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Antrag zur Bewertung des nicht-invasiven, multiparametrischen, komplexen Telemonitoring-basierten Managements von Patientinnen und Patienten mit Herzinsuffizienz NYHA II - III mit bereits stattgehabter Dekompensation gemäß § 135 Absatz 1 Satz 1 SGB V

Sehr geehrte Frau Dr. Lelgemann,

hiermit stellen wir den Antrag auf Bewertung des Managements von Patientinnen und Patienten mit Herzinsuffizienz NYHA (New York Heart Association) II - III mit bereits stattgehabter Dekompensation durch eine komplexe ärztliche Intervention, gesteuert durch ein nicht-invasives, multiparametrisches Telemonitoring auf der Rechtsgrundlage von § 135 Absatz 1 Satz 1 SGB V.

Hintergrund

Moderne Entwicklungen der Informations- und Kommunikationstechnologie haben es möglich gemacht, Informationen und Messwerte zum Gesundheitszustand der Patientin oder des Patienten zuhause oder an nahezu beliebigen Aufenthaltsorten, ohne persönlichen Praxis- oder Hausbesuch zu erheben und diese auf zentrale Server zu übertragen, wo sie ausgewertet und die Ergebnisse der behandelnden Ärztin oder dem behandelnden Arzt zur Verfügung gestellt werden. Dieses Monitoring ist grundsätzlich rund um die Uhr möglich.

Bei Patientinnen und Patienten, die an Herzinsuffizienz leiden, wurde eine Datenübertragung zur telemedizinischen Funktionsanalyse von implantierten Kardiovertern, Defibrillatoren und Aggregaten für die CRT (Cardiac Resynchronization Therapy) 2017 in den Leistungskatalog der GKV aufge-

nommen. Hierbei geht es lediglich darum, das regelrechte Funktionieren der Geräte zu überwachen und Störungen, die unter Umständen die Patientin oder den Patienten gefährden, frühzeitig zu erkennen.

Beim aktuell im Bewertungsverfahrens nach § 135 Absatz 1 Satz 1 SGB V befindlichen Telemonitoring mittels aktiver kardialer implantierbarer Aggregate, die zur Behandlung von ventrikulären Tachyarrhythmien sowie bei Herzinsuffizienz eingesetzt werden[1], werden Vitalparameter der Patientin oder des Patienten überwacht mit dem Ziel, die Sterblichkeit, die Morbidität bzw. Krankheitsereignisse zu verringern. In diesem Fall bleibt bislang in der Abfolge von Datenerhebung, -übertragung, -analyse, Rückmeldung an die behandelnde Ärztin oder den behandelnden Arzt und der dann erfolgenden Einflussnahme auf patientenrelevante Zielparameter, das letzte entscheidende Glied - die therapeutische Intervention - weitgehend undefiniert. Die Wirkungskette in ihrem Ineinandergreifen und in ihrer Umsetzung bleibt damit unklar. Die vorliegenden Studien sprechen z. B. davon, dass „die klinische Antwort auf die Beobachtungen des Telemonitorings im Ermessen des Studienarztes" gewählt wurde (Hindricks 2014). Dies lässt Fragen offen, worauf ein beobachteter Effekt des Telemonitorings ggf. basiert und wie das Versorgungsziel in der Routineversorgung realisiert werden kann.

In Bezug auf das Telemonitoring bei Patientinnen und Patienten, die ohne kardiale Aggregate behandelt werden, liegen aktuell weitergehende Erkenntnisse vor. Die Interventionen in der TIM-HF2-Studie, von der im August 2018 Ergebnisse (Koehler et al. 2018) und im September 2018 die Methodik (Koehler et al. 2018a) veröffentlicht wurden, weisen eine vollständige, auf einem Telemonitoring basierende Interventionskette einschließlich des Managements der Patientin oder des Patienten auf. Da hiermit zu einem nachvollziehbaren, für die praktische Umsetzung beschreibbaren Wirkprinzip des Telemonitoring-basierten Managements von Patientinnen oder Patienten mit Herzinsuffizienz eine Studie im deutschen Versorgungskontext mit positivem Ergebnis vorliegt, stellen wir einen Antrag auf Bewertung der Methode nach § 135 Absatz 1 Satz 1 SGB V.

Da derzeit auch eine Erprobung eines invasiven Telemonitorings von Patientinnen und Patienten mit Herzinsuffizienz mit Hilfe eines eigens dafür implantierten Drucksensors in Planung ist[2], decken mit dem vorliegenden Antrag die Verfahren und Beratungen des G-BA insgesamt ein breites Spektrum der verschiedenen Möglichkeiten der Fernüberwachung bei Patientinnen und Patienten mit Herzinsuffizienz ab.

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[1] https://www.g-ba.de/downloads/39-261-2571/2016-04-21_Einleitung-Beratungsverf-135_Telem-aktive-kardiale-Aggr.pdf

[2] https://www.g-ba.de/informationen/richtlinien/98/

Methode

Das Telemonitoring-basierte Management von Patientinnen und Patienten mit Herzinsuffizienz als Gegenstand des vorliegenden Antrages beschreibt eine nicht-invasive, multiparametrische Datenerfassung und eine dadurch ausgelöste komplexe ärztliche Intervention als Managementstrategie. Es ist somit als eine neue Untersuchungs- und Behandlungsmethode zu charakterisierten. Grundlage hierfür ist, dass die genannten Komponenten in wohldefinierter, transparenter und nachvollziehbarer Form zusammenwirken. Dieses Vorgehen geht weit über eine lediglich technisch verbesserte Umsetzung einer bereits etablierten Vorgehensweise mit Hilfe digitaler Informationstechnologie hinaus. Die Zahl der erfassten Messwerte (erhobene Parameter), die zeitlich konkret festgelegte tägliche Datenübertragung (Abtastrate), die Verarbeitung dieser Daten nach festgelegten Regeln über einen zentralen Server, welche eine Priorisierung kritischer Befunde erlaubt (Datenanalyse mit Priorisierung), die Sicherstellung, dass die Auswertungen der Daten zeitnah, entsprechend der Priorisierung von qualifiziertem Personal wahrgenommen werden und unverzüglich ein Management entsprechend bestehender Interventionsregeln bestimmt wird (Kenntnisnahme- und Entscheidungsfrist, Umsetzung von Interventionsregeln) sowie die Regelung der Kooperation zwischen dem ärztlichen Telemonitoringzentrum und den primär die Patientin oder den Patienten behandelnden Ärztinnen und Ärzten für einen lückenlosen Service (Sicherstellung der lückenlosen Handlungsfähigkeit) bilden ein in dieser Form bisher nicht etabliertes und in dieser Ausprägung weitgehend standardisiertes Regelkreismodell ärztlichen Handelns. Deshalb handelt es sich um eine Neue Untersuchungs- und Behandlungsmethode im Sinne von § 135 Absatz. 1 Satz 1 SGB V.

Im Einzelnen ist Bestandteil der Methode:

- Die Parameter der Patientinnen und Patienten werden nicht durch implantierte, sondern durch externe Geräte erfasst. Es wird eine Reihe von konkret definierten Parametern bzw. Messwerten überwacht (multiparametrisches Monitoring von Vitaldaten). Neben dem Körpergewicht des Patienten werden Blutdruck, Herzfrequenz, Sauerstoffsättigung im peripheren Kapillarblut und eine EKG-Aufzeichnung sowie eine Selbsteinschätzung des Patienten zu seinem Gesundheitsstatus erfasst.

- Die Parameter werden mindestens einmal täglich an eine zentrale Stelle (Telemonitoringzentrum) übertragen und dort nach festgelegten Kriterien analysiert. Beim Vorliegen bestimmter Befunde oder wenn vorher festgesetzte Grenzwerte über- oder unterschritten werden, wird der entsprechende Befund gemäß seiner Dringlichkeit für eine beschleunigte Kenntnisnahme durch qualifiziertes Personal im Telemonitoringzentrum priorisiert. Die Kenntnisnahme sämtlicher wesentlicher Befunde hat innerhalb einer definierten Frist von

wenigen Stunden - in der TIM-HF2-Studie vier Stunden - zu erfolgen (unverzügliche Kenntnisnahme auffälliger Befunde).

- Es besteht ein Katalog von definierten Interventionsregeln (SOPs, Standardized Operating Procedures), um bestimmte Therapieziele zu erreichen. In der TIM-HF2-Studie waren die Ziele eine Herzfrequenz von möglichst unter 75 Schlägen/min bei Sinusrhythmus und ein Blutdruck mit Werten nicht höher als 140 mmHg systolisch und 90 mmHg diastolisch. Patientinnen und Patienten mit neu aufgetretenem Vorhofflimmern sollten eine Antikoagulation und bei einem Grad der Herzschwäche von II bis IV nach NYHA Mineralocorticoid-Rezeptor-Antagonisten erhalten. Auch hier gilt, dass die Entscheidung über das entsprechende Management eines behandlungsbedürftigen Befundes innerhalb einer definierten Frist von wenigen bis maximal 24 Stunden nach dem Bekanntwerden des Befundes zu erfolgen hat.

- Zur Sicherstellung einer lückenlosen Handlungsfähigkeit bestehen Kooperationsregeln zwischen den primär behandelnden Ärztinnen und Ärzten der Patientin oder des Patienten und dem qualifizierten Personal des Telemonitoringzentrums. Die behandelnden Ärztinnen und Ärzte werden über neue Ereignisse und wichtige Befunde aus dem Telemonitoring unverzüglich, mit einer definierten Frist, unterrichtet. Entscheidungen über Therapiemaßnahmen werden grundsätzlich unter der Verantwortung der primär behandelnden Ärztinnen und Ärzte getroffen. Das Telemonitoringzentrum hat dabei zunächst nur beratende Funktion. Außerhalb der Dienstzeiten der primär behandelnden Ärztinnen und Ärzte wird die Entscheidung und Behandlung für den Notfall an das qualifizierte ärztliche Personal des Telemonitoringzentrums mit Facharztstandard delegiert.

- Das Telemonitoring-basierte Management umfasst zusätzlich zu der Messung, Übertragung, Analyse von Daten der Patientin oder des Patienten und der Benachrichtigung der behandelnden Ärztinnen und Ärzte komplexe Interventionskomponenten, darunter geplante und bedarfsgesteuerte direkte telefonische Kontakte mit der Patientin oder dem Patienten durch das Telemonitoringzentrum und die vorausgehende und begleitende Schulung der Patientin oder des Patienten zum richtigen Umgang mit der Erkrankung und der Umsetzung des Monitorings. Es umfasst insbesondere auch die eigenständige, unverzügliche, therapeutische Intervention des Telemonitoringzentrums durch dort tätige qualifizierte Ärztinnen und Ärzte für den Notfall wie oben beschrieben. Zu diesen eigenständigen Interventionen gehört die tägliche Medikamentenreview mit der bedarfsweisen, notfallmäßigen Neuverordnung oder Dosisanpassung von Medikamenten entsprechend der festgelegten Interventionsregeln zur Umsetzung einer leitliniengerechten Therapie. Die Ärztin-

nen und Ärzte im Zentrum können im Notfall den Notarzt benachrichtigen oder eine Krankenhauseinweisung vornehmen.

