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Telemedical Interventional Monitoring in Heart Failure (TIM-HF), a randomized, controlled intervention trial investigating the impact of telemedicine on mortality in ambulatory patients with heart failure: study design†

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Aims Remote patient management (telemonitoring) may help to detect early signs of cardiac decompensation, allowing optimization of and adherence to treatments in chronic heart failure (CHF). Two meta-analyses have suggested that telemedicine in CHF can reduce mortality by 30–35%. The aim of the TIM-HF study was to investigate the impact of telemedical management on mortality in ambulatory CHF patients.

Methods CHF patients [New York Heart Association (NYHA) II/III, left ventricular ejection fraction (LVEF) $\leq$35%] with a history of cardiac decompensation with hospitalization in the past or therapy with intravenous diuretics in the prior 24 months (no decompensation required if LVEF $\leq$ 25%) were randomized 1:1 to an intervention group of daily remote device monitoring (electrocardiogram, blood pressure, body weight) coupled with medical telephone support or to usual care led by the patients' local physician. In the intervention group, 24/7 physician-led medical support was provided by two central telemedical centres. A clinical event committee blinded to treatment allocation assessed cause of death and reason for hospitalization. The primary endpoint was total mortality. The first secondary endpoint was a composite of cardiovascular mortality or hospitalization due to heart failure. Other secondary endpoints included cardiovascular mortality, all-cause and cause-specific hospitalizations (all time to first event) as well as days lost due to heart failure hospitalization or cardiovascular death (in % of follow-up time), and changes in quality of life and NYHA class. Overall, 710 CHF patients were recruited. The mean follow-up was 21.5 $\pm$ 7.2 months, with a minimum of 12 months.

Perspective The study will provide important prospective outcome data on the impact of telemedical management in patients with CHF.

Keywords Chronic heart failure • Telemedicine • Intervention trial • Mortality • Hospitalization

†The list of participating investigators is provided in Appendix 1 and Appendix 2.

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Introduction

Modern telecommunication technologies have created new options for telemonitoring of patients with chronic heart failure (CHF). CHF results in poor life expectancy, impaired quality of life, and repeated hospitalizations, and is a considerable economic burden to society.[1] Despite advances in its treatment, the prognosis of CHF remains poor.[2]

Disease management programmes, mostly provided via heart failure clinics, have been reported to provide better care to CHF patients and to reduce healthcare utilization. In the last decade, in particular, the focus has been on the development of remote support systems for CHF patients. Remote patient management may help to optimize therapy, improve compliance, and enable early detection of signs and symptoms of cardiac decompensation. Two recent meta-analyses suggest that telemedical monitoring of CHF patients can improve rates and duration of hospitalization as well as overall survival.[3,4] These analyses reported that the reduction in mortality associated with telemedicine in CHF patients was between 17 and 47% during a reported median follow-up time of 6 months in randomized controlled trials (RCTs) and 12 months in cohort studies (*P*-values of 0.006 to <0.0001). To date, no study has prospectively investigated the impact of telemedical management on mortality in patients with CHF.

In the majority of telemedical studies reported so far, telemedical support was restricted to office hours only, which could limit efficacy. We aimed to overcome this shortcoming by using a dedicated telemedical centre with a permanent physician presence that provided service 24 h a day 7 days a week.

The Telemedical Interventional Monitoring in Heart Failure (TIM-HF) trial was a randomized, controlled intervention study designed to investigate whether telemedical care provided through dedicated 24/7 telemedical centres can reduce mortality in ambulatory CHF patients over a mean follow-up of 21 months, when compared with usual care. The first secondary endpoint was time to occurrence of the first of the following: cardiac death or hospitalization for heart failure. The present report provides details on the TIM-HF study design.

Study design

Overall trial design and planning

TIM-HF was an open, randomized, parallel group, prospective multi-centre clinical trial. Seven hundred and ten stable, ambulatory CHF patients were randomized in equal proportions to one of two intervention groups—home telemonitoring or usual care. Patients were followed for a minimum of 12 months (last randomized patient) and a maximum of 28 months (first randomized patient). The average follow-up was 21 months. The Clinical Trial Centre Leipzig (KKS), University Leipzig, Germany, acted as the coordinating centre for the trial.

