


A Review of Randomized Controlled Trials Utilizing Telemedicine for Improving Heart Failure Readmission: Can a Realist Approach Bridge the Translational Divide?

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ABSTRACT

BACKGROUND: Telemedicine and digital health technologies hold great promise for improving clinical care of heart failure. However, inconsistent and contradictory findings from randomized controlled trials have so far discouraged widespread adoption of digital health in routine clinical practice. We undertook this review study to summarize the study outcomes of the use of exploring the evidence for telemedicine in the clinical care of patients with heart failure and readmissions.

METHODS: We inspected the references of guidelines and searched PubMed for randomized controlled trials published over the past 10 years on the use of telemedicine for reducing readmission in heart failure. We utilized a modified realist review approach to identify the underlying contextual mechanisms for the intervention(s) in each randomized controlled trial, evaluating outcomes of the intervention and understanding how and under what conditions they worked. To provide uniformity, all extracted data were synthesized using adapted domains from the taxonomy for disease management created by the Disease Management Taxonomy Writing Group.

RESULTS: A total of 12 papers were eligible, 6 of them supporting and 6 others undermining the use of telemedicine for improving heart failure readmission. In general terms, those studies not supporting the use of telemedicine were multicentre, publicly funded, with large amount of participants, and long duration. The patients had also better rates of treatment with angiotensin-converting enzyme inhibitors/angiotensin II receptor blocker and beta-blockers, and telemonitoring and automatic transmission of vital signs were less utilized, in comparison with the studies in which telemedicine use was supported. The analysis of the environment, intensity, content of interventions, method of communication, quality of the underlying model of care and the ability, capability, and interest from health workers can help us to envisage probabilities of success of telemedicine use.

CONCLUSIONS: A realist lens may aid to understand whom and in which circumstances the use of telemedicine can add any substantial value to traditional models of care. Wider outcome criteria beyond major adverse cardiovascular events, for example, cost efficacy, should also be considered as appropriate for effecting guidelines on care delivery when robust prognostic therapeutics already exist.

KEYWORDS: Heart failure, readmission, technology, telemedicine, review

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Introduction

Heart failure (HF) is a major cause of mortality and hospitalization,¹ the later accounting for up to 2% of health care costs in the United States, Europe, and other developed nations^{2,3} which represents more than \$1 billion of health care costs.⁴ Heart failure readmissions reflect a complex interplay with

cardiovascular complications accounting for about half while comorbid factors account for the other half.⁵ Ambulatory support programmes such as rehabilitation are associated with improved major adverse cardiovascular outcomes (MACE).⁶ However, in real-world translation, such gains are limited due to disappointing rates of uptake and adherence,⁷ in part



attributable to access limitations and especially in sparsely populated areas.⁸

In the past years, telemedicine (broadly defined as the use of information and communications technology for the delivery of health care at a distance)⁹ has been proposed for the management of patients with HF. The use of telemedicine present potential advantages compared with traditional care delivery models, through overcoming geographical, temporal, and organizational barriers.¹⁰ However, the promising positive outcomes from the initial trials¹¹⁻¹³ have not been later corroborated by large prospective randomized clinical trials.¹⁴⁻¹⁶ Consequently, there is no evidence for superior outcomes with any particular model of care incorporating telecommunication technologies, in particular on improving MACE in HF.¹⁷

Realist analysis is an approach to review and synthesize research evidence on complex interventions, providing explanatory analysis not just 'whether' but rather 'what works, how, for whom, in what circumstances, in what respects, to what extent, and why' they work (or don't work), in particular contexts or settings.^{18,19} This approach has also the potential to enable the tailoring of interventions and policy to particular purposes, particular target groups and particular sets of circumstances²⁰ and perhaps to decrease unintended negative impacts of interventions.²¹ Hence, the success of an intervention through a realist lens depends on the characteristics of the participants, the institutions, and infrastructures, and in which environments the intervention is delivered.²² The aim of this review was to identify characteristics and contextual factors of telemedicine interventions in HF that could affect study outcomes by analysing the current literature through a realist lens.

Method

Source of search

We retrieved the randomized controlled trials (RCTs) included in the 2016 European Society of Cardiology (ESC) guidelines concerning the use of telemedicine in HF. Since the RCTs cited in the guidelines do not support the use of telemedicine for the management of people with HF, we searched for a comparable number of RCTs which are in favour of telemedicine in this context. For this purpose, we included MeSH terms and free text keywords pertaining to the main concepts of interest which were as follows: (a) HF and (b) technology and telemedicine. The search was limited to the records published since January 2009 and RCTs.

Eligibility criteria and study selection

We considered all RCTs addressing the use of telemedicine or remote patient management in the latest ESC guidelines.²³ In addition, we considered RCTs that met the following criteria: (a) HF was the only condition under study; (b) telemedicine was used as an intervention; (c) readmission as a main endpoint of the study showing an opposite outcome that the studies

included in the 2016 ESC guidelines; and (d) published in English language, in peer-reviewed journals in 2009 onward and indexed in PubMed. The exclusion criteria were as follows: (a) feasibility/pilot studies or protocol papers; (b) studies addressing several comorbidities; and (c) studies addressing outcomes from the implementation of implantable devices. The results of the electronic search were exported to an EndNote library and screened at title/abstract level. The full text of potentially relevant papers was obtained and inspected for eligibility. Figure 1 shows the flow diagram of the study search and selection process.

