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# Evaluation of the causes of sex disparity in heart failure trials

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## ABSTRACT

**Objectives** Cardiovascular disease is one of the leading causes of mortality and morbidity in women. Despite this, even in contemporary research, female patients are poorly represented in trials. This study aimed to explore reasons behind the sex disparity in heart failure (HF) trials.

**Methods** HF trials published in seven high-impact clinical journals (impact factor >20), between 2000 and 2020, were identified. Trials with over 300 participants of both sexes were included. Large HF registries, as well as population statistics, were also identified using the same criteria.

**Results** We identified 146 HF trials, which included 248 620 patients in total. The median proportion of female patients was 25.8%, with the lowest proportions seen in trials enrolling patients with ischaemic cardiomyopathy (17.9%), severe systolic dysfunction (left ventricular ejection fraction (LVEF) <35%) (21.4%) and those involving an invasive procedure (21.1%). The highest proportion of women was seen in trials assessing HF with preserved LVEF (51.6%), as well as trials including older participants (40.5%). Significant differences were seen between prevalence of female trial participants and population prevalence in all LVEF categories (25.8% vs 49.0%,  $p < 0.01$ ).

**Conclusions** A significant sex disparity was identified in HF trials, most visible in trials assessing patients with severely reduced LVEF and ischaemic aetiology. This is likely due to a complex interplay between enrolment bias and biological variation. Furthermore, the degree of both these aspects may vary according to trial type. Going forward, we should encourage all HF trials to appraise their recruitment log and suggest reasons for any reported sex disparity.

according to diagnosis.<sup>5 6</sup> A review of 740 CV trials found that women accounted for only 29% in HF, which, after adjustment for population prevalence, accounted for the lowest representation compared with all other CV pathologies.<sup>5</sup> In a systematic review of 317 trials investigating HF with reduced ejection fraction (HFrEF), 25.5% of participants were woman, with sex-related eligibility criteria, recruitment in ambulatory settings and male chief investigators all being associated with underenrolment of women.<sup>6</sup> Furthermore, while women are now equally represented in hypertension trials, the sex distribution in HF trials has been found to be static over a 30-year period.<sup>5 7</sup>

As such, policies and programmes have been introduced in an attempt to address this, on the assumption that this reflects selection bias.<sup>8 9</sup> Several journals have released statements prompting investigators that women should be routinely included in trials and that sex-specific analyses should be reported.<sup>10</sup> However, this assertion has not been directly assessed before and an alternative explanation may be that sex-specific differences may lead to different HF phenotypes in men and women. The aim of our study was to explore the relative impact of these factors on differential proportions of women being enrolled in HF trials. In brief, we compared proportions of patients in clinical trials, registries and population data as an indicator of enrolment bias and compared prevalence of women by aetiology and disease characteristics as an indicator of biological variation between men and women.

## METHODS

HF trials published in high-impact general medical or CV journals between 2000 and 2020 were identified using the search terms 'heart failure' (MeSH Major Topic) AND 'clinical trial' (Filter). Trials were included if they met the following criteria: published in the English language, >300 participants enrolled, both sexes enrolled and sexes of participants reported. In the case of serial publications, only the headline trial paper was included, with articles reporting post hoc or subgroup analyses excluded. The prevalence of female participants, trial design, study population as well as inclusion and exclusion criteria were recorded. Indicative journals were selected by an impact factor >20 (in 2021) and included four of the most widely read general medical journals (*New England Journal of Medicine*, *The Lancet*, *The British Medical Journal*,

## INTRODUCTION

Cardiovascular (CV) disease is the leading cause of mortality in women, accounting for 43%–49% of all deaths.<sup>1</sup> Within CV disease, heart failure (HF) is the only category for which the incidence, prevalence, hospitalisation rate and mortality continues to rise, attributed to the increasing burden of CV risk factors as well as improved survival from acute myocardial infarction.<sup>1 2</sup> However, patients enrolled in CV clinical trials have been predominantly male, which contrasts with much more balanced proportions encountered in clinical practice and population statistics.<sup>3 4</sup> Certainly, while female representation in CV trials has more than doubled in the last 40 years, this varies significantly



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*Journal of the American Medical Association*) and three specialist CV journals (*European Heart Journal*, *Journal of the American College of Cardiology*, *Circulation*).

Trials were subdivided into different clinically relevant criteria, including diagnostic investigations leading to recruitment, HF aetiology and left ventricular ejection fraction (LVEF).

HF registries were identified using a PubMed search encompassing the same terms in the above journals (online supplemental material). Population statistics were derived from publications in the same journals, which reported national healthcare datasets and primary and secondary care electronic healthcare records (online supplemental material). Ethical approval was not required as this is a retrospective analysis of published data.

Statistical analysis was performed using SPSS software (V.24.0; IBM Corp). Normally distributed data are expressed as mean and compared using the Student's t-test. Non-normal data are expressed as median (IQR) and compared using the Mann-Whitney U test. Study level prevalence data by sex was extracted from each trial; medians for each LVEF/aetiology subcategory were then calculated. All p values are two-sided with a significance threshold of  $p < 0.05$ .

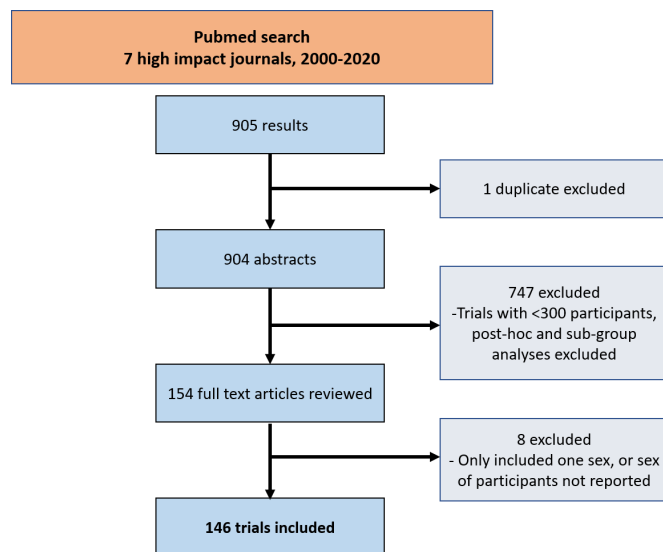
### Patient and public involvement

The initial motivation behind this work came from a Trial Steering Committee meeting for the ongoing trial REVIVED-BCIS2, which includes two patient representatives. It had been identified that very few female patients had been enrolled and the potential reasons behind this, as well as possible actions to address the issue, including this work, were discussed at length.

### RESULTS

The PubMed search yielded 905 trials, which were further screened as above (figure 1) and resulted in 146 randomised controlled trials (RCTs) being included in our analysis (table 1). This encompassed 238 813 patients. The overall proportion of women in RCTs was 25.8% (21.3%–36.0%) (figure 2).

Nineteen registries were identified, encompassing 583 742 patients (online supplemental table 2). The female prevalence in RCTs was markedly lower than that in registries (26% vs 40%,  $p < 0.01$ ) (figure 3). Significant differences were also seen



**Figure 1** Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram. Outline of inclusion and exclusion pathway.

**Table 1** Summary of trials, by design characteristics

Trial subtype	No of patients			Age
	Trials		Female proportion	
Invasive procedure/surgery	13	6852	21.1 (19.9–25.3)	64.7 (60.5–69.8)
Device trials	30	26328	23.6 (19.4–27.4)	64.9 (63.5–66.4)
Drug trials	79	180080	26.9 (21.9–40.1)	66.3 (62.8–70)
Outpatient care	18	19589	29.7 (22.8–41.7)	66.3 (63.6–70.9)
Diagnostic trials	10	7384	39.4 (32.6–48.8)	74 (63.1–77)
Older participants	5	4449	40.5 (37.0–55.1)	76 (76–76.5)
All invasive/procedural*	40	30680	23.3 (18.2–26.8)	64.9 (62.8–66.8)
All non-invasive	106	208133	28.8 (22–40.5)	66.3 (63–70)
All trials	146	238813	25.8 (21.3–36.0)	66 (63–69.5)

Age shown as median (IQR). Note some trials fit into more than one category, for example, device and outpatient care; medication and older participant. Invasive procedure—including percutaneous coronary intervention, intra-aortic balloon pump, impella, mitralclip, ablation trials. Outpatient care—for example, remote monitoring, outpatient HF follow up and education trials. Diagnosis—for example, early use of BNP, use of HF risk scores on admission, care bundle trials. Older participants—minimum age 45 (1 trial), 60 (1 trial), 70 (2 trials) and 75 (1 trial).  
\*Including any invasive coronary, valvular, surgical or device insertion procedure.  
BNP, B-type natriuretic peptide; HF, heart failure.

between prevalence of female trial participants and population prevalence (table 2). Of the different classifications of HF, the largest difference in sex-based representation was in all-comer HF trials (RCTs vs registries 8.4%,  $p = 0.08$ ; RCTs vs population 13.6%,  $p < 0.01$ ) (table 2).

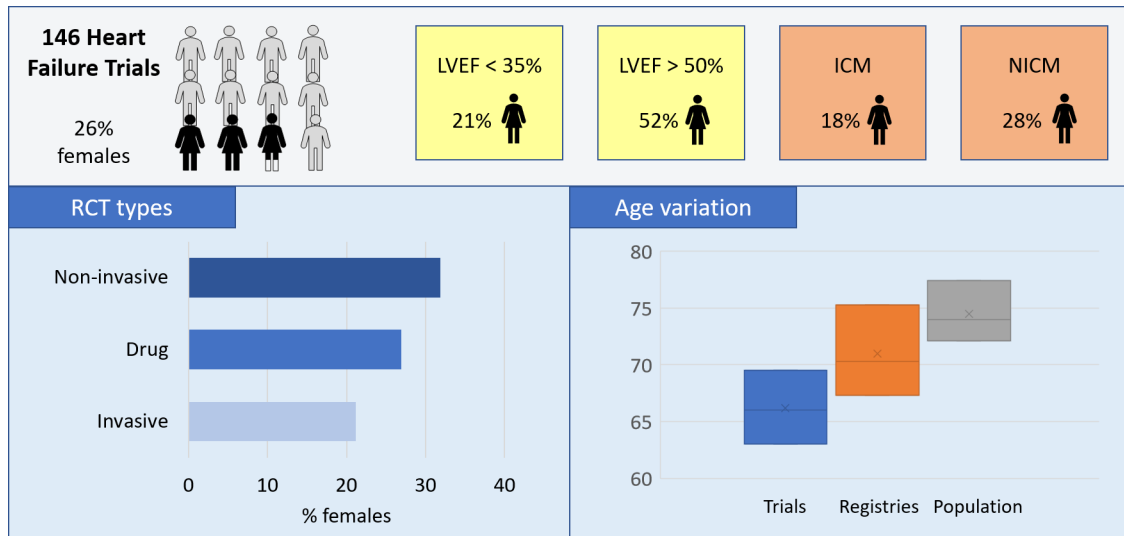
Trial populations had a lower median age compared with registries and population statistics (RCTs 66 years (63–69.5), registries 70.3 years (67.3–75.3), population 74 years (72.1–77.4)) (figure 2).

