Title: Reporting of lost to follow up and treatment discontinuation in device and pharmacotherapy trials in chronic heart failure: a systematic review

Abbreviated title: LTFU reporting in chronic heart failure trials

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ABSTRACT

Background

Loss to follow-up (LTFU) with unknown outcomes and premature treatment discontinuation, leaves uncertainty about the true efficacy and safety of a treatment and a lack of confidence in the results of any trial. We reviewed the extent of (and trends over time in) reporting loss to follow-up and treatment discontinuation in large studies in chronic heart failure published since 1990.

Methods and results

Online databases were systematically reviewed to identify randomized controlled clinical trials (RCTs) in CHF with > 400 participants and utilising all-cause mortality as a component of the primary or secondary endpoint. Assessments were made of documentation of LTFU, treatment discontinuation, inclusion of and completeness of a CONSORT diagram, and whether LTFU was differentiated from withdrawal of consent. 68 trials were identified, with more than 154, 000 participants. 83% of trials reported LTFU, although only 34% of these differentiated LTFU for vital status from withdrawal of consent. Reasons for treatment discontinuation in pharmacotherapy trials were infrequently reported (35%), particularly in a CONSORT diagram (20%). Use of a CONSORT diagram increased over time, although reporting of LTFU in the CONSORT diagram remained low overall at 35%.

Discussion

Participant flow through RCTs in CHF has not been uniformly reported, and use of a complete CONSORT diagram has been low, although appears to be improving. All study participants should be accounted for within a CONSORT diagram in any RCT to enable the practising cardiologist to interpret how the results should influence their clinical practice.

Keywords

Heart Failure; systematic review; lost to follow-up;

INTRODUCTION

Well-conducted prospective, randomized, double-blind, controlled trials are considered the gold-standard test of new treatments for disease, are at the core of evidence-based medicine and underpin clinical guidelines. The integrity of clinical trials may be threatened in a number of ways. One is when patients discontinue randomized therapy prematurely. If substantial numbers of patients stop active therapy it may not be possible to show a difference from placebo (or between one active substance and another). This problem may be compounded by patients randomly allocated to placebo receiving "open label" active therapy. However, the greatest contemporary threat is considered to be to patients discontinuing or withdrawing from the trial i.e. withdrawing from the protocol-specified assessments needed to evaluate efficacy and safety. Although related, these two problems are distinct in that withdrawal from study treatment should not necessarily lead to withdrawal from the trial. Although these two types of "withdrawal" are often confused by investigators and even trial sponsors. Withdrawal from trial follow-up or "loss to follow-up" (LTFU) has recently been raised as a concern by regulatory agencies.[1] LTFU, with unknown outcomes such as hospitalization and death in a substantial proportion of randomized patients, leaves uncertainty about the true efficacy and safety of a treatment and translates to a lack of confidence in the results of the trial. Consequently, it is crucial that both premature study drug discontinuation and LTFU should be minimized and that the frequency of occurrence of both should be clearly reported on completion of a trial. Efforts have been made to improve reporting of clinical trials with the publication of the CONsolidated Standards Of Reporting Trials (CONSORT) statement.[2-4] These statements were first published in 1996, and updated in 2001 and 2010. This guidance for authors includes a checklist and flow diagram detailing participants' status through a trial including LTFU and treatment discontinuation. Adherence to CONSORT guidance has been

shown to improve reporting of clinical trial data.[5] As pharmacological and device treatment is at the core of disease modifying therapy for all patients with chronic heart failure (CHF), we examined how robust the reporting of the RCTs underpinning the use of drugs and devices is in this condition. Specifically, we reviewed reporting of discontinuation of study-drug, LTFU and use of CONSORT figures in all large device and pharmacotherapy trials in CHF published since 1990.

METHODS

Literature search

Medline and Embase databases were searched with the terms "heart" or "cardiac" and "failure" as title or keywords. Standard filters were used to limit the search to include articles on or after January 1st 1990, including only human participants, published in the English language, and of RCTs. The search was carried out on January 7th 2015. Abstracts and publications were independently reviewed by two readers (RC and GW) (Figure 1). Discrepancies were resolved through discussion and review by a third reader (JM). Inclusion criteria were: RCTs of a pharmacologic or device (implantable cardioverter defibrillator or cardiac resynchronization therapy) intervention; studies in CHF; and 400 or more participants. Manuscripts were excluded if mortality was not a component of the pre-specified primary or secondary endpoint. We also excluded studies of acute heart failure and sub-group analyses.

Data extraction and analysis

Each manuscript was independently reviewed and by two readers (RC and GW). Disagreements and discrepancies were resolved by a third reviewer (JM). Tables, figures and text of the primary paper and appendix were reviewed and the following information gathered: trial characteristics (publication date, journal, total number of participants, number of participants per treatment arm, and mortality); documentation of LTFU and treatment discontinuation including reasons (for pharmacotherapy trials); and inclusion of and content of a CONSORT diagram. We documented whether LTFU was reported as loss of vital status only, loss of data pertaining to the primary endpoint, and whether "withdrawal of consent" was described. If the above data were not described in the primary results paper or appendix, then a search of subsequent sub-analyses and other sources of information were carried out (e.g. Food and Drug Administration (FDA) reports). Reporting of use of open-label therapy in the

placebo arm of pharmacotherapy trials was recorded. Potential availability of open-label pharmacotherapy was estimated by comparing FDA drug authorization dates to trial recruitment and follow-up dates. Weighted means (by number of participants) and standard deviation (SD) were calculated using the Bland and Kerry method.[6]

RESULTS

Table 1 summarizes the 68 qualifying RCTs in CHF which enrolled over 400 patients, and were published since 1990.[7-74] The details of the trials are shown in eTable 1- online supplement. A description of CHF trial acronyms is provided in eTable 2- online supplement. The majority of studies were published in the New England Journal of Medicine (n=32, 47%) or The Lancet (n=14, 21%). The most common primary endpoints were all-cause mortality or a composite mortality-morbidity endpoint. A composite endpoint was commonly used in more recent studies, and often included cardiovascular rather than all-cause mortality. Most pharmacotherapy studies were placebo controlled (n=42, 72%).

Discontinuation of study treatment

Nine of the 58 pharmacotherapy trials did not report rates of discontinuation of study drug for any reason other than death or because of an adverse event in the primary results paper, although these data were subsequently published in FDA reports for two trials (A-HeFT and Val-HeFT).[75] Of these 9, 3 reported rates of discontinuation for adverse events only. A description of the reasons for study drug discontinuation was provided in only 20 trials.

"Open label" use of study treatment

Of the 42 placebo-controlled, pharmacotherapy trials, 27 had open-label therapy available during the study. Of these 27 trials, 9 (33%) reported the use of open-label study-drug in patients assigned to placebo (i.e. SOLVD-T, DIG, PRIME-II, BEST, PEP-CHF, CORONA, GISSI-HF-rosuvastatin, GISSI-HF-n3-PUFA, , and TOPCAT).[8,17,19,31,41-2,47-8,60] The weighted mean reported use of open-label active drug in the placebo group was 7.9% (SD 8.4%).