Data extraction and collection

Two independent reviewers screened and categorized the results of each study. To provide uniformity in the analysis of the outcomes, all extracted data from the included RCTs were synthesized using adapted domains from a well-known taxonomy for disease management, created by the American Heart Association, and applicable for comparison across interventions.²⁴ Based on this system, the information obtained from each RCT was categorized into 8 different domains: (1) characteristics of the patient population, (2) recipient (who received support and data results), (3) intervention content (used guidelines, language), (4) delivery personnel (known to patient or not; possibility of patient to reply and how), (5) methods of communication (telephone, Internet), (6) intensity and complexity (how often, how frequently, duration of the intervention), (7) environment (hospital, homes, community), and (8) outcome measure (MACE, cost efficacy, patient satisfaction or proven non-inferiority).

To simplify data reviewing and table presentation, domain 1 was titled as 'Demographics', domains 2, 4, 6, and 7 were grouped and categorized as 'Characteristics/context of the trial', and domains 3 and 5 as 'Characteristics of the technology'. For domain 8, we collected the primary and secondary outcomes of the study and the presence of cost-analysis (Tables 1 and 2).

- (a) The domain 'Demographics' included the following: number of participants, mean age and sex of the participants, severity of the disease (according to the New York Heart Association [NYHA] function class), mean left ventricular ejection function (LVEF), and percentage of patients on medication (angiotensin-converting enzyme inhibitor [ACEi] and beta-blocker [BB]).
- (b) The domain 'Contextual factors' included the following: number of participating clinical sites (single or multi-centre), characteristics of the funding body, duration and the completion rates of the studies, and a short description of the work methodology.
- (c) The domain 'Characteristics of the technology' included the following: method of communication (telephone,

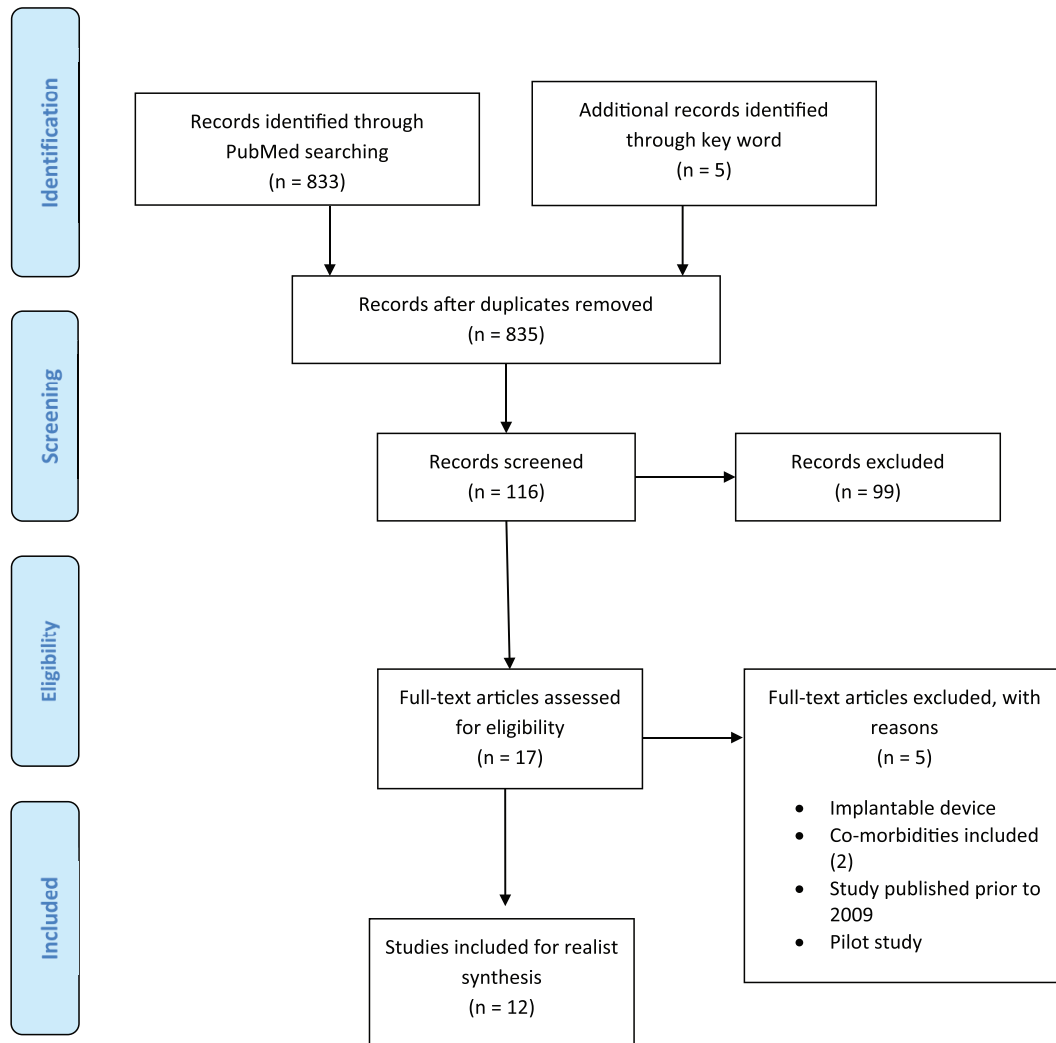


Figure 1. Search strategy.

wireless devices, Internet, or a combination of them) and whether automatic transmission of vital signs was included or not.

- (d) The domain ‘Outcomes’ included primary (P) and Secondary (S) outcomes of the study and whether usability, user’s satisfaction, quality of life (QoL), and cost-effectiveness were included for the study or not.

Finally, and following the domains described above, we compared the results from the studies supporting the use of telemedicine and the other for those which did not (Figure 2).