Indikationen und indikationsbezogene Zielsetzung

Die Diagnose einer Herzinsuffizienz wird aufgrund der Vorgeschichte der Patientin oder des Patienten, der Beschwerdesymptomatik und einer Ultraschalluntersuchung des Herzens zur Feststellung und Quantifizierung kardialer Funktionsstörungen gestellt. Von den Patientinnen und Patienten mit Herzinsuffizienz sind diejenigen besonders häufig stationär behandlungsbedürftig und von erhöhter Sterblichkeit betroffen, bei denen bereits eine schwerwiegende Verschlechterung des Krankheitsbildes im Sinne einer Dekompensation stattgefunden hat. Die Indikation zum Telemonitoring bei Herzinsuffizienz wurde in der TIM-HF2-Studie bei Patientinnen und Patienten mit sonografisch festgestellter, eingeschränkter Pumpleistung gestellt, bei denen in den letzten 12 Monaten ein stationärer Krankenhausaufenthalt wegen einer Dekompensation notwendig war. Außerdem wurde (aufgrund der Analyse der Daten der Vorgängerstudie) die Zielpopulation auf Patienten mit NYHA-Stadium II oder III sowie einer eingeschränkten Ejektionsfraktion von definiertem Ausmaß und ohne Hinweise auf eine depressive Symptomatik eingegrenzt, da erwartet werden konnte, dass insbesondere solche Patientinnen und Patienten von dem intensiven Telemonitoring profitierten.

Nutzen

Für die Bewertung der Methode wird als möglicher Nutzen eine Senkung der Sterblichkeit, der Morbidität und eine Verringerung der Häufigkeit von kardiovaskulär-bedingten Krankenhausaufenthalten gesehen (als Surrogate für Morbiditätsereignisse, die so gravierend sind, dass eine Krankenhausbehandlung erforderlich ist). So hat die TM-HF2-Studie eine signifikante Verringerung der Sterblichkeit sowie eine Verminderung der Tage aufgrund ungeplanter Krankenhausaufenthalte wegen kardiovaskulärer Probleme zeigen können (Koehler et al. 2018).

Notwendigkeit und Wirtschaftlichkeit

Die Herzinsuffizienz ist einer der häufigsten Gründe für eine stationäre Krankenhausaufnahme in Deutschland (2016: 455.680 Fälle mit Hauptdiagnose Herzinsuffizienz)[3]. Durch die Alterung der Gesellschaft werden in den kommenden Jahren die Fallzahlen vermutlich weiter steigen (Neumann et al. 2009). Die hier benannten Indikationen fallen in das Gebiet der Herz-Kreislauf-Erkrankungen, welche nach Berechnungen für das Jahr 2015 mit Ausgaben von rund 46 Milliarden Euro vor den psychischen Störungen, den Erkrankungen des Verdauungssystems und den Erkrankungen des Bewegungsapparates die kostenträchtigste Gruppe von Erkrankungen in Deutschland darstellt.[4] Fast 10 % davon werden für die Versorgung der Patientinnen und Patienten mit Herzinsuffizienz aufgewendet. Detailliertere Daten zu den Kosten der Versorgung der Patientinnen und Patienten mit Herzrhythmusstörungen wie auch zur Wirtschaftlichkeit der benannten Indikationen liegen nicht vor.

Alternative Behandlungsverfahren und vermeidbare Risiken

Die Alternative zum Management von Patientinnen und Patienten mit Herzinsuffizienz durch eine komplexe ärztliche Intervention gesteuert durch ein nicht-invasives, multiparametrisches Telemonitoring ist das konventionelle Management der Patienten mit ärztlichen Kontrollen im Rahmen von Praxis- oder Hausbesuchen gemäß von Leitlinien bzw. ein im Einzelnen im Hinblick auf die Kontakte von Patientinnen und Patienten mit Versorgungseinrichtungen und die Verwendung von Erkenntnissen über den jeweils aktuellen Gesundheitszustand im Rahmen dieser Kontakte wenig spezifiziertes Versorgungsgeschehen.

In Erwägung zu ziehen ist, dass unabhängig von ihrem Gesundheitszustand bestimmte Patientinnen und Patienten in eine kontinuierliche telemedizinische Überwachung nicht einwilligen werden oder dass von manchen die fortwährende Beobachtung des Krankheitsgeschehens als belastend empfunden wird, was sich negativ auf die notwendige Mitwirkung am Behandlungsprozess auswirken kann. Zu berücksichtigen sind auch datenschutzrechtliche Fragen und Fragen der Datensicherheit, da es sich bei den übermittelten Informationen um sensible persönliche Daten handelt.

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[3] Diagnosedaten der Krankenhäuser ab 2000 (Fälle, Berechnungs- und Belegungstage, durchschnittliche Verweildauer). Gliederungsmerkmale: Jahre, Behandlungsort, Alter, Geschlecht, Verweildauer, [ICD-10: I50, Jahr: 2016] (www.gbe-bund.de, 20.11.2018)

[4] https://www.destatis.de/DE/ZahlenFakten/GesellschaftStaat/Gesundheit/Krankheitskosten/Krankheitskosten.html

Priorisierung

Die Krankheitslast, die durch die zugrundeliegenden Erkrankungen verursacht wird, sollte bei der Priorisierung des Antrags berücksichtigt werden.

Mit freundlichen Grüßen

Dr. Diedrich Bühler

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Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial

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Summary

Background Remote patient management in patients with heart failure might help to detect early signs and symptoms of cardiac decompensation, thus enabling a prompt initiation of the appropriate treatment and care before a full manifestation of a heart failure decompensation. We aimed to investigate the efficacy of our remote patient management intervention on mortality and morbidity in a well defined heart failure population.

Methods The Telemedical Interventional Management in Heart Failure II (TIM-HF2) trial was a prospective, randomised, controlled, parallel-group, unmasked (with randomisation concealment), multicentre trial with pragmatic elements introduced for data collection. The trial was done in Germany, and patients were recruited from hospitals and cardiology practices. Eligible patients had heart failure, were in New York Heart Association class II or III, had been admitted to hospital for heart failure within 12 months before randomisation, and had a left ventricular ejection fraction (LVEF) of 45% or lower (or if higher than 45%, oral diuretics were being prescribed). Patients with major depression were excluded. Patients were randomly assigned (1:1) using a secure web-based system to either remote patient management plus usual care or to usual care only and were followed up for a maximum of 393 days. The primary outcome was percentage of days lost due to unplanned cardiovascular hospital admissions or all-cause death, analysed in the full analysis set. Key secondary outcomes were all-cause and cardiovascular mortality. This study is registered with ClinicalTrials.gov, number NCT01878630, and has now been completed.

Findings Between Aug 13, 2013, and May 12, 2017, 1571 patients were randomly assigned to remote patient management (n=796) or usual care (n=775). Of these 1571 patients, 765 in the remote patient management group and 773 in the usual care group started their assigned care, and were included in the full analysis set. The percentage of days lost due to unplanned cardiovascular hospital admissions and all-cause death was 4·88% (95% CI 4·55–5·23) in the remote patient management group and 6·64% (6·19–7·13) in the usual care group (ratio 0·80, 95% CI 0·65–1·00; p=0·0460). Patients assigned to remote patient management lost a mean of 17·8 days (95% CI 16·6–19·1) per year compared with 24·2 days (22·6–26·0) per year for patients assigned to usual care. The all-cause death rate was 7·86 (95% CI 6·14–10·10) per 100 person-years of follow-up in the remote patient management group compared with 11·34 (9·21–13·95) per 100 person-years of follow-up in the usual care group (hazard ratio [HR] 0·70, 95% CI 0·50–0·96; p=0·0280). Cardiovascular mortality was not significantly different between the two groups (HR 0·671, 95% CI 0·45–1·01; p=0·0560).

Interpretation The TIM-HF2 trial suggests that a structured remote patient management intervention, when used in a well defined heart failure population, could reduce the percentage of days lost due to unplanned cardiovascular hospital admissions and all-cause mortality.

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Introduction

Telemedicine allows health-care providers to remotely diagnose and treat patients using telecommunications as either an alternative to or alongside in-person visits.[1] Telemedicine has the potential to streamline and enable real-time consultation between caregivers through the same technology, to boost the provision of both timely and better-quality, personalised care for patients with chronic diagnoses.

Heart failure is a chronic disorder, the management of which could potentially benefit from a remote patient management approach.[2–5] One of the most challenging issues in the management of heart failure is to reduce hospital admission and readmission rates for worsening heart failure.[2]

Remote patient management includes a broad range of interventions, including uptitration of drugs in the outpatient setting, patient education, and management of

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Research in context

Evidence before this study

We reviewed randomised and non-randomised studies and meta-analyses published up to Dec 31, 2017, that addressed or discussed the use of telemedicine in patients with heart failure. We searched PubMed with the search terms "telemedicine", "remote monitoring", "telemonitoring" and "heart failure". We restricted the search to articles published in English and German. One randomised controlled trial (RCT) of invasive telemonitoring found a significantly lower rate of readmissions to hospital for heart failure resulting from remote patient management based on pulmonary artery pressure than with usual care. Another RCT measured multiple variables acquired remotely from implanted devices (implantable cardioverter defibrillator [ICD] or ICD plus cardiac resynchronisation therapy [CRT]) to manage patients with heart failure. This RCT showed a benefit in mortality for patients with heart failure with an indication for ICD or ICD plus CRT. On the basis of the results of these two RCTs, the 2016 European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure gave remote patient monitoring of patients with heart failure (with these two specific devices) a grade IIb recommendation, level of evidence B. No such recommendation exists for non-invasive remote patient management interventions. Within the past 10 years, non-invasive remote patient management strategies have been studied in several RCTs investigating the effect of remote patient management on mortality, morbidity, and quality of life in patients with heart failure. These RCTs have reported conflicting results because of major differences in the precise study populations investigated, the durations of the remote patient management interventions, the type of home-care devices used, and the interaction methods (including intensity and timing) between the patients, local physicians, heart failure specialists, and telemedical caregivers. Subgroup analyses of the TIM-HF trial suggested that remote patient management has a potential beneficial effect for patients with heart failure in functional New York Heart Association class II and III who were admitted to hospital for decompensated heart failure no more than 12 months before starting the remote patient management intervention and who did not have major depression, which is a common comorbidity in patients with heart failure.

Added value of this study

To the best of our knowledge, this is the first RCT to use a structured remote patient management intervention that was designed to be a true holistic approach for the management of patients with heart failure, involving cardiologists, general practitioners, nurses, other health-care providers, and the patient. The data transmitted to the telemedical centre was not just monitored; the Fontane system (telemedical analysis software) enabled the telemedical centre staff to provide tailored patient support and management using predefined algorithms and biomarker values obtained during follow-up visits. This approach enabled a risk profile to be defined for each patient and the subsequent individual patient care was tailored around this risk profile accordingly. Applying such a care concept, the telemedical centre was the central point for patient management, and such a unit requires physicians and heart failure nurses, and preferably a service that runs for 24 h a day, 7 days a week, and a modern information technology infrastructure, including a self-adapting software algorithm with prioritisation rules, to enable the tailored management of a large number of patients.

