The First Year of Noninvasive Remote Telemonitoring in Chronic Heart Failure Is not Cost Saving but Improves Quality of Life: The Randomized Controlled CardioBBEAT Trial

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Abstract

Introduction: Remote telemonitoring (RTM) for patients with chronic heart failure (HF) holds promise to improve prognosis and well-being beyond the standard of care (SoC). The CardioBBEAT trial assessed the health economic and clinical impact of an interactive bidirectional RTM system (Motiva®) versus SoC for patients with HF and a reduced ejection fraction (HFrEF), in Germany.

Methods: This multicenter, randomized controlled trial enrolled 621 patients with HFrEF (mean age 63.0±11.5 years, 88% men). The primary endpoint was the integrated effect of the intervention on total costs and nonhospitalized days alive after 12 months, reported as incremental cost-effectiveness ratio (ICER). Costs (in k€) were based on actual charges of patients’ statutory health insurance. Among secondary outcome measures were mortality and disease-specific quality of life.

Results: We found a neutral effect on nonhospitalized days alive (RTM mean 341±59 days, SoC 346±45 days; p = 0.298) associated with increased total costs (RTM 18.5±39.5 k€, SoC 12.8±22.0 k€; p = 0.046). This yielded an ICER of -1.15 k€/day. RTM did not impact mortality risk. All quality of life scales were consistently and meaningfully improved in the RTM group at 12 months compared to SoC (all p < 0.01).

Conclusions: The first 12 months of RTM were not cost-effective compared to SoC in patients with HFrEF, but associated with a relevant improvement in disease-specific quality of life. The balanced assessment of the potential benefit of RTM requires integration of both the societal and patient perspective. ClinTrials.gov (NCT02293252).

Keywords: telemonitoring, telemedicine, heart failure, health cost, ICER, quality of life, prognosis
Introduction

Heart failure (HF) is a clinical syndrome with serious health-economic implications. It is characterized by frequent repeat hospitalizations accounting for the commonest cause for hospitalization in the United States, Europe, and also Germany.\textsuperscript{1–3} Multiple evidence-based treatment options are available, including pharmacotherapy, invasive procedures, and device therapies.\textsuperscript{2} However, the syndrome of HF requires a multimodal, interdisciplinary treatment approach that needs to be structured, synchronized, and sustained over a long period of time.\textsuperscript{2} Repeated changes of substance classes, up-/down titrations of dosages, monitoring of side effects, and counseling of patients and relatives alike are frequent and time-consuming tasks of caregiver teams.

Effective self-care in these patients is highly desirable, but difficult to establish.\textsuperscript{2} Remote monitoring holds promise to support patient care, enhance self-empowerment, and improve hard clinical endpoints and health care cost.\textsuperscript{2,4} A wide range of monitoring strategies has been tested individually or in combinations, including biomarkers, remote telemonitoring (RTM) collecting clinical information, or information derived from implanted sensors or devices.\textsuperscript{4–8} However, meta-analyses and systematic reviews on telemonitoring in general and RTM in particular could not demonstrate consistent superiority when contrasted with appropriate comparators.\textsuperscript{4,9–11}

The health economic implications of RTM have not been studied in great depth. While some smaller studies suggested cost saving potential especially due to lower hospitalization rates,\textsuperscript{12} larger studies and meta-analyses were not conclusive.\textsuperscript{13–15} These limitations also apply, when these findings are considered in the context of the German health care system. The CardioBBEAT trial aimed to simultaneously assess the clinical and health economic impact of RTM for patients with HF and a reduced ejection fraction (HFrEF) in Germany, based on direct health care cost obtained from statutory insurances. We hypothesized that RTM will be cost effective and positively impact on hard clinical endpoints and patient well-being.

