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CLINICAL REVIEW
Controversies in cardiovascular medicine

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 con icting ndings 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 ndings of these observational studies with those of relevant RCTs. We identi ed 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 bene t, with 10 nding a neutral effect, and one a harmful effect.

Conclusion This comprehensive comparison of studies of non-randomized data with the ndings 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

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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)[118]	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)[119]	RCT	1986–1990	USA, Canada, Belgium	134–145[a]	6797	3396	3401	0.90 (0.84–0.95; $P < 0.0003$)	—
Jong, Canada, 2003 (X-SOLVD-Prevention)[119]	RCT	1986–1990	USA, Canada, Belgium	134[a]	4228	2111	2117	0.86 (0.79–0.93; $P < 0.001$)	—
Randomized controlled trials—neutral treatment effect									
SOLVD Investigators, USA, 1992 (SOLVD-Prevention)[120]	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)[119]	RCT	1986–1990	USA, Canada, Belgium	145[a]	2569	1285	1284	0.93 (0.85–1.01; $P < 0.01$)	—
Observational studies—beneficial treatment effect									
Masoudi, USA, 2004 (NHC)[26]	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)[121]	RCT	1999–2001	Multiregional	34[a]	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)[27]	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[28]	Prospective cohort study	2005–2010	China	52[a]	2154	1421	733	—	0.43 (0.33–0.57; $P < 0.001$)
Lund, Sweden, 2012 (Swedish HF Registry)[29]	Registry (PSM)	2000–2011	Sweden	12	4010	2005	2005	—	0.80 (0.74–0.86; $P < 0.001$)
Masoudi, USA, 2004 (NHC)[26]	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 (1. CHART-1)[30]	Prospective cohort study	2000–2005	Japan	36	543	385	158	—	0.67 (0.40–1.12; $P < 0.128$)

Continued

Table 2 *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)
Ushigome, Japan, 2015 (2. CHART-2)[30]	Prospective cohort study	2006–2010	Japan	36	1360	1061	299	—	0.83 (0.60–1.15; $P < 0.252$)
HFpEF (ACEI)									
Randomized controlled trials—neutral treatment effect									
Cleland, UK, 2006 (PEP-CHF)[122]	RCT (≥70 years)	2000–2003	Multiregional	26	850	424	426	1.09 (0.75–1.58; $P < 0.665$)	—
Observational studies—beneficial treatment effect									
Gomez-Soto, Spain, 2010[31]	Prospective cohort study (propensity score adjusted)	2001–2005	Spain	30[a]	1120	255	865	RR: 0.34 (0.23–0.46; $P < 0.001$)	0.67 (0.52–0.71)
Shah, USA, 2008 (NHC)[32]	Retrospective cohort study (≥65 years)	1998–1999, 2000–2001	USA	36	13 533	6413	7120	—	RR: 0.93 (0.89–0.98)
Tribouilloy, France, 2008[33]	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[34]	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; $P < 0.012$)
Observational studies—neutral treatment effect									
Mujib, USA, 2013 (OPTIMIZE-HF)[35]	Registry (PSM) (≥65 years)	2003–2004	USA	29[a]	2674	1337	1337	—	0.96 (0.88–1.05; $P < 0.373$)
Dauterman, USA, 2001 (Medicare)[36]	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)[37]	Registry	1995, 1996–1997	USA	6	302	137	165	OR: 0.72 (0.38–1.39)	OR: 0.61 (0.30–1.25)
Philbin, USA, 1997 (MISCHF)[38]	Registry	1995	USA	6	350	190	160	—	OR: 0.63 ($P < 0.15$–95% CI not reported)
HFpEF (ARB)									
Randomized controlled trials—neutral treatment effect									
Massie, USA, 2008 (I-PRESERVE)[123]	RCT	2002–2005	Multiregional	50	4128	2067	2061	1.00 (0.88–1.14; $P < 0.98$)	—
Yusuf, Canada, 2003 (CHARM-Preserved)[124]	RCT	1999–2000	Multiregional	37[a]	3023	1514	1509	1.02 (0.85–1.22; $P < 0.836$)	—
Observational studies—neutral treatment effect									
Patel, USA, 2012 (OPTIMIZE-HF)[39]	Registry (PSM) (≥65 years)	2003–2004	USA	72	592	296	296	0.93 (0.76–1.14; $P < 0.509$)	—