Implications of all the available evidence

Our study, along with findings from some of the previous RCTs, has shown that if a patient with heart failure is carefully chosen according to their profile (ie, they have had a recent admission to hospital for heart failure and do not show evidence of major depression) and a structured remote patient management intervention is used, the proportion of days lost due to unplanned cardiovascular hospital admissions or all-cause death during 1 year of follow-up is reduced compared with usual care. The key element in this holistic care concept is a telemedical centre with physicians and heart failure nurses available 24 h a day, every day, and able to act promptly according to the individual patient risk profile. The actions taken by the telemedical centre staff include changes in medication and admission to hospital, if needed, but also educational activities. Moreover, the study results were not influenced by geographical location. As a result, regional differences in the access to appropriate heart failure care might be reduced.

comorbidities. This approach is an advance over telemonitoring alone, which generally focuses only on the early detection of clinical deterioration.

Over the past decade, several randomised studies investigating telehealth interventions in heart failure have been published.[6–14] Because the finding of benefit for the interventions is inconsistent across these studies, and the interventions used were different in kind and intensity, the generalisability of the results for the management of heart failure is limited.[15–17] As such, the recent European Society of Cardiology guidelines only give limited recommendations based on two device-related telemonitoring solutions.[13,14]

Using data from the TIM-HF trial,[10] we investigated which heart failure patient profile could potentially benefit from our multifaceted remote patient management intervention with respect to hospital admissions and mortality. In one of the prespecified subgroup analyses in the TIM-HF trial, we noted that patients assigned to remote patient management without major depression (ie, with a Patient Health Questionnaire [PHQ-9] score <10) who had recently been admitted to hospital for worsening heart failure, had fewer days lost due to hospital admission for heart failure or for all-cause death than did those who had usual care alone.[18] Using these findings, we defined the heart failure

patient population to be included in the Telemedical Interventional Management in Heart Failure II (TIM-HF2) trial, which was undertaken to assess the effect of our remote patient management system on unplanned cardiovascular hospital admissions and mortality in this well defined heart failure population.[19]

Methods

Study design and participants

The TIM-HF2 trial was a prospective, randomised, controlled, parallel-group, unmasked (with randomisation concealment), multicentre trial with pragmatic elements introduced for data collection. Detailed methods are due to be published shortly.[19] The trial was done in Germany, and patients were recruited from 200 university, local, and regional hospitals, and cardiology and general practitioner (GP) practices. Patients were eligible for inclusion if they had been admitted to hospital for worsening heart failure within 12 months before randomisation, were in functional New York Heart Association class II or III, had a left ventricular ejection fraction of 45% or lower (or if more than 45%, were being treated with oral diuretics). Patients were excluded if they had major depression (ie, PHQ-9 score >9), were on haemodialysis, or had been admitted to hospital for any reason within 7 days before randomisation. In addition, patients with a left ventricular assist device or those who had undergone coronary revascularisation or cardiac resynchronisation therapy implantation within 28 days before randomisation were excluded, as were those who were scheduled for coronary revascularisation, transcatheter aortic valve implantation, mitral clip implantation, or cardiac resynchronisation therapy implantation 3 months after randomisation.

The TIM-HF2 trial was designed, implemented, and overseen by an independent steering committee. This report was prepared and submitted for publication by the steering committee. An independent data safety monitoring board reviewed safety data on an ongoing basis. The clinical endpoint committee, masked to study group assignment, adjudicated all deaths and hospitalisations using prospectively defined criteria in the clinical endpoint committee charter. The adjudicated data were used for outcomes regarding hospitalisations and deaths.[19] The study complied with good clinical practice in accordance with the Declaration of Helsinki and the laws and regulations applicable in Germany. Written approval from the appropriate ethics committees was obtained.

Patients provided written informed consent, granting permission for the telemedical centre to contact their health insurance company to cross check the hospital admissions reported by the investigators with those on file in the health insurance records. This process was approved by the German Federal Social Insurance Office and done for patients in both study groups.

Randomisation and masking

Potentially eligible patients were screened for eligibility, and those agreeing to participate and who provided written informed consent were then screened and had baseline measurements and assessments done. Eligible and willing patients were randomly assigned (1:1) using a secure web-based system to either remote patient management plus usual care (remote patient management group) or to usual care alone (usual care group). To ensure a balance of important clinical covariates between the two study groups, we used Pocock's minimisation algorithm with 10% residual randomness.[20] Randomisation was concealed but neither participants nor investigators were masked to group assignment in this open trial (for a full list of investigators see appendix p 5).

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See Online for appendix

Procedures

A description of the remote patient management system and intervention is due to be published shortly.[19] Briefly, the remote patient management intervention consisted of the following: a daily transmission of bodyweight, systolic and diastolic blood pressure, heart rate, analysis of the heart rhythm, peripheral capillary oxygen saturation (SpO_2) and a self-rated health status (scale range one to five) to the telemedical centre; a definition of a patient's risk category using the baseline and follow-up visit biomarker data in combination with the daily transmitted data; patient education; and co-operation between the telemedical centre, and the patient's GP and cardiologist.

The telemonitoring system, which was installed in the patient's home within 7 days after randomisation, was a multicomponent system with a three-channel electrocardiogram (ECG) device to collect either a 2 min or streaming ECG measurements (PhysioMem PM 1000, GETEMED Medizin und Informationstechnik AG, Teltow, Germany); a blood pressure measuring device (UA767PBT, A&D Company Ltd, Tokyo, Japan); and weighing scales (Seca 861, seca GmbH & Co KG, Hamburg, Germany). SpO_2 was collected using Masimo Signal Extraction Technology (Masimo Europe Ltd, Puchheim, Germany).

Patients were also provided with a mobile phone to be used to contact the telemedical centre directly in emergency situations. During the telemonitoring system installation process, certified nurses provided patient training on the system and initiated a heart failure patient education programme; the latter was continued monthly by structured telephone interviews with the patient. The monthly telephone interviews were an integral part of the remote patient management intervention. Combined with the daily data transmissions to the telemedical centre, the patient's clinical and symptomatic status and concomitant medications were assessed, in addition to adherence to the remote patient management intervention and other social and technical issues, which were discussed between the patient and the telemedical

centre nurse. The telemonitoring system used a wireless system with a digital tablet (Physio-Gate PG 1000, GETEMED Medizin und Informationstechnik AG) as the central structural element to transmit the data from the patient's home to the centre. This was done by using the mobile phone network (secured via a virtual private network tunnel). The telemedical centre was located at Charité–Universitätsmedizin Berlin; transmission of patient data was set at a fixed time daily. The data collection, transmission, and processing were done in strict compliance with state-of-the-art confidentiality and technical standards as approved by the relevant data protection offices in Germany.

The telemedical centre provided physician-led medical support and patient management 24 h a day, Monday to Sunday, for the entire study period using the Fontane system, a CE-marked telemedical analysis software (T-Systems International GmbH, Frankfurt, Germany). Algorithms were programmed and implemented in this system which guided patient management and allowed the telemedical centre physicians to act promptly (eg, concomitant medication change, initiation of an ambulatory assessment by a home physician, or to hospitalise the patient) and to piroritise high-risk patients. Patients were categorised as low or high risk using the combination of mid-regional pro-adrenomedullin (MR-proADM) values and the patient transmitted data—the risk category was revaluated every 3 months using the MR-proADM results obtained at each follow-up visit. The Fontane system also enabled direct communication between the telemedical centre staff and the patient, and the patient's GP and local cardiologists, all of whom were involved in the management of the patient. Via the Fontane system, the telemedical centre created a study-specific electronic patient file, which was accessible by both the telemedical centre staff and patient's care provider.

Patients allocated to the usual care group were followed up in accordance with the current guidelines for the management and treatment of patients with heart failure.[5] Throughout the study follow-up, the patient's GP and cardiologist were free to adjust or prescribe treatments in accordance with the patient's clinical condition.

Patients in both study groups were followed up for at least 365 days and up to 393 days after randomisation. All patients were seen by their treating cardiologist at the screening and baseline visit and at the final study visit; the latter was done on day 365 (28-day time window) after randomisation. In between, patient visits were scheduled at 3, 6, and 9 months, and were undertaken by the patient's GP or local cardiologist. At all visits, data were collected in a case report form which included vital signs and bodyweight, and patients were asked about the occurrence of hospital admissions since the last study contact.

To avoid contact information and data collection bias, given the daily contact with patients in the remote patient management group, a quality control system was implemented to ensure the accurate and complete reporting of hospital admissions in both the remote patient management plus usual care and usual care groups. This process required the cooperation of patients, investigators, and the patients' respective health insurance companies. The accuracy of data concerning hospital admissions was confirmed using data from the health insurance companies, and a cross check was done with the hospital admissions reported by the investigators.

Outcomes

The primary outcome was the percentage of days lost due to unplanned cardiovascular hospital admissions or death from any cause, comparing remote patient management plus usual care to usual care alone during the individual patient follow-up time. The main secondary outcomes were all-cause mortality and cardiovascular mortality during the individual patient follow-up time plus 28 days after the last study visit, to a maximum of 393 days; percentage of days lost due to unplanned cardiovascular hospital admissions, and percentage of days lost due to unplanned heart failure hospital admissions; change in Minnesota Living with Heart Failure Questionnaire (MLHFQ) global score; and change in N-terminal prohormone brain natriuretic peptide (NT-proBNP) and MR-proADM between randomisation and the final study visit. For a full list of outcomes, see appendix (p 2). Secondary outcomes not reported here will be reported in future publications.

Statistical analysis

We used data for specific subgroups from the TIM-HF trial for sample size calculations. For the patient subgroup that mirrored the population we intended to include in the TIM-HF2 trial, 19 days were lost due to all-cause death or unplanned cardiovascular hospital admissions at 12 months in the usual care group, and 12 days were lost for patients in the remote patient management group, which corresponds to a 38% reduction.[10,18] With an estimated pooled SD of 48, we calculated that 750 patients would be required in each group to detect this difference with a power of 80% and a two-sided α of 5%.

We prespecified all data analyses in a formal statistical analysis plan, which was finalised before database lock (July 16, 2018). We used R (version 3.4.4) and Stata (version 14.2) for all analyses. The primary and secondary efficacy analyses were performed on the full analysis set, in accordance with the intention-to-treat principle. The full analysis set consisted of all randomised patients who gave consent and began their assigned care.

Baseline characteristics are summarised as number of patients (%) for categorical variables and as mean (SD) for continuous variables; for all baseline laboratory tests, the median and IQR is used.

For the primary analysis of percentage of days lost due to all-cause death or unplanned cardiovascular hospital

admission, the proportion of follow-up time lost due to death or unplanned cardiovascular hospitalisation was defined as the number of days lost divided by the intended follow-up. For patients who died, the number of days lost between the date of death and the date of intended follow-up plus the number of days spent in hospital for cardiovascular reasons were counted. For patients who completed the study as planned or who withdrew prematurely from follow-up, the fraction of follow-up time was defined as number of days lost (due to cardiovascular hospitalisation) divided by the follow-up time realised (ie, up to the censoring date). For the primary outcome, a permutation test was used to compare the weighted averages of the percentage of days lost between the two groups. The two-sided permutation test p value was calculated as the fraction of permutations, which had an absolute value of the test statistic at least as large as the observed test statistic, when we applied a mid-p correction in case of equality. For this analysis 2000 randomly drawn permutations were used. Confidence intervals (CIs) were calculated using the method described by Garthwaite,[21] which is based on the Robbins-Monro method. In short, this method does a separate search for each endpoint of the CI by sequentially updating the estimates where the magnitude of steps is governed by the distance between the original test statistic and the test statistic for the permuted data, and the step number. Follow-up time was weighted using weighted arithmetic means, and annualised averages are presented.