Methods

TRIAL DESIGN, PATIENT SELECTION, AND FOLLOW-UP

CardioBBEAT was a multicenter, open, randomized controlled trial (RCT) with two prospective study arms, registered at ClinTrials.gov (Central Ethics Vote 0 1305–HB/ID). The study was conducted in accordance with the Declaration of Helsinki, guidelines of Good Clinical Practice, and national as well as local regulations. The research protocol was approved...
by the Ethics Committees (ECs) of the University of Bayreuth and respective local ECs, and data protection authorities. Written informed consent was obtained from all patients before any study-related procedure. Patients were enrolled at 10 study sites from 5 federal states in Germany (Berlin, Brandenburg, Bavaria, Hamburg, and North Rhine-Westphalia).

The detailed description of the study design and methods has been published previously. In brief, eligible patients had to have an objectively confirmed diagnosis of symptomatic HFrEF, that is, New York Heart Association (NYHA) functional class II–IV with a documented left ventricular ejection fraction ≤40%, and experienced an episode of HF-related hospitalization within the past 12 months. Key exclusion criteria were myocardial infarction or cardiogenic shock within the past 4 weeks, coronary intervention or cardiac surgery within the past 8 weeks or planned within the next 6 months, priority status on the heart transplantation list, severe chronic and pulmonary illness, or dialysis (for details refer to Hofmann et al.16).

Patients were randomized 1:1 using a centralized stacked technique. Patients predominantly managed by their general practitioner (GP) were cluster-randomized by GP practice to minimize carry-over effects. All patients were asked to participate in three trial-specific examinations at the time of enrolment, and after 6 and 12 months.16

STANDARD OF CARE

After discharge, GPs or outpatient medical specialists provided ambulatory care according to the principles described in the current guidelines of the European Society of Cardiology. Physicians could access and modify individual patient care plans to ensure best medical treatment. All study participants maintained a patient diary and were urged to document any health issue once a week.

INTERVENTION

Patients in the intervention arm received Standard of Care (SoC) enriched by RTM connecting them wirelessly to the participating care providers using the telemedicine platform Motiva® (Philips Medical Systems GmbH, Hamburg, Germany). Motiva is an interactive bidirectional patient management system that provides remote monitoring, motivates patients to manage their disease state, and enables physicians to keep in contact with the patients at home on a daily basis. Patients were asked to daily measure vital signs (blood pressure, heart rate, and weight). Through secure broadband connection, this information was transferred to a workstation of the responsible hospital, where it could be accessed by specialized staff. Patients regularly filled standardized questionnaires (addressing symptoms of cardiac de-compensation, hypo-/hypertension, and abnormal pulse rate) that were converted into actionable algorithms potentially triggering phone calls from responsible staff. Patients were actively called if monitored vital signs left predefined corridors.

In addition, patients received educational content via Motiva using the regular television screen (coaching materials, evaluations, reminders, and feedback regarding their health status).16 RTM equipment was installed and training on its use was provided to patients within 2 weeks after randomization.

OUTCOME MEASURES

The primary endpoint was the incremental cost-effectiveness ratio (ICER) established by the between-group difference in mean total cost (expressed in EUR x 1,000, k€) relating to “days alive and not in hospital nor inpatient care per potential days under study” within a follow-up period of 12 months. Secondary outcome measures were total mortality, and changes in health-related quality of life were assessed via the disease-specific Kansas City Cardiomyopathy Questionnaire (KCCQ), the World Health Organization well-being index (WHO-5), and the generic Short Form health survey with 36 questions using norm-based scoring (SF-36 v2).16 Functional capacity was assessed by the 6-minute walk test.

COST DATA

Cost data (reported in k€) were obtained from patients’ statutory health insurance companies thus reflecting the actually charged resource consumption, and included inpatient and outpatient care, rehabilitation, nursing, medication, and life-saving appliances. This information was validated using the records of the telemonitoring sites, GPs, medical specialists, and patients’ diaries. Technical costs for installing Motiva as well as costs for the RTM software system itself were not included in the analysis.