The lowest proportion of women was seen in trials exclusively enrolling patients with ischaemic cardiomyopathy (ICM vs NICM: 17.9% (11.7%–21.2%) vs 27.5% (25.8%–29.4%);  $p < 0.01$ , online supplemental table 4) and with severe LV systolic dysfunction (LVEF  $< 35\%$ ) only (table 2). The highest proportion of women was seen in trials recruiting patients with HF with preserved ejection fraction (HFpEF) (figure 4), as well as trials assessing only older patients (table 1).

Trials involving an invasive procedure or surgical treatment had the lowest prevalence of women (cumulative prevalence 21.2%, figure 2). Conversely, there was a higher proportion of women in studies investigating HF presentation including the use of risk scores (39.4%); these trials also had a higher median age (table 1).

Multiple trials reported outcomes by participant sex; two trials from either end of the female proportion spectrum are shown (online supplemental table 5). In all sex-specific analyses, women were older and had lower rates of smoking. Furthermore, some trials were identified to have an upper age limit, including GALATIC-HF, SCD-HEFT, PROTECT-2 and IABP-SHOCK-2. It was also identified that STICH and PARR-2 excluded women of childbearing age.

Among the registries that reported at least one sex-specific outcome ( $n = 16$ ), four did not find differences between sexes in the use of guideline-directed medical therapy, while four reported lower rates in women. Three registries specifically discussed investigations, one reporting lower use of echocardiography in women, one reporting lower use of coronary angiography and one reporting lower use of all procedure-orientated therapy (including angiography, percutaneous coronary intervention, haemodynamic support, coronary artery bypass



**Figure 2** Across all trials, the median proportion of women was 26%, with the lowest proportions seen in trials assessing patients with severely impaired left ventricular function and ischaemic cardiomyopathy. ICM, ischaemic cardiomyopathy; LVEF, left ventricular ejection fraction; NICM, non-ischaemic cardiomyopathy; non-invasive, outpatient care and diagnostic trials; RCTs, randomised controlled trials.

grafting and device implantation). Female patients were less likely to receive an implantable device, even after controlling for LVEF in two registries. Three registries reported that female patients were less likely to be followed up in specialised services. Five reported sex-specific mortality outcomes; three reported no significant differences (OPTIMIZE-HF, ADHERE-HFpEF, REPORT-HF) and two reported women had a higher mortality rate (ESC-HF-LT, GARFIELD-AF).

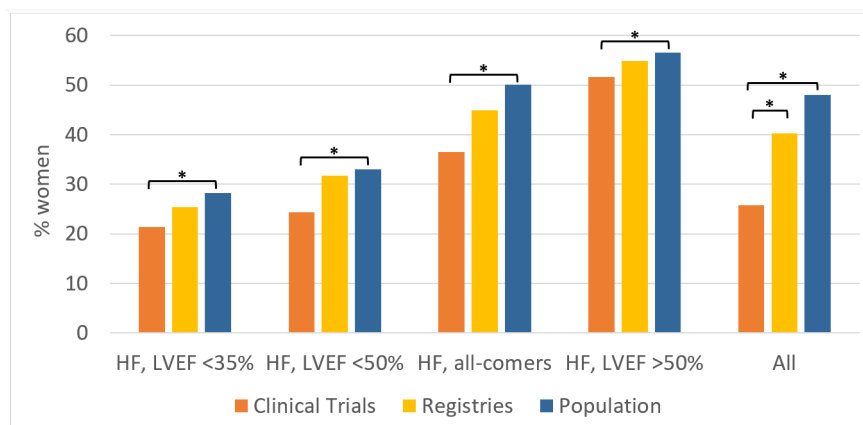
## DISCUSSION

We have found a major disparity in sex representation in HF trials, with a median female proportion of 26% across 146 randomised control trials. The novel findings of this study are: (1) a negative correlation between the proportion of women recruited and the degree of LV systolic dysfunction, with women less frequently recruited into HFrEF than HEpEF trials and (2) variation in proportion of women enrolled by HF aetiology, being least often represented in ischaemic cardiomyopathy; (3) marked variation in the proportions of women included in trials compared with registries or population series.

Although other authors have previously reported a sex disparity in individual HF trials and meta-analyses, an appraisal of the underlying reasons behind this has been missing. Furthermore, previous reports have regarded HF trials as a single entity, but as we have shown, HF is a broad description that encompasses heterogeneous conditions, each of which may be affected differentially by enrolment bias (encompassing physician-related selection bias and patient-related participation bias) and biological variation. The findings of our study show that the relative contribution of each determinant varies with the type of condition resulting in HF as well as the nature of the intervention being assessed in each trial. To this extent and the entry criteria into these trials are equally varied; therefore, there is a significant disparity in the types of patients that are recruited into these studies.

### Sex disparity in ICM

Trials for patients with ICM have the highest sex disparity, with only 26% of the participants being women. Furthermore, among trial of ICM itself, those designed to evaluate an invasive



**Figure 3** Female representation in research. Proportion of women in trials, registries and the population. HF, heart failure; LVEF, left ventricular ejection fraction.

**Table 2** Proportion of women in trials, registries and population statistics (median (IQR))

	Trial	Registries	Population	P value (trials to registries)	P value (trials to population)
HF, LVEF <35%	21.4 (17.7–25.7)	25.4 (23.7–27.2)	28.2 (26.0–30.4)	0.21	0.02
HF, LVEF <50%	24.3 (21.7–32.0)	31.7 (31.2–37.0)	33 (29.0–40.0)	0.14	0.03
All HF (no LVEF specified)	36.5 (29.2–47.2)	44.9 (33.9–52.8)	50.1 (48.0–51.8)	0.08	<0.01
HF, LVEF >50%	51.6 (48.6–52.0)	54.8 (50.8–61.0)	56.5 (52.2–64.8)	0.15	0.01
All	25.8 (21.3–36.0)	40.2 (32.3–52.8)	49.0 (38.2–53.4)	<0.01	<0.01

HF, heart failure; LVEF, left ventricular ejection fraction.

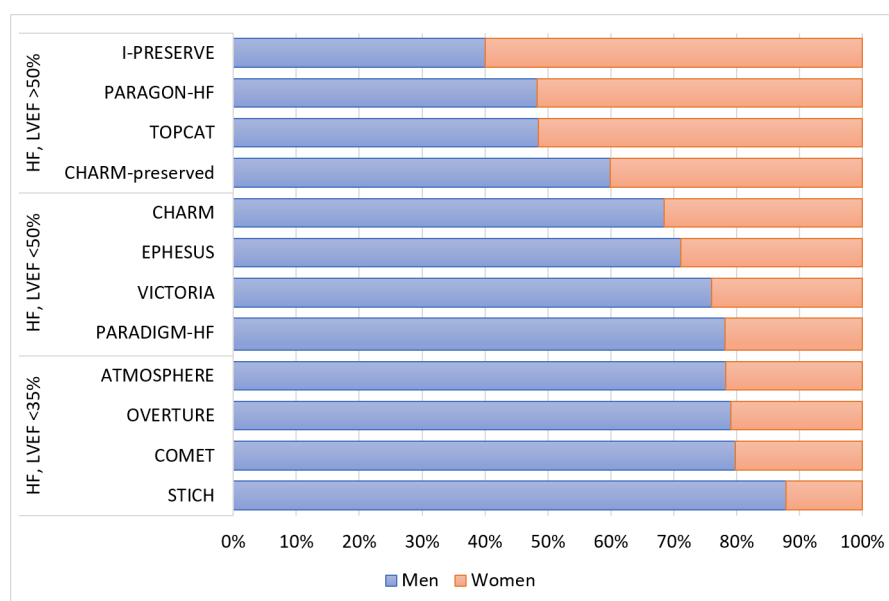
treatment (such as coronary artery bypass surgery) have the lowest prevalence of women. It has been previously reported that female patients are more likely to prefer lifestyle-based interventions as opposed to procedure-based interventions,<sup>5</sup> representing patient-related bias. Sex-based diagnostic and therapeutic biases have previously been demonstrated in clinical practice.<sup>11</sup> We identified that even after hospitalisation, female patients are less likely to be followed up in specialised cardiac services.<sup>12 13</sup> This may result in fewer opportunities for consideration of entering these patients into clinical trials.

While these represent enrolment bias, there is evidence to suggest that biological variation may also play a significant role in accounting for the sex disparity in ICM trials. Women have smaller epicardial coronary artery diameter, and yet, similar coronary flow reserve compared with men; this is achieved by higher baseline and hyperaemic coronary blood flow.<sup>14</sup> This has been hypothesised to reduce lipid accumulation and delay development of coronary plaques through enhanced wall shear stress.<sup>12</sup> Women, when presenting with an acute coronary syndrome, are less likely to have extensive coronary disease or functionally significant coronary artery stenoses<sup>15 16</sup>; therefore, making them less likely to develop ICM. Furthermore, oestradiol has been hypothesised to play a crucial role in preventing, or delaying the onset of, obstructive coronary artery disease in women. There is evidence that oestrogen increases myocyte resistance to ischaemia, with rodent studies finding superior post-ischaemic recovery of LV function and reduced infarct size

in female rats, hypothesised to occur via oestrogen-mediated protein kinase C signalling.<sup>17</sup> Indeed, in an HF registry of 9428 patients with HF, ischaemic heart disease was the aetiology in 49% of men and 28% of women<sup>18</sup>; this very closely mirrors our findings of 26% female prevalence in ICM trials. These provide a case in support for biological variation playing a significant contributory role in the sex disparity in trials investigating patients with ICM.