Patients were recruited from 165 cardiology, internal medicine, or general medicine practices located in four areas of varying economic status in Germany, i.e. Berlin, Brandenburg, Saxony-Anhalt, and Baden-Württemberg (Appendix 1). The diversity of outpatient clinic types and their distribution represented the regional differences within these four regions of varying infrastructure, where general medical care predominates in rural or scarcely populated territories in contrast to the medical specialist care in urban areas. Each participating site was not only responsible for the recruitment and follow-up of patients, but also for contingency patient management in collaboration with the telemedical centres. Each site recruited between 1 and 35 patients (average 4.3).

The study was conducted in accordance with the principles stated in the Declaration of Helsinki (1996), International Conference on Harmonization Good Clinical Practice, and local and national regulations. Written informed consent was obtained from all patients prior to any study-related procedures.

Patient selection

Optimally treated (i.e. with angiotensin receptor blockers, β-blockers, and diuretics), stable, ambulatory CHF patients, who had signed the informed consent form, were eligible to participate if they were aged at least 18 years and were in New York Heart Association (NYHA) class II or III with a left ventricular ejection fraction (LVEF) $\leq 35\%$. In addition, eligible patients must have had at least one episode of decompensation in the previous 24 months with hospitalization for worsening heart failure or treatment with intravenous loop diuretics (>40 mg furosemide per day). The requirement for the previous episode of decompensation was not necessary if the patient had an LVEF $\leq 25\%$ (measured twice within the past 6 months).

The main exclusion criteria were: the presence of a pre-existing condition (other than heart failure) which limited life expectancy (<1 year), foreseeable problems with patient compliance, presence of unstable angina, on the heart transplant list, planned treatment with an implantable cardioverter defibrillator (ICD), and/or cardiac resynchronization therapy (CRT) device (must have taken place at least 12 weeks prior to inclusion). The complete list of inclusion and exclusion criteria is provided in Table 1.

Data collection and visit schedules

A complete medical history and symptomatic status relating to CHF, NYHA class, vital signs, and concomitant treatment were collected on paper case report forms (CRFs) for each patient prior to randomization. After randomization, outpatient clinic visits were performed at 3-month intervals for the first 12 months and thereafter at intervals of 6 months, as well as at the end of the study. During these follow-up visits, vital signs were recorded in addition to CHF symptomatic status, NYHA class, and any changes made to concomitant treatment. In addition, patients completed a quality-of-life questionnaire (SF-36) and a questionnaire to assess depression (PHQ-9) at baseline and at all follow-up visits (months 3, 6, 9, 12, 18, and 24). Information relating to death from any cause, hospitalization, or emergency room admissions was reported on the specific form provided in the CRF.

Randomization

During the baseline visit, specific information concerning eligible patients was sent to the coordinating centre by fax. Patients were then assigned to one of the two treatment arms by a central computerized randomization system. In order to achieve a balance of potential risk factors in the treatment arms, Pocock's minimization

Table 1 Summary of key inclusion and exclusion criteria at screening

Inclusion criteria
1. Ambulatory CHF NYHA II or III
2. LVEF ≤ 35% and cardiac decompensation with hospitalization for heart failure or therapy with intravenous diuretics (>40 mg furosemide/day) within 24 months prior to enrolment
or
LVEF ≤ 25%, measured twice within past 6 months
3. Optimal medical treatment for CHF (β-blocker, ACE-inhibitor/ARB, diuretics) including ICD/CRT if indicated
4. Age ≥ 18 years
5. Informed consent
Exclusion criteria
1. Existence of any disease (HF excluded) reducing life expectancy to less than 1 year
2. Insufficient compliance to telemonitoring or study visits
3. Impairment to use the telemonitoring equipment or appear to study visits (e.g. dementia, impaired self-determination, lacking ability to communicate)
4. Pregnancy
5. Concurrent participation in other therapy trials
6. Hospitalization for cardiac decompensation within 7 days before inclusion in trial
7. Implanted cardiac assist system
8. Unstable angina pectoris
9. Congenital heart defect
10. Primary heart valve disease
11. Hypertrophic or restrictive cardiomyopathy
12. Arrhythmogenic right ventricular cardiomyopathy
13. Acute myocarditis diagnosis <1 year
14. Actively listed for heart transplantation
15. Planned revascularization or CRT implantation
16. Chronic renal insufficiency with creatinine >2.5 mg/dl
17. Liver cirrhosis
18. Known alcohol or drug abuse

