Association is not causation: treatment effects cannot be estimated from observational data in heart failure

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Aims

Treatment 'effects' are often inferred from non-randomized and observational studies. These studies have inherent biases and limitations, which may make therapeutic inferences based on their results unreliable. We compared the conflicting findings of these studies to those of prospective randomized controlled trials (RCTs) in relation to pharmacological treatments for heart failure (HF).

Methods and results

We searched Medline and Embase to identify studies of the association between non-randomized drug therapy and all-cause mortality in patients with HF until 31 December 2017. The treatments of interest were: angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, mineralocorticoid receptor antagonists (MRAs), statins, and digoxin. We compared the findings of these observational studies with those of relevant RCTs. We identified 92 publications, reporting 94 non-randomized studies, describing 158 estimates of the 'effect' of the six treatments of interest on all-cause mortality, i.e. some studies examined more than one treatment and/or HF phenotype. These six treatments had been tested in 25 RCTs. For example, two pivotal RCTs showed that MRAs reduced mortality in patients with HF with reduced ejection fraction. However, only one of 12 non-randomized studies found that MRAs were of benefit, with 10 finding a neutral effect, and one a harmful effect.

Conclusion

This comprehensive comparison of studies of non-randomized data with the findings of RCTs in HF shows that it is not possible to make reliable therapeutic inferences from observational associations. While trials undoubtedly leave gaps in evidence and enrol selected participants, they clearly remain the best guide to the treatment of patients.

Keywords

Heart failure • Pharmacotherapy • Associations • Observational studies • Randomized controlled trials

Introduction

Randomized controlled trials (RCTs) are widely acknowledged to be the gold standard test of whether or not a drug is beneficial.1–4 Although the biases and limitations of non-randomized, observational studies have been recognized for decades (Figure 1), studies of this type purporting to describe the effects of treatment continue to be published, even in high-impact journals.5–10 Indeed, the 'comparative effectiveness' and 'big data' movements have given non-randomized studies a new respectability in some peoples' eyes.11–13 Advocates point to the use of more sophisticated analytical techniques than in the past and increasingly larger 'real-world' datasets.14–17 If the findings of observational studies could validly determine the effect of treatments, such information would clearly be of considerable value. On the other hand, if such analyses are inherently flawed they serve only to cause confusion, e.g. the association between hormone replacement therapy...
and decreased risk of coronary heart disease (CHD), and decreased risk of coronary heart disease (CHD), and maybe worse, e.g. lead to discontinuation of effective therapy by physicians or patients misled by the findings.

There is a particularly strong evidence base for pharmacological treatments in heart failure (HF), making it an appropriate condition in which to compare treatment effects established in RCTs with those reported in non-randomized studies. We have, therefore, compared the conflicting results of non-randomized studies of the ‘effect’ of pharmacological treatments with those of RCTs using the same therapies for HF. Although many publications of this type have used the word 'effect', more correctly they have actually described associations between treatments and outcomes.

**Methods**

**Search strategy and eligibility criteria**

We conducted a comprehensive search of the electronic databases Medline and Embase to identify observational studies examining the association between non-randomized drug therapy and all-cause mortality in patients with HF. The drugs of interest were those included in all major HF guidelines: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors), and digoxin, where the effect on all-cause mortality had been tested in at least one large RCT. The term ‘heart failure’ was searched in title and keywords relating to outcome data and pharmacotherapy were searched in title or abstract to retrieve all potentially relevant articles (see Supplementary material online, figures S1–S5). The search, updated until 31 December 2017, was limited to studies of adults, published in the English language, with more than 100 participants in both the study drug and control groups, with a minimum follow-up period of six months. Studies of patients with left ventricular systolic dysfunction and/or HF after myocardial infarction were not included. We also excluded studies describing only subgroups of patients with HF, e.g. those with HF and chronic kidney disease, HF and diabetes etc. Bibliographies of meta-analyses, guidelines, reviews, and manuscripts identified through the search strategy were also hand-searched for additional eligible studies. The review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.

Non-randomized studies were considered for inclusion in this review if the following requirements were met:

1. Inclusion of patients with HF
2. Report of the ‘effect’ of the drug of interest on all-cause mortality
3. Estimate of treatment ‘effect’ provided as a multivariate-adjusted hazard ratio (HR), risk ratio/relative risk, or odds ratio

**Data extraction, synthesis, and risk of bias**

Data from the manuscripts identified through the search criteria were abstracted and tabulated by one reviewer (C.J.R.). The data were independently verified by a second reviewer (R.T.C.), with a third reviewer (J.J.M.) resolving any discrepancies. The articles retrieved were categorized according to HF phenotype, based on ejection fraction (EF), and drug class for comparison with the relevant randomized trials. For studies that reported more than one multivariable-adjusted ‘effect’ estimate, the estimate which had been adjusted for most confounders was used. A two-tailed P-value of 0.05 was considered significant.

The quality of each study was assessed with the Cochrane Collaboration Risk of Bias tool for RCTs and the Risk of Bias Assessment tool for Non-randomized Studies (RoBANS) tool for observational...
studies (see Supplementary material online, Tables S1 and S2). 24,25 Studies judged as having a low risk of bias have been presented separately from those with a high or unclear risk of bias in the Supplementary material online, Figures S6–S19.

Results

We identified 92 publications reporting 94 non-randomized studies. 26–117 Together, these described 158 estimates of the ‘effect’ of the six treatments of interest on all-cause mortality. These six treatments had been tested in 25 RCTs. 118–147 The results of our analyses are summarized in Table 1 and described in detail in Tables 2–6. The forest plots in the Supplementary material online, Figures S6–S19 illustrate the treatment effects/association between treatment and outcomes in the trials and observational studies, respectively, reported in Tables 2–6 and include a quality assessment of these trials/studies.

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers

Heart failure with reduced ejection fraction

Two landmark randomized trials in heart failure with reduced ejection fraction (HFrEF) demonstrated a reduction in mortality with an ACEI 118–120 and one further trial showed a consistent benefit with an ARB. 121 We identified one non-randomized study showing lower mortality in patients with HFrEF treated with an ACEI. 26 Most studies, however, examined patients treated with either an ACEI or ARB. Of six such studies, four reported an association between ACEI/ARB use and lower mortality, 26–29 whereas two did not. 30 Overall, therefore, in HFrEF five non-randomized estimates of treatment ‘effect’ found that use of an ACEI or ARB was associated with lower mortality and two did not (Table 2).

Heart failure with preserved ejection fraction

One moderately large randomized trial showed no effect of perindopril on mortality, although the estimate of treatment effect was not robust because of limited power. 122 However, two large RCTs showed no effect of irbesartan 123 and candesartan (in Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity—CHARM) 124 on mortality. Of eight observational studies examining ACEI use and outcome in heart failure with preserved ejection fraction (HFpEF), four suggested that use of this treatment was associated with a lower mortality, 31–34 whilst four did not 35–38 (Table 2). We identified one observational study of ARB use in patients with HFpEF which suggested no mortality benefit. 39 A further three non-randomized studies reported estimates of a treatment ‘effect’ for use of either an ACEI or ARB in HFpEF. One study found an association between ACEI/ARB use and better survival 39 and two studies did not. 40 Overall, therefore, in HFpEF, five non-randomized studies found that use of an ACEI or ARB was associated with lower mortality and seven did not (Table 2).

Mixed/unspecified heart failure phenotype

The CHARM Programme showed a neutral effect of candesartan on mortality in patients with HFpEF and HFrEF combined. 125 Nine non-randomized studies were identified, which reported 10 estimates of a
“treatment-effect” for use of either an ACEI or ARB in patients with HFrEF or HFpEF (i.e. both major HF phenotypes). Of these analyses, eight suggested a benefit \(^{40-46}\) and two reported a neutral effect \(^{30}\) (Table 2).

**Beta-blockers**

**Heart failure with reduced ejection fraction**

Several landmark RCTs demonstrated significant mortality benefit with the use of beta-blockers in HFrEF. \(^{128-131}\) Seventeen non-randomized studies reported 18 estimates of beta-blocker ‘treatment-effect’. Sixteen of these suggested beta-blocker use was associated with a lower mortality \(^{28,30,46-58}\) and two did not \(^{30,59}\) (Table 3).

**Heart failure with preserved ejection fraction**

The effect of beta-blockers on mortality was examined in one small randomized trial \(^{136}\) and a pre-specified subgroup analysis of a randomized trial which included patients with both HFrEF and HFpEF. \(^ {132}\) Overall, we identified 13 non-randomized studies of beta-blockers in HFpEF, of which nine reported an association between beta-blocker use and better survival, \(^ {32,46,50,51,55,60-63}\) whereas four did not \(^{30,53,64}\) (Table 3).

**Mixed/unspecified heart failure phenotype**

One moderately large RCT evaluated the effects of nebivolol in patients with both HFrEF and HFpEF, demonstrating a neutral effect on mortality. \(^{137}\) We identified 17 observational studies reporting 19 estimates of the ‘effect’ of treatment, with 17 suggesting benefit, \(^ {41,44-46,55,65-74}\) and two reporting no difference in outcome between those treated with and not treated with a beta-blocker \(^{30}\) (Table 3).

### Mineralocorticoid receptor antagonists

**Heart failure with reduced ejection fraction**

Two pivotal RCTs in HFrEF demonstrated the mortality and hospitalization benefits of MRAs. \(^ {138,139}\) In contrast, of 12 non-randomized studies only one concluded MRAs were of benefit, \(^ {75}\) with 10 finding a neutral effect, \(^ {30,54,76-82}\) and one suggesting a harmful effect \(^ {83}\) (Table 4).

**Heart failure with preserved ejection fraction**

One large RCT showed no effect of spironolactone on mortality in patients with HFpEF. \(^ {141}\) Two observational studies also found a neutral effect, \(^ {30,86}\) but a further non-randomized study reported an association between MRA use and lower mortality \(^ {84}\) (Table 4).

**Mixed/unspecified heart failure phenotype**

Of five studies of patients with a mixed HF phenotype, two suggested benefit, \(^ {84,86}\) and three reported a neutral effect \(^ {30,46}\) (Table 4).