Realist analysis approach

A realist analysis aims to identify underlying causal mechanisms that may help to understand how an intervention work and under what conditions.³⁴ The framework behind the realist approach is that specific contexts (C) of a trial interact with somewhat different mechanisms (M), which may trigger particular outcomes (O) (abbreviated as C-M-O).²² In this work, we conducted a systematic interpretive cross-case comparison

between supportive and undermining studies. Based on this realist approach, we discussed the importance and the implications that contextual factors may have in the designing and implementation of future telemedicine studies.

Results

A total of 12 papers were eligible and included in this review. In 6 of these studies, the outcomes of the intervention supported the use of telemedicine (to reduce readmission) and in 6 studies did not.

Studies supporting the use of telemedicine

The outcomes of 6 RCTs²⁵⁻³⁰ supported in general the use of telemedicine to reducing readmission in HF. In total, 2321 patients were included in these studies, with an average age of 73 years and approximately 43% female; 67% had moderate-to-severe decreased function class with a mean LVEF of 42%. In average, 42% of the patients had an ischemic etiology for their HF. Half of the studies were conducted at a single-centre, and mostly funded by private institutions/companies (except for

Table 1. Summary of demographics, context, and technology for the studies supporting the use of telemedicine in HF.

STUDY/DOMAINS	DEMOGRAPHICS	CHARACTERISTICS/CONTEXT OF THE TRIAL	CHARACTERISTICS OF THE TECHNOLOGY	OUTCOMES OF THE STUDY
Hale et al. ²⁵ US 2016	<ul style="list-style-type: none"> • Patient population • N = 25 (11) • Mean age = 71 years • Female = 64% • FC: 50% in II or III • Isch = NR • LVEF = 47% • Medication: NR 	<ul style="list-style-type: none"> • Recipient, delivery personnel, methods of communication, intensity and complexity, and environment • Multisite: 3 hospitals in the US • Fund = Presentcare Inc. • Dur: 3 months • Complet: 85% • WM: specialized nurses conducting TM and telephone calls 	<ul style="list-style-type: none"> • Intervention content and method of communication • Electronic device alerts when it is time to take medications. • Monitoring advisors contact participants when medications are not taken. • Combination of Internet-based TM and telephone support. 	<p>P: medication adherence S: health, depression, NYHA class, hospitalization, ED visits Usability: yes Satisfaction: yes QoL: yes Cost-effectiveness: no</p>
Comin-Colet et al. ²⁶ Spain 2016	<ul style="list-style-type: none"> • N = 178 (81) • Mean age = 77 years • Female = 41% • FC: 46% in I-II, 54% in III-IV • Isch = 35% • LVEF = 47% • Medication: ACE/ARB 61%, BB 84% 	<ul style="list-style-type: none"> • Single centre trial • Fund = Telefonica Solutions • Dur: 6 months • Complet: 100% • WM: project managers review all collected data (weight, HR, BP, symptoms reporting) 	<ul style="list-style-type: none"> • Home TM multichannel service: automatic transfer of biometric data, generation of warning alarms (out of range), and alerts (dysfunction of the household devices). • Internet-based TM and telephone support. 	<p>P: non-fatal HF event S: all-cause and cardiovascular mortality, unplanned readmissions (all-cause, HF and cardiovascular), changes in patient-centred outcomes (self-efficacy and QoL) Usability: no Satisfaction: no QoL: yes Cost-effectiveness: yes</p>
Pedone et al. ²⁷ Italy 2015	<ul style="list-style-type: none"> • N = 90 (50) • Mean age = 80 years • Female = 62% • FC: 87% in II or III • Isch = NR • LVEF = 46% • Medication: ACE/ARB 58%, BB 54% 	<ul style="list-style-type: none"> • Single centre trial • Fund: NR • Dur: 6 months • Complet: 64% • WM: Project managers review all collected data: Weight once a day; BP and HR twice a day, and pO2 3 times a day. The telephonic contacts were not scheduled 	<ul style="list-style-type: none"> • TM system and office-hours telephonic support provided by a geriatrician. • Automatic transfer of vital signs through the system. • The telephonic contacts were not scheduled; this channel of communication to report new symptoms or technical problems. • Internet-based TM and telephone-based communication channel to support patients. 	<p>P: combination of all-cause death and hospital admissions. S: NR Usability: no Satisfaction: no QoL: no Cost-effectiveness: no</p>

Table 1. (Continued)