DATA ANALYSIS

Baseline characteristics are summarized as number of patients (%) for categorical variables and as mean ± standard deviation for continuous variables. The ICER is the ratio of the difference in utility divided by difference in costs and consists of two components. The utility component was defined as number of days alive and not in hospital nor inpatient care. The cost component was defined as cost associated with utility generation. Each component was separately compared between random groups using a permutation test (Fisher-Pitman using the coin module in R). As cost data have a highly skewed distribution, a log-transformation was applied after adding 0.1 to account for zeros.

For the ICER, that is, the ratio, we calculated confidence intervals (CIs) both from conventional and reordered
Cost-effectiveness acceptability curves (CEACs) were generated to illustrate the probability for cost-effectiveness. The CEAC is a graph summarizing the impact of uncertainty on the result of an economic evaluation, frequently expressed as an ICER in relationship to possible values of the cost-effectiveness threshold.

Sensitivity analyses were run to assess the robustness of the principal results, for the full-analysis set and the complete-case population. The latter comprised all patients ($n = 377$) with complete documentation provided by statutory health insurances, defined as 99% coverage.

Cumulative incidence was visualized by Kaplan–Meier plots, and differences between curves were tested using the log-rank test. Cox proportional hazards regression was used to estimate the hazard ratio (HR) with 95% CI. Data on the number of hospitalizations (all-cause, HF related, cardiac, extended cardiac, and emergency) were compared using negative binomial models using time covered by health insurance data as offset. Changes in quality-of-life scales (KCCQ, SF-36, WHO-5) were analyzed using analysis of covariance, with the difference between the 12-month value and baseline as dependent variable, group as fixed factor, and the baseline value as adjustment variable. In addition, a mixed model was used to incorporate the data of the 6-month visit, which adds the individual patient as random effect. Analyses were performed with R version 3.4.4 (R Project for Statistical Computing, https://www.r-project.org/).

**Fig. 1.** Patient flow and availability for analyses. *One death in the control group, and two deaths in the intervention group occurred during a hospitalization that took place at the 12-month study end visit.*
Results

PATIENT DISPOSITION AND BASELINE CHARACTERISTICS

Between January 2010 and June 2013, 621 patients with a confirmed diagnosis of HFrEF were enrolled and randomly assigned to the two study groups: RTM, n = 302, and SoC, n = 319. During the 12-month study period, 46 patients died and 105 patients withdrew from the study, with no significant differences between groups, respectively. One patient was lost to follow-up. At the final visit, 472 patients (76.0%) were available for clinical investigations. Figure 1 shows the patient flow.

Baseline characteristics of study participants have been reported earlier,16 and were well balanced between groups (Supplementary Table S1). Mean age of patients was 63.0 – 11.5 years (quartiles 55, 72 years), 88% were men, and 26% were living alone. The predominant cause of HF was ischemic (59%), and baseline pharmacotherapy and cardiac resynchronization therapy and implantable cardioverter-defibrillator placement were well implemented. Most patients (61.2%) were in sinus rhythm, mean left ventricular ejection fraction was 30.4% – 7.4%, and mean 6-minute walk distance was 375 – 132 m.

OUTCOMES

Health cost data availability. Cost data could be gathered from 38 out of 55 health insurance companies, with 17 companies abrogating cooperation. This resulted in 492 patients available for health economic analysis amounting to 444 patient-years (for details refer to Fig. 1). Baseline characteristics were similar in patients with and without health care cost data (Supplementary Table S2), and in patients receiving RTM versus SoC among those with health care cost data (Supplementary Table S3).

Primary endpoint. Based on bootstrap distribution, the probability of SoC being the dominant strategy was 84.8%. By contrast, the respective probability of RTM dominating was 1.3%, and the probability of RTM being cost-effective was <14.4%. The respective number of days alive and out of hospital was similar for both groups: 341 ± 59 for RTM, and 346 ± 45 for SoC (p = 0.298). Respective total cost (in k€) were 18.5 ± 39.5 for RTM and 12.8 ± 22.0 for SoC (p = 0.046). This yielded an ICER of −1.15 k€/day.