### Statins

**Heart failure with reduced ejection fraction**

Two large RCTs showed a neutral effect of rosuvastatin on mortality in HFrEF (one trial included a small number of patients with HFpEF). \(^ {142,144}\) Sixteen non-randomized studies reported 17 estimates of the ‘effect’ of statin treatment in HFrEF. Of these, 14 reported an association between statin use and better

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**Table 1** Summary of the concordance between the effect of treatment on mortality in randomized controlled trials and the association between non-randomized use of the same treatments and mortality in observational studies in HF

| Treatment                          | Randomized controlled trials | Observational studies |
|------------------------------------|-----------------------------|-----------------------|
|                                    | Benefit                     | Neutral               | Harm     |
| HFrEF                              |                             |                       |          |
| ACEI/ARB                           | Benefit                     | 5                     | 2        | 0        |
| Beta-blocker                       | Benefit                     | 16                    | 2        | 0        |
| MRA                                | Benefit                     | 1                     | 10       | 1        |
| Statin                             | Neutral                     | 14                    | 3        | 0        |
| Digoxin                            | Neutral                     | 1                     | 4        | 5        |
| HFpEF                              |                             |                       |          |
| ACEI/ARB                           | Neutral                     | 5                     | 7        | 0        |
| Beta-blocker                       | Neutral                     | 9                     | 4        | 0        |
| MRA                                | Neutral                     | 1                     | 2        | 0        |
| Statin                             | —                           | —                     | —        | —        |
| Digoxin                            | Neutral                     | 1                     | 3        | 0        |
| Mixed/unspecified HF phenotype     |                             |                       |          |
| ACEI/ARB                           | Neutral                     | 8                     | 2        | 0        |
| Beta-blocker                       | Neutral                     | 17                    | 2        | 0        |
| MRA                                | —                           | 2                     | 3        | 0        |
| Statin                             | Neutral                     | 11                    | 1        | 0        |
| Digoxin                            | Neutral                     | 2                     | 7        | 7        |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MRA, mineralocorticoid receptor antagonist.
### Table 2  All-cause mortality in randomized and non-randomized ACEI/ARB HF studies

| First author, country, year of publication (study name) | Study design | Study period | Region | Mean follow-up (months) | Patients (n) | Study (n) | Control (n) | All-cause mortality—unadjusted HR (95% CI) | All-cause mortality—adjusted HR (95% CI) |
|--------------------------------------------------------|--------------|--------------|--------|-------------------------|--------------|-----------|------------|---------------------------------------------|------------------------------------------|
| **HFrEF (ACEI)**                                        |              |              |        |                         |              |           |            |                                             |                                          |
| Randomized controlled trials—beneficial treatment effect|              |              |        |                         |              |           |            |                                             |                                          |
| SOLVD Investigators, USA, 1991 (SOLVD-Treatment)        | RCT          | 1986–1989    | USA, Canada, Belgium | 41           | 2569         | 1285      | 1284       | RR: 0.84 (0.74–0.95; P < 0.004)            |                                           |
| Jong, Canada, 2003 (X-SOLVD Overall)                    | RCT          | 1986–1990    | USA, Canada, Belgium | 134–145      | 6797         | 3396      | 3401       | 0.90 (0.84–0.95; P < 0.0003)               |                                           |
| Jong, Canada, 2003 (X-SOLVD-Prevention)                 | RCT          | 1986–1990    | USA, Canada, Belgium | 134          | 4228         | 2111      | 2117       | 0.86 (0.79–0.93; P < 0.001)               |                                           |
| Randomized controlled trials—neutral treatment effect   |              |              |        |                         |              |           |            |                                             |                                          |
| SOLVD Investigators, USA, 1992 (SOLVD-Prevention)       | RCT          | 1986–1990    | USA, Canada, Belgium | 37           | 4228         | 2111      | 2117       | RR: 0.92 (0.79–1.08; P < 0.30)            |                                           |
| Jong, Canada, 2003 (X-SOLVD-Treatment)                  | RCT          | 1986–1990    | USA, Canada, Belgium | 145          | 2569         | 1285      | 1284       | 0.93 (0.85–1.01; P < 0.01)               |                                           |
| **Observational studies—beneficial treatment effect**   |              |              |        |                         |              |           |            |                                             |                                          |
| Masoudi, USA, 2004 (NHC)                               | Retrospective cohort study (≥65 years) | 1998–1999, 2000–2001 | USA | 12 | 17 456 | 12 069 | 13 600 | RR: 0.78 (0.75–0.81; P < 0.0001) | RR: 0.86 (0.82–0.90) |
| **HFrEF (ARB)**                                         |              |              |        |                         |              |           |            |                                             |                                          |
| Randomized controlled trials—neutral treatment effect   |              |              |        |                         |              |           |            |                                             |                                          |
| Granger, USA, 2003 (CHARM-Alternative)                  | RCT          | 1999–2001    | Multiregional | 34          | 2028         | 1013      | 1015       | 0.87 (0.74–1.03; P < 0.11)               | 0.83 (0.70–0.99; P < 0.033) |
| **HFrEF (ACEI + ARB)**                                  |              |              |        |                         |              |           |            |                                             |                                          |
| Observational studies—beneficial treatment effect       |              |              |        |                         |              |           |            |                                             |                                          |
| Sanam, USA, 2016 (Alabama HF Project)                   | Retrospective cohort study (PSM) (≥65 years) | 1998–2001 | USA | 12 | 954 | 477 | 477 | — | 0.77 (0.62–0.96; P < 0.020) |
| Liu, China, 2014                                        | Prospective cohort study | 2005–2010 | China | 52 | 2154 | 1421 | 733 | — | 0.43 (0.33–0.57; P < 0.001) |
| Lund, Sweden, 2012 (Swedish HF Registry)                | Registry (PSM) | 2000–2011 | Sweden | 12 | 4010 | 2005 | 2005 | — | 0.80 (0.74–0.86; P < 0.001) |
| Masoudi, USA, 2004 (NHC)                               | Retrospective cohort study (≥65 years) | 1998–1999, 2000–2001 | USA | 12 | 17 456 | 13 600 | 3856 | — | RR: 0.83 (0.79–0.88) |
| Observational studies—neutral treatment effect         |              |              |        |                         |              |           |            |                                             |                                          |
| Ushigome, Japan, 2015                                   | Prospective cohort study (1. CHART-1) | 2000–2005 | Japan | 36 | 543 | 385 | 158 | — | 0.67 (0.40–1.12; P < 0.128) |

Continued
| First author, country, year of publication (study name) | Study design | Study period | Region | Mean follow-up (months) | Patients (n) | Study (n) | Control (n) | All-cause mortality—un-adjusted HR (95% CI) | All-cause mortality—adjusted HR (95% CI) |
|------------------------------------------------------|--------------|--------------|--------|-------------------------|--------------|----------|-----------|-------------------------------------------|------------------------------------------|
| Ushigome, Japan, 2015 (2. CHART-2) | Prospective cohort study | 2006–2010 Japan | 36 | 1360 | 1061 | 299 | — | 0.83 (0.60–1.15; P < 0.252) |
| Cleland, UK, 2006 (PEP-CHF) | RCT (≥70 years) | 2000–2003 Multiregional | 26 | 850 | 424 | 426 | 1.09 (0.75–1.58; P < 0.665) | — |
| Gomez-Soto, Spain, 2010 | Prospective cohort study (propensity score adjusted) | 2001–2005 Spain | 30<sup>a</sup> | 1200 | 255 | 865 | RR: 0.34 (0.23–0.46; P < 0.001) | 0.67 (0.52–0.71) |
| Shah, USA, 2008 (NHC) | Retrospective cohort study (≥65 years) | 1998–1999, 2000–2001 USA | 36 | 13533 | 6413 | 7120 | — | RR: 0.93 (0.89–0.98) |
| Tribouilloy, France, 2008 | Prospective cohort study (PSM) | 2000 France | 60 | 240 | 120 | 120 | 0.61 (0.43–0.87; P < 0.006) | 0.58 (0.40–0.82; P < 0.002) |
| Grigorian Shamagian, Spain, 2006 | Prospective cohort study | 1991–2002 Spain | 31 | 416 | 210 | 206 | 0.56 (0.40–0.79; P < 0.001) | 0.63 (0.44–0.90; P < 0.012) |
| Mujib, USA, 2013 (OPTIMIZE-HF) | Registry (PSM) (≥65 years) | 2003–2004 USA | 29<sup>a</sup> | 2674 | 1337 | 1337 | — | 0.96 (0.88–1.05; P < 0.373) |
| Dauterman, USA, 2001 (Medicare) | Retrospective cohort study (≥65 years) | 1993–1994, 1996 USA | 12 | 430 | 206 | 224 | — | 1.15 (0.79–1.67; P < 0.46) |
| Philbin, USA, 2000 (MISCHF) | Registry | 1995, 1996–1997 USA | 6 | 302 | 137 | 160 | OR: 0.72 (0.38–1.39) | OR: 0.61 (0.30–1.25) |
| Philbin, USA, 1997 (MISCHF) | Registry | 1995 USA | 6 | 350 | 190 | 160 | — | OR: 0.63 (P < 0.15–95% CI not reported) |
| Massie, USA, 2008 (I-PRESERVE) | RCT | 2002–2005 Multiregional | 50 | 4128 | 2067 | 2061 | 1.00 (0.88–1.14; P < 0.98) | — |
| Yusuf, Canada, 2003 (CHARM-Preserved) | RCT | 1999–2000 Multiregional | 37<sup>a</sup> | 3023 | 1514 | 1509 | 1.02 (0.85–1.22; P < 0.836) | — |
| Patel, USA, 2012 (OPTIMIZE-HF) | Registry (PSM) (≥65 years) | 2003–2004 USA | 72 | 592 | 296 | 296 | 0.93 (0.76–1.14; P < 0.509) | — |