	DEMOGRAPHICS	CHARACTERISTICS/CONTEXT OF THE TRIAL	CHARACTERISTICS OF THE TECHNOLOGY	OUTCOMES OF THE STUDY
Villani et al. ²⁸ Italy 2014	<ul style="list-style-type: none"> N = 80 (40) Mean age = 72 years Female = 28% FC: mean 3 Isch = 54% LVEF: 32% ACEi/ARB: 91%, BB 51% 	<ul style="list-style-type: none"> Single centre trial Fund: Italian government Dur: 12 months Comple: 98% WM: study nurses review collected data and automatic questions. Staff call if necessary. 	<ul style="list-style-type: none"> The TM technology comprised a patient front-end, a medical front-end, and a web-based system for assisting with clinical decisions. The patient front-end operated through a PDA given to each patient leaving hospital. Internet-based TM and telephone support (call or SMS). 	<p>P: major adverse effect (including cardiovascular death or hospitalization lasting more than 3 days). Minor adverse event as any hospital stay less than 3 days</p> <p>S: clinical results including NYHA class, LVEF, BNP levels</p> <p>Usability: no</p> <p>Satisfaction: no</p> <p>QoL: no</p> <p>Cost-effectiveness: yes</p>
Krum et al. ²⁹ Australia 2013	<ul style="list-style-type: none"> N = 405 Mean age = 73 years Female = 37% Fx Class: 59% in II and 35% in III LVEF = 36% ACEi/ARB: 57%, BB: 61% 	<ul style="list-style-type: none"> Multisite: 127 clusters of general practitioners (GPs) Fund: NHMRC and the Australian Heart Foundation Dur: 12 months Comple: NR WM: patients were asked to answer automated questions relevant to HF on an at least a monthly basis 	<ul style="list-style-type: none"> Automated telemedicine system. Alerts were also set up within the system alerting nurse to follow up patients who reported symptoms warranting intervention. Telephone STC 	<p>P: (1) death, (2) hospital admission for heart failure, (3) withdrawal from study due to worsening heart failure, (4) 7-point global health assessment questionnaire with regard to overall well-being in comparison with baseline.</p> <p>S: secondary endpoints, comprised all-cause death and all-cause hospitalization as well as heart failure-related death and heart failure-specific hospitalization.</p> <p>Usability: no</p> <p>Satisfaction: no</p> <p>QoL: no</p> <p>Cost-effectiveness: no</p>
DIAL-study Ferrante et al. ³⁰ Argentina 2010	<ul style="list-style-type: none"> N = 1518 (760) Mean age = 65 years Female = 29% FC: 51% in I-II, 49% in III-IV Isch = 44% 80% had LVEF < 40% ACEi/ARB: 93%, BB 62% 	<ul style="list-style-type: none"> Multisite: 51 sites Fund: NR Dur: 12 months (extended to 36 months in a further analysis) Comple: NR WM: telephone intervention by specialized nurses 	<ul style="list-style-type: none"> STS to improve diet and treatment compliance, to promote exercise, to regularly monitor symptoms, weight, and edema, and to promote early visits if signs of clinical deterioration. None automatic transfer of vital data. Telephone STC 	<p>P: all-cause mortality, HF hospitalization</p> <p>S: NR</p> <p>Usability: no</p> <p>Satisfaction: no</p> <p>QoL: no</p> <p>Cost-effectiveness: no</p>

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; BB, beta-blockers; BP, blood pressure; Comple, % of patients who completed the programme; Dur, duration of the study; FC, function class, according to the New York Heart Association (NYHA); Fund, main funding organization; HF, heart failure; HR, heart rate; Isch, ischemic aetiology for HF; LVEF, left ventricular ejection fraction (mean); N, number of participants in the study (number of patients assigned to the intervention group); NHMRC, National Health and Medical Research Council; NR, not reported in the study; PDA, personal digital assistant; pO₂, peripheral oxygen saturation; QoL, quality of life; STC, structured telephone call; TM, telemonitoring; WM, work methodology.

Table 2. Summary of demographics, context, and technology for the studies not supporting the use of telemedicine in HF.

	DEMOGRAPHICS	CHARACTERISTICS/CONTEXT OF THE TRIAL	CHARACTERISTICS OF THE TECHNOLOGY	OUTCOMES OF THE STUDY
Study/domains	Patient population	Recipient, delivery personnel, intensity and complexity, and environment	Intervention content and method of communication	
BEAT-study Ong et al. ¹⁶ USA 2016	<ul style="list-style-type: none"> N = 1437 (715) Mean age = 73 years Female = 46% FC: 89% in II or III Isch = 52% LVEF = 31% Medication: ACE/ARB 90.9%, BB 84.3% 	<ul style="list-style-type: none"> Multisite: 6 medical centres in California Fund = Public (NHLBI) Dur: 6 months FC: 52% and coaching: 68% WM: specialized nurses conducting TM and telephone calls 	<ul style="list-style-type: none"> Combined health coaching telephone calls and a home-based TM system. Timely transfer of vital signs through the system (daily information on BP, HR, symptoms, and weight) Combination of telephone-based STC and the internet-based TM 	<p>P: readmission for any cause within 180 days after discharge</p> <p>S: all-cause readmission within 30 days, all-cause mortality at 30 and 180 days, and QoL at 30 and 180 days</p> <p>Usability: no</p> <p>Satisfaction: no</p> <p>QoL: no</p> <p>Cost-effectiveness: no</p>
Tele-HF Chaudhry et al. ¹⁴ USA 2010	<ul style="list-style-type: none"> N = 1653 (826) Mean age = 61 years Female = 43% FC: 87% in II or III Isch = 52% LVEF = 71% had LVEF < 40% Medication: ACE/ARB 82.9%, BB 82.9% 	<ul style="list-style-type: none"> Multisite: 33 cardiology practices Fund = NHLBI Dur: 6 months Compleat: 79% WM: nurses as site coordinators review weekly collected information. 	<ul style="list-style-type: none"> Patients enter data through a daily toll-free automated all to collect information about symptoms and weight. No automatic data transmission of vital signs. Telephone 	<p>P: composite of readmission for any reason or death from any cause within 180 days</p> <p>S: hospitalization for any reason or heart failure, death from any cause, number of days in hospital, and time to P and S outcomes.</p> <p>Usability: no</p> <p>Satisfaction: no</p> <p>QoL: no</p> <p>Cost-effectiveness: no</p>
TIM-HF. Koehler et al. ¹⁵ Germany 2011	<ul style="list-style-type: none"> N = 1437 (715) Mean age = 67 years Female = 19% FC: 89% in II or III Isch = 56% LVEF = 27% Medication: considered as 'Optimally treated' 	<ul style="list-style-type: none"> Multisite: 165 practices of 4 regions into the country. Fund: German government Dur: 26 months Compleat: 55% WM: nurses at specialized telemedical site reviewed all collected information. 	<ul style="list-style-type: none"> Bluetooth data transmission of vital signs. PDA transmit in encrypted form sent to 2 hospital-based telemedical centres. Wireless devices and Internet-based TM system. 	<p>P: composite of cardiovascular mortality or hospitalization due to heart failure</p> <p>S: cardiovascular mortality, all-cause hospitalizations, days lost due to HF hospitalization or cardiovascular death and changes in QoL and NYHA class</p> <p>Usability: no</p> <p>QoL: yes</p> <p>Satisfaction: no</p> <p>Cost-effectiveness: no</p>