Calculation of CIs based on conventional bootstrapping did not perform well.17 This is demonstrated in Figure 2A, where the 95% bootstrap CI (8.35 – 6.66) falsely excludes a circular sector of the bivariable distribution of effects and cost in a highly probable area. The method of reordered bootstraps17 yielded a 95% CI of (−∞, −0.26) U (0.50, ∞) k€/day, thus excluding areas that were extreme in the bivariable distribution (Fig. 2B).

Sensitivity analyses on the estimated ICER (k€/day) yielded consistency and are described in Supplementary Results.
Visualization of cost-effectiveness. Complementary CEACs were calculated (Graphical Abstract, A). They confirmed the low probability of RTM to be cost-effective for various scenarios, even for very large values of $\lambda$, that is, the amount society is willing to pay to get one more day out of hospital. Respective probabilities were <14.4% for primary endpoint, <25.5% for HF-related events, <17.6% for cardiac events, and <19.3% for extended cardiac events.

Mortality and rehospitalization. As a secondary endpoint, Kaplan–Meier curves display the estimated time-dependent survival rates for both groups (Fig. 3). We observed 20 events in the RTM group and 26 events in the SoC group, with no statistical difference between groups: HR 0.81 (95% CI 0.45–1.45; log-rank $p = 0.478$). During the 12-month follow-up period, 58% ($n = 139$) of patients in the RTM group underwent at least one hospitalization, similar to the 60% ($n = 150$) observed in the SoC group.

In total, 343 (RTM) and 342 (SoC) hospitalizations were recorded, resulting in an incidence of 1.5 (95% CI 1.3–1.8) hospitalizations per person-year in the RTM group and 1.4 (95% CI 1.2–1.7) in the SoC group; incidence rate ratio 1:1 (95% CI 0.86–1.40; $p = 0.452$). Also, no differences in specific types of hospitalizations (HF-related, cardiac, and emergency) were observed (Table 1). There were six hospitalizations for of left ventricular assist device implantation in the RTM group compared to only one in the SoC group ($p = 0.0086$; trend confirmed in sensitivity analysis limited to patients with complete information; Supplementary Table S4).

Quality of life. During the 12-month study period, diseasespecific and generic quality of life improved in both groups. The improvement in the RTM group was consistently and

| CAUSE OF HOSPITALIZATION | N (%| WITH HOSPITALIZATION | SUM OF HOSPITALIZATIONS | INCIDENCE RATE (95% CI) | IRR (95% CI) | P |
|--------------------------|-------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| All-cause                | 150 (59.8)                    | 342                     | 1.596 (1.181–1.685)     | 139 (57.7)              | 343 (1.396–1.468)        | 0.452                   |
| Heart failure related    | 44 (17.5)                     | 72                      | 0.299 (0.210–0.425)     | 39 (16.2)               | 60 (0.289–0.410)         | 0.900                   |
| Cardiac                  | 106 (42.2)                    | 191                     | 0.574 (0.407–0.730)     | 99 (41.1)               | 193 (0.671–0.834)        | 0.954                   |
| Cardiac                  | 66 (26.3)                     | 106                     | 0.444 (0.315–0.585)     | 68 (28.2)               | 121 (0.382–0.475)        | 0.216                   |
| Artificial heart implantation | 1 (0.4)                  | 6                       | 0.004 (0.001–0.028)     | 6 (2.3)                 | 1 (0.001–0.006)          | 0.004                   |

CI, confidence intervals; IRR, incidence rate ratio. RR with CI and $p$-values estimated using negative binomial regression.
meaningfully higher than in the SoC group regarding all reported scales (Graphical Abstract, B, and Table 2). In particular, the net gain in the KCCQ scale was larger than five points, compatible with a relevant clinical effect.\(^1\)\(^8\)

**6-Minute walk test.** Mean walking distance was virtually identical for both groups at baseline (374 ± 131 m for RTM; 376 ± 132 m for usual care). Walking distance in both groups was higher after 12 months, with no significant differences between groups: RTM, 405 ± 121 m versus SoC, 415 ± 133 m.