### Sex disparity in HFrEF versus HFpEF trials

After ICM, trials recruiting only patients with HFrEF have the highest sex disparity. Studies have consistently reported that women with HF have a higher mean LVEF, which may put them beyond the threshold for trial recruitment in HFrEF trials. They may also not tolerate target HF medication doses. The PARADIGM-HF inclusion criteria included LVEF  $\leq$ 35%, raised natriuretic peptide plasma concentration, a systolic blood pressure  $\geq$ 95 mm Hg, estimated glomerular filtration rate  $\geq$ 30 mL/min and a tolerated period of enalapril 20 mg daily (or equivalent). Norberg *et al*<sup>19</sup> applied these inclusion criteria to their real-life patient cohort and found that only 16% of their female patients would have been eligible to partake in the study, largely due to female patients not meeting target medication doses. Other work has identified that lower doses of prognostic medications are required in female patients to achieve similar benefits<sup>20 21</sup>; therefore, suitable female patients may be excluded.



**Figure 4** Sex prevalence in HF trials. Male and female prevalence in different HF trial categories; largest four trials from each subgroup shown. HF, heart failure; LVEF, left ventricular ejection fraction; trial acronyms\*: I-PRESERVE, PARAGON-HF, TOPCAT, CHARM-preserved, CHARM, EPHEBUS, Victoria, PARADIGM-HF, ATMOSPHERE, OVERTURE, comet, STICH, \*see online supplemental material.

This represents physician-related enrolment bias but also highlights the potential for oversight in trial design.

On the contrary, women are more susceptible to certain coronary vasomotor disorders due to sex-specific risk factors, such as systemic inflammation and endocrine changes. Oestradiol is generally protective against inflammation and reduced oestrogen levels post-menopause are associated with altered vascular function, heightened systemic inflammation and upregulation of the renin-angiotensin-aldosterone and sympathetic nervous systems.<sup>22</sup> These have all been implicated in the pathogenesis of HFpEF and serve as the reasons for why women may be biologically more likely to develop HFpEF than HFrEF.<sup>23</sup>

## Influence of patient and physician on likelihood of enrolment

### Patient-related enrolment bias

It has been demonstrated that women perceive higher personal harm from involvement in research and have been found to be less willing to partake in trials than their male counterparts.<sup>24</sup> This has been hypothesised to be related to cultural differences, greater childcare responsibilities and even related to the sex of researchers recruiting patients.<sup>5 25 26</sup>

### Physician-related enrolment bias

RCTs included a younger population than registries, and both RCTs and registries had a lower median age when compared with population statistics. Older patients are under-represented in trials,<sup>5</sup> with RCT patient cohorts being consistently younger compared with registry populations.<sup>27</sup> As female patients presenting with HF are more likely to have significant comorbidities and be of older age, they are more likely to meet exclusion criteria in such trials.<sup>6 27 28</sup> As identified here, some trials set an upper age limit or excluded women of childbearing age, both of which would disproportionately impact recruitment of female patients.<sup>6</sup> Other work has found that higher numbers of women are excluded during trial screening.<sup>7</sup> Van Spall *et al*<sup>27</sup> reported that common medical conditions and older age were the reason for trial exclusion in 81.3% and 38.5% of trials, respectively.

### Putting our findings into wider context

The sex disparity in HF trials may have implications on the management of female patients with HF. The majority of evidence-based pharmacotherapy, device and intervention strategies in HF management are currently based on populations comprised largely of male patients. Therefore, if the women are truly under-represented, then this represents a significant void that needs to be urgently addressed. However, and as is clearly evidenced by the arguments pertaining to biological variations between the sexes, we must be cautious when trying to achieve preconceived parity in sex representation in HF trials. There is certainly growing evidence that biological variation plays a significant role in the sex disparity seen in certain HF trials. It is probable that the interplay between enrolment bias and biological variation is complex and varies according to each study; for example, in trials enrolling patients with ICM, it may be that biological variation plays a more dominant role, while enrolment bias may play a dominant role in trials mandating invasive procedures before recruitment. Rather than striving to always achieve 50% female representation, researchers should make efforts to ascertain population prevalence, which in turn should influence trial design and eligibility criteria on the one hand and equitable recruitment strategies on the other hand. In this context, true equality may be best served by ensuring that every eligible patient has the same chance of being included in the appropriate

trial and initiatives, such as 'WIN-her', by *Boston Scientific* may go some way to achieving this.

## Limitations

The limitations of this study include that it is a retrospective analysis of published work, and therefore, reasons for individual patient exclusion cannot be explored in detail. Furthermore, we were unable to compare characteristics between men and women within trial cohorts unless this was reported by the original authors. Ideally, trial and registry recruitment would be followed prospectively and this should be an area for future work.

## CONCLUSIONS

Sex disparity exists in HF trials and across all subgroups, but most visible in trials assessing patients with severely reduced LVEF and ICM. This is likely due to a complex interplay between enrolment bias and biological variation. Furthermore, the degree of enrolment bias and biological variation may vary according to the study type. Going forward, we should encourage all trials recruiting patient with HF to appraise their recruitment log and suggest reasons for any reported sex-specific disparity.

## Key messages

### What is already known on this subject?

⇒ Female participation in cardiovascular clinical trials has consistently been lower than that of men. Compared with all other cardiovascular pathologies, this is most marked in heart failure (HF) trials. Although this sex disparity in HF research has been previously reported, reasons for this remain unclear, and until they are identified we cannot effectively address this issue.

### What might this study add?

⇒ This study identified a significant sex disparity in HF trials, with a negative correlation between the proportion of women recruited and the degree of left ventricular systolic dysfunction, with women less likely to be recruited into HF with reduced ejection fraction than HF with preserved ejection fraction trials and furthermore significant variation by HF aetiology with women less likely to be represented in ischaemic cardiomyopathy. While differential biology may account for some of the disparity, enrolment bias is also an important contributing factor, which must be addressed.

### How might this impact on clinical practice?

⇒ Given the sex disparity in HF trials, it may be argued that the guideline recommendations, based on the aforementioned trials, may not necessarily be generalisable to female patients with HF. In this work, we have described a number of recommendations for future HF research. Clinicians must be aware of unconscious biases in their management and investigation of female HF patients. Trial paperwork and design should encourage and support female participation. Inclusion and exclusion criteria should be reviewed to ensure female patients are not unwittingly penalised. There must be clear documentation of those screened but excluded, with consideration of simultaneous registries.

**Contributors** HM conceived the idea, conducted the search, analysed the results and drafted the manuscript. AS conducted the search, repeated all analyses and drafted the manuscript. MM and SMH supervised the work, reviewed and edited

the manuscript. DP conceived the idea, reviewed and edited the manuscript and is responsible for the overall content as the guarantor.

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**Patient and public involvement** Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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#### REFERENCES

- Virani SS, Alonso A, Aparicio HJ, et al. Heart disease and stroke Statistics-2021 update: a report from the American heart association. *Circulation* 2021;143:e254–743.
- Gheorghiadu M, Sopko G, De Luca L, et al. Navigating the crossroads of coronary artery disease and heart failure. *Circulation* 2006;114:1202–13.
- Foundation BH. Heart & Circulatory Disease Statistics 2021 BHF: Heart statistics publications, 2021. Available: <https://www.bhf.org.uk/what-we-do/our-research/heart-statistics/heart-statistics-publications>
- Galvao M, Kalman J, DeMarco T, et al. Gender differences in in-hospital management and outcomes in patients with decompensated heart failure: analysis from the acute decompensated heart failure national registry (adhere). *J Card Fail* 2006;12:100–7.
- Jin X, Chandramouli C, Allocco B, et al. Women's participation in cardiovascular clinical trials from 2010 to 2017. *Circulation* 2020;141:540–8.
- Whitelaw S, Sullivan K, Eliya Y, et al. Trial characteristics associated with under-enrolment of females in randomized controlled trials of heart failure with reduced ejection fraction: a systematic review. *Eur J Heart Fail* 2021;23:15–24.
- Scott PE, Unger EF, Jenkins MR, et al. Participation of Women in Clinical Trials Supporting FDA Approval of Cardiovascular Drugs. *J Am Coll Cardiol* 2018;71:1960–9.
- Ovseiko PV, Greenhalgh T, Adam P, et al. A global call for action to include gender in research impact assessment. *Health Res Policy Syst* 2016;14:50.
- Freedman LS, Simon R, Foulkes MA, et al. Inclusion of women and minorities in clinical trials and the NIH Revitalization Act of 1993--the perspective of NIH clinical trialists. *Control Clin Trials* 1995;16:277–85.
- Peters SAE, Woodward M, Jha V, et al. Women's health: a new global agenda. *BMJ Glob Health* 2016;1:e000080.
- Nguyen JT, Berger AK, Duval S, et al. Gender disparity in cardiac procedures and medication use for acute myocardial infarction. *Am Heart J* 2008;155:862–8.
- Haider A, Bengs S, Luu J, et al. Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome. *Eur Heart J* 2020;41:1328–36.
- Ghare MI, Chandrasekhar J, Mehran R, et al. Sex Disparities in Cardiovascular Device Evaluations: Strategies for Recruitment and Retention of Female Patients in Clinical Device Trials. *JACC Cardiovasc Interv* 2019;12:301–8.
- Lansky AJ, Ng VG, Maehara A, et al. Gender and the extent of coronary atherosclerosis, plaque composition, and clinical outcomes in acute coronary syndromes. *JACC Cardiovasc Imaging* 2012;5:S62–72.
- Mendes LA, Davidoff R, Cupples LA, et al. Congestive heart failure in patients with coronary artery disease: the gender paradox. *Am Heart J* 1997;134:207–12.
- Zandeck L, Janion-Sadowska A, Kurzawska J, et al. Clinical presentation and 3-year outcomes of patients with acute coronary syndromes and non-obstructive coronary arteries on angiography. *PLoS One* 2020;15:e0234735.
- Bae S, Zhang L. Gender differences in cardioprotection against ischemia/reperfusion injury in adult rat hearts: focus on Akt and protein kinase C signaling. *J Pharmacol Exp Ther* 2005;315:1125–35.
- Lainščak M, Milinković I, Polovina M, et al. Sex- and age-related differences in the management and outcomes of chronic heart failure: an analysis of patients from the ESC HFA EORP heart failure long-term registry. *Eur J Heart Fail* 2020;22:92–102.
- Norberg H, Bergdahl E, Lindmark K. Eligibility of sacubitril-valsartan in a real-world heart failure population: a community-based single-centre study. *ESC Heart Fail* 2018;5:337–43.
- Sullivan K, Doumouras BS, Santema BT, et al. Sex-Specific differences in heart failure: pathophysiology, risk factors, management, and outcomes. *Can J Cardiol* 2021;37:560–71.
- Tamargo J, Rosano G, Walther T, et al. Gender differences in the effects of cardiovascular drugs. *Eur Heart J Cardiovasc Pharmacother* 2017;3:163–82.
- Klein SL, Flanagan KL. Sex differences in immune responses. *Nat Rev Immunol* 2016;16:626–38.
- Sinha A, Rahman H, Webb A, et al. Untangling the pathophysiologic link between coronary microvascular dysfunction and heart failure with preserved ejection fraction. *Eur Heart J* 2021;42:4431–41.
- Ding EL, Powe NR, Manson JE, et al. Sex differences in perceived risks, distrust, and willingness to participate in clinical trials: a randomized study of cardiovascular prevention trials. *Arch Intern Med* 2007;167:905–12.
- Reza N, Tahhan AS, Mahmud N, et al. Representation of women authors in international heart failure guidelines and contemporary clinical trials. *Circ Heart Fail* 2020;13:e006605.
- Lau ES, Hayes SN, Volgman AS, et al. Does patient-physician gender concordance influence patient perceptions or outcomes? *J Am Coll Cardiol* 2021;77:1135–8.
- Van Spall HGC, Toren A, Kiss A, et al. Eligibility criteria of randomized controlled trials published in high-impact general medical journals: a systematic sampling review. *JAMA* 2007;297:1233–40.
- McMurray JJV, Jackson AM, Lam CSP, et al. Effects of Sacubitril-Valsartan versus valsartan in women compared with men with heart failure and preserved ejection fraction: insights from PARAGON-HF. *Circulation* 2020;141:338–51.