All survival analyses were done on a time-to-first event basis. Cumulative incidence curves for all-cause mortality were constructed according to the Kaplan-Meier method and the differences between curves were examined by the log-rank statistic. A competing risk analysis was used for cardiovascular mortality to take into account that the event of interest could not occur because of another previous fatal event. Cox-proportional hazards regression models were used to estimate (cause-specific) hazard ratios (HRs). Event rates are expressed as the number of events per 100 patient years of follow-up, taking into account the censoring of follow-up data.

Sensitivity analyses for mortality outcomes examined the robustness of the results using the full analysis set of all patients censored at day 393 after randomisation as defined in the statistical analysis plan. We analysed data for number of hospitalisation events by negative binomial models. For continuous variables such as the MLHFQ global score, changes in group means of both study groups at 12 months were compared by ANCOVA models adjusting for the baseline value. The biomarker test results were analysed using a log scale and ANCOVA models.

Compliance with the daily data transmissions to the telemedical centre was defined as the number of days between the day when the first data transmission was sent to the telemedical centre up to the end of the patient's individual follow-up minus any day when the patient was admitted to hospital for any reason.

A statistical test of interaction was done to assess whether the effect of the remote patient management on the primary outcome was consistent across the prespecified subgroups. Interaction tests for the subgroup analyses were done by adding the interaction term in the corresponding models.

This study is registered at ClinicalTrials.gov, number NCT01878630.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Aug 13, 2013, and May 12, 2017, 1571 patients were randomly assigned (796 to remote patient management plus usual care and 775 to usual care only, of which 765 in the remote patient management group and 773 in the usual care group were included in the full analysis set; figure 1). Baseline clinical and laboratory characteristics and the use of cardiovascular medications were similar

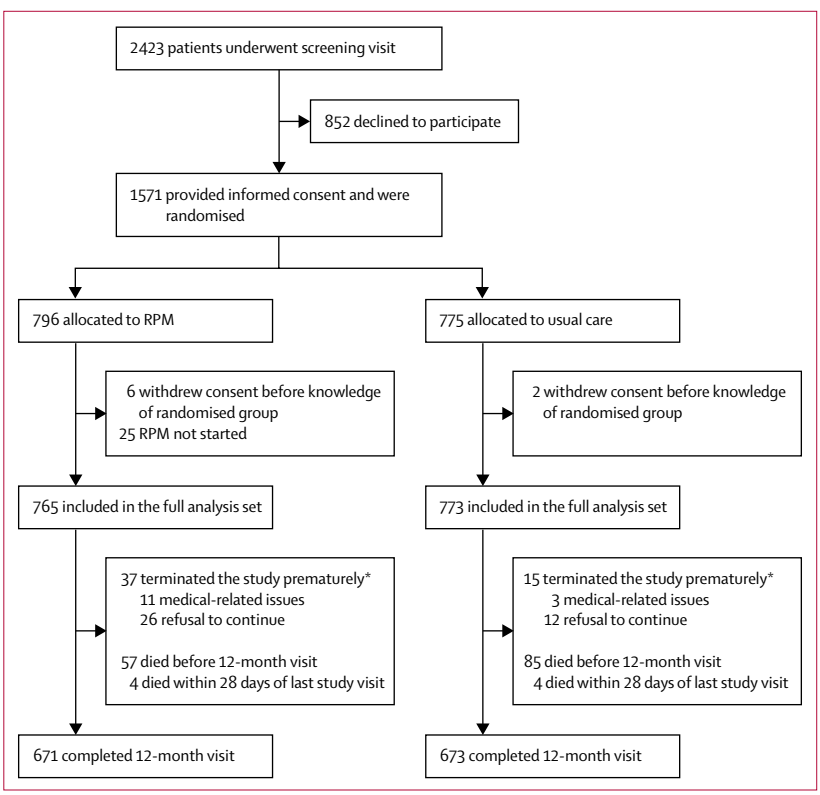

Figure 1: **Trial profile**
RPM=remote patient management. *Survival status known up to 393 days after randomisation for all patients who withdrew prematurely.

	Remote patient management (n=765)	Usual care (n=773)
Age (years)	70 (11)	70 (10)
Sex		
Male	533 (70%)	537 (69%)
Female	232 (30%)	236 (31%)
Living alone	213 (28%)	222 (29%)
Living in a urban area *vs* rural area		
Rural	457 (60%)	458 (59%)
Urban	308 (40%)	315 (41%)
NYHA class		
I	3 (0%)	8 (1%)
II	400 (52%)	396 (51%)
III	359 (47%)	367 (47%)
IV	3 (0%)	2 (0%)
LVEF	41 (13)	41 (13)
≤45%	492 (64%)	509 (66%)
>45%	273 (36%)	264 (34%)
<40%	342 (45%)	328 (42%)
40–50%	228 (30%)	272 (35%)
>50%	195 (25%)	173 (22%)
Days between discharge of last heart failure hospital admission and randomisation	92 (81)	93 (82)
≤30 days	192 (25%)	198 (26%)
31–90 days	281 (36%)	276 (36%)
>90 days	299 (39%)	291 (38%)
Bodyweight (kg)	87 (21)	88 (21)
Body-mass index (kg/m²)	30 (6)	30 (6)
Blood pressure (mm Hg)		
Systolic	126 (19)	125 (20)
Diastolic	74 (11)	74 (11)
Pulse (beats per min)	73 (14)	72 (14)
Primary cause of heart failure		
Ischaemic cause (coronary artery disease or myocardial infarction)	301 (39%)	323 (42%)
Hypertension	128 (17%)	146 (19%)
Dilated cardiomyopathy	176 (23%)	171 (22%)
Other	160 (21%)	133 (17%)
Cardiovascular risk factors		
Smoking status		
Unknown	24 (3%)	27 (3%)
Non-smoker	378 (49%)	385 (50%)
Former smoker	286 (37%)	304 (39%)
Smoker	77 (10%)	57 (7%)
Hyperlipidaemia		
Unknown	41 (5%)	39 (5%)
No	306 (40%)	318 (41%)
Yes	418 (55%)	415 (54%)
Diabetes mellitus	347 (45%)	355 (46%)

(Table 1 continues in next column)

	Remote patient management (n=765)	Usual care (n=773)
(Continued from previous column)		
Medical history		
Coronary revascularisation (PCI)	262 (34%)	298 (39%)
Coronary artery bypass surgery	134 (18%)	145 (19%)
TAVI	23 (3%)	30 (4%)
Mitral clip	26 (3%)	34 (4%)
Cardiac surgery for valves	86 (11%)	71 (9%)
Implantable cardioverter defibrillator	222 (29%)	234 (30%)
Cardiac resynchronisation therapy	118 (15%)	122 (16%)
Ablation of pulmonary veins	71 (9%)	52 (7%)
Laboratory measurements		
Haemoglobin (mmol/L)	8 (7–9)	8 (8–9)
Serum sodium (mmol/L)	140 (137–142)	140 (138–142)
Potassium (mmol/L)	5 (4–5)	5 (4–5)
Serum creatinine (µmol/L)	108 (87–141)	109 (88–148)
Estimated GFR (mL/min per 1·73m² of body surface area, Cockcroft-Gault)	60 (43–88)	60 (42–84)
NT-proBNP (pg/mL)	1407 (626–3142)	1488 (594–3069)
In patients with LVEF ≤45 (n=1001)	1728 (798–3858)	1798 (786–3667)
In patients with LVEF >45 (n=537)	1056 (468–2042)	1035 (405–1985)
MR-proADM (nmol/L)	1 (1–2)	1 (1–2)
Concomitant treatment		
ACE inhibitors or ARBs	628 (82%)	641 (83%)
ARN inhibitors	44 (6%)	47 (6%)
β blockers	702 (92%)	711 (92%)
Aldosterone antagonists	441 (58%)	405 (52%)
Loop diuretics	717 (94%)	721 (93%)
Thiazides	191 (25%)	185 (24%)
Other diuretics	4 (1%)	1 (0%)
Vitamin K antagonists	265 (35%)	272 (35%)
Antiplatelet therapy	103 (13%)	130 (17%)
NOACs	205 (27%)	208 (27%)
Platelet aggregation inhibitors	266 (35%)	267 (35%)
Lipid-lowering drugs	456 (60%)	453 (59%)
Insulin	170 (22%)	170 (22%)
Oral hypoglycaemic drugs	206 (27%)	185 (24%)
Ivabradine	22 (3%)	43 (6%)
Calcium antagonists	163 (21%)	188 (24%)
Nitrates	37 (5%)	48 (6%)
Digitalis glycosides	119 (16%)	133 (17%)
Antiarrhythmic drugs	99 (13%)	98 (13%)

Data are mean (SD) or n (%), median (IQR) for all laboratory tests. NYHA=New York Heart Association. LVEF=left ventricular ejection fraction. PCI=percutaneous coronary intervention. TAVI=transcatheter aortic valve implantation. GFR=glomerular filtration rate. NT-proBNP=N-terminal prohormone of brain natriuretic peptide. MR-proADM=mid-regional proadrenomedullin. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. ARN=angiotensin receptor-neprilysin. NOAC=novel oral anticoagulant.

Table 1: **Baseline characteristics**

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	Remote patient management (n=765)		Usual care (n=773)		Ratio, remote patient management *vs* usual care (95% CI)	p value
	Number of patients with event	Weighted average (95% CI)	Number of patients with event	Weighted average (95% CI)		
Percentage of days lost due to unplanned cardiovascular hospitalisation or death of any cause	265 (35%)	4·88% (4·55–5·23)	290 (38%)	6·64% (6·19–7·13)	0·80* (0·65–1·00)	0·0460
Days lost per year	..	17·8 days (16·6–19·1)	..	24·2 days (22·6–26·0)	..	..
All-cause mortality†	61 (8%)	7·86 (6·14–10·10)	89 (12%)	11·34 (9·21–13·95)	0·70‡ (0·50–0·96)	0·0280
Cardiovascular mortality†	39 (5%)	5·04 (3·68–6·90)	59 (8%)	7·51 (5·82–9·70)	0·67‡ (0·45–1·01)	0·0560

*Ratio of the weighted average. †Measured during individual patient follow-up time plus 28 days after the last study visit, to a maximum of 393 days. ‡Hazard ratio.

Table 2: **Primary and key secondary outcomes**

between the two groups (table 1). The mean age of all patients was 70 years (SD 10), and 70% were men.

For patients randomly assigned to receive remote patient management, 743 (97%) were at least 70% compliant with the daily transfer of data to the telemedical centre. Additionally, all patients were contacted within 24 h of missing data transmissions. Survival status was known for all patients up to the maximum follow-up for each patient (ie, up to day 393 after randomisation).

265 (35%) of 765 patients in the remote patient management group and 290 (38%) of 773 in the usual care group were admitted to hospital for an unplanned cardiovascular reason or died. The percentage of days lost due to unplanned cardiovascular hospital admissions or all-cause death was statistically reduced in patients allocated to remote patient management (4·88%, 95% CI 4·55–5·23) as compared with usual care (6·64%, 95% CI 6·19–7·13; ratio 0·80, 95% CI 0·65–1·00; p=0·0460; table 2). Patients assigned to remote patient management lost a weighted average of 17·8 days per year compared with 24·2 days per year for patients assigned to usual care for this outcome.