**Discussion**

The CardioBBEAT trial evaluated a 12-month period and observed no difference between the RTM and SoC group for the predefined primary endpoint incorporating measures for rehospitalization and mortality as well as health-associated costs. However, RTM induced consistent and clinically meaningful effects regarding an improved disease-specific and generic health-related quality of life.

There is a rich and controversial debate, whether noninvasive RTM for patients with HFrEF may offer clinical benefits or health economic advantages over SoC. In a meta-analysis based on 21 RCTs performed between 2000 and 2009 on 5,712 patients,\(^1\)\(^9\) RTM was associated with fewer hospitalizations for HF (incidence rate ratio 0.77; 95% CI 0.65–0.91, \(p < 0.001\)) and hospitalizations for any cause (0.87, 95% CI 0.79–0.96, \(p = 0.003\)). The difference in costs between RTM and SoC ranged from 0.3 to 1.0 k€, favoring RTM. In a budget impact meta-analysis, the adoption of a RTM strategy entailed a progressive and linear increase in costs saved.\(^1\)\(^9\) Notably, this analysis derived cost data from diagnosis-related group reimbursements, but not real cost data.

Further, according to a meta-analysis of 11 RCTs investigating cardiac implantable electronic devices, compared with SoC, device-based RTM was associated with a marked reduction in planned hospital visits and lower monetary costs (although survival was not affected).\(^2\)\(^0\) The most recent study conducted in Germany between 2013 and 2017 was the Telemedical Interventional Management in Heart Failure (TITM-HF) II trial, \(n = 1,538.8\) TIM-HF II examined a specific subgroup of patients identified in the TIM-HF I trial,\(^2\)\(^1\) potentially better suited for RTM than the broader HF population. The study showed that RTM in combination with a structured patient management program reduced all-cause mortality risk and the percentage of days lost due to unplanned hospital admission.\(^8\) While respective cost-effective analyses are still pending, this trial also showed that benefits vanished when stopping RTM.\(^2\)\(^2\)

Several other RCTs observed neutral effects. The Telemonitoring to Improve Heart Failure trial, \(n = 1,653\), aimed to reduce hospital readmissions. RTM included frequent phone-based interactions with patients utilizing a voice-response system. The primary endpoint was not met, and no differences were seen in the number of deaths, readmissions, or days in hospital between groups.\(^2\)\(^3\) The TIM-HF trial, \(n = 710\), investigated telemonitoring and structured feed-back and found no consistent benefit for RTM compared to SoC regarding differences in all-cause death, cardiovascular death, or HF

| SCORE         | \(N\) | ESTIMATED DIFFERENCE | 95% CONFIDENCE INTERVAL | \(p\)  |
|--------------|------|----------------------|-------------------------|-------|
| KCCQ\(^a\)  |      |                      |                         |       |
| Overall summary score | 416  | 5.5                  | 2.3–8.7                 | <0.001|
| Clinical summary score | 416  | 4.0                  | 0.7–7.3                 | 0.017 |
| WHO-5        |      |                      |                         |       |
| Raw value    | 409  | 1.3                  | 0.3–2.3                 | 0.010 |
| Percentage value | 409  | 5.0                  | 1.2–8.9                 | 0.010 |
| SF-36        |      |                      |                         |       |
| Physical component | 412  | 2.0                  | 0.5–3.5                 | 0.009 |
| Mental component | 412  | 2.7                  | 0.9–4.6                 | 0.004 |

\(^a\)Overall summary score includes the total symptom, physical function, social limitations and quality-of-life scores. Clinical Summary Score includes total symptom and physical function scores.

KCCQ, Kansas City Cardiomyopathy Questionnaire; SF-36, short-form 36 quality-of-life questionnaire; WHO-5, World Health Organization 5–item questionnaire.

Note: Difference refers to changes of 12-month value minus baseline value. Positive differences indicate advantages of remote telemonitoring.
hospitalizations. The Better Effectiveness After Transition–Heart Failure trial, \( n = 1,437 \), studied older adults hospitalized with HF and enhanced RTM by regular contact with the health care team providing protocol-driven instructions on medical care. This trial failed to show a reduced 6-month readmission rate.