## **SUPPLEMENTAL MATERIAL**

### **An Evaluation of the Causes of Sex Disparity in Heart Failure Trials**

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**Supplementary Table 1: Full Trial List**

Trial	Total no	Females	%	Age	Journal	Year	Notes	Sub-type
SERVE-HF	1325	127	9.6	69.5	NEJM	2015	CPAP, lvef<45%	2
CHART-1	315	32	10.2	61.9	EHJ	2017	ICM, stem cells	1,10 Y
CHRISTMAS	305	31	10.2	62.5	Lancet	2003	Carvediolol, ICM	2,11
STICH	1212	148	12.2	59.5	NEJM	2011	CABG	1,9,10 Y
BeAT-HF	408	53	13.0	62	JACC	2020	Baroreflex, LVEF <35	1,9 Y
MUSTT	2202	301	13.7	66.5	NEJM	2000	ICD	2,6 Y
ESSENTIAL II	950	133	14.0	62	EHJ	2009	Enoximone	1,11
REM-HF	1650	231	14.0	69.5	EHJ	2017	Remote monitoring	1,8
DOT-HF	335	47	14.0	64	Circ	2011	Implanted monitor	1,6 Y
CASTLE-AF	363	52	14.3	64	NEJM	2018	AF ablation	1,9 Y
WATCH	1587	234	14.7	63	Circ	2009	Warfarin/sapt, ef<35%	1,11
DAVID II	600	90	15.0	63.5	JACC	2009	Pacing	2,6 Y
MADIT-II	1232	192	15.6	64.5	NEJM	2002	LVEF <30	1,6 Y
PARR-2	430	67	15.6	63.5	JACC	2007	PET imaging	1,7,10
SENSE-HF	501	79	15.8	65	EHJ	2011	fluid monitor device	1,6 Y
EVITA	400	68	17.0	55	EHJ	2017	Vitamin D	1,11
RAFT	1798	308	17.1	66.2	NEJM	2010	ICD v CRT, LVEF <30%	1,6 Y
EARTH	642	113	17.6	60.3	Lancet	2004	Darusentan	1,11
AF-CHF	1376	248	18.0	67	NEJM	2008	AF in CCF, LVEF 27	1,11
Higgins et al	490	91	18.6	66	JACC	2003	CRT	1,6 Y
IN-TIME	664	128	19.3	65.5	Lancet	2014	Device monitoring	1,6,8
ACCLAIM	2408	476	19.8	64.3	Lancet	2008	IMT	1,8
MOMENTUM-3	366	73	19.9	59.5	NEJM	2018	LVAD	1,6,9 Y
VAL-HEFT	5010	1005	20.1	62.7	NEJM	2001	Valsartan	2,11
MACH-1	2590	521	20.1	62.8	Circ	2000	Mibefradil	1,11
PROTECT-2	452	91	20.1	67.5	Circ	2012	Impella/IABP	1,9,10 Y



WARCEF	2305	465	20.2	61	NEJM	2012	Warfarin v aspirin	1,11
COMET	3029	612	20.2	62	Lancet	2003	Carvedilol/metoprolol	1,11
OPTILINK-HF	1002	203	20.3	66.3	EHJ	2016	Fluid monitoring	1,8
MORE-CRT MPP	467	95	20.3	79.7	EHJ	2019	CRT	2,6 Y
ARTS-HF	458	94	20.5	71.3	EHJ	2013	Finerenone	2,11
COPERNICUS	2289	470	20.5	63.4	NEJM	2001	Carvedilol	1,11
BCIS-1	301	62	20.6	71	JAMA	2010	IABP	1,9,10 Y
REVERSE	610	128	21.0	62.5	Circ	2012	CRT, mild LVSD	2,6 Y
OVERTURE	5770	1211	21.0	63.4	Circ	2002	omapatrilat v enalapril	1,11
INOVATE-HF	707	149	21.1	61.4	JACC	2016	Vagus nerve	2,9 Y
OHCS	1193	254	21.3	66	JACC	2011	Atrial arrhythmia device	2,6
IMPRESS	573	122	21.3	64	Lancet	2000	omapatrilat v enalapril	2,11
FIGHT	300	64	21.3	61.5	JAMA	2016	Liraglutide	2,11
MOXCON	1934	420	21.7	64.2	EHJ	2003	ICM 62%, EF 25%	1,11
GISSI-HF	6975	1516	21.7	67	Lancet	2008	Fatty acids	5,11
ATMOSPHERE	7016	1525	21.7	63.3	NEJM	2016	Aliskiren	1,11
ENDURANCE	446	97	21.7	64.7	NEJM	2017	Lvad	1,6,9 Y
PARADIGM-HF	8399	1832	21.8	63.8	NEJM	2014	Entresto	2,11
BEST	2708	593	21.9	60	NEJM	2001	BB in EF<35	1,11
RENEWAL	2048	450	22.0	64.1	Circ	2004	Etanercept, EF<30	1,11
OPT-CHF	405	89	22.0	64.5	JACC	2008	Oxypurinol	2,11
EMPHASIS-HF	2737	610	22.3	68.6	NEJM	2011	Empagliflozin	1,11
TEN-HMS	426	97	22.8	67.2	JACC	2005	Tele monitoring	2,8
ASTRONAUT	1615	368	22.8	64.6	EHJ	2013	Aliskiren	2,11
COMMANDER HF	5022	1150	22.9	66.4	NEJM	2018	Rivaroxaban	2,10,11
ATOMIC-AHF	613	141	23.0	66	JACC	2016	Omecamtiv, LVEF<40	2,11
NorthStar	921	212	23.0	69	EHJ	2013	Long-term FU	2,8
MIRACLE-ICD	369	86	23.3	67.1	JAMA	2003	CRT	1,6 Y

SCD-HeFT	2521	588	23.3	60	NEJM	2005	Amiodarone v ICD	1,6 Y
DAPA-HF	4744	1109	23.4	66.3	NEJM	2019	Dapagliflozin	2,11
ARTS-HF	1066	250	23.5	71.2	EHJ	2016	Finerenone	2,11
CORONA	5011	1180	23.5	Not reported	JACC	2009	Rosuvastatin	5,11
MOOD-HF	372	89	23.9	62	JAMA	2016	Escitalopram	2,11
EMPEROR-reduced	3730	893	23.9	66.8	NEJM	2020	Empagliflozin	2,11
HeartMate II	309	74	23.9	54	Circ	2009	LVAD	1,6 Y
Cvlprit shock	646	155	24.0	70	NEJM	2017	Cardiogenic shock	5,9 Y
VICTORIA	5050	1212	24.0	67	NEJM	2020	Vericiguat	2,11
SHIFT	6558	1574	24.0	60.4	Lancet	2010	Ivabradine	1,11
RELEVANT	324	78	24.1	64.2	EHJ	2009	CRT, NICM	1,6,12 Y
Qili Qiangxin HF	491	121	24.6	57.3	JACC	2013	Qili Qiangxin	2,11
DAVID	506	125	24.7	65	JAMA	2002	Dual chamber v ICD	2,6 Y
ANDROMEDA	627	155	24.7	71.5	NEJM	2008	Dronedarone	1,11
MADIT CRT	1820	453	24.9	64.5	NEJM	2009	CRT	1,6 Y
SUPPORT	1147	287	25.0	66	EHJ	2015	Olmesartan	5,11
BLOCK-HF	691	174	25.2	73.4	NEJM	2013	CRT	2,6
MITRA-FR	304	77	25.3	36% >75	NEJM	2018	Mitraclip	2,9
EVEREST	4133	1058	25.6	65.8	JAMA	2007	Tolvaptan	2,11
ESSENTIAL I	900	234	26.0	62	EHJ	2009	Enoximone	1,11
ESCAPE	433	113	26.1	56	JAMA	2005	RH catheterisation	1,9 Y
CARE-HF	813	216	26.6	66.5	NEJM	2005	CRT	1,6 Y
ROSE-AHF	360	97	26.9	70	JAMA	2013	Dopamine/Nesiritide	5,11
EchoCRT	809	221	27.3	58	NEJM	2013	CRT in narrow QRS	1,6 Y
CHAMPION	550	151	27.5	61.5	Lancet	2011	Implantable monitor	5,6,8 Y
DANISH	1116	307	27.5	63.5	NEJM	2016	ICD in NICM	1,6,12 Y
TRUST	1339	370	27.6	63.5	Circ	2010	OP ICD	1,6
DOSE	308	86	27.9	66	NEJM	2011	diuretics	5,11

