Optimal effectiveness of heart failure management — an umbrella review of meta-analyses examining the effectiveness of interventions to reduce (re)hospitalizations in heart failure

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Abstract
Heart failure (HF) is a major health concern, which accounts for 1–2% of all hospital admissions. Nevertheless, there remains a knowledge gap concerning which interventions contribute to effective prevention of HF (re)hospitalization. Therefore, this umbrella review aims to systematically review meta-analyses that examined the effectiveness of interventions in reducing HF-related (re)hospitalization in HFrEF patients. An electronic literature search was performed in PubMed, Web of Science, PsycInfo, Cochrane Reviews, CINAHL, and Medline to identify eligible studies published in the English language in the past 10 years. Primarily, to synthesize the meta-analyzed data, a best-evidence synthesis was used in which meta-analyses were classified based on level of validity. Secondarily, all unique RCTs were extracted from the meta-analyses and examined. A total of 44 meta-analyses were included which encompassed 186 unique RCTs. Strong or moderate evidence suggested that catheter ablation, cardiac resynchronization therapy, cardiac rehabilitation, telemonitoring, and RAAS inhibitors could reduce (re)hospitalization. Additionally, limited evidence suggested that multidisciplinary clinic or self-management promotion programs, beta-blockers, statins, and mitral valve therapy could reduce HF hospitalization. No, or conflicting evidence was found for the effects of cell therapy or anticoagulation. This umbrella review highlights different levels of evidence regarding the effectiveness of several interventions in reducing HF-related (re)hospitalization in HFrEF patients. It could guide future guideline development in optimizing care pathways for heart failure patients.

Keywords Heart failure related hospitalizations · Interventions · Medication · Invasive therapy · Rehabilitations · Care pathways

Introduction
Heart failure (HF) is a major health concern, with mortality ranging from 5 to 40% [1], corresponding with a fivefold increased risk of death, compared to the general population [2]. It is even estimated that HF patients have a worse life expectancy than the majority of cancer patients, with a median survival of approximately 2 to 3 years [3, 4]. More than 400,000 patients in the USA are being diagnosed with HF, annually [5]. Moreover, prevalence rates...
are progressively rising and are expected to increase with 46% from 2012 to 2030 [6, 7].

In addition, heart failure is the diagnosis with the highest readmission rates among all diseases [8–11], as it accounts for 1 to 2% of all hospital admissions [12, 13]. In elderly people, it is the major cause of hospitalization [8]. Most patients are hospitalized at least once a year after diagnosis (i.e., 68 to 78% of patients) [8, 14, 15], and more than one-fourth is at risk of being readmitted within 30 days after initial diagnosis [8, 15–18]. Comparatively to prevalence rates, the total number of hospitalizations is also expected to rise, by 50% in the near future [19, 20].

Hospitalization places a great burden on patients [21]. Patients may experience various limitations in their activities of daily living [22–24], which highly impact their quality of life and level of satisfaction [21, 25]. Moreover, aside from a reduced quality of life, patients who are hospitalized have a significantly higher risk of death than non-hospitalized patients [26, 27]. Additionally, hospitalization due to HF places a great burden on the healthcare system, as it accounts for more than half of total healthcare costs [28, 29] corresponding with more than > 15 billion dollars a year for the American healthcare system [24, 30, 31]. HF is the most costly condition in western countries and since long time hospitalization for HF even exceeds the hospitalization costs for both cancer and myocardial infarction combined [32, 33]. Accordingly, hospitalization is judged as a highly important outcome measure in (inter) national literature and registries [34, 35].

Nevertheless, despite the rising prevalence rates, it seems that up to 40% of hospitalizations could be classified as preventable [36–40]. Therefore, the reduction of hospitalizations is the most promising factor as target to improve patients’ reported experiences or outcomes and to reduce the costs of HF management [25, 41, 42]. The combined measure of patient outcomes and costs are the main goal in value based healthcare, a well-known and promising strategy in healthcare in order to improve patient value [43–45].

Multiple previous studies examined the effect of various interventions to reduce (re)hospitalization in HF, mostly in patients with a left ventricular ejection fraction (LVEF) < 40% (i.e., patients with HFrEF) [46], but contrasting findings are found within the literature regarding the effectiveness of these interventions in reducing hospital admissions [47, 48]. Moreover, there is some considerable heterogeneity in strategies and methods used in previous studies [49]. Some studies, for example, focused on remote monitoring to prevent readmissions, while others examined quality improvement of interventions or transitional care systems [36, 37, 50–52]. Therefore, there remains a gap in information concerning which interventions could effectively contribute to effective prevention of HF hospitalization or readmission [47, 48, 53, 54].

Hence, even though multiple interventions have been included in the guidelines for treatment of HF [46, 55], there is a compelling need of a comprehensive overview of which types of interventions prove effective specifically in reducing HF hospitalizations, especially in HFrEF patients. This umbrella review therefore aims to systematically review all published meta-analyses conducted in the past 10 years that examined the incremental effect of different interventions in addition to standard care, to reduce (re)hospitalization in HFrEF patients, in order to highlight different levels of evidence regarding their effectiveness.

Methods

The systematic review protocol of this review was registered, in accordance with the PRISMA guidelines, at the International Prospective Register of Systematic Reviews (PROSPERO) on July 6, 2020 (registration number: 247872).

Search strategy

An electronic literature search was performed in PubMed, Web of Science, PsycInfo, Cochrane Reviews, CINAHL, and Medline to identify eligible studies published in the English language from January 2010 up to the end of June 2020. Search terms were developed using MeSH terms. Key words were related to (1) interventions, (2) heart failure, (3) hospitalization, and (4) meta-analysis (Table 1).

Ample differences existed in the classification of categories of interventions depicted in the existing literature. For example, previous reviews classified interventions in either educational interventions, pharmacological interventions, telemonitoring (TM), structured telephone support (STS), nurse home visits, nurse care management, and disease management clinics [41]; or discharge planning protocols, comprehensive geriatric assessments, discharge support arrangements, and educational interventions [56]; or case management interventions, clinical interventions, and multidisciplinary interventions [53]; or predischarge interventions, postdischarge interventions, and interventions bridging the transition [57]. A list of 4 categories of interventions was derived following a scoping review that combine the most common interventions aimed at reducing hospital (re) admissions, cardiac rehabilitation, care pathways, medication, and invasive treatment. Both general terms linked to the concept of interventions (e.g., programs, inventions, therapy) and terms for specific examples of (categories of) interventions were included in the search strategy.
Table 1: Search strategy for each database

| Database | Search terms |
|----------|-------------|
| PubMed | (((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((((telemedicine>Title/Abstract)) OR (telecare>Title/Abstract)) OR (teleconsultation>Title/Abstract)) OR (telecommunication>Title/Abstract)) OR (home monitoring>Title/Abstract)) OR (monitoring>Title/Abstract)) OR (tele>Title/Abstract)) OR (tele-med>Title/Abstract)) OR (telehealth>Title/Abstract)) OR (tele-health>Title/Abstract)) OR (remote consult>Title/Abstract)) OR (remote monitoring>Title/Abstract)) OR (remote patient monitoring>Title/Abstract)) OR (structured telephone support>Title/Abstract)) OR (structured scheduled telephone support>Title/Abstract)) OR (tele-telephone support>Title/Abstract)) OR (telecardiol>Title/Abstract)) OR (home care services>Title/Abstract)) OR (disease management>Title/Abstract)) OR (patient care team>Title/Abstract)) OR (patient discharge>Title/Abstract)) OR (patient care planning>Title/Abstract)) OR (home care services>Title/Abstract)) OR (manage>Title/Abstract)) OR (comprehensive discharge planning>Title/Abstract)) OR (discharge planning>Title/Abstract)) OR (hospital discharge>Title/Abstract)) OR (patient care planning>Title/Abstract)) OR (multidisciplinary care>Title/Abstract)) OR (care management>Title/Abstract)) OR (transition>Title/Abstract)) OR (comprehensive health care>Title/Abstract)) OR (process of care>Title/Abstract)) OR (comprehensive care>Title/Abstract)) OR (total quality management>Title/Abstract)) OR (guideline adherence>Title/Abstract)) OR (clinical competence>Title/Abstract)) OR (rehabilitation centers>Title/Abstract)) OR (exercise therapy>Title/Abstract)) OR (sports>Title/Abstract)) OR (physical exertion>Title/Abstract)) OR (erxercise>Title/Abstract)) OR (exercise>Title/Abstract)) OR (exercise>Title/Abstract)) OR (rehabtit>Title/Abstract)) OR (lifestyle intervent>Title/Abstract)) OR (life-style intervent>Title/Abstract)) OR (psychotherapy>Title/Abstract)) OR (psychotherap>Title/Abstract)) OR (psycholog>Title/Abstract)) OR (psycholog* intervent>Title/Abstract)) OR (self-care>Title/Abstract)) OR (relaxation therapy>Title/Abstract)) OR (counseling>Title/Abstract)) OR (cognitive therapy>Title/Abstract)) OR (behaviour therapy>Title/Abstract)) OR (behavior therapy>Title/Abstract)) OR (meditation>Title/Abstract)) OR (hypnotherap>Title/Abstract)) OR (psycho-educat>Title/Abstract)) OR (psychoeducat>Title/Abstract)) OR (motiv* intervent>Title/Abstract)) OR (education>Title/Abstract)) OR (self-management>Title/Abstract)) OR (action plan>Title/Abstract)) OR (medication>Title/Abstract)) OR (medication* treatment>Title/Abstract)) OR (pharmacotherapy>Title/Abstract)) OR (device* implantation>Title/Abstract)) OR (medication adherence>Title/Abstract)) OR (patient compliance>Title/Abstract)) OR (adherent>Title/Abstract)) OR (non-compliant>Title/Abstract)) OR (noncompliance>Title/Abstract)) OR (prescription drug>Title/Abstract)) OR (dosage forms>Title/Abstract)) OR (prescribed>Title/Abstract)) OR (pill>Title/Abstract)) OR (invasive HF monitoring>Title/Abstract)) OR (implanted monitoring devices>Title/Abstract)) OR (CRT>Title/Abstract)) OR (biventricular pacing>Title/Abstract)) OR (drug therapy>Title/Abstract)) OR (intervention>Title/Abstract)) OR (interven>Title/Abstract)) OR (immunization>Title/Abstract)) OR (e-health>Title/Abstract)) OR (program>Title/Abstract)) OR (mobile health>Title/Abstract)) OR (mhealth>Title/Abstract)) OR (after-hours care>Title/Abstract)) OR (integrated delivery of health care>Title/Abstract)) OR (managed care programs>Title/Abstract)) OR (technological interventions>Title/Abstract)) OR (inventions>Title/Abstract)) OR (automation>Title/Abstract)) OR (program evaluation>Title/Abstract)) OR (standard of care>Title/Abstract)) AND (((((heart failure>Title/Abstract)) OR (cardiac failure>Title/Abstract)) OR (congestive>Title/Abstract)) OR (left ventricular dysfunction>Title/Abstract)) OR (CHF>Title/Abstract))))) AND (((((readmission*hospitalization>Title/Abstract)) OR (rehospitalization>Title/Abstract)) OR (admission>Title/Abstract)) OR (re-admission>Title/Abstract)) OR (re-admission>Title/Abstract)) OR (length of stay>Title/Abstract))))) AND ((((meta analysis>Title/Abstract)) OR (meta-analysis>Title/Abstract)) OR (metaanaly>Title/Abstract)) OR (meta-analy>Title/Abstract)) OR (meta-analy>Title/Abstract)) OR (meta-analysis>Title/Abstract)) OR (meta analy>Title/Abstract)) OR (meta analy>Title/Abstract)) OR (meta-analy>Title/Abstract)) OR (meta-analy>Title/Abstract)) OR (meta-analy>Title/Abstract))|
### Table 1 (continued)

| Database | Search terms |
|----------|--------------|
| **Cochrane library** | #1: (Telemedicine):ti,ab,kw OR (telecare):ti,ab,kw OR (teleconsultation):ti,ab,kw OR (telecommunication):ti,ab,kw OR (home monitoring):ti,ab,kw OR (monitoring):ti,ab,kw OR (tele*:ti,ab,kw OR (tele med):ti,ab,kw OR (tele-med*):ti,ab,kw OR (telehealth*:ti,ab,kw OR (tele-health*:ti,ab,kw OR (remote patient monitoring):ti,ab,kw OR (structured telephonic support):ti,ab,kw OR (structured telephone support):ti,ab,kw OR (telephone support):ti,ab,kw OR (telecardiol*:ti,ab,kw OR (home care services):ti,ab,kw OR (disease management):ti,ab,kw OR (patient care team):ti,ab,kw OR (patient discharge):ti,ab,kw OR (patient education):ti,ab,kw OR (patient aftercare):ti,ab,kw OR (patient care planning):ti,ab,kw OR (home care services):ti,ab,kw OR (manage*:ti,ab,kw OR (comprehensive discharge planning):ti,ab,kw OR (discharge planning):ti,ab,kw OR (hospital discharge):ti,ab,kw OR (patient care planning):ti,ab,kw OR (multidisciplinary care):ti,ab,kw OR (care management):ti,ab,kw OR (transition*:ti,ab,kw OR (comprehensive health care):ti,ab,kw OR (process of care):ti,ab,kw OR (comprehensive care):ti,ab,kw OR (multidisciplinary care):ti,ab,kw OR (improve*:ti,ab,kw OR (promot*:ti,ab,kw OR (enhance*:ti,ab,kw OR (optimi*:ti,ab,kw OR (quality of health care):ti,ab,kw OR (improvement initiative):ti,ab,kw OR (process*: improvement):ti,ab,kw OR (management quality circles):ti,ab,kw OR (total quality management):ti,ab,kw OR (guideline adherence):ti,ab,kw OR (clinical competence):ti,ab,kw OR (rehabilitation centers):ti,ab,kw OR (exercise therapy):ti,ab,kw OR (rehabilitation:ti,ab,kw OR (sports):ti,ab,kw OR (physical exertion):ti,ab,kw OR (exertion):ti,ab,kw OR (exercise):ti,ab,kw OR (rehabilit*:ti,ab,kw OR (lifestyle interven*:ti,ab,kw OR (life-style interven*:ti,ab,kw OR (physiotherapy):ti,ab,kw OR (psychotherap*:ti,ab,kw OR (psychotherap*:ti,ab,kw OR (psychologist interven*:ti,ti,ab,kw OR (cognitive therapy):ti,ab,kw OR (behaviour therapy):ti,ab,kw OR (behavior therapy):ti,ab,kw OR (meditation):ti,ab,kw OR (hypnotherap*)ti,ab,kw OR (psycho-educat*:ti,ab,kw OR (psychoeduca*:ti,ab,kw OR (self-management):ti,ab,kw OR (action plan*:ti,ab,kw OR (Medication):ti,ab,kw OR (medication*: treatment):ti,ab,kw OR (pharmacotherapy):ti,ab,kw OR (device*: implantation):ti,ab,kw OR (medication adherence):ti,ab,kw OR (patient compliance):ti,ab,kw OR (adherent):ti,ab,kw OR (non-compliant):ti,ab,kw OR (noncompliance):ti,ab,kw OR (nonadherent):ti,ab,kw OR (nonadherence):ti,ab,kw OR (prescription drugs):ti,ab,kw OR (dosage forms):ti,ab,kw OR (prescribed):ti,ab,kw OR (pill* OR invasive HF monitoring):ti,ab,kw OR (implanted monitoring devices):ti,ab,kw OR (CRT*:ti,ab,kw OR (biventricular pacing):ti,ab,kw OR (drug therapy):ti,ab,kw OR (intervention):ti,ab,kw OR (interven*:ti,ab,kw OR (e-health):ti,ab,kw OR (program):ti,ab,kw OR (mobile health):ti,ab,kw OR (mhealth):ti,ab,kw OR (after-hours care):ti,ab,kw OR (integrated delivery of health care):ti,ab,kw OR (managed care programs):ti,ab,kw OR (technology interventions):ti,ab,kw OR (inventions):ti,ab,kw OR (automation):ti,ab,kw OR (program evaluation):ti,ab,kw OR (standard of care):ti,ab,kw OR (influenza):ti,ab,kw |