algorithm[5] (with 20% residual randomness) was used, with the following variables: NYHA class II or III, hospitalization for heart failure within 2 years prior to randomization, implanted defibrillator, region (Berlin-Brandenburg or Baden-Württemberg), age group (<60 or 60–70 or >70 years), known diabetes mellitus, known cerebrovascular disease, living alone or with partner, gender, presence of CRT, use of statins, and use of aldosterone receptor antagonists. Investigators were unaware of the randomization sequence.

Intervention group

The telemonitoring system used in the TIM-HF trial is based on a wireless Bluetooth system with a personal digital assistant (PDA) as the central structural element. The only prerequisite for this system to function once installed is the availability of a mobile phone network connection. Three measuring devices are integrated into the system, namely one to collect electrocardiogram (ECG) measurements, one to collect blood pressure measurements, and one to collect body weight. Each device is equipped with a Bluetooth chip and connected to the PDA. The patient performs the daily self-assessment of health status by using the PDA interface. A subgroup of patients in the intervention group performed a 6-min walk test using a telemedical accelerometer once a month (APM Medlogger; Aipermon GmbH & Co. KG, Munich, Germany) starting 3 months after randomization.[6]

The PDA uses the mobile phone network to transmit all data in an encrypted manner to a central server where the measurements are organized and sent to the local servers of the respective telemedical centres. The telemedical database was located in two hospital-based telemedical centres in Berlin and Stuttgart (Appendix 2). All procedures were in compliance with state-of-the-art confidentiality standards for electronic archiving of medical data as agreed with and certified by the relevant data protection offices. For authentication of the individual measurements, all data transmission incorporated unique device identification information. Privacy of data was ensured using dynamic encryption. To ensure patient safety, it was *a priori* required that total system availability (of all central components including server, software, and communication systems), including that of the mobile phone network, was no less than 94%. Further technical details on the telemedical technology used and the results of feasibility testing are described in a dedicated manuscript.[7]

The telemonitoring equipment was installed, and training was given to patients within 5 working days after randomization (2–3 days in most cases). Patients were instructed to submit daily measurements of blood pressure, body weight, and ECG measurements in addition to a self-assessed health status, to their respective telemedical centre located either in Berlin or in Stuttgart. The telemedical centres provided physician-led medical support 24 h a day, 7 days a week for the entire study period according to a structured programme using standard operating procedures. A structured telephone contact between the telemedical centre and the patient was made once a month to discuss disease status, assess symptoms of depression, to instruct the patient about dealing with emergency situations, and to solve any technical problems. Typically, the two telemedical centres worked in parallel caring for their respective patients. To further increase the efficacy of the overall telemedical structure, as of May 2009, the night-time service (8 p.m. to 7 a.m.) and the weekend and bank holiday service (1 p.m. to 7 a.m.) for the entire study population in the telemedicine treatment group was provided by the Berlin telemedical centre alone.

In addition to the PDA-centred system with its different assessment tools, the home of each patient in the telemedicine treatment group was equipped with a landline-based personal emergency response system, enabling a fast and direct connection via a loudspeaker between the patient's home and a physician at the responsible telemedical centre in the case of emergencies. It was also possible to initiate a live ECG stream (using the ECG device) and to perform oxygen saturation measurements (using an additional device) in such situations.

Besides the monthly contact, a member of the telemedical staff also contacted the patient when deemed necessary (according to the standard operating procedures related to changes in the

parameters assessed, clinical judgement, and the patient's clinical development) or if requested by the patient to verify measurements, give advice, or institute treatment. The telemedical staff informed the patient's general practitioner or caring physician by telephone or fax about any events, interventions, important findings from the monthly telephone contact, contacts with the emergency doctor, or any changes made to the patient's therapy as a result of new findings seen on the data transmitted to the telemedical centre. Overall responsibility for the patients' care remained with the local physician. The telemedical centre supported the local physician.