Continued

Table 2 *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[a]	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[a]	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[a]	7599	3803	3796	0.91 (0.83–1.00; $P < 0.055$)	0.90 (0.82–0.99; $P < 0.032$)

Continued

Table 2 *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)
Mixed/unspecified HF phenotype (ACEI + ARB)									
Observational studies—beneficial treatment effect									
Gastelurrutia, Spain, 2012 (75% HFrEF, 25% HFrEF)[45]	Prospective cohort study	2001–2008	Spain	44[a]	960	846	114	—	0.52 (0.39–0.69; *P* < 0.001)
Teng, Australia, 2010 (WAHMD) (24% HFrEF, 30% HFpEF, 46% unknown)[46]	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)[30]	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)[30]	Prospective cohort study	2006–2010	Japan	36	3676	2677	999	—	0.94 (0.76–1.15; *P* < 0.534)

[a]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'Anziano; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced 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	37[a]	655	426	229	—	0.72 (0.55–0.95; $P < 0.018$)
Bhatia, 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)[30]	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; $P < 0.001$)	0.3 (0.2–0.5; $P < 0.001$)
Liu, China, 2014[28]	Prospective cohort study	2005–2010	China	52[a]	2154	1471	683	—	0.75 (0.57–0.999; $P < 0.049$)
Lund, Sweden, 2014 (Swedish HF Registry)[50]	Registry (PSM)	2005–2012	Sweden	23[a]	6081	4054	2027	—	0.89 (0.82–0.97; $P < 0.005$)
El-Refai, USA, 2013[51]	Retrospective cohort study	2000–2008	USA	25[a]	1094	927	167	—	0.26 (0.17–0.40; $P < 0.001$)

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)
Xu, China, 2013[52]	Retrospective cohort study	2007–2012	China	31[a]	685	555	130	—	0.69 (0.50–0.95; $P < 0.021$)
Teng, Australia, 2010 (WAHMD)[46]	Retrospective cohort study	1996–2006	Australia	12	225	100	125	—	0.53 (0.32–0.87; $P < 0.011$)
Hernandez, USA, 2009 (OPTIMIZE-HF)[53]	Registry (≥65 years)	—	USA	12	3001	1800	1201	0.65 (0.57–0.73)	0.77 (0.68–0.87)
Miyagishima, Japan, 2009[54]	Retrospective cohort study	2000–2004	Japan	36	431	297	134	—	0.48 (0.32–0.73)
Fauchier, France, 2009 (41% HFrEF)[55]	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[56]	Registry (>70 years)	2002–2003	Spain	31[a]	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')[57]	Registry	1995–2004	Germany	31	278	166	112	—	0.57 (0.38–0.86)
Jost, Germany, 2005 (Ludwigshafen HF Registry) (2. 'Non-trial patients')[57]	Registry	1995–2004	Germany	31	397	204	193	—	0.72 (0.53–0.97)
Bobbio, Italy, 2003 (BRING-UP)[58]	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									
Ushigome, Japan, 2015 (1. CHART-1)[30]	Prospective cohort study	2000–2005	Japan	36	543	184	359	—	0.87 (0.50–1.50; $P < 0.610$)
Huan Loh, UK, 2007[59]	Retrospective cohort study	—	UK	36[a]	900	738	162	0.54 (0.40–0.73; $P < 0.001$)	0.73 (0.53–1.02; $P < 0.067$)
HFpEF									
Randomized controlled trials—neutral treatment effect									
Yamamoto, Japan, 2013 (J-DHF)[136]	PROBE	2004–2009	Japan	38	245	120	125	0.99 (0.53–1.86; $P < 0.975$)	—
van Veldhuisen, Netherlands, 2009 (SENIORS)[132]	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									
Ruiz, Spain, 2016[60]	Prospective cohort study (PSM)	2006–2015	Spain	22[a]	1970	985	985	RR: 0.76 (0.70–0.83; $P < 0.001$)	0.78 (0.71–0.85; $P < 0.001$)
Lund, Sweden, 2014 (Swedish HF Registry)[50]	Registry (PSM)	2005–2012	Sweden	23[a]	8244	5496	2748	—	0.93 (0.86–0.996; $P < 0.04$)
El-Refai, USA, 2013[51]	Retrospective cohort study	2000–2008	USA	25[a]	741	570	171	—	0.43 (0.27–0.68; $P < 0.001$)
Nevzorov, Israel, 2012[61]	Retrospective cohort study	2001–2005	Israel	24	345	154	191	—	0.69 (0.47–0.99; $P < 0.046$)