**Web of Science** | #1: (Telemedicine OR telecare OR teleconsultation OR telecommunication OR home monitoring OR monitoring OR tele*: OR tele med OR tele-med* OR telehealth*: OR remote patient monitoring OR structured telephonic support OR (structured telephone support OR (telephone support OR telecardiol*: OR home care services OR disease management OR patient care team OR patient discharge OR patient education OR patient aftercare OR patient care planning OR home care services OR manage* OR comprehensive discharge planning OR discharge planning OR hospital discharge OR patient care planning OR multidisciplinary care OR care management OR transition* OR comprehensive health care OR process of care OR comprehensive care OR multidisciplinary care OR improve* OR promot* OR enhance* OR optimi* OR quality of health care OR improvement initiative OR process* improvement OR management quality circles OR total quality management OR guideline adherence OR clinical competence OR *rehabilitation centers OR exercise therapy OR rehabilitation OR sports OR physical exertion OR exertion OR exercise OR rehabilit* OR lifestyle interven* OR life-style interven* OR psychotherapy OR psychotherap* OR psycholog* OR psycholog* interven* OR self-care OR relaxation therapy OR counseling OR cognitive therapy OR behaviour therapy OR meditation OR hypnotherap* OR psycho-educat* OR psychoeduca* OR motiv* interven* OR health education OR self-management OR action plan* OR Medication OR medication* treatment OR pharmacotherapy OR device* implantation OR medication adherence OR patient compliance OR adherent OR non-compliant OR noncompliance OR nonadherent OR nonadherence OR prescription drugs OR dosage forms OR prescribed OR pill* OR invasive HF monitoring OR implanted monitoring devices OR CRT OR biventricular pacing OR drug therapy OR intervention OR interven* OR e-health OR program OR mobile health OR mhealth OR after-hours care OR integrated delivery of health care OR managed care programs OR technological interventions OR inventions OR automation OR program evaluation OR standard of care) |

#2: TS = (meta analysis OR meta-analysis OR metaanaly* OR meta-analysis) |

#3: TS = (hospitalization* OR rehospitalization* OR admission* OR re-admission* OR readmission* OR length of stay) |

#4: TS = (*Heart failure OR cardiac failure OR congestive* OR left ventricular dysfunction OR CHF) |

#5: #4 AND #3 AND #2 AND #1
Table 1 (continued)

| Database | Search terms |
|----------|--------------|
| Psycinfo | TX (Telemedicine OR telecare OR teleconsultation OR telecommunication OR home monitoring OR monitoring OR tele* OR tele med OR tele-med* OR telehealth* OR tele-health* OR remote consult* OR remote monitoring OR remote patient monitoring OR structured telephone support OR structured scheduled telephone support OR telephone support OR telecardi* OR home care services OR disease management OR patient care team OR patient discharge OR patient education OR patient aftercare OR patient care planning OR home care services OR manage* OR comprehensive discharge planning OR discharge planning OR hospital discharge OR patient care planning OR multidisciplinary care OR care management OR transition* OR comprehensive health care OR process of care OR comprehensive care OR multidisciplinary care OR improve* OR promot* OR enhance* OR optimi* OR quality of health care OR improvement initiative OR process* OR improvement OR management quality circles OR total quality management OR guideline adherence OR clinical competence OR rehabilitation centers OR exercise therapy OR rehabilitation OR sports OR physical exertion OR exertion OR exercise OR rehabilit* OR lifestyle interven* OR life-style interven* OR psychotherapy OR psychotherap* OR psycholog* OR psycholog* interven* OR self-care OR relaxation therapy OR counseling OR cognitive therapy OR behaviour therapy OR behavior therapy OR meditation OR hypnotherap* OR psycho-educat* OR psychoeduca* OR motiv* interven* OR health education OR self-management OR action plan* OR Medication OR medication* treatment OR pharmacotherapy OR device* implantation OR medication adherence OR patient compliance OR adherent OR non-compliant OR noncompliance OR nonadherent OR nonadherence OR prescription drugs OR dosage forms OR prescribed OR pill* OR invasive HF monitoring OR implanted monitoring devices OR CRT OR biventricular pacing OR drug therapy OR intervention OR interven* OR e-health OR program OR mobile health OR mhealth OR after-hours care OR integrated delivery of health care OR managed care programs OR technological interventions OR inventions OR automation OR program evaluation OR standard of care) AND TX (meta analysis OR meta-analysis OR meta analy* OR metaanaly* OR meta-analy*) AND TX (hospitalization* OR rehospitalization* OR admission* OR re-admission* OR readmission* OR length of stay) AND TX (Heart failure OR cardiac failure) |
| Medline | AB (Telemedicine OR telecare OR teleconsultation OR telecommunication OR home monitoring OR monitoring OR tele* OR tele med OR tele-med* OR telehealth* OR tele-health* OR remote consult* OR remote monitoring OR remote patient monitoring OR structured telephone support OR structured scheduled telephone support OR telephone support OR telecardi* OR home care services OR disease management OR patient care team OR patient discharge OR patient education OR patient aftercare OR patient care planning OR home care services OR manage* OR comprehensive discharge planning OR discharge planning OR hospital discharge OR patient care planning OR multidisciplinary care OR care management OR transition* OR comprehensive health care OR process of care OR comprehensive care OR multidisciplinary care OR improve* OR promot* OR enhance* OR optimi* OR quality of health care OR improvement initiative OR process* OR improvement OR management quality circles OR total quality management OR guideline adherence OR clinical competence OR rehabilitation centers OR exercise therapy OR rehabilitation OR sports OR physical exertion OR exertion OR exercise OR rehabilit* OR lifestyle interven* OR life-style interven* OR psychotherapy OR psychotherap* OR psycholog* OR psycholog* interven* OR self-care OR relaxation therapy OR counseling OR cognitive therapy OR behaviour therapy OR behavior therapy OR meditation OR hypnotherap* OR psycho-educat* OR psychoeduca* OR motiv* interven* OR health education OR self-management OR action plan* OR Medication OR medication* treatment OR pharmacotherapy OR device* implantation OR medication adherence OR patient compliance OR adherent OR non-compliant OR noncompliance OR nonadherent OR nonadherence OR prescription drugs OR dosage forms OR prescribed OR pill* OR invasive HF monitoring OR implanted monitoring devices OR CRT OR biventricular pacing OR drug therapy OR intervention OR interven* OR e-health OR program OR mobile health OR mhealth OR after-hours care OR integrated delivery of health care OR managed care programs OR technological interventions OR inventions OR automation OR program evaluation OR standard of care) AND AB (meta analysis OR meta-analysis OR meta analy* OR metaanaly* OR meta-analy*) AND AB (hospitalization* OR rehospitalization* OR admission* OR re-admission* OR readmission* OR length of stay) AND AB (Heart failure OR cardiac failure OR congestive* OR left ventricular dysfunction OR CHF) |
Search results of all databases were combined, and duplicates were removed. Titles and abstracts were screened against the following inclusion criteria: (1) a meta-analysis was conducted, on (2) randomized controlled trials (RCTs), (3) that examined the effectiveness of (3.a) cardiac rehabilitation, or (3.b) care pathways, or (3.c) medication, or (3.d) invasive therapy, (4) in patients with an established diagnosis of chronic heart failure, (5) with an LVEF < 40, (6) with invasive therapy, (7) as compared to usual care, (8) conducted in the past 10 years, (9) followed patients for at least three months, and (11) were reported in English. Meta-analyses that included both RCTs and observational or cohort studies were not excluded. Yet only the included RCTs (and corresponding meta-analyzed effect sizes) were extracted and used for our analyses. Only meta-analyses that reported at least one meta-analyzed effect estimate for HF-related admissions were included. In order to assure objective assessment, the title and abstract screening were independently conducted by two researchers (FH, TG). In case of disagreement between reviewers, points of disagreement were discussed in order to reach consensus. For full-text screening, inter-rate reliability was calculated using Cohen’s kappa.

Studies were excluded when the patient population was not primarily diagnosed with heart failure (e.g., patients with diabetes and comorbid heart failure). Additionally, if studies examined HF patients in combination with other patient groups yet did not report data on the individual patient groups, the study was excluded, as we would otherwise be unable to make a distinction between the differences in patient groups. Furthermore, studies that only reported data on a combined endpoint (e.g., mortality in conjunction with HF-hospitalization) and meta-analyses that examined risk stratification, prognostic factors, or lifestyle advice in patients were excluded. Moreover, meta-analyses were also excluded when examining a specific subgroup of HF patients (e.g., patients with and LVAD) or when examining a broader category of patients that could possibly include HF patients (e.g., “older patients” in general).

### Quality assessment

The “A MeaSurement Tool to Assess systematic Reviews 2” (AMSTAR 2) was used to assess the methodological quality of included meta-analyses [58]. AMSTAR 2 consists of 16 items, of which 10 items were retained from the original AMSTAR tool. Response options for the items were “yes,” “partial yes,” and “no,” with “yes” responses denoting a positive result. The overall score of this tool was converted to high quality, moderate quality, low quality, and critically low quality. High quality was achieved when studies possessed no or one non-critical weakness; moderate quality was achieved when studies had more than one non-critical weakness; low quality was achieved when studies had one critical flaw, with or without a non-critical weakness; and critically low quality was achieved when studies exhibited more than one critical flaw with or without non-critical weaknesses. Critical domains are depicted in Table 2 [58]. In order to assure objective assessment, the quality assessment

| Database | Search terms |
|----------|--------------|
| CINAHL | AB ( Telemedicine OR telecare OR teleconsultation OR telecommunication OR home monitoring OR monitoring OR tele* OR tele med OR tele-med* OR telehealth* OR tele-health* OR remote consult* OR remote monitoring OR remote patient monitoring OR structured telephone support OR structured scheduled telephone support OR telephone support OR telecardiol* OR home care services OR disease management OR patient care team OR patient discharge OR patient education OR patient aftercare OR patient care planning OR home care services OR manage* OR comprehensive discharge planning OR discharge planning OR hospital discharge OR patient care planning OR multidisciplinary care OR care management OR transition* OR comprehensive health care OR process of care OR comprehensive care OR multidisciplinary care OR improve* OR promot* OR enhance* OR optimi* OR quality of health care OR improvement initiative OR process* improvement OR management quality circles OR total quality management OR guideline adherence OR clinical competence OR *rehabilitation centers OR exercise therapy OR *rehabilitation OR sports OR physical exertion OR exertion OR exercise OR rehabilit* OR lifestyle interven* OR life-style interven* OR psychotherapy OR psychotherap* OR psycholog* OR psycholog* interven* OR self-care OR relaxation therapy OR counseling OR cognitive therapy OR behaviour therapy OR behavior therapy OR meditation OR hypnotherap* OR psycho-educat* OR psychopeducat* OR motiv* interven* OR health education OR self-management OR action plan* OR Medication OR medication* treatment OR pharmacotherapy OR device* implantation OR medication adherence OR patient compliance OR adherent OR non-compliant OR noncompliance OR nonadherent OR nonadherence OR prescription drugs OR dosage forms OR prescribed OR pill* OR invasive HF monitoring OR implanted monitoring devices OR CRT OR biventricular pacing OR drug therapy OR intervention OR interven* OR e-health OR program OR mobile health OR mhealth OR after-hours care OR integrated delivery of health care OR managed care programs OR technological interventions OR inventions OR automation OR program evaluation OR standard of care) AND AB ( meta analysis OR meta-analysis OR meta analy* OR metaanaly* OR meta-analy*) AND AB ( hospitalization* OR rehospitalization* OR admission* OR re-admission* OR readmission* OR length of stay) AND AB ( Heart failure OR cardiac failure OR congestive* OR left ventricular dysfunction OR CHF)
was independently conducted by two researchers (GS, TG). In case of disagreement between reviewers, points of disagreement were discussed in order to reach consensus (RT).

**Data extraction**

A standardized extraction form was used to extract data from the included studies. Sociodemographic data (e.g., age, sex), number of participants, left ventricular ejection fraction, type of intervention and control, follow-up period, effect size, and conclusion were extracted from either the individual RCT or the meta-analysis in which the RCT was included. Only the most recent meta-analysis was included when multiple articles were written by the same authors on the same dataset. Comparisons were made between the different categories of interventions in terms of effectiveness in reducing HF-related (re)hospitalization. Interventions were classified as having a significant effect on HF-related (re)hospitalization (as compared to usual care) based on their own reported RR statistics, findings, and conclusions.

**Data synthesis**

Interventions were first classified into the four predefined categories (i.e., cardiac rehabilitation, care pathways, medication, and invasive therapy) and subsequently divided into more detailed classes of interventions (e.g., TM and STS) to examine the exact effect of all unique interventions.

**Primary analysis: meta-analyses**

To synthesize the data, a best-evidence synthesis was used as primary analysis, in which meta-analyses were classified based on level of internal and external validity [59]. The levels of evidence regarding the significance or non-significance of a relationship between the intervention and HF-related hospitalization among studies were ranked according to the following statements: (1) strong evidence: consistent findings (> 75% of the studies reported consistent findings) in multiple high quality studies; (2) moderate evidence: consistent findings (> 75% of the studies reported consistent findings) in one high-quality study and two or more moderate quality studies or in three or more weak quality studies; (3) limited evidence: generally consistent findings (> 75% of the studies reported consistent findings) in a high quality study or in two or fewer moderate quality studies; (4) no evidence: no studies could be found; (5) conflicting evidence: conflicting findings. 

**Secondary analysis: extracted RCTs**

It was expected that multiple meta-analyses would report identical RCTs, as it was previously found that the amount of redundancy and duplication among reviews is substantial [60, 61]. Therefore, the corrected covered area (CCA) was calculated, which is a measure of duplicates in meta-analyses divided by the frequency of duplicates, reduced by the number of original publications (Corrected covered area = \( N_\text{r} / r \)) [62]. A CCA of 0–5% is considered as slight overlap, while 6–10%, 11–15%, > 15% are respectively regarded as moderate, high, and very high overlap. In order to prevent bias as a result of duplicated data, a secondary analysis was conducted to control for the effects of overlap. All unique RCTs were extracted from the meta-analyses. Individual risk ratios (RRs) and 95% CIs for each intervention were calculated using Review Manager V.5.4. or extracted from the meta-analyses. The \( I^2 \)-statistic was used to present the heterogeneity of intervention effect. When the \( I^2 \)-statistic was statistically significant, a random-effects model was used in analyses. The RR-statistics found in our own meta-analyses were compared to the reported effects in the published meta-analyses.

**Results**

**Search results**

After removal of duplicate meta-analyses, 639 titles and abstracts were screened (see Fig. 1). A total of 202 full-text articles were assessed for eligibility, of which 44 were included in our analyses. Cohen’s kappa for full-text screening was 0.76, indicating substantial agreement [63]. Median year of publication of all included meta-analyses was 2018. The 44 included meta-analyses encompassed 348 RCTs of which 186 were unique RCTs regarding interventions to prevent HF hospitalization (Table 3). Of these 186 unique RCTs, 44 were classified as invasive therapy, 14 as cardiac rehabilitation, 60 as medication, and 67 as care pathways (Table 4). The CCA for cardiac revalidation was \( (14/14−14)/(86−45) = 5/14 = 36\% \), the CCA for invasive therapy was \( (41/630)/(45×15−45) = 41/630 = 7\% \), the CCA for medication was \( (40/836)/(64×14−60) = 40/836 = 5\% \), and the CCA for care pathways was \( (73/896)/(67×15−67) = 73/896 = 8\% \). This indicates a moderate to very high overlap in included RCTs [62].

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**Table 2** Critical domains of the AMSTAR 2

| Registered protocol before commencement of the review |
|--------------------------------------------------------|
| Risk of bias from individual studies being included in the review |
| Appropriateness of meta-analytical methods |
| Consideration of risk of bias when interpreting the results of the review |
| Assessment of presence and likely impact of publication bias |
Quality assessment

Overall, risk of bias was classified as relatively low (Table 5). Of the 44 meta-analyses, 11 scored critically low, 15 low, 1 moderate, and 17 high. Almost all meta-analyses registered their protocol before commencement of the review (item 2) and used appropriate meta-analytical methods (item 11). Reviews were mostly downgraded based on the lack of an adequate investigation of publication bias (item 15).

