Association of statin use and clinical outcomes in heart failure patients: a systematic review and meta-analysis

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Abstract

Background: The role of statins in patients with heart failure (HF) of different levels of left ventricular ejection fraction (LVEF) remains unclear especially in the light of the absence of prospective data from randomized controlled trials (RCTs) in non-ischemic HF, and taking into account potential statins' prosarcopenic effects. We assessed the association of statin use with clinical outcomes in patients with HF.

Methods: We searched PubMed, EMBASE, Scopus, Google Scholar and Cochrane Central until August 2018 for RCTs and prospective cohorts comparing clinical outcomes with statin vs non-statin use in patients with HF at different LVEF levels. We followed the guidelines of the 2009 PRISMA statement for reporting and applied independent extraction by multiple observers. Meta-analyses of hazard ratios (HRs) of effects of statins on clinical outcomes used generic inverse variance method and random model effects. Clinical outcomes were all-cause mortality, cardiovascular (CV) mortality and CV hospitalization.

Results: Finally we included 17 studies (n = 88,100; 2 RCTs and 15 cohorts) comparing statin vs non-statin users (mean follow-up 36 months). Compared with non-statin use, statin use was associated with lower risk of all-cause mortality (HR 0.77, 95% confidence interval [CI], 0.72–0.83, P < 0.0001, $I^2 = 63\%$), CV mortality (HR 0.82, 95% CI: 0.76–0.88, P < 0.0001, $I^2 = 63\%$), and CV hospitalization (HR 0.78, 95% CI: 0.69–0.89, P = 0.0003, $I^2 = 36\%$). All-cause mortality was reduced on statin therapy in HF with both EF < 40% and ≥ 40% (HR: 0.77, 95% CI: 0.68–0.86, P < 0.00001, and HR 0.75, 95% CI: 0.69–0.82, P < 0.00001, respectively). Similarly, CV mortality (HR 0.86, 95% CI: 0.79–0.93, P = 0.0003, and HR 0.83, 95% CI: 0.77–0.90, P < 0.00001, respectively), and CV hospitalizations (HR 0.80 95% CI: 0.64–0.99, P = 0.04 and HR 0.76 95% CI: 0.61–0.93, P = 0.009, respectively) were reduced in these EF subgroups. Significant effects on all clinical outcomes were also found in cohort studies' analyses; the effect was also larger and significant for lipophilic than hydrophilic statins.

Conclusions: In conclusion, statins may have a beneficial effect on CV outcomes irrespective of HF etiology and LVEF level. Lipophilic statins seem to be much more favorable for patients with heart failure.

Keywords: Statins, Heart failure, Mortality, Hospitalization, Meta-analysis

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Background

The management of heart failure (HF) remains a significant challenge. The most recent American College of Cardiology/American Heart Association (ACC/AHA) guidelines on the treatment of blood cholesterol have no recommendation regarding statin therapy in patients with New York Heart Association class II-IV HF [1]. Moreover, the recent European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of HF do not support the initiation of statin therapy in most patients with chronic HF and reduced left ventricular (LV) ejection fraction (HFrEF). However, in HF patients who already are under the treatment with statin therapy because of underlying coronary artery disease (CAD) and/or hyperlipidemia, continuation of this therapy should be considered [2].

The issue of whether or not to use statins in patients with HF remains controversial. More than half of patients with HF have LV mid-range EF (HFmrEF) and preserved LVEF (HFpEF) and mortality and morbidity of patients with these types of HF are also high [3, 4]. The pathophysiology of HFpEF is poorly understood, and the presence of a systemic pro-inflammatory state was also proposed [3, 4].

Statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors), apart from their lipid-lowering properties and mevalonate inhibition, exert their actions through multiple additional mechanisms [5]. These pleiotropic effects of statins may potentially influence the course of HF. Therefore, the aim of this meta-analysis was to assess the effect of statins on clinical outcomes in patients with HF.

Methods

We followed the guidelines of the 2009 PRISMA statement [6] for reporting. Due to the study design (meta-analysis), neither Institutional Review Board (IRB) approval nor patient informed consent was needed.