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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[62]	Prospective cohort study (propensity score adjusted)	2001–2005	Spain	30[a]	1085	378	707	RR: 0.37 (0.21–0.50; $P < 0.001$)	0.72 (0.58–0.84)
Teng, Australia, 2010 (WAHMD)[46]	Retrospective cohort study	1996–2006	Australia	12	284	101	183	—	0.62 (0.39–0.99; $P < 0.048$)
Fauchier, France, 2009 (35% HFpEF)[55]	Retrospective cohort study (AF)	2000–2004	France	29	1269	449	820	—	RR: 0.45 (0.26–0.80; $P < 0.006$)
Shah, USA, 2008 (NHC)[32]	Retrospective cohort study (≥65 years)	1998–1999, 2000–2001	USA	36	13 533	4562	8971	—	RR: 0.92 (0.87–0.97)
Dobre, Netherlands, 2007[63]	Prospective cohort study (propensity score adjusted)	2000–2005	Netherlands	25	443	227	216	—	0.57 (0.37–0.88; $P < 0.01$)
Observational studies—neutral treatment effect									
Ushigome, Japan, 2015 (1. CHART-1)[30]	Prospective cohort study	2000–2005	Japan	36	463	104	359	—	0.89 (0.45–1.75; $P < 0.734$)
Ushigome, Japan, 2015 (2. CHART-2)[30]	Prospective cohort study	2006–2010	Japan	36	2316	1018	1298	—	0.94 (0.73–1.22; $P < 0.654$)
Patel, USA, 2014 (OPTIMIZE-HF)[64]	Registry (PSM) (≥65 years)	2003–2004	USA	72	2198	1099	1099	—	0.99 (0.90–1.10; $P < 0.897$)
Hernandez, USA, 2009 (OPTIMIZE-HF)[53]	Registry (≥65 years)	—	USA	12	4153	1621	2532	0.87 (0.77–0.97)	0.94 (0.84–1.07)
Mixed/unspecified HF phenotype									
Randomized controlled trials—neutral effect									
Flather, UK, 2005 (SENIORS) (65% HFrEF, 35% HFpEF)[137]	RCT (≥70 years)	2000–2002	Multiregional	21	2128	1067	1061	0.88 (0.71–1.08; $P < 0.21$)	—
Observational studies—beneficial treatment effect									
Katz, Israel, 2016 (HFSIS) (38% HFrEF, 15% HFmrEF, 22% HFpEF, 26% unknown)[65]	Prospective cohort study	2003	Israel	120	2402	1481	921	—	0.83 (0.77–0.89; $P < 0.001$)
Maison, France, 2013[66]	Registry (propensity score adjusted)	2000	France	96	281	101	180	—	0.54 (0.34–0.84)
Gastelurrutia, Spain, 2012 (75% HFrEF, 25% HFrEF)[45]	Prospective cohort study	2001–2008	Spain	44[a]	960	776	184	—	0.51 (0.39–0.66; $P < 0.001$)
Marijon, France, 2010 (EVADEF)[67]	Prospective cohort study (ICD)	2001–2003	France	22	1030	721	309	0.53 (0.30–0.91; $P < 0.02$)	0.56 (0.32–0.98; $P < 0.04$)
Teng, Australia, 2010 (WAHMD) (24% HFrEF, 30% HFpEF, 46% unknown)[46]	Retrospective cohort study	1996–2006	Australia	12	944	318	626	—	0.68 (0.53–0.86; $P < 0.002$)
Fauchier, France, 2009 (41% HFrEF, 35% HFpEF, 24% unknown)[55]	Retrospective cohort study (AF)	2000–2004	France	29	1269	449	820	0.59 (0.45–0.78; $P < 0.0002$)	0.60 (0.43–0.84; $P < 0.003$)