Study characteristics

A total of 425,220 patients were included in the 44 meta-analyses and 186 RCTs (Table 4). RCTs included between 16 and 10,917 patients. The mean age of patients ranged from 33 to 96 years. Mean LVEF varied between 17 and 40%. Percentage of male patients ranged from 25 to 100%. Follow-up period ranged widely from 30 days to 10 years. Studies that tried to prevent hospital admissions with cardiac rehabilitation focused on either exercise only or multicomponent cardiac rehabilitation. Care pathways could be divided into either TM, STS, and self-management promotion programs or multidisciplinary clinics. Invasive therapy encompassed catheter ablation (CA), cardiac resynchronization therapy (CRT), mitral valve repair, or stem cell therapy. Medication subtypes were angiotensin-converting enzyme inhibitors (ACE), angiotensin II receptor blockers (ARBs), mineralocorticoid receptor antagonists (MRAs), beta-blockers, statins, anticoagulation, and a miscellaneous subcategory.
Table 3  Overlap between different meta-analyses in included RCTs

| Study                                      | Year | Included |
|--------------------------------------------|------|----------|
| Abraham et al. [87]                        | 2002 | x        |
| Abraham et al. [88]                        | 2004 |          |
| Adamson et al. [89]                        | 2003 | x        |
| Adamson et al. [90]                        | 2011 | x        |
| Al-khatib et al. [91]                      | 2010 | x        |
| Angermann et al. [92]                      | 2012 |          |
| Antonicelli et al. [93]                    | 2008 |          |
| Asgar et al. [94]                          | 2017 | x        |
| Assmus et al. [95]                         | 2006 |          |
| Assmus et al. [96]                         | 2013 | x x      |
| Atienza et al. [97]                        | 2004 |          |
| Austin et al. [98]                         | 2005 | x        |
| Australia/New Zealand Heart Failure Group [99] | 1997 |          |
| Bartunek et al. [100]                      | 2013 |          |
| Belardinelli et al. [101]                  | 1999 | x        |
| Belardinelli et al. [102]                  | 2012 | x        |
| Beller et al. [103]                        | 1995 |          |
| Bentkover et al. [104]                     | 2007 |          |
| Beta-Blocker evaluation of survival trial [105] | 2001 |          |
| Biannic et al. [106]                       | 2012 |          |
| Bielecka-Dabrowa et al. [107]              | 2009 | x        |
| Blue et al. [108]                          | 2001 |          |
| Boccanelli et al. [109]                    | 2009 |          |
| Böhmi et al. [110]                         | 2016 |          |
| Bolli et al. [111]                         | 2011 |          |
| Boriani et al. [112]                       | 2017 | x        |
| Boyne et al. [113]                         | 2012 |          |
| Bristow et al. [114]                       | 1996 |          |
| Brown et al. [115]                         | 1995 |          |
| Lok et al. [116]                           | 2007 | x        |
| Capomolla et al. [117]                     | 2002 |          |
| Cazeau et al. [118]                        | 2001 | x        |
| CDMR [119]                                 | 1988 |          |
| Chan et al. [120]                          | 2007 | x        |
| Chaudhry et al. [69]                       | 2010 |          |
| Chen et al. [121]                          | 2018 |          |
| Reference | Year |
|-----------|------|
| Chung [122] | 2021 |
| CIBIS [123] | 1994 |
| CIBIS-II [124] | 1999 |
| Cicoira et al. [125] | 2002 |
| Cleland et al. [126] | 2004 |
| Cline et al. [127] | 1998 |
| Cohn and Tognoni [128] | 2001 |
| Cokkinos et al. [129] | 2006 |
| Colucci et al. [130] | 1996 |
| Consensus et al. [241] | 2000 |
| Cowie et al. [131] | 2014 |
| Dalal et al. [132] | 2019 |
| Dar et al. [133] | 2009 |
| Dargie [134] | 2001 |
| Daubert et al. [135] | 2009 |
| Dendale et al. [136] | 2012 |
| Dewalt et al. [137] | 2012 |
| Di Biase et al. [138] | 2016 |
| DIG [139] | 1997 |
| Domenichini et al. [140] | 2016 |
| Domingo et al. [141] | 2011 |
| Domingues et al. [142] | 2011 |
| Dougherty et al. [143] | 2002 |
| Ducharme et al. [144] | 2005 |
| Dunagan et al. [145] | 2005 |
| Ekman et al. [146] | 1998 |
| Ellingsen et al. [147] | 2017 |
| Erhardt et al. [148] | 1995 |
| Fisher et al. [149] | 1994 |
| Fox et al. [150] | 2008 |
| Fragasso et al. [151] | 2006 |
| Gallagher et al. [152] | 2017 |
| Gasparini et al. [153] | 2006 |
| Gattis et al. [154] | 1999 |
| Giannini et al. [155] | 2016 |
| Giannuzzi et al. [156] | 2003 |
|                  | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 |
|------------------|---|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|
| Giordano et al. [157] | 2009 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | x |    |    | x |
| Goldberg et al. [158] | 2003 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Goldstein et al. [159] | 1999 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Granger et al. [160] | 2000 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Granger et al. [161] | 2003 |    |    |    |    |    |    |    |    |    | x |    |    |    |    |    |    |    |    |    |    |    |
| Hamaad et al. [162] | 2005 |    |    |    |    |    |    |    |    |    |    |    | x |    |    |    |    |    |    |    |    |    |
| Hambrecht et al. [163] | 1995 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Hambrecht et al. [164] | 2000 |    |    |    |    |    |    |    |    | x |    |    |    |    |    |    |    |    |    |    |    |    |
| Hamshere et al. [165] | 2015 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | x |    |    |    |    |
| Hanconk et al. [166] | 2012 |    |    |    |    |    | x |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Hansen et al. [167] | 2018 |    |    |    |    |    |    |    |    |    | x |    |    |    |    |    |    |    |    |    |    |    |
| Heldman et al. [168] | 2014 |    |    |    |    |    |    |    |    |    |    | x | x |    |    |    |    |    |    |    |    |    |
| Heldman et al. [168] | 2014 |    |    |    |    |    |    |    |    |    |    |    | x |    |    |    |    |    |    |    |    |    |
| Higgins et al. [169] | 2003 |    |    |    |    |    | x |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Hindricks et al. [170] | 2014 |    |    |    |    |    |    |    |    |    |    |    |    | x |    |    |    |    |    |    |    |    |
| Idris et al. [171] | 2015 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Jaarsma et al. [47] | 2008 |    |    |    |    |    |    |    |    |    |    |    |    |    | x |    |    |    |    |    |    |    |
| Jolly et al. [172] | 2009 |    |    |    |    |    |    |    |    |    |    | x |    |    |    |    | x |    |    |    |    |    |
| Jones and Wong [173] | 2013 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | x |    |    |    |    |
| Kashem et al. [174] | 2008 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Kasper et al. [175] | 2002 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | x |    |    |    |    |
| Koehler et al. [176] | 2011 |    |    |    |    |    |    |    |    |    |    |    |    | x |    |    | x |    |    |    |    |    |
| Komajda [177] | 2004 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Kraai et al. [178] | 2016 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Krum et al. [179] | 2013 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Krumholz et al. [180] | 2002 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Landolina et al. [181] | 2012 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | x |    |    |    |
| Laramee et al. [182] | 2003 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | x |    | x |    |    |
| Linde et al. [183] | 2002 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | x |    |    |
| Leclercq et al. [184] | 2007 |    |    |    |    |    |    |    |    |    |    |    | x |    |    |    |    |    |    |    |    |    |
| Linde et al. [185] | 2008 |    |    |    |    |    | x |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Liu et al. [186] | 2012 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | x |    |    |    |
| Luthje et al. [187] | 2015 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | x |    | x |    |    |
| Luttik et al. [188] | 2014 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    | x |    |    |    |    |
| Lyngå et al. [68] | 2012 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| MacDonald et al. [189] | 2011 |    |    |    |    |    |    |    |    |    |    |    | x |    |    |    |    |    | x |    |    |    |

Table 3 (continued)
| Study                                | Year |
|--------------------------------------|------|
| Maggioni et al. [190]                | 2002 |
| Margulies et al. [191]               | 2016 |
| Marrouche et al. [192]               | 2018 |
| Martinelli et al. [193]              | 2010 |
| Mathiasen et al. [194]               | 2015 |
| Menasché [195]                       | 2008 |
| Mcdonald et al. [196]                | 2002 |
| McMurray et al. [197]                | 2003 |
| MERIT-HF [198]                       | 1999 |
| Morgan et al. [199]                  | 2017 |
| Mortara et al. [200]                 | 2009 |
| Moss et al. [201]                    | 2002 |
| Moss et al. [202]                    | 2009 |
| Mozid et al. [203]                   | 2014 |
| Mueller et al. [204]                 | 2007 |
| Node et al. [205]                    | 2003 |
| Obadia et al. [206]                  | 2018 |
| Packer et al. [207]                  | 1993 |
| Packer et al. [208]                  | 1996 |
| Packer et al. [209]                  | 1996 |
| Packer et al. [210]                  | 2001 |
| Passino et al. [211]                 | 2006 |
| Patel et al. [212]                   | 2015 |
| Pütilä et al. [213]                  | 2014 |
| Perin et al. [214]                   | 2012 |
| Peters-klimm et al. [215]            | 2010 |
| Pfeffer et al. [216]                 | 1992 |
| Piepoli et al. [217]                 | 2008 |
| Pinter et al. [218]                  | 2009 |
| Pitt et al. [219]                    | 1999 |
| Pitt et al. [220]                    | 2003 |
| Pokushalov et al. [221]              | 2010 |
| Pokushalov et al. [222]              | 2011 |
| Prabhu et al. [223]                  | 2017 |
| Ramachandran et al. [224]            | 2007 |
| Rosano et al. [225]                  | 2003 |
Table 3 (continued)

| Reference                          | Year |
|-----------------------------------|------|
| Ruschitzka et al. [226]           | 2013 |
| Sarda et al. [227]                | 2016 |
| Scherr et al. [228]               | 2009 |
| Schou et al. [229]                | 2013 |
| Sisk et al. [230]                 | 2006 |
| Smith et al. [231]                | 2014 |
| Sola et al. [232]                 | 2006 |
| Yusuf et al. [233]                | 1991 |
| Yusuf et al. [234]                | 1992 |
| Spargias et al. [235]             | 1999 |
| Stone et al. [236]                | 2018 |
| Sturm et al. [237]                | 2000 |
| Swedberg et al. [238]             | 2010 |
| Takano et al. [239]               | 2013 |
| Tang et al. [240]                 | 2010 |
| Consensus et al. [241]            | 2000 |
| Thibault et al. [242]             | 2011 |
| Thibault et al. [243]             | 2013 |
| Tsuyuki et al. [244]              | 2004 |
| Tuunanen et al. [245]             | 2008 |
| Udelson et al. [246]              | 2010 |
| Uretsky et al. [247]              | 1993 |
| van Veldhuisen et al. [248]       | 2009 |
| van Veldhuisen et al. [249]       | 2011 |
| Villani et al. [250]              | 2007 |
| Villani et al. [251]              | 2014 |
| Vitale et al. [252]               | 2004 |
| Vizzardi et al. [253]             | 2010 |
| Vrtovec et al. [254]              | 2008 |
| Vuorinen et al. [255]             | 2014 |
| Weintraub et al. [256]            | 2010 |
| Wierczowiecki et al. [257]        | 2006 |
| Willenheimer et al. [258]         | 2001 |
| Wojnicz et al. [259]              | 2006 |
| Xie et al. [260]                  | 2010 |
| Yamada et al. [261]               | 2007 |
Table 3 (continued)