Search strategy

We searched PubMed, EMBASE, Scopus, Google Scholar, the Cochrane Central Registry of Controlled Trials and ClinicalTrial.gov until August 2018, using the following keywords: 'heart failure' OR 'HF' OR 'left ventricular dysfunction' OR 'heart failure with preserved ejection fraction' OR 'HFpEF' 'heart failure with reduced ejection fraction' OR 'HFrEF' OR 'heart failure with mid-range ejection fraction' OR 'HFmrEF' AND 'statin' OR 'statins' OR 'lipid-lowering therapy' OR 'dyslipidemia therapy' OR 'simvastatin' OR 'atorvastatin' OR 'rosuvastatin' OR 'pitavastatin' OR 'pravastatin' OR 'lovastatin' AND 'all-cause mortality', 'cardiovascular mortality', 'hospitalizations' AND 'lipid' OR 'lipids' OR 'cholesterol' OR 'lipoprotein' OR 'lipoproteins'. The details on the search strategy can be found in the Additional file 1. Additional searches for potential trials included the references of review articles, and abstracts at ESC, AHA, ACC, European Society of Atherosclerosis (EAS) and National Lipid Association (NLA) meetings. The literature search was limited to articles published in English and to studies in humans.

Study selection

We included randomized controlled trials (RCTs) and prospective cohort studies with HF patients with LVEF < 40% and ≥ 40%, i.e. involving all types of patients as per the 2016 ESC HF guidelines classification: preserved, mid-range and reduced ejection fraction (HFpEF, HFmrEF and HFrEF) [7]. Because most of studies were performed before 2016, we divided them into HFrEF studies (patients with LV EF < 40%) and both HFpEF and HFmrEF studies (patients with EF ≥40%). Other inclusion criteria were: follow-up ≥12 months, CV events as the primary or secondary outcomes, a control arm, ≥50 participants, and patients of 18 years or older.

Exclusion criteria were: (1) retrospective studies (2), follow-up < 12 months, and (3) ongoing trials. Two reviewers (AB-D and IB) independently evaluated each article separately. No filters were applied. The remaining articles were obtained in full-text and assessed again by the same two researchers. Disagreements were resolved by discussion with a third party (MB).

Outcome variables

Primary clinical outcomes were: all-cause mortality, cardiovascular (CV) mortality and CV hospitalization. We used study definitions for all outcomes. We evaluated the longest available follow-up according to per protocol definitions.

Data extraction

We independently extracted: 1) first author's name, 2) year of publication, 3) name of study, 4) country where the study was performed, 5) number of centers, 6) study design, 7) number of participants per arm 8) HF and statin, 9) mean follow-up, 10) age and sex of study participants, 10) baseline level of triglycerides (TGs) and total cholesterol (TC), 11) diabetes mellitus (DM) and arterial hypertension (HTN), and, 12) data regarding CV events. Discrepancies in extractions were resolved by discussion with a third author (MB).

Risk of bias assessment

Assessment of risk of bias RCTs was evaluated by the same investigators for each study and was performed independently using the Cochrane risk of bias tool [8]. Evaluated items were: random sequence generation (selection bias), allocation sequence concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcome reporting (reporting bias) and other potential sources of bias. The risk of bias in each study was judged to be "low", "high" or "unclear".

For the assessment of risk of bias in cohort studies we used the Newcastle-Ottawa Scale (NOS). Three domains were evaluated with the following items: a. Selection: 1) representativeness of the exposed cohort, 2) selection of the non-exposed cohort, 3) ascertainment of exposure and 4) demonstration that outcome of interest was not present at start of study; b. Comparability of exposed and non-exposed; and c. Exposure: 1) assessment of outcome, 2) was follow-up long enough for outcomes to occur?, and 3) adequacy of follow-up of cohorts. The risk of bias in each study was judged to be "good", "fair" or "poor" [9].