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)
Jordán, Spain, 2009 (BADAPIC) (77% HFrEF, 23% HFpEF)[68]	Registry	2000–2002	Spain	35	3162	2242	920	—	RR: 0.82 (0.47–0.95)
Dobre, Netherlands, 2007 (55% HFrEF, 45% HFpEF)[69]	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)[70]	Retrospective cohort study (≥65 years)	1998–2003	Canada	30	14 693	7584	7109	0.67 (0.64–0.70)	0.79 (0.75–0.83)
Keyhan, Canada, 2007 (2. male cohort)[70]	Retrospective cohort study (≥65 years)	1998–2003	Canada	30	13 144	6499	6645	0.64 (0.61–0.67)	0.76 (0.72–0.80)
Chan, USA, 2005 (CHS) (19% HFrEF, 36% HFpEF, 45% unknown)[71]	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)[41]	Prospective cohort study	1989–2001	Canada	32[a]	1041	475	566	—	OR: 0.52 (0.39–0.70)
Maggioni, Italy, 2003 (BRING-UP) (1. no BB vs. continued BB)[72]	Registry	1998	Italy	12	2226	771	1455	—	0.74 (0.55–0.99; $P < 0.045$)
Maggioni, Italy, 2003 (BRING-UP) (2. no BB vs. initiated BB)[72]	Registry	1998	Italy	12	2320	865	1455	—	0.60 (0.45–0.80; $P < 0.0003$)
McCullough, USA, 2003 (REACH)[73]	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)[44]	Retrospective cohort study (≥65 years) (propensity score adjusted)	1994–1998	Canada	21[a]	11 942	1162	10 780	—	0.72 (0.65–0.80)
McAlister, Canada, 1999 (78% HFrEF, 22% HFpEF)[74]	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)[30]	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)[30]	Prospective cohort study	2006–2010	Japan	36	3676	1886	1790	—	0.82 (0.68–1.00; $P < 0.055$)

[a]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: Évaluation Médico-Économique du Défibrillateur Automatique Implantable; 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; 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 Randomised Intervention Trial 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; 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.

Table 4 All-cause mortality in randomized and non-randomized MRA 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									
Zannad, USA, 2011 (EMPHASIS-HF)[138]	RCT	2006–2010	Multiregional	21[a]	2737	1364	1373	0.78 (0.64–0.95; $P < 0.01$)	0.76 (0.62–0.93; $P < 0.008$)
Pitt, USA, 1999 (RALES)[139]	RCT	1995–1996	Multiregional	24	1663	822	841	RR: 0.70 (0.60–0.82; $P < 0.001$)	—
Observational studies—beneficial treatment effect									
Hamaguchi, Japan, 2010 (JCARE-CARD)[75]	Prospective cohort study	2004–2005	Japan	26	946	435	511	0.75 (0.54–1.04; $P < 0.078$)	0.62 (0.41–0.93; $P < 0.02$)
Observational studies—neutral treatment effect									
Lam, USA, 2017 (Alabama HF Project)[76]	Retrospective cohort study (PSM)	1998–2001	USA	12	648	324	324	—	1.11 (0.83–1.49; $P < 0.483$)
Ushigome, Japan, 2015 (1. CHART-1)[30]	Prospective cohort study	2000–2005	Japan	36	543	116	427	—	1.39 (0.80–2.43; $P < 0.247$)
Ushigome, Japan, 2015 (2. CHART-2)[30]	Prospective cohort study	2006–2010	Japan	36	1360	493	867	—	1.23 (0.91–1.66; $P < 0.172$)
Frankenstein, Norway, 2013 (Norwegian HF Registry)[77]	Registry (PSM)	—	Norway, Germany	44	4832	1565	3267	1.08 (0.97–1.22; $P < 0.17$)	1.03 (0.88–1.20; $P < 0.74$)
Lee, USA, 2013 (KPNC)[78]	Retrospective cohort study	2006–2008	USA	30[a]	2358	521	1837	—	0.93 (0.60–1.44)
Lund, Sweden, 2013 (Swedish HF Registry)[79]	Registry (PSM)	2000–2012	Sweden	27[a]	18 852	6551	12 301	1.10 (1.04–1.15; $P < 0.001$)	1.05 (1.00–1.11; $P < 0.054$)
Pascual-Figal, Spain, 2013 (MUSIC)[80]	Prospective cohort study (PSM)	2003–2004	Spain	38[a]	362	181	181	1.25 (0.81–1.94; $P < 0.318$)	1.46 (0.84–2.55; $P < 0.185$)
Hernandez, USA, 2012 (GWTG-HF/Medicare)[81]	Registry	2005–2009	USA	36	5887	1070	4817	0.98 (0.90–1.06; $P < 0.58$)	1.05 (0.97–1.15; $P < 0.23$)
Miyagishima, Japan, 2009[54]	Retrospective cohort study	2000–2004	Japan	36	431	312	119	—	0.83 (0.54–1.30)
Ouzounian, Canada, 2007 (ICONS)[82]	Prospective cohort study	1997–2001	Canada	24	7816	644	7172	—	OR: 0.97 (0.79–1.20)
Observational studies—harmful treatment effect									
O'Meara, Canada, 2012 (AF-CHF)[83]	*Post hoc* analysis of RCT (AF)	2001–2005	Multiregional	37	1376	616	760	—	1.40 (1.10–1.80; $P < 0.005$)
HFpEF									
Randomized controlled trials—neutral treatment effect									
Pfeffer, USA, 2015 (TOPCAT-Americas subgroup)[140]	*Post hoc* analysis of RCT	2006–2012	USA, Canada, Brazil, Argentina	35	1767	886	881	0.83 (0.68–1.02; $P < 0.08$)	—