PIONEER-HF	881	246	27.9	61	NEJM	2019	Entresto	2,11
SURVIVE	1327	371	28.0	66.5	JAMA	2007	Levo v Dobutamine	1,11
HF-action	2331	653	28.0	59	JAMA	2009	Exercise	1
OPTIME-CHF	949	272	28.7	65.5	JAMA	2002	Milrinone	5,11
EPHESUS	6632	1918	28.9	64	NEJM	2003	Eplerenone	2,11
South Texas CHF Disease	1069	310	29.0	70.9	Circ	2004	Disease mx	5,8
DIAL	1518	444	29.2	65	BMJ	2005	OP telephone FU	5,8
ACTIV CHF	319	95	29.8	62	JAMA	2004	Tolvaptan	2,11
HEAAL	3834	1143	29.8	66	Lancet	2009	Losartan	2,11
WISDOM	525	158	30.1	61.7	JACC	2019	Communication	5,8
ELITE II	3152	977	31.0	71.4	Lancet	2000	Losartan/Captopril	2,11
VMAC	489	152	31.1	61.4	JAMA	2002	Nesiritide v GTN	5,11
RESPOND-CRT	998	311	31.2	67	EHJ	2017	CRT	1,6 Y
IABP Shock 2	600	187	31.2	69.5	NEJM	2012	Cardiogenic shock	5,9 Y
OUTSMART-HF	500	156	31.2	59	Circ	2020	CMR, NICM	5,7,12
CHARM	7599	2400	31.6	66	Lancet	2003	Candesartan	2,11
MIRACLE	453	144	31.9	64.3	NEJM	2002	CRT	1,6 Y
TIM-HF	1571	501	31.9	70	Lancet	2018	Telecommunications	1,8
GUIDE-IT	894	286	32.0	63	JAMA	2017	BNL, LVEF <40	2,7
SMART-AV	980	314	32.0	66	Circ	2010	CRT smart delay	2,6 Y
COMPANION	1520	495	32.6	66.8	NEJM	2004	CRT	1,6 Y
PROTECT	2033	671	33.0	70	JACC	2011	Rolofylline	5,11
DECREASE-HF	306	101	33.0	66.7	Circ	2007	CRT	1,6 Y
ASCEND-HF	7141	2391	33.5	67	NEJM	2011	Nesiritide	5,11
TRUE-AHF	2157	737	34.2	68.5	NEJM	2017	Ularitide	5,11
TIME-CHF	499	172	34.5	76.5	JAMA	2009	Intensive mx, age>60	2,3,7,8
BATTLESCARRED	364	131	36.0	76	JACC	2009	BNP	5,7
COAPT	614	221	36.0	72.2	NEJM	2018	Mitraclip	5,9 Y

GALACTIC	781	288	36.9	78	JAMA	2019	Vasodilators	1,11
SENIORS	2128	787	37.0	76	EIJ	2005	Nebivolol, >70	3,5,11
STAMINA-HeFT	319	118	37.0	69	Circ	2008	Erythropoietin	2,11
RELAX-AHF	1161	436	37.6	72	Lancet	2013	Serelaxin	5,11
BLAST-AHF	621	236	38.0	70	EIJ	2017	TRV027	5,11
CHARM-preserved	3023	1212	40.1	67.2	Lancet	2003	Candesartan	4,11
A-HeFT	1050	421	40.1	56.8	NEJM	2004	ISMN/hydralazine	2,11
RELAX-AHF-2	6545	2637	40.3	73	NEJM	2019	Serelaxin	5,11
VERITAS	1435	580	40.4	70	JAMA	2007	Tezosentan	5,11
SADHART-CHF	469	190	40.5	62.1	JACC	2010	Sertraline	2,3,11
RED-HF	2278	934	41.0	72	NEJM	2013	Erythropoietin	2,11
WHICH? II	787	323	41.0	74	EIJ	2017	Intensive mx	5,8
TELE-HF	1653	694	42.0	61	NEJM	2010	Telemonitoring	5,8
PRIMA	345	148	42.9	72	JACC	2010	BNP target	5,7,8
AFFIRM-AHF	1132	494	43.6	71.1	Lancet	2020	IV iron, ef<50%	2,11
NCT00490958	332	153	46.1	62.8	JACC	2010	Telmisartan dialysis	2,11
CONFIRM-HF	304	141	46.4	69.2	EIJ	2015	IV iron	2,11
IMPACT-HF	363	170	46.8	67	JACC	2004	Carvedilol, EF 25%	2,9,10,11
HART	902	424	47.0	63.6	JAMA	2010	Education, any EF	5,8
ACUTE	1983	951	48.0	81	Circ	2019	Risk score, HFH	5,7
socrates-preserved	477	229	48.0	73	EIJ	2017	Vericiguat	4,11
NCT00378950	605	291	48.1	60.7	Circ	2012	Education	5,8
RUSSLAN	504	244	48.4	67	EIJ	2002	Levosimendan, ICM	5,10,11
VITALITY-HFpEF	789	385	48.8	72.7	JAMA	2020	Vericiguat	4,11
ICON-RELOADED	1461	717	49.1	56.4	NEJM	2018	BNP in acute HF	5,7
TORIC	1377	689	50.0	68.5	EIJ	2002	Torasemide, any EF	5,11
PACT-HF	2494	1258	50.4	77.7	Circ	2019	Discharge care	5,8
PRIMA II	405	207	51.1	77.5	Circ	2018	BNP, acute HF	5,7

TOPCAT	3445	1775	51.5	68.7	NEJM	2014	Spironolactone	4,11
PARAGON-HF	4796	2479	51.7	72.7	NEJM	2019	Entresto	4,11
Aldo-DHF	422	219	51.9	67	JAMA	2013	Spiro, HFpEF	4,11
PANACHE	305	160	52.5	73.6	JAMA	2019	neladenoson bialanate	4,11
FAIR-HF	459	244	53.2	67.7	NEJM	2009	IV iron, LVEF <45	2,11
PEP-CHF	850	468	55.1	76	EHJ	2006	Perindopril in >70s	3,5,11
ELISABETH	503	298	59.2	87	JAMA	2020	ED care bundle, >75	3,5,7
I-PRESERVE	4128	2477	60.0	72	NEJM	2008	Irbesartan HFpEF	4,11

*Subtypes: 1. LVEF<35% 2. LVEF<50% 3. Older age group, 4. HFpEF, 5. HF all comers, 6. Device 7.*

*Diagnostics/scores 8. Outpatient care 9. Invasive procedure/surgery 10. ICM 11. Drug trial 12. NICM.*

*Invasive/procedural: Y.*

**Supplementary Table 2: Registries**

**Search term:** (*heart failure*[MeSH Major Topic]) AND (*registry*[Text Word]) AND ((*"The New England journal of medicine"*[Journal]) OR (*"Lancet (London, England)"*[Journal]) OR (*"British medical journal"*[Journal]) OR (*"JAMA"*[Journal]) OR (*"Journal of the American College of Cardiology"*[Journal]) OR (*"Circulation"*[Journal]) OR (*"European heart journal"*[Journal])) AND (2000:2021[*pdat*])

	No of females	Total patients	Female %	Age	Category	Started	Country
Duke CVD Databank	392	1411	27.8	62	ICM	1969	US
BIOSTAT-CHF	402	1710	23.5	67	HFrEF (<40%)	2010	Europe
IMPROVE-HF	10060	34810	28.9	68.7	HFrEF (<35%)	2007	US
ASIAN-HF	1153	5276	21.9	60.1	HFrEF (<35%)	2012	Asia
	597	1204	49.6	68.5	HFpEF		
CHAMP-HF	807	2588	31.2	68	HFrEF	2016	US
SWEDE-HF	10281	32421	31.7	72.6	HFrEF (<50%)	2003	Sweden
	5260	9640	54.5	77	HFpEF		
ESC-HF-LT	4011	12440	32.2	66.6	HHF/CHF	2015	Europe
ESC-HF pilot	1666	5118	32.6	67.1	AHF/CHF	2014	Europe
DATA-HELP	1489	4253	35.0	69	ICM	2009	Poland
	562	1310	42.9	64.1	NICM		
REPORT-HF	7003	18553	37.7	67	HHF	2015	International
GWTG-HF (by LVEF)	26966	70267	38.4	77.5	HFrEF (<50%)	2005	US
	25423	40354	63.0	78	HFpEF		
ADHERE-HFpEF	10346	25865	40.0	73.9	HFpEF	2001	International
GWTG-HF (by Dx)	41040	92361	44.4	76	ICM	2005	US
	36186	63652	56.8	72	NICM		
GARFIELD-AF	1903	4717	40.3	70.2	ICM	2010	International

	3128	7021	44.6	70.0	NICM		
OPTIMIZE-HF	7444	20118	37.0	70.4	HFrEF (<40%)	2003	US
	6849	10072	68.0	75.6	HFpEF		
ADHERE	54802	105388	52.0	74.2	AHF	2001	International
RICA	2226	4200	53.0	78	HHF	2008	Spain
EAHFE	3273	5845	56.0	79	AHF	2007	Spain
Euro Heart HFpEF	1739	3148	55.0	71	HFpEF	2000	Europe
Total	265,008	583,742	40.2	70.3			

**Supplementary Table 3: Population Statistics**

*(heart failure[MeSH Major Topic]) AND (registry[Text Word]) AND (("The New England journal of medicine"[Journal]) OR ("Lancet (London, England)"[Journal]) OR ("British medical journal"[Journal]) OR ("JAMA"[Journal]) OR ("Journal of the American College of Cardiology"[Journal]) OR ("Circulation"[Journal]) OR ("European heart journal"[Journal])) AND (2000:2021[pdat]). NB: if paper referred to a separate original source, this source was used as the reference.*