Statistical analysis

A two-tailed $p < 0.05$ was considered significant [10]. Study baseline characteristics were reported as median and range. Mean and standard deviation (SD) values were estimated using the method described by Hozoetet et al. [11]. Meta-analyses were performed with random effects models as we expected heterogeneity of effects among studies. The generic inverse variance method was used to combine log hazard ratios (log HR) and standard errors of the log HR (SElogHR). The log HRs were adjusted for a common set of confounders across studies, such as age and gender. Heterogeneity between studies was assessed using the Cochrane Q test and I^2 statistic. As a guide, $I^2 < 25\%$ indicated low, 25–50% moderate and > 50% high heterogeneity [12]. Publication bias was assessed using visual inspections of funnel plots and Egger's test. Subgroup analyses by EF level (< 40% vs ≥ 40%) and type of statin (lipophilic vs hydrophilic) were performed. Sensitivity analyses in cohort studies only were also done. Meta-analyses were conducted using RevMan 5.1 (The Cochrane Collaboration, Copenhagen, Denmark).

Results

Search results and trial flow

Of 578 articles initially identified, 281 studies were screened as potentially relevant. After excluding 222 studies, 59 full text articles were assessed. Among the remaining 59 trials checked for eligibility, 42 studies were excluded. After careful assessment, 17 articles met the inclusion criteria [13–29]: two RCTs (n = 9585) and 15 cohort studies (*n* = 78,515) (Fig. 1).
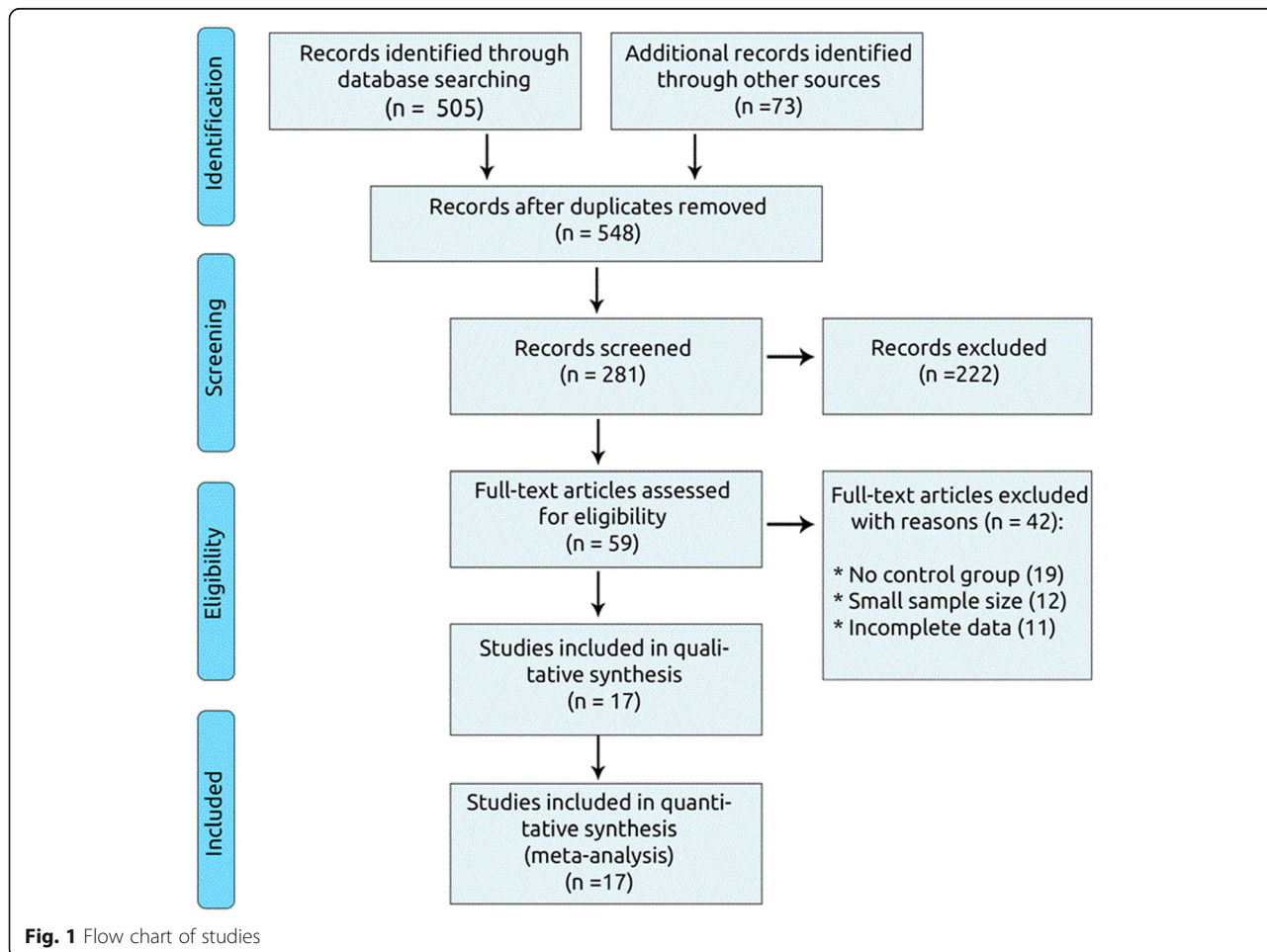
Fig. 1 Flow chart of studies