Loss to follow-up

LTFU for at least vital status (i.e. whether the patient was alive or dead at the end of the study) was reported in the primary results paper of all but eleven trials (Xamoterol-HF, V-HeFT II, FIRST, VEST, MACH-I, V-Heft III, Val-HeFT, IMPRESS, PRAISE II, CONTAK CD, and DEFINITE).[7,9,18,70,26,21,30,59,62,63] LTFU for vital status was not described in the primary results paper of Val-HeFT,[33] but was published in a subsequent FDA report.[75] The weighted mean LTFU reported was 1.4%, with a range from 0% to 14.8%. The weighted mean LTFU was higher in device trials compared to pharmacotherapy trials, 2.9% versus 1.3% respectively. Six trials of pharmacotherapy reported total LTFU of greater than 5% and the rate of LTFU did not seem to be related to trial duration: STAT-CHF (duration 45 months; LTFU 11.6%),[14] CIBIS III (14.6; 11.8%),[40] AF-CHF (37; 5.7%),[45] CIBIS-ELD (3; 9.4%),[55] SADHART-CHF (26.2; 6.2%),[54] and WATCH (21; 5.6%)[72] ; in the last 3 trials "withdrawal of consent" was assumed to equate to LTFU. Of the ten device trials, three reported LTFU of greater than 5%: MADIT-CRT (duration 29 months, LTFU 5.4%), BLOCK-HF (37, 14.8%), and ECHO-CRT (19, 6.4%). LTFU reporting improved over the period reviewed, with all but three studies from 2002 onwards reporting LTFU. In most trials it was not clear whether follow-up for outcomes other than death was complete or not. One notable exception was HEAAL.[51] In HEAAL, the authors reported that "the status for the primary endpoint [death from any cause or heart failure hospitalization] was unknown for 41 (2%) patients in the 150 mg [losartan] group and 54 (3%) of patients in the 50 mg group, and vital status was unknown for 48 (2%) and 62 (3%) patients, respectively". The WARCEF investigators also provided a CONSORT diagram in an online appendix which potentially included complete patient dispositions.[57] However, this was difficult to interpret, showing the number of patients with "complete follow-up or endpoint"

(745/1142 patients assigned to warfarin and 761/1163 assigned to aspirin), those experiencing a primary endpoint (302 and 320), the number in which only vital status was known (46 and 44) and those lost to follow-up (17 and 18), and we could not reconcile the numbers.

Withdrawal of consent

A further problem was the reporting of and interpretation of "withdrawal of consent". This has only been reported in more recent trials. When reported it was usually unclear whether "withdrawal of consent" necessarily equated to LTFU; examination of patient disposition in various trials suggested that in most it did (or was implied e.g. STAT-CHF, BEST, COMET, MOXCON, GISSI-HF, SHIFT, CIBIS-III, OPT-CHF, WARCEF, MADIT-CRT, BLOCK-HF, ECHO-CRT, and RAFT)[14,31,35,37,47-8,53,40,44,57,66-69] while in others it did not (ECHOS, SADHART-CHF, and CIBIS-ELD)[49,54,55] . One example of a trial that did report patient status clearly in this respect was OVERTURE where the authors reported "1.0% and 0.8%, respectively, were lost to follow-up for assessment of vital status; and 0.9% and 0.4%, respectively, withdrew consent to be monitored for end points".[34]

Provision of a CONSORT diagram

Of the 68 trials reviewed, 58 were published after the first CONSORT statement. Of these, 29 were published with a CONSORT-type figure in the main paper or as an appendix (table 2). Of these 29 trials, 12 were published in The Lancet, 8 in the New England Journal of Medicine, 2 in the European Journal of Heart Failure, 2 in the European Heart Journal, 2 in Circulation, 1 in Circulation Heart Failure, 1 in the Journal of the American Medical Association, and 1 in the Journal of the American College of Cardiology (table 3). Of the studies with a CONSORT diagram, most described LTFU within the flow diagram (24

studies). However, only 10 of the pharmacotherapy studies reported treatment discontinuation within the CONSORT diagram. Furthermore, only 3 studies provided reasons for treatment discontinuation within the CONSORT diagram (FUSION II, WATCH, and SADHART-CHF).[43,54,64] Prior to the first CONSORT statement in 1996, only one study of CHF reported patient flow through the study with a flow diagram (Xamoterol-HF).[7] Overall, CONSORT diagram use increased during the time period reviewed following each successive CONSORT guidance publication (table 2). Of the ten device trials, only the most recent trials (RAFT, BLOCK-HF, and ECHO-CRT) used a CONSORT diagram. Studies with a CONSORT diagram documented LTFU (either within the text, tables, or diagrams) more frequently (93%) than those without (76%). Similarly, treatment discontinuation was more frequently documented (either within the text, tables, or diagrams) in trials of pharmacotherapy with a CONSORT diagram (96%) than without (74%).

DISCUSSION

Loss of participants during the course of a randomized controlled trial (sometimes referred to as "dropouts" or "attrition")[76] can introduce bias that may make interpretation of the results of the trial difficult or even question their validity.[77-82] LTFU introduces bias if the characteristics of participants LTFU differ between the randomized groups and the characteristics that differ are related to the trial's outcomes, especially if the proportion of participants LTFU differs between treatment groups. [77-82] For example, patients who are sicker at baseline are more likely to experience worsening of their condition; worsening may lead to withdrawal from the trial and the patient may die. Both worsening and death may be important outcomes in the trial and, if missing, will result in the trial giving an incomplete report of the true picture of what happens to patients with the condition. Should withdrawal from the trial occur more commonly in one treatment group than the other (e.g. because of benefit or harm from the investigational therapy), this non-random loss of data will result in a biased assessment of the effect of treatment. The same considerations apply to adverse effects related to study treatment and reliable estimation of the overall risk-benefit ratio. Although it is often reported that serious bias does not occur until the proportion LTFU is >20% and that little bias is likely if the proportion is <5%,[77] this "rule-of-thumb" has been questioned and even a LTFU proportion of 5% is potentially important in trials with low event rates.[83] A concrete example of this is reflected in the FDA concern about the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome ACS 2–Thrombolysis In Myocardial Infarction 51 trial (ATLAS ACS 2-TIMI 51). Of the 15,526 patients randomized, 1,294 patients (8.3%) withdrew consent and vital status was not ascertained in 1,117 patients (7.2%); this number exceeded the total number of patients with a primary endpoint (n=1,002).[84] Indeed, the primary composite endpoint could not be evaluated in 2402 patients (15.5%). Consequently, transparency in relation to completeness of follow-up is a crucially important aspect of

the reporting of clinical trials; LTFU should be described in the primary trial publication, is an important consideration in the approval process for new treatments (as indicated above) and is part of the grading of levels of evidence used in some guidelines.[85] Use of a CONSORT figure is recommended as the means of providing this information.

We found that 11 of 68 CHF trials (16.1%) did not report LTFU. This is a similar proportion to that reported in a prior survey of 235 trials published in the 5 leading general medical journals,[82] although another similar analysis reported that assessment of LTFU was difficult from the descriptions given in the trial results papers.[80] Description of study drug discontinuation rates in pharmacotherapy trials was also incomplete, both overall (16% did not report discontinuation due to reasons other than death) and for specific reasons (only 35% reported reasons for specific discontinuation).

Reporting of LTFU and treatment discontinuation in CHF trials improved over the two decades analyzed. Inclusion of a CONSORT type diagram increased following the initial guidance in 1996, and with each subsequent CONSORT statement. Authors utilizing a CONSORT diagram were more likely to document LTFU and treatment discontinuation. Although most journals endorse the CONSORT approach (with the exception of the the American Heart Journal), inclusion of a CONSORT diagram varied between journals, with the Lancet, the Journal of the American Medical Association and Circulation Heart Failure having the highest proportional use of such diagrams. However, only 3 studies reported patient disposition completely within the CONSORT diagram (FUSION II, WATCH, and SADHART-CHF),[43,54,72] that is, detailed LTFU and treatment discontinuations, including the reasons for each. Of the 68 CHF trials included in this analysis, 32 were published in the New England Journal of Medicine but only 8 of these featured a CONSORT diagram in the primary paper or

appendix. This perhaps reflects the New England Journal of Medicine endorsing the CONSORT methodology in 2004, and instructions for authors state that authors may provide a CONSORT diagram. Since 2004, over half of CHF studies meeting the inclusion criteria for this review and published in the New England Journal of Medicine featured a CONSORT diagram. Other journals, such as the Lancet and the Journal of the American Medical Association are more explicit in their requirements for authors to comply with the CONSORT 2010 statement.