Usual care group

Patients randomized to the usual care group were followed by their treating physician who was instructed to ensure that the patients were optimally treated for their heart failure in accordance with the current standards and guidelines for treatment of patients with CHF.

Clinical Endpoint Committee

A Clinical Endpoint Committee (CEC), blinded to treatment allocation, will classify all deaths and hospitalizations using pre-defined criteria as detailed in the CEC charter (Appendix 3).

Study endpoints

The primary endpoint is all-cause mortality.

The first secondary endpoint is a composite of the combined rate of cardiovascular death and hospitalization for worsening heart failure. For this composite endpoint, patients will be followed for all hospitalizations for heart failure until death or the end of follow-up thus enabling the possibility to report event rates for each event.

Other secondary endpoints include:

- days lost due to death or heart failure hospitalization,
- cardiovascular mortality,
- rate of cardiovascular hospitalization at 6, 12 and 24 months
- rate of hospitalization for Heart Failure at 6, 12 and 24 months
- hospitalization for any reason,
- cardiovascular hospitalization,
- hospitalization for heart failure,
- duration of all hospitalizations for heart failure,
- NYHA functional class at 12 months and 24 months adjusted for baseline,
- SF-36 physical functioning score at 12 months and 24 months adjusted for baseline, and
- PHQ-9 depression score, 12 months and 24 months adjusted for baseline.

As for the first secondary endpoint, patients will be followed for all events until death or the end of follow-up.

Statistical considerations

Sample size

The sample size calculation was based on the assumption of a mortality rate of 27% in the control group and 17% in the intervention group. This corresponds to a relative risk (RR) of 0.63, which is comparable to the effect of remote patient management reported by Cleland *et al.*[8] (RR = 0.65) and more conservative than the findings of Goldberg *et al.*[9] (RR = 0.44). These were the only two study reports available and considered relevant when designing TIM-HF. In order to ensure a minimum power of 90% to detect the resulting hazard ratio of 0.59 at a two-sided type I error level of 0.05, where 114 events should be observed, 600 patients should be recruited when accounting for the overall event rate of 22% and a withdrawal from follow-up rate of 5%. In 2008, the sample size was increased to 710 patients and the follow-up extended by 12 months because at that time, there was a lower-than-anticipated event rate after 1 year of follow-up.

Statistical analysis

The essential features of the planned statistical analyses are as follows: two analysis populations will be distinguished—the full analysis set (FAS) and the per protocol analysis population. The FAS analysis population will consist of all patients who were randomized to either the intervention or the usual care group. The analysis will be performed according to the Intention-to-treat principle. Using Kaplan–Meier plots and log-rank tests to compare censored time-to-event data, the primary and time-to-event secondary endpoints, as defined by the CEC, will be analysed by the assigned treatment group. Effects of telemonitoring relative to usual care will be expressed as hazard ratios with 95% confidence intervals (CIs) using Cox proportional hazards models. NYHA class during follow-up will be compared by the Mann–Whitney test, stratified by the baseline NYHA class. Analysis of variance will be carried out for quality-of-life scores. The impact of compliance (i.e. frequency of data transfer to the telemedical centre) in the intervention group will be assessed by Cox regression for mortality and correlation analysis for quantitative outcomes. Prospectively defined sub-group analyses for the primary and first secondary endpoints will also be performed.

Subgroup analyses

Subgroup analyses will be performed for the following subgroups:

(1) male vs. female;
(2) defibrillator vs. no defibrillator;
(3) NYHA II vs. III;
(4) episode of HF decompensation (HF decompensation is defined as hospitalization within 24 months prior to randomization and/or treatment with IV diuretics within 24 months prior to randomization) prior to randomization vs. all others;
(5) GFR: $<$60 mL/min vs. all others;
(6) NT-proBNP: highest tertile vs. all others;
(7) MR-proADM: highest tertile vs. all others;
(8) MR-proANP: highest tertile vs. all others;
(9) PHQ depression score $>$10 points vs. all others;
(10) Age $\geq$70 years vs. $<$70 years;
(11) defibrillator at baseline and episode of HF decompensation prior to randomization (any time) vs. all others;
(12) LVEF (in %): above median vs. below median.