**Table 1** Main characteristics of studies included in the study

Study, year	Study design	Type of HF	Inclusion Criteria	Exclusion Criteria	Study comparison	Type of statins	Primary endpoints	Follow-up
Horwich et al. 2004	Prospective cohort	HFrEF	HF patients	EF > 40% Baseline incomplete data	Statins: Control	Not specified	All-cause mortality; mortality mortality	12 mo
Sola et al. 2005	Prospective cohort	HFrEF	HF patients EF ≤35% NYHA II-III	Prescribed statins > 1 year; intolerance to statins	Statins: Control	Atorvastatin Fluvastatin Pitavastatin Simvastatin	All-cause mortality; Hospitalization	24 5 mo
Fukuta et al. 2005	Prospective cohort	HFpEF	HF patients	EF < 50% Significant valvular disease; prosthetic valve	Statins: Control	Atorvastatin Simvastatin Pravastatin Fluvastatin	All-cause mortality; Hospitalizations	21 ± 12 mo
Hong et al. 2005	Prospective cohort	HFrEF	HF patients < 40%	HF patients with EF > 40%	Statins: Control	Simvastatin	All-cause mortality;	12 mo
Go et al. 2006	Prospective cohort	HFrEF	HF patients		Statins: Control	Not specified	All-cause mortality; Hospitalizations	28 mo
Kjekshus et al. 2007 CORONA	RCTs	HFrEF	HF patients, EF < 40%, NYHA II-IV	previous statin-induced myopathy or hypersensitivity decompensated HF	Statins: Control	Rosuvastatin	CV death Non-fatal MI Stroke	38.2 mo
Huan et al. 2007	Prospective cohort	HFrEF	HF patients with LVSD	HF patients with LVDD	Statins: Control	Not specified	All-cause mortality;	36 mo
Coleman et al. 2008	Prospective cohort	HFrEF	HF patients EF < 40%;und–ergoing ICD		Statins: Control	Not specified	All-cause Mortality VT/VF incidence	31 mo
Roik et al. 2008	Prospective cohort	HFpEF	HF patients with preserved EF	LVEF ≤45%, ACS cardiogenic shock severe AS, etc.	Statins: Control	Simvastatin Atorvastatin	All-cause mortality; Hospitalization	12 mo
Tevazzi et al. 2008 the GISSI-HF trial	RCTs	HFrEF	HF patients NYHA II-IV	Non-cardiac comorbidity (cancer)	Statins: Control	Rosuvastatin	All-cause mortality; Hospitalization	3.9 y
Gomez-Soto et al. 2010	Prospective cohort	HFpEF	HF patients with preserved EF	HF patients with reduced EF	Statins: Control	Not specified	All-cause mortality; CV mortality Hospitalization	34.6 mo
Kaneko et al. 2013	Prospective cohort	HFpEF	HF patients with EF ≥50%	Valvular heart disease EF < 50%	Statins: Control	Not specified	CV mortality Hospitalization	3 y
Yap et al. 2015	Prospective cohort	HFpEF	HF patients with EF ≥50%	Incomplete follow-up Non-documented EF	Statins: Control	Not specified	All-cause mortality;	2 y
Nochioka et al. 2015	Prospective cohort	HFpEF	HF patients with stages B-D	NR	Statins: Control	Not specified	All-cause mortality; Hospitalization	3 y
Alehagen U et al. 2015	Prospective cohort	HFpEF	HF patients with EF ≥50%	HF patients with EF < 50%	Statins: Control	Not specified	All-cause mortality;	12 mo
Alehagen et al. 2015	Prospective cohort	HFrEF	HF patients	HF patients with EF ≥50%	Statins: Control	Not specified	All-cause mortality;	24 mo
Tsujimoto et al. 2018	Prospective cohort	HFpEF	HF patients with preserved EF	HOCMP systemic illness with l Life expectancy < 3 y;		Not specified	All-cause mortality; CV and Non-CV mortality;	3.3 y