| Study                                      | Year | Outcome 1 | Outcome 2 | Outcome 3 | Outcome 4 | Outcome 5 |
|--------------------------------------------|------|-----------|-----------|-----------|-----------|-----------|
| Young et al. [262]                         | 2003 | x         |           |           |           |           |
| Zan [263]                                  | 2020 |           | x         |           |           |           |
| Zannad et al. [264]                        | 2011 | x         | x         | x         |           |           |
| Zannad et al. [265]                        | 2018 |           |           |           |           |           |
| Abraham et al. [87]                        | 2002 | x         |           | x         |           |           |
| Abraham et al. [88]                        | 2004 |           |           | x         |           |           |
| Adamson et al. [89]                        | 2003 |           |           |           |           |           |
| Adamson et al. [90]                        | 2011 |           |           |           |           |           |
| Al-khatib et al. [91]                      | 2010 |           |           |           |           |           |
| Angermann et al. [92]                      | 2012 |           | x         |           |           |           |
| Antonicelli et al. [93]                    | 2008 |           | x         |           |           |           |
| Asgar et al. [94]                          | 2017 |           |           |           |           |           |
| Assmus et al. [95]                         | 2006 |           |           |           |           |           |
| Assmus et al. [96]                         | 2013 |           |           |           |           |           |
| Atienza et al. [97]                        | 2004 | x         |           |           |           |           |
| Austin et al. [98]                         | 2005 |           |           |           |           |           |
| Australia/New Zealand Heart Failure Group  | 1997 |           |           |           |           | x         |
| Bartunek et al. [100]                      | 2013 |           |           |           |           |           |
| Belardinelli et al. [101]                  | 1999 |           |           |           |           | x         |
| Belardinelli et al. [102]                  | 2012 |           |           |           |           |           |
| Beller et al. [103]                        | 1995 |           |           |           |           | x         |
| Bentkover et al. [104]                     | 2007 |           |           |           |           | x         |
| Beta-Blocker evaluation of survival trial  | 2001 |           |           |           |           | x         |
| Biannic et al. [106]                       | 2012 |           |           |           |           |           |
| Bidecka-Dabrowa et al. [107]               | 2009 |           |           |           |           |           |
| Blue et al. [108]                          | 2001 | x         |           |           | x         | x         |
| Boccanelli et al. [109]                    | 2009 |           |           |           | x         | x         |
| Böhm et al. [110]                          | 2016 |           |           |           |           |           |
| Bolli et al. [111]                         | 2011 |           |           |           |           |           |
| Boriani et al. [112]                       | 2017 |           |           |           |           |           |
| Boyne et al. [113]                         | 2012 |           |           |           |           | x         |
| Bristow et al. [114]                       | 1996 |           |           |           |           | x         |
| Brown et al. [115]                         | 1995 |           |           |           |           | x         |
| Lok et al. [116]                           | 2007 | x         |           |           |           | x         |
| Reference               | Year | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 |
|------------------------|------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Capomolla et al. [117] | 2002 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Cazeau et al. [118]   | 2001 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| CDMR [119]            | 1988 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Chan et al. [120]     | 2007 |    |    |    | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Chaudhry et al. [69]  | 2010 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Chen et al. [121]     | 2018 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Chung [122]           | 2021 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| CIBIS [123]           | 1994 |    |    |    |    |    |    |    |    | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| CIBIS-II [124]        | 1999 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Cicoira et al. [125]  | 2002 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Cleland et al. [126]  | 2004 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Cline et al. [127]    | 1998 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Cohn and Tognoni [128]| 2001 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Cokkinos et al. [129] | 2006 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Colucci et al. [130]  | 1996 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Consensus et al. [241]| 2000 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Cowie et al. [131]    | 2014 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Dalal et al. [132]    | 2019 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Dar et al. [133]      | 2009 |    |    |    |    |    | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Dargie [134]          | 2001 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Daubert et al. [135]  | 2009 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Dendale et al. [136]  | 2012 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Dewalt et al. [137]   | 2012 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Di Biase et al. [138] | 2016 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| DIG [139]             | 1997 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Domenichini et al. [140]| 2016 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Domingo et al. [141]  | 2011 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Dominguez et al. [142]| 2011 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Doughty et al. [143]  | 2002 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Ducharme et al. [144] | 2005 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Dunagan et al. [145]  | 2005 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Ekman et al. [146]    | 1998 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Ellingsen et al. [147]| 2017 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Erhardt et al. [148]  | 1995 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Fisher et al. [149]   | 1994 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Fox et al. [150]      | 2008 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Author(s) et al. | Year | Reference |
|-----------------|------|-----------|
| Fragasso et al. [151] | 2006 | x | x |
| Gallagher et al. [152] | 2017 | | |
| Gasparini et al. [153] | 2006 | | |
| Gattis et al. [154] | 1999 | | |
| Giannini et al. [155] | 2016 | | |
| Giannuzzi et al. [156] | 2003 | x | |
| Giondano et al. [157] | 2009 | | x | x |
| Goldberg et al. [158] | 2003 | x | | x |
| Goldstein et al. [159] | 1999 | x | |
| Granger et al. [160] | 2000 | x | |
| Granger et al. [161] | 2003 | x | |
| Hamaad et al. [162] | 2005 | | |
| Hambrecht et al. [163] | 1995 | x | |
| Hambrecht et al. [164] | 2000 | | |
| Hamshere et al. [165] | 2015 | | |
| Hanconk et al. [166] | 2012 | | |
| Hansen et al. [167] | 2018 | | |
| Heldman et al. [168] | 2014 | | |
| Heldman et al. [168] | 2014 | | |
| Higgins et al. [169] | 2003 | x | | x |
| Hindricks et al. [170] | 2014 | | |
| Idris et al. [171] | 2015 | x | |
| Jaarsma et al. [47] | 2008 | x | |
| Jolly et al. [172] | 2009 | x | | x |
| Jones and Wong [173] | 2013 | x | x | x | x |
| Kashem et al. [174] | 2008 | x | | x | x |
| Kasper et al. [175] | 2002 | x | | x | x | x | x |
| Koehler et al. [176] | 2011 | | x | | x | x |
| Komajda et al. [177] | 2004 | | x | |
| Kraai et al. [178] | 2016 | | x | |
| Krum et al. [179] | 2013 | | x | |
| Krumholz et al. [180] | 2002 | | x | x | |
| Landolina et al. [181] | 2012 | | |
| Laramée et al. [182] | 2003 | x | | x | x | |
| Linde et al. [183] | 2002 | | |
| Leclercq et al. [184] | 2007 | | | | | |
| Study                        | Year | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 |
|-----------------------------|------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Linde et al. [185]          | 2008 |  x |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Liu et al. [186]            | 2012 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Luthje et al. [187]         | 2015 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Luttik et al. [188]         | 2014 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Lyngå et al. [68]           | 2012 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| MacDonald et al. [189]      | 2011 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Maggioni et al. [190]       | 2002 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Margulies et al. [191]      | 2016 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Marrouche et al. [192]      | 2018 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Martinelli et al. [193]     | 2010 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Mathiasen et al. [194]      | 2015 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Menasché [195]              | 2008 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Mcdonald et al. [196]       | 2002 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| McMurray et al. [197]       | 2003 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| MERIT-HF [198]              | 1999 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Morgan et al. [199]         | 2017 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Mortara et al. [200]        | 2009 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Moss et al. [201]           | 2002 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Moss et al. [202]           | 2009 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Mozid et al. [203]          | 2014 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Mueller et al. [204]        | 2007 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Node et al. [205]           | 2003 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Obadia et al. [206]         | 2018 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Packer et al. [207]         | 1993 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Packer et al. [208]         | 1996 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Packer et al. [209]         | 1996 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Packer et al. [210]         | 2001 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Passino et al. [211]        | 2006 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Patel et al. [212]          | 2015 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Pütilä et al. [213]         | 2014 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Perin et al. [214]          | 2012 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Peters-klimm et al. [215]   | 2010 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Pfeffer et al. [216]        | 1992 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Piepoli et al. [217]        | 2008 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Pinter et al. [218]         | 2009 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Pitt et al. [219]           | 1999 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Reference                          | Year | 23 | 24 | 25 | 26 | 27 | 28 | 29 | 30 | 31 | 32 | 33 | 34 | 35 | 36 | 37 | 38 | 39 | 40 | 41 | 42 | 43 | 44 |
|-----------------------------------|------|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Pitt et al. [220]                 | 2003 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Pokushalov et al. [221]          | 2010 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Pokushalov et al. [222]          | 2011 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Prabhu et al. [223]              | 2017 | x  | x  | x  | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Ramachandran et al. [224]        | 2007 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Rosano et al. [225]              | 2003 |    |    |    | x  | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Ruschitzka et al. [226]          | 2013 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Sarda et al. [227]               | 2016 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Scherr et al. [228]              | 2009 | x  | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Schou et al. [229]               | 2013 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Sisk et al. [230]                | 2006 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Smith et al. [231]               | 2014 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Sola et al. [232]                | 2006 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Yusuf et al. [233]               | 1991 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Yusuf et al. [234]               | 1992 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Spargias et al. [235]            | 1999 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Stone et al. [236]               | 2018 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Sturm et al. [237]               | 2000 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Swedberg et al. [238]            | 2010 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Takano et al. [239]              | 2013 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Tang et al. [240]                | 2010 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Consensus et al. [241]           | 2000 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Thibault et al. [242]            | 2011 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Thibault et al. [243]            | 2013 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Tsuyuki et al. [244]             | 2004 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Tuunanen et al. [245]            | 2008 | x  | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Udelson et al. [246]             | 2010 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Uretsky et al. [247]             | 1993 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| van Veldhuisen et al. [248]      | 2009 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| van Veldhuisen et al. [249]      | 2011 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Villani et al. [250]             | 2007 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Villani et al. [251]             | 2014 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Vitale et al. [252]              | 2004 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Vizzardi et al. [253]            | 2010 | x  |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Vrtovec et al. [254]             | 2008 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Vuorinen et al. [255]            | 2014 |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
Effect of interventions

Primary analysis: meta-analyses

Meta-analytic results of the 44 included meta-analyses are demonstrated in Table 6 and Fig. 2. According to our best-evidence synthesis, strong evidence suggests that CA, CR, and TM could prevent heart failure hospitalization. Furthermore, moderate evidence was found for the effectiveness of RAAS inhibitors, and CRT in reducing HF-related hospitalizations, while only limited evidence suggests the beneficial effects of beta-blockers, statins, mitral valve therapy, and multidisciplinary clinics or self-management promotion programs. There is conflicting evidence regarding the effect of cell therapy on HF hospitalization, and no evidence was found that anticoagulation should reduce HF-related hospitalizations.

Secondary analysis: extracted RCTs

In order to prevent bias as a result of duplicated data, all unique RCTs (N = 186) were extracted in a secondary analysis from the meta-analyses and compared to the results from our primary analysis.

Cardiac rehabilitation

A total of 14 studies examined the effects of cardiac rehabilitation. Of these individual studies, 1 reported a significant effect. When examined in a meta-analysis, a significant positive effect of cardiac rehabilitation was found (RR: 0.66, 95% CI: 0.44 | 0.97) (Fig. 3). This is in accordance with the general findings reported by the studied meta-analyses. Upon visual inspection, the funnel plots suggest no publication bias (Fig. 7).

Invasive therapy

There were 5 studies examining the effect of CA. Of these studies, 2 studies reported a significant effect. A positive effect of CA on HF-related hospitalization was found in our meta-analyses (RR: 0.57, 95% CI: 0.46 | 0.72) (Fig. 4). This is consistent with the general findings reported by the studied meta-analyses.

A total of 23 studies examined CRT to prevent HF-related hospitalization. Of these, 8 studies found a positive effect. Our meta-analysis suggested a positive effect of CRT (RR: 0.85, 95% CI: 0.78 | 0.92). This is in line with the general findings reported by the studied meta-analyses.

Of the 4 studies that examined mitral valve repair, 3 reported an effective reduction in HF-related hospitalization. Our meta-analyses suggested a positive effect (RR: 0.74,
## Table 4  Baseline characteristics of RCTs

| Included RCTs           | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control              | Follow-up period |
|-------------------------|------------------|-------------|-------|----------|--------|----------|-------------------------------|----------------------|-----------------|
| Beller et al. [103]     | 130              | 63          | 193   | 61       | 76     | 28       | Initial oral dose of 5 mg of lisinopril. The dose of diuretic therapy was adjusted based on the clinical condition of the patient, particularly to control edema. | Matching placebo     | 3 months        |
| Brown et al. [115]      | 116              | 125         | 241   | 62       | 82     | 25       | The 24-week double-blind treatment period beginning with 10 mg of fosinopril. In the ensuing 3 weeks, patients were titrated to 20 mg of study medication (level TI), as tolerated. | Matching placebo     | N/R             |
| CDMR [119]              | 200              | 100         | 300   | 57       | 83     | 25       | Captopril (25 to 50 mg, three times a day)                                      | Placebo              | 6 months        |
| Consensus et al. [241]  | 127              | 126         | 263   | 71       | 56     | <40      | Enalapril (2.5 to 40 mg/day)                                                   | Placebo              | 12 months       |
| Erhardt et al. [148]    | 155              | 153         | 308   | 64       | 76     | 27       | Fosinopril 10 mg                                                              | Matching placebo     | 12 weeks        |
| Pfieffer et al. [216]   | 1115             | 1116        | 2231  | 60       | 83     | 31       | Captopril                                                                    | Placebo              | 36 months       |
| Yusuf et al. [233]      | 1285             | 1284        | 2569  | 61       | 81     | 25       | Enalapril                                                                     | Placebo              | 41 months       |
| Yusuf et al. [234]      | 2111             | 2117        | 4228  | 59       | 89     | 28       | Enalapril                                                                     | Placebo              | 42 months       |
| Cleland et al. [126]    | 89               | 190         | 279   | 63       | 74     | <35      | Warfarin with INR of 2.5                                                      | Placebo or no antithrombotic therapy | 27 months       |
| Cokkinos et al. [129]   | 92               | 105         | 197   | 59       | 85     | 28       | Warfarin was supplied as 5-mg tablets. The daily dose was 2.5–10 mg, with a target INR of 2–3 | Placebo              | 19.5 months     |
| Zannad et al. [265]     | 2507             | 2515        | 5022  | 66       | 77     | 34       | Rivaroxaban 2.5 mg twice daily                                                | Placebo              | 21 months       |
| Cohn and Toghoni [128]  | 2511             | 2499        | 5010  | 63       | 80     | 27       | Valsartan was initiated at a dose of 40 mg twice daily, and the dose was doubled every 2 weeks until a target dose of 160 mg twice daily was reached | Placebo              | 23 months       |
| Granger et al. [160]    | 179              | 91          | 270   | 66       | 25     | 26       | Candesartan, 4 mg, 8 mg and 16 mg                                             | Matching placebo     | 12 months       |
| Granger et al. [161]    | 1013             | 1015        | 2028  | 66       | 68     | 30       | Candesartan, 4 mg, 8 mg, 16 mg, 32 mg                                         | Matching placebo     | 34 months       |
| Maggioni et al. [190]   | 185              | 181         | 366   | 63       | 71     | 28       | Valsartan                                                                     | Placebo              | 12 months       |
| McMurray et al. [197]   | N/R              | N/R         | 7599  | 67       | 40     | 54       | Candesartan                                                                   | Matching placebo     | N/R             |
| Spargias et al. [235]   | 1734             | 243         | 1977  | 67       | 74     | 40       | Ramipril                                                                      | Placebo              | N/R             |
Table 4 (continued)