Study status

The study protocol and amendments have been approved by relevant regulatory authorities and ethics committees. Patient enrolment started on 10 January 2008, and the last patient was recruited on 22 June 2009. The study is expected to report its results late autumn 2010.

Discussion

The TIM-HF trial investigates the effect of our telemedical management system compared with usual care on all-cause mortality. The first secondary endpoint of the TIM-HF trial is to evaluate whether telemedical care can improve a combined endpoint of cardiovascular death or heart failure hospitalization compared with usual care. TIM-HF is the first telemedical trial to prospectively investigate these outcomes in CHF patients over a mean follow-up of 21 months.

Other secondary endpoints include cause-specific mortality and hospitalization rates, and days lost to death or hospitalization, symptom status, and quality of life. TIM-HF has recruited 710 patients and the mean follow-up is 21 months, which is substantially longer than in other trials. Klersy *et al.*[3] reported that the mean follow-up in previous RCTs of remote patient monitoring was only 6 months which is too short to make recommendations for a clinical practice. One important practical question for healthcare providers—besides the question as to whether or not such systems are efficacious—will be about the duration of remote patient monitoring. Only longer-term intervention trials can possibly provide some guidance on this.

Several clinical trials of telemedical care have recently been reported, including the HOME-HF trial,[10] the INH study,[11] COACH,[12] the HHH study,[13] the DOT-HF study,[14] and the CHAT system.[15] Hence, two meta-analyses have recently been published regarding the overall impact of telemedical care on survival and hospitalization rates in CHF patients.[3,4]

The meta-analysis of Klersy *et al.*[3] reported on remote patient monitoring in CHF with a total of 6258 patients enrolled in RCTs (20 studies) and 2354 patients assessed in cohort studies (12 studies). Median follow-up was 6 and 12 months, respectively. The RCTs showed that telemedicine was associated with a significantly lower number of deaths (RR = 0.83, 95% CI: 0.73–0.95, $P = 0.006$). In the cohort studies, the effect was more pronounced (RR = 0.53, 95% CI: 0.29–0.96, $P < 0.001$). Also, hospitalizations overall and hospitalizations for heart failure were significantly lower in patients cared for using remote patient monitoring. The decrease in events was greater in cohort studies than in RCTs.

In the meta-analysis of Inglis *et al.*,[4] 25 studies were considered for analysis, 16 studies of structured telephone support (5613 participants), 11 studies of telemedicine (2710 participants), and 2 studies of both. Telemonitoring reduced all-cause mortality by 34% (RR = 0.66, 95% CI: 0.54–0.81, $P < 0.0001$), but structured telephone support was not associated with significantly reduced mortality. Telemonitoring also reduced CHF-related hospitalizations (RR = 0.79, 95% CI: 0.67–0.94, $P = 0.008$) as did structured telephone support (RR = 0.77, 95% CI: 0.68–0.87, $P < 0.0001$). For both structured telephone support and telemonitoring, Inglis *et al.*[4] reported that several studies documented improved quality of life and reduced healthcare costs and that the interventions were acceptable to patients.

Meta-analyses can provide strong arguments and have an impact on guideline recommendations in the absence of prospectively designed studies. TIM-HF is the first study to prospectively test whether overall mortality is reduced in CHF patients when structured telemedical care is provided compared with usual care. TIM-HF is a multi-centre randomized, controlled intervention study that will provide important information about the efficacy of telemedicine in CHF. TIM-HF will enable us to make statements about the health economic impact that telemedical therapy may have in CHF patients.

Author contributions

The study protocol was developed by F.K., M.S., S.L., G.G., and S.D.A. The first draft of the manuscript was written by F.K., S.W., S.S.K., B.-A.K., and S.D.A. All other authors contributed to critically revising the manuscript.

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Conflict of interest: S.D.A. is consultant for Robert Bosch Healthcare GmbH, Brahms GmbH and St. Jude Medical GmbH and receives honoraria for speaking from Brahms GmbH and St. Jude Medical GmbH.