Continued

Table 4 *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)
Pfeffer, USA, 2015 (TOPCAT-Russia/Georgia subgroup)[140]	*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)[141]	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[84]	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)[30]	Prospective cohort study	2006–2010	Japan	36	2316	491	1825	—	0.96 (0.72–1.29; $P < 0.808$)
Patel, USA, 2013 (OPTIMIZE-HF)[85]	Registry (PSM) (≥65 years)	2002–2008	USA	29	974	487	487	—	1.03 (0.89–1.20; $P < 0.693$)
Mixed/unspecified HF phenotype									
Observational studies—beneficial treatment effect									
Bonsu, Malaysia, 2017 (23% HFrEF, 18% HFmrEF, 59% HFpEF)[84]	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)[86]	Prospective cohort study	1989–2001	Canada	32[a]	1037	136	901	—	RR: 0.13 (0.04–0.42)
Observational studies—neutral treatment effect									
Ushigome, Japan, 2015 (1. CHART-1) (54% HFrEF, 46% HFpEF)[30]	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) (37% HFrEF, 63% HFpEF)[30]	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)[46]	Retrospective cohort study	1996–2006	Australia	12	944	154	790	—	0.87 (0.64–1.20; $P < 0.390$)

[a]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.

Table 5 All-cause mortality in randomized and non-randomized statin 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—neutral treatment effect									
Kjekshus, Norway, 2007 (CORONA)[142]	RCT	2003–2005	Europe, Russia, South Africa	33[a]	5011	2514	2497	0.95 (0.86–1.05; $P < 0.31$)	—
Takano, Japan, 2013 (PEARL)[143]	PROBE	2006–2008	Japan	36[a]	574	288	286	—	0.73 (0.44–1.20; $P < 0.211$)
Observational studies—beneficial treatment effect									
Alehagen, Sweden, 2015 (Swedish HF Registry)[87]	Registry (PSM)	2000–2012	Sweden	47[a]	10 762	5381	5381	—	0.81 (0.76–0.86; $P < 0.001$)
Liu, China, 2014[28]	Prospective cohort study	2005–2010	China	52[a]	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)[89]	*Post hoc* analysis of RCT (CRT)	2000–2002	USA	15–16[a]	1520	603	917	0.85 (0.67–1.07; $P < 0.15$)	0.77 (0.61–0.97; $P < 0.03$)
Coleman, USA, 2008[90]	Retrospective cohort study (ICD)	1997–2007	USA	31	1204	642	562	—	0.67 (0.53–0.85; $P < 0.001$)
Dickinson, 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)[59]	Retrospective cohort study	—	UK	36[a]	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)[93]	*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)[94]	*Post hoc* analysis of RCT	1997–1998	Multiregional	18[a]	3132	2734	398	0.61 (0.45–0.83; $P < 0.0007$)	0.61 (0.44–0.84; $P < 0.003$)
Anker, UK, 2006 (2. European Centres Study)[94]	Retrospective cohort study	1992–2000	Europe	24[a]	2068	705	1363	0.59 (0.49–0.72; $P < 0.0001$)	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[96]	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)

