Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-428 Tirzepatid

Stand: Oktober 2021

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Tirzepatid
zur Behandlung des Diabetes mellitus Typ 2

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Sulfonylharnstoffe Biguanide DPP-4-Hemmer (Gliptine) Glinide GLP-1-Rezeptor Agonisten (Glutide; Inkretinmimetika) Alpha-Glukosidasehemmer SGLT-2-Inhibitoren (Gliflozine) Thiazolidindione (Glitazone) Insuline und Analoga
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	– Beschlüsse über die Nutzenbewertung nach § 35a SGB V: o Linagliptin vom 21.02.2013 (erneute Nutzenbewertung) sowie Linagliptin (neues AWG) vom 16.05.2013 o Dapagliflozin sowie Dapagliflozin/Metformin (Neubewertung aufgrund neuer wissenschaftlicher Erkenntnisse) jeweils vom 19.12.2019 o Lixisenatid vom 05.09.2013 o Vildagliptin sowie Vildagliptin/Metformin vom 01.10.2013; Vildagliptin (erneute Nutzenbewertung) vom 21.05.2015 o Canagliflozin vom 04.09.2014 sowie Canagliflozin/Metformin vom 05.02.2015 o Insulin degludec vom 16.10.2014, Insulin degludec (neues AWG) vom 20.08.2015 sowie Insulin degludec (Neubewertung aufgrund neuer wissenschaftlicher Erkenntnisse) vom 16.05.2019

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Tirzepatid zur Behandlung des Diabetes mellitus Typ 2	
Kriterien gemäß 5. Kapitel § 6 VerfO	
	○ Albiglutid vom 19.03.2015 ○ Dulaglutid vom 16.07.2020 (Neubewertung aufgrund neuer wissenschaftlicher Erkenntnisse). ○ Insulin degludec/Liraglutid vom 15.10.2015 sowie Insulin degludec/Liraglutid (neues AWG) vom 04.02.2016 ○ Empagliflozin (erneute Nutzenbewertung) sowie Empagliflozin/Metformin vom 01.09.2016 ○ Sitagliptin, Sitagliptin/Metformin vom 15.12.2016 (erneute Nutzenbewertung nach Fristablauf) sowie Sitagliptin vom 22.3.2019 (erneute Nutzenbewertung nach Fristablauf) ○ Saxagliptin (erneute Bewertung nach Fristablauf) vom 15.12.2016 ○ Saxagliptin/Metformin (neues AWG) vom 01.10.2013; Saxagliptin/Metformin vom 15.12.2016 (erneute Nutzenbewertung nach Fristablauf) sowie Saxagliptin/Metformin (neues AWG) vom 01.02.2018 ○ Insulin glargin/Lixisenatid vom 16.08.2018 und Insulin glargin/Lixisenatid (nAWG) vom 15.10.2020. ○ Ertugliflozin/Sitagliptin vom 01.11.2018 ○ Empagliflozin/Linagliptin vom 22.11.2019. ○ Semaglutid vom 15.04.2021 – Bestehender Verordnungsausschluss (AM-RL, Anlage III): Glitazone – Bestehende Verordnungseinschränkungen (AM-RL, Anlage III): schnell wirkende/lang wirkende Insulinanaloga, Glinide, orale Antidiabetika, Harn- und Blutzuckerteststreifen – Richtlinie Methoden vertragsärztliche Versorgung (MVV-RL): Kontinuierliche interstitielle Glukosemessung mit Real-Time-Messgeräten (rtCGM) zur Therapiesteuerung bei insulinpflichtigem Diabetes mellitus – IQWiG- Rapid-Report zur LEADER Studie (Studie zu Liraglutid, Auftrag A17-09, Stand 23.08.2017)

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Tirzepatid zur Behandlung des Diabetes mellitus Typ 2	
Kriterien gemäß 5. Kapitel § 6 VerfO	
	– DMP Diabetes mellitus Typ 2 (Anforderungen an strukturierte Behandlungsprogramme für Diabetes mellitus Typ 2)
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff ATC-Code Handelsname	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel	
Tirzepatid ATC-Code /	<u>vorläufig geplantes Anwendungsgebiet lauf Beratungsanforderung</u> Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen als Zusatz zu Diät und körperlicher Aktivität angewendet - als Monotherapie, wenn die Anwendung von Metformin aufgrund einer Unverträglichkeit oder Kontraindikationen ungeeignet ist - zusätzlich zu anderen Arzneimitteln zur Behandlung des Diabetes mellitus
Biguanide	
Metformin A10BA02	Therapie des Diabetes mellitus Typ II; insbesondere bei übergewichtigen Patienten, bei denen allein durch Diät und körperliche Betätigung keine ausreichende Einstellung des Blutzuckerspiegels erreicht wurde.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
generisch	- Bei Erwachsenen kann Metformin Heumann in Form einer Monotherapie oder in Kombination mit anderen oralen Antidiabetika bzw. Insulin angewendet werden. - Bei Kindern ab 10 Jahren und bei Jugendlichen kann Metformin Heumann in Form einer Monotherapie oder in Kombination mit Insulin angewendet werden. - Bei übergewichtigen erwachsenen Patienten mit Diabetes mellitus Typ II konnte nach Versagen diätetischer Maßnahmen eine Senkung der Häufigkeit von diabetesbedingten Komplikationen unter Behandlung mit Metforminhydrochlorid als Therapie der ersten Wahl nachgewiesen werden. (siehe Abschnitt 5.1) (FI Metformin Heumann, Stand 11/2019)
Sulfonylharnstoffe	
Glibenclamid A10BB01 generisch	Nicht insulinabhängiger Diabetes mellitus bei Erwachsenen (NIDDM, Typ 2), wenn andere Maßnahmen wie konsequente Einhaltung der Diabetes-Diät, Gewichtsreduktion bei Übergewicht, ausreichende körperliche Betätigung nicht zu einer befriedigenden Einstellung des Blutglukosespiegels geführt haben. Glibenclamid AbZ® kann als Monotherapie oder in Kombination mit Metformin verwendet werden. (FI Glibenclamid, Stand 07/2018)
Glimepirid A10BB12 z.B. Amaryl®	Amaryl ist angezeigt zur Behandlung des Diabetes mellitus Typ 2, wenn eine Diät, körperliche Aktivität und Gewichtsreduktion allein nicht ausreichen. (FI Amaryl, Stand 04/2017)
Gliquidon A10BB08 Glurenorm®	Nicht-insulinabhängiger Diabetes mellitus bei Erwachsenen (NIDDM, Typ 2), wenn andere Maßnahmen wie konsequente Einhaltung der Diabetes-Diät, Gewichtsreduktion bei Übergewicht, ausreichende körperliche Betätigung nicht zu einer befriedigenden Einstellung des Blutglucosespiegels geführt haben. Glurenorm kann als Monotherapie oder in Kombination mit Metformin verwendet werden. (FI Glurenorm, Stand 10/2018)
Gliclazid	Nicht insulinabhängiger Diabetes mellitus (Typ II) bei Erwachsenen, sofern eine Diät, körperliche Aktivität und Gewichtsreduzierung

II. Zugelassene Arzneimittel im Anwendungsgebiet	
A10BB09 DIAMICRON UNO®	alleine nicht ausreichend sind, um den Blutzuckerspiegel einzustellen. (FI Diamicron, Stand 02/2020)
Alpha-Glucosidase-Inhibitoren	
Acarbose A10BF01 Acarbose AbZ®	Acarbose AbZ ist angezeigt zur Behandlung von Patienten mit nicht insulinabhängigem Diabetes mellitus (NIDDM, Diabetes mellitus Typ 2), wenn durch Diät und körperliche Betätigung keine ausreichende Blutzuckereinstellung erreicht wurde. Acarbose - 1 A Pharma kann in Kombination mit Metformin, einem Sulfonylharnstoff oder Insulin angewendet werden. (FI Acarbose, Stand 02/2014)
GLP-(Glucagon-like Peptide)-1-Rezeptor-Agonisten (Inkretinmimetika)	
Exenatide A10BX04 Byetta®	Byetta ist angezeigt zur Behandlung des Typ-2-Diabetes mellitus in Kombination mit - Metformin - Sulfonylharnstoffen - Thiazolidindionen - Metformin und einem Sulfonylharnstoff-Präparat - Metformin und einem Thiazolidindion-Präparat bei Erwachsenen, bei denen mit der maximal verträglichen Dosis dieser oralen Therapien eine angemessene Blutzuckerkontrolle nicht erreicht werden konnte. Byetta ist ebenfalls angezeigt als Kombinationstherapie mit Basalinsulin mit oder ohne Metformin und/oder Pioglitazon bei Erwachsenen, die mit diesen Arzneimitteln keine angemessene Blutzuckerkontrolle erreicht haben. (FI Byetta, Stand 02/2019)
Liraglutid A10BX07 Victoza®	Victoza wird zur Behandlung des unzureichend kontrollierten Diabetes mellitus Typ 2 bei Erwachsenen, Jugendlichen und Kindern ab dem Alter von 10 Jahren als Zusatz zu Diät und körperlicher Aktivität angewendet - als Monotherapie, wenn die Anwendung von Metformin aufgrund einer Unverträglichkeit oder Kontraindikation ungeeignet ist - zusätzlich zu anderen Arzneimitteln zur Behandlung des Diabetes mellitus.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
	Für Studienergebnisse hinsichtlich Kombinationen, Auswirkungen auf die glykämische Kontrolle und kardiovaskuläre Ereignisse, sowie untersuchten Populationen, siehe Abschnitte 4.4, 4.5 und 5.1. (FI Victoza, Stand 09/2020)
Insulin glargin/Lixisenatid A10AE54 Suliqua®	Suliqua wird als Ergänzung zu Diät und Bewegung zusätzlich zu Metformin mit oder ohne SGLT-2-Inhibitoren zur Behandlung von erwachsenen Patienten mit unzureichend kontrolliertem Diabetes mellitus Typ 2 zur Verbesserung der Blutzuckerkontrolle angewendet. (Zu Studienergebnissen hinsichtlich Wirkung auf die Blutzuckerkontrolle sowie der untersuchten Populationen siehe Abschnitt 4.4 und 5.1) (FI Suliqua, Stand 07/2020)
Dulaglutid A10BX14 Trulicity®	<u>Typ 2-Diabetes mellitus</u> Trulicity ist angezeigt zur Behandlung von Erwachsenen mit unzureichend kontrollie-tem Typ 2-Diabetes mellitus unterstützend zu Diät und Bewegung: • als Monotherapie, wenn die Einnahme von Metformin wegen Unverträglichkeit oder Kontraindikationen nicht angezeigt ist. • zusätzlich zu anderen Arzneimitteln zur Behandlung des Diabetes mellitus. Für Studienergebnisse hinsichtlich Kombinationen, Auswirkungen auf die glykämische Kontrolle und kardiovaskuläre Ereignisse, sowie untersuchten Populationen, siehe Abschnitte 4.4, 4.5 und 5.1. (FI Trulicity: Stand 11/2020)
Semaglutid A10BJ06 Ozempic®	Ozempic wird zur Behandlung des unzureichend kontrollierten Diabetes mellitus Typ 2 bei Erwachsenen als Zusatz zu Diät und körperlicher Aktivität angewendet - als Monotherapie, wenn die Anwendung von Metformin aufgrund einer Unverträglichkeit oder Kontraindikationen ungeeignet ist - zusätzlich zu anderen Arzneimitteln zur Behandlung des Diabetes mellitus. Für Studienergebnisse hinsichtlich Kombinationen, Auswirkungen auf die glykämische Kontrolle und kardiovaskuläre Ereignisse, sowie untersuchte Populationen, siehe Abschnitte 4.4, 4.5 und 5.1. (FI Ozempic, Stand 03/2021)

Gliptine (DPP (Dipeptidylpeptidase)-4 Hemmer)	
Saxagliptin A10BH03 Onglyza®	Onglyza ist bei erwachsenen Patienten mit Typ-2-Diabetes mellitus in Ergänzung zu einer Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle indiziert: - Als Monotherapie, wenn Metformin aufgrund von Unverträglichkeit oder Kontraindikationen ungeeignet ist. - In Kombination mit anderen Arzneimitteln zur Behandlung des Diabetes einschließlich Insulin, wenn diese den Blutzucker nicht ausreichend kontrollieren (siehe Abschnitte 4.4, 4.5 und 5.1 bezüglich vorhandener Daten für verschiedene Kombinationen) (FI Onglya, Stand 03/2020)
Saxagliptin/Metformin A10BD10 Komboglyze®	Komboglyze ist als Ergänzung zu Diät und Bewegung angezeigt, um die Blutzuckerkontrolle bei erwachsenen Patienten mit Typ-2-Diabetes mellitus zu verbessern: - Bei Patienten, die mit der maximal verträglichen Dosis von Metformin allein nicht ausreichend kontrolliert sind. - In Kombination mit anderen Arzneimitteln zur Behandlung des Diabetes einschließlich Insulin, bei Patienten, die mit Metformin und diesen Arzneimitteln nicht ausreichend kontrolliert sind (siehe Abschnitte 4.4, 4.5 und 5.1 bezüglich vorhandener Daten für verschiedene Kombinationen). - Bei Patienten, die bereits mit der Kombination von Saxagliptin und Metformin als separate Tabletten behandelt werden. (FI Komboglyze, Stand 03/2020)
Sitagliptin A10BH01 Januvia®	Bei erwachsenen Patienten mit Typ-2-Diabetes mellitus ist Januvia indiziert zur Verbesserung der Blutzuckerkontrolle: <u>Als Monotherapie:</u> - bei Patienten, bei denen Diät und Bewegung allein den Blutzucker nicht ausreichend senken und für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeit nicht geeignet ist. <u>Als orale Zweifachtherapie in Kombination mit:</u> - Metformin, wenn Diät und Bewegung plus eine Monotherapie mit Metformin den Blutzucker nicht ausreichend senken. - einem Sulfonylharnstoff, wenn Diät und Bewegung plus eine Monotherapie mit einem Sulfonylharnstoff in der höchsten vertragenen Dosis den Blutzucker nicht ausreichend senken und wenn Metformin aufgrund von Gegenanzeigen oder Unverträglichkeit nicht geeignet ist. - einem Peroxisomal Proliferator-activated Receptor gamma(PPARγ)-Agonisten (d. h. einem Thiazolidindion), wenn die Anwendung eines PPARγ-Agonisten angebracht ist und Diät und Bewegung plus Monotherapie mit einem PPARγ-Agonisten den Blutzucker nicht ausreichend senken. <u>Als orale Dreifachtherapie in Kombination mit</u>: - einem Sulfonylharnstoff und Metformin, wenn Diät und Bewegung plus eine Zweifachtherapie mit diesen Arzneimitteln den

	Blutzucker nicht ausreichend senken. - einem PPARγ-Agonisten und Metformin, wenn die Anwendung eines PPARγ-Agonisten angebracht ist und Diät und Bewegung plus eine Zweifachtherapie mit diesen Arzneimitteln den Blutzucker nicht ausreichend senken. Januvia ist auch zusätzlich zu Insulin indiziert (mit oder ohne Metformin), wenn Diät und Bewegung sowie eine stabile Insulindosis den Blutzucker nicht ausreichend senken. (FI Januvia, Stand 05/2020)
Sitagliptin/Metformin A10BD07 z.B. Janumet®	Für erwachsene Patienten mit Typ-2-Diabetes mellitus: Janumet ist zusätzlich zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle bei Patienten indiziert, bei denen eine Monotherapie mit Metformin in der höchsten vertragenen Dosis den Blutzucker nicht ausreichend senkt oder die bereits mit der Kombination von Sitagliptin und Metformin behandelt werden. Janumet ist in Kombination mit einem Sulfonylharnstoff (z. B. als Dreifachtherapie) zusätzlich zu Diät und Bewegung bei Patienten indiziert, bei denen eine Kombination aus der jeweils höchsten vertragenen Dosis von Metformin und eines Sulfonylharnstoffs nicht ausreicht, um den Blutzucker zu senken. Janumet ist als Dreifachtherapie in Kombination mit einem Peroxisomal Proliferator-activated Receptor gamma(PPARγ)-Agonisten (d. h. einem Thiazolidindion) zusätzlich zu Diät und Bewegung bei Patienten indiziert, bei denen die jeweils höchste vertragene Dosis von Metformin und einem PPARγ-Agonisten nicht ausreicht, um den Blutzucker zu senken. Janumet ist auch zusätzlich zu Insulin (d. h. als Dreifachtherapie) indiziert als Ergänzung zu Diät und Bewegung bei Patienten, bei denen eine stabile Insulindosis und Metformin allein den Blutzucker nicht ausreichend senken. (FI Janumet, Stand 09/2020)
Ertugliflozin/Sitagliptin A10BD24 Steglujan®	Bei Erwachsenen ab 18 Jahren mit Typ-2 Diabetes mellitus zusätzlich zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle: - bei Patienten, deren Blutzucker unter Metformin und/oder einem Sulfonylharnstoff und einem der in dem vorliegenden Arzneimittel enthaltenen Einzelwirkstoffe nicht ausreichend gesenkt werden kann. - bei Patienten, die bereits mit der Kombination aus Ertugliflozin und Sitagliptin in Form von einzelnen Tabletten behandelt werden. (Zu Studienergebnissen für die Kombinationen und die Wirkung auf die Blutzuckerkontrolle, siehe Abschnitte 4.4, 4.5 und 5.1.) (FI Steglujan, Stand 07/2020)
Vildagliptin A10BH02	Vildagliptin ist angezeigt zur Behandlung von Diabetes mellitus Typ 2 bei Erwachsenen: <u>Monotherapie</u>

Jalra®	- bei Patienten, die durch Diät und Bewegung allein nicht ausreichend therapiert sind und für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeiten nicht geeignet ist. <u>In einer oralen Zweifach-Kombinationstherapie mit:</u> - Metformin bei Patienten, deren Blutzucker trotz Monotherapie mit maximal verträglichen Dosen von Metformin unzureichend eingestellt ist, - einem Sulfonylharnstoff bei Patienten, deren Blutzucker trotz Monotherapie mit maximal verträglichen Dosen eines Sulfonylharnstoffs unzureichend eingestellt ist und bei denen Metformin wegen Kontraindikationen oder Unverträglichkeit ungeeignet ist, - einem Thiazolidindion bei Patienten mit ungenügender Blutzuckereinstellung, für die die Anwendung eines Thiazolidindions geeignet ist. <u>In orale Dreifach-Kombinationstherapie mit:</u> - einem Sulfonylharnstoff und Metformin, wenn Diät und Bewegung zusätzlich zu einer Zweifachtherapie mit diesen Arzneimitteln zu keiner adäquaten glykämischen Kontrolle führen. Vildagliptin ist auch für die Anwendung in Kombination mit Insulin indiziert (mit oder ohne Metformin), wenn Diät und Bewegung zusätzlich zu einer stabilen Insulindosis zu keiner adäquaten glykämischen Kontrolle führen. (FI Jalra: Stand 10/2020)
Vildagliptin/Metformin A10BD08 z.B. Eucreas®	Vildagliptin/Metformin ist für die Behandlung des Typ-2-Diabetes-mellitus indiziert: Vildagliptin/Metformin ist für die Behandlung von Erwachsenen indiziert, deren Blutzucker trotz Monotherapie mit der maximal verträglichen Dosis von Metformin alleine unzureichend eingestellt ist oder die bereits mit einer Kombination aus Vildagliptin und Metformin in separaten Tabletten behandelt werden. Vildagliptin/Metformin ist in Kombination mit einem Sulfonylharnstoff (d. h. Dreifachkombinationstherapie) zusätzlich zu Diät und Bewegung indiziert bei erwachsenen Patienten, die mit Metformin und einem Sulfonylharnstoff nicht ausreichend eingestellt werden können. Vildagliptin/Metformin ist als Dreifachkombinationstherapie mit Insulin zusätzlich zu Diät und Bewegung indiziert, um die glykämische Kontrolle bei erwachsenen Patienten zu verbessern, wenn eine stabile Insulindosis und Metformin allein zu keiner adäquaten glykämischen Kontrolle führen. (FI Eucreas: Stand 05/2020)

Selektive Natrium-Glucose-Cotransport-Inhibitoren (SGLT-2-Inhibitoren)	
Dapagliflozin A10BX09 Forxiga®	Zugelassenes Anwendungsgebiet: Forxiga ist bei erwachsenen Patienten indiziert zur Behandlung von unzureichend kontrolliertem - Typ-2-Diabetes mellitus zur Verbesserung der Blutzuckerkontrolle in Ergänzung zu einer Diät und Bewegung: o als Monotherapie, wenn Metformin aufgrund einer Unverträglichkeit als ungeeignet erachtet wird o zusätzlich zu anderen Arzneimitteln zur Behandlung des Typ-2-Diabetes. Zu Studienergebnissen im Hinblick auf Kombinationen von Behandlungen, die Wirkung auf die Blutzuckerkontrolle und kardiovaskuläre Ereignisse sowie die untersuchten Populationen, siehe Abschnitte 4.4, 4.5 und 5.1. […] (FI Forxiga, Stand 11/2020)
Dapagliflozin/Metformin A10BD15 z.B. Xigduo®	Xigduo ist bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus indiziert, als Ergänzung zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle: - bei Patienten, bei denen der Blutzucker mit der maximal verträglichen Dosis von Metformin allein nicht ausreichend kontrolliert wird - in Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin bei Patienten, bei denen der Blutzucker mit Metformin und diesen Arzneimitteln nicht ausreichend kontrolliert wird - bei Patienten, die bereits mit der Kombination aus Dapagliflozin und Metformin als separate Tabletten behandelt werden. (FI Xigduo, Stand 11/2019)
Empagliflozin A10BX12 Jardiance®	Jardiance wird zur Behandlung von Erwachsenen mit nicht ausreichend behandeltem Typ-2-Diabetes mellitus als Ergänzung zu Diät und Bewegung angewendet - als Monotherapie, wenn Metformin aufgrund einer Unverträglichkeit als ungeeignet erachtet wird - zusätzlich zu anderen Arzneimitteln zur Behandlung von Diabetes Zu Studienergebnissen im Hinblick auf Kombinationen, die Wirkung auf Blutzuckerkontrolle und kardiovaskuläre Ereignisse sowie die untersuchten Populationen siehe Abschnitte 4.4, 4.5 und 5.1. (FI Jardiance, Stand 09/2020)
Empagliflozin/Linagliptin A10BD19 Glyxambi®	Glyxambi, eine Fixdosiskombination aus Empagliflozin und Linagliptin, wird angewendet bei Erwachsenen ab 18 Jahren mit Typ-2-Diabetes mellitus: • zur Verbesserung der Blutzuckerkontrolle, wenn Metformin und/oder Sulfonylharnstoff (SH) und eine der Monosubstanzen von

	Glyxambi zur Blutzuckerkontrolle nicht ausreichen • wenn der Patient bereits mit der freien Kombination von Empagliflozin und Linagliptin behandelt wird. (FI Glyxambi, Stand 10/2020)
Ertugliflozin A10BK04 Steglatro®	Steglatro ist zur Behandlung von Erwachsenen mit unzureichend kontrolliertem Typ-2 Diabetes mellitus als Ergänzung zu Diät und Bewegung angezeigt: • Als Monotherapie, wenn Metformin aufgrund von Unverträglichkeit oder Gegenanzeigen nicht geeignet ist. • Zusätzlich zu anderen Arzneimitteln zur Behandlung von Diabetes. Zu Studienergebnissen im Hinblick auf die Kombinationen von Therapien, die Wirkung auf die Blutzuckerkontrolle, die kardiovaskulären Ereignisse und die untersuchten Populationen, siehe Abschnitte 4.4, 4.5 und 5.1. (FI Steglatro, Stand 10/2021)
Glinide	*Verordnungseinschränkung Anlage III – AM-RL*
Nateglinid A10BX03 Starlix®	Kombinationstherapie mit Metformin bei Patienten mit Typ-2-Diabetes, die nicht ausreichend mit einer maximal tolerierbaren Metformin-Dosis eingestellt werden können. (FI Starlix, Stand 05/2018)
Repaglinid A10BX02 z.B. Repaglinid AbZ®	Repaglinid ist indiziert bei Patienten mit Typ 2 Diabetes (NIDDM, nicht insulinabhängiger Diabetes mellitus), wenn der Blutzuckerspiegel durch Diät, Gewichtsreduktion und körperliche Aktivität alleine nicht mehr ausreichend reguliert werden kann. Repaglinid kann bei Typ 2 Diabetes-Patienten in Kombination mit Metformin eingenommen werden, falls die Blutzuckereinstellung mit Metformin allein nicht zufriedenstellend reguliert werden kann. Die Therapie sollte als Ergänzung zu Diät und körperlicher Bewegung begonnen werden, um die Blutzuckerwerte in Abhängigkeit von der Mahlzeit zu reduzieren. (FI Repaglinid, Stand 02/2016)
Glitazone	*Verordnungsausschluss Anlage III – AM-RL*
Humaninsuline	
Insulin human A10A C01	Zur Behandlung von Patienten mit Diabetes mellitus, die Insulin für die Aufrechterhaltung einer normalen Glukosehomöostase benötigen.

Berlinsulin H 30/70	(FI Berlininsulin, Stand 08/2020)
Insulinanaloga	*Verordnungseinschränkung Anlage III – AM-RL*
Insuline schnell wirkend: Insulin lispro, Insulin aspart, Insulin glulisin A10AB01-06 NovoRapid 100 I.E./ml	NovoRapid wird angewendet zur Behandlung von Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern ab dem Alter von 1 Jahr. (FI Novorapid, Stand 09/2020)
Insuline lang wirkend: Insulin detemir, Insulin glargin, Insulin degludec A10AE01-06 Lantus 100 I.E./ml	Insulin glargin: Zur Behandlung von Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern im Alter von 2 Jahren und älter. (Fachinformation Lantus, Stand 07/2020)

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-428 Tirzepatide, 2021-B-132-z Tirzepatide

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	22. Juni 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

ACP	American College of Physicians
AGI	Alpha-glucosidase inhibitor
AHA	Antihyperglycaemic agent
AHRQ	U.S. Agency for Healthcare Research and Quality
AMSTAR	A Measurement Tool to Assess systematic Reviews
ASCVD	Atherosclerotic cardiovascular disease
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BB	Basal-bolus
BI	Basal insulin
BMI	Body mass index
BP	Basal-plus
CKD	Chronic kidney disease
CV(D)	Cardiovascular (disease)
DBP	Diastolic blood pressure
DKA	Diabetic ketoacidosis
DPP-4(i)	Dipeptidyl peptidase-4 (inhibitor)
ECRI	ECRI Guidelines Trust
eGFR	the estimated glomerular filtration rate
EMA	European Medicines Agency
EMPA	Empagliflozin
ESRD	End-stage renal disease
FBG	Fasting blood glucose
FDA	U.S. Food and Drug Administration
FE	Fixed effects
FPG	Fasting plasma glucose
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GLP-1 (RA)	Glucagon-like peptide-1 (receptor agonits)
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTI	Genital tract infection
HbA1c	Haemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
HF	Heart failure

HR	Hazard Ratio
INS	Insulin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LDL-C	Low-density lipoprotein cholesterol
LoE	Level of Evidence
MACE	Major adverse cardiovascular events
MET	Metformin
MD	Mean difference
NAFLD	Non alcoholic fatty liver disease
NICE	National Institute for Health and Care Excellence
NMA	Network Meta-Analysis
NPH	Neutral protamine Hagedorn
NVL	Nationale VorsorgungsLeitlinie
OAD	Oral antidiabetic agent
OR	Odds Ratio
PBG	Postprandial blood glucose
PBO	Placebo
PPG	Postprandial glucose
RCT	Randomised controlled trial
RE	Random effects
RR	Relatives Risiko
SAE	(Serious) adverse events
SBP	Systolic blood pressure
SCD	Sudden cardiac death
SGLT-2(i)	Sodium–glucose cotransporter 2 (inhibitor)
SIGN	Scottish Intercollegiate Guidelines Network
SMPG	Self-monitored plasma glucose
SU	Sulfonylureas
T2DM	Type 2 diabetes mellitus
TRIP	Turn Research into Practice Database
TZD	Thiazolidinediones
UACR	Urine Albumin-to-Creatinine Ratio
UTI	Urinary tract infection
WHO	World Health Organization
WMD	Weighted mean difference

1 Indikation

Diabetes mellitus Typ 2 bei Erwachsenen

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Diabetes Mellitus Typ 2 durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 07.05.2021 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1977 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 117 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

G-BA, 2021 [28].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Semaglutid (Diabetes mellitus Typ 2) vom 15. April 2021

Anwendungsgebiet

Ozempic wird zur Behandlung des unzureichend kontrollierten Diabetes mellitus Typ 2 bei Erwachsenen als Zusatz zu Diät und körperlicher Aktivität angewendet

- als Monotherapie, wenn die Anwendung von Metformin aufgrund einer Unverträglichkeit oder Kontraindikationen ungeeignet ist
- zusätzlich zu anderen Arzneimitteln zur Behandlung des Diabetes mellitus.

Rybelsus wird zur Behandlung des unzureichend kontrollierten Diabetes mellitus Typ 2 bei Erwachsenen zur Verbesserung der glykämischen Kontrolle als Zusatz zu Diät und körperlicher Aktivität angewendet

- als Monotherapie, wenn die Anwendung von Metformin aufgrund einer Unverträglichkeit oder Kontraindikationen ungeeignet ist
- in Kombination mit anderen Arzneimitteln zur Behandlung des Diabetes mellitus.

a) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung allein den Blutzucker nicht ausreichend kontrollieren, und für die die Anwendung von Metformin aufgrund einer Unverträglichkeit nicht geeignet ist

a1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

a2) bei Patienten mit manifester kardiovaskulärer Erkrankung[1] in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2]

b) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit einem blutzuckersenkenden Arzneimittel (außer Insulin) den Blutzucker nicht ausreichend kontrollieren

b1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

b2) bei Patienten mit manifester kardiovaskulärer Erkrankung1 in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2]

c) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit mindestens zwei blutzuckersenkenden Arzneimitteln (außer Insulin) den Blutzucker nicht ausreichend kontrollieren

c1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

c2) bei Patienten mit manifester kardiovaskulärer Erkrankung[1] in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2]

d) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit Insulin (mit oder ohne einem anderen blutzuckersenkenden Arzneimittel) den Blutzucker nicht ausreichend kontrollieren

d1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

d2) bei Patienten mit manifester kardiovaskulärer Erkrankung[1] in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2]

Zweckmäßige Vergleichstherapie

a1) Sulfonylharnstoff (Glibenclamid oder Glimepirid)

a2) Sulfonylharnstoff (Glibenclamid oder Glimepirid)

b1)

- Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) oder
- Metformin + Empagliflozin oder
- Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder kontraindiziert ist

b2)

- Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) oder
- Metformin + Empagliflozin oder
- Metformin + Liraglutid[3] oder
- Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder kontraindiziert ist

c1)

- Humaninsulin + Metformin oder
- nur Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam ist

c2)

- Humaninsulin + Metformin oder
- Humaninsulin + Empagliflozin[3] oder
- Humaninsulin + Liraglutid[3] oder
- Humaninsulin, wenn die bestimmten Kombinationspartner gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind

d1) Die Optimierung des Humaninsulinregimes (ggf. + Metformin)

d2) Die Optimierung des Humaninsulinregimes (ggf. + Metformin *oder* Empagliflozin[3] *oder* Liraglutid[3])

Fazit / Ausmaß des Zusatznutzens

a1) Ein Zusatznutzen ist nicht belegt.

a2) Ein Zusatznutzen ist nicht belegt

b1) Ein Zusatznutzen ist nicht belegt.

b2) Ein Zusatznutzen ist nicht belegt.

c1) Ein Zusatznutzen ist nicht belegt.

c2) Ein Zusatznutzen ist nicht belegt.

d1) Ein Zusatznutzen ist nicht belegt.

d2) Ein Zusatznutzen ist nicht belegt.

1 manifeste kardiovaskuläre Erkrankung ist im vorliegenden Fall anhand der SUSTAIN 6-Studie (siehe Studienprotokoll, Marso et. al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes.

N Engl J Med 2016; 375:1834-1844. DOI: 10.1056/NEJMoa1607141) definiert und hier näherungsweise zusammengefasst als ≥ 50 Jahre mit mindestens einer kardiovaskulären Erkrankung (vorangegangener Herzinfarkt; Schlaganfall oder transitorische ischämische Attacke, Revaskularisation, > 50% Stenose, vorangegangene symptomatische koronare Herzerkrankung oder instabile Angina, asymptomatische kardiale Ischämie, chronisches Herzversagen (NYHA-Klasse II-III) oder chronisches Nierenversagen) oder ≥ 60 Jahre mit mindestens einem Risikofaktor für kardiovaskuläre Erkrankungen (Mikroalbuminurie oder Proteinurie, Bluthochdruck und linksventrikuläre Hypertrophie, linksventrikuläre systolische oder diastolische Dysfunktion oder Knöchel-Arm-Index < 0,9).
2 Insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker
3 Empagliflozin bzw. Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten

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G-BA, 2021 [31].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage III: Übersicht über Verordnungseinschränkungen und -ausschlüsse in der Arzneimittelversorgung durch die Arzneimittel-Richtlinie und aufgrund anderer Vorschriften (§ 34 Absatz 1 Satz 6 und Absatz 3 SGB V), Hinweise zur wirtschaftlichen Verordnungsweise von nicht verschreibungspflichtigen Arzneimitteln für Kinder bis zum vollendeten 12. Lebensjahr und für Jugendliche mit Entwicklungsstörungen bis zum vollendeten 18. Lebensjahr sowie Verordnungseinschränkungen und -ausschlüsse von sonstigen Produkten; zuletzt geändert am 20. Februar 2021

11. Antidiabetika, orale

Verordnungseinschränkung verschreibungspflichtiger Arzneimittel nach dieser Richtlinie. [4]

- ausgenommen nach erfolglosem Therapieversuch mit nichtmedikamentösen Maßnahmen.

Die Anwendung anderer therapeutischer Maßnahmen ist zu dokumentieren.

33. Insulinanaloga, schnell wirkende zur Behandlung des Diabetes mellitus Typ 2.

Verordnungseinschränkung verschreibungspflichtiger Arzneimittel nach dieser Richtlinie. [4]

Hierzu zählen:

- Insulin Aspart
- Insulin Glulisin
- Insulin Lispro

Diese Wirkstoffe sind nicht verordnungsfähig, solange sie mit Mehrkosten im Vergleich zu schnell wirkendem Humaninsulin verbunden sind. Das angestrebte Behandlungsziel ist mit Humaninsulin ebenso zweckmäßig, aber kostengünstiger zu erreichen. Für die Bestimmung der Mehrkosten sind die der zuständigen Krankenkasse tatsächlich entstehenden Kosten maßgeblich.

Dies gilt nicht für Patienten

- mit Allergie gegen den Wirkstoff Humaninsulin
- bei denen trotz Intensivierung der Therapie eine stabile adäquate Stoffwechsellage mit Humaninsulin nicht erreichbar ist, dies aber mit schnell wirkenden Insulinanaloga nachweislich gelingt
- bei denen aufgrund unverhältnismäßig hoher Humaninsulindosen eine Therapie mit schnell wirkenden Insulinanaloga im Einzelfall wirtschaftlicher ist.

33a. Insulinanaloga, lang wirkende zur Behandlung des Diabetes mellitus Typ 2.

Verordnungseinschränkung verschreibungspflichtiger Arzneimittel nach dieser Richtlinie. [4]

Hierzu zählen:

- Insulin glargin
- Insulin detemir

Diese Wirkstoffe sind nicht verordnungsfähig, solange sie - unter Berücksichtigung der notwendigen Dosierungen zur Erreichung des therapeutischen Zieles - mit Mehrkosten im Vergleich zu intermediär wirkendem Humaninsulin verbunden sind. Das angestrebte Behandlungsziel ist mit Humaninsulin ebenso zweckmäßig, aber kostengünstiger zu erreichen. Für die Bestimmung der Mehrkosten sind die der zuständigen Krankenkasse tatsächlich entstehenden Kosten maßgeblich.

Diese Regelungen gelten nicht für

- eine Behandlung mit Insulin glargin bei Patienten, bei denen im Rahmen einer intensivierten Insulintherapie auch nach individueller Therapiezielüberprüfung und individueller Anpassung des Ausmaßes der Blutzuckersenkung in Einzelfällen ein hohes Risiko für schwere Hypoglykämien bestehen bleibt,
- Patienten mit Allergie gegen intermediär wirkende Humaninsuline.

49. Glitazone zur Behandlung des Diabetes mellitus Typ 2.

Verordnungsausschluss verschreibungspflichtiger Arzneimittel nach dieser Richtlinie. [3]

Hierzu zählen:

- Pioglitazon
- Rosiglitazon

50. Glinide zur Behandlung des Diabetes mellitus Typ 2.

Verordnungseinschränkung verschreibungspflichtiger Arzneimittel nach dieser Richtlinie. [4]

- Nateglinid
- Repaglinid

Ausgenommen ist die Behandlung von niereninsuffizienten Patienten mit einer Kreatinin-Clearance < 25 ml / min mit Repaglinid, soweit keine anderen oralen Antidiabetika in Frage kommen und eine Insulintherapie nicht angezeigt ist.

52. Harn- und Blutzuckerteststreifen bei Patienten mit Diabetes mellitus Typ 2, die nicht mit Insulin behandelt werden

Verordnungseinschränkung nach § 92 Absatz 1 Satz 1 Halbsatz 3 SGB V in Verbindung mit § 16 Absatz 1 AM-RL

ausgenommen bei instabiler Stoffwechsellage. Diese kann gegeben sein bei interkurrenten Erkrankungen, Ersteinstellung auf oder Therapieumstellung bei oralen Antidiabetika mit hohem Hypoglykämierisiko (grundsätzlich je Behandlungssituation bis zu 50 Teststreifen)

[3] Verordnungsausschluss nach dieser Richtlinie (§ 92 Abs. 1 Satz 1 Halbsatz 3 SGB V in Verbindung mit § 16 Abs. 1 und 2 AM-RL).
[4] Verordnungseinschränkung nach dieser Richtlinie (§ 92 Abs. 1 Satz 1 Halbsatz 3 SGB V in Verbindung mit § 16 Abs. 1 und 2 AM-RL).

G-BA, 2020 [30].

Richtlinie des Gemeinsamen Bundesausschusses zur Zusammenführung der Anforderungen an strukturierte Behandlungsprogramme nach § 137f Abs. 2 SGB V (DMP-Anforderungen-Richtlinie/DMP-A-RL) in der Fassung vom 20. März 2014, veröffentlicht im Bundesanzeiger (BAnz AT 2 6. Juni 2014 B3 AT 26. August 2014 B2), in Kraft getreten am 1. Juli 2014; zuletzt geändert am 17. Dezember 2020, veröffentlicht im Bundesanzeiger (BAnz AT 14. Januar 2021 B4); Inkrafttreten: 1. Januar 2021

Anlage 1 Anforderungen an strukturierte Behandlungsprogramme für Diabetes mellitus Typ 2

1 Behandlung nach dem aktuellen Stand der medizinischen Wissenschaft unter Berücksichtigung von evidenzbasierten Leitlinien oder nach der jeweils besten, verfügbaren Evidenz sowie unter Berücksichtigung des jeweiligen Versorgungssektors (§ 137f Abs. 2 Satz 2 Nr. 1 des Fünften Buches Sozialgesetzbuch, SGB V)

…

1.3 Therapie des Diabetes mellitus Typ 2

1.3.1 Therapieziele

Die Therapie dient der Erhöhung der Lebenserwartung sowie der Erhaltung oder der Verbesserung der von einem Diabetes mellitus Typ 2 beeinträchtigten Lebensqualität. Dabei sind in Abhängigkeit z. B. von Alter und Begleiterkrankungen der Patientin oder des Patienten folgende individuelle Therapieziele anzustreben:

- Vermeidung von Symptomen der Erkrankung (z. B. Polyurie, Polydipsie, Abgeschlagenheit) einschließlich der Vermeidung neuropathischer Symptome, Vermeidung von Nebenwirkungen der Therapie (insbesondere schwere oder rezidivierende Hypoglykämien) sowie schwerer hyperglykämischer Stoffwechselentgleisungen,
- Reduktion des erhöhten Risikos für kardiale, zerebrovaskuläre und sonstige makroangiopathische Morbidität und Mortalität,
- Vermeidung der mikrovaskulären Folgeschäden (insbesondere Retinopathie mit schwerer Sehbehinderung oder Erblindung, Niereninsuffizienz mit der Notwendigkeit einer Nierenersatztherapie),
- Vermeidung des diabetischen Fußsyndroms mit neuro-, angio- und/oder osteoarthropathischen Läsionen und von Amputationen.

1.5 Blutglukosesenkende medikamentöse Therapie

1.5.1 Grundsätze der Wirkstoffauswahl

Bei der Wirkstoffauswahl zur antidiabetischen Therapie sind neben der Beachtung von Zulassung, Verordnungsfähigkeit und Kontraindikationen prinzipiell folgende Kriterien zu berücksichtigen:

- Beleg der Wirksamkeit anhand klinisch relevanter mikro- und makrovaskulärer Endpunkte
- Eignung von Wirkungsmechanismus, Wirkungs- und Nebenwirkungsprofil (z. B. Risiko von Hypoglykämien und Gewichtszunahme), Arzneimittelinteraktionen und Pharmakokinetik für die individuelle Indikationsstellung
- individuelle Wirkung und Verträglichkeit
- Patientensicherheit
- individuelle Patientenbedürfnisse im Sinne eines „shared-decision-making“.

Kontrollierte Studien mit klinischen Endpunkten (Tod, Infarkt, Herzinsuffizienz, Niereninsuffizienz, Amputation etc.) sind das wichtigste Instrument zum Wirksamkeitsnachweis einer Therapie und daher auch wichtigste Grundlage aller Therapieentscheidungen.

Antidiabetika mit gesicherter günstiger Beeinflussung klinischer Endpunkte:

- Metformin
- Sulfonylharnstoffe (SH) Glibenclamid und Gliclazid
- Insulin.

Antidiabetika ohne gesicherte günstige Beeinflussung klinischer Endpunkte:

- Alpha-Glukosidasehemmer
- DPP-4-Inhibitoren (Dipeptidyl-Peptidase-4-Inhibitoren, Gliptine)
- SGLT2-Inhibitoren (Gliflozine), außer Empagliflozin in der unten genannten Indikation
- Glinide
- GLP-1-Rezeptoragonisten (Inkretinmimetika, GLP-1-Analoga) außer Liraglutid in der unten genannten Indikation
- Andere Antidiabetika (z. B. Glimepirid).

Patientinnen und Patienten mit manifester kardiovaskulärer Erkrankung, die mit Medikamenten zur Behandlung kardiovaskulärer Risikofaktoren behandelt werden, können bei unzureichender Kontrolle des Diabetes mellitus / bei unzureichender Blutzuckerkontrolle von Empagliflozin in Kombination mit mindestens einem weiteren oralen Antidiabetikum und/oder mit Insulin profitieren.

1.5.2 Primärtherapie (Monotherapie)

Metformin ist bevorzugt zu verwenden. Sulfonylharnstoffe (Glibenclamid und Gliclazid) können als Alternative bei Unverträglichkeiten gegenüber Metformin eingesetzt werden. Eine Überlegenheit für Insulin als Ersttherapie gegenüber diesen oralen Antidiabetika in Monotherapie ist nicht belegt. Bei hohem Ausgangsblutzucker und HbA1c-Wert und erforderlicher starker Wirkung kann auch im Rahmen der Ersttherapie der Einsatz von Insulin notwendig sein.

1.5.3 Therapieeskalation/Kombinationstherapie

Reicht die primäre Monotherapie nicht aus, um das HbA1c-Ziel zu erreichen, kann eine Kombination mehrerer Antidiabetika helfen, den Blutzucker besser zu kontrollieren. Für entsprechende Therapieregime sind Langzeitstudien zu berücksichtigen, die einen Nutzen in Bezug auf klinische Endpunkte bzw. die Langzeitsicherheit belegen. Eine Nutzen-Schaden-Abwägung muss sorgfältig vorgenommen werden.

G-BA, 2020 [29].

Richtlinie des Gemeinsamen Bundesausschusses zu Untersuchungs- und Behandlungsmethoden der vertragsärztlichen Versorgung (Richtlinie Methoden vertragsärztliche Versorgung), zuletzt geändert am 17. Dezember 2020

20. Kontinuierliche interstitielle Glukosemessung mit Real-Time-Messgeräten (rtCGM) zur Therapiesteuerung bei Patientinnen und Patienten mit insulinpflichtigem Diabetes mellitus

§ 1 Beschreibung der Methode

Bei der Intervention der Kontinuierlichen interstitiellen Glukosemessung mit Real-Time-Messgeräten (rtCGM) wird mittels eines Sensors kontinuierlich der Glukosegehalt in der interstitiellen Flüssigkeit des Unterhautfettgewebes gemessen. Anschließend überträgt ein mit dem Sensor verbundener Transmitter die Messwerte automatisch an das Empfangsgerät. Es werden kontinuierlich Messwerte und der Trend zum Glukosegehalt ausgegeben. Anhand einer Alarmfunktion mit individuell einstellbaren Grenzwerten warnt das Gerät vor dem Erreichen zu hoher oder zu niedriger Glukosewerte.

§ 2 Indikation

(1) Die Kontinuierliche interstitielle Glukosemessung mit Real-Time-Messgeräten (rtCGM) darf zu Lasten der gesetzlichen Krankenversicherung erbracht werden

1. bei Patientinnen und Patienten mit insulinpflichtigem Diabetes mellitus,

2. die einer intensivierten Insulinbehandlung bedürfen, in dieser geschult sind und diese bereits anwenden,

3. insbesondere dann, wenn die zwischen Ärztin oder Arzt und Patientin oder Patient festgelegten individuellen Therapieziele zur Stoffwechseleinstellung auch bei Beachtung der jeweiligen Lebenssituation der Patientin oder des Patienten nicht erreicht werden können

4. und wenn die Voraussetzungen des § 3 vorliegen.

(2) Als intensiviert ist eine Insulintherapie anzusehen, bei der die Patientin oder der Patient entsprechend ihres oder seines Lebensstils den Zeitpunkt und die Zusammensetzung der Mahlzeit selbst frei festlegt und dementsprechend die Dosierung des Mahlzeiteninsulins anhand der Menge der aufzunehmenden Kohlenhydrate und der Höhe des präprandialen Blutzuckerspiegels steuert.

§ 3 Vorgaben zur Qualitätssicherung

(1) Im Rahmen der vertragsärztlichen Versorgung darf die Kontinuierliche interstitielle Glukosemessung mit Real-Time-Messgeräten (rtCGM) nur bei Erfüllung der in den folgenden Absätzen aufgeführten Qualitätssicherungsvorgaben durchgeführt werden:

(2) Zur Durchführung der Methode rtCGM im Rahmen der vertragsärztlichen Versorgung berechtigt sind:

1. Fachärzte für Innere Medizin und Endokrinologie und Diabetologie oder

2. Fachärzte für Innere Medizin, für Allgemeinmedizin oder für Kinder- und Jugendmedizin jeweils mit der Anerkennung „Diabetologie“ oder „Diabetologe Deutsche Diabetes Gesellschaft (DDG)“ bzw. mit vergleichbarer Qualifikation oder

3. Fachärzte für Kinder- und Jugendmedizin mit der Anerkennung „Kinder- Endokrinologie und -Diabetologie“.

Die in der Richtlinie verwendeten Facharzt-, Schwerpunkt- und Zusatzbezeichnungen richten sich nach der (Muster-) Weiterbildungsordnung der Bundesärztekammer und schließen auch diejenigen Ärzte ein, welche eine entsprechende Bezeichnung nach altem Recht führen.

(3) Die Patientin oder der Patient muss zeitnah im Zuge der Verordnung und vor der ersten Anwendung des rtCGM über die Schulungsinhalte zur intensivierten Insulintherapie (ICT und gegebenenfalls zur Insulinpumpe) hinausgehend, hinsichtlich der sicheren Anwendung des Gerätes, insbesondere der Bedeutung der Blutglukose-Selbstmessung und der durch das Gerät zur Verfügung gestellten Trends unter Berücksichtigung des individuellen Bedarfs und eventuell vorhandener Vorkenntnisse geschult werden.

(4) Die Ärztin oder der Arzt und die Patientin oder der Patient legen gemeinsam ein individuelles Therapieziel unter Nutzung der rtCGM fest. Die Ärztin oder der Arzt dokumentiert das Therapieziel und im Verlauf der weiteren Behandlung die Zielerreichung.

(5) Das eingesetzte Gerät muss ein zugelassenes Medizinprodukt zur Kontinuierlichen interstitiellen Glukosemessung mit Real-Time-Messung (rtCGM) sein. Anhand einer Alarmfunktion mit individuell einstellbaren Grenzwerten muss das Gerät vor dem Erreichen zu hoher oder zu niedriger Glukosewerte warnen können. Das Empfangsgerät kann in eine Insulinpumpe integriert sein.

(6) Soweit der Einsatz des Gerätes eine Verwendung, Erhebung, Verarbeitung oder Nutzung personenbezogener oder personen-beziehbarer Daten vorsieht, muss sichergestellt sein, dass diese allein zum Zwecke der Behandlung der Patientin oder des Patienten erfolgen und eine Nutzung ohne Zugriff Dritter, insbesondere der Hersteller, möglich ist.

G-BA, 2020 [48].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Oktober 2020 - Insulin glargin/Lixisenatid (neues Anwendungsgebiet: Diabetes Mellitus Typ 2, Kombination mit Metformin und mit SGLT-2-Inhibitoren)

Anwendungsgebiet

Suliqua wird als Ergänzung zu Diät und Bewegung zusätzlich zu Metformin mit oder ohne SGLT-2-Inhibitoren zur Behandlung von erwachsenen Patienten mit unzureichend kontrolliertem Diabetes mellitus Typ 2 zur Verbesserung der Blutzuckerkontrolle angewendet.

Der vorliegende Beschluss bezieht sich auf die neue Kombinationstherapie bestehend aus Insulin glargin/Lixisenatid + Metformin + SGLT-2-Inhibitoren.

a) Erwachsene Patienten mit Diabetes mellitus Typ 2, die durch die Behandlung mit mindestens zwei blutzuckersenkenden Arzneimitteln (außer Insulin) nicht ausreichend kontrolliert sind

Zweckmäßige Vergleichstherapie

- Humaninsulin + Metformin oder
- Humaninsulin + Empagliflozin oder
- Humaninsulin + Liraglutid oder
- Humaninsulin, wenn die bestimmten Kombinationspartner gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind

  Empagliflozin bzw. Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten[1]

Ausmaß des Zusatznutzens

Ausmaß und Wahrscheinlichkeit des Zusatznutzens von Insulin glargin/Lixisenatid + Metformin + SGLT-2-Inhibitoren gegenüber der zweckmäßigen Vergleichstherapie:

Ein Zusatznutzen ist nicht belegt.

1 zur Operationalisierung siehe Studienprotokolle: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI 10.1056/NEJMoa1504720 bzw. Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827

G-BA, 2020 [27].

Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie (AM-RL): Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V; Dulaglutid (Erneute Nutzenbewertung aufgrund neuer wissenschaftlicher Erkenntnisse gem. §13: Diabetes mellitus Typ 2) vom 16. Juli 2020

Anwendungsgebiet

Trulicity ist angezeigt zur Behandlung von Erwachsenen mit unzureichend kontrolliertem Typ 2 Diabetes mellitus unterstützend zu Diät und Bewegung:

- als Monotherapie, wenn die Einnahme von Metformin wegen Unverträglichkeit oder Kontraindikationen nicht angezeigt ist
- zusätzlich zu anderen Arzneimitteln zur Behandlung des Diabetes mellitus.

a) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung allein den Blutzucker nicht ausreichend kontrollieren, und für die die Anwendung von Metformin aufgrund einer Unverträglichkeit nicht geeignet ist.

b) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin) den Blutzucker nicht ausreichend kontrollieren

c) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit mindestens zwei blutzuckersenkenden Arzneimitteln (außer Insulin) den Blutzucker nicht ausreichend kontrollieren

d) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit Insulin (mit oder ohne einem anderen blutzuckersenkenden Arzneimittel) den Blutzucker nicht ausreichend kontrollieren

d1) bei Patienten ohne Niereninsuffizienz

d2) bei Patienten mit moderater oder schwerer Niereninsuffizienz gemäß einer chronischen Nierenerkrankung CKD Stadium 3 und 4, definiert über einen eGFRWert < 60 bis ≥ 15 ml/min/1,73 m2

Zweckmäßige Vergleichstherapie

a) Sulfonylharnstoff (Glibenclamid oder Glimepirid)

b)

- Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) oder
- Metformin + Empagliflozin oder
- Metformin + Liraglutid

  Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten[1]

c)

- Humaninsulin + Metformin oder
- Humaninsulin + Empagliflozin oder
- Humaninsulin + Liraglutid oder
- Humaninsulin, wenn die bestimmten Kombinationspartner gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind

Empagliflozin bzw. Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulärenRisikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten[2]

d) d1) Die Optimierung des Humaninsulinregimes (ggf. + Metformin oder Empagliflozin oder Liraglutid)

Empagliflozin bzw. Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder bLipidsenker erhalten[2]

d2) Die Optimierung des Humaninsulinregimes (ggf. + Metformin oder Liraglutid) Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten[1]

Ausmaß des Zusatznutzens

a) Zusatznutzen nicht belegt

b) Zusatznutzen nicht belegt

c) Zusatznutzen nicht belegt

d) d1) Anhaltspunkt für einen geringen Zusatznutzen

d2) Anhaltspunkt für einen geringen Zusatznutzen

1 zur Operationalisierung siehe Studienprotokoll: Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2nDiabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827

2 zur Operationalisierung siehe Studienprotokolle: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI 10.1056/NEJMoa1504720 bzw. Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827

G-BA, 2019 [57].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 22. November 2019 - Empagliflozin/Linagliptin

Anwendungsgebiet

Glyxambi ist eine Fixdosiskombination aus Empagliflozin und Linagliptin, wird angewendet bei Erwachsenen ab 18 Jahren mit Typ-2-Diabetes mellitus:

• zur Verbesserung der Blutzuckerkontrolle, wenn Metformin und/oder Sulfonylharnstoff (SH) und eine der Monosubstanzen von Glyxambi zur Blutzuckerkontrolle nicht ausreichen

• wenn der Patient bereits mit der freien Kombination von Empagliflozin und Linagliptin[1] behandelt wird.

Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit mindestens zwei blutzuckersenkenden Arzneimitteln (außer Insulin, hier Metformin und/oder Sulfonylharnstoff und Empagliflozin oder Linagliptin1) den Blutzucker nicht ausreichend kontrollieren

Zweckmäßige Vergleichstherapie

- Humaninsulin + Metformin oder
- Humaninsulin + Empagliflozin[2] oder

- Humaninsulin + Liraglutid[2] oder
- Humaninsulin, wenn die bestimmten Kombinationspartner gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

1 Linagliptin als Monopräparat ist derzeit in Deutschland nicht in Verkehr.

2 Empagliflozin bzw. Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten (zur Operationalisierung siehe Studienprotokolle: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI 10.1056/NEJMoa1504720 bzw. Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827).

G-BA, 2019 [51].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. Oktober 2014 / 16. Mai 2019 / 4. Juli 2019 - Insulin degludec

Anwendungsgebiet

Behandlung des Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern ab dem Alter von 1 Jahr.

„In der Mono- oder Kombinationstherapie

a) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit mindestens zwei blutzuckersenkenden Arzneimitteln (außer Insulin) den Blutzucker nicht ausreichend kontrollieren

b) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit Insulin (mit oder ohne einem anderen blutzuckersenkenden Arzneimittel) den Blutzucker nicht ausreichend kontrollieren

Zweckmäßige Vergleichstherapie

a)

- Humaninsulin + Metformin oder
- Humaninsulin + Empagliflozin[1] ode
- Humaninsulin + Liraglutid[1] od
- Humaninsulin, wenn die bestimmten Kombinationspartner gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind

b) Die Optimierung des Humaninsulinregimes (ggf. + Metformin oder Empagliflozin[1] oder Liraglutid[1])

Ausmaß des Zusatznutzens

a) Ein Zusatznutzen ist nicht belegt.

b) Ein Zusatznutzen ist nicht belegt.

1 Empagliflozin bzw. Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, eines insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten (zur Operationalisierung siehe Studienprotokolle: Zinman et al.

G-BA, 2019 [53].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 19. Dezember 2019 - Dapagliflozin/Metformin (Neubewertung aufgrund neuer Wissenschaftlicher Erkenntnisse: Diabetes mellitus Typ 2)

Anwendungsgebiet

Xigduo® ist bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus indiziert, als Ergänzung zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle:

– bei Patienten, bei denen der Blutzucker mit der maximal verträglichen Dosis von Metformin allein unzureichend kontrolliert wird

– in Kombination mit anderen Arzneimitteln zur Behandlung des Diabetes bei Patienten, die mit Metformin und diesen Arzneimitteln unzureichend kontrolliert sind

– bei Patienten, die bereits mit der Kombination aus Dapagliflozin und Metformin als separate Tabletten behandelt werden.

a) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin, hier Metformin) den Blutzucker nicht ausreichend kontrollieren

a1) bei Patienten ohne hohes kardiovaskuläres Risiko[1]

a2) bei Patienten mit hohem kardiovaskulärem Risiko[1], die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2] erhalten

b) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit mindestens zwei blutzuckersenkenden Arzneimitteln (darunter Metformin, außer Insulin) den Blutzucker nicht ausreichend kontrollieren

b1) bei Patienten ohne hohes kardiovaskuläres Risiko[1]

b2) bei Patienten mit hohem kardiovaskulärem Risiko[1], die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2] erhalten

c)Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit Insulin (mit einem anderen blutzuckersenkenden Arzneimittel, hier Metformin) den Blutzucker nicht ausreichend kontrollieren

c1) bei Patienten ohne hohes kardiovaskuläres Risiko[1]

c2) bei Patienten mit hohem kardiovaskulärem Risiko1, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren2 erhalten

Zweckmäßige Vergleichstherapie

a1)

- Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) oder
- Metformin + Empagliflozin

a2)

- Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) oder
- Metformin + Empagliflozin oder
- Metformin + Liraglutid[3]

b1) Humaninsulin + Metformin

b2)

- Humaninsulin + Metformin oder
- Humaninsulin + Empagliflozin[3] oder
- Humaninsulin + Liraglutid[3] oder
- Humaninsulin, wenn die bestimmten Kombinationspartner gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind

c1) Die Optimierung des Humaninsulinregimes (ggf. + Metformin)

c2) Die Optimierung des Humaninsulinregimes (ggf. + Metformin oder Empagliflozin[3] oder Liraglutid[3])

Fazit / Ausmaß des Zusatznutzens

a1) Ein Zusatznutzen ist nicht belegt.

a2) Anhaltspunkt für einen geringen Zusatznutzen.

b1) Ein Zusatznutzen ist nicht belegt.

b2) Anhaltspunkt für einen geringen Zusatznutzen.

c1) Ein Zusatznutzen ist nicht belegt.

c2) Anhaltspunkt für einen geringen Zusatznutzen.

1 hohes kardiovaskuläres Risiko ist im vorliegenden Fall anhand der DECLARE-TIMI 58-Studie (siehe Studienprotokoll, Wiviott et. al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019; 380(4):347-357. DOI: 10.1056/NEJMoa1812389) definiert und hier näherungsweise zusammengefasst als ≥ 40 Jahre mit mindestens einer kardiovaskulären Erkrankung (ischämische Herzkrankheit, zerebrovaskuläre Erkrankung oder periphere arterielle Verschlusskrankheit) oder Frauen ≥ 60 Jahre und Männer ≥ 55 Jahre mit mindestens einem Risikofaktor für kardiovaskuläre Erkrankungen (Dyslipidämie, Hypertonie, aktuelles Rauchen mit ≥ 5 Zigaretten / Tag für mindestens ein Jahr zum Zeitpunkt der Randomisierung)2 Insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker
3 Empagliflozin bzw. Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten (zur Operationalisierung siehe Studienprotokolle: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI 10.1056/NEJMoa1504720 bzw. Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827).

G-BA, 2019 [33].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL): Anlage XII - (Frühe) Nutzenbewertung nach § 35a SGB V; Ertugliflozin/ Sitagliptin; Geltende Fassung zum Beschluss vom 1. November 2018 / 4. Juli 2019

Anwendungsgebiet

Steglujan ist bei Erwachsenen ab 18 Jahren mit Typ-2 Diabetes mellitus zusätzlich zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle angezeigt:

- bei Patienten, deren Blutzucker unter Metformin und/oder einem Sulfonylharnstoff und einem der in Steglujan enthaltenen Einzelwirkstoffe nicht ausreichend gesenkt werden kann.

- bei Patienten, die bereits mit der Kombination aus Ertugliflozin und Sitagliptin in Form von einzelnen Tabletten behandelt werden[1].

Vergleichstherapie

Erwachsene Patienten mit Diabetes mellitus Typ 2, die durch die Behandlung mit mindestens zwei blutzuckersenkenden Arzneimitteln (außer Insulin, hier Metformin und/oder Sulfonylharnstoff und Ertugliflozin oder Sitagliptin) nicht ausreichend kontrolliert sind:

- Humaninsulin + Metformin oder
- Humaninsulin + Empagliflozin[2] oder
- Humaninsulin + Liraglutid oder
- Humaninsulin, wenn die bestimmten Kombinationspartner gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

1 Ertugliflozin als Monopräparat ist derzeit in Deutschland nicht in Verkehr.
2 Empagliflozin bzw. Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten (zur Operationalisierung siehe Studienprotokolle: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI 10.1056/NEJMoa1504720 bzw. Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827).

G-BA, 2019 [49].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. August 2018 / 4. Juli 2019 - Insulin glargin/Lixisenatid.

Anwendungsgebiet

Suliqua wird in Kombination mit Metformin zur Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen zur Verbesserung der Blutzuckerkontrolle angewendet, wenn Metformin allein oder Metformin in Kombination mit einem anderen oralen blutzuckersenkenden Arzneimittel oder mit Basalinsulin den Blutzuckerspiegel nicht ausreichend reguliert

a) Erwachsene Patienten mit Diabetes mellitus Typ 2, die durch die Behandlung mit mindestens zwei blutzuckersenkenden Arzneimitteln (ausschließlich orale, inklusive Metformin) nicht ausreichend kontrolliert sind

Zweckmäßige Vergleichstherapie:

- Humaninsulin + Metformin oder
- Humaninsulin + Empagliflozin[1] oder
- Humaninsulin + Liraglutid[1] oder
- Humaninsulin, wenn die bestimmten Kombinationspartner gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind.

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

b) Erwachsene Patienten mit Diabetes mellitus Typ 2, die durch die Behandlung mit Insulin (mit einem anderen blutzuckersenkenden Arzneimittel, hier Metformin) nicht ausreichend kontrolliert sind

Zweckmäßige Vergleichstherapie:

- Die Optimierung des Humaninsulinregimes (ggf. + Metformin oder Empagliflozin[1] oder Liraglutid[1])

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

1) Empagliflozin bzw. Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten (zur Operationalisierung siehe Studienprotokolle: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI 10.1056/NEJMoa1504720 bzw. Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827).

G-BA, 2019 [52].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 19. Dezember 2019 - Dapagliflozin (Neubewertung aufgrund neuer Wissenschaftlicher Erkenntnisse: Diabetes mellitus Typ 2)

Anwendungsgebiet

„Forxiga ist bei erwachsenen Patienten indiziert zur Behandlung von unzureichend kontrolliertem Typ-2-Diabetes mellitus in Ergänzung zu einer Diät und Bewegung

– als Monotherapie, wenn Metformin aufgrund einer Unverträglichkeit als ungeeignet erachtet wird

– zusätzlich zu anderen Arzneimitteln zur Behandlung des Typ-2-Diabetes.

a) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung allein den Blutzucker nicht ausreichend kontrollieren, und für die die Anwendung von Metformin aufgrund einer Unverträglichkeit nicht geeignet ist

a1) bei Patienten ohne hohes kardiovaskuläres Risiko[1]

a2) bei Patienten mit hohem kardiovaskulärem Risiko[1], die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2] erhalten

b) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin) den Blutzucker nicht ausreichend kontrollieren

b1) bei Patienten ohne hohes kardiovaskuläres Risiko[1]

b2) bei Patienten mit hohem kardiovaskulärem Risiko[1], die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2] erhalten

c) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit mindestens zwei blutzuckersenkenden Arzneimitteln (außer Insulin) den Blutzucker nicht ausreichend kontrollieren

c1) bei Patienten ohne hohes kardiovaskuläres Risiko[1]

c2) bei Patienten mit hohem kardiovaskulärem Risiko[1], die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2] erhalten

d) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit Insulin (mit oder ohne einem anderen blutzuckersenkenden Arzneimittel) den Blutzucker nicht ausreichend kontrollieren

d1) bei Patienten ohne hohes kardiovaskuläres Risiko[1]

d2) bei Patienten mit hohem kardiovaskulärem Risiko[1], die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2] erhalten

Zweckmäßige Vergleichstherapie:

a1) Sulfonylharnstoff (Glibenclamid, Glimepirid)

a2) Sulfonylharnstoff (Glibenclamid oder Glimepirid)

b1)

- Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) oder
- Metformin + Empagliflozin

b2)

- Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) oder
- Metformin + Empagliflozin oder
- Metformin + Liraglutid[3]

c1)

- Humaninsulin + Metformin oder
- nur Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam ist

c2)

- Humaninsulin + Metformin oder
- Humaninsulin + Empagliflozin3 oder
- Humaninsulin + Liraglutid3 oder
- Humaninsulin, wenn die bestimmten Kombinationspartner gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind

d1) Die Optimierung des Humaninsulinregimes (ggf. + Metformin)

d2) Die Optimierung des Humaninsulinregimes (ggf. + Metformin oder Empagliflozin[3] oder Liraglutid[3])

Fazit / Ausmaß des Zusatznutzens / Ergebnis

a1) Ein Zusatznutzen ist nicht belegt.

a2) Ein Zusatznutzen ist nicht belegt.

b1) Ein Zusatznutzen ist nicht belegt.

b2) Anhaltspunkt für einen geringen Zusatznutzen.

c1) Ein Zusatznutzen ist nicht belegt.

c2) Anhaltspunkt für einen geringen Zusatznutzen.

d1) Ein Zusatznutzen ist nicht belegt.

d2) Anhaltspunkt für einen geringen Zusatznutzen.

1 hohes kardiovaskuläres Risiko ist im vorliegenden Fall anhand der DECLARE-TIMI 58-Studie (siehe Studienprotokoll, Wiviott et. al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2019; 380(4):347-357. DOI: 10.1056/NEJMoa1812389) definiert und hier näherungsweise zusammengefasst als ≥ 40 Jahre mit mindestens einer kardiovaskulären Erkrankung (ischämische Herzkrankheit, zerebrovaskuläre Erkrankung oder periphere arterielle Verschlusskrankheit) oder Frauen ≥ 60 Jahre und Männer ≥ 55 Jahre mit mindestens einem Risikofaktor für kardiovaskuläre Erkrankungen (Dyslipidämie, Hypertonie, aktuelles Rauchen mit ≥ 5 Zigaretten / Tag für mindestens ein Jahr zum Zeitpunkt der Randomisierung).
2 Insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker
3 Empagliflozin bzw. Liraglutid nur für Patienten mit manifester kardiovaskulärer Erkrankung, die weitere Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker erhalten (zur Operationalisierung siehe Studienprotokolle: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI 10.1056/NEJMoa1504720 bzw. Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827).

G-BA, 2019 [46].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Dezember 2016 / 22. März 2019 / 4. Juli 2019 - Sitagliptin

Anwendungsgebiet

Bei erwachsenen Patienten mit Typ-2-Diabetes mellitus ist Januvia®/Xelevia® indiziert zur Verbesserung der Blutzuckerkontrolle:

Als Monotherapie:

- bei Patienten, bei denen Diät und Bewegung allein den Blutzucker nicht ausreichend senken und für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeit nicht geeignet ist.

Als orale Zweifachtherapie in Kombination mit:

- Metformin, wenn Diät und Bewegung plus eine Metformin-Monotherapie den Blutzucker nicht ausreichend senken.
- einem Sulfonylharnstoff, wenn Diät und Bewegung plus eine Sulfonylharnstoff-Monotherapie in der höchsten vertragenen Dosis den Blutzucker nicht ausreichend senken und wenn Metformin aufgrund von Gegenanzeigen oder Unverträglichkeit nicht geeignet ist.
- einem Peroxisomal Proliferator activated Receptor gamma (PPARγ)-Agonisten (d.h. einem Thiazolidindion), wenn die Anwendung eines PPARγ-Agonisten angebracht ist und Diät und Bewegung plus Monotherapie mit einem PPARγ-Agonisten den Blutzucker nicht ausreichend senken.[2]

Als orale Dreifachtherapie in Kombination mit:

- einem Sulfonylharnstoff und Metformin, wenn Diät und Bewegung plus eine Zweifachtherapie mit diesen Arzneimitteln den Blutzucker nicht ausreichend senken.

- einem PPARγ-Agonisten und Metformin, wenn die Anwendung eines PPARγ-Agonisten angebracht ist und Diät und Bewegung plus eine Zweifachtherapie mit diesen Arzneimitteln den Blutzucker nicht ausreichend senken.[2]

Januvia®/Xelevia® ist auch zusätzlich zu Insulin indiziert (mit oder ohne Metformin), wenn Diät und Bewegung sowie eine stabile Insulindosis den Blutzucker nicht ausreichend senken.

a) Für die Monotherapie bei Patienten, bei denen Diät und Bewegung allein den Blutzucker nicht ausreichend senken und für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeit nicht geeignet ist:

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

b) Erwachsene Patienten mit Diabetes mellitus Typ 2, bei denen Diät und Bewegung und die Behandlung mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin, hier Metformin) den Blutzucker nicht ausreichend kontrollieren:

Zweckmäßige Vergleichstherapie:

- Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) oder
- Metformin + Empagliflozin oder
- Metformin + Liraglutid[3]

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Anhaltspunkt für einen geringen Zusatznutzen.

c) In Kombination mit einem Sulfonylharnstoff, wenn Diät und Bewegung plus eine Sulfonylharnstoff-Monotherapie in der höchsten vertragenen Dosis den Blutzucker nicht ausreichend senken und wenn Metformin aufgrund von Gegenanzeigen/ Unverträglichkeit nicht geeignet ist:

Zweckmäßige Vergleichstherapie

Humaninsulin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: ggf. Therapie nur mit Humaninsulin)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

d) In Kombination mit einem Sulfonylharnstoff und Metformin, wenn Diät und Bewegung plus eine Zweifachtherapie mit diesen Arzneimitteln den Blutzucker nicht ausreichend senken:

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

e) In Kombination mit Insulin (mit und ohne Metformin), wenn Diät und Bewegung sowie eine stabile Insulindosis den Blutzucker nicht ausreichend senken:

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

1 Zulassungen vom 29.07.2009 (a), 21.03.2007 (b), 19.12.2007 (c), 02.06.2009 (d), 09.11.2009 (e).
2 Aufgrund des Verordnungsausschlusses der Glitazone zur Behandlung des Diabetes mellitus Typ 2 (AM-Richtlinie, Anlage III) entfällt diese Wirkstoffkombination für die Nutzenbewertung von Sitagliptin nach § 35a SGB V.
3 Liraglutid in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker und nur für Patienten mit manifester kardiovaskulärer Erkrankung (zur Operationalisierung siehe Studienprotokoll: Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827)

G-BA, 2018 [32].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. Februar 2018 - Saxagliptin/Metformin

Anwendungsgebiet

Komboglyze ist als Ergänzung zu Diät und Bewegung angezeigt, um die Blutzuckerkontrolle bei erwachsenen Patienten mit Typ-2-Diabetes mellitus zu verbessern:

- Bei Patienten, die mit der maximal verträglichen Dosis von Metformin allein nicht ausreichend kontrolliert sind.
- In Kombination mit anderen Arzneimitteln zur Behandlung des Diabetes einschließlich Insulin, bei Patienten, die mit Metformin und diesen Arzneimitteln nicht ausreichend kontrolliert sind.
- Bei Patienten, die bereits mit der Kombination von Saxagliptin und Metformin als separate Tabletten behandelt werden.

Hinweis: Der vorliegende Beschluss bezieht sich nur auf die Kombination von Saxagliptin/Metformin mit anderen Arzneimitteln außer Insulin oder Sulfonylharnstoffen zur Behandlung des Diabetes.

Zweckmäßige Vergleichstherapie

- Humaninsulin + Metformin oder
- Humaninsulin + Empagliflozin[1] oder
- Humaninsulin + Liraglutid[1] oder

- Humaninsulin, wenn Metformin und Empagliflozin[1] und Liraglutid[1] gemäß Fachinformation unverträglich oder kontraindiziert oder aufgrund eines fortgeschrittenen Diabetes mellitus Typ 2 nicht ausreichend wirksam sind

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

1 Empagliflozin und Liraglutid in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren, insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker und nur für Patienten mit manifester kardiovaskulärer Erkrankung (zur Operationalisierung siehe Studienprotokolle: Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI: 10.1056/NEJMoa1504720 bzw. Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes, N Engl J Med 2016; 375:311-322. DOI: 10.1056/NEJMoa1603827)

G-BA, 2016 [37].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. September 2016 - Empagliflozin

Anwendungsgebiet

Jardiance® ist bei Erwachsenen mit Typ-2-Diabetes mellitus zur Verbesserung der Blutzuckerkontrolle angezeigt als:

- Monotherapie: Wenn Diät und Bewegung allein zur Blutzuckerkontrolle nicht ausreichen, bei Patienten, bei denen die Anwendung von Metformin aufgrund einer Unverträglichkeit als ungeeignet erachtet wird.
- Add-on-Kombinationstherapie: In Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin, wenn diese zusammen mit Diät und Bewegung zur Blutzuckerkontrolle nicht ausreichen (siehe Abschnitte 4.4, 4.5 und 5.1 für zurzeit vorliegende Daten zu verschiedenen Kombinationen).

a) In der Monotherapie, wenn Diät und Bewegung allein den Blutzucker nicht ausreichend kontrollieren und eine Anwendung von Metformin aufgrund von Unverträglichkeit als ungeeignet erachtet wird

a1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

Vergleichstherapie:

Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens:

Ein Zusatznutzen ist nicht belegt.

a2) bei Patienten mit manifester kardiovaskulärer Erkrankung1 in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren2

Vergleichstherapie:

Sulfonylharnstoff (Glibenclamid oder Glimepirid) in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren[2]

Ausmaß des Zusatznutzens:

Ein Zusatznutzen ist nicht belegt.

b) In Kombination mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin), wenn dieses den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert

b1) In der Zweifachkombination mit Metformin

b1.1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

Vergleichstherapie:

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens:

Anhaltspunkt für einen geringen Zusatznutzen.

b1.2) bei Patienten mit manifester kardiovaskulärer Erkrankung1 in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren2:

Vergleichstherapie:

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren[2]

Ausmaß des Zusatznutzens:

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

b2) In der Zweifachkombination mit einem anderen blutzuckersenkenden Arzneimittel außer Metformin und Insulin

b2.1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung1

Vergleichstherapie:

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen.)

Ausmaß des Zusatznutzens:

Ein Zusatznutzen ist nicht belegt.

b2.2) bei Patienten mit manifester kardiovaskulärer Erkrankung1 in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren2

Vergleichstherapie:

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid) in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren[2]

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen.)

Ausmaß des Zusatznutzens:

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

c) In Kombination mit mindestens zwei anderen blutzuckersenkenden Arzneimitteln, wenn diese den Blutzucker zusätzlich zu Diät und Bewegung nicht ausreichend kontrollieren

c1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung1

Vergleichstherapie:

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß des Zusatznutzens:

Ein Zusatznutzen ist nicht belegt.

c2) bei Patienten mit manifester kardiovaskulärer Erkrankung1 in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren2

Vergleichstherapie:

Metformin + Humaninsulin in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren[2]

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß des Zusatznutzens:

Anhaltspunkt für einen beträchtlichen Zusatznutzen.

d) In Kombination mit Insulin (mit oder ohne orales Antidiabetikum)

d1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung[1]

Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

d2) bei Patienten mit manifester kardiovaskulärer Erkrankung[1] in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren2

Vergleichstherapie:

Metformin + Humaninsulin in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren[2]

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß und Wahrscheinlichkeit des Zusatznutzens

Anhaltspunkt für einen beträchtlichen Zusatznutzen

1 manifeste kardiovaskuläre Erkrankung ist im vorliegenden Fall anhand der EMPA-REG-Outcome-Studie (siehe Studienprotokoll, Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI: 10.1056/NEJMoa1504720) definiert und hier näherungsweise zusammengefasst als mind. eine der folgenden Bedingungen: bestätigter Myokardinfarkt, klinisch relevante koronare Eingefäßerkrankung mit ≥ 50% Stenose, koronare Mehrgefäßerkrankung, instabile Angina Pectoris mit angiografischem Nachweis einer koronaren Herzerkrankung, ischämischer oder hämorrhagischer Schlaganfall oder periphere arterielle Verschlusserkrankung mit klinischer relevanter Durchblutungsstörung.

G-BA, 2016 [38].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. September 2016 - Empagliflozin/Metformin

Anwendungsgebiet

Synjardy® ist bei Erwachsenen ab 18 Jahren mit Typ-2-Diabetes mellitus zusätzlich zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle angezeigt

- bei Patienten, die unter der maximal verträglichen Dosis von Metformin allein unzureichend eingestellt sind.
- bei Patienten, die mit Metformin in Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin unzureichend eingestellt sind (siehe Abschnitte 4.5 und 5.1 für zurzeit vorliegende Daten zu verschiedenen Kombinationen).
- bei Patienten, die bereits mit der Kombination aus Empagliflozin und Metformin in Form getrennter Tabletten behandelt werden.

a) Zweifachkombination Empagliflozin mit Metformin bei Patienten, die unter der maximal verträglichen Dosis von Metformin zusätzlich zu Diät und Bewegung unzureichend eingestellt sind:

a1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung1

Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid) + Metformin

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

a2) bei Patienten mit manifester kardiovaskulärer Erkrankung1 in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren2

Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid) + Metformin in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren[2]

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

b) Kombinationstherapie mit anderen blutzuckersenkenden Arzneimitteln (außer Insulin) bei Patienten, die mit Metformin in Kombination mit diesen anderen blutzuckersenkenden Arzneimitteln (außer Insulin) zusätzlich zu Diät und Bewegung unzureichend eingestellt sind:

b1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung1

Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

b2) bei Patienten mit manifester kardiovaskulärer Erkrankung1 in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren2

Vergleichstherapie

Humaninsulin + Metformin in Kombination mit weiterer Medikation zur Behandlung kardiovaskulärer Risikofaktoren2

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

c) Kombinationstherapie mit Insulin bei Patienten, die mit Metformin in Kombination mit Insulin zusätzlich zu Diät und Bewegung unzureichend eingestellt sind:

c1) bei Patienten ohne manifeste kardiovaskuläre Erkrankung1

Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

c2) bei Patienten mit manifester kardiovaskulärer Erkrankung1 in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren2

Vergleichstherapie

Humaninsulin + Metformin in Kombination mit weiterer Medikation zur Behandlung der kardiovaskulären Risikofaktoren

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

1 manifeste kardiovaskuläre Erkrankung ist im vorliegenden Fall anhand der EMPA-REG-Outcome-Studie (siehe Studienprotokoll, Zinman et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28. DOI: 10.1056/NEJMoa1504720) definiert und hier näherungsweise zusammengefasst als mind. eine der folgenden Bedingungen: bestätigter Myokardinfarkt, klinisch relevante koronare Eingefäßerkrankung mit ≥ 50% Stenose, koronare Mehrgefäßerkrankung, instabile Angina Pectoris mit angiografischem Nachweis einer koronaren Herzerkrankung, ischämischer oder hämorrhagischer Schlaganfall oder periphere arterielle Verschlusserkrankung mit klinischer relevanter Durchblutungsstörung.

2 Insbesondere Antihypertensiva, Antikoagulanzien und/oder Lipidsenker

G-BA, 2016 [39].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum

Beschluss vom 4. Februar 2016 - Insulin degludec/Liraglutid (neues Anwendungsgebiet: Diabetes mellitus Typ 2 in Kombination mit oralen Antidiabetika)

Anwendungsgebiet

Xultophy wird zur Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen angewendet, um in Kombination mit oralen blutzuckersenkenden Arzneimitteln die Blutzuckerkontrolle zu verbessern, wenn diese Mittel allein oder in Kombination mit einem GLP-1-Rezeptor-Agonisten oder Basalinsulin den Blutzuckerspiegel nicht ausreichend regulieren.

Vergleichstherapie

Metformin plus Humaninsulin

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [45].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Dezember 2016 - Sitagliptin/Metformin

Anwendungsgebiet

Für erwachsene Patienten mit Typ-2-Diabetes mellitus:

Janumet®/Velmetia® ist zusätzlich zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle bei Patienten indiziert, bei denen eine Monotherapie mit Metformin in der höchsten vertragenen Dosis den Blutzucker nicht ausreichend senkt oder die bereits mit der Kombination von Sitagliptin und Metformin behandelt werden.

Janumet®/Velmetia® ist in Kombination mit einem Sulfonylharnstoff (z. B. als Dreifachtherapie) zusätzlich zu Diät und Bewegung bei Patienten indiziert, bei denen eine Kombination aus der jeweils höchsten vertragenen Dosis von Metformin und eines Sulfonylharnstoffs nicht ausreicht, um den Blutzucker zu senken.

Janumet®/Velmetia® ist als Dreifachtherapie in Kombination mit einem Peroxisomal Proliferator activated Receptor gamma (PPARγ)-Agonisten (d. h. einem Thiazolidindion) zusätzlich zu Diät und Bewegung bei Patienten indiziert, bei denen die jeweils höchste vertragene Dosis von Metformin und einem PPARγ-Agonisten nicht ausreicht, um den Blutzucker zu senken.2

Janumet®/Velmetia® ist auch zusätzlich zu Insulin (d. h. als Dreifachtherapie) indiziert als Ergänzung zu Diät und Bewegung bei Patienten, bei denen eine stabile Insulindosis und Metformin allein den Blutzucker nicht ausreichend senken.

a) Zweifachkombination Sitagliptin/Metformin zusätzlich zu Diät und Bewegung zur Verbesserung der Blutzuckerkontrolle bei Patienten, bei denen eine Monotherapie mit Metformin in der höchsten vertragenen Dosis den Blutzucker nicht ausreichend senkt:

Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

b) Dreifachkombination Sitagliptin/Metformin mit Sulfonylharnstoff zusätzlich zu Diät und Bewegung bei Patienten, bei denen eine Kombination aus der jeweils höchsten vertragenen Dosis von Metformin und eines Sulfonylharnstoffs nicht ausreicht, um den Blutzucker zu senken:

Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist.)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

c) Dreifachkombination Sitagliptin/Metformin mit Insulin als Ergänzung zu Diät und Bewegung bei Patienten, bei denen eine stabile Insulindosis und Metformin allein den Blutzucker nicht ausreichend senken:

Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist.)

Fazit / Ausmaß des Zusatznutzens / Ergebnis

Ein Zusatznutzen ist nicht belegt.

G-BA, 2016 [43].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Dezember 2016 – Saxagliptin

Anwendungsgebiet

Onglyza ist bei erwachsenen Patienten ab 18 Jahren mit Typ-2-Diabetes mellitus zur Verbesserung der Blutzuckerkontrolle indiziert:

Als Monotherapie bei Patienten, die durch Diät und Bewegung allein nicht ausreichend kontrolliert sind und für die Metformin aufgrund von Kontraindikationen oder Unverträglichkeit ungeeignet ist.[2]

Als orale Zweifachtherapie in Kombination mit

- Metformin, wenn eine Metformin-Monotherapie, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert.
- einem Sulfonylharnstoff bei Patienten, für die die Anwendung von Metformin ungeeignet erscheint, wenn eine Sulfonylharnstoff-Monotherapie, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert.
- einem Thiazolidindion bei Patienten, für die die Anwendung eines Thiazolidindions geeignet erscheint, wenn eine Thiazolidindion-Monotherapie, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert.[3]

Als orale Dreifachtherapie

- in Kombination mit Metformin und einem Sulfonylharnstoff, wenn diese Behandlung allein, mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert.

Als Kombinationstherapie mit Insulin (mit oder ohne Metformin), wenn diese Behandlung allein, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert.

a) In Kombination mit Metformin, wenn eine Metformin-Monotherapie, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) In Kombination mit einem Sulfonylharnstoff bei Patienten, für die die Anwendung von Metformin ungeeignet erscheint, wenn eine Sulfonylharnstoff-Monotherapie, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert:

Zweckmäßige Vergleichstherapie

Humaninsulin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: ggf. Therapie nur mit Humaninsulin)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) Als orale Dreifachtherapie in Kombination mit Metformin und einem Sulfonylharnstoff, wenn diese Behandlung allein, mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert:

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

d) In Kombination mit Insulin (mit oder ohne Metformin), wenn diese Behandlung allein, zusammen mit einer Diät und Bewegung, den Blutzucker nicht ausreichend kontrolliert:

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

2 Die Monotherapie ist nicht Bestandteil des hier zugrunde liegenden, befristeten Beschlusses für die Nutzenbewertung nach § 35a SGB V von Saxagliptin.
3 Aufgrund des Verordnungsausschlusses der Glitazone zur Behandlung des Diabetes mellitus Typ 2 (AM-Richtlinie, Anlage III) entfällt diese Wirkstoffkombination für die Nutzenbewertung von Saxagliptin nach § 35a SGB V.

G-BA, 2016 [44].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Dezember 2016 - Saxagliptin/Metformin

Anwendungsgebiet

Komboglyze® ist als Ergänzung zu Diät und Bewegung angezeigt, um die Blutzuckerkontrolle bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus zu verbessern, die mit der maximal verträglichen Dosis von Metformin allein nicht ausreichend kontrolliert sind, oder die bereits mit der Kombination von Saxagliptin und Metformin als separate Tabletten behandelt werden.

Komboglyze® ist auch in Kombination mit Insulin (d. h. als Dreifach-Kombinationstherapie) als Ergänzung zu Diät und Bewegung angezeigt, um die Blutzuckerkontrolle bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus zu verbessern, wenn Insulin und Metformin allein den Blutzucker nicht ausreichend kontrollieren.

Komboglyze® ist auch in Kombination mit einem Sulfonylharnstoff (d. h. als Dreifach-Kombinationstherapie) als Ergänzung zu Diät und Bewegung angezeigt, um die Blutzuckerkontrolle bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus zu verbessern, wenn die maximal verträgliche Dosis sowohl von Metformin als auch des Sulfonylharnstoffs den Blutzucker nicht ausreichend kontrolliert.[2]

a) Zweifachkombinationstherapie Saxagliptin/Metformin bei erwachsenen Patienten im Alter von 18 Jahren und älter, die mit der maximal verträglichen Dosis von Metformin allein nicht ausreichend kontrolliert sind:

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Dreifachkombination Saxagliptin/Metformin mit Insulin als Ergänzung zu Diät und Bewegung, um die Blutzuckerkontrolle bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus zu verbessern, wenn Insulin und Metformin allein den Blutzucker nicht ausreichend kontrollieren:

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

2 Die Kombination mit einem Sulfonylharnstoff ist nicht Bestandteil des hier zugrunde liegenden, befristeten Beschlusses für die Nutzenbewertung nach § 35a SGB V von Saxagliptin/Metformin.

G-BA, 2015 [47].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 15. Oktober 2015 - Insulin degludec/Liraglutid

Anwendungsgebiet

Xultophy® wird zur Behandlung des Diabetes mellitus Typ 2 bei Erwachsenen angewendet, um in Kombination mit oralen blutzuckersenkenden Arzneimitteln die Blutzuckerkontrolle zu verbessern, wenn diese Mittel allein oder in Kombination mit einem GLP-1-Rezeptor-Agonisten oder Basalinsulin den Blutzuckerspiegel nicht ausreichend regulieren

a) Insulin degludec/Liraglutid in Kombination mit oralen Antidiabetika zur Behandlung des Diabetes mellitus Typ 2, wenn eine orale antidiabetische Kombinationstherapie zur Blutzuckerkontrolle nicht ausreicht:

Vergleichstherapie

Metformin plus Humaninsulin

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet oder Metformin in Kombination mit Insulin nicht ausreichend wirksam ist, ist Humaninsulin als Therapieoption einzusetzen)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Insulin degludec/Liraglutid in Kombination mit oralen Antidiabetika zur Behandlung des Diabetes mellitus Typ 2, wenn diese oralen Antidiabetika in Kombination mit Basalinsulin zur Blutzuckerkontrolle nicht ausreichen:

b1) in der Kombination mit Metformin:

Vergleichstherapie

Humaninsulin plus ggf. Metformin

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt[1]:

b2) in Kombination mit oralen Antidiabetika (außer Metformin):

Vergleichstherapie

Humaninsulin plus ggf. Metformin

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

1 Die vergleichende Bewertung erfolgt auf der Grundlage eines direkten Vergleichs von Insulin degludec/Liraglutid in Kombination mit Metformin gegenüber der Kombination aus einem langwirksamen Insulin-Analogon (Insulin glargin) mit Metformin.

G-BA, 2015 [54].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 19. März 2015/ 16. Juli 2015 - Albiglutid

Anwendungsgebiet

Albiglutid (Eperzan®) ist bei erwachsenen Patienten mit Typ 2 Diabetes zur Verbesserung der Blutzuckereinstellung indiziert als:

Monotherapie

- Wenn Diät und Bewegung allein zur Blutzuckereinstellung nicht ausreichen bei Patienten, für die die Anwendung von Metformin aufgrund von Kontraindikationen oder Unverträglichkeit als ungeeignet angesehen wird.

Kombinationstherapie

- In Kombination mit anderen blutzuckersenkenden Arzneimitteln einschließlich Basalinsulin, wenn diese zusammen mit Diät und Bewegung den Blutzucker nicht ausreichend senken (für verfügbare Daten zu den verschiedenen Kombinationen siehe Abschnitt 4.4 und 5.1).

a) In der Monotherapie, wenn Diät und Bewegung allein zur Blutzuckereinstellung nicht ausreichen bei Patienten, für die die Anwendung von Metformin aufgrund von Kontraindikationen oder Unverträglichkeit als ungeeignet angesehen wird

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) In Kombination mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin), wenn dieses den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend senkt

b1) In der Zweifachkombination mit Metformin

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Hinweis für einen geringen Zusatznutzen

b2) In der Zweifachkombination mit einem anderen blutzuckersenkenden Arzneimittel außer Metformin und Insulin

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) In Kombination mit mindestens zwei anderen blutzuckersenkenden Arzneimitteln, wenn diese den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend senken

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

d) In Kombination mit Insulin (mit oder ohne orale Antidiabetika)

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich ist.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2015 [55].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 20. August 2015 - Insulin degludec (neues Anwendungsgebiet: Diabetes mellitus, Patienten ab 1 Jahr)

Anwendungsgebiet

Behandlung des Diabetes mellitus bei Erwachsenen, Jugendlichen und Kindern ab dem Alter von 1 Jahr.

Der vorliegende Beschluss bezieht sich ausschließlich auf das neu zugelassene Anwendungsgebiet vom 30. Januar 2015 (größere Änderung des Typs 2 nach Anhang 2 Nummer 2 Buchstabe a der Verordnung (EG) Nr. 1234/2008 der Kommission vom 24. November 2008 über die Prüfung von Änderungen der Zulassungen von Human- und Tierarzneimitteln), d. h. auf die Behandlung des Diabetes mellitus bei Jugendlichen und Kindern ab dem Alter von 1 Jahr.

a) Behandlung des Diabetes mellitus Typ 1 bei Jugendlichen und Kindern ab 1 Jahr:

Zweckmäßige Vergleichstherapie

Humaninsulin

Ausmaß des Zusatznutzens[1]

Ein Zusatznutzen ist nicht belegt.

b) Behandlung des Diabetes mellitus Typ 2 bei Jugendlichen und Kindern ab 1 Jahr in der Monotherapie:

Zweckmäßige Vergleichstherapie

Humaninsulin

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) Behandlung des Diabetes mellitus Typ 2 bei Jugendlichen und Kindern ab 1 Jahr in Kombination mit anderen Antidiabetika:

Zweckmäßige Vergleichstherapie

Humaninsulin plus Metformin

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

1 Die vergleichende Bewertung erfolgt auf der Grundlage eines direkten Vergleichs von Insulin degludec in Kombination mit einem kurzwirksamen Insulin-Analogon (Insulin aspart) gegenüber der Kombination aus einem langwirksamen Insulin-Analogon (Insulin detemir) mit einem kurzwirksamen Insulin-Analogon (Insulin aspart).

G-BA, 2015 [36].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. Oktober 2013 / 23. Januar 2014 / 21. Mai 2015 – Vildagliptin

Anwendungsgebiet

Galvus®/Jalra® /Xiliarx® ist angezeigt zur Behandlung von Diabetes mellitus Typ 2

Als Monotherapie bei Patienten, die durch Diät und Bewegung allein nicht ausreichend therapiert sind und für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeiten nicht geeignet ist.

In einer oralen Zweifach-Kombinationstherapie mit

- Metformin bei Patienten, deren Blutzucker trotz Monotherapie mit maximal verträglichen Dosen von Metformin unzureichend eingestellt ist,
- einem Sulfonylharnstoff bei Patienten, deren Blutzucker trotz Monotherapie mit maximal verträglichen Dosen eines Sulfonylharnstoffs unzureichend eingestellt ist und bei denen Metformin wegen Kontraindikationen oder Unverträglichkeit ungeeignet ist,
- einem Thiazolidindion bei Patienten mit ungenügender Blutzuckereinstellung, für die die Anwendung eines Thiazolidindions geeignet ist.1

In einer oralen Dreifach-Kombinationstherapie mit einem Sulfonylharnstoff und Metformin, wenn Diät und Bewegung zusätzlich zu einer Zweifachtherapie mit diesen Arzneimitteln zu keiner adäquaten glykämischen Kontrolle führen.

Vildagliptin ist auch für die Anwendung in Kombination mit Insulin indiziert (mit oder ohne Metformin), wenn Diät und Bewegung zusätzlich zu einer stabilen Insulindosis zu keiner adäquaten glykämischen Kontrolle führen.

a) Monotherapie, bei Patienten, die durch Diät und Bewegung allein nicht ausreichend therapiert sind und für die Metformin aufgrund von Gegenanzeigen oder Unverträglichkeiten nicht geeignet ist:

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Zweifachkombination Vildagliptin mit Metformin bei Patienten, deren Blutzucker trotz Monotherapie mit maximal verträglichen Dosen von Metformin unzureichend eingestellt ist:

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid) + Metformin

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

1 Aufgrund des Verordnungsausschlusses der Glitazone zur Behandlung des Diabetes mellitus Typ 2 (AM-Richtlinie, Anlage III) entfällt dieses Anwendungsgebiet für die Nutzenbewertung von Vildagliptin nach § 35a SGB V.

G-BA, 2015 [41].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 5. Februar 2015 - Canagliflozin/Metformin.

Anwendungsgebiet

Vokanamet wird angewendet bei Erwachsenen im Alter von 18 Jahren und älter mit Typ-2-Diabetes-mellitus zusätzlich zu Diät und Bewegung zur Blutzuckerkontrolle:

- bei Patienten, bei denen Metformin in den maximal verträglichen Dosen allein den Blutzucker nicht ausreichend kontrolliert,
- bei Patienten, bei denen Metformin in den maximal verträglichen Dosen zusammen mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin den Blutzucker nicht ausreichend kontrolliert (siehe Abschnitte 4.4, 4.5 und 5.1 für Daten zu verschiedenen Kombinationstherapien)
- bei Patienten, die bereits Canagliflozin und Metformin als separate Tabletten erhalten.

a) Kombinationstherapie mit Metformin, wenn Metformin in der maximal verträglichen Dosis den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid) + Metformin

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Kombinationstherapie mit anderen blutzuckersenkenden Arzneimitteln außer Insulin, wenn der Blutzucker mit Metformin und diesen Arzneimitteln zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert wird

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist).

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) Kombinationstherapie mit Insulin, wenn der Blutzucker mit Metformin und Insulin zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert wird

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist).

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 [42].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 5. September 2013 / 23. Januar 2014 – Lixisenatid.

Anwendungsgebiet

Lyxumia® wird angewendet bei Erwachsenen zur Behandlung des Typ-2-Diabetes mellitus in Kombination mit oralen blutzuckersenkenden Arzneimitteln und/oder Basalinsulin, wenn diese zusammen mit Diät und Bewegung den Blutzucker nicht ausreichend senken.

a) Add-on Kombinationstherapie mit Metformin, wenn Metformin den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend senkt:

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid) + Metformin

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Add-on Zweifach-Kombination mit einem oralen Antidiabetikum (außer Metformin), wenn dieses zusammen mit einer Diät und Bewegung den Blutzucker nicht ausreichend senkt:

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) Add-on Dreifach-Kombination mit oralen Antidiabetika, wenn diese zusammen mit einer Diät und Bewegung den Blutzucker nicht ausreichend senken:

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist)

Ausmaß des Zusatznutzens

Ein Zusatznutzen gilt als nicht belegt.

d) Add-on Kombination mit einem Basalinsulin mit oder ohne Metformin, wenn Basalinsulin (mit oder ohne Metformin) zusammen mit einer Diät und Bewegung den Blutzucker nicht ausreichend senkt:

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder nicht ausreichend wirksam ist)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 [56].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 21. Februar 2013 / 23. Januar 2014 – Linagliptin

Anwendungsgebiet

Trajenta® ist bei erwachsenen Patienten mit Diabetes mellitus Typ 2 zur Verbesserung der Blutzuckerkontrolle indiziert:

als Monotherapie

- bei Patienten, wenn Diät und Bewegung allein zur Blutzuckerkontrolle nicht ausreichen und für die Metformin wegen Unverträglichkeit ungeeignet oder aufgrund einer Nierenfunktionsstörung kontraindiziert ist.

als Kombinationstherapie

- in Kombination mit Metformin, wenn Diät und Bewegung sowie eine Metformin-Monotherapie zur Blutzuckerkontrolle nicht ausreichen,
- in Kombination mit einem Sulfonylharnstoff und Metformin, wenn Diät und Bewegung sowie eine Zweifachtherapie mit diesen beiden Arzneimitteln zur Blutzuckerkontrolle nicht ausreichen.

a) Monotherapie

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid, Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen gilt als nicht belegt.

b) Zweifachkombinationstherapie: Linagliptin + Metformin

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid, Glimepirid) + Metformin

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 [50].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 16. Mai 2013 / 23. Januar 2014 - Linagliptin (neues Anwendungsgebiet: Diabetes mellitus Typ 2, Kombinationstherapie mit Insulin mit oder ohne Metformin)

Anwendungsgebiet

Trajenta® ist bei erwachsenen Patienten mit Diabetes mellitus Typ 2 zur Verbesserung der Blutzuckerkontrolle indiziert:

- in Kombination mit Insulin mit oder ohne Metformin, wenn diese Behandlung alleine mit Diät und Bewegung zur Blutzuckerkontrolle nicht ausreichen.

Dreifachkombination Saxagliptin/Metformin mit Sulfonylharnstoff, wenn die maximal verträgliche Dosis sowohl von Metformin als auch des Sulfonylharnstoffs den Blutzucker nicht ausreichend kontrolliert

Zweckmäßige Vergleichstherapie

Zweifachkombination von Metformin + Humaninsulin.

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation unverträglich oder nicht ausreichend wirksam ist.)

Ausmaß des Zusatznutzens

Da die erforderlichen Nachweise nicht vollständig vorgelegt worden sind, gilt der Zusatznutzen im Verhältnis zur zweckmäßigen Vergleichstherapie als nicht belegt (§ 35a Abs. 1 Satz 5 SGB V).

G-BA, 2014 [35].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. Oktober 2013 / 23. Januar 2014 - Vildagliptin/Metformin

Anwendungsgebiet

Eucreas®/ Icandra®/ Zomarist® ist für die Behandlung des Typ-2-Diabetes-mellitus indiziert:

- Eucreas®/ Icandra®/ Zomarist® ist für die Behandlung von Erwachsenen indiziert, deren Blutzucker trotz Monotherapie mit der maximal verträglichen Dosis von Metformin alleine unzureichend eingestellt ist oder die bereits mit einer Kombination aus Vildagliptin und Metformin in separaten Tabletten behandelt werden.
- Eucreas®/ Icandra®/ Zomarist® ist in Kombination mit einem Sulfonylharnstoff (d. h. Dreifachkombinationstherapie) zusätzlich zu Diät und Bewegung indiziert bei Patienten, die mit Metformin und einem Sulfonylharnstoff nicht ausreichend eingestellt werden können.
- Eucreas®/ Icandra®/ Zomarist® ist als Dreifachkombinationstherapie mit Insulin zusätzlich zu Diät und Bewegung indiziert, um die glykämische Kontrolle bei Patienten zu verbessern, wenn eine stabile Insulindosis und Metformin allein zu keiner adäquaten glykämischen Kontrolle führen.

a) Zweifachkombination Vildagliptin/Metformin bei Patienten, deren Blutzucker trotz Monotherapie mit der maximal verträglichen Dosis von Metformin alleine unzureichend eingestellt ist:

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) Dreifachkombination Vildagliptin/Metformin mit Sulfonylharnstoff bei Patienten, die mit Metformin und einem Sulfonylharnstoff nicht ausreichend eingestellt werden können:

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) Kombination Vildagliptin/Metformin mit Insulin, wenn eine stabile Insulindosis und Metformin allein zu keiner adäquaten glykämischen Kontrolle führen:

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 [40].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 4. September 2014 – Canagliflozin.

Anwendungsgebiet

Invokana® wird angewendet bei Erwachsenen im Alter von 18 Jahren und älter mit Typ-2-Diabetes-mellitus zur Blutzuckerkontrolle als:

Monotherapie

- Bei Patienten, bei denen Diät und Bewegung allein den Blutzucker nicht ausreichend kontrollieren und eine Anwendung von Metformin aufgrund von Unverträglichkeit oder Gegenanzeigen als ungeeignet erachtet wird.

Kombinationstherapie

- Als Kombinationstherapie mit anderen blutzuckersenkenden Arzneimitteln einschließlich Insulin, wenn diese den Blutzucker, zusammen mit Diät und Bewegung, nicht ausreichend kontrollieren (siehe Abschnitte 4.4, 4.5 und 5.1 für verfügbare Daten zu den verschiedenen Kombinationstherapien).

a) In der Monotherapie, wenn Diät und Bewegung allein den Blutzucker nicht ausreichend kontrollieren und eine Anwendung von Metformin aufgrund von Unverträglichkeit oder Gegenanzeigen als ungeeignet erachtet wird

Zweckmäßige Vergleichstherapie

Sulfonylharnstoff (Glibenclamid oder Glimepirid)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

b) In Kombination mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin), wenn dieses den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert (Kombination mit Metformin)

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

c) In Kombination mit einem anderen blutzuckersenkenden Arzneimittel (außer Insulin), wenn dieses den Blutzucker zusammen mit einer Diät und Bewegung nicht ausreichend kontrolliert (Kombination mit einem Sulfonylharnstoff)

Zweckmäßige Vergleichstherapie

Metformin + Sulfonylharnstoff (Glibenclamid oder Glimepirid)

(Hinweis: Wenn Metformin gemäß Fachinformation nicht geeignet ist, ist Humaninsulin als Therapieoption einzusetzen.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

d) In Kombination mit mindestens zwei anderen blutzuckersenkenden Arzneimitteln, wenn diese den Blutzucker zusätzlich zu Diät und Bewegung nicht ausreichend kontrollieren

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

e) In Kombination mit Insulin (mit oder ohne orales Antidiabetikum)

Zweckmäßige Vergleichstherapie

Metformin + Humaninsulin

(Hinweis: Therapie nur mit Humaninsulin, wenn Metformin gemäß Fachinformation nicht ausreichend wirksam oder unverträglich.)

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt.

G-BA, 2014 [34].

Richtlinie über die Verordnung von Arzneimitteln in der vertragsärztlichen Versorgung (AM-RL); Anlage XII: (Frühe) Nutzenbewertung nach § 35a SGB V; Geltende Fassung zum Beschluss vom 1. Oktober 2013 / 23. Januar 2014 - Saxagliptin/Metformin (neues Anwendungsgebiet: Diabetes mellitus, Kombination mit einem Sulfonylharnstoff).

Anwendungsgebiet

Komboglyze® ist auch in Kombination mit einem Sulfonylharnstoff (d. h. als Dreifach-Kombinationstherapie) als Ergänzung zu Diät und Bewegung angezeigt, um die Blutzuckerkontrolle bei erwachsenen Patienten im Alter von 18 Jahren und älter mit Typ-2-Diabetes mellitus zu verbessern, wenn die maximal verträgliche Dosis sowohl von Metformin als auch des Sulfonylharnstoffs den Blutzucker nicht ausreichend kontrolliert.

Dreifachkombination Saxagliptin/Metformin mit Sulfonylharnstoff, wenn die maximal verträgliche Dosis sowohl von Metformin als auch des Sulfonylharnstoffs den Blutzucker nicht ausreichend kontrolliert

Zweckmäßige Vergleichstherapie

Humaninsulin + Metformin

(Hinweis: ggf. Therapie nur mit Humaninsulin, wenn Metformin nicht ausreichend wirksam ist).

Ausmaß des Zusatznutzens

Ein Zusatznutzen ist nicht belegt

IQWiG, 2017 [65].

Bewertung der Studie LEADER zu Liraglutid; Rapid Report; Auftrag A17-09

Fragestellung

Bewertung der Langzeitstudie LEADER im Anwendungsgebiet Diabetes mellitus Typ 2 hinsichtlich patientenrelevanter Endpunkte.

Methodik

Population: Erwachsene Patientinnen und Patienten mit Diabetes mellitus Typ 2 mit einem HbA1c-Wert von ≥ 7,0 % und einem Alter von mindestens 50 Jahren. Bei Patientinnen und Patienten ab 50 Jahren musste dabei zusätzlich eine kardiovaskuläre Erkrankung vorliegen, bei Patientinnen und Patienten ab 60 Jahren war das Vorliegen mindestens eines Risikofaktors für eine kardiovaskuläre Erkrankung ausreichend.

Intervention: Liraglutid + antidiabetischen Standardtherapie (blutzuckersenkende und kardiovaskuläre Therapie) OHNE GLP-1-Rezeptoragonisten, DPP-4-Inhibitoren oder Pramlintid

Komparator: Placebo + antidiabetischen Standardtherapie (blutzuckersenkende und kardiovaskuläre Therapie) OHNE GLP-1-Rezeptoragonisten, DPP-4-Inhibitoren oder Pramlintid

Endpunkte: Mortalität, Morbidität, gesundheitsbezogene Lebensqualität und Nebenwirkungen

Ergebnisse

Eingeschlossene Patienten: 9340

Qualität der Studie: Trotz des überwiegend niedrigen Verzerrungspotenzials auf Studien- und Endpunktebene ist die Aussagesicherheit der Studie niedrig, da im Verlauf der Studie bei einem Großteil der Patientinnen und Patienten die Studienvorgaben zur blutzucker- und blutdrucksenkenden Therapieeskalation nicht ausreichend umgesetzt wurden. Daher ist auch die Aussagesicherheit für jeden einzelnen patientenrelevanten Endpunkt der Studie LEADER niedrig.

Studienergebnisse:

- Gesamtmortalität: statistisch signifikanter Unterschied zugunsten von Liraglutid.
- Major Adverse Cardiovascular Event (MACE):
  - zusammengesetzt aus kardiovaskulärem Tod, nicht tödlichem Myokardinfarkt und nicht tödlichem Schlaganfall
  - statistisch signifikanter Unterschied zugunsten von Liraglutid. Dies gilt auch für die Einzelkomponente kardiovaskulärer Tod.
  - keine statistisch signifikanten Unterschiede für weitere Endpunkte
- SUE: unzureichend interpretierbar
- SUE oder nicht schwerwiegendes Medical Event of Special Interest (MESI): statistisch signifikanter Unterschied zuungunsten von Liraglutid für Erkrankungen des Gastrointestinaltrakts insgesamt sowie für die Einzelereignisse Diarrhö, Übelkeit und Erbrechen.
- Abbruch wegen SUE oder nicht schwerwiegendem MESI: statistisch signifikanter Unterschied zugunsten der Vergleichsbehandlung. Patientinnen und Patienten im Liraglutidarm brachen die Behandlung häufiger aufgrund eines SUE oder nicht schwerwiegenden MESI ab.
- Hypoglykämien:
  - Für den Endpunkt symptomatische Hypoglykämien mit einem Plasmaglukosewert < 56 mg/dl zeigte sich ein statistisch signifikanter Unterschied zugunsten von Liraglutid.

- Für die Endpunkte symptomatische Hypoglykämien mit einem Plasmaglukosewert ≤ 70 mg/dl und schwere Hypoglykämien zeigten sich keine statistisch signifikanten Unterschiede zwischen den Behandlungsgruppen.