The robustness of reporting of trials of device therapy in CHF has previously been questioned.[86] The proportion of studies reporting LTFU was similar between device and pharmacotherapy trials, at 80 and 84% respectively. However, the weighted mean LTFU was higher in device versus pharmacotherapy trials at 2.9 and 1.3% respectively. Use of a CONSORT figure to describe patient flow differed between the two types of CHF trial studied, with 46% of pharmacotherapy and 30% of device trials using a CONSORT figure. However, use of a CONSORT figure did improve latterly, with the 3 most recent device studies reporting patient flow with a CONSORT figure, although there was ambiguity regarding withdrawal of consent and whether this represented withdrawal from follow-up. Not only did reporting of LTFU and CONSORT diagram use improve over the period of study but the weighted average proportion of participants LTFU in the trials analysed was lower than in prior studies: 1.4% (range 0-14.8%) compared with 6% (2-14%) reported by Akl et al and 7% (0.1- 48%) by Dumville et al.[78,82] The reason for the difference between the current and prior studies is not clear but cannot be attributed entirely to year of publication. However, our findings reassure the practicing cardiologists about the robustness of reporting of RCTs of pharmacotherapy and device therapy in CHF.

Despite these encouraging trends, there is room for further improvement. Confusing terminology is still often used, making interpretation of participant flow through a trial difficult. The term LTFU was often used in an ambiguous fashion, especially in trials where the primary endpoint was not all-cause mortality. A minority of trials differentiated LTFU for vital status from LTFU with respect to the primary endpoint e.g. a mortality-morbidity composite. This issue has also been highlighted by Toerien et al in a recent review of reporting participant flow in RCTs published in six major journals.[80] Another confusing term used in the trials reviewed was "withdrawal" of participants. Does this mean withdrawal from the study treatment, from some planned follow-up/study procedures (e.g. in-person visits) or from all active follow-up? What about passive follow-up e.g. through medical records or death registers? A particular problem in more recent trials is the term "withdrawal of consent". It is often not clear whether this precludes any further follow-up of participants, even for vital status. Indeed, "withdrawal of consent" may have a different implication for follow-up, depending on the country of recruitment. Some countries require a patient be removed from passive follow up if they withdraw consent to participate in the study (e.g. Germany), where others (United Kingdom) can passively follow patients up for endpoint analyses through use of national databases unless the patient explicitly requests that this does not happen. We recommend that the phrase "withdrawal of consent" not be used in a non-specific way and that, instead, patients are asked to list, from a menu of options, what sort of follow-up they are willing to accept even if they do not wish to continue to return for study visits. These might include telephone follow-up, in person, contact with a primary care physician, follow up through medical records and tracking through national registers or public records. Of course, the patient may choose to refuse any form of follow-up at all. These details should be made explicitly clear to the reader, and we have provided examples of less ambiguous phrases. Other useful metrics which help in the interpretation of LTFU but infrequently reported are the number/proportion of patients discontinuing study follow-up

after experiencing a primary non-fatal endpoint (as opposed to the number/proportion discontinuing before any recognized event) and the proportion of overall potential follow-up time for which endpoint ascertainment took place. The latter was reported in SADHART-CHF.[54] With the growing internationalization of trials it may also be appropriate to report study-treatment discontinuation rates and LTFU by region or country.[87-88]

Reporting of the other aspects of the conduct of trials that might affect their integrity i.e. premature discontinuation of randomized therapy and cross-over to "open label" active therapy was also limited. The latter consideration only applies to a limited number of studies i.e. where the treatment under investigation (or something very similar) is available for prescription and is difficult to fully evaluate e.g. because such treatment may not be available in all countries included in the trial. The former consideration is, however, applicable to all trials of pharmacologic therapy. As described above, we found description of discontinuation rates to be incomplete, both overall and for specific reasons. Overall rates of discontinuation of study drug can be reported in the CONSORT diagram. We believe that all prescribers of therapies and patients who take therapies also have the right to see a detailed breakdown of causes of discontinuation of study drug. We suspect that word restrictions by journals may limit the reporting of such information although the increasing availability of online supplementary appendices alongside papers should remove this obstacle. A useful related metric infrequently described is the time spent on each randomized therapy. This was only reported in SADHART-CHF.[54]

RECOMMENDATIONS FOR RCT REPORTING

We believe that documentation of patients flow through a study should be standardised. LTFU, treatment discontinuation and withdrawal of consent should be defined, subcategorised and systematically recorded. The time points during follow up of these occurrences should be documented. This will allow readers to make an informed decision regarding the results, and therefore how a trial should influence the reader's practice. Authors should make clear the numbers of participants for whom the primary end point status was unknown and differentiate this from loss of vital status, rather than use vague terms such as "withdrawal". Authors should detail numbers of participants who stop blinded therapy and take open-label therapy (where appropriate). Authors should also detail time spent in the study for all participants, especially those not completing the study protocol and full follow-up. This will allow readers to interpret the potential effect that participants drop-out may have on the trial results. It is our opinion that the CONSORT diagram should be adapted to include these data (figure 2). Specifically, we believe the follow-up section of the CONSORT diagram should include the number of participants with unknown primary end point status, unknown vital status, number of participants who discontinue study intervention (including reasons and those who take open label therapy), and the duration of follow-up. At the very least, utilising a CONSORT diagram should be mandatory when reporting a clinical trial.

The main limitation of this study is that we limited our analysis to trials of device and pharmacotherapy and we did not include the other treatment options available in CHF (such as remote monitoring, exercise prescription, or ventricular-assist devices), or acute heart failure trials. This was because we wished to examine reporting of LTFU, and robustness of trial reporting in general, in classes of therapy that have been shown to reduce mortality in patients with CHF.

CONCLUSION

The findings of this systematic review are not only important to those involved in the design and reporting of RCTs, but also to the practising Cardiologist. Although reporting of LTFU in RCTs of device and pharmacotherapy in CHF has improved, this could and should be more complete. However, the proportion of participants LTFU in CHF trials was less than reported in other conditions, reassuring the practising Cardiologist that the evidence-base for device and pharmacotherapy in CHF is particularly robust. Nevertheless, Cardiologists should pay close attention to the reporting of LTFU when interpreting the results of RCTs, and, ultimately, in deciding how RCTs should influence their clinical practice. LTFU during RCTs should be fully reported in a CONSORT diagram to allow readers to better interpret the results.

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Clinical Perspective

Loss to follow-up (LTFU) with unknown outcomes and premature treatment discontinuation, leaves uncertainty about the true efficacy and safety of a treatment and a lack of confidence in the results of any trial. We systematically reviewed the extent of (and trends over time in) reporting LTFU and treatment discontinuation in large studies in chronic heart failure (CHF). 68 trials were identified, with more than 154, 000 participants. 83% of trials reported LTFU, although only 34% of these

differentiated LTFU for vital status from withdrawal of consent. Reasons for treatment discontinuation in pharmacotherapy trials were infrequently reported (35%), particularly in a CONSORT diagram (20%). Over the time period studied, participant flow through RCTs in CHF was not uniformly reported, and use of a complete CONSORT diagram was low, although appears to be improving. The practicing cardiologist can, however, be assured that evidence based guidelines for treating CHF with device and pharmacotherapy are based on robustly reported clinical trials. Specifically, the number of trials describing participants LTFU in device and pharmacotherapy trials is high, with lower reported rates of patients LTFU compared to other conditions. However, the reporting of LTFU could and should be complete, and the practicing cardiologist should pay close attention to this metric when considering whether to change their clinical practice based upon any RCT.