Diagnosis	Population studied	Proportions of females	Age	Reference
All HF	UK	All - 49%; HF+IHD - 43%	76.7	Conrad et al Lancet 2017
HFpEF / HFrEF	UK	HFpEF - 71%; HFrEF 41.5%	83	Dulai, Br J Cardiol 2016
HFpEF / HFrEF	Italy	HFpEF - 51%; HFrEF - 30%	77	Iorio EJHF 2018
All HF	UK	All - 36.4%	Not reported for HF alone	BHF Heart Circulatory Disease Statistics 2019
All HF	Minnesota	All - 57%	74	Roger JAMA 2004
HFrEF / HFpEF	Minnesota	HFpEF 64%; HFrEF 42%	76.4	Gerber JAMA 2015
All HF	Italy	All - 51.7%; HFpEF 50.9%, HFrEF 29%; HF+IHD - 40.7%	Not reported; 63% 55-75 years	Piccini C 2017
All HF	US	All - 45%	57	Loehr, AJC 2008
All HF	Portugal	HFpEF 73.3%; HFrEF 28.2%	68.1	Ceia EJHF 2002
All HF	UK	All - 49%	77.8	Lawson, Lancet 2019
All HF	UK	HF+IHD - 42%; HFpEF - 65%; HFrEF - 40%	78	Lee Circ 2009
All HF	US	All - 52%; HFpEF 55.9%; HFrEF - 29%	74	Gottdiener AIM 2002
All HF	Minnesota	HFpEF - 55.7%; HFrEF - 34.6%	73.0	Owan NEJM 2006
All HFH	Denmark	Hfpef - 50%; HFrEF - 33%; HFrEF (<35%) - 24%	71.7	Gustafsson EHJ 2004



All HF	US	HFpEF – 57.1%, HFrEF (<35%) - 32.6%	72.4	Gurwitz 2013 AJM
All HF	UK	All - 51.2%	79.7	Koudstaal EJHF 2017
IHD/ICM	International	HF+IHD - 41.3%	Not reported	Moran 2014 Circ
ICM/NICM	US	NICM - 48%; HF+IHD - 33%	61.6	Bart, JACC 1997
Total			74	

**Supplementary Table 4: Summary of trials and registries; divided by LVEF and aetiology.**

Category	Registries		Trials	
	Number of patients	Female prevalence	Number of patients	Female prevalence
Unspecified LVEF	151544	44.9 [33.9-52.8]	58,101	36.5 [29.2-47.2]
<b>LVEF</b>				
HF, LVEF <35%	40086	25.4 [23.7-27.2]	88,787	21.4 [17.7-25.7]
HF, LVEF <50%	127104	31.7 [31.2-37.0]	84,348	24.3 [21.7-32.0]
HF, LVEF >50%	90283	54.8 [50.8-61.0]	17,385	51.6 [48.6-52.0]
<b>Aetiology</b>				
ICM	102742	37.7 [33.2-41.3]	8541	17.9 [11.7-21.2]
NICM	71983	44.6 [43.8-50.7]	1940	27.5 [25.8-29.4]
<b>Total</b>	<b>583,742</b>	<b>40.2 [32.3-52.8]</b>	<b>238,813</b>	<b>25.8 [21.3-36.0]</b>

**Supplementary Table 5: Trials reporting sex-specific characteristics and outcomes.**

Trial	Females	Age (yrs)	Baseline characteristics	Outcomes
STICH	12%	59.3 (males 63.4)	Women had higher BMI, higher rates of diabetes, hypertension, hyperlipidemia. Lower rates of smoking.	Overall all-cause and CV mortality lower in women. No difference in rates of surgical deaths (despite higher preoperative risk). No significant interaction between sex and treatment group for mortality of CV hospitalisation.
MUSTT	14%	53% women <70y/o (67% of men)	Women were more likely to have a history of HF and recent angina. No differences in LVEF, presence of 3 vessel coronary artery disease, prior coronary artery bypass graft or other revascularization.	On EP testing, Men were more likely to have inducible sustained VT than women. Over a 2 year period, there were no significant differences in risk of arrhythmic death or cardiac arrest (9% v 12% in men) or overall mortality (32% vs 21% in men).
TOPCAT	50%	72.1 (males 71.0)	Women had less <u>coronary artery disease</u> , tobacco use, atrial <u>fibrillation</u> , <u>chronic obstructive pulmonary disease</u> , and diabetes	Compared to men, women demonstrated a significantly greater increase in creatinine at 4 months. In the spironolactone arm, event rates were also numerically lower in women

			mellitus. Women had higher LVEF, blood pressure, BMI but lower eGFR and hemoglobin	than in men, of which the differences in all-cause mortality and non-CV mortality were statistically significant.
PARAGON-HF	52%	73.6 (males 71.8	Women had more obesity, less coronary disease, and lower eGFR and NT-proBNP levels than men. Median lvef 60% in women, 55% in men. Lower rates of smoking.	In the control group women had more HFH and less CV death. Greater reduction in events for women than men (primarily driven by reduction in HFH - 33% relative risk reduction in women versus men). Greater improvement in quality of life scores in men.

*NT-proBNP* : N-terminal pro-B-type natriuretic peptide; *HFH*: heart failure hospitalisation, *eGFR*: estimated glomerular filtration rate

**Trial Acronyms in Figure 4**

I-PRESERVE - Irbesartan in Heart Failure With Preserved Systolic Function

PARAGON-HF - Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Receptor Blocker Global Outcomes in HF with Preserved Ejection Fraction

TOPCAT - Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist

CHARM-preserved - Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity (Clinical Study of Candesartan in Patients With Heart Failure and Preserved Left Ventricular Systolic Function)

CHARM - Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity

EPHESUS - Evaluation of Perceptions, Knowledge and Compliance With tHE Guidelines for Secondary Prevention in Real Life Practice: A Survey on the Under-treatment of hypercholeSterolemia

VICTORIA - VerICiguaT GIObal Study in Subjects With Heart Failure With Reduced EjectIon FrAction

PARADIGM-HF - Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Converting–Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial

ATMOSTPHERE - Aliskiren Trial of Minimizing OutcomeS in Patients With HEart Failure

OVERTURE - Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events

COMET - Carvedilol Or Metoprolol European Trial

STICH - Surgical Treatment for Ischemic Heart Failure

## **SUPPLEMENTAL MATERIAL**

### **An Evaluation of the Causes of Sex Disparity in Heart Failure Trials**

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**Supplementary Table 1: Full Trial List**

Trial	Total no	Females	%	Age	Journal	Year	Notes	Sub-type
SERVE-HF	1325	127	9.6	69.5	NEJM	2015	CPAP, lvef<45%	2
CHART-1	315	32	10.2	61.9	EHJ	2017	ICM, stem cells	1,10 Y
CHRISTMAS	305	31	10.2	62.5	Lancet	2003	Carvediolol, ICM	2,11
STICH	1212	148	12.2	59.5	NEJM	2011	CABG	1,9,10 Y
BeAT-HF	408	53	13.0	62	JACC	2020	Baroreflex, LVEF <35	1,9 Y
MUSTT	2202	301	13.7	66.5	NEJM	2000	ICD	2,6 Y
ESSENTIAL II	950	133	14.0	62	EHJ	2009	Enoximone	1,11
REM-HF	1650	231	14.0	69.5	EHJ	2017	Remote monitoring	1,8
DOT-HF	335	47	14.0	64	Circ	2011	Implanted monitor	1,6 Y
CASTLE-AF	363	52	14.3	64	NEJM	2018	AF ablation	1,9 Y
WATCH	1587	234	14.7	63	Circ	2009	Warfarin/sapt, ef<35%	1,11
DAVID II	600	90	15.0	63.5	JACC	2009	Pacing	2,6 Y
MADIT-II	1232	192	15.6	64.5	NEJM	2002	LVEF <30	1,6 Y
PARR-2	430	67	15.6	63.5	JACC	2007	PET imaging	1,7,10
SENSE-HF	501	79	15.8	65	EHJ	2011	fluid monitor device	1,6 Y
EVITA	400	68	17.0	55	EHJ	2017	Vitamin D	1,11
RAFT	1798	308	17.1	66.2	NEJM	2010	ICD v CRT, LVEF <30%	1,6 Y
EARTH	642	113	17.6	60.3	Lancet	2004	Darusentan	1,11
AF-CHF	1376	248	18.0	67	NEJM	2008	AF in CCF, LVEF 27	1,11
Higgins et al	490	91	18.6	66	JACC	2003	CRT	1,6 Y
IN-TIME	664	128	19.3	65.5	Lancet	2014	Device monitoring	1,6,8
ACCLAIM	2408	476	19.8	64.3	Lancet	2008	IMT	1,8
MOMENTUM-3	366	73	19.9	59.5	NEJM	2018	LVAD	1,6,9 Y
VAL-HEFT	5010	1005	20.1	62.7	NEJM	2001	Valsartan	2,11
MACH-1	2590	521	20.1	62.8	Circ	2000	Mibefradil	1,11
PROTECT-2	452	91	20.1	67.5	Circ	2012	Impella/IABP	1,9,10 Y