Die positiven und negativen Effekte von Liraglutid zusätzlich zu einer antidiabetischen Standardtherapie, die sich aus der Studie LEADER ergeben, unterscheiden sich je nach Ausprägung einer Nierenfunktionsstörung zu Studienbeginn

Patientengruppe mit einer eGFR < 60 ml/min/1,73 m2

Tabelle 1: Positive und negative Effekte von Liraglutid + antidiabetische Standardtherapie im Vergleich zu Placebo + antidiabetische Standardtherapie in der Studie LEADER (berechnet nach MDRD)

Positive Effekte	**Negative Effekte**
Mortalität ▪ Gesamtmortalität	
Morbidität ▪ MACE[a] ▪ nicht tödlicher Schlaganfall ▪ alle Schlaganfälle ▪ stationäre Behandlung aufgrund von Herzinsuffizienz[b]	
Nebenwirkungen ▪ symptomatische Hypoglykämien (Plasmaglukose < 56 mg/dl)	Nebenwirkungen ▪ SUE oder nicht schwerwiegendes MESI ▫ Erkrankung des Gastrointestinaltrakts (Diarrhö, Übelkeit, Erbrechen)
a: kombinierter Endpunkt, bestehend aus den Einzelkomponenten kardiovaskulärer Tod, nicht tödlicher Myokardinfarkt und nicht tödlicher Schlaganfall b: gilt nur für die Patientengruppe mit einer kardiovaskulären Erkrankung eGFR: geschätzte glomeruläre Filtrationsrate; MACE: Major Adverse Cardiovascular Event; MDRD: Modification of Diet in Renal Disease; MESI: Medical Event of Special Interest; SUE: schwerwiegendes unerwünschtes Ereignis	

Patientengruppe mit einer eGFR ≥ 60 ml/min/1,73 m2

Tabelle 2: Positive und negative Effekte von Liraglutid + antidiabetische Standardtherapie im Vergleich zu Placebo + antidiabetische Standardtherapie in der Studie LEADER (berechnet nach MDRD)

Positive Effekte	Negative Effekte
Mortalität ▪ Gesamtmortalität	
Morbidität ▪ stationäre Behandlung aufgrund von Herzinsuffizienz[a]	
Nebenwirkungen ▪ symptomatische Hypoglykämien (Plasmaglukose < 56 mg/dl)	Nebenwirkungen ▪ SUE oder nicht schwerwiegendes MESI ▫ Erkrankung des Gastrointestinaltrakts (Diarrhö, Übelkeit, Erbrechen) ▪ Abbruch wegen SUE oder nicht schwerwiegendem MESI
a: gilt nur für die Patientengruppe mit einer kardiovaskulären Erkrankung eGFR: geschätzte glomeruläre Filtrationsrate; MACE: Major Adverse Cardiovascular Event; MDRD: Modification of Diet in Renal Disease; MESI: Medical Event of Special Interest; SUE: schwerwiegendes unerwünschtes Ereignis	

Fazit

Insgesamt ist unklar, ob die in der Studie beobachteten Effekte zu den kardiovaskulären Endpunkten auf Liraglutid zurückzuführen sind oder auf die unterschiedliche Behandlungsqualität in den Behandlungsgruppen. Demgegenüber ist die Hypoglykämierate in der Interventionsgruppe trotz forcierter Titration von Liraglutid und insgesamt stärkerer Blutzuckersenkung geringer als in der Kontrollgruppe, sodass für diesen Endpunkt von einem substanzspezifischen Effekt von Liraglutid ausgegangen werden kann.

3.2 Cochrane Reviews

Gnesin F et al., 2020 [61].

Metformin monotherapy for adults with type 2 diabetes mellitus

Fragestellung

To assess the effects of metformin monotherapy in adults with type 2 diabetes mellitus.

Methodik

Population:

- Adults (18 years or more) with type 2 diabetes mellitus (T2DM).

Intervention:

- Metformin monotherapy

Komparator:

- No intervention or other glucose-lowering drugs (sulphonylureas, insulin, thiazolidinediones, DPP-4i, glucagon-like peptide 1-analogue, meglitinides)

Endpunkte:

- Primary outcomes: All-cause mortality, Serious adverse events, Health-related quality of life.
- Secondary outcomes: Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, End-stage renal disease, Blindness, Severe hypoglycaemia

Recherche/Suchzeitraum:

- Identification of eligible studies was based on the results of the AHRQ report (Bolen S, Tseng E, Hutfless S, Segal JB, Suarez-Cuervo C, Berger Z, et al. Diabetes medications for adults with type 2 diabetes: an update. Comparative Effectiveness Review No. 173. Rockville (MD): Agency for Healthcare Research and Quality 2016 Apr. AHRQ Publication No. 16-EHC013-EF 2016.)
- Search was topped-up with their own search strategy from 2014 to December 2019: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE Ovid, Embase Ovid, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform

Qualitätsbewertung der Studien:

- Cochrane 'Risk of bias' assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 18 completed trials in qualitative synthesis (n= 10,680)
- 14 completed trials in meta-analyses

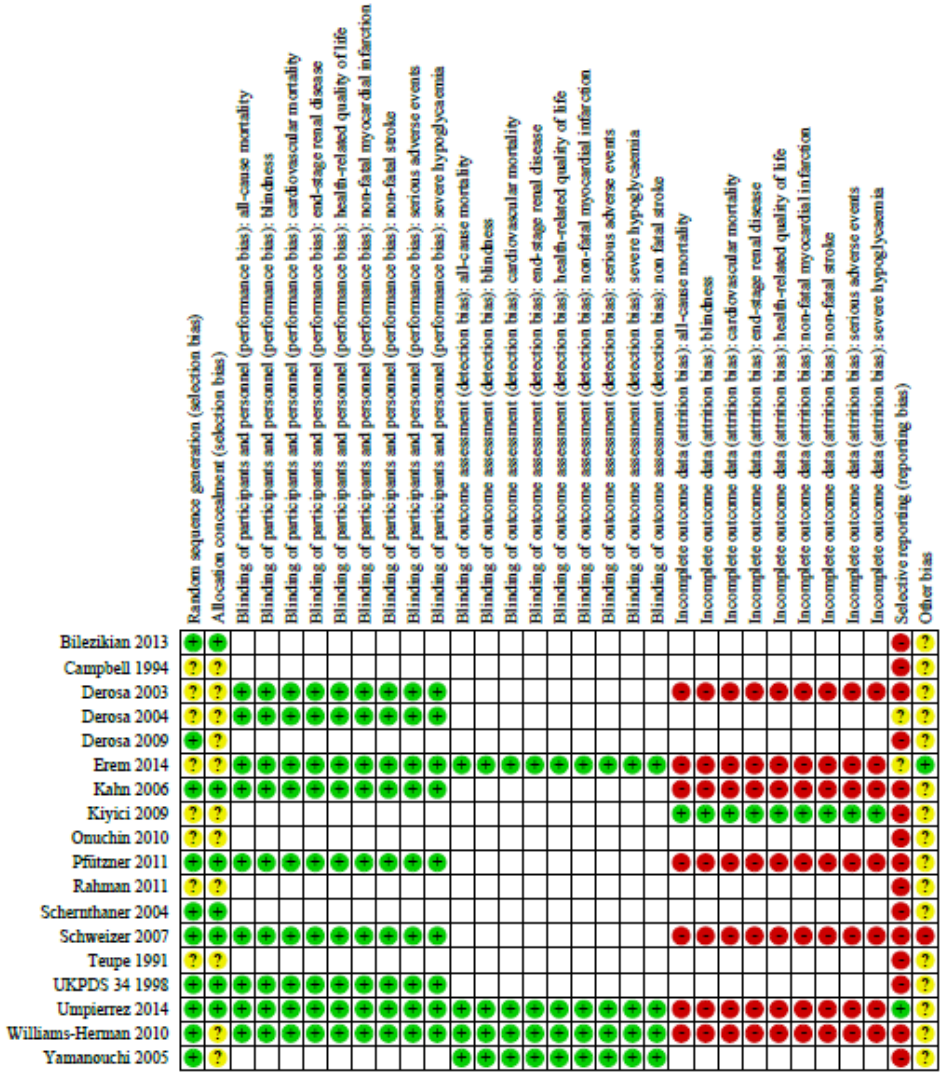
Charakteristika der Population:

- Two trials compared metformin monotherapy with no intervention (Kiyici 2009; Teupe 1991). Seven trials compared metformin monotherapy with sulphonylureas (Campbell 1994; Derosa 2004; Erem 2014; Kahn 2006; Rahman 2011; UKPDS 34 1998; Yamanouchi 2005). Two trials compared metformin monotherapy with insulin (Onuchin 2010; UKPDS

34 1998). Seven trials compared metformin monotherapy with thiazolidinediones (Bilezikian 2013; Derosa 2009; Erem 2014; Kahn 2006; Kiyici 2009; Schernthaner 2004; Yamanouchi 2005). Three trials compared metformin monotherapy with dipeptidyl peptidase 4-inhibitors (Pfützner 2011; Schweizer 2007; Williams-Herman 2010). One trial compared metformin monotherapy with a glucagon-like peptide 1-analogue (Umpierrez 2014). One trial compared metformin monotherapy with meglitinides (Derosa 2003).

- Mean and median duration of T2DM was approximately 3.7 years and 3.3 years, respectively.
- Two trials included only female participants (Bilezikian 2013; Onuchin 2010). In the remaining trials, the percentage of female participants ranged from 41% to 74%.
- Most participants were White people.
- Mean age of trial participants ranged from approximately 50.7 years to 64.0 years.
- Mean HbA1c at baseline ranged from 6.4% to 11.8%. Mean BMI at baseline ranged from 24.7 kg/m2 to 34 kg/m2.
- The most frequent cointervention/comedication was diet and exercise. Four trials reported comorbidities of participants (Derosa 2009; Erem 2014; Kiyici 2009; Onuchin 2010). The most frequent comorbidity was hypertension.

<u>Qualität der Studien:</u>



Studienergebnisse:

Summary of findings 1. Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus insulin

Metformin monotherapy compared with insulin for adults with type 2 diabetes

Patient: people with type 2 diabetes

Settings: outpatients

Intervention: metformin monotherapy

Comparison: insulin

Outcomes	Insulin	Metformin	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality	**Not reported**				
Serious adverse events	**Not reported**				
Health-related quality of life (Short Form-36 version 2 questionnaire) Follow-up: 1 year	See comment		91 (1)	⊕⊖⊖⊖ **very low** [a]	No substantial difference in mental or physical health-related quality of life between the intervention groups

Summary of findings 2. Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus sulphonylureas

Metformin monotherapy compared with sulphonylureas for adults with type 2 diabetes

Patient: people with type 2 diabetes

Settings: outpatients

Intervention: metformin monotherapy

Comparison: sulphonylureas (glibenclamide/glyburide, gliclazide, glipizide, glimepiride)

Outcomes	Sulphonylureas (glibenclamide/glyburide, gliclazide, glipizide, glimepiride)	Metformin	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 1-4 years	See comment		3129 (4)	⊕⊖⊖⊖ **very low** [a]	3 trials: no participant died (Campbell 1994; Derosa 2004; Erem 2014) 1 trial: 31/1454 participants (2.1%) in the metformin group died vs 31/1441 participants (2.2%) in the sulphonylurea group (Kahn 2006)
Serious adverse events (SAE) Follow-up: 1-4 years	See comment		3081 (3)	⊕⊖⊖⊖ **very low** [a]	2 trials: no SAE occurred (Derosa 2004; Erem 2014) 1 trial: 331/1454 participants (22.8%) in the metformin group experienced a SAE compared with 308/1441 participants (21.4%) in the sulphonylurea group (Kahn 2006)
Health-related quality of life	**Not reported**				
Cardiovascular mortality (CVM) Follow-up: 1-4 years	See comment		2940 (2)	⊕⊖⊖⊖ **very low** [a]	1 trial: no CVM was observed (Erem 2014) 1 trial: 4/1455 participants (0.3%) in the metformin group died of cardiovascular reasons vs 8/1447 participants (0.6%) in the sulphonylurea group (Kahn 2006)
Non-fatal myocardial infarction (NFMI) Follow-up: 1-4 years	See comment		3047 (3)	⊕⊖⊖⊖ **very low** [a]	2 trials: no NFMI occurred (Erem 2014; Yamanouchi 2005) 1 trial: 21/1454 participants (1.4%) in the metformin group experienced a NFMI vs 15/1441 participants (1.0%) in the sulphonylurea group (Kahn 2006)
Non-fatal stroke (NFS) Follow-up: 1-4 years	See comment		72 (1)	⊕⊖⊖⊖ **very low** [a]	1 trial: no NFS occurred (Yamanouchi 2005)
End-stage renal disease	**Not reported**				

CI: confidence interval; **NFMI**: non-fatal myocardial infarction; **NFS**: non-fatal stroke; **SAE**: serious adverse event.

Summary of findings 3. Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus thiazolidinediones

Metformin monotherapy compared with thiazolidinediones for adults with type 2 diabetes

Patient: people with type 2 diabetes

Settings: outpatients

Intervention: metformin monotherapy

Comparison: thiazolidinediones (pioglitazone, rosiglitazone)

Outcomes	Thiazolidinediones (pioglitazone, rosiglitazone)	Metformin monotherapy	Relative effect (95% CI)	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 1-4 years	**16 per 1000**	**14 per 1000** (9 to 22)	**RR 0.88** (0.55 to 1.39)	4402 (5)	⊕⊖⊖⊖ **very low** [a]	2 trials: no deaths occurred (Erem 2014; Kiyici 2009) 1 trial contributed 65/71 events (91.5%) (Kahn 2006)
Serious adverse events (SAE) Follow-up: 1-4 years	**220 per 1000**	**209 per 1000** (184 to 239)	**RR 0.95** (0.84 to 1.09)	3208 (4)	⊕⊖⊖⊖ **very low** [a]	2 trials: no SAE occurred (Erem 2014; Kiyici 2009).
Health-related quality of life	**Not reported**					
Cardiovascular mortality (CVM) Follow-up: 1-4 years	**3 per 1000**	**2 per 1000** (1 to 7)	**RR 0.71** (0.21 to 2.39)	3211 (4)	⊕⊖⊖⊖ **very low** [a]	2 trials: no deaths due to cardiovascular reasons occurred (Erem 2014; Kiyici 2009)
Non-fatal myocardial infarction (NFMI) Follow-up: 1-4 years	See comment			3020 (3)	⊕⊖⊖⊖ **very low** [a]	2 trials: no NFMI occurred (Erem 2014; Yamanouchi 2005) 1 trial: 21/1454 participants (1.4%) in the metformin group experienced a NFMI vs 25/1456 participants (1.7%) in the thiazolidinedione group
Non-fatal stroke (NFS) Follow-up: 1-4 years	See comment			72 (1)	⊕⊖⊖⊖ **very low** [a]	1 trial: no NFS occurred (Yamanouchi 2005)
End-stage renal disease	Not reported					

Summary of findings 4. Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus dipeptidyl-peptidase 4 inhibitors

Metformin monotherapy compared with dipeptidyl peptidase-4 inhibitors for adults with type 2 diabetes

Patient: people with type 2 diabetes

Settings: outpatients

Intervention: metformin monotherapy

Comparison: dipeptidyl peptidase-4 inhibitors (saxagliptin, sitagliptin, vildagliptin)

Outcomes	Dipeptidyl peptidase-4 inhibitors (saxagliptin, sitagliptin, vildagliptin)	Metformin monotherapy	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 1.5-2 years	See comment		1977 (3)	⊕⊝⊝⊝ **very low** [a]	1 trial: 5/328 (1.5%) participants in the metformin group died vs 2/335 (0.6%) participants in the saxagliptin group (Pfützner 2011) 1 trial: 1/364 (0.3%) participants in the metformin group died vs 0/179 in the sitagliptin group (Williams-Herman 2010) 1 trial: 4/252 (1.6%) participants in the metformin group died vs 3/519 (0.6%) in the vildagliptin group (Schweizer 2007)
Serious adverse events (SAE) Follow-up: 1.5-2 years	See comments		1977 (3)	⊕⊝⊝⊝ **very low** [a]	1 trial: 15/328 (4.5%) participants in the metformin group experienced a SAE vs 16/335 (4.8%) participants in the saxagliptin group (Pfützner 2011) 1 trial: 16/364 (4.4%) participants in the metformin group experienced a SAE vs 13/179 (7.2%) participants in the sitagliptin group (Williams-Herman 2010) 1 trial: 13/252 (5.2%) participants in the metformin group experienced a SAE vs 35/519 (6.7%) participants in the vildagliptin group (Schweizer 2007)
Health-related quality of life	**Not reported**				
Cardiovascular mortality (CVM) Follow-up: 1.5-2 years	See comment		1206 (2)	⊕⊝⊝⊝ **very low** [a]	1 trial: no deaths due to cardiovascular reasons occurred (Williams-Herman 2010). 1 trial: 3/328 (0.9%) participants in the metformin group died due to cardiovascular disease vs 2/335 (0.6%) participants in the saxagliptin group (Pfützner 2011)
Non-fatal myocardial infarction (NFMI) Follow-up: 1.5-2 years	See comment		543 (1)	⊕⊝⊝⊝ **very low** [a]	1 trial: 1/364 (0.3%) participants in the metformin group experienced a NFMI vs 0/179 participants in the sitagliptin group (Williams-Herman 2010)
Non-fatal stroke (NFS) Follow-up: 1.5-2 years	See comment		543 (1)	⊕⊝⊝⊝ **very low** [a]	1 trial: no NFS occurred (Williams-Herman 2010)

Summary of findings 5. Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus glucagon like peptide-1 analogues

Metformin monotherapy compared with glucagon like peptide-1 analogues for adults with type 2 diabetes

Patient: people with type 2 diabetes

Settings: outpatients

Intervention: metformin monotherapy

Comparison: glucagon like peptide-1 analogues (dulaglutide)

Outcomes	Glucagon like peptide-1 analogues (dulaglutide)	Metformin monotherapy	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality Follow-up: 1 year	See comment		807 (1)	⊕⊝⊝⊝ **very low** [a]	1 trial: no deaths occurred (Umpierrez 2014)
Serious adverse events (SAE) Follow-up: 1 year	See comment		807 (1)	⊕⊝⊝⊝ **very low** [a]	1 trial: 16/268 (6.0%) participants in the metformin group experienced a SAE vs 35/539 (6.5%) participants in the dulaglutide group (Umpierrez 2014)
Cardiovascular mortality (CVM) Follow-up: 1 year	See comment		807 (1)	⊕⊝⊝⊝ **very low** [a]	1 trial: no deaths due to cardiovascular reasons occurred (Umpierrez 2014)
Non-fatal myocardial infarction (NFMI) Follow-up: 1 year	See comment		807 (1)	⊕⊝⊝⊝ **very low** [a]	1 trial: 0/268 participants in the metformin group experienced a NFMI vs 1/539 (0.2%) participants in the dulaglutide group (Umpierrez 2014)
Non-fatal stroke (NFS) Follow-up: 1 year	See comment		807 (1)	⊕⊝⊝⊝ **very low** [a]	1 trial: 0/268 participants in the metformin group experienced a NFS vs 1/539 (0.2%) participants in the dulaglutide group (Umpierrez 2014)

Summary of findings 6. Summary of findings of metformin monotherapy for adults with type 2 diabetes mellitus: metformin versus meglitinides

Metformin monotherapy compared with another glucose-lowering drug for adults with type 2 diabetes					
Patient: people with type 2 diabetes					
Settings: outpatients					
Intervention: metformin monotherapy					
Comparison: meglitinide					
Outcomes	**Metiglinide (repaglinide)**	**Metformin monotherapy**	**No of participants (trials)**	**Certainty of the evidence (GRADE)**	**Comments**
All-cause mortality	**Not reported**				
Serious adverse events	See comment		112 (1)	See comment	1 trial: no SAE occurred (Derosa 2003)

Anmerkung/Fazit der Autoren

The amount of evidence for our primary and secondary outcomes was very limited. Neither metformin nor any of the comparators were clearly favoured in any of the outcomes. There were fewer reported cases of severe hypoglycaemia with metformin compared to sulphonylurea. Furthermore, metformin was favoured in the majority of our explorative outcomes. However, many of these results suffered from lack of data and heterogeneity, and were not robust in sensitivity analyses.

Semlitsch T et al., 2020 [99].

(Ultra-)long-acting insulin analogues versus NPH insulin (human isophane insulin) for adults with type 2 diabetes mellitus

Fragestellung

To compare the effects of long-term treatment with (ultra-)longacting insulin analogues (insulin glargine U100 and U300, insulin detemir and insulin degludec) with NPH insulin (human isophane insulin) in adults with type 2 diabetes mellitus

Methodik

Population:

- Adults (aged 18 years and older) with type 2 diabetes mellitus and not pregnant

Intervention:

- Long-acting insulin analogues (insulin glargine U100 or insulin detemir) or ultra-long-acting insulin analogues (insulin glargine U300 or insulin degludec).

Komparator:

- NPH insulin

Endpunkte:

- Primary outcomes: Diabetes-related complications, Hypoglycaemic episodes, Health-related quality of life.
- Secondary outcomes: All-cause mortality, Adverse events other than hypoglycaemia, Socioeconomic effects, HbA1c.

Recherche/Suchzeitraum:

- Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE Ovid, Embase Ovid, ClinicalTrials.gov, World Health Organization International Clinical Trials Registry Platform
- Until November 2019

Qualitätsbewertung der Studien:

- Cochrane 'Risk of bias' assessment tool

Ergebnisse

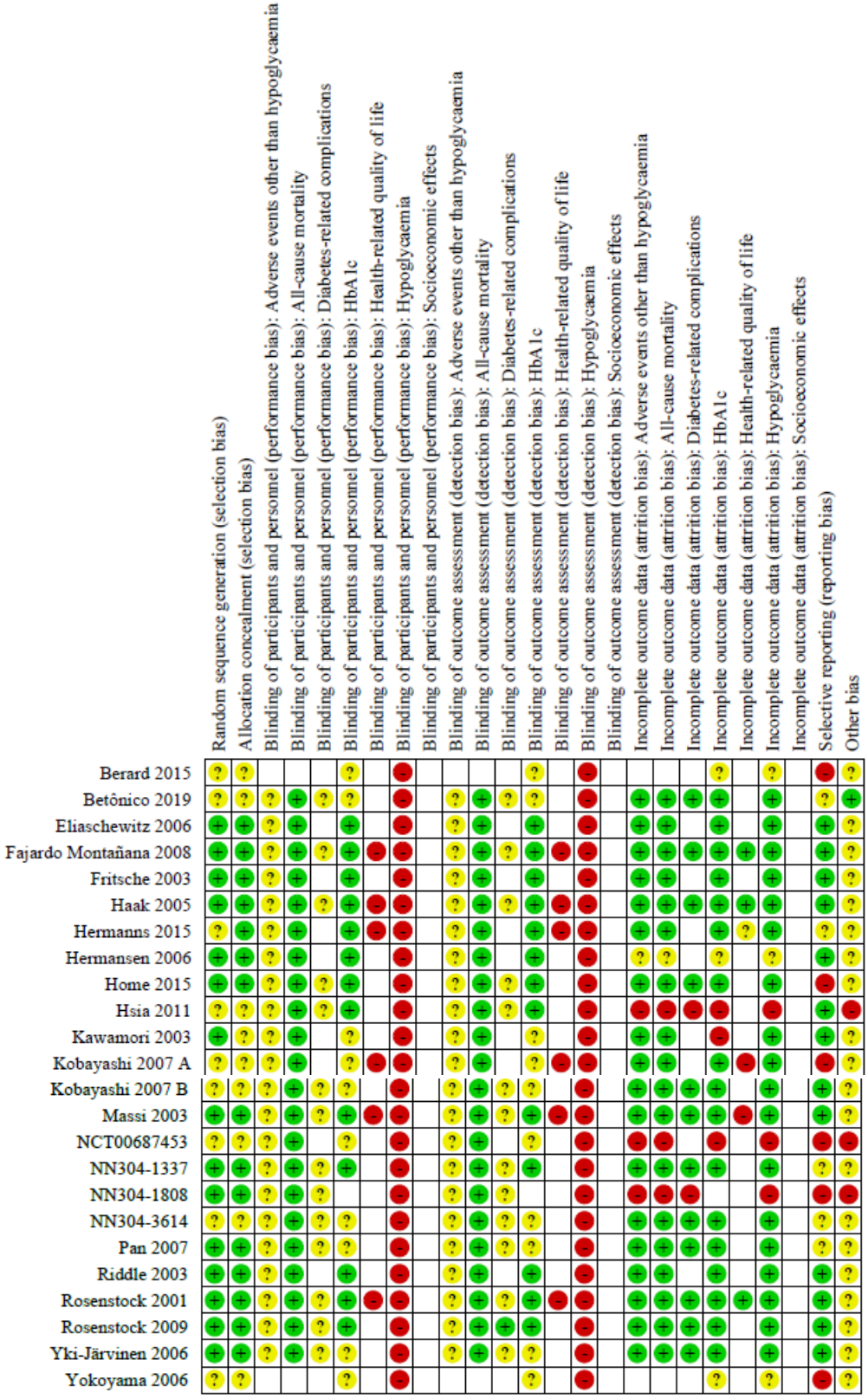
Anzahl eingeschlossener Studien:

- 24 studies (n=8677)
- Only trials reporting on subcutaneously administered insulin were considered for inclusion in this review

Charakteristika der Population:

- Glargine U100 vs NPH
  - Sixteen trials compared NPH to insulin glargine (Berard 2015; Eliaschewitz 2006; Fritsche 2003; Hermanns 2015; Home 2015; Hsia 2011; Kawamori 2003; Massi 2003; NCT00687453; Pan 2007; Betônico 2019; Riddle 2003; Rosenstock 2001; Rosenstock 2009; Yki-Järvinen 2006; Yokoyama 2006).
  - Overall, 6330 people with type 2 diabetes mellitus were randomised to the different comparison groups. Individual sample sizes ranged from 24 to 1024 participants per study. Between 60% and 95% of randomised participants finished the trials.
- Detemir vs NPH
  - Eight trials compared NPH insulin to insulin detemir (Fajardo Montañana 2008; Haak 2005; Hermansen 2006; Kobayashi 2007 A; Kobayashi 2007 B; NN304-1337; NN304-1808; NN304-3614).
  - Overall, 2347 people with type 2 diabetes mellitus were randomized to the different comparison groups. Individual sample sizes ranged from 60 to 505 per study. Between 48% and 95% of participants finished the trial.

Qualität der Studien:



Studienergebnisse:

SUMMARY OF FINDINGS

Summary of findings 1. Insulin glargine versus NPH insulin for type 2 diabetes mellitus

Insulin glargine vs NPH insulin for type 2 diabetes mellitus

Patient: participants with type 2 diabetes mellitus

Intervention: insulin glargine

Comparison: NPH insulin (human isophane insulin)

Outcomes	Risk for NPH insulin	Risk for insulin glargine	Relative effect (95% CI)	No of participants (trials)	Certainty of the evidence (GRADE)	Comments
Diabetes-related complications (1) Fatal MI (2) Fatal stroke (3) Progression in retinopathy (4) Amputations (5) ESRD Follow-up: 6 months to 36 weeks	(1) See comment (2) See comment **(3) 101 per 1000** (4) See comment (5) See comment	(1) See comment (2) See comment **(3) 104 per 1000** (60 to 178) (4) See comment (5) See comment	(1) + (2) See comment (3) **RR 1.03** (0.60 to 1.77) (4) + (5) See comment	(1) 934 (4 RCTs) (2) 934 (4 RCTs) (3) 1947 (5 RCTs) (4) 34 (1 RCT) (5) 34 (1 RCT)	(1) + (2) ⊕⊝⊝⊝ **Very low**[a] (3) ⊕⊝⊝⊝ **Very low**[b] (4) + (5) ⊕⊝⊝⊝ **Very low**[c]	(1) 1 trial reported 3/352 participants in the glargine 100 IU group vs 0/349 participants in the NPH group experienced fatal MI; 3 additional trials with 233 participants reported that no fatal MI occurred. (2) No fatal strokes occurred. (3) The 95% prediction interval ranged between 0.22 and 4.83. (4) + (5) 1 trial reported that no amputation or ESRD occurred.
Hypoglycaemic episodes (1) Severe hypoglycaemia (2) Serious hypoglycaemia (3) Confirmed hypoglycaemia (BG < 75 mg/dL) (4) Confirmed hypoglycaemia (BG < 55 mg/dL) (5) Confirmed nocturnal hypoglycaemia (BG < 75 mg/dL)	(1) **37 per 1000** (2) **27 per 1000** (3) **572 per 1000** (4) **180 per 1000** (5) **351 per 1000**	(1) **25 per 1000** (17 to 37) (2) **20 per 1000** (14 to 29) (3) **526 per 1000** (486 to 578) (4) **159 per 1000** (146 to 173) (5) **274 per 1000** (239 to 312)	(1) **RR 0.68** (0.46 to 1.01) (2) **RR 0.75** (0.52 to 1.09) (3) **RR 0.92** (0.85 to 1.01) (4) **RR 0.88** (0.81 to 0.96) (5) **RR 0.78** (0.68 to 0.89)	(1) 6164 (14 RCTs) (2) 4685 (10 RCTs) (3) 4115 (7 RCTs) (4) 4388 (8 RCTs) (5) 4225 (8 RCTs)	(1) ⊕⊝⊝⊝ **Very low**[d] (2) ⊕⊕⊝⊝ **Low**[e] (3) ⊕⊝⊝⊝ **Very low**[f] (4) ⊕⊕⊕⊝ **Moderate**[g] (5) ⊕⊝⊝⊝	(1) The 95% prediction interval ranged between 0.33 and 1.40. (2) The 95% prediction interval ranged between 0.48 and 1.16. (3) The 95% prediction interval ranged between 0.69 and 1.22. (4) The 95% prediction interval ranged between 0.79 and 0.98. (5) The 95% prediction interval ranged between 0.53 and 1.14.
(6) Confirmed nocturnal hypoglycaemia (BG < 55 mg/dL) Follow-up: 24 weeks to 5 years	(6) **115 per 1000**	(6) **85 per 1000** (74 to 98)	(6) **RR 0.74** (0.64 to 0.85)	(6) 4759 (8 RCTs)	**Very low**[f] (6) ⊕⊕⊕⊝ **Moderate**[g]	(6) The 95% prediction interval ranged between 0.62 and 0.88.
HRQoL Follow-up: 28 weeks to 48 weeks	See comment			1228 (3 RCTs)	⊕⊝⊝⊝ **Very low**[h]	3 trials reported no statically significant differences between glargine groups and NPH groups in HRQoL total scores (W-BQ22; EQ-5) or any subscales.
All-cause mortality Follow-up: 24 weeks to 5 years	**8 per 1000**	**9 per 1000** (5 to 15)	**Peto OR 1.06** (0.62 to 1.82)	6173 (14 RCTs)	⊕⊕⊝⊝ **Low**[i]	—
AEs other than hypoglycaemia (1) SAE (2) Overall AE (3) AE leading to discontinuation Follow-up: 24 weeks to 5 years	(1) **135 per 1000** (2)**662 per 1000** (3) **17 per 1000**	(1) **132 per 1000** (117 to 148) (2) **669 per 1000** (649 to 682) (3)**20 per 1000** (14 to 30)	(1) **RR 0.98** (0.87 to 1.10) (2) **RR 1.01** (0.98 to 1.03) (3) **RR 1.21** (0.84 to 1.76)	(1) 5499 (13 RCTs) (2) 6170 (14 RCTs) (3) 6149 (13 RCTs)	(1) + (2) (+3) ⊕⊕⊕⊝ **Moderate**[j]	(1) The 95% prediction interval ranged between 0.86 and 1.12. (2) The 95% prediction interval ranged between 0.99 and 1.03. (3) The 95% prediction interval ranged between 0.79 and 1.84.
Socioeconomic effects	Not reported					
HbA1c Follow-up: 24 weeks to 5 years	The mean change in HbA1c ranged across control groups from –2.12% to +0.1%	The mean change in HbA1c in the intervention groups was **0.07% lower** (0.18% lower to 0.03% higher)	—	5809 (16 RCTs)	⊕⊕⊝⊝ **Low**[k]	The 95% prediction interval ranged between –46% and 0.32%.

Summary of findings 2. Insulin detemir versus NPH insulin for type 2 diabetes mellitus

Insulin detemir vs NPH insulin for type 2 diabetes mellitus						
Patient: participants with type 2 diabetes mellitus **Intervention:** insulin detemir **Comparison:** NPH insulin (human isophane insulin)						
Outcomes	**Risk for NPH insulin**	**Risk for insulin detemir**	**Relative effect (95% CI)**	**No of participants (trials)**	**Certainty of the evidence (GRADE)**	**Comments**
Diabetes-related complications (1) Fatal MI (2) Fatal stroke (3) Progression in retinopathy (4) Amputations (5) ESRD Follow-up: 24 weeks to 26 weeks	(1) + (2) See comment **(3) 25 per 1000** (4) + (5) See comment	(1) + (2) See comment **(3) 37 per 1000** (17 to 82) (4) + (5) See comment	(1) + (2) See comment (3) **RR 1.50** (0.68 to 3.32) (4) + (5) See comment	(1) + (2) 271 (1 RCT) (3) 972 (2 RCTs) (4) + (5) 271 (1 RCT)	(1) + (2) + (3) + (4) + (5) ⊕⊝⊝⊝ **Very low**[a]	(1) + (2) 1 trial reported that no fatal MI or fatal stroke occurred. (3) – (4) + (5) 1 trial reported that no amputation or ESRD occurred.
Hypoglycaemic episodes (1) Severe hypoglycaemia (2) Serious hypoglycaemia (3) Confirmed hypoglycaemia (BG < 75 mg/dL) (4) Confirmed hypoglycaemia (BG < 55 mg/dL) (5) Confirmed nocturnal hypoglycaemia (BG < 75 mg/dL) (6) Confirmed nocturnal hypoglycaemia (BG < 55 mg/dL) Follow-up: 24 weeks to 7 months	(1) **17 per 1000** (2) **11 per 1000** (3) **562 per 1000** (4) **493 per 1000** (5) **309 per 1000** (6) **40 per 1000**	(1) **8 per 1000** (3 to 21) (2) **2 per 1000** (0 to 7) (3) **410 per 1000** (343 to 484) (4) **237 per 1000** (158 to 350) (5) **176 per 1000** (145 to 210) (6) **13 per 1000** (6 to 25)	(1) **RR 0.45** (0.17 to 1.20) (2) **Peto OR 0.16** (0.04 to 0.61) (3) **RR 0.73** (0.61 to 0.86) (4) **RR 0.48** (0.32 to 0.71) (5) **RR 0.57** (0.47 to 0.68) (6) **RR 0.32** (0.16 to 0.63)	(1) 1804 (5 RCTs) (2) 1777 (5 RCTs) (3) 1718 (4 RCTs) (4) 1718 (4 RCTs) (5) 1718 (4 RCTs) (6) 1718 (4 RCTs)	(1) ⊕⊝⊝⊝ **Very low**[b] (2) ⊕⊕⊝⊝ **Low**[c] (3) ⊕⊕⊝⊝ **Low**[d] (4) + (5) + (6) ⊕⊕⊝⊝ **Low**[e]	(1) The 95% prediction interval ranged between 0.09 and 2.21. (2) – (3) The 95% prediction interval ranged between 0.36 and 1.48. (4) The 95% prediction interval ranged between 0.20 and 1.13. (5) The 95% prediction interval ranged between 0.39 and 0.84. (6) The 95% prediction interval ranged between 0.07 and 1.42.
Health-related quality of life Follow-up: 26 weeks to 36 weeks	See comment			873 (3 RCTs)	⊕⊝⊝⊝ **Very low**[b]	3 trials reported no statically significant difference between detemir groups and NPH groups in HRQoL total scores (ITR-QOLN; DHP-2; SF-36) or any subscales.
All-cause mortality Follow-up: 24 weeks to 48 weeks	**5 per 1000**	**4 per 1000** (1 to 13)	**Peto OR 0.74** (0.20 to 2.65)	2328 (8 RCTs)	⊕⊕⊝⊝ **Low**[f]	—
AEs other than hypoglycaemia (1) SAE (2) Overall AE (3) AE leading to discontinuation Follow-up: 24 weeks to 48 weeks	(1) **71 per 1000** (2)**611 per 1000** (3) **18 per 1000**	(1) **62 per 1000** (45 to 85) (2) **629 per 1000** (586 to 678) (3)**22 per 1000** (12 to 40)	(1) **RR 0.88** (0.64 to 1.20) (2) **RR 1.03** (0.96 to 1.11) (3) **RR 1.22** (0.67 to 2.25)	(1) 2328 (8 RCTs) (2) 2328 (8 RCTs) (3) 2328 (8 RCTs)	(1) + (2) (+3) ⊕⊝⊝⊝ **Moderate**[g]	(1) The 95% prediction interval ranged between 0.60 and 1.30. (2) The 95% prediction interval ranged between 0.94 and 1.13. (3) The 95% prediction interval ranged between 0.57 and 2.62.
Socioeconomic effects	Not reported					
HbA1c Follow-up:	The mean change in HbA1c ranged across control groups	The mean change in HbA1c in the intervention groups was **0.13% higher** (0.02% lower to 0.28% higher)	—	2233 (7 RCTs)	⊕⊕⊝⊝ **Low**[h]	The 95% prediction interval ranged between –0.28% and 0.54%.

						from −1.9% to −0.32%	

AE: adverse event; **BG:** blood glucose; **CI:** confidence interval; **DHP-2:** Diabetes Health Profile 2; **ESRD:** end-stage renal disease; **HbA1c:** glycosylated haemoglobin A1c; **HRQoL:** health-related quality of life; **ITR-QOLN:** insulin therapy-related quality of life at night; **MD:** mean difference; **MI:** myocardial infarction; **NPH:** neutral protamine Hagedorn; **OR:** odds ratio; **RR:** risk ratio; **SAE:** serious adverse event; **SF-36:** 36-item Short Form Health Survey.

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded three levels because of risk of bias and serious imprecision (very sparse data) – see Appendix 2.
[b]Downgraded three levels because of risk of bias and serious imprecision – see Appendix 2.
[c]Downgraded two levels because of risk of bias and imprecision – see Appendix 2.
[d]Downgraded two levels because of risk of bias and inconsistency – see Appendix 2.
[e]Downgraded two levels because risk of bias and imprecision – see Appendix 2.
[f]Downgraded two levels because of serious imprecision – see Appendix 2.
[g]Downgraded one level because of imprecision – see Appendix 2.
[h]Downgraded two levels because of inconsistency and imprecision – see Appendix 2.

Anmerkung/Fazit der Autoren

With regard to diabetes complications information on myocardial infarction, stroke, amputations and end-stage renal disease was available from few trials only with a small number of events. No trustworthy inferences could be drawn from these results. There were more data on retinopathy; however, meta-analyses did not result in statistically or clinically relevant differences between treatment with glargine or detemir and NPH.

There were no clear differences for all-cause mortality when comparing treatment with long-acting insulin-analogues to NPH treatment. Information was available from almost all included trials and the number of people dying during a trial was low.

Treatment of people with type 2 diabetes mellitus with insulin glargine and insulin detemir compared to NPH insulin resulted in no substantial diDerences in hypoglycaemic episodes, HbA1c lowering was comparable between treatments. Serious hypoglycaemia was somewhat lower following insulin detemir treatment compared to NPH insulin. Both insulin glargine and insulin detemir showed lower confirmed (nocturnal) hypoglycaemia rates in comparison to NPH insulin.

Madsen KS et al., 2019 [77].

Metformin and second- or third-generation sulphonylurea combination therapy for adults with type 2 diabetes mellitus

Fragestellung

To assess the effects of metformin and sulphonylurea (second- or third-generation) combination therapy for adults with type 2 diabetes mellitus

Methodik

Population:

- T2DM

Intervention:

- Metformin plus second- or third-generation sulphonylurea (M +S) combination therapy

Komparator:

- Metformin plus another glucose-lowering intervention as a combination therapy (e.g. metformin plus dipeptidylpeptidase-4 inhibitor, metformin plus insulin)
- Metformin plus placebo
- Metformin monotherapy

Endpunkte:

- Primary endpoints: All-cause mortality, Health-related quality of life, Serious adverse events
- Secondary outcomes: Cardiovascular mortality, Non-fatal myocardial infarction, Heart failure, Non-fatal stroke, Amputation of lower extremity, Blindness or severe vision loss, End-stage renal disease, Non-serious adverse events, Hypoglycaemia, Socio-economic effects

Recherche/Suchzeitraum:

- CENTRAL, MEDLINE, Embase, ClinicalTrials.gov and WHO ICTRP. The date of the last search was March 2018
- We included trials with a minimum duration of intervention of 52 weeks

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 32 RCTs randomising 28,746 people.

Charakteristika der Population:

- Two trials had both a placebo group and an active comparator group (Ahrén 2014; Nauck 2013), the rest of the included trials had an active comparator group.
- The mean age of the participants ranged from 52 years to 73 years.
- One trial only included participants aged 65 years and more (Schernthaner 2015).
- Mean HbA1c at baseline ranged from 7.3% to 9.3%.
- Metformin was administered in all intervention and comparator arms and was mostly given in doses of 500 mg/day to 3000 mg/day
- The included trials used different types of sulphonylureas; 16 trials administered a second-generation sulphonylurea and 16 trials administered a third-generation sulphonylurea.

Qualität der Studien:

- None of the 32 included trials in our review was classified as having low risk of bias in all 'Risk of bias' domains.
- The description of randomization and allocation in the included trials was insufficient in eight trials (Ahrén 2014; Del Prato 2014; Filozof 2010; Gerich 2005; Matthews 2010; NCT00367055; Petrica 2009; Petrica 2011).
- Eleven trials had insufficient reporting of one or more outcomes of relevance for our review and, therefore, we classified them as having high risk of bias for selective outcome reporting bias (Derosa 2005; Derosa 2009a; Derosa 2009b; Derosa 2010; Derosa 2011a; Derosa 2011b; Filozof 2010; Gerich 2005; Maffioli 2013; Petrica 2009;

Petrica 2011). We were able to assess one or more of our predefined outcomes in all the included trials.

- For all the comparisons, we judged the certainty of the evidence to be low or very low mainly because of very limited data, various risk of bias and imprecision.
- Most trials received financial funding from the pharmaceutical industry. It is known that trials receiving funding or provision of free drugs or devices from a pharmaceutical company show more favourable results and conclusions compared to trials sponsored y other sources (Lundh 2017).

Studienergebnisse:

- All Cause Mortality

Outcomes	Metformin + antidiabetic drug	Metformin + sulphonylurea	Relative effect (95% CI)	No. of partic-ipants (trials)	Certainty of the evidence (GRADE)	Comments
All-cause mortality (N)						
M + GLP1-A Follow-up: 2-3 years	**7 per 1000**	**8 per 1000** (4 to 19)	**RR 1.15** (0.49 to 2.67)	2594 (3)	⊕⊕⊖⊖[a1] **Low**	
M + DPP4-I Follow-up: 1-3 years	**4 per 1000**	**5 per 1000** (3 to 9)	**RR 1.32** (0.76 to 2.28)	11,694 (9)	⊕⊕⊖⊖ **Low**[b1]	
M + thiazolidinedione Follow-up: 1-5.5 years	**34 per 1000**	**37 per 1000** (29 to 48)	**RR 1.09** (0.85 to 1.40)	6654 (6)	⊕⊕⊖⊖ **Low**[c1]	
M + nateglinide Follow-up: 1-2 years	See comment			874 (3)	⊕⊕⊖⊖ **Low**[d1]	1 participant died in each intervention group
M + SGLT2-I Follow-up: 2-4 years	**6 per 1000**	**6 per 1000** (3 to 13)	**RR 0.96** (0.44 to 2.09)	5134 (4)	⊕⊖⊖⊖ **Very low**[e1]	
Serious adverse events (N)						
M + GLP1-A Follow-up: 2-3 years	**126 per 1000**	**114 per 1000** (92 to 140)	**RR 0.90** (0.73 to 1.11)	2594 (3)	⊕⊖⊖⊖ **Very low**[a3]	
M + DPP4-I Follow-up: 1-3 years	**124 per 1000**	**132 per 1000** (120 to 146)	**RR 1.07** (0.97 to 1.18)	11,694 (9)	⊕⊖⊖⊖ **Very low**[b3]	
M + thiazolidinedione Follow-up: 1-5.5 years	**200 per 1000**	**202 per 1000** (186 to 222)	**RR 1.01** (0.93 to 1.11)	6654 (6)	⊕⊖⊖⊖ **Very low**[c3]	
M + nateglinide Follow-up:	**60 per 1000**	**101 per 1000** (32 to 313)	**RR 1.68** (0.54 to 5.21)	874 (3)	⊕⊕⊖⊖ **Low**[d3]	
M + SGLT2-I Follow-up: 2-4 years	**124 per 1000**	**126 per 1000** (94 to 170)	**RR 1.02** (0.76 to 1.37)	5134 (4)	⊕⊖⊖⊖ **Very low**[e3]	

Non-fatal stroke (N)						
M + GLP1-A	**Not reported**[a4]					
M + DPP4-I Follow-up: 1-2 years	**3 per 1000**	**6 per 1000** (2 to 18)	**RR 2.21** (0.74 to 6.58)	5093 (4)	⊕⊖⊖⊖ **Very low**[b4]	
M + thiazolidinedione Follow-up: 1-4.8 years	**10 per 1000**	**13 per 1000** (7 to 25)	**RR 1.29** (0.67 to 2.47)	3123 (2)	⊕⊖⊖⊖ **Very low**[c4]	
M + nateglinide Follow-up: 52 weeks	See comment			233 (1)	⊕⊖⊖⊖ **Very low**[d4]	No non-fatal stroke was reported
M + SGLT2-I Follow-up: 2 years	**4 per 1000**	**3 per 1000** (1 to 13)	**RR 0.87** (0.22 to 3.34)	2775 (2)	⊕⊖⊖⊖ **Very low**[e4]	
Non-fatal myocardial infarction (N)						
M + GLP1-A Follow-up: 2-3 years	**6 per 1000**	**3 per 1000** (1 to 16)	**RR 0.57** (0.12 to 2.82)	1575 (2)	⊕⊖⊖⊖ **Very low**[a5]	
M + DPP4-I Follow-up: 1-3 years	**3 per 1000**	**5 per 1000** (2 to 10)	**RR 1.45** (0.69 to 3.07)	6874 (6)	⊕⊖⊖⊖ **very low**[b5]	
M + thiazolidinedione Follow-up: 1-4.8 years	**11 per 1000**	**14 per 1000** (8 to 24)	**RR 1.21** (0.68 to 2.14)	3718 (3)	⊕⊖⊖⊖ **Very low**[c5]	
M + nateglinide Follow-up: 1 year	See comment			446 (2)	⊕⊕⊖⊖ **Low**[d5]	In 1 trial 2/101 (2%) participants had a non-fatal myocardial infarction in the M +S group compared with 0/112 partici-pant in the metformin plus nateglinide group
M + SGLT2-I Follow-up: 2-4 years	**6 per 1000**	**8 per 1000** (3 to 24)	**RR 1.43** (0.49 to 4.18)	2264 (2)	⊕⊖⊖⊖ **Very low**[e5]	

Anmerkung/Fazit der Autoren

There is no firm evidence whether metformin plus sulphonylurea combination compared with metformin plus another glucose-lowering agent or metformin monotherapy increases benefit or harm for most patient-important outcomes (all-cause mortality, serious adverse events, macrovascular complications (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke) and microvascular complications (amputation of lower extremity, blindness or severe vision loss, end-stage renal disease)).

There were more reported hypoglycaemic episodes with metformin plus sulphonylurea combination in comparison to all other metformin-antidiabetic agent combinations. The risk of hypoglycaemia increases with low glucose level targets which may not apply to the majority of elderly people with diabetes.

3.3 Systematische Reviews

Systematische Reviews zu DPP-4 Inhibitoren

Gillani SW et al., 2020 [58].

Clinical Review: Safety and Efficacy Comparison between Sulfonylureas and Dipeptidyl Peptidase-4 Inhibitors as Second-Line Therapies in Type 2 Diabetes Mellitus

Fragestellung

The objective of this systematic review is to analyze variables of interest in Type 2 diabetes including fasting blood glucose (FBG), post-prandial blood glucose (PPBG), hemoglobin A1c (HbA1c), microvascular complications, and cardiovascular outcomes in order to determine the shift towards the newer class of medications for type 2 diabetes.

Methodik

Population:

- Type 2 diabetes, patients who were on metformin therapy for a sufficient amount of time, as defined by the trial's protocol, who were then initiated on either a sulfonylurea (glipizide or glimepiride) or a DPP-4 inhibitor (saxagliptin or linagliptin).
- Patients with any acute and chronic health conditions were included in the search. Patients who were not initiated on metformin therapy as first-line treatment or were diagnosed with Type 1 diabetes were not included in this study.

Intervention/ Komparator:

- Sulfonylureas and Dipeptidyl Peptidase-4 Inhibitors
- 2. line

Endpunkte:

- FBG, post-prandial blood glucose, HbA1c, microvascular complications, and cardiovascular outcomes

Recherche/Suchzeitraum:

- ScienceDirect was the primary source used to obtain literature through journals such as the International Journal of Clinical Practice, Diabetes Research and Clinical Practice, Cardiovascular Diabetology, and The Journal of the American Medical Association. Other databases and individual journal websites such as PubMed, New England Journal of Medicine, and Google Scholar were also used during the literature search.
- The literature search focused on articles ranging from 2005-2019

Qualitätsbewertung der Studien:

- Good Research for Comparative Effectiveness (GRACE)

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 studies

Charakteristika der Population:

Table 1. Characteristics of studies extracted.

Article Number	Authors	Drug and Dose	Sample Size (n)	Age Cohort (years)	Outcome Measures Extracted from Articles	Treatment Period	Population
[1]	M. Feinglos *et al.* (2005)	Glipizide GITS 2.5 mg OR placebo	122	30-80	HbA1c, FPG	16 weeks	White (90/122)
[2]	B. Goke *et al.* (2013)	Glipizide 5-20 mg OR Saxagliptin 5 mg	858	25-83	HbA1c, FPG	104 weeks (52-week initial phase, 52-week extension phase)	White (714/858)
[3]	G. Schernthaner *et al.* (2015)	Glimepiride ≤6 mg OR Saxagliptin 5 mg/	720	≥65	HbA1c	52 weeks	White (707/720)
[4]	W. Yang *et al.* (2011)	Saxagliptin 5 mg OR placebo	530	54 (average)	HbA1c, FPG, PPBG	24 weeks	Chinese (326/530)
[5]	R. Weitgasser *et al.* (2002)	Glimepiride 0.5 mg->4 mg	1,770 (284 follow-up)	23-93 (35-90 follow-up)	HbA1c	1.5 years	N/A
[6]	B. Gallwitz *et al.* (2012)	Glimepiride 1-4 mg OR linagliptin 5 mg	1,552	18-80	HbA1c	2 years	White (1,319/1,552)
[7]	M. Sjostrand *et al.* (2014)	Saxagliptin 5 mg	431	105 (average)	HbA1c, FPG, PPBG	24 weeks	Chinese
[8]	C. Ott *et al.* (2014)	Saxagliptin 5 mg	50	18-75	HbA1c, FPG, PPBG, RCF	12 weeks	N/A
[9]	T. Jax *et al.* (2017)	Glimepiride 1-4 mg OR linagliptin 5 mg	42	18-70	HbA1c, FMVD	4 weeks	Germans
[10]	J. Rosenstock *et al.* (2019)	Glimepiride 1-4 mg OR linagliptin 5 mg	6,042	64 (average)	HbA1c, 3P-MACE	5.9 years	White (4,407/6,042)

*HbA1c = Hemoglobin A1c, FPG = Fasting plasma glucose, FMVD = Flow-mediated vasodilation, PPBG = Post-prandial blood glucose, RCF = Retinal capillary flow.

Qualität der Studien:

Table 2. Quality assessment *via* GRACE.

-	M. Feinglos *et al.* (2005) [4]	B. Goke *et al.* (2013) [6]	G. Schernthaner *et al.* (2015) [12]	W. Yang *et al.* (2011) [18]	R. Weitgasser *et al.* (2002) [17]	B. Gallwitz *et al.* (2012) [5]	M. Sjostrand *et al.* (2014) [13]	C. Ott *et al.* (2014) [9]	T. Jax *et al.* (2017) [8]	J. Rosenstock *et al.* (2019) [15]
Were treatment and/or important details of treatment exposure adequately recorded for the study purpose in the data source(s)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the primary outcomes adequately recorded for the study purpose (*e.g.*, available in sufficient detail through data source(s))?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the primary clinical outcome(s) measured objectively rather than subject to clinical judgment (*e.g.*, opinion about whether the patient's condition has improved)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were primary outcomes validated, adjudicated, or otherwise known to be valid in a similar population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

- **(Table 2) Contd....**

-	M. Feinglos *et al.* (2005) [4]	B. Goke *et al.* (2013) [6]	G. Schernthaner *et al.* (2015) [12]	W. Yang *et al.* (2011) [18]	R. Weitgasser *et al.* (2002) [17]	B. Gallwitz *et al.* (2012) [5]	M. Sjostrand *et al.* (2014) [13]	C. Ott *et al.* (2014) [9]	T. Jax *et al.* (2017) [8]	J. Rosenstock *et al.* (2019) [15]
Was the primary outcome(s) measured or identified in an equivalent manner between the treatment/ intervention group and the comparison group(s)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were important covariates that may be known confounders or effect modifiers available and recorded?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was the study (or analysis) population restricted to new initiators of treatment or those starting a new course of treatment?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
If one or more comparison groups were used, were they concurrent comparators? If not, did the authors justify the use of historical comparisons group(s)?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were important covariates, confounding and effect modifying variables taken into account in the design and/or analysis?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is the classification of exposed and unexposed person-time free of "immortal time bias"?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were any meaningful analyses conducted to test key assumptions on which primary results are based on?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Studienergebnisse:

- Comparison between Sulfonylureas and DPP-4 Inhibitorson Fasting Plasma Glucose
  - In a study by M. Feinglos et al., [4] there was a significant reduction in fasting plasma glucose with 154 mg/dL + 4 mg/dL as the baseline, decreasing to 132 mg/dL + 4 mg/dL by the final visit after the use of glipizide GITS 2.5 mg with metformin. In the second article, the baseline FPG in the saxagliptin group was 161.9 mg/dL + 2.0 and 160.5 mg/dL + 1.9 in the glipizide group with an adjusted mean change of -12.5 mg/dL + 1.9 and -9.8 mg/dL + 2.0. In article 4, there was a significant adjusted mean change in fasting plasma glucose of -1.14 mmol/L versus -0.58 mmol/L for saxagliptin plus metformin and placebo plus metformin, respectively. However, another study [7] presents saxagliptin with its adjusted mean change of fasting plasma glucose as -0.41. Fasting plasma glucose in an article [8] did not reach statistical significance with the use of saxagliptin.
- Comparison between Sulfonylureas and DPP-4 inhibitors on post-Prandial Blood Glucose
  - There was an adjusted mean change of post-prandial blood glucose of -2 mmol/L and -1 mmol/L of saxagliptin plus metformin versus placebo plus metformin, respectively [4]. Literature also [7] presents saxagliptin with its adjusted mean change for PPBG as - 168. A significant reduction with saxagliptin was also noted for postprandial glucose (9.27 ± 0.4 versus 10.1 ± 0.4 mmol/L; p = 0.001) compared to placebo [8].
- Comparison between Sulfonylureas and DPP-4 Inhibitors on Hemoglobin A1c

- In a study by M. Feinglos et al., [4] there was a significant reduction in A1c with the baseline from 7.45% + 0.1% to 6.80% +0.1% in patients who participated in the treatment arm of glipizide GITS 2.5 mg plus metformin. In contrast, B. Goke et al., [6] focused on both glipizide with metformin and saxagliptin with metformin with the baseline mean of both 7.65% + 0.04 and an adjusted mean of -0.41 + 0.04 and -0.35 + 0.04 with saxagliptin and glipizide respectively (95% CI, -0.17 to 0.06). In the study by G.
- Schernthaner et al., [12] an adjusted mean change from baseline in HbA1c was -0.44 (-0.51, -0.37), showing no significant difference with both glimepiride and saxagliptin. The 4th article began the HgA1c baseline at an average of 7.9% for both saxagliptin and placebo with an adjusted mean change of -0.78 and -0.37, respectively, by the end of the trial. Over the span of 1.5 years, Raimund Weitgasser et al. [17] showed an adjusted mean change ranging from month 4, year 1, to year 1.5 with values of -1.4, -1.5, and -1.7% respectively for A1c. Aside from previous trials that had a significant difference in hemoglobin A1c, B. Gallwitz et al. [5] presented with non-inferiority between glimepiride and linagliptin, their adjusted mean difference for A1c (-0.36 and -0.16, respectively). In contrast, another article [7] focuses on saxagliptin with its adjusted mean change as -0.33%.

- Comparison between Sulfonylureas and DPP-4 Inhibitors on Microvascular and Cardiovascular Complications
  - Linagliptin presented with significantly fewer cardiovascular events [6] compared to glimepiride. Retinal capillary flow (RCF), as mentioned in an article [8], significantly reduced after the use of saxagliptin (288 ± 13.2); RCF was used to determine microvascular complications with the use of a DPP-4 inhibitor. Under fasting conditions, linagliptin significantly improved microvascular function as shown by a 34% increase in hyperaemia area (P = 0.045 vs glimepiride), a 34% increase in resting blow flow (P = 0.011 vs glimepiride, P = 0.003 vs placebo), and a 25% increase in peak blood flow (P = 0.009 vs glimepiride, P = 0.003 vs placebo). In a study by Ott el al. [9], findings for the primary endpoint of change in fasting flow-mediated vasodilation, the adjusted gMean ratios (90% CI) on day 28 to baseline were 0.89 (0.70-1.13) for linagliptin, 1.00 (0.80- 1.26) for glimepiride and 1.00 (0.79-1.28) for placebo (Fig. 2). No statistically significant differences in fasting flow-mediated vasodilation were observed between the treatments (P > 0.1 for all comparisons). The last article (CAROLINA trial) focuses on 3P-MACE as the primary endpoint with 0.98 (0.84 to 1.14) as the hazard ratio and odds ratio, respectively (Table 3).
- Safety Profile between Sulfonylureas and DPP-4 Inhibitors
  - Safety variables such as adverse effects and events of hypoglycaemia were not analyzed in this review due to the comparative article by Farah et al., addressing these variables. A general trend from the articles indicated that low hypoglycemic risk was associated with linagliptin or saxagliptin compared to glimepiride and glipizide. In a couple of articles chosen, the following information evidently describes the difference in hypoglycemic events in DPP-4 inhibitors and sulfonylureas. With glipizide GITS 2.5 mg and metformin in the first article, there was an increase in hypoglycemia in 9 patients, with hypoglycemia defined as point-of-care testing measured at <60 mg/dL with symptoms, <50 mg/dL without symptoms, or a fasting plasma glucose of <55 mg/dL without symptoms. With hypoglycemia in the study by B. Goke et al., [6]

achieving an HbA1c of <7%, caused more hypoglycemic events in patients who were taking glipizide with metformin versus saxagliptin with metformin; 13.4% of patients achieved HbA1c <7% without hypoglycemic events compared to 22.2% of patients who achieved an HbA1c of <7% without hypoglycemic events. According to G. Schernthaner et al., [12] the incidence of confirmed/severe hypoglycaemia was greater in the glimepiride group compared to the saxagliptin group with the glimepiride group achieving a target A1c more than the saxagliptin group. It should be noted that in another study [6], linagliptin presented with significant fewer cardiovascular events compared to glimepiride (Table 4).

Anmerkung/Fazit der Autoren

Despite the higher efficacious characteristics of sulfonylureas in lowering HbA1c, due to its reported hypoglycemic effects, DPP-4 inhibitors may be considered as a clinically stable choice for second-line therapy after completing maximally tolerated doses of metformin. Sulfonylureas are considered better than DPP-4 inhibitors for treatment in patients with cardiovascular disease history and hypoglycemia.

Pan Z et al., 2020 [94].

Efficacy and safety of DPP-IV inhibitors combined with basal insulin in the treatment of type 2 diabetes

Fragestellung

To evaluate the efficacy and safety of dipeptidyl peptidase IV (DPP-IV) inhibitors when added to insulin therapy in patients with type 2 diabetes mellitus (T2DM).

Methodik

Population:

- T2DM

Intervention:

- DPP-IVi/INS
- duration ≥12 weeks

Komparator:

- insulin-alone (with or without placebo)

Endpunkte:

- glycemic control

Recherche/Suchzeitraum:

- PubMed, EMBASE, the Web of Science, and the Cochrane Library

Qualitätsbewertung der Studien:

- Cochrane Riski of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 16

Charakteristika der Population:

TABLE 1 Characteristics of the included studies

Number	First author (publication)	country	Study duration, wk	Single-center or multicenter	Diabetes duration, y	Number of baseline samples		Sex (male/female)		Age		Intervention measures		Relevant variables	Drug treatment sequence
						Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
No.1	Villabell (2010) [16]	USA	24	100 clinical sites	12.5	322	319	157/49	169/53	58.3 ± 9.1	57.2 ± 9.3	Saxagliptin +insulin	placebo +insulin	HbAlc (%), 2h PPG (mmol/L), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.2	Barnett (2012) [17]	USA	24	multicenter	12	304	151	120/184	68/83	57.2 ± 9.43	57.3 ± 9.27	Saxagliptin + insulin	placebo +insulin	HbAlc (%), 2h PPG (mmol/L), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.3	Hong (2012) [18]	Korean	24	single-center	15.8	61	63	33/28	32/31	58.8 ± 14.3	59.6 ± 13.0	Saxagliptin +insulin	placebo + insulin	HbAlc (%), 2h PPG (mmol/L), FBG (mmol/L), Hypoglycemia	DPP-IVi therapy was added on to insulin
No.4	Yki-Jarvinen (2013) [19]	19 countries	24	19 clinical sites	>5	631	630	329/302	329/301	59.7 ± 69.9	60.4 ± 10.0	Linagliptin +insulin	placebo +insulin	HbAlc (%), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
NO.5	Kadowaki (2013) [20]	Japan	16	60 clinical sites	14	129	137	53/76	57/80	59.3 ± 9.9	59.1 ± 10.1	Sitagliptin +insulin	placebo +insulin	HbAlc (%), 2h PPG (mmol/L), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.6	Kaku (2014) [21]	Japan	12	37 clinical sites	14.5	90	89	50/40	47/40	62.9 ± 8.22	62.4 ± 9.88	Alogliptin + insulin	placebo +insulin	HbAlc (%), FBG (mmol/L), Hypoglycemia, AEs	DPP-IVi therapy was added on to insulin
No.7	Hirose (2015) [22]	Japan	12	28 clinical sites	12.9	44	44	55/23	56/22	58.5 ± 9.6	60.1 ± 9.1	Vildagliptin +insulin	placebo +insulin	HbAlc (%)	DPP-IVi therapy was added on to insulin
No.8	Sato (2015) [23]	Japan	24	single-center	19.5	25	24	16/9	18/6	66 ± 8	66 ± 13	Sitagliptin +insulin	placebo +insulin	HbAlc (%), 2h PPG (mmol/L), FBG (mmol/L), Hypoglycemia	DPP-IVi therapy was added on to insulin

TABLE 1 (Continued)

Number	First author (publication)	country	Study duration, wk	Single-center or multicenter	Diabetes duration, y	Number of baseline samples		Sex (male/female)		Age		Intervention measures		Relevant variables	Drug treatment sequence
						Intervention	Control	Intervention	Control	Intervention	Control	Intervention	Control		
No.9	Mathieu (2015) [24]	USA	24	multicenter	13.5	329	329	151/178	164/165	59.3 ± 8.9	58.3 ± 9.7	Sitagliptin +insulin	placebo +insulin	HbAlc (%), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.10	Ning (2016) [25]	China	24	22 clinical sites	11.3	146	147	61/85	66/81	57.8 ± 9.1	58.4 ± 9.6	Vildagliptin +insulin	placebo +insulin	HbAlc (%), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.11	Mita (2016) [26]	Japan	104	12 clinical sites	NA	137	137	83/61	82/30	63.8 ± 9.7	63.6 ± 1.0	Sitagliptin +insulin	placebo +insulin	HbAlc (%), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.12	Kadowaki (2017) [27]	Japan	16	62 clinical sites	NA	117	115	69/44	70/45	63.1 ± 10.3	63.7 ± 10.1	Saxagliptin +insulin	placebo +insulin	HbAlc (%), 2h PPG (mmol/L), FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.13	Cao (2017) [28]	China	16	single-center	6	33	32	18/15	18/14	52.1 ± 9.6	49.8 ± 11.2	Sitagliptin +insulin	Insulin	HbA1c (%), Hypoglycemia	NA
No.14	Chen (2018) [29]	China	24	22 clinical sites	NA	234	232					Saxagliptin +insulin	placebo +insulin	2hPPG (mmol/L), FBG (mmol/L), Hypoglycemia	DPP-IVi therapy was added on to insulin
No.15	Ledesma (2019) [30]	Japan	24	multicenter	NA	151	151	92/59	91/60	72.5 ± 5.1	72.5 ± 5.6	Linagliptin +insulin	placebo +insulin	FBG (mmol/L), Hypoglycemia, SAEs, AEs	DPP-IVi therapy was added on to insulin
No.16	Munch (2020) [31]	France	12	6 clinical sites	23.5	32	33	17/16	15/18	69.7 ± 9.6	71.3 ± 7.3	Vildagliptin +insulin	Insulin	HbAlc (%), Hypoglycemia, SAEs	DPP-IVi therapy was added on to insulin

Abbreviations: 2hPPG, 2-hour postprandial blood glucose; AE, adverse event; FBG, fasting blood glucose; DPP-IVi, dipeptidyl peptidase IV inhibitor; HbA1c, glycosylated hemoglobin; NA, not available; SAE, serious adverse event.

Qualität der Studien:

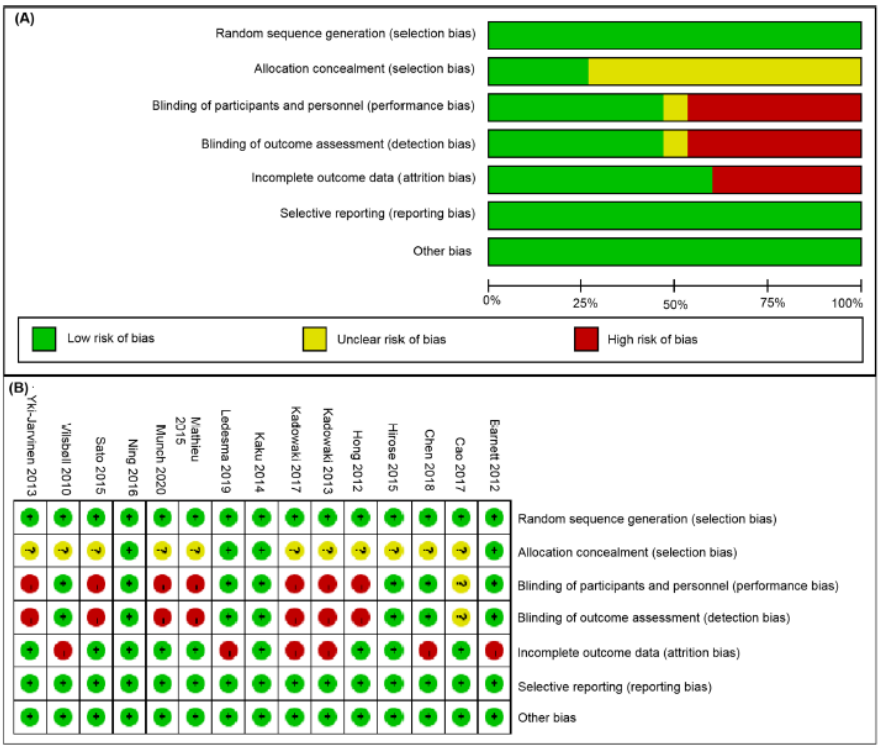


FIGURE 2 Risk of bias graph (A) and summary (B). In Figure 2B, green represents a low risk of bias, while red represents a high risk of bias. Yellow represents unclear risk of bias

Studienergebnisse:

- Glycosylated hemoglobin (HbA1c) was significantly decreased in the DPP-IV inhibitors with insulin (DPP-IVi/INS) group compared with the insulin-alone (with or without placebo) group (WMD = −0.62%; 95% CI: −0.74, −0.49; P < .05).
- Consistent with this finding, the fasting blood glucose (FBG)-lowering effect (WMD = −0.61 mmol/L; 95% CI: −0.77, −0.45; P < .05) and 2-hour postprandial glucose (2hPPG)-lowering efficacy (WMD = −2.39 mmol/L; 95% CI: −2.81, −1.97; P < .05) in the DPP-IVi/INS group were also significantly better than in the insulin-alone group.
- Regarding safety indicators, compared with the insulin-alone group, DPP-IVi/INS treatments had no association with the risk of adverse effects, including hypoglycemia, adverse events (AEs), and serious adverse events (SAEs).

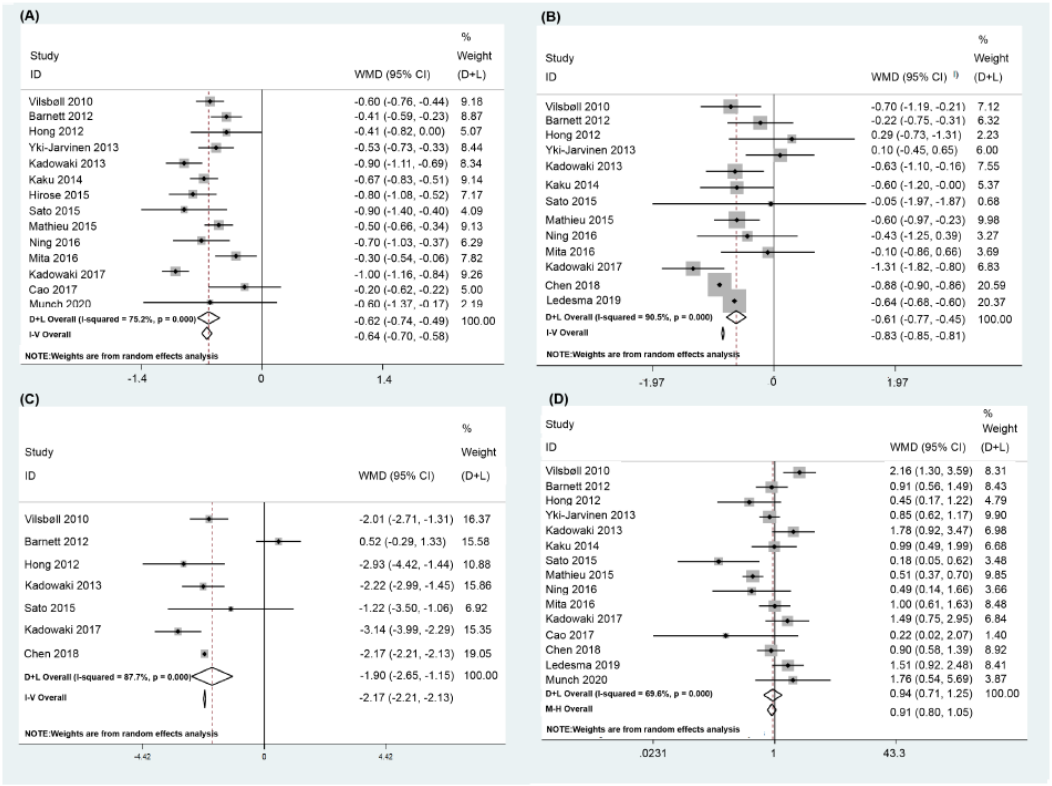
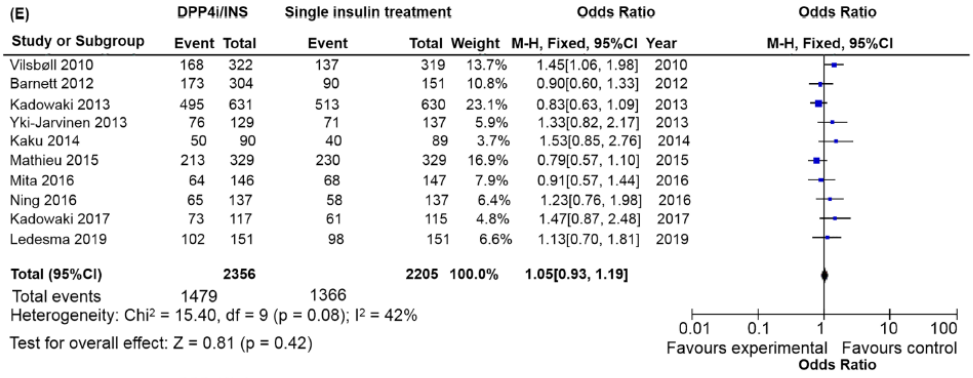
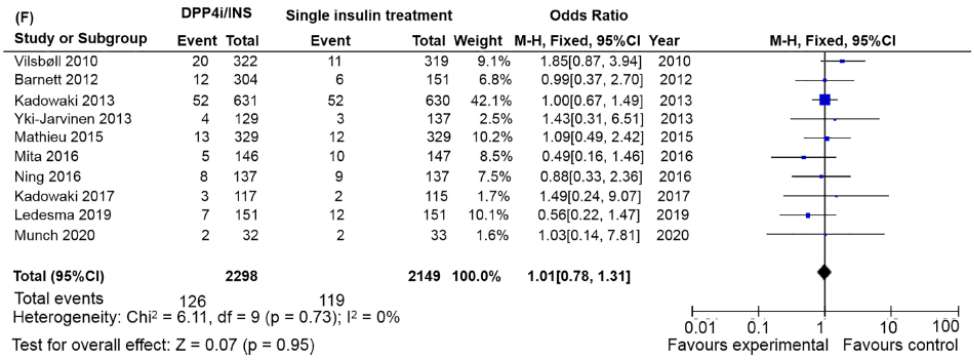


FIGURE 3 Outcomes of the comparison of the HbA1c (A), FBG (B), 2hPPG (C), hypoglycemia (D), adverse events (F) and severe adverse reactions (E) of the DPP4i/INS group with those of the insulin alone group in patients with T2DM by forest plots





Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis demonstrated that compared with the insulin-alone group, DPP-IVi/INS improved glycemic control without leading to any known AEs or SAEs. We recommend that T2DM patients have DPP-IVi/INS therapy for improved glycemic

control, especially T2DM patients with inadequate glycemic control who are on insulin treatment alone.

Shibuki K et al., 2020 [100].

Meta-Analysis of 11 Heterogeneous Studies regarding Dipeptidyl Peptidase 4 Inhibitor Add-On Therapy for Type 2 Diabetes Mellitus Patients Treated with Insulin

Fragestellung

We conducted a meta-analysis of randomized controlled trials, which compared the efficacy and safety of adding DPP-4 inhibitors or placebo to insulin therapy; the level of hemoglobin A1c (HbA1c) in the patients was >7.0%, and the duration of treatment was ≥8 weeks.

Methodik

Population:

- Patients with type 2DM (≥18 years old, HbA1c ≥ 7:0%, excluding pregnant women), who had been treated with a fixed dose of insulin (insulin lispro, insulin aspart, insulin glulisine, insulin neural, insulin isophane, insulin glargine, insulin detemir, or insulin degludec; single agent or in combination with metformin) for more than 8 weeks before DPP-4 treatment

Intervention:

- received an additional DPP-4 inhibitor (sitagliptin, alogliptin, vildagliptin, saxagliptin, linagliptin, anagliptin, or teneligliptin) at the standard dosage coadministered with the insulin therapy

Komparator:

- received placebo instead of a DPP-4 inhibitor with the insulin therapy

Endpunkte:

- changes in HbA1c from the baseline (ΔHbA1c) and the incidence of hypoglycemia

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, the Cochrane Library, ClinicalTrials.gov, and pharmaceutical company sites as sources of information.
- A comprehensive literature search was conducted from September 1, 2015, to December 31, 2016.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 studies (n = 4654 patients)

Charakteristika der Population:

	Number of patients (experimental vs. control)	Country	Type 2 DM duration[a] (years)	HbA1c (%)	FPG (mg/dL)	BMI (kg/m^2)	Therapy duration (weeks)
Fonseca et al. [33]	296 (144/152)	Germany, Finland, Spain, USA	14.7	8.40	161.8	33.1	24
Rosenstock et al. [34]	259 (130/129)	13 countries	12.8	9.30	190.8	32.4	26
Vilsbøll et al. [35]	641 (322/319)	22 countries	12.0	8.60	177.1	31.0	24
Kothny et al. [36]	449 (228/221)	11 countries	13.0	8.80	NA	28.9	24
Barnett et al. [37]	455 (304/151)	11 countries	11.9	8.70	173.3	32.3	52
Kadowaki et al. [38]	266 (129/137)	Japan	14.0	8.90	165.0	25.2	16
Kaku et al. [39]	179 (90/89)	Japan	14.9	8.43	154.9	24.3	12
Mathieu et al. [40]	658 (329/329)	27 countries	13.4	8.80	176.4	32.1	24
Durán-Garcia et al. [41]	950 (475/475)	19 countries	NA	8.30	151.2	31.0	52
Hirose et al. [42]	156 (78/78)	Japan	12.9	8.10	160.2	25.7	12
Ning et al. [43]	293 (146/147)	China, Thailand, Philippines, Singapore	11.3	8.70	171.0	26.2	24

[a]Abbreviations: DM: diabetes mellitus; HbA1c: hemoglobin A1c; FPG: fasting plasma glucose; BMI: body mass index; NA: not available.

Qualität der Studien:

- There were a few risks of bias that would affect the assessment of efficacy and safety
- of DPP-4 inhibitors.

Studienergebnisse:

- The mean ΔHbA1c between the DPP-4 inhibitor and placebo groups was -0.61% (95% confidence interval (CI): -0.74 to -0.48, I2 = 73:4%). There was substantial heterogeneity among the 11 studies, but 74.1% of this variability was explained by the difference in BMI. The odds ratio for the incidence of hypoglycemia was 1.02 (95% CI: 0.74 to 1.42, I2 = 63:8%), with substantial heterogeneity due to differences in the definition of hypoglycemia among the studies.
-
- Figure 1: Forest plot for ΔHbA1c in the random-effects model. Each square indicates the mean difference (MD) and the bar indicates the 95% confidence interval (CI) from an eligible study. The size of each square corresponds to the weight of that study. The diamond and its width represent the combined MD and 95% CI, respectively. ΔHbA1c: change in hemoglobin A1c; SD: standard deviation.

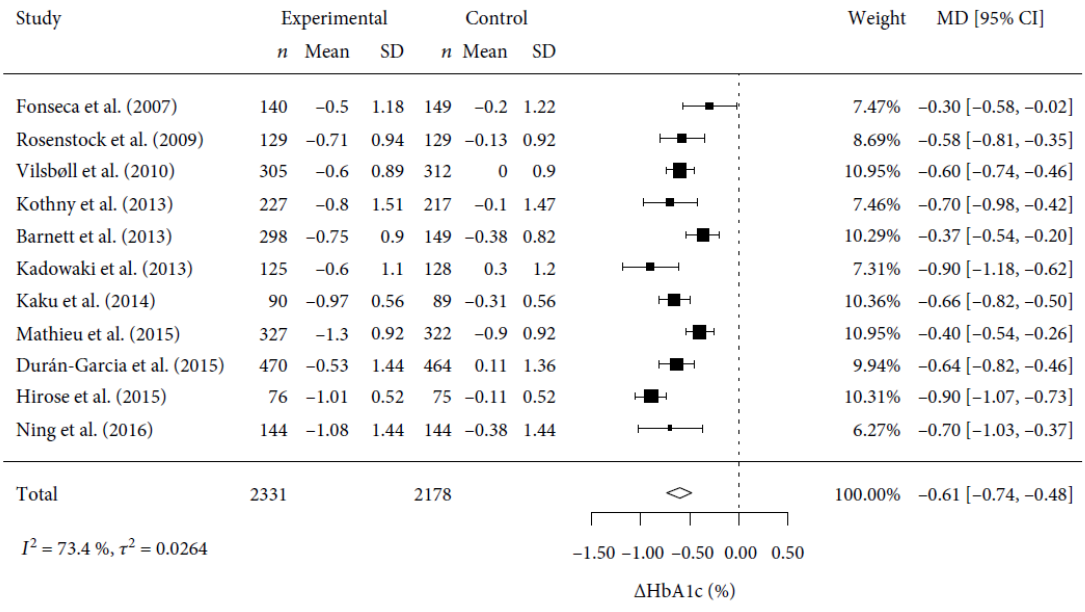


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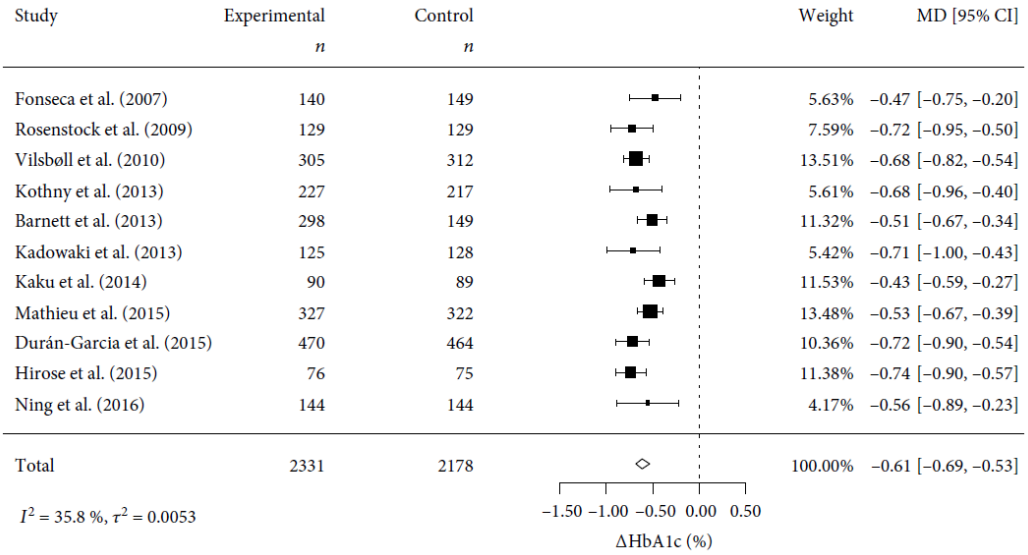
Figure 3: Forest plot for corrected ΔHbA1c based on the BMI in each study. BMI: body mass index; ΔHbA1c: change in hemoglobin A1c; MD: mean difference; CI: confidence interval.



- Figure 5: Forest plot for hypoglycemic incidence in the random-effects model. Each square indicates the odds ratio (OR) and the bar indicates the 95% confidence interval (CI) from an eligible study. The size of each square corresponds to the weight of that study. The diamond and its width represent the combined OR and 95% CI, respectively.

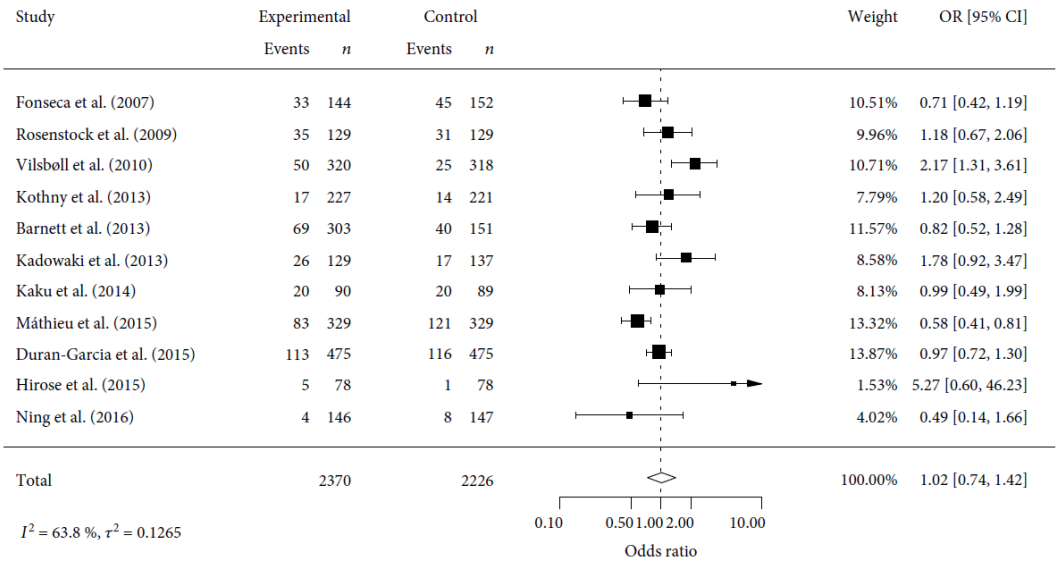


Table 3: Summary of the results of existing meta-analyses.

	ΔHbA1c (%)	Odds ratio for hypoglycemic incidence
Chen et al. [11]	-0.52% (-0.59 to -0.44, I^2 = 0%, 7 studies)	1.04 (0.83 to 1.31, I^2 = 58.5%, 7 studies)
Kim et al. [12]	-0.58% (-0.70 to -0.46, I^2 = 76.4%, 9 studies)	0.94 (0.84 to 1.05, I^2 = 71.7%, 9 studies)
Yang et al. [13]	-0.53% (-0.63 to -0.43, I^2 = 99%, 7 studies)	1.02 (0.91 to 1.16, I^2 = NR[a], 7 studies)
Wang et al. [14]	-0.54% (-0.66 to -0.42, I^2 = 82%, 22 studies)	0.92 (0.78 to 1.10, I^2 = 60%, 22 studies)
Present study	-0.61% (-0.74 to -0.48, I^2 = 73.4%, 11 studies)	1.02 (0.74 to 1.42, I^2 = 63.8%, 11 studies)

[a]Abbreviation: NR: not reported.

Anmerkung/Fazit der Autoren

The addition of DPP-4 inhibitors to insulin therapy for adult patients with type 2 DM can significantly reduce HbA1c levels without increasing the occurrence of hypoglycemia. BMI and hypoglycemia definition could explain the heterogeneity in the clinical trials.

Yang J et al., 2020 [108].

Effect of Dipeptidyl Peptidase 4 Inhibitors Used in Combination with Insulin Treatment in Patients with Type 2 Diabetes: A Systematic Review and Metaanalysis

Fragestellung

To evaluate the efficacy and safety of dipeptidyl peptidase 4 inhibitors (DPP4i) used in combination with insulin in patients with type 2 diabetes mellitus (T2DM).

Methodik

Population:

- Adult patients with T2DM

Intervention:

- Addition of DPP4i to insulin therapy (either with regimens of basal insulin, basal and premeal bolus of insulin, or premixed insulin)

Komparator:

- insulin controls, with or without background therapy with other OADs

Endpunkte:

- Efficacy outcomes [HbA1c, fasting plasma glucose (FPG), 2-hour postprandial glucose PPG-2h), total daily insulin dose; the number of participants achieving the target HbA1c\7%)]
- Safety outcomes (body weight and incidence of hypoglycemia).

Recherche/Suchzeitraum:

- searched the MEDLINE, Embase, and Cochrane library databases
- RCT published through June 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 21 RCTs with 3697 patients

Charakteristika der Population:

- Sudy duration was 12-104 weeks. Male proportion in studies ranges from 34%- 76.6%.

Qualität der Studien:

- There were 12 studies not clearly describing the methods of random sequence generation and/ or allocation concealment (selection bias). Two trials showed a high

risk of performance and detection bias. Also, risk of performance and detection bias was unclear in four trials, and the risk was judged to be low for the other studies.

- Two, one, and two studies were considered to have an unclear risk for incomplete outcome data, selective reporting, and other bias, respectively, and the risks were considered low for the others.

Studienergebnisse:

- Efficacy Outcomes
- Change in HbA1c All enrolled studies involving
- 6851 patients with T2DM assessed the change in HbA1c levels. The combination therapy of insulin and a DDP4i led to a greater reduction in HbA1c level as compared with the control (WMD = - 0.57%; 95% CI - 0.66, - 0.48; p\0.0001). A significant heterogeneity among studies was detected (I^2 = 82%, p\0.01). Subgroup analysis showed that control-adjusted reductions in HbA1c from baseline were observed in both the insulin-stable subgroup (WMD = - 0.64%; 95% CI - 0.74, - 0.53) and insulin-flexible subgroup (WMD = - 0.43%; 95% CI - 0.56, - 0.30) (Fig. 2).

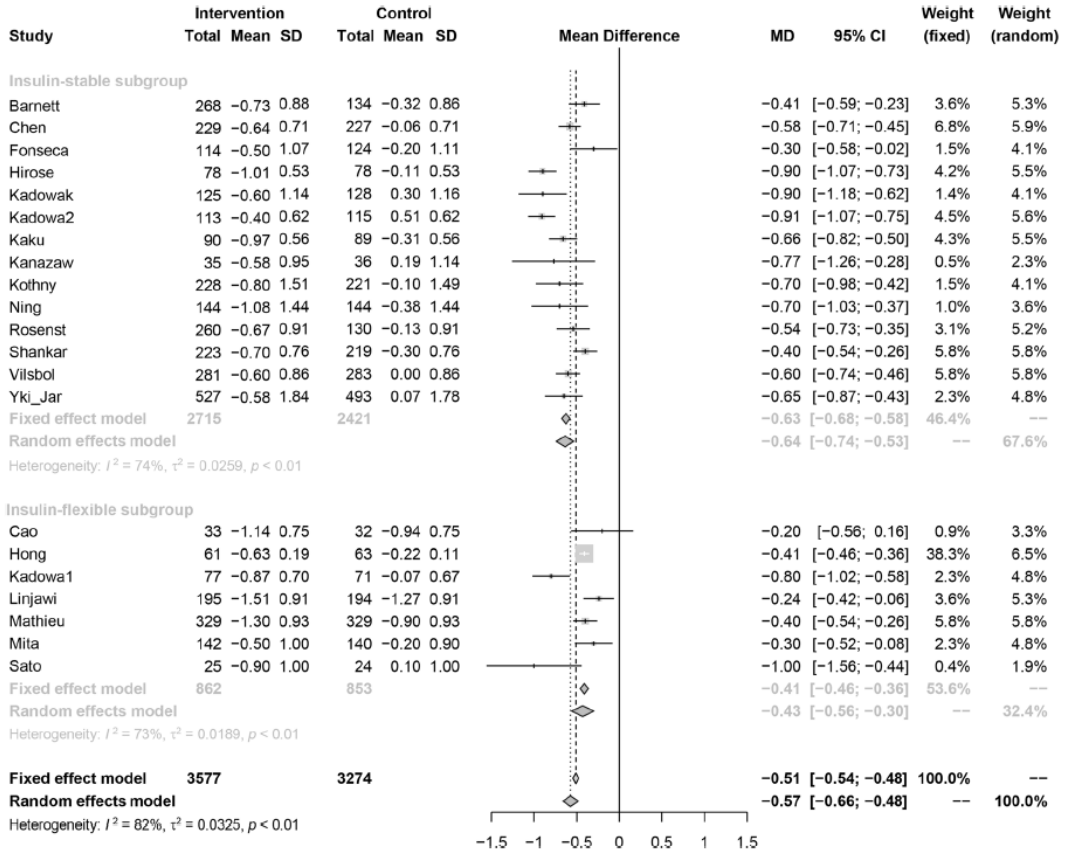


Fig. 2 Results assessed by forest plots for the change in HbA1c from baseline (%)

- Achievement of HbA1c Target Goal
- Eighteen studies assessed the proportion of patients achieving the target HbA1c (\7%). The combination therapy of DPP4i and insulin was associated a higher likelihood of achieving this goal (OR 3.45; 95% CI 2.58, 4.63; p\0.0001). Significant heterogeneity among studies was detected (I^2 = 62%, p\0.01). In subgroup analysis, the combination therapy of DPP4i and insulin demonstrated a greater chance to achieve the target HbA1c goal in comparison with the control treatment in both the insulinstable

subgroup (OR 4.33; 95% CI 2.90, 6.48) and insulin-flexible subgroup (OR 2.43; 95% CI 1.71, 3.46) (Fig. 3).

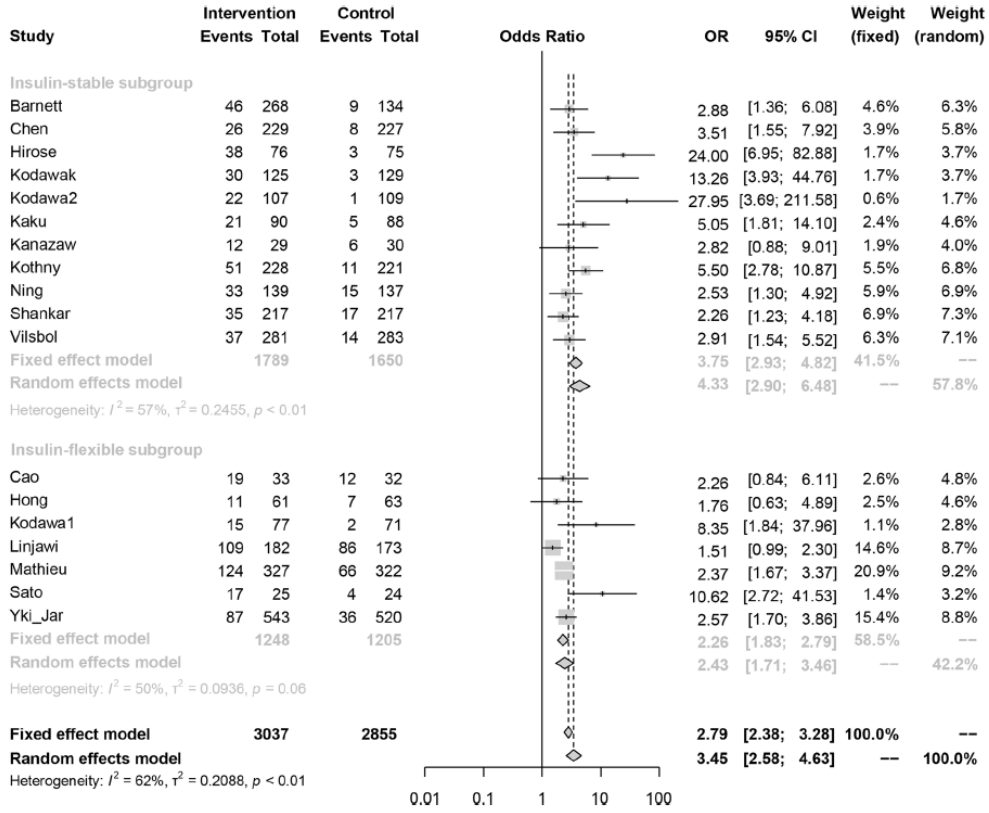


Fig. 3 Results assessed by forest plots for odds ratio (OR) in terms of achieving HbA1c < 7.0%

- Change in FPG
- Pooled analysis of 16 studies assessed the change in FPG. The FPG change from baseline was significant between the DPP4i/insulin and control groups (WMD = - 0.53 mmol/L; 95% CI - 0.72, - 0.34; p\0.0001). The heterogeneity among studies was not significant (I^2 = 37%, p = 0.07). Subgroup analysis revealed that the difference in the adjusted change from baseline for the DPP4i/insulin group compared with the control was - 0.64 mmol/L (95% CI - 0.84, - 0.44) in the insulin-stable subgroup and - 0.27 mmol/L (95% CI - 0.66, 0.11) in the insulin-flexible subgroup (Supplementary Fig. 3).
- Change in PPG-2h
- Seven studies were used for the analysis of the PPG-2h change from baseline, which was significant between DPP4i/ insulin and control groups (WMD = - 1.91 mmol/L; 95% CI - 2.24, - 1.58; p\0.0001). The heterogeneity among studies was not significant (I^2 = 5%, p = 0.39). Subgroup analysis showed that the control-adjusted mean change in PPG-2h from baseline was - 1.85 mmol/L (95% CI - 2.18, - 1.53) and - 2.55 mmol/L (95% CI - 3.67, - 1.43) in the insulinstable and insulin-flexible subgroups, respectively (Supplementary Fig. 4).
- Change in Daily Dosage of Insulin Use
- For the change in daily insulin dose from baseline, 11 studies were included for the analysis, of which seven studies examined patients on stable insulin dose regimens while the other four studies examined patients with insulin dose titration. DPP4i/insulin treatment led to a greater not differ between treatment with DPP4i/insulin and control (symptomatic hypoglycemia, OR 1.08, 95% CI 0.69, 1.68, p = 0.7484; significant heterogeneity among studies with I^2 = 79%, p\0.01; and severe

hypoglycemia, OR 1.00, 95% CI 0.66, 1.52, p = 0.9863; nonsignificant heterogeneity among studies with I2 = 0%, p = 0.98) (Supplementary Figs. 6 and 7).

- Among studies with a stable insulin dosage, DPP4i/insulin treatment caused an increased risk of symptomatic hypoglycemia (OR 1.64; 95% CI 1.20, 2.25; p\0.05) compared with the control. For studies with flexible insulin dosing, DPP4i/insulin did not increase the likelihood of symptomatic hypoglycemia (OR 0.71; 95% CI 0.45, 1.14; p[0.05) (Supplementary Fig. 6).
- Irrespective of the subgroup, the risk of developing severe hypoglycemia was not significantly different with DPP4i/insulin relative to the control treatment (Supplementary Fig. 7).
- Change in Body Weight
- The change in body weight from baseline did not differ significantly between patients receiving DPP4i/insulin and control treatment (WMD = 0.02 kg; 95% CI - 0.30, 0.34; p = 0.8931). The heterogeneity among studies was significant (I^2 = 77%, p\0.01). Subgroup analysis revealed that the adjusted mean change in body weight from baseline was 0.02 kg (95% CI - 0.16, 0.19) in the insulin-stable group and - 0.33 kg (95% CI - 1.51, 0.85) in the insulin-flexible group (Supplementary Fig. 8).

Anmerkung/Fazit der Autoren

The addition of DPP4i to insulin is associated with a statistically significant reduction in glycemic control as measured by HbA1c, fasting plasma glucose, and 2-h postprandial glucose, without increasing the risk of hypoglycemia and weight gain. These conclusions were also observed in both stable-dose and flexible-dose insulin subgroups.

Bae JH et al., 2019 [3].

Effects of Dipeptidyl Peptidase-4 Inhibitors on Renal Outcomes in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis

Fragestellung

In the present study, we performed a systematic review and meta-analysis of RCTs to investigate the effects of DPP-4 inhibitors on individual renal outcomes including ESRD compared with placebo or other antidiabetic agents in patients with type 2 diabetes.

Methodik

Population:

- type 2 diabetes

Intervention:

- DPP-4 inhibitors

Komparator:

- placebo or other antidiabetic agents

Endpunkte:

- renal outcomes including changes in UACR or eGFR, and the development of microalbuminuria, macroalbuminuria, doubling of serum creatinine levels, renal failure, end-stage renal disease (ESRD), renal replacement therapy (RRT), dialysis, or kidney transplantation

Recherche/Suchzeitraum:

- MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials to Sep 2017
- eligible studies were at least 12 weeks of study duration

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

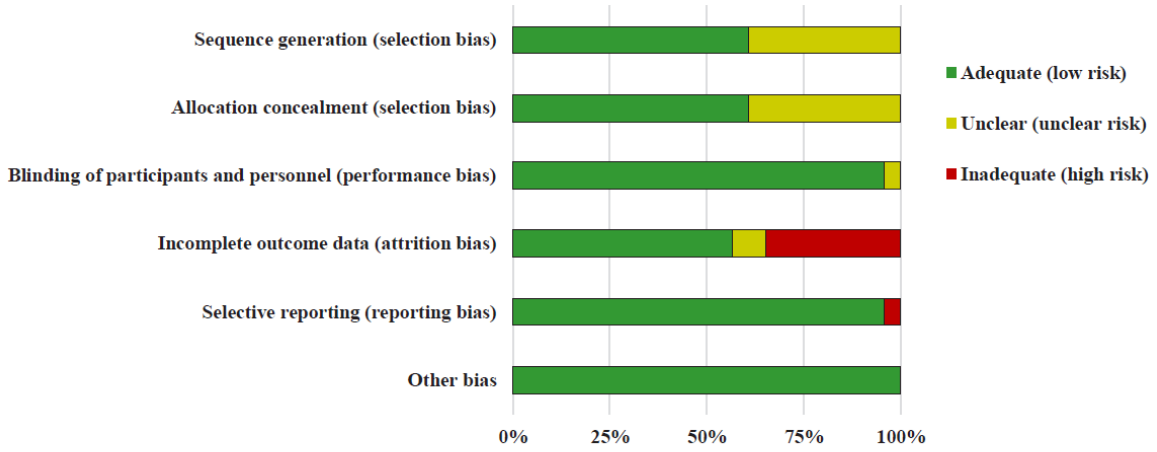
Anzahl eingeschlossener Studien:

- 23 RCTs in 19 publications (n=41359)

Charakteristika der Population:

- The number of participants in individual studies ranged from 36 to 16,492.
- The study duration of two studies lasted up to 4 years [12,14], and one study reported results with a median duration of 2.1 years [11]. The remaining studies had 12 to 160 weeks of study duration.
- Baseline eGFR of participants was ≥60 mL/min/1.73 m2 in five studies [30-34] and ≥30 mL/min/1.73 m2 in five studies [12,14,15,23,35]. Two studies did not describe inclusion or exclusion criteria for baseline eGFR or serum creatinine levels [36,37].

Qualität der Studien:



Supplemental Fig. S1. Study quality and risk of bias assessment.

Studienergebnisse:

eGFR

- DPP-4 inhibitors showed a small but significant decline in eGFR compared with controls ([WMD, −1.11 mL/min/1.73 m2; 95% CI, −1.78 to −0.44; P=0.001], [SMD, −0.07; 95% CI, −0.12 to −0.02; P= 0.009]).
- The test for heterogeneity showed moderate heterogeneity across the studies (I2=40.5%, P=0.064 on the test of WMD; I2=43.2%, P=0.048 on the test of SMD).

Development, progression, and regression of albuminuria

- DPP-4 inhibitors significantly reduced the risk of developing microalbuminuria (RR, 0.89; 95% CI, 0.80 to 0.98; P=0.022) and macroalbuminuria (RR, 0.77; 95% CI, 0.61 to 0.97; P= 0.027) compared with controls. However, the effects of DPP-4 inhibitors on incident albuminuria were mainly driven by one large trial (Supplemental Fig. S3) [11]. There was

no heterogeneity across the studies on both microalbuminuria (I2=0.0%, P=0.471) and macroalbuminuria (I2=1.3%, P=0.363) (Fig. 4A, B).

Development of ESRD

- DPP-4 inhibitors did not reduce the risk of developing ESRD in patients with type 2 diabetes compared with controls (RR, 0.93; 95% CI, 0.76 to 1.14; P=0.475) (Fig. 4D). There was no heterogeneity across the studies (I2=0.0%, P=0.853).

Anmerkung/Fazit der Autoren

In conclusion, our systematic review and meta-analysis demonstrated that DPP-4 inhibitors had renoprotective effects by reducing the risk of development or progression of albuminuria without affecting the risk of ESRD in patients with type 2 diabetes compared with placebo or other antidiabetic agents.

Dai D et al., 2019 [15].

Efficacy and hypoglycemic risk of sitagliptin in obese/overweight patients with type 2 diabetes compared with GLP-1 receptor agonists.

Fragestellung

To assess the efficacy and hypoglycemic risk of sitagliptin versus that of GLP-1 receptor agonists in the management of obese/overweight patients with T2DM.

Methodik

Population:

T2DM patients

Intervention/Komparator:

Sitagliptin vs. GLP-1 receptor agonists

Endpunkte:

Decreases in hemoglobin A1c (HbA1C) levels, the percentage of patients achieving an HbA1C goal of <7%, weight loss, decreases in fasting plasma glucose (FPG) and postprandial plasma glucose (PPG), and decreases in systolic blood pressure (SBP) and diastolic blood pressure (DBP); incidence of hypoglycemia

Recherche/Suchzeitraum:

EMBASE, PubMed, Cochrane Library, and ClinicalTrials.gov until March 2018

Qualitätsbewertung der Studien:

Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 studies

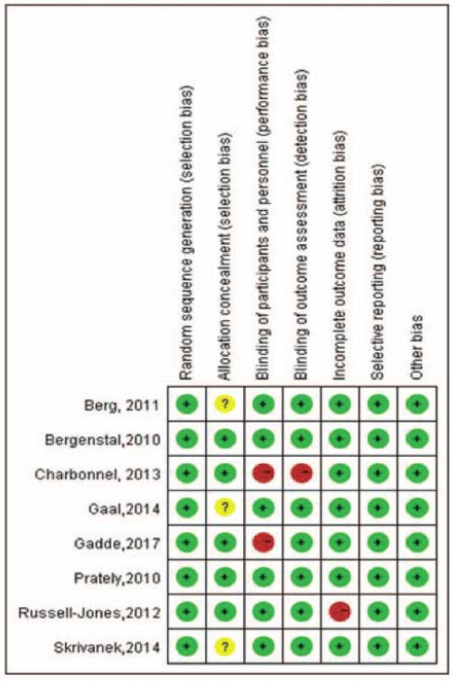
Charakteristika der Population:

- Seven RCTs were parallel studies, and 1 was a crossover study.

- Patients had been treated with a stable metformin regimen in 7 trials and metformin or thiazolidinedione in 1 trial.
- The mean BMI at baseline ranged from 31kg/m2 to 36.8kg/m2 in the sitagliptin group and 31kg/m2 to 36.8kg/m2 in the GLP-1 receptor agonist group.
- The mean values of HbA1C at baseline ranged from 8.1% to 8.5% in the sitagliptin group and 8.1% to 8.6% in the GLP-1 receptor agonist group.
- 1240 patients were included in the sitagliptin group, and 75.8% were White, 7.2% were Black, 7.7% were Asian (a study by Charbonnel et al did not report this value) and 9.3% were other races
- 1378 patients were included in the GLP-1 receptor agonist group, and 76.2% were White, 6.1% were Black, 6.4% were Asian (a study by Charbonnel et al did not report this value), and 11.3% were other races.

Qualität der Studien:

- The participants of all 8 trials were randomly allocated, 5 studies adequately described the methods of randomization and others did not mention it. There were no differences in the baseline characteristics between the sitagliptin group and the GLP-1 receptor agonist group. Studies by Charbonel et al and Gadde et al were not blinded to the participants. All 8 studies clearly reported participants withdrawing from the trial and accounted for it.



- Figure 3. Risk of bias for the included studies.

Studienergebnisse:

- Compared with GLP-1 receptor agonists, sitagliptin was less effective at reducing HbA1c (0.42 [0.27, 0.56]), FPG (0.78 [0.36, 1.19]), PPG (2.61 [1.35, 3.87]), and body weight (1.42 [0.71, 2.14]).
- Conversely, there were no significant differences in SBP reduction (0.38 [-1.14, 1.89]), DBP reduction (-0.30 [-1.00, 0.39]), and hypoglycemic risk (1.09 [0.50, 2.35]).
-

Summary of meta-analyses for outcome measures from included studies.

Outcome	No. of studies contributing data	Risk Ratio (95% CI), sitagliptin vs GLP-1 receptor agonists	Mean Difference (95% CI), sitagliptin vs GLP-1 receptor agonists	No. of participants of experimental group	No. of participants of control group	I^2 heterogeneity, %	P
Decrease in HbA_{1C}	7		0.42 [0.27, 0.56]	1376	1473	68	<.00001
participants achieving HbA_{1C} goal of <7.0%	7	0.70 [0.58, 0.83]		1391	1493	80	<.0001
Decrease in FPG	8		0.78 [0.36, 1.19]	1418	1514	86	.0003
Decrease in PPG	3		2.61 [1.35, 3.87]	238	242	75	<.00001
Decrease in body weigh	6		1.42 [0.71, 2.14]	1115	1226	85	<.00001
Decrease in SBP	5		0.38 [−1.14, 1.89]	954	1073	50	.63
Decrease in DBP	5		−0.30 [−1.00, 0.39]	954	1073	5	.4
Participants experiencing hypoglycemia	8	1.09 [0.50, 2.35]		1543	1666	77	.84

DBP = diastolic blood pressure, FPG = fasting plasma glucose, HbA_{1C} = hemoglobin A_{1C}, PPG = postprandial plasma glucose, SBP = systolic blood pressure.

Subgroup analysis:

Factor	Studies, n	Mean Difference (95% CI), sitagliptin vs GLP-1 receptor agonists	Risk Ratio (95% CI), sitagliptin vs GLP-1 receptor agonists	I^2 (%)	P
Subgroup analyses for decrease in HbA1c (%)					
Type of GLP-1 receptor agonists					
Exenatide	3	0.48 [0.33, 0.63]		2	< .00001
liraglutide	2	0.37 [0.24, 0.50]		0	< .00001
Formulation of GLP-1 receptor agonists					
Long-acting GLP-1 receptor agonists	4	0.54 [0.42, 0.66]		19	< .00001
Short-acting GLP-1 receptor agonists	3	0.27 [0.06, 0.48]		66	.01
the potential confounding factor (studies might enroll participants with BMI <25 kg/m^2)					
Studies excluding the potential confounding factor	3	0.42 [0.06, 0.79]		87	.02
Studies including the potential confounding factor	4	0.39 [0.28, 0.49]		0	< .00001
Subgroup analyses for the percentage of patients achieving HbA1c goal of <7.0%					
Type of GLP-1 receptor agonists					
Exenatide	3			50	<.00001
liraglutide	2		0.68[0.39, 1.18]	92	.17
Formulation of GLP-1 receptor agonists					
Long-acting GLP-1 receptor agonists	4		0.64 [0.56, 0.73]	29	<.00001
Short-acting GLP-1 receptor agonists	3		0.77 [0.55, 1.07]	85	.12
the potential confounding factor (studies might enroll participants with BMI <25 kg/m^2)					
Studies excluding the potential confounding factor	3		0.68[0.49, 0.94]	83	.02
Studies including the potential confounding factor	4		0.71[0.56, 0.89]	78	.003
Subgroup analyses for decrease in FPG (mmol/l)					
Type of GLP-1 receptor agonists					
Exenatide	4	0.66 [0.09, 1.22]		80	.02
liraglutide	2	1.13 [0.85, 1.41]		0	<.00001
Formulation of long-acting GLP-1 receptor agonists					
Long-acting GLP-1 receptor agonists	4	1.08 [0.72, 1.44]		56	<.00001
Short-acting GLP-1 receptor agonists	4	0.52 [−0.16, 1.21]		90	.13
the potential confounding factor (studies might enroll participants with BMI <25 kg/m^2)					
Studies excluding the potential confounding factor	4	0.52 [−0.30, 1.35]		93	.21
Studies including the potential confounding factor	4	1.08 [0.85, 1.31]		7	<.00001
Subgroup analyses for weight loss (kg)					
Formulation of GLP-1 receptor agonists					
Long-acting GLP-1 receptor agonists	4	1.33 [0.31, 2.36]		90	.01
Short-acting GLP-1 receptor agonists	2	1.65 [1.09, 2.20]		0	<.00001
the potential confounding factor (studies might enroll participants with BMI <25 kg/m^2)					
Studies excluding the potential confounding factor	3	1.82 [1.24, 2.41]		49	<.00001
Studies including the potential confounding factor	3	1.01 [−0.16, 2.19]		89	.09

Anmerkung/Fazit der Autoren

In conclusion, for obese/overweight patients, sitagliptin might exert a less potent effect regarding HbA1C, FPG, PPG, and weight reduction than GLP-1 receptor agonists; however, there was no difference in hypoglycemic risk. Meanwhile, long-acting GLP-1 receptor agonists seemed more effective in reducing FPG.