The rate of all-cause death was 7·9 per 100 person-years of follow-up in the remote patient management group and 11·3 per 100 person-years of follow-up in the usual care group (HR 0·70, 95% CI 0·50–0·96; p=0·0280; table 2; figure 2). The difference between the remote patient management and usual care groups with respect to death from a cardiovascular cause was not statistically significant (HR 0·67, 95% CI 0·45–1·01; p=0·0560; table 2; appendix p 3).

Patients assigned to remote patient management lost fewer days than the usual care group for unplanned hospital admissions due to worsening heart failure (mean 3·8 days per year [95% CI 3·5–4·1] *vs* 5·6 days per year [5·2–6·0], respectively). The percentage of days lost for this outcome for the remote patient management and usual care groups was 1·04% (95% CI 0·96–1·11) and 1·53% (1·43–1·64), respectively (ratio 0·80, 95% CI 0·67–0·95; p=0·0070). Comparing remote patient management with the usual care group,

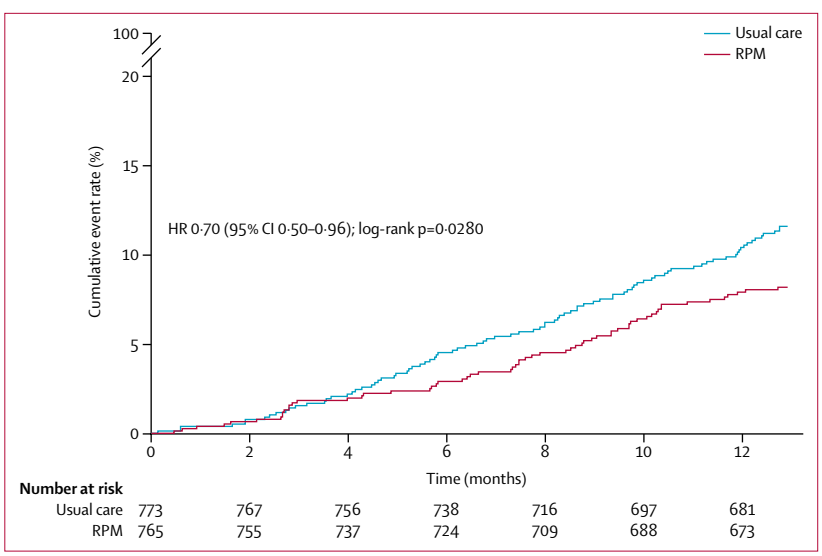

Figure 2: **Kaplan-Meier cumulative event curve for all-cause death**
HR=hazard ratio. RPM=remote patient management.

similar results were obtained for the sensitivity analysis done for all-cause mortality (ratio 0·74, 95% CI 0·54–1·02; p=0·0633).

The percentage of days lost due to unplanned cardiovascular hospital admissions was 1·71% (95% CI 1·59–1·83) for the remote patient management group and 2·29% (2·13–2·45) for the usual care group (ratio 0·89, 95% CI 0·74–1·07; p=0·208).

The change from baseline in the Minnesota Living with Heart Failure Questionnaire (MLHFQ) global score at 12 months, was not statistically different between the remote patient management and usual care group (table 3).

Figure 3 shows the results of the subgroup analyses for the primary outcome. We noted no effect of prespecified subgroups on the difference between treatment groups for the primary outcome.

2251 unplanned hospital admissions were reported and classified by the clinical endpoint committee (appendix p 4). Of these hospitalisations, 262 (14 in the remote patient management group and 248 in the usual care

	Remote patient management (n=765)		Usual care (n=773)		Mean difference* (95% CI)	p value
	Patients (n)	Mean (95% CI)	Patients (n)	Mean (95% CI)		
Quality of life						
Change in MLHFQ global score from baseline to 12 months†	649	−3·08 (−4·42 to −1·75)	624	−1·98 (−3·34 to −0·61)	−1·11 (−3·01 to 0·80)	0·26
Biomarker values						
Change in NT-proBNP (pg/mL) from baseline to 12 months†	664	−24·66% (−29·68 to 19·29)	628	−18·72% (−24·28 to−12·75)	−7·31% (−16·03 to 2·31)	0·13
In patients with LVEF ≤45%	423	−34·30% (−39·94 to 28·12)	410	−27·16% (−33·51 to −20·20)	−9·80% (−20·64 to 2·52)	0·11
In patients with LVEF >45%	241	−3·71% (−12·99 to 6·56)	218	−0·68% (−10·73 to 10·49)	−3·04% (−16·32 to 12·33)	0·68
Change in MR-proADM (nmol/L) from baseline to 12 months†	665	8·44% (5·99 to 10·94)	628	3·76% (1·35 to 6·23)	4·50% (1·14 to 7·98)	0·0084

MLHFQ=Minnesota Living with Heart Failure Questionnaire. NT-proBNP=N-terminal prohormone of brain natriuretic peptide. LVEF=left ventricular ejection fraction. MR-proADM=mid-regional proadrenomedullin. *Mean difference in change in the remote patient management group *vs* change in the usual care group. †Data obtained at final study visit performed at a maximum of 393 days after randomisation.

Table 3: **Other secondary outcomes**

group) were identified during the cross-check verification procedure with health insurance records.

1 026 078 vital parameters were transmitted to the telemedical centre (a median of 1421 per patient [range 6–3962]); table 4 provides a summary of the data transmitted and actions taken.

Discussion

The findings of TIM-HF2 show that remote patient management in a well defined heart failure population results in fewer days lost due to unplanned cardiovascular hospitalisations and all-cause mortality compared with the usual care group over a maximum follow-up of 393 days. The number of days lost was reduced from 24 days in the usual care group to 18 days in the remote patient management group. The primary outcome composite was driven mainly by reduction in mortality, and in particular cardiovascular mortality, rather than in unplanned cardiovascular hospital admissions.

The main objective in investigating a telemedical approach for heart failure management is to prevent and to treat disease exacerbations in addition to promoting patient self-empowerment.[1,5] The TIM-HF2 holistic approach of interaction between patients, (local) heart failure caregivers, and a telemedical centre enabled an intensive and instantaneous outpatient management of heart failure on a daily basis. Remote patient management is not just confined to monitoring of patients; it should also cover a spectrum of interventions relating to patient management including concomitant medication management, evaluation of comorbidities, and patient education. Ideally, remote patient management technology should be intuitive for both patients and care providers, enabling actionable feedback and a sustainable approach to the management of chronic diseases, with heart failure being just one example.

On the basis of an extensive review of the data from the TIM-HF trial,[10,18] we evaluated the heart failure population that could potentially benefit from our remote patient management and which outcome would be the most appropriate and clinically meaningful to use. We decided to exclude patients with major depression, evaluated using the PHQ-9D questionnaire, on the basis of the subgroup analyses of the TIM-HF data. The PHQ-9D questionnaire used in this context is widely available and sufficiently simple to use.

Remote patient management has the inherent risk of increasing the number of hospital admissions, but given the nature of our remote patient management intervention, the duration of stay should be shorter; the latter is an important consideration for patients and for payers. We therefore opted to use percentage of days lost due to unplanned cardiovascular hospital admissions or all-cause death as the primary outcome. We believe this is a clinically meaningful outcome for this patient population, and that the average difference of 6 days per year lost for remote patient management compared with usual care is clinically meaningful for patients, doctors, and payers. Based on our findings, five patients would need to use our remote patient management system for 1 year to gain 1 month during which they are alive and not being admitted to hospital for unplanned cardiovascular reasons, compared with usual care.

Another factor that was important in the management of patients with our remote patient management intervention and might have contributed to the success of the trial, was that we did not just monitor the data that were transmitted daily to the telemedical centre—the data were used by the telemedical centre team to guide the patient care. Together with the transmitted data and the biomarker data, we could define a risk category for each patient and hence tailor and individualise care for each patient. We believe that this real-time approach to the management of this specific heart failure population helped achieve a timely provision of personalised and quality care. Specifically, we think that the uptitration of guideline-recommended treatments as

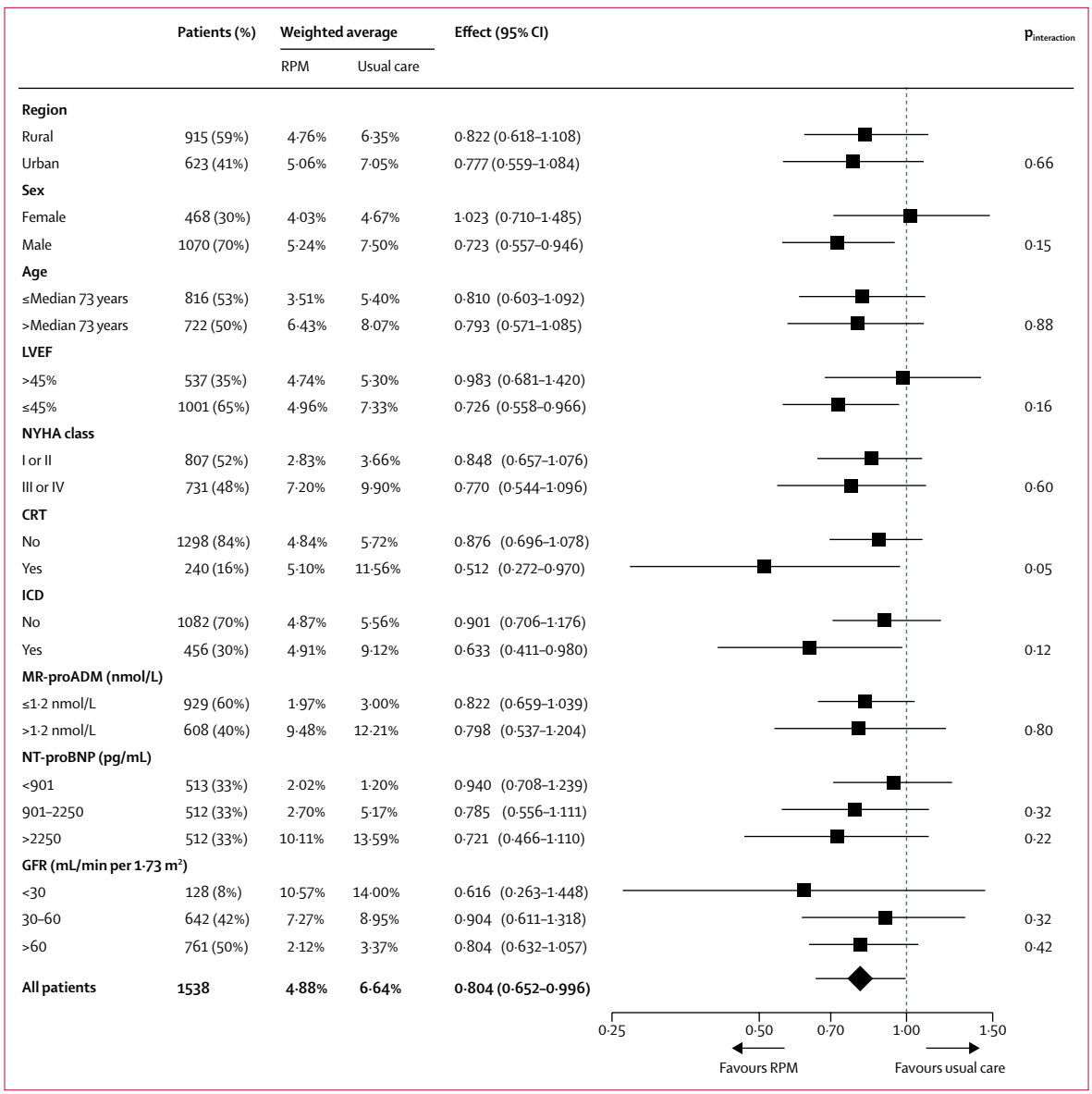

Figure 3: **Forest plot of subgroup analyses for percentage of days lost due to unplanned cardiovascular hospital admissions and all-cause mortality**
RPM=remote patient management. LVEF=left ventricular ejection fraction. NYHA=New York Heart Association. CRT=cardiac resynchronisation therapy. ICD=implantable cardioverter defibrillator. MR-proADM=mid-regional proadrenomedullin. NT-proBNP=N-terminal prohormone of brain natriuretic peptide. GFR=glomerular filtration rate.

well as the timely increase and decrease of diuretics conferred a substantial proportion of the benefit seen. We speculate that daily contact with patients enables a timely management of arrhythmias.