| Included RCTs                                      | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention          | Control                   | Follow-up period |
|---------------------------------------------------|------------------|-------------|-------|----------|--------|-----------|-----------------------|--------------------------|------------------|
| Sturm [237]                                        | 51               | 49          | 100   | 52       | 90     | 17        | Atenolol              | Placebo                 | 24 months        |
| Australia/New Zealand Heart Failure Research Collaborative Group [99] | 208              | 207         | 415   | 67       | 80     | 29        | Carvedilol            | Matching placebo        | 19 months        |
| Beta-Blocker evaluation of survival trial [105]    | 1354             | 1354        | 2708  | 60       | 79     | 23        | Initial oral dose of 3 mg of bucindolol, which was repeated twice daily for 1 week | Placebo                 | 24 months        |
| Bristow et al. [114]                               | 261              | 84          | 345   | 60       | 78     | 23        | Low-dose Carvedilol (6.25 mg BID), medium-dose Carvedilol (12.5 mg BID), and high-dose Carvedilol (25 mg BID) | Placebo                 | 6 months         |
| CIBIS [123]                                        | 320              | 321         | 641   | N/R      | N/R    | 25        | 2.5 mg Bisoprolol     | 2.5 mg placebo          | 1.9 years        |
| CIBIS-II [124]                                     | N/R              | N/R         | N/R   | N/R      | N/R    | 28        | Bisoprolol 1.25 mg    | Placebo                 | 1.3 years        |
| Colucci et al. [130]                               | 232              | 134         | 366   | 55       | 86     | 23        | Carvedilol            | Placebo                 | 213 days         |
| Dargie [134]                                       | 975              | 984         | 1959  | 63       | 74     | 33        | Carvedilol            | Identical looking placebo | 1.3 years        |
| Fisher et al. [149]                                | 25               | 25          | 50    | 63       | 100    | 22        | Metoprolol, from 6.25 to 12.5 mg twice a day to 12.5 mg three times a day to 25 mg twice a day | Placebo                 | 6 months         |
| Goldstein et al. [159]                             | 40               | 20          | 60    | N/R      | N/R    | 27        | The initial dose of approximately 12.5 mg Metoprolol (one half of a 25 mg tablet) was administered once daily. The dose of metoprolol was increased to 25 mg and subsequently increased in steps of 50 mg to 100 mg and finally to 150 mg once daily | Matching placebo         | 26 weeks         |
| Komajda [177]                                      | N/R              | N/R         | 572   | N/R      | N/R    | <40       | Enalapril              | Matching placebo         | N/R              |
| Merit-HF [198]                                     | 1990             | 2001        | 3991  | 64       | 78     | 28        | Metoprolol            | Placebo                 | 1 year           |
| Packer et al. [208]                                | 133              | 145         | 278   | 61       | 73     | 22        | Carvedilol, 25–50 mg BID | Placebo                 | 6 months         |
| Packer et al. [209]                                | 696              | 398         | 1094  | 58       | 77     | 23        | Carvedilol            | Placebo                 | 6.5 months       |
| Packer et al. [210]                                | 1156             | 1133        | 2289  | 63       | 80     | 20        | Carvedilol            | Placebo                 | 10.4 months      |
| van Veldhuisen et al. [248]                        | 678              | 681         | 1359  | 76       | 70     | 29        | Nebivolol             | Placebo                 | 21 months        |
| Di Biase [138]                                     | 102              | 101         | 203   | 74       | 60     | 29        | PVI + LAPWI + SVC1 + CFAE | AMIO therapy            | 24 months        |
| Jones and Wong [173]                               | 26               | 26          | 52    | 63       | 87     | 22        | PVI + linear then CFAEs | Rate control            | 12 months        |
| MacDonald et al. [189]                             | 22               | 19          | 41    | 63       | 78     | 20        | PVI ± linear lesions + CFAEs | Rate control            | 6 months         |
| Included RCTs                  | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                              | Control                               | Follow-up period |
|-------------------------------|------------------|-------------|-------|----------|--------|-----------|-------------------------------------------|---------------------------------------|-----------------|
| Marrouche et al. [192]        | 179              | 184         | 363   | 85       | 61     | 32        | PVI+/- additional lesions at discretion of operator | Rate and/or rhythm control           | 38 months       |
| Prabhu et al. [223]           | 33               | 33          | 66    | 91       | 61     | 35        | PVI+ LAPWI                                | Rate control                          | 6 months        |
| DIG [139]                     | 3397             | 3403        | 6800  | 64       | 78     | 29        | Digoxin                                   | Placebo                              | 37 months       |
| Packer et al. [207]           | 85               | 93          | 178   | 61       | 76     | 28        | Digoxin                                   | Placebo                              | 3 months        |
| Uretsky et al. [247]          | 42               | 46          | 88    | 64       | 90     | 29        | Digoxin                                   | Withdrawal of digoxin                 | 3 months        |
| Assmus et al. [95]            | 24               | 23          | 47    | 61       | 100    | 39-41     | Intracoronary infusion of BMC or CPC      | No cell infusion                      | 3 months        |
| Assmus et al. [96]            | 64               | 39          | 103   | 65       | 90     | 32-37     | Intracoronary infusion of BMCS            | Cell-free medium (placebo)            | 45.7 months     |
| Bartunek et al. [100]         | 32               | 15          | 47    | 59       | 91     | 28        | Patients in the cell therapy arm received bone marrow–derived cardiopoietic stem cells meeting quality release criteria | Standard of care comprising a beta-blocker, an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, and a diuretic with dosing and schedule tailored for maximal benefit and tolerability in accordance with practice guidelines for heart failure management | 2 years         |
| Bolli et al. [111]            | 16               | 7           | 23    | 57       | 100    | 30        | Autologous CSCs were isolated from the right atrial appendage and re-infused intracoronarily 4±1 months after surgery; | No treatment                          | 12 months       |
| Hamshere et al. [165]         | 15               | 15          | 30    | 56       | 86     | 42        | G-CSF + BMSC                               | Peripheral placebo (saline)           | 12 months       |
| Heldman et al. [168]          | 22               | 11          | 33    | 60       | 95     | 38-40     | Mesenchymal stem cell group or bone marrow mononuclear cell group | Placebo                               | 12 months       |
| Heldman et al. [168]          | 38               | 21          | 59    | 61       | 100    | 36        | Mesenchymal stem cell group or bone marrow mononuclear cell group | Placebo                               | 12 months       |
| Mathiasen et al. [194]        | 40               | 20          | 60    | 66       | 90     | 28        | BMSC                                      | Placebo                               | 6 months        |
| Menasché [195]                | 63               | 34          | 97    | 61       | 100    | 29        | Cell suspension                           | Placebo solution consisting of the suspension medium without skeletal myoblasts | 72 months       |
| Mozid et al. [203]            | 14               | 2           | 16    | 70       | 94     | 31        | G-CSF + BMSC                              | Placebo                               | 6 months        |
| Patel et al. [212]            | 24               | 6           | 30    | 59       | 100    | 26        | BMAC infusion                             | Standard heart failure care           | 12 months       |
| Included RCTs       | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                                                                                     | Follow-up period |
|--------------------|------------------|-------------|-------|----------|--------|----------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|-----------------|
| Pätilä et al. [213]| 20               | 19          | 39    | 65       | 95     | 37       | Injections of BMMC or vehicle intra-operatively into the myocardial infarction border area | Controls received only vehicle medium by syringes                                              | 12 months       |
| Perin et al. [214] | 20               | 10          | 30    | 61       | 80     | 39       | Transendocardial delivery of ABMMNCs                                           | Placebo                                                      | 6 months         |
| Austin et al. [98] | 100              | 100         | 200   | 60       | 66     | 85% < 35 | An 8-week cardiac rehabilitation program that was coordinated by the clinical nurse specialist. Patients attended classes twice weekly for a period of 2.5 h | Eight weekly monitoring of clinical status (functional performance, fluid status, cardiac rhythm, laboratory assessment) in the cardiology outpatients by the clinical nurse specialist | 8 weeks          |
| Belardinelli et al. [101] | 50           | 49          | 99    | 59       | 88     | 28       | The exercise group underwent exercise training for 14 months                   | The control group did not exercise                                                             | 14 months        |
| Belardinelli et al. [102] | 63           | 60          | 123   | 59       | 78     | 37       | The trained group underwent an ET program for 10 years. The training program consisted of 3 sessions per week at the hospital for 2 months, then 2 supervised sessions the rest of the year. Every 6 months, patients exercised at the hospital, and then they returned to a coronary club, where they exercised the rest of the year | The nontrained group was not provided with a formal ET program                                  | 120 months       |
| Chen et al. [121]  | 19               | 18          | 27    | 61       | 36     | 36       | Outpatient cardiac rehabilitation for 1 week, before starting home-based cardiac rehabilitation. Home-based cardiac rehabilitation was conducted by requesting the interventional group to carry out aerobic exercise at least 3 times per week, for a duration of at least 30 min each time | Instructed to maintain both their standard medical care and previous activity levels          | 3 months         |
| Cowie et al. [131] | 30               | 16          | 46    | 64       | 91     |          | The hospital group attended a physiotherapist-led class                         | A DVD and booklet (replicating the class) was created for home use. Controls followed their usual HFNS care | 5 years          |
| Included RCTs | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention | Control | Follow-up period |
|---------------|-----------------|-------------|-------|----------|--------|-----------|--------------|---------|-----------------|
| Dalal et al. [132] | 107 | 109 | 216 | 70 | 78 | 35 | REACH-HF manual for patients with a choice of two structured exercise programs | No cardiac rehabilitation approach that included medical management according to national and local guidelines, including specialist heart failure nurse care | 12 weeks |
| Ellingsen et al. [147] | 78 | 81 | 261 | 60 | 81 | 29 | HIIT and MCT had 3 supervised sessions per week on a treadmill or bicycle. HIIT included four 4-min intervals aiming at 90 to 95% of maximal heart rate separated by 3-min active recovery periods of moderate intensity. MCT sessions aimed at 60 to 70% of maximal heart rate | Patients were advised to exercise at home according to current recommendations and attended a session of moderate-intensity training at 50 to 70% of maximal heart rate every 3 weeks | 3 months |
| Giannuzzi et al. [156] | 45 | 45 | 90 | 60 | N/R | 25 | The exercise protocol consisted of supervised continuous sessions of 30-min bicycle ergometry > 3 times a week (3 to 5 times) at 60% of the peak V̇O₂ achieved at the initial symptom-limited exercise testing. In addition to supervised sessions, patients were asked to take a brisk daily walk for > 30 min and intermittent unsupervised sessions of calisthenics (30 min) as part of the home-based exercise program | Educational support, but no formal exercise protocol | 6 months |
| Hambrecht et al. [163] | 12 | 10 | 22 | 52 | 27 | 26 | Patients assigned to the training program remained in an intermediate care ward for the initial 3 weeks. Training sessions were conducted individually under strict supervision for the first 3 weeks. Patients exercised six times daily for 10 min on a bicycle ergometer | Patients assigned to the control group spent 3 days in an intermediate care ward for baseline evaluation. After discharge, medical therapy was continued, and patients were supervised by their private physicians | 6 months |
| Included RCTs               | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                                                      | Follow-up period |
|----------------------------|------------------|-------------|-------|----------|--------|-----------|--------------------------------------------------------------------------------|--------------------------------------------------------------|-----------------|
| Hambrecht et al. [164]     | 36               | 37          | 73    | 54       | 100    | 27        | 2 weeks of in-hospital ergometer exercise for 10 min 4 to 6 times per day, followed by 6 months of home-based ergometer exercise training for 20 min per day at 70% of peak oxygen uptake | No intervention                                             | 6 months        |
| Jolly et al. [172]         | 84               | 85          | 169   | 66       | 75     | <40       | Three supervised exercise sessions to plan an individualized exercise program. These were followed by a home-based program, with home visits at 4, 10, and 20 weeks, telephone support at 6, 15, and 24 weeks, and a manual with details about safe progressive exercise and self-monitoring of frequency, duration, and intensity | Specialist heart failure nurse input in primary and secondary care through clinic and home visits that included the provision of information about heart failure, advice about self-management and monitoring of their condition, and titration of beta-blocker therapy | 3 months        |
| Mueller et al. [204]       | 25               | 25          | 50    | 55       | 100    | <40       | Five indoor cycling sessions were performed weekly for a duration of 30 min, and all subjects walked outdoors for 45 min twice daily. Training duration was one month | Control subjects received usual clinical care, including verbal encouragement to remain physically active | 1 month         |
| Passino et al. [211]       | 44               | 41          | 85    | N/R      | N/R    | 35        | The training group underwent a nine-month training program. The training program consisted of cycling on a bike for a minimum of 3 days per week, 30 min per day | Control patients continued their usual lifestyle             | 9 months        |
| Willenheimer et al. [258]  | 27               | 27          | 54    | N/R      | N/R    | 35        | Patients carried out cycle ergometer interval training at a heart rate corresponding to 80% of peak VO2 ± 5 beats/min, for as long as possible during each interval | Control patients were asked not to change their degree of physical activity during the active study period | 6 months        |
| Abraham et al. [87]        | 228              | 225         | 453   | 64       | 68     | 22        | Atrial-synchronized biventricular pacing | No pacing for six months, during which time medications for heart failure were to be kept constant | 6 months        |
Table 4 (continued)

| Included RCTs                  | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                                                                 | Follow-up period |
|-------------------------------|------------------|-------------|-------|----------|--------|-----------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------|
| Abraham et al. [88]           | 101              | 85          | 186   | 64       | 89     | 25        | Optimal medical treatment with active CRT and active ICD therapy               | Optimal medical treatment and active ICD therapy                        | 6 months         |
| Bentkover et al. [104]        | 36               | 36          | 72    | 79       | 79     | < 35      | Biventricular pacing and ICD                                                | ICD alone                                                   | 6 months         |
| Cazeau et al. [118]           | 29               | 29          | 58    | 63       | 75     | 23        | Atriobiventricular (active) pacing                                          | Ventricular inhibited (inactive) pacing                                 | 3 months         |
| Chung [122]                   | 9                | 9           | 18    | 76       | 76     | 30        | A CRT–defibrillator device with LV coronary venous lead system              | A dual-chamber ICD                                                      | 12 months        |
| Daubert et al. [135]          | 82               | 180         | 262   | 81       | 81     | 28        | Patients who had undergone successful implantation were randomly assigned in a 2-to-1 scheme to a CRT ON group for 24 months | CRT OFF                                                            | 24 months        |
| Gasparini et al. [153]        | 33               | 36          | 69    | 67       | 94     | 26        | BiV CRT                                                                      | LV                                                                     | 12 months        |
| Higgins et al. [169]          | 245              | 245         | 490   | 66       | 84     | 22        | CRT-D                                                                        | ICD                                                                    | 6 months         |
| Linde et al. [183]            | 25               | 18          | 43    | 66       | 84     | 30        | Biventricular VVIR pacing during two 3-month periods                        | Right-univentricular VVIR pacing during two 3-month periods             | 3 months         |
| Leclercq et al. [184]         | 25               | 19          | 44    | 74       | 100    | 27        | Biventricular VVIR pacing during two 3-month periods                        | Right-univentricular VVIR pacing during two 3-month periods             | 3 months         |
| Linde et al. [185]            | 419              | 191         | 610   | 79       | 79     | 27        | Active CRT                                                                   | Control                                                               | 12 months        |
| Martinelli et al. [193]       | 27               | 27          | 54    | 59       | 68     | 30        | Device was initially programmed to BiVP, crossed to RVP and crossed back to BiVP | Device was initially programmed to RVP, crossed to BiVP and crossed back to RVP | 18 months        |
| Moss et al. [201]             | 742              | 490         | 1232  | 65       | 85     | 23        | ICD                                                                           | Conventional medical therapy                                             | 20 months        |
| Moss et al. [202]             | 1089             | 731         | 1820  | 75       | 75     | 24        | Cardiac-resynchronization therapy with biventricular pacing                 | ICD alone                                                             | 2.4 years        |
| Piepoli et al. [217]          | 44               | 45          | 89    | 72       | 72     | 24        | CRT-P/CRT-D                                                                  | Medical                                                                | 12 months        |
| Pinter et al. [218]           | 36               | 36          | 72    | 79       | 79     | 23        | CRT-D                                                                        | ICD                                                                    | 6 months         |
| Pokushalov et al. [221]       | 91               | 87          | 178   | 90       | 90     | 29        | CRT-P + CABG                                                                 | CABG                                                                  | 18 months        |
| Pokushalov et al. [222]       | 13               | 13          | 26    | 96       | 96     | 27        | BMMMC+ active CRT                                                           | BMMMC+ inactive CRT                                                   | 6 months         |
| Ruschitzka et al. [226]       | 404              | 405         | 809   | 72       | 72     | 27        | CRT capability turned on                                                   | CRT capability turned off                                           | 19.4 months      |
| Tang et al. [240]             | 894              | 904         | 1798  | 83       | 83     | 23        | ICD + CRT                                                                    | ICD alone                                                             | 40 months        |
| Thibault et al. [242]         | 60               | 61          | 121   | 75       | 75     | 24        | biventricular CRT                                                           | LV CRT                                                                | 6 months         |
| Thibault et al. [243]         | 44               | 41          | 85    | 71       | 71     | 25        | CRT-D                                                                        | ICD                                                                    | 12 months        |
Table 4 (continued)

| Included RCTs                        | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                                      | Follow-up period |
|--------------------------------------|------------------|-------------|-------|----------|--------|-----------|--------------------------------------------------------------------------------|----------------------------------------------|------------------|
| Young et al. [262]                   | 182              | 187         | 369   | 68       | 78     | 24        | Combined CRT and ICD capabilities                                              | ICD activated, CRT off                      | 6 months         |
| Fragasso et al. [151]                | 34               | 31          | 65    | 65       | 96     | 35        | Trimeperazine, 20 mg three times daily                                         | Placebo                                      | 13 months        |
| Rosano et al. [225]                  | 16               | 16          | 32    | 66       | 75     | 33        | 20 mg t.d.s. trimetazidine                                                    | Placebo t.d.s                                | 6 months         |
| Tuunanen et al. [245]                | 12               | 7           | 19    | 58       | 79     | 34        | Trimetazidine                                                                | Placebo                                      | 3 months         |
| Vitale et al. [252]                  | 23               | 24          | 47    | 78       | 85     | 29        | Placebo                                                                         | Placebo                                      | 6 months         |
| Margulies et al. [191]               | 154              | 146         | 300   | 62       | 69     | 25        | Liraglutide                                                                    | Placebo                                      | 6 months         |
| Fox et al. [150]                     | 5479             | 5438        | 10,917| 60       | 83     | 32        | Ivabradine 7.5 MG BID                                                          | Placebo                                      | 19 months        |
| Swedberg et al. [238]                | 3241             | 3264        | 6505  | 65       | 76     | 29        | Ivabradine 7.5 MG BID                                                          | Placebo                                      | 22.9 months      |
| Asgar et al. [94]                    | 50               | 42          | 92    | 75       | 77     | 38        | Treated with the MitraClip                                                    | This retrospective comparator group consisted of medically managed patients | 22–33 months     |
| Giannini et al. [155]                | 60               | 60          | 120   | 76       | 70     | 34        | MitraClip                                                                      | Optimal medical therapy                      | 17 months        |
| Obadia et al. [206]                  | 152              | 152         | 304   | 71       | 79     | 33        | Percutaneous mitral-valve repair                                               | Medical therapy alone                        | 12 months        |
| Stone et al. [236]                   | 302              | 312         | 614   | 73       | 67     | 31        | Transcatheter mitral-valve repair plus medical therapy                         | Medical therapy alone                        | 16.5 months      |
| Boccanelli et al. [109]              | 188              | 193         | 381   | 63       | 84     | 40        | Canrenone                                                                      | Placebo                                      | 12 months        |
| Chan et al. [120]                    | 23               | 25          | 48    | 63       | 83     | 27        | Candesartan 8 mg and spironolactone 25 mg once daily                          | Candesartan 8 mg and a matching identical placebo once daily | 12 months        |
| Cicoira et al. [125]                 | 54               | 52          | 106   | 67       | 86     | 33        | Spironolactone treatment, at an initial dose of 25 mg once daily              | Placebo                                      | 12 months        |
| Pitt et al. [219]                    | 822              | 841         | 1663  | 65       | 73     | 25        | Spironolactone, 25 mg                                                         | Matching placebo                             | 24 months        |
| Pitt et al. [220]                    | 3319             | 3313        | 6632  | 64       | 71     | 33        | Eplerenone                                                                    | Placebo                                      | 16 months        |
| Udelson et al. [246]                 | 116              | 109         | 225   | 63       | 84     | 27        | Eplerenone, 50 mg/d                                                           | Placebo                                      | 9 months         |
| Vizzardi et al. [253]                | 65               | 65          | 130   | 65       | N/R    | 36        | 25 mg of spironolactone once daily                                            | Matching placebo                             | 44 months        |
| Zannad et al. [264]                  | 1364             | 1373        | 2737  | 69       | 78     | 26        | Eplerenone 50 mg/d                                                           | Placebo                                      | 21 months        |
| Atienza et al. [97]                  | 164              | 174         | 338   | 68       | 60     | 36        | 1 individual session prior to discharge by nurse, 1 visit to physician, 3-monthly follow-up visits and tele-monitoring | Usual care (discharge planning according to protocol) | 509 days         |
### Table 4 (continued)