Table 2. (Continued)

	DEMOGRAPHICS	CHARACTERISTICS/CONTEXT OF THE TRIAL	CHARACTERISTICS OF THE TECHNOLOGY	OUTCOMES OF THE STUDY
INH-study Angermann et al. ³¹ Germany 2012	<ul style="list-style-type: none"> N = 715 (352) Mean age = 68 years Female = 29% FC: 94% in II or III Isch = 55% LVEF: 30% ACEi/ARB: 89%, BB: 81% 	<ul style="list-style-type: none"> Multisite: 9 hospitals of 2 regions into the country. Fund: German government Dur: 3 months Complet: No patient was lost to follow-up WM: specialized nurses delivered the programme 	<ul style="list-style-type: none"> Nurse-coordinated disease management programme where standardized questions on cardiac monitoring and written intervention templates pursue monitoring and education. Telephone-based STC 	<p>P: composite of time to all-cause death or rehospitalization</p> <p>S: cardiovascular and all-cause death or hospitalization separately, time to, number and duration of readmissions, number of patient days alive and not hospitalized, changes in NYHA class, heart failure medication, cardiac hospitalization.</p> <p>Usability: no</p> <p>QoL: yes</p> <p>Satisfaction: no</p> <p>Cost-effectiveness: no</p>
WISH-study Lynga et al. ³² Sweden 2010	<ul style="list-style-type: none"> N = 344 (179) Mean age = 74 years Female = 24% FC: 94% in II or III Isch = 47% LVEF: 61% had LVEF < 30% ACEi/ARB: 99%, BB: 91% 	<ul style="list-style-type: none"> Multisite: 6 public hospitals in Sweden Fund: Swedish Governmental Agency for Innovation Dur: 12 months Complet: 93% in the intervention group WM: study nurses checked collected weight 3 times/week 	<ul style="list-style-type: none"> Daily electronic transmission of body weight to a HF clinic through an Electronic scale (Zenico Medical systems AB) to install at home. Wireless weigh scale and the Internet 	<p>P: cardiac rehospitalization</p> <p>S: all-cause hospitalization, death from any cause and composite endpoint of cardiac hospitalization and death from any cause.</p> <p>Usability: no</p> <p>QoL: no</p> <p>Satisfaction: no</p> <p>Cost-effectiveness: no</p>
TEHAF-study Boyne et al. ³³ Netherlands 2012	<ul style="list-style-type: none"> N = 382 (197) Mean age = 71 years Female = 42% FC: 96% in II or III Isch = 50% LVEF: 36% ACEi/ARB: 93%, BB: 82% 	<ul style="list-style-type: none"> Multisite: 3 hospitals in the Netherlands Fund: province of Limburg grant, 2 heart foundations, and Astra Zeneca ACEi/ARB: 93%, BB: 82% Dur: 12 months Complet: 81% completed follow-up WM: study nurses check daily pre-set dialogues about symptoms, knowledge, and behaviour which were transferred into risk profiles and sent to nurse's desktop 	<ul style="list-style-type: none"> The Health-Buddy@ collects specific disease through a device connected to a landline phone. Nurse may interact on high-risk profiles such as lack of adherence and depression. Telephone-based STC 	<p>P: time to first heart failure hospitalization</p> <p>S: combined endpoint of heart failure admission and all-cause death, number of readmission for heart failure and days in hospital for heart failure or other causes, mortality, and number of visits to the heart failure clinic</p> <p>Usability: no</p> <p>Satisfaction: no</p> <p>Cost-effectiveness: no</p>

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; BB, beta-blockers; BP, blood pressure; Complet, % of patients who completed the programme; Dur, duration of the study; FC, function class, according to the New York Heart Association (NYHA); Fund, main funding organization; HF, heart failure; HR, heart rate; Isch, ischemic aetiology for HF; LVEF, left ventricular ejection fraction (mean); N, number of participants in the study (number of patients assigned to the intervention group); NR, not reported in the study; PDA, personal digital assistant; pO₂, peripheral oxygen saturation; QoL, quality of life; STC, structured telephone call; TM, telemonitoring; WM, work methodology.