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Figure Legends

Figure 1: Flow diagram of literature search to identify randomized controlled trials of pharmacotherapy and device use in chronic heart failure trials

Figure 2: Suggested modified CONSORT Flow Diagram

TABLES

Table 1: Summary trial characteristics

Trial characteristic	All Trials	Pharmacology Trials	Device Trials
Number of studies, n	68	58	10
Number of patients			
Total, n	154 579	143 058	11 521
mean, n	2273	2467	1152
Publication range	1990-2014	1990-2014	2002-2013
Journal, n (%)			
AHJ	1 (2)	1 (1)	-
Circulation	7 (10)	7 (12)	-
Circulation HF	1 (2)	1 (2)	-
EHJ	4 (6)	4 (7)	-
EJHF	3 (6)	3 (5)	-
JACC	4 (6)	2 (3)	2 (20)
JACC HF	1 (2)	1 (2)	-
JAMA	1 (2)	1 (2)	-
Lancet	14 (21)	14 (24)	-
NEJM	32 (47)	24 (41)	8 (80)
Primary Endpoint, n (%)			
Composite endpoint	35 (52)	28 (48)	7 (70)
All-cause mortality	27 (40)	24 (41)	3 (30)
Cardiovascular mortality	1 (2)	1 (2)	-
Other	5 (7)	5 (9)	-
Placebo controlled, n (%)	48 (71)	42 (72)	6 (60)

AHJ = American Heart Journal; EHJ =European Heart Journal; EJHF = The European Journal of Heart Failure; HF = heart failure;
JACC = Journal of the American College of Cardiology; JAMA = Journal of the American Medical Association; NEJM = New England Journal of Medicine

Table 2: Reporting of lost to follow up in relation to CONSORT statement publication

	All trials	Before 1996 CONSORT statement	After 1996 CONSORT statement	After 2001 CONSORT statement	After 2010 CONSORT statement
Year of publication	1990-2014	1990-1996	1997-2001	2002-2010	2011-2014
Number of trials, n (%)	68 (100)	10 (17)	19 (33)	30 (44)	9 (13)
Lost to follow up, n (%)					
LTFU reported*					
Primary paper/ appendix	57 (84)	8 (80)	13 (68)	28 (93)	8 (89)
Subsequent paper / Other source	1 (2)	0	1 (5)	0	0
LTFU reported both arms*	57 (84)	7 (70)	14 (74)	28 (93)	8 (89)
"Withdrawal of consent" described	20 (29)	1 (10)	1 (5)	13 (43)	5 (56)
Treatment discontinuation, n (%†)					
Documented for any reason	49 (85)	9 (90)	14 (74)	20 (91)	6 (86)
Both arms	48 (83)	9 (90)	14 (74)	19 (86)	6 (86)
Breakdown of reasons detailed	20 (35)	5 (50)	3 (16)	10 (46)	2 (29)
Documented for adverse events only	3 (5)	1 (10)	2 (11)	0	0
Placebo group taking open-label drug	9 (33+)	1 (25+)	3 (30+)	4 (50+)	1 (20+)
CONSORT diagram, n (%)					
In primary paper/ appendix	30 (44)	NA	7 (37)	15 (50)	7 (78)
Treatment discontinuation detailed	10 (17†)	NA	5 (26†)	4 (18†)	1 (14†)
Breakdown of reasons detailed	3 (5†)	NA	0†	3 (14†)	0†

LTFU = lost to follow up; NA= not applicable.
*For at least vital status
+Percentage of placebo controlled trials with available open-label therapy
† Percenentage of trials of pharmacotherapy

Table 3: CONSORT diagram reporting per journal after 1996 guidance

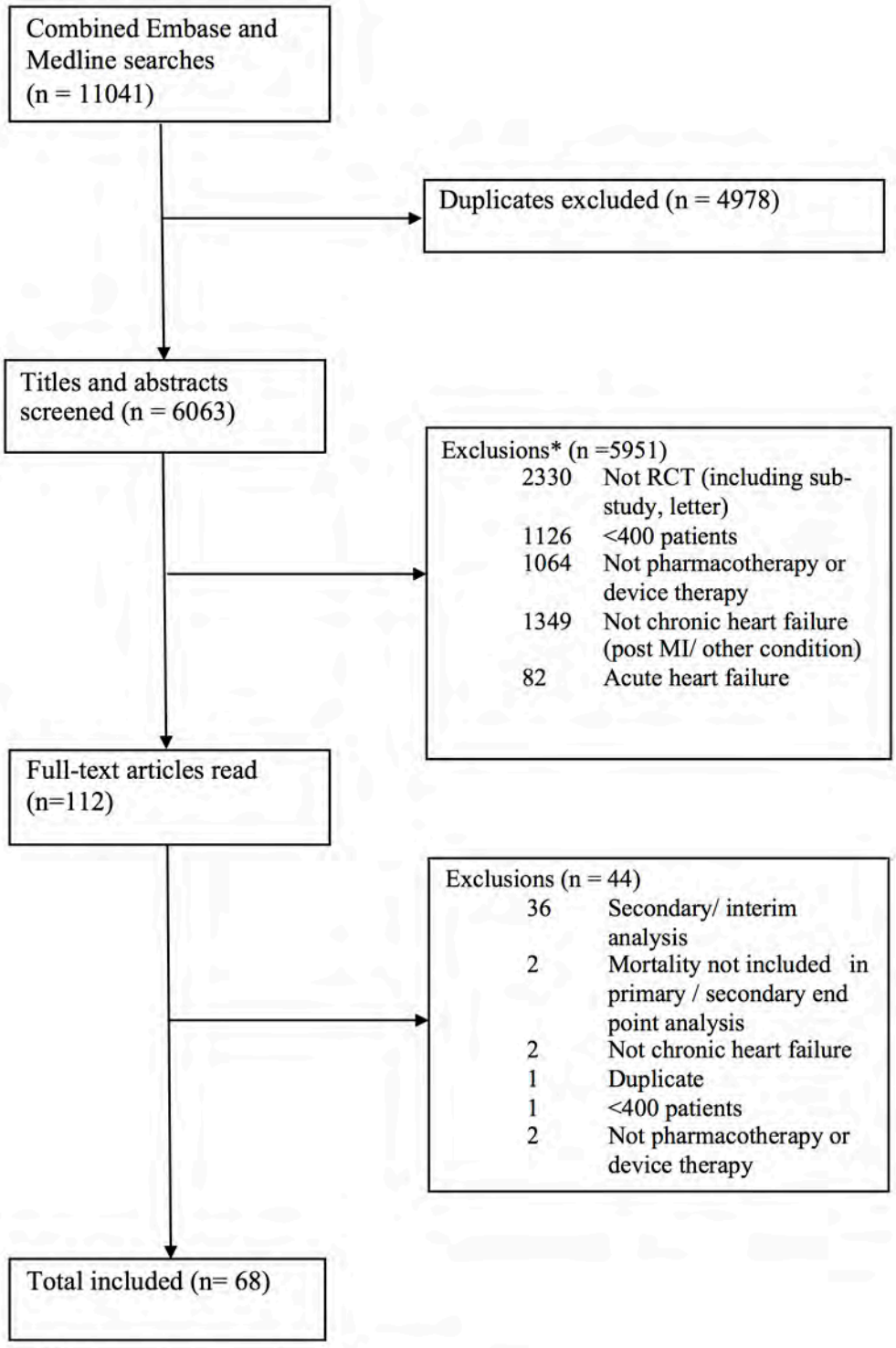
	n	CONSORT diagram in primary paper/ appendix n (%)	LTFU reported in CONSORT diagram n (%)	Treatment Discontinuation Reported in CONSORT n (%†)	Reason for treatment discontinuation detailed in CONSORT n (%†)
Journal					
AHJ	1	0	-	-	-
Circulation	6	2 (33)	2 (33)	1 (17)	1 (17)
Circulation HF	1	1 (100)	1 (100)	1 (100)	1 (100)
EHJ	4	2 (50)	2 (50)	0	1
EJHF	3	2 (67)	1 (33)	1 (33)	0
JACC	4	1 (25)	1 (25)	1 (50)	1(50)
JACC HF	1	0	-	-	-
JAMA	1	1 (100)	1 (100)	1 (100)	0
Lancet	12	12 (100)	8 (66)	4 (33)	0
NEJM	25	8 (32)	8 (32)	1 (6)	0