Similarly, in the 12-month CardioBBEAT trial investigating a high-risk HF population, days spent alive and out of hospital, number of rehospitalizations, and total mortality were similar between groups, and there was no signal suggesting that RTM may improve cost expenditure in that time frame. As mentioned, CardioBBEAT is the first study that used actual and not estimated cost data to quantify the economic impact of chronic HF as data for costing were retrieved directly from patients’ statutory health insurances. Other than projected, complete health insurance data were not available for 28% of patient days overall, and missing cost data had to be imputed. A linear imputation method assuming “data missing at random” was chosen, as the probability of missingness was related to observed data but not to unobserved data.

Findings in predefined sensitivity analyses were consistent. Patients were well treated and cared for according to European Society of Cardiology guidelines exemplified by high uptake of standard HF pharmacotherapy, close supervision, and telephone support by study nurses. This might have attenuated the benefits offered by telemedicine in this particular setting. From this trial, at least three important lessons may be learnt. First, innovations in care targeting treatment and/or monitoring come at costs that need to be weighed and agreed by health policy makers, payors, and patients alike. CardioBBEAT investigated a high-risk group of patients with HFrEF that was representative in risk, but about 10 years younger than the “typical” patient with HFrEF in Germany. Accordingly, the 12-month mortality risk was considerably lower than observed in the general HF population, yet, in line with modern pharmacotherapy trials, for example, the PARADIGM-HF trial. Hence, the 12-month period might have been too short to capture the full potential of this complex intervention in a complex patient population. It would be important to extend study periods to observe the selective attrition of particularly susceptible patient groups and account for problems arising from competing risk.

Second, it might be very difficult if not impossible to compare (and integrate into meta-analyses) the effects generated by different RTM approaches and care programs utilizing different components in different health care settings. Trials investigating complex interventions usually exhibit unique features regarding study design and reporting, and perception by health policy makers. In this context, CardioBBEAT provides data that may be generalizable to the German health perspective, but not necessarily so to other health care systems.

Third, improvement of quality of life is one of the explicit goals of HF management, and patient related outcomes are accepted endpoints in pharmacotherapy or device trials. In CardioBBEAT, we observed consistent improvement on all quality-of-life scales in both groups, which argues for excellent background care in this trial. However, effects were meaningfully greater in the RTM group (e.g., 5.5 points change in KCCQ overall summary score) compared to SoC. This effect occurred fairly fast, was clinically relevant, and expected to translate into a >10% relative risk reduction in HF-related hospitalization or death.

LIMITATIONS AND STRENGTHS

Baseline characteristics of participants were well balanced in general, but differed regarding NYHA functional class, heart rhythm, and renal function. However, estimates were robust and consistent in adjusted analyses. We studied relatively younger patients with HF. Age itself may not be an obstacle for RTM, however, evidence in this age group is limited. Furthermore, cost data were obtained as costs paid by insurance companies; the actual consumption of resources could not be determined.

Conclusions

In CardioBBEAT, simultaneous assessment of clinical effects and health cost expenditure in patients with HFrEF treated with versus without RTM yielded neutral effects on survival as well as days alive and out of hospital, and failed to provide a positive cost effectiveness ratio. However, RTM meaningfully improved disease-specific and generic quality of life compared to SoC. Whether and how RTM will be implemented within the German health care system will depend on the balanced weighing of risks, benefits, and costs—from a perspective that encompasses not only the payor but also the individual patient and the society.