Both the education and the involvement of patients in the heart failure management and treatment strategy might also help in preventing a worsening heart failure episode, because patients will be able to identify worsening signs and symptoms early. This holistic approach might further help to increase adherence to the pharmacological heart failure treatment, because of the circle of patients' measurements and telemedical centre-given feedback.[19]

TIM-HF2 was undertaken in a large population drawn from a wide variety of practices throughout Germany in both metropolitan and rural areas. In our subgroup analysis, we noted no difference in effect between patients located in rural and metropolitan areas. This validates the concept that remote patient management can be used to harmonise the provision of health care across areas of great socioeconomic variability, at least in the setting of care for patients with chronic heart failure.

There are several specific trial design and execution issues that need attention when performing telemedical and remote patient management studies to mitigate

	Number of interventions	Median (range) per patient
Evaluation of patient-transmitted vital parameters*	1026078	1421·0 (6–3962)
Patient case review by TMC physicians and nurses	38694	36·0 (0–273)
Monthly structured telephone interview	9189	12·0 (1–13)
TMC initiated contact with patient for evaluation of key vital parameters	4324	4·0 (0–37)
TMC initiated contact with patient after discharge, physician appointment, and for validation of medication list	6037	7·0 (1–27)
TMC initiated medication changes	3546	3·0 (0–57)
TMC initiated scheduled 3-month medical report sent to patient's local physician (GP or cardiologist)	2812	4·0 (0– 4)
TMC physician and patient telephone consultations	1535	1·0 (0–40)
TMC initiated contact with health-care professionals	863	0·0 (0–21)
Patient home heart failure education including caregivers	765	1·0 (1–1)
TMC initiated emergency department visits	30	NA
TMC initiated unplanned cardiovascular hospital admissions	57	NA
TMC initiated unplanned non-cardiovascular hospital admissions	13	NA

*Vital parameters are bodyweight, blood pressure, self-rated health status, and electrocardiogram including peripheral capillary oxygen saturation. TMC=telemedicine centre. GP=general practitioner. NA=not applicable; only the total number is known, and not the median per patient.

Table 4: **Selected interventions of TMC physicians and nurses in the remote patient management group**

patient contact and data collection bias. Given the nature of remote patient management interventions, care providers are in contact much more frequently with patients assigned to the intervention than those in the usual care group, so are privy to much more information about these patients, which might include hospital admissions. We can confirm that the telemedical centre actions indeed triggered a number of hospital admissions in patients assigned to remote patient management. We will need to explore in future research the nature, duration, and effect of these hospitalisations. Nevertheless, the total number of admissions was lower in the remote patient management group than in the usual care group; hence, we speculate that the telemedical centre-triggered hospitalisations prevented hospital stays of longer duration.

Without a procedure cross-validating all hospital admissions with the respective health insurance provider, any study design would include an information bias against telemedical interventions to show a positive effect. We suggest that all telemedical studies aiming to document reductions in hospital admission rates need to include such procedures. More frequent contact with patients (here daily *vs* every 3 months in the usual care group) also carries the risk of more patients withdrawing from the study in the intervention group than in the control group. This was indeed the case in TIM-HF2. We aimed to avoid this bias as much as possible and hence included a grace period of up to 28 days for analysis of days lost after any premature withdrawal, but data protection issues prevented us from doing such analyses for hospitalisation to day 393 in all patients. For death, however, we could do a sensitivity analysis to day 393, which largely confirms the results for all-cause mortality.

Remote patient management in TIM-HF2 did not positively effect general measures of quality of life. We will need to explore this further. Exclusion of patients with major depression resulted in a cohort with a relatively good quality of life at baseline; hence, it was difficult to detect any improvement at the end of the study. The interventions provided by the telemedical centre did not significantly affect biomarker concentrations (namely NT-proBNP). Imaging data were not collected for this trial, so we are unable to discuss the association between the biomarkers and imaging data.

Over the entire study period, four physicians and five registered nurses worked as full-time staff in the telemedical centre during daytime hours (Monday to Sunday from 0800 h to 1600 h). In addition, during the night shift (daily from 1600 h to 0800 h), one physician was on-call on site and one physician was on-call at home.

Our study had several limitations. Our remote patient management was tailor-made to the German health-care system with specific emphasis on the interaction between a telemedical centre and local caregivers. The applicability of using our remote patient management in other health-care systems will require specific adaptations in two remote patient management elements: patient education (eg, depending on cultural differences) and in the interaction between caregivers (eg, depending on the given heart failure care structure).

In conclusion, the TIM-HF2 trial suggests that in a carefully selected population using a structured and holistic remote patient management intervention, the time spent in hospital for unplanned cardiovascular reasons is significantly reduced compared with usual care. Also, all-cause mortality is reduced by this intervention.

Contributors

FK contributed to the research conception and design, data acquisition, data analysis and interpretation, manuscript drafting, critical revision of manuscript, obtaining funding, and supervising the work. KK, OD, SP, B-AK, and SDA contributed to research conception and design, data acquisition, data analysis and interpretation, manuscript drafting, and critical revision of manuscript. KW and EV contributed to statistical analysis, data analysis and interpretation, manuscript drafting, and critical revision of manuscript. MO, CZ, HN, SSt, US, CA, RP, FE, SSp, SMS, JB, BW, CS, MT, HD, SW, and PCS contributed to data acquisition, and critical revision of manuscript. CB, LB, GD, GG, and KS contributed to data acquisition, research conception and design, and critical revision of manuscript.

Declaration of interests

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Telemedical Interventional Management in Heart Failure II (TIM-HF2), a randomised, controlled trial investigating the impact of telemedicine on unplanned cardiovascular hospitalisations and mortality in heart failure patients: study design and description of the intervention

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Background Heart failure (HF) is a complex, chronic condition that is associated with debilitating symptoms, all of which necessitate close follow-up by health care providers. Lack of disease monitoring may result in increased mortality and more frequent hospital readmissions for decompensated HF. Remote patient management (RPM) in this patient population may help to detect early signs and symptoms of cardiac decompensation, thus enabling a prompt initiation of the appropriate treatment and care before a manifestation of HF decompensation.

Objective The objective of the present article is to describe the design of a new trial investigating the impact of RPM on unplanned cardiovascular hospitalisations and mortality in HF patients.

Methods The TIM-HF2 trial is designed as a prospective, randomised, controlled, parallel group, open (with randomisation concealment), multicentre trial with pragmatic elements introduced for data collection. Eligible patients with HF are randomised (1:1) to either RPM + usual care or to usual care only and are followed for 12 months. The primary outcome is the percentage of days lost due to unplanned cardiovascular hospitalisations or all-cause death. The main secondary outcomes are all-cause and cardiovascular mortality.

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Conclusion The TIM-HF2 trial will provide important prospective data on the potential beneficial effect of telemedical monitoring and RPM on unplanned cardiovascular hospitalisations and mortality in HF patients.
Trial registration: ClinicalTrials.gov Identifier NCT01878630.

Keywords Chronic heart failure • Telemonitoring • Remote patient management • Hospitalisation

Introduction

Modern heart failure (HF) care programmes focus on the improvement of ambulatory HF care to reduce the risk of recurrent HF hospitalisations.[1] In the year following a HF hospitalisation, the rate of hospital readmission is approximately 50% and the 1-year mortality rate is 15–20%.[1,2] Current telemedicine HF concepts are holistic programmes which include telemonitoring and telemedical interventions, guideline-based ambulatory care and structured patient education grouped together and known as remote patient management (RPM).[3]

Many randomised controlled trials have investigated the impact of RPM in HF patients on different clinical outcomes — including BEAT-HF,[4] CardioBBEAT,[5] TIM-HF,[6,7] REM-HF,[8] OptiLink HF,[9] IN-TIME,[10] and CHAMPION.[11] The results from these studies are not consistent between each other with respect to morbidity and mortality. This may be explained by the differences in RPM interventions used and the nature of the heterogeneous patient populations included in the studies. Despite the differences in the study designs and the RPM interventions used (including invasive or non-invasive telemonitoring), one suggestion is that unstable HF patients with a recent (i.e. $\leq$ 12 months) hospitalisation for HF before starting RPM appear to have a subsequent lower HF readmission rate, have reduced mortality and an improvement in quality of life. A recent meta-analysis suggests that nurse home visits and disease management clinics can decrease all-cause mortality and readmissions after a recent hospitalisation for HF.[12]

In 2016, the European Society of Cardiology (ESC) recommended class IIb for telemonitoring with invasive telemedical devices in the actual guidelines for the treatment of acute and chronic HF.[13] A meta-analysis of data from completed clinical trials evaluating haemodynamic-guided care for HF patients concluded that haemodynamic-guided HF management using permanently implanted sensors and frequent evaluation of filling pressures was superior to traditional clinical management strategies in reducing the risk of hospitalisations in patients who remain symptomatic.[14]

The TIM-HF trial[6,7] enabled us to critically appraise the procedures and processes which were implemented for this trial, and based on the lessons learnt, we proceeded to design the Telemedical Interventional Management in Heart Failure II (TIM-HF2) trial. The TIM-HF2 trial is designed to assess the impact of RPM on mortality and morbidity in a HF population, also taking into consideration regional settings (i.e. rural vs. metropolitan). We present the design of the TIM-HF2 trial in addition to providing a description of the RPM system and approach which we plan to use in this study.

Study design

The TIM-HF2 trial is a prospective, randomised, controlled, parallel group, open (with randomisation concealment), multicentre trial with pragmatic elements introduced for data collection (ClinicalTrials.gov Identifier: NCT01878630). The study conduct is guided by good clinical practice (GCP), in accordance with the Declaration of Helsinki and the laws and regulations applicable in Germany. Written approval from the appropriate Ethics Committees is required and each patient must provide written informed consent. The TIM-HF2 Steering Committee (see online supplementary *Appendix S1*) and TMC staff members designed the trial and wrote the study protocol. An independent Data Safety Monitoring Board (DSMB) reviewed patient data periodically, as defined in the DSMB charter. A Clinical Endpoint Committee (CEC), blinded to treatment allocation, is appointed to adjudicate all deaths and hospitalisations using pre-defined criteria as detailed in the CEC charter (see online supplementary *Appendix S2*).