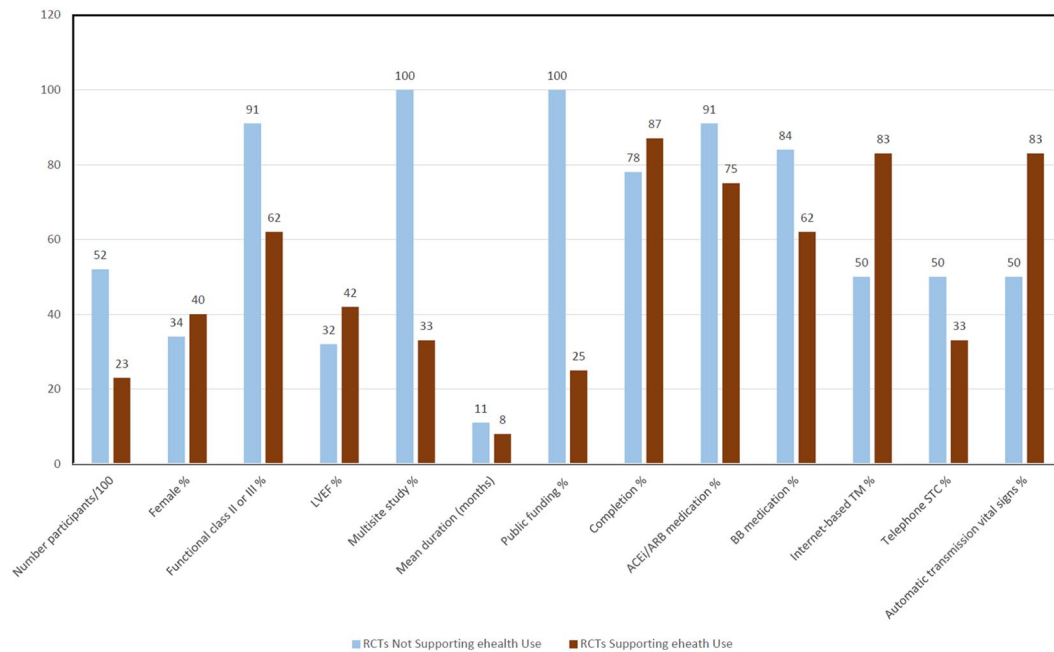


Figure 2. Comparison of the accumulative results (%) of supportive and non-supportive trials. ACEi indicates angiotensin-converting enzyme inhibitor; BB, beta-blockers; LVEF, left ventricular ejection function; STC, structured telephone call; TM, telemonitoring.

Pedone et al study, which was granted by a government research organization). The total (added) duration of the studies was 51 months (mean: 8.5 months). Standard medical treatment was reported in 5 of the 6 studies, presenting mean rates of ACEi/ARB and BB treatment of 72% and 62%, respectively. The mean duration of these studies was 8.5 months.

In 4 of the 6 studies (67%), automated transmission of vital signs through a telemonitoring (TM) system was tested. Structured telephone call (STC) was implemented in 2 studies (33%). The costs and cost-savings of the telemedicine intervention were specified in 2 of the 5 studies and in 1 of them was concluded that the costs of the integrated technology-based management were more expensive than usual care although the cost of adverse events was significantly lower.²⁸

Studies undermining the use of telemedicine

Of the outcomes of 6 RCTs,^{14-16,31-33} 5 of them included at the 2016 ESC guidelines for HF management²³ did not, in global terms, support the use of telemedicine in patients with HF, compared with usual care. In total, 5241 participants were included with an average age of 69 years and approximately 34% female. Most of the included patients had a moderate-to-severe decreased function class (91% in NYHA function class II and III) and, from the studies reporting mean LVEF (4 of 6), the mean value was 31%. In average, 52% of the patients had an ischemic etiology for their HF. All studies were conducted as multisite studies in different regions or clinical sites in the same country. All were conducted in public hospitals, and the studies were mainly

supported and funded by public governmental funds. The total (added) duration of the studies was 52 months (mean: 12 months). The participants of these studies presented optimal rates of standard medical HF treatment, with 91% on treatment with ACE-blocker and 84%, respectively. The mean duration of the studies was 12 months.

In 3 studies (50%), no Internet-based TM of health data was transmitted. Telephone-based interventions were present in most of the studies as a supportive tool and in 3 of them, in the form of STC; 3 of the 6 studies (50%) included the automatic transmission of vital signs to the TM system. All studies included readmission as a primary outcome measure of the study, either as a single primary endpoint or as a combined endpoint with all-cause death. No study addressed the satisfaction complaints of the users with the technology or the possible economic savings derived from telemedicine adoption.

Comparison of quantifiable results (in %) from non-supportive and supportive studies

All results from non-supportive and supportive studies were represented in a comparative manner, as shown in Figure 2.

Demographics. A larger number of participants were included in the studies not supporting the use of telemedicine (5241 vs 2296). Of them, 34% were females (vs 40%). The percentage of participants in NYHA functional class II and III was 91% (vs 77%). Of all the included studies, only 2 (one in the supportive and the other in the non-supportive group) specifically reported the percentage of patients with a LVEF > 40% (HF with

preserved ejection fraction [HFpEF]; 29% of the included patients in Chaudry's study [non-supportive] vs 20% in Ferrante's study [supportive]). In general, the mean LVEF was lower in the not-supportive studies compared to the supportive ones (32% vs 42%).

Context. All non-supportive studies were conducted in more than one clinical setting and funded by a public organization, meanwhile, only 50% of the supportive studies presented these characteristics. Completion rates were 78% versus 87% and the mean duration of the studies differed from 11 months for the non-supportive to 8 months for the supportive ones. In relation to medication, ACE and BB were, in general, more utilised in the patients participating in non-supportive studies (91% vs 72% for ACE and 84% vs 62% for BB).

Technology. Internet-based TM was used in 50% of the non-supportive studies and in almost 70% of the supportive RCTs (same percentages regarding the automatic transmission of vital signs). Telephone SCS was utilized in 50% of the non-supportive RCTs and slightly above 30% in the supportive ones.

Discussion

Readmission for HF remains a challenge in the treatment of affected patients. Strategies to reduce readmissions include the use of remote monitoring in the hope that, the early detection of clinical worsening may provide an avenue through which therapeutic interventions can be made to prevent a readmission.³⁵ However, to date, no clear evidence has demonstrated the efficacy of this strategy in reducing admissions. According to the realist lens, we have analysed a variety of factors, inherent and specific to each study that can trigger different mechanisms to produce different outcomes in response to similar interventions. Hence, the results from an intervention may differ depending, for example, on the characteristics of the site where the intervention occurs, including the attitude that clinicians and patients adopt in response to the technology utilized. In an effort to achieve a better understanding of these 'surrounding' factors, we applied a realist lens to this study in which dissimilarities in a patient population, context, and technology could explain divergent results from similar interventions. We decided to exclude the implantable devices studies in this review, as we considered that the characteristics of the population included in these studies (more often patients presenting a more advanced stage of disease) along with a more homogeneous context among the study centres and the funding sources (generally conducted in main public hospitals) could interfere in the results of our analysis. Finally, to provide a systematic base to this discussion, we have utilized the Taxonomy domain covered by Krumholz et al²⁴ basis to model a realist approach.