Chen K et al., 2018 [10].

Direct head-to-head comparison of glycaemic durability of dipeptidyl peptidase-4 inhibitors and sulphonylureas in patients with type 2 diabetes mellitus: A meta-analysis of long-term randomized controlled trials

Fragestellung

the aim of the present study was to perform a meta-analysis of long-term randomized controlled trials (RCTs) to compare the glycaemic durability of DPP-4 inhibitors and SUs in patients with T2DM, as reflected by the change in HbA1c levels from an intermediate time point (26 or 52 weeks) to 104 weeks of treatment

Methodik

Population:

- confirmed T2DM

Intervention/ Komparator:

- oral DPP-4 inhibitor treatment group or an oral SU group
- treatment duration of at least 2 years (104 weeks)

Endpunkte:

- primary outcome: change in HbA1c level from an intermediate time point (26 or 52 weeks) to 104 weeks of treatment

Recherche/Suchzeitraum:

- Medline (PubMed), Embase (Ovid), and CENTER (Cochrane Library) databases
- The final search was performed on January 25, 2017.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Of the eight included RCTs, one included two interventional arms with different doses of alogliptin (12.5 and 25 mg once daily), and these were included as two comparisons.

Charakteristika der Population:

TABLE 1 Baseline patient and clinical characteristics of the included studies

Study	Design	N	Mean age, years	Sex, % men	BMI, kg/m²	Baseline HbA1c, %	T2DM duration, years	Add-on therapy	Extension study	DPP-4 inhibitor dose	SU dose	Intermediate time point, weeks	Final time point, weeks	Drop out, %, and handling strategy
Foley 2009	R, DB	811	54.8	55.8	30.7	8.7	2.2	N	N	Vildagliptin, 50 mg twice daily	Gliclazide, 80-320 mg once daily	24, 52	104	25.7%, LOCF
Ahren 2010	R, DB	258	57.5	53.6	31.8	7.3	5.7	Y, Metformin	Y	Vildagliptin, 50 mg twice daily	Glimepiride, 2-6 mg once daily	24, 52	104	NR
Matthews 2010	R, DB	1357	57.5	53.5	31.6	7.2	5.7	Y, Metformin	N	Vildagliptin, 50 mg twice daily	Glimepiride, 2-6 mg once daily	24, 53	104	37.6%, LOCF
Seck 2010	R, DB	504	57.3	60.1	31.1	7.3	5.8	Y, Metformin	N	Sitagliptin, 100 mg once daily	Glipizide, 5-20 mg once daily	24, 54	104	56%, OC
Gallwitz 2012	R, DB	504	59.8	60.5	30.3	7.7	NR	Y, Metformin	N	Linagliptin, 5 mg once daily	Glimepiride, 1-4 mg once daily	28, 52	104	23%, LOCF
Goke 2013	R, DB	312	57.5	52.4	31.4	7.7	5.5	Y, Metformin	Y	Saxagliptin, 5 mg once daily	Glipizide, 5-20 mg once daily	24, 52	104	73%, LOCF
Ahren 2014	R, DB	602	55.1	50.1	NR	8.2	6.2	Y, Metformin	N	Sitagliptin, 100 mg once daily	Glimepiride, 2-4 mg once daily	24, 52	104	33%, LOCF
Del 2014, 12.5 mg	R, DB	1317	55.4	48.9	31.2	7.6	5.6	Y, Metformin	N	Alogliptin, 12.5 mg once daily	Glipizide, 5-20 mg once daily	26, 52	104	22%, LOCF
Del 2014, 25 mg	R, DB	1322	55.4	50.8	31.2	7.6	5.5	Y, Metformin	N	Alogliptin, 25 mg once daily	Glipizide, 5-20 mg once daily	26, 52	104	22%, LOCF

Abbreviations: BMI, body mass index; DB, double-blind; LOCF, last observation carried forward; N, no; NR, not reported; OC, observed cases; R, randomized; Y, yes.

Qualität der Studien:

- Keine Angaben

Studienergebnisse:

- Treatment with DPP-4 inhibitors was associated with significantly smaller changes in HbA1c levels from 24 to 28 weeks to 104 weeks (MD −0.16%, 95% CI −0.21 to −0.11; P < .001; Figure 1A) and 52 weeks to 104 weeks (MD −0.06%, 95% CI −0.10 to −0.02; P = .001; Figure 1B) compared with SUs, with no considerable heterogeneity (I2 = 0%). A

sensitivity analysis based on the omission of the study including medication-naïve patients showed similar results (24-28 weeks: MD −0.15%, 95% CI −0.20 to −0.10, P < .001; 52 weeks: MD −0.06%, 95% CI −0.10 to −0. 02, P = .003).

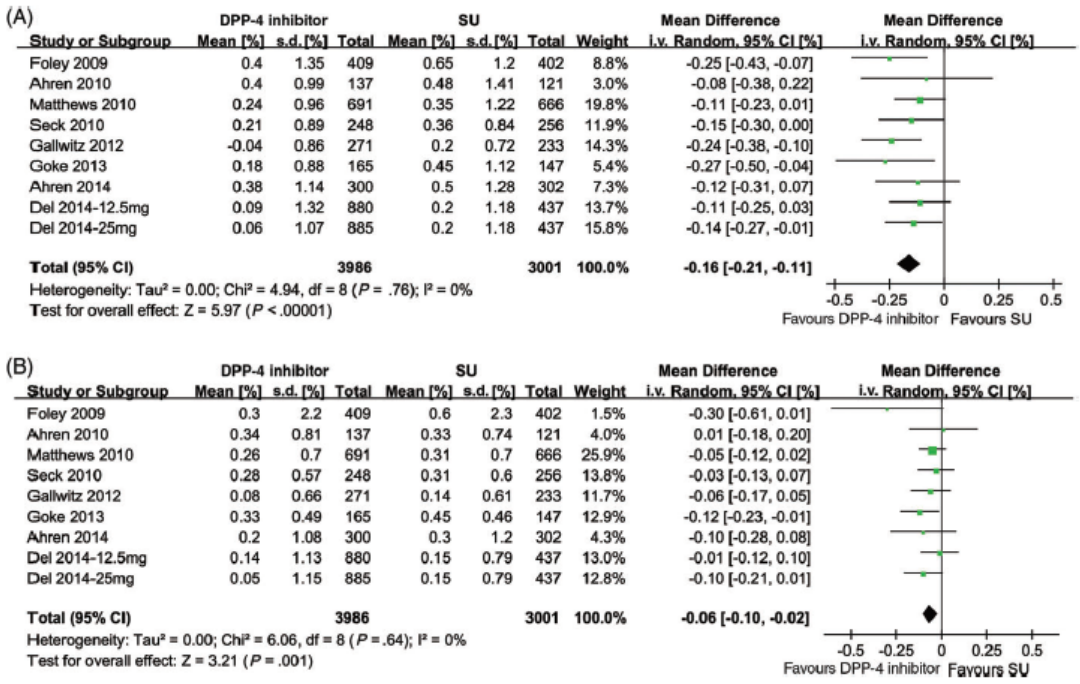


FIGURE 1 Forest plots for the comparative glycaemic durability of DPP-4 inhibitors and SUs. A, Changes in HbA1c levels from 24 to 28 to 104 weeks of treatment; B, changes in HbA1c levels from 52 to 104 weeks of treatment. i.v., intravenous; s.d., standard deviation

Anmerkung/Fazit der Autoren

These results suggest that long-term treatment with DPP-4 inhibitors confers better durability of glycaemic response than treatment with SUs in patients with T2DM, which may indicate that DPP-4 inhibitors better preserve islet β-cell function compared with SUs.

Men P et al., 2018 [83].

Efficacy and safety of saxagliptin in patients with type 2 diabetes: A systematic review and meta-analysis

Fragestellung

This systematic review synthesized currently available evidence to provide a better understanding of the comparative efficacy and safety of saxagliptin in treating type 2 diabetes.

Methodik

Population:

- patients over 18 years of age with type 2 diabetes

Intervention:

- saxagliptin (as monotherapy or in dual or triple therapy)

Komparator:

- placebo or other active antidiabetic interventions (as monotherapy or in dual or triple therapy)

Endpunkte:

- HbA1c, proportion of patients achieving HbA1c targets of <7%, fasting plasma glucose (FPG) concentration, overall and serious adverse events, body weight, confirmed hypoglycemia, heart failure, pancreatitis, arthralgia, and other adverse events

Recherche/Suchzeitraum:

- To March 2018 in PubMed, Embase, the Cochrane Library, Web of Science, and 2 Chinese databases

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 30 trials involving 29,938 participants

Charakteristika der Population:

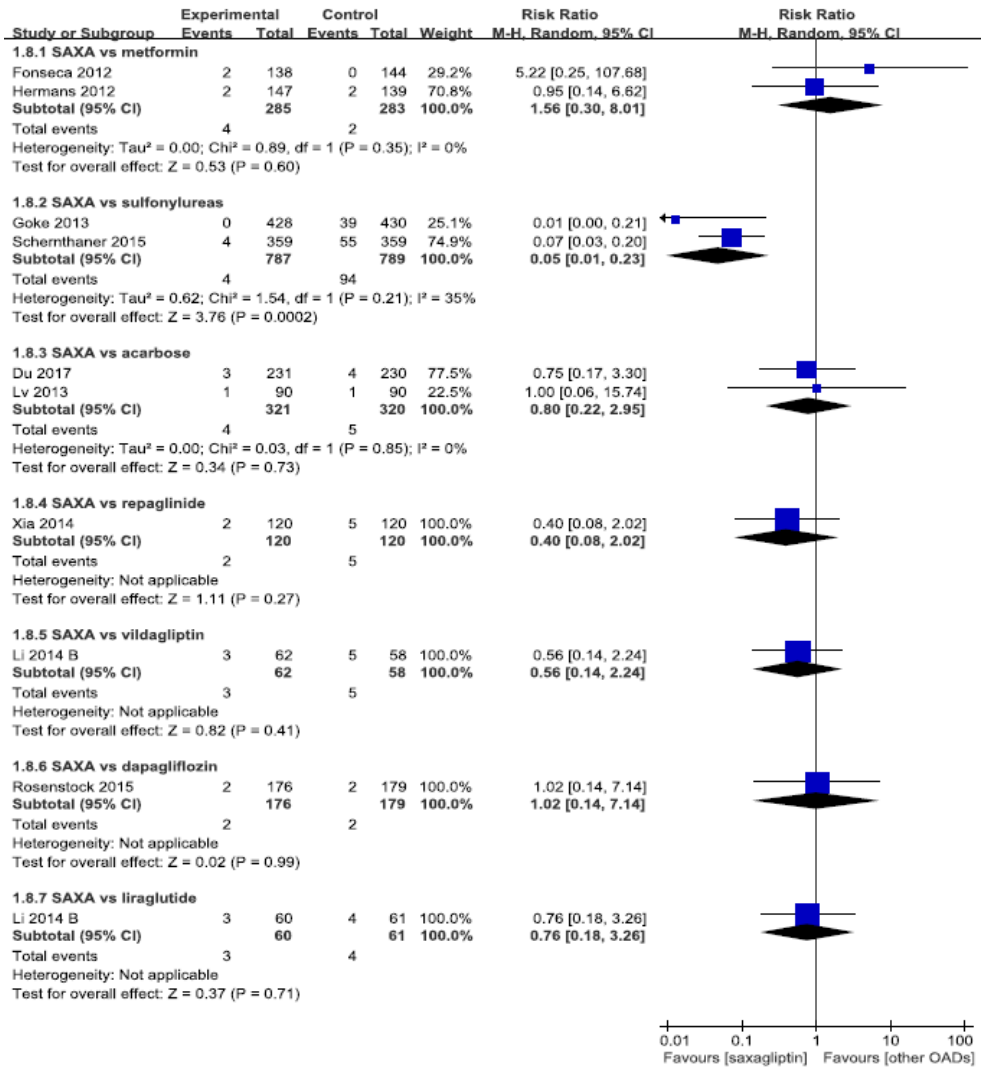
- Only RCTs involving >150 patients.
- demographics of the patient populations were comparable
  - mean age of 42.0 to 72.6 years
  - mean duration of type 2 diabetes ranged from 0.4 to 16.7 years
  - mean baseline HbA1c levels between 7.6% and 10.7%.

Qualität der Studien:

- Random sequence generation adequate in 25 trials, and allocation concealment adequately described in 16 trials. Two trials were considered to be at high risk of performance and detection bias. All studies were judged to be at low risk of attrition, reporting and other bias.

Studienergebnisse:

- HbA1c of <7%: Proportin significantly greater with saxagliptin as add-on (RR 1.67, 95% CI 1.55 to 1.81; p < 0.00001) or compared to metformin (RR 1.30, 95% CI 1.04 to 1.63; p = 0.02) and acarbose (RR 2.38, 95% CI 1.17 to 4.83; p = 0.02). However, no significant differences were observed in comparisons comparisons of saxagliptin with other active comparators
- FPG: significantly greater reductions of saxagliptin as add-on therapy to other andtidiabetic agents: (WMD −14,08 mg/dL, 95% CI −15.82 to −12.34; p < 0.00001); added to metformin, saxagliptin produced a significantly smaller reduction in FPG compared with sulfonylureas (WMD 9.05 mg/dL, 95% CI 6.18 to 11.93; p < 0.00001), liraglutide (WMD 7.60 mg/dL, 95% CI 1.76 to 13.44; p = 0.01) and dapagliflozin (WMD 18.00 mg/ dL, 95% CI 10.10 to 25.90; p < 0.00001). However, no significant differences were observed when saxagliptin was compared with other active comparators
- Hypoglycemia: Compared with sulfonylureas, saxaglitpin significantly reduced the risk of hypoglycemia by 95% (see figure). No significant differences were observed in comparison with other active comparators, including other DPP-4 inhibitors.



- Body weight: Saxagliptin was inferior to liraglutide (WMD 5.10 kg, 95% CI 1.66 to 8.54; p = 0.004) and dapagliflozin (WMD 2.40 kg, 95% CI 1.69 to 3.11; p < 0.00001). However, treatment with saxagliptin was associated with significantly less effect on body weight than sulfonylureas (WMD −2.34 kg, 95% CI −3.31 to −1.36; p < 0.00001). In comparison with other DPP-4 inhibitors, changes in body weight were similar.
- Overall and serious adverse events: Reduction in AE vs acarbose (RR 0.71, 95% CI 0.57 to 0.89; p = 0.03) and liraglutide (RR 0.41, 95% CI 0.24 to 0.71; p = 0.001) when added to metformin, no other significant differences.
- Other adverse events:
  - Pancreatitis and heart failure: no significant difference vs placebo and SU
  - Arthralgia: saxagliptin could significantly reduced the risk of arthralgia vs sitagliptin (RR 0.20, 95% CI 0.04 to 0.90; p = 0.04), but not compared with other active treatments.
  - saxagliptin was not associated with any increased risks of upper respiratory tract infection, urinary tract infection and nasopharyngitis compared with both placebo and active comparators

Anmerkung/Fazit der Autoren

In conclusion, Generally, saxagliptin has similar efficacy compared with most oral antidiabetic drugs, while may be more effective than acarbose. Saxagliptin is safe in the treatment of T2D, especially having a better safety profile than acarbose and sulfonylureas.

Kommentare zum Review

- Die Ergebnisse der Studien mit Placebo als Komparator wurden nicht dargestellt, genau wie die Ergebnisse zu Sagagliptin 2,5 mg.

Yang WY et al., 2018 [109].

Addition of dipeptidyl peptidase-4 inhibitors to insulin treatment in type 2 diabetes patients: A meta-analysis

Fragestellung

To evaluate the efficacy and safety of combining insulin therapy with dipeptidyl peptidase-4 (DPP-4) inhibitors compared with combining insulin therapy with a placebo or other antihyperglycemic agents

Methodik

Population:

- type 2 diabetes patients

Intervention:

- addition of DPP-4 inhibitors with insulin

Komparator:

- addition of a placebo or other active hypoglycemic agents to insulin therapy

Endpunkte:

- glucose control (primary outcome)

Recherche/Suchzeitraum:

- MEDLINE (PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE
- until December 2016

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 36

Charakteristika der Population:

- 7 studies that compared a placebo with a combination of a DPP-4 inhibitor and insulin (DPP4i/INS), 3 studies that compared a placebo with a combination of metformin and insulin (MET/INS), 7 studies that compared a placebo with a combination of

thiazolidinedionesin and insulin (TZD/INS), 5 studies that compared a placebo with a combination of an alpha-glucosidase inhibitor and insulin (AGI/INS), 7 studies that compared a placebo with a combination of a GLP-1 receptor agonist and insulin (GLP-1RA/INS) and 8 studies that compared a placebo with a combination of SGLT-2i and insulin (SGLT- 2i/INS

Qualität der Studien:

- All the included studies were randomized, placebo-controlled trials. Most studies reported age, sex, diabetes duration, HbA1c, BMI, bodyweight between the comparison groups at baseline. Overall, the risk of bias was low.

Studienergebnisse:

- Efficacy outcomes
- Changes in HbA1c
- The HbA1c-lowering efficacy was significantly greater with DPP-4i/INS than with PBO/INS (WMD -0.53%, 95% CI: -0.63, -0.43, P < 0.01; Figure 2; Table 1). The placebo-corrected HbA1c change from baseline was greater with MET/INS than with DPP-4i/INS (P < 0.05). There was no significant difference in the placebo-corrected HbA1c change from baseline between DPP-4i/INS and AGI/INS, TZD/INS, GLP-1RA/INS and SGLT-2i/INS (P > 0.05).

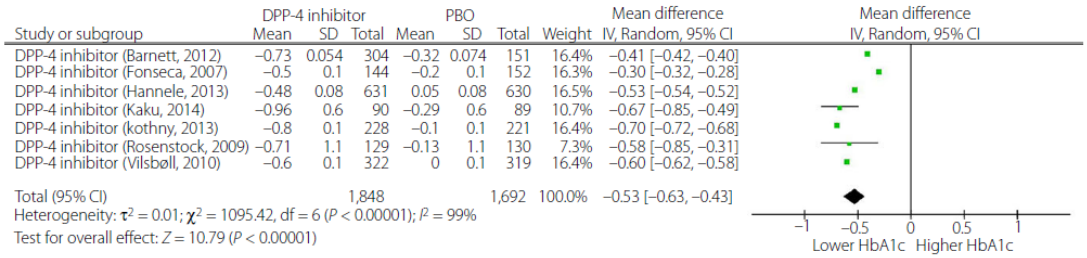


Figure 2 | Change from baseline in glycated hemoglobin (HbA1c) of dipeptidyl peptidase-4 (DPP-4) inhibitor/insulin treatment. CI, confidence interval; PBO, placebo.

Table 1 | Comparisons of glycated hemoglobin change from baseline in different treatment groups

	No. studies	No. participants (active agents vs PBO)	WMD from baseline	95% CI	*P*-value
HbA1c change from baseline (%)					
DPP-4i/INS	7	1,848/1,692	−0.53	−0.63, −0.43	<0.01*
MET/INS	3	127/135	−0.88	−1.11, −0.64	<0.01*
AGI/INS	5	375/367	−0.55	−1.12, 0.01	0.06
TZD/INS	7	758/760	−0.61	−0.80, −0.41	<0.01*
SGLT-2i/INS	8	1,658/1,585	−0.66	−0.79, −0.53	<0.01*
GLP-1RA/INS	7	1,393/1,223	−0.74	−1.07, −0.41	<0.01*

*P-value < 0.05. AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; INS, insulin; MET, metformin; PBO, placebo; TZD, thiazolidinediones; SGLT-2i, sodium–glucose cotransporter 2 inhibitor; WMD, weighted mean difference.

- Changes in FPG
- When DPP4i/INS treatment was compared with PBO/INS treatment, the change in FPG was not significant (WMD -0.32 mmol/L, 95% CI: -0.75, 0.11, P = 0.14; I^2 = 100%, random effects model was used; Table 2). The difference in the placebo-corrected FPG change from baseline between DPP-4i/INS and MET/INS, AGI/INS, TZD/INS, GLP-1RA/INS and SGLT-2i/INS treatments was not significant (P > 0.05).

Table 2 | Comparisons of fasting plasma glucose change from baseline in different treatment groups

	No. studies	No. participants (active agents vs PBO)	WMD from baseline	95% CI	*P*-value
FPG change from baseline (mmol/L)					
DPP-4i/INS	7	1,848/1,692	−0.32	−0.75, 0.11	0.14
MET/INS	3	127/135	−0.72	−1.58, 0.14	0.10
AGI/INS	4	268/267	−0.02	−0.30, 0.26	0.87
TZD/INS	6	750/750	−1.16	−3.15, 0.83	0.25
SGLT-2i/INS	6	800/753	−0.63	−1.39, 0.13	0.10
GLP-1RA/INS	7	1,393/1,223	−0.46	−0.87, -0.05	<0.05*

*P-value < 0.05. AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; INS, insulin; MET, metformin; PBO, placebo; SGLT-2i, sodium–glucose cotransporter 2 inhibitor; SU, sulfonylurea; TZD, thiazolidinediones; WMD, weighted mean difference.

- Changes in PPG
  - The PPG-lowering efficacy was significantly greater with DPP-4i/INS than with PBO/INS (WMD -1.65 mmol/L, 95% CI: -2.34, -0.96, P < 0.01; I^2 = 100%, random effects model was used; Table 3). The placebo-corrected PPG change from baseline was greater with SGLT-2i/INS than with DPP-4i/INS (P < 0.05). The placebo-corrected PPG change from baseline between DPP-4i/INS and AGI/INS and GLP-1RA/INS treatments was not significantly different (P > 0.05).

Table 3 | Comparisons of postprandial plasma glucose change from baseline in different treatment groups

	No. studies	No. participants (active agents vs PBO)	WMD from baseline	95% CI	*P*-value
PPG change from baseline (mmol/L)					
DPP-4i/INS	2	626/470	−1.65	−2.34, −0.96	<0.01
AGI/INS	3	208/207	−1.76	−4.19, 0.66	0.15
GLP-1RA/INS	3	705/547	−2.87	−8.98, 3.23	0.36
SGLT-2i/INS	2	146/83	−2.62	−2.86, −2.37	<0.01

AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; INS, insulin; PBO, placebo; PPG, postprandial plasma glucose; SGLT-2i, sodium–glucose cotransporter 2 inhibitor; WMD, weighted mean difference.

- Changes in bodyweight
  - When DPP4i/INS treatment was compared with PBO/INS treatment, the change in bodyweight was not significant (WMD 0.18 kg, 95% CI: -0.08, 0.44, P = 0.17; Table 4). When placebo-corrected, bodyweight was significantly decreased with SGLT-2i/INS and GLP-1RA/INS compared with DPP-4i/INS (P < 0.05), and was significantly increased with TZD/INS compared with DPP-4i/INS (P < 0.05). There was no significant difference in placebo-corrected bodyweight change from baseline between DPP-4i/INS and AGI/INS treatments (P > 0.05).

Table 4 | Comparisons of bodyweight change from baseline in different treatment groups

	No. studies	No. participants (active agents vs PBO)	WMD from baseline	95% CI	*P*-value
Bodyweight change from baseline (kg)					
DPP-4i/INS	7	1,848/1,692	0.18	−0.08, 0.44	0.17
MET/INS	3	127/135	−2.66	−3.91, −1.41	<0.01*
AGI/INS	4	268/267	−0.70	−2.15, 0.75	0.34
TZD/INS	6	655/656	1.88	0.29, 3.46	0.02*
SGLT-2i/INS	7	994/946	−1.89	−2.31, −1.48	<0.01*
GLP-1RA/INS	7	1,393/1,223	−1.70	−2.53, −0.88	<0.01*

*P-value < 0.05. AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; INS, insulin; MET, metformin; PBO, placebo; SGLT-2i, sodium–glucose cotransporter 2 inhibitor; TZD, thiazolidinediones; WMD, weighted mean difference.

- Changes in the dosage of insulin use
  - The change in daily insulin doses was significantly greater with DPP-4i/INS than with PBO/INS (WMD -2.17 units/day, 95% CI: -3.18, -1.15, P < 0.01; I2 = 99%, random effects model was used; Table 5). The placebo-corrected daily insulin dosage was significantly decreased with TZD/INS compared with DPP-4i/ INS (P < 0.05). Comparisons of the placebo-corrected insulin dosage change from baseline between DPP-4i/INS and AGI/ INS, GLP-1RA/INS and SGLT-2i/INS treatments showed that the difference was not significant (P > 0.05).

Table 5 | Comparisons of daily insulin dosage change from baseline in different treatment groups

	No. studies	No. participants (active agents vs PBO)	WMD from baseline	95% CI	*P*-value
Daily insulin dosage change from baseline (U/day)					
DPP-4i/INS	4	1,307/1,154	−2.17	−3.18, −1.15	<0.01*
AGI/INS	2	142/141	0.28	−2.85, 3.40	0.86
TZD/INS	5	518/524	−16.15	−25.89, −6.42	<0.01*
SGLT-2i/INS	3	545/490	−6.00	−12.28, 0.27	0.06
GLP-1RA/INS	7	1,393/1,223	−3.39	−4.74, −2.04	<0.01*

*P-value < 0.05. AGI, alpha-glucosidase inhibitors; CI, confidence interval; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated hemoglobin; INS, insulin; PBO, placebo; SGLT-2i, sodium–glucose cotransporter 2 inhibitor; TZD, thiazolidinediones; U, unit; WMD, weighted mean difference.

-
- Safety outcomes
- In the subgroup analysis of safety outcomes, we analyzed the incidence of hypoglycemia and severe hypoglycemia.
- The risk of hypoglycemia or severe hypoglycemia between treatment with DPP4i/INS and PBO/INS was similar (I2 = 48% for the incidence of hypoglycemia, I2 = 41% for the incidence of severe hypoglycemia, fixed effects model was used). In the AGI/INS treatment group, the risk of hypoglycemia significantly increased compared with the PBO/INS treatment group (RR 1.39, 95% CI: 1.07, 1.81, P = 0.01).
- There was no significant difference in the risk of hypoglycemia or severe hypoglycemia in the other treatment groups compared with the PBO/INS group (Table 6). The placebo-corrected risk of hypoglycemia or severe hypoglycemia between DPP-4i/INS and MET/INS, TZD/ INS, GLP-1RA/INS and SGLT-2i/INS treatments showed no significant difference (P > 0.05).

Anmerkung/Fazit der Autoren

Treatment with DPP-4 inhibitors combined with insulin improved glycemic control without an increased risk of hypoglycemia or weight gain compared with insulin treatment alone.

Systematische Reviews zu GLP-1 Inhibitoren

Huthmacher JA et al., 2020 [64].

Efficacy and Safety of Short- and Long-Acting Glucagon-Like Peptide 1 Receptor Agonists on a Background of Basal Insulin in Type 2 Diabetes: A Meta-analysis

Fragestellung

To compare the efficacy and safety of short- and long-acting glucagon-like peptide 1 receptor agonists (GLP-1 RAs), both used in combination with basal insulin, in patients with type 2 diabetes

Methodik

Population:

- T2DM

Intervention:

- a combination of GLP-1 RA and basal insulin therapy

Komparator:

- basal insulin ± placebo

Endpunkte:

- Reductions in HbA1c, fasting plasma glucose, body weight
- adverse events, prevalence of hypoglycemia, and proportion of patients prematurely discontinuing drug treatment

Recherche/Suchzeitraum:

- PubMed
- published before 31 December 2018

Qualitätsbewertung der Studien:

- Jadad score and the Risk of Bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 14

Charakteristika der Population:

Table 1—Overview of the individual design of studies used for the present meta-analysis comparing the efficacy and safety of short- and long-acting GLP-1 RAs in combination with basal insulin

Study	Publication year	Trial duration (weeks)	GLP-1 RA	Basal insulin	Use of placebo	Combination of GLP-1 RA and basal insulin	Study design	Titration of basal insulin during trial	Target dose of GLP-1 RA
Short-acting GLP-1 RAs added to basal insulin									
Buse et al. (13)	2011	30	Exenatide (twice a day)	Insulin glargine	Yes	Free	Double blind	Yes	20 μg/day
Seino et al. (14)	2012	24	Lixisenatide	Basal insulin[a]	Yes	Free	Double blind	No	20 μg/day
Riddle et al. (15)	2013	24	Lixisenatide	Basal insulin[a]	Yes	Free	Double blind	No	20 μg/day
Riddle et al. (16)	2013	24	Lixisenatide	Insulin glargine	Yes	Free	Double blind	Yes	20 μg/day
Yang et al. (17)	2018	24	Lixisenatide	Basal insulin[a]	Yes	Free	Double blind	No	20 μg/day
Aroda et al. (18)	2016	30	Lixisenatide	Insulin glargine	No	Fixed (iGlarLixi)	Open label	Yes	5–20 μg/day[b]
Rosenstock et al. (19)	2016	30	Lixisenatide	Insulin glargine	No	Fixed (iGlarLixi)	Open label	Yes	5–20 μg/day[b]
Rosenstock et al. (20)	2016	24	Lixisenatide	Insulin glargine	No	Fixed (iGlarLixi)	Open label	Yes	5–20 μg/day[b]
Long-acting GLP-1 RAs added to basal insulin									
Ahmann et al. (21)	2015	26	Liraglutide	Basal insulin[a]	Yes	Free	Double blind	No	1.8 mg/day
Guja et al. (22)	2018	28	Exenatide (once a week)	Insulin glargine	Yes	Free	Double blind	Yes	2.0 mg/week
Pozzilli et al. (23)	2017	28	Dulaglutide	Insulin glargine	Yes	Free	Double blind	Yes	1.5 mg/week
Rodbard et al. (24)	2018	30	Semaglutide	Basal insulin[a]	Yes	Free	Double blind	No	1.0 mg/week
Buse et al. (25)	2014	26	Liraglutide	Insulin degludec	No	Fixed (iDegLira)	Double blind	Yes	0.6–1.8 mg/day[b]
Gough et al. (26)	2014	26	Liraglutide	Insulin degludec	No	Fixed (iDegLira)	Open label	Yes	0.36–1.8 mg/day[b]

[a]Different compounds of basal insulin were used; a detailed presentation is given in Supplementary Tables 6 and 8. [b]As per result of the titration process.

Qualität der Studien:

- The quality of the studies (…) was found to be sufficient for the inclusion of all retrieved publications.

Studienergebnisse:

- *Primary* End Point
- All studies analyzed indicated a significant reduction in HbA1c with GLP-1 Ras plus basal insulin versus basal insulin ± placebo (Fig. 1A). This resulted in overall significant differences when looking not only at all GLP-1 RAs (Δ 20.7% [95% CI 21.2; 20.2], 28 mmol/mol [213; 22], P = 0.006) but also for the subgroups of short-acting (Δ 20.5% [20.7; 20.3], 25 mmol/mol [27; 23], P , 0.0001) and long-acting (Δ 21.0% [21.2; 20.8], 211 mmol/mol [213; 28], P , 0.0001) GLP-1 RAs (Fig. 1A).
- Secondary End Points
- HbA1c Target Achievement

- The difference in proportions of patients achieving an HbA1c ,7.0% (,53 mmol/ mol) (Fig. 1B) or 6.5% (,48 mmol/mol) (Supplementary Fig. 3) was significantly greater for long-acting GLP-1 RAs.

- Fasting Plasma Glucose

- Nearly all studies using long-acting GLP-1 RAs reported a significant reduction in fasting plasma glucose compared with administration of basal insulin ± placebo, while for most short-acting GLP-1 RAs, no significant reduction was observed (Fig. 1C). This resulted in overall insignificant differences when looking at all GLP-1 RAs (Δ 20.5 mmol/L [95% CI 21.2; 0.2], P 5 0.18) and short-acting GLP-1 RAs (Δ 20.1 mmol/L [20.4; 0.2], P 5 0.35) but in a highly significant difference for the long-acting GLP-1 RAs (Δ 20.9 mmol/L [21.2; 20.5], P =0.0001) (Fig. 1C).

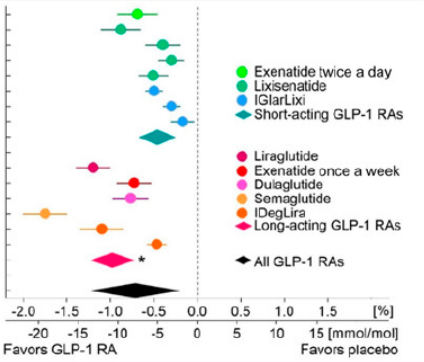
- Body Weight

- Body weight was almost uniformly reduced in most studies except for one using lixisenatide (Fig. 1C). The effect for all GLP-1 RAs was significant (Δ 22.0 kg [95% CI 23.4; 20.6], P 5 0.005), as was the effect in both subgroups representing short-acting (Δ21.3 kg [21.7;20.8], P , 0.0001) and long-acting (Δ 22.7 kg [23.3; 22.1], P , 0.0001) GLP-1 RAs. Semaglutide had the largest effect on body weight, again explaining some of the observed heterogeneity.

- Figure1— Forest plot of reductions inHbA1c (A), the proportion of patients achieving anHbA1c target,7.0%(B),and reductions in fasting plasma glucose (C) and body weight (D) in patients with type 2 diabetes treated with short- or long-acting GLP-1 RAs in combination with basal insulin. Forest plots show the difference in means(A, C, andD) and the risk difference (B) between the interventionarm (GLP-1RA1basal insulin) and comparatorarm (placebo1 basal insulin or basal insulin alone). Color codes for the various GLP-1 RAs are shown in panel A. Filled circles indicate the results for individual studies, while rhombuses indicate results of the meta-analysis. Measures of heterogeneity are also shownin all panels (Q, I2, t2, and related P values) for all GLP-1 Ras

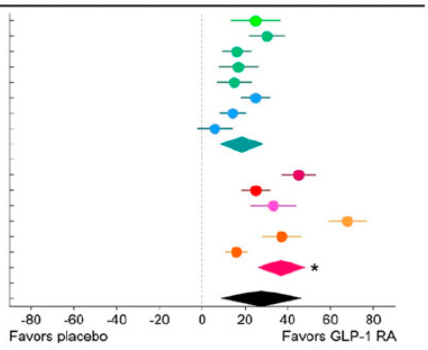
Study/ publication	Difference in means	95% Confidence interval	Weight [%]	Z-value	P-value
A. HbA_{1c} reduction [%]					
Buse et al. 2011 (13)	-0.69	-0.92; -0.46	11.6	-5.78	< 0.0001
Seino et al. 2012 (14)	-0.88	-1.11; -0.65	11.6	-7.43	< 0.0001
Riddle et al. 2013 a (15)	-0.40	-0.60; -0.20	12.1	-3.93	< 0.0001
Riddle et al. 2013 b (16)	-0.30	-0.45; -0.15	12.7	-3.92	< 0.0001
Yang et al. 2018 (17)	-0.51	-0.68; -0.34	12.5	-5.83	< 0.0001
Aroda et al. 2016 (18)	-0.50	-0.60; -0.40	13.3	-9.82	< 0.0001
Rosenstock at al. 2016 a (19)	-0.30	-0.40; -0.20	13.3	-5.89	< 0.0001
Rosenstock et al. 2016 b (20)	-0.17	-0.30; -0.04	12.9	-2.48	0.013
All short-acting GLP-1 RAs	**-0.46**	**-0.67; -0.26**	-	**-4.42**	**< 0.0001**
Ahmann et al. 2015 (21)	-1.20	-1.40; -1.00	16.8	-11.79	< 0.0001
Guja et al. 2018 (22)	-0.73	-0.93; -0.53	16.8	-7.17	< 0.0001
Pozzilli et al. 2017 (23)	-0.77	-0.97; -0.57	16.7	-7.39	< 0.0001
Rodbard et al. 2018 (24)	-1.75	-2.00; -1.50	15.7	-13.51	< 0.0001
Buse et al. 2014 (25)	-1.10	-1.35; -0.85	15.8	-8.65	< 0.0001
Gough et al. 2014 (26)	-0.47	-0.58; -0.36	18.3	-8.38	< 0.0001
All long-acting GLP-1 RAs	**-0.99**	**-1.23; -0.75**	-	**-8.03**	**< 0.0001**
All GLP-1 RAs	**-0.72**	**-1.23; -0.20**	-	**-2.74**	**0.006**

* Difference between short- and long-acting GLP-1 RAs [%]: Δ -0.53, 95% CI: -0.88 ; -0.18 , p= 0.007
Heterogeneity of all GLP-1 RAs: Q-value: 231.98; df (Q): 13; P-value: < 0.0001; I^2: 94.40 %; Tau^2: 0.11



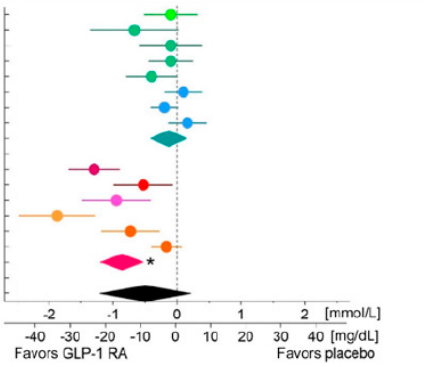
Study/publication	Risk difference	95% Confidence interval	Weight [%]	Z-Value	P-Value
B. Achievement of HbA1c target < 7.0%					
Buse et al. 2011 (13)	25.0	13.2; 36.8	11.39	4.16	<0.0001
Seino et al. 2012 (14)	30.4	22.1; 38.7	12.51	7.16	<0.0001
Riddle et al. 2013 a (15)	16.3	9.4; 23.2	12.89	4.61	<0.0001
Riddle et al. 2013 b (16)	17.0	7.9; 26.1	12.26	3.65	0.00026
Yang et al. 2018 (17)	15.0	6.6; 23.4	12.49	3.51	0.00045
Aroda et al. 2016 (18)	25.0	18.1; 31.9	12.89	7.07	<0.0001
Rosenstock at al. 2016 a (19)	14.3	8.3; 20.3	13.12	4.68	<0.0001
Rosenstock et al. 2016 b (20)	6.0	-2.5; 14.5	12.45	1.38	0.17
All short-acting GLP-1 RAs	**18.6**	**9.1; 28.0**	-	**3.85**	**<0.0001**
Ahmann et al. 2015 (21)	45.2	37.3; 53.1	16.79	11.27	<0.0001
Guja et al. 2018 (22)	25.1	18.2; 32.0	17.13	7.11	<0.0001
Pozzilli et al. 2017 (23)	33.4	22.7; 44.1	15.64	6.14	<0.0001
Rodbard et al. 2018 (24)	68.0	59.2; 76.8	16.44	15.20	<0.0001
Buse et al. 2014 (25)	37.2	28.2; 46.2	16.36	8.13	<0.0001
Gough et al. 2014 (26)	16.0	10.7; 21.3	17.63	5.90	<0.0001
All long-acting GLP-1 RAs	**37.2**	**26.3; 48.1**	-	**6.70**	**<0.0001**
All GLP-1 RAs	**27.7**	**9.4; 45.9**	-	**2.97**	**0.0030**

* Difference between short- and long-acting GLP-1 RAs: Δ -18.6, 95% CI: -34.7 ; -2.62 , p=0.03
Heterogeneity of all GLP-1 RAs: Q-value: 185.45; df (Q): 13; P-value: < 0.0001; I^2: 92.99 %; Tau^2: 0.02



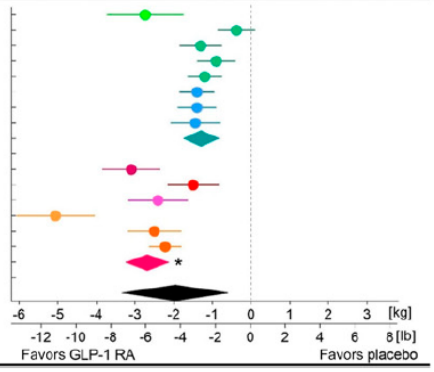
Study/ publication	Difference in means	95% Confidence interval	Weight [%]	Z-value	P-value
C. Fasting plasma glucose reduction [mmol/L]					
Buse et al. 2011 (13)	-0.10	-0.52; 0.32	12.2	-0.47	0.64
Seino et al. 2012 (14)	-0.67	-1.36; 0.02	8.3	-1.89	0.06
Riddle et al. 2013 a (15)	-0.10	-0.60; 0.40	10.9	-0.39	0.69
Riddle et al. 2013 b (16)	-0.10	-0.45; 0.25	13.2	-0.56	0.57
Yang et al. 2018 (17)	-0.40	-0.80; 0.00	12.5	-1.97	0.049
Aroda et al. 2016 (18)	0.10	-0.20; 0.40	14.0	0.65	0.51
Rosenstock at al. 2016 a (19)	-0.20	-0.42; 0.02	15.1	-1.78	0.07
Rosenstock et al. 2016 b (20)	0.16	-0.14; 0.46	13.9	1.03	0.30
All short-acting GLP-1 RAs	**-0.14**	**-0.42; 0.15**	-	**-0.94**	**0.35**
Ahmann et al. 2015 (21)	-1.30	-1.70; -0.90	17.8	-6.39	< 0.0001
Guja et al. 2018 (22)	-0.53	-0.99; -0.07	16.3	-2.24	0.025
Pozzilli et al. 2017 (23)	-0.95	-1.49; -0.41	14.8	-3.48	0.0005
Rodbard et al. 2018 (24)	-1.88	-2.48; -1.28	13.6	-6.17	< 0.0001
Buse et al. 2014 (25)	-0.73	-1.19; -0.27	16.4	-3.12	0.002
Gough et al. 2014 (26)	-0.17	-0.41; 0.07	21.1	-1.39	0.16
All long-acting GLP-1 RAs	**-0.87**	**-1.21; -0.53**	-	**-5.04**	**< 0.0001**
All GLP-1 RAs	**-0.50**	**-1.22; 0.22**	-	**-1.35**	**0.18**

* Difference between short- and long-acting GLP-1 RAs [mmol/L]: Δ -0.73, 95% CI: -1.22 ; -0.25, p=0.007
Heterogeneity of all GLP-1 RAs: Q-value: 82.67; df (Q): 13; P-value: < 0.0001; I^2: 84.28 %; Tau^2: 0.19



D. Body weight reduction [kg]					
Buse et al. 2011 (13)	-2.74	-3.74; -1.74	9.0	-5.40	< 0.0001
Seino et al. 2012 (14)	-0.38	-0.87; 0.11	13.2	-1.52	0.13
Riddle et al. 2013 a (15)	-1.30	-1.85; -0.75	12.7	-4.64	< 0.0001
Riddle et al. 2013 b (16)	-0.90	-1.40; -0.40	13.1	-3.54	0.0004
Yang et al. 2018 (17)	-1.20	-1.65; -0.75	13.5	-5.24	< 0.0001
Aroda et al. 2016 (18)	-1.40	-1.85; -0.95	13.5	-6.11	< 0.0001
Rosenstock at al. 2016 a (19)	-1.40	-1.90; -0.90	13.1	-5.50	< 0.0001
Rosenstock et al. 2016 b (20)	-1.44	-2.09; -0.79	11.9	-4.36	< 0.0001
All short-acting GLP-1 RAs	**-1.29**	**-1.74; -0.83**	-	**-5.49**	**< 0.0001**
Ahmann et al. 2015 (21)	-3.10	-3.85; -2.35	16.3	-8.12	< 0.0001
Guja et al. 2018 (22)	-1.50	-2.16; -0.84	17.4	-4.43	< 0.0001
Pozzilli et al. 2017 (23)	-2.41	-3.18; -1.64	16.0	-6.12	< 0.0001
Rodbard et al. 2018 (24)	-5.06	-6.08; -4.04	13.1	-9.77	< 0.0001
Buse et al. 2014 (25)	-2.50	-3.20; -1.80	16.9	-7.02	< 0.0001
Gough et al. 2014 (26)	-2.22	-2.64; -1.80	20.4	-10.37	< 0.0001
All long-acting GLP-1 RAs	**-2.69**	**-3.25; -2.13**	-	**-9.43**	**< 0.0001**
All GLP-1 RAs	**-1.98**	**-3.35; -0.60**	-	**-2.82**	**0.005**

* Difference between short- and long-acting GLP-1 RAs [kg]: Δ -1.40, 95% CI: -2.20 ; -0.60 , p=0.002
Heterogeneity of all GLP-1 RAs: Q-value: 121.25; df (Q): 13; P-value: < 0.0001; I^2: 89.28 %; Tau^2: 0.71



- Adverse Events
  - Nausea, vomiting, and diarrhea were reported in a small proportion of those treated with insulin ± placebo but occurred with greater prevalence in those treated by GLP-1

RAs with basal insulin (Table 2). Among patients treated with GLP-1 RAs and basal insulin, the proportion with nausea was approximately twofold higher in the case of short-acting GLP-1 RAs (P = 0.0001). Vomiting was observed more frequently (57%) with short-acting GLP-1 RAs (P = 0.0001) as well. There were no major differences regarding diarrhea (Table 2).

Table 2—Overview of adverse events and withdrawals from studies used for the present meta-analysis comparing the efficacy and safety of short- and long-acting GLP-1 RAs in combination with basal insulin

Study, publication year	Patients, *n*		Nausea, *n* (%)		Vomiting, *n* (%)		Diarrhea, *n* (%)		Withdrawals because of adverse events, *n* (%)		Withdrawals because of any reason, *n* (%)	
	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo	GLP-1 RA	Placebo
Short-acting GLP-1 RAs added to basal insulin												
Buse et al. (13), 2011	137	122	56 (40.9)	10 (8.2)	25 (18.2)	5 (4.1)	25 (18.2)	10 (8.2)	13 (9.5)	1 (0.8)	26 (19.0)	22 (18.0)
Seino et al. (14), 2012	154	157	61 (39.6)	7 (4.5)	28 (18.2)	3 (1.9)	10 (6.5)	4 (2.5)	14 (9.1)	5 (3.2)	21 (13.6)	13 (8.3)
Riddle et al. (15), 2013	328	167	86 (26.2)	14 (8.4)	27 (8.2)	1 (0.6)	24 (7.3)	9 (5.4)	26 (7.9)	4 (2.4)	53 (16.2)	20 (12.0)
Riddle et al. (16), 2013	223	223	61 (27.4)	11 (4.9)	21 (9.4)	3 (1.3)	15 (6.7)	7 (3.1)	19 (8.5)	9 (4.0)	29 (13.0)	12 (5.4)
Yang et al. (17), 2018	223	223	51 (22.9)	12 (5.4)	25 (11.2)	2 (0.9)	NA	NA	8 (3.6)	4 (1.8)	32 (14.3)	18 (8.1)
Aroda et al. (18), 2016	366	365	38 (10.4)	2 (0.5)	13 (3.6)	2 (0.5)	16 (4.4)	10 (2.7)	12 (3.3)	3 (0.8)	29 (7.9)	10 (2.7)
Rosenstock et al. (19), 2016	468	466	45 (9.6)	17 (3.6)	15 (3.2)	7 (1.5)	42 (9.0)	20 (4.3)	12 (2.6)	9 (1.9)	29 (6.2)	27 (5.8)
Rosenstock et al. (20), 2016	161	162	12 (7.5)	0 (0.0)	4 (2.5)	1 (0.6)	5 (3.1)	6 (3.7)	6 (3.7)	0 (0.0)	11 (6.8)	3 (1.9)
All short-acting GLP-1 RA	2,060	1,885	410 (19.9)	73 (3.9)	158 (7.7)	24 (1.3)	137 (7.5)	66 (4.0)	110 (5.3)	35 (1.9)	230 (11.2)	125 (6.6)
Long-acting GLP-1 RAs added to basal insulin												
Ahmann et al. (21), 2015	225	225	50 (22.2)	7 (3.1)	20 (8.9)	2 (0.9)	24 (10.7)	11 (4.9)	12 (5.3)	3 (1.3)	35 (15.6)	51 (22.7)
Guja et al. (22), 2018	231	230	12 (5.2)	9 (3.9)	1 (0.4)	3 (1.3)	11 (4.8)	8 (3.5)	7 (3.0)	5 (2.2)	19 (8.2)	23 (10.0)
Pozzilli et al. (23), 2017	150	150	18 (12.0)	2 (1.3)	9 (6.0)	0 (0.0)	17 (11.3)	6 (4.0)	6 (4.0)	2 (1.3)	12 (8.0)	16 (10.7)
Rodbard et al. (24), 2018	131	133	22 (16.8)	6 (4.5)	15 (11.5)	4 (3.0)	9 (6.9)	2 (1.5)	10 (7.6)	1 (0.8)	16 (12.2)	13 (9.8)
Buse et al. (25), 2014	199	199	13 (6.5)	7 (3.5)	NA	NA	13 (6.5)	7 (3.5)	1 (0.5)	3 (1.5)	32 (16.1)	35 (17.6)
Gough et al. (26), 2014	833	413	73 (8.8)	15 (3.6)	32 (3.8)	6 (1.5)	66 (7.9)	19 (4.6)	10 (1.2)	8 (1.9)	90 (10.8)	47 (11.4)
All long-acting GLP-1 RAs	1,769	1,350	170 (9.6)*	46 (3.4)	77 (4.9)†	15 (1.3)	130 (7.3)¶	53 (3.9)	46 (2.6)**	22 (1.6)	204 (11.5)‡	185 (13.7)

NA, not available. *Odds ratio 0.43 (95% CI 0.18; 0.52), $P < 0.0001$. †Odds ratio 0.55 (95% CI 0.41; 0.72), $P < 0.0001$. ¶$P = 0.41$. **Odds ratio 0.43 (95% CI 0.34; 0.67), $P < 0.0001$. ‡Odds ratio 1.04 (95% CI 0.85; 1.26), $P = 0.72$; however, with placebo, the odds ratio was 2.24 (1.76; 2.83), $P < 0.0001$, and the 95% CIs for verum and placebo studies did not overlap, indicating a significant difference ($P < 0.05$) between short- and long-acting GLP-1 RAs relative to placebo.

- Hypoglycemia
- The proportion of patients reporting symptomatic hypoglycemia was higher in patients treated with GLP-1 RAs and basal insulin than in those treated with basal insulin 6 placebo (P = 0.020) (Supplementary Table 10). Patients treated in studies using short-acting GLP-1 RAs and basal insulin had slightly higher proportions reporting symptomatic hypoglycemic episodes compared with those using longacting GLP-1 RAs (27.3 vs. 24.4%, P 5=0.048) (Supplementary Table 10). Proportions of patients reporting severe episodes of hypoglycemia were low and not significantly different between studies using short- and long-acting GLP-1 Ras (Supplementary Table 10).

Anmerkung/Fazit der Autoren

In conclusion, the results of our metaanalysis indicate that long-acting GLP-1 RAs should preferentially be combined with basal insulin, since this combination results in not only better overall glycemic control (HbA1c) but also improved fasting plasma glucose concentrations and lower body weight. This combination also has advantages regarding gastrointestinal adverse events.

Avgerinos I et al., 2019 [2].

Glucagon-like peptide-1 receptor agonists and microvascular outcomes in type 2 diabetes: A systematic review and metaanalysis.

Fragestellung

We conducted a systematic review and meta-analysis of RCTs to clarify the effect of GLP-1 RAs on renal and diabetic retinopathy-related outcomes in adults with T2DM.

Methodik

Population:

- in adults with T2DM

Intervention:

- GLP-1 RA

Komparator:

- placebo or another antidiabetic agent

Endpunkte:

- primary outcomes: change from baseline in urinary albumin-to-creatinine ratio (UACR, mg/g) and incidence of diabetic retinopathy.
- Secondary outcomes: change from baseline in estimated glomerular filtration rate (eGFR, mL/min/1.73 m2) and in glycated haemoglobin (HbA1c, %), and incidence of macular oedema, retinal detachment, retinal haemorrhage, or vitreous haemorrhage

Recherche/Suchzeitraum:

- MEDLINE, Embase and the Cochrane Library up to June 11, 2018,
- RCTs with treatment duration of at least 12 weeks

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 60 RCTs (60 077 participants)

Charakteristika der Population:

- Twenty-six trials assessed liraglutide, while exenatide, lixisenatide, dulaglutide and semaglutide were assessed in 9, 7, 10 and 8 trials, respectively.
- Study duration ranged from 12 weeks to 3.8 years, and was ≥52 weeks in 26 trials, while HbA1c levels at baseline ranged from 7.1% to 10.3%.

Qualität der Studien:

- Overall risk of bias was high in most studies assessing change from baseline in UACR or incidence of diabetic retinopathy, mainly because of the high discontinuation rate, missing data, or the need for imputation of mean and standard deviation values

Studienergebnisse:

Outcome	Comparison	Studies included, *n*	Number of participants analysed, n		Effect estimate WMD/ OR[a] (95% CI)	I^2, %
			GLP-1 RA	Comparator		
Mean change in UACR from baseline (mg/g)	GLP-1 RAs vs. placebo	19	11 923	9643	−2.55 (−4.37, −0.73)	45
	GLP-1 RAs vs. active comparator	17	4454	2850	−5.52 (−10.89, −0.16)	41
Mean change in eGFR from baseline (ml/min/1.73 m^2)	GLP-1 RAs vs. placebo	14	9329	7861	−0.97 (−1.84, −0.11)	69
	GLP-1 RAs vs. active comparator	10	3790	1897	0.03 (−0.70, 0.76)	25
Diabetic retinopathy	GLP-1 RAs vs. placebo	15	16 525	15 099	1.01 (0.89, 1.16)	0
	GLP-1 RAs vs. active comparator	18	6960	4233	0.95 (0.67, 1.35)	0
Macular oedema	GLP-1 RAs vs. placebo	9	8339	7252	0.84 (0.44, 1.57)	0
	GLP-1 RAs vs. active comparator	6	1940	1817	1.14 (0.34, 3.84)	0
Retinal detachment	GLP-1 RAs vs. placebo	8	10 588	10 143	1.20 (0.52, 2.80)	0
	GLP-1 RAs vs. active comparator	8	3528	2190	0.67 (0.26, 1.74)	0
Retinal haemorrhage	GLP-1 RAs vs. placebo	8	8170	7126	0.93 (0.42, 2.08)	0
	GLP-1 RAs vs. active comparator	10	3682	2185	0.79 (0.34, 1.88)	0
Vitreous haemorrhage	GLP-1 RAs vs. placebo	6	10 748	9964	1.93 (1.09, 3.42)	0
Mean change in HbA1c from baseline (%)	GLP-1 RAs vs. placebo	28	14 489	12 336	−0.88 (−1.01, −0.74)	93
	GLP-1 RAs vs. active comparator	30	9426	6024	−0.37 (−0.51, −0.24)	94

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; GLP-1 RAs, glucagon-like peptide-1 receptor agonists; HbA1c, glycated haemoglobin; NE, not estimable; OR, odds ratio; UACR, urinary albumin-to-creatinine ratio; WMD, weighted mean difference.
[a] For change in UACR, eGFR and HbA1c, the effect estimate is weighted mean difference, while for diabetic retinopathy, macular oedema, retinal detachment, retinal haemorrhage and vitreous haemorrhage, the effect estimate is odds ratio, along with 95% confidence interval.

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis provides some reassurance that GLP-1 RAs are safe in terms of their effect on diabetic retinopathy and albuminuria or change in eGFR. Caution may be warranted for incidence of vitreous haemorrhage.

Maiorino MI et al., 2019 [79].

The good companions: insulin and glucagon-like peptide-1 receptor agonist in type 2 diabetes. systematic review and meta-analysis o randomized controlled trials

Fragestellung

We provided an updated systematic review with meta-analysis of randomized controlled trials (RCTs) assessing the metabolic effects of combination therapy of insulin and GLP- 1RA (combo) in comparison with other injectable therapy

Methodik

Population:

- type 2 diabetic patients

Intervention/Komparator:

- compared both free or fixed combo of short- and long-acting GLP-1RAs and insulin with other injectable treatment strategy, had at least duration of 8 weeks,

Endpunkte:

- HbA1c and weight change, safety (hypoglycemia)

Recherche/Suchzeitraum:

- MEDLINE (via Pubmed), Cochrane Central Register of Controlled Trials, Google Scholar, and ClinicalTrials.gov to March 21, 2019.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

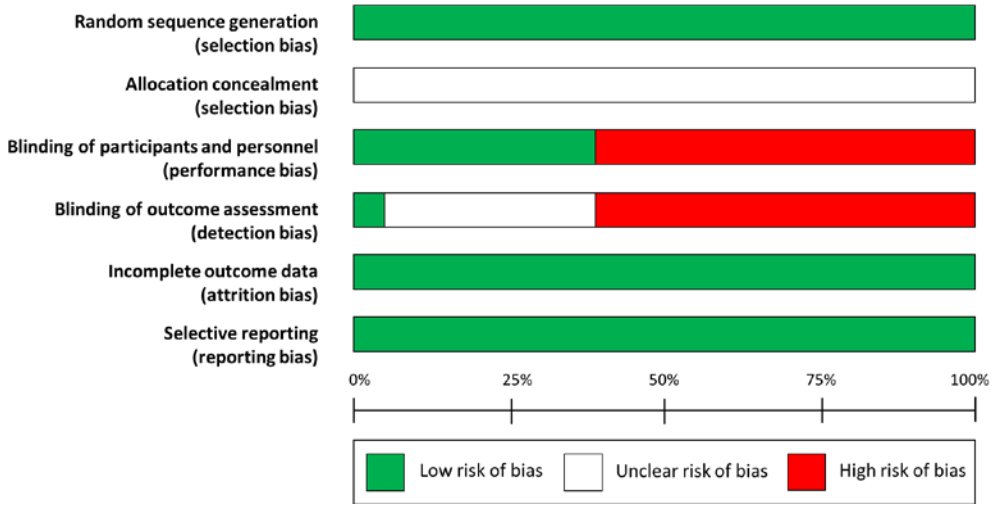
Anzahl eingeschlossener Studien:

- 36 RCTs (n=14636)

Charakteristika der Population:

- Most RCTs were multinational and received industry funding [19–27,29–45,47–52]; six studies [21,22,36,46,53,54] focused on Asian population.
- All trials were of parallel-group design, 14 were double-blind [19,22–25,29–31,36–37,39–42] and the remaining utilised an open-label design. The trials had a duration ranging from 8 to 52 weeks.
- The participants in all trials were adults (>18 years old) with type 2 diabetes; only one study [51] included patients with moderate-severe kidney disease. Mean patients' age ranged from 42 to 66 years, and mean baseline HbA1c levels ranged from 6.9% to 9.0%, with a median of 8.3% (IQR 7.8–8.5%) in the intervention groups and 8.2% (IQR 7.7–8.5%) in the comparator groups.

Qualität der Studien:



Outcome measure	N of studies	Limitations	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of evidence
HbA1c change	36	no serious limitations	no serious	very serious	no serious	no serious	undetected	moderate
HbA1c <7%	31	no serious limitations	no serious	very serious	no serious	some imprecision	suspected	low
Risk of hypoglycemia	30	no serious limitations	no serious	very serious	no serious	some imprecision	suspected	low
Weight change	35	no serious limitations	no serious	very serious	no serious	no serious	suspected	low

Studienergebnisse:

Table 2 – Pre-planned subgroup analysis

Parameter	Comparisons	Patients	Controls	Estimate (95% CI)	p-value	I^2	p-value of Q test
HbA1c (%)				**WMD**			
Combination therapy of insulin and GLP-1RA							
Vs placebo/intensification/GLP-1RA	27	5196	4965	−0.71 (−0.82, −0.59)	<0.001	91.4	<0.001
Vs Basal-plus/Basal-bolus	15	2328	2147	−0.08 (−0.15, −0.01)	0.038	58.7	0.002
Combo with short-acting GLP-1RA	16	2786	3147	−0.29 (−0.44, −0.14)	<0.001	93.7	<0.001
Combo with long-acting GLP-1RA	26	4738	3965	−0.63 (−0.78, −0.47)	<0.001	93.3	<0.001
All trials	42	7524	7112	−0.49 (−0.61, −0.38)	<0.001	94.2	<0.001
HbA1c < 7%				**RR**			
Combination therapy of insulin and GLP-1RA							
Vs placebo/intensification/GLP-1RA	27	5196	4965	2.23 (1.88, 2.65)	<0.001	93.5	<0.001
Vs Basal-plus/Basal-bolus	10	2205	2022	1.07 (0.99, 1.15)	0.077	15.3	0.302
Combo with short-acting GLP-1RA	12	2676	3034	1.57 (1.28, 1.93)	<0.001	92.4	<0.001
Combo with long-acting GLP-1RA	25	4725	3953	1.91 (1.61, 2.27)	<0.001	92.1	<0.001
All trials	37	7401	6987	1.77 (1.56, 2.01)	<0.001	92.1	<0.001
Hypoglycemia				**RR**			
Combination therapy of insulin and GLP-1RA							
Vs placebo/intensification/GLP-1RA	25	5111	4889	1.26 (1.06, 1.49)	0.008	82.2	<0.001
Vs Basal-plus/Basal-bolus	10	1628	1735	0.64 (0.52, 0.79)	<0.001	82.0	<0.001
Combo with short-acting GLP-1RA	15	2775	3132	1.02 (0.81, 1.28)	0.866	84.8	<0.001
Combo with long-acting GLP-1RA	20	3964	3492	1.04 (0.85, 1.27)	0.733	87.6	<0.001
All trials	35	6739	6624	1.03 (0.88, 1.19)	0.728	86.4	<0.001
Weight (Kg)				**WMD**			
Combination therapy of insulin and GLP-1RA							
Vs placebo/intensification/GLP-1RA	26	5022	4793	−1.8 (−2.6, −1.1)	<0.001	97.1	<0.001
Vs Basal-plus/Basal-bolus	15	2328	2147	−3.6 (−4.5, −2.7)	<0.001	92.5	<0.001
Combo with short-acting GLP-1RA	16	2786	3147	−2.2 (−3.1, −1.4)	<0.001	96.0	<0.001
Combo with long-acting GLP-1RA	25	4564	3793	−2.7 (−3.6, −1.7)	<0.001	97.2	<0.001
All trials	41	7350	6940	−2.5 (−3.1, −1.8)	<0.001	96.8	<0.001

RR, relative risk; WMD, weighted mean difference.

Anmerkung/Fazit der Autoren

Combination therapy of GLP-1RA and insulin could represent a valuable treatment strategy to improve metabolic control in the management of type 2 diabetes. This combination presents a higher efficacy associated with a slight increase of hypoglycemia and weight loss when compared with other injectable therapy (insulin up-titration or GLP-1RA alone), and similar efficacy when compared with insulin regimens (basal-plus or basal-bolus), with low risk of hypoglycemicevents and more weight loss.

Andreadis P et al., 2018 [1].

Semaglutide for type 2 diabetes mellitus: A systematic review and meta-analysis

Fragestellung

We conducted a systematic review and meta-analysis of RCTs comparing semaglutide with placebo or other antidiabetic agents in patients with T2DM to summarize all available evidence concerning the efficacy and safety of semaglutide.

Methodik

Population:

- Adult patients with T2DM

Intervention:

- Subcutaneous semaglutide

Komparator:

- placebo or with another antidiabetic agent

Endpunkte:

- Our primary outcome was change from baseline in HbA1c.
- Secondary efficacy outcomes included change in body weight, systolic and diastolic blood pressure and heart rate
- Safety: nausea, vomiting, diarrhoea, any hypoglycaemia and severe hypoglycaemia acute pancreatitis and diabetic retinopathy because of the association of semaglutide

Recherche/Suchzeitraum:

- Medline (via PubMed), Embase (via Ovid) and the Cochrane Library. in January 2018
- RCTs with treatment duration of at least 12 weeks

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 12 studies, with 9501 patients

Charakteristika der Population:

- Subcutaneous semaglutide was compared with placebo or with another antidiabetic agent in 6 studies and 7 studies, respectively, while 1 trial compared both subcutaneous and oral semaglutide with placebo.
- The antidiabetic agents used in control arms included sitagliptin, insulin glargine, liraglutide, exenatide extended-release (ER) or dulaglutide while, in 1 study, control treatment was chosen by trial clinicians from among dipeptidyl peptidase-4 inhibitors, metformin, sulphonylureas, glinides, α-glucosidase inhibitors and thiazolidinediones.
- Two studies enrolled treatment-naïve patients, whereas the remaining trials recruited patients receiving single or dual antidiabetic therapy.
- Duration of intervention in most trials ranged from 12 to 56 weeks, with the exception of the SUSTAIN-6 trial, a dedicated cardiovascular outcomes study, that had a duration of 104 weeks.
- Participants' mean age and mean baseline HbA1c ranged from 52.7 to 64.7 years and from 7.3% to 8.7%, respectively.

Qualität der Studien:

- Risk of bias within studies was deemed low for 8 studies and high for 2 studies, mainly because of missing outcome data. Furthermore, there were some concerns about 1 study because of lack of information concerning the randomization process,8 and we did not assess risk of bias for 1 study because it did not provide data for our primary outcome.

Study ID	Randomization process	Deviations from intended interventions	Mising outcome data	Measurement of the outcome	Selection of the reported result	Overall Bias
Ahmann 2016	Low	Low	Low	Low	Low	Low
Ahren 2017	Low	Low	Low	Low	Low	Low
Aroda 2017	Low	Low	Low	Low	Low	Low
Davies 2017	Low	High	High	Low	Low	High
Kaku 2018	Low	Low	Low	Low	Low	Low
Marso 2017	Low	Low	Low	Low	Low	Low
Nauck 2016	Low	Low	High	Low	Low	High
Pratley 2018	Low	Low	Low	Low	Low	Low
Rodbard 2016	Some concerns	Low	Low	Low	Low	Some concerns
Seino 2017	Low	Low	Low	Low	Low	Low
Sorli 2017	Low	Low	Low	Low	Low	Low

Studienergebnisse:

Heart rate

- In comparisons against other antidiabetic agents (WMD, 1.53, 95% CI, 0.89-2.17; I2 = 58% and WMD, 2.03, 95% CI, 1.47-2.60; I2 = 65% for semaglutide 0.5 and 1 mg, respectively).

Hypoglycaemia

- Results were similar for semaglutide 1 mg when compared to antidiabetic agents (OR, 0.72, 95% CI, 0.51-1.03; I2 = 37%).
- Results for semaglutide 0.5 mg, showing a decrease in the incidence of any hypoglycaemia compared to any other agent (OR, 0.52, 95% CI, 0.31-0.87; I2 = 47%)

Adverse events

- Nausea; any other comparator: n=7 OR: 2.60 (95% KI: 2.18-3.10), I^2: 84%
- Vomiting: any other comparator; n=6 OR 2.06 (1.61-2.63),; I^2: 51%
- Diarrhea: any other comparator; n=7; OR 1.84 (1.52-2.23), I^2: 74%

Anmerkung/Fazit der Autoren

In conclusion, a once weekly subcutaneous dose of semaglutide In efficacious in lowering HbA1c, body weight and systolic blood pressure, compared to both placebo and other antidiabetic agents, including several other GLP-1 RAs. However, it is associated with an increased incidence of gastrointestinal adverse events and its relationship with diabetic retinopathy-related outcomes requires further examination through post-approval pharmacovigilance studies.

Kommentare zum Review

- Studien mit vorbehandelten und nicht vorbehandelten Patienten in Meta-Analyse gepoolt
- Autoren erhielten Förderungen seitens pharmazeutischer Unternehmer

Castellana M et al., 2018 [7].

GLP-1 receptor agonist added to insulin versus basal-plus or basal-bolus insulin therapy in type 2 diabetes: A systematic review and meta-analysis

Fragestellung

We conducted a systematic review and meta-analysis to compare the effects of GLP-1RA/insulin combinations versus BP/BB.

Methodik

Population:

- patients with type 2 diabetes

Intervention:

- short-acting GLP-1RA added to basal insulin (1)
- long-acting GLP-1RA added to basal insulin (2)
- long-acting GLP-1RA added to prandial insulin (3)
- fixed-ratio combinations of GLP-1RA and basal insulin (4)

Komparator:

- basal-plus (BP) or basal-bolus (BB) insulin

Endpunkte:

- Primary: HbA1c change
- Secondary: body weight change, total daily insulin dose, incidence of hypoglycaemic events discontinued patients due to lack of efficacy

Recherche/Suchzeitraum:

- on 15 July 2018 in PubMed, Scopus, CENTRAL, and ClinicalTrials.gov

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 trials with 5308 adult patients
  - 3 studies exenatide, 3 lixisenatide, 2 albiglutide, 2 dulaglutide, 2 liraglutide, and 1 IDegLira
  - 3 studies 3 armed

Charakteristika der Population:

- type 2 diabetes mellitus, with HbA1c of 6% to 11%
- Prescreening therapy: 96% of basal insulin, 27% on prandial insulin, 82% on metformin

Qualität der Studien:

- Random sequence generation and allocation concealment adequate in 8 trials; 4 not reported
- risk of performance and detection bias: high risk, all 13 trials were open label

- Discontiuation rate between 0-30%; significant betweens arms in 2 studies
- No selective reporting bias
- Industry sponsored: 9 trials

Studienergebnisse:

- Subgroups: Interventions 1-4
- Change in HbA1c (Baseline to last available follow-up): not significant I2 = 52%
    - Subgroup long-acting GLP-1RA added to prandial insulin: -0.16%; 95% CI, -0.29 to -0.04; p=0.01
- body weight change: reduction with GLP-1RA -3.72 kg; CI, -4.49 to -2.95; p<0.001; I2 =89%
    - consistent in all subgroups
    - high heterogeneity in all analysis (total and subgroup)
- total daily insulin dose: GLP-1RA added to insulin was associated with a reduction -30.3 IU/day; 95% CI, -41.2 to -19.3; p<0.001; I2 = 94%
    - consistent in all subgroups
    - high heterogeneity in all analysis
- hypoglycaemic events: GLP-1RA added to insulin showed to be superior to BP/BB insulin (RR = 0.46; 95% CI, 0.38-0.55; p< 0.001; I2 = 99%)
    - consistent in all subgroups
    - high heterogeneity in all analysis
- discontinuation due to lack of efficacy: no difference

Anmerkung/Fazit der Autoren

In patients with type 2 diabetes mellitus, a combination therapy with GLP-1RA and insulin proved to be as effective as BP/BB insulin on HbA1c, while leading to a significant weight loss, reduced risk of hypoglycaemia, and use of less insulin dose. Since the addition of GLP-1RA could exert the same glucose-lowering effects of up to 60 IU/day of insulin, a significant number of patients on BP/BB could be potentially shifted to GLP-1RA/insulin regimens.

Kommentare zum Review

- Es ist zu beachten, dass alle Studien open-label waren. Zudem bestand eine starke Heterogenität. Die Autoren führen dazu aus: This could be due to (1) characteristics of GLP-1RA in each subgroup (ie, exenatide versus lixisenatide), (2) trial design, and (3) patients characteristics other than the extracted ones. HbA1c at baseline was between 6% and 11%.

Li X et al., 2018 [74].

The safety and efficacy of once-weekly glucagon-like peptide-1 receptor agonist semaglutide in patients with type 2 diabetes mellitus: a systemic review and meta-analysis.

Fragestellung

To investigate the safety and efficacy of once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist semaglutide as monotherapy or add-on to other antihyperglycaemic agents (AHAs) in patients with type 2 diabetes mellitus (T2DM).

Methodik

Population:

- T2DM patients

Intervention/Komparator:

- semaglutide with placebo or other antihyperglycaemic agents (AHAs)

Endpunkte:

- reduction in HbA1c, reduction in SMPG, reduction in FPG, number of participants achieving HbA1c <7.0%, weight loss, AEs, SAEs and hypoglycaemic events (severe or BG-confirmed symptomatic)

Recherche/Suchzeitraum:

- PubMed, Embase, Cochrane library and ClinicalTrials.gov were searched from the inception to January 18, 2018

Qualitätsbewertung der Studien:

- Cochrane approach

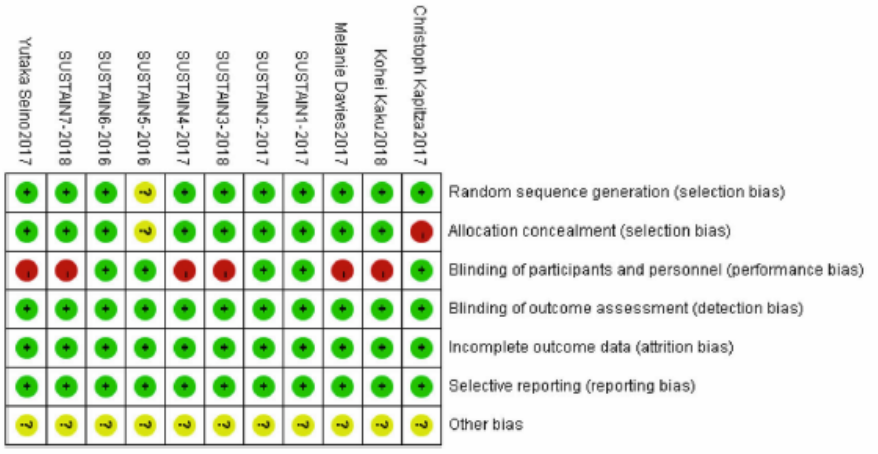
Ergebnisse

Anzahl eingeschlossener Studien:

- A total of 11 studies with 9519 patients
- Among 11 trials, 5 trials compared the efficacy and safety of semaglutide with placebo and 6 trials compared the efficacy and safety of semaglutide with other AHAs. In the included studies, the diabetes duration ranged from 3.62 to 14.3 years and the treatment duration ranged from 12 to 104 weeks.

Qualität der Studien:

Fig. 2 Risk of bias graph and summary for included studies



Studienergebnisse:

- The results revealed that compared with placebo or other AHAs, semaglutide had further reduced
  - the level of haemoglobin A1c (HbA1c) [MD 1.03%, 95% CI (0.85%, 1.22%), p < 0.00001],
  - weight [MD 3.61 kg, 95% CI (3.05 kg, 4.17 kg), p < 0.00001]

  - and significantly increased participants who achieved HbA1c < 7.0% [RR 2.26, 95% CI (1.89, 2.70), p < 0.00001] in T2DM patients.
- Semaglutide had a significant increase in
  - the incidence of adverse events (AEs) [RR 1.06, 95% CI (1.02, 1.11), p < 0.0001] and
  - an analogous incidence in serious adverse events (SAEs) [RR 0.94, 95% CI (0.86, 1.02), p = 0.11] and
  - hypoglycaemic events (severe or blood glucose (BG)-confirmed symptomatic) [RR 0.93, 95% CI (0.74, 1.16), p = 0.50] compared with the control group.

Anmerkung/Fazit der Autoren

In conclusion, semaglutide had a favourable efficacy and safety as monotherapy or add-on to other AHAs in the treatment of T2DM patients. It may be a superior choice for T2DM patients with obesity or T2DM patients who have a poor adherence to daily AHAs. Semaglutide is generally well tolerated and has obviously better efficacy than either placebo or other AHAs in treating T2DM.

Maiorino MI, et al. 2018 [78].

Free and fixed-ratio combinations of basal insulin and GLP-1 receptor agonists versus basal insulin intensification in type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials

Fragestellung

What is the effect of GLP-1RA and insulin combination, as compared with insulin intensification, on glycaemic control in type 2 diabetes?

Methodik

Population:

- Patients with T2DM

Intervention:

- free or fixed combo basal insulin and GLP-1

Komparator:

- up-titration of basal insulin

Endpunkte:

- decrease of HbA1c; secondary endpoints: proportion of patients at the HbA1c target <7% (53 mmol/ mol), the incidence of hypoglycaemic events, and change in body weight

Recherche/Suchzeitraum:

- 23.February 2018 in PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews and ClinicalTrials.gov

Qualitätsbewertung der Studien:

- Cochrane Collaboration Risk-of-Bias tool
- Jadad score

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 RCTs with 6176 patients

Charakteristika der Population:

- Heterogene Hintergrundtherapie:
  - 6x Metformin, 2x Metformin x Glitazon, 2x Metfomin ± SU/Glinide, 1x Metformin ± OAD
  - Insulin: 3x None, 8x Basal Insulin at different UI/daily

Qualität der Studien:

- Cochrane risk of bias tool: three common biases blinding of participants (5x high), blinding of outcome assessment (2x high and 4x unclear), and allocation concealment (all unclear)
- median score of methodologic quality: 4.0; 6 studies had a score ≥4, indicating high quality

Studienergebnisse:

Parameter	Comparisons (n)	Intervention/control (n)	Estimate (95% CI)	*P* value	I^2	*P* value Q Test
HbA1c change (%)			WMD			
All	11	3386/2790	−0.53 (−0.66, −0.40)	<0.001	87.6	<0.001
Free combo	5	1070/893	−0.57 (−0.77, −0.38)	<0.001	80.7	<0.001
Fixed combo	6	2316/1897	−0.50 (−0.67, −0.33)	<0.001	91.0	<0.001
HbA1c < 7%			RR			
All	11	3386/2790	1.69 (1.42, 2.00)	<0.001	91.6	<0.001
Free combo	5	1070/893	2.08 (1.53, 2.84)	<0.001	80.7	<0.001
Fixed combo	6	2316/1897	1.48 (1.23, 1.77)	<0.001	92.3	<0.001
Hypoglycaemia			RR			
All	11	3386/2790	0.97 (0.84, 1.12)	0.684	71.6	<0.001
Free combo	5	1070/893	1.13 (0.95, 1.36)	0.166	35.3	0.186
Fixed combo	6	2316/1897	0.87 (0.72, 1.04)	0.114	72.9	0.002
Weight change (kg)			WMD			
All	11	3386/2790	−1.9 (−2.3, −1.4)	<0.001	83.4	<0.001
Free combo	5	1070/893	−1.7 (−2.3, −1.1)	<0.001	76.4	0.002
Fixed combo	6	2316/1897	−2.0 (−2.6, −1.4)	<0.001	86.0	<0.001

- Decrease of HbA1c:
  - significantly greater than insulin up-titration (-0.53%, 95% CI −0.66, -0.40%, P < 0.001)
  - high heterogeneity (I^2=87.6%, p<0.001) and evidence of publication bias (Egger test, p=0.043)
  - free and fixed combos reduced HbA1c in a similar way (-0.57% and -0.50% respectively)
- HbA1c target of <7%
  - likelihood of achieving the HbA1c target was 69% higher in favour of the combination
  - high heterogeneity (I2 = 91.6%, p<0.001), and evidence of publication bias (P < 0.001)
  - likelyhood for both subroups was significantly higher than in insulin intensification groups
- risk of any hypoglycaemia: not significantly different
- body weight decrease

- grater in the combo therapy (-1.9 kg, 95% CI -2.3, -1.4, p<.001), evident in both subgroups
- high heterogeneity (I2 = 83.4%)

Anmerkung/Fazit der Autoren

In conclusion, combo strategies, either free or fixed, represent a good option to intensify basal insulin therapy in patients with type 2 diabetes who need amelioration of glycaemic control. On the other hand, long-term effectiveness is still uncertain, owing to the limited duration of the trials published to date.

Kommentare zum Review

- Hohe Heterogenität zwischen den Studien, sowie Hinweise auf einen Publikationsbias limitieren die Aussagekraft der Ergebnisse. Zur Heterogenität tragen neben den verschiedenen Vortherapien auch die unterschiedlichen GLP-1RA und zusätzliche eingenommene OADs bei.

Mishriky BM et al., 2018 [87].

Comparing once-weekly semaglutide to incretin-based therapies in patients with type 2 diabetes: a systematic review and meta-analysis

Fragestellung

to compare once-weekly semaglutide to incretin-based therapies – defined as either dipeptidyl peptidase-4 inhibitors (DPP-4i) or other glucagon-like peptide-1 receptor agonist (GLP- 1RA) – in patients with type 2 diabetes.

Methodik

Population:

- Patients with type 2 diabetes

Intervention:

- once-weekly subcutaneous semaglutide

Komparator:

- incretin-based therapy (i.e., any other DPP-4i or GLP-1RA)

Endpunkte:

- primary: change in HbA1c
- Secondary: change in body weight, change in FPG, change in blood pressure, number of patients achieving goal haemoglobin A1c < 7.0% and ≤ 6.5%, number of patients achieving goal haemoglobin A1c < 7.0% without hypoglycaemia or weight gain, numbers of patients with body weight loss ≥ 5% and ≥10%, number of patients requiring rescue medications, and incidence of side effects.

Recherche/Suchzeitraum:

- Up to March 14th, 2018 in MEDLINE the Cochrane Central Register of Controlled trials, EMBASE, Web of Science and CINAHL

Qualitätsbewertung der Studien:

- Cochrane risk of bias and the 7-point modified Oxford Score

Ergebnisse

Anzahl eingeschlossener Studien:

- Five trials with 3769 patients
  - 3 vs another GLP-1RA
  - 2 vs DPP-4i (Sitagliptin)

Charakteristika der Population:

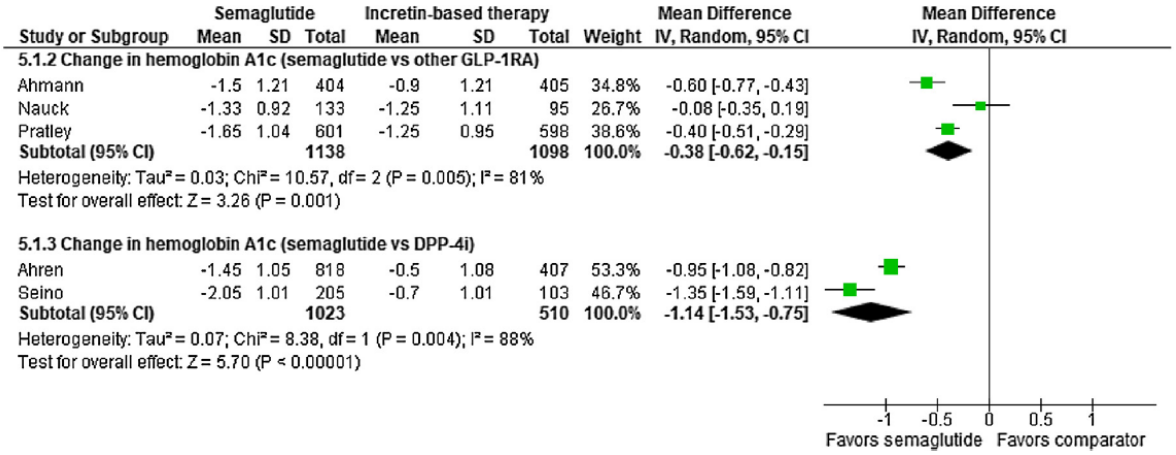
- Three trials investigated semaglutide as add-on therapy, one as added to either diet/exercise or metformin, and one as monotherapy.
- The primary outcome for four trials was the change in haemoglobin A1c over time, and one was the treatment-emergent adverse events.

Qualität der Studien:

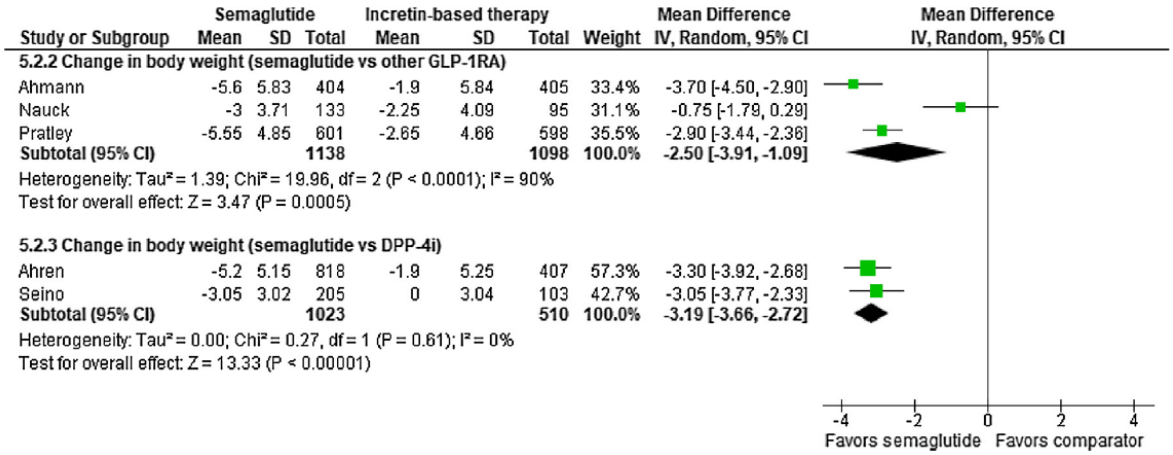
- Just mentioned in the supplement online

Studienergebnisse:

- Change in HbA1c



- HbA1c < 7.0%, ≤ 6.5% and composite outcome:
  - GLP-1RA: Pooled results favoured semaglutide [RR (95% CI) = 1.33 (1.06, 1.68), I2 = 88%, 1.52 (1.09, 2.12), I2 = 87% and 1.63 (1.10, 2.43), I2 = 93%, respectively]
  - DPP-4i: pooled favoured semaglutide [RR (95% CI) = 2.22 (1.77, 2.77), I2 = 58%, 3.70 (2.14, 6.39), I2 = 80%, and 3.17 (1.94, 5.19), I2 = 80%, respectively]
- Change in body weight



  - Patients with body weight loss ≥ 5% and ≥10%: significantly higher vs both comparators

- Adverse effects:
  - GLP-1RA Semaglutide-treated patients had a significantly higher incidence of adverse effects leading to discontinuation of study drug, nausea, and vomiting
  - DPP-4i Semaglutide-treated patients had a significantly higher incidence of adverse effects leading to discontinuation of study drug, vomiting, and diarrhoea

Anmerkung/Fazit der Autoren

The present systematic review and meta-analysis suggests that once-weekly semaglutideproduces greaterreductions in haemoglobin A1c, weight, and blood pressure when compared to other GLP-1RA or DPP-4i while requiring less need for rescue medications. In addition, the number of patients achieving glycaemic goals was higher in semaglutide-treated patients compared to either other GLP-1RAor DPP-4i. Furthermore, the number of patients achieving weight loss was higher in semaglutide-treated patients compared to other GLP-1RA or DPP-4i. However, while semaglutide seems more potent compared to other incretin-based therapies, it was associated with an increased risk for nausea, vomiting, diarrhoea and adverse effects leading to discontin- uation of the medication.

Kommentare zum Review

- Signifikante Heterogenität zwischen den Studien, da verschiedene GLP-1RA Komperatoren gepoolt wurden und sowohl Monotherapien als auch add-on einbezogen wurden.
- für den Vergleich von oralem Semaglutid vs. injizierbare GLP-1 RA siehe auch **Nuhoho et al., 2019 [92],** welche zum gleichen Ergebnis kommt: "orally administered semaglutide 14 mg QD was associated with a significantly greater reduction in HbA1c at 26 ± 4 weeks vs most GLP-1 RA comparators"

Wei ZG et al., 2018 [105].

PRISMA—efficacy and safety of lixisenatid for type 2 diabetes mellitus A meta-analysis of randomized controlled trials

Fragestellung

The objective of this metaanalysis was to systematically evaluate the efficacy and safety of lixisenatide in patients with T2DM.

Methodik

Population:

- patients ages>18 years, with inadequately controlled type 2 diabetes and a glycated hemoglobin (HbA1c) level of 7–10%

Intervention/Komparator:

- lixisenatide or placebo was administered subcutaneously, with or without oral antidiabetic agents (OADs)/insulin

Endpunkte:

- HbA1c, FPG, body weight, and rescue therapy, safety

Recherche/Suchzeitraum:

- MEDLINE, EMBASE, Cochrane library, ClinicalTrials.gov, Google, Web of Science, and the Chinese Science Citation Database were searched up to March 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

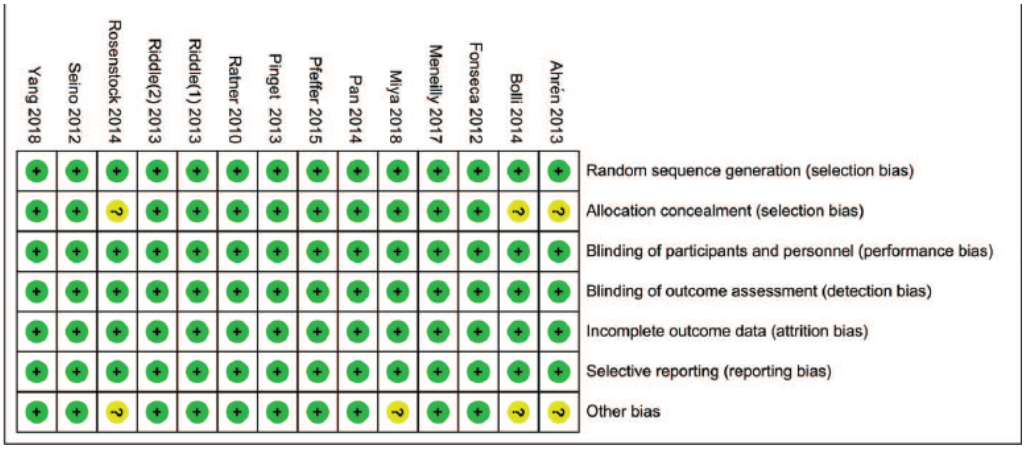
Anzahl eingeschlossener Studien:

- Fourteen eligible multicenterRCTs[5,6,14,18–28] were included finally, with a total sample size of 11,947

Charakteristika der Population:

- The baseline HbA1c level was 7 to 10% in all studies, and the follow-up durations were 24 weeks,[6,18–24,26,28] 13 weeks,[5] 12 weeks,[14,27] and 25 months.[25]
- Lixisenatide 20mg once daily was subcutaneously administered in most of the included studies. Metformin, [5,18–25,28] sulfonylurea, [6,18–21,25] thiazolidinedione, [24,25] pioglitazone,[22] and insulin [6,23–25,28] were used in different studies for glycemic control.

Qualität der Studien:

- 

Studienergebnisse:

Outcomes	Study	I^2%	Random effects model WMD/RR (95% CI)	P
Efficacy				
HbA1c	7	66	−0.48 (−0.60, −0.36)	<.00001
HbA1c<7.0%	11	58	1.94 (1.73–2.16)	<.00001
HbA1c<6.5%	10	43	3.03 (2.54–3.63)	<.00001
Fasting plasma glucose	7	28	−0.43 (−0.62, −0.25)	<.00001
Body weight	6	0	−1.34 (−2.67,−0.02)	0.05
Rescue therapy	9	0	0.39 (0.30–0.51)	<.00001
Glucose excursion	5	93[#]	−3.91 (−4.72, −3.10)	<.00001
2-hour PPG	5	92[&]	−4.31 (−5.50, −3.12)	<.00001
Safety				
Any adverse events (AE)	12	46	1.14 (1.08–1.19)	<.00001
Discontinuation due to AE	14	0	1.79 (1.57–2.05)	<0.00001
Serious adverse events	13	0	0.94 (0.86–1.04)	.49
Death*	6	0	0.64 (0.18, 2.32)	.49
Gastrointestinal disorders	13	74	2.23 (1.86–2.68)	<.00001
Nausea	12	30	4.09 (3.38–4.95)	<.00001
Vomiting	12	18	5.57 (3.88–7.98)	<.00001
Diarrhea	10	7	1.28 (1.05–1.55)	.01
Symptomatic hypoglycemia	14	0	1.59 (1.35–1.89)	<.0001
Severe hypoglycemia	5	0	0.74 (0.40–1.36)	.33
Injection-site reactions	9	0	2.05 (1.43–2.95)	.0001
Allergic reaction	6	0	2.11 (0.68–6.54)	.20

Anmerkung/Fazit der Autoren

Compared to placebo, lixisenatide could significantly reduce the levels of HbA1c, FPG, and PPG, and higher proportion of lixisenatide-treated patients achieved the HbA1c targets of<7.0% and<6.5% in lixisenatide-treatment group. It increased the incidence of mild-to-moderate gastrointestinal AEs and symptomatic hypoglycemia, but it was not associated with serious AEs, death, or severe hypoglycemia. In conclusion, lixisenatide was effective and relatively well tolerated in patients with inadequately controlled T2DM.

Singh S et al., 2017 [101].

Glucagon-like peptide-1 receptor agonists compared with basal insulins for the treatment of type 2 diabetes mellitus: a systematic review and meta-analysis

Fragestellung

This systematic review and metaanalysis assessed the clinical efficacy and safety of GLP-1 RAs compared with basal insulins.

Methodik

Population:

- adults with type 2 diabetes inadequately controlled with oral antihyperglycemic drugs

Intervention:

- GLP-1 RAs

Komparator:

- basal insulins

Endpunkte:

- change from baseline to 26 weeks (10 weeks) of treatment in haemoglobin A1c (HbA1c) and weight, proportion of patients experiencing hypoglycaemia

Recherche/Suchzeitraum:

- from database inception to September 9, 2016

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 RCTs meta-analysed

Charakteristika der Population:

-

Qualität der Studien:

- selection bias assessed as unclear in
  - 7 trials for random sequence generation and in
  - 4 trials for allocation concealment
- all trials open label
- attrition bias (see incomplete outcome data) was assessed to be low in
  - 12 trials (percentage of patients lost to follow-up reported as 0%-3% in all arms) and
  - unclear in 3 trials

Studienergebnisse:

- Body weight
  - mean difference in bodyweight for insulin glargine vs. …
  - exenatide 10 µg: −4.31 kg (95% CI, −4.71, −3.90; I2 = 76%),
  - exenatide 2 mg LAR: −2.85 kg (95% CI, −3.20, −2.49; I2 = 96.5%),
  - liraglutide 1.8 mg: −4.65 kg (95% CI, −5.08, −4.22; I2 = 89.1%), and
  - dulaglutide 0.75 mg: −1.98 kg (95% CI, −2.32, −1.64, I2 = 91%)
  - mean weight reduction was seen with all GLP-1 RAs
- Hypoglycaemia
  - interpretation of analysis limited by inconsistent definitions and reporting
- Gastrointestinal events
  - meta-analyses not conducted as reporting across studies was insufficient to allow meaningful analyses

Anmerkung/Fazit der Autoren

Although weight reduction is seen with all GLP-1 RA's, only the once-weekly agents, exenatide LAR and dulaglutide, demonstrate significant HbA1c reductions when compared to basal insulins.

De Buitléir C et al., 2021 [16].

Efficacy and safety of a sodium-glucose co-transporter-2 inhibitor versus placebo as an add-on therapy for people with type 2 diabetes inadequately treated with metformin and a dipeptidyl peptidase-4 inhibitor: a systematic review and metaanalysis of randomised controlled trials.

Fragestellung

to assess the efficacy, safety and tolerability of sodium-glucose co-transporter-2 inhibitors vs placebo as add-on therapy after metformin and dipeptidyl peptidase-4 inhibitor dual therapy in type 2 diabetes.

Methodik

Population:

- People with type 2 diabetes

Intervention/Komparator:

- sodium-glucose cotransporter-2 inhibitors vs placebo as add-on therapy after metformin and dipeptidyl peptidase-4 inhibitor therapy

Endpunkte:

- HbA1c, fasting plasma glucose (FPG), 2-h postprandial glucose, weight, and blood pressure, safety outcomes

Recherche/Suchzeitraum:

- PubMed, www.clinicaltrials.gov and Cochrane Central Register of Controlled Trials up until 14 August 2020

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Six randomised controlled trials (1661 participants)

Charakteristika der Population:

- The percentage of female participants ranged from 35.5% to 56.3%, with the mean age ranging from 54.3 to 59.7 years, and the mean duration of diabetes ranging from ≤1 year to 11.6 years. The mean baseline HbA1c ranged from 63 mmol/mol (7.9%) to 69 mmol/mol (8.5%)

Qualität der Studien:

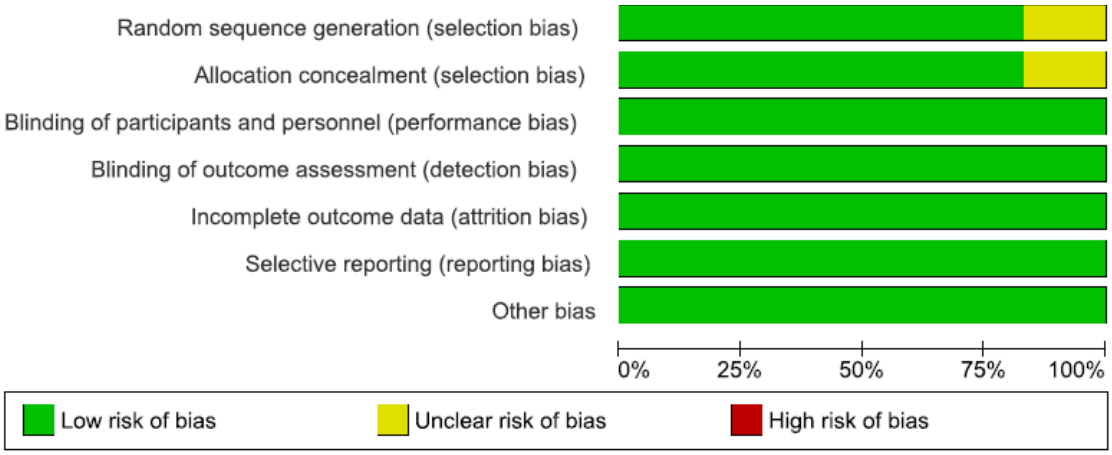


FIGURE 2 Risk-of-bias graph: review authors' judgements about each risk-of-bias item presented as percentages across all included studies

Studienergebnisse:

- Compared with placebo, sodium-glucose co-transporter-2 inhibitor treatment, as add-on to metformin and dipeptidyl peptidase-4 inhibitor therapy, was associated with a significant reduction in HbA1c level [mean difference –8 mmol/mol, 95% CI –10, –6 (–0.7%, 95% CI –0.9, –0.6); P < 0.00001], in fasting plasma glucose level [mean difference –1.70 mmol/l, 95% CI –1.91, –1.49; P < 0.00001], in weight (mean difference –1.76 kg, 95% CI –2.04, –1.48; P < 0.00001) and in blood pressure (systolic blood pressure: mean difference –3.6 mmHg, 95% CI –4.8, –2.4; P < 0.00001; diastolic blood pressure: mean difference –1.5 mmHg; 95% CI –2.4, –0.6; P = 0.002).
- Genital mycotic infections (odds ratio 7.37, 95% CI 3.06, 17.76; P < 0.00001) were more common with sodium-glucose co-transporter-2 inhibitors, but there was no significant statistical difference in urinary tract infections (odds ratio 1.16, 95% CI 0.63, 2.13; P = 0.64), in hypoglycaemia (odds ratio 1.36, 95% CI 0.61, 3.04; P = 0.45), or in discontinuation rates due to adverse events (odds ratio 1.52, 95% CI 0.78, 2.97; P = 0.22) between the two groups.

Anmerkung/Fazit der Autoren

In summary, this systematic review and meta-analysis showed that, in comparison with placebo, add-on therapy with an SGLT2 inhibitor is significantly more effective in lowering HbA1c, FPG, weight, and blood pressure in people with type 2 diabetes and inadequate glycaemic control on metformin and a DPP-4 inhibitor. Importantly, more participants achieved HbA1c levels <53 mmol/mol (7%) with add-on therapy of SGLT2 inhibitor than placebo. Discontinuation due to adverse events was similar despite higher risk of genital mycotic infections.

Kommentare zum Review

- Siehe auch: Molugulu et al., 2017 [89] - Conclusion: The combined therapy of SGLT2 inhibitor and metformin is more effective in HbA1c reduction and weight reduction as compared to monotherapy using metformin alone. (intervention: SGLT2 inhibitor+metformin, comparison: placebo + metformin / metformin)

Escobar C et al., 2021 [22].

SGLT2 inhibitors and GLP1 agonists administered without metformin compared to other glucose-lplowering drugs in patients with type 2 diabetes mellitus to prevent cardiovascular events: A systematic review.

Fragestellung

To assess the efficacy of glucagon-like peptide-1 receptor agonists (GLP1-RAs) and sodium-glucose co-transporter 2 (SGLT2) inhibitors, administered without metformin on cardiovascular outcomes in type 2 diabetes patients.

Methodik

Population:

- adult type 2 diabetes patients

Intervention/Komparator

- SGLT2 inhibitors, and GLP1-RAs not combined with metformin

Komparator:

- other glucose-lowering drugs (including metformin)

Endpunkte:

- cardiovascular outcomes presented individually like myocardial infarction, stroke, heart failure, ischemic heart disease, cardiovascular mortality and all-cause mortality.

Recherche/Suchzeitraum:

- EMBASE (February 2019), the Cochrane Central Registry of Controlled Trials (CENTRAL) and MEDLINE (through PubMed), up to 6th November 2020

Qualitätsbewertung der Studien:

- Cochrane Risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 5 RCTs

Charakteristika der Studien/Population:

- 3 studies assessed a GLP1-RA (LEADER, liraglutide; EXSCEL, exenatide and HARMONY, albiglutide) and 2 studies a SGLT2 inhibitor (EMPA-REG, empagliflozin and CANVAS, canagliflozin).
- The trials included a total of 50,725 participants, of whom 10,013 did not receive metformin. More than a half of participants had type 2 diabetes for 10 or more years and more than two-thirds of them had a history of MACE or cardiovascular risk factors (from 65% to 99.9%). The mean age of the participants was 64 years old and between 64% and 71% of patients were men
- Follow-up varied across trials, from 1.6 years in HARMONY study to 7 years in EXSCEL.
- The intervention group received a GLP1-RA or a SGLT2 inhibitor and were compared with placebo. All groups received standard plus other glucose-lowering drugs at baseline, except for a subgroup of patients in the LEADER study that did not receive any other glucose-lowering drugs.

Qualität der Studien:

- Although we rated the five included RCTs as having a low RoB since randomization was not stratified by metformin use in any of the trials and it is unknown whether all risk factors were balanced in the studied subgroup population not taking metformin, we considered that the risk of selection bias was unclear. In consequence, we rated the global RoB of the included studies as moderate.

Studienergebnisse:

Outcomes	Anticipated absolute effects* (95% CI) Risk with other treatments	Risk with GLP1-RAs without metformin	Relative effect (95% CI)	N participants (studies)	Certainty of the evidence[a,b] (GRADE)
SGLT2 inhibitors without metformin compared to placebo for prevention of cardiovascular events					
MACE	165 per 1000	85 per 1000 (72–101)	HR 0.68 (0.57–0.81)	5141 (2 RCTs[3,25,26])	⨁⨁◯◯ LOW
Cardiovascular death	88 per 1000	44 per 1000 (50–64)	HR 0.50 (0.34–0.72)	1827 (1 RCT[3,26])	⨁⨁⨁◯ VERY LOW
First occurrence of stroke	78 per 1000	17 per 1000 (10–28)	HR 0.22 (0.13–0.36)	1827 (1 RCT[3,26])	⨁⨁⨁◯ VERY LOW
GLP1-RAs without metformin compared to placebo for prevention of cardiovascular events					
MACE	165 per 1000	132 per 1000 (117–147)	HR 0.80 (0.71–0.89)	6951 (3 RCTs[8,11,33])	⨁⨁◯◯ LOW
All cause of death	148 per 1000	121 per 1000 (98–149)	HR 0.82 (0.66–1.01)	2200 (1 RCT[33])	⨁⨁⨁◯ VERY LOW
Cardiovascular death	94 per 1000	75 per 1000 (56–100)	HR 0.80 (0.60–1.06)	2092 (1 RCT[33])	⨁⨁⨁◯ VERY LOW
Non-fatal myocardial infarction	87 per 1000	65 per 1000 (49–88)	HR 0.75 (0.56–1.01)	2195 (1 RCT[33])	⨁⨁⨁◯ VERY LOW
Non-fatal stroke	46 per 1000	30 per 1000 (19–46)	HR 0.65 (0.42–100)	2198 (1 RCT[33])	⨁⨁⨁◯ VERY LOW
Cerebrovascular disease (Albiglutide)	120 per 1000	93 per 1000 (73–117)	HR 0.75 (0.58–0.97)	2495 (1 RCT[33])	⨁⨁⨁◯ VERY LOW
Hospitalization for instable angina	27 per 1000	29 per 1000 (18–48)	HR 1.07 (0.66–1.76)	2211 (1 RCT[33])	⨁⨁⨁◯ VERY LOW
Hospitalization for heart failure	83 per 1000	66 per 1000 (49–89)	HR 0.80 (0.59–1.07)	2208 (1 RCT[33])	⨁⨁⨁◯ VERY LOW

GRADE Working Group grades of evidence: High certainty: We are greatly confident that the true effect; Moderate certainty: We are moderately confident in the effect estimate; Low certainty: Our confidence in the effect estimate is limited; Very low certainty: We have very little confidence in the effect estimate.

CI: confidence interval; HR: hazard ratio.

[a]The certainty of the evidence was low due to the risk of bias of the studies and indirectness.

[b]The certainty of the evidence was very low due to the risk of bias of the studies, imprecision in the results and indirectness.

Anmerkung/Fazit der Autoren

SGLT2 inhibitors and GLP1-RAs provided without metformin at baseline may reduce the risk of MACE in comparison with placebo in type 2 diabetes patients at increased risk of cardiovascular events.

Fernandes GC et al., 2021 [25].

Association of SGLT2 inhibitors with arrhythmias and sudden cardiac death in patients with type 2 diabetes or heart failure: A meta-analysis of 34 randomized controlled trials

Fragestellung

to perform a systematic review of the literature and meta-analysis of arrhythmia endpoints in randomized controlled trials of SGLT2is use for T2DM or HF.

Methodik

Population:

- adult patients older than 18 years with diagnosed type 2 diabetes, HF, or both

Intervention:

- SGLT2i

Komparator:

- Placebo or active control

Endpunkte:

- incident atrial arrhythmias (atrial fibrillation and atrial flutter), incident ventricular arrhythmias (ventricular tachycardia, ventricular fibrillation, ventricular flutter, ventricular arrhythmia, and torsades de pointes), SCD (sudden cardiac death, sudden death, and cardiac arrest; as these diagnoses may represent different mechanisms and were not adjudicated, data for this outcome are presented individually for each component and cumulatively), and cumulative incidence of events

Recherche/Suchzeitraum:

- MEDLINE (via PubMed) and ClinicalTrials.gov
- The database search was performed on December 31, 2020.

Qualitätsbewertung der Studien:

- Cochrane tool for assessing risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 34 randomized trials, 25 placebo-controlled and 9 active-controlled, totaling 63,166 patients: 35,883 (56.8%) in the SGLT2i group and 27,273 (43.2%) in the control group.

Charakteristika der Population:

- Follow-up ranged from 24 weeks to 5.7 years, providing 177,087 patient-years. The mean age ranged from 53 to 67 years; 63% were male and 75% white.
- SGLT2is used were dapagliflozin (11 studies, 25,210 patients), canagliflozin (10 studies, 19,732 patients), empagliflozin (9 studies, 12,066 patients) and ertugliflozin (4 studies, 3158 patients). The study population had T2DM for all studies except for 1, DAPA-HF,3 which included patients with symptomatic HF and ejection fraction 40% and had 42% of patients with T2DM.
- 16/34 received background therapy

Qualität der Studien:

- There was no study with a high risk of bias.