Continued
| First author, country, year of publication (study name) | Study design | Study period | Region | Mean follow-up (months) | Patients (n) | Study (n) | Control (n) | All-cause mortality—unadjusted HR (95% CI) | All-cause mortality—adjusted HR (95% CI) |
|------------------------------------------------------|--------------|--------------|--------|-------------------------|-------------|-----------|------------|------------------------------------------|------------------------------------------|
| **HfPEF (ACEI + ARB)** | | | | | | | | | | |
| Observational studies—beneficial treatment effect | | | | | | | | | |
| Lund, Sweden, 2012 (Swedish HF Registry)29 | Registry (PSM) | 2000–2011 Sweden | 12 | 6658 | 3329 | 3329 | — | 0.91 (0.85–0.98; $P < 0.008$) |
| Observational studies—neutral treatment effect | | | | | | | | | |
| Ushigome, Japan, 2015 (1. CHART-1)30 | Prospective cohort study | 2000–2005 Japan | 36 | 463 | 304 | 159 | — | 0.86 (0.51–1.47; $P < 0.592$) |
| Ushigome, Japan, 2015 (2. CHART-2)30 | Prospective cohort study | 2006–2010 Japan | 36 | 2316 | 1619 | 697 | — | 1.01 (0.77–1.32; $P < 0.924$) |
| Mixed/unspecified HF phenotype (ACEI) | | | | | | | | | |
| Randomized controlled trials—beneficial treatment effect | | | | | | | | | |
| Cohn, USA, 1991 (V-HeFT-II)125 | RCT | 1986–1990 USA | 24 | 804 | 403 | 401 (H-ISDN) RR: 0.72 (P < 0.016–95% CI not reported) | — | |
| CONSENSUS Trial Study Group, Sweden, 1987 (CONSENSUS)126 | RCT | 1985–1986 Sweden, Norway, Finland | 12 | 245 | 127 | 126 | RR: 0.69 (P < 0.001–95% CI not reported) | — | |
| Observational studies—beneficial treatment effect | | | | | | | | | |
| Keyhan, Canada, 2007 (1. female cohort)40 | Retrospective cohort study (≥65 years) | 1998–2003 Canada | 12 | 14 693 | 9801 | 4892 | 0.75 (0.71–0.78) | 0.80 (0.76–0.85) |
| Keyhan, Canada, 2007 (2. male cohort)40 | Retrospective cohort study (≥65 years) | 1998–2003 Canada | 12 | 13 144 | 9419 | 3725 | 0.62 (0.59–0.65) | 0.71 (0.67–0.75) |
| Tandon, Canada, 2004 (75% HFrEF, 25% HfPEF)41 | Prospective cohort study | 1989–2001 Canada | 32 | 1041 | 878 | 163 | — | OR: 0.60 (0.39–0.91) |
| Pedone, Italy, 2004 (GIFA)42 | Prospective cohort study (≥65 years) | 1998 Italy | 10 | 818 | 550 | 268 | 0.56 (0.41–0.78) | 0.60 (0.42–0.88) |
| Ahmed, USA, 2003 (Medicare)43 | Retrospective cohort study (PSM) | 1994 USA | 36 | 1090 | 528 | 562 | 0.77 (0.66–0.91) | 0.81 (0.69–0.97) |
| Sin, Canada, 2002 (19% HFrEF, 36% HfPEF, 45% unknown)44 | Retrospective cohort study (≥65 years) (propensity score adjusted) | 1994–1998 Canada | 21 | 11 942 | 4908 | 7034 | — | 0.59 (0.55–0.62) |
| Mixed/unspecified HF phenotype (ARB) | | | | | | | | | |
| Randomized controlled trials—neutral treatment effect | | | | | | | | | |
| Pfeffer, USA, 2003 (CHARM Overall Programme) (60% HFrEF, 40% HfPEF)127 | RCT | 1999–2001 Multiregional | 40 | 7599 | 3803 | 3796 | 0.91 (0.83–1.00; $P < 0.055$) | 0.90 (0.82–0.99; $P < 0.032$) |

Continued
| First author, country, year of publication (study name) | Study design | Study period | Region | Mean follow-up (months) | Patients (n) | Study (n) | Control (n) | All-cause mortality—un-adjusted HR (95% CI) | All-cause mortality—adjusted HR (95% CI) |
|--------------------------------------------------------|--------------|--------------|--------|-------------------------|--------------|----------|------------|------------------------------------------|------------------------------------------|
| Mixed/unspecified HF phenotype (ACEI + ARB) | Observational studies—beneficial treatment effect | gastelurrutia, Spain, 2012 (75% HFrEF, 25% HFrEF) | Prospective cohort study | 2001–2008 | Spain | 44 | 960 | 846 | 114 | — | 0.52 (0.39–0.69; P < 0.001) |
| | Teng, Australia, 2010 (WAHMD) (24% HFrEF, 30% HFpEF, 46% unknown) | Retrospective cohort study | 1996–2006 | Australia | 12 | 944 | 701 | 243 | — | 0.71 (0.57–0.89; P < 0.003) |
| | Observational studies—neutral treatment effect | Ushigome, Japan, 2015 (1. CHART-1) (54% HFrEF, 46% HFpEF) | Prospective cohort study | 2000–2005 | Japan | 36 | 1006 | 689 | 317 | — | 0.79 (0.55–1.14; P < 0.208) |
| | | Ushigome, Japan, 2015 (2. CHART-2) (37% HFrEF, 63% HFpEF) | Prospective cohort study | 2006–2010 | Japan | 36 | 3676 | 2677 | 999 | — | 0.94 (0.76–1.15; P < 0.534) |

*Median. —, Not reported; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CHARM, Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity; CHART, Chronic Heart Failure Analysis and Registry in the Tohoku district; CI, confidence interval; CONSENSUS, Cooperative North Scandinavian Enalapril Survival Study; GIFA, Gruppo Italiano di Farmacovigilanza nell’Aria; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; H-ISDN, hydralazine-isosorbide dinitrate; HR, hazard ratio; I-PRESERVE, Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction; MISCHF, Management to Improve Survival in Congestive Heart Failure; NHC, National Heart Care; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; OR, odds ratio; PEP-CHF, Perindopril in Elderly People with Chronic Heart Failure; PSM, propensity score matched study; RCT, randomized controlled trial; RR, risk ratio/relative risk; SOLVD, Studies of Left Ventricular Dysfunction; V-HeFT-II, Vasodilator Heart Failure Trial II; WAHMD, Western Australia Hospital Morbidity Data; X-SOLVD, Extended follow-up of the SOLVD trials.
**Table 3**  All-cause mortality in randomized and non-randomized beta-blocker HF studies

| First author, country, year of publication (study name) | Study design | Study period | Region | Mean follow-up (months) | Patients (n) | Study (n) | Control (n) | All-cause mortality—unadjusted HR (95% CI) | All-cause mortality—adjusted HR (95% CI) |
|-------------------------------------------------------|-------------|-------------|--------|------------------------|-------------|----------|------------|------------------------------------------|------------------------------------------|
| **HFrEF**                                             |             |             |        |                        |             |          |            |                                          |                                          |
| Randomized controlled trials—beneficial treatment effect |             |             |        |                        |             |          |            |                                          |                                          |
| Packer, USA, 2001 (COPERNICUS) 128                    | RCT         | 1997–2000   | Multiregional | 10           | 2289        | 1156     | 1133       | RR: 0.65 (0.52–0.81; P < 0.00013)           |                                          |
| MERIT-HF Study Group, Sweden, 1999 (MERIT-HF) 129      | RCT         | 1997–1998   | Europe, USA | 12           | 3991        | 1990     | 2001       | RR: 0.66 (0.53–0.81; P < 0.0001)           |                                          |
| CIBIS Investigators, UK, 1999 (CIBIS-II) 130            | RCT         | —           | Europe   | 16           | 2647        | 1327     | 1320       | 0.66 (0.54–0.81; P < 0.0001)               |                                          |
| Packer, USA, 1996 (US Carvedilol HF Study Group) 131   | RCT         | 1993–1995   | USA      | 7            | 1094        | 696      | 398        | RR: 0.35 (0.20–0.61; P < 0.001)            |                                          |
| **Randomized controlled trials—neutral treatment effect** |             |             |        |                        |             |          |            |                                          |                                          |
| van Veldhuisen, Netherlands, 2009 (SENIORS) 132         | Pre-specified subgroup analysis of RCT (EF <35%; ≥70 years) | 2000–2002 | Europe | 21           | 1359        | 678      | 681        | 0.84 (0.66–1.08)                          |                                          |
| BEST Investigators, USA, 2001 (BEST) 133                | RCT         | 1995–1998   | USA, Canada | 24           | 2708        | 1354     | 1354       | 0.90 (0.78–1.02; P > 0.10)                |                                          |
| ANZ HF Research Collaborative Group, New Zealand, 1997 (ANZ) 134 | RCT (IHD) | —           | Australia, New Zealand | 19   | 415         | 207     | 208        | RR: 0.76 (0.42–1.36; P < 0.1)             |                                          |
| CIBIS Investigators, France, 1994 (CIBIS-I) 135         | RCT         | 1989–1992   | Europe   | 23           | 641         | 320      | 321        | RR: 0.80 (0.56–1.15)                      |                                          |
| **Observational studies—beneficial treatment effect**   |             |             |        |                        |             |          |            |                                          |                                          |
| Cadrin-Tourigny, Canada, 2017 (AF-CHF) 47               | Post hoc analysis of RCT (PSM) (AF) | 2001–2005 | Multiregional | 37a          | 655        | 426      | 229        | 0.72 (0.55–0.95; P < 0.018)               |                                          |
| Bhata, USA, 2015 (Alabama HF Project) 48                | Retrospective cohort study (PSM) (≥65 years) | 1998–2001 | USA   | 48           | 760         | 380      | 380        | 0.81 (0.67–0.98)                          |                                          |
| Ushigome, Japan, 2015 (2. CHART-2) 50                   | Prospective cohort study | 2006–2010 | Japan   | 36           | 1360        | 870      | 490        | 0.59 (0.44–0.81; P < 0.001)               |                                          |
| Del Carlo, Brazil, 2014 49                              | Retrospective cohort study | 1992, 1994, 1996, 1999, 2005–2006 | Brazil   | 12           | 333         | 199     | 134        | 0.3 (0.2–0.5; P < 0.001)                  |                                          |
| Liu, China, 2014 28                                      | Prospective cohort study | 2005–2010 | China   | 52a          | 2154        | 1471     | 683        | 0.75 (0.57–0.99; P < 0.049)               |                                          |
| Lund, Sweden, 2014 (Swedish HF Registry) 50             | Registry (PSM) | 2005–2012 | Sweden  | 23a          | 6081        | 4054     | 2027       | 0.89 (0.82–0.97; P < 0.005)               |                                          |
| El-Refai, USA, 2013 51                                   | Retrospective cohort study | 2000–2008 | USA    | 25a          | 1094        | 927      | 167        | 0.26 (0.17–0.40; P < 0.001)               |                                          |