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Authors’ Contributions

H.V. made substantial contributions to conception and design of the study, is principal investigator and head of...
clinical trial, member of steering committee, performed the clinical interpretation of data, and wrote the first version of the article. D.B. made substantial contributions to the development and management of the study, performed the acquisition as well as economic analysis and interpretation of data, and codrafted the article. K.N. made substantial contributions to the development and coordination of the study, is head of health economics evaluation, member of steering committee, sponsor, and revised the article critically. R.H. made substantial contributions to the development, implementation, and management of the study, performed the economic analysis and interpretation of data, and revised the article critically. E.V. made substantial contributions to conception and design of the study, drafted parts of the article, performed the statistical analysis, and contributed to the interpretation of data. K.W. made substantial contributions to conception and design of the study, supervised the statistical analysis, is member of steering committee and revised the article critically.

E.F. made substantial contributions to conception and design of the study, is principal investigator and head of clinical trial, member of steering committee, and revised the article critically.

S.S. is principal investigator and codrafted the article. E.N. made substantial contributions to conception and design of the study, is head of health economics evaluation, member of steering committee, sponsor, and revised the article critically. All authors read and approved the final article.

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Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

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Supplementary Material

Supplementary Data

REFERENCES

1. Christ M, Störk S, Dörr M, Heppner HJ, Müller C, Wachter R, et al. Heart failure epidemiology 2000–2013: Insights from the German Federal Heart Monitoring System. *Eur J Heart Fail* 2016;18:1009–1018.

2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016;37:2129–2200.

3. Störk S, Handrock R, Jacob J, Walker J, Calado F, Lahoz R, et al. Epidemiology of heart failure in Germany: A retrospective database study. *Clin Res Cardiol* 2017;106:913–922.

4. Emani S. Remote monitoring to reduce heart failure readmissions. *Curr Heart Fail Rep* 2017;14:40–47.

5. Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB, et al. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: Complete follow-up results from the CHAMPION randomised trial. *Lancet* 2016;387:463–461.

6. Angermann CE, Störk S, Gelbrich G, Faller H, Jahn R, Frantz S, et al. Mode of action and effects of standardized collaborative disease management on mortality and morbidity in patients with systolic heart failure: The Interdisciplinary Network for Heart Failure (INH) study. *Circ Heart Fail* 2012;5:25–35.

7. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A, et al. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): A randomised controlled trial. *Lancet* 2014;384:583590.

8. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan BA, et al. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): A randomised, controlled, parallel-group, unmasked trial. *Lancet* 2018;392:1047–1057.

9. Bashi N, Karunanithi M, Fatehi F, Ding H, Walters D. Remote monitoring of patients with heart failure: An overview of systematic reviews. *J Med Internet Res* 2017;19:e18.

10. Potb A, Cameron C, Hsieh S, Wells G. Comparative effectiveness of different forms of telemedicine for individuals with heart failure (HF): A systematic review and network meta-analysis. *PloS One* 2015;10:e0119881.

11. Xiang R, Li L, Liu SX. Meta-analysis and meta-regression of telemedicine programmes for patients with chronic heart failure. *J Telemed Telecare* 2013;19:249–259.
12. Comin-Colet J, Enjuanes C, Verdu-Rotellí JM, Linas A, Ruiz-Rodríguez P, Gonzalez-Robledo G, et al. Impact on clinical events and healthcare costs of adding telemedicine to multidisciplinary disease management programmes for heart failure: Results of a randomized controlled trial. *J Telemed Telecare* 2016;22:282295.

13. Achleitner D. Policy expectations and reality of telemedicine—A critical analysis of health care outcomes, costs and acceptance for congestive heart failure. *J Telemed Telecare* 2014;20:192–200.

14. Grustam AS, Severens JL, van Nijnatten J, Koymans R, Vrijhoef HJ. Cost-effectiveness of telehealth interventions for chronic heart failure patients: A literature review. *Int J Technol Assess Health Care* 2014;30:99–68.

15. Henderson C, Knapp M, Fernandez JL, Beecham J, Hirani SP, Cartwright M, et al. Cost effectiveness of telehealth for patients with long term conditions (whole systems demonstrator telehealth questionnaire study). *BMJ* 2013;346:f1035.