Studienergebnisse:

Atrial arrhythmias

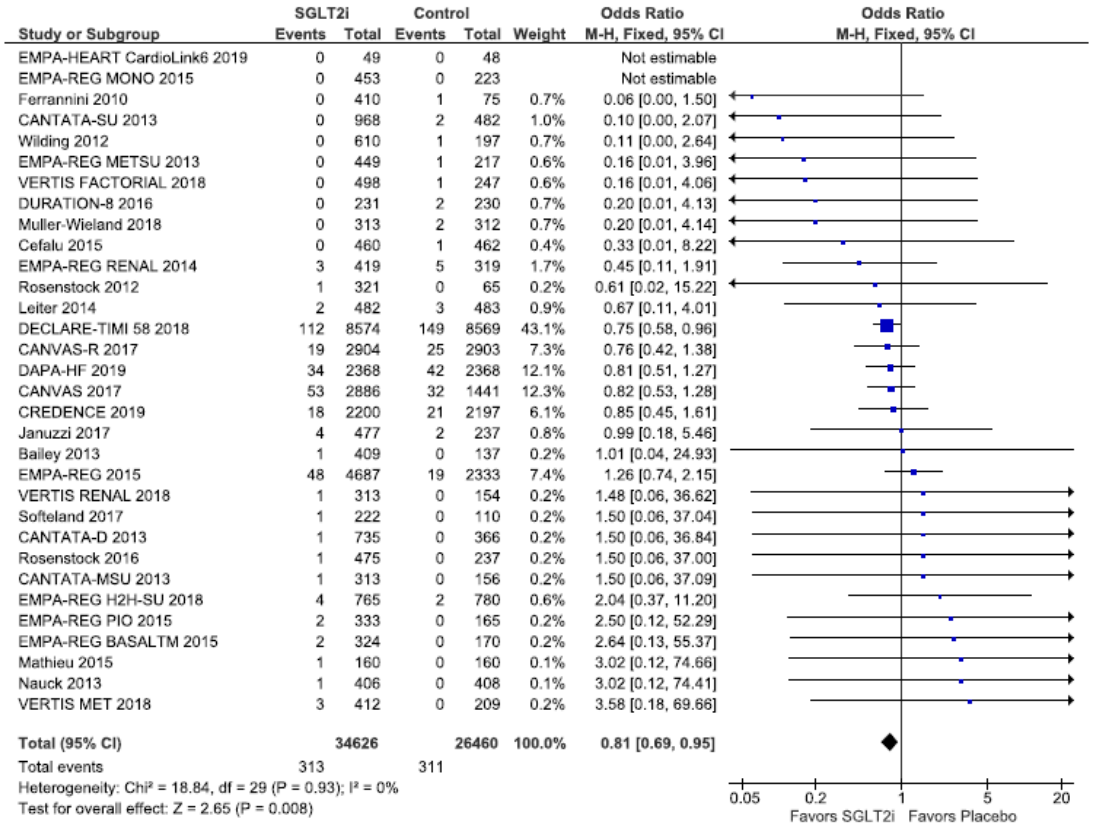


Figure 2 Incident atrial arrhythmias with sodium-glucose cotransporter 2 inhibitors (SGLT2is) vs control in patients with diabetes or heart failure. Summary statistic favors SGLT2is (odds ratio 0.81; 95% confidence interval [CI] 0.69–0.95; $P = .008$) with a significant reduction in incident atrial fibrillation or flutter compared with placebo or active control. M-H = Mantel-Haenszel.

- Subgroup analyses, including only studies of diabetes and only placebo-controlled trials, yielded results similar to overall analysis (OR 0.81; 95% CI 0.68–0.96; P 5 .01 and OR 0.82; 95% CI 0.69–0.96; P 5 .01, respectively). For the 9 active-controlled trials, there were only 7 atrial arrhythmia events in the SGLT2i group and 7 in the control group.
- In subgroup analysis based on SGLT2i used, only dapagliflozin was associated with a significantly reduced risk of atrial arrhythmias (OR 0.74; 95% CI 0.60–0.91; P 5 .005).

Ventricular arrhythmias and SCD

- The risk of incident ventricular arrhythmias was not significantly different between SGLT2is and control. In subgroup analysis, there were 4 trials in the canagliflozin group and 5 trials in each dapagliflozin and empagliflozin groups, and all showed no significant differences between treatment and control groups
- SGLT2i treatment was associated with a significant 28% relative reduction in the odds of the SCD component of this variable when compared with placebo (OR 0.72; 95% CI 0.54–0.97; P 5 .03). The overall analysis of the composite SCD outcome demonstrated no significant difference.

Anmerkung/Fazit der Autoren

SGLT2is are associated with a significantly reduced risk of incident atrial arrhythmias and may be associated with a reduced risk of SCD in patients with type 2 diabetes. More specifically designed studies are needed to confirm these benefits in patients with type 2 diabetes and, in particular, HF. Prospective trials are warranted to confirm the antiarrhythmic effect of SGLT2is and to investigate whether this is related to improvement in HF and a class or drug-specific effect.

Gebrie D., et al., 2021 [26].

Cardiovascular safety and efficacy of metformin-SGLT2i versus metformin-sulfonylureas in type 2 diabetes: systematic review and meta-analysis of randomized controlled trials.

Fragestellung

to compare the cardiovascular safety and efficacy of combination therapy of metformin-SGLT2Is and metformin-sulfonylureas in patients with T2DM.

Methodik

Population:

- Patients with T2DM

Intervention:

- A combination of metformin with any of the SGLT2Is, which could be dapagliflozin, canagliflozin, empagliflozin, or ertugliflozin

Komparator:

- A combination of metformin with any of sulfonylureas compounds, which could be gliclazide, glipizide, glyburide, glibenclamide, or glimepiride.

Endpunkte:

- All-cause mortality, Serious adverse events (SAEs), Cardiovascular mortality, Non-fatal myocardial infarction, Non-fatal stroke, Hypoglycemia, Changes in HbA1c, Change in body weight, Changes in fasting plasma glucose (FPG), Changes in systolic blood pressure (SBP), Changes in diastolic blood pressure (DBP), Changes in low-density lipoprotein cholesterol (LDL-C), Changes in high-density lipoprotein cholesterol (HDL-C)

Recherche/Suchzeitraum:

- MEDLINE, PubMed, Embase, The Cochrane Library and ClinicalTtrials.gov up to 15 August 2019

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 RCTs with 10,974 patients

Charakteristika der Population:

- patients with T2DM who were in either of the two combination therapies at least for a year

Qualität der Studien:

- The studies were found to be “low risk of bias”

Studienergebnisse:

- The pooled analysis showed no significant difference in all-cause mortality (risk ration [RR] = 0.93, 95% CI [0.52, 1.67]), serious adverse events (RR = 0.96, 95% CI [0.79, 1.17]) and adverse events (RR = 1.00, 95% CI [0.99, 1.02]) between the two, but in hypoglycemia (RR = 0.13, 95% CI [0.10, 0.17], $P < 0.001$).

- Participants taking metformin-sodium glucose cotransporter-2 inhibitors showed a significantly greater reduction in HbA1c (mean difference [MD] = − 0.10%, 95% CI [− 0.17, − 0.03], body weight (MD = − 4.57 kg, 95% CI [− 4.74, − 4.39], systolic blood pressure (MD = − 4.77 mmHg, 95% CI [− 5.39, − 4.16]), diastolic blood pressure (MD = − 2.07 mmHg, 95% CI [− 2.74, − 1.40], and fasting plasma glucose (MD = − 0.55 mmol/L, 95% CI [− 0.69, − 0.41]), $p < 0.001$.

Anmerkung/Fazit der Autoren

Combination therapy of metformin and sodium-glucose cotransporter-2 inhibitors are a safe and efficacious alternative to combination therapy of metformin and sulfonylureas for patients with T2DM who are at risk of cardiovascular comorbidity. However, there remains a need for additional long-term randomized controlled trials as available studies are very limited and heterogeneous.

Li C et al., 2021 [69].

Sodium-glucose co-transporter-2 inhibition and ocular outcomes in patients with type 2 diabetes: A systematic review and meta-analysis.

Fragestellung

To assess SGLT2 inhibitors versus placebo on DR or other ocular events in adults with type 2 diabetes.

Methodik

Population:

- Adults with type 2 diabetes

Intervention:

- SGLT2 inhibitors

Komparator:

- Placebo

Endpunkte:

- eye-related adverse events (AEs)

Recherche/Suchzeitraum:

- MEDLINE and EMBASE for the period from database inception date to October 11, 2019

Qualitätsbewertung der Studien:

- Cochrane risk-of-bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 studies, involving 39 982 patients with a mean follow-up of 2.8 years

Charakteristika der Population:

TABLE 1 Baseline characteristics of included randomized placebo-controlled trials and trial participants

First author (year)	Name	Intervention	Background treatments (%)	No	Age, years	Male, %	Median follow-up, weeks	HbA1c, mmol/mol	Duration of diabetes, years	History of retinopathy, %
Zinman[4] (2015)	EMPA-REG OUTCOME	Empagliflozin, 10/25 mg	Insulin (48.2); sulphonylureas (42.8); metformin (74.0); TZD (4.3); GLP-1 (2.8); DPP-4 (11.3); RAAS (80.7); beta-blockers (64.9); statins (77.0)	7020	63	71.5	161.8	65.0	>10 57.1%	22.0
Neal[5] (2017)	CANVAS Program	Canagliflozin, 100/300 mg	Insulin (50.2); sulphonylureas (43.0); metformin (77.2); TZD (4.9); GLP-1 (4.0); DPP-4 (12.4); antithrombotic (73.6); RAAS (80.0); beta-blockers (53.5); statins (74.9)	10 142	63	64.2	126.1	66.1	13.5	21.0
Perkovic[6] (2019)	CREDENCE	Canagliflozin, 100 mg	Insulin (65.5); sulphonylureas (28.8); metformin (57.8); GLP-1 (4.2); DPP-4 (17.1); TZD (3.1); antithrombotic (59.6); RAAS (99.9); beta-blockers (40.2); statins (69.0)	4401	63	66.1	136.7	67.2	15.8	42.8
Wiviott[7] (2019)	DECLARE-TIMI 58	Dapagliflozin, 10 mg	Insulin (40.9); sulphonylureas (42.7); metformin (82.0); TZD (0); GLP-1 (4.4); DPP-4 (16.8); antiplatelet agents (61.1); RAAS (81.3); beta-blockers (52.6%); statins/ezetimibe (75.0)	17 160	64	62.6	219.2	67.2	11.0	NR
Kashiwagi[8] (2015–1)	EMIT	Ipragliflozin, 50	Sulphonylureas (100); RAAS (NR); beta-blockers (NR); statins/ezetimibe (NR)	245	60	65.8	24.0	68.3	10.5	NR
Kashiwagi[9] (2015–2)	SPOTLIGHT	Ipragliflozin, 50 mg	Pioglitazone (100); RAAS (NR); beta-blockers (NR); statins/ezetimibe (NR)	152	56	74.2	24.0	67.2	6.8	NR
Inagaki[10] (2016)	NR	Canagliflozin, 100 mg	Insulin (100); RAAS (NR); beta-blockers (NR); statins/ezetimibe (NR)	146	58	63.7	16.0	73.8	13.8	41.8
Yang[11] (2016)	NR	Dapagliflozin, 5/10 mg	Metformin (100); RAAS (NR); beta-comblockers (NR); statin/ezetimibe (NR)	444	54	54.3	24.0	65.0	4.9	NR
Yang[12] (2018)	NR	Dapagliflozin 10 mg	Insulin (100); sulphonylureas (11.0); metformin (45.2); TZD (4.0); GLP-1 (NR); DPP-4 (5.5); RAAS (NR); beta-blockers (13.6); statins/ezetimibe (NR)	272	58	47.8	24.0	69.4	12.5	NR

Abbreviations: CANVAS Program, Canagliflozin Cardiovascular Assessment Program; CREDENCE, Canagliflozin and Renal Endpoints in Diabetes with Established Nephropathy Clinical Evaluation Trial; DECLARE-TIMI 58, Dapagliflozin Effect on Cardiovascular Events Trial; EMPA-REG Outcome, Empagliflozin Cardiovascular Outcome Event Trial in Type 2 diabetes Mellitus; EMIT study, A Study to Assess the Efficacy and Safety of ASP1941 in Combination With Sulphonylurea in Type 2 Diabetic Patients; SPOTLIGHT, A Study to Assess the Efficacy and Safety of ASP1941 in Combination With Pioglitazone in Type 2 Diabetic Patients; TZD, thiazolidinediones; GLP-1, glucagon-like peptide-1; DPP-4, dipeptidyl peptidase-4; RAAS, renin angiotensin aldosterone system; HbA1c, glycated haemoglobin; NR, not reported.
Participants are included in the intention-to-treat analysis. Values for age, gender, HbA1c and duration of diabetes are mean.

Qualität der Studien:

- Trials were generally of high quality

Studienergebnisse:

- There were 1414 total ocular events, of which 624 were retinopathy events.
- SGLT2 inhibition was not associated with a change in the risk of total ocular events (RR 0.97, 95% CI 0.85, 1.11) or retinopathy (RR 0.98, 95% CI 0.84, 1.16), with consistent effects across studies (P for heterogeneity = 0.35 and 0.45, respectively).

Anmerkung/Fazit der Autoren

In conclusion, the use of SGLT2 inhibitors, as compared to placebo, was not associated with an increase or decrease in the risk of total ocular events or retinopathy in patients with type 2 diabetes.

Coelho F., et al., 2020 [13].

Effects of sodium-glucose co-transporter 2 inhibitors on liver parameters and steatosis: A meta-analysis of randomized clinical trials.

Fragestellung

to summarize the evidence on the effects of sodium-glucose co-transporter 2 (SGLT2) inhibitors on liver structure and function.

Methodik

Population:

- Patients with T2D

Intervention/Komparator:

- SGLT2 inhibitors with placebo or other oral antidiabetic drugs

Endpunkte:

- liver function and/or structure

Recherche/Suchzeitraum:

- PubMed, Web of Science and ClinicalTrials.gov from their inception to April 2019

Qualitätsbewertung der Studien:

- Cochrane Collaboration's risk of bias assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- Twenty studies. A total of 1950 patients with T2D, with or without NAFLD, were treated with SGLT2 inhibitors for at least 8 weeks, and 1900 patients were used as controls.

Charakteristika der Population:

- Five studies only included participants with NAFLD

Qualität der Studien:

- 9 studies were considered of Good Quality by the Cochrane Collaboration's risk of bias assessment tool while the remaining eleven were considered of Fair Quality.

Studienergebnisse:

- SGLT2 inhibitors induced a significant decrease in serum alanine (-7.43U/ L, [95%CI -12.14, - 2.71], $p < 0.01$), in aspartate aminotransferases (- 2.83U/L, [- 4.71, - 0.95], $p < 0.01$), as well as in gamma glutamyl transferase (- 8.21U/L, [- 9.52,-6.91], $p < 0.01$), and an increase in total plasma bilirubin (8.19% [0.79, 15.59], $p < 0.01$), comparing with placebo or other oral antidiabetic drugs.
- SGLT2 inhibitors treatment was associated with a decrease in liver steatosis (- 3.39% [-6.01, - 0.77], $p < 0.0.1$).

Anmerkung/Fazit der Autoren

In conclusion, SGLT2 inhibitors seem to improve hepatic function and structure. Further prospective and randomized clinical trials are needed, particularly in patients with NAFLD, in order to evaluate the efficacy and safety of these drugs. Validation of SGLT2 inhibitors as an effective pharmacological approach to NAFLD may result in a paradigm shift with positive prognostic changes for this pathology, which is now considered the most common liver disease in developed countries.

Ding L et al., 2020 [20].

Comparing the Efficacy and Safety of Glucagon-Like Peptide 1 Receptor Agonists with Sodium-Glucose Cotransporter 2 Inhibitors for Obese Type 2 Diabetes Patients Uncontrolled on Metformin: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Fragestellung

This study aims to conduct a systematic review and meta-analysis of RCTs to compare the efficacy and safety outcomes of GLP-1RAs and SGLT-2is for obese T2D patients uncontrolled on metformin.

Methodik

Population:

- T2D patients who showed inadequate response to stable and optimized metformin monotherapy, with a body mass index ≥30 kg/m2

Intervention/Komparator:

- GLP-1 RAs vs SGLT-2is

Endpunkte:

- Primary outcome: mean change from baseline in HbA1c.
- Secondary outcomes: the mean change from baseline in fasting blood glucose (FBG), PBG, and bodyweight. Safety outcomes were overall adverse events (AEs) and AEs of specific interest including hypoglycemia, urinary tract infections, and gastrointestinal events

Recherche/Suchzeitraum:

- PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Ovid, and Web of Science
- until 14 May 2020

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool; GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 RCTs enrolling 2066 obese T2D patients

Charakteristika der Population:

- The mean age of participants (range from 54 to 58 years), the proportion of women (range from 43% to 52%), and the mean length of diabetes (range from 7.1 to 7.7 years) were similar across three RCTs. The follow-up time ranged from 26 to 52 weeks. And the mean baseline HbA1c ranged from 8.1 to 9.3%. Of all the 2066 participants, 48.5% were female and most of them were white.
- Two classes of long-acting GLP-1RAs were evaluated: semaglutide (orally 14 mg/week, subcutaneously 1 mg/week) and exenatide (subcutaneously 2 mg/week)
- Three classes of orally SGLT-2is were examined: empagliflozin (25 mg/day), canagliflozin (300 mg/day), and dapagliflozin (10 mg/day).

Qualität der Studien:

Study	Random sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective reporting	Other bias	Bias risk
Rodbard 2019	Yes	Yes	No	Yes	No	Unclear	B
Lingvay 2019	Yes	Yes	Yes	Yes	No	Unclear	A
Jabbour 2018	Yes	Yes	Yes	Yes	No	Unclear	A

A indicates low risk, B indicates unclear, C indicates high risk.

Studienergebnisse:

Table 2: Summary of findings and strength of evidence.

Outcome	Studies (patients)	Mean differences/relative effect (95% CI)	I^2	Certainty of the evidence
HbA1c (%)	3 (2066)	MD: −0.40 (−0.54, −0.25)	44%	Low[1,2]
FBG (mmol/L)	3 (2066)	MD: −0.17 (−0.31, −0.04)	0	Low[1,2]
PBG (mmol/L)	2 (1609)	MD: −0.32 (−0.49, −0.14)	44%	Low[1,2]
Bodyweight (kg)	3 (2066)	MD: −0.26 (−0.93, 0.42)	77%	Very Low[1,2,3]
Adverse events	3 (2068)	RR: 1.03 (0.98, 1.09)	0	Low[1,2]
Hypoglycemia	2 (1605)	RR: 1.38 (0.96, 1.98)	35%	Low[1,2]
Urinary tract infections	2 (1249)	RR: 0.98 (0.60, 1.58)	0	Moderate[2]
Gastrointestinal events	2 (1249)	RR: 1.62 (1.37, 1.93)	0	Moderate[2]

HbA1c: glycated haemoglobin, FBG: fasting blood glucose, PBG: postprandial blood glucose, CI: confidence interval, RR, risk ratio; MD, mean difference. [1]Study limitations for one of the trail lacked of blinding. [2]Strongly suspected publication bias for all the trials were sponsored by companies. [3]Inconsistency for substantial heterogeneity.

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- Glycemic control
  - GLP-1RAs significantly reduced HbA1c by 0.40% (95% CI: −0.54, −0.25; p < 0.00001) compared with SGLT-2is.

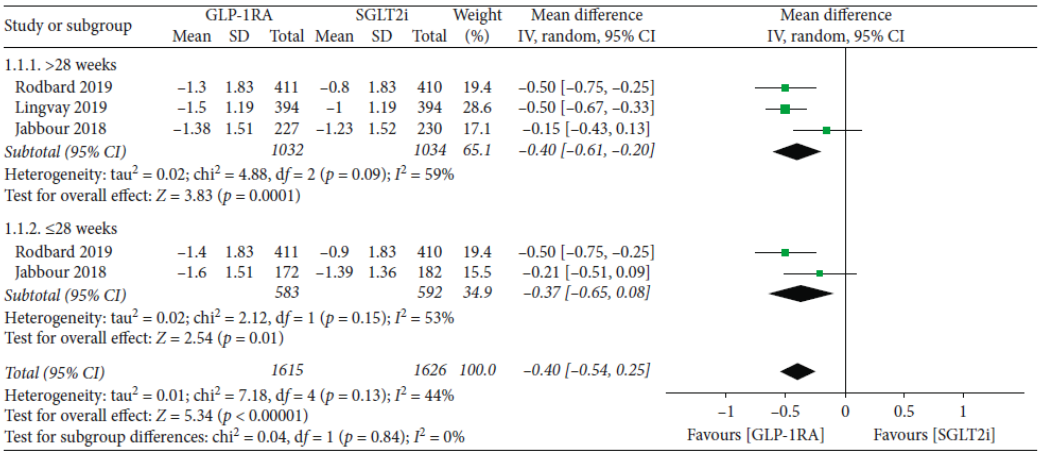

Figure 2: Forest plot for meta-analyses comparing the effect of GLP-1RAs with SGLT-2is in HbA1c. GLP-1RAs: glucagon-like peptide 1 receptor agonists, SGLT-2is: sodium-glucose cotransporter 2 inhibitors, HbA1c: glycated haemoglobin, CI: confidence interval, SD: standard deviation.

  -
  - FBG and PBG were also detected, and both of them showed significant decreases in GLP-1RAs treatment compared with SGLT-2is. GLP-1Ras lowered FBG by 0.17 mmol/L (95% CI: −0.31, −0.04; p = 0.01), and reduced PBG by 0.32 mmol/L (95% CI: −0.49, −0.14; p = 0.0003) compared with SGLT-2is.
- Body weight
  - Pooled results of the mean change of bodyweight from baseline showed no significant difference between the treatment of GLP-1RAs and SGLT-2is with a substantial heterogeneity (I2 = 77%). However, restricting the analysis to the class of semaglutide of GLP-1RAs revealed a significant reduction of bodyweight by 0.75 kg (95% CI: −1.18, −0.31; p = 0.0007) compared with SGLT-2is
- Adverse events
  - The overall occurrence of AEs was not significantly different between the treatment of GLP-1RAs and SGLT-2is. Some AEs of specific interest were also detected. No statistically significant differences were found in the occurrence of hypoglycaemia and urinary tract between GLP-1RAs and SGLT-2is group, while the occurrence of gastrointestinal events was higher in GLP-1RAs compared with that in SGLT-2is (RR: 1.62; 95% CI: 1.37, 1.93; p < 0.00001).

Anmerkung/Fazit der Autoren

To sum up, the study highlighted that GLP-1RAs are superior to SGLT-2is in the treatment for obese T2D patients uncontrolled on metformin in glycemic control without an increase

in total AEs except for a higher occurrence in gastrointestinal events. Weight loss benefit was shown in the treatment of semaglutide. Future large longer-term followup clinical trials are needed to provide more evidence about the sustainable effects and safety of GLP-1RAs compared with SGLT-2is.

Katsiki N et al., 2020 [67].

Fixed-dose combination of empagliflozin and linagliptin for the treatment of patients with type 2 diabetes mellitus: A systematic review and meta-analysis

Fragestellung

The present meta-analysis evaluated the efficacy and safety of empagliflozin + linagliptin combination compared with either monotherapy.

Methodik

Population:

- patients with T2DM aged ≥18 years

Intervention:

empagliflozin + linagliptin

Komparator:

- Either drug alone (empagliflozin or linagliptin)

Endpunkte:

- change in FPG, HBA1c, weight, BMI, SBP and DBP

Recherche/Suchzeitraum:

- Medline, Embase, CINAHL, PsycINFO and Cochrane CENTRAL,
- until October 20, 2019

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool for randomized trials

Ergebnisse

Anzahl eingeschlossener Studien:

- six RCTs (n = 2857 patients)

Charakteristika der Population:

- The studies altogether enrolled 2,857 patients with T2DM aged ≥18 years on diet + exercise ± metformin.
- Across all studies, the mean age of the patients ranged from 54.6 to 59.9 years, 39.7% of the participants were women and 47.6% had been diagnosed over 5 years prior to their enrolment in the RCTs. Empagliflozin + linagliptin combination was administered as a fixed-dose regimen (in 2 trials) or free combination (in 4 trials).

Qualität der Studien:

Supplementary Table 2. Quality of bias assessment of the included studies according to the Cochrane guidelines.

First Author, Year of Publication	Random Sequence Generation	Allocation Concealment	Selective Reporting	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Other Bias
Søfteland 2017	L	L	L	H	L	H	L
Kawamori 2017	L	L	L	L	L	L	L
Kaku 2019	L	H	L	L	L	L	L
Tinahones 2017	L	L	L	L	L	L	H
Lewin 2015	L	L	L	L	L	H	L
DeFronzo 2015	L	L	L	L	L	L	L

- L, low risk of bias; H, high risk of bias; U, unclear risk of bias.

Studienergebnisse:

- Significantly higher reductions in HbA1c, body weight and fasting plasma glucose (FPG) were observed with the combination therapy (either empagliflozin 10 mg + linagliptin 5 mg or empagliflozin 25 mg + linagliptin 5 mg) compared with linagliptin 5 mg over 24 weeks.
- Furthermore, HbA1c and FPG were significantly more decreased with the combination (either empagliflozin 10 mg + linagliptin 5 mg or empagliflozin 25 mg + linagliptin 5 mg) compared with empagliflozin (10 or 25 mg) monotherapy; body weight was lowered equally.
- Patients with T2DM on combination therapy had a significantly greater likelihood of attaining HbA1c <7% over 24 weeks than those on monotherapies.
- In relation to blood pressure (BP), with empagliflozin 10 mg + linagliptin 5 mg systolic BP was lower than with linagliptin 5 mg, but the difference fell just short of statistical significance (P = 0.084, Table 1), probably because of the rather large heterogeneity (I2 = 61%).
- Furthermore, no differences were found in adverse events between the combination and monotherapy groups. The findings were robust to leave-one-out sensitivity analyses.

TABLE 1 Pooled results comparing empagliflozin + linagliptin fixed dose combination with linagliptin or empagliflozin monotherapies over 24 weeks

Outcomes	Summary of studies	Empagliflozin 10 mg + linagliptin 5 mg vs. linagliptin 5 mg	Empagliflozin 25 mg + linagliptin 5 mg vs. linagliptin 5 mg	Empagliflozin 10 mg + linagliptin 5 mg vs. empagliflozin 10 mg	Empagliflozin 25 mg + linagliptin 5 mg vs. empagliflozin 25 mg
HbA1c (%)	No. of studies pooled	4	3	4	3
	Sample size	561/462	378/371	500/505	379/380
	WMD (95% CI)	[−0.72 (−1.04, −0.40), $P < 0.001$; $I^2 = 90.0\%$]	[−0.52 (−0.68, −0.37), $P < 0.001$; $I^2 = 43.0\%$]	[−0.50 (−0.73, −0.26), $P < 0.001$; $I^2 = 85.4\%$]	[−0.40 (−0.66, −0.14), $P < 0.001$; $I^2 = 82.2\%$]
Percentage of patients with HbA1c ≥7% at baseline who achieve HbA1c <7%	No. of studies pooled	4	3	4	3
	Sample size	561/462	378/371	500/505	379/380
	OR (95% CI)	[3.89 (2.79, 5.41), $P < 0.001$; $I^2 = 0.0\%$]	[3.20 (2.25, 4.55), $P < 0.001$; $I^2 = 0.0\%$]	[3.70 (2.58, 5.32), $P < 0.001$; $I^2 = 0.0\%$]	[3.18 (1.81, 5.59), $P < 0.001$: $I^2 = 58.9\%$]
Weight (kg)	No. of studies pooled	4	3	3	3
	Sample size	561/462	378/371	393/397	379/380
	WMD (95% CI)	[−2.08 (−2.62, −1.53), $P < 0.001$; $I^2 = 55.7\%$]	[−1.96 (−2.59, −1.33), $P < 0.001$ $I^2 = 37.4\%$]	[0.07 (−0.57, 0.71), $P = 0.826$; $I^2 = 43.1\%$]	[0.00 (−0.47, 0.48), $I^2 = 43.1\%$]
Fasting plasma glucose (mmol/L)	No. of studies pooled	4	3	4	3
	Sample size	561/462	378/371	500/505	379/380
	WMD (95% CI)	[−1.60 (−2.21, −1.00), $P < 0.001$; $I^2 = 88.1\%$]	[−1.52 (−2.02, −1.02), $P < 0.001$; $I^2 = 74.7\%$]	[−0.60 (−0.78, −0.41), $P < 0.001$; $I^2 = 0.0\%$]	[−0.54 (−0.93, −0.15), $P < 0.001$; $I^2 = 61.5\%$]
Systolic blood pressure (mmHg)	No. of studies pooled	2	—[a]	2	—[a]
	Sample size	291/201		229/231	
	WMD (95% CI)	[−3.02 (−6.45, 0.41), $P = 0.084$; $I^2 = 61.0\%$]		[−1.24 (−3.26, 0.78), $P = 0.230$; $I^2 = 0.0\%$]	
Diastolic blood pressure (mmHg)	No. of studies pooled	2	—[a]	2	—[a]
	Sample size	291/201		229/231	
	WMD (95% CI)	[−0.67 (−2.04, 0.69), $P = 0.333$; $I^2 = 0.0\%$]		[−1.30 (−2.60, 0.00), $P = 0.051$, $I^2 = 0.0\%$]	
All adverse events (%)	No. of studies pooled	4	3	4	3
	Sample size	565/466	380/373	500/505	382/387
	RR (95% CI)	[0.93 (0.84, 1.03), $P = 0.163$; $I^2 = 24.5\%$]	[0.96 (0.80, 1.14), $P = 0.610$; $I^2 = 70.2\%$]	[0.91 (0.84, 1.00), $P = 0.038$; $I^2 = 0.0$]	[1.02 (0.92, 1.13), $P = 0.779$; $I^2 = 14.2\%$]
Drug-related adverse events (%)	No. of studies pooled	4	3	4	3
	Sample size	565/466	380/373	500/505	382/387
	RR (95% CI)	[1.48 (0.79, 2.77), $P = 0.223$; $I^2 = 57.2\%$]	[1.41 (0.96, 2.08), $P = 0.083$; $I^2 = 0.0\%$]	[0.95 (0.69, 1.30), $P = 0.732$; $I^2 = 0.0\%$]	[1.01 (0.67, 1.50), $P = 0.980$; $I^2 = 27.9\%$]
Adverse events leading to discontinuation (%)	No. of studies pooled	4	3	1.034	3
	Sample size	565/466	380/373	500/505	382/387
	RR (95% CI)	[1.28 (0.47, 3.46), $P = 0.632$; $I^2 = 16.0\%$]	[1.15 (0.22, 5.94), $P = 0.864$; $I^2 = 52.9\%$]	[0.69 (0.30, 1.55), $P = 0.362$; $I^2 = 29.7\%$]	[1.26 (0.59, 2.69), $P = 0.554$; $I^2 = 0.0\%$]

Confirmed hypoglycaemia (%)	No. of studies pooled	4	3	4	3
	Sample size	565/466	380/373	500/505	382/387
	RR (95% CI)	[0.55 (0.17, 1.83), $P = 0.331$ $I^2 = 0.0\%$]	[1.54 (0.50, 4.70), $P = 0.452$; $I^2 = 0.0\%$]	[0.83 (0.22, 3.12), $P = 0.629$; $I^2 = 0.0\%$]	[0.71 (0.25, 2.06), $P = 0.530$; $I^2 = 0.0\%$]
Urinary tract infections	No. of studies pooled	4	3	4	3
	Sample size	565/466	380/373	500/505	382/387
	RR (95% CI)	[1.04 (0.69, 3.47), $P = 0.866$; $I^2 = 0.0\%$]	[0.87 (0.53, 1.43), $P = 0.584$; $I^2 = 3.8\%$]	[0.96 (0.66, 1.40), $P = 0.841$; $I^2 = 0.0\%$]	[1.11 (0.72, 1.71), $I^2 = 13.6\%$]
Genital infections	No. of studies pooled	4	3	4	3
	Sample size	565/466	380/373	500/505	382/387
	RR (95% CI)	[1.53 (0.68, 1.56), $P = 0.306$; $I^2 = 0.0\%$]	[1.73 (0.77, 3.92), $P = 0.186$; $I^2 = 0.0\%$]	[0.74 (0.40, 1.38), $P = 0.342$; $I^2 = 0.0\%$]	[0.51 (0.18, 1.48), $P = 0.216$; $I^2 = 58.2\%$]

Abbreviations: CI, confidence interval; HbA1c, glycated haemoglobin; OR, odds ratio; RR, risk ratio; WMD, weighted mean difference.
[a]No pooled data (<2 studies with available data).

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Anmerkung/Fazit der Autoren

The present meta-analysis demonstrated superior efficacy and similar safety of empagliflozin (10 or 25 mg) + linagliptin 5 mg compared with empagliflozin (10 or 25 mg) or linagliptin 5 mg monotherapies in patients with T2DM inadequately controlled with diet + exercise ± metformin, facilitating the achievement of their glycaemic control. The available FDCs of these drugs (i.e. empagliflozin 10 mg + linagliptin 5 mg, empagliflozin 25 mg + linagliptin 5 mg) can simplify drug dosing regimen, decrease pill burden and enhance treatment adherence, which might represent an important therapeutic option in routine clinical practice.

Li WJ et al., 2020 [73].

SGLT2 inhibitors and atrial fibrillation in type 2 diabetes: a systematic review with meta-analysis of 16 randomized controlled trials.

Fragestellung

to pool data from all placebo-controlled RCTs that evaluated AF/AFL outcomes of SGLT2 inhibitors, from which we gained more reliable assessments of the efficacy and safety of specific results overall and in relevant subgroups.

Methodik

Population:

- Patients with type 2 diabetes

Intervention:

- SGLT2 inhibitors

Komparator:

- Placebo

Endpunkte:

- AF/AFL (the composite of new-onset and recurrent AF/AFL), all-cause mortality, HF, cerebrovascular events, and myocardial infarction, urinary tract infections, HbA1c, body weight loss, systolic blood pressure (SBP) and diastolic blood pressure (DBP).

Recherche/Suchzeitraum:

- PubMed, EMBASE and ClinicalTrials.gov) from their inception to January 2020

Qualitätsbewertung der Studien:

- Cochrane risk-of-bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 16 trials consisting of 38,335 patients

Charakteristika der Population:

- The proportion of females ranged from 33.1% to 54.4%. Among the included studies, 12 trials
- Across all sixteen studies, the median follow-up duration was 1.8 years

Qualität der Studien:

- In 16 trials, most studies were of considerably high methodological quality, indicating minimal selection bias or implementation bias. All data were considerably complete and bias from the blinding method did not appear in any of the included studies.

Studienergebnisse:

- Incorporated data demonstrated that compared to placebo, SGLT2 inhibitors significantly reduced AF/AFL (RR: 0.76; 95% CI 0.65–0.90; p = 0.001) and all-cause mortality (RR: 0.91; 95% CI 0.83–0.99; p = 0.03).

- AF/AFL reductions were not modified by age, body weight, glycated haemoglobin (HbA1c), or systolic blood pressure (SBP) at baseline (all p-interactions > 0.3).
- SGLT2 inhibitors also significantly reduced heart failure events (RR: 0.73; 95% CI 0.64–0.84; p < 0.00001), HbA1c (WMD: − 0.62%; 95% CI − 0.89 to − 0.34; p < 0.00001), body weight (WMD: − 2.12 kg; 95% CI − 2.91 to − 1.34; p < 0.00001), SBP (WMD: − 3.34 mmHg; 95% CI − 4.12 to − 2.56; p < 0.00001), and diastolic blood pressure (DBP) (WMD: − 1.11 mmHg; 95% CI − 1.62 to − 0.60; p < 0.0001).
- Of note, cerebrovascular events and myocardial infarction did not increase in patients taking SGLT2 inhibitors.

Anmerkung/Fazit der Autoren

Overall, the pleiotropic effects of SGLT2 inhibitors have a great benefit of reducing AF/AFL and all-cause mortality events in a broad type 2 diabetes population, regardless of baseline characteristics including age, HbA1c, systolic blood pressure and body weight.

Liu J, et. al., 2020 [76].

Sodium-glucose co-transporter-2 inhibitors and the risk of diabetic ketoacidosis in patients with type 2 diabetes: A systematic review and meta-analysis of randomized controlled trials.

Fragestellung

to assess the effects of sodium-glucoseco-transporter-2 (SGLT2) inhibitors on diabetic ketoacidosis (DKA) in patients with type 2 diabetes.

Methodik

Population:

- adult patients with type 2 diabetes

Intervention/Komparator:

- SGLT2 inhibitor against no additional treatment, placebo or active antidiabetic drugs

Endpunkte:

- Events of DKA

Recherche/Suchzeitraum:

- PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov from inception to 13 June 2019

Qualitätsbewertung der Studien:

- Cochrane risk-of-bias (RoB 2) tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 39 RCTs enrolling 60 580 patients

Charakteristika der Population:

- The length of follow-up ranged from 12 to 218.4 weeks (median 28 weeks), the mean age of patients ranged from 52.6 to 69.6 years, mean BMI from 24.8 to 35.6 kg/m2, mean baseline HbA1c from 6.9% (52 mmol/mol) to 9.3% (78 mmol/mol), mean FPG from 5.0 to 17.9 mmol/L and mean duration of diabetes from 1.0 to 15.9 years across trials

Qualität der Studien:

- All trials adequately generated their randomization sequence, but one did not report the concealed allocation, and no trials suggested a problem with the randomization process. Among 39 trials, 37 (94.9%) blinded patients and caregivers, the other two open-label trials suggested judgements of “some concerns”. Twenty-one (53.8%) trials had infrequent missing outcome data. All trials were free of bias in measurement of outcomes and in selection reporting. The baseline characteristics were generally balanced between treatment and control groups in each trial.

Studienergebnisse:

- SGLT2 inhibitors were statistically associated with an increased risk of DKA versus control (SGLT2 inhibitors: 62/34 961 [0.18%] vs. control: 23/25 211 [0.09%], Peto odds ratio [OR] 2.13, 95% confidence interval [CI] 1.38 to 3.27, I2 = 8%; RD 1.7 more events, 95% CI 0.6 more to 3.4 more events per 1000 over 5 years; high-quality evidence).
- Sensitivity analyses showed similar results. The subgroup analyses by mean age (interaction P = 0 .02) and length of follow-up (interaction P = 0 .03) showed a larger relative effect among older patients (aged ≥60 years) and those with longer use of SGLT2 inhibitors (>52 weeks).

Anmerkung/Fazit der Autoren

In conclusion, our study shows that SGLT2 inhibitors increase the risk of DKA in patients with type 2 diabetes with high-quality evidence. Although this drug-related DKA is probably rare and non-fatal, patients taking SGLT2 inhibitors should be fully aware of this risk, especially older patients and those with long-term use of SGLT2 inhibitors. Further real-world surveillance of DKA in patients receiving these drugs is warranted to identify those at higher risk.

Mantsiou C et al., 2020 [81].

Glucagon-like peptide-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors as combination therapy for type 2 diabetes: A systematic review and meta-analysis

Fragestellung

To evaluate the efficacy and safety of combination therapy with a GLP-1RA and an SGLT2i in patients with type 2 diabetes

Methodik

Population:

- adults with type 2 diabetes

Intervention:

- combination of a GLP-1RA and an SGLT2i (GLP-1RA/SGLT2i)

Komparator:

- placebo or an active control (including individual GLP-1RAs or SGLT2is)

Endpunkte:

- HbA1c, body weight, systolic blood pressure, diastolic blood pressure and estimated glomerular filtration rate (eGFR)
- all-cause mortality and cardiovascular mortality, and the numbers of patients who experienced at least one event of severe hypoglycaemia (as defined in each study), myocardial infarction, stroke and hospitalization for heart failure.

Recherche/Suchzeitraum:

- MEDLINE, EMBASE and the Cochrane library up to 2 December 2019

Qualitätsbewertung der Studien:

- revised Cochrane Collaboration's Risk of Bias Tool version 2.0 for change in HbA1c, body weight and systolic blood pressure
- GRADE) approach to rate the certainty of evidence in effect estimates for the three aforementioned outcomes

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 trials

Charakteristika der Studien/Population:

Comparisions

- 3 studies evaluated the combination of GLP-1RA/SGLT2i as simultaneous initiation therapy versus isolated GLP-1RA and SGLT2i.
- 3 studies compared a GLP-1RA with placebo as add-on therapy in patients already treated with an SGLT2i,
- 1 study was a post hoc subgroup analysis of the CANVAS (CANagliflozin cardioVascular Assessment Study) trial programme comparing an SGLT2i with placebo as add-on therapy in patients already treated with a GLP-1RA.

Population

- In all RCTs, patients continued receiving their background antidiabetic treatment, which was mostly metformin or metformin plus a sulphonylurea.
- Across the included trials, mean baseline HbA1c ranged from 8.0% to 8.2% in all studies, except for the DURATION-8 trial, in which mean HbA1c at baseline was 9.3%.
- Mean body weight, body mass index and systolic blood pressure at baseline ranged from 90.9 to 91.7 kg, 31.9 to 37.4 kg/m2 and 127.9 to 136.7 mmHg, respectively.
- Across all trials, mean participant's age ranged from 52.3 to 61.0 years

Qualität der Studien:

Overall risk of bias for change in HbA1c was deemed to be of some concern in three studies and low in four studies. .

GRADE Assessment:

Supplementary table S3. Summary of GRADE assessment.

Outcome	Comparator	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall
HbA_{1c}	GLP-1 RA	serious	very serious	serious	not serious	undetected	very low
	SGTL2i	serious	very serious	serious	not serious	undetected	very low
Body weight	GLP-1 RA	serious	serious	serious	not serious	undetected	very low
	SGLT2i	serious	very serious	serious	not serious	undetected	very low
Systolic blood pressure	GLP-1 RA	serious	serious	serious	not serious	undetected	very low
	SGLT2i	serious	very serious	serious	not serious	undetected	very low

Abbreviations: GLP-1 RA, glucagon-like peptide 1 receptor agonist; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; HbA_{1c}, glycated hemoglobin; SGLT2i, sodium glucose co-transporter 2 inhibitor.

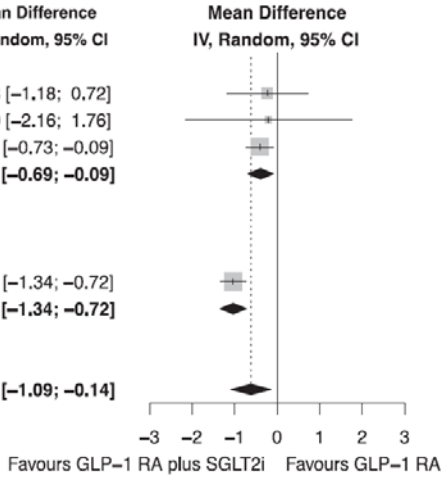
Studienergebnisse:

Change from baseline in HbA1c (%)

GLP-1RA/SGLT2i vs GLP-1RA:

(A)

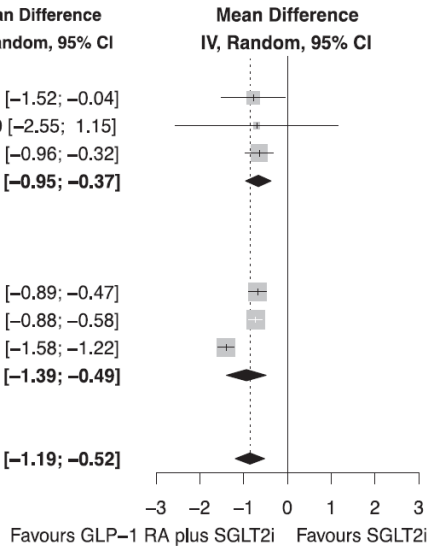
Study or Subgroup	GLP–1 RA plus SGLT2i Mean	SD	Total	GLP–1 RA Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Simultaneous initiation of GLP–1 RA plus SGLT2i								
Ali 2020[36]	–1.67	1.12	15	–1.44	1.51	15	16.3%	–0.23 [–1.18; 0.72]
Ikonomidis 2018[28]	–1.50	3.58	20	–1.30	2.68	20	5.2%	–0.20 [–2.16; 1.76]
Jabbour 2018[21]	–1.70	1.66	228	–1.29	1.81	227	39.0%	–0.41 [–0.73; –0.09]
Total (95% CI)			**263**			**262**	**60.5%**	**–0.39 [–0.69; –0.09]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.16$, df = 2 ($P = 0.92$); $I^2 = 0\%$								
Sequential addition of SGLT2i to GLP–1 RA								
Fulcher 2016[24]	–0.86	0.71	65	0.17	0.71	30	39.5%	–1.03 [–1.34; –0.72]
Total (95% CI)			**65**			**30**	**39.5%**	**–1.03 [–1.34; –0.72]**
Heterogeneity: not applicable								
Total (95% CI)			**328**			**292**	**100.0%**	**–0.61 [–1.09; –0.14]**
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 8.79$, df = 3 ($P = 0.03$); $I^2 = 66\%$								



GLP-1RA/SGLT2i vs SGLT2i.:

(B)

Study or Subgroup	GLP–1 RA plus SGLT2i Mean	SD	Total	SGLT2i Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Simultaneous initiation of GLP–1 RA plus SGLT2i								
Ali 2020[36]	–1.67	1.12	15	–0.89	0.93	15	11.0%	–0.78 [–1.52; –0.04]
Ikonomidis 2018[28]	–1.50	3.58	20	–0.80	2.24	20	2.9%	–0.70 [–2.55; 1.15]
Jabbour 2018[21]	–1.70	1.66	228	–1.06	1.82	230	19.5%	–0.64 [–0.96; –0.32]
Total (95% CI)			**263**			**265**	**33.4%**	**–0.66 [–0.95; –0.37]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.12$, df = 2 ($P = 0.94$); $I^2 = 0\%$								
Sequential addition of GLP–1 RA to SGLT2i								
Blonde 2020[33]	–1.00	0.86	195	–0.32	0.83	95	21.8%	–0.68 [–0.89; –0.47]
Ludvik 2018[34]	–1.27	0.74	266	–0.54	0.74	133	22.6%	–0.73 [–0.88; –0.58]
Zinman 2019[35]	–1.50	0.74	151	–0.10	0.86	151	22.2%	–1.40 [–1.58; –1.22]
Total (95% CI)			**612**			**379**	**66.6%**	**–0.94 [–1.39; –0.49]**
Heterogeneity: $Tau^2 = 0.15$; $Chi^2 = 38.05$, df = 2 ($P < 0.01$); $I^2 = 95\%$								
Total (95% CI)			**875**			**644**	**100.0%**	**–0.85 [–1.19; –0.52]**
Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 41.09$, df = 5 ($P < 0.01$); $I^2 = 88\%$								



Severe hypoglycaemia

- Combination treatment with GLP-1RA /SGLT2i did not increase the incidence of severe hypoglycaemia compared with
  - GLP-1RA (OR = 1.38, 95% CI 0.14 to 13.14, I2 = 0%, three studies) or
  - SGLT2i (OR = 2.39, 95% CI 0.47 to 12.27, I2 = 0%, five studies)

Mortality and cardiovascular outcomes

Supplementary table S5. Effect of GLP-1 RA plus SGLT2i on incidence of all-cause mortality, cardiovascular mortality, myocardial infarction and stroke compared to GLP-1 RA and SGLT2i.

Outcome	Comparator	Studies contributing data, n	Participants analyzed, n		Participants with outcome, n		Overall effect estimate, OR (95% CI)	I^2, %
			GLP-1 RA plus SGLT2i	Comparator	GLP-1 RA plus SGLT2i	Comparator		
Incidence of all-cause mortality	GLP-1 RA	3	311	275	3	1	1.98 (0.33; 11.85)	0
	SGLT2i	5	881	639	5	2	1.51 (0.40; 5.68)	0
Incidence of cardiovascular mortality	GLP-1 RA	3	311	275	1	1	1.00 (0.13; 7.42)	0
	SGLT2i	5	881	639	1	1	1.00 (0.19; 5.16)	0
Incidence of myocardial infarction	GLP-1 RA	2	246	245	0	3	0.28 (0.03; 3.06)	0
	SGLT2i	4	679	539	0	4	0.31 (0.06; 1.58)	0
Incidence of stroke	GLP-1 RA	2	246	245	1	1	1.00 (0.10; 9.73)	0
	SGLT2i	4	679	539	2	2	0.97 (0.20; 4.82)	0

Abbreviations: CI, confidence interval; GLP-1 RA, glucagon-like peptide 1 receptor agonist; OR, odds ratio; SGLT2i, sodium glucose co-transporter 2 inhibitor.

Anmerkung/Fazit der Autoren

In conclusion, based on data from a limited number of RCTs, combination therapy with a GLP-1RA and an SGLT2i seems to reduce HbA1c and systolic blood pressure without increasing the risk of severe hypoglycaemia compared with either GLP-1RA or SGLT2i alone. Combination therapy with GLP-1RA/SGLT2i can also reduce body weight compared with either GLP-1RA or SGLT2i in the short term, while long-term data from one trial suggest that combination therapy was similar to SGLT2i in terms of body weight reduction. Currently, the available research evidence does not allow for a valid assessment of the long-term effectiveness, effect on cardiovascular outcomes or differences between types of GLP-1RA/SGLT2i combinations.

Kommentare zum Review

- Für den Vergleich von GLP-1RA/SGLT2i vs SGLT2i siehe auch SR von
  - Castellana M et al. 2019 [8],
  - Patoulias et al. 2019 [95]

  welche zur gleichen Schlussfolgerung kommen.

Zhang X et al., 2020 [113].

Long-term renal outcomes associated with sodium glucose cotransporter 2 inhibitors in patients with type 2 diabetes mellitus: A systematic review and meta-analysis.

Fragestellung

to investigate the renal outcomes associated with SGLT2 inhibitors in patients with type 2 diabetes (T2DM) in the long term.

Methodik

Population:

- Adult patients with T2DM

Intervention/Komparator:

- SGLT2 inhibitors with placebo or other kinds of anti-diabetic treatments

Endpunkte:

- Renal outcomes

Recherche/Suchzeitraum:

- PubMed and ClinicalTrials.gov up to August 2, 2019

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

- 39 studies involving 35 trials. The total number of participants was 60 656, ranging from 180 to 17 160 across different trials

Charakteristika der Population:

- The mean age of patients in all trials included was over 50 years old. Large proportion of participants was obese according to the relatively high BMI (>28 kg/m2) in most studies. All patients were previously diagnosed with T2DM and most patients received background anti-diabetic medications except for the intervention therapies. Four trials included patients with impaired renal function

Qualität der Studien:

- Most trials were rated at low risk of bias for all items assessed. All trials were RCTs, but the process of random sequence generation, allocation concealment, and blinding were not clearly described in several trials. The interventions were slightly adjusted in the early phase in one trial.

Studienergebnisse:

- Compared with placebo or other anti-diabetic medications, SGLT2 inhibitors were associated with significant lower incidence of composite renal outcome and acute renal failure or injury in patients with T2DM.
- The risk of progression of albuminuria also appeared to be decreased.
- No significant changes of estimated glomerular filtration rate levels or urine albumin-creatinine ratios were found in patients receiving SGLT2 inhibitors.

Anmerkung/Fazit der Autoren

In conclusion, this meta-analysis indicated overall renal safety and beneficial effects of SGLT2 inhibitors in patients with T2DM in the long term. Future trials and real-world studies are warranted to further clarify the renal effects of SGLT2 inhibitors, both in the general population with T2DM and in patients with T2DM and CKD.

Zhou Y et al., 2020 [117].

Meta-analysis on the efficacy and safety of SGLT2 inhibitors and incretin based agents combination therapy vs. SGLT2i alone or add-on to metformin in type 2 diabetes

Fragestellung

determine whether sodium-glucose cotransporter type 2 inhibitors (SGLT2is) and incretin-based agents combination therapy produces more benefits than SGLT2is alone in patients with type 2 diabetes mellitus (T2DM).

Methodik

Population:

- drug-naive or metformin failure patients with T2DM

Intervention:

- SGLT2is plus incretin-based agents (SGLT2is/DPP4is or SGLT2is/GLP-1RAs)

Komparator:

- SGLT2is alone or plus placebo

Endpunkte:

- Primary outcome: change in HbA1c from baseline.
- Secondary outcomes: change in body weight and SBP from baseline, and the incidence of AEs including genital infection, urinary tract infection (UTI), gastrointestinal disorder, and hypoglycemia.

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane Library
- Until February 2019

Qualitätsbewertung der Studien:

- Cochrane Collaboration's risk-of-bias assessment tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 articles with 7350 participants

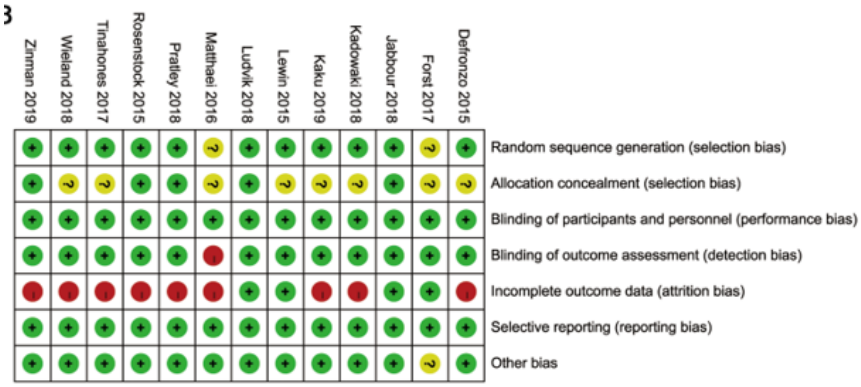
Charakteristika der Population:

- Five studies compared the simultaneous combination of SGLT2is and DPP4is versus SGLT2is in drug-naive or metformin failure patients, while the other eight studies compared the addition of incretin-based agents with a placebo as add-on therapy in patients inadequately controlled with SGLT2is. Overall, there were four combined types of SGLT2is/DPP4is (Canagliflozin/Teneligliptin, Dapagliflozin/Saxagliptin, Empagliflozin/

Linagliptin, and Ertugliflozin/Sitagliptin), and three types of SGLT2is/ GLP-1RAs (Dapagliflozin/Exenatide, SGLT2is/Dulaglutide, and SGLT2is/Semaglutide). In articles including the same patients as a part of an extension period, we only included the most complete or longest follow-up data to avoid duplicating results.

-

Qualität der Studien:

- 

Studienergebnisse:

- Combination with SGLT2is and DPP4is
  - A total of nine RCTs comparing SGLT2is/DPP4is with SGLT2is were included.
  - Results showed that compared with SGLT2is alone, SGLT2is/DPP4is further reduced HbA1c by 0.47% (95% CI, 0.58%-0.37%), without significant difference in body weight or SBP change.
  - In aspect of safety profile, the increased incidence of genital infection seen with SGLT2is is significantly attenuated with DPP4is combination (RR, 0.73; 95% CI, 0.54-0.97), while no significant differences were detected concerning AEs related to UTI or hypoglycemia with SGLT2is/DPP4is versus SGLT2is.
- Combination with SGLT2is and GLP-RAs
  - Results comparing SGLT2is/GLP-1RAs with SGLT2is showed that combination with GLP-1RAs further reduced HbA1c by 0.80% (WMD, −0.8%; 95% CI, −1.14% to −0.45%), body weight by 1.46 kg (WMD, −1.46; 95% CI, −2.38 to −0.54 kg), SBP by 2.88 mmHg (WMD, −2.88; 95% CI, −4.52 to −1.25 mmHg).
  - In aspect of safety profile, SGLT2is/GLP-1RAs together did not change the risk for genital infection, UTI or hypoglycemia, but significantly increased the risk for gastrointestinal disorders than SGLT2is alone (RR, 1.66; 95% CI, 1.14-2.47)

Anmerkung/Fazit der Autoren

In conclusion, combination with SGLT2is and incretin-based agents is both efficacious and safe compared with SGLT2is alone in T2DMs. In particular, combination with GLP-1RAs shows a subadditive glucose reduction, an additive weight loss, and a super-additive SBP decrease to a larger extent than DPP4is, while combination with DPP4is ameliorates the potential risk for genital infection seen with SGLT2is.

Bae JH et al., 2019 [4].

Effects of Sodium-Glucose Cotransporter 2 Inhibitors on Renal Outcomes in Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis of Randomized Controlled Trials.

Fragestellung

In this regard, we conducted this systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the effects of SGLT2 inhibitors on individual renal outcomes compared with placebo or other antidiabetic drugs in patients with type 2 diabetes.

Methodik

Population:

- Patients with Type 2 Diabetes

Intervention:

- SGLT2 inhibitors

Komparator:

- placebo or other antidiabetic drugs

Endpunkte:

- renal outcomes: changes in urine albumin-to-creatinine ratio (UACR) or eGFR, and incident microalbuminuria, macroalbuminuria, doubling of serum creatinine, renal failure, end-stage renal disease (ESRD), RRT, dialysis, or kidney transplantation

Recherche/Suchzeitraum:

- MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from inception to September 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

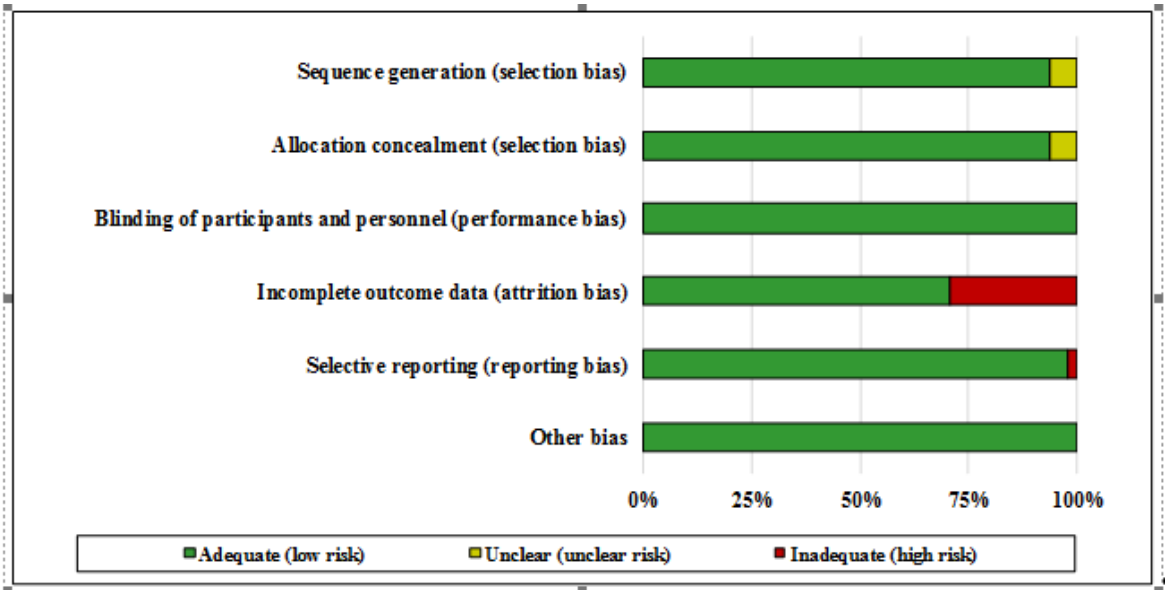
Anzahl eingeschlossener Studien:

- 48 RCTs (n= 58,165 (n=34,661 in the SGLT2 inhibitor group and n=23,504 in the control group).

Charakteristika der Population:

- The number of participants in each study ranged from 114 to 10,142. Three studies had a duration of 187 to 296 weeks whereas the remaining studies had a duration ranging from 12 to 104 weeks.
- The baseline eGFR of the participants was ≥55 (or 60) mL/min/1.73 m2 in 24 studies, ≥30 mL/min/1.73 m2 in 14 studies, ≥20 mL/ min/1.73 m2 and in 1 study. In one study, 74 of 741 participants had an eGFR of ≥15 and <30 mL/min/1.73 m2 at baseline.

Qualität der Studien:



Studienergebnisse:

eGFR

- The changes in eGFR were not significantly different between SGLT2 inhibitors and controls (WMD, 0.19 mL/min/1.73 m2; 95% CI, −0.44 to 0.82; P = 0.552) (Fig. 4A,B). The test for heterogeneity for this showed substantial heterogeneity across the studies (I2 = 79.6%; P < 0.001). There was a large discrepancy noted in estimated treatment effects between fixed effect and random effects models, depending on weights given to two large trials20,22.
- SGLT2 inhibitors significantly slowed the decline in eGFR in patients with >52 weeks of treatment duration compared with controls.
- In the meta-regression, the decline in eGFR were slower in patients with a higher baseline eGFR (P = 0.116) and a longer duration of follow-up (P = 0.038)

ESRD

- SGLT2 inhibitors significantly reduced the risk of ESRD compared with controls (RR, 0.70; 95% CI, 0.57 to 0.87; P = 0.001) (Fig. 5D).
- The number of events was 151 of 15,212 and 194 of 10,694 participants in the SGLT2 inhibitor and control groups, respectively.
- Heterogeneity was regarded as not significant across the studies (I2 = 0.1%; P = 0.433).

Anmerkung/Fazit der Autoren

Our meta-analysis demonstrated that SGLT2 inhibitors had beneficial effects on the kidney by lowering the risk of albuminuria development or progression and reducing the risk of ESRD compared with placebo or other antidiabetic drugs in patients with type 2 diabetes. In addition, the renoprotective effects of SGLT2 inhibitors were greater in patients with a higher UACR and GFR, and a long duration of treatment.

Kommentare zum Review

- Siehe auch: Feng C et al., 2019 [24]

Chen Z et al., 2019 [11].

Sodium-Glucose Co-Transporter 2 Inhibitors Compared with Sulfonylureas in Patients with Type 2 Diabetes Inadequately Controlled on Metformin: A Meta-Analysis of Randomized Controlled Trials

Fragestellung

to collectively compare the efficacy, safety, and durability of SGLT2 inhibitors with Sulfunylureas (SUs) as second-line therapy in patients with T2DM with inadequate glycemic control on metformin.

Methodik

Population:

- T2DM

Intervention/Komparator:

- SGLT2 inhibitors vs. SUs add on to Metformin

Endpunkte:

- Primary outcomes: HbA1c and weight between baseline and end of intervention, and number of participants with any hypoglycemic episodes. Hypoglycemic events include documented hypoglycemia (episodes with a capillary or plasma glucose level ≤ 3.9 mmol/L with or without symptoms), and symptomatic hypoglycemia (episodes with clinical symptoms reported by the investigator as hypoglycemia, biochemical documentation not required).
- Secondary outcomes were as follows: changes from baseline in fasting plasma glucose (FGP), systolic and diastolic blood pressures (SBP and DBP); and incidence of genital tract infection, urinary tract infection, and serious adverse events at the end of intervention.

Recherche/Suchzeitraum:

- PubMed, EMBASE, and Cochrane Central Register of Controlled Trials published up to 10 January 2018
- RCTs had at least 8-week follow-up periods

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

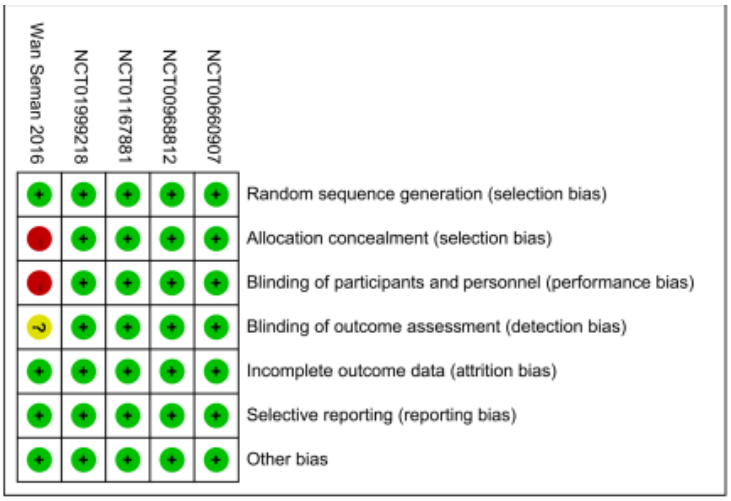
- 5 RCTs (n=4300)

Charakteristika der Population:

- Mean duration of the five trials was 96 weeks (range 12–208 weeks). Patients had a mean baseline HbA1c of 7.78% (range 7.65–7.92), mean baseline body mass index (BMI) of 30.8 kg/m2 (29.8–31.5), and mean duration of diabetes of 6.5 years (5.5–7.5).
- Two trials (NCT00660907, Wan) compared dapagliflozin with SUs, one trial (NCT00968812) compared canagliflozin with a SU, one trial (NCT01167881) compared empagliflozin with a SU, and one study (NCT01999218) compared ertugliflozin with a SU.

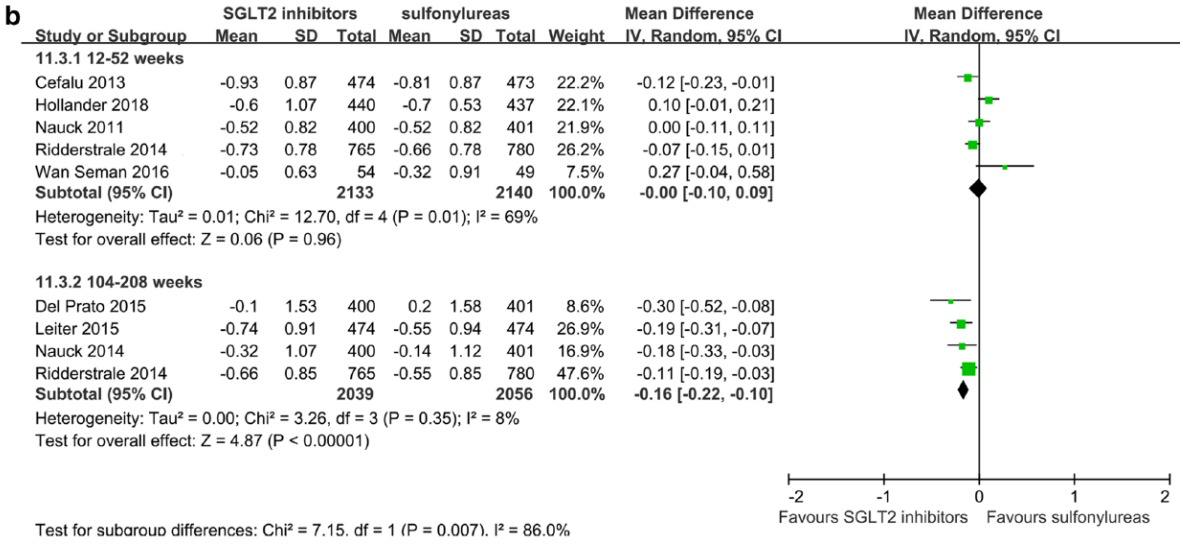
- Outcomes of three trials (NCT00660907, NCT00968812, NCT01167881) were assessed at different durations of follow-up, and two trials (NCT00968812, NCT01999218) used two doses of SGLT2 inhibitors

Qualität der Studien:

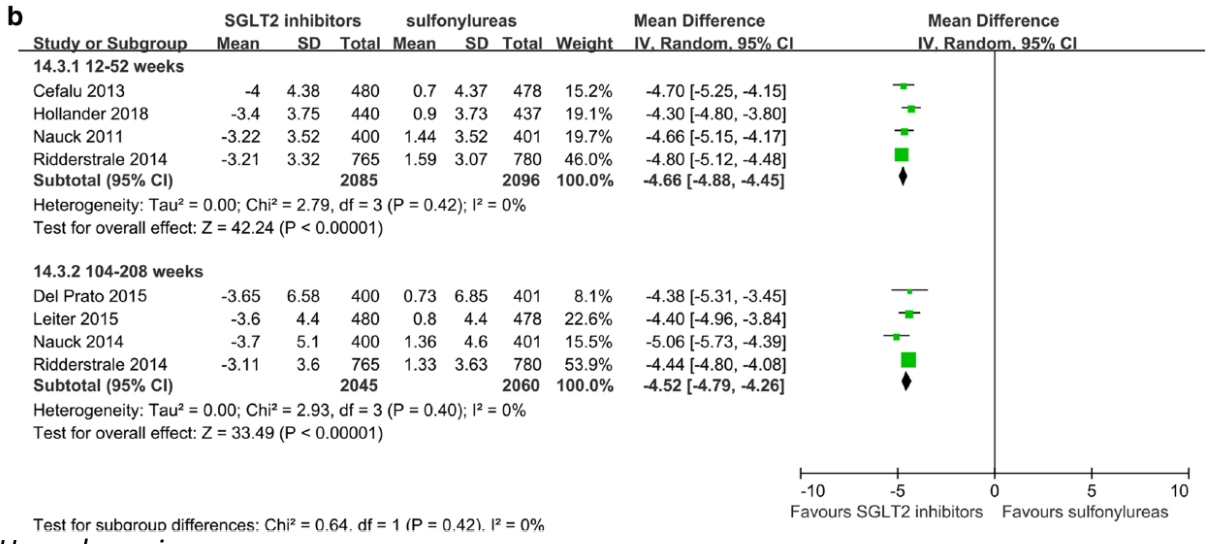


Studienergebnisse:

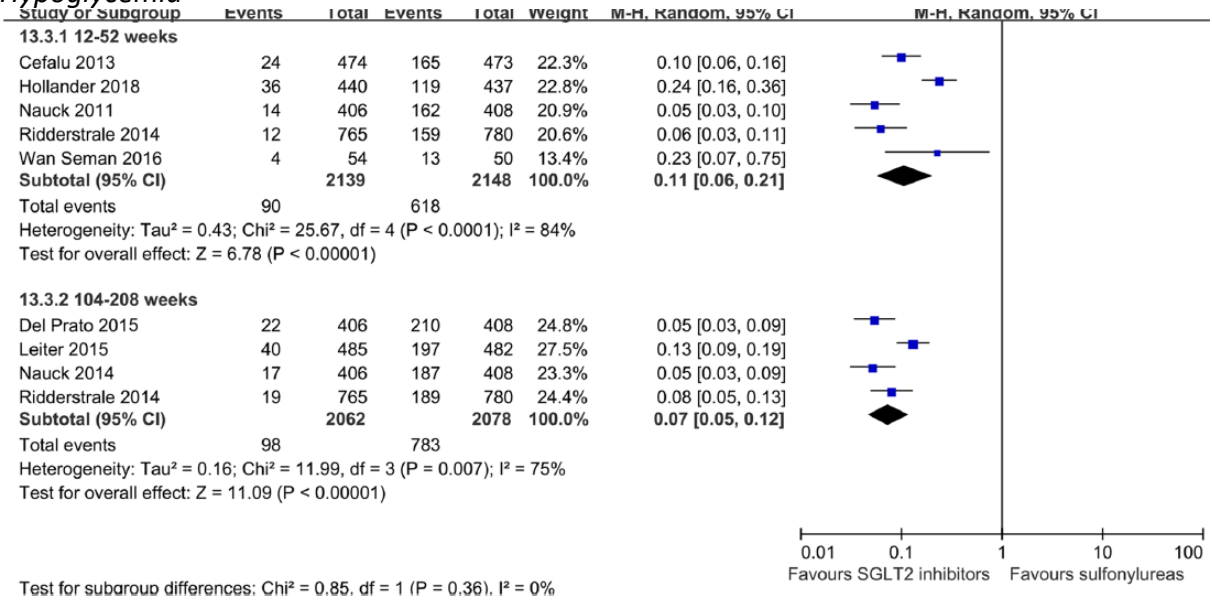
HbA1c



Weight



Hypoglycemia



Safety

- SGLT2 inhibitors led to greater reductions in FGP (MD − 0.53 [− 0.75, − 0.32] mmol/L, p < 0.00001), SBP (MD − 5.00 [− 5.77, − 4.22] mmHg, p < 0.00001), and DBP (MD − 2.19 [− 2.91, − 1.46] mmHg, p < 0.00001), whereas the incidence of genital tract infection (OR 5.54 [3.63, 8.45], p < 0.00001) was significantly higher after SGLT2 inhibitor treatment compared with SUs (Table 3).
- There was no significant difference in the incidence of urinary tract infection (OR 1.17 [0.96, 1.43], p = 0.12) and serious adverse events (OR 1.02 [0.69, 1.52], p = 0.92) between the two groups

Anmerkung/Fazit der Autoren

Despite similar glycemic efficacy over a relatively short term, SGLT2 inhibitors are more effective over a longer term than SUs as add-on treatment to metformin. In addition, SGLT2 inhibitors produce less hypoglycemic events and lead to greater reductions in weight and blood pressure compared with SUs. Finally, SGLT2 inhibitors appear to be well tolerated apart from genital tract infection, which is frequent but usually mild. Therefore, SGLT2 inhibitors might be effective and well tolerated second-line agents for patients with T2DM who have not achieved good glycemic control on metformin alone.

Dicembrini I et al., 2019 [19].

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors and cancer: A meta-analysis of randomized controlled trials

Fragestellung

to assess the effects of SGLT-2 inhibitors on the overall incidence of malignancies and on different types of cancer, summarizing the results of trials with a duration of at least 1 year.

Methodik

Population:

- Type 2 diabetes

Intervention:

- SGLT-2 inhibitors (ie, canagliflozin 100/300 mg, dapagliflozin 5/10 mg, empagliflozin 10/25 mg, ertugliflozin 5/15 mg, ipragliflozin 25/50 mg, luseogliflozin 2.5/5 mg and tofogliflozin 20 mg)

Komparator:

- Placebo or active control other than SGLT-2 inhibitors. Sergliflozin and remogliflozin were discontinued

Endpunkte:

- All types of cancer and several site-specific cancers (ie breast, pulmonary, gastrointestinal, hepatic, pancreatic, skin, prostate and bladder)
- Nephrolithiasis

Recherche/Suchzeitraum:

- Medline up to 1 December 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

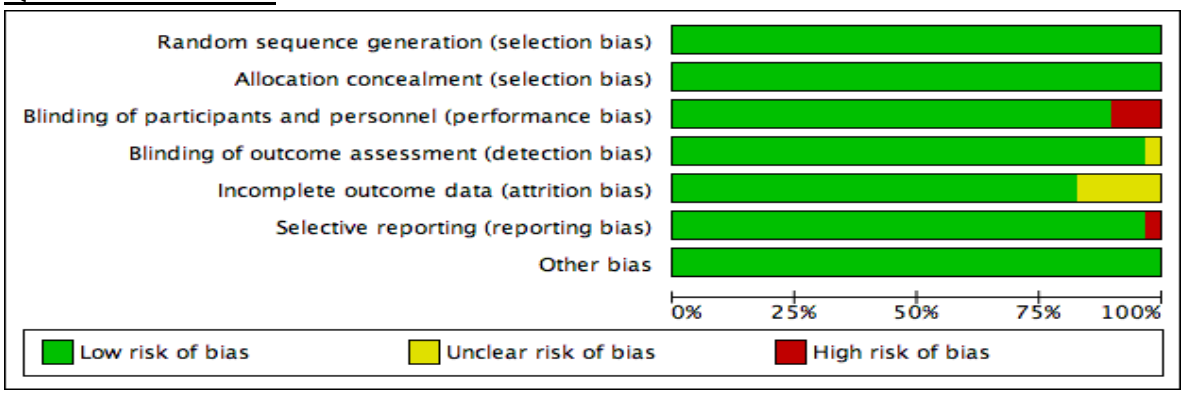
Anzahl eingeschlossener Studien:

- 27 trials (n=27744)

Charakteristika der Population:

- Mean duration of treatment of 84 weeks.
- Mean age, duration of diabetes, baseline HbA1c and BMI of enrolled patients at baseline were 59.0, 8.3 years, 8.0% and 30.9 Kg/m2, respectively.

Qualität der Studien:



Studienergebnisse:

- Among the 1659 cases of cancer (938 and 721 in patients treated with SGLT2-is and comparators, respectively), 197 (11.9%) were prostate cancers, 121 (7.3%) were skin cancers, 107 (6.5%) were breast cancers, 126 (7.6%) were gastrointestinal tract cancers, 106 (6.4%) were bladder cancers, 88 (5.3%) were respiratory airways cancers, 36 (2.2%) were kidney cancers, 29 (1.7%) were pancreas cancers, 23 were female genital tract cancers (1.4%) and 17 (1.0%) were liver cancers.
- No difference was observed in the overall incidence of malignancies between patients allocated to SGLT-2is and those allocated to comparators (MH-OR 0.98 [0.77–1.24]), with no evidence of heterogeneity. No significant difference in the effect on overall malignancies was observed when trials with different comparators, (Figure 1) or with different SGLT- 2 inhibitors (Figure 2), were analysed separately
- No association of SGLT-2 inhibitors with nephrolithiasis was observed (MH-OR 0.85 [0.57–1.26). I2 statistics did not suggest any relevant heterogeneity.
- In subgroup analyses, risk of nephrolithiasis was 1.04 [0.51–2.13], 0.70 [0.35–1.41], 0.82 [0.43–1.60], and 1.48 [0.06–36.34], all p > 0.50, for canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, respectively.
- When comparing SGLT-2 inhibitors with different comparators, the risk of nephrolithiasis was 0.69 [0.17–2.79], 0.87 [0.57–1.33], and 1.17 [0.06–24.66] (all p > 0.050) versus insulin secretagogues, placebo, and metformin, respectively.
- Similarly, non between-group difference was detected in the risk of renal colic (MH-OR 0.70 [0.24–2.01]), hydronephrosis (MH-OR 1.06 [0.41–2.72]), and urinary retention (MH-OR 1.29 [0.63–2.64];

Anmerkung/Fazit der Autoren

In conclusion, available data from randomized trials do not suggest a detrimental effect of SGLT-2 inhibitors on the incidence of malignancies in general, or on the incidence of bladder cancer in particular. Further data should be collected from observational databases for a longer-term assessment.
In conclusion, based on the results of available randomized controlled trials, treatment with SGLT-2 inhibitors appears to be neither beneficial nor detrimental with respect to nephrolithiasis. The possible effects of SGLT-2 inhibitors on urinary concentrations and solubility of urate and oxalate are not sufficient to determine relevant differences in clinical outcomes.

Kommentare zum Review

- Siehe auch: Cosentino C et al., 2019 [14]

Dorsey-Trevino EG et al., 2020 [21].

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors and microvascular outcomes in patients with type 2 diabetes: systematic review and meta-analysis

Fragestellung

We conducted a systematic review of randomized trials to estimate the effectiveness of SGLT-2 inhibitors on patient important outcomes—that patients perceive and value—and surrogate outcomes—laboratory parameters that are oblivious to patient's perception—of microvascular complications in adult patients with type 2 diabetes.

Methodik

Population:

- adult patients with type 2 diabetes

Intervention:

- SGLT-2 inhibitors

Komparator:

- Active treatment or placebo

Endpunkte:

- end-stage renal disease (ESRD) defined as the need for continuous renal replacement therapy or renal transplant, chronic renal disease stage > II, and renal death
- diabetes-related blindness, vitreous hemorrhage, retinal detachment, severe macular edema, and retinal artery occlusion
- pain, numbness, sensory loss (touch or vibration), and quality of life, wound healing, ulcers, or limb amputation

Recherche/Suchzeitraum:

- Ovid, EMBASE, Web of Science, Scopus from each database's inception to May 05, 2019

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

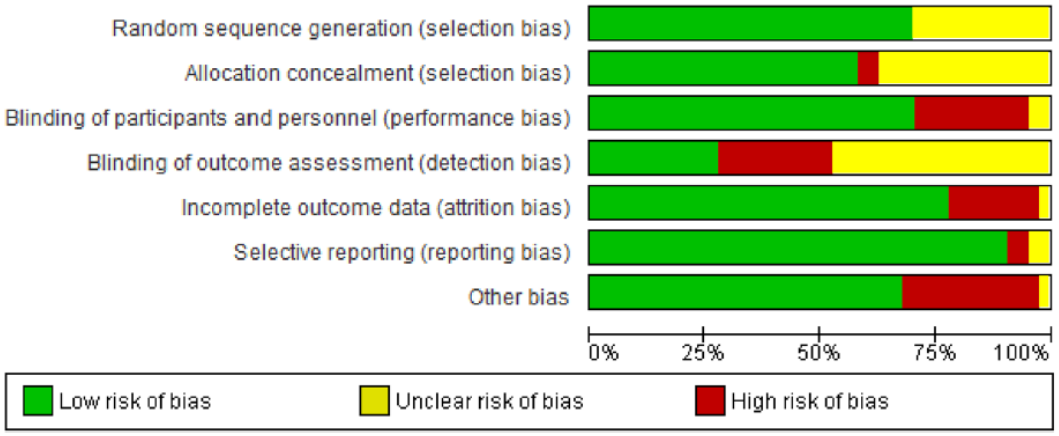
Anzahl eingeschlossener Studien:

- 40 RCTs

Charakteristika der Population:

- n=57560
- duration between 8 and 208 weeks

Qualität der Studien:

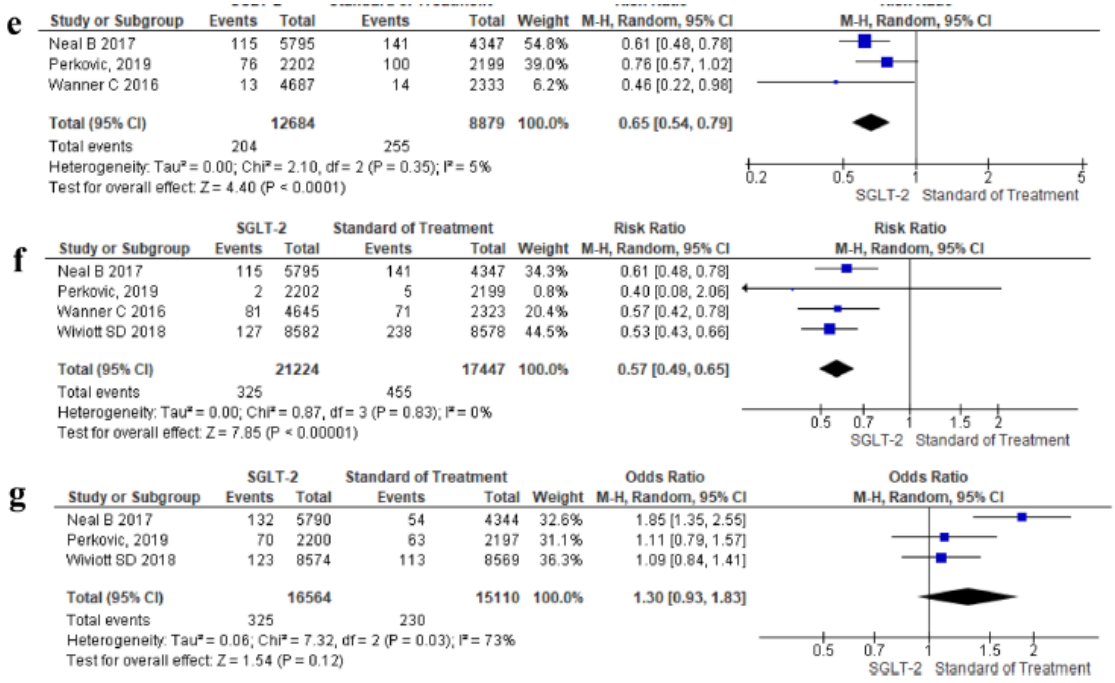


Studienergebnisse:

Renal microvascular outcomes

- a 35% reduction in the risk of renal replacement therapy (0.65, 95% CI 0.54–0.79 I2 = 5% 3 RCTs)
- a 43% reduction of death from renal causes (0.57, 95% CI 0.49–0.65 I2 = 0% 4 RCTs)

Pooled analysis of (e) Renal-Replacement Therapy, (f) Renal Death, (g) Amputation



Anmerkung/Fazit der Autoren

Based on limited evidence dominated by four high-quality RCTs, SGLT-2 inhibitors may reduce the risk of patient important renal outcomes. This inference is weakened by the inconsistent effect of treatment on known precursors of these outcomes, the lack of blind independent adjudication of these endpoints, and the difficulty of attributing these effects to the use of these drugs. Their effects on other microvascular outcomes remain uncertain.

Giugliano D et al., 2019 [60].

Type 2 diabetes and risk of heart failure: a systematic review and meta-analysis from cardiovascular outcome trials

Fragestellung

We performed a meta-analysis of randomized controlled trials (RCTs) that evaluated the effect of dipeptidyl peptidase- 4 inhibitors (DPP-4i), glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and sodium glucose co-transporter-2 inhibitors (SGLT-2i) on heart failure (HF) risk in patients with type 2 diabetes (T2D).

Methodik

Population:

- T2D

Intervention/Komparator:

- add-on therapy with any DPP-4i, GLP-1RA, or SGLT-2i with placebo

Endpunkte:

- hospitalization for HF, MACE (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke)

Recherche/Suchzeitraum:

- PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and ClinicalTrials. Gov on 10 November 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

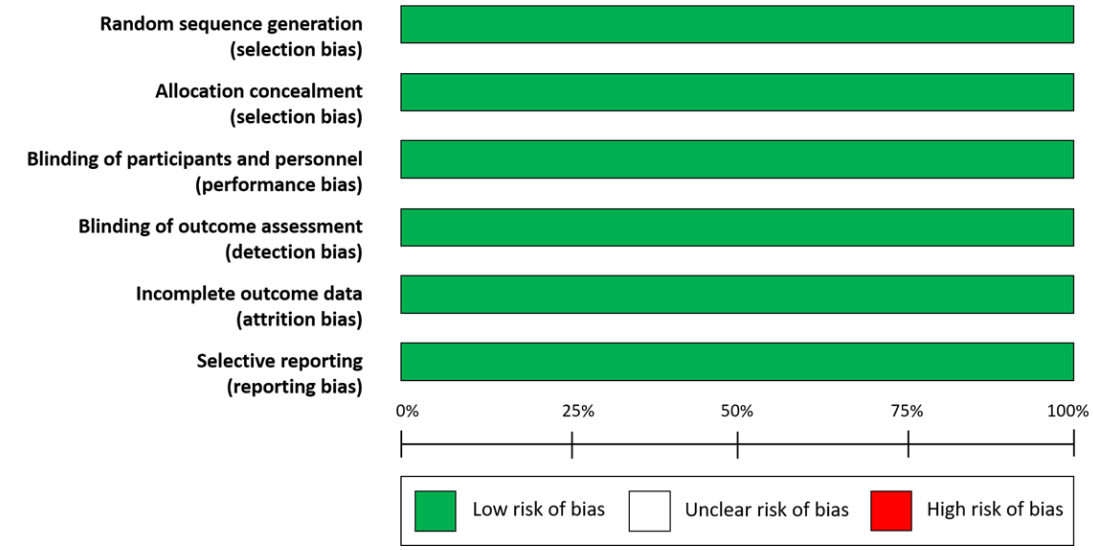
Anzahl eingeschlossener Studien:

- 12 RCTs (n=120765)

Charakteristika der Population:

- The participants were all patients with T2D (>18 years old).
- All trials were multinational and sponsored by industry. The trials have been published between 2013 and 2018, with 3 studies published in 2018. All trials were of parallel-group double-blind design, and their mean duration ranged from 1.5 to 4.2 years.
- The baseline HbA1c level ranged from 7.3% to 8.7%, but was almost identical between groups (drug vs placebo) within the same trial.
- The populations studied ranged in size from 3297 (SUSTAIN-6) to 17,160 (DECLARE) and were of similar age (range: 60–66 years).

Qualität der Studien:



Studienergebnisse:

Outcome	Trials (*n*)	Estimate (HR)	95% CI	*P* value	I^2 (%)	*P* value *Q* test
HF						
All	12	0.90	0.80–1.01	0.068	69.2	<0.001
DPP-4i	4	1.05	0.90–1.24	0.531	60.0	0.058
GLP-1 RAs	5	0.91	0.83–1.00	0.058	0	0.717
SGLT-2i	3	0.69	0.61–0.79	<0.001	0	0.741
MACE						
All	12	0.92	0.87–0.96	0.001	45.8	0.041
DPP-4i	4	0.99	0.94–1.05	0.798	0	0.948
GLP-1 RAs	5	0.88	0.80–0.96	0.005	58.8	0.045
SGLT-2i	3	0.89	0.83–0.96	0.001	0	0.550
CV mortality						
All	12	0.90	0.83–0.97	0.009	48.3	0.031
DPP-4i	4	0.98	0.89–1.08	0.655	2.6	0.379
GLP-1 RAs	5	0.88	0.80–0.96	0.004	0	0.518
SGLT-2i	3	0.81	0.63–1.05	0.116	79.9	0.007
Non-fatal MI						
All	12	0.93	0.87–0.99	0.018	27.6	0.174
DPP-4i	4	1.00	0.92–1.10	0.928	0	0.445
GLP-1 RAs	5	0.90	0.80–1.01	0.063	50.9	0.087
SGLT-2i	3	0.88	0.79–0.97	0.011	0	0.935
Non-fatal stroke						
All	12	0.95	0.88–1.03	0.203	8.6	0.361
DPP-4i	4	1.00	0.87–1.14	0.949	0	0.664
GLP-1 RAs	5	0.87	0.77–0.99	0.028	6.0	0.373
SGLT-2i	3	1.02	0.87–1.19	0.803	25.7	0.260
All-cause mortality						
All	12	0.92	0.86–0.98	0.013	55.4	0.010
DPP-4i	4	1.01	0.93–1.09	0.792	14.1	0.322
GLP-1 RAs	5	0.89	0.83–0.95	0.001	0	0.663
SGLT-2i	3	0.83	0.70–0.99	0.013	75.2	0.018

Anmerkung/Fazit der Autoren

In conclusion, the findings of this meta-analysis suggest that SGLT-2i are useful in the prevention and treatment of HF in T2D patients. Future CV outcome trials of glucoselowering therapies should enroll a proportion of patients with baseline HF similar to the prevalence of HF in the general population with T2D.

Liao HW et al., 2019 [75].

Sodium-glucose cotransporter 2 inhibitor plus pioglitazone vs pioglitazone alone in patients with diabetes mellitus: A systematic review and meta-analysis of randomized controlled trials.

Fragestellung

To evaluate the efficacy and safety of combined therapy with sodium-glucose cotransporter 2 (SGLT-2) inhibitors plus pioglitazone versus pioglitazone alone in type 2 diabetic patients.

Methodik

Population:

- Patients had a history of type 2 diabetes mellitus

Intervention/Komparator:

- SGLT-2 inhibitor plus pioglitazone vs. pioglitazone

Endpunkte:

- HbA1c, fasting glucose, body weight, hypoglycaemia, death, heart failure, urinary tract infection, genital tract infection

Recherche/Suchzeitraum:

- PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and clinicaltrials.gov from 1966 to September 2018

Qualitätsbewertung der Studien:

- Cochrane approach

Ergebnisse

Anzahl eingeschlossener Studien:

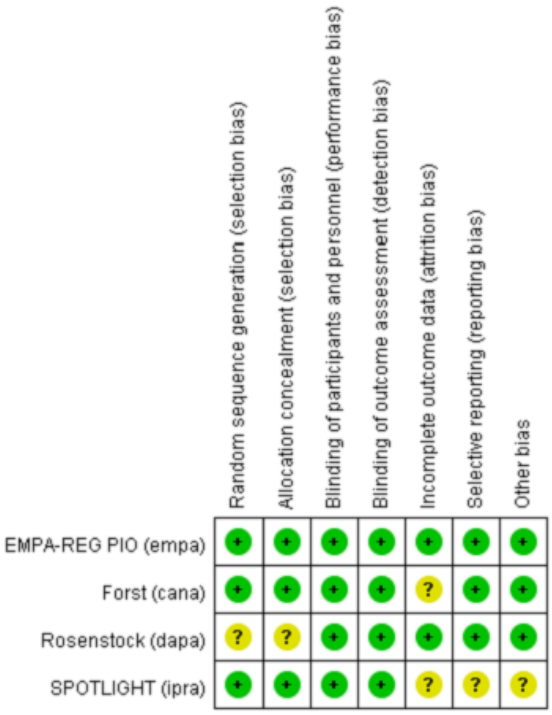
- Four randomized controlled trials with 1411 diabetic patients

Charakteristika der Population:

- About 938 participants were randomly assigned to the active group which received SGLT-2 inhibitor and background treatment with pioglitazone with or without metformin while 473 were randomly assigned to control group which received pioglitazone with or without metformin.

Qualität der Studien:

- The quality of a body of evidence was found to be low to moderate in most end-points.



Studienergebnisse:

- Pooling data from included trials showed that HbA1c change was significantly larger in both low-dose SGLT-2 inhibitors (MD: −0.59%, 95% CI: −0.77 to −0.41%; P < 0.001) and high dose SGLT-2 inhibitors (MD: −0.65%, 95% CI: −0.78 to −0.53%; P < 0.001) plus pioglitazone than pioglitazone alone in 24-26 weeks.
- Favourable outcomes were also found in achieving HbA1c <7% in SGLT-2 inhibitor plus pioglitazone (OR: 3.21, 95% CI: 1.99 to 5.16; P < 0.001).
- Pooling data from included trials showed fasting glucose reduction was larger in both low-dose SGLT-2 inhibitor plus pioglitazone (mean difference: −28.23 mg/dL, 95% CI: −36.57 to −19.89 mg/dL, P < 0.001) and high-dose SGLT-2 inhibitor plus pioglitazone (mean difference: −29.46 mg/dL, 95% CI: −35.58 to −23.34 mg/ dL, P < 0.001) than pioglitazone alone.
- Low-dose and high-dose SGLT-2 inhibitors plus pioglitazone were associated with larger weight change than pioglitazone alone (low-dose: mean difference: −2.22 kg, 95% CI −2.67 to −1.77 kg, P < 0.001; high-dose: mean difference: −2.27 kg, 95% CI −3.36 to −1.17 kg, P < 0.001).
- Both low-dose (mean difference: −4.04 mm Hg, 95% CI: −5.57 to −2.51 mm Hg, P < 0.001) and high-dose (mean difference: −3.72 mm Hg, 95% CI: −5.30 to −2.14 mm Hg, P < 0.001) SGLT-2 inhibitors combined with pioglitazone had a better systolic blood pressure control than pioglitazone at the end of core period.
- Pooling data from included trials showed that both low-dose (mean difference: −3.00 mm Hg, 95% CI: −4.47 to −1.54 mm Hg, P < 0.001) and high-dose (mean difference: −2.34 mm Hg, 95% CI: −3.34 to −1.35 mm Hg, P < 0.001) SGLT-2 inhibitors combined with pioglitazone had a better diastolic blood pressure control than pioglitazone at the end of core period.
- The risks of death, heart failure, hypoglycaemia and urinary tract infection were not different between active and control groups although genital tract infection was more frequently seen in SGLT-2 inhibitor group (OR: 4.04, 95% CI: 2.09 to 7.81, P < 0.001).

Anmerkung/Fazit der Autoren

In conclusion, in this meta-analysis of randomized controlled trials comparing an SGLT-2 inhibitor plus pioglitazone vs pioglitazone, we found that an SGLT-2 inhibitor plus pioglitazone was associated with better glycaemic control, and reduced body weight and blood pressure, without any increase in hypoglycaemia, death or urinary tract infection. However, genital tract infection increased with combination therapy. Large randomized controlled trials might be warranted to evaluate whether such combination therapy is beneficial for cardiovascular outcomes in diabetic patients with high cardiovascular risks

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Milder TY et al., 2019 [85].

Combination Therapy with an SGLT2 Inhibitor as Initial Treatment for Type 2 Diabetes: A Systematic Review and Meta-Analysis.

Fragestellung

To compare the efficacy and safety of (i) sodium-glucose cotransporter 2 (SGLT2) inhibitor combination therapy in treatment-naïve type 2 diabetes adults; (ii) initial high and low dose SGLT2 inhibitor combination therapy.

Methodik

Population:

- Treatment-naïve (defined as no pharmacotherapy for at least 12 weeks prior to randomisation) adults with type 2 diabetes

Intervention/Komparator:

- All dosing regimens of combination therapy that included an SGLT2 inhibitor that were compared to monotherapy (each agent in the combination)

Endpunkte:

- HbA1c, change in body weight, blood pressure (BP), adverse events including hypoglycaemia, genital and urinary tract infections (UTIs)

Recherche/Suchzeitraum:

- PubMed, Embase and Cochrane Library were searched from inception through to April 2018

Qualitätsbewertung der Studien:

- Cochrane approach / GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- Four studies (n = 3749 subjects) compared initial combination SGLT2 inhibitor and metformin therapy, to either metformin monotherapy or SGLT2 inhibitor monotherapy.
- Studies evaluated the combination of metformin and empagliflozin, dapagliflozin or canagliflozin.

Charakteristika der Population:

- Participants in these four studies had a mean baseline HbA1c which ranged from 8.7%–9.1% and a mean body weight which ranged from 83–91 kg.

- One study (n = 667 subjects) compared combination therapy with an SGLT2 inhibitor (empagliflozin) and linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor to monotherapy with each agent in the combination. Participants in this study had a mean baseline HbA1c of 8.0% and mean body weight of 88 kg.

Qualität der Studien:

- In general, the majority of the domains for the five studies were considered to have a low risk of bias.

Studienergebnisse:

- In 4 RCTs (n = 3749) there was moderate quality evidence that SGLT2 inhibitor/metformin combination therapy resulted in a greater reduction in HbA1c (MD (95% CI); -0.55% (-0.67, -0.43)) and weight (-2.00 kg (-2.34, -1.66)) compared with metformin monotherapy, and a greater reduction in HbA1c (-0.59% (-0.72, -0.46)) and weight (-0.57 kg (-0.89, -0.25)) compared with SGLT2 inhibitor monotherapy.
- The high dose SGLT2 inhibitor/metformin combination resulted in a similar HbA1c but greater weight reduction; -0.47 kg (-0.88, -0.06) than the low dose combination therapy.
- The RR of genital infection with combination therapy was 2.22 (95% CI 1.33, 3.72) and 0.69 (95% CI 0.50, 0.96) compared with metformin and SGLT2 inhibitor monotherapy, respectively.
- The RR of diarrhoea was 2.23 (95% CI 1.46, 3.40) with combination therapy compared with SGLT2 inhibitor monotherapy.

Anmerkung/Fazit der Autoren

Initial SGLT2 inhibitor/metformin combination therapy has glycaemic and weight benefits compared with either agent alone and appears relatively safe. High dose SGLT2 inhibitor/metformin combination therapy appears to have modest weight, but no glycaemic benefits compared with the low dose combination therapy.

Wang A et al., 2020 [103].

Effects of sodium-glucose cotransporter 2 inhibitors on risk of venous thromboembolism in patients with type 2 diabetes: A systematic review and meta-analysis

Fragestellung

Therefore, we performed this meta-analysis of published and unpublished randomized controlled trials (RCTs) to evaluate the effects of SGLT2 inhibitors on risk of VTE in patients with T2D.

Methodik

Population:

- Adult patients with T2D

Intervention:

- SGLT2 inhibitors

Komparator:

- placebo or other active antidiabetic drugs regardless of background treatments

Endpunkte:

- Venous thromboembolism

Recherche/Suchzeitraum:

- PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) from inception to May 2018 + Update April 2019
- RCTs with duration of follow-up of at least 12 weeks

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

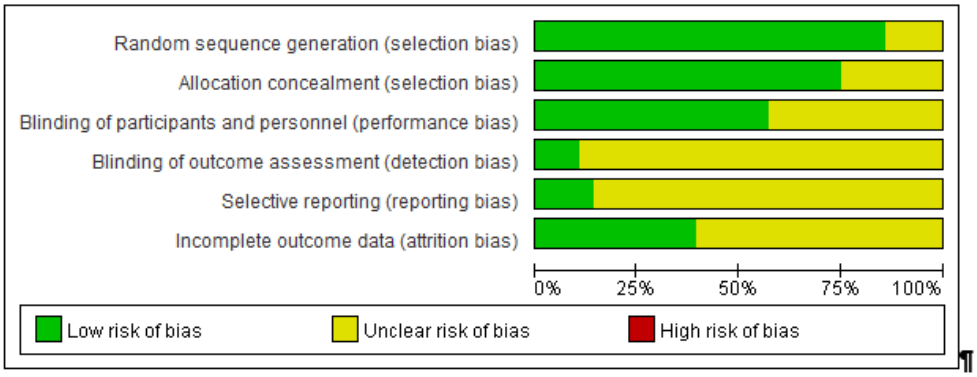
- 29 eligible RCTs (n=56035)

Charakteristika der Population:

- The duration of follow-up ranged from 24 to 218 weeks; mean age of study population ranged from 51.6 to 68.5 years; and the mean HbA1c values among all participants ranged from 7.7% to 8.9%.

Qualität der Studien:

Figure S1. Risk of bias assessment results with risk of each bias presented as percentages across all included trials.



Studienergebnisse:

TABLE 2 Subgroup analyses of the effects of SGLT2 inhibitors on risk of venous thromboembolism in patients with type 2 diabetes

Subgroup Analyses	No. of Trials	SGLT2 Inhibitors (n/N)	Controls (n/N)	Risk Ratio (95% CI)	Heterogeneity (I^2, %)	Difference Between Subgroups (*P* Value)
Subgroup by type of SGLT2 inhibitor						
Empagliflozin	10	35/8450	23/4934	0.78 (0.47-1.31)	0	0.73
Dapagliflozin	8	29/11 571	25/10 516	1.02 (0.59-1.75)	0	
Canagliflozin	8	61/10 799	42/7938	1.11 (0.75-1.64)	0	
Ertugliflozin	3	3/1218	2/609	0.70 (0.12-4.18)	20	
Subgroup by type of control[a]						
Placebo	20	122/27 440	86/21 024	1.00 (0.76-1.32)	0	0.56
Other active drugs	10	6/5046	6/2973	0.71 (0.23-2.15)	0	
Subgroup by mode of therapy						
Monotherapy	5	6/2033	2/1108	0.83 (0.18-3.82)	0	0.83
Add-on therapy	24	122/30 005	90/22 889	1.00 (0.75-1.33)	0	

Anmerkung/Fazit der Autoren

In conclusion, our meta-analysis found no association between SGLT2 inhibitors on risk of VTE among patients with T2D. Further prospective studies are required to confirm our findings.

Zelniker TA et al., 2019 [112].

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Fragestellung

The goal of the present meta-analysis was to combine data from all the large-scale placebo-controlled cardiovascular outcome trials of SGLT2i to gain more reliable estimates of the efficacy and safety of specific outcomes overall and in relevant subgroups.

Methodik

Population:

- Patients were stratified into those with established ASCVD versus patients with multiple risk factors (MRFs) for ASCVD

Intervention:

- SGLT2 inhibitors

Komparator:

- placebo

Endpunkte:

- Major adverse cardiovascular events (the composite of myocardial infarction, stroke, or cardiovascular death); the composite of cardiovascular death or hospitalization for heart failure, their individual components
- A standardised composite of renal outcomes including worsening eGFR, end-stage renal disease, or renal death
- Safety endpoints: non-traumatic lower limb amputations, fractures, and diabetic ketoacidosis

Recherche/Suchzeitraum:

- PubMed and Embase up to Sept 24, 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 trials1–3 (n=34322)

Charakteristika der Population:

	EMPA-REG OUTCOME[1]	CANVAS Program[2]	DECLARE-TIMI 58[3]
Drug	Empagliflozin	Canagliflozin	Dapagliflozin
Doses analysed	10 mg, 25 mg (once daily)	100 mg, 300 mg (once daily)	10 mg (once daily)
Median follow-up time, years	3·1	2·4	4·2
Trial participants	7020	10142	17160
Age, mean	63·1	63·3	63·9
Women	2004 (28·5%)	3633 (35·8%)	6422 (37·4%)
Patients with established atherosclerotic cardiovascular disease	7020 (100%)	6656 (65·6%)	6974 (40·6%)
Patients with a history of heart failure	706 (10·1%)	1461 (14·4%)	1724 (10·0%)
Patients with eGFR <60 mL/min per 1·73 m²	1819 (25·9%)	2039 (20·1%)	1265 (7·4%)

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR=estimated glomerular filtration rate.

Table: **Randomised controlled phase 3/4 clinical trials of sodium-glucose cotransporter-2 inhibitors**

Qualität der Studien:

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias) (patient-reported outcomes)	Blinding of outcome assessment (detection bias) (Mortality)	Incomplete outcome data addressed (attrition bias) (Short-term outcomes (2-6 weeks))	Incomplete outcome data addressed (attrition bias) (Longer-term outcomes (>6 weeks))	Selective reporting (reporting bias)
EMPA-REG Outcome	Low	Low	Low	Low	Low	Low	Low	Low
CANVAS Program	Low	Low	Low	Low	Low	Low	Low	Low
DECLARE-TIMI 58	Low	Low	Low	Low	Low	Low	Low	Low

Studienergebnisse:

Major adverse cardiac event (myocardial infarction, stroke, cardiovascular death)

- In total, 3342 (9·7%) of 34 322 patients had a major adverse cardiac event in the trials. Of those events, 2588 (77·4%) occurred in the group with established atherosclerotic cardiovascular disease.
- Overall, SGLT2i reduced the risk of a major adverse cardiac event by 11% (HR 0·89 [95% CI 0·83–0·96], p=0·0014).
- However, this effect was entirely restricted to a 14% reduction in patients with atherosclerotic cardiovascular disease (HR 0·86 [0·80 to 0·93]), whereas no treatment effect was found in patients with multiple risk factors (1·00 [0·87–1·16], p for interaction=0·0501)

Myocardial infarction

- 1604 (4·7%) patients had a myocardial infarction (80·5% of which occurred in patients with atherosclerotic cardiovascular disease), SGLT2i reduced the risk of myocardial infarction by 11% (HR 0·89 [95% CI 0·80–0·98], p=0·0177)
- SGLT2i reduced myocardial infarction (HR 0·85 [0·76–0·95]) in patients with atherosclerotic cardiovascular disease

Stroke

- 1060 (3·1%) had a stroke (73·1% of which occurred in patients with atherosclerotic cardiovascular disease), SGLT2i had no effect on stroke (HR 0·97 [0·86–1·10], p=0·64

Cardiovascular death

- 1256 (3·7%) had cardiovascular death (78·6% of which occurred in patients with the disease). SGLT2i reduced the risk of cardiovascular death by 16% (HR 0·84 [0·75–0·94], p=0·0023, but with high heterogeneity [I^2=79·9%])
- SGLT2i reduced cardiovascular death (HR 0·80 [0·71–0·91]) in patients with atherosclerotic cardiovascular disease

All cause death

- SGLT2i significantly reduced the risk for allcause death by 15% (HR 0·85 [95% CI 0·78–0·93], p=0·0002), but with high heterogeneity (I^2=75·2%;).
- In patients with atherosclerotic cardiovascular disease the HR was 0·83 (0·75–0·92) and in those with multiple risk factors it was 0·90 (0·77–1·05, p for interaction=0·69;).
- Similarly, in patients with history of heart failure the HR was 0·80 (0·67–0·95) and in those without a history of heart failure it was 0·88 (0·80–0·97, p for interaction=0·63).

Composite of cardiovascular death or hospitalisation for heart failure

- SGLT2i significantly reduced the risk for the composite of cardiovascular death or hospitalisation for heart failure by 23% (HR 0·77 [95% CI 0·71–0·84], p<0·0001), and hospitalisation for heart failure by 31% (0·69 [0·61–0·79], p<0·0001)
- The effect on hospitalization for heart failure alone was robust, with an approximately 30% reduction in relative risk in both subgroups

Composite of worsening of renal function, end-stage renal disease, renal death

- SGLT2i were renoprotective and reduced the composite of worsening of renal function, end-stage renal disease, or renal death by 45% (HR 0·55 [95% CI 0·48–0·64], p<0·0001).
- This effect was similarly robust both in patients with atherosclerotic cardiovascular disease (HR 0·56 [95% CI 0·47– 0·67]) and those with multiple risk factors, (0·54 [0·42–0·71], p for interaction=0,71)

Safety outcomes

- Diabetic ketoacidosis showed a consistent increased risk of almost two times higher in patients given SGLT2i than those given placebo (2·20 [1·25–3·87], p=0·0060), but the event rates were low (<one per 1000 patient-years)

Anmerkung/Fazit der Autoren

In conclusion, SGLT2i have moderate benefits on atherosclerotic major adverse cardiovascular events that appear confined to patients with established atherosclerotic cardiovascular disease. However, robust reductions in hospitalisation for heart failure and progression of renal disease are seen regardless of baseline atherosclerotic risk category or a history of heart failure.

Kommentare zum Review

- Siehe auch: Yamani N et al., 2020 [107]
- Siehe auch: Giugliano et al., 2020 [59] – This review included the same three CVOTs as the review by Zelniker et al., 2019. Here, the effect of SGLT-si on MACE risk in patients with T2D stratified by age and by statin use was the focus: In conclusion, the results of our meta-analyses are reassuring and confirm that the efficacy profile of gliflozins is unchanged by age and is not dependent on concomitant statins' use.

Cho YK et al., 2018 [12].

Efficacy and safety of combination therapy with SGLT2 and DPP4 inhibitors in the treatment of type 2 diabetes: A systematic review and meta-analysis

Fragestellung

Comparing the efficacy of SGLT2i/DPP4i vs. that of either a DPP4i or a SGLT2i.