Continued
| First author, country, year of publication (study name) | Study design | Study period | Region | Mean follow-up (months) | Patients | Study | Control | All-cause mortality—unadjusted HR (95% CI) | All-cause mortality—adjusted HR (95% CI) |
|-----------------------------------------------------|--------------|--------------|--------|------------------------|----------|-------|---------|------------------------------------------|----------------------------------|
| Xu, China, 2013                                      | Retrospective cohort study | 2007–2012 | China | 31a | 685 | 555 | 130 | — | 0.69 (0.50–0.95; P < 0.021) |
| Teng, Australia, 2010 (WAHMD)                         | Retrospective cohort study | 1996–2006 | Australia | 12 | 225 | 100 | 125 | — | 0.53 (0.32–0.87; P < 0.011) |
| Hernandez, USA, 2009 (OPTIMIZE-HF)                    | Registry (≥65 years) | — | USA | 12 | 3001 | 1800 | 1201 | 0.65 (0.57–0.73) | 0.77 (0.68–0.87) |
| Miyagishima, Japan, 2009                              | Retrospective cohort study | 2000–2004 | Japan | 36 | 431 | 297 | 134 | — | 0.48 (0.32–0.73) |
| Fauchier, France, 2009 (41% HFpEF)                    | Retrospective cohort study (AF) | 2000–2004 | France | 29 | 1269 | 449 | 820 | — | RR: 0.60 (0.40–0.89; P < 0.01) |
| Pascual-Figal, Spain, 2008                            | Registry (>70 years) | 2002–2003 | Spain | 31a | 272 | 139 | 133 | 0.45 (0.31–0.65; P < 0.001) | 0.53 (0.34–0.80; P < 0.003) |
| Jost, Germany, 2005 (Ludwigshafen HF Registry)(1. ‘Trial patients’)) | Registry | 1995–2004 | Germany | 31 | 278 | 166 | 112 | — | 0.57 (0.38–0.86) |
| Jost, Germany, 2005 (Ludwigshafen HF Registry)(2. ‘Non-trial patients’)) | Registry | 1995–2004 | Germany | 31 | 397 | 204 | 193 | — | 0.72 (0.53–0.97) |
| Bobbio, Italy, 2003 (BRING-UP)                        | Prospective cohort study | 1998 | Italy | 12 | 2843 | 1582 | 1261 | RR: 0.46 (0.38–0.57) | 0.64 (0.48–0.86) |
| Observational studies—neutral treatment effect        | Prospective cohort study | 2000–2005 | Japan | 36 | 543 | 184 | 359 | — | 0.87 (0.50–1.50; P < 0.06) |
| Ushigome, Japan, 2015 (1. CHART-1)                    | Prospective cohort study | 2000–2005 | Japan | 36 | 900 | 738 | 162 | RR: 0.76 (0.70–0.83; P < 0.001) | 0.73 (0.53–1.02; P < 0.067) |
| Huan Loh, UK, 2007                                    | Retrospective cohort study | — | UK | 36a | 900 | 738 | 162 | 0.54 (0.40–0.73; P < 0.001) | 0.73 (0.53–1.02; P < 0.067) |
| HFpEF                                                 | PROBE         | 2004–2009 | Japan | 38 | 245 | 120 | 125 | 0.99 (0.53–1.86; P < 0.975) | — |
| van Veldhuisen, Netherlands, 2009 (SENIORS)           | Pre-specified subgroup analysis of RCT (EF >35%) (≥70 years) | 2000–2002 | Europe | 21 | 752 | 380 | 372 | 0.91 (0.62–1.33; P < 0.718) | — |
| Observational studies—beneficial treatment effect     | Prospective cohort study (PSM) | 2006–2015 | Spain | 22a | 1970 | 985 | 985 | RR: 0.76 (0.70–0.83; P < 0.001) | 0.78 (0.71–0.85; P < 0.001) |
| Ruiz, Spain, 2016                                    | Registry (PSM) | 2005–2012 | Sweden | 23a | 8244 | 5496 | 2748 | — | 0.93 (0.86–0.99; P < 0.04) |
| Lund, Sweden, 2014 (Swedish HF Registry)              | Retrospective cohort study | 2000–2008 | USA | 25a | 741 | 570 | 171 | — | 0.43 (0.27–0.68; P < 0.001) |
| El-Refai, USA, 2013                                   | Retrospective cohort study | 2001–2005 | Israel | 24 | 345 | 154 | 191 | — | 0.69 (0.47–0.99; P < 0.046) |

Continued
Table 3 Continued

| First author, country, year of publication (study name) | Study design | Study period | Region | Mean follow-up (months) | Patients (n) | Study (n) | Control (n) | All-cause mortality—unadjusted HR (95% CI) | All-cause mortality—adjusted HR (95% CI) |
|--------------------------------------------------------|--------------|--------------|--------|-------------------------|-------------|----------|------------|--------------------------------------------|----------------------------------------|
| Gomez-Soto, Spain, 2011 (propensity score adjusted)    | Prospective cohort study                          | 2001–2005 | Spain  | 30*                     | 1085        | 378      | 707        | RR: 0.37 (0.21–0.50; P < 0.001)               | 0.72 (0.58–0.84)                        |
| Teng, Australia, 2010 (WAHMD)                          | Retrospective cohort study                         | 1996–2006 | Australia | 12                     | 284        | 101      | 183        | RR: 0.62 (0.39–0.99; P < 0.048)               | RR: 0.45 (0.26–0.80; P < 0.006)          |
| Fauchier, France, 2009 (35% HFpEF)                     | Retrospective cohort study (AF)                    | 2000–2004 | France  | 29                     | 1269       | 449      | 820        | RR: 0.59 (0.45–0.80; P < 0.001)               | RR: 0.68 (0.53–0.86; P < 0.002)          |
| Shah, USA, 2008 (NHC)                                 | Retrospective cohort study (≥65 years)             | 1998–1999, 2000–2001 | USA  | 36                     | 13 533     | 4562     | 8971       | RR: 0.92 (0.87–0.97)                           | RR: 0.92 (0.87–0.97)                    |
| Dobre, Netherlands, 2007 (propensity score adjusted)  | Prospective cohort study                           | 2000–2005 | Netherlands | 25                     | 443        | 227      | 216        | RR: 0.57 (0.37–0.88; P < 0.01)                | RR: 0.57 (0.37–0.88; P < 0.01)          |
| Observational studies—neutral treatment effect         |              |              |        |                         |             |         |            |                                            |                                        |
| Ushigome, Japan, 2015 (1. CHART-1)                     | Prospective cohort study                           | 2000–2005 | Japan  | 36                     | 463        | 104      | 359        | RR: 0.89 (0.45–1.75; P < 0.734)              | RR: 0.94 (0.73–1.22; P < 0.654)         |
| Ushigome, Japan, 2015 (2. CHART-2)                     | Prospective cohort study                           | 2006–2010 | Japan  | 36                     | 2316       | 1018     | 1298       | RR: 0.99 (0.90–1.10; P < 0.897)              | RR: 0.94 (0.84–1.07)                    |
| Patel, USA, 2014 (OPTIMIZE-HF)                         | Registry (PSM) (≥65 years)                         | 2003–2004 | USA  | 72                     | 2198       | 1099     | 1099       | RR: 0.77 (0.60–0.98; P < 0.04)               | RR: 0.60 (0.43–0.84; P < 0.003)         |
| Hernandez, USA, 2009 (OPTIMIZE-HF)                     | Registry (≥65 years)                               | —         | USA  | 12                     | 4153       | 1621     | 2532       | RR: 0.87 (0.77–0.97)                           | RR: 0.84 (0.77–0.97)                    |
| Mixed/unspecified HF phenotype                         |              |              |        |                         |             |         |            |                                            |                                        |
| Randomized controlled trials—neutral effect            |              |              |        |                         |             |         |            |                                            |                                        |
| Flather, UK, 2005 (SENIORS) (65% HFrEF, 35% HFpEF)    | RCT (≥70 years)                                    | 2000–2002 | Multiregional | 21                     | 2128       | 1067     | 1061       | RR: 0.88 (0.71–1.08; P < 0.21)               | RR: 0.88 (0.71–1.08; P < 0.21)          |
| Observational studies—beneficial treatment effect      |              |              |        |                         |             |         |            |                                            |                                        |
| Katz, Israel, 2016 (HFSIS) (38% HFrEF, 15% HFrEF, 22% HFpEF, 26% unknown) | Prospective cohort study                           | 2003 | Israel  | 120                    | 2402       | 1481     | 921        | RR: 0.83 (0.77–0.89; P < 0.001)              | RR: 0.83 (0.77–0.89; P < 0.001)         |
| Maison, France, 2013                                   | Registry (propensity score adjusted)               | 2000 | France  | 96                     | 281        | 101      | 180        | RR: 0.54 (0.34–0.84)                           | RR: 0.54 (0.34–0.84)                    |
| Gastelurrutia, Spain, 2012 (75% HFrEF, 25% HFpEF)     | Prospective cohort study                           | 2001–2008 | Spain  | 44*                    | 960        | 776      | 184        | RR: 0.51 (0.39–0.66; P < 0.001)              | RR: 0.51 (0.39–0.66; P < 0.001)         |
| Marijon, France, 2010 (EVADEF)                        | Prospective cohort study (ICD)                     | 2001–2003 | France  | 22                     | 1030       | 721      | 309        | RR: 0.56 (0.32–0.98; P < 0.04)               | RR: 0.68 (0.53–0.86; P < 0.002)         |
| Teng, Australia, 2010 (WAHMD) (24% HFrEF, 30% HFpEF, 46% unknown) | Retrospective cohort study                         | 1996–2006 | Australia | 12                     | 944        | 318     | 626        | RR: 0.68 (0.53–0.86; P < 0.002)              | RR: 0.68 (0.53–0.86; P < 0.002)         |
| Fauchier, France, 2009 (14% HFrEF, 35% HFpEF, 24% unknown) | Retrospective cohort study (AF)                    | 2000–2004 | France  | 29                     | 1269       | 449      | 820        | RR: 0.59 (0.45–0.78; P < 0.0002)             | RR: 0.59 (0.45–0.78; P < 0.0002)         |
| First author, country, year of publication (study name) | Study design | Study period | Region | Mean follow-up (months) | Patients (n) | Study (n) | Control (n) | All-cause mortality—unadjusted HR (95% CI) | All-cause mortality—adjusted HR (95% CI) |
|--------------------------------------------------------|--------------|--------------|--------|------------------------|-------------|-----------|------------|------------------------------------------|----------------------------------------|
| Jordań, Spain, 2009 (BADAPIC) (77% HFrEF, 23% HFpEF) | Registry     | 2000–2002    | Spain  | 35                      | 3162        | 2242      | 920        | RR: 0.82 (0.47–0.95)                       |                                        |
| Dobre, Netherlands, 2007 (55% HFrEF, 45% HFpEF)     | Prospective cohort study (propensity score adjusted) | 2000–2004 | Netherlands | 22          | 625        | 308       | 317        | 0.55 (0.39–0.78; P < 0.001)                |                                        |
| Keyhan, Canada, 2007 (1. female cohort)              | Retrospective cohort study (≥65 years) | 1998–2003 | Canada  | 30                      | 14693       | 7584      | 7109       | 0.67 (0.64–0.70)                           | 0.79 (0.75–0.83)                       |
| Keyhan, Canada, 2007 (2. male cohort)                | Retrospective cohort study (≥65 years) | 1998–2003 | Canada  | 30                      | 13144       | 6499      | 6645       | 0.64 (0.61–0.67)                           | 0.76 (0.72–0.80)                       |
| Chan, USA, 2005 (CHS) (19% HFrEF, 36% HFpEF, 45% unknown) | Prospective cohort study (≥65 years) | 1989–2000 | USA    | 120                     | 950         | 157       | 793        | 0.74 (0.56–0.98)                           | 0.74 (0.56–0.98)                       |
| Tandon, Canada, 2004 (75% HFrEF, 25% HFpEF)         | Prospective cohort study | 1989–2001 | Canada  | 32          | 1041        | 475       | 566        | OR: 0.52 (0.39–0.70)                       |                                        |
| Maggioni, Italy, 2003 (BRING-UP) (1. no BB vs. continued BB) | Registry | 1998          | Italy  | 12                      | 2226        | 771       | 1455       | 0.74 (0.55–0.99; P < 0.005)                |                                        |
| Maggioni, Italy, 2003 (BRING-UP) (2. no BB vs. initiated BB) | Registry | 1998          | Italy  | 12                      | 2320        | 865       | 1455       | 0.60 (0.45–0.80; P < 0.0003)               |                                        |
| McCullough, USA, 2003 (REACH)                        | Retrospective cohort study | 1995–1998 | USA    | 12                      | 1317        | 647       | 670        | OR: 0.75 (0.57–0.98; P < 0.04)             |                                        |
| Sin, Canada, 2002 (19% HFrEF, 36% HFpEF, 45% unknown) | Prospective cohort study (≥65 years) (propensity score adjusted) | 1994–1998 | Canada  | 21          | 11942       | 1162      | 10780      | 0.72 (0.65–0.80)                           |                                        |
| McAlister, Canada, 1999 (78% HFrEF, 22% HFpEF)       | Prospective cohort study | 1989–1995 | Canada  | 17                      | 566         | 147       | 419        | OR: 0.5 (P < 0.006–95% CI not reported)    |                                        |
| Observational studies—neutral treatment effect      |              |              |        |                        |             |           |            |                                          |                                        |
| Ushigome, Japan, 2015 (1, CHART-1) (54% HFrEF, 46% HFpEF) | Prospective cohort study | 2000–2005 | Japan  | 36                      | 1006        | 288       | 718        | 0.96 (0.63–1.44; P < 0.829)               |                                        |
| Ushigome, Japan, 2015 (1, CHART-2) (37% HFrEF, 63% HFpEF) | Prospective cohort study | 2006–2010 | Japan  | 36                      | 3676        | 1886      | 1790       | 0.82 (0.68–1.00; P < 0.055)               |                                        |