AHJ = American Heart Journal; EHJ =European Heart Journal; EJHF = The European Journal of Heart Failure; HF= heart failure;
JACC = Journal of the American College of Cardiology; JACC HF= Journal of the American College of Cardiology Heart failure;
JAMA = Journal of the American Medical Association; NEJM = New England Journal of Medicine;
† Percenentage of trials of pharmacotherapy

Table 4: Proposed Terminology for reporting of loss to follow-up in clinical trials

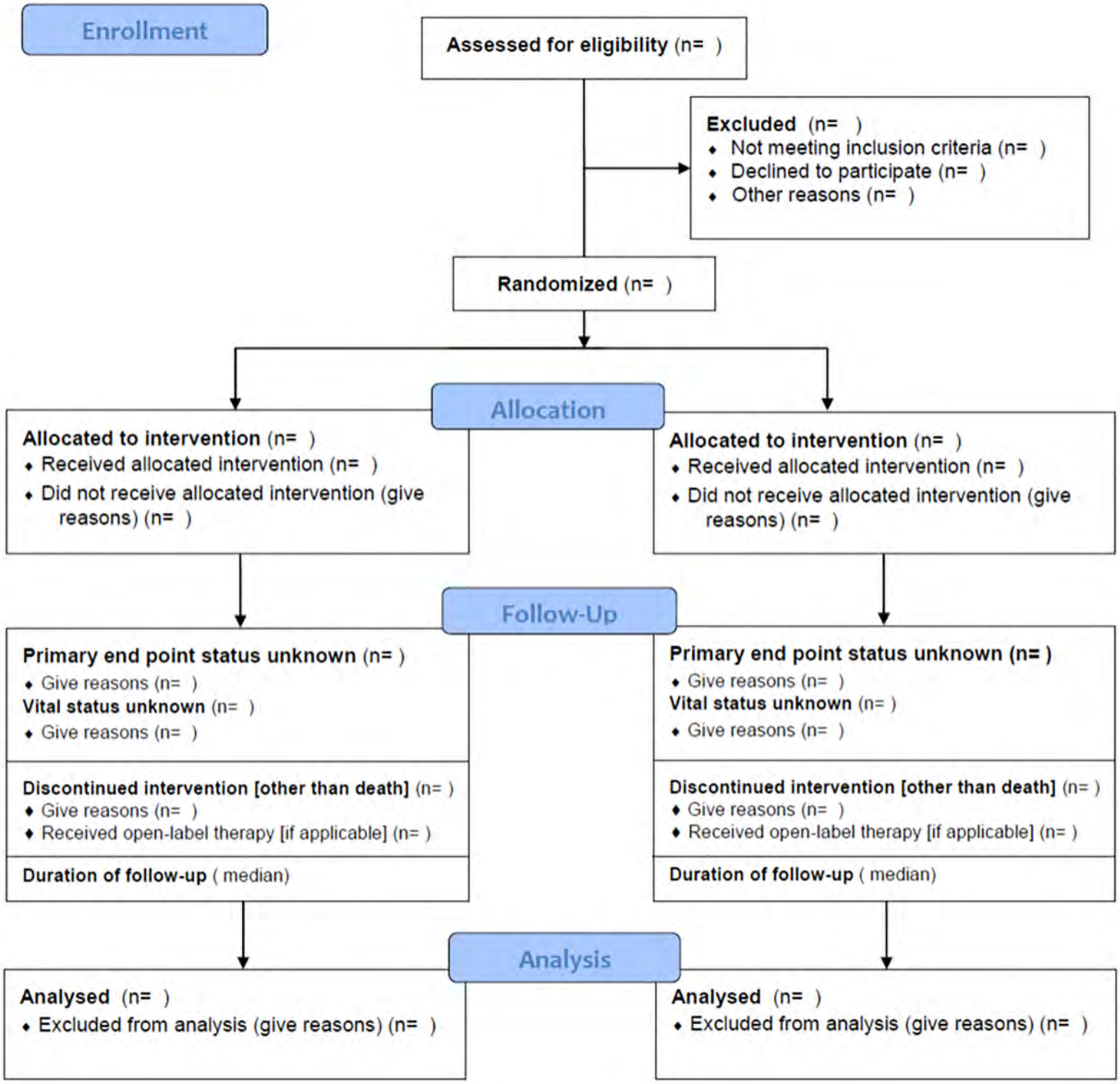
Current Phrase	**Proposed Alternative Phrase(s)**
Lost to follow-up	Lost to follow-up for vital status only Lost to follow-up for primary end point
Withdrawal of consent	Withdrawal of consent to study drug use Withdrawal of consent to attend study visits Withdrawal of consent to follow-up via medical/ death records Withdrawal of consent to any kind of follow-up

Figure 1: Flow diagram of literature search to identify randomized controlled trials of pharmacotherapy and device use in chronic heart
failure trials



* Most had more than one reason for exclusion
RCT = randomized controlled trial; MI = myocardial infarction

Figure 2: Suggested modified CONSORT Flow Diagram



eTable 1-A: Summary of heart failure trials with two comparative arms listed by date of publication

Trial	Year of Publication /Journal	Patients	Treatment Comparison		Primary End-point	Duration of Follow-up (months)	Deaths n (%)		Treatment Discontinuation (other than death) n (%)		Loss to Follow-up n (%)	
			A (n)	B (n)			A	B	A	B	A	B
PHARMACOLOGY TRIALS												
Xamoterol-HF[1]	1990/LANC	516	xamoterol (352)	mp (164)	mortality (any cause)	3.2†	32 (9.2)	6 (3.7)	67 (19.0)	19 (11.6)	NR	NR
SOLVD-Treatment[2]	1991/NEJM	2569	enalapril (1285)	mp (1284)	mortality (any cause)	41.4†	452 (35.2)	510 (39.7)	418* (32.5)	532* (41.4)	1 (0.1)	1 (0.1)
V-HeFT II[3]	1991/NEJM	804	enalapril 5mg & mp qd (403)	mp & H-ISDN (401)	mortality (any cause)	30†	132 (32.8)	153 (38.2)	89* (22)	Hydralazine/ ISDN 117* (29)/125* (31)	NR	NR
PROMISE[4]	1991/NEJM	1088	milrinone (561)	mp (527)	mortality (any cause)	6.1	168 (29.9)	127 (24.1)	71 (12.7)	46 (8.7)	0 (0.0)	0 (0.0)
SOLVD-Prevention[5]	1992/NEJM	4228	enalapril (2117)	mp (2111)	mortality (any cause)	37.4†	313 (14.8)	334 (15.8)	508 (24.0)	570 (27.0)	4 (0.2)	3 (0.2)
CIBIS-I[6]	1994/CIRC	641	bisoprolol (320)	mp (321)	mortality (any cause)	22.8†	53 (16.6)	67 (20.9)	75 (23.4)	82 (25.5)	1 (0.2)	
GESICA[7]	1994/LANC	516	amiodarone (260)	standard therapy (256)	mortality (any cause)	13†	87 (33.6)	106 (41.4)	NR	NR	7 (2.7)	12 (4.7)
STAT-CHF[8]	1995/NEJM	674	amiodarone (336)	mp (338)	mortality (any cause)	45	131 (39.0)	143 (42.3)	90 (26.8)	78 (23.1)	†46 (13.7)	†32 (9.5)
USCP[9]	1996/NEJM	1094	carvedilol (696)	mp (398)	mortality (any cause) and / or hospitalisation (CV causes)	6.5	22 (3.2)	31 (7.8)	77 * (11)	68* (17)	0 (0.0)	0 (0.0)
PRAISE I[10]	1996/NEJM	1153	amlodipine (571)	mp (582)	mortality (any cause) /or hospitalisation (CV causes)	13.8	190 (33.3)	223 (38.3)	82 (14.4)	94 (16.2)	0 (0.0)	0 (0.0)
DIG[11]	1997/NEJM	6800	digoxin (3397)	mp (3403)	mortality (any cause)	37†	1181 (34.8)	1194 (35.1)	992* (29.2)	1093* (32.1)	47 (1.4)	46 (1.4)
FIRST[12]	1997/AHJ	471	epoprostenol (237)	standard therapy (234)	mortality (any cause)	NR	114 [a] (48)	87* (37)	NR	NR	NR	NR
PRIME II[13]	1997/LANC	1906	ibopamine (953)	mp (953)	mortality (any cause)	11.5† /12†	232 (24.3)	193 (20.3)	259 (27.2)	222 (23.3)	24 (2.5)	27 (2.8)