WARCEF	2305	465	20.2	61	NEJM	2012	Warfarin v aspirin	1,11
COMET	3029	612	20.2	62	Lancet	2003	Carvedilol/metoprolol	1,11
OPTILINK-HF	1002	203	20.3	66.3	EHJ	2016	Fluid monitoring	1,8
MORE-CRT MPP	467	95	20.3	79.7	EHJ	2019	CRT	2,6 Y
ARTS-HF	458	94	20.5	71.3	EHJ	2013	Finerenone	2,11
COPERNICUS	2289	470	20.5	63.4	NEJM	2001	Carvedilol	1,11
BCIS-1	301	62	20.6	71	JAMA	2010	IABP	1,9,10 Y
REVERSE	610	128	21.0	62.5	Circ	2012	CRT, mild LVSD	2,6 Y
OVERTURE	5770	1211	21.0	63.4	Circ	2002	omapatrilat v enalapril	1,11
INOVATE-HF	707	149	21.1	61.4	JACC	2016	Vagus nerve	2,9 Y
OHCS	1193	254	21.3	66	JACC	2011	Atrial arrhythmia device	2,6
IMPRESS	573	122	21.3	64	Lancet	2000	omapatrilat v enalapril	2,11
FIGHT	300	64	21.3	61.5	JAMA	2016	Liraglutide	2,11
MOXCON	1934	420	21.7	64.2	EHJ	2003	ICM 62%, EF 25%	1,11
GISSI-HF	6975	1516	21.7	67	Lancet	2008	Fatty acids	5,11
ATMOSPHERE	7016	1525	21.7	63.3	NEJM	2016	Aliskiren	1,11
ENDURANCE	446	97	21.7	64.7	NEJM	2017	Lvad	1,6,9 Y
PARADIGM-HF	8399	1832	21.8	63.8	NEJM	2014	Entresto	2,11
BEST	2708	593	21.9	60	NEJM	2001	BB in EF<35	1,11
RENEWAL	2048	450	22.0	64.1	Circ	2004	Etanercept, EF<30	1,11
OPT-CHF	405	89	22.0	64.5	JACC	2008	Oxypurinol	2,11
EMPHASIS-HF	2737	610	22.3	68.6	NEJM	2011	Empagliflozin	1,11
TEN-HMS	426	97	22.8	67.2	JACC	2005	Tele monitoring	2,8
ASTRONAUT	1615	368	22.8	64.6	EHJ	2013	Aliskiren	2,11
COMMANDER HF	5022	1150	22.9	66.4	NEJM	2018	Rivaroxaban	2,10,11
ATOMIC-AHF	613	141	23.0	66	JACC	2016	Omecamtiv, LVEF<40	2,11
NorthStar	921	212	23.0	69	EHJ	2013	Long-term FU	2,8
MIRACLE-ICD	369	86	23.3	67.1	JAMA	2003	CRT	1,6 Y

SCD-HeFT	2521	588	23.3	60	NEJM	2005	Amiodarone v ICD	1,6 Y
DAPA-HF	4744	1109	23.4	66.3	NEJM	2019	Dapagliflozin	2,11
ARTS-HF	1066	250	23.5	71.2	EHJ	2016	Finerenone	2,11
CORONA	5011	1180	23.5	Not reported	JACC	2009	Rosuvastatin	5,11
MOOD-HF	372	89	23.9	62	JAMA	2016	Escitalopram	2,11
EMPEROR-reduced	3730	893	23.9	66.8	NEJM	2020	Empagliflozin	2,11
HeartMate II	309	74	23.9	54	Circ	2009	LVAD	1,6 Y
Cvlprit shock	646	155	24.0	70	NEJM	2017	Cardiogenic shock	5,9 Y
VICTORIA	5050	1212	24.0	67	NEJM	2020	Vericiguat	2,11
SHIFT	6558	1574	24.0	60.4	Lancet	2010	Ivabradine	1,11
RELEVANT	324	78	24.1	64.2	EHJ	2009	CRT, NICM	1,6,12 Y
Qili Qiangxin HF	491	121	24.6	57.3	JACC	2013	Qili Qiangxin	2,11
DAVID	506	125	24.7	65	JAMA	2002	Dual chamber v ICD	2,6 Y
ANDROMEDA	627	155	24.7	71.5	NEJM	2008	Dronedarone	1,11
MADIT CRT	1820	453	24.9	64.5	NEJM	2009	CRT	1,6 Y
SUPPORT	1147	287	25.0	66	EHJ	2015	Olmesartan	5,11
BLOCK-HF	691	174	25.2	73.4	NEJM	2013	CRT	2,6
MITRA-FR	304	77	25.3	36% >75	NEJM	2018	Mitraclip	2,9
EVEREST	4133	1058	25.6	65.8	JAMA	2007	Tolvaptan	2,11
ESSENTIAL I	900	234	26.0	62	EHJ	2009	Enoximone	1,11
ESCAPE	433	113	26.1	56	JAMA	2005	RH catheterisation	1,9 Y
CARE-HF	813	216	26.6	66.5	NEJM	2005	CRT	1,6 Y
ROSE-AHF	360	97	26.9	70	JAMA	2013	Dopamine/Nesiritide	5,11
EchoCRT	809	221	27.3	58	NEJM	2013	CRT in narrow QRS	1,6 Y
CHAMPION	550	151	27.5	61.5	Lancet	2011	Implantable monitor	5,6,8 Y
DANISH	1116	307	27.5	63.5	NEJM	2016	ICD in NICM	1,6,12 Y
TRUST	1339	370	27.6	63.5	Circ	2010	OP ICD	1,6
DOSE	308	86	27.9	66	NEJM	2011	diuretics	5,11



PIONEER-HF	881	246	27.9	61	NEJM	2019	Entresto	2,11
SURVIVE	1327	371	28.0	66.5	JAMA	2007	Levo v Dobutamine	1,11
HF-action	2331	653	28.0	59	JAMA	2009	Exercise	1
OPTIME-CHF	949	272	28.7	65.5	JAMA	2002	Milrinone	5,11
EPHESUS	6632	1918	28.9	64	NEJM	2003	Eplerenone	2,11
South Texas CHF Disease	1069	310	29.0	70.9	Circ	2004	Disease mx	5,8
DIAL	1518	444	29.2	65	BMJ	2005	OP telephone FU	5,8
ACTIV CHF	319	95	29.8	62	JAMA	2004	Tolvaptan	2,11
HEAAL	3834	1143	29.8	66	Lancet	2009	Losartan	2,11
WISDOM	525	158	30.1	61.7	JACC	2019	Communication	5,8
ELITE II	3152	977	31.0	71.4	Lancet	2000	Losartan/Captopril	2,11
VMAC	489	152	31.1	61.4	JAMA	2002	Nesiritide v GTN	5,11
RESPOND-CRT	998	311	31.2	67	EHJ	2017	CRT	1,6 Y
IABP Shock 2	600	187	31.2	69.5	NEJM	2012	Cardiogenic shock	5,9 Y
OUTSMART-HF	500	156	31.2	59	Circ	2020	CMR, NICM	5,7,12
CHARM	7599	2400	31.6	66	Lancet	2003	Candesartan	2,11
MIRACLE	453	144	31.9	64.3	NEJM	2002	CRT	1,6 Y
TIM-HF	1571	501	31.9	70	Lancet	2018	Telecommunications	1,8
GUIDE-IT	894	286	32.0	63	JAMA	2017	BNL, LVEF <40	2,7
SMART-AV	980	314	32.0	66	Circ	2010	CRT smart delay	2,6 Y
COMPANION	1520	495	32.6	66.8	NEJM	2004	CRT	1,6 Y
PROTECT	2033	671	33.0	70	JACC	2011	Rolofylline	5,11
DECREASE-HF	306	101	33.0	66.7	Circ	2007	CRT	1,6 Y
ASCEND-HF	7141	2391	33.5	67	NEJM	2011	Nesiritide	5,11
TRUE-AHF	2157	737	34.2	68.5	NEJM	2017	Ularitide	5,11
TIME-CHF	499	172	34.5	76.5	JAMA	2009	Intensive mx, age>60	2,3,7,8
BATTLESCARRED	364	131	36.0	76	JACC	2009	BNP	5,7
COAPT	614	221	36.0	72.2	NEJM	2018	Mitraclip	5,9 Y

GALACTIC	781	288	36.9	78	JAMA	2019	Vasodilators	1,11
SENIORS	2128	787	37.0	76	EHJ	2005	Nebivolol, >70	3,5,11
STAMINA-HeFT	319	118	37.0	69	Circ	2008	Erythropoietin	2,11
RELAX-AHF	1161	436	37.6	72	Lancet	2013	Serelaxin	5,11
BLAST-AHF	621	236	38.0	70	EHJ	2017	TRV027	5,11
CHARM-preserved	3023	1212	40.1	67.2	Lancet	2003	Candesartan	4,11
A-HeFT	1050	421	40.1	56.8	NEJM	2004	ISMN/hydralazine	2,11
RELAX-AHF-2	6545	2637	40.3	73	NEJM	2019	Serelaxin	5,11
VERITAS	1435	580	40.4	70	JAMA	2007	Tezosentan	5,11
SADHART-CHF	469	190	40.5	62.1	JACC	2010	Sertraline	2,3,11
RED-HF	2278	934	41.0	72	NEJM	2013	Erythropoietin	2,11
WHICH? II	787	323	41.0	74	EHJ	2017	Intensive mx	5,8
TELE-HF	1653	694	42.0	61	NEJM	2010	Telemonitoring	5,8
PRIMA	345	148	42.9	72	JACC	2010	BNP target	5,7,8
AFFIRM-AHF	1132	494	43.6	71.1	Lancet	2020	IV iron, ef<50%	2,11
NCT00490958	332	153	46.1	62.8	JACC	2010	Telmisartan dialysis	2,11
CONFIRM-HF	304	141	46.4	69.2	EHJ	2015	IV iron	2,11
IMPACT-HF	363	170	46.8	67	JACC	2004	Carvedilol, EF 25%	2,9,10,11
HART	902	424	47.0	63.6	JAMA	2010	Education, any EF	5,8
ACUTE	1983	951	48.0	81	Circ	2019	Risk score, HFH	5,7
socrates-preserved	477	229	48.0	73	EHJ	2017	Vericiguat	4,11
NCT00378950	605	291	48.1	60.7	Circ	2012	Education	5,8
RUSSLAN	504	244	48.4	67	EHJ	2002	Levosimendan, ICM	5,10,11
VITALITY-HFpEF	789	385	48.8	72.7	JAMA	2020	Vericiguat	4,11
ICON-RELOADED	1461	717	49.1	56.4	NEJM	2018	BNP in acute HF	5,7
TORIC	1377	689	50.0	68.5	EHJ	2002	Torasemide, any EF	5,11
PACT-HF	2494	1258	50.4	77.7	Circ	2019	Discharge care	5,8
PRIMA II	405	207	51.1	77.5	Circ	2018	BNP, acute HF	5,7