Median. —, Not reported; AF, atrial fibrillation cohort; AF-CHF, Atrial Fibrillation and Congestive Heart Failure; ANZ, Australia/New Zealand; BADAPIC, Registry of the Working Group on Heart Failure, Heart Transplantation and Other Therapeutic Alternatives of the Spanish Society of Cardiology; BB, beta-blocker; BEST, Beta-blocker Evaluation in Survival Trial; BRING-UP, Beta-Blockers in Patients With Congestive Heart Failure: Guided Use in Clinical Practice; CHS, Cardiovascular Health Study; CHART, Chronic Heart Failure Analysis and Registry in the Tohoku district; CI, confidence interval; CIBIS, Cardiac Insufficiency Bisoprolol Study; COPERNICUS, Carvedilol Prospective Randomized Cumulative Survival; EF, ejection fraction; EVADEF, Evaluation Médico-Economique du Défibrillateur Automatique Implantable; HF, heart failure; HFrEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFSIS, National Heart Failure Survey in Israel; HR, hazard ratio; ICD, implantable cardioverter defibrillator cohort; IHD, ischaemic heart disease cohort; J-DHF, Japanese Diastolic Heart Failure; MERIT-HF, Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NHCS, National Heart Care; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; OR, odds ratio; PROBE, prospective randomized open blind endpoint study; PSM, propensity score matched study; RCT, randomized controlled trial; REACH, Resource Utilization Among Congestive Heart Failure; RR, risk ratio/relative risk; SENIORS, Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure; ‘Trial patients’, patients meeting the inclusion criteria of the MERIT-HF trial; ‘Non-trial patients’, patients not meeting the inclusion criteria of the MERIT-HF trial; WAHMD, Western Australia Hospital Morbidity Data.
| First author, country, year of publication (study name) | Study design | Study period | Region | Mean follow-up (months) | Patients (n) | Study (n) | Control (n) | All-cause mortality—unadjusted HR (95% CI) | All-cause mortality—adjusted HR (95% CI) |
|--------------------------------------------------------|-------------|--------------|--------|-------------------------|-------------|-----------|------------|------------------------------------------|----------------------------------------|
| **HFpEF**                                               |             |              |        |                         |             |           |            |                                          |                                        |
| **Randomized controlled trials—neutral treatment effect** |             |              |        |                         |             |           |            |                                          |                                        |
| Pfeffer, USA, 2015 (TOPCAT-Americas subgroup)           | Post hoc analysis of RCT | 2006–2012 | USA, Canada, Brazil, Argentina | 35          | 1767 | 886       | 881       | 0.83 (0.68–1.02; P < 0.08) | —                                      |
| **Observational studies—harmful treatment effect**      |             |              |        |                         |             |           |            |                                          |                                        |
| O'Meara, Canada, 2012 (AF-CHF)                          | Post hoc analysis of RCT | 2001–2005 | Multiregional | 37          | 1376 | 616       | 760       | 1.40 (1.10–1.80; P < 0.005) | —                                      |

**Table 4** All-cause mortality in randomized and non-randomized MRA HF studies

*Association is not causation*
| First author, country, year of publication (study name) | Study design | Study period | Region | Mean follow-up (months) | Patients (n) | Study (n) | Control (n) | All-cause mortality—unadjusted HR (95% CI) | All-cause mortality—adjusted HR (95% CI) |
|------------------------------------------------------|--------------|--------------|--------|------------------------|--------------|-----------|------------|------------------------------------------|----------------------------------------|
| Pfeffer, USA, 2015 (TOPCAT-Russia/Georgia subgroup)  | Post hoc analysis of RCT | 2006–2012 | Russia, Georgia | 44 | 1678 | 836 | 842 | 1.12 (0.80–1.55; P < 0.51) | — |
| Pitt, USA, 2014 (TOPCAT) | RCT | 2006–2012 | Multiregional | 40 | 3445 | 1722 | 1723 | 0.91 (0.77–1.08; P < 0.295) | 0.88 (0.74–1.05; P < 0.151) |
| Observational studies—beneficial treatment effect | Bonsu, Malaysia, 2017 | Retrospective cohort study | 2009–2013 | Ghana | 60 | 878 | 227 | 651 | — | 0.66 (0.49–0.89; P < 0.006) |
| Observational studies—neutral treatment effect | Ushigome, Japan, 2015 (2. CHART-2) | Prospective cohort study | 2006–2010 | Japan | 36 | 2316 | 491 | 1825 | — | 0.96 (0.72–1.29; P < 0.808) |
| Patel, USA, 2013 (OPTIMIZE-HF) | Registry (PSM) (≥65 years) | 2002–2008 | USA | 29 | 974 | 487 | 487 | — | 1.03 (0.89–1.20; P < 0.693) |
| Observational studies—neutral treatment effect | Bonsu, Malaysia, 2017 (23% HFrEF, 18% HFmrEF, 59% HFpEF) | Retrospective cohort study | 2009–2013 | Ghana | 60 | 1488 | 417 | 1071 | — | 0.81 (0.65–0.99; P < 0.049) |
| Sligl, Canada, 2004 (75% HFrEF, 25% HFpEF) | Prospective cohort study | 1989–2001 | Canada | 32 | 1037 | 136 | 901 | — | RR: 0.13 (0.04–0.42) |
| Observational studies—neutral treatment effect | Ushigome, Japan, 2015 (1. CHART-1) | Prospective cohort study | 2000–2005 | Japan | 36 | 1006 | 182 | 824 | — | 1.36 (0.89–2.07; P < 0.154) |
| Ushigome, Japan, 2015 (2. CHART-2) | Prospective cohort study | 2006–2010 | Japan | 36 | 3676 | 984 | 2692 | — | 1.14 (0.93–1.39; P < 0.223) |
| Teng, Australia, 2010 (34% HFrEF, 19% HFpEF, 47% unknown) | Retrospective cohort study | 1996–2006 | Australia | 12 | 944 | 154 | 790 | — | 0.87 (0.64–1.20; P < 0.390) |