Trial	Year of Publication /Journal	Patients	Treatment Comparison		Primary End-point	Duration of Follow-up (months)	Deaths n (%)		Treatment Discontinuation (other than death) n (%)		Loss to Follow-up n (%)	
			A (n)	B (n)			A	B	A	B	A	B
AUST-NZ[14]	1997/LANC	415	carvedilol (207)	mp (208)	changes in left ventricular ejection fraction + treadmill exercise duration	19†	20 (9.7)	26 (12.5)	41 (19.8)	30 (14.4)	0 (0.0)	0 (0.0)
V-Heft III[15]	1997/CIRC	450	felodipine ER (224)	mp (226)	(1)Exercise tolerance / sign + symptoms HF (2) Mortality and hospitalisation	18†	31 (13.8)	29 (12.8)	22 (10.0)	17 (7.8)	NR	NR
ELITE[16]	1997/LANC	722	losartan (352)	captopril (370)	Tolerability	-	17 (4.8)	32 (8.7)	64 (18.2)	106 (28.6)	0 (0.0)	0 (0.0)
CIBIS-II[17]	1999/LANC	2647	bisoprolol (1327)	mp (1320)	mortality (any cause)	15.6†	156 (11.8)	228 (17.3)	194 (14.6)	192 (14.5)	5 (0.4)	1 (0.07)
RALES[18]	1999/NEJM	1663	spironolac-tone (822)	mp (841)	mortality (and cause)	24†	284 (34.5)	386 (45.9)	222 (27.0)	211 (25.1)	0 (0.0)	0 (0.0)
DIAMOND-HF[19]	1999/NEJM	1518	dofetilide (762)	mp (756)	mortality (any cause)	18	311 (40.8)	317 (41.9)	NR	NR	0 (0.0)	0 (0.0)
MACH-I[20]	1999/CIRC	2590	mibefradil (1295)	mp (1295)	mortality (any cause)	18.6† /19.5‡	350 (27.0)	319 (24.6)	NR	NR	NR	NR
ATLAS[21]	1999/CIRC	3164	lisinopril (1568)	lisinopril & mp (1596)	mortality (any cause)	45.7	666 (42.4)	717 (44.9)	427* (27.2)	488* (30.6)	0 (0.0)	0 (0.0)
MERIT-HF[22]	2000/JAMA	3991	metoprolol (1990)	mp (2001)	mortality (any cause) hospitalisation (any cause)	12†	145 (7.3)	217 (10.8)	310 (15.6)	279 (13.9)	0 (0.0)	0 (0.0)
ELITE-II[23]	2000/LANC	3152	losartan & mp (1578)	captopril & mp (1574)	mortality (any cause)	18	280 (17.7)	250 (15.9)	125 (7.9)	221 (14)	1 (0.1)	1 (0.1)
IMPRESS[24]	2000/LANC	573	omipatrilat (289)	Lisinopril (284)	Improvement in maximum exercise treadmill test performance	-	7 (2)	10 (4)	24 (8.3)	24 (8.4)	NR	NR
BEST[25]	2001/NEJM	2708	bucindolol (1354)	mp (1354)	mortality (any cause)	24†	411 (30.4)	449 (33.2)	311* (23)	339* (25)	5§ (0.4)	3§ (0.2)
COPERNICUS[26]	2001/NEJM	2289	carvedilol (1156)	mp (1133)	mortality (any cause)	10.4†	130 (11.2)	190 (16.8)	231* (20)	283* (25)	0 (0.0)	0 (0.0)
Val-HeFT[27]	2001/NEJM	5010	valsartan (2511)	mp (2499)	mortality (any cause)	23†	495 (20)	484 (20)	NR	NR	NA	NA
OVERTURE[28]	2002/CIRC	5770	omapatrilat (2886)	enalapril (2884)	mortality (any cause) or HFH	14.5†	477 (16.5)	509 (17.6)	774* (26.8)	730* (25.3)	55*§ (1.9)	35*§ (1.2)

Trial	Year of Publication /Journal	Patients	Treatment Comparison		Primary End-point	Duration of Follow-up (months)	Deaths n (%)		Treatment Discontinuation (other than death) n (%)		Loss to Follow-up n (%)	
			A (n)	B (n)			A	B	A	B	A	B
COMET[29]	2003/LANC	3029	carvedilol (1511)	metoprolol (1518)	mortality (any cause) or hospitalisation (any cause)	58†	512 (33.9)	600 (39.5)	481 (31.9)	483 (31.8)	13§ (0.9)	20§ (1.3)
CHARM[30]	2003/LANC	7601	candesart-an (3803)	mp (3796)	mortality (any cause)	37.7	886 (23.3)	945 (24.9)	660 (17.4)	529 (13.9)	7 (0.2)	3 (0.1)
MOXCON[31]	2003/EJHF	1934	moxonidine SR (990)	mp (944)	mortality (any cause)	-	54 (5.5)	32 (3.4)	58 (5)	34 (4)	30§ (3.0)	23§ (2.4)
A-HeFT[32]	2004/NEJM	1050	H- ISDN (518)	mp (532)	composite score	10†	32 (6.2)	54 (10.2)	NA	NA	0 (0.0)	0 (0.0)
SENIORS[33]	2005/EHJ	2128	nebivolol (1067)	mp (1061)	mortality (any cause) or hospitalisation (CV causes)	21†	169 (15.8)	192 (18.0)	285 (26.7)	261 (24.6)	16 (1.5)	21 (2.0)
CIBIS-III[34]	2005/CIRC	1010	bisoprolol (505)	enalapril (505)	mortality (any cause) or hospitalisation (any cause)	14.6†	65 (12.9)	73 (14.5)	101 (20.0)	89 (17.6)	60§ (11.9)	59§ (11.7)
PEP-CHF[35]	2006/EHJ	850	perindopril (424)	mp (426)	mortality (any cause) or HFH	26.2	56 (13.2)	53 (12.4)	170* (40) [at 18 months]	153* (36) [at 18 months]	4 (0.9)	0 (0.0)
CORONA[36]	2007/NEJM	5011	rosuvastatin (2514)	mp (2497)	mortality (CV causes) or non-fatal MI or non-fatal stroke	32.8	728 (29.0)	759 (30.4)	490 (19.5)	546 (21.9)	0 (0.0)	1 (0.04)
FUSION II[37]	2008/CIRC HF	911	Nestiritide (605)	mp (306)	Mortality (all causes) or CV/ renal hospitalisation	3	56 (9.5)	29 (9.6)	72 (12.0)	35 (11.4)	4 (0.7)	1 (0.3)
OPT-CHF[38]	2008/JACC	405	oxypurinol (203)	mp (202)	mortality (any cause) morbidity (for HF) quality of life	6†	10 (4.9)	6 (3.0)	36 (8.9)		6‖ (3.0)	7‖ (3.5)
AF-CHF[39]	2008/NEJM	1376	rhythm control (682)	rate control (694)	mortality (CV causes)	37†	217 (31.8)	228 (32.9)	142 (20.8)	66 (9.5)	35 (5.1)	44 (6.3)
ANDROMEDA[40]	2008/NEJM	627	dronedarone (310)	mp (317)	mortality (any cause) or HFH	2	25 (8.1)	12 (3.8)	NR	NR	0 (0.0)	0 (0.0)
GISSI-HF Rosuvastatin[41]	2008/LANC	4574	rosuvastatin (2285)	mp (2289)	time to death and / or HFH	46.8	657 (28.8)	644 (28.1)	790 (34.6)	831 (36.3)	28§ (1.2)	31§ (1.4)
GISSI-HF n3-PUFA[42]	2008/LANC	6975	n-3 PUFA (3494)	mp (3481)	time to death and / or HFH	46.8	955 (27.1)	1014 (29.7)	1004 (28.7)	1029 (29.6)	34§ (1.0)	46§ (1.3)
ECHOS[43]	2008/EJHF	1000	nolomirole (501)	mp (499)	mortality (any cause) HFH	12†	138 (27.5)	143 (28.7)	32 (6.4)	25 (5.0)	26§ (5.2)	18§ (3.6)
I-PRESERVE[44]	2008/NEJM	4128	irbesartan (2067)	mp (2061)	mortality (any cause) hospitalisation (CV causes)	49.5†	445 (21.5)	436 (21.2)	702 [a] (34.0)	684 [a] (33)	29 (1.4)	44 (2.1)