Patient population

Although generally collected in the trials, the respective authors have not signalled age and sex to influence their study outcomes. Our comparative findings neither support any relevant differences. Comorbidities and severity of disease were also generally reported in the studies but from our results, most of the included patients in the trials presented similar rates of comorbidities and most of the included patients presented a moderate-to-severe depressed function class. In this regard, even if the mean LVEF was consistently reported, only 2 authors considered the importance of reporting the percentage of patients with HFpEF. This is a very important observation as the different outcomes of the trials could be explained by variable representation of reduced versus preserved EF patients and the debate whether or not the management of each phenotype should be similar or different remains open. In addition, although 'standard care' is well established for HFrEF (such as the use of ACEi/ARB and BB), there is less consensus and guidance on the treatment of HFpEF. Thereby, it could appear that studies supporting the use of telemedicine patients were not receiving optimal medical treatment in terms of lower use of ACEi/ARB and BB. However, these studies included more patients with LVEF > 40% in whom no treatment with a class I recommendation has been established so we may conclude that it is not possible to directly compare these studies without accounting for the number of patients with preserved LVEF.

Notably, none of the studies addressed the level of literacy of the participants, that is, the magnitude of use or the grade of acceptance of technologies such as computers, smartphones and wearable devices, and/or their use of social media such as Facebook or Twitter.

Recipient

The characteristics of nominated patients and control group and their support channels (GP/specialist/allied health/hospitals) may play an important role to predetermine the outcomes of a given intervention. In general, underlying social and educational characteristics of the participants and the functioning of the health structures have not been deeply explained, as they may have been considered 'out of the scope' in traditional clinical trials.

The intervention content

Optimal medication management is an important factor that could explain study outcome differences. The adoption of telemedicine may not have the same opportunity to show benefits in a stable and optimally well-treated population of HF patients compared with a more unstable population with a higher risk for prompt worsening. The importance of these factors can be observed at the TIM-HF and the BEAT-HF studies. In the TIM-HF population, although

medication rates were not specifically reported, only 10% experienced a cardiac event during the 24 months of the study. In addition, also the control group of the study was followed up by highly trained clinicians of an exclusively dedicated HF out-patient services were responsible to follow up all participants, including those in the control group of the study. The BEAT-HF had an extremely well-treated cohort of patients, including the control group, which could contribute to explain failure to reduce readmission following telemedicine use in this study.

Delivery personnel

Multiple options depend on locations and availability of personnel. In general, beyond general terms, such as 'specialized nurses', we have failed finding information on the capacity or the educative level of personnel resources aimed to deliver productive interactions between patients and care providers.

Method of communication

The success of telemedicine may rely on the capacity of the technology to facilitate a prompt detection of clinical deterioration signs, enabling counteractive interventions to prevent worsening and eventually prevent readmission.³⁶ Hence, automated transmission of vital signs into the chosen technology (including weight, heart rate, blood pressure, and electrocardiogram) could theoretically increase the possibility of success. From our review, this hypothesis could be corroborated as most of the trials supporting the use of telemedicine presented some kind of automated transmission of vital signs. On the contrary, the Tele-HF, INH, and TEHAF trials, which failed to identify any impact on MACE were not designed to deliver timely monitoring of physiological health data. In fact, previous studies analysing the effects of intensive nursing support after hospital discharge in comparison with standard care but without technology support failed identifying possible benefits on improving MACEs.³⁷

Intensity and complexity

The duration, frequency, and complexity of a telemedicine programme are highly relevant to pre-determine the adherence to the intervention which may, in turn, contribute to determine the outcomes of this intervention. As an example, the BEAT-study and the Tele-HF, considered as an example of the largest telemedicine studies in HF, concluded that daily automated monitoring did not show significant differences in MACE compared with usual care. However, the low adherence to the programmes in these studies could have affected their results and their subsequent conclusions. In fact, the experience from the DIAL-study, another large long-term study utilizing similar approach (expert nursing staff collected health data via phone and encouraged patients to adhere to the programme)

showed good adherence of patients with significant reduction of readmission in this cohort of patients.

Environment

The characteristics of the settings in which the telemedicine solutions have been trialled (small clinics vs large hospitals, rural vs urban or even funding sources of a study) could play an important role to determine the outcomes of a given intervention.

From our review, those interventions with a fewer number of participants, funded or co-funded by private companies/organizations, conducted during shorter periods of time at homogeneous single clinical settings (though academic medical centres) have supported the use of telemedicine. As an exemption, we appreciated divergent results in a study conducted in multiple settings of rural areas²⁹ (in contrast with the majority of studies conducted in urban populations), which may support the hypothesis that the characteristics of the settings in which the telemedicine solutions are trialled are highly relevant.²⁰ We have shown that most of the multi-centre larger RCTs, granted by public or governmental organizations, showed less probabilities to demonstrate significant clinical benefits. However, private funded single-sited studies were more prompt to address and report the economic outcomes of their interventions. Large, public funded, multisite RCTs did not mention economic analysis in their results.