Study Committees

Principal Investigator: Friedrich Koehler.

Steering Committee Members: Stefan D. Anker (Chair), Friedrich Koehler, Udo Sechtem, Karl Stangl, Michael Böhm, and Herbert Boll.

Critical Event Committee Members: Wilhelm Haverkamp (Berlin, Chair), Markus Haass (Mannheim), Matthias John (Schwedt/Oder), and Martin Middeke (München).

Data Safety Monitoring Board: Christian Opitz (Berlin, Chairman), Rainer Dietz (Berlin), Goetz Gelbrich (statistician, Leipzig).

Appendix 1

Local investigators who participated in the study

Name	First name	City
Abele	Peter	Stuttgart
Aigeldinger	Erwin	Remshalden
Anders	Carola	Berlin
André	Thomas	Mühlacker
Arend	Ute	Vetschau/Spreewald
Asci	Tayfun	Waiblingen
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Bassen-auf dem Brinke	Alexandra	Berlin
Bauer	Gerhard	Bad Mergentheim
Becker	Hans-Joachim	Heidenheim
Behroz	Abdullah	Heidelberg
Beling	Mark	Berlin
Biewener	Hans-Ullrich	Baden-Baden
Boden	Ulrich	Oranienburg
Boitz	Martin	Berlin
Bondke	Christina	Berlin
Boron	Janusz	Leonberg
Borst	Ulrich	Esslingen
Brendel	Ralph	Zehdenick
Brunk	Katharina	Schwedt/Oder
Bubeck	Otto	Stuttgart
Buhr	Marianne	Berlin
Byrtus	Martin	Villingen-Schwenningen
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Dieckmann	Lutz	Wittenberge
Doster	Gerhard	Stuttgart
Drescher	Matthias	Brieselang
Ehlert	Annette	Pritzwalk
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Engelsing	Meike	Berlin
Etzold	Erika	Berlin
Fassbender	Manuel	Berlin
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Continued

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Hagenow	Andreas	Elsterwerda
Hahn	Rüdiger	Stuttgart
Hartmann	Susanne	Reutlingen
Haufe	Corina	Dreetz
Haufe	Stefan	Rastatt
Hechler	Rüdiger	Prenzlau
Heda	Barbara	Bad Liebenwerda
Hein	Konrad	Böblingen
Herbst	Ingo	Potsdam
Herpolsheimer	Frank	Cottbus
Hess	Karl-Michael	Schorndorf
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Hotz	Holger	Berlin
Hudelmaier	Azra	Stuttgart
Hueck	Christian	Berlin
Jaehn	Thomas	Forst
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Kannenberg	Jörg	Kyritz
Kempf	Peter	Titisee-Neustadt
Kendzia	Alexander	Berlin
Kiesel	Erhard	Crinitz
Kleinbach	Klaus	Kirchheim unter Teck
Knapp	Markus	Schwäbisch Hall
Knorpp	Rudolf	Fellbach-Schmiden
Kobel	Michael	Rüdersdorf
Konietzko	Agathe	Konstanz
Kraiß	Martin	Stuttgart
Krause-Allmendinger	Helmut	Ludwigsburg
Kühlkamp	Volker	Konstanz
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Kurth	Carsten	Waldshut-Tiengen
Laskos	Klaus	Berlin
Lenz	Lutz	Welzheim
Löffler	Richard	Weil am Rhein
Lokies	Jan	Berlin
Löprich	Bruno	Baden-Baden
Lorenz	Lucian	Pforzheim
Lötsch	Manuela	Strausberg
Mahler	Hans	Schwäbisch Gmünd
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Martens	Hellmut	Stuttgart