*Median.*

—, Not reported; AF, atrial fibrillation cohort; AF-CHF, Atrial Fibrillation and Congestive Heart Failure; CHART, Chronic Heart Failure Analysis and Registry in the Tohoku district; CI, confidence interval; EMPHASIS-HF, Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure; GWTG-HF, Get With The Guidelines Heart Failure; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; ICONS, Improving Cardiovascular Outcomes in Nova Scotia; JCare-CARD, Japanese Cardiac Registry of Heart Failure in Cardiology; KPNC, Kaiser Permanente Northern California; MRA, mineralocorticoid receptor antagonist; MUSIC, Multi-Sensor Monitoring in Congestive Heart Failure; OPTIMIZE-HF, Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure; OR, odds ratio; PSM, propensity score matched study; RALES, Randomized Aldactone Evaluation Study; RCT, randomized controlled trial; RR, risk ratio/relative risk; TOPCAT, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist Trial.
| First author, country, year of publication (study name) | Study design | Study period | Region | Mean follow-up (months) | Patients (n) | Study (n) | Control (n) | All-cause mortality—unadjusted HR (95% CI) | All-cause mortality—adjusted HR (95% CI) |
|--------------------------------------------------------|--------------|--------------|--------|------------------------|-------------|----------|------------|------------------------------------------|----------------------------------------|
| **HFrEF**                                               |              |              |        |                        |             |          |            |                                          |                                        |
| Kjekshus, Norway, 2007 (CORONA) [14]                    | RCT          | 2003–2005    | Europe, Russia, South Africa | 33a         | 5011       | 2514     | 2497       | 0.95 (0.86–1.05; P < 0.31) | —                                     |
| Takano, Japan, 2013 (PEARL) [14]                        | PROBE        | 2006–2008    | Japan  | 36a                    | 574         | 288      | 286        | —                                         | 0.73 (0.44–1.20; P < 0.211) |
| **Observational studies—beneficial treatment effect**   |              |              |        |                        |             |          |            |                                          |                                        |
| Alehagen, Sweden, 2015 (Swedish HF Registry) [57]       | Registry (PSM) | 2000–2012    | Sweden | 47a                    | 10 762      | 5381     | 5381       | —                                         | 0.81 (0.76–0.86; P < 0.001) |
| Liu, China, 2014 [48]                                   | Prospective cohort study | 2005–2010    | China  | 52a                    | 2154        | 936      | 1218       | —                                         | 0.50 (0.37–0.67; P < 0.001) |
| Gomez-Soto, Spain, 2010 (56% HFrEF) [88]                | Prospective cohort study (propensity score adjusted) | 2001–2005    | Spain  | 34                      | 2573        | 1343     | 1230       | —                                         | 0.20 (0.09–0.31; P < 0.001) |
| Sumner, USA, 2009 (COMPANION) [59]                      | Post hoc analysis of RCT (CRT) | 2000–2002    | USA    | 15–16a                  | 15 200      | 603      | 917        | 0.85 (0.67–1.07; P < 0.15) | 0.77 (0.61–0.97; P < 0.03) |
| Coleman, USA, 2008 [50]                                 | Retrospective cohort study (ICD) | 1997–2007    | USA    | 31                      | 1204        | 642      | 562        | —                                         | 0.67 (0.53–0.85; P < 0.001) |
| Dokinson, USA, 2007 (SCD-HeFT) [91]                     | Post hoc analysis of RCT | 1997–2001    | North America, New Zealand | 46          | 2521      | 965      | 1556       | —                                         | 0.70 (0.58–0.83; P < 0.001) |
| Huan Loh, UK, 2007 (1. no statin vs. initiated statin)  | Retrospective cohort study | —            | UK     | 36a                    | 479         | 102      | 377        | 0.52 (0.32–0.84) | 0.50 (0.30–0.83) |
| Krum, Australia, 2007 (CIBIS-II) [92]                   | Post hoc analysis of RCT | —            | Europe | 16                      | 2647        | 226      | 2421       | 0.57 (0.37–0.94) | 0.60 (0.39–0.94; P < 0.02) |
| Krum, Australia, 2007 (Val-HeFT) [70]                   | Post hoc analysis of RCT | 1997–1999    | Multiregional | 23          | 5010      | 1602     | 3408       | —                                         | 0.81 (0.70–0.94; P < 0.005) |
| Anker, UK, 2006 (1. ELITE-II) [74]                      | Post hoc analysis of RCT | 1997–1998    | Multiregional | 18a         | 3132      | 2734     | 398        | 0.61 (0.45–0.83; P < 0.06) | 0.61 (0.44–0.84; P < 0.03) |
| Anker, UK, 2006 (2. European Centres Study) [74]        | Retrospective cohort study | 1992–2000    | Europe  | 24a                    | 2068        | 705      | 1363       | 0.59 (0.49–0.72; P < 0.0007) | 0.58 (0.44–0.77; P < 0.0001) |
| Goldberger, USA, 2006 (DEFINITE) [95]                   | Post hoc analysis of RCT (non-ischaemic DCM) | 1998–2002    | USA    | 29                      | 458         | 110      | 348        | 0.22 (0.09–0.55; P < 0.001) | 0.23 (0.09–0.58; P < 0.04) |
| Ray, Canada, 2005 [76]                                  | Retrospective cohort study (66–85 years) | 1995–2001    | Canada | 24                      | 28 828      | 1146     | 27 682     | 0.50 (0.43–0.59) | 0.67 (0.57–0.78) |

Association is not causation
| First author, country, year of publication (study name) | Study design | Study period | Region | Mean follow-up (months) | Patients (n) | Study (n) | Control (n) | All-cause mortality—unadjusted HR (95% CI) | All-cause mortality—adjusted HR (95% CI) |
|---------------------------------------------------------|--------------|--------------|--------|-------------------------|--------------|-----------|------------|----------------------------------------|----------------------------------------|
| Mozaffarian, USA, 2004 (PRAISE)69                       | Post hoc analysis of RCT | 1992–1994 | USA    | 15                      | 1153         | 134       | 1019       | 0.38 (0.23–0.64)                        | 0.44 (0.26–0.75)                        |
| Observational studies—neutral treatment effect          |              |              |        |                         |              |           |            |                                        |                                        |
| Ushigome, Japan, 2015 (CHART-2)30                        | Prospective cohort study | 2006–2010 | Japan  | 36                      | 1360         | 515       | 845        | —                                     | 0.84 (0.60–1.17; P < 0.299)             |
| Ouzounian, Canada, 2009 (EFFECT) (23% HFrEF)98           | Retrospective cohort study | 1999–2001 | Canada | 60                      | 6451         | 5330      | 1121       | —                                     | 0.84 (0.70–1.02; P < 0.07)              |
| Huan Loh, UK, 2007 (2. no statin vs. continued statin)59 | Retrospective cohort study | —         | UK     | 36                      | 760          | 377       | 383        | 0.74 (0.52–1.05)                        | 0.82 (0.55–1.23)                        |
| Mixed/unspecified HF phenotype                           |              |              |        |                         |              |           |            |                                        |                                        |
| Tavazzi, Italy, 2008 (GISSI-HF Rosuvastatin) (90% HFrEF, 10% HfPef)144 | RCT (≥60 years) | 2002–2005 | Italy  | 47                      | 4574         | 2285      | 2289       | 1.03 (95.5% CI 0.92–1.15; P < 0.660)     | 1.00 (95.5% CI 0.90–1.12; P < 0.943)    |
| Observational studies—beneficial treatment effect       |              |              |        |                         |              |           |            |                                        |                                        |
| Bonsu, Malaysia, 2017 (23% HFrEF, 18% HfPef, 59% HFrEF)99 | Retrospective cohort study (IPTW) | 2009–2013 | Ghana | 60                      | 1488         | 552       | 936        | —                                     | 0.79 (0.65–0.96; P < 0.019)             |
| Ballo, Italy, 2016100                                    | Retrospective cohort study | —         | Italy  | 12                      | 2088         | 643       | 1445       | —                                     | 0.65 (0.51–0.83; P < 0.001)             |
| Gastelurrutia, Spain, 2012 (75% HFrEF, 25% HFrEF)45     | Prospective cohort study | 2001–2008 | Spain | 44                      | 960          | 591       | 369        | 0.45 (0.37–0.54; P < 0.001)             | 0.66 (0.53–0.83; P < 0.001)             |
| Gomez-Soto, Spain, 2010 (56% HFrEF, 44% HFrEF)88        | Prospective cohort study (propensity score adjusted) | 2001–2005 | Spain | 34                      | 2573         | 1343      | 1230       | —                                     | 0.71 (0.59–0.83)                        |
| Jordán, Spain, 2009 (BADAPIC) (77% HFrEF, 23% HfPef)68  | Registry | 2000–2002 | Spain  | 35                      | 3162         | 1305      | 1857       | —                                     | RR: 0.73 (0.45–0.88; P < 0.001)         |
| Nevzorov, Israel, 2009 (61% HFrEF, 39% HfPef)101        | Retrospective cohort study (IHD) | 2001–2005 | Israel | 12                      | 656          | 238       | 418        | OR: 0.63 (0.40–0.87; P < 0.006)          | 0.66 (0.40–0.97; P < 0.035)             |
| Ouzounian, Canada, 2009 (EFFECT)98                       | Retrospective cohort study (PSM) | 1999–2001 | Canada | 60                      | 1442         | 721       | 721        | —                                     | 0.85 (0.72–1.00; P < 0.05)              |
| Ryan, UK, 2009 (THIN) (1. statin before HF diagnosis)102 | Retrospective cohort study | 1995–2004 | UK     | 24                      | 10 914       | 2185      | 8239       | —                                     | 0.53 (0.40–0.70; P < 0.001)             |
| Ryan, UK, 2009 (THIN) (2. statin after HF diagnosis)93   | Retrospective cohort study | 1995–2004 | UK     | 24                      | 8729         | 191       | 8538       | —                                     | 0.68 (0.46–0.99; P < 0.047)             |
| Foody, USA, 2006 (NHC) (48% HFrEF, 52% HfPef)103        | Retrospective cohort study (≥65 years) | 1998–1999, 2000–2001 | USA | 36                      | 54 960       | 9163      | 45 797     | 0.67 (0.65–0.69; P < 0.001)             | 0.82 (0.79–0.85; P < 0.001)             |

Continued
Association is not causation

Table 5

| First author, country, year of publication | Study design | Study period | Region | Mean follow-up (months) | Patients (n) | Study | Control | All-cause mortality-adjusted HR (95% CI) |
|------------------------------------------|-------------|--------------|--------|-------------------------|-------------|-------|---------|----------------------------------------|
| Go, USA, 2006 (KPNC) (25% HFrEF, 26% HFpEF, 49% unknown) | Retrospective cohort | 1996–2004 USA | 29 | 24,598 | 12,648 | 11,960 | — | 0.76 (0.72–0.80; P < 0.001) |
| Ushigome, Japan, 2015 (CHART-2) (37% HFrEF, 63% HFpEF) | Prospective cohort study | 2006–2010 Japan | 36 | 3676 | 1332 | 2344 | — | 0.81 (0.65–1.02; P = 0.068) |

Discussion

Heart failure with preserved ejection fraction

The use of statins has not been evaluated in a randomized trial in patients with HFrEF, therefore, no relevant non-randomized studies were identified.