Continued

Table 5 *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)
Mozaffarian, USA, 2004 (PRAISE)[97]	*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[a]	760	377	383	0.74 (0.52–1.05)	0.82 (0.55–1.23)
Mixed/unspecified HF phenotype									
Randomized controlled trials—neutral treatment effect									
Tavazzi, Italy, 2008 (GISSI-HF Rosuvastatin) (90% HFrEF, 10% HFpEF)[144]	RCT (≥60 years)	2002–2005	Italy	47[a]	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% HFmrEF, 59% HFpEF)[99]	Retrospective cohort study (IPTW)	2009–2013	Ghana	60	1488	552	936	—	0.79 (0.65–0.96; $P < 0.019$)
Ballo, Italy, 2016[100]	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[a]	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% HFpEF)[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)[102]	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[a]	54 960	9163	45 797	0.67 (0.65–0.69; $P <$ 0.001)	0.82 (0.79–0.85; $P < 0.001$)

Continued

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)[145]	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)[105]	Prospective cohort study (PSM) (SR/AF)	2001–2008	Spain	46[a]	2842	1421	1421	—	0.92 (0.89–0.95; $P < 0.005$)
Observational studies—neutral treatment effect									
Ushigome, Japan, 2015 (1. CHART-1)[30]	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)[30]	Prospective cohort study (SR/AF)	2006–2010	Japan	36	1360	586	774	—	1.10 (0.80–1.51; $P < 0.558$)
Fauchier, France, 2009 (41% HFrEF)[55]	Retrospective cohort study (AF)	2000–2004	France	29	1269	591	678	—	RR: 0.79 (0.54–1.16; $P < 0.23$)
Dhaliwal, USA, 2008[106]	Retrospective cohort study (SR/AF)	2002–2004	USA	10[a]	347	155	192	1.15 (0.85–1.55; $P < 0.371$)	1.11 (0.81–1.53; $P < 0.521$)
Observational studies—harmful treatment effect									
Al-Khateeb, Saudi Arabia, 2017[107]	Retrospective cohort study (PSM) (SR/AF)	2000–2015	Saudi Arabia	43[a]	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)[108]	Retrospective cohort study (SR/AF)	2006–2008	USA	30[a]	2891	529	2362	—	1.72 (1.25–2.36)
Butler, USA, 2010 (Val-HeFT)[109]	*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)[110]	*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)[110]	*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)[146]	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)[105]	Prospective cohort study (PSM) (SR/AF)	2001–2008	Spain	46[a]	2842	1421	1421	—	0.86 (0.79–0.92; $P < 0.008$)
Observational studies—neutral treatment effect									
Ushigome, Japan, 2015 (1. CHART-1)[30]	Prospective cohort study (SR/AF)	2000–2005	Japan	36	463	249	214	—	0.92 (0.55–1.54; $P < 0.764$)
Ushigome, Japan, 2015 (2. CHART-2)[30]	Prospective cohort study (SR/AF)	2006–2010	Japan	36	2316	335	1981	—	1.07 (0.81–1.41; $P < 0.632$)

Continued

Table 6 *Continued*

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									
Randomized controlled trials—neutral treatment effect									
Rich, USA, 2001 (DIG Overall)[147]	RCT (SR)	1991–1993	USA, Canada	37	7788	3889	3899	RR: 0.99 (0.92–1.07; $P < 0.7815$)	—
Observational studies—beneficial treatment effect									
Ahmed, USA, 2014 (Alabama HF Project) (57% HFrEF, 25% HFpEF, 18% unknown)[111]	Retrospective cohort study (PSM) (SR/AF)	1998–2001	USA	12	1842	921	921	—	0.83 (0.70–0.98)
Andrey, Spain, 2011 (51% HFrEF, 49% HFpEF)[105]	Prospective cohort study (PSM) (SR/AF)	2001–2008	Spain	46[a]	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	—	30 035	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 (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)[42]	Prospective cohort study (SR/AF)	1998	Italy	10	818	539	279	—	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	34[a]	8102	4051	4051	—	1.29 (1.15–1.44)
Katz, Israel, 2016 (HFSIS) (38% HFrEF, 15% HFmrEF, 22% HFpEF, 26% unknown)[65]	Prospective cohort study (SR/AF)	2003	Israel	120	2402	380	2022	—	1.27 (1.16–1.42; $P < 0.001$)
Madelaire, Denmark, 2016[115]	Retrospective cohort study (PSM) (SR)	1996–2012	Denmark	32[a]	15 981	5327	10 654	—	1.19 (1.15–1.24; $P < 0.001$)

Continued

and enrol selected participants, they clearly remain the best guide to the treatment of patients.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Conflict of interest: P.S.J. 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, Cardiorentis, 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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