| Included RCTs       | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                                                                                     | Follow-up period |
|---------------------|------------------|-------------|-------|----------|--------|-----------|--------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|------------------|
| Blue et al. [108]   | 84               | 81          | 165   | 75       | 48     | Severe 40%| Planned home visits of decreasing frequency, supplemented by telephone contact as needed. The aim was to educate the patient about heart failure and its treatment, optimize treatment (drugs, diet, exercise), monitor electrolyte concentrations, teach self-monitoring and management, liaise with other health care and social workers as required, and provide psychological support. | Patients in the usual care group were managed as usual by the admitting physician and, subsequently, general practitioner. They were not seen by the specialist nurses after hospital discharge. | 12 months       |
| Lok et al. [116]    | 118              | 122         | 240   | 71       | 79     | 31        | An intensive follow-up of the patients during 1 year at a HF outpatient clinic led by a HF physician and a cardiovascular nurse. Verbal and written comprehensive education was imparted about the disease and the aetiology, medication, compliance and possible adverse events. Patients were advised about individualized diet with salt and fluid restriction, weight control, early recognition of worsening HF, when to call a healthcare provider, and about physical exercise and rest. An appointment with a dietician was made. The nurse asked the patient about his or her social and medical circumstances and performed a short physical examination. The physician assessed the clinical condition of the patient, the laboratory results and ECG, performed a physical examination, and, together with the nurse, proposed a treatment regimen. | Their routine care was no doubt largely according to the guideline of the European Society of Cardiology prevailing at that time (version 2001), with optimal application of medical therapy including the target dose or high dose of HF medication. | 12 months       |
### Table 4 (continued)

| Included RCTs                  | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                              | Follow-up period |
|-------------------------------|------------------|-------------|-------|----------|--------|-----------|--------------------------------------------------------------------------------|---------------------------------------|------------------|
| Capomolla et al. [117]         | 112              | 122         | 234   | 56       | 84     | 31        | The objectives of the multidisciplinary staff are prevention and functional recovery of consequences of acute hemodynamic instability | Patients were referred to their primary care physician and cardiologist. During follow-up the process of care was driven by the patient’s needs into a heterogeneous range of emergency room management, hospital admission, and outpatient access | 12 months         |
| Cline et al. [127]             | 80               | 110         | 190   | 76       | 55     | 36        | The education program consisted of two 30-min information visits by a nurse during primary hospitalization and a 1-h information visit for patients and family 2 weeks after discharge | Routine clinical practice             | 1 year           |
| Dendale et al. [136]           | 80               | 80          | 160   | 76       | 65     | 33        | Patients were seen in the outpatient heart failure clinic with additional planned visits at 3 and 6 months. Daily patient telemonitoring was conducted with specified alert limits set for each patient. Alterations in patient status were forwarded to the general practitioner and heart failure clinic for subsequent patient follow-up and management | Usual care                           | 6 months         |
| Included RCTs        | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                                                                                                           | Follow-up period |
|---------------------|------------------|-------------|-------|----------|--------|----------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------|-----------------|
| Dewalt et al. [137] | 303              | 302         | 605   | 61       | 52     | <40      | The intervention began with a 1-h educational session with a clinical pharmacist or health educator during a regular clinic visit. Patients were given an educational booklet designed for low literacy patients and a digital scale. As part of the educational session, patients were taught to identify signs of heart failure exacerbation, perform daily weight assessment, and adjust their diuretic dose. The program coordinator then made scheduled follow-up phone calls and monthly during months. | Patients enrolled in the control group received a general heart failure education pamphlet written at approximately the 7th grade level and continued with usual care from their primary physician | 12 months       |
| Doughty et al. [143]| 100              | 97          | 197   | 74       | 56     | 34       | One-on-one education with the study nurse was initiated at the first clinic visit. A patient diary, for daily weights, medication record, clinical notes and appointments, and educational booklet were provided. Group education sessions (each lasting 1.5–2 h) were offered, two within 6 weeks of hospital discharge and a further after 6 months. Continued under the care of their GP with additional follow-up measures as usually recommended by the medical team responsible for their in-patient care |                                                                                                                                                                           | 12 months       |
| Ducharme et al. [144]| 115             | 115         | 230   | 70       | 73     | 35       | Patients in the intervention group were referred to a multidisciplinary specialized heart failure outpatient clinic where they were evaluated by the study team within 2 weeks of hospital discharge. Received treatment and appropriate follow-up according to the standards of the attending physicians but without further direct contact with the research team or the planned intervention |                                                                                                                   | 6 months        |
Table 4 (continued)

| Included RCTs          | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                         | Follow-up period |
|------------------------|------------------|-------------|-------|----------|--------|-----------|--------------------------------------------------------------------------------|----------------------------------|-----------------|
| Ekman et al. [146]     | 79               | 79          | 158   | N/R      | N/R    | 43        | The structured-care program was based on a nurse monitored, outpatient clinic, run in cooperation with the study doctors, who were responsible for optimal pharmacological treatment | Usual care                      | 5 months        |
| Gallagher et al. [152] | 20               | 20          | 40    | 64       | 75     | 25        | A licensed clinical social worker reviewed adherence data daily during the first 7 days after discharge and weekly thereafter and contacted participants who were nonadherent for two or more days per week. During these phone calls, the social worker inquired about consequences of nonadherence, and assessed and responded to reasons for missed doses | For participants assigned to passive monitoring, adherence data were recorded but not monitored by the study team | 1 months        |
| Hancock et al. [166]   | 16               | 12          | 28    | 85       | 44     | 43        | An assessment visit by a consultant cardiologist who initiated a plan of treatment, followed by visits at one to two weekly intervals within the home by heart failure specialist nurses. The HFSNs enacted the plan, including blood tests, assessment of symptoms and signs, educational advice, and medication titration | Routine care                     | 6 months        |
| Jaarsma et al. [47]    | 340              | 339         | 679   | 72       | 66     | 34        | (A) 2 individual session by cardiologist, 9 visits to nurse, possibility to contact nurse (B) 2 individual sessions by cardiologist, 18 visits to nurse, 2 home visits, 2 multidisciplinary sessions, follow-up telephone contact by nurse | Usual care (standard management by cardiologist) | 18 months       |
Table 4 (continued)

| Included RCTs       | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                                                                 | Follow-up period |
|---------------------|------------------|-------------|-------|----------|--------|-----------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------|
| Kasper et al. [175] | 102              | 98          | 200   | 62       | 61     | 27        | Patients received nurse-led care coordination linked to a multidisciplinary team composed of a heart failure nurse, cardiologist, and patient’s primary care physician. Patients were contacted via telephone at preplanned intervals after discharge, in addition to scheduled visits within the community | Patients received unrestricted follow-up care from their primary physicians, who received a baseline heart failure management plan, as documented in the patient’s chart | 6 months         |
| Krumholz et al. [180] | 44               | 44          | 88    | 74       | 57     | 38        | The study intervention was based on five sequential care domains for chronic illness, including patient knowledge of the illness, the relation between medications and illness, the relation between health behaviors and illness, knowledge of early signs and symptoms of decompensation and where and when to obtain assistance | Patients assigned to the control group received all usual care treatments and services ordered by their physicians | 12 months        |
| Liu et al. [186]    | 53               | 53          | 200   | 63       | 66     | 29        | The patient was cared for by an HF team consisting of 3 cardiologists specialized in HF care, one psychologist, one dietary assistant, and two case managers | The primary care physician was responsible for patient evaluation, treatment and clinic visits. Neither scheduled follow-up nor specialized HF nurses were available | 6 months         |
| Luttik et al. [188] | 92               | 97          | 200   | 73       | 63     | 32        | Follow-up by the HF clinic | Follow-up by their GP | 12 months |
| Lyngå et al. [68]   | 166              | 153         | 344   | 73       | 75     | 57% < 30 | Patients randomized to the IG were given an electronic scale to install in their homes | The patients in the CG were informed to contact the HF clinic on a special telephone in the case of a weight gain of .2 kg in 3 days | 12 months        |
| Included RCTs                  | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                                                                 | Follow-up period |
|-------------------------------|------------------|-------------|-------|----------|--------|-----------|------------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------|
| Mcdonald et al. [196]         | 51               | 47          | 98    | 71       | 66     | 37        | Patients systematically received specialist nurse-led education and specialist dietitian consults on three or more occasions during the index admission. The education program focused on daily weight monitoring, disease and medication understanding, and salt restriction | Patients underwent investigations for HF, including echocardiography and right and left heart catheterization where indicated. Optimal medical therapy was administered | 3 months         |
| Schou et al. [229]            | 460              | 460         | 200   | 69       | 63     | 32        | Patients allocated to an extended follow-up completed the following program: visits at 1–3-month intervals at the discretion of the investigators | Usual care by a GP                                                   | 9 months         |
| Smith et al. [231]            | 92               | 106         | 198   | 63       | 66     | 30        | The intervention began with four weekly group visit appointments followed by a 5th “booster” appointment held 6 months after randomization | HF care from their existing treatment team both during and after hospitalization | 12 months        |
| Tsuyuki et al. [244]          | 140              | 136         | 276   | 74       | 55     | 31        | The essential components of the patient support program were simplified into 5 basic areas: salt and fluid restriction, daily weighing, exercise alternating with rest periods, proper medication use, and knowing when to call their physician (early recognition of worsening symptoms) | Usual care                                                   | 6 months         |
| Wierzchowiecki et al. [257]   | 64               | 65          | 129   | 81       | N/R    | 36        | Multidisciplinary care                                                                                                     | Routine care                                          | 6 months         |
| Bielecka-Dabrowa et al. [107] | 41               | 27          | 68    | 57       | 85     | 29        | Atorvastatin 40 mg daily for 2 months (8 weeks) and next 10 mg for 4 months                                             | DCM was treated according to present standards without statin therapy | 6 months         |
| Hamaad et al. [162]           | 12               | 9           | 23    | 67       | 86     | 32        | Atorvastatin, 40 mg once daily                                                                                             | Placebo                                                | 32.8 months      |
| Node et al. [205]             | 23               | 25          | 48    | 48       | 69     | 34        | Simvastatin                                                                                                                | Placebo                                                | 3.5 months       |
| Sola et al. [232]             | 54               | 54          | 108   | 33       | 63     | 33        | Atorvastatin                                                                                                               | No statin treatment                                       | 12 months        |
| Takano et al. [239]           | 288              | 286         | 577   | 63       | N/R    | 34        | Pitavastatin                                                                                                               | Control                                                | 35.5 months      |
| Vrtovec et al. [254]          | 55               | 55          | 110   | 62       | 61     | 25        | Atorvastatin (10 mg/day)                                                                                                    | No statins                                              | 12 months        |
| Wojnicz et al. [259]          | 36               | 38          | 74    | 38       | 81     | 28        | Atorvastatin                                                                                                               | Placebo                                                | 6 months         |
| Included RCTs                                      | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                        | Control                        | Follow-up period |
|--------------------------------------------------|------------------|-------------|-------|----------|--------|-----------|-------------------------------------|--------------------------------|------------------|
| Xie et al. [260]                                  | N/R              | N/R         | 81    | N/R      | N/R    | 38        | Atorvastatin (10–20 mg/day)         | Routine treatment             | 12 months        |
| Yamada et al. [261]                               | 19               | 19          | 38    | 64       | 79     | 34        | Atorvastatin 10 mg/day              | Conventional treatment        | 31 months        |
| Angermann et al. [92]                             | 352              | 363         | 715   | 69       | 71     | 30        | Included the following elements:   | Standard postdischarge planning, which typically included treatment plans, comprehensive discharge letters, and fixed appointments with GPs or cardiologists within 7–14 days |
|                                                  |                  |             |       |          |        |           | (1) in-hospital face-to-face contact between specialist nurse, patient, and relatives to explain the intervention, practice supervision of blood pressure, heart rate and symptoms; (2) telephone-based structured monitoring; (3) up titration of heart failure medication; (4) needs-adjusted specialist care, which nurses coordinated with patients’ physician(s); (5) measures for appropriate education and supervision of interveners to ensure high intervention quality | | |
| Chaudhry et al. [69]                               | 826              | 827         | 1653  | 61       | 52     | 71% < 40  | Structured (daily) telephone-based monitoring (of symptoms and weight) via an interactive voice response system | Standard optimal care. Followed by local physician. Guideline based therapy | 6 months          |
| Domingues et al. [142]                            | 48               | 63          | 111   | 63       | 68     | 29        | Structured (weekly for 1st month, every 15 days for following 2 months) telephone-based education and monitoring signs and symptoms of decompensation | Usual care that consisted of the follow-up of the patient at the return appointment at the outpatient clinic without any telephone contact | 3 months          |
| Dunagan et al. [145]                               | 76               | 75          | 151   | 70       | 44     | 75% < 40  | The intervention group received additional education from study nurses during scheduled telephone contact | Educational packet describing the causes of HF, the basic principles of treatment, their role in routine care and monitoring of their condition, and appropriate strategies for managing a HF exacerbation | 12 months         |
| Included RCTs       | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                                           | Follow-up period |
|--------------------|------------------|-------------|-------|----------|--------|-----------|--------------------------------------------------------------------------------|---------------------------------------------------|------------------|
| Gattis et al. [154] | 90               | 91          | 181   | 67       | 68     | 30        | Clinical pharmacist-led medication review and patient education. Regularly scheduled telephone contact (at 2, 12 and 24 weeks) to detect clinical deterioration early | Usual care                                           | 6 months         |
| Krum et al. [179]   | 188              | 217         | 405   | 73       | 61     | 36        | Nurse-led telephone monitoring. Participant responded to computer-generated CHF self-monitoring questions by pressing the numbers on the touch-phone keypad. Nurse survey incoming calls daily and responded to preset variations to participant’s parameters | Usual care involved standard general practice management of heart failure | 12 months        |
| Laramee et al. [182]| 141              | 146         | 287   | 71       | 54     | <40       | Four major components were (1) early discharge planning and coordination of care, (2) individualized and comprehensive patient and family education, (3) 12 weeks of enhanced telephone follow-up and surveillance, and (4) promotion of optimal CHF medications and medication doses (ACEIs or ARBs and BBs) | Standard care, typical of a tertiary care hospital, and all conventional treatments requested by the attending physician | 3 months         |
| Mortara et al. [200]| 301              | 160         | 461   | 60       | 85     | 29        | The patients enrolled in HT strategies 2 and 3 transmitted weekly records of the following data to the coordinating center via an automated interactive voice response system: weight; heart rate; systolic arterial pressure; dyspnea score; asthenia score; oedema score; changes in therapy; and blood results | Patients allocated to the control arm were discharged as normal from the hospital | 12 months        |
Table 4 (continued)