Methodik

Population:

- Patients with T2DM

Intervention:

- SGLT2i/DPP4i as combined treatment

Komparator:

- DPP4i + placebo or SGLT2i + placebo

Endpunkte:

- HbA1c; Secondary outcomes: fasting plasma glucose (FPG), body weight, proportion of subjects achieving the therapeutic goal of an HbA1c < 7.0%, risk of hypoglycaemia

Recherche/Suchzeitraum:

- Bis 31 Mai 2017 in PuMed, Embase and Cochrane Library

Qualitätsbewertung der Studien:

- Cochrane Collaboration tool for assessing risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 RCTs (1 Study included 2 separate RCTs)
  - 8 RCT SGLT2i/DPP4i vs.DPP4i with 2220 Patients
  - 5 RCT SGLT2i/DPP4i vs.SGLT2i with 1681 Patients
  - 3 RCTs included in both meta-analyses as they included both comparisons

Charakteristika der Population:

- Metformin as background therapy: 9 RCTs
- Simultaneaous combination treatment 3 RCTs
- Additional efficacy and safety of SGLT2i or DPP4i in 10 trials (placebo added)

Author (year)	Background therapy	Interventions	Duration (weeks)	Patients (*n*)	Age (years)	Male (%)	BMI (kg/m^2)	HbA_{1c} (%)	HbA_{1c} (mmol/mol)	FPG (mg/dL)
Defronzo (2015) [20]	Metformin	Empagliflozin 25 mg	24	134	57.1	53.7	30.6	7.9	62.8	154.6
		+linagliptin 5 mg		140	55.5	46.4	31.8	8.0	64.2	159.9
		Empagliflozin 25 mg		128	56.2	50.0	30.6	8.0	64.2	156.3
		Linagliptin 5 mg								
Lewin (2015) [19]	None	Empagliflozin 25 mg	24	134	54.2	52.2	31.8	8.0	63.8	156.1
		+linagliptin 5 mg		133	56.0	57.9	31.2	8.0	63.8	152.8
		Empagliflozin 25 mg		133	53.8	56.4	31.9	8.1	64.5	156.0
		Linagliptin 5 mg								
Rosenstock (2015) [18]	Metformin	Dapagliflozin 10 mg	24	179	53	47	31.8	8.9	74.0	180.0
		+saxagliptin 5 mg		179	54	53	31.8	9.0	75.2	192.0
		Dapagliflozin 10 mg		176	55	50	31.5	8.9	73.4	185.0
		Saxagliptin 5 mg								
Jabbour (2014) [24]	Metformin + sitagliptin 100 mg	Dapagliflozin 10 mg	24	223	54.8	57.0	NA	7.9	62.8	162.2
		Placebo		224	55.0	52.7	NA	8.0	63.9	163.0
Mathieu (2015) [26]	Metformin + saxagliptin 5 mg	Dapagliflozin 10 mg	24	160	55.2	43.7	31.2	8.2	66.6	179.0
		Placebo		160	55.0	47.5	32.2	8.2	65.8	177.0
Rodbard (2016) [27]	Metformin + sitagliptin 100 mg	Canagliflozin 100 mg	26	107	57.4	61.7	32.3	8.5	69.4	185.5
		or 300 mg		106	57.5	51.9	31.7	8.4	68.3	180.4
		Placebo[b]								
Kadowaki (2017) [25]	Teneligliptin 20 mg	Canagliflozin 100 mg	24	70	58.4	77.1	25.5	8.2	65.9	173.9
		Placebo		68	56.0	77.9	26.4	7.9	62.5	166.3
Søfteland (2017) [28]	Metformin + linagliptin 5 mg	Empagliflozin 25 mg	24	110	55.4	64.5	29.9	8.0	63.6	169.2
		Placebo		108	55.9	55.6	29.6	8.0	63.6	163.8
Matthaei (2015) [29]	Metformin + dapagliflozin 10 mg	Saxagliptin 5 mg	24	153	54.7	47.7	31.4	8.0	63.6	164.0
		Placebo		162	54.5	46.9	31.4	7.9	62.4	158.0
Tinahones (a)[a] (2017) [22]	Metformin + empagliflozin 10 mg	Linagliptin 5 mg	24	122	56.6	56.6	31.3	8.0	64.4	159.5
		Placebo		125	56.8	56.0	30.8	8.0	64.3	157.1
Tinahones (b)[a] (2017) [22]	Metformin + empagliflozin 25 mg	Linagliptin 5 mg	24	110	56.6	47.3	30.8	7.8	61.9	152.1
		Placebo		110	56.1	57.3	32.0	7.9	62.6	155.4

Data are means (continuous variables) or percentages (dichotomous variables) unless otherwise indicated. BMI: body mass index; FPG: fasting plasma glucose; HbA_{1c}: haemoglobin A_{1c}; NA: not available.

[a] Tinahones et al. [22] comprised two separate trials of linagliptin 5 mg/empagliflozin 10 mg or placebo/empagliflozin 10 mg plus metformin (Tinahones [a]) or linagliptin 5 mg/empagliflozin 25 mg or placebo/empagliflozin 25 mg plus metformin (Tinahones [b])

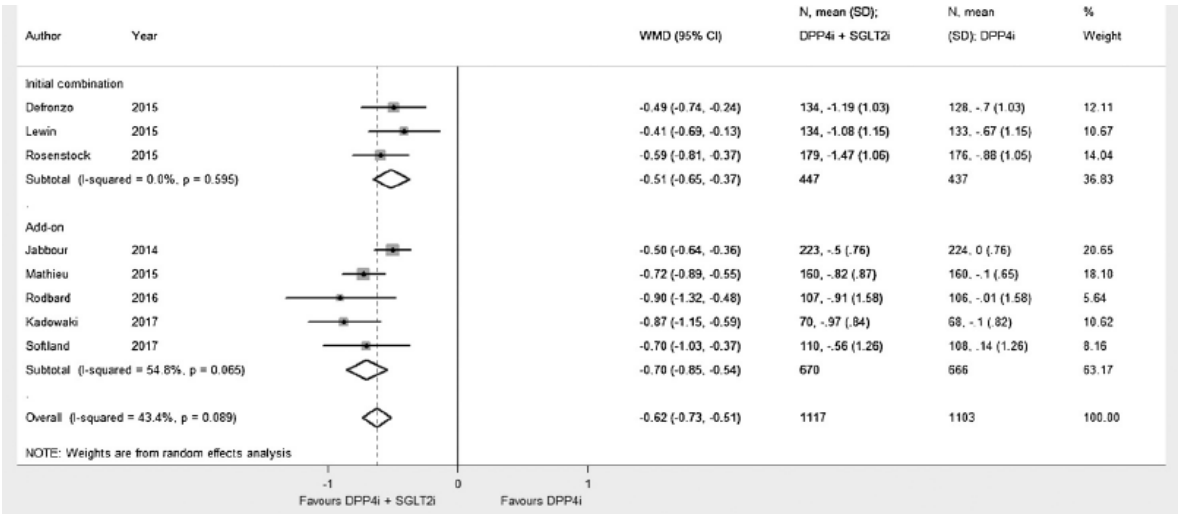
[b] 6 weeks after starting canagliflozin 100 mg, the dose was increased to 300 mg (or from placebo to matching placebo) if all of the following criteria were met: baseline estimated glomerular filtration rate ≥ 70 mL/min/1.73 m^2; fasting self-monitored blood glucose ≥ 5.6 mmol/L (≥ 100 mg/dL); no volume-depletion-related adverse events within 2 weeks of dose increase.

Qualität der Studien:

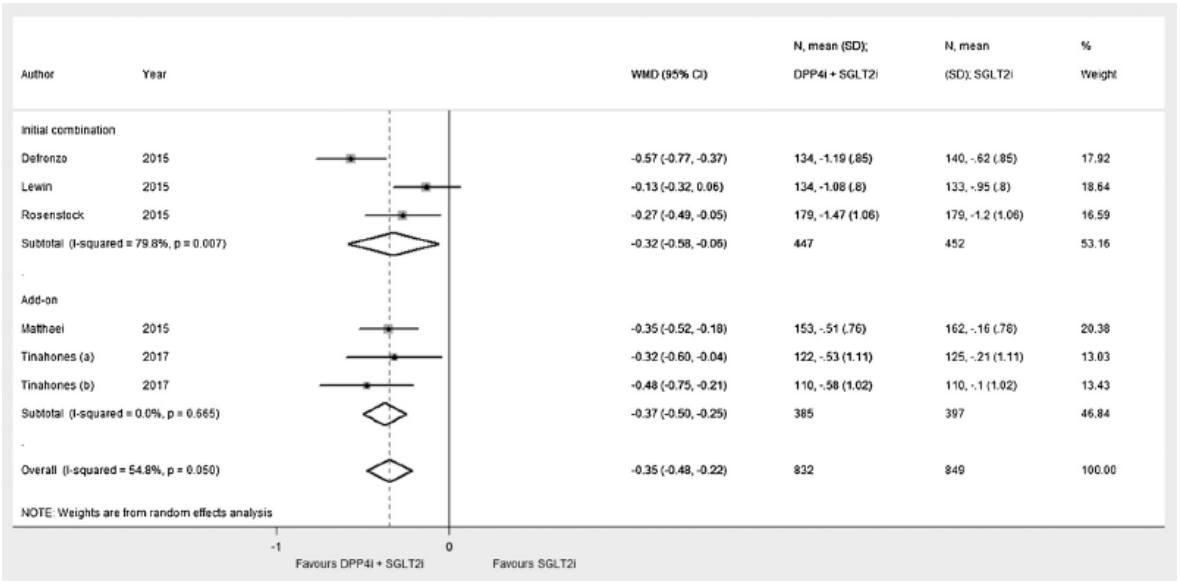
- funnel plots and Egger's regression test (HbA1c), no obvious asymmetrical distribution or small-study effect was detected

Studienergebnisse:

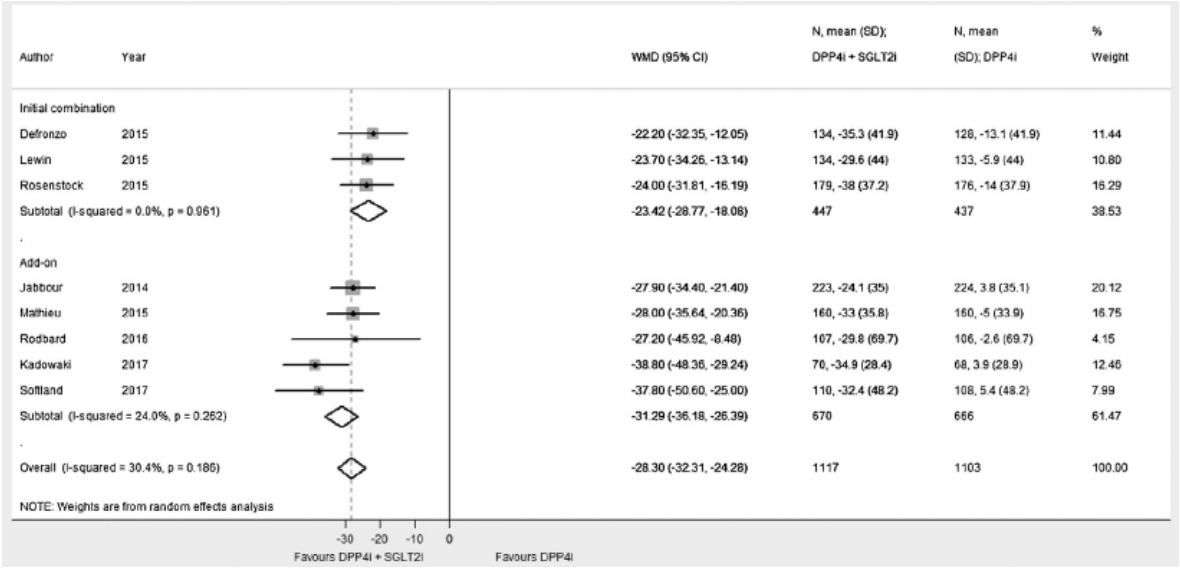
- HbA1c reduction
  - SGLT2i/DPP4i vs DPP4i:



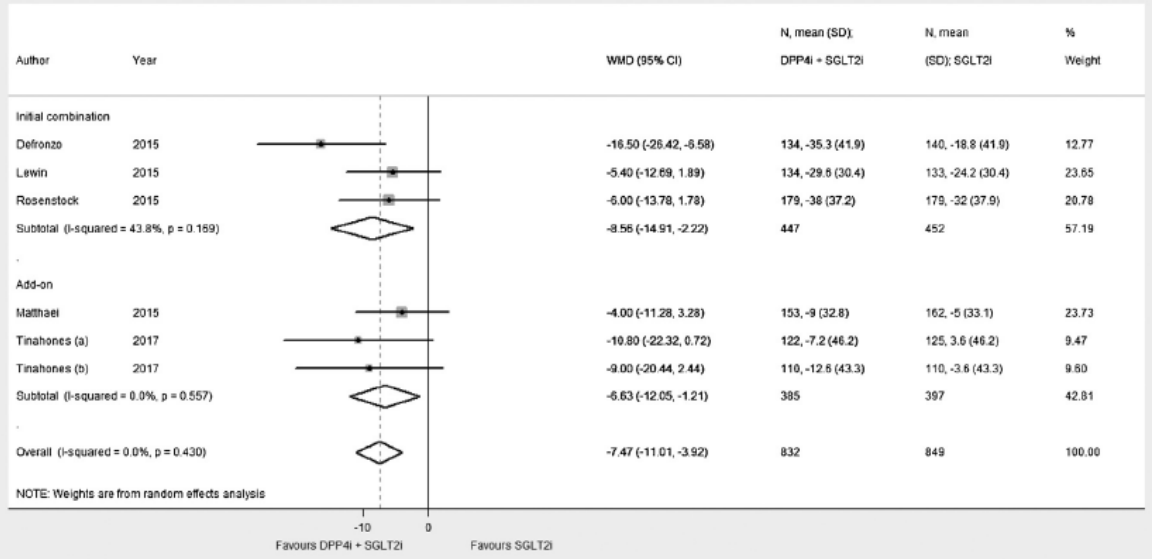
SGLT2i/DPP4i vs SGLT2i:



- Changes in FPG
  - SGLT2i/DPP4i vs DPP4i:



- SGLT2i/DPP4i vs SGLT2i:



- proportion of participants attaining the HbA1c target of < 7.0%
  - SGLT2i/DPP4i vs DPP4i: RR: 2.03, 95% CI: 1.73–2.39; P < 0.001
  - SGLT2i/DPP4i vs. SGLT2i: RR: 1.74, 95% CI: 1.46–2.08; P < 0.001
  - The difference was significant regardless of the manner of combination
- Change of body weight from baseline
  - SGLT2i/DPP4i vs DPP4i: WMD: -1.75 kg, 95% CI: -2.02 to -1.49 kg; P < 0.001
  - SGLT2i/DPP4i vs. SGLT2i: WMD: 0.29 kg, 95% CI: -0.14 to 0.71 kg; P = 0.191
  - No significant differences observed vs. SGLT2i; result similar regardless of combination
- Change of SBP from Baseline
  - SGLT2i/DPP4i vs DPP4i: WMD: -2.50 mmHg, 95% CI: -3.77 to -1.24 mmHg; P < 0.001
  - SGLT2i/DPP4i vs. SGLT2i: not significant
- Hypoglycaemia: risk of hypoglycaemia was low and similar between treatment groups
- genital infections
  - SGLT2i/DPP4i vs DPP4i: higher risk (RR: 2.94, 95% CI: 1.23 to 7.00; P = 0.015)
  - SGLT2i/DPP4i vs SGLT2i: lower risk (RR: 0.42, 95% CI: 0.18 to 0.99; P = 0.046)

Anmerkung/Fazit der Autoren

Combined therapy with SGLT2i/DPP4i is effective and safe. However, interestingly, a marked additional glucose-lowering effect is evident when SGLT2i is combined with or added to DPP4i, but not vice versa. In addition, baseline HbA1c levels significantly influence the glucose-lowering effects of SGLT2i in combination with DPP4i and, thus, further studies are needed to elucidate the underlying mechanism of this effect.

Kommentare zum Review

- Li D et al., 2018 [70] führten eine Meta-Analyse mit einer fast identischen Fragestellung durch. Obwohl dieser Review 3 zusätzliche Studien einschloss (jeweils asiatische Patienten und SGLT2i in unterschiedlichen Dosierungen) war die Schlussfolgerung vergleichbar:

- „In conclusion, compared with monotherapy, SGLT2 inhibitor/ DPP-4 inhibitor combination therapy was efficacious in treatment naïve patients or metformin-treated patients. However, this combination therapy might be associated with a higher risk of genital infections and increased levels of TC, HDL-C and LDL-C than those associated with a DPP-4 inhibitor. Low doses of an SGLT2 inhibitor might be prioritised when combination therapy is required."
- Min SH et al., 2018 [86] führten ebenfalls einen SR inklusive Metaanalyse zur Kombinationstherapie von SGLT2i/DPP4i durch, jedoch nur im Vergleich zu DPP4i. Die 7 eingeschlossenen RCTs waren mit einer Ausnahme (Insuline und weitere OADs waren als Begleittherapie erlaubt) ebenfalls in der Metaanalyse von Cho YK et al., 2018 [12] enthalten. Die Ergebnisse und Schlussfolgerungen waren vergleichbar:
- „In conclusion, the SGLT2 inhibitor and DPP4 inhibitor combination therapy improves glycemic control and reduces body weight without increasing the risk of hypoglycemia and UTI in patients with inadequately controlled type 2 diabetes."

Fadini GP et al., 2018 [23].

Dipeptidyl peptidase-4 inhibitors moderate the risk of genitourinary tract infections associated with sodium-glucose co-transporter-2 inhibitors

Fragestellung

In the present study, we evaluated whether combination therapy with an SGLT2 inhibitor and a dipeptidyl peptidase-4 (DPP-4) inhibitor is associated with a lower risk of GUTI than the SGLT2 inhibitor therapy alone.

Methodik

Population:

- D2T

Intervention:

- DPP-4 inhibitor/SGLT2 inhibitor combination therapy

Komparator:

- treatment with an SGLT2 inhibitor alone

Endpunkte:

- frequency of genital tract infection (GTIs), and of urinary tract infection (UTIs) separately and combined (GUTIs

Recherche/Suchzeitraum:

- PubMed and then in ISI Web of Science, Scopus, www.clinicalttrials.gov, and Cochrane Central Register of Controlled Trials
- AERSmine query strings

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

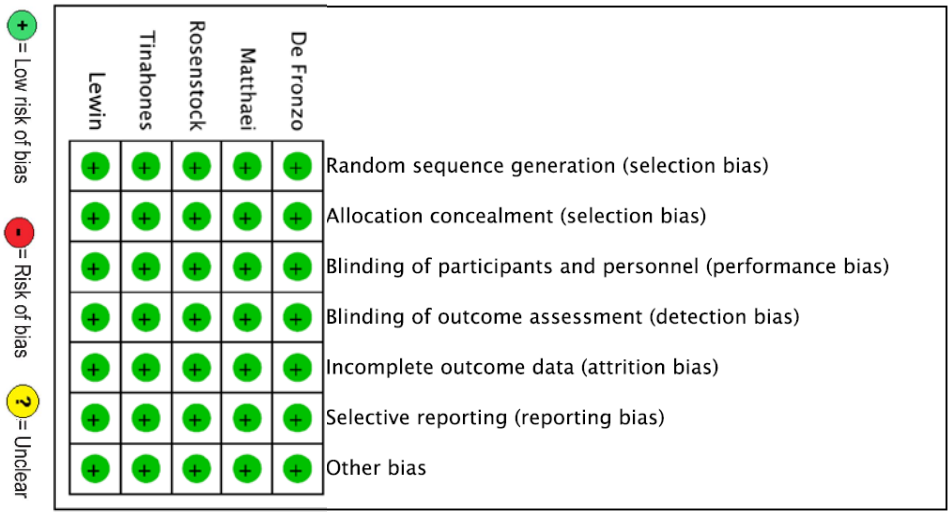
Anzahl eingeschlossener Studien:

- 5 RCTs

Charakteristika der Population:

- The five trials reported the results of adding the DPP-4 inhibitors saxagliptin or linagliptin vs placebo to a baseline therapy composed of the SGLT2 inhibitor dapagliflozin or empagliflozin, respectively, for 24 weeks,7,8 or the dual add-on of a combination therapy with saxagliptin/ dapagliflozin or linagliptin/empagliflozin vs the single add-on of dapagliflozin or empagliflozin, respectively, for 24 or 52 weeks.9–11

Qualität der Studien:



Studienergebnisse:

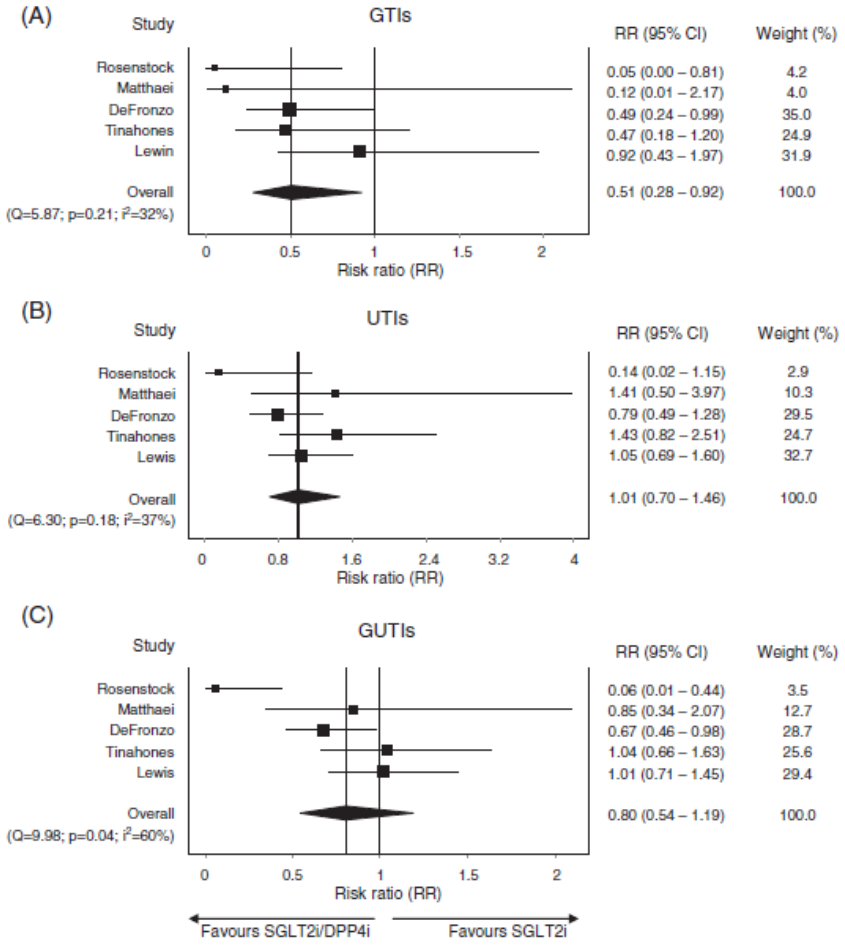


FIGURE 1 Meta-analysis forest plots. The forest plots are shown for UTIs (A), GTIs (B) and combined GUTIs (C). RRs with 95% CIs in each study and in the pooled estimate are given in the tables on the right. The random effects model was used

For GTIs, the RR was 0.51 (95% confidence interval [CI] 0.28-0.92) in favour of the DPP-4 inhibitor/SGLT2 inhibitor combination, with no heterogeneity (Figure 1A). For UTIs, the overall RR was 1.01 (95% CI 0.70-1.46; Figure 1B), and for combined GUTIs the RR was 0.80 (95% CI 0.43-1.19; Figure 1C), with significant heterogeneity.

Anmerkung/Fazit der Autoren

Our meta-analysis of five high-quality RCTs indicates a 49% lower GTI risk in patients who received a DPP-4 inhibitor in combination with an SGLT2 inhibitor as compared with patients who received an SGLT2 inhibitor alone. A lower rate was not observed in the frequency of UTIs. This is not surprising as, in RCTs, SGLT2 inhibitors typically increase the risk of GTIs, but not that of UTIs.

Li D et al., 2018 [71].

Risks of diabetic foot syndrome and amputation associated with sodium glucose co-transporter 2 inhibitors: A Meta-analysis of Randomized Controlled Trials.

Fragestellung

to evaluate the association between SGLT2i and risk of diabetic foot syndrome and amputation in patients with T2D, and to clarify whether the increased risk of amputations is a drug-specific effect or a class effect.

Methodik

Population:

- Patients with type 2 diabetes

Intervention:

- SGLT2i

Komparator:

- Placebo or other OADs

Endpunkte:

- Diabetic foot syndrome and amputation were identified using pre-specified lists from the Medical Dictionary for Regulatory Activities (MedDRA)

Recherche/Suchzeitraum:

- To June 2017 PubMed, Embase and CENTRAL

Qualitätsbewertung der Studien:

- Cochrane risk-of-bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 RCTs with 26,167 participants

Charakteristika der Population:

- Different Background therapies in the trials

Qualität der Studien:

- Thirteen RCTs were judged low risk of bias because they reported adequate random sequence generation and allocation concealment. Eight RCTs were low risk of performance bias, and six RCTs were low risk of detection bias. However, twelve RCTs reported the occurrence of events of interest online but not in the published paper, and judged unclear risk of reporting bias. All RCTs were judged low risk of attrition bias owing to the clear elaboration of discontinuation situation.

Studienergebnisse:

- Diabetic foot syndrome risk: only nine studies reported at least one case with **no significant** differences between SGLT2i and comparators
- Amputation risk: only four RCTs reported at least one case; No RCT was available to evaluate the amputation risk of dapagliflozin. SGLT2i as a class were **not significantly** associated with increased risk of amputation as compared with comparators

- Subgroupmeta-analysis showed that canagliflozin (OR 1.89, 95% CI 1.37–2.60), but not empagliflozin (OR 0.71, 95% CI: 0.71–1.48), was significantly associated with an increase in amputation risk.

Anmerkung/Fazit der Autoren

Current evidence from available RCTs suggests that SGLT2i, as a class, are not significantly associated with increased risk of diabetic foot syndrome. However, canagliflozin, but not empagliflozin, may increase the risk of amputations. Although the underlying mechanism remains uncertain, SGLT2i, especially canagliflozin, should be used with caution in patients who are at high risk of amputation.

Li J et al., 2018 [72].

Efficacy and safety of sodium-glucose cotransporter 2 inhibitors as add-on to metformin and sulfonylurea treatment for the management of type 2 diabetes: a meta-analysis.

Fragestellung

To evaluate the efficacy and safety of sodium-glucose cotransporter 2 (SGLT2) inhibitors as add-on to metformin and sulfonylurea treatment for type 2 diabetes management.

Methodik

Population:

- Adult T2DM patients having inadequate control on disease with metformin and SU therapy.

Intervention/Komparator:

- SGLT2 inhibitor as add-on to metformin and SU treatment compared to placebo or a suitable non-SGLT2 comparator drug

Endpunkte:

- HbA1c, FPG) levels, and body weight.
- systolic and diastolic blood pressure, and the blood levels of HDL-chol, LDL-chol, and triglycerides, and eGFR.
- Safety endpoints were the incidence of hypoglycemia and hyperglycemia, incidence of genital and uri nary tract infections, and incidence of ketoacidosis during treatment period

Recherche/Suchzeitraum:

- Embase, Google Scholar, Medline/PubMed, Scopus, Ovid SP, and Web of Science databases: October 2017

Qualitätsbewertung der Studien:

- Cochrane Risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 trials

Charakteristika der Studien/ Population:

- 3,321 patients treated with SGLT2 vs 1,318 placebo treated patients and 504 comparator (dipeptidyl dipeptidase 4 (DPP4) inhibitors) treated patients as add-on to metformin and SU treatment.
- canagliflozin was used in 3 studies, and empagliflozin in 2 and dapagliflozin in 2 studies.
- 5 studies compared a SGLT2 inhibitor against a placebo-controlled group whereas 2 studies used a DPP4 inhibitor drug as a comparator.
- Five studies investigated 2 doses of SGLT2 inhibitors.
- Age, percentage of males and BMI of the SGLT2 inhibitor treated patients were 56.85 years [95% confidence interval (CI): 56.24, 57.45], 52.12% [50.46, 53.77], and 29.72 kg/m2 [28.39, 31.06] and those of control patients were 56.69 years [56.11, 57.26], 51.55% [49.91, 53.20] and 29.36 kg/m2 [28.06, 30.65], respectively.

Qualität der Studien:

- Quality of the included RCTs was high

Studienergebnisse:

HbA1C

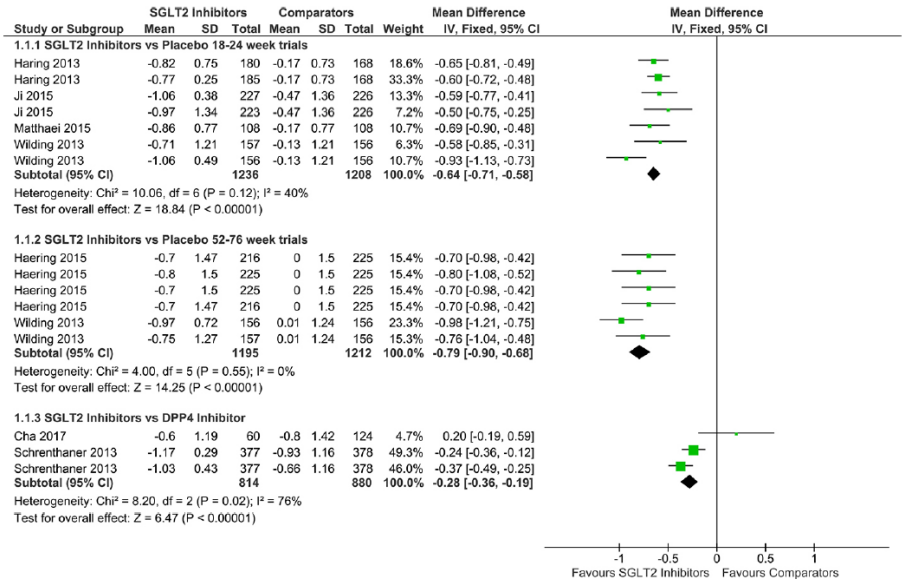


Fig. 2 Forest graph showing the mean differences in the changes in percent HbA1c between SGLT2 inhibitors and comparators.

Safety

Table 4 Outcomes of the safety meta-analysis (odds ratios [95% confidence interval]) between SGLT2 inhibitors-treated and placebo-treated groups in the incidence of adverse events (AEs).

Safety endpoint	*n*	Overall	Low dose	High dose
Any AE/s	2,695	1.02 [0.88, 1.17]; $p = 0.82$	0.98 [0.80, 1.19]; $p = 0.82$	1.07 [0.86, 1.32]; $p = 0.56$
Drug-related AEs	2,695	1.61 [1.37, 1.89]; $p < 0.0001$	1.63 [1.30, 2.05]; $p < 0.0001$	1.58 [1.25, 2.00]; $p < 0.00001$
Serious AEs	2,695	0.68 [0.51, 0.90]; $p = 0.007$	0.76 [0.52, 1.11]; $p = 0.16$	0.58 [0.38, 0.89]; $p = 0.01$
AEs causing discontinuation	2,695	1.09 [0.78, 1.52]; $p = 0.62$	0.95 [0.59, 1.52]; $p = 0.82$	1.25 [0.78, 1.99]; $p = 0.35$
Male genital tract infections	2,695	2.73 [1.29, 5.75]; $p = 0.009$	3.04 [1.10, 8.38]; $p = 0.03$	2.38 [0.79, 7.20]; $p = 0.12$
Female genital tract infections	2,695	4.71 [2.63, 8.44]; $p < 0.00001$	6.59 [2.57, 16.93]; $p < 0.0001$	3.63 [1.71, 7.70]; $p = 0.00008$
Urinary tract infections	2,680	1.31 [1.02, 1.67]; $p = 0.03$	1.37 [0.98, 1.91]; $p = 0.06$	1.24 [0.87, 1.77]; $p = 0.24$
Hypoglycemia	2,244	1.75 [1.43, 2.15]; $p < 0.00001$	1.88 [1.42, 2.50]; $p < 0.001$	1.62 [1.20, 2.187]; $p < 0.001$
Hyperglycemia	1,284	0.30 [0.22, 0.42]; $p < 0.00001$	0.30 [0.19, 0.47]; $p < 0.00001$	0.31 [0.20, 0.48]; $p < 0.00001$

Anmerkung/Fazit der Autoren

As add-on to metformin and sulfonylurea, SGLT2 inhibitors are found significantly more efficacious than placebo and DPP4 inhibitors in improving HbA1c, FPG, and body weight. Systolic and diastolic blood pressures, HDL-cholesterol and triglyceride levels also significantly improved with SGLT2 inhibitor treatment in comparison with placebo controlled patients. Incidence of genital tract infections and hypoglycemic events was significantly higher in SGLT2 inhibitor treated group whereas hyperglycemic events were significantly higher in control group.

Wang K et al., 2018 [104].

SGLT-2 Inhibitors and DPP-4 Inhibitors as Second-Line Drugs in Patients with Type 2 Diabetes: A Meta-Analysis of Randomized Clinical Trials

Fragestellung

To directly compare the efficacy and safety of SGLT-2 inhibitors to those of DPP-4 inhibitors and provide a basis for the selection of second-line drugs in patients with T2DM.

Methodik

Population:

- Patientes with T2DM

Intervention:

- SGLT-2 inhibitors, mono or combined with other drugs

Komparator:

- DPP-4 inhibitors, mono or combined with other drugs

Endpunkte:

- HbA1c, fasting plasma glucose (FPG) levels, body weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), triglycerides (TG) and adverse events

Recherche/Suchzeitraum:

- To July 2018 in PubMed, MEDLINE, the Cochrane Library, EMBASE, Web of Science, CNKI, and Biomedical database

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool
- Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Ergebnisse

Anzahl eingeschlossener Studien:

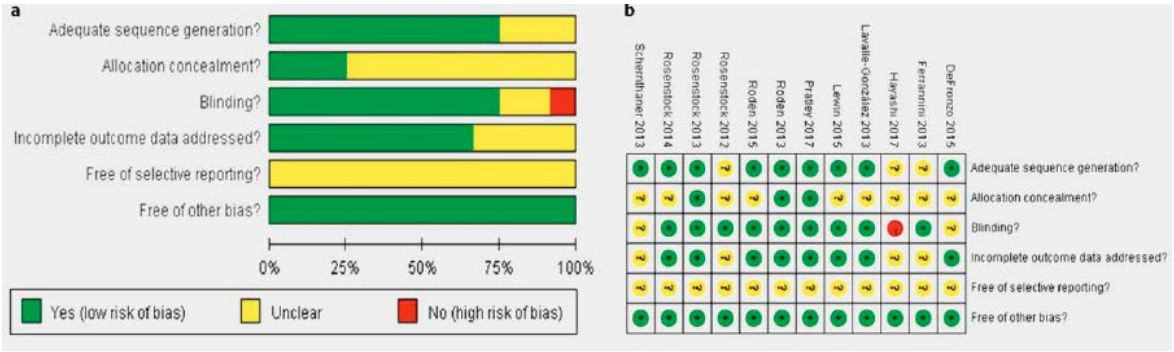
- 12 RCTs including 4342 patients

Charakteristika der Population:

- Background therapy
  - metformin (6 RCTs); None (3 RCTs); metformin + SU (1 RCT); SU, Metformin or α-Glucosidase inhibitor (1 RCT); glimepiride or insulin glargine (1 RCT)
- no significant differences in baseline characteristics

Qualität der Studien:

- Risk of bias of the included studies was low to unclear.



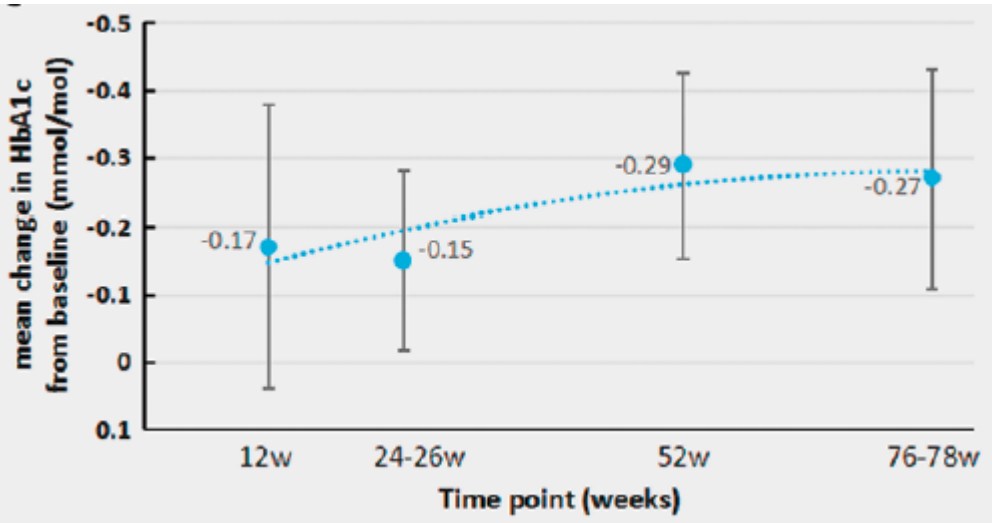
Studienergebnisse:

- The following table shows the study results. Significant outcomes are highlighted yellow. Outcomes at different timepoints from one study are pooled together (eg. Week 26 and 52)

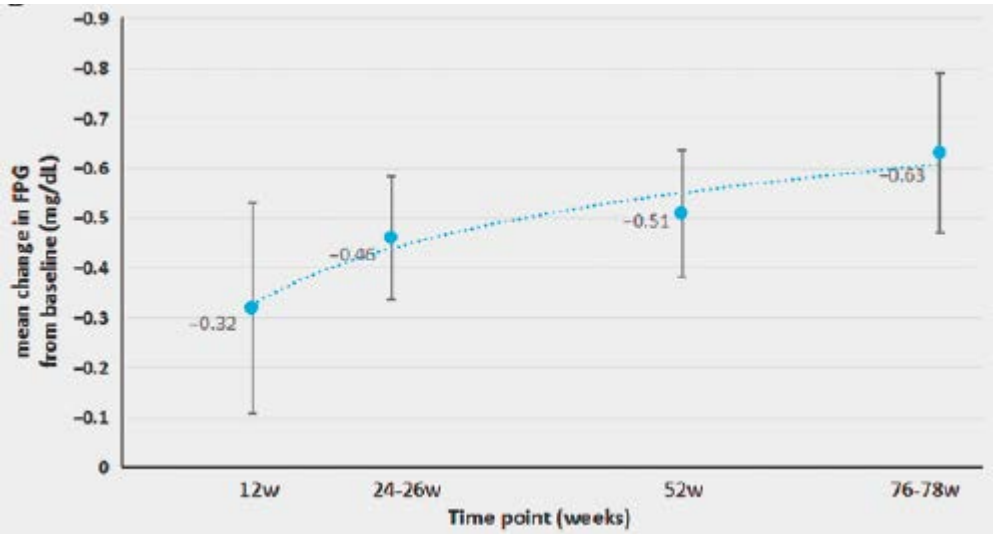
Outcomes	No. of participants (Studies)	Relative effect (95 % CI)	Quality of the evidence
HbA1c	4261(12)	SMD −0.22 (−0.30 to −0.14)	MODERATE[abg]
FPG	4261(12)	SMD −0.48 (−0.56 to −0.41)	MODERATE[abg]
Body weight	4269(12)	SMD −0.72 (−0.81 to −0.63)	LOW[abcg]
Systolic blood pressure	3796(10)	SMD −0.30 (−0.35 to −0.25)	MODERATE[acg]
Diastolic blood pressure	3301(9)	SMD −0.26 (−0.33 to −0.20)	LOW[ac]
Total cholesterol	1997(6)	SMD 0.12 (0.03 to 0.21)	LOW[ac]
HDL-cholesterol	2677(7)	SMD 0.48 (0.39 to 0.57)	LOW[abcg]
LDL-cholesterol	2671(7)	SMD 0.13 (0.05 to 0.20)	VERY LOW[acd]
Triglycerides	1961(6)	SMD 0.03 (−0.06 to 0.12)	VERY LOW[acd]
ADR	4260(11)	OR 1.01 (0.95 to 1.07)	LOW[acdg]
Urinary tract infection	4260(11)	OR 0.96 (0.77 to 1.21)	LOW[acdg]
Genital infection	3722(9)	OR 4.49 (2.96 to 6.83)	MODERATE[acefg]
Hypoglycaemia	2234(7)	OR 0.77 (0.40 to 1.46)	VERY LOW[acd]
Headache	938(5)	OR 0.64 (0.35 to 1.15)	VERY LOW[acd]
Pollakiuria	1758(4)	OR 2.24 (1.05 to 4.79)	MODERATE[acefg]
Nasopharyngitis	1430(4)	OR 0.75 (0.52 to 1.08)	VERY LOW[acd]
Back pain	1125(4)	OR 0.60 (0.34 to 1.05)	MODERATE[acg]
Hypertension	855(3)	OR 0.28 (0.12 to 0.66)	MODERATE[acg]
Hyperglycaemia	1572(5)	OR 0.43 (0.28 to 0.67)	LOW[ac]
Diarrhoea	843(3)	OR 1.17 (0.52 to 2.66)	VERY LOW[acde]
Upper respiratory tract infection	984(3)	OR 0.96 (0.61 to 1.52)	VERY LOW[bcd]
Event consistent with volume depletion	984(3)	OR 0.55 (0.16 to 1.86)	LOW[cd]

[a]Limitations in study design or execution (risk of bias), [b]Inconsistency in results, [c]Indirectness of evidence, [d]Imprecision of results, [e]Publication bias, [f]Magnitude of the effect, [g]Dose-response gradient.

- changes in HbA1c between SGLT-2 inhibitors and DPP-4 inhibitors by week



- changes in FPG between SGLT-2 inhibitors and DPP-4 inhibitors by week



- Sensitivity analysis showed no differences

Anmerkung/Fazit der Autoren

In this meta-analysis of 12 randomized controlled trials directly comparing the efficacy and safety between SGLT-2 and DPP-4 inhibitors, SGLT-2 inhibitors were found to be superior to DPP-4 inhibitors for treating type 2 diabetes. The results indicate that these two novel second-line antidiabetic agents both have advantages and disadvantages and thus should be chosen with caution to best suit each individual patient, especially as an add-on therapy after the failure of metformin or another anti-diabetic drug.

Kommentare zum Review

- Es ist zu beachten, dass die Ergebnisse der Studien zu verschiedenen Zeitpunkten (z.B. Woche 24 und 52) miteinander gepoolt wurden, sodass Studien mit drei Erhebungszeitpunkten dreifach in die Metaanalyse eingeflossen sind. Mögliche Verzerrungen hierdurch können nicht ausgeschlossen werden. Ausgenommen sind die Endpunkte HbA1c und FPG, für die auch separate Schätzer berechnet wurden.
- Weiterhin ist die heterogene Vor- bzw. Hintergrundtherapie zu beachten wobei diese in 6 Studien aus Metformin bestand. Diese Studien wurden auch von einem weiteren SR von Mishriky BM et al., 2018 [88] (insgesamt 7 Studien), der SGLT-2 Inhibitoren mit DPP-4 Inhibitoren als add-on Therapie zu Metformin verglich, eingeschlossen. Auch hier zeigten sich vergleichbare Ergebnisse, mit signifikant niedrigeren HbA1c Werte und reduziertem Körpergewicht, bei vermehrten Genitalinfektionen bei SGLT-2 Inhibitoren.

Zhang YJ et al., 2018 [114].

Efficacy and safety of empagliflozin for type 2 diabetes mellitus Meta-analysis of randomized controlled trials

Fragestellung

We carried out this meta-analysis to assess the efficiency and safety of EMPA (10 and 25mg once daily) compared with placebo both as monotherapy and as addon therapy to OAD in patients with T2DM.

Methodik

Population:

- T2DM

Intervention:

- EMPA

Komparator:

- Placebo, placebo as add-on to other antidiabetes therapy

Endpunkte:

- change from baseline in hemoglobin A1c (HbA1c), proportion of patients with HbA1c ≥7.0% at baseline who reached HbA1c <7.0% at last follow-up; changes from baseline in fasting plasma glucose (PFG); changes from baseline in body weight, proportion of patients with >5.0% reduction in body weight; change from baseline in systolic and diastolic blood pressures

Recherche/Suchzeitraum:

- Cochrane Central Register of Controlled Trials (CENTRAL), Web of Knowledge, and Pubmed up to May 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

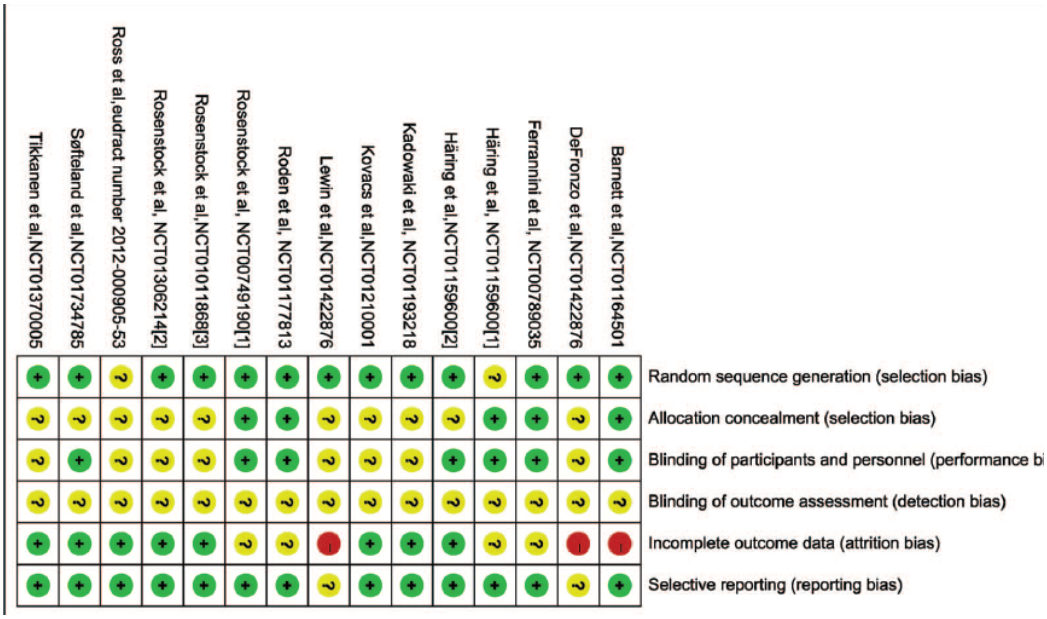
Anzahl eingeschlossener Studien:

- 15 studies (n=7891)

Charakteristika der Population:

There were 3 trials comparing EMPA vs placebo as monotherapy[13,17,18]; 3 trials comparing EMPA vs placebo as add-on to metformin[4,15,20]; 1 trial comparing EMPA vs placebo as add-on to metformin plus sulfonylurea[16]; 2 trial comparing EMPA vs placebo as add-on to metformin plus linagliptin[6,23]; 1 trial comparing EMPA vs placebo as add-on to pioglitazone or pioglitazone plus metformin[21]; 2 trials comparing EMPA vs placebo as add-on to insulin with or without OADs[3,19]; 1 trial comparing EMPA vs placebo as add-on to linagliptin[2]; 2 trials comparing EMPA vs placebo with other OADs unclear.[5,22]

Qualität der Studien:



Studienergebnisse:

Subgroup analysis of efficacy effect sizes (e.g., change from baseline in HbA1c, proportion of patient with HbA1c >7% who had HbA1c <7% and change from baseline in FPG) according to concomitant therapy of EMPA on type 2 diabetes mellitus.

	Change from baseline in HbA1c (%)			Proportion of patient with HbA1c>7% who had HbA1c<7%			change from baseline in FPG		
	No. of study	No. of participants	WMD (95% CI) Heterogeneity	No. of study	No. of participants	RR (95% CI) heterogeneity	No. of study	No. of participants	WMD (95% CI) heterogeneity
EMPA monotherapy	3	1335	−0.74 (−0.84, −0.64) $P=.54$, $I^2=0\%$	2	1019	4.63 (1.64, 13.09) $P=.07$, $I^2=69\%$	3	1335	−2.01 (−2.52, −1.49) $P=.004$, $I^2=82\%$
EMPA add-on to metformin	3	1351	−0.58 (−0.71, −0.46) $P=.12$, $I^2=53\%$	2	1054	1.90 (1.33, 2.71) $P=.27$, $I^2=17\%$	3	1707	−1.48 (−1.67, −1.29) $P=.41$, $I^2=0\%$
EMPA add-on to metformin plus sulfonylurea	1	666	−0.63 (−0.75, −0.51) not applicable	1	627	3.18 (2.04, 4.95) not applicable	1	666	−1.60 (−1.86, −1.34) not applicable
EMPA add-on to metformin plus linagliptin	2	715	−0.68 (−0.78, −0.58) $P=.39$, $I^2=0\%$	2	677	1.85 (1.42, 2.39) $P=.51$, $I^2=0\%$	2	721	−1.64 (−2.21, −1.07) $P=.06$, $I^2=71\%$
EMPA add-on to pioglitazone or pioglitazone plus metformin	1	501	−0.54 (−0.71, −0.38) not applicable	1	466	3.49 (1.97, 6.19) not applicable	1	496	−1.44 (−1.80, −1.08) not applicable
EMPA add-on to insulin with or without OAD	2	701	−0.47 (−0.62, −0.32) $P=.40$, $I^2=0\%$	2	1045	1.81 (1.37, 2.39) $P=.52$, $I^2=0\%$	2	840	−0.92 (−1.25, −0.59) $P=.88$, $I^2=0\%$
EMPA add-on to linagliptin	1	402	−0.73 (−0.94, −0.53) not applicable	1	370	1.82 (1.39, 2.39) not applicable	1	402	−1.52 (−1.91, −1.13) not applicable
EMPA with background OAD therapy unclear	2	1547	−0.56 (−0.73, −0.40) $P=.04$, $I^2=76\%$	1	290	3.09 (1.35, 7.04) not applicable	2	1561	−1.28 (−1.76, −0.80) $P=.04$, $I^2=76\%$
Overall effect	15	7218	−0.62 (−0.67, −0.57) $P=.03$, $I^2=45\%$	13	6122	2.20 (1.68, 2.87) $P<.00001$, $I^2=82\%$	15	7728	−1.52 (−1.72, −1.32) $P<.00001$, $I^2=79\%$

95% CI = 95% confidence interval, EMPA = empagliflozin, HbA1c = hemoglobin A1c, No = number, OAD = other oral antidiabetic agent, PFG = fasting plasma glucose, RR = relative risk, WMD = weight mean difference.

	Change from baseline in body weight		
	No. of study	No. of participants	WMD (95% CI) heterogeneity
EMPA monotherapy	3	1335	−1.87 (−2.19, −1.54) P=.28, I^2=22%
EMPA add-on to metformin	3	1814	−1.81 (−2.11, −1.52) P=.56, I^2=0%
EMPA add-on to metformin plus sulfonylurea	1	666	−1.88 (−2.25, −1.52) not applicable
EMPA add-on to metformin plus linagliptin	2	725	−2.49 (−2.90, −2.08) P=.75, I^2=0%
EMPA add-on to pioglitazone or pioglitazone plus metformin	1	498	−1.88 (−2.36, −1.41) not applicable
EMPA add-on to insulin with or without OAD	2	846	−2.56 (−3.26, −1.86) P=.62, I^2=0%
EMPA add-on to linagliptin	1	402	−1.50 (−2.45, −0.54) not applicable
EMPA with backgroud OAD therapy unclear	2	1561	−1.68 (−1.93, −1.43) P=.49, I^2=0%
Overall effect	15	7847	−1.91 (−2.07, −1.75) P=.13, I^2=30%

Anmerkung/Fazit der Autoren

In summary, it is demonstrated that EMPA therapy can improve glycemia, weight and blood pressure control, and was well tolerated except for increased genital infections in patients with T2DM. We recommend that EMPA should be offered to patients with T2DM, especially to patient who are overweight or at risk for body weight gain. As for combination therapy, we recommend EMPA firstly added to metformin, metformin plus sulfonylurea, metformin plus linagliptin, pioglitazone or pioglitazone plus metformin, insulin with or without OAD and linagliptin.

Yang Y et al., 2017 [110].

Safety and efficiency of SGLT2 inhibitor combining with insulin in subjects with diabetes: Systematic review and meta-analysis of randomized controlled trials

Fragestellung

We aimed to assess the safety and efficiency of the novel sodium glucose co-transporter 2 (SGLT2) inhibitor in combinations with insulin for type 1 and type 2 diabetes mellitus (T1DM and T2DM).

Methodik

Population:

- more than 18 years old, HbA1c between 7% and 12%, treated by insulin who were diabetes mellitus diagnosed by WHO diagnostic criteria

Intervention:

- SGLT2 inhibitors plus insulin versus placebo plus insulin or only insulin no matter the dose and kind of SGLT2 inhibitor and insulin

Komparator:

- placebo combined with insulin or only insulin in which the insulin method was same to experimental group

Endpunkte:

- adverse reactions including hypoglycemia, UTI, and GTI, the effective indicators including HbA1c and fasting plasma glucose (FPG)

Recherche/Suchzeitraum:

- from January 2010 to December 2016

Qualitätsbewertung der Studien:

- Cochrance System Evaluate Method

Ergebnisse

Anzahl eingeschlossener Studien:

- 9 with 3069 Patients

Charakteristika der Population:

- 8 of 9 studies double-blinded, randomized, placebo-controlled trials,
- 1 study randomized no placebo control trail,
- 2 studies IIa pilot trials;
- 1 study single-center,
- 6 studies multicentre
- experimental group in 9 studies SGLT2 inhibitor combined with insulin,
  - SGLT2 inhibitors were respectively dapagliflozin (3 studies), empagliflozin (3 studies), sapagniflozin (1 study), canagliflozin (1 study), and tofogliflozin (1 study),
  - control group were placebo with insulin or insulin itself
- Insulin therapy was not limited as long as the insulin therapy was the same in both 2 groups
- Intervention duration ranged from 2 to 78 weeks

Qualität der Studien:

- studies had low risk of bias

Studienergebnisse:

- Body weight
  - reduction was 2.53kg with SGLT2 inhibitors as add-on treatment in DM2 compared with placebo
  - n=696, MD -2,53 kg, 95%CI [-3,50 to -1,56], P<.00001
- Risk of GTI
  - events of GTI higher in SGLT2 inhibitors group compared with control group (OR 4,28, 95%CI [2,00-9,16], P=.0002)
- Risk of hypoglycemia and UTI
  - no statistical difference in the incidence of hypoglycemia (but a tendency to increase) and urinary infection

Anmerkung/Fazit der Autoren

SGLT2 inhibitors have improved the HbA1c, FPG, and body weight when combined with insulin and decreased the dose of insulin without increasing the risk of hypoglycemia. However, SGLT2 inhibitor was proved to be related to the events of GTI, despite SGLT2 inhibitors

appeared to be well tolerated. We suggest that more monitoring should be done to prevent the events of GTI, and more randomized controlled trials should be planned next step

Systematische Reviews zu Metformin oder Insulin Therapien

Monami M et al., 2021 [90].

Effect of metformin on all-cause mortality and major adverse cardiovascular events: An updated meta-analysis of randomized controlled trials.

Fragestellung

to perform a systematic review and meta-analysis on the effect of metformin on on major adverse cardiovascular events (MACEs) and all-cause mortality.

Methodik

Population:

- Patients with type 2 diabetes

Intervention:

- metformin

Komparator:

- current care or other active comparators or placebo

Endpunkte:

- MACE and all-cause mortality at ≥52 weeks

Recherche/Suchzeitraum:

- MEDLINE and EMBASE search on August 31st, 2020

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool
- GRADE for overall quality of evidence

Ergebnisse

Anzahl eingeschlossener Studien:

- 3 trials fulfilling the inclusion criteria was identified for MACE and 13 for all-cause mortality.

Charakteristika der Studien/ Population:

All-cause mortality

- Mean trial duration: 131 weeks;
- most of the trials with active comparators
- mean age 55 years

MACE

- the 2 trials compared metformin vs active comparators
- trial duraion were 256 and 577 weeks;

Qualität der Studien:

- Risk of bias was generally low, with the exception of blinding procedures.

Studienergebnisse:

MACE:

- Metformin was associated with a lower risk of MACEs compared with comparator treatments (n = 2 RCTs; MH-OR 0.52 [0.37, 0.73]), p < 0.001 (moderate quality of evidence)

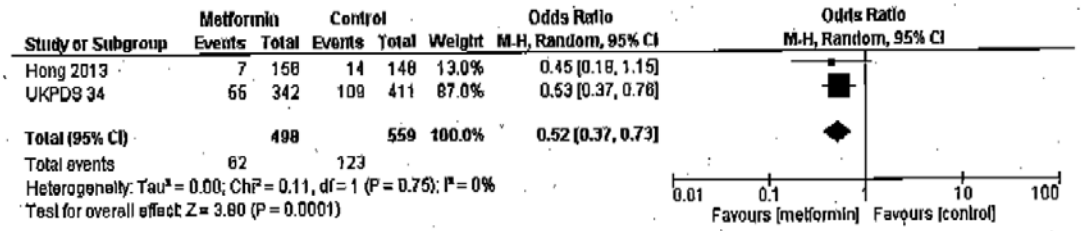


Figure 1 Risk of major adverse cardiovascular events (MACE) with metformin *versus* other active comparators approved by EMA and currently used in Europe (MH–OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals).

All-cause mortality

- Overall: no sign. stat. difference:

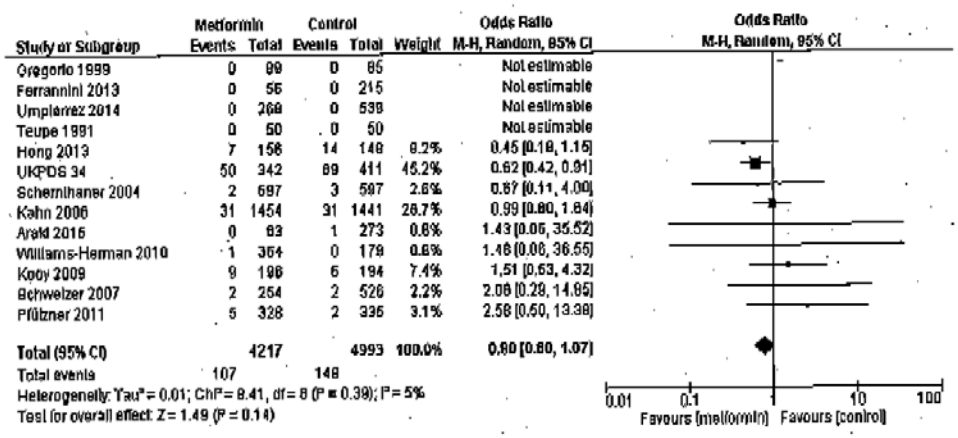


Figure 2 Risk of all-cause mortality with metformin *versus* other active comparators approved by EMA and currently used in Europe (MH–OR, 95% CI: Mantel-Haenzel Odds Ratio, with 95% of Confidence Intervals).

- No significant stat. Difference in risk of all-cause mortality for metformin in comparison with different classes of anti-hyperglycaemic drugs

Anmerkung/Fazit der Autoren

This meta-analysis suggests that metformin is associated with a lower risk of MACE, when compared with other anti-hyperglycaemic drugs.

Home PD et al., 2020 [62].

Efficacy and safety of iGlarLixi versus IDegLira in adults with type 2 diabetes inadequately controlled by glucagon-like peptide-1 receptor agonists: a systematic literature review and indirect treatment comparison

Fragestellung

To estimate the relative treatment effect between the fixed-ratio combinations iGlarLixi and IDegLira (glucagon-like peptide 1 receptor agonist with basal insulin) in people with type 2 diabetes inadequately controlled on a glucagon-like peptide 1 receptor agonist.

Methodik

Population:

- T2DM

Intervention:

- fixed-ratio combinations iGlarLixi

Komparator:

- IDegLira (glucagon-like peptide 1 receptor agonist with basal insulin)

Endpunkte:

- change in HbA1c; proportion reaching HbA1c <6.5% (<48 mmol/mol) and HbA1c <7.0% (<53 mmol/mol) targets relative to the respective GLP-1RA arm, change in fasting plasma glucose (FPG); parameters derived from selfmonitored plasma glucose (SMPG) profiles; change in body weight;
- incidence and event rate of hypoglycaemia, including total, symptomatic, severe, confirmed and combinations thereof. Treatment emergent adverse events (AEs)

Recherche/Suchzeitraum:

- MEDLINE (Medical Literature Analysis and Retrieval System Online), Embase and CENTRAL (Cochrane Central Register of Controlled Trials), published between January 2005 and January 2019
- Recent conference proceedings searched in Embase included those from the International Diabetes Federation, ADA and EASD from 2017 to 2018. Additional literature was identified by 'hand search' review of the reference lists of the articles found via the database search.

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool for assessing risk of bias in randomized trials

Ergebnisse

Anzahl eingeschlossener Studien:

- 2

Charakteristika der Population:

TABLE 1 Baseline demographics and disease characteristics in DUAL III and LixiLan-G

		LixiLan-G[12]		DUAL III[15]	
		iGlarLixi (n = 257)	GLP-1RA (n = 257)	IDegLira (n = 292)	GLP-1RA (n = 146)
Age, years		59.2 ± 9.6	60.0 ± 10.3	58.3 ± 9.9	58.4 ± 8.8
Sex, male		49	56	52.4	48.6
Race					
Asian		1.2	1.6	2.1	1.4
Black		4.7	2.7	5.1	8.2
White		93.8	94.9	92.1	89.7
Other		0.4	0.8	0.6	0.7
BMI, kg/m^2		32.8 ± 4.4	33.0 ± 4.4	32.9 ± 4.4	33.0 ± 4.1
Body weight, kg		–	–	95.6 ± 16.6	95.5 ± 17.3
HbA1c	%	7.9 ± 0.6	7.9 ± 0.5	7.8 ± 0.6	7.7 ± 0.6
	mmol/mol	63 ± 7[a]	63 ± 5[a]	62 ± 6	61 ± 7
FPG	mmol/L	9.1 ± 2.1	9.5 ± 1.9	9.0 ± 2.1	9.4 ± 2.3
	mg/dL	163 ± 38	170 ± 35	162 ± 38	169 ± 42
Fasting SMPG	mmol/L	8.6 ± 3.1	8.8 ± 3.3	8.7 ± NR	9.1 ± NR
	mg/dL	155 ± 56	158 ± 59	157 ± NR	164 ± NR
Duration of T2D, years		11.2 ± 7.4	11.0 ± 6.1	10.4 ± 5.8	10.4 ± 5.8
Previous GLP-1RA					
Liraglutide		52.5	56.4	79.5	79.5
Exenatide		7.0	3.5	20.5	20.5
Dulaglutide		21.0	19.8	–	–
Exenatide ER		17.5	18.7	–	–
Albiglutide		1.9	1.6	–	–
Previous OAD use					
Metformin alone		85.2[b]	81.3[b]	74.3	74.0
Metformin + SU		–	–	20.9	21.9
Metformin + pioglitazone		4.7	8.6	2.4	2.7
Metformin + SU + pioglitazone		–	–	2.4	1.4
Metformin + SGLT2 inhibitor		10.1	10.1	–	–

Note: Data are presented as % or mean ± SD.
Abbreviations: BMI, body mass index; ER, extended release; FPG, fasting plasma glucose; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; OAD, oral antihyperglycaemic drug; SD, standard deviation; SGLT2, sodium glucose cotransporter 2; SMPG, self-measured plasma glucose; SU, sulphonylurea; T2D, type 2 diabetes.
[a]Not reported in paper, but calculated from reported percentage data.
[b]Not reported in paper, but as all participants were taking metformin with or without pioglitazone and with or without an SGLT2 inhibitor this was calculated using metformin + pioglitazone use and metformin + SGLT2 inhibitor use.

-

Qualität der Studien:

- Keine Angaben

Studienergebnisse:

- Blood glucose control
- The mean HbA1c reduced from 7.8 ± 0.6% (62 ± 7 mmol/mol) at baseline to 6.4 ± 0.8% (46 ± 9 mmol/mol) at week 26 for IDegLira and from 7.8 ± 0.6% (62 ± 7 mmol/mol) at baseline to 6.7 ± 0.8% (50 ± 9 mmol/mol) at week 26 for iGlarLixi (Table 2).12,15 The results of the ITC analysis showed the mean difference between IDegLira and iGlarLixi in the change in HbA1c from baseline to week 26 was −0.36 (95% CrI −0.58, −0.14) %-units [−3.9 (−6.3, −1.5) mmol/mol; Figure 1A]. In both trials, HbA1c targets were ≤6.5% (≤48 mmol/mol) and <7.0% (<53 mmol/mol); more participants reached HbA1c targets with IDegLira or iGlarLixi than GLP-1RAs, but absolute attainment differed between studies for the GLP-1RA arms (Table 2).12,15 Adjusting for this, the relative risk of IDegLira compared with iGlarLixi for the ≤6.5% target was 0.94 (95% CrI 0.65, 1.39) and for the <7.0% target was 1.04 (95% CrI 0.85, 1.27; Figure 1B). The mean difference between IDegLira and iGlarLixi for change in FPG from baseline to week 26 was significant in

favour of IDegLira: −1.00 (95% CrI −1.57, −0.43) mmol/L. In LixiLan-G, participants collected a seven-point SMPG profile (postprandial 2 h after meals) on two separate days at baseline and week 26.12 In DUAL III, participants measured a nine-point SMPG profile adding a 04:00 h and following day breakfast test (postprandial 90 min after meals), at baseline and week 26.15 In both trials, pre- and post-breakfast and mean pre- and postprandial SMPG values were significantly lower with the FRC than the GLP-1RA comparator (Table S4).12,15 However SMPG levels at baseline and week 26 were highly variable in the GLP-1RA arms. Mean differences in pre- and post-breakfast, as well as daily average pre- and postprandial SMPG did not favour either FRC statistically, but credible intervals were wide (Figure 1A).

TABLE 2 Glucose control and body weight outcomes in DUAL III and LixiLan-G

	LixiLan-G[12]		DUAL III[15]	
	iGlarLixi (n = 252)	GLP-1RA (n = 253)	IDegLira (n = 292)	GLP-1RA (n = 146)
HbA1c, %				
Baseline	7.8 ± 0.6	7.8 ± 0.6	7.8 ± 0.6	7.7 ± 0.5
Week 26	6.7 ± 0.8	7.4 ± 0.8	6.4 ± 0.8	7.4 ± 1.0
LS mean difference, *P*	−0.6 (−0.8, −0.5), <0.0001		NC	
Difference, *P*	NC		−0.94 (−1.11, −0.78), <0.001	
HbA1c, mmol/mol[a]				
Baseline	62 ± 7	62 ± 7	62 ± 6	61 ± 7
Week 26	50 ± 9	57 ± 9	46 ± 9	57 ± 11
LS mean difference, *P*	−7 (−9, −6), <0.0001		NC	
Difference, *P*	NC		−10 (−12, −9), <0.001	
HbA1c target attainment (26 weeks)				
≤6.5% (≤48 mmol/mol), %	41	10	63	23
Difference, *P*	30.6 (23.6, 37.6), <0.0001		NC	
Estimated odds ratio, *P*	NC		7.5 (4.6, 12.4), <0.001	
<7.0% (<53 mmol/mol), %	61.9	26.6	75	36
Difference, *P*	36.1 (28.1, 44.0), <0.001		NC	
Odds ratio, *P*	NC		6.84 (4.28 to 10.94), <0.001	
FPG, mmol/L				
Baseline, mean ± SD	9.1 ± 2.1	9.5 ± 1.9	9.0 ± 2.1	9.4 ± 2.3
Week 26, mean ± SD	6.9 ± 1.7	8.7 ± 2.0	6.0 ± 1.6	8.8 ± 2.7
LS mean difference, *P*	−1.7 (−2.0 to −1.3), <0.0001		NC	
Difference, *P*	NC		−2.6 (−3.0 to −2.3), <0.001	
FPG, mg/dL				
Baseline, mean ± SD	163 ± 38	170 ± 35	162 ± 38[b]	169 ± 42[b]
Week 26, mean ± SD	124 ± 30	156 ± 36	108 ± 29[b]	158 ± 49[b]
LS mean difference, *P*	−30 (−36 to −24), <0.0001		NC	
Difference, *P*	NC		−48 (−55 to −41)[b], <0.001	
Body weight, kg				
Baseline, mean ± SD	NR	NR	95.6 ± 16.6	95.5 ± 17.3
Week 26, mean ± SD	+1.9 ± NR	−1.2 ± NR	+2.0 ± 3.9	−0.8 ± 3.0
LS mean difference, *P*	+3.0 (2.42 to 3.64), NR		NC	
Difference, *P*	NC		+2.9 (2.2 to 3.6), <0.001	

Note: Data are mean ± SD, %, difference (95% CrI), or *P* value.

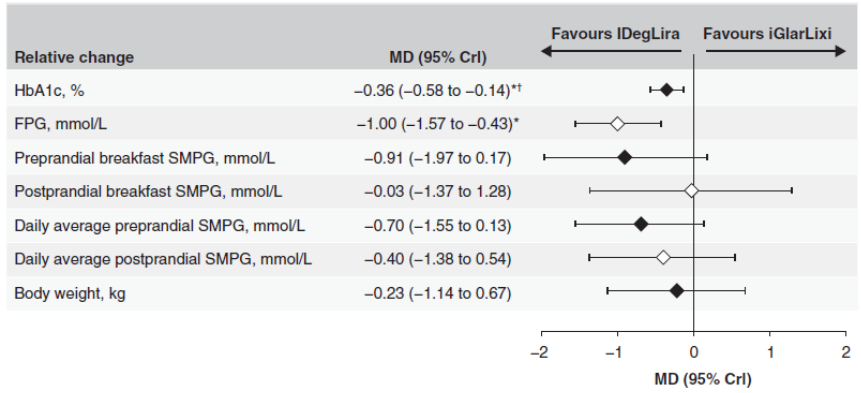
Note: The table includes only data as presented in the LixiLan-G and DUAL III publications, except week 26 FPG and FPG treatment difference data for DUAL III, which was only provided in mg/dL and then converted during our analyses to mmol/L. HbA1c mmol/mol data were also converted from percentage data.

Abbreviations: CrI, credible interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; LS, least squares; NC, not calculated in publication; NR, not reported in publication; SD, standard deviation.

[a]Not reported in the manuscript but calculated from reported % data.

[b]Calculated from mmol/L data.

A



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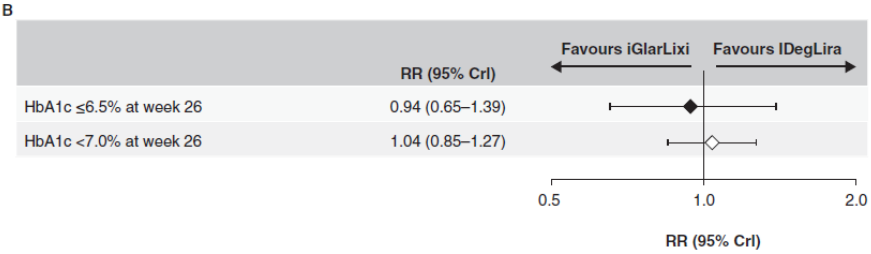

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- Body weight
  - In both trials, mean weight increased in the FRC group relative to the GLP-1RA group (Table 2)12,15; however, comparative analyses did not suggest differences in weight at week 26 between IDegLira and iGlarLixi.

TABLE 2 Glucose control and body weight outcomes in DUAL III and LixiLan-G

	LixiLan-G[12]		DUAL III[15]	
	iGlarLixi (n = 252)	GLP-1RA (n = 253)	IDegLira (n = 292)	GLP-1RA (n = 146)
HbA1c, %				
Baseline	7.8 ± 0.6	7.8 ± 0.6	7.8 ± 0.6	7.7 ± 0.5
Week 26	6.7 ± 0.8	7.4 ± 0.8	6.4 ± 0.8	7.4 ± 1.0
LS mean difference, *P*	−0.6 (−0.8, −0.5), <0.0001		NC	
Difference, *P*	NC		−0.94 (−1.11, −0.78), <0.001	
HbA1c, mmol/mol[a]				
Baseline	62 ± 7	62 ± 7	62 ± 6	61 ± 7
Week 26	50 ± 9	57 ± 9	46 ± 9	57 ± 11
LS mean difference, *P*	−7 (−9, −6), <0.0001		NC	
Difference, *P*	NC		−10 (−12, −9), <0.001	
HbA1c target attainment (26 weeks)				
≤6.5% (≤48 mmol/mol), %	41	10	63	23
Difference, *P*	30.6 (23.6, 37.6), <0.0001		NC	
Estimated odds ratio, *P*	NC		7.5 (4.6, 12.4), <0.001	
<7.0% (<53 mmol/mol), %	61.9	26.6	75	36
Difference, *P*	36.1 (28.1, 44.0), <0.001		NC	
Odds ratio, *P*	NC		6.84 (4.28 to 10.94), <0.001	
FPG, mmol/L				
Baseline, mean ± SD	9.1 ± 2.1	9.5 ± 1.9	9.0 ± 2.1	9.4 ± 2.3
Week 26, mean ± SD	6.9 ± 1.7	8.7 ± 2.0	6.0 ± 1.6	8.8 ± 2.7
LS mean difference, *P*	−1.7 (−2.0 to −1.3), <0.0001		NC	
Difference, *P*	NC		−2.6 (−3.0 to −2.3), <0.001	
FPG, mg/dL				
Baseline, mean ± SD	163 ± 38	170 ± 35	162 ± 38[b]	169 ± 42[b]
Week 26, mean ± SD	124 ± 30	156 ± 36	108 ± 29[b]	158 ± 49[b]
LS mean difference, *P*	−30 (−36 to −24), <0.0001		NC	
Difference, *P*	NC		−48 (−55 to −41)[b], <0.001	
Body weight, kg				
Baseline, mean ± SD	NR	NR	95.6 ± 16.6	95.5 ± 17.3
Week 26, mean ± SD	+1.9 ± NR	−1.2 ± NR	+2.0 ± 3.9	−0.8 ± 3.0
LS mean difference, *P*	+3.0 (2.42 to 3.64), NR		NC	
Difference, *P*	NC		+2.9 (2.2 to 3.6), <0.001	

Note: Data are mean ± SD, %, difference (95% CrI), or *P* value.
Note: The table includes only data as presented in the LixiLan-G and DUAL III publications, except week 26 FPG and FPG treatment difference data for DUAL III, which was only provided in mg/dL and then converted during our analyses to mmol/L. HbA1c mmol/mol data were also converted from percentage data.
Abbreviations: CrI, credible interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; LS, least squares; NC, not calculated in publication; NR, not reported in publication; SD, standard deviation.
[a]Not reported in the manuscript but calculated from reported % data.
[b]Calculated from mmol/L data.

-
- Hypoglycaemia
  - Table 3 presents the proportions of participants with hypoglycaemia and event rates as reported in the DUAL III and LixiLan-G trials. Comparisons of hypoglycaemic episodes were limited by differing definitions and plasma glucose cut-offs for hypoglycaemia, sulphonylurea use in DUAL III but not in LixiLan-G, and the very low rates of hypoglycaemia in the GLP-1RA comparator arms (Table 3). Accordingly, hypoglycaemia results are only presented descriptively. In DUAL III, hypoglycaemia was defined as confirmed hypoglycaemia with plasma glucose ≤3.1 mmol/L (≤56 mg/dL) or severe hypoglycaemia that required third-party assistance, whereas in LixiLan-G, hypoglycaemia was documented symptomatic with plasma glucose ≤3.9 mmol/L (≤70 mg/dL) and for a separate analysis <3.0 mmol/L (<54 mg/dL).

TABLE 3 Hypoglycaemia outcomes in the DUAL III and LixiLan-G studies

	LixiLan-G[12]		DUAL III[15]	
	iGlarLixi (n = 255)	GLP-1RA (n = 256)	IDegLira (n = 291)	GLP-1RA (n = 145)
Confirmed [≤3.1 mmol/L (≤56 mg/dL)] or severe hypoglycaemia[a], n (%); events per patient-year				
All participants	NR	NR	93 (32); 2.82	4 (2.8); 0.12
SU-treated participants	NR	NR	31/68 (46); 6.34	4/34 (12); 0.51
No SU			62/223 (28); 1.75	0/111 (0); 0
Nocturnal (00:01–05:59 h) confirmed [≤3.1 mmol/L (≤56 mg/dL)], n (%); events per patient-year				
All participants	NR	NR	32 (11); 0.45	1 (0.7); 0.02
Documented symptomatic [≤3.9 mmol/L (≤70 mg/dL)], n (%); events per patient-year				
All participants (no SU)	71 (27.8); 1.54	6 (2.3); 0.08	NR	NR
Documented symptomatic [<3.0 mmol/L (<54 mg/dL)], n (%); events per patient-year				
All participants (no SU)	24 (9.4); 0.25	1 (0.4); <0.01	NR	NR
Severe hypoglycaemia,[a] n (%)				
All participants	1 (0.4)	0	1 (0.3)	0

Abbreviations: GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, glycated haemoglobin; NR, not reported in publication; SU, sulphonylurea.
[a]An event requiring the assistance of another person.

- Incidence of confirmed hypoglycaemia (≤3.1 mmol/L) in participants with no sulphonylurea use was 28% for IDegLira in DUAL III versus 0% for the GLP-1RA arm. Incidence of documented symptomatic hypoglycaemia (<3.0 mmol/L) was 9.4% for iGlarLixi in LixiLan-G versus 0.4% for its GLP-1RA arm. Hypoglycaemia event occurred in each FRC arm of each study, versus none in the comparator groups.
- Safety
  - In LixiLan-G, 63.9% of participants in the iGlarLixi group and 47.3% in the GLP-1RA group reported at least one AE. The most commonly reported AEs across treatment groups were nasopharyngitis, nausea and diarrhoea. Nausea occurred in 8.6% and 2.3% of participants in the iGlarLixi and GLP-1RA groups. Serious AEs were reported in 3.9% of the iGlarLixi group and 3.5% of the GLP-1RA group. Discontinuations due to an AE occurred in 3.5% and 0% of participants, respectively. In DUAL III, AE were reported by 65.6% of participants in the IDegLira group and 63.4% in the GLP-1RA group. The most commonly reported AEs across treatment groups were nasopharyngitis, upper respiratory tract infection, increased lipase, headache and diarrhoea.
  - Nausea occurred in 3.1% of participants in the IDegLira group and 4.1% of the GLP-1RA group. Serious AEs were reported in 3.1% of the IDegLira group and 2.1% of the GLP-1RA group. One participant treated with IDegLira and two with GLP-1RA discontinued due to AEs.15 No unexplained or unexpected serious AEs occurred in either trial.

Anmerkung/Fazit der Autoren

Results of this indirect treatment comparison using two studies suggest iGlarLixi and IDegLira appear to offer similar benefits for HbA1c target achievement. However, the findings suggest differences in other glycaemia results and hypoglycaemia, which may reflect differences in study design and titration approaches.

Mannucci E et al., 2020 [80].

Effect of insulin secretagogues on major cardiovascular events and all-cause mortality: A meta-analysis of randomized controlled trials.

Fragestellung

to perform a systematic review and meta-analysis on the effect of insulin secretagogues (sulfonylureas and glinides) on on major adverse cardiovascular events (MACEs) and all-cause mortality.

Methodik

Population:

- Patients with type 2 diabetes

Intervention:

- insulin secretagogues (glibenclamide, gliclazide, glimepiride, glipizide, chlorpropamide, repaglinide, nateglinide)

Komparator:

- active comparators or placebo

Endpunkte:

- MACE and all-cause mortality at ≥52 weeks

Recherche/Suchzeitraum:

- MEDLINE up to January 1st, 2020.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias tool
- GRADE for overall quality of evidence

Ergebnisse

Anzahl eingeschlossener Studien:

- 46 RCTs for all-cause mortality, 14 for MACE

Charakteristika der Studien/ Population:

All-cause mortality

- Mean trial duraion 140 weeks; all trials with active comparators
- mean 58 years

MACE

- all trials on sulfonylureas and none on glinides
- Mean trial duraion 162 weeks; all trials with active comparators
- Mean age 56 years

Qualität der Studien:

- The overall quality of all included RCTs was high for all items, with the exception of performance bias in 11 open-label trials (all cause mortality) / in 2 open-label trials (MACE).

Studienergebnisse:

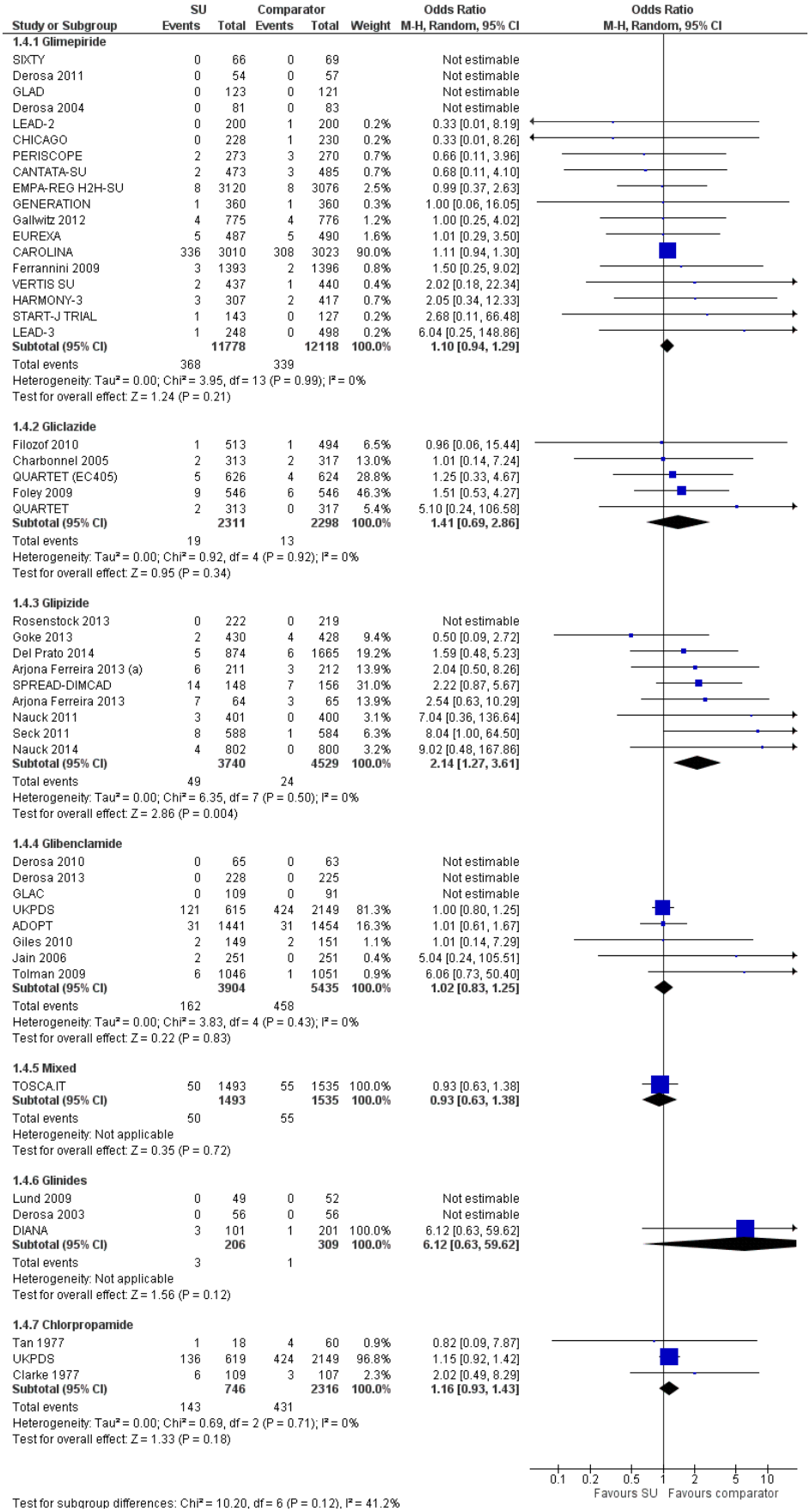
MACE (14 RCTs)

- Insulin secretagogues were not significantly associated with an increased risk of MACEs in comparison with controls (MH-OR 1.08 [95% CI 0.96, 1.22] I^2=11%, p = 0.20), quality of evicence: high

When considering trials in which insulin secretagogues were given as first-line treatment (i.e. monotherapy) [9,11–14] the MH–OR was 1.08 [0.95, 1. 22], p = 0.27, whereas in those in which *insulin secretagogues* were administered as add-on therapy the MH–OR *was* 0.87 [0.59, 1. 30], p = 0.51.

All-cause mortality

- insulin secretagogues were associated with a significantly increased risk of all-cause mortality (MH-OR 1.11 [1.00, 1.23] I^2=0%, p = 0.04), quality of evicence: high
- Risk of all-cause mortality with individual insulin secretagogues versus other comparators approved by EMA and currently used in Europe (MH-OR, 95% CI: Mantel-Haenzel Odds Ratio, 95% of Confidence Intervals):


SU
Comparator
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
1.4.1 Glimepiride
SIXTY 0 66 0 69 Not estimable
Derosa 2011 0 54 0 57 Not estimable
GLAD 0 123 0 121 Not estimable
Derosa 2004 0 81 0 83 Not estimable
LEAD-2 0 200 1 200 0.2% 0.33 [0.01, 8.19]
CHICAGO 0 228 1 230 0.2% 0.33 [0.01, 8.26]
PERISCOPE 2 273 3 270 0.7% 0.66 [0.11, 3.96]
CANTATA-SU 2 473 3 485 0.7% 0.68 [0.11, 4.10]
EMPA-REG H2H-SU 8 3120 8 3076 2.5% 0.99 [0.37, 2.63]
GENERATION 1 360 1 360 0.3% 1.00 [0.06, 16.05]
Gallwitz 2012 4 775 4 776 1.2% 1.00 [0.25, 4.02]
EUREXA 5 487 5 490 1.6% 1.01 [0.29, 3.50]
CAROLINA 336 3010 308 3023 90.0% 1.11 [0.94, 1.30]
Ferrannini 2009 3 1393 2 1396 0.8% 1.50 [0.25, 9.02]
VERTIS SU 2 437 1 440 0.4% 2.02 [0.18, 22.34]
HARMONY-3 3 307 2 417 0.7% 2.05 [0.34, 12.33]
START-J TRIAL 1 143 0 127 0.2% 2.68 [0.11, 66.48]
LEAD-3 1 248 0 498 0.2% 6.04 [0.25, 148.86]
Subtotal (95% CI) 11778 12118 100.0% 1.10 [0.94, 1.29]
Total events 368 339
Heterogeneity: Tau² = 0.00; Chi² = 3.95, df = 13 (P = 0.99); I² = 0%
Test for overall effect: Z = 1.24 (P = 0.21)
1.4.2 Gliclazide
Filozof 2010 1 513 1 494 6.5% 0.96 [0.06, 15.44]
Charbonnel 2005 2 313 2 317 13.0% 1.01 [0.14, 7.24]
QUARTET (EC405) 5 626 4 624 28.8% 1.25 [0.33, 4.67]
Foley 2009 9 546 6 546 46.3% 1.51 [0.53, 4.27]
QUARTET 2 313 0 317 5.4% 5.10 [0.24, 106.58]
Subtotal (95% CI) 2311 2298 100.0% 1.41 [0.69, 2.86]
Total events 19 13
Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 4 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)
1.4.3 Glipizide
Rosenstock 2013 0 222 0 219 Not estimable
Goke 2013 2 430 4 428 9.4% 0.50 [0.09, 2.72]
Del Prato 2014 5 874 6 1665 19.2% 1.59 [0.48, 5.23]
Arjona Ferreira 2013 (a) 6 211 3 212 13.9% 2.04 [0.50, 8.26]
SPREAD-DIMCAD 14 148 7 156 31.0% 2.22 [0.87, 5.67]
Arjona Ferreira 2013 7 64 3 65 13.9% 2.54 [0.63, 10.29]
Nauck 2011 3 401 0 400 3.1% 7.04 [0.36, 136.64]
Seck 2011 8 588 1 584 6.3% 8.04 [1.00, 64.50]
Nauck 2014 4 802 0 800 3.2% 9.02 [0.48, 167.86]
Subtotal (95% CI) 3740 4529 100.0% 2.14 [1.27, 3.61]
Total events 49 24
Heterogeneity: Tau² = 0.00; Chi² = 6.35, df = 7 (P = 0.50); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)
1.4.4 Glibenclamide
Derosa 2010 0 65 0 63 Not estimable
Derosa 2013 0 228 0 225 Not estimable
GLAC 0 109 0 91 Not estimable
UKPDS 121 615 424 2149 81.3% 1.00 [0.80, 1.25]
ADOPT 31 1441 31 1454 16.3% 1.01 [0.61, 1.67]
Giles 2010 2 149 2 151 1.1% 1.01 [0.14, 7.29]
Jain 2006 2 251 0 251 0.4% 5.04 [0.24, 105.51]
Tolman 2009 6 1046 1 1051 0.9% 6.06 [0.73, 50.40]
Subtotal (95% CI) 3904 5435 100.0% 1.02 [0.83, 1.25]
Total events 162 458
Heterogeneity: Tau² = 0.00; Chi² = 3.83, df = 4 (P = 0.43); I² = 0%
Test for overall effect: Z = 0.22 (P = 0.83)
1.4.5 Mixed
TOSCA.IT 50 1493 55 1535 100.0% 0.93 [0.63, 1.38]
Subtotal (95% CI) 1493 1535 100.0% 0.93 [0.63, 1.38]
Total events 50 55
Heterogeneity: Not applicable
Test for overall effect: Z = 0.35 (P = 0.72)
1.4.6 Glinides
Lund 2009 0 49 0 52 Not estimable
Derosa 2003 0 56 0 56 Not estimable
DIANA 3 101 1 201 100.0% 6.12 [0.63, 59.62]
Subtotal (95% CI) 206 309 100.0% 6.12 [0.63, 59.62]
Total events 3 1
Heterogeneity: Not applicable
Test for overall effect: Z = 1.56 (P = 0.12)
1.4.7 Chlorpropamide
Tan 1977 1 18 4 60 0.9% 0.82 [0.09, 7.87]
UKPDS 136 619 424 2149 96.8% 1.15 [0.92, 1.42]
Clarke 1977 6 109 3 107 2.3% 2.02 [0.49, 8.29]
Subtotal (95% CI) 746 2316 100.0% 1.16 [0.93, 1.43]
Total events 143 431
Heterogeneity: Tau² = 0.00; Chi² = 0.69, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.33 (P = 0.18)
Test for subgroup differences: Chi² = 10.20, df = 6 (P = 0.12), I² = 41.2%
0.1 0.2 0.5 1 2 5 10
Favours SU Favours comparator

Anmerkung/Fazit der Autoren.

This meta-analysis suggests that insulin secretagogues are associated with an increased risk of all-cause mortality when compared with placebo or other anti-hyperglycaemic drugs.

Zhou W et al., 2019 [116].

Insulin Degludec, a Novel Ultra-Long-Acting Basal Insulin versus Insulin Glargine for the Management of Type 2 Diabetes: A Systematic Review and Meta- Analysis

Fragestellung

Therefore, we performed a systematic review and meta-analysis of randomized controlled trials (RCTs) to establish the effect of insulin degludec versus insulin glargine on key outcomes in the treatment of patients with T2DM, including glycemic control, hypoglycamia, body weight gain, and SAEs.

Methodik

Population:

- Patients with T2DM

Intervention:

- insulin degludec

Komparator:

- insulin glargine

Endpunkte:

- changes in glycated hemoglobin (HbA1c), changes in laboratory-measured fasting plasma, glucose (FPG) or proportion of participants with, HbA1c ≤ 7.0% OR proportion of participants experiencing ≥ 1 hypoglycemic event or changes in body weight or proportion of participants with major adverse cardiovascular events (MACEs), or proportion of participants with SAEs

Recherche/Suchzeitraum:

- PubMed, Embase, Web of Science, and Cochrane Library databases published prior to 13 August 2018

Qualitätsbewertung der Studien:

- Cochrane risk of bias

Ergebnisse

Anzahl eingeschlossener Studien:

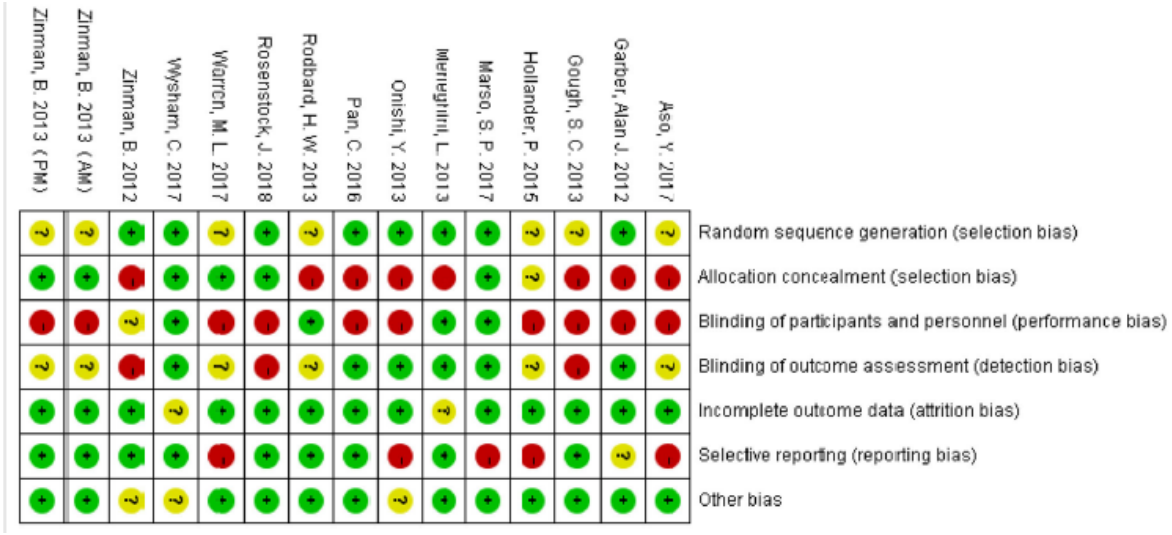
- 15 RCTs (with data for 16,694 participants)

Charakteristika der Population:

- Mean trial duration was 43.3 (range 24–104) weeks.
- Patients had a mean baseline HbA1c of 8.31% (range 7.6–8.86%), mean baseline FPG of 165.7 (range 137–186) mg/dL, mean baseline BMI of 30.9 (range 24.6–36.2) kg/ m2, and mean duration of diabetes of 11.1 (range 8–16.4) years.

- Of the 15 RCTs, 12 were carried out in multiple countries, two in the USA, and one in Japan. In the two crossover trials, participants were switched directly to the other intervention without a washout perio.
- In 13 trials used Insulin degludec was administered once daily in 13 trials and three times per week in only two trials.

Qualität der Studien:



Studienergebnisse:

Glycemic Control

- Ten studies (containing 11 trials) that included 7719 patients in the insulin degludec group and 6279 patients in the insulin glargine group reported the change in HbA1c between baseline and the end of the intervention.
- A random-effects model was used for this analysis (I2 = 66.5%). A pooled analysis of all 11 trials revealed that insulin glargine led to a greater mean reduction in HbA1c than did insulin degludec (WMD 0.07, 95% CI 0.01, 0.13, P = 0.019), with statistically significant between-study heterogeneity (P\0.1, I2 [50%).
- Subgroup analysis (P = 0.204, I2 = 27%) based on the background treatment (insulin-naı¨ve vs. insulin) was also performed to demonstrate that there was no statistically significant difference between the two treatment groups regarding changes in the HbA1c level (WMD 0.03, 95% CI 0.00, 0.07, P = 0.08;

Hypoglycemic Events

- Pooled analysis of the 12 studies (8903 participants; I2 = 43.5%) that assessed the proportion of participants experiencing ≥ 1 hypoglycemic event showed a lower incidence of all confirmed hypoglycemic episodes when participants were treated with insulin degludec, as compared to treatment insulin glargine, but the difference was not statistically significant
- RR 0.98, 95% CI 0.93, 1.03, P = 0.43

Body weight Control

- Six studies that included 6713 patients in the insulin degludec group and 5431 patients in the insulin glargine group reported changes in body weight.
- A random-effect model was applied for this analysis (P = I2 = 79%). Pooling the data of these studies showed that insulin degludec led to a greater mean weight gain than did

insulin glargine, but the difference was not statistically significant (WMD 0.23, 95% CI - 0.14, 0.61, P = 0.22;

Serious Adverse Events

- Thirteen studies that included 9961 patients in the insulin degludec group and 7310 patients in the insulin glargine group reported the proportion of participants with SAEs
- Insulin degludec was associated with a lower ratio of participants with SAEs as compared to insulin glargine, but the difference was not statistically significant (RR 0.97, 95% CI 0.92, 1.02, P = 0.20)

Anmerkung/Fazit der Autoren

Findings from our meta-analysis show that insulin degludec has an overall beneficial effect on the management of type 2 diabetes as compared to insulin glargine, mainly manifesting in the lower risks of severe and nocturnal hypoglycemia.

Zaccardi F et al., 2017 [111].

Comparison of glucose-lowering agents after dual therapy failure in type 2 diabetes: A systematic review and network meta-analysis of randomized controlled trial.

Fragestellung

To assess the evidence supporting the choice of third-line agents in adults with inadequately controlled type 2 diabetes.

Methodik

Population:

- adult patients with type 2 diabetes with sub-optimal glucose control on dual therapy with metformin and a second-line agent (“dual therapy failure”)

Intervention/Komparator:

- third-line glucose-lowering agents added to metformin-based dual treatments

Endpunkte:

- cardiometabolic outcomes (HbA1c, fasting plasma glucose [FPG], body weight, systolic and diastolic blood pressure, total cholesterol, LDL and HDL cholesterol, and triglycerides) and hypoglycaemia

Recherche/Suchzeitraum:

- between January 2000 and July 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 43 with 16 590 participants
- metformin combined with: sulphonylureas (SUs) in 20 RCTs; thiazolidinediones (TZDs) in 10; basal or rapid-acting insulin in 6; dipeptidyl peptidase-4 (DPP-4) inhibitors in 3;

glucagon-like peptide-1 receptor agonists (GLP-1RAs) in 2; and sodium-glucose co-transporter-2 (SGLT-2) inhibitors in 2

Qualität der Studien:

- overall risk of bias: low, high and unclear in 31 (63.3%), 3 (6.1%) and 15 (30.6%) studies, respectively
- high or unclear domain-specific bias was lowest for selective reporting (20.4%) and highest for incomplete outcome data (34.7%)
- almost all studies were supported by one or more pharmaceutical companies (other bias)

Studienergebnisse:

- Direct pairwise comparisons for HbA1c, fasting plasma glucose, and body weight, by outcome, background therapy, and RCTs duration

Outcome	Drug A	Drug B	Metformin + Sulphonylurea (24-36 weeks)			
			No. of		Mean Difference (95% CI)	I^2 (p-value)
			RCT	Part.		
HbA1c (%)	DPP-4i	Placebo	5	2146	-0.65 (-0.78, -0.52)	59.5 (0.042)
	Basal	GLP-1RA	4	2191	0.21 (-0.03, 0.45)	86.9 (0.000)
	SGLT-2i	Placebo	3	959	-0.73 (-0.92, -0.54)	69.9 (0.036)
FPG (mmol/l)	DPP-4i	Placebo	4	1678	-0.76 (-0.99, -0.53)	10.5 (0.341)
	SGLT-2i	Placebo	3	959	-1.71 (-1.95, -1.47)	0.0 (0.512)
Body weight (kg)	Basal	GLP-1RA	4	2141	3.50 (2.93, 4.07)	69.5 (0.020)
	SGLT-2i	Placebo	3	961	-1.96 (-2.29, -1.62)	0.0 (0.747)
	GLP-1RA	Placebo	2	832	-0.91 (-1.52, -0.29)	26.3 (0.244)
	Basal	Placebo	2	557	2.74 (1.39, 4.09)	77.0 (0.037)
	DPP-4i	Placebo	2	1190	0.52 (0.07, 0.98)	51.8 (0.150)

Outcome	Drug A	Drug B	Metformin + Thiazolidinedione (24-36 weeks)			
			No. of		Mean Difference (95% CI)	I^2 (p-value)
			RCT	Part.		
HbA1c (%)	GLP-1RA	Placebo	4	1337	-0.88 (-1.14, -0.61)	81.1 (0.001)
	SGLT-2i	Placebo	2	477	-0.68 (-0.86, -0.51)	35.3 (0.214)
	DPP-4i	Placebo	2	573	-0.70 (-0.87, -0.53)	0.0 (0.366)
FPG (mmol/l)	GLP-1RA	Placebo	3	982	-1.57 (-2.26, -0.88)	85.6 (0.001)
	DPP-4i	Placebo	2	572	-0.77 (-1.15, -0.38)	10.5 (0.291)
Body weight (kg)	GLP-1RA	Placebo	4	1284	-2.40 (-2.86, -1.95)	5.5 (0.365)

- Direct pairwise comparisons for hypoglycaemia, by outcome, background therapy, and RCTs duration

Drug A	Drug B	Metformin + Sulphonylurea (24-36 weeks)				
		No. of			Odds Ratio (95% CI)	I^2 (p-value)
		RCT	Part.	Hypo*		
DPP-4i	Placebo	5	2280	293	3.06 (1.52, 6.14)	54.0 (0.069)
Basal	GLP-1RA	3	1684	523	1.58 (0.86, 2.90)	84.1 (0.002)
SGLT-2i	Placebo	3	972	77	1.77 (1.02, 3.07)	14.9 (0.309)
Basal	Placebo	2	557	166	2.76 (1.49, 5.11)	55.6 (0.134)
GLP-1RA	Placebo	2	832	180	2.33 (1.62, 3.35)	0.0 (0.351)

Drug A	Drug B	Metformin + Thiazolidinedione (24-36 weeks)				
		No. of			Odds Ratio (95% CI)	I^2 (p-value)
		RCT	Part.	Hypo*		
GLP-1RA	Placebo	4	1408	122	2.85 (1.71, 4.74)	8.6 (0.350)
DPP-4i	Placebo	3	847	40	1.38 (0.69, 2.76)	0.0 (0.514)

Drug A	Drug B	Metformin + Sulphonylurea (52-54 weeks)				
		No. of			Odds Ratio (95% CI)	I^2 (p-value)
		RCT	Part.	Hypo*		
SGLT-2i	Placebo	2	530	46	1.62 (0.87, 3.02)	0.0 (0.428)

*Hypo: Participants with hypoglycaemia event(s), Comparisons with only one study are not shown. CI: Confidence interval; Part.: = Participants; Basal: Basal (long-acting) insulin; DPP-4i: Dipeptidyl peptidase-4 inhibitor; GLP-1RA: Glucagon-like peptide-1 receptor agonist; SGLT-2i: Sodiumglucose cotransporter-2 inhibitor.

Anmerkung/Fazit der Autoren

Moderate-quality evidence supports the choice of a third-line agent only in patients on metformin combined with a SU or a TZD, with SGLT-2 inhibitors performing generally better than other drugs. In suggesting third-line agents, future guidelines should recognize the widely differing evidence on the various dual therapy failures.

Kommentare zum Review

- Funding information: F.Z. is a Clinical Research Fellow funded with an unrestricted Educational Grant from Sanofi-Aventis to the University of Leicester. The funding source had no involvement in this study.

Netzwerk-Metaanalysen

Cha AS et al., 2021 [9].

Microvascular Benefits of New Antidiabetic Agents: A Systematic Review and Network Meta-Analysis of Kidney Outcomes

Fragestellung

To characterize the risk of developing a composite kidney outcome among patients receiving a new antidiabetic medication of the SGLT-2i, GLP-1ra, and DPP-4i drug classes.

Methodik

Population:

- Adults with T2DM

Intervention/Komparator

- new antidiabetic medication of the SGLT-2i, GLP-1ra, and DPP-4i drug classes

Endpunkte:

- composite kidney outcome

Recherche/Suchzeitraum:

- MEDLINE: March 2020

Qualitätsbewertung der Studien:

Revised cochrane risk of bias tool (RoB2)

NMA-Methodik/Überprüfung der zentralen Annahmen

- network meta-analysis was conducted within a Bayesian framework using a fixed-effects model with uninformative priors
- qualitative assessment of transitivity was conducted where transitivity was defined as the assessement of the validity of logical inference based on a similar distribution of potential modifiers across included studies.
- A heterogeneity statistic was calculated to quantify the % total variation across the studies.
- The consistency assumption did not appply, since this analysis did not include both direct and indirect evidence

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 trials

Table 4. Baseline Demographic Characteristics Across Included Studies

Clinical trial program	Year of publication	NCT identifier(s)	Drug class	Treatment drug	Sample size	Mean age ± SD	Female (%)	HbA_{1c} (%) ± SD	Duration of T2DM (years)	eGFR ± SD (mL/min/1.73m^2)	Inclusion criteria by eGFR (mL/min/1.73m^2)	Median follow-up time (years)
CANVAS-R	2017	01032629	SGLT-2i	Canagliflozin	5795	63.2 ± 8.3	35.1	8.2 ± 0.9	13.5 ± 7.7	76.7 ± 20.3	≥30	2.42 years
		01989754		Placebo	4347	63.4 ± 8.2	36.7	8.2 ± 0.9	13.7 ± 7.8	76.7 ± 20.8		
CREDENCE	2019	02065791	SGLT-2i	Canagliflozin	2202	62.9 ± 9.2	34.6	8.3 ± 1.3	15.5 ± 8.7	56.3 ± 18.2	30-90	2.62 years
				Placebo	2199	63.2 ± 9.2	33.3	8.3 ± 1.3	16.0 ± 8.6	56.0 ± 18.3		
DECLARE- TIMI 58	2018	01730534	SGLT-2i	Dapagliflozin	8582	63.9 ± 6.8	36.9	8.3 ± 1.2	11.0 (6.0–16.0)[a]	85.4 ± 15.8	≥60	4.2 years
				Placebo	8578	64.0 ± 6.8	37.9	8.3 ± 1.2	10.0 (6.0–16.0)[a]	85.1 ± 16.0		
EMPA-REG OUTCOME[b]	2016	01131676	SGLT-2i	Empagliflozin	4685	63.1 ± 8.3	28.8	8.07 ± 0.85	2670 (57.0)[a]	74.1 ± 14.8	≥30	3.1 years
				Placebo	2333	63.3 ± 8.5	28.0	8.08 ± 0.84	1339 (57.4)[a]	73.8 ± 14.3		
LEADER	2016	01179048	GLP-1ra	Liraglutide	4668	64.2 ± NR	35.5	8.7 ± NR	12.8 ± 8.0	80.2 ± NR	[d]33	3.84 years
				Placebo	4672	64.4 ± NR	36.0	8.7 ± NR	12.9 ± 8.1	80.6 ± NR		
SUSTAIN-6[b]	2016	01720446	GLP-1ra	Semaglutide	1648	64.6 ± 7.2	38.5	8.7 ± 1.45	14.2 ± 8.2	NR	<60	2.1 years
				Placebo	1649	64.6 ± 7.5	40.0	8.7 ± 1.5	13.6 ± 7.95	NR		
CARMELINA	2019	01897532	DPP-4i	Linagliptin	3494	66.1 ± 9.1	38.5	7.9 ± 1.0	15.0 ± 9.6	54.7 ± 25.1	15-75	2.2 years
				Placebo	3485	65.6 ± 9.1	35.7	8.0 ± 1.0	14.5 ± 9.3	54.5 ± 24.9		

Abbreviations: eGFR, estimated glomerular filtration rate; DPP-4i, dipeptidyl peptidase-4 inhibitor; eGFR, estimated glomerular filtration rate; GLP-1ra, glucagon-like peptide 1 analogues; HbA1c, glycated hemoglobin A1 NCT, National Clinical Trial; NR, not reported; SGLT-2i, sodium-glucose co-transporter 2 inhibitors; T2DM, type 2 diabetes mellitus.

[a]Median (IQR) reported

[b]Weighted averaged calculated for reported baseline demographics

[c]Duration of T2DM reported as interval of >10 years since diagnosis of T2DM, N(%)

[d]Prespecified enrollment requirement of approximately 400 patients with moderate renal impairment and 200 patients with severe kidney impairment

Qualität der Studien:

Table 3. Risk of Bias Assessment

Clinical trial program	Domain 1: risk of bias arising from the randomization process	Domain 2: risk of bias due to deviations from the intended interventions (effect of ASSIGNMENT to intervention)	Domain 2: risk of bias due to deviations from the intended interventions (effect of ADHERING to intervention)	Domain 3: missing outcome data	Domain 4: risk of bias in measurement of the outcome	Domain 5: risk of bias in selection of the reported result	Overall risk-of-bias judgment
CANVAS-R	Low	Low	Low	Low	Low	Low	Low
CREDENCE	Low	Low	Low	Some Concerns	Low	Low	Low
DECLARE-TIMI 58	Low	Low	Low	Low	Low	Low	Low
CARMELINA	Low	Low	Low	Low	Low	Low	Low
EMPA-REG OUTCOME	Low	Low	Some Concerns	Some Concerns	Low	Low	Some Concerns
LEADER	Low	Low	Missing/NI	Low	Low	Low	Low
SUSTAIN-6	Low	Low	Some Concerns	Low	Low	Low	Low

Studienergebnisse:

Direktvergleichende Evidenz: keine Angaben

NMA

- Included studies were generally comparable in mean age, glycated hemoglobin A1c (HbA1c), and mean duration of T2DM at baseline, there are slight onkly differences in study design and baseline demographic characteristics
- heterogeneity statistic was low

Netzwerkgeometrie

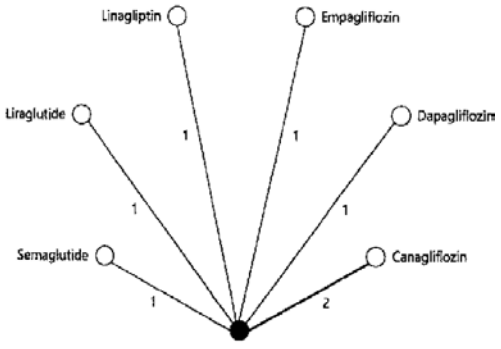


Figure 2. Network star diagram.

Results

Table 5. Composite Kidney Outcome League Table

Dapagliflozin						
0.87 (0.67, 1.12)	Empagliflozin					
0.84 (0.64, 1.09)	0.96 (0.78, 1.19)	Canagliflozin				
0.83 (0.5, 1.22)	0.95 (0.67, 1.36)	0.99 (0.69, 1.42)	Semaglutide			
0.68 (0.52, 0.89)	0.78 (0.63, 0.96)	0.81 (0.65, 1.02)	0.82 (0.57, 1.17)	Liraglutide		
0.51 (0.39, 0.66)	0.59 (0.47, 0.72)	0.61 (0.49, 0.76)	0.62 (0.43, 0.88)	0.75 (0.60, 0.93)	Linagliptin	
0.53 (0.43, 0.66)	0.61 (0.53, 0.70)	0.63 (0.54, 0.74)	0.64 (0.46, 0.88)	0.78 (0.67, 0.91)	1.04 (0.89, 1.22)	Placebo

Results reported as HR (95% credible interval).