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Merz	Gerhard	Bietigheim-Bissingen
Metz	Werner	Leonberg
Metzler	Jörg	Schwäbisch Gmünd
Mies	Peter	Stuttgart
Möller	Christine	Berlin
Möller	Swetlana	Berlin
Morgan	Paul	Berlin
Moser	Bernd	Stuttgart
Mulzer	Johanna	Berlin
Natour	Mohammed	Heidelberg
Neeb	Bernd	Berlin
Niedrig	Kristina	Luckenwalde
Nowzohour	Djafar	Berlin
Oeder	Robert	Berlin
Petcu	George	Stuttgart
Pfeiffer	Wilhelm	Ditzingen
Pinkwart	Lutz-Ulrich	Berlin
Plappert	Bernhard	Calw
Pomiersky	Christian	Tuttlingen
Pötsch	Thomas	Berlin
Pricelius	Sabine	Berlin
Pulvermüller	Frank	Heilbronn
Putze	Kersten	Stuttgart
Raible	Rudolf	Berlin
Rathert	Bernhard	Karlsruhe
Reich	Christiane	Waiblingen
Rek	Birgit	Stuttgart
Ritter	Berthold	Emmendingen
Röder	Frank	Schwaikheim
Rommel	Theophil	Ditzingen
Rösch	Dieter	Schwäbisch Gmünd
Saurbier	Bernward	Freiburg/Breisgau
Scheuermann	Oliver	Kornwestheim
Schiefer	Christina	Klettwitz
Schlick	Matthias	Karlsruhe
Schmitt	Frank	Stuttgart
Scholz	Harald	Luckau
Scholz	Thomas	Berlin
Schultze	Dietrich	Stuttgart
Schumm	Wolfram	Filderstadt
Schwehr	Udo	Seelbach
Schwerecke	Anke	Templin
Seifart	Christoph	Berlin
Seyfferth	Thomas	Reutlingen
Sieroslawski	Ludwig	Bad Waldsee
Simon	Josef	Schwäbisch Gmünd
Sinn	Lutz	Bad Säckingen
Sommerfeldt	Antje	Berlin

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Name	First name	City
Spangenberg	Birgit	Berlin
Steffens	Cornelius	Berlin
Stiller	Wolfgang	Wittstock
Strähle	Erwin	Aichtal-Aich
Szerdahelyi	Ulrike	Berlin
Tamm	Angelika	Wittenberg
Tardel	Johannes	Stuttgart
Theiss	Alexander	Lauchringen
Thriemer	Martin	Stuttgart
Tiede	Nikolaus	Bad Krozingen
Toncar-Pflumm	Gisela	Mössingen
Toursarkissian	Nicole	Berlin
Treiber	Dietmar	Fellbach
Ulfert	Günther	Backnang
Vogel-Sührig	Christian	Oranienburg
Vogt	Dierk-Christian	Ludwigsburg
Waldenmaier	Stefan	Esslingen
Weber	Bernhard	Backnang
Wehr	Gabriele	Gerlingen
Weiss	Gerhard	Gosheim
Wickenhäuser	Bernhard	Leinfelden-Echterdingen
Wild	Beate	Potsdam
Willberg	Heinz-Andreas	Potsdam
Zeddies	Heike	Schöneiche
Zeisler	Marianne	Oranienburg
Zieger	Stefan	Esslingen
Zietz	Hertraud	Herzberg

Appendix 2

Telemedical investigators

Telemedical Centre Berlin (Charité Universitätsmedizin Berlin)

Name	First Name
Blunert	Judith
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Dübel	Hans-Peter
Dziurla	René
Fiß	Gunnar
Gläß	Christine
Heinold	Marrett
Kim	Simone
Köhler	Friedrich
Köhler	Kerstin

Continued

Continued

Name	First Name
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Lücke	Stephanie
Prescher	Sandra
Schannor	Brunhilde
Sellmer	Sibylle
van der Spek	Daniel
Winkler	Sebastian

Telemedical Centre Stuttgart (Robert-Bosch-Krankenhaus Stuttgart)

Name	First Name
Basrai	Daniel
Braun	Gregor
Derin	Tüley
Eckert	Joachim
Heinrich	Christian
Honold	Marcus
Kiebler	Reiner
Lang	Alexandra
Looser	Alexandra
Maier	Cosima
Müller-Dittner	Esther
Rüßner	Ilona
Schieber	Michael
Sieprath	Sonja
Victor	Achim

TIM-HF Consultant for Nephrology

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Appendix 3

CEC classification criteria

Death

Death will be classified as cardiovascular, non-cardiovascular, or unknown. Further classification will be for the mode of death (sudden, non-sudden) and if death was due to heart failure. The following definitions are used.