Abbreviations: HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; CV: cardiovascular; ACS: acute coronary syndrome; AS: aortic stenosis; NR: non-reported; mo: months; y: years

Table 2 Main characteristics of patients enrolled among trials included in the meta-analysis

| Study, year	Arms	No	EF %	Age Year	BMI	Male %	DM %	HTN %	Smoking %	TC mmol/L	Triglyceride mmol/L
Horwich et al. 2004	S	200	≤40%	57 ± 11	28.2 ± 6.2	82	33	64	80	4.32 ± 1.25	1.87 ± 1.3
	C	250	≤40%	48 ± 13	26.9 ± 6.2	70	16	43	66	4.2 ± 1.5	1.98 ± 2.17
Sola et al. 2005	S	225	≤35%	55.4 ± 6.4	24.3 ± 3.8	62	24	41	34	NR	2.8 ± 0.5
	C	191	≤35%	53.8.4 ± 5.7	23.5 ± 4.3	63	27	36	30	NR	2.9 ± 0.4
Fukuta et al. 2005	S	69	≥50%	65 ± 2	NR	51	34	87	NR	6.07 ± 2.22	2.31 ± 2.21
	C	68	≥50%	65 ± 16	NR	45	12	72	NR	4.67 ± 1	1.64 ± 0.90
Hong et al. 2005	S	106	≤40%	61.8 ± 10.3	NR	72	32	41	57	NR	NR
	C	96	≤40%	60.9 ± 10.4	NR	75	28	44	52	NR	NR
Go et al. 2006	S	12,648	≤40%	69.6 ± 10.3	NR	62	55.7	89	NR	5.37 ± 1.14	NR
	C	11,950	≤40%	72.9 ± 11.4	NR	60	41.3	83	NR	5.68 ± 1.22	NR
Kjekshus et al. 2007	S	2514	≤40%	73 ± 7.1	27 ± 4.5	76	30	63	9	5.36 ± 1.11	2.01 ± 1.33
	C	2497	≤40%	73 ± 7.0	27 ± 4.6	76	29	63	8	5.35 ± 1.06	1.99 ± 1.23
Huan et al. 2007	S	377	≤40%	74 ± 4	26.5	66	NR	NR	75	5.1 ± 0.25	NR
	C	102	≤40%	74 ± 3	28.1	77	NR	NR	72	5.5 ± 0.3	NR
Coleman et al. 2008	S	642	≤30%	67.5 ± 13	NR	80.7	31.5	43.8	NR	NR	NR
	C	562	≤30%	64.5 ± 10.8	NR	76.2	30.2	34.9	NR	NR	NR
Roik et al. 2008	S	103	≥45%	69 ± 11	28.6 ± 4.8	50.5	25	76	43	4.57 ± 1.37	1.64 ± 1.08
	C	43	≥45%	66 ± 16	27.2 ± 4.9	58	12	58	34	4.57 ± 1.03	1.62 ± 1.05
Tavazzi et al. 2008 the GISSI-HF trial	S	2285	33.4	68 ± 1	27·1 ± 4.6	78.6	25	53.5	14.1	NR	NR
	C	2289	33.4	68 ± 1	27.71 ± 4.4	76.8	27.4	55.1	14	NR	NR
Gomez-Soto et al. 2010	S	1343	≥47%	71.5 ± 6.9	NR	51.6	36.8	45.6	33	NR	NR
	C	1230	≥47%	69.8 ± 7.8	NR	43.9	47.7	48.5	31	NR	NR
Kaneko et al. 2013	S	459	≥50%	65.6 ± 11.7*	24.3 ± 3.6*	76.2*	32.4*	64.5*	24.2*	NR	NR
	C	665	≥50%							NR	NR
Yap et al. 2015	S	457	≥50%	73.1 ± 10.6*	26.5*	35.3*	47.1*	80.3*	NR	NR	NR
	C	293	≥50%						NR	NR	NR
Nochioka et al. 2015	S	1163	≥50%	69.0 ± 11.0	67.5	45	33.8	85	45	NR	1.51 ± 0.82
	C	1961	≥50%	69.7 ± 12.9	64	40.8	20.9	76.7	40.8	NR	1.4 ± 0.81
Alehagen U et al. 2015	S	3427	≥50%	78 ± 12	29 ± 6	54	31	62	NR	NR	NR
	C	5713	≥50%	75 ± 9	27 ± 6	42	28	64	NR	NR	NR
Alehagen et al. 2015	S	10,345	< 40%	72 10	27 ± 5	75	33	48	41	NR	NR
	C	11,519	< 40%	72 ± 14	26 ± 5	68	18	39	49	NR	NR
Tsujimoto et al. 2018	S	1765	≥50%	69 ± 9.6	NR	55	42.9	93.1	10.5	NR	NR
	C	1613	≥50%	68.1 ± 9.6	NR	42	20.8	89.8	10.6	NR	NR