16. Hofmann R, Völler H, Nagels K, Bindl D, Vettorazzi E, Dittmar R, et al. First outline and baseline data of a randomized, controlled multicenter trial to evaluate the health economic impact of home telemonitoring in chronic heart failure—CardioBBEAT. *Trials* 2015;16:343.

17. Wang H, Zhao H. A study on confidence intervals for incremental cost-effectiveness ratios. *Biom J* 2008;50:505–514.

18. Speritus J, Peterson E, Conard MW, Heidenreich PA, Krumholz HM, Jones P, et al. Monitoring clinical changes in patients with heart failure: A comparison of methods. *Am J Heart* 2005;150:707–715.

19. Inglis SC, Clark RA, McAlister FA, Stewart S, Cleland JG. Which components of heart failure programmes are effective? A systematic review and meta-analysis of the outcomes of structured telephone support or telemonitoring as the primary component of chronic heart failure management in 8323 patients: Abridged Cochrane review. *Eur J Heart Fail* 2011;13:1028–1040.

20. Kleersy C, Boriani G, De Silvestri A, Mairesse GH, Braunschweig F, Scotti V, et al. Effect of telemonitoring of cardiac implantable electronic devices on healthcare utilization: A meta-analysis of randomized controlled trials in patients with heart failure. *Eur J Heart Fail* 2016;18:195–204.

21. Koehler F, Winkler S, Schieber M, Sechtem U, Vrijhoef HJ. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: The temedical interventional monitoring in heart failure study. *Circulation* 2011;123:1873–1880.

22. Koehler F, Koehler K, Prescher S, Kirwan BA, Wegscheider K, Vettorazzi E, et al. Mortality and morbidity 1 year after stopping a remote patient management intervention: Extended follow-up results from the temedical interventional management in patients with heart failure II (TIM-HF2) randomised trial. *Lancet Digit Health* 2020;2:e16–e24.

23. Chaudhry SI, Mattera JA, Curtis JP, Speritus JA, Herrin J, Lin Z, et al. Telemonitoring in patients with heart failure. *N Engl J Med* 2010;363:2301–2309.

24. Ong MK, Romano PS, Edgington S, Aromow HU, Auerbach AD, Black JT, et al. Effectiveness of remote patient monitoring after discharge of hospitalized patients with heart failure: The better effectiveness after transition heart failure (BEAT-HF) randomized clinical trial. *JAMA Intern Med* 2016;176:310–318.

25. Little RJ, Rubin DB. Statistical analysis with missing data. Hoboken, New Jersey: John Wiley & Sons, 2014.

26. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkalla AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993–1004.

27. van Walraven C, McAlister FA. Competing risk bias was common in Kaplan-Meier risk estimates published in prominent medical journals. *J Clin Epidemiol* 2016;69:170–173 e178.

28. Piotrowicz E, Pencina MJ, Opolski G, Zareba W, Banach M, Kowalik I, et al. Effects of a 9-week hybrid comprehensive telerehabilitation program on long-term outcomes in patients with heart failure: The telerehabilitation in heart failure patients (TELEREH-HF) randomized clinical trial. *JAMA Cardio* 2020;5:300–308.

29. Medical Research Council (MRC) & National Institute for Health Research (NIHR). A framework for the development and evaluation of RCTs for complex interventions to improve health—Update 2019. Available at https://mrc.ukri.org/documents/pdf/complex-interventions-guidance/(last accessed December 31, 2021).

30. Food and Drug Administration (FDA). Medical device development tool qualification decision: Summary for Kansas City Cardiomyopathy Questionnaire (KCCQ). *2016*. Available at https://www.fda.gov/media/108301/download(last accessed December 31, 2021).

31. Kosiborod M, Soto GE, Jones PG, Krumholz HM, Weintraub WS, Deedwania P, et al. Identifying heart failure patients at high risk for near-term cardiovascular events with serial health status assessments. *Circulation* 2007;115:1975–1981.

32. Lemay G, Azad N, Struthers C. Utilization of home telementoring in patients 75 years of age and over with complex heart failure. *J Telemed Telecare* 2013;19:18–22.

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