Cardiovascular death

A death will be considered to be 'cardiovascular' when it is due to cardiovascular causes which includes, but is not limited to the following: acute myocardial infarction, arrhythmia, heart failure, pulmonary embolism, cerebrovascular disease (e.g. stroke). etc.

Non-cardiovascular death

Death due to non-cardiovascular causes includes, but is limited to the following: death from suicide, violence, or accident; death from infection, but non-cardiovascular; death from renal failure, but non-cardiovascular; death from respiratory insufficiency, but non-cardiovascular; death from cancer; death from other non-cardiovascular causes.

Death from unknown causes

This category applies to death with an unknown cause despite available data, and not attributable to any of the above categories. All attempts will be made to obtain adequate data for classification in an effort to minimize the number of subjects falling into this category.

Death from unclassifiable causes due to lack of data

This applies to death where review and classification are not possible because of lack of data. Such cases will be classified as 'Unknown'.

Sudden cardiac death

Sudden cardiac death is defined as natural death due to cardiac causes, preceded by abrupt loss of consciousness within 1 h of the onset of acute symptoms; pre-existing heart disease may have been known to be present, but the time and mode of death are unexpected. If a patient was asymptomatic or without evidence of a deteriorating medical condition and seen alive within 24 h prior to being found dead, this will be considered to be a 'sudden, presumed arrhythmic death' and hence classified as 'cardiovascular death' and as 'sudden cardiac death'.

Non-sudden cardiac death

Any death due to a cardiovascular reason that is not classified as sudden cardiac death.

Death due to heart failure

Death resulting from mechanical dysfunction of the heart (even if the terminal event was likely to be an arrhythmia or sudden cardiac death) will be classified as heart failure death when preceded by persistent or frequently recurrent NYHA class IV symptoms, an escalating need for supportive therapy and often by evidence of organ failure (e.g. renal). Subjects with cardiogenic shock or pulmonary oedema resistant to therapy are included in this category.

Hospitalization

Hospitalization is defined as a hospital admission resulting in an overnight stay with date change (even if total duration is less than 24 h). It also includes emergency room visits with a date change. Hospitalizations for diagnostic procedures, elective interventions (such as a device battery change), or rehabilitative measures are considered to be planned hospitalizations and will not be counted as hospitalization event. For a hospitalization

considered as a planned hospitalization, the patient must not have had signs or symptoms of worsening disease and must not have been in need for intensified therapy at any time during the hospitalization.

Hospitalizations will be classified as cardiovascular hospitalizations, hospitalization for or with worsening heart failure or as 'other' hospitalization. The following definitions will be used.

Cardiovascular hospitalization

Cardiovascular hospitalization will be defined as a hospitalization due to cardiovascular disease or development of a cardiovascular condition during a hospitalization that is considered to have caused a prolonged hospital stay. Cardiovascular diseases include heart failure, angina, myocardial infarction, syncope, arrhythmia, stroke, transient ischaemic attack, acute peripheral vascular emergencies, pulmonary embolism, or other cardiovascular conditions.

Hospitalization for or with worsening heart failure

A cardiovascular hospitalization will be classified as 'for or with worsening heart failure' if the reason for admission is worsening heart failure or worsening heart failure is one of the major components of the admission. Hospitalization for or with worsening heart failure includes heart failure-induced supraventricular or ventricular arrhythmias, acute coronary syndromes, or renal dysfunction due to drug effects or worsening of cardiac function. The CEC diagnosis will be made using the following two criteria:

(1) presence of two typical heart failure signs or symptoms OR objective evidence for worsening heart failure AND
(2) treatment for heart failure is started or intensified.

If the patient developed heart failure during hospitalization (but heart failure was not the reason or a major component of the respective hospital admission), this will not be judged a 'hospitalization for or with worsening heart failure' but will be deemed a 'cardiovascular hospitalization', if the respective criteria are fulfilled.

Other hospitalizations

Hospital admissions not related to cardiovascular disease will be classified as 'other hospitalization' (i.e. non-cardiovascular hospitalization).

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