Anmerkung/Fazit der Autoren

Compared with placebo, dapagliflozin was associated with the greatest reduction in risk of developing the composite kidney outcome (hazard ratio 0.53; 95% credible interval, 0.43-0.66) followed by empagliflozin, canagliflozin, semaglutide, and liraglutide. Linagliptin did not show a significant reduction in risk of the outcome.

Our analysis has several limitations.

- there may be presence of residual confounding due to some differences in baseline demographic characteristics and follow up periods across the included studies.

Results of this analysis were limitied to currently available trial date. Many drugs in the new antidiabetic agent classes are not included in the analyses, such as lixisenatide, dulaglutide, alogliptin and sitagliptin.

Lautsch D et al., 2021 [68].

Comparative Efficacy of Dual and Single Initiation of Add-On Oral Antihyperglycemic Agents in Type 2 Diabetes Uncontrolled on Metformin Alone: A Systematic Literature Review and Network Meta-Analysis

Fragestellung

Bayesian network meta-analysis to evaluate the comparative efficacy of single and dual initiated approved oral doses of SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1 receptor agonist (all in combination with metformin) at 24–26 weeks in adult T2DM patients uncontrolled on metformin in RCTs.

Methodik

Population:

- adults (age ≥ 18 years) with T2DM and uncontrolled HbA1c (HbA1c>7.0%) while on metformin

Intervention:

Approved doses of the following oral therapies and their combinations (dose reported as once daily if not otherwise specified):

- Metformin + SGLT-2i (ertugliflozin 5mg/15mg, canagliflozin 100mg/300mg, dapagliflozin 5 mg/10 mg, empagliflozin 10 mg/25 mg)
- Metformin + DPP-4i (saxagliptin 2.5 mg/5 mg, linagliptin 5mg, alogliptin 25mg, sitagliptin 100mg, vildagliptin 50mg twice per day)

- Metformin + DPP-4i + SGLT-2i (DPP-4i: saxagliptin 2.5mg/5mg, linagliptin 5mg, alogliptin, vildagliptin, sitagliptin 100mg; SGLT-2i: ertugliflozin 5mg/15mg, canagliflozin 100 mg/300 mg, dapagliflozin 5 mg/10 mg, empagliflozin 10 mg/25 mg)
- Metformin + oral GLP-1 RA (semaglutide 7 mg/14 mg)

Komparator:

Same as interventions, and metformin + placebo (dosing studies that only included metformin were excluded)

Endpunkte:

- Continuous outcomes—Changes in HbA1c (%), weight (kg), SBP (mmHg), DBP (mmHg)
- Binary outcomes—HbA1c within target range (exploratory outcome: expected range defined as: HbA1c\7.0%)

…at 24–26 weeks of follow-up.

Recherche/Suchzeitraum:

- Embase, MEDLINE+Cochrane Library on November 2019

Qualitätsbewertung:

- Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB2) to perform quality assessment of individual studies

NMA-Methodik

- Bayesian NMA: fixed effects (FE) and random effects (RE) Bayesian NMA models.
- Überprüfung der zentralen Annahmen der NMA:
  - The feasibility of conducting an NMA was assessed by evaluating the formation of treatment networks across included studies and by recognizing any differences in patients or study design characteristics that are potential modifiers of treatment effects. The NMA feasibility assessment was performed on all outcomes of interest as per the PICOTS criteria.
  - To understand how effect modifiers might impact the results of evidence synthesis, imbalances of effect modifiers across studies (i.e., heterogeneity) or across comparisons (i.e., inconsistency) were tested. Tests of inconsistency were performed based on methods presented in NICE DSU TSD 4 [17] to evaluate the agreement of indirect evidence and direct evidence.
  - To assess the impact of study heterogeneity on the results, sensitivity analyses were performed for all outcomes by excluding studies with heterogeneity in effect modifiers.

Ergebnisse

Anzahl eingeschlossener Studien:

- 25 unique RCTs

Charakteristika der Studien/Population

- 14 studies included SGLT-2 inhibitors with or without DPP-4 inhibitors,
  - 6 studies reported the dual initiation of SGLT- 2 and DPP-4 inhibitors,
    - 4 studies assessed the combination of dapagliflozin +saxagliptin
    - 1 study on the combination of empagliflozin + linagliptin
    - 1 study on ertugliflozin + sitagliptin

- 10 studies included DPP-4 inhibitors only,
- 1 study included a GLP-1 receptor agonist single initiation therapy.
- The treatment groups were comparable within and across the included studies in terms of the mean baseline age (range 52.7–60.8 years) and mean baseline SBP (range 126–138.8 mmHg).
- Some differences were found in terms of mean baseline HbA1c (range 7.2–9.3%), which could potentially influence the outcome on attaining HbA1c<7%. However, it was decided that the levels of baseline HbA1c were acceptable for comparison and differences were not egregious enough to exclude studies based on this factor, and we opted in favor of maintaining a comprehensive evidence base.
- The mean baseline weight ranged from 67.9 to 97.7 kg, with six Asian studies reporting relatively lower mean baseline weight of B 71.6 kg across treatment groups. Likewise, the mean baseline body mass index (BMI) was relatively lower in the six Asian studies (mean BMI B 26.4) compared to the other included studies (mean BMI range 28.7–33.3).
- Other potential effect modifiers, such as background therapy regimen, proportion of females, and duration of diabetes, were found to be relatively similar across all studies.

Qualität der Studien:

- low overall risk of bias was observed for 84% of the included studies,
- some concerns were observed for three studies,
- one study (PIONEER 2) presented high risk of bias owing to its open-label comparison of empagliflozin 25 mg versus semaglutide 14 mg

Studienergebnisse:

Direkte Evidenz: Meta-Analyse: k.A. (nur Ergebnisse der 25 Einzelstudien verfügbar)

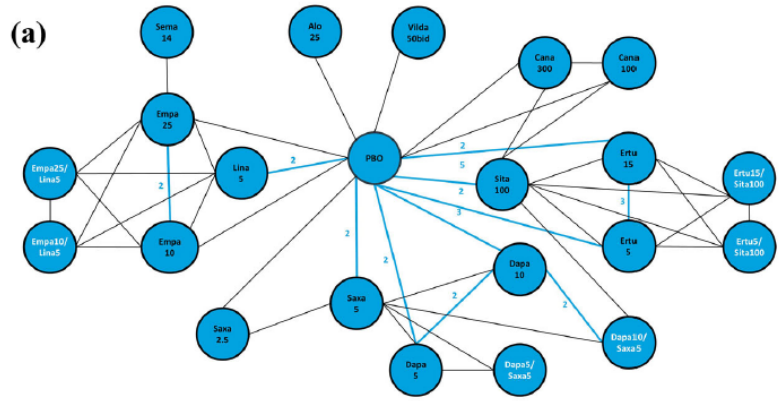
NMA

The NMA was found to be feasible for all outcomes.

- The patients and study design characteristic were considered similar across the included studies, except that low weight and BMI were observed for six Asian studies, and potential high risk of bias was observed with the PIONEER 2 openlabel study. Sensitivity analyses were conducted to remove these studies to assess the impact of these potential effect modifiers.
- inconsistencies were identified within loops of the network. This suggests that there were differences between the direct and indirect comparisons. Differences were observed between NMA and inconsistency models, with DIC differences ranging from 1.2 to 11.1 points. However, the detected inconsistency was at an acceptable level and therefore should not impact the overall interpretation.

Mean change from baseline to 24 (± 2) weeks in HbA1c (N = 25 studies)

Network diagram for change from baseline in HbA1c:

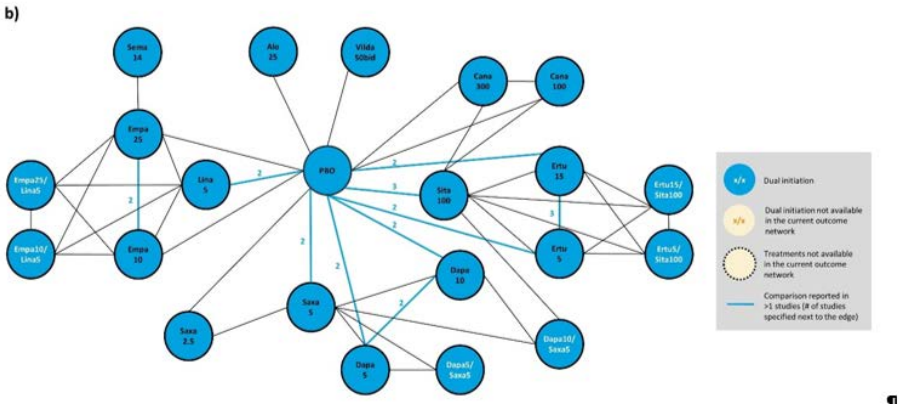


Results

- All the dual and single initiation therapies demonstrated statistically significant reductions (i.e., improvement) in HbA1c from baseline compared to placebo
- pairwise comparison between active treatments indicated more favorable results with dual initiation therapies than single initiation therapies (siehe Table 3 im Anhang).
  - o the change in HbA1c from baseline was statistically significantly greater with ertugliflozin 5mg + sitagliptin 100mg and ertugliflozin 15 mg + sitagliptin 100 mg dual initiation therapies than with all single initiation therapies except semaglutide 14 mg.
  - o Semaglutide 14 mg had no statistically significant difference compared with all dual initiation therapies.

Proportion of patients with HbA1c <7% (N = 21 studies)

Network diagram



Results

- The odds of achieving the HbA1c target (<7%) were statistically significantly higher for all dual initiation therapies and 14 out of 15 single initiation therapies (except dapagliflozin 5 mg) compared to placebo
- pairwise comparison league tables fort he proportion of
- patients achieving HbA1c<7% are provided in supplementary table 7 (siehe Anhang)

Sensitivitätsanalysen

- Sensitivity Analysis Results In the sensitivity analyses removing the PIONEER 2 open-label study, results were consistent with the base case analysis, and no substantial

impact was observed for the comparative efficacy among active treatments versus placebo

- Removing the six Asian studies with low baseline weight and BMI also did not alter the direction of treatment effect or statistical significance for change in HbA1c and proportion of patients achieving the HbA1c target (<7%).

Anmerkung/Fazit der Autoren

Add-on dual initiation therapies, particularly ertugliflozin + sitagliptin, demonstrated significantly better outcomes than most single initiation therapies in reducing HbA1c, weight, and SBP over 24–26 weeks of follow-up in T2DM patients uncontrolled on metformin alone.

Kommentare zum Review

- Hier nur Ergebnisse zu HbA1c dargestellt
- Für Effekte von Ertugliflozin + sitagliptin siehe auch McNeill AM et al. 2019 [82]

Qiu M et al., 2021 [97].

Comparative Efficacy of Glucagon-like Peptide 1 Receptor Agonists and Sodium Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular Events in Type 2 Diabetes: A Network Meta-analysis.

Fragestellung

To assess the comparative efficacy of different GLP-1 RAs and SGLT2is on MACE endpoint in type 2 diabetic subgroups with or without cardiorenal disease, and to identity the most efficacious drug interventions for different diabetic subgroups

Methodik

Population:

- type 2 diabetic adults
- Subgroups of interest were type 2 diabetic adults
  - with/without cardiovascular disease (CVD),
  - with/without heart failure (HF), and
  - with/without chronic kidney disease (CKD).

Intervention:/Komparator:

- SGLT2is or GLP-1 RAs

Endpunkte:

- MACE (defined as a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)

Recherche/Suchzeitraum:

- In PubMed and Embase from the date of database inception to May 3, 2020

Qualitätsbewertung der Studien:

Cochrane risk of bias tool

NMA-Methodik/ Überprüfung der zentralen Annahmen

- fixed-effects network meta-analysis within the Bayesian framework
- I2 statistic was used to measure statistical heterogeneity. When substantial heterogeneity (ie, I2 .50%) was observed, we conducted sensitivity analysis by using the random-effects model instead of the fixed-effects model to conduct network metaanalysis.
- When the evidence network had more than one closed loop, we built the node-splitting model to test for the inconsistency between direct and indirect evidences.

Ergebnisse

Anzahl eingeschlossener Studien:

- 11 trials

Charakteristika der Studien /Population:

- The 11 trials in total assessed the efficacy of 10 drug interventions (ie, empagliflozin, canagliflozin, dapagliflozin, lixisenatide, liraglutide, subcutaneous semaglutide, exenatide, albiglutide, dulaglutide, and oral semaglutide) versus placebo.
  - Canagliflozin was assessed in 2 trials
  - each of the other drug interventions was assessed in only 1 trial.
- Trials were similar in key patient characteristics (ie, age, sex, race, diabetes duration):

Table S1 Similarity assessment for included trials

Study id	Study name	Intervention	Mean age (years)	Women (%)	White (%)	Mean diabetes duration (years)
1	EMPA-REG OUTCOME	Empagliflozin	63.1	28.5	72.4	57.1% *
2	CANVAS Program	Canagliflozin	63.3	35.8	78.3	13.5
3	DECLARE–TIMI 58	Dapagliflozin	63.9	37.4	79.6	10.5
4	CREDENCE	Canagliflozin	63.0	33.9	66.6	15.8
5	ELIXA	Lixisenatide	60.0	31.0	75.0	9.2
6	LEADER	Liraglutide	64.0	36.0	77.0	12.8
7	SUSTAIN-6	Subcutaneous semaglutide	65.0	39.0	83.0	13.9
8	EXSCEL	Exenatide	62.0	38.0	76.0	13.1
9	Harmony Outcomes	Albiglutide	64.0	31.0	70.0	14.2
10	REWIND	Dulaglutide	66.0	46.0	76.0	10.6
11	PIONEER 6	Oral semaglutide	66.0	32.0	72.0	14.9

* indicates that the proportion of participants with type 2 diabetes duration >10 years is 57.1%, and the average diabetes duration of participants in the EMPA-REG OUTCOME trial is not available.

Qualität der Studien:

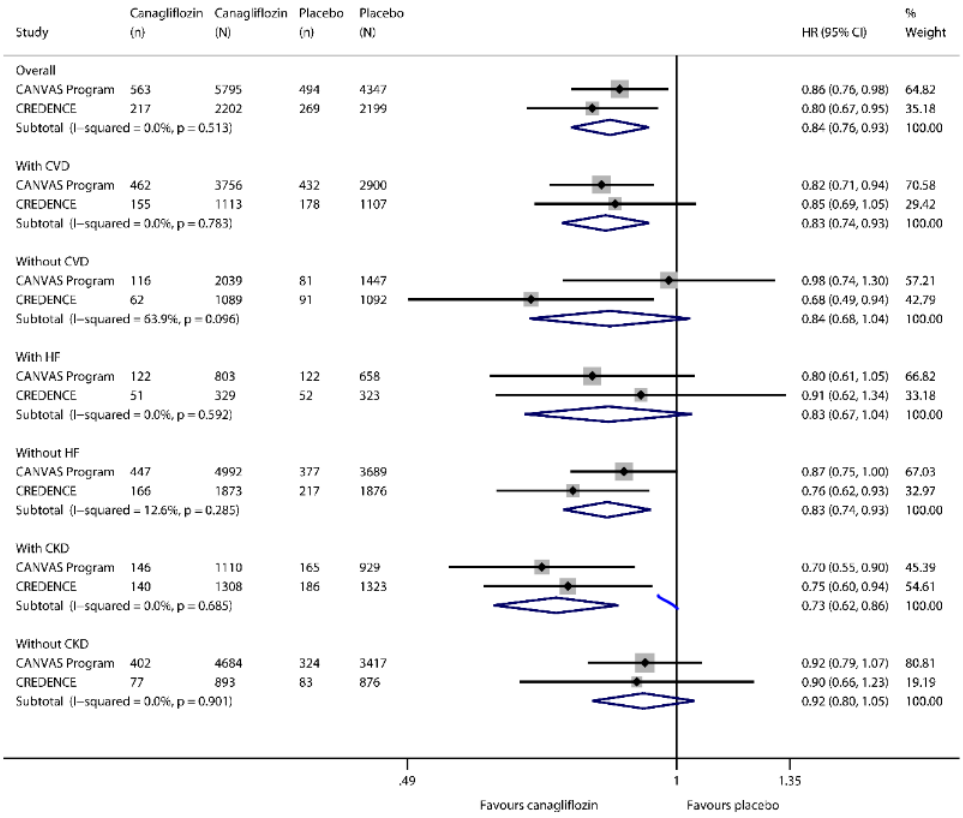
- All the included trials had low risk of bias

Studienergebnisse:

Direktvergleichende Evidenz nach Subgruppen:

Angaben nur für Canagliflozin trials; Endpunkt MACE

Fig. S4 Meta-analysis and heterogeneity test for two canagliflozin trials, stratified by type 2 diabetic subpopulations

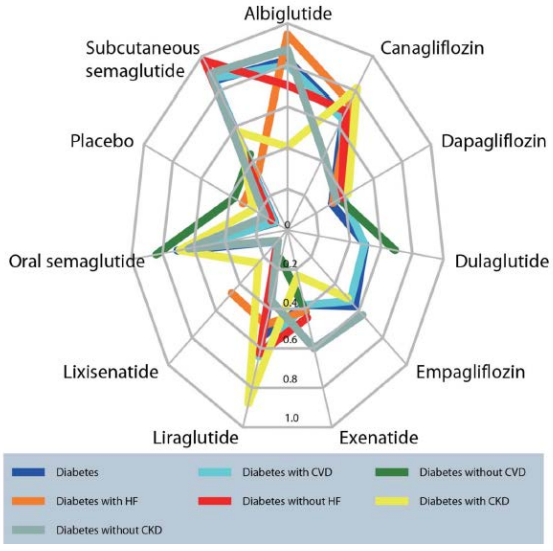


NMA

Endpunkt MACE

- No substantial heterogeneity was not observed in all diabetic subgroups except for the diabetic subgroup withoutCVD (I2 = 63.9%). For this subgroup, sensitivity analysis) revealed the robustness of the network meta-analysis results.
- No test for inconsistency because there was not a closed loop in any evidence network

Netzwerkgeometrie



Results

Gesamtpopulation

Table S2A. Pairwise comparison results from network meta-analysis for people with type 2 diabetes

Albiglutide	1.07 (0.9, 1.28)	1.19 (1, 1.42)	1.13 (0.94, 1.35)	1.1 (0.9, 1.35)	1.17 (0.99, 1.38)	1.12 (0.94, 1.33)	**1.31 (1.07, 1.59)**	1.01 (0.71, 1.45)	**1.28 (1.11, 1.47)**	0.95 (0.71, 1.26)
0.93 (0.78, 1.11)	**Canagliflozin**	1.11 (0.96, 1.28)	1.05 (0.9, 1.22)	1.03 (0.86, 1.23)	1.09 (0.94, 1.25)	1.04 (0.89, 1.2)	**1.22 (1.03, 1.44)**	0.94 (0.67, 1.33)	**1.19 (1.08, 1.32)**	0.88 (0.68, 1.15)
0.84 (0.71, 1)	0.9 (0.78, 1.04)	**Dapagliflozin**	0.95 (0.81, 1.1)	0.92 (0.77, 1.1)	0.98 (0.85, 1.12)	0.94 (0.81, 1.09)	1.1 (0.92, 1.3)	0.85 (0.6, 1.2)	1.08 (0.97, 1.19)	0.8 (0.61, 1.04)
0.89 (0.74, 1.06)	0.95 (0.82, 1.11)	1.06 (0.91, 1.23)	**Dulaglutide**	0.98 (0.81, 1.18)	1.03 (0.89, 1.2)	0.99 (0.85, 1.16)	1.16 (0.97, 1.38)	0.9 (0.63, 1.27)	**1.14 (1.02, 1.27)**	0.84 (0.64, 1.1)
0.91 (0.74, 1.11)	0.97 (0.82, 1.17)	1.08 (0.91, 1.29)	1.02 (0.85, 1.23)	**Empagliflozin**	1.06 (0.89, 1.26)	1.01 (0.84, 1.21)	1.19 (0.97, 1.45)	0.92 (0.64, 1.32)	**1.16 (1.01, 1.34)**	0.86 (0.65, 1.15)
0.86 (0.72, 1.01)	0.92 (0.8, 1.06)	1.02 (0.89, 1.17)	0.97 (0.84, 1.12)	0.95 (0.8, 1.12)	**Exenatide**	0.96 (0.83, 1.1)	1.12 (0.95, 1.32)	0.87 (0.62, 1.23)	1.1 (1, 1.21)	0.81 (0.62, 1.06)
0.9 (0.75, 1.07)	0.96 (0.83, 1.12)	1.07 (0.92, 1.24)	1.01 (0.86, 1.18)	0.99 (0.82, 1.18)	1.05 (0.91, 1.21)	**Liraglutide**	1.17 (0.99, 1.4)	0.91 (0.64, 1.29)	**1.15 (1.03, 1.28)**	0.85 (0.65, 1.11)
0.76 (0.63, 0.93)	**0.82 (0.69, 0.97)**	0.91 (0.77, 1.08)	0.86 (0.72, 1.03)	0.84 (0.69, 1.03)	0.89 (0.76, 1.05)	0.85 (0.72, 1.01)	**Lixisenatide**	0.77 (0.54, 1.11)	0.98 (0.85, 1.12)	**0.73 (0.55, 0.96)**
0.99 (0.69, 1.42)	1.06 (0.75, 1.5)	1.18 (0.83, 1.66)	1.11 (0.78, 1.58)	1.09 (0.75, 1.56)	1.15 (0.82, 1.62)	1.1 (0.78, 1.56)	1.29 (0.9, 1.85)	**Osemaglutide**	1.27 (0.91, 1.76)	0.94 (0.62, 1.42)
0.78 (0.68, 0.9)	**0.84 (0.76, 0.93)**	0.93 (0.84, 1.03)	**0.88 (0.79, 0.98)**	**0.86 (0.74, 0.99)**	0.91 (0.83, 1)	**0.87 (0.78, 0.97)**	1.02 (0.89, 1.17)	0.79 (0.57, 1.1)	**Placebo**	**0.74 (0.58, 0.95)**
1.05 (0.79, 1.4)	1.13 (0.87, 1.48)	1.26 (0.97, 1.64)	1.19 (0.91, 1.56)	1.16 (0.87, 1.55)	1.23 (0.95, 1.6)	1.17 (0.9, 1.54)	**1.38 (1.04, 1.82)**	1.07 (0.71, 1.61)	**1.35 (1.06, 1.73)**	**Ssemaglutide**

Results are presented as HRs (95% CIs) of the column-defining treatment versus the row-defining treatment. Red bold font indicates statistical significance. Osemaglutide, Oral semaglutide; Ssemaglutide, Subcutaneous semaglutide.

Subgroup: people with diabetes with CVD

Table S2B. Pairwise comparison results from network meta-analysis for people with type 2 diabetes with CVD

Albiglutide	1.06 (0.89, 1.27)	1.15 (0.95, 1.4)	1.11 (0.9, 1.38)	1.1 (0.9, 1.35)	1.15 (0.97, 1.37)	1.06 (0.89, 1.28)	**1.31 (1.07, 1.59)**	1.06 (0.73, 1.55)	**1.28 (1.12, 1.48)**	0.92 (0.69, 1.24)
0.94 (0.78, 1.13)	**Canagliflozin**	1.09 (0.91, 1.29)	1.05 (0.86, 1.28)	1.04 (0.86, 1.25)	1.09 (0.93, 1.27)	1 (0.85, 1.18)	**1.23 (1.03, 1.47)**	1 (0.69, 1.45)	**1.21 (1.07, 1.35)**	0.87 (0.65, 1.16)
0.87 (0.72, 1.05)	0.92 (0.77, 1.09)	**Dapagliflozin**	0.97 (0.79, 1.19)	0.96 (0.79, 1.16)	1 (0.85, 1.18)	0.92 (0.78, 1.1)	1.13 (0.94, 1.37)	0.92 (0.63, 1.34)	1.11 (0.98, 1.26)	0.8 (0.6, 1.07)
0.9 (0.73, 1.11)	0.95 (0.78, 1.16)	1.04 (0.84, 1.27)	**Dulaglutide**	0.99 (0.8, 1.23)	1.04 (0.86, 1.25)	0.95 (0.78, 1.16)	1.17 (0.95, 1.45)	0.96 (0.65, 1.4)	1.15 (0.98, 1.35)	0.83 (0.61, 1.12)
0.91 (0.74, 1.11)	0.96 (0.8, 1.16)	1.05 (0.86, 1.27)	1.01 (0.82, 1.26)	**Empagliflozin**	1.05 (0.88, 1.25)	0.97 (0.8, 1.16)	1.19 (0.97, 1.45)	0.97 (0.66, 1.41)	**1.16 (1.01, 1.35)**	0.84 (0.62, 1.13)
0.87 (0.73, 1.03)	0.92 (0.79, 1.07)	1 (0.85, 1.17)	0.97 (0.8, 1.17)	0.95 (0.8, 1.14)	**Exenatide**	0.92 (0.79, 1.07)	1.13 (0.96, 1.34)	0.92 (0.64, 1.33)	**1.11 (1.01, 1.23)**	0.8 (0.61, 1.06)
0.94 (0.78, 1.13)	1 (0.85, 1.18)	1.08 (0.91, 1.29)	1.05 (0.86, 1.28)	1.04 (0.86, 1.25)	1.08 (0.93, 1.26)	**Liraglutide**	**1.23 (1.03, 1.47)**	1 (0.69, 1.45)	**1.21 (1.07, 1.35)**	0.87 (0.65, 1.15)
0.76 (0.63, 0.93)	**0.81 (0.68, 0.97)**	0.88 (0.73, 1.06)	0.85 (0.69, 1.05)	0.84 (0.69, 1.03)	0.88 (0.75, 1.05)	**0.81 (0.68, 0.97)**	**Lixisenatide**	0.81 (0.56, 1.19)	0.98 (0.86, 1.12)	**0.71 (0.52, 0.95)**
0.94 (0.64, 1.37)	1 (0.69, 1.45)	1.08 (0.75, 1.58)	1.05 (0.71, 1.54)	1.03 (0.71, 1.52)	1.08 (0.75, 1.56)	1 (0.69, 1.45)	1.23 (0.84, 1.79)	**Osemaglutide**	1.2 (0.85, 1.71)	0.87 (0.56, 1.35)
0.78 (0.68, 0.9)	**0.83 (0.74, 0.93)**	0.9 (0.79, 1.02)	0.87 (0.74, 1.02)	**0.86 (0.74, 0.99)**	**0.9 (0.82, 0.99)**	**0.83 (0.74, 0.93)**	1.02 (0.89, 1.17)	0.83 (0.58, 1.18)	**Placebo**	**0.72 (0.55, 0.94)**
1.08 (0.8, 1.46)	1.15 (0.86, 1.53)	1.25 (0.93, 1.67)	1.21 (0.89, 1.64)	1.19 (0.89, 1.61)	1.25 (0.95, 1.65)	1.15 (0.87, 1.54)	**1.41 (1.05, 1.91)**	1.15 (0.74, 1.78)	**1.39 (1.07, 1.8)**	**Ssemaglutide**

Results are presented as HRs (95% CIs) of the column-defining treatment versus the row-defining treatment. Red bold font indicates statistical significance. Osemaglutide, Oral semaglutide; Ssemaglutide, Subcutaneous

Subgroup: people with diabetes without CVD

Table S2C. Pairwise comparison results from network meta-analysis for people with type 2 diabetes without CVD

Canagliflozin	1.21 (0.92, 1.58)	1.04 (0.79, 1.35)	1.18 (0.85, 1.65)	1.43 (0.96, 2.12)	0.61 (0.18, 2.08)	1.19 (0.96, 1.48)	1.19 (0.48, 2.98)
0.83 (0.63, 1.09)	**Dapagliflozin**	0.86 (0.68, 1.09)	0.98 (0.72, 1.33)	1.19 (0.82, 1.72)	0.51 (0.15, 1.72)	0.99 (0.84, 1.17)	0.99 (0.4, 2.47)
0.96 (0.74, 1.26)	1.16 (0.92, 1.47)	**Dulaglutide**	1.14 (0.84, 1.54)	1.38 (0.96, 2)	0.59 (0.17, 1.99)	1.15 (0.98, 1.35)	1.15 (0.47, 2.84)
0.85 (0.61, 1.18)	1.02 (0.75, 1.38)	0.88 (0.65, 1.19)	**Exenatide**	1.21 (0.8, 1.84)	0.52 (0.15, 1.77)	1.01 (0.78, 1.3)	1.01 (0.4, 2.56)
0.7 (0.47, 1.04)	0.84 (0.58, 1.22)	0.72 (0.5, 1.05)	0.82 (0.54, 1.26)	**Liraglutide**	0.42 (0.12, 1.48)	0.83 (0.6, 1.16)	0.83 (0.32, 2.17)
1.64 (0.48, 5.55)	1.98 (0.58, 6.65)	1.7 (0.5, 5.73)	1.94 (0.56, 6.62)	2.36 (0.67, 8.18)	**Osemaglutide**	1.96 (0.58, 6.51)	1.96 (0.44, 8.8)
0.84 (0.68, 1.04)	1.01 (0.85, 1.19)	0.87 (0.74, 1.02)	0.99 (0.77, 1.28)	1.2 (0.86, 1.67)	0.51 (0.15, 1.71)	**Placebo**	1 (0.41, 2.45)
0.84 (0.34, 2.09)	1.01 (0.41, 2.51)	0.87 (0.35, 2.15)	0.99 (0.39, 2.5)	1.2 (0.46, 3.1)	0.51 (0.11, 2.29)	1 (0.41, 2.44)	**Ssemaglutide**

Results are presented as HRs (95% CIs) of the column-defining treatment versus the row-defining treatment. Red bold font indicates statistical significance.

Osemaglutide, Oral semaglutide; Ssemaglutide, Subcutaneous semaglutide.

Subgroup: people with diabetes with HF

Table S2D. Pairwise comparison results from network meta-analysis for people with type 2 diabetes with HF

Albiglutide	1.19 (0.85, 1.68)	**1.44 (1.03, 2.03)**	**1.39 (1.02, 1.9)**	1.34 (0.93, 1.93)	1.35 (0.95, 1.93)	**1.43 (1.11, 1.84)**	1.47 (0.86, 2.52)
0.84 (0.6, 1.18)	**Canagliflozin**	1.21 (0.88, 1.66)	1.16 (0.87, 1.55)	1.13 (0.8, 1.58)	1.13 (0.81, 1.58)	1.2 (0.96, 1.5)	1.23 (0.73, 2.09)
0.69 (0.49, 0.97)	0.83 (0.6, 1.13)	**Dapagliflozin**	0.96 (0.72, 1.28)	0.93 (0.66, 1.31)	0.94 (0.67, 1.31)	0.99 (0.79, 1.24)	1.02 (0.61, 1.73)
0.72 (0.53, 0.98)	0.86 (0.65, 1.15)	1.04 (0.78, 1.39)	**Exenatide**	0.97 (0.71, 1.33)	0.97 (0.72, 1.32)	1.03 (0.86, 1.23)	1.06 (0.64, 1.76)
0.74 (0.52, 1.07)	0.89 (0.63, 1.25)	1.07 (0.76, 1.52)	1.03 (0.75, 1.42)	**Liraglutide**	1.01 (0.7, 1.44)	1.06 (0.82, 1.38)	1.1 (0.64, 1.89)
0.74 (0.52, 1.06)	0.88 (0.63, 1.24)	1.07 (0.76, 1.5)	1.03 (0.76, 1.4)	0.99 (0.69, 1.42)	**Lixisenatide**	1.06 (0.83, 1.36)	1.09 (0.64, 1.86)
0.7 (0.54, 0.9)	0.84 (0.67, 1.05)	1.01 (0.81, 1.26)	0.97 (0.81, 1.16)	0.94 (0.72, 1.22)	0.95 (0.74, 1.21)	**Placebo**	1.03 (0.64, 1.65)
0.68 (0.4, 1.16)	0.81 (0.48, 1.37)	0.98 (0.58, 1.65)	0.94 (0.57, 1.56)	0.91 (0.53, 1.57)	0.92 (0.54, 1.57)	0.97 (0.61, 1.56)	**Ssemaglutide**

Results are presented as HRs (95% CIs) of the column-defining treatment versus the row-defining treatment. Red bold font indicates statistical significance.

Ssemaglutide, Subcutaneous semaglutide.

Subgroup: people with diabetes without HF

Table S2E. Pairwise comparison results from network meta-analysis for people with type 2 diabetes without HF

Albiglutide	1.01 (0.82, 1.25)	1.12 (0.91, 1.38)	1.1 (0.9, 1.34)	1.04 (0.84, 1.28)	1.27 (0.99, 1.62)	**1.22 (1.02, 1.45)**	0.78 (0.56, 1.1)
0.99 (0.8, 1.22)	**Canagliflozin**	1.11 (0.94, 1.3)	1.08 (0.93, 1.26)	1.02 (0.87, 1.21)	**1.25 (1.02, 1.54)**	**1.2 (1.07, 1.35)**	0.77 (0.56, 1.05)
0.89 (0.72, 1.1)	0.9 (0.77, 1.06)	**Dapagliflozin**	0.98 (0.84, 1.14)	0.92 (0.79, 1.08)	1.13 (0.92, 1.38)	1.09 (0.97, 1.21)	**0.7 (0.51, 0.95)**
0.91 (0.74, 1.12)	0.92 (0.79, 1.08)	1.02 (0.88, 1.19)	**Exenatide**	0.94 (0.81, 1.11)	1.15 (0.95, 1.41)	1.11 (1, 1.23)	**0.71 (0.52, 0.97)**
0.97 (0.78, 1.19)	0.98 (0.83, 1.15)	1.08 (0.92, 1.27)	1.06 (0.9, 1.24)	**Liraglutide**	1.22 (1, 1.5)	**1.18 (1.05, 1.32)**	0.75 (0.55, 1.03)
0.79 (0.62, 1.01)	**0.8 (0.65, 0.98)**	0.88 (0.72, 1.08)	0.87 (0.71, 1.06)	0.82 (0.67, 1)	**Lixisenatide**	0.96 (0.81, 1.14)	**0.62 (0.44, 0.86)**
0.82 (0.69, 0.98)	**0.83 (0.74, 0.93)**	0.92 (0.83, 1.03)	0.9 (0.81, 1)	**0.85 (0.76, 0.96)**	1.04 (0.88, 1.23)	**Placebo**	**0.64 (0.48, 0.86)**
1.28 (0.91, 1.8)	1.3 (0.95, 1.78)	**1.44 (1.05, 1.96)**	**1.41 (1.03, 1.92)**	1.33 (0.97, 1.82)	**1.62 (1.16, 2.27)**	**1.56 (1.17, 2.09)**	**Ssemaglutide**

Results are presented as HRs (95% CIs) of the column-defining treatment versus the row-defining treatment. Red bold font indicates statistical significance.

Ssemaglutide, Subcutaneous semaglutide.

Subgroup: people with diabetes with CKD

Table S2F. Pairwise comparison results from network meta-analysis for people with type 2 diabetes with CKD

Albiglutide	0.78 (0.58, 1.06)	0.99 (0.68, 1.45)	0.95 (0.67, 1.34)	1.09 (0.81, 1.46)	0.74 (0.54, 1.02)	1.09 (0.77, 1.53)	0.8 (0.42, 1.52)	1.08 (0.84, 1.38)	0.9 (0.57, 1.44)
1.27 (0.95, 1.72)	**Canagliflozin**	1.26 (0.91, 1.76)	1.21 (0.9, 1.62)	**1.39 (1.1, 1.74)**	0.95 (0.73, 1.23)	**1.39 (1.04, 1.85)**	1.02 (0.55, 1.87)	**1.37 (1.16, 1.62)**	1.15 (0.75, 1.77)
1.01 (0.69, 1.48)	0.79 (0.57, 1.1)	**Dapagliflozin**	0.96 (0.65, 1.4)	1.1 (0.79, 1.53)	0.75 (0.53, 1.06)	1.1 (0.75, 1.6)	0.81 (0.42, 1.55)	1.09 (0.81, 1.45)	0.91 (0.56, 1.49)
1.06 (0.75, 1.5)	0.83 (0.62, 1.12)	1.05 (0.72, 1.53)	**Empagliflozin**	1.15 (0.86, 1.54)	0.78 (0.57, 1.08)	1.15 (0.82, 1.62)	0.84 (0.45, 1.59)	1.14 (0.89, 1.46)	0.96 (0.6, 1.52)
0.92 (0.68, 1.24)	**0.72 (0.57, 0.91)**	0.91 (0.65, 1.27)	0.87 (0.65, 1.17)	**Exenatide**	**0.68 (0.53, 0.88)**	1 (0.75, 1.33)	0.74 (0.4, 1.35)	0.99 (0.84, 1.17)	0.83 (0.54, 1.27)
1.35 (0.98, 1.85)	1.06 (0.81, 1.37)	1.33 (0.94, 1.89)	1.27 (0.93, 1.75)	**1.46 (1.13, 1.89)**	**Liraglutide**	**1.46 (1.07, 2)**	1.07 (0.58, 2)	**1.45 (1.19, 1.77)**	1.22 (0.78, 1.89)
0.92 (0.65, 1.3)	**0.72 (0.54, 0.96)**	0.91 (0.63, 1.33)	0.87 (0.62, 1.22)	1 (0.75, 1.33)	**0.68 (0.5, 0.93)**	**Lixisenatide**	0.73 (0.39, 1.38)	0.99 (0.78, 1.26)	0.83 (0.53, 1.32)
1.25 (0.66, 2.37)	0.98 (0.53, 1.81)	1.24 (0.65, 2.39)	1.19 (0.63, 2.25)	1.36 (0.74, 2.51)	0.93 (0.5, 1.73)	1.36 (0.73, 2.57)	**Osemaglutide**	1.35 (0.75, 2.42)	1.13 (0.56, 2.3)
0.93 (0.73, 1.19)	**0.73 (0.62, 0.86)**	0.92 (0.69, 1.23)	0.88 (0.69, 1.12)	1.01 (0.86, 1.19)	**0.69 (0.57, 0.84)**	1.01 (0.8, 1.28)	0.74 (0.41, 1.33)	**Placebo**	0.84 (0.57, 1.24)
1.11 (0.69, 1.76)	0.87 (0.57, 1.32)	1.09 (0.67, 1.78)	1.05 (0.66, 1.67)	1.2 (0.78, 1.84)	0.82 (0.53, 1.27)	1.2 (0.76, 1.9)	0.88 (0.43, 1.79)	1.19 (0.8, 1.76)	**Ssemaglutide**

Results are presented as HRs (95% CIs) of the column-defining treatment versus the row-defining treatment. Red bold font indicates statistical significance. Osemaglutide, Oral semaglutide; Ssemaglutide,

Subgroup: people with diabetes without CKD

Table S2G. Pairwise comparison results from network meta-analysis for people with type 2 diabetes without CKD

Albiglutide	**1.27 (1.02, 1.58)**	**1.31 (1.07, 1.6)**	1.16 (0.91, 1.5)	1.19 (0.97, 1.47)	**1.3 (1.05, 1.61)**	**1.49 (1.16, 1.91)**	1.12 (0.72, 1.75)	**1.39 (1.17, 1.65)**	0.93 (0.65, 1.34)
0.79 (0.63, 0.98)	**Canagliflozin**	1.03 (0.87, 1.23)	0.92 (0.73, 1.15)	0.94 (0.79, 1.12)	1.03 (0.85, 1.24)	1.17 (0.93, 1.47)	0.88 (0.58, 1.35)	1.09 (0.95, 1.25)	0.73 (0.52, 1.04)
0.76 (0.62, 0.93)	0.97 (0.82, 1.15)	**Dapagliflozin**	0.89 (0.72, 1.1)	0.91 (0.78, 1.06)	0.99 (0.84, 1.17)	1.14 (0.92, 1.4)	0.86 (0.56, 1.3)	1.06 (0.95, 1.17)	0.71 (0.5, 1)
0.86 (0.67, 1.1)	1.09 (0.87, 1.37)	1.13 (0.91, 1.4)	**Empagliflozin**	1.02 (0.83, 1.27)	1.12 (0.9, 1.4)	1.28 (0.99, 1.66)	0.96 (0.62, 1.51)	1.19 (0.99, 1.43)	0.8 (0.55, 1.17)
0.84 (0.68, 1.03)	1.07 (0.89, 1.27)	1.1 (0.94, 1.29)	0.98 (0.78, 1.21)	**Exenatide**	1.09 (0.92, 1.3)	**1.25 (1.01, 1.55)**	0.94 (0.62, 1.44)	**1.16 (1.04, 1.31)**	0.78 (0.55, 1.1)
0.77 (0.62, 0.95)	0.98 (0.81, 1.17)	1.01 (0.85, 1.19)	0.89 (0.71, 1.12)	0.91 (0.77, 1.09)	**Liraglutide**	1.14 (0.91, 1.42)	0.86 (0.56, 1.32)	1.06 (0.94, 1.21)	0.71 (0.5, 1.01)
0.67 (0.52, 0.86)	0.85 (0.68, 1.07)	0.88 (0.71, 1.09)	0.78 (0.6, 1.01)	**0.8 (0.65, 0.99)**	0.88 (0.7, 1.09)	**Lixisenatide**	0.76 (0.48, 1.17)	0.93 (0.78, 1.12)	**0.62 (0.43, 0.91)**
0.89 (0.57, 1.38)	1.13 (0.74, 1.74)	1.17 (0.77, 1.78)	1.04 (0.66, 1.62)	1.06 (0.7, 1.62)	1.16 (0.76, 1.78)	1.32 (0.85, 2.07)	**Osemaglutide**	1.23 (0.82, 1.86)	0.83 (0.49, 1.39)
0.72 (0.61, 0.86)	0.92 (0.8, 1.05)	0.95 (0.85, 1.05)	0.84 (0.7, 1.01)	**0.86 (0.77, 0.97)**	0.94 (0.83, 1.07)	1.07 (0.9, 1.29)	0.81 (0.54, 1.22)	**Placebo**	**0.67 (0.49, 0.93)**
1.08 (0.74, 1.55)	1.37 (0.96, 1.94)	1.41 (1, 1.98)	1.25 (0.86, 1.82)	1.28 (0.91, 1.8)	1.4 (0.99, 1.98)	**1.6 (1.1, 2.31)**	1.21 (0.72, 2.02)	**1.49 (1.08, 2.06)**	**Ssemaglutide**

Results are presented as HRs (95% CIs) of the column-defining treatment versus the row-defining treatment. Red bold font indicates statistical significance. Osemaglutide, Oral semaglutide; Ssemaglutide,

SUCRA:

- The maximum SUCRA values accompanied albiglutide and subcutaneous semaglutide for people with diabetes, for people with diabetes with CVD, and for people with diabetes without CKD; accompanied oral semaglutide for people with diabetes without CVD; accompanied albiglutide for people with diabetes with HF; accompanied subcutaneous semaglutide for people with diabetes without HF; and accompanied canagliflozin and liraglutide for people with diabetes with CKD.

Anmerkung/Fazit der Autoren

In conclusion, different SGLT2is and GLP-1 RAs have different efficacy in preventing MACE in type 2 diabetes, and the most efficacious drugs vary with patient comorbidities. Subcutaneous semaglutide and albiglutide are most effective for type 2 diabetes with CVD, albiglutide is most effective for type 2 diabetes with HF, and canagliflozin and liraglutide are most effective for type 2 diabetes with CKD.

Kommentare zum Review

- Limitation: Keine Angaben zur Untersuchung der Transitivitätsannahme; jedoch Information darüber, dass die Studien hinsichtlich key patient characteristics ähnlich waren

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Men P et al., 2020 [84].

Comparison of lixisenatide in combination with basal insulin versus other insulin regimens for the treatment of patients with type 2 diabetes mellitus inadequately controlled by basal insulin: systematic review, network meta-analysis and cost-effectiveness analysis.

Fragestellung

To evaluate the comparative efficacy and safety of lixisenatide combined with basal insulin (BI) versus intensive premix insulin (premix), BI plus prandial insulin with the main meal (basal-plus) or progressively covering all meals (basal-bolus) in patients with type 2 diabetes mellitus (T2DM) inadequately controlled by BI

Methodik

Protocol of this SLR and NMA has been registered on PROSPERO

Population:

- Adult T2DM patients inadequately controlled on basal insulin

Intervention:

- Lixisenatide in combination with basal insulin
- Premix insulin regimen (twice daily or third daily)
- Basal-bolus regimen (basal insulin + prandial insulin covering all meals (3 shots)
- Basal-plus regimen (basal insulin + prandial insulin with the main meal (1 shot))

Komparator:

- Any insulin intervention of interest in an approved dose

Endpunkte:

- Mean changes in the HbA1c from baseline
- Mean changes in the FPG from baseline

- Mean change in body weight from baseline
- Incidence and event per patient of systematic hypoglycemia

Recherche/Suchzeitraum:

- Syst. search in PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure (CNKI) and Wanfang databases from January 1998 to January 2018

Qualitätsbewertung der Studien:

- Using Cochrane Collaborations Risk of Bias tool

NMA-Methodik/Überprüfung der zentralen Annahmen

- Bayesian framework with random-effects hierarchical models
- The node-splitting method was used to assess the inconsistency of the model by separating evidence on a particular comparison into direct and indirect evidence
- Heterogeneity among the studies was assessed using the I2 test.
- GRADE assessment for rating the quality of treatment effect estimates from NMA

Ergebnisse

Anzahl eingeschlossener Studien:

- 8 RCT

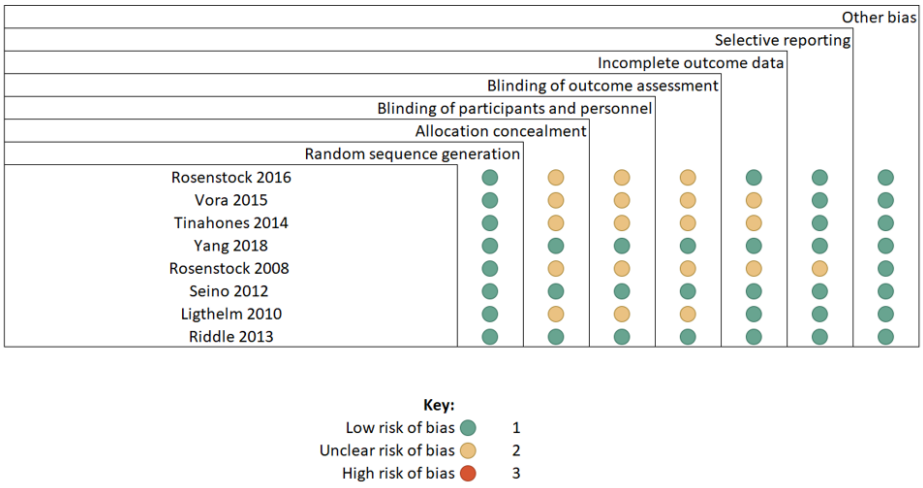
Studiencharakteristika:

- The baseline characteristics, including age, gender, BMI, HbA1c, treatment duration and diabetes duration, were similar across the studies
- Patients in the included trials had a mean age of 57.3 years, a BMI of 30.9 kg/m2, a baseline HbA1c of 8.6%, and a diabetes duration of 12.0 years.
- All but one of the treatment durations was 24 weeks.
- Besides the insulin treatments (with or without lixisenatide), most of the patients were allowed to receive background OAD therapy (metformin for most).

Qualität der Studien:

- The majority of included studies possessed low and/or moderate risk of bias.
  - Random sequence generation was adequate in all of the eight trials.
  - We did not identify any studies with definite high risk of bias

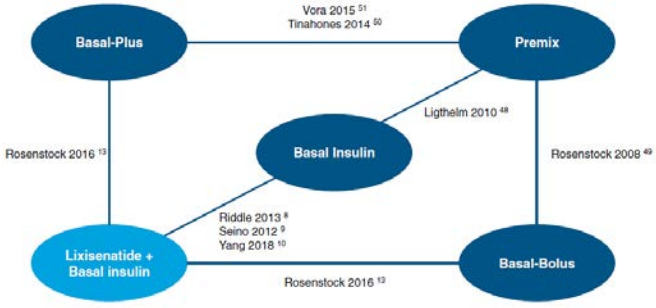
Appendix S9 Quality assessment for included trials



Studienergebnisse:

NMA

Netzwerkgeometrie



Results for direct evidence, indirect evidence and mixed treatment effect

Parameter	Direct evidence		Indirect evidence		Network meta-analysis	
	MD (95% CI)	Quality of evidence	MD (95% CI)	Quality of evidence	MD (95% CI)	Quality of evidence
Changes in the HbA1c from baseline (%)						
Lixi + BI vs. Premix	--	--	-0.654 (-1.406,0.098)	low	-0.124 (-0.498, 0.250)	low
Lixi + BI vs. Basal-Plus	0.000 (-0.374,0.374)	high	-0.623 (-1.119,-0.127)	moderate	-0.229 (-0.607, 0.150)	high
Lixi + BI vs. Basal-Bolus	0.200 (-0.298,0.698)	high	0.180 (-0.594,0.954)	moderate	0.090 (-0.310, 0.490)	high
Changes in the body weight from baseline (kg)						
Lixi + BI vs. Premix	--	--	-1.181 (-2.71,0.348)	low	-2.276 (-2.909, -1.643)	low

Lixi + BI vs. Basal-Plus	-0.400 (-1.252,0.452)	high	-0.913 (-1.958,0.132)	moderate	-1.732 (-2.375, -1.089)	high
Lixi + BI vs. Basal-Bolus	-2.000 (-2.832,-1.168)	high	-3.213 (-4.508,-1.918)	moderate	-2.354 (-3.054, -1.654)	high
Incidence of symptomatic hypoglycemia						
Lixi + BI vs. Premix	--	--	0.568 (0.098,3.281)	moderate	0.654 (0.458, 0.933)	moderate
Lixi + BI vs. Basal-Plus	0.770 (0.500,1.188)	high	0.310 (0.022,4.317)	moderate	0.754 (0.548, 1.038)	high
Lixi + BI vs. Basal-Bolus	0.601 (0.257,1.404)	high	0.230 (0.005,10.568)	low	0.599 (0.430, 0.834)	high
Event per patient of symptomatic hypoglycemia						
Lixi + BI vs. Premix	--	--	0.698 (0.517,0.941)	moderate	0.589 (0.353, 0.995)	moderate
Lixi + BI vs. Basal-Plus	0.835 (0.731,0.953)	high	0.756 (0.575,0.993)	moderate	0.805 (0.475, 1.376)	high
Lixi + BI vs. Basal-Bolus	0.501 (0.327,0.767)	high	1.049 (1.098,1.002)	moderate	0.624 (0.360, 1.103)	high

Abbreviations: basal-plus: basal insulin plus prandial insulin with the main meal; basal-bolus: basal insulin plus prandial insulin covering all meal; BI: basal insulin; CI: confidence interval; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; MD: mean difference; premix: intensive premixed insulin; RR: risk ratio

Anmerkung/Fazit der Autoren

In conclusion, lixisenatide combined with BI is shown to have a comparable glycaemic control ability, but is superior to premix, basal-plus and basal-bolus in terms of weight control and hypoglycaemia risk.

Kommentare zum Review

- Limitation: Keine Angaben zur Untersuchung der Transitivitätsannahme; jedoch Festlegung enger Einschlusskriterien der Studien; Studien hinsichtlich der Baselinecharakteristika Alter, BMI, HbA1c, Krankheitsdauer ähnlich

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Tsapas A et al., 2020 [102].

Comparative Effectiveness of Glucose-Lowering Drugs for Type 2 Diabetes. A Systematic Review and Network Meta-analysis.

Fragestellung

This systematic review and network meta-analysis of randomized controlled trials assesses the long-term effects of antidiabetic drugs on clinically important outcomes in clinically relevant subpopulations.

Methodik

Population:

- adults with type 2 diabetes

Intervention/ Komparator:

- glucose-lowering drugs that had been approved or had pending applications for regulatory authorization in Europe or the United States.
- Comparisons among the following single interventions were included:
  - metformin,
  - sulphonylureas,
  - pioglitazone,
  - dipeptidyl peptidase-4 (DPP-4) inhibitors,
  - GLP-1 RAs,
  - SGLT-2 inhibitors,
  - basal insulin, basal–bolus insulin regimens (including basal-plus insulin), premixed insulins,
  - a-glucosidase inhibitors,
  - meglitinides,
  - or placebo.

In each comparison, background treatment was defined as the antidiabetic medication therapy used in both the intervention and control groups after randomization. Eligible background therapy was either no background treatment (monotherapy) or metformin-based background treatment (metformin only or metformin plus any other antidiabetic medication).

Endpunkte:

- primary outcomes: change from baseline in HbA1c level and all-cause mortality
- Secondary outcomes: severe hypoglycemia, cardiovascular death, stroke, myocardial infarction, hospitalization for heart failure, diabetic retinopathy, and amputation
- data for end-stage renal disease

Recherche/Suchzeitraum:

- We searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials from inception through 18 December 2019 (without language restrictions)

Qualitätsbewertung der Studien

revised Cochrane Collaboration Risk of Bias tool RoB2.0.

NMA-Methodik/Überprüfung der zentralen Annahmen für eine NMA

- Initially, we did pairwise meta-analyses and then explored the transitivity assumption that a network meta-analysis approach was appropriate by comparing the distribution of potential effect modifiers across treatment comparisons (duration of diabetes, age, hemoglobin A1c level at baseline, and body mass index)
- We did frequentist random-effects network metaanalyses and calculated mean differences (MDs) for the change in hemoglobin A1c level and odds ratios (ORs) and 95% CIs for dichotomous outcomes, assuming a common heterogeneity variable across all comparisons. In case of sparse networks, we used a fixed-effects model, given that the common between-study heterogeneity cannot be estimated reliably in such networks

- We evaluated heterogeneity by comparing the magnitude of the common between-study variance for each outcome with empirical distributions of heterogeneity variances
- We evaluated consistency in the networks both locally by comparing direct with indirect evidence and globally by using the design-by-treatment interaction mode

Ergebnisse

Anzahl eingeschlossener Studien:

- 453 trials assessing 21 antidiabetic interventions from 9 drug classes

Charakteristika der Studien/Population:

- In 134 trials (41 862 patients), treatment interventions were used as monotherapy, of which 101 studies were in drug-naive patients, whereas the remaining studies recruited patients who had received antidiabetic treatment in the past but had all prior medication withdrawn at randomization.
- In 296 trials (264 087 patients), treatment interventions were used as an add-on to metformin-based therapy (metformin only or metformin plus any other antidiabetic medication). The remaining 23 studies (14 525 patients) included both groups that evaluated treatments as monotherapy and groups with patients receiving background metformin-based therapy. The median duration of trials was 26 weeks (interquartile range, 24 to 52 weeks).
- Three hundred studies had a double-blind design, 127 were open label, and 5 were single-blind; blinding status was unclear in the remaining studies.
- Mean hemoglobin A1c level at baseline was 8.3% (SD, 0.76%), and mean body weight was 85.1 kg (SD, 9.17).
- The median HbA1c level was 8.2% (interquartile range, 7.9% to 8.7%) in monotherapy trials and 8.2% (interquartile range, 8.0% to 8.5%) in trials with drugs as an add-on to metformin-based therapy.
- The median duration of diabetes across all trials was 6.9 years (interquartile range, 4.6 to 9.3 years).

Qualität der Studien:

- Regarding change in hemoglobin A1c level, 224 trials (58%) had low overall risk of bias.
- For allcause mortality, overall risk of bias was low in 80 trials(20%), whereas 292 trials (74%) had high risk of bias

Studienergebnisse:

Direkte Evidenz: siehe Anhang (Tsapas 2020 [102]. Pairwise meta-analysis results)

NMA

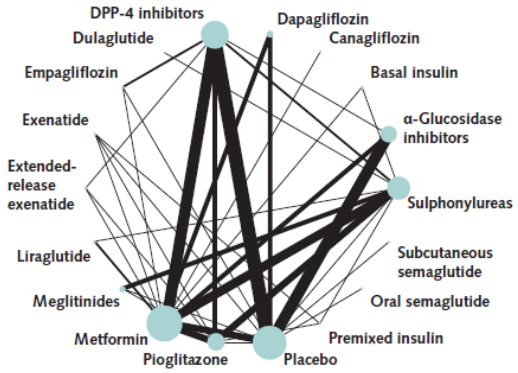
- On the basis of the distribution of potential effect modifiers (duration of diabetes, age, hemoglobin A1c level at baseline, and body mass index) across all treatment comparisons, eligible trials were deemed sufficiently similar to assume that a network meta-analysis was appropriate
- There was no evidence of heterogeneity for any outcome except for change in hemoglobin A1c level in both subnetworks and for diabetic retinopathy and amputation in the subnetwork of patients at increased cardiovascular risk receiving metformin-based background therapy

- The design-by-treatment interaction model did not identify global inconsistency in any of the networks, except for change in hemoglobin A1c level in the network of drug-naive patients. Local inconsistency in all analyses was generally low

Drug-Naive Patients

Glycemic Outcomes

Netzwerkgeometrie HbA1c



Results

- All treatments reduced HbA1c level compared with placebo, with MDs ranging from -1.48% (95% CI, -2.15% to -0.81%) for subcutaneous semaglutide to -0.60% (CI, -0.75% to -0.46%) for DPP-4 inhibitors (moderate confidence).

12.1.1. Change in HbA1c

aGIs										
0.39 (-0.23, 1.01)	Basal insulin									
-0.12 (-0.33, 0.08)	-0.51 (-1.12, 0.09)	DPP-4i								
0.40 (0.12, 0.69)	0.02 (-0.62, 0.65)	**0.53 (0.28, 0.78)**	GLP-1 RAs							
0.04 (-0.29, 0.36)	-0.35 (-1.01, 0.31)	0.16 (-0.14, 0.47)	**-0.37 (-0.73, -0.01)**	Meglitinides						
0.19 (-0.01, 0.38)	-0.20 (-0.79, 0.39)	**0.31 (0.17, 0.45)**	-0.22 (-0.47, 0.03)	0.15 (-0.15, 0.45)	Metformin					
0.17 (-0.07, 0.41)	-0.22 (-0.83, 0.39)	**0.29 (0.10, 0.48)**	-0.24 (-0.51, 0.03)	0.13 (-0.19, 0.45)	-0.02 (-0.19, 0.16)	Pioglitazone				
0.36 (-0.21, 0.93)	-0.03 (-0.83, 0.78)	0.49 (-0.07, 1.04)	-0.04 (-0.59, 0.50)	0.32 (-0.28, 0.93)	0.18 (-0.37, 0.72)	0.19 (-0.35, 0.74)	Premixed insulin			
0.11 (-0.16, 0.37)	-0.28 (-0.91, 0.35)	**0.23 (0.01, 0.45)**	-0.30 (-0.60, 0.01)	0.07 (-0.28, 0.42)	-0.08 (-0.29, 0.13)	-0.06 (-0.32, 0.20)	-0.25 (-0.83, 0.33)	SGLT-2i		
0.12 (-0.10, 0.33)	-0.27 (-0.88, 0.33)	**0.24 (0.06, 0.42)**	**-0.29 (-0.55, -0.03)**	0.08 (-0.20, 0.36)	-0.07 (-0.24, 0.10)	-0.05 (-0.25, 0.15)	-0.25 (-0.80, 0.30)	0.01 (-0.25, 0.26)	SU	
-0.73 (-0.91, -0.56)	**-1.12 (-1.73, -0.52)**	**-0.61 (-0.75, -0.47)**	**-1.14 (-1.38, -0.89)**	**-0.77 (-1.06, -0.48)**	**-0.92 (-1.06, -0.77)**	**-0.90 (-1.10, -0.70)**	**-1.09 (-1.65, -0.54)**	**-0.84 (-1.06, -0.63)**	**-0.85 (-1.03, -0.67)**	Placebo

Treatments are reported in alphabetical order. Treatment estimates are MDs and 95% CIs in the column-defining treatment compared to the row-defining treatment. MDs lower than 0 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=Sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

- All treatments reduced HbA1c level to a similar extent with metformin, except for DPP-4 inhibitors (MD, 0.32% [CI, 0.17% to 0.46%]), which were also inferior to liraglutide, subcutaneous semaglutide, pioglitazone, and sulphonylureas.

12.2. Mean differences for comparisons between drug classes and individual GLP-1 RAs and SGLT-2 inhibitors

12.2.1. Change in HbA_{1c}

aGIs																
0.39 (-0.24, 1.02)	Basal insulin															
0.28 (-0.39, 0.96)	-0.11 (-0.99, 0.78)	Canagliflozin														
0.09 (-0.23, 0.42)	-0.30 (-0.96, 0.37)	-0.19 (-0.89, 0.51)	Dapagliflozin													
-0.13 (-0.34, 0.08)	-0.52 (-1.14, 0.10)	-0.42 (-1.07, 0.24)	-0.22 (-0.52, 0.08)	DPP-4i												
0.55 (-0.12, 1.23)	0.16 (-0.73, 1.05)	0.27 (-0.65, 1.19)	0.46 (-0.25, 1.18)	**0.68 (0.02, 1.35)**	Dulaglutide											
0.08 (-0.31, 0.47)	-0.31 (-1.01, 0.39)	-0.20 (-0.94, 0.53)	-0.01 (-0.46, 0.44)	0.21 (-0.14, 0.57)	-0.47 (-1.22, 0.27)	Empagliflozin										
0.25 (-0.22, 0.71)	-0.14 (-0.89, 0.60)	-0.04 (-0.81, 0.74)	0.16 (-0.35, 0.67)	0.38 (-0.06, 0.82)	-0.31 (-1.09, 0.48)	0.17 (-0.39, 0.72)	Exenatide									
0.18 (-0.39, 0.74)	-0.21 (-1.02, 0.60)	-0.11 (-0.94, 0.73)	0.09 (-0.51, 0.69)	0.31 (-0.23, 0.85)	-0.37 (-1.22, 0.47)	0.10 (-0.54, 0.74)	-0.07 (-0.75, 0.61)	Exenatide ER								
0.72 (-0.02, 1.45)	0.33 (-0.61, 1.26)	0.43 (-0.53, 1.39)	0.62 (-0.14, 1.39)	**0.85 (0.12, 1.57)**	0.16 (-0.80, 1.13)	0.64 (-0.16, 1.43)	0.47 (-0.37, 1.30)	0.54 (-0.36, 1.43)	Liraglutide							
0.04 (-0.29, 0.37)	-0.35 (-1.02, 0.32)	-0.24 (-0.96, 0.47)	-0.05 (-0.45, 0.35)	0.17 (-0.14, 0.48)	-0.51 (-1.21, 0.19)	-0.04 (-0.50, 0.42)	-0.21 (-0.72, 0.31)	-0.14 (-0.75, 0.47)	-0.67 (-1.45, 0.10)	Meglitinides						
0.18 (-0.02, 0.39)	-0.21 (-0.81, 0.40)	-0.10 (-0.74, 0.54)	0.09 (-0.19, 0.38)	**0.32 (0.17, 0.46)**	-0.37 (-1.03, 0.30)	0.10 (-0.26, 0.47)	-0.06 (-0.50, 0.37)	0.01 (-0.53, 0.54)	-0.53 (-1.25, 0.18)	0.14 (-0.16, 0.45)	Metformin					
0.15 (-0.10, 0.40)	-0.24 (-0.86, 0.39)	-0.13 (-0.80, 0.53)	0.06 (-0.27, 0.39)	**0.28 (0.09, 0.48)**	-0.40 (-1.07, 0.27)	0.07 (-0.32, 0.46)	-0.09 (-0.54, 0.35)	-0.03 (-0.57, 0.52)	-0.56 (-1.30, 0.17)	0.11 (-0.22, 0.44)	-0.03 (-0.21, 0.15)	Pioglitazone				
0.29 (-0.31, 0.89)	-0.10 (-0.93, 0.74)	0.01 (-0.86, 0.87)	0.20 (-0.44, 0.84)	0.42 (-0.16, 1.01)	-0.26 (-1.13, 0.60)	0.21 (-0.46, 0.89)	0.04 (-0.55, 0.64)	0.11 (-0.67, 0.89)	-0.42 (-1.34, 0.49)	0.25 (-0.39, 0.89)	0.11 (-0.47, 0.69)	0.14 (-0.43, 0.71)	Premixed insulin			
0.37 (-0.31, 1.04)	-0.02 (-0.92, 0.88)	0.08 (-0.85, 1.01)	0.27 (-0.44, 0.99)	0.50 (-0.17, 1.17)	-0.19 (-1.12, 0.75)	0.29 (-0.46, 1.03)	0.12 (-0.67, 0.90)	0.19 (-0.67, 1.04)	-0.35 (-1.33, 0.63)	0.33 (-0.39, 1.04)	0.18 (-0.49, 0.85)	0.21 (-0.47, 0.90)	0.07 (-0.80, 0.95)	Semaglutide PO		
0.75 (0.06, 1.44)	0.36 (-0.55, 1.27)	0.46 (-0.48, 1.40)	0.65 (-0.07, 1.38)	**0.88 (0.20, 1.56)**	0.19 (-0.75, 1.14)	0.67 (-0.09, 1.42)	0.50 (-0.30, 1.29)	0.57 (-0.29, 1.43)	0.03 (-0.96, 1.02)	0.71 (-0.02, 1.44)	0.56 (-0.12, 1.24)	0.59 (-0.10, 1.29)	0.45 (-0.43, 1.34)	0.38 (-0.55, 1.31)	Semaglutide SC	
0.12 (-0.10, 0.35)	-0.27 (-0.89, 0.35)	-0.16 (-0.83, 0.50)	0.03 (-0.29, 0.35)	**0.25 (0.06, 0.45)**	-0.43 (-1.07, 0.21)	0.04 (-0.34, 0.43)	-0.12 (-0.58, 0.33)	-0.06 (-0.61, 0.50)	-0.59 (-1.32, 0.13)	0.08 (-0.21, 0.37)	-0.06 (-0.24, 0.11)	-0.03 (-0.24, 0.18)	-0.17 (-0.75, 0.42)	-0.24 (-0.92, 0.44)	-0.62 (-1.32, 0.07)	SU

Treatments are reported in alphabetical order. Treatment estimates are MDs and 95% CIs in the column-defining treatment compared to the row-defining treatment. MDs lower than 0 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. ER=extended release. PO=per os, SC=subcutaneous. SU=sulphonylureas.

- For all treatments, there was no difference versus placebo or metformin in the incidence of severe hypoglycemia (59 studies; 24 479 patients).

12.1.2. Severe hypoglycemia

aGIs												
0.83 (0.04, 19.11)	Basal insulin											
1.15 (0.26, 4.99)	1.39 (0.07, 26.45)	DPP-4i										
1.53 (0.25, 9.25)	1.85 (0.08, 41.48)	1.34 (0.32, 5.63)	GLP-1 RAs									
1.25 (0.06, 27.72)	1.51 (0.03, 89.20)	1.09 (0.06, 20.91)	0.81 (0.04, 18.04)	Meglitinides								
1.12 (0.27, 4.66)	1.36 (0.08, 23.43)	0.98 (0.41, 2.34)	0.73 (0.18, 2.91)	0.90 (0.05, 17.51)	Metformin							
1.20 (0.17, 8.41)	1.45 (0.06, 34.64)	1.04 (0.24, 4.57)	0.78 (0.13, 4.59)	0.96 (0.04, 24.18)	1.06 (0.24, 4.74)	Pioglitazone						
0.95 (0.05, 18.81)	1.15 (0.02, 54.94)	0.83 (0.05, 13.18)	0.62 (0.04, 9.88)	0.76 (0.01, 39.17)	0.85 (0.06, 12.93)	0.80 (0.05, 13.17)	Premixed insulin					
1.47 (0.25, 8.63)	1.78 (0.08, 39.33)	1.28 (0.34, 4.90)	0.96 (0.17, 5.50)	1.18 (0.05, 26.15)	1.31 (0.37, 4.61)	1.23 (0.19, 7.94)	1.55 (0.08, 29.52)	SGLT-2i				
0.59 (0.12, 2.89)	0.72 (0.04, 12.39)	0.52 (0.16, 1.71)	0.39 (0.09, 1.72)	0.48 (0.02, 10.00)	0.53 (0.19, 1.44)	0.50 (0.09, 2.60)	0.62 (0.04, 9.20)	0.40 (0.09, 1.88)	SU			
0.88 (0.22, 3.45)	1.06 (0.05, 20.96)	0.77 (0.28, 2.07)	0.57 (0.15, 2.24)	0.70 (0.04, 11.36)	0.78 (0.28, 2.19)	0.73 (0.14, 3.77)	0.92 (0.06, 14.97)	0.60 (0.15, 2.33)	1.48 (0.43, 5.10)	Placebo		

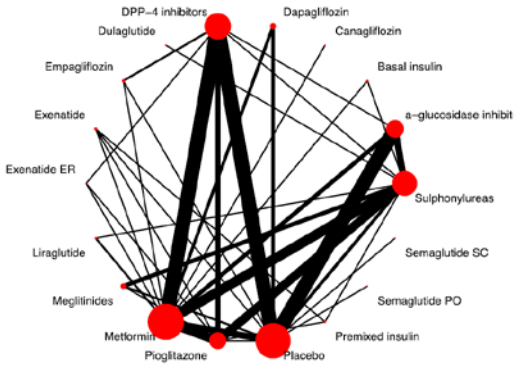
Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=Sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

Mortality and Vascular Outcomes

- We did not identify any trials exclusively recruiting drug-naive patients at increased cardiovascular risk; hence, for mortality and vascular outcomes, all trials in drug-naive patients were analyzed in a single network. Of note, patients in these trials likely had low underlying cardiovascular risk given that no cardiovascular deaths were reported among patients in the placebo groups.

Netzwerkgeometrie All cause mortality (P: at low cardiovascular risk)

5.2.1. All-cause mortality



Results

- All medications had a neutral effect on all-cause mortality (97 studies; 31 489 patients), cardiovascular death (91 studies; 24 212 patients), stroke (16 studies; 10 744 patients), myocardial infarction (27 studies; 15 286 patients), or hospitalization for heart failure (8 studies; 2560 patients). The confidence in these estimates was generally deemed very low

14.1.1. All-cause mortality

aGIs										
1.07 (0.06, 20.65)	Basal insulin									
1.40 (0.52, 3.83)	1.31 (0.08, 22.80)	DPP-4i								
1.18 (0.27, 5.07)	1.10 (0.05, 23.14)	0.84 (0.23, 3.01)	GLP-1 RAs							
1.12 (0.19, 6.75)	1.04 (0.04, 26.20)	0.80 (0.15, 4.19)	0.95 (0.13, 6.79)	Meglitinides						
1.08 (0.41, 2.82)	1.00 (0.06, 16.63)	0.77 (0.43, 1.38)	0.91 (0.27, 3.07)	0.96 (0.19, 4.83)	Metformin					
1.19 (0.36, 3.95)	1.11 (0.06, 20.38)	0.85 (0.34, 2.10)	1.01 (0.26, 4.01)	1.06 (0.19, 5.99)	1.11 (0.50, 2.48)	Pioglitazone				
0.62 (0.07, 5.70)	0.58 (0.02, 18.26)	0.44 (0.05, 3.56)	0.53 (0.06, 4.93)	0.55 (0.04, 7.12)	0.58 (0.07, 4.45)	0.52 (0.06, 4.30)	Premixed insulin			
1.55 (0.39, 6.12)	1.44 (0.07, 29.24)	1.10 (0.35, 3.47)	1.31 (0.27, 6.44)	1.38 (0.20, 9.33)	1.44 (0.48, 4.31)	1.30 (0.34, 4.91)	2.49 (0.25, 24.88)	SGLT-2i		
1.05 (0.40, 2.77)	0.98 (0.06, 16.30)	0.75 (0.40, 1.39)	0.89 (0.26, 3.05)	0.94 (0.19, 4.61)	0.98 (0.64, 1.49)	0.88 (0.39, 2.01)	1.70 (0.23, 12.76)	0.68 (0.22, 2.15)	SU	
0.91 (0.37, 2.23)	0.85 (0.05, 15.33)	0.65 (0.31, 1.35)	0.77 (0.22, 2.76)	0.81 (0.16, 4.23)	0.85 (0.41, 1.77)	0.77 (0.28, 2.10)	1.47 (0.18, 12.34)	0.59 (0.18, 1.91)	0.87 (0.41, 1.85)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=Sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas..

14.1.2. Cardiovascular mortality

aGIs										
1.13 (0.06, 21.93)	Basal insulin									
1.08 (0.36, 3.31)	0.96 (0.05, 17.90)	DPP-4i								
1.24 (0.28, 5.54)	1.10 (0.05, 23.74)	1.15 (0.28, 4.67)	GLP-1 RAs							
1.17 (0.19, 7.18)	1.03 (0.04, 26.12)	1.08 (0.18, 6.48)	0.94 (0.13, 7.02)	Meglitinides						
1.12 (0.39, 3.18)	0.99 (0.06, 16.91)	1.03 (0.45, 2.37)	0.90 (0.24, 3.31)	0.96 (0.17, 5.42)	Metformin					
1.28 (0.36, 4.56)	1.13 (0.06, 21.46)	1.18 (0.39, 3.61)	1.03 (0.24, 4.40)	1.09 (0.18, 6.49)	1.14 (0.42, 3.15)	Pioglitazone				
0.61 (0.05, 7.97)	0.54 (0.01, 21.55)	0.57 (0.04, 7.12)	0.49 (0.04, 6.35)	0.52 (0.03, 9.04)	0.55 (0.05, 6.53)	0.48 (0.04, 5.64)	Premixed insulin			
1.73 (0.36, 8.28)	1.53 (0.07, 34.35)	1.60 (0.38, 6.70)	1.39 (0.23, 8.24)	1.48 (0.18, 12.12)	1.55 (0.42, 5.76)	1.35 (0.27, 6.67)	2.83 (0.18, 44.79)	SGLT-2i		
1.13 (0.37, 3.39)	1.00 (0.06, 17.06)	1.04 (0.35, 3.09)	0.91 (0.23, 3.61)	0.96 (0.19, 4.82)	1.01 (0.40, 2.57)	0.88 (0.32, 2.44)	1.84 (0.17, 20.17)	0.65 (0.14, 3.04)	SU	
0.90 (0.36, 2.22)	0.79 (0.04, 14.61)	0.83 (0.35, 1.94)	0.72 (0.19, 2.69)	0.77 (0.14, 4.19)	0.80 (0.34, 1.87)	0.70 (0.23, 2.14)	1.47 (0.12, 17.90)	0.52 (0.13, 2.07)	0.80 (0.29, 2.17)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=Sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas..

14.1.3. Myocardial infarction

DPP-4i						
0.79 (0.10, 6.34)	GLP-1 RAs					
0.82 (0.34, 2.01)	1.04 (0.13, 8.41)	Metformin				
0.68 (0.21, 2.16)	0.86 (0.10, 7.21)	0.83 (0.28, 2.42)	Pioglitazone			
1.06 (0.26, 4.32)	1.34 (0.15, 12.28)	1.29 (0.36, 4.57)	1.55 (0.32, 7.45)	SGLT-2i		
0.99 (0.35, 2.78)	1.25 (0.15, 10.67)	1.20 (0.67, 2.16)	1.45 (0.48, 4.41)	0.93 (0.23, 3.74)	SU	
0.70 (0.17, 2.86)	0.89 (0.13, 5.85)	0.85 (0.20, 3.57)	1.03 (0.21, 4.96)	0.66 (0.15, 2.88)	0.71 (0.15, 3.25)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=Sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas..

14.1.4. Stroke

DPP-4i					
2.07 (0.17, 25.55)	GLP-1 RAs				
0.99 (0.31, 3.18)	0.48 (0.04, 5.32)	Metformin			
1.08 (0.16, 7.45)	0.52 (0.04, 7.74)	1.10 (0.17, 7.27)	SGLT-2i		
1.14 (0.30, 4.29)	0.55 (0.05, 6.10)	1.16 (0.60, 2.22)	1.06 (0.15, 7.64)	SU	
0.51 (0.10, 2.67)	0.25 (0.02, 2.63)	0.52 (0.09, 2.92)	0.47 (0.09, 2.36)	0.45 (0.07, 2.75)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=Sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

14.1.5. Hospitalization for heart failure

DPP-4i						
0.93 (0.01, 127.86)	GLP-1 RAs					
1.23 (0.15, 10.06)	1.32 (0.01, 180.78)	Metformin				
1.19 (0.08, 17.22)	1.28 (0.01, 171.38)	0.97 (0.07, 14.15)	Pioglitazone			
2.00 (0.04, 101.15)	2.14 (0.00, 1161.53)	1.63 (0.02, 140.12)	1.68 (0.01, 193.37)	SGLT-2i		
1.21 (0.02, 64.30)	1.30 (0.00, 446.64)	0.99 (0.02, 39.39)	1.01 (0.03, 40.52)	0.61 (0.00, 161.39)	SU	
0.47 (0.02, 9.26)	0.51 (0.01, 25.77)	0.39 (0.02, 7.57)	0.40 (0.02, 7.47)	0.24 (0.00, 32.65)	0.39 (0.01, 29.77)	Placebo

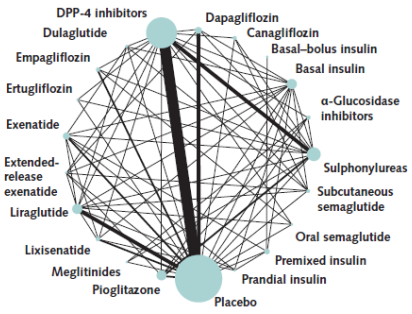
Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=Sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas..

We did not do meta-analyses for diabetic retinopathy and amputation because of a paucity of pertinent data.

<u>Patients on Metformin-Based Background Therapy</u>

Glycemic Outcomes

Netzwerkgeometrie HbA1C



Results

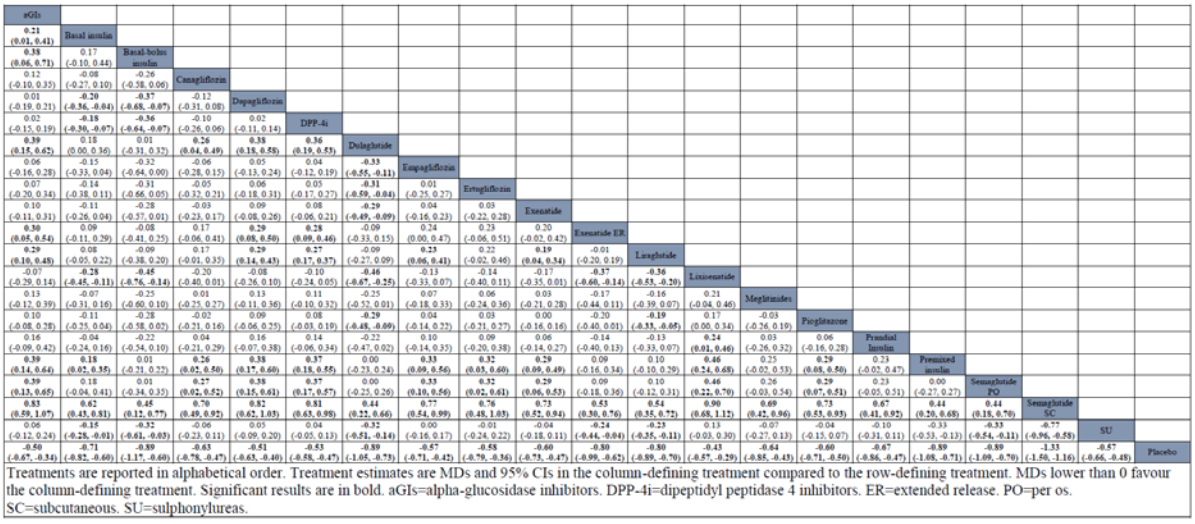
- The greatest placebo-subtracted reductions in HbA1c level were seen with GLP-1 RAs, premixed insulin, and basal–bolus insulin regimens. Subcutaneous semaglutide was more efficacious in lowering HbA1c level than all other treatments (MD vs. placebo, -1.33% [CI, -1.50% to -1.16%]). The confidence in effect estimates for change in HbA1c level was high to moderate.

16.1.1. Change in HbA_{1c}

aGIs												
0.21 (0.01, 0.41)	Basal insulin											
0.42 (0.09, 0.75)	0.20 (-0.07, 0.48)	Basal-bolus insulin										
0.02 (-0.16, 0.19)	**-0.20 (-0.32, -0.08)**	**-0.40 (-0.69, -0.11)**	DPP-4i									
0.27 (0.09, 0.45)	0.06 (-0.05, 0.16)	-0.15 (-0.43, 0.13)	**0.25 (0.18, 0.33)**	GLP-1 RAs								
0.14 (-0.12, 0.39)	-0.08 (-0.31, 0.16)	-0.28 (-0.64, 0.07)	0.12 (-0.09, 0.34)	-0.13 (-0.35, 0.09)	Meglitinides							
0.10 (-0.09, 0.29)	-0.11 (-0.26, 0.03)	**-0.32 (-0.62, -0.02)**	0.08 (-0.03, 0.19)	**-0.17 (-0.29, -0.05)**	-0.04 (-0.27, 0.19)	Pioglitazone						
0.25 (-0.01, 0.51)	0.04 (-0.16, 0.24)	-0.17 (-0.50, 0.16)	**0.24 (0.03, 0.44)**	-0.02 (-0.21, 0.17)	0.11 (-0.18, 0.40)	0.15 (-0.07, 0.37)	Prandial insulin					
0.42 (0.18, 0.67)	0.21 (0.04, 0.38)	0.01 (-0.21, 0.22)	**0.41 (0.22, 0.60)**	0.16 (-0.03, 0.34)	**0.29 (0.01, 0.57)**	**0.33 (0.11, 0.54)**	0.17 (-0.07, 0.42)	Premixed insulin				
0.04 (-0.14, 0.22)	**-0.17 (-0.30, -0.04)**	**-0.38 (-0.67, -0.08)**	0.03 (-0.06, 0.11)	**-0.23 (-0.32, -0.13)**	-0.10 (-0.32, 0.13)	-0.06 (-0.19, 0.07)	-0.21 (-0.42, 0.00)	**-0.38 (-0.58, -0.19)**	SGLT-2i			
0.07 (-0.11, 0.25)	**-0.15 (-0.28, -0.01)**	**-0.35 (-0.65, -0.05)**	0.05 (-0.04, 0.14)	**-0.20 (-0.30, -0.10)**	-0.07 (-0.28, 0.14)	-0.03 (-0.15, 0.08)	-0.18 (-0.40, 0.03)	**-0.36 (-0.56, -0.16)**	0.03 (-0.08, 0.14)	SU		
-0.50 (-0.67, -0.34)	**-0.72 (-0.83, -0.61)**	**-0.92 (-1.21, -0.64)**	**-0.52 (-0.58, -0.46)**	**-0.77 (-0.84, -0.71)**	**-0.64 (-0.86, -0.43)**	**-0.60 (-0.71, -0.50)**	**-0.75 (-0.95, -0.56)**	**-0.93 (-1.12, -0.74)**	**-0.55 (-0.62, -0.47)**	**-0.57 (-0.66, -0.48)**	Placebo	

Treatments are reported in alphabetical order. Treatment estimates are MDs and 95% CIs in the column-defining treatment compared to the row-defining treatment. MDs lower than 0 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. ER=extended release. PO=per os. SC=subcutaneous. SU=sulphonylureas.

16.2.1. Change in HbA_{1c}



Treatments are reported in alphabetical order. Treatment estimates are MDs and 95% CIs in the column-defining treatment compared to the row-defining treatment. MDs lower than 0 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. ER=extended release. PO=per os. SC=subcutaneous. SU=sulphonylureas.

- Sulphonylureas, premixed insulin, and basal–bolus insulin were associated with an increase in the incidence of severe hypoglycemia (252 studies; 261 559 patients)., the confidence for severe hypoglycemia was generally moderate to low.

16.1.2. Severe hypoglycemia

aGIs											
0.97 (0.28, 3.37)	Basal insulin										
0.59 (0.15, 2.31)	0.61 (0.34, 1.10)	Basal-bolus insulin									
1.34 (0.41, 4.40)	1.39 (0.92, 2.10)	**2.27 (1.15, 4.50)**	DPP-4i								
1.41 (0.43, 4.65)	1.46 (0.99, 2.16)	**2.40 (1.23, 4.68)**	1.05 (0.90, 1.23)	GLP-1 RAs							
1.18 (0.17, 8.11)	1.23 (0.24, 6.25)	2.01 (0.36,11.17)	0.88 (0.18, 4.29)	0.84 (0.17, 4.08)	Meglitinides						
0.99 (0.28, 3.58)	1.03 (0.53, 1.99)	1.68 (0.71, 3.97)	0.74 (0.43, 1.28)	0.70 (0.41, 1.22)	0.84 (0.16, 4.43)	Pioglitazone					
0.71 (0.18, 2.83)	0.73 (0.35, 1.55)	1.20 (0.50, 2.86)	0.53 (0.25, 1.09)	0.50 (0.24, 1.02)	0.60 (0.11, 3.39)	0.71 (0.29, 1.75)	Prandial insulin				
0.66 (0.18, 2.44)	0.68 (0.43, 1.08)	1.11 (0.78, 1.59)	**0.49 (0.27, 0.88)**	**0.46 (0.26, 0.82)**	0.55 (0.10, 2.97)	0.66 (0.30, 1.44)	0.93 (0.42, 2.05)	Premixed insulin			
1.72 (0.52, 5.73)	**1.78 (1.15, 2.77)**	**2.92 (1.45, 5.89)**	**1.28 (1.03, 1.61)**	1.22 (0.98, 1.52)	1.46 (0.30, 7.14)	1.73 (0.98, 3.07)	**2.44 (1.15, 5.14)**	**2.63 (1.44, 4.80)**	SGLT-2i		
0.26 (0.07, 0.87)	**0.26 (0.15, 0.45)**	**0.43 (0.20, 0.93)**	**0.19 (0.13, 0.27)**	**0.18 (0.12, 0.26)**	0.22 (0.04, 1.05)	**0.26 (0.14, 0.48)**	**0.36 (0.16, 0.81)**	0.39 (0.20, 0.77)	**0.15 (0.10, 0.22)**	SU	
1.42 (0.43, 4.65)	1.47 (0.99, 2.19)	**2.41 (1.23, 4.73)**	1.06 (0.94, 1.20)	1.01 (0.91, 1.11)	1.20 (0.25, 5.84)	1.43 (0.83, 2.45)	2.01 (0.98, 4.13)	**2.17 (1.23, 3.84)**	0.83 (0.68, 1.01)	**5.57 (3.84, 8.08)**	Placebo

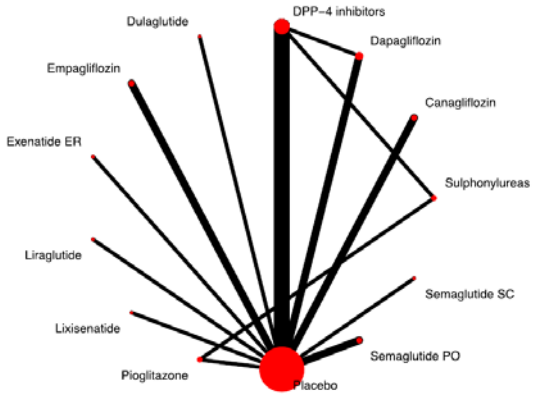
Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. ER=extended release. PO=per os. SC=subcutaneous. SU=sulphonylureas.

Mortality and Cardiovascular Outcomes

a) Patients at Increased Cardiovascular Risk

Netzwerkgeometrie all-cause mortality

6.2.1 All-cause mortality



Results

- **all-cause mortality:** Compared with placebo, all-cause mortality (21 studies; 145 694 patients) was reduced with oral semaglutide (OR, 0.50 [CI, 0.31 to 0.83]), empagliflozin (OR, 0.67 [CI, 0.55 to 0.81]), liraglutide (OR, 0.84 [CI, 0.73 to 0.97]), extended-release exenatide (OR, 0.86 [CI, 0.76 to 0.98]), and dapagliflozin (OR, 0.89 [CI, 0.80 to 0.99]) The confidence in these effect estimates was high to moderate.

18.1.1. All-cause mortality

DPP-4i					
1.15 (0.99, 1.33)	GLP-1 RAs				
0.99 (0.77, 1.27)	0.86 (0.67, 1.11)	Pioglitazone			
1.16 (0.99, 1.35)	1.01 (0.87, 1.17)	1.17 (0.91, 1.51)	SGLT-2i		
0.94 (0.76, 1.15)	0.82 (0.64, 1.05)	0.95 (0.72, 1.25)	0.81 (0.63, 1.04)	SU	
1.00 (0.89, 1.11)	**0.87 (0.79, 0.96)**	1.01 (0.80, 1.27)	**0.86 (0.77, 0.96)**	1.06 (0.85, 1.34)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. DPP-4i =dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i,=sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

  - On the basis of indirect comparisons, oral semaglutide and empagliflozin also had a favorable effect compared with canagliflozin, dapagliflozin, DPP-4 inhibitors, dulaglutide, extended-release exenatide, lixisenatide, pioglitazone, subcutaneous semaglutide, and sulphonylureas.

18.2.1. All-cause mortality

Canagliflozin												
1.10 (0.93, 1.30)	Dapagliflozin											
0.97 (0.83, 1.12)	0.88 (0.77, 1.00)	DPP-4i										
1.09 (0.91, 1.30)	0.99 (0.84, 1.17)	1.13 (0.98, 1.30)	Dulaglutide									
1.45 (1.15, 1.83)	**1.32 (1.06, 1.65)**	**1.50 (1.22, 1.85)**	**1.33 (1.06, 1.67)**	Empagliflozin								
1.13 (0.95, 1.35)	1.03 (0.87, 1.21)	**1.17 (1.01, 1.35)**	1.04 (0.87, 1.23)	**0.78 (0.62, 0.98)**	Exenatide ER							
1.16 (0.96, 1.41)	1.06 (0.88, 1.26)	**1.20 (1.02, 1.41)**	1.06 (0.88, 1.29)	0.80 (0.63, 1.02)	1.03 (0.85, 1.24)	Liraglutide						
1.04 (0.82, 1.31)	0.94 (0.75, 1.18)	1.07 (0.87, 1.32)	0.95 (0.75, 1.20)	**0.71 (0.54, 0.94)**	0.92 (0.73, 1.15)	0.89 (0.70, 1.14)	Lixisenatide					
0.97 (0.77, 1.22)	0.88 (0.71, 1.10)	1.01 (0.82, 1.23)	0.89 (0.71, 1.12)	**0.67 (0.51, 0.88)**	0.86 (0.69, 1.08)	0.84 (0.66, 1.06)	0.94 (0.71, 1.23)	Pioglitazone				
1.94 (1.16, 3.24)	**1.76 (1.06, 2.93)**	**2.00 (1.21, 3.31)**	**1.78 (1.06, 2.96)**	1.33 (0.78, 2.27)	**1.71 (1.03, 2.86)**	1.67 (0.99, 2.80)	**1.87 (1.10, 3.19)**	**1.99 (1.17, 3.39)**	Semaglutide PO			
0.94 (0.64, 1.38)	0.86 (0.59, 1.25)	0.98 (0.67, 1.41)	0.86 (0.59, 1.27)	**0.65 (0.43, 0.98)**	0.83 (0.57, 1.22)	0.81 (0.55, 1.20)	0.91 (0.60, 1.37)	0.97 (0.64, 1.46)	**0.49 (0.26, 0.90)**	Semaglutide SC		
0.90 (0.73, 1.11)	**0.81 (0.67, 0.99)**	0.93 (0.80, 1.08)	0.82 (0.67, 1.01)	**0.62 (0.48, 0.80)**	**0.79 (0.64, 0.98)**	**0.77 (0.62, 0.96)**	0.87 (0.67, 1.12)	0.92 (0.73, 1.16)	0.46 (0.27, 0.78)	0.95 (0.64, 1.42)	SU	
0.98 (0.86, 1.11)	**0.89 (0.80, 0.99)**	1.01 (0.94, 1.09)	0.89 (0.79, 1.01)	**0.67 (0.55, 0.81)**	**0.86 (0.76, 0.98)**	**0.84 (0.73, 0.97)**	0.94 (0.77, 1.15)	1.00 (0.83, 1.21)	**0.50 (0.31, 0.83)**	1.04 (0.72, 1.49)	1.09 (0.92, 1.29)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. DPP-4i =dipeptidyl peptidase 4 inhibitors, ER=extended release, PO=per os, SC=subcutaneous, SU=sulphonylureas.

- **cardiovascular death**

- Compared with placebo, oral semaglutide, empagliflozin, and liraglutide were associated with lower odds of cardiovascular death (21 studies; 145 694 patients) The confidence in these effect estimates was high to moderate

10.1.2. Cardiovascular mortality

DPP-4i					
1.12 (0.93, 1.34)	GLP-1 RAs				
0.98 (0.70, 1.37)	0.88 (0.63, 1.23)	Pioglitazone			
1.14 (0.94, 1.38)	1.02 (0.85, 1.23)	1.16 (0.83, 1.63)	SGLT-2i		
1.05 (0.78, 1.40)	0.94 (0.67, 1.32)	1.07 (0.70, 1.64)	0.92 (0.65, 1.30)	SU	
0.97 (0.85, 1.11)	**0.87 (0.77, 0.99)**	0.99 (0.73, 1.35)	**0.85 (0.74, 0.97)**	0.93 (0.67, 1.27)	Placebo

- Empagliflozin had a favorable effect on cardiovascular death compared with several other treatments, including canagliflozin, dapagliflozin, DPP-4 inhibitors, dulaglutide, extended-release exenatide, pioglitazone, and sulphonylureas (Figure 3).

Figure 3. Network meta-analysis results for cardiovascular death (left lower half) and hospitalization for heart failure (right upper half) in patients at increased cardiovascular risk receiving metformin-based background therapy:

Canagliflozin	0.97† (0.76–1.22)	*0.68† (0.55–0.84)*	0.76† (0.59–1.00)	1.10† (0.80–1.54)	*0.76† (0.58–0.98)*	0.82† (0.63–1.07)	0.75† (0.55–1.03)	*0.51† (0.37–0.69)*	0.85‡ (0.46–1.56)	0.66† (0.43–1.00)	0.83† (0.58–1.17)	*0.72* (0.60–0.87)*
1.05† (0.85–1.30)	Dapagliflozin	*0.70* (0.59–0.84)*	0.79† (0.62–1.01)	1.14† (0.84–1.56)	*0.78† (0.62–0.99)*	0.85† (0.67–1.08)	0.78† (0.58–1.04)	*0.53† (0.39–0.70)*	0.88‡ (0.48–1.60)	0.68† (0.45–1.02)	0.86† (0.61–1.19)	*0.75* (0.64–0.86)*
0.98† (0.82–1.16)	0.92† (0.78–1.10)	DPP-4 inhibitors	1.13† (0.91–1.40)	*1.63† (1.22–2.18)*	1.12† (0.90–1.38)	1.22† (0.98–1.50)	1.11† (0.84–1.46)	*0.75† (0.57–0.98)*	1.25‡ (0.70–2.26)	0.97‡ (0.66–1.43)	1.22† (0.92–1.62)	1.06† (0.96–1.17)
1.06† (0.85–1.32)	1.00‡ (0.81–1.24)	1.08† (0.90–1.30)	Dulaglutide	*1.45† (1.04–2.01)*	0.99† (0.76–1.29)	1.08† (0.82–1.41)	0.98‡ (0.71–1.35)	*0.66† (0.48–0.91)*	1.11‡ (0.60–2.05)	0.86‡ (0.56–1.31)	1.08‡ (0.76–1.54)	0.94‡ (0.78–1.14)
1.57† (1.19–2.08)	*1.49† (1.14–1.96)*	*1.62† (1.26–2.07)*	*1.49† (1.13–1.97)*	Empagliflozin	*0.68† (0.49–0.95)*	0.74† (0.54–1.03)	*0.68† (0.47–0.98)*	*0.46† (0.32–0.67)*	0.77‡ (0.41–1.46)	*0.59† (0.37–0.94)*	0.75† (0.50–1.12)	*0.65* (0.50–0.85)*
1.09† (0.88–1.34)	1.03‡ (0.83–1.27)	1.11† (0.94–1.33)	1.03‡ (0.83–1.28)	*0.69† (0.52–0.91)*	Extended-release exenatide	1.09† (0.84–1.42)	0.99‡ (0.72–1.36)	*0.67† (0.49–0.92)*	1.12‡ (0.61–2.07)	0.87‡ (0.57–1.32)	1.09‡ (0.77–1.56)	0.95‡ (0.79–1.15)
1.24† (0.98–1.57)	1.17† (0.93–1.48)	*1.27† (1.04–1.55)*	1.17† (0.92–1.49)	0.79† (0.59–1.05)	1.14† (0.90–1.44)	Liraglutide	0.91† (0.67–1.25)	*0.62† (0.45–0.84)*	1.03‡ (0.56–1.90)	0.80† (0.52–1.21)	1.00‡ (0.71–1.43)	0.87† (0.73–1.05)
0.98† (0.74–1.28)	0.93† (0.71–1.21)	1.00‡ (0.78–1.28)	0.92† (0.70–1.22)	*0.62† (0.45–0.86)*	0.90† (0.69–1.18)	0.79† (0.59–1.05)	Lixisenatide	*0.68† (0.47–0.97)*	1.13‡ (0.60–2.13)	0.87‡ (0.56–1.38)	1.10‡ (0.74–1.63)	0.96† (0.74–1.24)
0.99‡ (0.74–1.32)	0.94† (0.71–1.25)	1.01† (0.78–1.31)	0.94† (0.70–1.25)	*0.63† (0.45–0.88)*	0.91† (0.69–1.21)	0.80† (0.59–1.08)	1.01‡ (0.73–1.41)	Pioglitazone	1.68† (0.89–3.16)	1.29† (0.82–2.04)	*1.63† (1.10–2.41)*	1.42† (1.10–1.83)
1.88† (1.00–3.52)	1.78† (0.95–3.33)	*1.93† (1.04–3.57)*	1.78† (0.95–3.34)	1.19‡ (0.62–2.29)	1.73† (0.93–3.24)	1.52† (0.80–2.87)	1.93† (1.01–3.69)	1.90† (0.99–3.66)	Oral semaglutide	0.77‡ (0.39–1.54)	0.97‡ (0.51–1.87)	0.85‡ (0.47–1.51)
1.01‡ (0.64–1.57)	0.96‡ (0.61–1.49)	1.03‡ (0.67–1.59)	0.95‡ (0.61–1.49)	0.64† (0.40–1.03)	0.93‡ (0.59–1.45)	0.81† (0.52–1.29)	1.03‡ (0.64–1.66)	1.02‡ (0.63–1.65)	0.54† (0.26–1.12)	Subcutaneous semaglutide	1.26† (0.78–2.04)	1.10‡ (0.75–1.60)
1.00‡ (0.76–1.33)	0.95† (0.72–1.25)	1.03‡ (0.83–1.28)	0.95† (0.72–1.26)	*0.64† (0.46–0.88)*	0.92† (0.70–1.22)	0.81† (0.60–1.09)	1.03‡ (0.74–1.42)	1.01‡ (0.73–1.41)	0.53† (0.28–1.02)	1.00‡ (0.62–1.61)	Sulphonylureas	0.87† (0.65–1.17)
0.96† (0.83–1.12)	0.91† (0.79–1.06)	0.99* (0.90–1.08)	0.91† (0.78–1.07)	*0.61* (0.49–0.77)*	0.89† (0.76–1.03)	*0.78† (0.65–0.93)*	0.99‡ (0.79–1.24)	0.97† (0.76–1.24)	*0.51† (0.28–0.94)*	0.96‡ (0.63–1.45)	0.96† (0.76–1.21)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs of the column-defining treatment compared with the row-defining treatment for cardiovascular death. Treatment estimates are ORs and 95% CIs of the row-defining treatment compared with the column-defining treatment for hospitalization for heart failure. Odds ratios less than 1 favor the column-defining treatment for cardiovascular death and the row-defining treatment for hospitalization for heart failure. Significant results are italicized and highlighted in light green. DPP-4 = dipeptidyl peptidase-4; OR = odds ratio.
* High level of confidence in effect estimate.
† Moderate level of confidence in effect estimate.
‡ Low level of confidence in effect estimate.

- **hospitalization for heart failure:**

18.1.5. Hospitalization for heart failure

DPP-4i					
1.14 (0.99, 1.31)	GLP-1 RAs				
0.75 (0.57, 0.98)	**0.66 (0.50, 0.86)**	Pioglitazone			
1.47 (1.27, 1.70)	**1.29 (1.12, 1.49)**	**1.97 (1.49, 2.59)**	SGLT-2i		
1.22 (0.92, 1.62)	1.07 (0.79, 1.47)	**1.63 (1.10, 2.41)**	0.83 (0.60, 1.14)	SU	
1.06 (0.96, 1.17)	0.93 (0.85, 1.03)	**1.42 (1.10, 1.83)**	**0.72 (0.65, 0.80)**	0.87 (0.65, 1.17)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. DPP-4i =dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i,=sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

- The odds of hospitalization for heart failure were increased with pioglitazone compared with placebo (OR, 1.42 [CI, 1.10 to 1.83]) or other treatments (Figure 3).

- The confidence in effect estimates for hospitalization for heart failure was moderate.

Stroke / Myocardial infarction

- Compared with placebo, GLP-1 RAs reduced the incidence of stroke (OR, 0.84 [CI, 0.75 to 0.93]).

18.1.4. Stroke

DPP-4i					
1.18 (0.99, 1.39)	GLP-1 RAs				
1.21 (0.90, 1.61)	1.03 (0.77, 1.37)	Pioglitazone			
0.98 (0.82, 1.17)	**0.83 (0.71, 0.98)**	0.81 (0.60, 1.09)	SGLT-2i		
0.87 (0.68, 1.12)	**0.74 (0.55, 0.99)**	0.72 (0.51, 1.02)	0.89 (0.66, 1.20)	SU	
0.99 (0.87, 1.12)	**0.84 (0.75, 0.93)**	0.82 (0.63, 1.07)	1.01 (0.89, 1.14)	1.14 (0.86, 1.50)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. DPP-4i =dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i,=sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

- In terms of individual agents, the odds of stroke were lower with subcutaneous semaglutide (OR, 0.61 [CI, 0.37 to 0.99]) and dulaglutide (OR, 0.76 [CI, 0.62 to 0.94]). The confidence in these effect estimates was high to moderate.

18.2.3. Stroke

Canagliflozin												
0.91 (0.70, 1.19)	Dapagliflozin											
0.94 (0.74, 1.19)	1.03 (0.82, 1.29)	DPP-4i										
1.21 (0.91, 1.62)	**1.33 (1.01, 1.76)**	**1.29 (1.01, 1.66)**	Dulaglutide									
0.78 (0.55, 1.10)	0.86 (0.61, 1.20)	0.83 (0.61, 1.14)	**0.64 (0.45, 0.92)**	Empagliflozin								
1.08 (0.82, 1.43)	1.18 (0.90, 1.55)	1.15 (0.91, 1.46)	0.89 (0.67, 1.19)	1.38 (0.98, 1.96)	Exenatide ER							
1.07 (0.80, 1.43)	1.18 (0.89, 1.55)	1.14 (0.89, 1.46)	0.88 (0.66, 1.19)	1.37 (0.97, 1.95)	0.99 (0.75, 1.32)	Liraglutide						
0.83 (0.55, 1.24)	0.91 (0.61, 1.35)	0.88 (0.61, 1.28)	0.68 (0.45, 1.03)	1.06 (0.68, 1.67)	0.77 (0.51, 1.15)	0.77 (0.51, 1.16)	Lixisenatide					
1.13 (0.81, 1.58)	1.24 (0.90, 1.72)	1.21 (0.90, 1.61)	0.93 (0.66, 1.31)	1.45 (0.98, 2.15)	1.05 (0.75, 1.47)	1.06 (0.75, 1.49)	1.37 (0.88, 2.13)	Pioglitazone				
1.19 (0.58, 2.48)	1.31 (0.63, 2.71)	1.27 (0.62, 2.60)	0.98 (0.47, 2.05)	1.53 (0.72, 3.27)	1.11 (0.53, 2.30)	1.11 (0.54, 2.32)	1.44 (0.66, 3.16)	1.05 (0.50, 2.23)	Semaglutide PO			
1.53 (0.90, 2.57)	1.67 (1.00, 2.81)	1.62 (0.98, 2.68)	1.26 (0.74, 2.13)	**1.96 (1.12, 3.43)**	1.41 (0.84, 2.38)	1.42 (0.84, 2.41)	**1.84 (1.01, 3.35)**	1.35 (0.77, 2.34)	1.28 (0.54, 3.00)	Semaglutide SC		
0.82 (0.58, 1.15)	0.90 (0.64, 1.25)	0.87 (0.68, 1.12)	**0.67 (0.47, 0.95)**	1.05 (0.70, 1.56)	0.76 (0.54, 1.06)	0.76 (0.54, 1.08)	0.99 (0.63, 1.54)	0.72 (0.51, 1.02)	0.68 (0.32, 1.45)	**0.53 (0.31, 0.93)**	SU	
0.93 (0.76, 1.13)	1.02 (0.85, 1.22)	0.99 (0.87, 1.12)	**0.76 (0.62, 0.94)**	1.19 (0.89, 1.58)	0.86 (0.70, 1.05)	0.87 (0.70, 1.07)	1.12 (0.79, 1.59)	0.82 (0.63, 1.07)	0.78 (0.38, 1.57)	**0.61 (0.37, 0.99)**	1.14 (0.86, 1.50)	Placebo

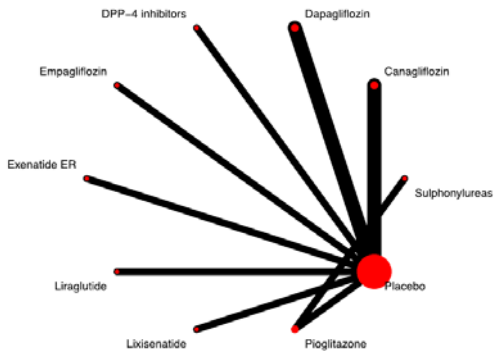
Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. DPP-4i =dipeptidyl peptidase 4 inhibitors. ER=extended release. PO=per os. SC=subcutaneous. SU=sulphonylureas.

- No differences were evident among any treatments for myocardial infarction.

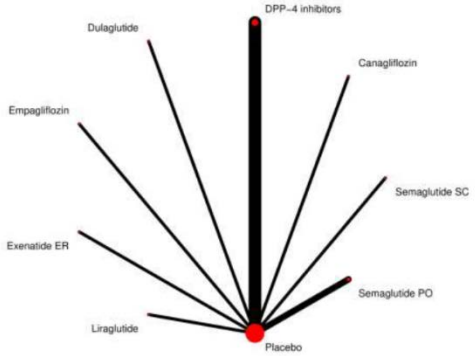
Diabetic retinopathy, amputation, end-stage renal disease

Netwerkgeometrie

6.2.7. Amputation



6.2.6. Diabetic retinopathy



Results

- The odds of diabetic retinopathy (12 studies; 95 664 patients) were similar to placebo for all treatments, except for subcutaneous semaglutide (OR, 1.75 [CI, 1.10 to 2.78]).
- The odds of amputation (11 studies; 93 922 patients) versus placebo were increased with canagliflozin (OR, 1.61 [CI, 1.27 to 2.05]) and reduced with liraglutide (OR, 0.65 [CI, 0.45 to 0.96]).
- The network for end-stage renal disease included 11 studies with 98 379 patients. Compared with placebo, SGLT-2 inhibitors reduced the odds of end-stage renal disease (OR, 0.63 [CI, 0.50 to 0.79]). This effect was consistent for dapagliflozin (OR, 0.32 [CI, 0.13 to 0.79]), empagliflozin (OR, 0.46 [CI, 0.22 to 0.98]), and canagliflozin (OR, 0.69 [CI, 0.54 to 0.88]).
- The confidence in effect estimates for diabetic retinopathy, amputation, and end-stage renal disease was low.

b) Patients at Low Cardiovascular Risk

Results

- **all-cause mortality:** When treatments were analyzed as drug classes, GLP-1 RAs were associated with reduced odds of all-cause mortality (292 studies; 136 942 patients) versus placebo (OR, 0.64 [CI, 0.45 to 0.91]).