Abbreviations: S: statins; C: control; HTN: hypertension; DM: diabetes mellitus; TC: total cholesterol; EF: ejection fraction; NR: not-reported; *: only whole group represented
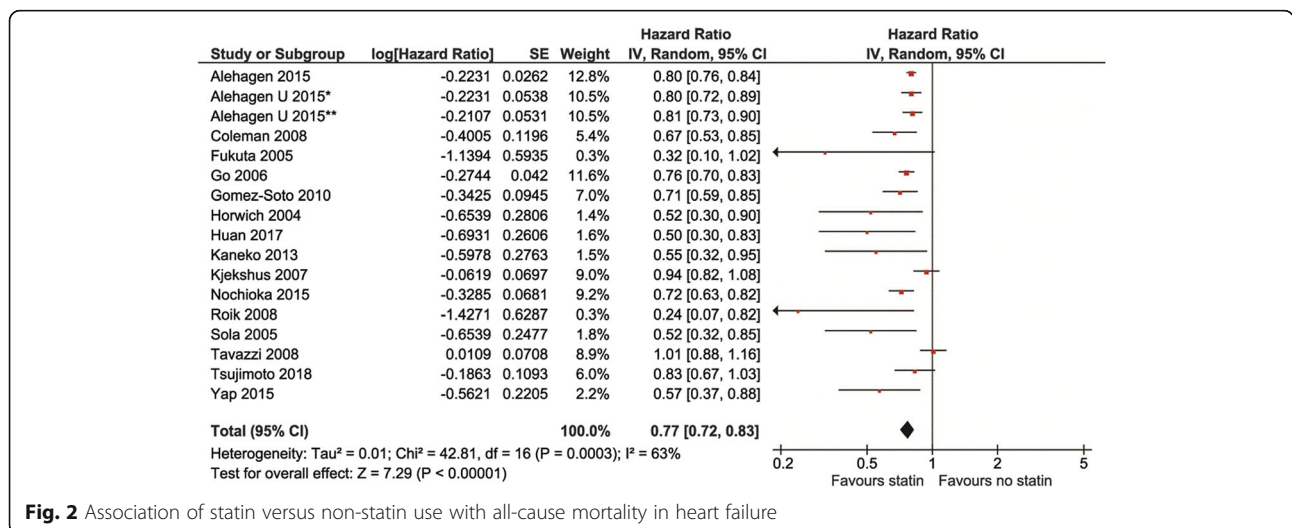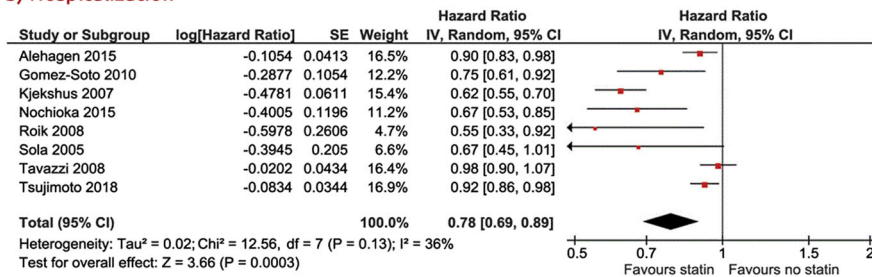