Mixed/unspecified heart failure phenotype

One large statin trial included patients with both HFrEF and HFpEF and showed no effect of treatment on mortality.144 Eleven observational studies reported 12 estimates of the ‘effect’ of a statin in patients with a mixture of HFrEF and HFpEF phenotypes, or where EF was not specified. Of these, 11 reported an association between statin use and better outcome, and only one describing no relationship between treatment and mortality.30 (Table 5).

Digoxin

Heart failure with reduced ejection fraction

A single RCT, the Digitalis Investigators Group (DIG) trial, showed that, in sinus rhythm, digoxin had a neutral effect on death but reduced the risk of HF hospitalization.145 Nine non-randomized studies reported 10 estimates of the ‘effect’ of digoxin treatment in HFrEF, with five concluding digoxin was harmful, with four reporting a neutral effect,146 and one suggesting digoxin was beneficial146 (Table 6).

Heart failure with preserved ejection fraction

A single randomized trial of modest size, the DIG ancillary trial in HFpEF (n = 988), showed no effect of digoxin on mortality in patients with HFpEF in sinus rhythm, although the estimate of the effect of treatment was not robust because of limited power.146 Four observational studies were identified, one suggesting that non-randomized digoxin treatment was beneficial,105 and three showing a neutral association between treatment and mortality.30,55 (Table 6).

Mixed/unspecified heart failure phenotype

The combined main and ancillary DIG trials showed a neutral effect of digoxin on mortality.147 Fourteen observational studies reported effect estimates for digoxin in patients with HFrEF and HFpEF in combination, or where EF was not specified. These studies reported 16 estimates of ‘treatment-effect’. Seven found an association between the use of digoxin and a higher mortality, and two suggested better outcomes associated with digoxin use.105,111 (Table 6).

Discussion

There is a particularly strong evidence base for the treatment of HF, making it an appropriate condition in which to compare treatment effects established in RCTs with those estimated in non-randomized and observational studies.

Looking first at patients with HFrEF, six observational studies (reporting seven ‘effect’ estimates) fulfilled our inclusion criteria, and examined the association between treatment with an ACEI/ARB and mortality. Of these, five showed a lower mortality in patients with HFrEF compared to control patients (Table 5).
### Table 6  All-cause mortality in randomized and non-randomized digoxin HF studies

| First author, country, year (study name) | Study design | Study period | Region | Mean follow-up (months) | Patients (n) | Study (n) | Control (n) | All-cause mortality—unadjusted HR (95% CI) | All-cause mortality—adjusted HR (95% CI) |
|----------------------------------------|--------------|--------------|--------|-------------------------|--------------|-----------|------------|------------------------------------------|----------------------------------------|
| **HFrEF**                              |              |              |        |                         |              |           |            |                                          |                                        |
| Randomized controlled trials—neutral treatment effect |              |              |        |                         |              |           |            |                                          |                                        |
| Digoxin Investigation Group, USA, 1997 (DIG Main Trial) | RCT (SR)     | 1991–1993    | USA, Canada | 37                        | 6800         | 3397      | 3403       | RR: 0.99 (0.91–1.07; P < 0.80)             | —                                      |
| Observational studies—beneficial treatment effect |              |              |        |                         |              |           |            |                                          |                                        |
| Andrey, Spain, 2011 (51% HFrEF) | Prospective cohort study (PSM) (SR/AF) | 2001–2008 | Spain | 46^                        | 2842         | 1421      | 1421       | —                                        | 0.92 (0.89–0.95; P < 0.005)               |
| Observational studies—neutral treatment effect |              |              |        |                         |              |           |            |                                          |                                        |
| Ushigome, Japan, 2015 (1. CHART-1) | Prospective cohort study (SR/AF) | 2000–2005 | Japan | 36                        | 543          | 229       | 314        | —                                        | 0.99 (0.61–1.61; P < 0.978)               |
| Ushigome, Japan, 2015 (2. CHART-2) | Prospective cohort study (SR/AF) | 2006–2010 | Japan | 36                        | 1360         | 586       | 774        | —                                        | 1.10 (0.80–1.51; P < 0.558)               |
| Poulsen, France, 2009 (41% HFpEF) | Retrospective cohort study (AF) | 2000–2004 | France | 29                        | 1269         | 591       | 678        | —                                        | RR: 0.79 (0.54–1.16; P < 0.23)            |
| Daliwal, USA, 2008 | Retrospective cohort study (SR/AF) | 2002–2004 | USA | 10^                        | 347          | 155       | 192        | 1.15 (0.85–1.55; P < 0.37)                 | 1.11 (0.81–1.53; P < 0.521)               |
| Observational studies—harmful treatment effect |              |              |        |                         |              |           |            |                                          |                                        |
| Al-Khateeb, Saudi Arabia, 2017 | Retrospective cohort study (PSM) (SR/AF) | 2000–2015 | Saudi Arabia | 43^                        | 1075         | 325       | 750        | 1.81 (1.33–2.45; P < 0.001)                | 1.74 (1.20–2.38; P < 0.0001)             |
| Freeman, USA, 2013 (KPNC) | Retrospective cohort study (SR/AF) | 2006–2008 | USA | 30^                        | 2891         | 529       | 2362       | —                                        | 1.72 (1.25–2.36)                         |
| Butler, USA, 2010 (Val-HeFT) | Post hoc analysis of RCT (SR/AF) | — | Multiregional | 23                        | 5010         | 1636      | 3374       | 1.46 (1.23–1.64; P < 0.001)                | 1.28 (1.05–1.57; P < 0.02)               |
| Domanski, USA, 2005 (SOLVD) (1. female cohort) | Post hoc analysis of RCT (SR/AF) | 1986–1989 | USA, Canada, Belgium | 39                        | 988          | 370       | 618        | 1.48 (1.10–2.00; P < 0.01)                | 1.36 (1.03–1.80; P < 0.03)               |
| Domanski, USA, 2005 (SOLVD) (2. male cohort) | Post hoc analysis of RCT (SR/AF) | 1986–1989 | USA, Canada, Belgium | 39                        | 5809         | 1874      | 3935       | 1.37 (1.20–1.56; P < 0.0001)              | 1.42 (1.26–1.61; P < 0.0001)             |
| **HFpEF**                              |              |              |        |                         |              |           |            |                                          |                                        |
| Randomized controlled trials—neutral treatment effect |              |              |        |                         |              |           |            |                                          |                                        |
| Ahmed, USA, 2006 (DIG Ancillary Trial) | RCT (SR)     | 1991–1993    | USA, Canada | 37                        | 988          | 492       | 496        | 0.99 (0.76–1.28; P < 0.925)                | —                                      |
| Observational studies—beneficial treatment effect |              |              |        |                         |              |           |            |                                          |                                        |
| Andrey, Spain, 2011 (49% HFpEF) | Prospective cohort study (PSM) (SR/AF) | 2001–2008 | Spain | 46^                        | 2842         | 1421      | 1421       | —                                        | 0.86 (0.79–0.92; P < 0.008)               |
| Observational studies—neutral treatment effect |              |              |        |                         |              |           |            |                                          |                                        |
| Ushigome, Japan, 2015 (1. CHART-1) | Prospective cohort study (SR/AF) | 2000–2005 | Japan | 36                        | 463          | 249       | 214        | —                                        | 0.92 (0.65–1.54; P < 0.764)               |
| Ushigome, Japan, 2015 (2. CHART-2) | Prospective cohort study (SR/AF) | 2006–2010 | Japan | 36                        | 2316         | 335       | 1981       | —                                        | 1.07 (0.81–1.41; P < 0.632)               |
| First author, country, year (study name) | Study design | Study period | Region | Mean follow-up (months) | Patients (n) | Study (n) | Control (n) | All-cause mortality—unadjusted HR (95% CI) | All-cause mortality—adjusted HR (95% CI) |
|----------------------------------------|--------------|--------------|--------|------------------------|-------------|-----------|------------|------------------------------------------|----------------------------------------|
| Fauchier, France, 2009 (35% HFpEF)55  | Retrospective cohort study (AF) | 2000–2004 France | 29 | 1269 | 591 | 678 | — | RR: 1.21 (0.77–1.89; P < 0.42) |  |
| Mixed/unspecified HF phenotype         |              |              |        |                        |             |           |            |                                          |                                        |
| Rich, USA, 2001 (DIG Overall)147      | RCT (SR)     | 1991–1993 USA, Canada | 37 | 7788 | 3899 | 3899 | — | RR: 0.99 (0.92–1.07; P < 0.7815) |  |
| Observational studies—beneficial treatment effect | | | | | | | | | 0.83 (0.70–0.98) |  |
| Ahmed, USA, 2014 (Alabama HF Project) | Retrospective cohort study (PSM) (SR/AF) | 1998–2001 USA | 12 | 1842 | 921 | 921 | — |  |  |
| Andrey, Spain, 2011 (51% HFrEF, 49% HFpEF)106 | Prospective cohort study (PSM) (SR/AF) | 2001–2008 Spain | 46a | 2842 | 1421 | 1421 | — |  | 0.90 (0.84–0.97) |  |
| Observational studies—neutral treatment effect | | | | | | | | |  |
| Ushigome, Japan, 2015 (1. CHART-1) (54% HFrEF, 46% HFpEF)30 | Prospective cohort study (SR/AF) | 2000–2005 Japan | 36 | 1006 | 478 | 528 | — | 0.97 (0.69–1.38; P < 0.875) |  |
| Ushigome, Japan, 2015 (2. CHART-2) (37% HFrEF, 63% HFpEF)30 | Prospective cohort study (SR/AF) | 2006–2010 Japan | 36 | 3676 | 921 | 2755 | — | 1.06 (0.87–1.31; P < 0.555) |  |
| Flory, USA, 2012 (THIN) (1. female cohort)112 | Retrospective cohort study (SR/AF) | 1986–2008 UK | — | 30035 | 10 808 | 19 227 | — | 1.00 (0.96–1.06) |  |
| Flory, USA, 2012 (THIN) (2. male cohort)112 | Retrospective cohort study (SR/AF) | 1986–2008 UK | — | 27 194 | 9487 | 17 707 | — | 1.00 (0.95–1.06) |  |
| Fauchier, France, 2009 (41% HFrEF, 35% HFpEF, 24% unknown)55 | Retrospective cohort study (SR/AF) | 2000–2004 France | 29 | 1269 | 591 | 678 | — | 0.90 (0.66–1.24; P < 0.53) |  |
| Hallberg, Sweden, 2007 (RIKS-HIA) (58% HFrEF, 42% HFpEF) (1. AF cohort)113 | Registry (propensity score adjusted) | 1995–2003 Sweden | 12 | 16 960 | 7758 | 9202 | RR: 1.07 (1.01–1.14) | RR: 1.00 (0.94–1.06) |  |
| Pedone, Italy, 2004 (GIFA)12 | Prospective cohort study (SR/AF) | 1998 Italy | 10 | 818 | 539 | 297 | — | 0.75 (0.51–1.10) |  |
| Observational studies—harmful treatment effect | | | | | | | | |  |
| Eisen, USA, 2017 (ENGAGE AF-TIMI 48) (41% HFrEF, 34% HFpEF, 24% unknown)114 | Post hoc analysis of RCT (IPTW) (AF) | 2008–2010 Multiregional | 34a | 8102 | 4051 | 4051 | — | 1.29 (1.15–1.44) |  |
| Katz, Israel, 2016 (HFSIS) (38% HFrEF, 15% HFMrEF, 22% HFpEF, 26% unknown)45 | Prospective cohort study (SR/AF) | 2003 Israel | 120 | 2402 | 380 | 2022 | — | 1.27 (1.16–1.42; P < 0.001) |  |
| Madelaine, Denmark, 2016115 | Retrospective cohort study (PSM) (SR) | 1996–2012 Denmark | 32a | 15 981 | 5327 | 10 654 | — | 1.19 (1.15–1.24; P < 0.001) |  |