Trial	Year of Publication /Journal	Patients	Treatment Comparison		Primary End-point	Duration of Follow-up (months)	Deaths n (%)		Treatment Discontinuation (other than death) n (%)		Loss to Follow-up n (%)	
			A (n)	B (n)			A	B	A	B	A	B
HEAAL[45]	2009/LANC	3834	losartan (1921)	losartan & mp (1913)	mortality (any cause) HFH	56.4	635 (33.1)	665 (34.8)	544 (28.3)	522 (27.3)	89 (4.6)	116 (6.1)
ESSENTIAL[46]	2009/ EHJ	1854	enoximone (926)	mp (928)	mortality (any cause) or hospitalisation (CV causes)	16.6	196 (21)	203 (22)	134 (14.5)	120 (12.9)	67 (7.2)	58 (6.3)
SHIFT[47]	2010/LANC	6505	ivabradine (3241)	mp (3264)	mortality (CV causes) or HFH	22.9	503 (15.5)	552 (16.8)	682 (20.9)	605 (18.4)	75§ (2.3)	59§ (1.8)
SADHART-CHF[48]	2010/ JACC	469	sertraline 50mg (234)	mp (235)	Change in depression score and composite CV status	26.2†	68 (29.1)	61 (26)	85¶ (36.3)	75¶ (31.9)	12§¶ (5.1)	17§¶ (7.2)
CIBIS-ELD[49]	2011/EJHF	876	bisoprolol (431)	carvedilol (445)	tolerability	3†	9 (2.1)	4 (0.9)	46 (11.0)	51 (11.0)	36§ (8.3)	45§ (10.1)
EMPHASIS-HF[50]	2011/NEJM	2737	eplerenone (1364)	mp (1373)	mortality (CV causes) or HFH	21	171 (12.5)	213 (15.5)	222 (16.3)	228 (16.7)	17 (1.2)	15 (1.0)
WARCEF[51]	2012/NEJM	2305	warfarin & mp (1142)	aspirin & mp (1163)	mortality (any cause) or ischemic stroke or intracerebral hemorrhage	42†	268 (23.4)	263 (22.6)	NR	NR	77§ (6.7)	82§ (7.0)
RED-HF[52]	2013/NEJM	2278	darbopotin (1136)	mp (1142)	mortality (any cause) or first HFH	27	474 (41.7)	458 (40.1)	368 (32.4)	412 (36.1)	13 (1.1)	21 (1.8)
PRAISE II[53]	2013/JACC -HF	1654	amlodipine (827)	mp (827)	mortality (all cause)	33	278 (33.6)	262 (31.6)	122 (14.8)	120 (14.5)	NR	NR
TOPCAT[54]	2014/NEJM	3445	spironolact-one (1722)	mp (1723)	mortality (CV causes) or HFH or aborted cardiac arrest	40†	252 (14.6)	274 (15.9)	590 (34.3)	541 (31.4)	67 (3.9)	65 (3.8)
PARADIGM-HF[55]	2014/NEJM	8399	LCZ696 (4187)	enalapril (4212)	mortality (CV causes) or HFH	27	711 (17)	835 (19.8)	746 (17.8)	833 (19.8)	11 (0.3)	9 (0.2)
DEVICE TRIALS												
CONTAK CD[56]	2003/JACC	490	CRT (245)	CRT off (245)	Progression of HF (all cause mortality/ HFH / VT/VF requiring intervention)	3,6	11 (4.5)	16 (6.5)	NA	NA	NR	NR
DEFINITE[57]	2004/NEJM	458	ICD + medical Rx (229)	Medical Rx (229)	mortality (any cause)	29†	28 (12.2)	40 (17.5)	NA	NA	NR	NR
CARE-HF[58]	2005/NEJM	813	CRT + medical Rx (409)	Medical Rx (404)	mortality (any cause) hospitalisation (CV causes)	29†	82 (20.0)	120 (29.7)	NA	NA	0	0
REVERSE[59]	2008/JACC	610	CRT ON (419)	CRT OFF (191)	HF clinical composite score (mortality, HFH, discontinued blinded Rx, worsening NYHA class)	12†	9 (2.1)	3 (1.6)	NA	NA	0	0
MADIT-CRT[60]	2009/NEJM	1820	CRT-ICD (1089)	ICD only (731)	mortality (any cause) or nonfatal heart failure events	29†	74 (6.8)	53 (7.3)	NA	NA	44 (4.0) §	55 (7.5) §

Trial	Year of Publication /Journal	Patients	Treatment Comparison		Primary End-point	Duration of Follow-up (months)	Deaths n (%)		Treatment Discontinuation (other than death) n (%)		Loss to Follow-up n (%)	
			A (n)	B (n)			A	B	A	B	A	B
RAFT[61]	2010/NEJM	1798	CRT-ICD (894)	ICD only (904)	mortality (CV causes) or HFH	40†	186 (20.8)	236 (26.1)	NA	NA	10 (1.1) §	5 (0.6) §
BLOCK HF[62]	2013/NEJM	691	BIVENT pacing (349)	Right ventricular pacing (342)	mortality (any cause) or HF treatment with IV diuretic or ≥ 15% increase LVESVI	37†	75 (21.5)	90 (26.3)	NA	NA	52 (14.9) §	50 (14.6) §
ECHO CRT[63]	2013/NEJM	809	CRT ON (404)	CRT OFF (405)	mortality (CV causes) or HFH	19†	46 (11.3)	30 (7.4)	NA	NA	18 (4.5) §	34 (8.4) §

eTable 1-B: Summary of heart failure trials with three comparative arms listed by date of publication