TOPCAT	3445	1775	51.5	68.7	NEJM	2014	Spironolactone	4,11
PARAGON-HF	4796	2479	51.7	72.7	NEJM	2019	Entresto	4,11
Aldo-DHF	422	219	51.9	67	JAMA	2013	Spiro, HFpEF	4,11
PANACHE	305	160	52.5	73.6	JAMA	2019	neladenoson bialanate	4,11
FAIR-HF	459	244	53.2	67.7	NEJM	2009	IV iron, LVEF <45	2,11
PEP-CHF	850	468	55.1	76	EHJ	2006	Perindopril in >70s	3,5,11
ELISABETH	503	298	59.2	87	JAMA	2020	ED care bundle, >75	3,5,7
I-PRESERVE	4128	2477	60.0	72	NEJM	2008	Irbesartan HFpEF	4,11

*Subtypes: 1. LVEF<35% 2. LVEF<50% 3. Older age group, 4. HFpEF, 5. HF all comers, 6. Device 7.*

*Diagnostics/scores 8. Outpatient care 9. Invasive procedure/surgery 10. ICM 11. Drug trial 12. NICM.*

*Invasive/procedural: Y.*

**Supplementary Table 2: Registries**

**Search term:** (*heart failure*[MeSH Major Topic]) AND (*registry*[Text Word]) AND (("The New England journal of medicine"[Journal]) OR ("Lancet (London, England)"[Journal]) OR ("British medical journal"[Journal]) OR ("JAMA"[Journal]) OR ("Journal of the American College of Cardiology"[Journal]) OR ("Circulation"[Journal]) OR ("European heart journal"[Journal])) AND (2000:2021[mdat])

	No of females	Total patients	Female %	Age	Category	Started	Country
Duke CVD Databank	392	1411	27.8	62	ICM	1969	US
BIOSTAT-CHF	402	1710	23.5	67	HFrEF (<40%)	2010	Europe
IMPROVE-HF	10060	34810	28.9	68.7	HFrEF (<35%)	2007	US
ASIAN-HF	1153	5276	21.9	60.1	HFrEF (<35%)	2012	Asia
	597	1204	49.6	68.5	HFpEF		
CHAMP-HF	807	2588	31.2	68	HFrEF	2016	US
SWEDE-HF	10281	32421	31.7	72.6	HFrEF (<50%)	2003	Sweden
	5260	9640	54.5	77	HFpEF		
ESC-HF-LT	4011	12440	32.2	66.6	HHF/CHF	2015	Europe
ESC-HF pilot	1666	5118	32.6	67.1	AHF/CHF	2014	Europe
DATA-HELP	1489	4253	35.0	69	ICM	2009	Poland
	562	1310	42.9	64.1	NICM		
REPORT-HF	7003	18553	37.7	67	HHF	2015	International
GWTG-HF (by LVEF)	26966	70267	38.4	77.5	HFrEF (<50%)	2005	US
	25423	40354	63.0	78	HFpEF		
ADHERE-HFpEF	10346	25865	40.0	73.9	HFpEF	2001	International
GWTG-HF (by Dx)	41040	92361	44.4	76	ICM	2005	US
	36186	63652	56.8	72	NICM		
GARFIELD-AF	1903	4717	40.3	70.2	ICM	2010	International

	3128	7021	44.6	70.0	NICM		
OPTIMIZE-HF	7444	20118	37.0	70.4	HFrEF (<40%)	2003	US
	6849	10072	68.0	75.6	HFpEF		
ADHERE	54802	105388	52.0	74.2	AHF	2001	International
RICA	2226	4200	53.0	78	HHF	2008	Spain
EAHFE	3273	5845	56.0	79	AHF	2007	Spain
Euro Heart HFpEF	1739	3148	55.0	71	HFpEF	2000	Europe
Total	265,008	583,742	40.2	70.3			

**Supplementary Table 3: Population Statistics**

*(heart failure[MeSH Major Topic]) AND (registry[Text Word]) AND (("The New England journal of medicine"[Journal]) OR ("Lancet (London, England)"[Journal]) OR ("British medical journal"[Journal]) OR ("JAMA"[Journal]) OR ("Journal of the American College of Cardiology"[Journal]) OR ("Circulation"[Journal]) OR ("European heart journal"[Journal])) AND (2000:2021[pdat]). NB: if paper referred to a separate original source, this source was used as the reference.*

Diagnosis	Population studied	Proportions of females	Age	Reference
All HF	UK	All - 49%; HF+IHD - 43%	76.7	Conrad et al Lancet 2017
HFpEF / HFrEF	UK	HFpEF - 71%; HFrEF 41.5%	83	Dulai, Br J Cardiol 2016
HFpEF / HFrEF	Italy	HFpEF - 51%; HFrEF - 30%	77	Iorio EJHF 2018
All HF	UK	All - 36.4%	Not reported for HF alone	BHF Heart Circulatory Disease Statistics 2019
All HF	Minnesota	All - 57%	74	Roger JAMA 2004
HFrEF / HFpEF	Minnesota	HFpEF 64%; HFrEF 42%	76.4	Gerber JAMA 2015
All HF	Italy	All - 51.7%; HFpEF 50.9%, HFrEF 29%; HF+IHD - 40.7%	Not reported; 63% 55-75 years	Piccini C 2017
All HF	US	All - 45%	57	Loehr, AJC 2008
All HF	Portugal	HFpEF 73.3%; HFrEF 28.2%	68.1	Ceia EJHF 2002
All HF	UK	All - 49%	77.8	Lawson, Lancet 2019
All HF	UK	HF+IHD - 42%; HFpEF - 65%; HFrEF - 40%	78	Lee Circ 2009
All HF	US	All - 52%; HFpEF 55.9%; HFrEF - 29%	74	Gottdiener AIM 2002
All HF	Minnesota	HFpEF - 55.7%; HFrEF - 34.6%	73.0	Owan NEJM 2006
All HFH	Denmark	Hfpef - 50%; HFrEF - 33%; HFrEF (<35%) - 24%	71.7	Gustafsson EHJ 2004

All HF	US	HFpEF – 57.1%, HFrEF (<35%) - 32.6%	72.4	Gurwitz 2013 AJM
All HF	UK	All - 51.2%	79.7	Koudstaal EJHF 2017
IHD/ICM	International	HF+IHD - 41.3%	Not reported	Moran 2014 Circ
ICM/NICM	US	NICM - 48%; HF+IHD - 33%	61.6	Bart, JACC 1997
Total			74	

**Supplementary Table 4: Summary of trials and registries; divided by LVEF and aetiology.**

Category	Registries		Trials	
	Number of patients	Female prevalence	Number of patients	Female prevalence
Unspecified LVEF	151544	44.9 [33.9-52.8]	58,101	36.5 [29.2-47.2]
<b>LVEF</b>				
HF, LVEF <35%	40086	25.4 [23.7-27.2]	88,787	21.4 [17.7-25.7]
HF, LVEF <50%	127104	31.7 [31.2-37.0]	84,348	24.3 [21.7-32.0]
HF, LVEF >50%	90283	54.8 [50.8-61.0]	17,385	51.6 [48.6-52.0]
<b>Aetiology</b>				
ICM	102742	37.7 [33.2-41.3]	8541	17.9 [11.7-21.2]
NICM	71983	44.6 [43.8-50.7]	1940	27.5 [25.8-29.4]
<b>Total</b>	<b>583,742</b>	<b>40.2 [32.3-52.8]</b>	<b>238,813</b>	<b>25.8 [21.3-36.0]</b>

**Supplementary Table 5: Trials reporting sex-specific characteristics and outcomes.**

Trial	Females	Age (yrs)	Baseline characteristics	Outcomes
STICH	12%	59.3 (males 63.4)	Women had higher BMI, higher rates of diabetes, hypertension, hyperlipidemia. Lower rates of smoking.	Overall all-cause and CV mortality lower in women. No difference in rates of surgical deaths (despite higher preoperative risk). No significant interaction between sex and treatment group for mortality of CV hospitalisation.
MUSTT	14%	53% women <70y/o (67% of men)	Women were more likely to have a history of HF and recent angina. No differences in LVEF, presence of 3 vessel coronary artery disease, prior coronary artery bypass graft or other revascularization.	On EP testing, Men were more likely to have inducible sustained VT than women. Over a 2 year period, there were no significant differences in risk of arrhythmic death or cardiac arrest (9% v 12% in men) or overall mortality (32% vs 21% in men).
TOPCAT	50%	72.1 (males 71.0)	Women had less <u>coronary artery disease</u> , tobacco use, atrial <u>fibrillation</u> , <u>chronic obstructive pulmonary disease</u> , and diabetes	Compared to men, women demonstrated a significantly greater increase in creatinine at 4 months. In the spironolactone arm, event rates were also numerically lower in women



			mellitus. Women had higher LVEF, blood pressure, BMI but lower eGFR and hemoglobin	than in men, of which the differences in all-cause mortality and non-CV mortality were statistically significant.
PARAGON-HF	52%	73.6 (males 71.8	Women had more obesity, less coronary disease, and lower eGFR and NT-proBNP levels than men. Median lvef 60% in women, 55% in men. Lower rates of smoking.	In the control group women had more HFH and less CV death. Greater reduction in events for women than men (primarily driven by reduction in HFH - 33% relative risk reduction in women versus men). Greater improvement in quality of life scores in men.

*NT-proBNP* : N-terminal pro-B-type natriuretic peptide; *HFH*: heart failure hospitalisation, *eGFR*: estimated glomerular filtration rate

**Trial Acronyms in Figure 4**

I-PRESERVE - Irbesartan in Heart Failure With Preserved Systolic Function

PARAGON-HF - Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Receptor Blocker Global Outcomes in HF with Preserved Ejection Fraction

TOPCAT - Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist

CHARM-preserved - Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity (Clinical Study of Candesartan in Patients With Heart Failure and Preserved Left Ventricular Systolic Function)

CHARM - Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity

EPHESUS - Evaluation of Perceptions, Knowledge and Compliance With tHE Guidelines for Secondary Prevention in Real Life Practice: A Survey on the Under-treatment of hypercholeSterolemia

VICTORIA - VerICiguaT GIObal Study in Subjects With Heart Failure With Reduced EjectIon FrAction

PARADIGM-HF - Prospective Comparison of Angiotensin Receptor–Neprilysin Inhibitor with Angiotensin-Converting–Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial

ATMOSTPHERE - Aliskiren Trial of Minimizing OutcomeS in Patients With HEart Failure

OVERTURE - Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events

COMET - Carvedilol Or Metoprolol European Trial

STICH - Surgical Treatment for Ischemic Heart Failure