| Included RCTs | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention | Control | Follow-up period |
|---------------|-----------------|-------------|-------|----------|--------|-----------|--------------|---------|-----------------|
| Peters-klimm et al. [215] | 97 | 100 | 197 | 70 | 72 | 38 | The design of the intervention addressed 4 elements: delivery system design, self-management support, decision support, clinical information systems | No case management was applied | 12 months |
| Ramachandran et al. [224] | 25 | 25 | 50 | 45 | 78 | 21 | Intervention group participants were managed in the heart failure clinic and received disease, medication and self-management education and telephonic disease management which consisted of reinforcement of information and drug dose modification | Usual care in the heart failure clinic | 6 months |
| Sisk et al. [230] | N/R | N/R | 32 | 59 | 38 | 29 | An in-person appointment was arranged for each intervention participant, which included symptom and disease education and referral to additional patient services (if required). Follow-up telephone calls consisted of participant assessment, recording of admission information reinforcement of self-monitoring and administration of a food-frequency questionnaire | Usual care patients received federal consumer guidelines for managing systolic dysfunction but no other intervention | 12 months |
| Adamson et al. [89] | N/R | N/R | 32 | 59 | 38 | 29 | Permanent right-ventricular implantable hemodynamic monitor system similar to a single-lead pacemaker | Historical controls | 17 months |
| Adamson et al. [90] | 198 | 202 | 400 | 55 | 69 | 23 | Expert disease management conforming to consensus recommendations coupled with hemodynamic information from the IHM | The control group received expert disease management with frequent and random nursing calls | 12 months |
| Al-khatib et al. [91] | 76 | 75 | 151 | 63 | 62 | 25 | Remote monitoring of ICDs using the Medtronic CareLink transmission monitor | Quarterly ICD interrogations in clinic classified as standard of care | 12 months |
| Included RCTs               | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                                                                 | Follow-up period |
|---------------------------|------------------|-------------|-------|----------|--------|-----------|------------------------------------------------------------------------------|-------------------------------------------------------------------------|-----------------|
| Antonicelli et al. [93]   | 28               | 29          | 57    | 78       | 61     | 35        | Patients were contacted by telephone at least once a week by the team to obtain information on symptoms and adherence to prescribed treatment, as well as blood pressure, heart rate, bodyweight and 24-h urine output data for the previous day. A weekly ECG transmission was also required. Evaluation of these parameters was followed by reassessment of the therapeutic regimen and modification whenever needed. | Standard care based on routinely scheduled clinic visits from a team specialized in CHF patient management | 12 months       |
| Biannic et al. [106]      | 35               | 38          | 73    | 78       | 79     | 32        | TM during 3 months, after which participants all received usual care up until 1 year | Usual care                                                   | 3 months        |
| Böhm et al. [110]         | 497              | 505         | 1002  | 66       | 80     | 27        | Telemedicine alerts enabled, triggered by intrathoracic fluid index threshold crossing, which was programmed at the investigator’s discretion. The fluid status monitoring algorithm detects changes in thoracic impedance resulting from accumulation of intrathoracic fluid as an early sign of developing cardiac decompensation | To not transmit alerts                               | 23 months       |
| Boriani et al. [112]      | 428              | 437         | 865   | 66       | 76     | 27        | Received a monitor for scheduled remote device checks, and automatic alerts for lung fluid accumulation atrial tachyarrhythmia, and system integrity were enabled. In-office device checks were requested to re-arm alerts which had been temporarily inactivated due to previous transmissions | In-office follow-ups alone | 24 months       |
| Included RCTs                  | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                                                                 | Follow-up period |
|-------------------------------|------------------|-------------|-------|----------|--------|-----------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------|------------------|
| Boyne et al. [113]            | 185              | 197         | 382   | 71       | 59     | 36        | The patients in the intervention arm received a device, with a liquid crystal display and four keys, connected to a landline phone. Daily pre-set dialogues were communicated about symptoms, knowledge, and behaviour, being answered by touching one of the keys and sent to a server and to the nurses’ desktop. | Nurse-led usual care was given according to the latest European Society of Cardiology guidelines, including oral and written educational information, and psychosocial support as needed | 12 months       |
| Capomolla et al. [310]         | 67               | 66          | 133   | 57       | 88     | 29        | The objectives of the multidisciplinary staff are prevention and functional recovery of consequences of acute hemodynamic instability. The team members also have the task of creating, analyzing, and correcting the organization that supports the process of treatment identified in an individual care plan. | Patients were referred to their primary care physician and cardiologist. During follow-up, the process of care was driven by the patient’s needs into a heterogeneous range of emergency room management, hospital admission, and outpatient access | 11 months       |
| Dar et al. [133]              | 91               | 91          | 182   | 72       | 66     | 61% < 40  | Home telemonitoring. Daily measurement, manual transmission of weight, blood pressure, heart rate, oxygen saturation and symptoms. | Standard care                                               | 6 months         |
| Domenichini et al. [140]      | 39               | 41          | 80    | 68       | 94     | 29        | The OptiVolw or CorVueTM functions and alarms activated as Group 1, whereas the alarms were not activated | Patients were instructed to record their weight, blood pressure, and heart rate each morning before breakfast | 12 months       |
| Domingo et al. [141]          | 44               | 48          | 92    | 66       | 71     | 36        | Motiva System with educational videos, motivational messages. |                                              | 12 months       |
Table 4 (continued)

| Included RCTs          | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                                                      | Follow-up period |
|------------------------|------------------|-------------|-------|----------|--------|----------|-----------------------------------------------------------------------------|--------------------------------------------------------------|-----------------|
| Giordano et al. [157]  | 230              | 230         | 460   | 57       | 85     | 28       | Patient telemonitoring involving medical and nursing professionals. Daily transmission of cardiac parameters was monitored by a cardiologist, general practitioner and nurse, who assessed the patient's clinical status, providing consultation or triage. Nurse-driven telephone contacts to assess patient status and treatment regimen adherence were conducted weekly, or biweekly, dependent on patient status | Referred to their primary care physician. A structured follow-up with the cardiologist at 12 months in the hospital outpatient department and the appointment with the primary care physician within 2 weeks from the discharge were planned | 12 months       |
| Goldberg et al. [158] | 138              | 142         | 280   | N/R      | N/R    | 22       | The system includes an electronic scale placed in patients' homes. Patients were instructed to weigh themselves and respond to yes/no questions about heart failure related symptoms twice daily. The attending physician individualized the symptom questions and weight goals for each patient at the time of enrollment | Patients were instructed to contact their physician for weight increases of more than a prespecified amount or if their symptoms of heart failure worsened. These patients were asked to bring a copy of their home weight log to study visits | 6 months        |
| Hansen et al. [167]   | 102              | 108         | 210   | 63       | 83     | 28       | Receive quarterly automated follow-up via telemetry | Receive quarterly personal contact with a physician | 13 months       |
| Hindricks et al. [170]| 331              | 333         | 664   | 66       | 81     | 26       | In the telemonitoring group, transmitted data were reviewed by study investigators according to their clinical routine. In parallel, transmitted data were reviewed by a central monitoring unit composed of trained study nurses and supporting physicians. | In the control group, no study participant had access to telemonitoring data until study completion. All patients were treated according to European guidelines | 12 months       |
| Idris et al. [171]    | 14               | 14          | 28    | 63       | 39     | 23       | Daily remote monitoring of blood pressure, heart rate, oxygen saturation, and weight via the telemonitoring system for 3 months | Standard care | 3.6 months       |
Table 4 (continued)

| Included RCTs       | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control   | Follow-up period |
|---------------------|------------------|-------------|-------|----------|--------|-----------|------------------------------------------------------------------------------|-----------|-----------------|
| Kashem et al. [174] | 24               | 24          | 48    | 54       | 74     | 25        | Blood pressure, pulse, steps/day, and weight together with symptoms were entered. The most recent laboratory data and medication were entered by the practice staff, and the patient was instructed to review medications and laboratory values and transmit any questions to the practice | Usual care | 12 months       |
| Koehler et al. [176]| 354              | 356         | 710   | 67       | 82     | 27        | The system is based on a wireless Bluetooth device, together with a personal digital assistant, as the central structural element. Data transfer was performed with the use of cell phone technologies. The patient performed a daily self-assessment and the data were transferred to the responsible telemedical center | Usual care | 26 months       |
| Koehler et al. [311]| N/R              | N/R         | 710   | 67       | 81     | < 30      | The system is based on a wireless Bluetooth device together with a personal digital assistant as the central structural element. The patient performed a daily self-assessment and the data was transferred to the telemedical center which provided physician-led medical support 24 h a day, 7 days a week for the entire study period | Usual care | 24 months       |
| Included RCTs          | N (intervention) | N (control) | Total  | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                                                                 | Follow-up period |
|-----------------------|------------------|-------------|--------|----------|--------|----------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------|
| Kraai et al. [178]    | 94               | 83          | 177    | 69       | 37     | 27       | Patients in the telemonitoring group received telemonitoring devices at home consisting of a weighing scale, blood pressure equipment, an ECG-device and a health-monitor. The instruction was to record weight and blood pressure once a day and an ECG in case of starting or up-titration of Beta-blockers. After receiving the data from the above-mentioned devices, the health-monitor generated standard health-related questions regarding the patients' health status | The ICT-guided-DSM group followed the normal HF-routine of the individual hospitals, like any other HF-patient, without limitations to the visits | 9 months         |
| Landolina et al. [181]| 101              | 99          | 200    | 68       | 79     | 31       | ICD-OptiVol                                                                 | Remote transmission off                                                  | 16 months        |
| Lüthje et al. [187]   | 89               | 87          | 176    | 66       | 77     | 32       | The device determines a representative impedance daily and compares this with a roving reference value. Whenever daily impedance drops below the reference, a cumulative, absolute difference is calculated, and called fluid index | Standard in-office visits were performed every 3 months                  | 15 months        |
| Morgan et al. [199]   | 824              | 826         | 1650   | 70       | 86     | 30       | Remote monitoring via an electronic care record form management system       | Usual care                                                             | 34 months        |
| Sarda et al. [227]    | 89               | 94          | 183    | 72       | 76     | <35      | CRT-D with TM                                                                | CRT-D with traditional ambulatory monitoring                           | 12 months        |
| Scherr et al. [228]   | 54               | 54          | 108    | 66       | 79     | 25       | Pharmacological treatment with telemedical surveillance for 6 months        | Pharmacological treatment                                               | 6 months         |
| Soran et al. [312]    | 160              | 155         | 315    | 76       | 31     | 24       | Home-based disease management program to monitor and to detect early signs and symptoms of heart failure using telecommunication equipment | Patient 1-on-1 education, an effort to use evidenced-based optimal medical treatment, and a commercially available digital home scale with management by primary physician | 6 months         |
### Table 4 (continued)

| Included RCTs | N (intervention) | N (control) | Total | Mean age | % Male | Mean LVEF | Intervention                                                                 | Control                                      | Follow-up period |
|---------------|------------------|-------------|-------|----------|--------|----------|--------------------------------------------------------------------------------|----------------------------------------------|------------------|
| van Veldhuisen [249] | 167              | 168         | 335   | 86       | 86     | 25       | Information available to physicians and patients as an audible alert in case of preset threshold crossings | Information and an alert were not available | 15 months        |
| Villani et al. [250] | 30               | 30          | 60    | 69       | 75     | 31       | N/A                                                                            | N/A                                          | 12 months        |
| Villani et al. [251] | 40               | 40          | 80    | 72       | 74     | 32       | The patient front-end operated through a personal digital assistant given to each patient leaving hospital. The cardiologist decided what variables should be followed up (e.g., heart rate, body weight, blood pressure, ECG) and the frequency of monitoring (e.g., daily for blood pressure and body weight, weekly for the ECG) according to the patient's clinical characteristics | Usual care                                   | 1 year           |
| Vuorinen et al. [255] | 47               | 47          | 94    | 58       | 83     | 27       | A patient regularly reported their most important health parameters to the nurse using a mobile phone app. At the beginning of the study, the patients were given a home-care package including a weight scale, a blood pressure meter, a mobile phone, and self-care instructions. The patients were advised to carry out and report the measurements together with the assessment of symptoms once a week | A multidisciplinary care approach including patient guidance and support for self-care has been adopted at the clinic | 6 months         |
| Weintraub et al. [256] | 95               | 93          | 188   | 69       | 66     | 32       | Specialized primary and networked care in heart failure disease management program | Disease management program in conjunction with the AHM system | 3 months         |
95% CI: 0.64 | 0.86), which is in agreement with the general findings reported by the studied meta-analyses.

Stem cell therapy was in 0 of the 13 studies related to reduced HF-related hospitalization, which is in line with our meta-analyzed result (RR: 0.71, 95% CI: 0.45 | 1.14) and the conflicting evidence suggested by the studied meta-analyses.

The funnel plots indicate no, or only minimal publication bias (Fig. 7).

Medication

ACE inhibitors (5/18 studies; RR: 0.64, 95% CI: 0.49 | 0.85), MRAs (4/9 studies; RR: 0.77, 95% CI: 0.71 | 0.83), ARBs (4/5 studies; RR: 0.77, 95% CI: 0.72 | 0.84), beta-blockers (8/16 studies; RR: 0.78, 95% CI: 0.74 | 0.83), and statins (2/9 studies; RR: 0.51, 95% CI: 0.36 | 0.72) showed a significant effect of reduced hospitalizations in our meta-analyses (Fig. 5). This is in line with the general findings reported by the studied meta-analyses.

Anticoagulation (RR: 0.99, 95% CI: 0.91 | 1.08) was in none of the studies (0/3) able to reduce HF-related hospitalizations. This absence of an effect was also reported by the studied meta-analyses.

The asymmetry in the medication funnel plots suggests some publication bias towards significant effectiveness of medication in reducing HF-related hospitalizations (Fig. 7).

Care pathways

Multidisciplinary clinics or self-management promotion programs (10/23 studies; RR: 0.79, 95% CI: 0.73 | 0.85) and TM (12/33 studies; RR: 0.86, 95% CI: 0.81 | 0.92) were related to less HF-related hospitalizations (Fig. 6). This is in agreement with findings reported by the studied meta-analyses. STS (1/11 studies; RR: 0.85, 95% CI: 0.85 | 1.04) was not related to reductions in HF-related hospitalizations. This is in contrast to findings from the meta-analyses. Visual inspection of the funnel plots did not suggest publication bias (Fig. 7).

Discussion

Heart failure is a major health concern, with the highest readmission rates among all diseases [8–11]. Yet, up to 40% of hospitalizations could be classified as preventable [36–40]. This umbrella review therefore aimed to systematically review all published meta-analyses conducted in the past 10 years that examined the incremental benefit of interventions in addition to standard care, in reducing HF-related (re)hospitalization, in order to provide a comprehensive overview of different levels of evidence with regard to
Table 5 AMSTAR 2 scores

| Item | AMSTAR 2 scores | Judgment |
|------|-----------------|----------|
| 2a   | ●●● ●●● ●●● ●●● | Critically low |
| 9b   | ●●● ●●● ●●● ●●● | Low |
| 11c  | ●●● ●●● ●●● ●●● | High |
| 13d  | ●●● ●●● ●●● ●●● | Low |
| 14e  | ●●● ●●● ●●● ●●● | High |

a Registered protocol before commencement of the review
b Risk of bias from individual studies being included in the review
c Appropriateness of meta-analytical method
d Consideration of risk of bias when interpreting the results of the review
e Assessment of presence and likely impact of publication bias
| Author, year | Category | Sig | Conclusion | Statistics |
|--------------|----------|-----|------------|------------|
| Adamson et al. [266] | Care pathways | ✓ | *Haemodynamic-guided HF management* is superior in reducing long-term HF-hospitalization risk | HR: 0.63 (0.54–0.73) |
| Alotaibi et al. [269] | Care pathways | ✓ | A significant reduction in HF-hospitalizations in patients undergoing catheter ablation | RR: 0.56 (0.44–0.71) |
| Carbo et al. [275] | Care pathways | ✓ | We found reduction trends in HF-related admissions due to m-Health | SMD: −0.43 (−0.83|−0.02) |
| Driscoll et al. [277] | Care pathways | ✓ | *Nurse-led titration* may result in a significant reduction in hospital admissions | RR: 0.51 (0.36–0.72) |
| Gandhi et al. [281] | Care pathways | × | Multidisciplinary heart failure clinics failed to show a reduction in HF hospitalization | OR: 0.68 |
| Halawa et al. [282] | Care pathways | × | Usage of *intra-cardiac devices* is not linked to improving rates of HF admission | OR: 1.25 (0.92–1.69) |
| Inglis et al. [285] | Care pathways | ✓ | Both *STS* and *TM* reduced HF-related hospitalizations | RR: 0.77 (0.68–0.87) |
| Inglis et al. [286] | Care pathways | ✓ | *STS* and *TM* improve outcomes for patients with CHF | RR: 0.77 (0.68–0.87) |
| Jonkman et al. [288] | Care pathways | × | No specific program characteristics were consistently associated with better effects of self-management interventions | RR: 0.96 (0.92–0.995) |
| Klersy et al. [290] | Care pathways | ✓ | *TM* was associated with a significantly lower number of hospitalizations for HF | IRR: 0.77 (0.65–0.91) |
| Pandor et al. [296] | Care pathways | × | There were no major effects on HF-related hospitalization for *STS HM (HR: 1.03, 95% CrI: 0.66, 1.54)* or *TM* with medical support during office hours | HR: 1.03 (0.66, 1.54) |
| Thomas et al. [300] | Care pathways | ✓ | Specialist clinics for patients with HF can reduce the risk of unplanned admissions | RR: 0.51 (0.41–0.63) |
| Tse et al. [302] | Care pathways | ✓ | Hospitalization rates can be reduced by remote patient monitoring using either *TM* or *hemodynamic monitoring* | HR: 0.73 (0.65–0.83) |
| Uminksi et al. [305] | Care pathways | ✓ | *A post-discharge virtual ward* can provide added benefits to usual care to reduce HF-related hospital admissions | RR: 0.61 (0.49–0.76) |
| Xiang et al. [306] | Care pathways | ✓ | *Telehealth* had a significant overall effect on CHF hospitalization | RR: 0.72 (0.61–0.85) |
| Bjarnason-Weherens et al. [273] | CR | ✓ | Exercise-based intervention reduces the level of hospitalizations due to HF | RR: 0.59 (0.12–2.91) |
| Taylor et al. [299] | CR | ✓ | *ExCR* did reduce HF-specific hospitalization | RR: 0.59 (0.42–0.84) |
| Agasthi et al. [267] | Invasive therapy | ✓ | *CA* was associated with significantly lower rate of HF-readmission | RR: 0.58 (0.46–0.81) |
| Al-Majed et al. [268] | Invasive therapy | ✓ | *CRT* reduces HF-hospitalization in patients | RR: 0.69 (0.58–0.82) |
| AlTurki et al. [270] | Invasive therapy | ✓ | *RM* showed benefit in reducing HF-related hospitalization when compared to standard of care | RR: 0.95 (0.78–1.16) |
| Benito-González et al. [271] | Invasive therapy | ✓ | TMVR with *MitraClip® system* was related to a significant reduction in hospitalizations for HF | HR: 0.65 (0.46–0.92) |
| Bertaina et al. [272] | Invasive therapy | ✓ | *MitraClip for FMR* in patients with LV dysfunction is associated with a considerable reduction of HF-hospitalization | OR: 0.49 (0.24–1.00) |
| Fisher et al. [279] | Invasive therapy | ✓ | *Cell treatment* is associated with a significant reduction of rehospitalization caused by worsening HF | RR: 0.39 (0.22–0.70) |
| Fisher et al. [280] | Invasive therapy | × | *Cell therapy* does not appear to reduce the risk of rehospitalization for HF | RR: 0.62 (0.36–1.04) |
| Ma et al. [293] | Invasive therapy | ✓ | *CA* reduced risks of HF readmission | RR: 0.58 (0.46–0.66) |
| Malik and Aronow [294] | Invasive therapy | ✓ | *CA* was effective in reducing hospitalization for HF | OR: 0.41 (0.28–0.59) |
| Moschonas et al. [295] | Invasive therapy | ✓ | In patients randomized to AFA, there were significant improvements in unplanned hospitalization rates | RR: 0.58 (0.46–0.73) |
| Tu et al. [303] | Invasive therapy | ✓ | *CRT* had a marked effect in reducing new hospitalizations for worsening HF | RR: 0.69 (0.60–0.79) |
Table 6  (continued)