Trial	Year of Publication /Journal	Patients	Treatment Comparison			Primary End-point	Duration of Follow-up (months)	Deaths n (%)			Treatment Discontinuation (other than death) n (%)			Loss to Follow-up n (%)		
			A (n)	B (n)	C (n)			A	B	C	A	B	C	A	B	C
PHARMACOLOGY TRIALS																
VEST[64]	1998/NEJM	3833	Vesn-arino-ne 30mg (1275)	Vesn-arino-ne 60mg (1275)	mp (1283)	mortality (any cause)	9†	268 (21.0)	292 (22.9)	242 (18.9)	NR	NR	NR	NR	NR	NR
NETWORK[65]	1998/NEJM	1532	Enala-pril 5mg (506)	Enala-pril 10mg (510)	Enala-pril 20mg (516)	mortality (any cause) / HFH / worsening HF	6†	21 (4.2)	17 (3.3)	15 (2.9)	85 (16.8)	91 (17.8)	130 (25.2)	0	1 (0.2)	3 (0.6)
WATCH[66]	2009/CIRC	1587	Warfar-in (540)	Aspir-in 162mg (523)	Clopi-dogrel 75mg (524)	mortality (all cause) / nonfatal MI / CVA	21	92 (17.0)	94 (18.0)	96 (18.3)	110 (20.4)	100 (19.1)	102 (19.5)	35 (6.5)	24 (4.6)	30 (5.7)
DEVICE TRIALS																
COMPANION[67]	2004/NEJM	1520	Medic-al Rx (308)	CRT (617)	CRT-D (595)	mortality (any cause) hospitalisation (any cause)	12-16	77 (25)	131 (21.2)	105 (17.6)	NA	NA	NA	28 (9)	6 (1)	6 (1)
SCD HeFT[68]	2005/NEJM	2521	Amio-darone (845)	ICD (829)	mp (847)	mortality (any cause)	46	240 (28.4)	182 (21.9)	244 (28.8)	NA	NA	NA	0	0	0

AHJ = American Heart Journal; BIVENT= biventricular; CIRC = Circulation; CIRC HF= Circulation Heart Failure; CRT = cardiac resynchronisation therapy; EHJ =European Heart Journal; EJHF = The European Journal of Heart Failure; H-ISDN= hydralazine + isosorbide dinitrate; HF= heart failure; HFH = heart failure hospitalisation; ICD= implantable cardioverter defibrillator; JACC = Journal of the American College of Cardiology; JAMA = Journal of the American Medical Association; LANC = The Lancet; mp = matching placebo; LVESVI= left ventricular end systolic volume index; NA= not applicable; NEJM = New England Journal of Medicine; NR= not recorded; Rx = treatment; VT= ventricular tachycardia; VF= ventricular fibrillation.

* = Calculated from percentages

† = mean (others median)

§= Includes withdrawal of consent

||= Further 22 patients withdrew consent, but not detailed in both treatment arms

¶= assessed after three months of follow-up.

eTable 2- Chronic heart failure trial acronym definitions

Trial Acronym	Name
AF-CHF[39]	Atrial Fibrillation and Congestive Heart Failure
A-HeFT[32]	African-American Heart Failure Trial
ANDROMEDA[40]	Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease
ATLAS[21]	Assessment of Treatment with Lisinopril and Survival
AUST-NZ[14]	Australia/ NewZealand heart failure research collaborative group
BEST[25]	Beta-blocker Evaluation of Survival Trial
BLOCK HF[62]	Biventricular versus Right Ventricular Pacing in Heart Failure Patients with Atrioventricular Block
CARE-HF[58]	Cardiac Resynchronization — Heart Failure
CHARM[30]	Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity
CIBIS I[6]	Cardiac Insufficiency Bisoprolol Study I
CIBIS II[17]	Cardiac Insufficiency Bisoprolol Study II
CIBIS III[34]	Cardiac Insufficiency Bisoprolol Study III
CIBIS-ELD[49]	Cardiac Insufficiency Bisoprolol Study in Elderly
COMET[29]	Carvedilol Or Metoprolol European Trial
COMPANION[67]	Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure
COPERNICUS[26]	Carvedilol Prospective Randomized Cumulative Survival Study
CORONA[36]	Controlled Rosuvastatin Multinational Trial in Heart Failure
DIAMOND-HF[19]	Danish Investigations of Arrhythmia and Mortality on Dofetilide
DEFINITE[57]	Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation
DIG[11]	Digitalis Investigation Group
EchoCRT[63]	Echocardiography Guided Cardiac Resynchronization Therapy
ECHOS[43]	EchoCardiography and Heart Outcome Study
ELITE[16]	Evaluation of Losartan in the Elderly
ELITE II[23]	Evaluation of Losartan in the Elderly II
EMPHASIS-HF[50]	Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure
ESSENTIAL[46]	Studies of Oral Enoximone Therapy in Advanced heart failure
FIRST[12]	Flolan International Randomized Survival Trial
FUSION II[37]	Follow-Up Serial Infusions of Nesiritde trial
GESICA[7]	Groupo de Estudio de la Sobrevida en la Insuficiencia Cardiaca en Argentina
GISSI-HF n3-PUFA[42]	Gruppo Italiano per lo Studio della Sopravvivenza nell'Insuffi cienza cardiaca Heart Failure trial- n3-PUFA
GISSI-HF Rosuvastatin[41]	Gruppo Italiano per lo Studio della Sopravvivenza nell'Insuffi cienza cardiaca Heart Failure trial- rosuvastatin
HEAAL[45]	Heart failure Endpoint evaluation of Angiotensin II Antagonist Losartan study
IMPRESS[24]	Comparison of vasopeptidase inhibitor, omapatrilat, and lisinopril on exercise tolerance and morbidity in patients with heart failure
I-PRESERVE[44]	Irbesartan in heart failure with Preserved systolic function trial
MACH-I[20]	Mortality Assessment in Congestive Heart Failure Trial
MADIT-CRT[60]	Multicenter Au- tomatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy
MERIT-HF[22]	Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure
MOXCON[31]	MOXonidine CONgestive heart failure trial

NETWORK[65]	Clinical outcome with enalapril in symptomatic chronic heart failure; a dose comparison
OPT-CHF[38]	The Efficacy and Safety Study of Oxypurinol Added to Standard Therapy in Patients With New York Heart Association Class III-IV Congestive Heart Failure
OVERTURE[28]	Omipatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events
PARADIGM-HF[55]	Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial
PEP-CHF[35]	Perindopril in Elderly People with Chronic Heart Failure study
PRAISE I[10]	Prospective Randomized Amlodipine Survival Evaluation
PRAISE II[53]	Prospective Randomized Amlodipine Survival Evaluation II
PRIME II[13]	Prospective Randomised Study of Ibopamine on Mortality and Efficacy II
PROMISE[4]	Prospective Ransomized Milirinone Survival Evaluation
RALES[18]	Randomized Aldactone Evaluation Study
RAFT[61]	Resynchronization–Defibrillation for Ambulatory Heart Failure Trial
REVERSE[59]	REsynchronization reVErses Remodeling in Systolic left vEntricular dysfunction
RED-HF[52]	Reduction of Events by Darbepoetin Alfa in Heart Failure
SADHART-CHF[48]	Sertraline Against Depression and Heart Disease in Chronic Heart Failure
SCD-HeFT[68]	Sudden Cardiac Death in Heart Failure Trial
SENIORS[33]	Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure
SHIFT[47]	Systolic Heart failure treatment with the If inhibitor ivabradine Trial
SOLVD-Prevention[5]	Studies of Left ventricular dysfunction- prevention
SOLVD-Treatment[2]	Studies of Left ventricular dysfunction- treatment
STAT-CHF[8]	Survival Trial of Anti-arrhythmic Therapy in Congestive Heart Failure
TOPCAT[54]	Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist
USCP[9]	US Carvedilol Heart Failure Program
Val-HeFT[27]	Valsartan Heart Failure Trial
VEST[64]	VESnarinone Trial
V-HeFT II[3]	Veterans Adminstration Cooperative Vasodilator-Heart Failure Trial II
V-HeFT III[15]	Veterans Adminstration Cooperative Vasodilator-Heart Failure Trial III
WARCEF[51]	Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction
WATCH[66]	Warfarin/Aspirin Study in Heart Failure
Xalmeterol-HF[1]	Xamoterol in severe heart failure

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