20.1.1. All-cause mortality

aGIs											
1.26 (0.38, 4.14)	Basal insulin										
0.59 (0.10, 3.50)	0.46 (0.12, 1.84)	Basal-bolus insulin									
1.16 (0.40, 3.36)	0.92 (0.49, 1.72)	1.98 (0.45, 8.66)	DPP-4i								
1.42 (0.48, 4.24)	1.13 (0.65, 1.98)	2.44 (0.57, 10.34)	1.23 (0.82, 1.83)	GLP-1 RAs							
0.72 (0.16, 3.32)	0.57 (0.15, 2.22)	1.23 (0.18, 8.28)	0.62 (0.18, 2.16)	0.51 (0.14, 1.80)	Meglitinides						
1.13 (0.35, 3.63)	0.90 (0.39, 2.05)	1.93 (0.40, 9.32)	0.98 (0.51, 1.87)	0.79 (0.39, 1.59)	1.57 (0.40, 6.10)	Pioglitazone					
0.81 (0.21, 3.17)	0.64 (0.29, 1.44)	1.38 (0.32, 5.94)	0.70 (0.28, 1.75)	0.57 (0.24, 1.34)	1.12 (0.25, 5.09)	0.71 (0.24, 2.09)	Prandial insulin				
0.88 (0.24, 3.32)	0.70 (0.36, 1.37)	1.51 (0.45, 5.05)	0.76 (0.33, 1.78)	0.62 (0.28, 1.38)	1.23 (0.28, 5.35)	0.78 (0.29, 2.15)	1.10 (0.48, 2.49)	Premixed insulin			
0.96 (0.31, 2.94)	0.76 (0.38, 1.55)	1.64 (0.36, 7.46)	0.83 (0.52, 1.34)	0.67 (0.40, 1.13)	1.33 (0.37, 4.81)	0.85 (0.41, 1.79)	1.19 (0.45, 3.16)	1.09 (0.44, 2.71)	SGLT-2i		
1.03 (0.34, 3.08)	0.82 (0.41, 1.61)	1.76 (0.39, 7.88)	0.89 (0.60, 1.31)	0.72 (0.45, 1.17)	1.43 (0.42, 4.89)	0.91 (0.47, 1.78)	1.27 (0.49, 3.32)	1.16 (0.48, 2.83)	1.07 (0.65, 1.76)	SU	
0.92 (0.32, 2.60)	0.73 (0.40, 1.32)	1.57 (0.36, 6.78)	0.79 (0.58, 1.08)	**0.64 (0.45, 0.91)**	1.27 (0.37, 4.36)	0.81 (0.43, 1.54)	1.14 (0.46, 2.79)	1.04 (0.45, 2.38)	0.95 (0.62, 1.48)	0.89 (0.59, 1.36)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

- incidence of **myocardial infarction** (131 studies; 91 152 patients) was lower with GLP-1 RAs and SGLT-2 inhibitors than placebo,

20.1.3. Myocardial infarction

aGIs											
0.33 (0.03, 3.61)	Basal insulin										
0.23 (0.01, 3.87)	0.69 (0.14, 3.25)	Basal-bolus insulin									
0.43 (0.05, 3.94)	1.28 (0.50, 3.30)	1.87 (0.31, 11.25)	DPP-4i								
0.61 (0.06, 5.73)	1.82 (0.79, 4.23)	2.66 (0.47, 15.18)	1.42 (0.85, 2.37)	GLP-1 RAs							
1.14 (0.06, 21.58)	3.43 (0.33, 36.10)	5.00 (0.30, 82.65)	2.67 (0.30, 23.65)	1.88 (0.21, 17.20)	Meglitinides						
0.38 (0.03, 4.72)	1.15 (0.26, 5.18)	1.68 (0.20, 14.32)	0.90 (0.27, 3.04)	0.63 (0.18, 2.26)	0.34 (0.03, 4.02)	Pioglitazone					
0.31 (0.03, 3.84)	0.95 (0.34, 2.67)	1.38 (0.24, 8.03)	0.74 (0.22, 2.49)	0.52 (0.17, 1.60)	0.28 (0.02, 3.28)	0.82 (0.15, 4.43)	Prandial insulin				
0.23 (0.02, 3.10)	0.71 (0.25, 1.98)	1.03 (0.32, 3.29)	0.55 (0.14, 2.16)	0.39 (0.11, 1.42)	0.21 (0.02, 2.65)	0.61 (0.10, 3.70)	0.75 (0.20, 2.81)	Premixed insulin			
0.72 (0.08, 6.80)	2.18 (0.82, 5.83)	3.18 (0.52, 19.54)	1.70 (1.04, 2.78)	1.20 (0.68, 2.10)	0.64 (0.07, 5.74)	1.89 (0.53, 6.73)	2.31 (0.66, 8.02)	3.09 (0.77, 12.46)	SGLT-2i		
0.31 (0.03, 2.84)	0.94 (0.35, 2.50)	1.36 (0.22, 8.37)	0.73 (0.48, 1.10)	**0.51 (0.29, 0.90)**	0.27 (0.03, 2.33)	0.81 (0.23, 2.85)	0.99 (0.29, 3.44)	1.33 (0.33, 5.34)	**0.43 (0.26, 0.71)**	SU	
0.39 (0.04, 3.57)	1.17 (0.47, 2.93)	1.71 (0.29, 10.14)	0.92 (0.63, 1.34)	**0.64 (0.42, 0.99)**	0.34 (0.04, 3.06)	1.02 (0.30, 3.42)	1.24 (0.38, 4.09)	1.66 (0.43, 6.39)	**0.54 (0.35, 0.84)**	1.25 (0.79, 2.00)	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

- odds of diabetic retinopathy (38 studies; 25 151 patients) were increased with sulphonylureas (OR versus placebo, 2.48 [CI, 1.02 to 6.07]).

20.1.6. Diabetic retinopathy

aGIs									
15.20 (0.48, 485.76)	Basal insulin								
11.01 (0.41, 298.56)	0.72 (0.24, 2.19)	DPP-4i							
16.71 (0.61, 459.01)	1.10 (0.39, 3.14)	1.52 (1.00, 2.29)	GLP-1 RAs						
2.97 (0.12, 73.13)	0.20 (0.00, 12.26)	0.27 (0.00, 14.77)	0.18 (0.00, 9.83)	Meglitinides					
6.10 (0.17, 212.35)	0.40 (0.08, 2.06)	0.55 (0.14, 2.17)	0.36 (0.10, 1.38)	2.05 (0.03, 138.19)	Pioglitazone				
11.72 (0.39, 356.27)	0.77 (0.20, 2.93)	1.06 (0.42, 2.68)	0.70 (0.31, 1.60)	3.94 (0.07, 237.02)	1.92 (0.40, 9.21)	Prandial insulin			
10.55 (0.36, 306.86)	0.69 (0.19, 2.48)	0.96 (0.42, 2.20)	0.63 (0.30, 1.33)	3.55 (0.06, 205.66)	1.73 (0.39, 7.77)	0.90 (0.30, 2.74)	SGLT-2i		
5.99 (0.24, 147.32)	0.39 (0.11, 1.48)	0.54 (0.25, 1.21)	0.36 (0.15, 0.84)	2.02 (0.04, 101.72)	0.98 (0.21, 4.56)	0.51 (0.16, 1.67)	0.57 (0.20, 1.63)	SU	
14.88 (0.54, 413.39)	0.98 (0.34, 2.83)	1.35 (0.77, 2.37)	0.89 (0.56, 1.41)	5.01 (0.09, 279.26)	2.44 (0.70, 8.50)	1.27 (0.49, 3.27)	1.41 (0.61, 3.26)	**2.48 (1.02, 6.07)**	Placebo

Treatments are reported in alphabetical order. Treatment estimates are ORs and 95% CIs in the column-defining treatment compared to the row-defining treatment. ORs lower than 1 favour the column-defining treatment. Significant results are in bold. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. GLP-1 RAs=glucagon-like peptide 1 receptor agonists. SGLT-2i=sodium-glucose co-transporter 2 inhibitors. SU=sulphonylureas.

- All drug classes were similar to placebo in terms of cardiovascular death (263 studies; 118 419 patients), stroke (106 studies; 76 660 patients), hospitalization for heart failure (27 studies; 12 570 patients), and amputation (16 studies; 8921 patients).
- When GLP-1 RAs and SGLT-2 inhibitors were analyzed as individual agents, all treatments were similar to placebo in terms of all-cause mortality and cardiovascular outcomes.
- The confidence in most effect estimates in this subnetwork was very low because of imprecision and within-study bias

Anmerkung/Fazit der Autoren

In conclusion, the use of metformin as first-line treatment of drug-naive patients at low cardiovascular risk seems justified. Given the lack of pertinent evidence, we could not reach a conclusion about the optimal initial treatment of drug-naive patients at increased cardiovascular risk. In patients at low cardiovascular risk receiving metformin-based background therapy, choice among available agents should be based on their effect on other efficacy and safety outcomes because of lack of difference in vascular outcomes. For patients at increased cardiovascular risk receiving metformin-based background therapy, the optimal choice between specific GLP-1 RAs and SGLT-2 inhibitors should be based on the cardiovascular profile of individual agents and guided by patients' personal preferences and therapeutic priorities.

Kommentare zum Review

- Vergleich von GLP-1 RA and SGLT-2 Inhibitoren siehe auch NMA von Palmer et al. 2021 [93], welche zu ähnlichen Ergebnissen mit Ausnahme des EP Mortality kommt:
  - "Both classes of drugs lowered all cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and kidney failure (high certainty evidence). "
  - "SGLT-2 inhibitors reduced all-cause mortality (0.88 (0.79 to 0.97); 2, 7, 12, 16, and 23 fewer per 1000 in five years for very low, low, moderate, high, and very high risk patients respectively, moderate to high certainty)) and admission to hospital for heart failure more than GLP-1 receptor agonists, and GLP-1 receptor agonists reduced non-fatal stroke more than SGLT-2 inhibitors (which appeared to have no effect)."
- Vergleich zwischen bzw. von GLP-1 RAs und SGLT-2 inhibitors siehe auch NMA von Hussein H et al. 2020 [63] mit vergleichbaren HbA1c- Ergebnissen:
  - „Compared with placebo, all treatments improved HbA1c. Long-acting GLP-1RAs reduced HbA1c compared with short-acting GLP-1RAs and SGLT-2is, with semaglutide showing greater reduction compared with placebo [24weeks: −1.49% (95% credible interval: −1.76,−1.22); 52 weeks: −1.38% (−2.05, −0.71)] and all other treatments"

Kanters S et al., 2019 [66].

Comparative efficacy of once-weekly semaglutide versus SGLT-2 inhibitors in patients inadequately controlled with one to two oral antidiabetic drugs: a systematic literature review and network meta-analysis

Fragestellung

To conduct an SLR and NMA to determine the efficacy of once-weekly semaglutide relative to SGLT-2is licensed in both Europe and North America among patients (aged ≥18 years) with T2D with inadequate glycaemic control using 1–2 OADs.

Methodik

Population:

- adults aged 18 years or older with T2D inadequately controlled with 1–2 prior OADs;

Intervention:

- semaglutide 1.0 or 0.5 mg doses of once-weekly, or any approved doses of SGLT-2is that are licensed in Europe and North America

Komparator:

- SGLT-2is: Empagliflozin 10 mg and 25 mg once daily, Canagliflozin 100 mg and 300 mg once daily, Dapagliflozin 5 mg and 10 mg once daily
- Other treatments that are connected with once-weekly once-weekly semaglutide and/or a SGLT-2i

Endpunkte:

- change from baseline HbA1c, weight, body mass index (BMI), and systolic blood pressure (SBP), postprandial blood glucose (PPG), fasting plasma glucose (FPG), proportion of patients achieving <7% or ≤6.5% HbA1c, proportion of patients achieving ≥5 or 10% wt loss,

- safety outcomes and triple composite outcome (based on reaching <7.0% HbA1c, having no hypoglycaemic events and no weight gain)

Recherche/Suchzeitraum:

- MEDLINE, EMBASE and CENTRAL through Ovid from January 1994 to 5 April 2016, with updates on 3 October 2016 and 16 August 2017

Qualitätsbewertung der Studien:

- Cochrane risk of bias

NMA-Methodik/Überprüfung der zentralen Annahmen

- feasibility assessment was conducted to assess:

  (1) whether the RCT evidence for the interventions of interest formed a connected evidence network for each outcome of interest and time point;

  (2) the homogeneity of outcomes reported and data time points and

  (3) the distribution of study characteristics, subject characteristics and disease definitions that may impact treatment effects across direct comparisons of the evidence network for outcomes and time points of interest
- Analyses were performed within a Bayesian framework,

Ergebnisse

Anzahl eingeschlossener Studien:

- 21 trials

Charakteristika der Population:

- A majority of the trials were multicentre, phase III, double-blind trials. The only open-label trials were SUSTAIN 3 and SUSTAIN 7.
- Duration of follow-up was reported in all 21 trials, ranging from 24 to 104 weeks; mean age ranged from 53.5 to 61.0 years; mean weight at baseline ranged from 76.9 to 96.0 kg; mean SBP ranged from 126 to 135 mm Hg and mean baseline HbA1c ranged from 7.2% to 9.3%.

Qualität der Studien:

- The trials were considered to have low-risk of bias based onCochrane RoB Assessment tool.
- The only source of high-risk bias came from the lack of blinding and selective reporting in few included trials.

Studienergebnisse:

Direkte Evidenz: keine Angaben

NMA

- NMA was not possible for the following outcomes: proportion of patients achieving ≤6.5% HbA1c, proportion of patients achieving ≥5 or 10% wt loss, BMI, PPG (mmol/L), safety outcomes and triple composite outcome. This was either because the network was disconnected between onceweekly semaglutide and SGLT-2is or the data were not available at 26±4 weeks.
- The following sensitivity analyses were conducted: (i) removal of 3 trials with more than 40% Asian patients (this is due to Asian ethnicity being a well-recognised effect

modifier in diabetic therapeutics due to a greater level of ß-cell dysfunction in East Asians); and (ii) removal of one trial with high cardiovascular risk.

- In our feasibility assessment, we observed differences between different direct comparisons in the distribution of the following characteristics: sex, disease duration, weight at baseline, HbA1c at baseline, number of OADs failed at baseline. We conducted metaregression analyses using these variables.
- No evidenceof inconsistency was observed in any of the outcomes.

Netzwerkgeometrie

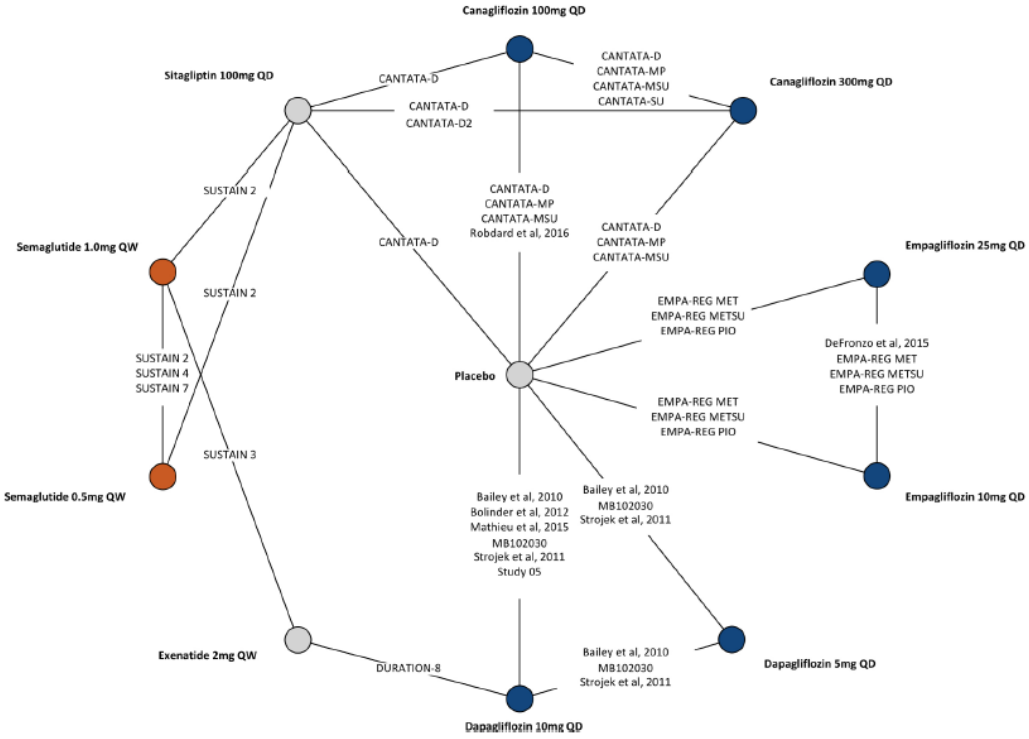


Figure 2 Overall network of evidence of semaglutide, SGLT-2is and other treatments for type II diabetes that is uncontrolled using 1-2 oral antidiabetics.

Relative efficacy with 95% credible intervals comparing HbA1c (%) in once-weekly semaglutide versus SGLT-2is

	Mean difference for HbA_{1c} (%) random-effect NMA			OR of patients achieving HbA_{1c} <7.0% from fixed-effect NMA		
	Placebo	Once-weekly semaglutide 0.5 mg	Once-weekly semaglutide 1.0 mg	Placebo	Once-weekly semaglutide 0.5 mg	Once-weekly semaglutide 1.0 mg
Placebo	–	−1.12 (−1.35 to −0.89)	−1.38 (−1.59 to −1.16)	–	9.45 (6.57 to 13.52)	12.80 (9.05 to 18.11)
Once-weekly semaglutide 0.5 mg	1.12 (0.89 to 1.35)	–	−0.26 (−0.38 to −0.13)	0.11 (0.07 to 0.15)	–	1.35 (1.09 to 1.68)
Once-weekly semaglutide 1.0 mg	1.38 (1.16 to 1.59)	0.26 (0.13 to 0.38)	–	0.08 (0.06 to 0.11)	0.74 (0.60 to 0.92)	–
Canagliflozin 100 mg once daily	0.67 (0.55 to 0.80)	−0.45 (−0.68 to −0.21)	−0.71 (−0.92 to −0.48)	0.43 (0.34 to 0.55)	4.07 (2.86 to 5.83)	5.52 (3.91 to 7.81)
Canagliflozin 300 mg once daily	0.82 (0.69 to 0.95)	−0.30 (−0.52 to −0.07)	−0.56 (−0.76 to −0.33)	0.25 (0.20 to 0.32)	2.38 (1.66 to 3.41)	3.22 (2.27 to 4.56)
Dapagliflozin 5 mg once daily	0.43 (0.29 to 0.57)	−0.70 (−0.96 to −0.43)	−0.95 (−1.20 to −0.69)	0.40 (0.27 to 0.57)	3.74 (2.33 to 6.08)	5.08 (3.21 to 8.09)
Dapagliflozin 10 mg once daily	0.58 (0.48 to 0.68)	−0.55 (−0.78 to −0.29)	−0.80 (−1.02 to −0.57)	0.29 (0.22 to 0.37)	2.70 (1.83 to 4.02)	3.66 (2.53 to 5.30)
Empagliflozin 10 mg once daily	0.59 (0.45 to 0.71)	−0.53 (−0.80 to −0.27)	−0.79 (−1.04 to −0.53)	0.27 (0.19 to 0.37)	2.53 (1.57 to 4.09)	3.43 (2.13 to 5.49)
Empagliflozin 25 mg once daily	0.61 (0.48 to 0.74)	−0.51 (−0.78 to −0.25)	−0.77 (−1.02 to −0.51)	0.22 (0.16 to 0.30)	2.06 (1.27 to 3.39)	2.80 (1.74 to 4.52)

Each cell represents the comparison (mean difference and 95% CrI) of the column treatment versus the row treatment. All bolded values are statistically meaningful at the 0.05 significance level.
NMA, network meta-analysis; SGLT-2is, sodium-glucose cotransporter 2 inhibitors.

- once-weekly semaglutide was more efficacious at reducing HbA1c relative to SGLT-2is, at both doses.
- once-weekly semaglutide was statistically significantly better than all SGLT-2is in achieving target HbA1c levels of <7%

Anmerkung/Fazit der Autoren

Limitation

While the population of interest was patients with inadequate glycaemic control using 1–2 OADs, a large number of studies only included patients on OAD monotherapy while others only included patients on dual therapy, which may have affected the homogeneity of the population. The pooling of such populations was required to ensure network connectivity, and models adjusting for these differences through metaregression suggest minimal impact from these differences.

Conclusion

Using an SLR and NMA, this study provided evidence in support of improved efficacy using once-weekly semaglutide relative to SGLT-2is licensed in Europe and North America for the treatment of patients with inadequate glycaemic control using 1–2 OADs.

Results of the NMA demonstrated that across most efficacy outcomes (HbA1c, target HbA1c<7%, weight loss and FPG), once-weekly semaglutide had the highest estimated efficacy. There was very strong evidence that once-weekly semaglutide led to larger decreases in both HbA1c and weight. Specifically, the magnitude of the differences was large and clinically meaningful.

Kommentare zum Review

- Nur Ergebnisse zu HbA1C dargestellt.

Zheng SL et al., 2018 [115].

Association Between Use of Sodium-Glucose Cotransporter 2 Inhibitors, Glucagon-like Peptide 1 Agonists, and Dipeptidyl Peptidase 4 Inhibitors With All-Cause Mortality in Patients With Type 2 Diabetes: A Systematic Review and Meta-analysis

Fragestellung

The purpose of this network meta-analysis was to compare the efficacy of SGLT-2 inhibitors, DPP-4 inhibitors, and GLP-1 agonists in reducing mortality and cardiovascular outcomes in participants with type 2 diabetes and their relative safety profiles

Methodik

Population:

- Patients with T2DM

Intervention/Komparator:

- SGLT-2 inhibitors, GLP-1 agonists, and DPP-4 inhibitors at market-approved doses with each other or with a control group (defined as placebo or no treatment)

Endpunkte:

- primary outcome: all-cause mortality.
- Secondary outcomes: cardiovascular mortality, heart failure events, myocardial infarction (MI) (all and nonfatal), unstable angina, and stroke (all and nonfatal).
- Safety end points: adverse events (any, serious, and leading to study withdrawal), and hypoglycemia (minor and major)
- Cardiovascular outcome trials:
  - composite cardiovascular outcome (cardiovascular mortality, nonfatal MI, nonfatal stroke)
  - Additional drug class–specific safety (UTI, GI, acute pancreatitis, retinopathy)

Recherche/Suchzeitraum:

- Up to October 11, 2017 MEDLINE, EMBASE, and CENTRAL

Qualitätsbewertung der Studien:

- Cochrane Collaboration risk of bias tool

NMA-Methodik/ Überprüfung der zentralen Annahmen

- Fixed- or random-effects models were selected for each outcome based on the deviance information criterion (DIC), using the model with the smallest value. Analyses were performed using Markov-chain Monte Carlo methods.
- The probability that each treatment class ranked in a given position from best to worst was estimated and presented in ranking plots.
- Transitivity assumes similarity between sets of trials with respect to important effect modifiers. This was assessed by constructing summary tables organized by pair-wise comparisons to qualitatively assess baseline clinical similarity of trial populations.
- Between study heterogeneity was assessed using the I^2 statistic.
- Inconsistency was evaluated by node-splitting analysis, and quantitative assessment of inconsistency was achieved by comparing the difference in direct and indirect estimates.

Ergebnisse

Anzahl eingeschlossener Studien:

- 236 RCTs with 176 310 participants

Charakteristika der Studien/Population:

Table. Study Participant Characteristics[a]

Drug Type	No. of Trials	Total No. Randomized	Mean (SD) Men, %	Age, y	BMI	HbA_{1c}, %
DPP-4 inhibitor vs control	83	67 958	54.7 (9.4)	57.9 (5.3)	29.3 (2.9)	8.16 (0.61)
GLP-1 agonist vs control	65	55 740	55.1 (11.4)	57.1 (3.8)	31.5 (3.5)	8.11 (0.36)
SGLT-2 inhibitor vs control	65	40 009	57.9 (10.4)	58.0 (3.7)	29.3 (5.0)	8.05 (0.32)
DPP-4 inhibitor vs GLP-1 agonist	14	8024	50.9 (7.5)	52.9 (4.4)	32.6 (2.3)	8.2 (0.20)
DPP-4 inhibitor vs SGLT-2 inhibitor	8	4121	56.0 (5.5)	55.5 (2.1)	30.9 (1.2)	8.0 (0.39)
GLP-1 agonist vs SGLT-2 inhibitor	1	458				

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; DPP-4, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HbA_{1c}, hemoglobin A_{1c}; SLGT2, sodium-glucose cotransporter 2.

[a] The Table represents data from studies stratified by the intervention and comparator. Control refers to placebo or no treatment. There was 1 study assessing GLP-1 agonist compared with a SGLT-2 inhibitor.

- The baseline characteristics of studies were deemed sufficiently similar based on sex, age, body mass index (BMI), and hemoglobin A1c (HbA1c) levels to permit network comparison.
- baseline cardiovascular disease and background medical therapy for participants in cardiovascular outcome trials were deemed similar, although 2 studies enrolled participants after being diagnosed with acute coronary syndrome.

Qualität der Studien:

- 104 (44.1%) were low risk of bias across all domains. Three (1.3%) were high risk of bias for allocation concealment, 16 (6.8%) for blinding, and 58 (24.6%) for attrition bias. No studies were high risk of bias for sequence allocation or detection.
- There was no evidence of publication bias (Egger test, 0.10; P = .27)

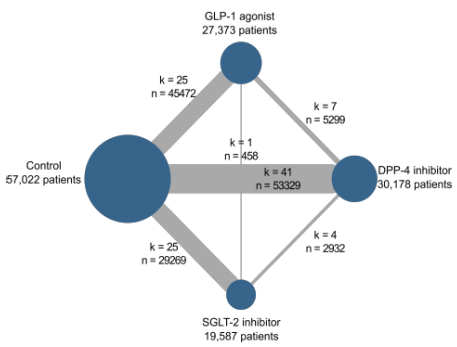
Studienergebnisse:

Direkte Evidenz –Metaanalyse : keine Information

NMA

Mortality

Netzwerkgeometrie

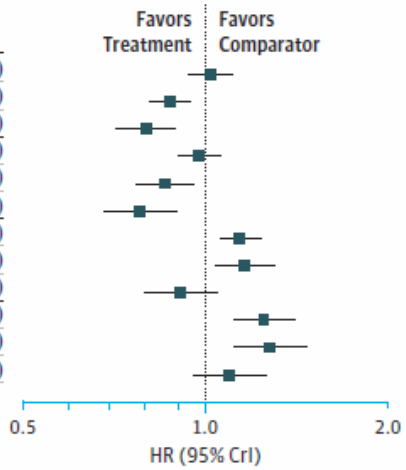


Results

A Primary outcome: all-cause mortality, 97 trials; $I^2 = 12\%$

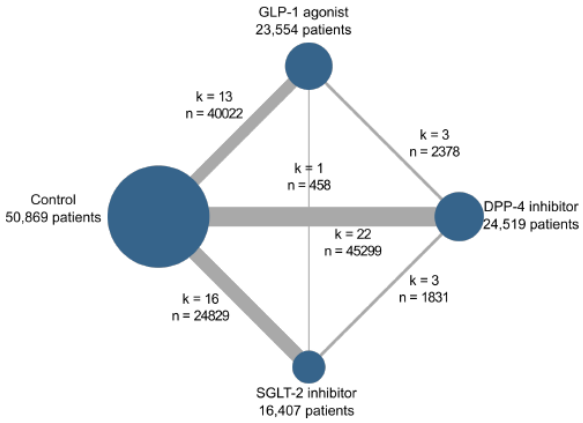
Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.1 (-0.3 to 0.6)	1.02 (0.94 to 1.11)
GLP-1 agonist		-0.6 (-1.0 to -0.3)	0.88 (0.81 to 0.94)
SGLT-2 inhibitor		-1.0 (-1.5 to -0.6)	0.80 (0.71 to 0.89)
Control	vs DPP-4 inhibitor	-0.1 (-0.4 to 0.2)	0.98 (0.90 to 1.06)
GLP-1 agonist		-0.5 (-0.9 to -0.2)	0.86 (0.77 to 0.96)
SGLT-2 inhibitor		-0.9 (-1.2 to -0.4)	0.78 (0.68 to 0.90)
Control	vs GLP-1 agonist	0.6 (0.3 to 1.0)	1.14 (1.06 to 1.23)
DPP-4 inhibitor		0.7 (0.2 to 1.3)	1.17 (1.04 to 1.30)
SGLT-2 inhibitor		-0.4 (-0.9 to 0.2)	0.91 (0.79 to 1.04)
Control	vs SGLT-2 inhibitor	0.9 (0.4 to 1.5)	1.25 (1.12 to 1.40)
DPP-4 inhibitor		1.0 (0.4 to 1.7)	1.28 (1.11 to 1.47)
GLP-1 agonist		0.4 (-0.1 to 0.9)	1.10 (0.96 to 1.26)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	88	2955 (5.2)	57022
DPP-4 inhibitor	49	1171 (3.9)	30178
GLP-1 agonist	32	1195 (4.4)	27373
SGLT-2 inhibitor	29	714 (3.6)	19587



Cardiovascular mortality

Netzwerkgeometrie

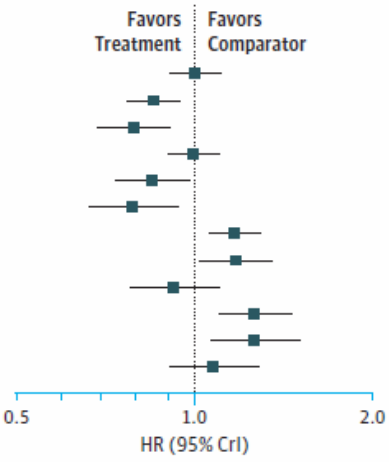


Results

B Cardiovascular mortality, 56 trials; $I^2 = 19\%$

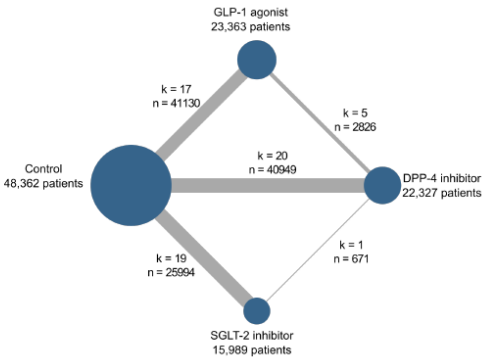
Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.0 (-0.3 to 0.4)	1.00 (0.91 to 1.11)
GLP-1 agonist		-0.5 (-0.8 to -0.1)	0.85 (0.77 to 0.94)
SGLT-2 inhibitor		-0.8 (-1.1 to -0.3)	0.79 (0.69 to 0.91)
Control	vs DPP-4 inhibitor	0.0 (-0.3 to 0.3)	1.00 (0.90 to 1.10)
GLP-1 agonist		-0.5 (-0.8 to -0.1)	0.85 (0.74 to 0.98)
SGLT-2 inhibitor		-0.7 (-1.1 to -0.2)	0.79 (0.66 to 0.94)
Control	vs GLP-1 agonist	0.5 (0.2 to 0.9)	1.17 (1.06 to 1.30)
DPP-4 inhibitor		0.5 (0.1 to 1.1)	1.18 (1.02 to 1.36)
SGLT-2 inhibitor		-0.2 (-0.7 to 0.3)	0.93 (0.78 to 1.10)
Control	vs SGLT-2 inhibitor	0.8 (0.3 to 1.3)	1.27 (1.10 to 1.46)
DPP-4 inhibitor		0.8 (0.2 to 1.5)	1.27 (1.07 to 1.51)
GLP-1 agonist		0.2 (-0.3 to 0.8)	1.08 (0.91 to 1.29)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	50	1833 (3.6)	50869
DPP-4 inhibitor	27	763 (3.1)	24519
GLP-1 agonist	19	704 (3.0)	23554
SGLT-2 inhibitor	19	468 (2.5)	18407



Heart failure

Neztwerkgeometrie

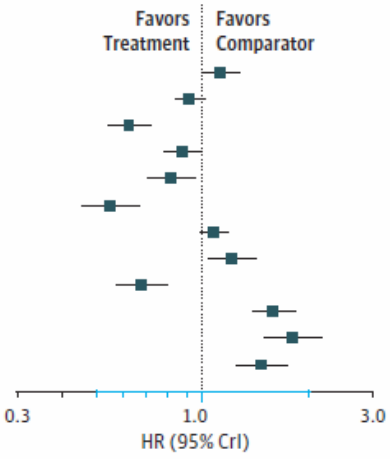


Results

C Heart failure events, 58 trials; $I^2 = 19\%$

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	0.4 (0.0 to 0.8)	1.13 (1.00 to 1.28)
GLP-1 agonist		-0.2 (-0.5 to 0.1)	0.93 (0.84 to 1.02)
SGLT-2 inhibitor		-1.1 (-1.3 to -0.8)	0.62 (0.54 to 0.72)
Control	vs DPP-4 inhibitor	-0.3 (-0.5 to 0.0)	0.88 (0.78 to 1.00)
GLP-1 agonist		-0.4 (-0.7 to -0.1)	0.82 (0.70 to 0.95)
SGLT-2 inhibitor		-1.1 (-1.3 to -0.8)	0.55 (0.46 to 0.67)
Control	vs GLP-1 agonist	0.2 (-0.1 to 0.5)	1.08 (0.98 to 1.18)
DPP-4 inhibitor		0.6 (0.1 to 1.1)	1.22 (1.05 to 1.42)
SGLT-2 inhibitor		-0.9 (-1.2 to -0.5)	0.67 (0.57 to 0.80)
Control	vs SGLT-2 inhibitor	1.0 (0.6 to 1.4)	1.60 (1.39 to 1.84)
DPP-4 inhibitor		1.3 (0.8 to 2.0)	1.81 (1.50 to 2.18)
GLP-1 agonist		0.8 (0.4 to 1.3)	1.48 (1.25 to 1.76)

Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	55	1370 (2.8)	48362
DPP-4 inhibitor	24	544 (2.4)	22327
GLP-1 agonist	21	638 (2.7)	23363
SGLT-2 inhibitor	19	266 (1.7)	15989

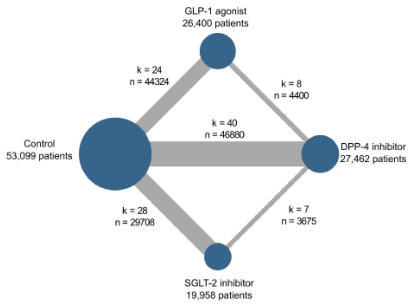


Unstable Angina:

- There was no significant difference between drug classes. No drug class was associated with reduction in unstable angina

Myocardial infarction:

Netzwerkgeometrie

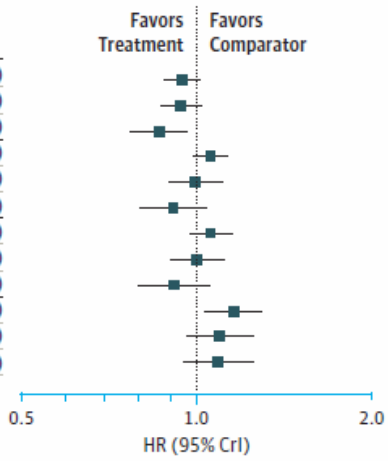


Results

A All myocardial infarction, 97 trials; I^2 = 15%

Treatment	Comparator	Absolute RD (95% CrI), %	HR (95% CrI)
DPP-4 inhibitor	vs Control	-0.2 (-0.5 to 0.0)	0.94 (0.88 to 1.01)
GLP-1 agonist		-0.2 (-0.5 to 0.1)	0.94 (0.87 to 1.02)
SGLT-2 inhibitor		-0.6 (-0.9 to -0.1)	0.86 (0.77 to 0.97)
Control	vs DPP-4 inhibitor	0.1 (0.0 to 0.3)	1.06 (0.99 to 1.13)
GLP-1 agonist		0.0 (-0.2 to 0.2)	1.00 (0.90 to 1.11)
SGLT-2 inhibitor		-0.2 (-0.4 to 0.1)	0.91 (0.80 to 1.04)
Control	vs GLP-1 agonist	0.3 (-0.1 to 0.6)	1.06 (0.98 to 1.15)
DPP-4 inhibitor		0.0 (-0.4 to 0.5)	1.00 (0.90 to 1.12)
SGLT-2 inhibitor		-0.3 (-0.9 to 0.2)	0.92 (0.80 to 1.05)
Control	vs SGLT-2 inhibitor	0.4 (0.1 to 0.8)	1.16 (1.04 to 1.30)
DPP-4 inhibitor		0.3 (-0.1 to 0.6)	1.10 (0.96 to 1.25)
GLP-1 agonist		0.2 (-0.1 to 0.6)	1.09 (0.95 to 1.25)

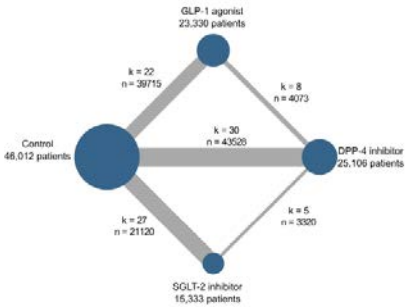
Treatment	No. of Trials	No. With Events (%)	Total No. of Patients
Control	87	2133 (4.0)	53099
DPP-4 inhibitor	50	616 (2.2)	27462
GLP-1 agonist	30	1140 (4.3)	26400
SGLT-2 inhibitor	32	505 (2.5)	19958



#

Stroke

Netzwerkgeometrie



Results

All stroke

6 trials, 1848 events, 68,343 patients, 195,748 patient-years

	Placebo	DPP-4i	GLP-1a	SGLT-2i
Placebo 892 events, 32,986 patients	Reference	0.97 (0.80-1.17)	1.12 (0.94-1.31)	1.05 (0.86-1.29)
DPP-4i 335 events, 15,612 patients	1.03 (0.85-1.25)	Reference	1.15 (0.89-1.48)	1.09 (0.82-1.44)
GLP-1a 427 events, 15,058 patients	0.90 (0.76-1.06)	0.87 (0.68-1.12)	Reference	0.94 (0.73-1.23)
SGLT-2i 194 events, 4687 patients	0.95 (0.77-1.17)	0.92 (0.69-1.22)	1.06 (0.81-1.37)	Reference

- No drug class was associated with reduction in all stroke compared with the control groups; however, GLP-1 agonists were associated with reduction in nonfatal stroke compared with the control groups (HR,0.87 [95%CrI,0.76 to 0.99]; absolute RD -0.3% [95%CrI, -0.5%to -0.02%]).
- There was no associated difference between drug classes for nonfatal stroke.

Safety Endpoints

- any hypoglycemia:
  - DPP-4 inhibitors (HR, 1.29 [95% CrI, 1.12 to 1.50]); GLP-1 agonists (HR, 1.44 [95% CrI, 1.25 to 1.66]), and SGLT-2 inhibitors (HR, 1.24 [95% CrI, 1.06 to 1.45]) were all associated with increased risk compared with the control groups
  - no significant differences for major hypoglycaemia

- no difference between drug classes for any or major hypoglycemia.

- Serious adverse events: SGLT-2 inhibitors associated with a reduction compared with the control groups (HR, 0.90 [95%CrI, 0.85 to 0.96]), DPP-4 inhibitor (HR,0.91 [95% CrI, 0.84 to 0.98], and GLP-1 agonist (HR,0.92 [95%CrI,0.85 to 0.99]).
- adverse events leading to trial withdrawal: GLP-1 agonists increased risk compared with the control groups (HR, 2.00 [95%CrI, 1.70 to 2.37]), SGLT-2 inhibitors (HR, 1.80 [95% CrI, 1.44 to 2.25]), and DPP-4 inhibitors (HR, 1.93 [95%CrI, 1.59 to 2.35]).

Individual Drug Types:

- For 16 individual drug types compared with the control groups, all-cause mortality was reduced only with 1 SGLT-2 inhibitor: empagliflozin (HR, 0.68 [95% CrI, 0.57 to 0.82]), and 2 GLP-1 agonists: liraglutide (HR, 0.85 [95% CrI, 0.75 to 0.98]) and exenatide (HR, 0.86 [95% CrI, 0.77 to 0.97]).
- No DPP-4 inhibitor individually reduced all-cause mortality.

Drug Class Rankings:

- For all-cause and cardiovascular mortality, SGLT-2 inhibitors were most likely to rank best, GLP-1 agonists second best, and DPP-4 inhibitors worst.
- The SGLT-2 inhibitors were most likely to rank best for heart failure and MI outcomes
- GLP-1 agonists were most likely to rank best for stroke outcomes.

Frequentist Meta-analysis:

- Frequentist network meta-analysis findings were similar to those using the Bayesian approach

Fazit der Autoren

In this network meta-analysis, the use of SGLT-2 inhibitors or GLP-1 agonists was associated with lower mortality than DPP-4 inhibitors or placebo or no treatment. Use of DPP-4 inhibitors was not associated with lower mortality than placebo or no treatment.

3.4 Leitlinien

Bundesärztekammer et al., 2021 [6].

Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF),

Nationale VersorgungsLeitlinie: Typ-2-Diabetes (Teilpublikation der Langfassung; 2. Auflage; Version 1)

Zielsetzung/Fragestellung

Die hohe Prävalenz und Inzidenz des Typ-2-Diabetes in Deutschland sowie eine große Variationsbreite in der Versorgungsqualität verlangen verstärkte Bemühungen um die Optimierung der Versorgung von Menschen mit Typ-2-Diabetes. Hierzu gehört die verlässliche Beschreibung der angemessenen Diagnostik, Therapie und Rehabilitation, basierend auf dem aktuellen Stand der wissenschaftlichen Erkenntnis, der klinischen Erfahrung der multidisziplinären Leitliniengruppe und der Praxis. Auf diesem Weg soll die Qualität der Versorgung verbessert und die Stellung der Menschen mit Typ-2-Diabetes gestärkt werden. Zudem kann die Berücksichtigung der Empfehlungen zu einer Effizienzsteigerung und damit zur Kostendämpfung im Gesundheitswesen beitragen.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche und Auswahl der Literatur – trifft zu;
- systematische Bewertung der Evidenz – trifft zu;
  - Übersichtsarbeiten: AMSTAR-Tool
  - Randomisierten kontrollierten Studien: Cochrane-Risk-of-Bias-Tool
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

Recherche/Suchzeitraum:

- initialen Recherche: März 2018; Up-Date-Recherche: Dezember 2019
- Medline, Cochrane-Datenbank, U.S. Agency for Healthcare Research and Quality (AHRQ)

LoE

- endpunktbezogene Bewertung: GRADE

GoR

Empfehlungsgrad	Beschreibung	Formulierung	Symbol
A	Starke Positiv-Empfehlung	soll	⇑⇑
B	Abgeschwächte Positiv-Empfehlung	sollte	⇑
0	Offene Empfehlung	kann	⇔
B	Abgeschwächte Negativ-Empfehlung	sollte nicht	⇓
A	Starke Negativ-Empfehlung	soll nicht	⇓⇓

Sonstige methodische Hinweise

- Die Vorgehensweise zur Erstellung der NVL ist im Leitlinienreport [5] beschrieben.

Empfehlungen: 2 Medikamentöse Therapie des Glukosestoffwechsels

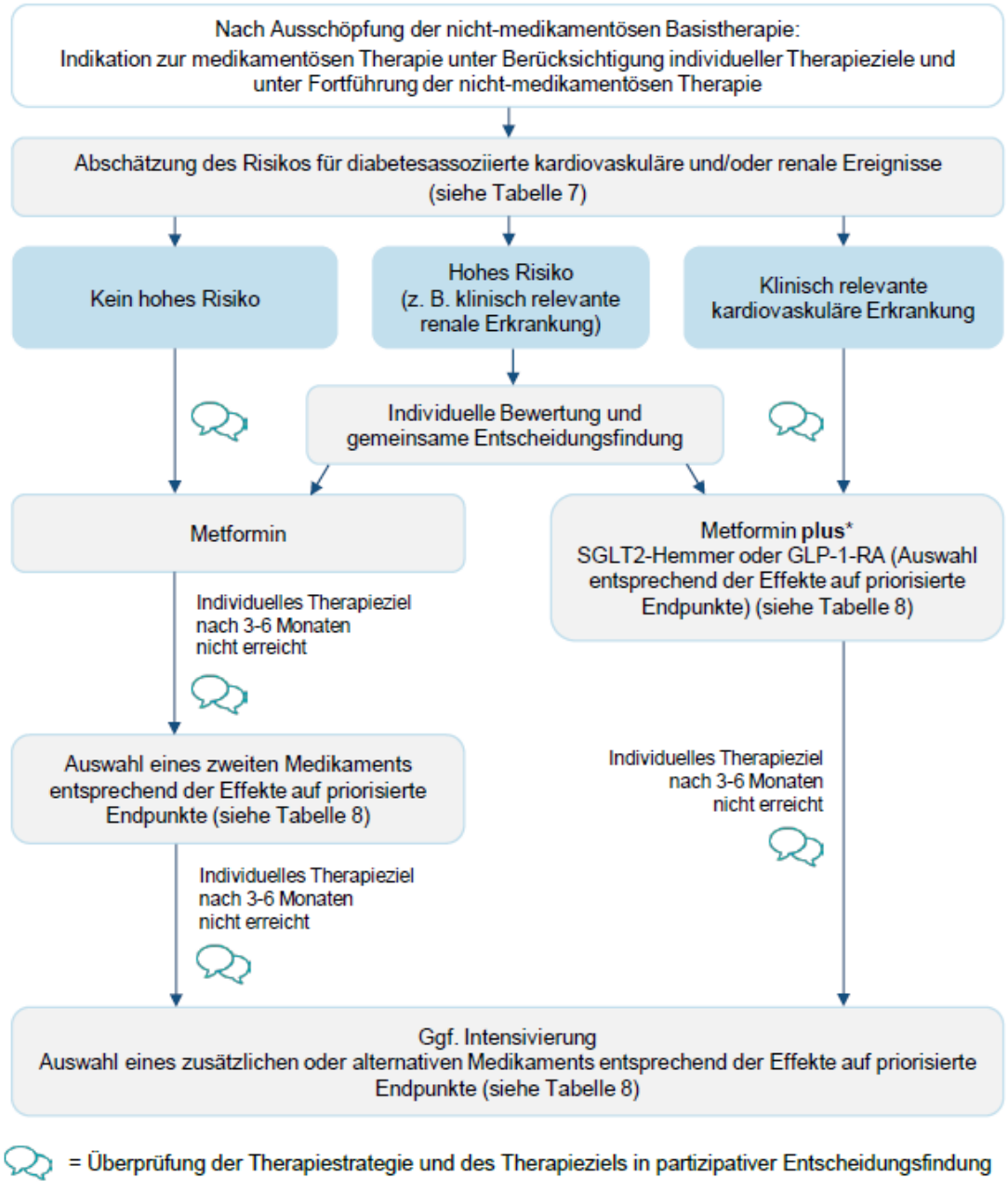
2.2 Allgemeine Therapieprinzipien für nicht-medikamentöse und medikamentöse Therapie

- **2-1:** ⇑⇑ Vor jeder Therapie-Eskalation sollen Ursachen für die Nicht-Erreichung bisher vereinbarter Therapieziele evaluiert und berücksichtigt werden.
- **2-2:** ⇑⇑ Bei Menschen mit Typ-2-Diabetes soll eine Therapie-Deeskalation oder eine Veränderung der Therapiestrategie regelmäßig geprüft werden, insbesondere:
  - wenn die negativen Effekte der Therapie auf die Sicherheit und die Lebensqualität der/des Betroffenen überwiegen;
  - wenn die individuelle Situation dafür spricht, dass prognostische Aspekte eine geringere Rolle spielen als die aktuelle Lebensqualität;
  - wenn das individuelle Therapieziel unterschritten wird;
  - bei Multimorbidität und Polymedikation;
  - bei Auftreten von akuten Erkrankungen.

- Die Empfehlungen 2-1 und 2-2 beruhen auf einem Expert*innenkonsens und beschreiben gute klinische Praxis.

2.3 Algorithmus Medikamentöse Therapie des Typ-2-Diabetes

- **2-3:** ⇑⇑ Ist bei Menschen mit Typ-2-Diabetes, unter Berücksichtigung der individuellen Therapieziele und nach Ausschöpfung der nicht-medikamentösen Basistherapie, eine medikamentöse Therapie des Glukosestoffwechsels indiziert, soll der Therapie-Algorithmus angewendet werden.
- Die in Empfehlung 2-3 genannten Voraussetzungen, die erfüllt sein sollen, um den Algorithmus anzuwenden, beruhen auf einem Expert*innenkonsens und beschreiben gute klinische Praxis.



= Überprüfung der Therapiestrategie und des Therapieziels in partizipativer Entscheidungsfindung

*Bei einem HbA1c von ≤ 7% liegen keine Daten für die Wirksamkeit einer Kombinationstherapie bei Menschen mit Typ-2-Diabetes ohne Herzinsuffizienz vor.

Der Algorithmus bezieht sich nicht auf Patient*innen mit schwerer Stoffwechseldekompensation bzw. Notfallsituationen. Aktuelle Fachinformationen sind zu berücksichtigen.

Abbildung 6: Algorithmus medikamentöse Therapie des Typ-2-Diabetes

- Beispiele kardiovaskulärer Risikofaktoren
  - (biologisches) Alter, Geschlecht (männlich > weiblich), Diabetesdauer, Lebensstil/Ernährung/Bewegungsmangel, familiäre/genetische Disposition, Hypertonie, Dyslipidämie, Adipositas, Niereninsuffizienz, Albuminurie, Raucherstatus, starke Stoffwechselinstabilität und schwere Hypoglykämien, linksventrikuläre Hypertrophie, subklinische Arteriosklerose bzw. subklinische kardiovaskuläre Erkrankung
  - Die hier aufgeführten Risikofaktoren beruhen auf einem Expert*innenkonsens. Für mehrere Faktoren wurden von einzelnen Fachgesellschaften an anderer Stelle Grenzwerte für ein erhöhtes Risiko festgelegt (Gewicht, Blutdruck, Lipide). Da einzelne geringgradige Grenzwertüberschreitungen keine große Risikoerhöhung zur Folge haben, ist eine umfassende integrative Beurteilung der beeinflussenden Risikofaktoren wichtig. Es ist zu bedenken, dass mit steigendem Alter und zunehmender Schwere der Komorbiditäten die Wahrscheinlichkeit abnimmt, von einer zusätzlichen Intervention zu profitieren. Die Reihenfolge der Aufzählung stellt keine Gewichtung dar.

2.5 Wirkstoffe

Tabelle 8: Orientierende, vergleichende Betrachtung der Substanzklassen (als Ergänzung zum Algorithmus Medikamentöse Therapie des Typ-2-Diabetes)

Diese Tabelle ist eine zusammenfassende Interpretation der Evidenz. Für die ausführliche Darstellung der Evidenz zu den einzelnen Wirkstoffgruppen siehe Evidenztabellen [15].

Medikament	Gesamt-mortalität	Kardiovaskuläre Endpunkte	Mikrovaskuläre Endpunkte[1]	Renale Endpunkte	Hypoglykämien	HbA1c, Gewicht	Anmerkungen/ Ausgewählte Sicherheitshinweise
Metformin	(↓)	(↓)	(0)	(0)	↔	HbA1c ↓↓ Gewicht: ↔↓	▪ Risiko der Laktatazidose ▪ bei Krankheit („sick days“) pausieren
SGLT2-Inhibitoren							▪ Risiko genitaler Infektionen, atypischer Ketoazidose, Fournier-Gangrän ▪ bei Krankheit („sick days“) pausieren ▪ Gewichtsreduktion (bei Frailty unerwünscht)
Empagliflozin	↓ senkt*	MACE: ↓ senkt CV-Tod: ↓ senkt HHI: ↓ senkt	k. A.	↓ senkt	↔	HbA1c ↓↓ Gewicht: ↓	
Canagliflozin	0	MACE: ↓ senkt CV-Tod: 0 HHI: ↓ senkt	k. A.: Retinopathie, Neuropathie Amputationen 0 bis ↑	↓ senkt	↔	HbA1c ↓↓ Gewicht: ↓	
Dapagliflozin	0*	MACE: 0 CV-Tod: 0 HHI: ↓ senkt	k. A.: Retinopathie, Neuropathie; Amputationen: 0.	↓ senkt	↔	HbA1c ↓↓ Gewicht: ↓	

Medikament	Gesamt-mortalität	Kardiovaskuläre Endpunkte	Mikrovaskuläre Endpunkte[1]	Renale Endpunkte	Hypoglykämien	HbA1c, Gewicht	Anmerkungen/ Ausgewählte Sicherheitshinweise
GLP-1-RA							▪ gastrointestinale Nebenwirkungen, Gallensteine ▪ bei den meisten Wirkstoffen Injektionen notwendig ▪ Gewichtsreduktion (bei Frailty unerwünscht)
Liraglutid	↓ senkt*	MACE: ↓ senkt CV-Tod: ↓ senkt HHI: 0	Retinopathie: 0 k. A.: Neuropathie, Amputationen	↓ senkt	↔	HbA1c: ↓↓ Gewicht: ↓	
Exenatid	↓ senkt*	MACE: 0 CV-Tod: 0 HHI: 0	k. A.: Retinopathie, Neuropathie Amputationen: 0	k. A.	↔	HbA1c: ↓↓ Gewicht: ↓	
Semaglutid s.c.	0*	MACE: ↓ senkt CV-Tod: 0 HHI: 0	Retinopathie: ↑ k. A.: Neuropathie, Amputationen	↓ senkt	↔	HbA1c: ↓↓ Gewicht: ↓	
Semaglutid oral	↓ senkt*	MACE: 0 CV-Tod: ↓ senkt HHI: 0	k. A.: Retinopathie, Neuropathie, Amputationen	k. A.	k. A.	HbA1c: ↓↓ Gewicht: ↓	
Lixisenatid	0*	MACE: 0 CV-Tod: 0 HHI: 0	k. A.: Retinopathie, Amputationen, Neuropathie	k. A.	↔	HbA1c: ↓↓ Gewicht: ↓	
Albiglutid	0*	MACE: ↓ senkt CV-Tod: 0 HHI: k. A.	Retinopathie: 0 k. A.: Neuropathie, Amputationen	k. A.	↔	HbA1c: ↓↓ Gewicht: ↓	
Dulaglutid	0	MACE: ↓ senkt CV-Tod: 0 HHI: 0	Retinopathie: 0 k. A.: Amputationen, Neuropathie	↓ senkt	↔	HbA1c: ↓↓ Gewicht: ↓	

Medikament	Gesamt-mortalität	Kardiovaskuläre Endpunkte	Mikrovaskuläre Endpunkte[1]	Renale Endpunkte	Hypoglykämien	HbA1c, Gewicht	Anmerkungen/ Ausgewählte Sicherheitshinweise
Sulfonylharnstoffe	(0)	MACE: k. A. CV-Tod: (0) HHI: (0)	(0 bis ↓)	(0 bis ↓)	↑↑	HbA1c: ↓↓ Gewicht: ↑	▪ Risiko schwerer prolongierter Hypoglykämien
DPP-4-Inhibitoren	(0)	MACE: k. A. CV-Tod: (0) HHI: (0)	(0)	(0)	↔	HbA1c: ↓ Gewicht: ↔	▪ Risiko für Pankreatitis, entzündliche Darmerkrankungen
Ggf. ab Stufe 3 des Algorithmus							
Insulin	(0)	(0)	(↓)	(0)	↑↑	HbA1c: ↓↓ (dosisabhängig) Gewicht: ↑↑	▪ Risiko für Hypoglykämien, besonders zu Therapiebeginn ▪ Lipohypertrophien ▪ Injektionen nötig

Legende

Effektangaben: ↓: positiver Effekt (Endpunkt wurde in den Studien seltener erreicht); ↑: negativer Effekt (Endpunkt wurde in den Studien häufiger erreicht); 0: der Endpunkt wurde nicht beeinflusst; k. A.: keine Angabe (die Effektgrößen wurden in der Hauptpublikation nicht, oder ohne Konfidenzintervall angegeben); renale Endpunkte: bei SGLT2-Inhibitoren und GLP-1-RA bezogen auf renale Kompositendpunkte.
Annahmen in Klammern () stammen aus Studien mit niedriger methodischer Qualität, oder es lag keine ausreichende Evidenz zur Beurteilung vor.

Hypoglykämien: ↑: erhöhtes Risiko; ↔: geringes Risiko, k. A.: keine Angabe (Hypoglykämien: Intervention > Placebo, Angabe ohne Konfidenzintervall)

HbA1c: ↓: Senkung

Gewicht: ↑: Gewichtszunahme; ↓: Gewichtsabnahme

Gesamtmortalität: *: Die Studie war nicht für den Endpunkt Gesamtmortalität gepowert

Abkürzungen: MACE: i. d. R. kardiovaskulärer Tod, Schlaganfall, Myokardinfarkt (Definitionen teils heterogen); CV-Tod: kardiovaskulärer Tod; HHI: Herzinsuffizienz-bedingte Hospitalisierung.

[1]Mikrovaskuläre Endpunkte: Retinopathie, Neuropathie, Amputationen

Daten zu renalen Endpunkten zu Empagliflozin aus [44]

Evidenzdarstellung

2.5.1 Metformin

- Cochrane-Review [45], AHRQ-Review [46], Cochrane-Review [47], NVL von 2014 [2]

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2.5.2 SGLT2-Inhibitoren (Gliflozine)

- 4 RCTs [36,40,44,52,53,54,56], Metanalyse [35]

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2.5.3 GLP-1-Rezeptoragonisten (GLP-1-RA)

- RCTs [69-73,38,39], Marktrücknahme Albiglutid [74,75]

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2.5.4 Sulfonylharnstoffe (Glibenclamid, Gliclazid, Glimepirid)

- Cochrane-Review [85], AHRQ-Review [46] RCTs [86-88], NVL von 2014 [2]

Referenzen aus Leitlinien

2. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medi-zinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Therapie des Typ-2-Diabetes - Langfassung, 1. Auflage. Version 4. 2014 [cited: 2017-01-12]. DOI: 10.6101/AZQ/000213. http://doi.org/10.6101/AZQ/000213.
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2.5.5 DPP-4-Hemmer

- AHRQ-Review [46] , RCTs [86], Cochrane Review [89]

Referenzen aus Leitlinien

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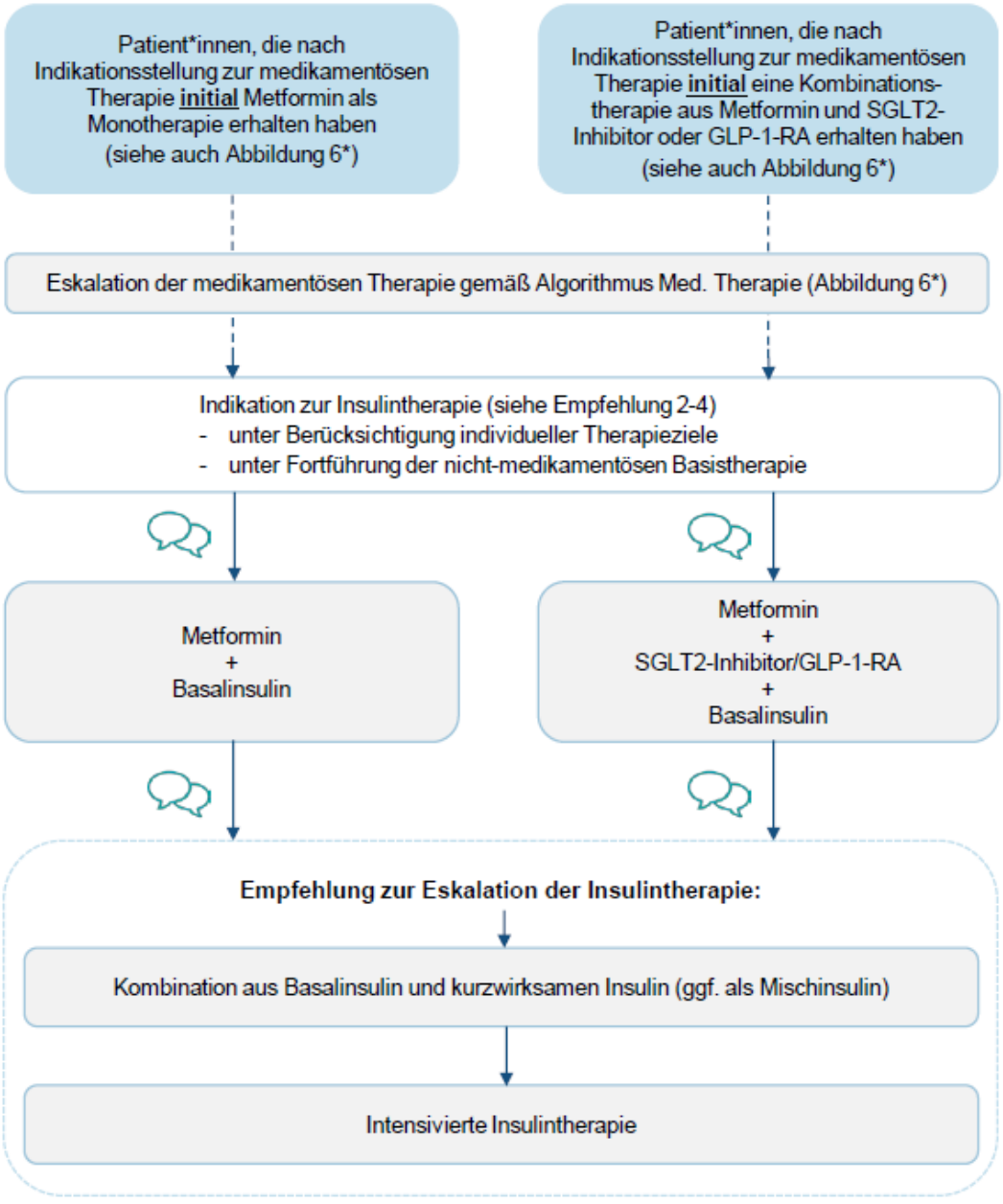
86. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Out-comes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. JAMA 2019; 322(12):1155–66. DOI: 10.1001/jama.2019.13772. http://www.ncbi.nlm.nih.gov/pubmed/31536101.
89. Richter B, Bandeira-Echtler E, Bergerhoff K, et al. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev 2008(2):CD006739. DOI: 10.1002/14651858.CD006739.pub2. http://www.ncbi.nlm.nih.gov/pubmed/18425967.

2.5.5 Insuline

- **2-4:** ⇑⇑ Bei Menschen mit Typ-2-Diabetes soll die Indikation zur Insulintherapie in folgen-den Situationen geprüft werden:
  - bei Nicht-Erreichen des individuellen Therapieziels trotz Ausschöpfung der nicht-medikamentösen Maßnahmen und medikamentösen Therapie (Kombi-nation aus oralen Antidiabetika mit/ohne s.c. zu verabreichenden GLP-1-RA gemäß Abbildung 6);
  - bei metabolischen Entgleisungen, z. B. bei Erstdiagnose (unklare diagnostische Situation, Typ-1-Diabetes nicht sicher ausgeschlossen);
  - bei Gabe von diabetogenen Medikamenten (z. B. Glukokortikoide), bei schweren Infekten, Traumata oder größeren Operationen, (eventuell nur temporär);
  - bei stark eingeschränkter Nierenfunktion (in Abhängigkeit vom individuellen Therapieziel).
- **2-5:** ⇑⇑ Die Deeskalation der Insulintherapie soll bei Menschen mit Typ-2-Diabetes in folgenden Situationen geprüft werden: Wenn
  - die Indikation (z. B. akute Erkrankung, metabolische Entgleisung, Verschlechterung der Nierenfunktion) nicht mehr besteht;
  - die Zielwerte des Glukosestoffwechsels erreicht sind oder unterschritten wer-den;
  - Hypoglykämien auftreten;
  - sich das individuelle Therapieziel ändert (z. B. in Folge von Multimorbidität).

  Die Empfehlungen basieren auf einem Expert*innenkonsens sowie indirekt auf der Evidenz zur Wirksamkeit der Insulinbehandlung und beschreiben gute klinische Praxis.
- Algorithmus der Insulintherapie:



= Überprüfung der Therapiestrategie und des Therapieziels in partizipativer Entscheidungsfindung
Die Kontraindikationen der eingesetzten Wirkstoffe sind zu beachten (z. B. bei stark eingeschränkter Nierenfunktion).

- * Abbildung 6: Algorithmus Medikamentöse Therapie des Typ-2-Diabetes

Abbildung 7: Algorithmus Insulintherapie

- Der Algorithmus schließt an den Algorithmus zur Medikamentösen Therapie des Typ-2-Diabetes (siehe Abbildung 6) an und ist als dessen Fortführung beim Einsatz von Insulin zu verstehen.
- **2-6:** ⇑⇑ Die Wahl der Insulinart und des Insulinschemas soll sich an der Lebenssituation der Patient*innen orientieren.

Evidenz

- Cochrane-Reviews [99,100,102,103], Beobachtungsstudie [104]

Referenzen aus Leitlinien

99. Goudswaard AN, Furlong NJ, Rutten GE, et al. Insulin monotherapy versus combinations of insulin with oral hypoglycaemic agents in patients with type 2 diabetes mellitus. Cochrane Database Syst Rev 2004(4):CD003418. http://www.ncbi.nlm.nih.gov/pubmed/15495054.
100. Vos RC, van Avendonk MJ, Jansen H, et al. Insulin monotherapy compared with the addition of oral glucose-lowering agents to insulin for people with type 2 diabetes already on insulin therapy and inadequate glycaemic control. Cochrane Database Syst Rev 2016; 9(9):CD006992. DOI: 10.1002/14651858.CD006992.pub2. http://www.ncbi.nlm.nih.gov/pub-med/27640062.
102. Fullerton B, Siebenhofer A, Jeitler K, et al. Short-acting insulin analogues versus regular human insulin for adult, non-preg-nant persons with type 2 diabetes mellitus. Cochrane Database Syst Rev 2018; 12:CD013228. DOI: 10.1002/14651858.CD013228. http://www.ncbi.nlm.nih.gov/pubmed/30556900.
103. Horvath K, Jeitler K, Berghold A, et al. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. Cochrane Database Syst Rev 2007(2):CD005613. DOI: 10.1002/14651858.CD005613.pub3. http://www.ncbi.nlm.nih.gov/pubmed/17443605.
104.Mertes B, Gödde S, Piorkowski M, et al. Successful Treatment with Bedtime Basal Insulin Added to Metformin without Weight Gain or Hypoglycaemia over Three Years. Journal of clinical medicine 2020; 9(4). DOI: 10.3390/jcm9041153. http://www.ncbi.nlm.nih.gov/pubmed/32316649

2.6 Therapiemöglichkeiten bei höhergradiger Niereninsuffizienz (eGFR < 30 ml/min/1,73 m2)

- Bei Patient*innen mit einer eGFR < 30 ml/min/1,73 m2 ist eine Therapie mit Metformin kontraindiziert [51]. In Abhängigkeit der metabolischen Situation ist bei dieser Patientengruppe initial häufig eine Insulintherapie indiziert. Dies kann auch nur vorübergehend sein. Es ist wichtig, regelmäßig zu prüfen, ob die Therapie an die Nierenfunktion angepasst ist.
- Die Leitliniengruppe schlägt vor, Patient*innen mit höhergradiger Niereninsuffizienz, bei denen die individuellen Therapieziele nach Ausschöpfung der nicht-medikamentösen Therapie nicht erreicht worden sind, unter Berücksichtigung des jeweiligen Zulassungsstatus und der Fachinformation mit einem der folgenden Wirkstoffen zu behandeln (alphabetische Reihenfolge): DPP-4-Inhibitoren oder Glinide oder GLP-1-RA oder Insulin.
- Werden die individuellen Therapieziele nicht erreicht, schließt sich eine Kombination aus Basalinsulin mit einem der oben genannten Wirkstoffe an (immer unter Berücksichtigung der Nierenfunktion). Die nächste Eskalationsstufe sieht eine Kombination von Basalinsulin mit kurzwirksamem Insulin bzw. eine Intensivierung der Insulintherapie vor. Die Auswahl der Medikamente erfolgt im Sinne der partizipativen Entscheidungsfindung unter Berücksichtigung der individuellen Therapieziele, Kontextfaktoren, sowie Vor- und Nachteile der Wirkstoffe. Bei dialysepflichtigen Patient*innen kann eine Anpassung des Insulinschemas an die Behandlungstage mit und ohne Nierenersatztherapie erforderlich sein

51. European Medicines Agency (EMA). Anwendung von Metformin zur Behandlung von Diabetes nun auf Patienten mit mittel-schwerer Nierenfunktionsbeeinträchtigung ausgeweitet. Empfehlungen für Patienten mit Nierenfunktionsbeeinträchtigung in den Produktinformationen aktualisiert. EMA/868987/2016. 2016 [cited: 2020-06-04]. https://www.ema.europa.eu/en/docu-ments/referral/metformin-article-31-referral-use-metformin-treat-diabetes-now-expanded-patients-moderately-re-duced_de.pdf.

2.7 Weitere Blutglukose-senkende Wirkstoffe

- Neben den oben genannten Wirkstoffgruppen wurden in der NVL Therapie des Typ-2-Diabetes aus 2014 [2] alpha-Glukosidasehemmer, Glinide und Glitazone genannt. Diese Wirkstoffe sind seltenen Sondersituationen vorbehalten und wurden im Rahmen der Leitlinienarbeit nicht näher betrachtet

2.Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medi-zinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Therapie des Typ-2-Diabetes - Langfassung, 1. Auflage. Version 4. 2014 [cited: 2017-01-12]. DOI: 10.6101/AZQ/000213. http://doi.org/10.6101/AZQ/000213.

NICE et al., 2015/2020 [91].

National Institute for Health and Care Excellence

Type 2 diabetes in adults: management - Clinical Guideline Update

Zielsetzung/Fragestellung

This guideline contains recommendations for managing type 2 diabetes in adults, and focuses on patient education, dietary advice, managing cardiovascular risk, managing blood glucose levels, and identifying and managing long-term complications.

Methodik

Grundlage der Leitlinie

Update der Leitlinie von 2015

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

Recherche/Suchzeitraum:

- searches undertaken between July 2012 and June 2013; re-run searches in June 2014
- Cochrane Database of Systematic Reviews –CDSR (Wiley); Cochrane Central Register of Controlled Trials –CENTRAL (Wiley); Database of Abstracts of Reviews of Effects –DARE (Wiley); Health Technology Assessment Database –HTA (Wiley); EMBASE (Ovid); MEDLINE (Ovid); MEDLINE In-Process (Ovid)

LoE

- Grading of Recommendations Assessment, Development and Evaluation (GRADE)

GoR

- Interventions that must (or must not) be used: We usually use ‘must’ or ‘must not’ only if there is a legal duty to apply the recommendation. Occasionally we use ‘must’ (or ‘must not’) if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
- Interventions that should (or should not) be used – a ‘strong’ recommendation: We use ‘offer’ (and similar words such as ‘refer’ or ‘advise’) when we are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective. We use similar forms of words (for example, ‘Do not offer...’) when we are confident that an intervention will not be of benefit for most patients.
- Interventions that could be used: We use ‘consider’ when we are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values and preferences than for a strong recommendation, and so the healthcare professional should spend more time considering and discussing the options with the patient.

Sonstige methodische Hinweise

- Die Empfehlungen zur Therapie eines Diabetes Typ 2 wurden nicht aktualisiert und sind aus dem Jahr 2015:
  - "December 2020: We have amended recommendations 1.7.17 and 1.7.20 [managing complications] to bring them in line with the diabetic eye screening programme. The evidence for these recommendations has not been reviewed, and they are marked."

Empfehlungen

Algorithmus siehe Anhang

Initial drug treatment (2015)

- 1.6.19 Offer standard-release metformin as the initial drug treatment for adults with type 2 diabetes. [new 2015]
- 1.6.20 Gradually increase the dose of standard-release metformin over several weeks to minimise the risk of gastrointestinal side effects in adults with type 2 diabetes. [new 2015]
- 1.6.21 If an adult with type 2 diabetes experiences gastrointestinal side effects with standard-release metformin, consider a trial of modified-release metformin. [new 2015]
- 1.6.22 In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73m2:
  - Stop metformin if the eGFR is below 30 ml/minute/1.73m2.
  - Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45 ml/minute/1.73m2. [2015]
- 1.6.23 In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment with:
  - a dipeptidyl peptidase-4 (DPP-4) inhibitor or
  - pioglitazone or
  - a sulfonylurea. [new 2015]
- 1.6.24 In adults with type 2 diabetes, do not offer or continue pioglitazone if they have any of the following:
  - heart failure or history of heart failure
  - hepatic impairment
  - diabetic ketoacidosis
  - current, or a history of, bladder cancer
  - uninvestigated macroscopic haematuria. [new 2015]

Treatment with sodium–glucose cotransporter 2 (SGLT-2) inhibitors may be appropriate for some adults with type 2 diabetes if metformin is contraindicated or not tolerated (see NICE's guidance on canagliflozin, dapagliflozin and empagliflozin as monotherapies for treating type 2 diabetes).

First intensification of drug treatment (2015)

- 1.6.25 In adults with type 2 diabetes, if initial drug treatment with metformin has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider dual therapy with:
  - metformin and a DPP-4 inhibitor or
  - metformin and pioglitazone or
  - metformin and a sulfonylurea. [new 2015]

- 1.6.26 In adults with type 2 diabetes, if metformin is contraindicated or not tolerated and initial drug treatment has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider dual therapy with:
  - a DPP-4 inhibitor and pioglitazone or
  - a DPP-4 inhibitor and a sulfonylurea or
  - pioglitazone and a sulfonylurea. [new 2015]

Treatment with combinations of medicines including sodium–glucose cotransporter 2 (SGLT-2) inhibitors may be appropriate for some people with type 2 diabetes; see the NICE guidance on canagliflozin in combination therapy for treating type 2 diabetes, dapagliflozin in combination therapy for treating type 2 diabetes and empagliflozin in combination therapy for treating type 2 diabetes.

Second intensification of drug treatment (2015)

- 1.6.27 In adults with type 2 diabetes, if dual therapy with metformin and another oral drug (see recommendation 1.6.25) has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider either:
  - triple therapy with:
    - metformin, a DPP-4 inhibitor and a sulfonylurea or
    - metformin, pioglitazone and a sulfonylurea or
  - starting insulin-based treatment (see recommendations 1.6.32–1.6.34). [new 2015]
- 1.6.28 If triple therapy with metformin and 2 other oral drugs (see recommendation 1.6.27) is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who:
  - have a BMI of 35 kg/m2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or
  - have a BMI lower than 35 kg/m2and:
    - for whom insulin therapy would have significant occupational implications or
    - weight loss would benefit other significant obesity-related comorbidities. [new 2015]
- 1.6.29 Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months). [2015]
- 1.6.30 In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, and if dual therapy with 2 oral drugs (see recommendation 1.6.26) has not continued to control HbA1c to below the person's individually agreed threshold for intensification, consider insulin-based treatment (see recommendations 1.6.32–1.6.34). [new 2015]
- 1.6.31 In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team [8]. [new 2015]

Treatment with combinations of medicines including SGLT-2 inhibitors [5],[6] may be appropriate for some people with type 2 diabetes; see the NICE guidance on canagliflozin in combination therapy for treating type 2 diabetes, dapagliflozin in combination therapy for treating type 2 diabetes, dapagliflozin in triple therapy for treating type 2 diabetes and empagliflozin in combination therapy for treating type 2 diabetes.

Insulin-based treatments (2015)

- 1.6.32 When starting insulin therapy in adults with type 2 diabetes, use a structured programme employing active insulin dose titration that encompasses:
  - injection technique, including rotating injection sites and avoiding repeated injections at the same point within sites
  - continuing telephone support
  - self-monitoring
  - dose titration to target levels
  - dietary understanding
  - DVLA guidance (At a glance guide to the current medical standards of fitness to drive)
  - management of hypoglycaemia
  - management of acute changes in plasma glucose control
  - support from an appropriately trained and experienced healthcare professional. [2015]
- 1.6.33 When starting insulin therapy in adults with type 2 diabetes, continue to offer metformin for people without contraindications or intolerance. Review the continued need for other blood glucose lowering therapies. [new 2015]
- 1.6.34 Start insulin therapy for adults with type 2 diabetes from a choice of a number of insulin types and regimens:
  - Offer NPH insulin injected once or twice daily according to need.
  - Consider starting both NPH and short-acting insulin (particularly if the person's HbA1c is 75 mmol/mol [9.0%] or higher), administered either separately or as a pre-mixed (biphasic) human insulin preparation.
  - Consider, as an alternative to NPH insulin, using insulin detemir or insulin glargine if:
    - the person needs assistance from a carer or healthcare professional to inject insulin, and use of insulin detemir or insulin glargine would reduce the frequency of injections from twice to once daily or
    - the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or
    - the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs.
  - Consider pre-mixed (biphasic) preparations that include short-acting insulin analogues, rather than pre-mixed (biphasic) preparations that include short-acting human insulin preparations, if:
    - a person prefers injecting insulin immediately before a meal or
    - hypoglycaemia is a problem or
    - blood glucose levels rise markedly after meals. [2015]
- 1.6.35 Consider switching to insulin detemir or insulin glargine from NPH insulin in adults with type 2 diabetes:
  - who do not reach their target HbA1c because of significant hypoglycaemia or
  - who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached or
  - who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to one of the long-acting insulin analogues was made or

  - who need help from a carer or healthcare professional to administer insulin injections and for whom switching to one of the long-acting insulin analogues would reduce the number of daily injections. [2015]
- 1.6.36 Monitor adults with type 2 diabetes who are on a basal insulin regimen (NPH insulin, insulin detemir or insulin glargine) for the need for short-acting insulin before meals (or a pre-mixed [biphasic] insulin preparation). [2015]
- 1.6.37 Monitor adults with type 2 diabetes who are on pre-mixed (biphasic) insulin for the need for a further injection of short-acting insulin before meals or for a change to a basal bolus regimen with NPH insulin or insulin detemir or insulin glargine, if blood glucose control remains inadequate. [2015]

Treatment with combinations of medicines including SGLT-2 inhibitors may be appropriate for some people with type 2 diabetes; see the NICE guidance on canagliflozin in combination therapy for treating type 2 diabetes, dapagliflozin in combination therapy for treating type 2 diabetes and empagliflozin in combination therapy for treating type 2 diabetes.

Diabetes Canada, 2020 [18].

Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update

Zielsetzung/Fragestellung

Based on a careful review of this evidence, the updated recommendations provide more specific treatment guidance for clinicians and people living with type 2 diabetes. We now have more evidence to recommend certain agents over others for patients with CVD, a history of HF, CKD and in those 60 years or older with multiple CV risk factors.

Methodik

Grundlage der Leitlinie

Update der Leitlinie von 2018 (siehe Diabetes Canada, 2018 [17].)

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – unklar (wird nicht explizit aufgeführt, dies ist allerding ein update der 2018 Leitlinie, was darauf schließen lässt, dass Empfehlungen aktuell gehalten werden).

Recherche/Suchzeitraum:

- Leveraging the search methods and PICO questions used for the 2018 Canada Clinical Practice Guidelines, a systematic search of the literature for relevant articles published from October 2017 to October 2019 was performed
- MEDLINE, EMBASE, CINAHL, the Cochrane Central Register of Trials, and PsycINFO

LoE

Studies of treatment and prevention	
Level 1A	Systematic overview or meta-analysis of high-quality RCTs a) Comprehensive search for evidence b) Authors avoided bias in selecting articles for inclusion c) Authors assessed each article for validity d) Reports clear conclusions that are supported by the data and appropriate analyses OR Appropriately designed RCT with adequate power to answer the question posed by the investigators a) Patients were randomly allocated to treatment groups b) Follow up at least 80% complete c) Patients and investigators were blinded to the treatment* d) Patients were analyzed in the treatment groups to which they were assigned e) The sample size was large enough to detect the outcome of interest
Level 1B	Non-randomized clinical trial or cohort study with indisputable results
Level 2	RCT or systematic overview that does not meet Level 1 criteria
Level 3	Non-randomized clinical trial or cohort study; systematic overview or meta-analysis of level 3 studies
Level 4	Other

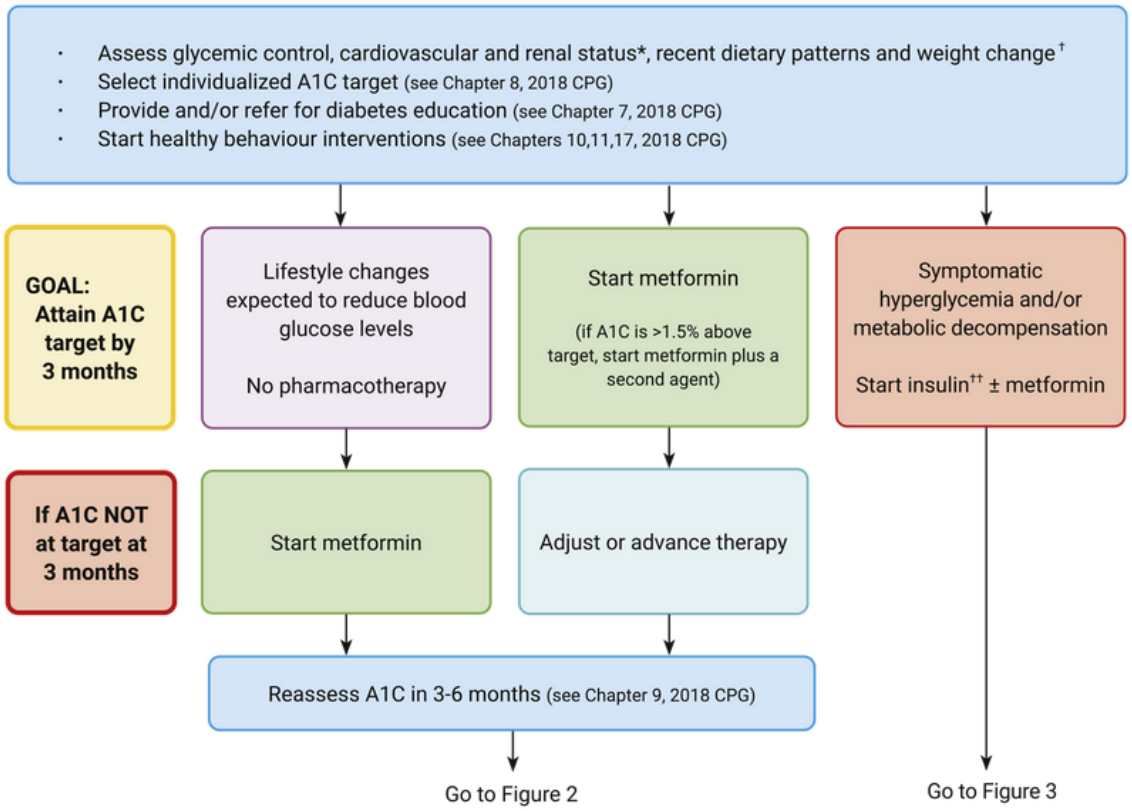
GoR

Table 2
Criteria for assigning grades of recommendations for clinical practice

Grade	Criteria
Grade A	The best evidence was at Level 1
Grade B	The best evidence was at Level 2
Grade C	The best evidence was at Level 3
Grade D	The best evidence was at Level 4 or consensus

Recommendations

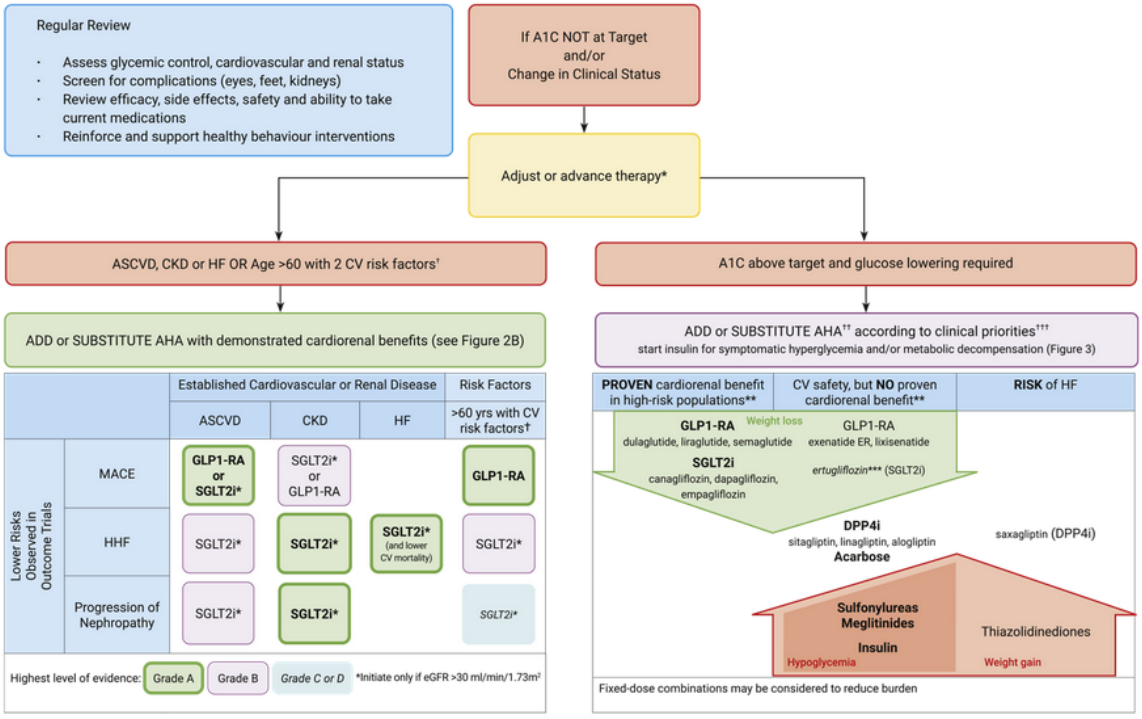
Figure 1
At diagnosis of type 2 diabetes.



* In individuals **with** atherosclerotic cardiovascular disease, history of heart failure (with reduced ejection fraction) or chronic kidney disease, agents with cardiorenal benefits (Figures 2A and 2B) may be considered (see Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update – The User's Guide).
† Unintentional weight loss should prompt consideration of other diagnoses (e.g. type 1 diabetes or pancreatic disease).
†† Reassess need for ongoing insulin therapy once type of diabetes is established and response to health behaviour interventions is assessed.
A1C, glycated hemoglobin; *CPG*, clinical practice guidelines.

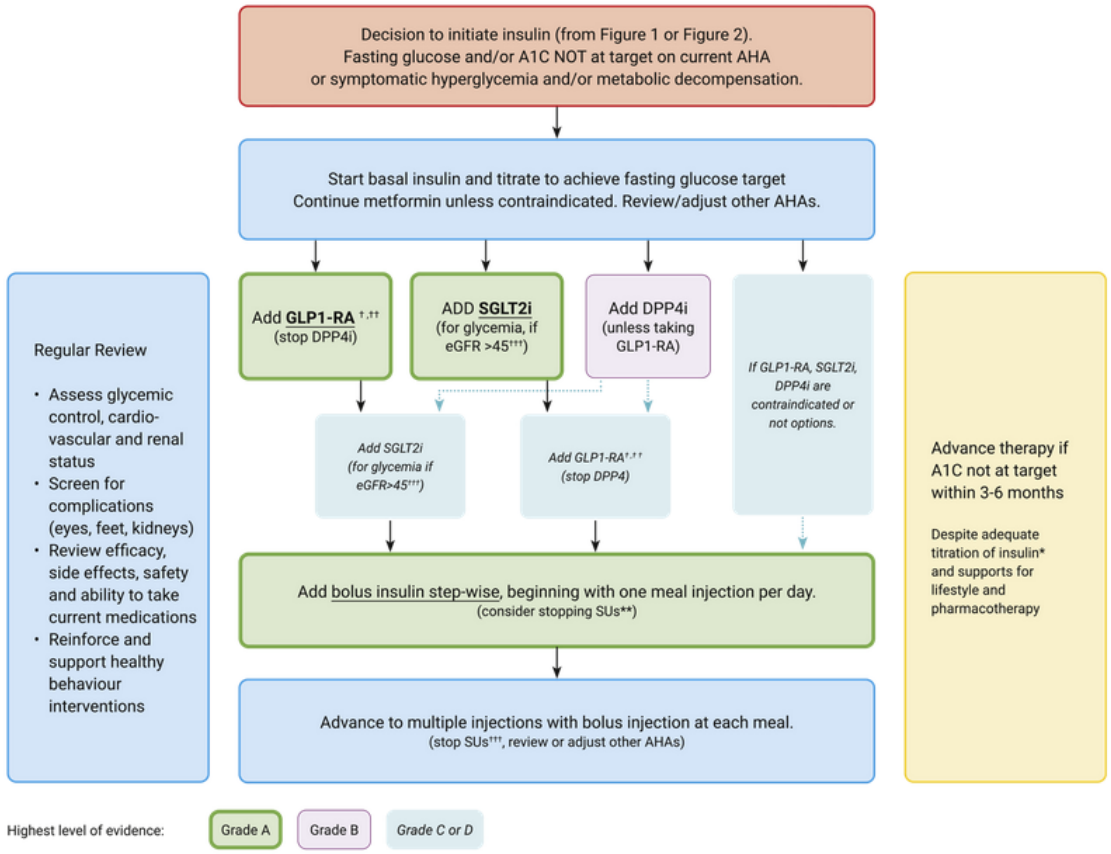
Figure 2A

Reviewing, adjusting or advancing therapy in type 2 diabetes.



* Changes in clinical status may necessitate adjustment of glycemic targets and/or deprescribing.
† Tobacco use; dyslipidemia (use of lipid-modifying therapy or a documented untreated low-density lipoprotein (LDL) ≥3.4 mmol/L, or high-density lipoprotein-cholesterol (HDL-C) <1.0 mmol/L for men and <1.3 mmol/L for women, or triglycerides ≥2.3 mmol/L); or hypertension (use of blood pressure drug or untreated systolic blood pressure [SBP] ≥140 mmHg or diastolic blood pressure [DBP] ≥95 mmHg).
†† All antihyperglycemic agents (AHAs) have Grade A evidence for effectiveness to reduce blood glucose levels.
††† Consider degree of hyperglycemia, costs and coverage, renal function, comorbidity, side effect profile and potential for pregnancy.
** In CV outcome trials performed in people with atherosclerotic cardiovascular disease (ASCVD), chronic kidney disease (CKD), heart failure (HF) or at high cardiovascular (CV) risk.
*** VERTIS (CV outcome trial for ertugliflozin) presented at American Diabetes Association (ADA) June 2020 showed noninferiority for major adverse CV events (MACE). Manuscript not published at time of writing.
A1C, glycated hemoglobin; *DPP4i*, dipeptidyl peptidase-4 inhibitors; *eGFR*, estimated glomerular filtration rate; *GLP1-RA*, glucagon-like peptide-1 receptor agonists; *exenatide ER*, exenatide extended-release; *HHF*, hospitalization for heart failure; *SGLT2i*, sodium-glucose cotransporter 2 inhibitors; *yrs*, years.

Figure 3
Starting or advancing insulin in type 2 diabetes.



* Titration of basal insulin to achieve FPG target without hypoglycemia.
† And titrate dose of GLP1-RA, as tolerated.
†† Or fixed-ratio combination.
††† If eGFR >30 ml/min/1.73m², may be used for cardiorenal benefit.
** Sulfonylureas or meglitinides.
AHAs, antihyperglycemic agents; *A1C*, glycated hemoglobin; *DPP4i*, dipeptidyl peptidase-4 inhibitors; *eGFR*, estimated glomerular filtration rate; *GLP1-RA*, glucagon-like peptide-1 receptor agonists; *SGLT2i*, sodium-glucose cotransporter 2 inhibitors; *SU*, sulfonylureas.

Treatment of People With Newly Diagnosed Type 2 Diabetes

- 1) Healthy behaviour interventions should be initiated at type 2 diabetes diagnosis [Grade B, Level 2 (36)] and reinforced and maintained throughout. Metformin may be introduced at the time of diagnosis, in conjunction with healthy behaviour interventions [Grade D, Consensus].
- 2) If glycemic targets are not achieved within 3 months using healthy behaviour interventions alone, antihyperglycemic therapy should be added to reduce the risk of microvascular complications [Grade A, Level 1A (37)]. Metformin should usually be selected before other agents due to its low risk of hypoglycemia and weight gain [Grade A, Level 1A (26)], and long-term experience with this agent [Grade D, Consensus].
- 3) If A1C values are ≥1.5% above target, initiating metformin in combination with a second antihyperglycemic agent should be considered to increase the likelihood of reaching target [Grade B, Level 2 (38-40) for SGLT2i (41); for DPP4i (42,43)].
- 4) Individuals with metabolic decompensation (e.g. marked hyperglycemia, ketosis or unintentional weight loss) should receive insulin with or without metformin, until glycemic control is achieved OR type of diabetes is established [Grade D, Consensus].

Reassessment and Monitoring

- 5) Glycemic control, cardiovascular and renal status should be reviewed regularly (at least annually). Healthy behaviour interventions should be reinforced and supported. Efficacy, side effects and adherence to existing antihyperglycemic therapy should be assessed [Grade D, Consensus].
- 6) Dose adjustments, substitutions and/or addition of antihyperglycemic medications should be made in order to maintain A1C or attain target A1C within 3 to 6 months [Grade D, Consensus].
- 7) If glycemic targets are not achieved with existing antihyperglycemic medication(s), or the individual's clinical status changes, other classes of agents should be used (either by addition or replacement) to reduce cardiorenal outcomes and/or improve glycemic control; or glycemic targets should be reassessed [Grade D, Consensus].
- 8) For adults with type 2 diabetes with metabolic decompensation (e.g. marked or symptomatic hyperglycemia, ketosis or unintentional weight loss), insulin should be used (see #12-16, below) [Grade D, Consensus].

Advancement or Adjustment of Treatment in People With Type 2 Diabetes

- 9) In adults with type 2 diabetes WITH atherosclerotic cardiovascular disease (ASCVD), HF and/or CKD, treatment should include agents from the following classes with demonstrated CV or renal benefits (see Figures 2A).
  - a) In adults with type 2 diabetes and ASCVD, a GLP1-RA or SGLT2i with CV or renal benefit should be used to reduce the risk of:
    - i) MACE [Grade A, Level 1A (6,10) for liraglutide and dulaglutide; Grade B, Level 2 for subcutaneous semaglutide (7); Grade A, Level 1A (12) for empagliflozin; Grade B, Level 2 (15) for canagliflozin].
    - ii) HHF [Grade B, Level 2 (12,15,17) for empagliflozin, canagliflozin and dapagliflozin].
    - iii) Progression of nephropathy [Grade B, Level 2 (44,15,17) for empagliflozin, canagliflozin and dapagliflozin].
  - b) In adults with type 2 diabetes and a history of HF (reduced ejection fraction <40%):
    - i) An SGLT2i should be used to reduce the risk of HHF or CV death, if the eGFR is >30 mL/min/ 1.73m2 [Grade A, Level 1A (19) for dapagliflozin; Grade A, Level 1 (18) for empagliflozin and canagliflozin].
    - ii) TZD and saxagliptin should be avoided due to their higher risk of HF [Grade A, Level 1A (21,45,46)].
  - c) In adults with type 2 diabetes and CKD and an estimated eGFR >30 mL/min/1.73m2:
    - i) An SGLT2i should be used to reduce the risk of: (1) Progression of nephropathy [Grade A, Level 1A (16) for canagliflozin; Grade A, Level 1 (18) for empagliflozin and dapagliflozin]. (2) HHF [Grade A, Level 1 (18) for canagliflozin, dapagliflozin and empagliflozin]. (3) MACE [Grade B, Level 2 for canagliflozin (16), Grade C, Level 3 (12) for empagliflozin].
    - ii) A GLP1-RA may be considered to reduce the risk of MACE (Grade B, Level 2 (6,7) for liraglutide and semaglutide).
- 10) In adults with type 2 diabetes requiring treatment advancement or adjustment to improve glycemic control, the choice of antihyperglycemic medication should be individualized according to clinical priorities (see Figure 2A) [Grade B, Level 2 (26)].

- a) In adults with type 2 diabetes aged 60 years or older with at least 2 CV risk factors, inclusion of the following classes in glycemic management should be considered:
  - i) A GLP1-RA with proven CV outcome benefit to reduce the risk of MACE [Grade A, Level 1A (10) for dulaglutide; Grade B, Level 2 (6) for liraglutide and Grade C, Level 2 (7) subcutaneous semaglutide]; OR
  - ii) An SGLT2i with proven cardiorenal outcome benefit if estimated GFR is >30 mL/min/1.73m2 to reduce the risk of (1) HHF [Grade B Level 2 (15,17) for dapagliflozin and canagliflozin]. (2) Progression of nephropathy [Grade C, Level 3 (15,17) for canagliflozin and dapagliflozin].
- b) If reducing risk of hypoglycemia is a priority: Incretin agents (DPP4i or GLP1-RA), SGLT2i, acarbose and/or pioglitazone should be considered as add-on medication to improve glycemic control with a lower risk of hypoglycemia than other agents [Grade A, Level 1A (26,28,29,47,48,49,74)].
- c) If weight loss is a priority: A GLP1-RA and/or SGLT2i should be considered as add-on medication to improve glycemic control with more weight loss than other agents [Grade A, Level 1A (26,28,29,30,47,48,49].

Initiating Insulin Treatment in Patients With Type 2 Diabetes

- 11) In people not achieving glycemic targets on existing noninsulin antihyperglycemic medication(s), the addition of a basal insulin regimen should be considered over premixed insulin or bolus-only regimens, if lower risk of hypoglycemia and/or preventing weight gain are priorities [Grade B, Level 2 (50)].
- 12) In adults with type 2 diabetes treated with basal insulin therapy, if minimizing risk of hypoglycemia is a priority:
  - a) Long-acting insulin analogues (insulin glargine U-100, glargine U-300, detemir, degludec) should be considered over NPH insulin to reduce the risk of nocturnal and symptomatic hypoglycemia [Grade A, Level 1A (51-56)].
  - b) Insulin degludec or insulin glargine U-300 (57) may be considered over insulin glargine U-100 to reduce overall and nocturnal hypoglycemia [Grade B, Level 2 for individuals with >1 risk factor for hypoglycemia (58,59)]; [Grade C, Level 3 for other individuals without risk factors for hypoglycemia (56)]; and severe hypoglycemia in patients at high CV risk [Grade C, Level 3 (60)]

Treatment Advancement or Adjustment for People With Type 2 Diabetes Treated With Insulin

- 13) In adults with type 2 diabetes receiving insulin, doses should be adjusted and/or additional antihyperglycemic medication(s) should be added if glycemic targets are not achieved [Grade D, Consensus].
  - a) A GLP1-RA should be considered as add-on therapy [Grade A, Level 1A (61,62)], before initiating bolus insulin or intensifying insulin to improve glycemic controlwith potential benefits ofweight loss and lower hypoglycemia risk compared to single or multiple bolus insulin injections [Grade A, Level 1A (63-71)].
  - b) An SGLT2i should be considered as add-on therapy to improve glycemic control with potential benefits of weight loss and lower hypoglycemia risk compared to additional insulin [Grade A, Level 1A (72-74)].
  - c) A DPP4i may be considered as add-on therapy to improve glycemic control with potential benefits of less weight gain and lower hypoglycemia risk compared to additional insulin [Grade B, Level 2 (72,75-77)].

- 14) When bolus insulin is added to antihyperglycemic agents, rapid-acting analogues may be considered over shortacting (regular) insulin for greater improvement in glycemic control [Grade B, Level 2 (78,79) for aspart].
- 15) Bolus insulin may be initiated using a stepwise approach (starting with 1 injection at 1 meal and additional mealtime injections as needed) to achieve similar A1C reduction with lower hypoglycemia risk compared to initiating bolus injections at every meal [Grade B, Level 2 (80)].

Safety Considerations for Pharmacotherapy of Type 2 Diabetes

- 16) All individuals with type 2 diabetes currently using or starting therapy with insulin or insulin secretagogues should be counselled about the prevention, recognition and treatment of hypoglycemia [Grade D, Consensus].
- 17) Pharmacotherapy may need to be temporarily adjusted during acute illness or around the time of some investigations:
  - a) Metformin and SGLT2i should be temporarily withheld during acute illnesses associated with risk for dehydration or procedures associated with high risk of acute kidney injury [Grade D, Consensus]
  - b) Insulin and insulin secretagogue doses should be decreased or held to reduce risk for hypoglycemia if oral intake is reduced [Grade D, Consensus].
- 18) SGLT2i should be temporarily withheld prior to major surgical procedures and during acute infections and serious illness to reduce the risk of ketoacidosis [Grade D, Consensus]. Particular caution should be paid to this risk in people following low-carbohydrate eating patterns (81) or with suspected insulin deficiency [Grade D, Consensus].

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World Health Organization (WHO), 2018 [106].

Guidelines on second-and third-line medicines and type of insulin for the control of blood glucose levels in non-pregnant adults with diabetes mellitus

Leitlinienorganisation/Fragestellung

- To consider the use of DPP-4 inhibitors, SGLT-2 inhibitors, and TZDs as second- and third-line treatment after metformin and sulfonylurea for controlling hyperglycaemia in type 2 diabetes in non-pregnant adults, including whether these oral agents are preferable to insulin.
- To provide guidance regarding the use of insulin analogues for type 1 and type 2 diabetes.
- The scope has been limited to agents for glycaemic control because that field is a dynamic one and has seen more change in evidence and practice in recent years than have other aspects of diabetes management
- Evidence-based protocols for managing diabetes in primary health care, including managing CVD risk and screening for complications, are available in the WHO PEN 2013 and are not repeated in this guideline.

Methodik

<u>Grundlage der Leitlinie</u>

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

- Update of the WHO PEN recommendations on the choice of second- and third-line treatment for type 2 diabetes based
- WHO established three groups: WHO Guideline Steering Group, Guidelines Development Group and external Peer Review Group
- developed in accordance with the WHO Handbook for Guideline Development. In brief, the WHO Steering Group, in collaboration with the Guideline Development Group developed key questions and rated outcomes to identify those critical for the guideline development
- SR of the evidence were used to build Summary of Findings tables according GRADE
- Outcome rating for recommendations: development of outcome lists, then rating of the Guideline Group if it is critical (rated 7-9), important (rated 4-6) or not important (rated 1-3)
- SR identified in literature search assessment with AMSTAR
- Deciding upon recommendations at Guideline Group met in Geneva in March 2017 on basis of evidence-to-decision tables incorporating Systematic reviews and GRADE tables

<u>Recherche/Suchzeitraum:</u>

- In Pubmed from 2006.

- Es existiert nur ein Datum für den Beginn des Suchzeitraums. Das Ende ist ausschließlich mit „current“ angegeben. Aus den eingeschlossenen Dokumenten kann auf das Jahr 2016 geschlossen werden.

LoE

The following levels of assessment of the evidence were used in the GRADE profiles:

Evidence level	Rationale
High ⊕⊕⊕⊕	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate ⊕⊕⊕O	Further research is likely to have an important impact on our confidence in the effect and may change the estimate.
Low ⊕⊕OO	Further research is very likely to have an impact on the estimate of effect and is likely to change the estimate.
Very low ⊕OOO	Any estimate of effect is very uncertain.

GoR

The recommendations in these guidelines were graded into two categories:

- **A strong recommendation** is one for which the Guideline Group was confident that the desirable effects of adhering to the recommendation outweigh the undesirable effects.
- **A weak** or **conditional recommendation** is one for which the Guideline Group concluded that the desirable effects of adhering to the recommendation probably outweigh the undesirable effects, but the Guideline Group was not confident about these trade-offs.

Empfehlungen:

Hypoglycaemic agents for second-line treatment in type 2 diabetes

- Give a sulfonylurea to patients with type 2 diabetes who do not achieve glycaemic control with metformin alone or who have contraindications to metformin (strong recommendation, moderate quality evidence)
- Remarks: Glibenclamide should be avoided in patients aged 60 years and older. Sulfonylureas with a better safety record for hypoglycaemia (e.g. gliclazide) are preferred in patients for whom hypoglycaemia is a concern (people who are at risk of falls, people who have impaired awareness of hypoglycaemia, people who live alone, people who drive or operate machinery as part of their job).
- The WHO PEN protocol recommends a target fasting blood glucose of <7 mmol/L (126 mg/dl). However, an individualized approach is encouraged in setting the patient's target level for glycaemic control, taking into account their comorbidities, risks from medication side-effects and their likely benefit from tight glycaemic control in view of life expectancy.

The evidence summary for second-line treatment intensification (adding medicines to metformin) was obtained from the systematic review and network meta-analysis carried out by the Methods and Applications Group for Indirect Treatment Comparisons (MAGIC) for the Canadian Agency for Drugs and Technologies in Health (CADTH) (6). The systematic review included 166 Randomized Controlled Trials (RCTs) that reported at least one of the outcomes of interest. The network meta-analysis included sulfonylureas, DPP-4 inhibitors, SGLT-2 inhibitors, TZDs and basal insulins, as well as bolus insulins, biphasic insulins, meglitinides, alpha-glucosidase inhibitors, and glucagon-like peptide-1 (GLP-1) agonists (which were not of interest to the guidelines).

All evaluated hypoglycaemic agents added to metformin performed similarly in lowering HbA1c compared to placebo. DPP-4 inhibitors performed less well compared to sulfonylurea (mean difference 0.12%, 95% CI: 0.01, 0.24) and TZD (mean difference 0.19%, 95% CI: 0.05, 0.33). There was lower risk of severe hypoglycaemia with DPP-4 inhibitors (OR 0.14, 95% CI: 0.07, 0.26) and SGLT-2 inhibitors (OR 0.09, 95% CI: 0.02, 0.44) compared to sulfonylurea. DPP-4 inhibitors and SGLT-2 inhibitors were associated with weight loss, while TZDs and basal insulin were associated with weight gain. Evidence on quality of life and microvascular complications was not available. There were no significant differences for CVD incidence (myocardial infarction (MI) or stroke) or CVD mortality, but the network meta-analysis (NMA) model was not robust (very few events and a large number of trials with no events). In a separate analysis of patients at high risk of CVD, there was no significant difference in CVD mortality.

Hypoglycaemic agents for third-line treatment in type 2 diabetes

- Introduce human insulin treatment to patients with type 2 diabetes who do not achieve glycaemic control with metformin and/or sulfonylurea (strong recommendation, very low-quality evidence)
- If insulin is unsuitable, a DPP-4 inhibitor, SGLT-2 inhibitor or a TZD may be added (weak recommendation, very low-quality evidence)

Remark: Insulin treatment could be unsuitable when circumstances make its use difficult (e.g. persons who live alone and are dependent on others to inject them with insulin).

The evidence summary for third line treatment (medicines added to metformin and sulfonylurea) was obtained from a systematic review and network meta-analysis that was published in 2016 (12). Five trials evaluated triple therapy. The network meta-analysis included DPP-4 inhibitors, SGLT-2 inhibitors, TZDs, basal insulin (medicines of interest to this guideline) as well as meglitinides, alpha-glucosidase inhibitors, GLP-1 agonists, and basal-bolus insulin (medicines not of interest for these guidelines).
All drug classes lowered HbA1c to a similar extent. TZDs (mean difference: -0.86%, 95% CI: -0.25, -1.48) and basal insulin (mean difference: -0.86%, 95% CI: -0.18, -1.55) were the only two medicines that performed significantly better than placebo in lowering HbA1c. DPP-4 inhibitors (mean difference: -0.23kg, 95% CI: -0.46, 0.00) and SGLT-2 inhibitors (mean difference: -0.33kg, 95% CI: -0.59, -0.07) were associated with a lower body weight compared to TZDs. There were very few events of CVD mortality and no significant differences between treatments. Insufficient observations were available to generate evidence networks for CVD incidence. There were no data for the critical outcomes severe hypoglycaemia and quality of life.

Insulin

- Use human insulin to control blood glucose levels in adults with type 1 diabetes, and in adults with type 2 diabetes for whom insulin is indicated (strong recommendation, low-quality evidence)

Remark: Recommendation 4 covers both short-acting (regular human insulin – RHI) and intermediate-acting human insulin (NPH insulin). The recommendation is strong because evidence of better effectiveness of insulin analogues is lacking and human insulin has a better resource-use profile.

- Consider long-acting insulin analogues to control blood glucose levels in adults with type 1 or type 2 diabetes who have frequent severe hypoglycaemia with human insulin (weak recommendation, moderate-quality evidence for severe hypoglycaemia)

Remark: Recommendation 5 is a weak recommendation reflecting the lack of, or very low-quality, evidence for any of the long-term outcomes such as chronic diabetes complications and mortality, and the considerable higher costs for long-acting insulin analogues compared to intermediate-acting human insulin.

Summary of the evidence:

[…] The third systematic review evaluated long-acting insulin analogues versus NPH insulin for type 2 diabetes (42)

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Scottish Intercollegiate Guidelines Network (SIGN), 2017 [98].

Pharmacological management of glycaemic control in people with type 2 diabetes

Leitlinienorganisation/Fragestellung

In adults with type 2 diabetes what is the evidence that

- metformin or sulphonylureas,
- alpha-glucosidase inhibitors or thiazolidinediones,
- DPP-4 inhibitors or GLP-1 receptor agonists,
- SGLT2 inhibitors or
- insulin

affect mortality, cardiovascular morbidity and mortality, microvascular morbidity, HbA1c, weight, hypoglycaemia and other adverse events?

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft teilweise zu (keine formalen Konsensusprozesse beschrieben, aber Begutachtungsverfahren durch unabhängige externe Experten);
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

- rapid systematic literature review based on a series of structured key questions
- AHRQ reviews plus NICE guidelines plus systematic review of primary literature
- SIGN methodological checklists used for critical appraisal, specialist review, public consultation
- members declare all financial interests, whether direct or indirect

Recherche/Suchzeitraum:

- 2011-2016
- Cochrane Central Register of Controlled Trials (CENTRAL), National Institute for Health Research-Health Technology Assessment (NIHR-HTA), Medline, Medline In-Process, Embase and the Cochrane Library

LoE/GoR

KEY TO EVIDENCE STATEMENTS AND RECOMMENDATIONS	
LEVELS OF EVIDENCE	
1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion
RECOMMENDATIONS	
Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation). The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation. Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence, and the balance of benefits and harms of the options.	
R	For **'strong'** recommendations on interventions that **'should'** be used, the guideline development group is confident that, for the vast majority of people, the intervention (or interventions) will do more good than harm. For **'strong'** recommendations on interventions that **'should not'** be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.
R	For **'conditional'** recommendations on interventions that should be **'considered'**, the guideline development group is confident that the intervention will do more good than harm for most patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.
GOOD-PRACTICE POINTS	
✓	Recommended best practice based on the clinical experience of the guideline development group.

Sonstige methodische Hinweise

- no process of consensus described

4 Metformin

- R: Metformin should be considered as the first-line oral treatment option for people with type 2 diabetes. (GoR conditional)

5 Sulphonylureas

- R: Sulphonylureas should be considered as first-line oral agents in people who are intolerant of, or have contraindications to metformin. (GoR conditional)
- R: Sulphonylureas should be considered as add-on second-line treatment to other oral therapies and may be useful in triple oral therapy. (GoR conditional)

- Sulphonylurea therapy is associated with hypoglycaemia (caution should be taken in the elderly) and weight gain.