Study population, recruitment and randomisation

Eligible patients are patients with HF, with a history of a HF hospitalisation within 12 months prior to randomisation. At the time of randomisation, patients must be in New York Heart Association (NYHA) class II or III with either left ventricular ejection fraction (LVEF) $\leq$ 45% or, if LVEF > 45%, patients must be treated with oral diuretics. The inclusion and exclusion criteria are shown in *Table 1*.

In total, 113 sites located in 14 metropolitan areas with more than 200 000 inhabitants and/or with a medical university (i.e. Berlin, Dresden, Hamburg, Stuttgart, Frankfurt am Main, Leipzig, Hannover), and in 11 rural areas in Germany (namely: Brandenburg, Bavaria, Thuringia, Saxony, Saxony-Anhalt, Hesse, Baden-Württemberg, Lower Saxony, Mecklenburg-Western Pomerania, North Rhine-Westphalia, Saarland) are included. Forty-three sites are hospitals, 10 sites are university hospitals, and 60 sites are local cardiologist practices. In addition, 87 general practitioners (GPs) collaborate in the study by screening and following up their patients (for the list of all involved primary site investigators, see online supplementary *Appendix S3*).

Patients are randomised to either RPM + usual care (RPM group) or to usual care only (UC group) via a secure web-based randomisation system located at the Clinical Trial Centre Leipzig (CTC). To achieve a balance of potential risk factors in the treatment arms, Pocock's minimisation algorithm was used,[15] utilizing 12 baseline variables with 10% residual randomness (see online supplementary *Table S1*).

Table 1 Main inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Diagnosed with HF – NYHA class II or III • Echocardiographically determined left ventricular ejection fraction ≤45% or > 45% + oral diuretic prescribed • Hospitalisation due to decompensated HF within the last 12 months before randomisation • Depression score PHQ-9 < 10 • Written informed consent obtained	• Hospitalisation within the last 7 days before randomisation • Implanted cardiac assist system • Acute coronary syndrome within the last 7 days before randomisation • High urgent listed for heart transplantation • Planned revascularisation, transcatheter aortic valve implantation, MitraClip and/or CRT implantation within 3 months after randomisation • Revascularisation and/or CRT implantation within 28 days before randomisation • Known alcohol or drug abuse • Terminal renal insufficiency with haemodialysis • Impairment or unwillingness to use the telemonitoring equipment (e.g. dementia, impaired self-determination, lacking ability to communicate) • Existence of any disease reducing life expectancy to less than 1 year • Age < 18 years • Pregnancy • Participation in other treatment studies or remote patient management programmes (register studies possible)

CRT, cardiac resynchronisation therapy; HF, heart failure; NYHA, New York Heart Association; PHQ, Patient Health Questionnaire.

The RPM intervention consists of the following elements:

- A daily transfer of body weight, blood pressure (systolic/diastolic), heart rate, analysis of the heart rhythm as derived from a 2 min 3-channel electrocardiogram (ECG), peripheral capillary oxygen saturation (SpO_2) and a self-rated health status (scale range 1–5)
- Identification of a patient risk category using the baseline and follow-up visit biomarker values
- Patient education, and
- Cooperation between the telemedical centre (TMC), the patient's GP and cardiologist ('doc-to-doc telemedical scenario') with respect to patient management.

Patients randomised to the UC group are followed in accordance with the current standards (i.e. ESC guidelines for HF management) at the discretion of their treating physicians.[13]

Study assessments and follow-up

The planned follow-up per patient is 365 days and five outpatient visits are scheduled over this time period. After randomisation, outpatient visits are planned at 3, 6, and 9 months and the final study visit should be performed at 365 + 28 days — i.e. up to maximally 393 days post-randomisation (*Figure 1*). The assessments performed at each visit are displayed in *Table 2*.

Home telemonitoring system

In accordance with the study protocol, the home telemonitoring system should be installed in the patient's home within 7 days of randomisation. The RPM system used is based on a Bluetooth system with a digital tablet (Physio-Gate® PG 1000, GETEMED Medizin- und Informationstechnik AG) as the central structural element to transmit vital measurements from the home of the patient to the TMC at the Charité - Universitätsmedizin Berlin. Four measuring devices are part of the system: a 3-channel ECG device to collect a 2 min or streaming ECG measurement (PhysioMem® PM 1000 GETEMED Medizin- und Informationstechnik AG), a device to collect peripheral capillary oxygen saturation (SpO_2; Masimo Signal Extraction Technology (SET®), a system to collect blood pressure (UA767PBT, A&D Ltd.) and a body weighing scales (Seca 861, seca GmbH & Co KG). Each device is equipped with a Bluetooth chip and connected to the digital tablet.

The TMC software used is 'Fontane' (eHealth Connect 2.0, T-Systems International GmbH), which was specifically developed for use in the TIM-HF2 study. The key innovation of Fontane is a novel self-adapting TMC middleware, which consists of three key components:

- An algorithm for the transmitted patient data to identify critical values or missing data, which allows for an immediate identification of the patients requiring immediate (medical) attention,
- Telecommunication software for a direct communication between TMC staff, patients, GPs, and local cardiologists, as well as
- Electronic health records for all relevant medical information (e.g. medication plan; reports about previous hospitalisation; laboratory data).

Patients are provided with a mobile phone (DORO Easy 510/Doro HandlePlus 334gsm, Doro AB) to call the TMC directly in case of emergency. In such situations, it is also possible to initiate a live ECG stream using the ECG device. The tablet uses the mobile network to transmit the patient data automatically in an encrypted manner (GSM-encryption via VPN-Tunnel) to a central server of the TMC in Berlin provided by project partner Deutsche Telekom AG. The combination of measurements and personal data

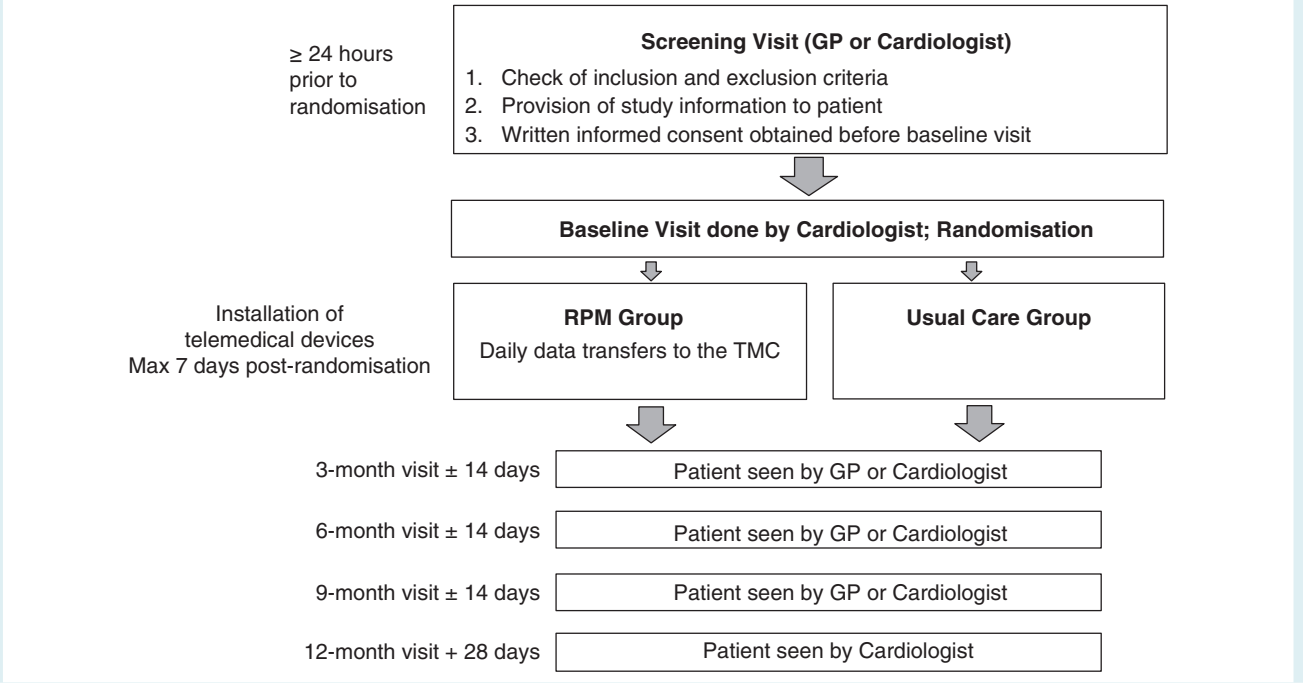

Figure 1 Trial flowchart. GP, general practitioner; RPM, remote patient management; TMC, telemedical centre.

with distinct information codes are only executed at a server at the Charité - Universitätsmedizin Berlin. To ensure patient safety, it is required a priori that the average transmission time to get the data to the TMC must be < 90 s. The availability of the mobile network connection is provided by the provider Deutsche Telekom AG. The complete data collection process, transmission and processing is done in strict compliance with state-of-the-art confidentiality and technical standards as agreed with and certified by the relevant data protection officer. For authentication of the individual measurements, all data transmissions incorporated unique device identification information. A service level agreement with the technical provider is concluded for first and second level support and corresponding service and escalation concepts.

In February 2013, the system was successfully tested in terms of safety, stability and performance during a pilot study done over 1 month in healthy volunteers at 50 different sites in rural (Brandenburg) and metropolitan areas (Berlin). The main outcome of the pilot study was a total system availability > 99%. The Fontane system obtained a European Conformity marking (CE) in 2013.

Registered nurses of the TMC install the telemonitoring equipment and train the patients and their families during home visits within 7 working days after randomisation. In addition, the nurses assess patients' self-care capabilities, give them information about their chronic disease (nursing assessment) and initiate a HF patient education programme, which is continued with monthly structured telephone interviews. According to the study protocol, the patients are instructed to measure daily, blood pressure, ECG tracing SpO_2, body weight and self-rated health status on a 5-point Likert scale using the tablet interface at defined time intervals.

All patients receive UC for the treatment and management of HF at the discretion of their treating physician.[13]

24/7 Telemedical support

The TMC provides physician-led medical support 24/7 for the entire study period according to standard operating procedures.

Within the Fontane system, algorithms are programmed and run on the transmitted data. The output is used by the TMC physicians and nurses to prioritise the workload and workflow so that patients presenting with any of the data cut-off limits as shown in *Table 3* are managed with priority.

Monthly, a structured telephone contact between the nurses and the patient is planned to discuss disease status, assess symptoms of depression or any other illness. In addition, the telemedical staff members initiate telephone contact when deemed appropriate — e.g. when there are changes in disease status, in case of technical problems, to verify vital sign measurements, to give advice, or to institute or change concomitant treatments.

Biomarker-guided approach

At the baseline visit and at each follow-up visit, biomarkers are taken and analysed by an independent laboratory. The results are sent to the CTC and the TMC. According to defined cut-off values for mid-regional pro-adrenomedullin (MR-proADM), patients are risk categorised as follows: low risk patients (MR-proADM ≤ 1.2 nmol/L) and high risk patients (MR-proADM > 1.2 nmol/L).