Association is not causation
Table 6

| First author, country, year (study name) | Study design | Study period | Region | Patients | Study Control | All-cause mortality—untreated, adjusted HR (95% CI) |
|----------------------------------------|--------------|--------------|---------|----------|---------------|--------------------------------------------------|
| Shah, Canada, 2014 (AFFIRM)            | Retrospective cohort study (PSM) | 1998–2012 Canada | 37 | 27 972 | 13 986 | 1.14 (1.11–1.17) |
| Whitehead, USA, 2013 (AFFIRM)          | Multiregional | 1989–2001 Canada | 32 | 1041 | 671 | 1.51 (1.10–2.07) |
| Hallberg, Sweden, 2007 (RKS-HIA)      | Post hoc analysis of RCT | 2005 | 12 | 22 345 | 18 549 | 1.35 (1.26–1.44) |
| Tandon, Canada, 2004 (75% HFrEF, 25% HFpEF) | Prospective cohort study (PSM) | 1989–2001 Canada | 113 | — | — | 1.41 (1.09–1.84) |

Mean follow-up (months) 37 1076 42 12 3701 370

Table continued

| Mean follow-up (months) | Study period | Region | Patients | Study Control | All-cause mortality—untreated, adjusted HR (95% CI) |
|-------------------------|--------------|---------|----------|---------------|--------------------------------------------------|
| —                       | 1998–2012 Canada | 37 | 27 972 | 13 986 | 1.14 (1.11–1.17) |
| —                       | Multiregional | 1989–2001 Canada | 32 | 1041 | 671 | 1.51 (1.10–2.07) |
| —                       | 2005 | 12 | 22 345 | 18 549 | 1.35 (1.26–1.44) |
| —                       | 1989–2001 Canada | 113 | — | — | 1.41 (1.09–1.84) |

Mean follow-up (months) 37 1076 42 12 3701 370

The non-randomized analyses of beta-blockers in HFrEF also showed good agreement with the RCTs, with 16 of 18 analyses converging. However, this was not the case in observational studies of patients with a mixed HF phenotype, where the study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial had shown a neutral effect on mortality. Of the 19 non-randomized analyses, 17 showed a lower mortality among patients of this type treated with a beta-blocker.

However, the picture was quite different for MRAs, which reduce mortality in HFrEF. Of 12 observational studies, one reported lower mortality in patients treated with a MRA, 10 did not find a better or worse outcome (i.e. were neutral), and one found a higher mortality (worse outcome) in the MRA treated patients. It is worth exploring this discordance in more detail. By far the largest study included 18 852 patients from Sweden and is worth examining in detail.

Another notable example of a discrepancy between observational data and randomized trials does address issues of safety and generalisability. All but three of a remarkable 17 observational ‘effect
estimates suggested that statins have a mortality benefit in HFrEF, yet two large independent RCTs showed no effect of this type of treatment on death. In patients with the mixed/unspecified HF phenotype, a further 11 of 12 analyses reported an association of statin use with mortality benefit. Again, it is instructive to examine one of the observational studies in detail. Go et al. used a Kaiser Permanente dataset with almost 25 000 patients to conduct careful propensity score-adjusted analyses of outcome related to statin treatment; the authors also used time-varying covariate adjustment for statin initiation during follow-up. The adjusted HR for all-cause mortality in patients treated with a statin (compared with those who were not) was 0.66 (95% CI 0.61–0.71) in individuals with CHD and 0.60 (95% CI 0.54–0.67) in those without CHD. Apart from the improbably large ‘reduction’ in mortality (34–40%), the similar ‘effect’ in patients with and without CHD seems unlikely given everything we know about the actions of statins. Moreover, the prior arguments made about generalisability and safety would need to be inverted here as the observational datasets included broad populations of patients with HF, presumably, receiving less intense monitoring than in the clinical trials.

Even in HFrEF, there are clearly discrepant findings between a large observational dataset and two randomized trials with an ARB and one trial with an ACEI. Once again, the most obvious example involves the Swedish HF registry. As previously, the authors of this study used an age- and propensity score-matched cohort. The adjusted HR for all-cause mortality in patients treated with an ACEI or ARB, compared with those not treated with one of these agents, was 0.90 (95% CI 0.85–0.96; P = 0.001). The authors also described a ‘dose–response’ relationship whereby the HR for high-dose treatment compared with no treatment was 0.85 (95% CI 0.78–0.83) and compared with low-dose treatment was 0.94 (95% CI 0.87–1.02). For this study, the authors used the issue of generalisability to explain why they saw benefit compared with the prior trials, in contradistinction to the case for MRAs where the opposite argument was made. Specifically, in this case, with ACEIs and ARBs, they argued that the broader, older and higher-risk population in the registry responded favourably to treatment compared with the more selected participants enrolled in the trials.

Much has been written recently in relation to the safety of digoxin in atrial fibrillation. Indeed, in a very illustrative example of the unreliability of observational data, Bavendiek et al. highlighted how in three separate and independent post hoc analyses of the same dataset, digoxin treatment was variably associated with increased all-cause mortality, was not associated with increased mortality and, in the third analysis, was associated with decreased in mortality in patients with an EF less than 30%. In HF, there is the same type of discrepancy between observational data and the single large RCT in HFrEF, an ancillary trial in HFrEF, and the combined analysis of the effect of digoxin in both HF phenotypes. In each of these analyses, digoxin had a neutral effect on all-cause mortality. A total of 30 observational analyses variously show better, worse, and neutral outcomes.

Why the non-randomized analyses of outcomes related to use of ACEI/ARB and beta-blockers in HFrEF were generally (but not absolutely) concordant with the RCTs, in contrast to the other treatments examined, is an interesting question. There may be less confounding by indication, i.e. ACEIs/ARBs and beta-blockers are recommended in essentially all patients with HFrEF, whereas digoxin and, at least until recently, MRAs were reserved for patients with more advanced HF. There may also have been particularly strong publication bias making it difficult to report studies suggesting that use of ACEIs/ARBs or beta-blockers is not associated with better outcomes (or even associated with worse outcomes). Of course, with both treatments there is also a strong selection bias whereby the sickest patients are least likely to be prescribed (and to tolerate) these therapies. The opposite consideration may apply to the non-randomized studies showing an association between treatments such as statins and lower mortality, with the possibility of other biases such as the ‘healthy-user effect’ not fully adjusted for.

Although our analyses show that the findings of non-randomized studies of the association between treatment use and outcomes are frequently inconsistent, they do not mean observational studies/registries are of no value. Registry-based analyses may be all that is available where randomized trials are not possible, such as in rare diseases or for rare outcomes. The latter forms the basis of pharmaco-epidemiological surveillance for rare adverse effects of drugs not identified in clinical trials. Non-randomized analyses may provide information on under-studied groups or subgroups excluded from clinical trials. However, the results of such analyses must be interpreted with caution, especially if the results of different analyses of this type conflict. Registries serve an important function in describing the use (or under-use) of evidence-based therapies in the ‘real-world’, often leading to initiatives to improve prescribing. Perhaps the greatest value of registries is the potential they offer to conduct more ‘real-world’ randomized trials, i.e. to randomize patients in a registry to treatment and follow their outcomes within the registry. This approach has been pioneered in a study of thrombus aspiration in ST-segment elevation myocardial infarction using the Swedish Coronary Angiography and Angioplasty Registry and a similar approach is now being used to conduct the Spironolactone Initiation Registry Randomized Interventional Trial in Heart Failure with Preserved Ejection Fraction (SPIRIT-HFpEF) in the Swedish HF Registry.

Our study has a number of strengths and limitations. The strengths include the robust evidence base in HF, with often more than one randomized trial supporting the use or avoidance of specific therapies. There is a specific limitation in relation to the effect of MRAs in HFrEF. In the single, prospective, RCT, ineligible patients were included, and study drug was not administered, at certain investigative sites. As a result, the integrity of the trial has been questioned, as has the overall treatment effect observed. Examination of the effect of therapy in regions where the trial is thought to have been conducted as intended suggested possible benefit of spironolactone, compared with placebo. Consequently, the effect of spironolactone in this RCT and in the one observational analysis which suggested no benefit from MRA therapy may not be in agreement.

**Conclusion**

This comprehensive comparison of the robust evidence base in HF with an increasing number of non-randomized data shows that it is not possible to make reliable therapeutic inferences from observational associations. While trials undoubtedly leave gaps in evidence...
Supplementary material

Supplementary material is available at European Heart Journal online.

Conflict of interest: PSJ reports having received consulting fees from Novartis, research funding from Boehringer Ingelheim and serving on an advisory board for Vifor Pharma, all outside the submitted work. J.J.V.M. reports payments for trial-related activities to the University of Glasgow from Novartis, Cardioresents, Amgen, Oxford University/Bayer, GlaxoSmithKline, Theracos, Abbvie, DalCor, Pfizer, Merck, AstraZeneca, Bristol Myers Squibb, and Kidney Research UK (KRUK)/Kings College Hospital, London/Vifor-Fresenius Pharma, all outside the submitted work.

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