| Author, year | Category       | Sig  | Conclusion                                                                                     | Statistics                |
|--------------|----------------|------|-----------------------------------------------------------------------------------------------|---------------------------|
| Turagam et al. [304] | Invasive therapy | √    | CA was associated with reductions in HF hospitalizations                                      | RR: 0.60 (0.39–0.93)    |
| Bonsu et al. [274]    | Medication     | √    | Superiority of lipophilic statin treatment in decreasing hospitalization for worsening HF       | OR: 0.49 (0.36–0.67)²    |
| De Vecchis and Ariano [276] | Medication | √    | ARA use in patients with heart failure was associated with a significant reduction in hospitalization | OR: 0.73 (0.61–0.89)    |
| Emdin et al. [278]     | Medication     | √    | RAAS inhibition overall reduces the risk for hospitalization for HF                          | RR: 0.80 (0.77–0.83)    |
| Gandhi et al. [313]    | Medication     | √    | In patients with acute advanced CHF concomitant hypertonic saline administration decreased HF-rehospitalization | RR: 0.50 (0.33–0.76)    |
| Hartmann et al. [283]  | Medication     | ×    | Ivasradine showed no significant effect for hospitalization due to HF                        | RR: 0.87 (0.68–1.12)    |
| Iturki al. [284]       | Medication     | √    | The use of AldoAs may exert beneficial effects in reducing re-hospitalization for cardiac causes | RR: 0.62 (0.52–0.74)    |
| Japp et al. [287]      | Medication     | √    | MRAs did improve hospitalizations                                                              | HR: 0.62 (0.47–0.82)    |
| Kang et al. [289]      | Medication     | √    | There was a trend towards reduced HF hospitalization risk with RAS inhibitors                 | RR: 0.91 (0.83–1.01)    |
| Komajda et al. [291]   | Medication     | √    | Disease-modifying medications resulted in the progressive improvement in hospitalization outcomes | HR: 0.25 (0.07–0.99)    |
| Le et al. [292]        | Medication     | √    | Significant relative risk reduction of CV hospitalization was observed in those assigned to AAs | RR: 0.79 (0.68–0.91)    |
| Shah et al. [297]      | Medication     | ×    | Pooled analysis of these trials suggests no consistent benefit of RAS inhibition with regard to HF hospitalization | OR: 0.90 (0.80–1.02)    |
| Sulaica et al. [298]   | Medication     | ×    | No difference was noted between the anticoagulation and placebo group in regard to hospitalization for HF | OR: 0.97 (0.80–1.18)    |
| Thomsen et al. [301]   | Medication     | √    | Drugs targeting the renin–angiotensin–aldosterone system, beta-blockers, digoxin, and CRT significantly reduced the risk of HF hospitalization | RR: 0.71 (0.65–0.78)⁶   |
| Zhang et al. [307]     | Medication     | √    | The beneficial effects of TMZ have been demonstrated by the decrease of hospitalization        | RR: 0.43 (0.21–0.91)    |
| Zhang et al. [308]     | Medication     | ×    | Our meta-analysis suggests that liraglutide treatment has no important influence on hospitalization for HF | RR: 1.18 (0.88–1.58)    |
| Zhou and Chen [309]    | Medication     | √    | TMZ treatment in CHF patients may reduce hospitalization for cardiac causes                      | RR: 0.43 (0.21–0.91)    |

HF heart failure, CA catheter ablation, CR cardiac rehabilitation, CRT cardiac resynchronization therapy, STS structured telephone support, UF ultrafiltration, TMZ Trimetazidine, TM telemonitoring

¹ Lipostatin
² Rosuvastatin
³ Structured telephone support
⁴ Telemonitoring
⁵ ACE
⁶ ARB
⁷ ARA
⁸ Beta-blocker
⁹ Digoxin
¹⁰ Ivasradine
¹¹ CRT
¹² ICD
¹³ Hemodynamic monitoring
the different interventions that aim to reduce HF-related (re)hospitalization.

Even though previous studies did examine the effectiveness of interventions in treatment for heart failure in general, this umbrella review highlights different levels of evidence regarding the effectiveness of several interventions in reducing HF-related hospitalization. All different categories of interventions (i.e., cardiac rehabilitation, invasive treatment, 

### Interventions reporting HF-related hospitalization from 44 included reviews (n = 186)

| Intervention Type | Medication (n = 60) | Cardiac rehabilitation (n = 14) | Invasive therapy (n = 45) | Care pathways (n = 67) |
|-------------------|---------------------|--------------------------------|--------------------------|------------------------|
| Meta-analyzed results | Statistically significant reductions | Statistically significant reductions | Statistically significant reductions | Statistically significant reductions |
| Best-evidence system | Strong / moderate evidence | Strong / moderate evidence | Conflicting / no evidence | Strong / moderate evidence |
| Individual RCTs | ACE (5/8) | MRA (4/9) | Beta-blocker (8/16) | Multidisciplinary care pathways (9/14) |
| | ARB (4/7) | Statin (2/5) | Angiotensin II receptor blockers (8/16) | Self-management promotion (10/23) |
| | Anticoagulation (6/7) | Cardiac resynchronization therapy (3/4) | Catheter ablation (2/5) | |
| | | CT (1/7) | Structured telephone support (1/2) | |
| | | | Multidisciplinary care pathways (1/3) | |

**Fig. 2** Effects of different interventions on HF-related hospitalization in meta-analyzed and single-study results. ACE, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; MRA, mineralocorticoid receptor antagonists; CR, cardiac rehabilitation; CRT, cardiac resynchronization therapy; CA, catheter ablation; TM, telemetry; STS, structured telephone support.

**Fig. 3** Forest plot of RR for HF-related hospitalization between cardiac rehabilitation and control. Random effects model.
medication, and care pathways) entail interventions that prove able to statistically significantly reduce HF-related hospitalizations. Strong or at least moderate evidence was found for the beneficial effects of CA, CRT, ACE inhibitors, MRAs, ARBs, CR, TM, and STS. Limited evidence was found for the ability of beta-blockers, statins, mitral valve repair, and multidisciplinary clinics or self-management promotion programs to reduce hospitalization rates. Conflicting or no evidence was found for the effects of anticoagulation and stem cell therapy.

The findings of this umbrella review were generally supported by the American Heart Association and European Society of Cardiology heart failure guidelines [46, 64]. Yet, evidence for effectiveness was still lacking for several interventions in these guidelines. A couple of interventions proposed in the guidelines had low levels of evidence, as they were only supported by a single randomized clinical trial. Although these guidelines do not solely focus on the prevention of (re)hospitalization, this umbrella review now provides additional evidence for the effectiveness of ARBs (e.g., Valsartan) and telemonitoring as effective in the prevention of (re)hospitalization in heart failure. Therefore, the results of this review may be used in addition in clinical practice, as well as by policymakers, as a guideline in deciding what treatment option might help prevent hospitalization in at risk heart failure patients.

Effectiveness of reported interventions was measured in terms of a reduced risk for heart failure related

![Table](raw_data:image.png)

**Fig. 4 (A–D)** Forest plots of RR for HF-related hospitalization between (A) catheter ablation, (B) cardiac resynchronization therapy, (C) mitral valve therapy, and (D) stem cell therapy, and control. Fixed effects model.
hospitalizations. However, it would be naïve to suggest that this equals the clinical, genuine effect of treatment. Non-effectiveness of treatment could also be related to non-adherence or non-acceptance of the intervention by the patient, since it is estimated that non-adherence ranges between 30 and 50% in patients with chronic illnesses [65]. And non-adherence not only holds for medication, yet also for cardiac rehabilitation [66, 67] and telemonitoring [68, 69]. It has been shown that worsening of HF is often related to non-adherence of patients [70] and is in fact associated with 10% of hospitalizations [65, 71] and a 10% increased risk of readmission [72]. The other way around, reductions in non-adherence are found to result in less hospital admissions [73].

Differences in non-adherence to different forms of interventions were also found. For example, patients are found to be more adherent to ACE-inhibitors (77.8%) as compared to beta-blockers (69.8%) [74]. These differences could be explained by cognitions of patients regarding the efficacy of the intervention and the usability of the intervention [75]. Moreover, low health literacy or simply a lack of knowledge about the syndrome could also contribute to non-adherence [76–78]. In clinical practice, one should therefore educate patients about the importance of disease management with medication, invasive therapy, cardiac rehabilitation, and care pathways [65, 79].

Moreover, when implementing interventions in practice, one should not only focus on effectiveness, yet also incorporate, for example, the costs of the intervention. Especially, since HF is the most costly condition in western countries, with at least twice the costs of the estimated consumption of healthcare in the general population in a year [32, 33, 80], mainly due to HF-related hospitalization [28, 29]. Research has shown that, in terms of cost-effectiveness, medication treatment with beta-blockers, ARBs, or ACE inhibitors could be preferred over more cost expensive therapies as device therapy with CRT [81, 82]. More specifically, with regard to specific forms of medication, ivabradine seems a cost-effective treatment option, while this does not hold for valsartan [82]. In addition, general HF treatment combined with telemonitoring has been found to be between 27 and 52% more cost-efficient than usual care alone [83, 84]. Furthermore, telemonitoring seems not only cost-efficient; but nowadays, with the pandemic consequences of COVID-19...
it seems more desired than ever [85]. The pandemic served as a catalyst, as both healthcare professionals as patients wanted optimal care in a time of reduced ambulatory outpatient clinics, with being compliant to social distancing [84]. Our review shows, in addition, that, even though the terms are interchangeably used to both describe some form of “remote care,” telemonitoring and structured telephone support have different levels of effectiveness with regard to prevention of heart failure related (re)hospitalizations, which should be accounted for in clinical practice.

In this umbrella review, we only aimed to provide an overview of effective treatment options for prevention of heart failure (re)hospitalization. Consequently, no conclusions could be drawn regarding the hierarchy of effectiveness based upon this review. In future research, it should be examined what factors contribute to effectiveness of interventions, as our study only showed that particular interventions could reduce heart failure hospitalizations, but not why per se. Research should focus on the effective mechanisms of care pathway programs, for example, or on determinants of successful implementations of interventions for heart failure.

The aim of our review was to assess interventions which are currently used in clinical practice and examined in large populations. Our results are based upon meta-analyses performed within the past 10 years. Yet, most

### Table 1

| Study or Subgroup       | log[Risk Ratio] | SE   | Weight | Risk Ratio IV, Random, 95% CI | Risk Ratio IV, Random, 95% CI |
|-------------------------|----------------|------|--------|-------------------------------|-------------------------------|
| Beller 1995             | -1.0217        | 1.1456 | 1.4%   | 0.36 [0.04, 3.40]             |                               |
| Brown 1995              | -1.0239        | 1.1475 | 1.4%   | 0.36 [0.04, 3.40]             |                               |
| CDMP 1987               | -1.2739        | 0.6444 | 4.2%   | 0.28 [0.08, 0.99]             |                               |
| Consensus 2000          | 0              | 0     | Not estimable |                               |
| Erhardt 1995            | -1.5171        | 0.5409 | 5.8%   | 0.22 [0.08, 0.63]             |                               |
| Pfeffer 1992            | -0.2231        | 0.1035 | 42.2%  | 0.80 [0.65, 0.98]             |                               |
| SOLVD 1991              | 0              | 0     | Not estimable |                               |
| SOLVD 1992              | -0.3857        | 0.0893 | 44.9%  | 0.68 [0.57, 0.81]             |                               |
| Total (95% CI)          | 100.0%         | 0.64 [0.49, 0.85] |                               |

Heterogeneity: Tau^2 = 0.03; Chi^2 = 9.06, df = 5 (P = 0.11); I^2 = 45%

Test for overall effect: Z = 3.10 (P = 0.001)

### Fig. 5 (A–F) Forest plots of RR for HF-related hospitalization between (A) angiotensin-converting enzyme inhibitors, (B) angiotensin II receptor blockers, (C) mineralocorticoid receptor antagonists, (D) beta-blockers, (E) statins, and (F) anticoagulation, and control. Fixed effects model
recent innovative treatment options are probably underrepresented. For example, no study examined the effects of SGLT-II inhibitors, while the European Society of Cardiology stated that SGLT-II inhibitors could be preferred in heart failure patients [86]. Future studies should examine whether the use of SGLT-II inhibitors could show effective in reducing hospitalization. Moreover, as the aim of our review was to assess interventions which are currently used in clinical practice and examined in large populations, we expected to find multiple meta-analyses examining the same interventions. A large amount of overlap in RCTs in included meta-analyses was found. This stresses the importance of registration of protocols and knowing whether the intended research subject has a significantly different research objective than existing, or outdated reviews [62].
To conclude, this umbrella review highlights different levels of evidence regarding the effectiveness of several interventions in reducing HF-related hospitalization in HFrEF patients. It provides an overview of all, known, meta-analyses conducted in the past 10 years that examined interventions to prevent heart failure related hospitalizations. All different categories of interventions entail interventions that prove able to statistically significantly reduce HF-related hospitalizations. Most evidence was found for the beneficial effects of angiotensin-converting enzyme inhibitors (ACE), mineralocorticoid receptor antagonists (MRAs), angiotensin II receptor blockers (ARBs), cardiac rehabilitation, and telemonitoring. The results of this review may be used in clinical practice, as well as by policymakers, to guide treatment for heart failure patients at risk of hospitalization.
Fig. 7 (A–D) Funnel plots of the effects of (A) cardiac rehabilitation, (B) telemonitoring, (C) medication, and (D) invasive therapy
Fig. 7 (continued)
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Author contribution All authors made substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data. All authors participated in drafting the article or revising it critically for important intellectual content gave final approval of the version to be submitted and any revised version.

Declarations

Ethical approval The study has been performed in accordance with the ethical standards in the 1964 Declaration of Helsinki and with relevant regulations of the US Health Insurance Portability and Accountability Act (HIPAA).

Conflict of interest The authors declare no competing interests.

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