Table 2 Study flow

	Screening	Baseline	3-Month visit	6-Month visit	9-Month visit	Final visit (365 days or within + 28 days)
Informed consent and patient information	X	X				
Review inclusion/exclusion criteria	X	X				
Randomisation		X				
Physical examination		X				X
Registration medication		X				X
Echocardiography		X				
12-channel ECG		X				X
Laboratory tests: haemoglobin, haematocrit, leucocytes, thrombocytes, sodium, potassium, creatinine		X	X	X	X	X
Cardiac biomarkers: NT-proBNP, MR-proADM, MR-proANP, procalcitonin		X	X	X	X	X
Health questionnaires: MLHFQ, EQ-5D-3 L, PHQ-9D, G9-EHFScBS		X				X
Registration of events: hospitalisation, emergency, death			X	X	X	X

EQ-5D-3 L, EuroQol-5 Dimensions-3 Levels; G9-EHFScBS, German 9-Item European Heart Failure Self-care Behaviour Scale; MLHFQ, Minnesota Living with Heart Failure Questionnaire; MR-proADM, mid-regional pro-adrenomedullin; MR-proANP, mid-regional pro-A type natriuretic peptide; NT-proBNP, N-terminal pro-B type natriuretic peptide; PHQ-9D, Patient Health Questionnaire nine questions in German.

Table 3 Algorithm-guided prioritisation rules of the incoming vital parameters in the Fontane software

- Bradycardia, heart rate < 50 b.p.m.
- Tachycardia, heart rate > 100 b.p.m.
- Ventricular tachycardia
- New-onset atrial fibrillation
- PQ interval > 200 ms
- QRS duration ≥ 120 ms
- QTc interval > 460 ms
- SpO_2 < 94%
- Body weight (weight gain > 1 kg in 1 day, > 2 kg in 3 days; > 2.5 kg in 8 days)
- Blood pressure systolic: < 90 or > 140 mmHg; diastolic < 40 or > 90 mmHg
- Self-rated health status (grades from 1-very good to 5-very bad): deterioration of about 2 grades starting from 1, or grade 4 or 5)

SpO_2, peripheral capillary oxygen saturation.

High risk patients are primarily followed by TMC physicians ('doctors care'), and low risk patients by registered TMC nurses ('nurse care'). After each follow-up visit, patients are categorised in accordance with the new biomarker sample results.

Concomitant medication review

Patients allocated to the RPM group undergo a daily structured review of their concomitant medications based on the transmitted data. In consent with the study site physicians, the TMC physicians will optimise concomitant treatments as appropriate to achieve the following targets:

- Heart rate < 75 b.p.m. for patients in sinus rhythm.
- Blood pressure control: systolic < 140 mmHg and diastolic < 90 mmHg.
- Patients with new-onset atrial fibrillation: use of anticoagulant therapy as a long-term treatment and antiarrhythmic therapy.
- Patients in NYHA class II–IV: instigate the use of mineralocorticoid receptor antagonists where possible.

The aim is to ensure that patients are prescribed the maximally tolerated doses to achieve these targets and, in addition, diuretic doses are adapted in case of weight gain and worsening symptoms.

The telemedical team informs the patients' GP or caring physician by telephone, fax or email about any new events or important clinical findings from the monthly telephone contact, contacts with the emergency doctor, or any intervention made to the patients' therapy as a result of measured telemedical vital parameters. The TMC only advices the patient's primary physician — it is the latter who has the overall responsibility to instigate the medical management of the patients.

Other data collection processes

To avoid information collection bias, given the daily contact with patients in the RPM group, we have implemented a quality control process to ensure the accurate and complete reporting of hospitalisations in both the RPM and UC groups. Patients are asked to sign an informed consent including their permission for the TMC to contact their health insurance company to cross check the hospitalisations reported by the investigators with those on file in the health insurance records. This process was approved by the German Federal Social Insurance Office, Bonn.

Study outcomes

The primary outcome is the days lost (%) due to unplanned cardiovascular hospitalisations or all-cause death, comparing RPM with UC only during the individual follow-up time.

The main secondary outcomes include:

a. All-cause mortality during the individual follow-up time (+ 28 days from the final study visit to a maximum of 393 days).
b. Cardiovascular mortality during the individual follow-up time (+ 28 days from the final study visit to a maximum of 393 days).
c. Days (%) lost due to unplanned cardiovascular hospitalisations during the individual follow-up time.
d. Days (%) lost due to HF hospitalisations during the individual follow-up time.
e. Change in the Minnesota Living with Heart Failure Questionnaire (MLHFQ) Global score between baseline and 365 days.
f. Change in the levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) and of MR-proADM between baseline and 365 days.

The following recurrent event analyses will be performed:

a. Unplanned cardiovascular hospitalisations and cardiovascular mortality.
b. Unplanned cardiovascular hospitalisations and all-cause mortality.
c. Unplanned HF hospitalisations and cardiovascular mortality.
d. Unplanned HF hospitalisations and all-cause mortality.

Pre-specified subgroups

Subgroup analyses will be performed for the primary outcome to assess the consistency of intervention effects across the following subgroups:

- Metropolitan vs. rural area of medical care.
- Male vs. female.
- Above/below median age.
- LVEF $\leq$ 45% vs. LVEF > 45%.
- NYHA functional class I/II vs. III/IV.
- Cardiac resynchronisation therapy (CRT) at baseline yes/no.
- Implantable cardioverter defibrillator (ICD) at baseline yes/no.
- MR-proADM at baseline $\leq$ 1.2 nmol/L vs. > 1.2 nmol/L.
- Tertiles of NT-proBNP baseline levels.
- Estimated glomerular filtration rate groups < 30/30–60/ > 60 mL/min.

Statistical considerations

Sample size

The sample size calculation was based on a subgroup of 333 patients of the TIM-HF trial (NCT00543881) with Patient Health Questionnaire (PHQ-9D) score < 10 and a hospitalisation due to decompensated HF within 12 months before randomisation.[7] At month 6, this subgroup of patients showed a 55% difference in the endpoint days lost due to unplanned cardiovascular hospitalisations and death in favour of the telemedical patients while at the 12-month follow-up time point, this difference was 36%. Based on these results of TIM-HF, a sample size of 1500 patients is planned for TIM-HF2 with an equal group size of 750 patients in the RPM and UC groups to detect a reduction in the primary outcome of 38% with a two-sided alpha of 5% with a power of 80%.

Statistical analyses

All analyses will be performed using the Full Analysis Set (FAS) in accordance with the intention-to-treat principle. Patients who are randomised to the RPM group, but for whom the RPM intervention was not installed, will be replaced.

The per protocol population will be a subset of the FAS population and will only include those patients with no major protocol deviation.

Analysis methods

Due to the expected skewed distribution, the primary outcome will be tested using a permutation test with weighting for the amount of follow-up time. All-cause and cardiovascular mortality will be analysed by Kaplan–Meier curves and log-rank tests. Cardiovascular mortality will be analysed taking competing risks into account with cumulative incidence curves and cause-specific hazard ratios. Recurrent events will be analysed by negative binomial tests, with sensitivity analysis according to WLW method or joint frailty models. Quality of life and biomarkers will be analysed by analysis of covariance. Further details will be given in a separate statistical analysis plan.

Individual patient follow-up will be defined as the time between randomisation and the actual or planned final study visit, which should take place plus maximally 28 days after day 365, i.e. a maximum of 393 days after randomisation. For patients who die before day 365, their intended follow-up will be calculated up to day 365. For patients who withdraw from follow-up prematurely — i.e. withdraw consent for further participation — their intended follow-up will be calculated up to the day of withdrawal of informed consent.

For the mortality-related secondary outcomes, the expanded individual follow-up time is defined as the time as of randomisation to the final study visit date + 28 days to a maximum of 393 days.

Discussion

The TIM-HF2 trial can be categorised as an RPM trial using non-invasive multi-parameter telemonitoring technology. The home telemonitoring devices for vital parameter measurement we implement for this trial have already been used in the TIM-HF study.[6,7]

Remote patient management devices come in different ways. Some implantable devices (e.g. CRT/ICD devices) today have remote data transfer functionality and these data can be used for RPM. Several other systems exist that use body weight or blood pressure data for RPM purposes. The home monitoring devices we use in TIM-HF2 are commercially available, but the system of systematic data processing and the TMC infrastructure we use is innovative. To the best of our knowledge, the combination of a vital parameter transfer from the home of the patient to an analytical machine in a TMC is used for the very first time under the conditions of a RPM clinical trial. In this setting, the TMC staff collaborates with a multidisciplinary team of health care providers (including cardiologists, nurses, and GPs) as well as the patient. The identification of high and low risk patients is supported by the use of biomarker data. This holistic approach also aims to increase adherence to the pharmacologic HF treatment.[16]

Selection of the population to be included in the TIM-HF2 trial

Based on our experiences in the TIM-HF study,[6,7] we extensively evaluated the data to identify the most optimal HF subpopulation that could potentially best benefit from this type of health care management, and the best endpoint to study. In the TIM-HF trial, the patients that seemed to fair better were patients who had a recent hospitalisation for HF and who did not present with major depression as defined by the German Version of the PHQ-9 (PHQ-9D) score. The patient selection criteria in the TIM-HF2 trial reflect these findings.

Another important factor of consideration when determining the best treatment strategy for HF patients is their domicile — i.e. rural or urban. In contrast to metropolitan areas with relatively easy access to a high number of cardiologists, rural area HF care in Germany is dominated by GPs.[17] Stakeholders have the expectation that RPM will be able to provide the same level of care and access to specialised care as that easily accessible in a metropolitan setting. We took this factor into consideration when designing the TIM-HF2 trial, and hence we aim to have a proportion of more than 60% of sites located in rural areas.

Rationale for the selection of the primary outcome

We selected the primary outcome as days (%) lost due to unplanned cardiovascular hospitalisations and all-cause mortality for two reasons. It is an appropriate outcome in RPM trials in HF patients, which was first used as a primary endpoint in the Trans-European Network Home-Care Management System (TEN-HMS) study.[18] Moreover, the primary outcome of TIM-HF2 is a patient centric outcome by definition, reflecting the most key patient expectations for his/her HF care, i.e. to be alive and to remain outside the hospital.

If this primary endpoint is positive, the TIM-HF2 trial would demonstrate that RPM with integrated biomarker assessment is beneficial for a large subgroup of HF patients following recent hospitalisation and excluding those with evidence of major depression. Importantly, the study includes patients with reduced, mid-range and preserved LVEF.[19,20]

We believe that this real-time approach to the management of specific HF populations is the way forward to provide timely, personalised and quality care to this chronically ill patient population. Both the education and the involvement of patients in the HF management and treatment strategy may also help in preventing a 'full-blown' manifestation of a worsening HF episode as patients will be able to identify worsening signs and symptoms early. The results of our study are expected in 2018.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Study Committees.

Appendix S2. Clinical event classification criteria.

Appendix S3. List of primary site investigators, nurses and study management.

Table S1. Stratification factors for the minimisation process in randomisation as per Pocock's minimisation algorithm for TIM-HF2.

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