Outcome measure

Readmission was included in all studies as a primary endpoint, either alone or as a composite along with mortality. Most of the secondary endpoints included hospitalization for any reason or HF, death from any cause, and the number of days in hospital. Only in the BEAT-study, the QoL of the patients, the satisfaction with care, and use of medication were included during the individual telephone interviews along the study, although they were not finally evaluated as an endpoint or outcome of the study.

Future Work

Following the results and the discussion structure of this review, we propose some considerations for future studies:

1. Age, sex, and co-morbidities may be less relevant to predict the outcomes of a telemedicine intervention in people with HF, whereas the literacy level of the users and their prior acceptance of technology represent relevant factors which need to be addressed.
2. The capacity of telemedicine to anticipate decompensation signs with enough lead time to permit prompt and timely intervention seems only be possible when a whole feedback loop is functioning. In fact, some of the critical parameters used in telemedicine could capture deterioration too late to

- provide a meaningful intervention. The produced data flow must be captured in a timely fashion, adequately interpreted and responded to, which implies a well-trained telehealth workforce. Patients must promptly receive and implement treatment recommendations from the caregivers and, finally, the system must provide timely feedback to confirm resolution of the problem or indicate the need for further intervention. Disruptions or delay in execution of any of the components in this feedback loop will blunt the potential effect of the technology.³⁸
3. The ability to prevent HF hospitalizations is dependent on delivery of an effective medical intervention. The trials used for this review were highly variable in their protocol-directed delivery of medical interventions. For example, changes in heart rate, weight, or other symptoms capture by telemedicine did not require specific medication adjustments and follow up monitoring to ensure an expected response to a delivered intervention was not always mandated. In other words, if a patient's weight increased, it was not required to increase medications until weight decreased again, or to escalate changes in medications if weight did not decrease. Such factors are extremely important when contemplating the success or failure of an approach to reduce HF readmissions as the presence or absence of required medical action may be the single most important factor in determining the success versus failure of a telemedicine trial. We may conclude that the type of medical management used, and the grade of adherence to the 'protocol-driven patient management plan' should be additional comparative domains to analyse in future studies.
 4. It is uncertain whether the results from small, homogeneous, single centre clinical trials can be generalized to larger community-based populations. However, conducting small-scale telemedicine projects testing a small number of elements and allowing for an iterative approach, that is, trial and error, with subsequent refinement, could enable the development the specific diverse elements to be brought together for further larger trials.
 5. The levels of satisfaction from all users in respect to the intervention, including possible impact on the QoL of the patients and on staff workload have not been, in general, included in the current literature. In this regard, the introduction of person-centred participatory design methodology and systematic analysis of qualitative outcomes, such as user's satisfaction and QoL,³⁹ can lead to improve the outcomes of further interventions. This engagement with the potential telemedicine customers may represent the best opportunity for progress by partnering with local systems who are engaged with the complexity of their ideas group, empowering them to devise technological solutions which work (or not) to augment their capacities to care, optimize, remotely monitor, remotely educate/train, and rapidly intervene in deteriorating states, often within their limited resources.
 6. The description of the characteristics of the usual care (control) group from which the telemedicine intervention compares with should be emphasized for future studies. This approach will allow us to contextualize the real impact of our intervention and the context in which this intervention may (or may not) work.
 7. The adoption of telemedicine in HF care should be able to demonstrate non-inferiority (or superiority) results. However, demonstrating superiority of a new solution in terms of quality or cost effectiveness of treatment could not be always indispensable, as the telemedicine/e-health solution/application can, even with similar clinical results, have other types of advantages, including saving travelling time or other costs such as parking.⁴⁰ In this regard, the more sophisticated the telemedicine solution under trial, the higher the associated costs, and the lower the chance to demonstrate a substantial benefit in terms of cost-effectiveness.
 8. Finally, it could be concluded that the heterogeneity of all the components analysed in the reviewed studies could in part explain the disparity of outcomes and the inconsistency of results when analysing in literature the efficacy of telemedicine to reduce readmission in HF. In fact, the recent publication of the TIM-HF 2 study⁴¹ (that, for chronological reasons, could not be included in this review) utilized the gained knowledge from the TIM-HF¹⁵ demonstrating that a structured and holistic telemedicine intervention was able to reduce all-cause mortality and time spent in hospital in a selected population of patients with HF.

Limitations of This Study

One of the limitations of this study is that we did not adopt an overarching definition of telemedicine. The term telemedicine may also refer to implantable technological solutions including intra-arterial hemodynamic sensors in the pulmonary artery and implantable intra-cardiac devices (ICDs, pacemakers), which can be used in a 'remote' fashion to manage HF. However, for methodological reasons explained above in the discussion, the present review has not compared the results of RCTs trialling implantable devices. This work would require a separate review and analysis that could be motivated as a complementary information to the present review.

Conclusion

To realize potential and measurable benefits of telemedicine and innovative communication technologies in HF populations, complex challenges of integration in real clinical settings must be faced. By using a realist approach, we have highlighted the impact that contextual factors may have on the outcomes from existing large RCTs. The pre-existing model of care, the grade of adoption of the technology from all users, the method

of communication between patients and caregivers, and the ability, capability, and motivation from the caregivers to maintain the integrity of feedback loops (collect, process, and react on the generated health data) are important factors to determine to whom and in which circumstances may telemedicine contribute to improve readmission in HF.

Author Contributions

MG and FF conceived and designed the study; MG, NG, and FF analysed the data; MG wrote the first draft of the manuscript. MG, NG, FF, and PI contributed to the writing of the manuscript. MG, FF, NB, PI, CN, and BO jointly developed the structure and arguments for the paper. All authors agree with manuscript results and conclusions, made critical revisions, and approved the final version of the manuscript.

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