6 Thiazolidinediones

6.1 PIOGLITAZONE

- R: Pioglitazone should be considered, usually as dual or triple therapy, for lowering HbA1c. (GoR conditional)
- R: Pioglitazone should not be used in patients with heart failure. (GoR strong)
- R: The risk of fracture should be considered during long-term use of pioglitazone. (GoR conditional)
- Patients prescribed pioglitazone should be made aware of the increased risk of peripheral oedema, heart failure, weight gain, bladder cancer and fractures.

6.2 ROSIGLITAZONE

In September 2010 the European Medicines Agency (EMA) completed a review of rosiglitazone containing medicines at the request of the European Commission, following reports of an increase in the risk of cardiovascular problems with rosiglitazone. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of rosiglitazone did not outweigh its risks, and that the marketing authorisation for all rosiglitazone-containing medicines should be suspended across the European Union (EU). The marketing authorisation for Avandia (rosiglitazone) in the EU was suspended on 11 July 2015 when the holder of the MA decided not to apply for a renewal. Further information can be found on the EMA website (www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2016/06/WC500208350.pdf).

In February 2011 the U.S. Food and Drug Administration (FDA) notified the public that information on the cardiovascular risks of rosiglitazone has been added to the physician labelling and patient Medication Guide. Following re-evaluation of contemporary evidence on the cardiovascular safety of rosiglitazone, restrictions on its use were reduced in 2013 and, ultimately, removed in 2015. From December 2015, distribution of rosiglitazone-containing medicines is no longer restricted in the USA. Further details are available on the FDA website (www.fda.gov/Drugs/DrugSafety/ucm376389.htm).

7 Dipeptidyl peptidase-4 inhibitors

- R: DPP-4 inhibitors should be considered, usually as dual or triple therapy, for lowering HbA1c. (GoR conditional)

8 Sodium glucose co-transporter 2 inhibitors

- R: SGLT2 inhibitors should be considered as an add-on therapy to metformin in people with type 2 diabetes. (GoR conditional)
- R: In individuals with type 2 diabetes and established cardiovascular disease, SGLT2 inhibitors with proven cardiovascular benefit (currently empagliflozin and canagliflozin) should be considered. (GoR conditional)

9 Glucagon-like peptide-1 receptor agonists

- R: GLP-1 receptor agonist therapy should be considered in people with a body mass index of ≥30 kg/m2 (or ethnicity-adjusted equivalent) in combination with oral glucose-lowering drugs or basal insulin (or both) as third- or fourth-line treatment, when adequate glycaemic control has not been achieved with these drugs.

- R: GLP-1 receptor agonist therapy should be considered as an alternative to insulin in people for whom treatment with combinations of oral glucose-lowering drugs has been inadequate. (GoR conditional)
- R: For individuals with type 2 diabetes and established cardiovascular disease, GLP-1 receptor agonist therapies with proven cardiovascular benefit (currently liraglutide) should be considered. (GoR conditional)

10 Insulin

10.1 CONTINUING ORAL AGENTS WHEN INITIATING BASAL INSULIN

- R: Oral metformin therapy should be continued when insulin therapy is initiated to maintain or improve glycaemic control. (GoR strong)

Consider stopping or reducing sulphonylurea therapy when insulin therapy is initiated. The benefits and risks of continuing other glucose-lowering agents should also be reviewed at this time on an individualised basis.

10.2 CHOOSING BASAL INSULIN

- R: Once-daily bedtime NPH insulin should be used when adding insulin to metformin. (GoR strong) Basal insulin analogues should be considered according to hypoglycaemia risk, for example in those who suffer from recurrent episodes of hypoglycaemia or require assistance with insulin injections. (GoR conditional)

Careful clinical judgement must be applied to ensure insulin therapy is not delayed inappropriately.

10.3 INSULIN INITIATION AND INTENSIFICATION

- R: When commencing insulin therapy, bedtime basal insulin should be initiated and the dose titrated against morning (fasting) glucose. (GoR strong) If the HbA1c level does not reach target then addition of prandial insulin should be considered. (GoR conditional)

10.3.1 INTENSIFYING WITH PREMIXED PREPARATIONS

Aim to optimise insulin dose and regimen to achieve target glycaemia while minimising the risk of hypoglycaemia and weight gain.

10.3.2 INTENSIFYING WITH RAPID-ACTING INSULIN ANALOGUES VERSUS HUMAN INSULIN

- R: Soluble human insulin or rapid-acting insulin analogues can be used when intensifying insulin regimens to improve or maintain glycaemic control. (GoR conditional)

Qaseem A et al., 2017 [96].

American College of Physicians (ACP)

Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of Physicians

Leitlinienorganisation/Fragestellung

The purpose of this ACP guideline is to present the updated evidence regarding the oral pharmacologic treatment of (all adults with) type 2 diabetes; it replaces the 2012 ACP guideline on the same topic.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium – trifft zu;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt – trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz – trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt – trifft nicht zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt – trifft teilweise zu (Evidenzverknüpfung nur indirekt);

- Regelmäßige Überprüfung der Aktualität gesichert – trifft zu.

- Systematic AHRQ literature review (5) based on a series of key questions, systematic review of primary literature
- Jadad and Downs and Black methodological checklists used for critical appraisal
- Meta-analysis conducted if feasible, peer review, public consultation, all financial interests of the members discussed and managed

5. Bolen S, et al. Diabetes Medications for Adults with Type 2 Diabetes: An Update. Comparative Effectiveness Review no. 173. (Prepared by the Johns Hopkins University Evidence-based Practice Center under contract no. 290-2012-00007-I.) Rockville: Agency for Healthcare Research and Quality; 2016.

Recherche/Suchzeitraum:

- April 2009 through March 2015 and updated through December 2015
- MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials

LoE/GoR

Table 1. The American College of Physicians' Guideline Grading System*

Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	**Benefits Finely Balanced With Risks and Burden**
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak
Insufficient evidence to determine net benefits or risks		

* Adopted from the classification developed by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) workgroup.

Sonstige methodische Hinweise

- no process of consensus described

Recommendation 1:

ACP recommends that clinicians prescribe metformin to patients with type 2 diabetes when pharmacologic therapy is needed to improve glycemic control. (Grade: strong recommendation; moderate-quality evidence)

Recommendation 2:

ACP recommends that clinicians consider adding a sulfonylurea, a thiazolidinedione, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin to improve glycemic control when a second oral therapy is considered. (Grade: weak recommendation; moderate-quality evidence.) ACP recommends that clinicians and patients select among medications after discussing benefits, adverse effects, and costs.

Table 1 contain further details about the comparative effectiveness and safety evidence.

Appendix Table 1. Summary of Clinical Outcomes for Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus

Intervention*, by Outcome	Strength of Evidence	Studies, n	Summary†
All-cause mortality			
Monotherapy vs. monotherapy			
Metformin vs. pioglitazone	Low	5	Neither treatment favored for short-term mortality
Metformin vs. rosiglitazone	Low	4	Metformin favored
Metformin vs. SU (shorter-duration studies)	Low	4	Neither favored for short-term mortality
Metformin vs. SU (longer-duration studies)	Low	9	Metformin favored for long-term mortality
Metformin vs. DPP-4 inhibitors	Low	6	Neither treatment favored for short-term mortality
Metformin vs. SGLT-2 inhibitors	Low	4	Neither treatment favored
Pioglitazone vs. DPP-4 inhibitors	Low	2	Neither treatment favored
SU vs. DPP-4 inhibitors	Low	1	DPP-4 inhibitors favored for short-term mortality
Metformin vs. metformin combination			
Metformin vs. metformin + rosiglitazone	Low	6	Metformin monotherapy favored: OR, 2.51 (95% CI, 0.66–9.52) ‡
Metformin vs. metformin + SU	Low	5	Neither treatment favored for short-term mortality
Metformin vs. metformin + DPP-4 inhibitors (<2 y)	Low	14	Neither treatment favored for short-term mortality
Metformin vs. metformin + SGLT-2 inhibitors (shorter duration)	Low	6	Neither treatment favored for short-term mortality
Metformin vs. metformin + SGLT-2 inhibitors (long-duration studies)	Low	2	Neither treatment favored
Combination vs. combination			
Metformin + rosiglitazone vs. metformin + SU	Low	3	Neither treatment favored for short-term mortality
Metformin + SU vs. metformin + DPP-4 inhibitors (longer duration)	Low	6	Metformin + DPP-4 inhibitors favored for long-term mortality: OR, 0.64 (CI, 0.27–1.52) ‡
Metformin + SU vs. metformin + SGLT-2 inhibitors (longer duration)	Low	3	Neither treatment favored for long-term mortality
Metformin + DPP-4 inhibitors vs. metformin + SGLT-2 inhibitors	Low	2	Neither favored for short-term mortality
Cardiovascular mortality			
Monotherapy vs. monotherapy			
Metformin vs. pioglitazone	Low	2	Neither treatment favored
Metformin vs. rosiglitazone	Low	1	Neither treatment favored
Metformin vs. SU (longer-duration studies)	Moderate§	5	Metformin favored: range in RR from RCTs, 0.6–0.7; adjusted HR from observational studies, 0.6–0.9
Metformin vs. DPP-4 inhibitors	Low	3	DPP-4 inhibitors favored for short-term mortality
Rosiglitazone vs. SU (longer-duration studies)	Low	1	Rosiglitazone favored
Metformin vs. metformin combination			
Metformin vs. metformin + rosiglitazone	Low	5	Metformin favored for short-term mortality
Metformin vs. metformin + DPP-4 inhibitor	Low	7	Metformin + DPP-4 inhibitors favored for short-term mortality
Combination vs. combination			
Metformin + SU vs. metformin + DPP-4 inhibitors (104 wk follow-up)	Low	5	Metformin + DPP-4 inhibitors favored for long-term CVD mortality
Metformin + SU vs. metformin + SGLT-2 inhibitor (longer-duration studies)	Low	2	Metformin + SGLT-2 inhibitors favored
Cardiovascular morbidity			
Monotherapy vs. monotherapy			
Metformin vs. rosiglitazone	Low	5	Metformin favored for long-term CVD morbidity
Metformin vs. pioglitazone	Low	5	Neither treatment favored
Metformin vs. SU	Low	7	Metformin favored for long-term CVD morbidity: range in RR from RCTs, 0.7–1.6; adjusted HR from observational studies, 0.3–0.9
Rosiglitazone vs. SU	Low	4	SU favored for long-term CVD morbidity
Pioglitazone vs. SU	Low	3	Pioglitazone favored for short-term CVD morbidity
SU vs. DPP-4 inhibitors	Low	2	DPP-4 inhibitor favored for short-term CVD morbidity
Metformin vs. metformin combination			
Metformin vs. metformin + rosiglitazone (shorter duration)	Low	6	Metformin favored for short-term CVD morbidity
Metformin vs. metformin + SU (shorter duration)	Low	1	Metformin favored for short-term CVD morbidity
Metformin vs. metformin + SGLT-2 inhibitor (shorter duration)	Low	1	Metformin favored for short-term CVD
Combination vs. combination			
Metformin + pioglitazone vs. metformin + DPP-4 inhibitor (shorter duration)	Low	2	Metformin + DPP-4 inhibitor favored for short-term cardiovascular morbidity
Metformin + rosiglitazone vs. metformin + DPP-4 inhibitor (shorter duration)	Low	2	Metformin + rosiglitazone favored for short-term CVD morbidity
Metformin + SU vs. metformin + DPP-4 inhibitor (long-term nonfatal MI)	Low	2	Metformin + DPP-4 inhibitor favored for long-term nonfatal MI
Metformin + SU vs. metformin + SGLT-2 inhibitor (long-term)	Low	1	Neither favored

(Continued on following page)

Appendix Table 1–Continued

Intervention*, by Outcome	Strength of Evidence	Studies, *n*	Summary†
Nephropathy			
Monotherapy vs. monotherapy			
Metformin vs. SU (shorter-duration studies)	Low	4	Metformin favored
TZD vs. SU (mainly shorter-duration studies)	Low	7	TZD favored for short-term nephropathy outcomes
SU vs. DPP-4 inhibitors (shorter-duration study)	Low	1	Neither treatment favored
Metformin vs. metformin combination			
Metformin + TZD vs. metformin + SU (shorter-duration study)	Low	2	Metformin + TZD favored
Metformin + TZD vs. metformin + DPP-4 (shorter-duration study)	Low	1	Neither treatment favored
Neuropathy			
Metformin vs. metformin + DPP-4 inhibitor (shorter-duration study)	Low	1	Metformin favored
Metformin + TZD vs. metformin + SU (shorter-duration study)	Low	1	Neither treatment favored

CVD = cardiovascular disease; DPP-4 = dipeptidyl peptidase-4; HR = hazard ratio; MI = myocardial infarction; OR = odds ratio; RCT = randomized, controlled trial; RR = relative risk; SGLT-2 = sodium-glucose cotransporter-2; SU = sulfonylurea; TZD = thiazolidinedione.
* Only comparisons that were evaluated by at least 1 randomized controlled trial are listed. All other comparisons were considered to have insufficient evidence due to a lack of available evidence. Unless otherwise specified, conclusions for the clinical outcomes are short term (1 y or shorter), because few longer-duration studies evaluated this outcome.
† Unless otherwise specified, the estimates are the pooled mean between-group differences (95% CIs).
‡ Effect is not statistically significant.
§ Grade given by the evidence reviewers. The Clinical Guidelines Committee reviewed the individual studies and found the 2 trials to be underpowered, with no significant reductions in cardiovascular mortality with metformin versus sulfonylureas, and therefore considered the quality of evidence to be low.

Harms

- Metformin: increased risk for gastrointestinal side effects
- Sulfonylureas: increased risk for hypoglycemia compared with other drugs
- Thiazolidinediones: increased risk for heart failure
- SGLT-2 inhibitors: increased genital mycotic infections

Clinical Considerations

- Nonpharmacologic therapy includes dietary modifications, regular exercise, lifestyle modifications, and weight loss.
- Management of type 2 diabetes often involves pharmacologic and nonpharmacologic therapies and includes patient education, evaluation, patient self-management for microvascular and macrovascular complications, treatment of hyperglycemia, and minimization of cardiovascular and other long-term risk factors.
- Initiation of pharmacologic therapy is an important approach for the effective management of type 2 diabetes when weight loss or lifestyle modification fails.
- Metformin monotherapy effectively decreases glycemic levels when used in monotherapy and combination therapy with a second agent. Metformin also reduces body weight.
- Although combination therapy reduces HbA1c levels more effectively than monotherapy, it is associated with more adverse events.
- The DPP-4 inhibitors saxagliptin and alogliptin may increase the risk for heart failure, especially in patients who already have heart or kidney disease.
- Metformin is considered safe for patients with mild chronic kidney disease and some patients with moderate kidney impairment (but is contraindicated in those with an estimated glomerular filtration rate <30 mL/min/1.73 m2).

COMPARATIVE BENEFITS OF ORAL MEDICATIONS FOR TYPE 2 DIABETES

Evidence from new studies (52 randomized, controlled trials and 13 observational studies, mostly 1 year or less in duration) was either low quality or insufficient for evaluating clinical outcomes, such as mortality, cardiovascular mortality and morbidity, retinopathy, nephropathy, and neuropathy.

- All-Cause Mortality

8. Hong J, Zhang Y, Lai S, Lv A, Su Q, Dong Y, et al; SPREADDIMCAD Investigators. Effects of metformin versus glipizide on cardiovascular outcomes in patients with type 2 diabetes and coronary artery disease. Diabetes Care. 2013;36:1304-11.
9. Kahn SE, Haffner SM, Heise MA, Herman WH, Holman RR, Jones NP, et al; ADOPT Study Group. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006;355: 2427-43.
10. Andersson C, Olesen JB, Hansen PR, Weeke P, Norgaard ML, Jørgensen CH, et al. Metformin treatment is associated with a low risk of mortality in diabetic patients with heart failure: a retrospective nationwide cohort study. Diabetologia. 2010;53:2546-53.
11. Schramm TK, Gislason GH, Vaag A, Rasmussen JN, Folke F, Hansen ML, et al. Mortality and cardiovascular risk associated with different insulin secretagogues compared with metformin in type 2 diabetes, with or without a previous myocardial infarction: a nationwide study. Eur Heart J. 2011;32:1900-8.
12. Wheeler S, Moore K, Forsberg CW, Riley K, Floyd JS, Smith NL, et al. Mortality among veterans with type 2 diabetes initiating metformin, sulfonylurea or rosiglitazone monotherapy. Diabetologia. 2013;56:1934-43.
13. Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al. Increase in overall mortality risk in patients with type 2 diabetes receiving glipizide, glyburide or glimepiride monotherapy versus metformin: a retrospective analysis. Diabetes Obes Metab. 2012;14: 803-9.
14. Corrao G, Romio SA, Zambon A, Merlino L, Bosi E, Scavini M. Multiple outcomes associated with the use of metformin and sulphonylureas in type 2 diabetes: a population-based cohort study in Italy. Eur J Clin Pharmacol. 2011;67:289-99.
15. Pantalone KM, Kattan MW, Yu C, Wells BJ, Arrigain S, Jain A, et al. The risk of developing coronary artery disease or congestive heart failure, and overall mortality, in type 2 diabetic patients receiving rosiglitazone, pioglitazone, metformin, or sulfonylureas: a retrospective analysis. Acta Diabetol. 2009;46:145-54.
16. Wang CP, Lorenzo C, Espinoza SE. Frailty attenuates the impact of metformin on reducing mortality in older adults with type 2 diabetes. J Endocrinol Diabetes Obes. 2014;2:1031.

- Cardiovascular Mortality

8 – 11 und 16 (siehe oben)

17. Johnson JA, Simpson SH, Toth EL, Majumdar SR. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with type 2 diabetes. Diabet Med. 2005;22:497-502.

- Cardiovascular and Cerebrovascular Morbidity

8 – 16 (siehe oben)

- Retinopathy, Nephropathy, and Neuropathy

All randomized, controlled trials were short term, and evidence for all comparisons was insufficient or low quality, thus inconclusive for these outcomes.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 5 of 12, May 2021) am 06.05.2021

#	Suchfrage
#1	MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#2	(t2dm OR dmt2 OR niddm OR mody):ti
#3	(diabetes OR dm):ti
#4	("adult onset" OR "maturity onset" OR (non NEXT insulin NEXT dependan*) OR (noninsulin NEXT dependan*) OR "slow onset" OR (ketosis NEXT resistan*) OR "type 2" OR "type II" OR t2 OR tII OR (t NEXT 2) or (t NEXT II)):ti
#5	#3 AND #4
#6	#1 OR #2 OR #5
#7	#6 with Cochrane Library publication date Between May 2016 and May 2021

Systematic Reviews in Medline (PubMed) am 06.05.2021

#	Suchfrage
1	"diabetes mellitus, type 2"[MeSH Terms]
2	(T2DM[Title/Abstract] OR DMT2[Title/Abstract] OR NIDDM[Title/Abstract] OR MODY[Title/Abstract])
3	(Diabetes[Title/Abstract] OR dm[Title/Abstract])
4	"adult onset"[Title/Abstract] OR "maturity onset"[Title/Abstract] OR (non insulin dependan*[Title/Abstract]) OR noninsulin dependan*[Title/Abstract] OR "slow onset"[Title/Abstract] OR ketosis resistan*[Title/Abstract] OR "type 2"[Title/Abstract] OR "type II"[Title/Abstract] OR "T 2"[Title/Abstract] OR T2[Title/Abstract] OR TII[Title/Abstract] OR "T II"[Title/Abstract]
5	(#3 AND #4)
6	(#1 OR #2 OR #5)
7	(metformin[MeSH Terms]) OR metformin[Title/Abstract] OR Dimethylbiguanidine[Title/Abstract] OR Dimethylguanylguanidine[Title/Abstract] OR Glucophage[Title/Abstract]
8	((Dipeptidyl-Peptidase IV Inhibitors[MeSH Terms]) OR gliptin*[Title/Abstract]) OR dpp4 inhibitor*[Title/Abstract] OR dppIV inhibitor*[Title/Abstract]
9	((("Dipeptidyl Peptidase"[Title/Abstract] OR Dipeptidylpeptidase[Title/Abstract] OR dpp[Title/Abstract])) AND (4[Title/Abstract] OR IV[Title/Abstract])) AND inhibitor*[Title/Abstract]
10	("Sodium-Glucose Transporter 2"[MeSH Terms]) OR "Sodium-Glucose Transporter 2 Inhibitors"[MeSH Terms] OR Gliflozin*[Title/Abstract] OR sglt2 inhibitor*[Title/Abstract] OR SGLT2i[Title/Abstract]
11	((((sodium[Title/Abstract] AND glucose[Title/Abstract])) AND (2[Title/Abstract] OR II[Title/Abstract])) AND (transporter[Title/Abstract] OR cotransporter[Title/Abstract] OR co-transporter[Title/Abstract])) AND inhibitor*[Title/Abstract]
12	((sglt[Title/Abstract]) AND (2[Title/Abstract] OR II[Title/Abstract])) AND inhibitor*[Title/Abstract]

#	Suchfrage
13	(Sulfonylurea Compounds[MeSH Terms]) OR (Sulfonylurea*[Title/Abstract] OR Sulphonylurea*[Title/Abstract])
14	(Glycoside Hydrolase Inhibitors[MeSH Terms]) OR "Glycoside Hydrolase Inhibitor*"[Title/Abstract]
15	((alpha[Title/Abstract]) AND (Amylase[Title/Abstract] OR Glucosidase[Title/Abstract])) AND inhibitor*[Title/Abstract]
16	insulins[MeSH Terms] OR insulin*[Title]
17	Incretins[MeSH Terms] OR incretin*[Title/Abstract]
18	Hypoglycemic Agents[MeSH Terms] OR glinid*[Title/Abstract] OR Antidiabetics[Title] OR Antihyperglycemics[Title] OR Antihyperglycaemics[Title] OR Hypoglycemics[Title] OR Hypoglycaemics[Title]
19	(Antidiabetic*[Title] OR Antihyperglycemic*[Title] OR Antihyperglycaemic*[Title] OR Hypoglycemic*[Title] OR Hypoglycaemic*[Title]) AND (Agent*[Title] OR drug*[Title] OR effect*[Title])
20	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
21	#6 AND #20
22	(#21) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology

#	Suchfrage
	report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
23	(#22) AND ("2016/05/01"[PDAT] : "3000"[PDAT])
24	(#23) NOT "The Cochrane database of systematic reviews"[Journal]
25	(#24) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 06.05.2021

#	Suchfrage
1	"diabetes mellitus, type 2"[MeSH Terms]
2	(T2DM[Title/Abstract] OR DMT2[Title/Abstract] OR NIDDM[Title/Abstract] OR MODY[Title/Abstract])
3	(Diabetes[Title/Abstract] OR dm[Title/Abstract])
4	"adult onset"[Title/Abstract] OR "maturity onset"[Title/Abstract] OR (non insulin dependan*[Title/Abstract]) OR noninsulin dependan*[Title/Abstract] OR "slow onset"[Title/Abstract] OR ketosis resistan*[Title/Abstract] OR "type 2"[Title/Abstract] OR "type II"[Title/Abstract] OR "T 2"[Title/Abstract] OR T2[Title/Abstract] OR TII[Title/Abstract] OR "T II"[Title/Abstract]
5	(#3 AND #4)
6	(#1 OR #2 OR #5)
7	(metformin[MeSH Terms]) OR metformin[Title/Abstract] OR Dimethylbiguanidine[Title/Abstract] OR Dimethylguanylguanidine[Title/Abstract] OR Glucophage[Title/Abstract]
8	((Dipeptidyl-Peptidase IV Inhibitors[MeSH Terms]) OR gliptin*[Title/Abstract]) OR dpp4 inhibitor*[Title/Abstract] OR dppIV inhibitor*[Title/Abstract]
9	((("Dipeptidyl Peptidase"[Title/Abstract] OR Dipeptidylpeptidase[Title/Abstract] OR dpp[Title/Abstract])) AND (4[Title/Abstract] OR IV[Title/Abstract])) AND inhibitor*[Title/Abstract]
10	("Sodium-Glucose Transporter 2"[MeSH Terms]) OR "Sodium-Glucose Transporter 2 Inhibitors"[MeSH Terms] OR Gliflozin*[Title/Abstract] OR sglt2 inhibitor*[Title/Abstract] OR SGLT2i[Title/Abstract]
11	((((sodium[Title/Abstract] AND glucose[Title/Abstract])) AND (2[Title/Abstract] OR II[Title/Abstract])) AND (transporter[Title/Abstract] OR cotransporter[Title/Abstract] OR co-transporter[Title/Abstract])) AND inhibitor*[Title/Abstract]
12	((sglt[Title/Abstract]) AND (2[Title/Abstract] OR II[Title/Abstract])) AND inhibitor*[Title/Abstract]
13	(Sulfonylurea Compounds[MeSH Terms]) OR (Sulfonylurea*[Title/Abstract] OR Sulphonylurea*[Title/Abstract])
14	(Glycoside Hydrolase Inhibitors[MeSH Terms]) OR "Glycoside Hydrolase Inhibitor*"[Title/Abstract]

#	Suchfrage
15	((alpha[Title/Abstract]) AND (Amylase[Title/Abstract] OR Glucosidase[Title/Abstract])) AND inhibitor*[Title/Abstract]
16	insulins[MeSH Terms] OR insulin*[Title]
17	Incretins[MeSH Terms] OR incretin*[Title/Abstract]
18	Hypoglycemic Agents[MeSH Terms] OR glinid*[Title/Abstract] OR Antidiabetics[Title] OR Antihyperglycemics[Title] OR Antihyperglycaemics[Title] OR Hypoglycemics[Title] OR Hypoglycaemics[Title]
19	(Antidiabetic*[Title] OR Antihyperglycemic*[Title] OR Antihyperglycaemic*[Title] OR Hypoglycemic*[Title] OR Hypoglycaemic*[Title]) AND (Agent*[Title] OR drug*[Title] OR effect*[Title])
20	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
21	#6 AND #20
22	(#21) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
23	(#22) AND ("2016/05/01"[CRDT] : "3000"[CRDT])
24	(#23) NOT (retracted publication [pt] OR retraction of publication [pt])

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Anhang

Abbildung 1: Algorithm for blood glucose lowering therapy in adults with type 2 diabetes [91]

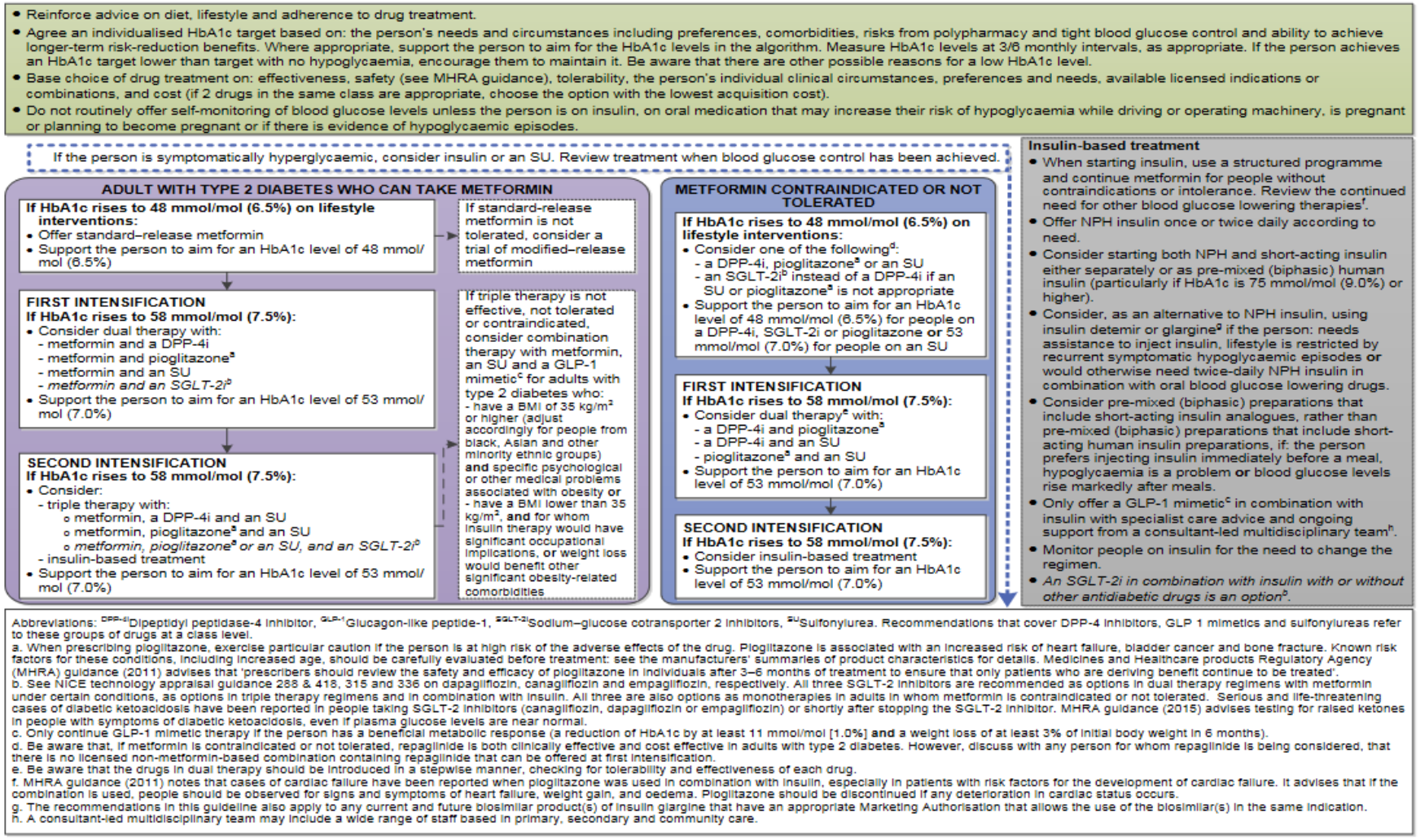

Abbildung 2: Lautsch et al., 2021 [68].: Table 3

Table 3 League table presenting pairwise treatment comparisons in mean difference (95% CrI) for change in mean HbA1c (%) from baseline

Alo25	Cana100	Cana300	Dapa10	Dapa10 /Saxa5	Dapa5	Dapa5/Saxa5
Alo25	0.16 (− 0.28, 0.60)	0.31 (− 0.13, 0.75)	0.09 (− 0.32, 0.48)	**0.49 (0.06, 0.91)**	− 0.01 (− 0.42, 0.39)	0.37 (− 0.09, 0.84)
	Cana100	0.15 (− 0.11, 0.41)	− 0.08 (− 0.35, 0.20)	**0.32 (0.02, 0.63)**	− 0.17 (− 0.46, 0.12)	0.21 (− 0.15, 0.58)
		Cana300	− 0.23 (− 0.50, 0.06)	0.17 (− 0.13, 0.48)	**− 0.32 (− 0.61, − 0.03)**	0.06 (− 0.30, 0.43)
			Dapa10	**0.40 (0.20, 0.60)**	− 0.09 (− 0.28, 0.08)	**0.29 (0.00, 0.58)**
				Dapa10 /Saxa5	**− 0.50 (− 0.74, − 0.26)**	− 0.11 (− 0.43, 0.21)
					Dapa5	**0.38 (0.12, 0.65)**
						Dapa5/Saxa5

Alo25	Dapa5	Dapa5/Saxa5	Empa10	Empa10/Lina5	Empa25	Empa25/Lina5	Ertu15
Alo25	− 0.01 (− 0.42, 0.39)	0.37 (− 0.09, 0.84)	0.07 (− 0.36, 0.49)	**0.51 (0.04, 0.97)**	0.09 (− 0.34, 0.51)	**0.62 (0.15, 1.08)**	0.29 (− 0.12, 0.68)
	− 0.17 (− 0.46, 0.12)	0.21 (− 0.15, 0.58)	− 0.09 (− 0.41, 0.23)	0.35 (− 0.02, 0.72)	− 0.07 (− 0.40, 0.24)	**0.46 (0.08, 0.83)**	0.12 (− 0.16, 0.40)
	− 0.32 (− 0.61, − 0.03)	0.06 (− 0.30, 0.43)	− 0.24 (− 0.56, 0.08)	0.20 (− 0.17, 0.57)	− 0.22 (− 0.55, 0.10)	0.31 (− 0.07, 0.68)	− 0.03 (− 0.31, 0.25)
	− 0.09 (− 0.28, 0.08)	**0.29 (0.00, 0.58)**	− 0.02 (− 0.28, 0.24)	**0.42 (0.10, 0.74)**	0.00 (− 0.26, 0.26)	**0.53 (0.21, 0.85)**	0.20 (− 0.02, 0.42)
	− 0.50 (− 0.74, − 0.26)	− 0.11 (− 0.43, 0.21)	**− 0.42 (− 0.71, − 0.12)**	0.02 (− 0.33, 0.37)	**− 0.40 (− 0.70, − 0.10)**	0.13 (− 0.22, 0.48)	− 0.20 (− 0.45, 0.05)
	Dapa5	**0.38 (0.12, 0.65)**	0.08 (− 0.20, 0.35)	**0.52 (0.19, 0.85)**	0.10 (− 0.18, 0.37)	**0.63 (0.29, 0.96)**	**0.29 (0.05, 0.53)**
		Dapa5/Saxa5	− 0.30 (− 0.66, 0.05)	0.14 (− 0.27, 0.53)	− 0.29 (− 0.64, 0.07)	0.25 (− 0.16, 0.65)	− 0.09 (− 0.42, 0.24)
			Empa10	**0.44 (0.18, 0.70)**	0.02 (− 0.18, 0.22)	**0.55 (0.29, 0.81)**	0.22 (− 0.06, 0.49)
				Empa10/Lina5	**− 0.42 (− 0.68, − 0.16)**	0.11 (− 0.18, 0.39)	− 0.23 (− 0.55, 0.10)
					Empa25	**0.53 (0.27, 0.79)**	0.20 (− 0.07, 0.47)
						Empa25/Lina5	− 0.33 (− 0.66, 0.00)
							Ertu15

Alo25	Ertu15 /Sita100	Ertu5	Ertu5/Sita100	Lina5	PBO
Alo25	**0.71 (0.26, 1.16)**	0.22 (− 0.18, 0.62)	**0.68 (0.23, 1.13)**	0.11 (− 0.30, 0.51)	**− 0.50 (− 0.87, − 0.14)**
	0.55 (0.21, 0.90)	0.06 (− 0.22, 0.35)	**0.52 (0.18, 0.86)**	− 0.05 (− 0.35, 0.24)	**− 0.66 (− 0.90, − 0.42)**
	0.40 (0.06, 0.75)	− 0.09 (− 0.37, 0.20)	**0.37 (0.03, 0.71)**	− 0.20 (− 0.50, 0.09)	**− 0.81 (− 1.05, − 0.57)**
	0.63 (0.33, 0.93)	0.14 (− 0.09, 0.36)	**0.60 (0.29, 0.90)**	0.02 (− 0.21, 0.25)	**− 0.58 (− 0.73, − 0.44)**
	0.22 (− 0.09, 0.55)	**− 0.26 (− 0.52, − 0.01)**	0.20 (− 0.13, 0.52)	**− 0.38 (− 0.64, − 0.11)**	**− 0.98 (− 1.19, − 0.78)**
	0.72 (0.41, 1.04)	0.23 (− 0.01, 0.47)	**0.69 (0.37, 1.01)**	0.12 (− 0.13, 0.36)	**− 0.49 (− 0.66, − 0.32)**
	0.34 (− 0.04, 0.72)	− 0.15 (− 0.48, 0.17)	0.31 (− 0.08, 0.70)	− 0.27 (− 0.60, 0.06)	**− 0.87 (− 1.15, − 0.59)**
	0.64 (0.31, 0.99)	0.15 (− 0.12, 0.43)	**0.61 (0.27, 0.96)**	0.04 (− 0.18, 0.25)	**− 0.57 (− 0.78, − 0.35)**
	0.20 (− 0.18, 0.59)	− 0.29 (− 0.61, 0.04)	0.17 (− 0.21, 0.57)	**− 0.40 (− 0.67, − 0.14)**	**− 1.01 (− 1.29, − 0.72)**
	0.62 (0.28, 0.97)	0.13 (− 0.14, 0.41)	**0.59 (0.25, 0.94)**	0.02 (− 0.20, 0.23)	**− 0.59 (− 0.80, − 0.37)**

Alo25	Ertu15 /Sita100	Ertu5	Ertu5/Sita100	Lina5	PBO
	0.09	**− 0.40 (− 0.72, − 0.06)**	0.06 (− 0.33, 0.46)	**− 0.51 (− 0.78, − 0.25)**	**− 1.12 (− 1.40, − 0.83)**
	(− 0.29, 0.48)				
	0.43 (0.18, 0.68)	− 0.06 (− 0.20, 0.08)	**0.40 (0.14, 0.65)**	− 0.18 (− 0.42, 0.06)	**− 0.78 (− 0.95, − 0.62)**
	Ertu15/Sita100	**− 0.49 (− 0.74, − 0.24)**	− 0.03 (− 0.32, 0.26)	**− 0.60 (− 0.93, − 0.29)**	**− 1.21 (− 1.48, − 0.95)**
		Ertu5	**0.46 (0.20, 0.71)**	− 0.12 (− 0.36, 0.12)	**− 0.72 (− 0.89, − 0.55)**
			Ertu5/Sita100	**− 0.57 (− 0.90, − 0.26)**	**− 1.18 (− 1.45, − 0.91)**
				Lina5	**− 0.60 (− 0.77, − 0.43)**
					PBO

Alo25	Saxa2.5	Saxa5	Sema14	Sita100	Vilda50bid
Alo25	0.07 (− 0.39, 0.52)	0.02 (− 0.39, 0.41)	0.49 (− 0.02, 0.99)	0.22 (− 0.17, 0.61)	0.01 (− 0.48, 0.49)
	− 0.09 (− 0.45, 0.27)	− 0.15 (− 0.43, 0.13)	0.33 (− 0.10, 0.75)	0.06 (− 0.17, 0.30)	− 0.15 (− 0.55, 0.25)
	− 0.24 (− 0.61, 0.13)	**− 0.30 (− 0.58, − 0.01)**	0.18 (− 0.25, 0.60)	− 0.09 (− 0.33, 0.15)	− 0.30 (− 0.70, 0.10)
	− 0.02 (− 0.32, 0.28)	− 0.07 (− 0.25, 0.11)	**0.40 (0.02, 0.78)**	0.13 (− 0.05, 0.32)	− 0.08 (− 0.43, 0.28)
	− 0.42 (− 0.74, − 0.09)	**− 0.47 (− 0.69, − 0.25)**	0.00 (− 0.40, 0.40)	**− 0.27 (− 0.47, − 0.05)**	**− 0.48 (− 0.86, − 0.10)**
	0.08 (− 0.23, 0.39)	0.02 (− 0.16, 0.21)	**0.50 (0.11, 0.89)**	**0.23 (0.02, 0.44)**	0.02 (− 0.35, 0.38)
	− 0.30 (− 0.68, 0.06)	**− 0.36 (− 0.62, − 0.09)**	0.12 (− 0.34, 0.56)	− 0.15 (− 0.46, 0.16)	− 0.36 (− 0.79, 0.06)
	0.00 (− 0.34, 0.35)	− 0.05 (− 0.32, 0.21)	**0.42 (0.08, 0.76)**	0.15 (− 0.09, 0.40)	− 0.06 (− 0.44, 0.33)
	− 0.44 (− 0.83, − 0.05)	**− 0.49 (− 0.81, − 0.17)**	− 0.02 (− 0.40, 0.36)	− 0.29 (− 0.59, 0.02)	**− 0.50 (− 0.92, − 0.07)**
	− 0.02 (− 0.36, 0.33)	− 0.07 (− 0.34, 0.19)	**0.40 (0.13, 0.67)**	0.13 (− 0.11, 0.39)	− 0.08 (− 0.46, 0.31)
	− 0.55 (− 0.94, − 0.15)	**− 0.60 (− 0.93, − 0.28)**	− 0.13 (− 0.51, 0.25)	**− 0.40 (− 0.71, − 0.08)**	**− 0.61 (− 1.03, − 0.18)**
	− 0.22 (− 0.54, 0.11)	**− 0.27 (− 0.50, − 0.04)**	0.20 (− 0.18, 0.59)	− 0.06 (− 0.24, 0.12)	− 0.28 (− 0.63, 0.08)
	− 0.64 (− 1.02, − 0.26)	**− 0.70 (− 1.01, − 0.39)**	− 0.22 (− 0.67, 0.21)	**− 0.49 (− 0.75, − 0.23)**	**− 0.70 (− 1.12, − 0.29)**
	− 0.15 (− 0.48, 0.17)	− 0.21 (− 0.43, 0.02)	0.27 (− 0.12, 0.65)	0.00 (− 0.18, 0.18)	− 0.21 (− 0.57, 0.15)
	− 0.61 (− 0.99, − 0.23)	**− 0.67 (− 0.97, − 0.36)**	− 0.19 (− 0.64, 0.25)	**− 0.46 (− 0.72, − 0.20)**	**− 0.67 (− 1.09, − 0.25)**
	− 0.04 (− 0.36, 0.29)	− 0.09 (− 0.32, 0.14)	**0.38 (0.03, 0.73)**	0.11 (− 0.10, 0.33)	− 0.10 (− 0.46, 0.27)
	0.57 (0.29, 0.84)	**0.51 (0.36, 0.67)**	**0.99 (0.64, 1.33)**	**0.72 (0.59, 0.85)**	**0.51 (0.19, 0.83)**
	Saxa2.5	− 0.05 (− 0.33, 0.22)	0.42 (− 0.02, 0.86)	0.15 (− 0.14, 0.45)	− 0.06 (− 0.48, 0.36)
		Saxa5	**0.47 (0.09, 0.85)**	**0.21 (0.01, 0.40)**	− 0.01 (− 0.36, 0.35)
			Sema14	− 0.27 (− 0.63, 0.11)	− 0.48 (− 0.95, 0.00)
				Sita100	− 0.21 (− 0.56, 0.13)

Alo25	Ertu15 /Sita100	Ertu5	Ertu5/Sita100	Lina5	PBO
	0.09 (− 0.29, 0.48)	**− 0.40 (− 0.72, − 0.06)**	0.06 (− 0.33, 0.46)	**− 0.51 (− 0.78, − 0.25)**	**− 1.12 (− 1.40, − 0.83)**
	0.43 (0.18, 0.68)	− 0.06 (− 0.20, 0.08)	**0.40 (0.14, 0.65)**	− 0.18 (− 0.42, 0.06)	**− 0.78 (− 0.95, − 0.62)**
	Ertu15/Sita100	**− 0.49 (− 0.74, − 0.24)**	− 0.03 (− 0.32, 0.26)	**− 0.60 (− 0.93, − 0.29)**	**− 1.21 (− 1.48, − 0.95)**
		Ertu5	**0.46 (0.20, 0.71)**	− 0.12 (− 0.36, 0.12)	**− 0.72 (− 0.89, − 0.55)**
			Ertu5/Sita100	**− 0.57 (− 0.90, − 0.26)**	**− 1.18 (− 1.45, − 0.91)**
				Lina5	**− 0.60 (− 0.77, − 0.43)**
					PBO

Alo25	Saxa2.5	Saxa5	Sema14	Sita100	Vilda50bid
Alo25	0.07 (− 0.39, 0.52)	0.02 (− 0.39, 0.41)	0.49 (− 0.02, 0.99)	0.22 (− 0.17, 0.61)	0.01 (− 0.48, 0.49)
	− 0.09 (− 0.45, 0.27)	− 0.15 (− 0.43, 0.13)	0.33 (− 0.10, 0.75)	0.06 (− 0.17, 0.30)	− 0.15 (− 0.55, 0.25)
	− 0.24 (− 0.61, 0.13)	**− 0.30 (− 0.58, − 0.01)**	0.18 (− 0.25, 0.60)	− 0.09 (− 0.33, 0.15)	− 0.30 (− 0.70, 0.10)
	− 0.02 (− 0.32, 0.28)	− 0.07 (− 0.25, 0.11)	**0.40 (0.02, 0.78)**	0.13 (− 0.05, 0.32)	− 0.08 (− 0.43, 0.28)
	− 0.42 (− 0.74, − 0.09)	**− 0.47 (− 0.69, − 0.25)**	0.00 (− 0.40, 0.40)	**− 0.27 (− 0.47, − 0.05)**	**− 0.48 (− 0.86, − 0.10)**
	0.08 (− 0.23, 0.39)	0.02 (− 0.16, 0.21)	**0.50 (0.11, 0.89)**	**0.23 (0.02, 0.44)**	0.02 (− 0.35, 0.38)
	− 0.30 (− 0.68, 0.06)	**− 0.36 (− 0.62, − 0.09)**	0.12 (− 0.34, 0.56)	− 0.15 (− 0.46, 0.16)	− 0.36 (− 0.79, 0.06)
	0.00 (− 0.34, 0.35)	− 0.05 (− 0.32, 0.21)	**0.42 (0.08, 0.76)**	0.15 (− 0.09, 0.40)	− 0.06 (− 0.44, 0.33)
	− 0.44 (− 0.83, − 0.05)	**− 0.49 (− 0.81, − 0.17)**	− 0.02 (− 0.40, 0.36)	− 0.29 (− 0.59, 0.02)	**− 0.50 (− 0.92, − 0.07)**
	− 0.02 (− 0.36, 0.33)	− 0.07 (− 0.34, 0.19)	**0.40 (0.13, 0.67)**	0.13 (− 0.11, 0.39)	− 0.08 (− 0.46, 0.31)
	− 0.55 (− 0.94, − 0.15)	**− 0.60 (− 0.93, − 0.28)**	− 0.13 (− 0.51, 0.25)	**− 0.40 (− 0.71, − 0.08)**	**− 0.61 (− 1.03, − 0.18)**
	− 0.22 (− 0.54, 0.11)	**− 0.27 (− 0.50, − 0.04)**	0.20 (− 0.18, 0.59)	− 0.06 (− 0.24, 0.12)	− 0.28 (− 0.63, 0.08)
	− 0.64 (− 1.02, − 0.26)	**− 0.70 (− 1.01, − 0.39)**	− 0.22 (− 0.67, 0.21)	**− 0.49 (− 0.75, − 0.23)**	**− 0.70 (− 1.12, − 0.29)**
	− 0.15 (− 0.48, 0.17)	− 0.21 (− 0.43, 0.02)	0.27 (− 0.12, 0.65)	0.00 (− 0.18, 0.18)	− 0.21 (− 0.57, 0.15)
	− 0.61 (− 0.99, − 0.23)	**− 0.67 (− 0.97, − 0.36)**	− 0.19 (− 0.64, 0.25)	**− 0.46 (− 0.72, − 0.20)**	**− 0.67 (− 1.09, − 0.25)**
	− 0.04 (− 0.36, 0.29)	− 0.09 (− 0.32, 0.14)	**0.38 (0.03, 0.73)**	0.11 (− 0.10, 0.33)	− 0.10 (− 0.46, 0.27)
	0.57 (0.29, 0.84)	**0.51 (0.36, 0.67)**	**0.99 (0.64, 1.33)**	**0.72 (0.59, 0.85)**	**0.51 (0.19, 0.83)**
	Saxa2.5	− 0.05 (− 0.33, 0.22)	0.42 (− 0.02, 0.86)	0.15 (− 0.14, 0.45)	− 0.06 (− 0.48, 0.36)
		Saxa5	**0.47 (0.09, 0.85)**	**0.21 (0.01, 0.40)**	− 0.01 (− 0.36, 0.35)
			Sema14	− 0.27 (− 0.63, 0.11)	− 0.48 (− 0.95, 0.00)
				Sita100	− 0.21 (− 0.56, 0.13)

Alo25	Saxa2.5	Saxa5	Sema14	Sita100	Vilda50bid
					Vilda50bid

The results presented in the table correspond to pairwise comparison of the treatment in the row vs. the treatment in the column. Posterior median of mean difference is presented with 95% credible interval. For difference in mean change from baseline, lower values (< 0) indicate more favorable results. For example, the mean difference for Alo25 vs. placebo is − 0.50, indicating Alo25 had a 0.50% greater reduction in HbA1c than placebo. Credible intervals not including 0 indicate statistically significant differences, which are highlighted in bold in the table

Alo alogliptin, *bid* twice a day, *Cana* canagliflozin, *Dapa* dapagliflozin, *Empa* empagliflozin, *Ertu* ertugliflozin, *Lina* linagliptin, *Lira* liraglutide, *N/A not applicable*, *Pbo* placebo, *Saxa* saxagliptin, *Sema* semaglutide, *Sita* sitagliptin, *Vilda* vildagliptin

Lautsch et al., 2021 [68].: Table 7

Supplementary Table 7. League table presenting pairwise treatment comparisons in odds ratio (95% CrI) for number of patients meeting HbA1c target (<7%)

Alo25	Cana100	Cana300	Dapa10	Dapa10/ Saxa5	Dapa5	Dapa5/ Saxa5	Empa10	Empa10/ Lina5	Empa25	Empa25/ Lina5	Ertu15	Ertu15/ Sita100	Ertu5	Ertu5/ Sita100	Lina5	PBO	Saxa2.5	Saxa5	Sema14	Sita100	Vilda50bid
Alo25	1.54 (0.64, 3.70)	0.94 (0.39, 2.24)	1.76 (0.76, 4.00)	0.57 (0.24, 1.35)	**3.15 (1.38, 7.22)**	1.05 (0.41, 2.64)	1.00 (0.41, 2.52)	**0.32 (0.11, 0.86)**	0.91 (0.37, 2.29)	**0.27 (0.10, 0.74)**	1.01 (0.44, 2.27)	0.48 (0.19, 1.16)	1.22 (0.53, 2.72)	0.42 (0.17, 1.03)	0.84 (0.35, 2.02)	**3.58 (1.72, 7.46)**	1.75 (0.69, 4.43)	1.76 (0.79, 3.94)	**0.30 (0.10, 0.86)**	0.97 (0.44, 2.10)	1.76 (0.66, 4.59)
	Cana100	0.61 (0.35, 1.04)	1.14 (0.60, 2.09)	**0.37 (0.19, 0.70)**	**2.04 (1.08, 3.90)**	0.68 (0.32, 1.45)	0.65 (0.31, 1.35)	**0.20 (0.09, 0.48)**	0.59 (0.28, 1.23)	**0.17 (0.07, 0.40)**	0.66 (0.36, 1.18)	**0.31 (0.15, 0.61)**	0.79 (0.43, 1.42)	**0.27 (0.13, 0.54)**	0.55 (0.27, 1.07)	**2.32 (1.38, 3.83)**	1.14 (0.52, 2.40)	1.14 (0.62, 2.06)	**0.20 (0.08, 0.49)**	0.63 (0.37, 1.02)	1.14 (0.49, 2.59)
		Cana300	1.87 (0.99, 3.50)	0.61 (0.31, 1.15)	**3.36 (1.78, 6.44)**	1.11 (0.52, 2.43)	1.07 (0.51, 2.23)	**0.34 (0.14, 0.79)**	0.97 (0.46, 2.04)	**0.28 (0.12, 0.67)**	1.08 (0.59, 1.94)	0.51 (0.25, 1.01)	1.30 (0.71, 2.34)	**0.45 (0.22, 0.90)**	0.90 (0.45, 1.76)	**3.82 (2.28, 6.36)**	1.88 (0.86, 3.97)	**1.88 (1.02, 3.40)**	**0.32 (0.13, 0.80)**	1.03 (0.62, 1.68)	1.86 (0.82, 4.25)
			Dapa10	**0.32 (0.20, 0.53)**	**1.79 (1.19, 2.78)**	0.59 (0.32, 1.12)	0.57 (0.30, 1.12)	**0.18 (0.08, 0.40)**	0.52 (0.27, 1.01)	**0.15 (0.07, 0.34)**	**0.58 (0.34, 0.98)**	**0.27 (0.14, 0.52)**	0.69 (0.41, 1.17)	**0.24 (0.12, 0.46)**	**0.48 (0.26, 0.87)**	**2.04 (1.39, 3.02)**	1.00 (0.52, 1.92)	1.00 (0.66, 1.53)	**0.17 (0.07, 0.41)**	**0.55 (0.35, 0.87)**	1.00 (0.47, 2.15)
				Dapa10/ Saxa5	**5.55 (3.25, 9.77)**	1.83 (0.94, 3.72)	1.75 (0.87, 3.63)	0.55 (0.24, 1.27)	1.61 (0.79, 3.29)	0.47 (0.20, 1.08)	**1.78 (1.01, 3.12)**	0.84 (0.42, 1.64)	**2.15 (1.22, 3.76)**	0.74 (0.37, 1.45)	1.48 (0.78, 2.86)	**6.30 (3.97,10.08)**	**3.10 (1.53, 6.18)**	**3.10 (1.92, 5.05)**	0.53 (0.22, 1.29)	**1.70 (1.07, 2.69)**	**3.08 (1.40, 6.94)**
					Dapa5	**0.33 (0.19, 0.56)**	**0.32 (0.16, 0.62)**	**0.10 (0.04, 0.22)**	**0.29 (0.15, 0.56)**	**0.08 (0.04, 0.19)**	**0.32 (0.18, 0.55)**	**0.15 (0.08, 0.29)**	**0.39 (0.22, 0.65)**	**0.13 (0.07, 0.26)**	**0.27 (0.14, 0.48)**	1.14 (0.75, 1.68)	0.56 (0.28, 1.05)	**0.56 (0.36, 0.83)**	**0.10 (0.04, 0.22)**	**0.31 (0.19, 0.49)**	0.56 (0.26, 1.18)
						Dapa5/ Saxa5	0.96 (0.43, 2.11)	**0.30 (0.12, 0.74)**	0.88 (0.40, 1.91)	**0.26 (0.10, 0.62)**	0.97 (0.48, 1.89)	**0.46 (0.20, 0.99)**	1.17 (0.58, 2.27)	**0.40 (0.18, 0.87)**	0.81 (0.38, 1.67)	**3.43 (1.90, 6.07)**	1.69 (0.77, 3.52)	1.69 (0.98, 2.84)	**0.29 (0.11, 0.74)**	0.93 (0.48, 1.72)	1.68 (0.70, 3.98)
							Empa10	**0.31 (0.17, 0.58)**	0.91 (0.58, 1.43)	**0.27 (0.14, 0.49)**	1.01 (0.52, 1.94)	0.47 (0.22, 1.00)	1.21 (0.63, 2.32)	**0.42 (0.19, 0.90)**	0.84 (0.49, 1.43)	**3.58 (2.09, 6.09)**	1.76 (0.79, 3.82)	1.75 (0.94, 3.30)	**0.30 (0.15, 0.61)**	0.97 (0.52, 1.77)	1.75 (0.76, 4.04)
								Empa10/ Lina5	**2.90 (1.57, 5.34)**	0.85 (0.43, 1.65)	**3.19 (1.46, 7.06)**	1.50 (0.62, 3.66)	**3.85 (1.74, 8.49)**	1.33 (0.55, 3.22)	**2.66 (1.42, 5.08)**	**11.32 (5.71,22.67)**	**5.58 (2.24,13.46)**	**5.57 (2.59,11.94)**	0.96 (0.42, 2.16)	**3.06 (1.44, 6.46)**	**5.54 (2.18,14.28)**
									Empa25	**0.29 (0.16, 0.54)**	1.10 (0.58, 2.11)	0.52 (0.24, 1.11)	1.33 (0.69, 2.54)	**0.46 (0.21, 0.99)**	0.92 (0.54, 1.56)	**3.91 (2.30, 6.66)**	1.92 (0.87, 4.17)	**1.92 (1.02, 3.59)**	**0.33 (0.19, 0.57)**	1.06 (0.57, 1.94)	1.92 (0.83, 4.43)
										Empa25/ Lina5	**3.79 (1.71, 8.31)**	1.77 (0.73, 4.30)	**4.56 (2.08,10.02)**	1.57 (0.65, 3.83)	**3.16 (1.66, 6.05)**	**13.43 (6.74,27.02)**	**6.60 (2.62,16.20)**	**6.60 (3.06,14.26)**	1.13 (0.50, 2.57)	**3.63 (1.70, 7.72)**	**6.57 (2.57,17.06)**
											Ertu15	**0.47 (0.28, 0.78)**	1.20 (0.90, 1.61)	**0.42 (0.25, 0.69)**	0.83 (0.46, 1.51)	**3.54 (2.45, 5.17)**	1.74 (0.88, 3.41)	**1.74 (1.06, 2.86)**	**0.30 (0.13, 0.70)**	0.96 (0.64, 1.41)	1.73 (0.83, 3.67)
												Ertu15/ Sita100	**2.56 (1.54, 4.26)**	0.89 (0.50, 1.56)	1.78 (0.87, 3.64)	**7.54 (4.38,13.04)**	**3.71 (1.66, 8.16)**	**3.70 (1.97, 6.98)**	0.64 (0.25, 1.63)	**2.04 (1.19, 3.44)**	**3.69 (1.60, 8.61)**
													Ertu5	**0.35 (0.21, 0.57)**	0.69 (0.38, 1.25)	**2.94 (2.04, 4.28)**	1.45 (0.73, 2.84)	1.44 (0.89, 2.38)	**0.25 (0.11, 0.58)**	0.80 (0.53, 1.18)	1.44 (0.69, 3.06)
														Ertu5/ Sita100	2.01 (0.97, 4.09)	**8.51 (4.94,14.89)**	**4.19 (1.88, 9.24)**	**4.18 (2.23, 7.95)**	0.72 (0.28, 1.86)	**2.30 (1.35, 3.92)**	**4.16 (1.80, 9.88)**
															Lina5	**4.24 (2.71, 6.74)**	2.08 (0.99, 4.33)	**2.08 (1.19, 3.71)**	**0.36 (0.17, 0.76)**	1.15 (0.66, 1.98)	2.08 (0.94, 4.58)
																PBO	**0.49 (0.27, 0.87)**	**0.49 (0.35, 0.69)**	**0.08 (0.04, 0.18)**	**0.27 (0.20, 0.36)**	**0.49 (0.26, 0.93)**
																	Saxa2.5	1.00 (0.58, 1.77)	**0.17 (0.07, 0.45)**	0.55 (0.29, 1.04)	1.00 (0.42, 2.43)
																		Saxa5	**0.17 (0.08, 0.39)**	**0.55 (0.36, 0.84)**	1.00 (0.48, 2.08)
																			Sema14	**3.20 (1.41, 7.19)**	**5.81 (2.15,15.64)**
																				Sita100	1.81 (0.89, 3.74)
																					Vilda50bid

Tsapas 2020 [102]. Pairwise meta-analysis results

Pairwise meta-analysis results for glucose-lowering drugs given as monotherapy in drug naïve patients.

Outcome/Comparison		Number of trials	Effect estimate MD/OR (95% CI)	Heterogeneity I^2 (%)
Change from baseline in HbA_{1c} (all patients)				
aGIs vs	Placebo	12	-0.80 (-0.98, -0.63)	63.7
	SU	4	0.30 (-0.17, 0.77)	82.5
Dapagliflozin vs	Placebo	3	-0.65 (-0.98, -0.32)	87.8
DPP-4i vs	Pioglitazone	4	0.34 (0.22, 0.45)	8.8
	Placebo	14	-0.54 (-0.62, -0.45)	42.4
	SU	2	0.08 (-0.08, 0.24)	0.0
Empagliflozin vs	DPP-4i	2	-0.20 (-0.31, -0.09)	0.0
Meglitinide vs	Placebo	2	-0.40 (-0.62, -0.19)	82.4
	SU	4	-0.19 (-0.41, 0.02)	65.0
Metformin vs	AGIs	4	-0.02 (-0.13, 0.09)	0.0
	Dapagliflozin	3	0.08 (-0.23, 0.38)	74.4
	DPP-4i	12	-0.28 (-0.40, -0.15)	79.9
	Liraglutide	2	0.37 (-0.79, 1.54)	68.0
	Pioglitazone	8	-0.04 (-0.13, 0.06)	26.2
	Placebo	7	-1.22 (-1.98, -0.45)	98.0
	SU	10	0.04 (-0.06, 0.15)	0.0
Pioglitazone vs	SU	7	0.04 (-0.17, 0.25)	35.7
SU vs	Placebo	2	-0.81 (-1.01, -0.60)	55.2
All-cause mortality (patients at low cardiovascular risk)				
aGIs vs.	Placebo	13	1.08 (0.36, 3.25)	0.0
	SU	6	1.00 (0.20, 5.01)	0.0
Dapagliflozin vs	Placebo	3	1.00 (0.09, 10.55)	0.0
DPP-4i vs	Pioglitazone	4	0.79 (0.11, 5.47)	0.0
	Placebo	13	1.00 (0.36, 2.75)	0.0
Empagliflozin vs	DPP-4i	2	1.30 (0.22, 7.78)	46.1
Meglitinide vs	Placebo	2	1.00 (0.06, 17.77)	0.0
	SU	4	1.00 (0.14, 7.20)	0.0
Metformin vs	AGIs	4	1.00 (0.14, 7.18)	0.0
	Dapagliflozin	3	0.77 (0.14, 4.39)	0.0
	DPP-4i	13	1.36 (0.62, 2.98)	0.0
	Liraglutide	2	1.00 (0.06, 16.36)	0.0
	Pioglitazone	8	0.97 (0.32, 2.91)	0.0
	Placebo	6	1.00 (0.20, 5.10)	0.0
	SU	9	0.99 (0.62, 1.59)	0.0
Pioglitazone vs	SU	8	0.66 (0.18, 2.37)	0.0
SU vs	Placebo	3	1.00 (0.10, 10.13)	0.0

Cardiovascular mortality (patients at low cardiovascular risk)				
aGIs vs.	Placebo	13	1.08 (0.36, 3.25)	0.0
	SU	6	1.00 (0.20, 5.01)	0.0
Dapagliflozin vs	Placebo	3	1.00 (0.09 , 10.55)	0.0
DPP-4i vs	Pioglitazone	4	1.00 (0.13, 7.6)	0.0
	Placebo	12	1.18 (0.38, 3.70)	0.0
Meglitinide	Placebo	2	1.00 (0.06, 17.77)	0.0
	SU	4	1.00 (0.14, 7.20)	0.0
Metformin	AGIs	4	1.00 (0.14, 7.18)	0.0
	Dapagliflozin	2	1.02 (0.14, 7.20)	0.0
	DPP-4i	12	1.08 (0.38, 3.09)	0.0
	Liraglutide	2	1.00 (0.06, 16.36)	0.0
	Pioglitazone	7	1.00 (0.22, 4.45)	0.0
	Placebo	6	1.00 (0.20, 5.10)	0.0
	SU	8	1.00 (0.25, 4.04)	0.0
Pioglitazone vs	SU	8	0.80 (0.21, 3.00)	0.0
SU vs	Placebo	3	1.00 (0.10, 10.13)	0.0
Hospitalization for heart failure (patients at low cardiovascular risk)				
Metformin vs	DPP-4i	3	1.00 (0.10, 10.13)	0.0
Myocardial infarction (patients at low cardiovascular risk)				
Metformin vs	DPP-4i	10	1.67 (0.66, 4.19)	0.0
DPP-4i vs	Pioglitazone	3	0.72 (0.14, 3.77)	0.0
	Placebo	3	1.27 (0.23, 6.93)	0.0
Metformin vs	Dapagliflozin	3	0.63 (0.12, 3.28)	0.0
	Pioglitazone	4	0.47 (0.09, 2.49)	0.0
	SU	3	1.26 (0.69, 2.30)	0.0
Pioglitazone vs	SU	3	1.00 (0.20, 5.00)	0.0
Diabetic retinopathy (patients at low cardiovascular risk)				
Metformin vs	DPP-4i	2	1.00 (0.062, 16.27)	0.0
Severe hypoglycemia (all patients)				
aGIs vs.	Placebo	5	1.00 (0.16, 6.23)	0.0
Dapagliflozin	Placebo	2	1.00 (0.06, 17.41)	0.0
Metformin vs	DPP-4i	11	1.00 (0.36, 2.81)	0.0
DPP-4i vs	Pioglitazone	4	1.00 (0.13, 7.6)	0.0
	Placebo	9	1.00 (0.26, 3.89)	0.0
Empagliflozin vs	DPP-4i	2	1.75 (0.11, 26.73)	0.0
Meglitinide vs	Placebo	2	1.00 (0.06, 17.77)	0.0
	AGIs	3	1.00 (0.10, 9.70)	0.0
Metformin vs	Dapagliflozin	3	1.00 (0.10, 9.95)	0.0
	Pioglitazone	3	1.00 (0.10, 9.88)	0.0
	Placebo	3	2.08 (0.28, 15.64)	0.0
	SU	5	0.31 (0.10, 1.02)	0.0
SU vs	Placebo	2	3.52 (0.36, 34.67)	0.0

Stroke				
Dapagliflozin vs	Placebo	2	1.31 (0.22, 7.82)	46.5
Metformin vs	DPP-4i	7	1.26 (0.38, 4.22)	0.0
DPP-4i vs	Placebo	3	0.86 (0.13, 5.52)	0.0

Treatment estimates are mean differences (MDs) and 95% confidence intervals (CIs) for change in glycated hemoglobin (HbA_{1c}) and odds ratios (ORs) and 95% CIs for the remaining outcomes. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. ER=extended release. po=per os. sc=subcutaneous.SU=sulphonylureas.

Pairwise meta-analysis results for glucose-lowering drugs given as add-on to metformin-based therapy.

Outcome/Comparison		Number of trials	Effect estimate MD/OR (95% CI)	Heterogeneity I^2 (%)
Glycemic outcomes				
Change from baseline in HbA_{1c}				
aGIs vs.	DPP-4i	2	0.09 (0.00, 0.19)	0.0
	Pioglitazone	2	0.29 (-0.20, 0.77)	83.0
	Placebo	8	-0.59 (-0.74, -0.45)	0.0
Basal insulin vs	DPP-4i	5	0.01 (-0.68, 0.70)	94.5
	Pioglitazone	3	-0.59 (-0.95, -0.23)	0.0
	Placebo	6	-0.75 (-0.88, -0.62)	69.3
	Prandial insulin	3	0.13 (-0.00, 0.26)	0.0
	Premixed insulin	8	0.14 (0.08, 0.20)	0.0
Basal bolus insulin vs	Premixed insulin	8	0.01 (-0.14, 0.16)	61.3
Canagliflozin vs	DPP-4i	2	-0.22 (-0.51, 0.08)	90.3
	Placebo	8	-0.56 (-0.77, -0.36)	95.1
Dapagliflozin vs	DPP-4i	4	-0.07 (-0.34, 0.20)	63.1
	Placebo	15	-0.49 (-0.61, -0.37)	89.0
	SU	2	-0.06 (-0.52, 0.40)	92.3

DPP-4i vs	Pioglitazone	7	0.03 (-0.17, 0.24)	85.4
	Placebo	68	-0.55 (-0.61, -0.47)	93.9
	SU	18	0.04 (-0.12, 0.20)	97.7
Dulaglutide vs	Placebo	5	-0.73 (-0.86, -0.61)	65.8
	Basal insulin	3	-0.25 (-0.36 to -0.13)	14.9
Empagliflozin vs	DPP-4i vs	2	-0.17 (-0.38, 0.03)	0.0
	Placebo	10	-0.55 (-0.66, -0.45)	71.9
Ertugliflozin vs	Placebo	4	-0.57 (-0.83, -0.31)	86.9
Exenatide vs	Basal insulin	3	0.05 (-0.09, 0.18)	0.0
	Placebo	11	-0.68 (-0.87, -0.49)	75.2
	Prandial insulin	3	-0.02 (-0.14, 0.09)	0.0
	Premixed insulin	2	0.44 (-0.20, 1.09)	89.2
	SU	3	0.16 (-0.24, 0.56)	90.6
Exenatide ER vs	Basal insulin	2	-0.30 (-0.52, -0.09)	53.9
	DPP-4i	2	-0.52 (-0.77, -0.28)	22.3
	Placebo	3	-0.66 (-0.82, -0.50)	0.0
Liraglutide vs	Basal insulin	4	0.03 (-0.18, 0.23)	71.7
	DPP-4i	6	-0.39 (-0.61, -0.17)	85.9
	Placebo	20	-0.75 (-0.90, -0.60)	90.1
	Prandial insulin	3	-0.21 (-0.54, 0.11)	75.1
	SU	2	-0.19 (-0.41, 0.04)	64.3
Lixisenatide vs	Placebo	11	-0.44 (-0.55, -0.33)	70.2
Meglitinide vs	Placebo	2	-0.60 (-1.02, -0.18)	74.1
	SU	5	-0.07 (-0.33, 0.18)	92.9
Pioglitazone vs	Placebo	12	-0.65 (-0.84, -0.46)	90.8
	SU	14	-0.08 (-0.21, 0.06)	74.6
Semaglutide po vs	DPP-4i	2	-0.36 (-0.54, -0.18)	39.0
	Placebo	4	-0.84 (-1.02, -0.66)	77.3
Semaglutide sc vs	Placebo	4	-1.34 (-1.76, -0.93)	95.4
SU vs	Placebo	8	-0.66 (-1.04, -0.29)	92.9

Severe hypoglycemia				
aGIs vs.	DPP-4i	2	1.00 (0.06, 16.13)	0.0
	Placebo	6	1.33 (0.30, 6.01)	0.0
Basal insulin vs	DPP-4i	3	2.16 (0.40, 11.81)	0.0
	Pioglitazone	2	1.00 (0.06, 16.74)	0.0
	Placebo	6	1.59 (0.35 , 7.24)	0.0
	Premixed insulin	8	0.75 (0.47, 1.20)	0.0
Basal bolus insulin vs	Premixed insulin	8	1.12 (0.79, 1.60)	0.0
Canagliflozin vs	DPP-4i	3	1.12 (0.55, 2.31)	0.0
	Placebo	5	1.05 (0.65, 1.68)	0.0
Dapagliflozin vs	DPP-4i	2	1.00 (0.06, 16.25)	0.0
	Placebo	10	0.72 (0.53, 1.00)	0.0
	SU	2	0.25 (0.03, 2.24)	0.0
DPP-4i vs	Pioglitazone	6	1.52 (0.43, 5.41)	0.0
	Placebo	57	1.07 (0.95, 1.22)	0.0
	SU	17	0.15 (0.09, 0.23)	0.0
Dulaglutide vs	Basal insulin	3	0.56 (0.29, 1.08)	0.0
	Placebo	5	0.89 (0.64, 1.24)	0.0
Empagliflozin vs	Placebo	9	0.89 (0.61, 1.30)	0.0
Ertugliflozin vs	Placebo	4	1.00 (0.21, 4.83)	0.0
Exenatide vs	Basal insulin	2	0.87 (0.35, 2.17)	0.0
	Placebo	9	1.50 (0.42, 5.41)	0.0
	Prandial insulin	3	0.37 (0.10, 1.39)	0.0
	Premixed insulin	2	0.12 (0.01, 1.23)	21.0
Exenatide ER vs	Basal insulin	2	1.00 (0.06, 16.08)	0.0
	DPP-4i	2	1.00 (0.06, 16.50)	0.0
	Placebo	4	1.13 (0.94, 1.36)	0.0
Liraglutide vs	Basal insulin	4	3.03 (0.90, 10.17)	0.0
	DPP-4i	6	1.20 (0.28, 5.10)	0.0
	Placebo	14	0.78 (0.61, 0.98)	0.0
	Prandial insulin	3	0.70 (0.21, 2.34)	0.0
Lixisenatide vs	Placebo	12	0.89 (0.54, 1.49)	0.0
Meglitinide vs	Placebo	3	1.00 (0.10, 10.15)	0.0
	SU	2	0.26 (0.02, 2.68)	0.0
Pioglitazone vs	Placebo	6	1.96 (1.00, 3.84)	0.0
	SU	5	0.11 (0.03, 0.37)	30.8
Semaglutide po vs	Placebo	2	1.75 (0.89, 3.43)	0.0
Semaglutide sc vs	Placebo	4	1.08 (0.91, 1.27)	0.0
SU vs	Placebo	7	2.42 (0.72, 8.17)	0.0

Mortality and vascular endpoints in patients at increased cardiovascular risk				
All-cause mortality				
Canagliflozin vs	Placebo	2	0.98 (0.86, 1.11)	74.3
Dapagliflozin vs	Placebo	2	0.89 (0.80, 0.99)	47.8
Empagliflozin vs	Placebo	2	0.67 (0.55, 0.81)	0.0
DPP-4i vs	Placebo	4	1.02 (0.94, 1.09)	13.8
Semaglutide po vs	Placebo	2	0.50 (0.31, 0.83)	0.0
Cardiovascular mortality				
Canagliflozin vs	Placebo	2	0.96 (0.83, 1.12)	77.0
Dapagliflozin vs	Placebo	2	0.91 (0.79, 1.06)	49.6
Empagliflozin vs	Placebo	2	0.61 (0.49, 0.77)	0.0
DPP-4i vs	Placebo	4	0.99 (0.91, 1.08)	0.0
Semaglutide po vs	Placebo	2	0.51 (0.28, 0.94)	0.0
Amputation				
Canagliflozin vs	Placebo	2	1.65 (1.30, 2.08)	88.2
Dapagliflozin vs	Placebo	2	1.11 (0.86,1.42)	0.0
Hospitalization for heart failure				
Canagliflozin vs	Placebo	2	0.72 (0.60, 0.86)	58.2
Dapagliflozin vs	Placebo	2	0.74 (0.64, 0.86)	0.0
DPP-4i vs	Placebo	4	1.06 (0.96, 1.18)	53.5
Semaglutide po vs	Placebo	2	0.84 (0.47, 1.50)	0.0
Myocardial infarction				
Canagliflozin vs	Placebo	2	0.96 (0.81, 1.14)	0.0
Empagliflozin vs	Placebo	2	0.92 (0.74, 1.13)	0.0
DPP-4i vs	Placebo	4	1.01 (0.92, 1.10)	0.0
Semaglutide po vs	Placebo	2	1.12 (0.71, 1.76)	0.0
Diabetic retinopathy				
DPP-4i vs	Placebo	4	1.19 (0.99, 1.43)	62.1
Semaglutide po vs	Placebo	2	1.23 (0.91, 1.68)	0.0
Stroke				
Canagliflozin vs	Placebo	2	0.93 (0.76, 1.13)	45.4
Empagliflozin vs	Placebo	2	1.19 (0.89, 1.58)	0.0
DPP-4i vs	Placebo	4	0.99 (0.87, 1.13)	0.0
Semaglutide po vs	Placebo	2	0.78 (0.38, 1.56)	0.0

Mortality and vascular endpoints in patients at low cardiovascular risk				
All-cause mortality				
aGIs vs.	DPP-4i	2	1.00 (0.06, 16.13)	0.0
	Pioglitazone	2	1.00 (0.06, 16.20)	0.0
	Placebo	9	1.00 (0.27, 3.72)	0.0
Basal insulin vs	DPP-4i	5	0.53 (0.11, 2.60)	0.0
	Pioglitazone	3	1.00 (0.10, 9.98)	0.0
	Placebo	6	0.78 (0.20, 3.01)	0.0
	Prandial insulin	3	0.36 (0.11, 1.15)	0.0
	Premixed insulin	8	0.62 (0.31, 1.23)	0.0
Basal bolus insulin vs	Premixed insulin	8	1.68 (0.60, 4.65)	0.0
Canagliflozin vs	DPP-4i	3	1.18 (0.27, 5.22)	0.0
	Placebo	5	1.00 (0.23, 4.27)	0.0
Dapagliflozin vs	DPP-4i	2	3.02 (0.31, 29.09)	0.0
	Placebo	14	1.44 (0.66, 3.15)	0.0
	SU	2	0.45 (0.10, 2.03)	0.0
DPP-4i vs	Pioglitazone	7	0.91 (0.28, 2.96)	0.0
	Placebo	66	0.77 (0.53, 1.12)	0.0
	SU	19	0.76 (0.47, 1.22)	0.0
Dulaglutide vs	Basal insulin	3	0.43 (0.12, 1.50)	0.0
	Placebo	4	1.40 (0.29, 6.73)	0.0
Empagliflozin vs	Placebo	8	1.35 (0.45, 4.08)	0.0
Ertugliflozin vs	Placebo	4	0.76 (0.21, 2.69)	0.0
Exenatide vs	Basal insulin	2	1.00 (0.06, 16.33)	0.0
	Placebo	10	1.00 (0.27, 3.68)	0.0
	Prandial insulin	2	2.00 (0.18, 22.57)	0.0
	Premixed insulin	2	0.59 (0.04, 7.91)	0.0
	SU	3	1.00 (0.32, 3.10)	0.0
Exenatide ER vs	Basal insulin	2	0.97 (0.10, 9.38)	0.0
	DPP-4i	2	0.50 (0.05, 5.51)	0.0
	Placebo	3	1.00 (0.24, 4.13)	0.0
Liraglutide vs	Basal insulin	4	1.00 (0.14, 7.14)	0.0
	DPP-4i	6	0.67 (0.19, 2.33)	0.0
	Placebo	20	0.86 (0.43, 1.72)	0.0
	Prandial insulin	3	1.00 (0.10, 9.68)	0.0
Lixisenatide vs	Placebo	11	0.55 (0.26, 1.18)	0.0
Meglitinide vs	Placebo	3	1.13 (0.20, 6.45)	0.0
	SU	4	1.53 (0.31, 7.50)	0.0
Pioglitazone vs	Placebo	12	1.12 (0.42, 3.00)	0.0

	SU	11	0.64 (0.22, 1.89)	0.0
Semaglutide po vs	DPP-4i	2	0.49 (0.13, 1.76)	0.0
	Placebo	2	2.52 (0.39, 16.21)	0.0
Semaglutide sc vs	Placebo	3	1.00 (0.10, 10.08)	0.0
SU vs	Placebo	8	0.70 (0.22, 2.18)	0.0
Cardiovascular mortality				
aGIs vs.	DPP-4i	2	1.00 (0.06, 16.13)	0.0
	Pioglitazone	2	1.00 (0.06, 16.20)	0.0
	Placebo	9	1.00 (0.27, 3.72)	0.0
Basal insulin vs	DPP-4i	4	1.00 (0.13, 7.49)	0.0
	Pioglitazone	3	1.00 (0.10, 9.98)	0.0
	Placebo	6	1.00 (0.24, 4.21)	0.0
	Prandial insulin	2	0.16 (0.03, 0.88)	0.0
	Premixed insulin	6	0.83 (0.36, 1.93)	0.0
Basal bolus insulin vs	Premixed insulin	8	1.34 (0.46, 3.88)	0.0
Canagliflozin vs	DPP-4i	2	3.13 (0.29, 33.70)	0.0
	Placebo	5	1.00 (0.23, 4.27)	0.0
Dapagliflozin vs	Placebo	10	0.84 (0.27, 2.65)	0.0
	SU	2	0.25 (0.03, 2.24)	0.0
DPP-4i vs	Pioglitazone	7	1.13 (0.29, 4.43)	0.0
	Placebo	59	0.87 (0.56, 1.35)	0.0
	SU	17	0.69 (0.36, 1.33)	0.0
Dulaglutide vs	Basal insulin	2	0.24 (0.04, 1.58)	0.0
	Placebo	4	1.23 (0.16, 9.23)	0.0
Empagliflozin vs	Placebo	7	1.50 (0.40, 5.55)	0.0
Ertugliflozin vs	Placebo	4	0.67 (1.15, 3.01)	0.0
Exenatide vs	Basal insulin	2	1.00 (0.06, 16.33)	0.0
	Placebo	10	1.00 (0.27, 3.68)	0.0
	Prandial insulin	2	2.00 (0.18, 22.57)	0.0
	Premixed insulin	2	0.59 (0.04, 7.91)	0.0
	SU	2	1.00 (0.06, 16.18)	0.0
Exenatide ER vs	DPP-4i	2	1.00 (0.06, 16.50)	0.0
	Placebo	3	1.00 (0.13, 7.63)	0.0
Liraglutide vs	Basal insulin	4	1.00 (0.14, 7.14)	0.0
	DPP-4i	5	0.47 (0.10, 2.15)	0.0
	Placebo	20	0.84 (0.39, 1.79)	0.0
	Prandial insulin	3	1.00 (0.10, 9.68)	0.0
Lixisenatide vs	Placebo	11	0.71 (0.28, 1.80)	0.0
Meglitinide vs	Placebo	3	1.13 (0.20, 6.45)	0.0
	SU	3	1.00 (0.10, 10.08)	0.0

Pioglitazone vs	Placebo	12	1.09 (0.37, 3.15)	0.0
	SU	11	1.00 (0.30, 3.28)	0.0
Semaglutide po vs	DPP-4i	2	0.54 (0.08, 3.57)	7.1
Semaglutide sc vs	Placebo	3	1.00 (0.10, 10.08)	0.0
SU vs	Placebo	8	0.80 (0.21, 2.99)	0.0
Amputation				
Basal insulin vs	DPP-4i	2	0.48 (0.04, 5.38)	0.0
DPP-4i vs	Placebo	2	0.59 (0.08, 4.49)	0.0
	SU	2	1.71 (0.13, 23.08)	0.0
Empagliflozin vs	Placebo	3	1.00 (0.09, 11.10)	0.0
Ertugliflozin vs	Placebo	2	3.27 (0.25, 42.75)	0.0
Liraglutide vs	Placebo	2	1.00 (0.06, 17.93)	0.0
Hospitalization for heart failure				
Basal insulin vs	DPP-4i	2	1.98 (0.17, 22.49)	0.0
DPP-4i vs	Placebo	8	0.81 (0.23, 2.87)	0.0
	SU	3	0.60 (0.08, 4.54)	0.0
Liraglutide vs	Basal insulin	2	0.50 (0.04, 5.54)	0.0
	Placebo	6	0.84 (0.21, 3.44)	0.0
Pioglitazone vs	SU	2	2.00 (0.18, 22.48)	0.0
Semaglutide po vs	DPP4i	2	0.21 (0.03, 1.35)	0.0
Myocardial infarction				
Basal insulin vs	DPP-4i	2	0.51 (0.04, 5.90)	0.0
	Placebo	2	1.00 (0.06, 17.41)	0.0
	Premixed insulin	5	0.57 (0.26, 1.28)	53.2
Basal bolus insulin vs	Premixed insulin	6	1.16 (0.40, 3.33)	0.0
Canagliflozin vs	DPP-4i	2	0.37 (0.05, 2.59)	0.0
	Placebo	2	0.65 (0.18, 2.28)	0.0
Dapagliflozin vs	DPP-4i	3	1.00 (0.17, 5.78)	0.0
	Placebo	10	0.51 (0.21, 1.24)	0.0
	SU	2	0.33 (0.05, 2.12)	0.0
DPP-4i vs	Pioglitazone	2	0.47 (0.06, 3.81)	0.0
	Placebo	37	0.92 (0.60, 1.40)	0.0
	SU	11	0.74 (0.47, 1.16)	22.7
Dulaglutide vs	Basal insulin	3	0.44 (0.14, 1.38)	6.1
	Placebo	3	0.78 (0.18, 3.38)	24.1
Empagliflozin vs	Placebo	6	1.00 (0.35, 2.83)	0.0
Ertugliflozin vs	Placebo	3	0.82 (0.28, 2.42)	0.0
Exenatide ER vs	Placebo	3	0.23 (0.04, 1.37)	0.0
Liraglutide vs	Basal insulin	2	1.00 (0.10, 9.70)	0.0
	DPP-4i	3	1.13 (0.20, 6.43)	0.0

	Placebo	9	1.30 (0.58, 2.93)	0.0
	Prandial insulin	2	0.50 (0.05, 5.53)	0.0
Lixisenatide vs	Placebo	9	0.64 (0.31, 1.32)	0.0
Meglitinide vs	SU	2	0.22 (0.02, 2.24)	0.0
Pioglitazone vs	Placebo	4	1.10 (0.20, 5.89)	0.0
SU vs	Placebo	6	0.87 (0.31, 2.39)	0.0
Diabetic retinopathy				
Basal insulin vs	Placebo	2	0.68 (0.17, 2.83)	0.0
DPP-4i vs	Placebo	7	1.75 (0.67, 4.59)	0.0
	SU	2	0.51 (0.21, 1.26)	0.0
Empagliflozin vs	Placebo	3	1.50 (0.15, 14.54)	0.0
Liraglutide vs	Basal insulin	2	0.56 (0.12, 2.63)	0.0
	DPP-4i	2	1.71 (0.13, 23.36)	0.0
	Placebo	5	0.89 (0.49, 1.64)	0.0
Semaglutide po vs	DPP-4i	2	0.70 (0.44, 1.11)	0.0
Semaglutide sc vs	Placebo	2	0.80 (0.29, 2.21)	68.1
Stroke				
Basal insulin vs	Placebo	4	0.60 (0.13, 2.76)	0.0
	Premixed insulin	7	0.70 (0.27, 1.84)	0.0
Dapagliflozin vs	DPP-4i	2	3.01 (0.31, 29.02)	0.0
	Placebo	4	0.91 (0.21, 3.92)	0.0
	SU	2	3.01 (0.31, 28.99)	0.0
DPP-4i vs	Pioglitazone	4	0.76 (0.18, 3.14)	0.0
	Placebo	29	0.84 (0.50, 1.44)	0.0
	SU	10	0.45 (0.22, 0.91)	0.0
Dulaglutide vs	Basal insulin	3	0.86 (0.25, 2.94)	0.0
	Placebo	2	2.07 (0.17, 25.56)	0.0
Empagliflozin vs	Placebo	5	1.84 (0.51, 6.68)	0.0
Ertugliflozin vs	Placebo	3	0.79 (0.15, 4.10)	0.0
Exenatide ER vs	Placebo	2	1.38 (0.15, 12.86)	0.0
Liraglutide vs	Basal insulin	3	0.60 (0.08, 4.57)	0.0
	DPP-4i	2	0.50 (0.04, 5.61)	0.0
	Placebo	7	0.95 (0.32, 2.81)	0.0
Lixisenatide vs	Placebo	5	0.76 (0.27, 2.16)	0.0
Pioglitazone vs	Placebo	4	1.26 (0.25, 6.51)	0.0
Semaglutide sc vs	Placebo	2	1.71 (0.13, 23.18)	0.0

Treatment estimates are mean differences (MDs) and 95% confidence intervals (CIs) for change in glycated hemoglobin (HbA_{1c}) and odds ratios (ORs) and 95% CIs for the remaining outcomes. aGIs=alpha-glucosidase inhibitors. DPP-4i=dipeptidyl peptidase 4 inhibitors. ER=extended release. po=per os. sc=subcutaneous. SU=sulphonylureas.

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2021-B-428

Kontaktdaten

Deutsche Diabetes Gesellschaft (DDG)

Deutsche Gesellschaft für Endokrinologie

Indikation

Behandlung des unzureichend kontrollierten Diabetes mellitus Typ 2 bei Erwachsenen als Zusatz zu Diät und körperlicher Aktivität

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Der Behandlungsstandard ist in der aktuellen, im März 2021 veröffentlichten 2. Auflage der Nationalen Versorgungs-Leitlinie (NVL) zur Behandlung des Typ 2 Diabetes (T2D) festgelegt (1). Die Empfehlungen in der NVL sind aufgrund der Evidenzlage ähnlich den internationalen Empfehlungen der amerikanischen- und europäischen Diabetesgesellschaften (ADA und EASD) und der Europäischen Gesellschaft für Kardiologie (ESC) und unter den beteiligten deutschen Fachgesellschaften und der ÄZQ konsentiert (2-4). Auch die Praxisempfehlungen der Deutschen Diabetes Gesellschaft (DDG) sind mit der NVL im Einklang.

Die 2. Auflage NVL Diabetes, die sich ganz wesentlich von der 1. Auflage durch neue Evidenzlage bezüglich kardiovaskulärer und kardiorenaler Parameter bei der Behandlung des T2D unterscheidet, stellt die partizipative Entscheidungsfindung (PEF) in den Vordergrund und gibt Hinweise auf Kriterien die bei der Entscheidungsfindung zu Therapiezielen eine Rolle spielen können. Erstmals wurden in den o.g. Leitlinien daher unterschiedliche Patientenkollektive mit T2D in Abhängigkeit ihres kardiovaskulären- und kardiorenalen Risikos aufgeführt, für die unterschiedliche Therapiealgorithmen (s.u.) nach der Einleitung einer Standardtherapie mit Metformin empfohlen werden (1).

Durch eine bessere medizinische Versorgung der Menschen mit Diabetes hat die Sterblichkeit durch Diabetes in den letzten Dekaden abgenommen. Nach wie vor haben Menschen mit Diabetes jedoch ein zwei- bis dreifach erhöhtes Risiko für einen frühzeitigeren Tod bei einer durchschnittlich vier bis sechs Jahre kürzeren Lebenserwartung im Vergleich zur gleichaltrigen, nicht an Diabetes erkrankten Bevölkerung. Bei allen Todesfällen in Deutschland sind 16 Prozent mit einem Typ-2-Diabetesassoziiert, Folge- und Begleiterkrankungen, vor allem diabetesbedingte kardiovaskuläre Erkrankungen sind die Ursache hierfür (5).

Unverändert wird in den o.g. Leitlinien nach Implementierung und Fortsetzung nicht-medikamentöser Maßnahmen (Kontrolle des Körpergewichtes, körperliche Aktivität, kein Nikotinkonsum) Metformin als erste medikamentöse Therapie empfohlen. Schätzungsweise 75% der Menschen mit der Diagnose eines T2D sind in das Disease Management Programm (DMP) Diabetes eingeschrieben und erhalten im Rahmen dieses Programms Metformin und die im Rahmen des DMP vorgesehenen Monitoringintervalle für Kontrolluntersuchungen. Für die glykämischen Behandlungsziele ist ein individueller Zielkorridor für den HbA1c-Wert in der NVL beschrieben.

Im Unterschied zu den o.g. Leitlinien der Diabetesgesellschaften und der NVL schlagen die ESC Guidelines zur Behandlung von Patienten mit Diabetes oder Prä-Diabetes und einem hohen oder sehr hohen kardiovaskulären Risiko nicht Metformin als Erstlinienmedikation vor, sondern direkt die Gabe eines SGLT-2-Inhibitors (SGLT-2i) oder eines GLP-1-Rezeptoragonisten (GLP-1RA) mit nachgewiesenem kardiovaskulärem Nutzen (4). Metformin wird dann

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in der nächsten Therapieeskalationsstufe empfohlen, wenn mit einer der beiden erstgenannten Substanzen das HbA1c-Ziel nicht erreicht wird. Die Empfehlungen der ESC basieren darauf, dass die kardioprotektiven Wirkungen von manchen SGLT-2i und GLP-1-RA auf einem wesentlich solideren Studienmaterial beruhen als für Metformin.

1. *https://www.leitlinien.de/nvl/diabetes Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF). Nationale VersorgungsLeitlinie Typ-2-Diabetes – Teilpublikation der Langfassung, 2. Auflage. Version 1. 2021 [cited: 2021-05-17]. DOI: 10.6101/AZQ/000475*
2. *Davies MJ, et al. Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2018; 61(12): 2461-2498. doi: 10.1007/s00125-018-4729-5*
3. *American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes—2021. Diabetes Care 2021; 44(Suppl 1): S111-S124. https://doi.org/10.2337/dc21-S009*
4. *Cosentino F, et al, ESC Scientific Document Group. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 20207; 41(2): 255-323. doi: 10.1093/eurheartj/ehz486*
5. *Jacobs E, et al. Burden of Mortality Attributable to Diagnosed Diabetes: A Nationwide Analysis Based on Claims Data from 65 Million People in Germany. Diabetes Care 2017; 40(12): 1703-1709. https://doi.org/10.2337/dc17-0954*

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von Erwachsenen mit unzureichend kontrollierten Diabetes mellitus Typ 2, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Nach den oben zitierten Leitlinien sollen Menschen mit klinisch relevanter kardiovaskulärer- oder kardiorenaler Vorerkrankung zusätzlich zur Metformintherapie entweder einen SGLT-1i oder einen GLP-1RA erhalten, der in einer RCT einen entsprechenden Vorteil gezeigt hat (1-4, 6-13). Diese Therapieempfehlung gilt nach Auffassung der Diabetesgesellschaften der ESC und der Kidney Disease Improving Global Outcomes (KDIGO) Diabetes Work Group unabhängig vom vorliegenden HbA1c-Wert (1-4, 14). Bei bestehender Herzinsuffizienz oder chronischer Nierenerkrankung (CKD) sollte ein SGLT-2i bevorzugt gegeben werden, bei einer atherosklerotischen Herz- und Gefäßerkrankung (ASCVD) sollte ein GLP-1RA gewählt werden (1-4). Bezüglich Menschen mit T2D und CKD sei zusätzlich auf die entsprechende Abfrage "Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6 2021-B-013" hingewiesen. In Deutschland sind als SGLT-2i mit Überlegenheitsdaten aus kardiovaskulären Sicherheitsstudien Dapagliflozin und Empagliflozin verfügbar. Beide haben vom G-BA einen Zusatznutzen in bestimmten Indikationen bei Menschen mit T2D und kardiovaskulärer Vorerkrankung in der Nutzenbewertung erhalten (15,16).

Als GLP-1RA mit kardiovaskulären Vorteilen in RCTs sind in Deutschland Dulaglutid, Liraglutid und Semaglutid verfügbar. Dulaglutid hat vom G-BA einen Zusatznutzen in bestimmten Indikationen bei Menschen mit T2D und kardiovaskulärer Vorerkrankung in der Nutzenbewertung erhalten (17). Im DMP sind Empagliflozin als SGLT-2i und

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Liraglutid als GLP-1RA darüber hinaus als Antidiabetika mit gesicherter günstiger Beeinflussung klinischer Endpunkte explizit genannt: "Patientinnen und Patienten mit manifester kardiovaskulärer Erkrankung, die mit Medikamenten zur Behandlung kardiovaskulärer Risikofaktoren behandelt werden, können bei unzureichender Kontrolle des Diabetes mellitus / bei unzureichender Blutzuckerkontrolle von Empagliflozin oder Liraglutid in Kombination mit mindestens einem weiteren oralen Antidiabetikum und/oder mit Insulin profitieren" (18).

Die Indikationen zu einer Insulintherapie bei T2D und auch die diesbezügliche Therapie-Deeskalation sind in der NVL explizit genannt (Abb. 7 und Tab. 2-4 & 2-5) (1). Aus Sicht der Diabetesgesellschaften ist als ein Therapieziel die Vermeidung von therapiebedingten Hypoglykämien ein wichtiger Teilaspekt bei der grundsätzlichen Therapiewahl, dies gilt es besonders bei der Therapie mit Insulin und Sulfonylharnstoffen zu beachten (1-4).

6. Marso SP, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016; 375(4): 311-322. doi: 10.1056/NEJMoa1603827
7. Marso SP, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016; 375: 1834-1844. doi: 10.1056/NEJMoa1607141
8. Husain M, et al. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2019; 381(9): 841-851. doi: 10.1056/NEJMoa1901118
9. Gerstein HC, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019; 394(10193): 121-130. doi: 10.1016/S0140-6736(19)31149-3
10. Zinman B, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. N Engl J Med. 2015; 373: 2117-2128. doi: 10.1056/NEJMoa1504720
11. Wanner C, et al. Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes. N Engl J Med. 2016; 375: 323-34. doi: 10.1056/NEJMoa1515920
12. Neal B, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med. 2017; 377(7): 644-657. doi: 10.1056/NEJMoa1611925
13. Wiviott SD, et al. Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2019; 380: 347-357. doi: 10.1056/NEJMoa1812389
14. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. Kidney Int. 2020;98(4S):S1-S115. doi: 10.1016/j.kint.2020.06.019
15. https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/469/#beschluesse [cited: 2021-05-17]
16. https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/220/#beschluesse [cited: 2021-05-17]
17. https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/517/#beschluesse [cited: 2021-05-17]
18. https://www.g-ba.de/beschluesse/3662/ [cited: 2021-05-17]

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

2021-B-428

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Fachgesellschaft: Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM)

Indikation

Behandlung des unzureichend kontrollierten Diabetes mellitus Typ 2 bei Erwachsenen als Zusatz zu Diät und körperlicher Aktivität

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Aktuell gibt es ein erhebliches Ausmaß an Überdiagnostik und Übertherapie eines Typ-2-Diabetes. Im DMP Nordrhein (kvno.de/s/LigYQQm7Kbd6B8k/download) hatten knapp 40% der eingeschlossenen Patient*innen ein HbA1c <6,5%, waren also entweder unnötig medikalisiert worden – oder hatten keinen Diabetes (mehr). Für den Nutzen einer medikamentösen HbA1c-Senkung <7,0% gibt es keine ausreichende Evidenz (IQWIG Nutzenbewertung einer langfristigen normnahen Blutzuckersenkung bei Patienten mit Diabetes mellitus Typ 2: Rapid Report A05-10; 2013).

Die Übersterblichkeit durch einen Diabetes sinkt in den industrialisierten Ländern des Westens laufend (Kim, D., Ki A.L., Cholankeril, G. et al. (2019). Trends in overall, cardiovascular and cancer-related mortality among individuals with diabetes reported on death certificates in the United States between 2007 and 2017. *Diabetologia 62,* 1185–1194. https://www.doi.org/10.1007/s00125-019-4870-9). Anders als bei unter 55-Jährigen, bei denen ein Diabetes die Gesamtsterblichkeit mehr als verdoppelt, ist bei über 70-Jährigen außer bei sehr hohen HbA1c-Werten nicht mehr von einer Übersterblichkeit auszugehen (Tancredi, M., Rosengren, A., Svensson, A-M. et al. (2015). Excess mortality among persons with type 2 diabetes. *N Engl J Med 373,* 1720–1732. https://www.doi.org/10.1056/ NEJMoa1504347).

Im DMP Nordrhein (Zitat s.o.) waren 26,7% der betreuten Personen 66-75, weitere 34,2% über/gleich 76 Jahre alt. Auch wenn die Inzidenz einer terminalen Niereninsuffizienz bei Menschen mit Diabetes 6-fach häufiger ist als bei Personen ohne Diabetes, sinkt diese bei Personen mit Typ-2-Diabetes von Jahr zu Jahr um 3% - bei Menschen ohne Diabetes übrigens nicht. (Claessen H, Narres M, Kvitkina T et al. Renal replacement therapy in people with and without diabetes in Germany, 2010-2016: an analysis of more than 25 million inhabitants. Diabetes Care 2021;44:1-9).

--Bei der Nationalen VersorgungsLeitlinie Typ-2-Diabetes (BÄK, KBV, AWMF (2021) (Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften). Nationale VersorgungsLeitlinie (**NVL**) Typ-2- Diabetes, Teilpublikation der Langfassung: https://www.leitlinien.de/nvl/diabetes) waren sich alle beteiligten Fachgesellschaften darüber einig, dass Metformin trotz des ernüchternden Ergebnisses eines aktuellen Cochrane-Reviews (Gnesin, F., Braun Thuesen, A.J., Kähler, L.A. et al. (2020). Metformin monotherapy for adults with type 2 diabetes mellitus. *Cochrane Database of Systematic Reviews 2020; Issue 6,* No.:CD012906. https://www.doi.org/10.1002/14651858. CD012906.pub2) als Blutglukose senkendes Medikament der ersten Wahl anzusehen ist – Metformin senkt stark die Blutglukose, ist gut verträglich und gut mit anderen Medikamenten kombinierbar.

Hinsichtlich des anzustrebenden HbA1c-Korridors sind sich die Fachgesellschaften nur in einem relativ weiten Bereich einig. Die DEGAM (**DEGAM** (2021). Typ-2-Diabetes. DEGAM-Anwenderversion als Addendum zur Nationalen VersorgungsLeitlinie (NVL) Typ-2-Diabetes. AWMF-Register-Nr. nvl-001. https://www. degam.de/files/Inhalte/Leitlinien-Inhalte/Dokumente/ Interdisziplinaere%20Leitlinien/NVL-001_Typ-2-Diabetes/ DEGAM%20Anwenderversion/NVL001%20Diabetes_av_ DEGAM2021.pdf; alternativ: tinyurl.com/m4ndpxdk) empfiehlt für die medikamentöse Therapie eines Diabetes einen Korridor von 7,0-8,0% und sieht nur selten eine Indikation, eine medikamentöse Therapie bei Werten <7% aufrechtzuerhalten. Alle Fachgesellschaften haben die Deeskalation einer zu aggressiven Therapie als relevante Empfehlung in die NVL aufgenommen.

Ebenso wenig einig sind sich die Fachgesellschaften hinsichtlich des nächsten Kombinationspartners nach Versagen von bzw. mit Metformin. Die DEGAM empfiehlt dann bei Patient*innen ohne kardiovaskuläre Erkrankungen als nächstes Glibenclamid. Die ADOPT-Studie (Kahn, S.E., Haffner S.M., Heise M.A. et al. (2006). Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy (**ADOPT** study). *N Engl J Med 355,* 2427–4243. https://www.doi.org/10.1056/NEJMoa066224) und die CAROLINA-Studie (Rosenstock, J., Kahn S.E., Johansen, O.E. et al. (2019). Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The **CAROLINA** Randomized Clinical Trial. *JAMA 322*(12), 1155–1166. https:// www.doi.org/10.1001/jama.2019.13772) zeigten, dass Sulfonylharnstoffe nicht kardiotoxisch sind.

Kontaktdaten

Fachgesellschaft: Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM)

Indikation

Behandlung des unzureichend kontrollierten Diabetes mellitus Typ 2 bei Erwachsenen als Zusatz zu Diät und körperlicher Aktivität

Sie sind starke Senker der Blutglukose und führen erheblich seltener zu Therapieversagen als beispielsweise DPP4-Hemmer (Palmer, S.C., Mavridis, D., Nicolucci, A. et al. (2016). Comparison of clinical outcomes and adverse events associated with glucose lowering drugs in patients with type 2 diabetes: A Meta-Analyses. *JAMA 316,* 313–324. https://www. doi.org/10.1001/jama.2016.9400).
Um Hypoglykämien, die wesentlichste unerwünschte Wirkung der Sulfonylharnstoffe, zu vermeiden, empfiehlt die DEGAM bei Therapie mit Glibenclamid, das HbA1c nicht unter 7,5% zu senken.
Wenn die Kombination von Metformin mit Glibenclamid nicht ausreicht, das individuelle HbA1c-Ziel zu erreichen, empfiehlt die DEGAM – dann wieder in Übereinstimmung mit DDG und DGIM – Empagliflozin bzw. Liraglutid, , sofern dies zu einer Glukosesenkung führt, was bei der geringen antihyperglykämischen Wirkung oft nicht der Fall ist. In einer aktuellen Metaanalyse (Palmer, S., Tendal, B., Mustafa, R. et al. (2021). Sodium-glucose cotransporter protein-2 (SGLT-2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists for type 2 diabetes: systematic review and network meta-analysis of randomized controlled trials. *BMJ 372,* m4573. https://www.doi. org/10.1136/bmj.m4573) konnte gezeigt werden, dass auch bei Patient*innen ohne bislang präzedente kardiovaskuläre Ereignisse diese beiden Substanzen das kardiovaskuläre Risiko und die Mortalität senken können, allerdings mit einer derart hohen Number-needed-to-treat, dass hier eine Übernahme in die Regelversorgung nur bedingt anbietet, es sei denn dass damit die Vermeidung einer Insulintherapie möglich ist. Zudem sind Empagliflozin und Liraglutid aktuell nach der Arzneimittelrichtlinie nur nach kardiovaskulären Ereignissen verordnungsfähig. Dagegen ist ihr Nutzen bei hohem Risiko für kardiovaskuläre Erkrankungen klar nachgewiesen und wird übereinstimmend von allen Fachgesellschaften bei unzureichender Einstellung als add on zu Metformin empfohlen (NVL Diabetes). Bei Herzinsuffizienz besteht für bestimmte Subgruppen eine eigenständige Indikation für SGLT2-Hemmer (Addendum zur NVL Herzinsufffizienz, wird demnächst publiziert)
Empagliflozin und Liraglutid senken beide das HbA1c nicht stark. Es wird also nicht ganz selten vorkommen, dass bei stark erhöhten HbA1c-Werten bei Personen ohne kardiovaskuläre Vorerkrankungen Insulin hinzugefügt werden muss. Die DEGAM empfiehlt hier vorrangig NPH-Insulin zur Nacht (Mertes, B., Gödde, S., Piorkowski, M. et al. (2020). Successful treatment with bedtime basal insulin added to metformin without weight gain or hypoglycemia over three years. *J Clin Med 9,* 1153. https://doi.org/10.3390/jcm9041153), eine intensivierte Insulintherapie sollte wegen deren besonders hohem Risiko für schwere Hypoglykämien (Müller, N., Lehmann, T., Klöss, A. et al. (2020). Changes in incidence of severe hypoglycaemia in people with type 2 diabetes from 2006 to 2016: analysis based on health insurance data in Germany considering the anti-hyperglycaemic medication. *Diabet Med 37,* 1326–1332. https://www.doi. org/10.1111/dme.14294) nach Möglichkeit vermieden werden.

Begleitend zu den medikamentösen Optionen sind die Lebensstilfaktoren weiterhin sehr wichtig. Ohne adäquate, umsetzbare und flächendeckend verfügbare Ernährungs- und Lebensstilkonzepte sind viele medikamentöse Ansätze tatsächlich zu hinterfragen.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von Erwachsenen mit unzureichend kontrollierten Diabetes mellitus Typ 2, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Personen mit Typ-2-Diabetes, bei denen es bereits zu kardiovaskulären Erkrankungen gekommen war, sollten eine der beiden Substanzen, für die eine Mortalitäts-Senkung nachgewiesen werden konnte (Zinman, B., Wanner, C., Lachin J.M. et al (2015). Empagliflocin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med 373,* 2117–2128. https://www.doi.org/10.1056/ NEJMoa1504720) (Marso, S.P., Daniels G.H., Brown-Frandsen, K. et al. (2016). Liraglutide and cardiovascular outcomes in type 2 diabetes (**LEADER**). *N Engl J Med 375,* 311–322. https://www.doi. org/10.1056/NEJMoa1603827), angeboten bekommen.
Nach Auffassung der DEGAM ist nicht ganz sicher von einem Gruppeneffekt bei SGLT-2-Hemmern und GLP-1-Rezeptor-Agonisten auszugehen – für andere SGLT-2-Hemmer als Empagliflozin (Neal B, Perkovic V, Mahaffey K et al for the CANVAS program collaborative group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. N Engl J Med 2017; 377:644-657) (Wiviott S, Bonaca M, Mosenzo O et al for the DECLARE TIMI 58 investigators. Dapagliflozin and cardiovascular outcome in diabetes. N Engl J Med 2019;380: 347-357) (Bhatt D, Szarek M, Pitt et al for the SCORED investigators. Sotagliflozin in Patients with Diabetes and Chronic Kidney Disease. N Engl J Med 2021; 384:129-139) (Heerspink H, Stefánsson B, Correa-Rotter R et al for the

Kontaktdaten

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DPA-CKD trial committee and investigators. Dapagliflozin in Patients with Chronic Kidney Disease. N Engl J Med 2020; 383:1436-1446) und für andere GLP-1-Rezeptor-Agonisten als Liraglutid (Pfeffer M, Blaggett B, Diaz R et al for the ELICA investigators. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med 2015;373:2247-57) (Marso S, Bain S, Consoli A et al for the SUSTAIN-6 investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2016;375:1834-44) (Holman R, Bethel M, Mentz R et al for the EXSCEL study group. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med 2017;377:1228-39) (Hernandez A, Green J, Janmohamed S et al for the Harmony outcomes committees and investigators. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled Trial. Lancet 2018;203:30-38) (Husain M, Birkenfeld A, Donsmark M et al for the PIONEER 6 investigators. Oral Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med 2019; 381:841-851) (Gerstein H, Colhoun H, Dagenais G et al for the REWIND investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121-130) ist die Datenlage hinsichtlich Senkung von primärem Endpunkt und Gesamtmortalität weniger überzeugend.

Alle Diabetes-Studien zu SGLT-2-Hemmern und GLP-1-Rezeptor-Agonisten eint Zweierlei:
- das HbA1c bei Studien-Einschluss lag nie unter 7,0%
- die Patient*innen waren zuvor bereits antihyperglykämisch vorbehandelt gewesen.

Empfehlungen von DGK und DDG, allen Patient*innen mit Diabetes und kardiovaskulärem Ereignis sofort mit dem Ereignis auch SGLT-2-Hemmer oder GLP-1-Analoga zu verordnen, werden darum von der DEGAM kritisch in Frage gestellt. Vielmehr empfiehlt die DEGAM den Einsatz dieser Substanzgruppen bei kardiovaskulär Vorerkrankten dann, wenn das individuelle HbA1c-Ziel allein mit Metformin nicht erreicht werden konnte.

Bei Patient*innen mit schwerer Herzinsuffizienz (McMurray J, Solomon S, Inzucchi S et al for the DAPA-HF trial committee and investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. N Engl J Med 2019; 381:1995-2008) (Packer M, Anker S, Butler J et al for the EMPEROR-reduced trial investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. N Engl J Med 2020; 383:1413-1424) (Bhatt D, Szarek M, Cannon C et al for the SOLOIST-WHF trial investigators. N Engl J Med 2021; 384:117-128) (Cosentino F, Cannon C, Cherney D et al on behalf of the VERTIS CV investigators. Efficacy of Ertugliflozin on Heart Failure–Related Events in Patients With Type 2 Diabetes Mellitus and Established Atherosclerotic Cardiovascular Disease. Circulation 2020;142:2205-2215) gelten andere Kriterien: hier wurde der Mortalitätsbenefit völlig unabhängig von der Präsenz eines Diabetes erzielt. Es handelte sich hier also nicht um eine Diabetes-Therapie, sondern um eine aus anderen Gründen erfolgreiche Behandlung einer trotz Standardtherapie weiterhin symptomatischen Herzinsuffizienz).