Fig. 2 Association of statin versus non-statin use with all-cause mortality in heart failure
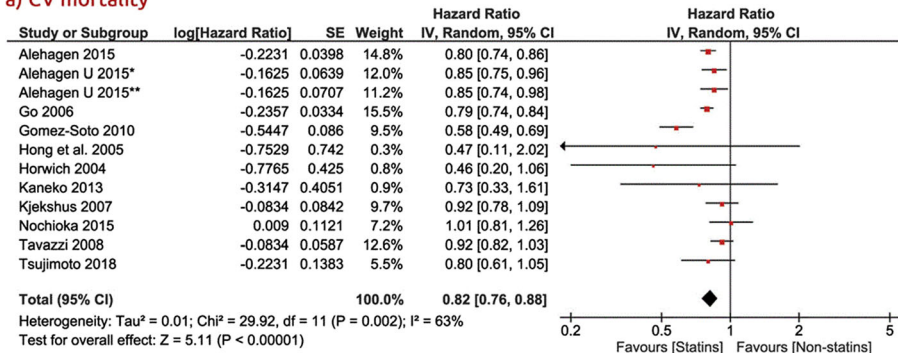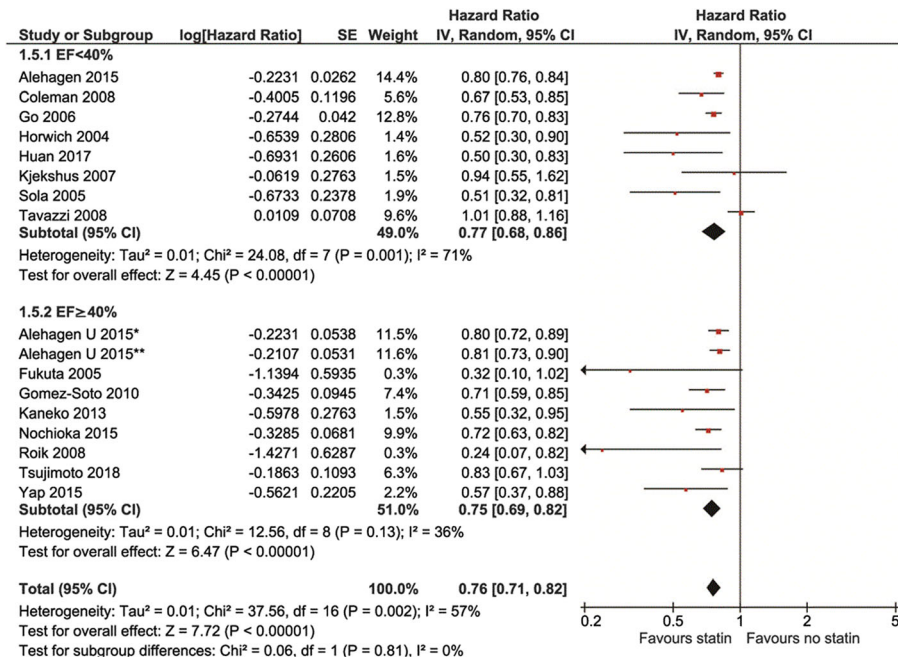
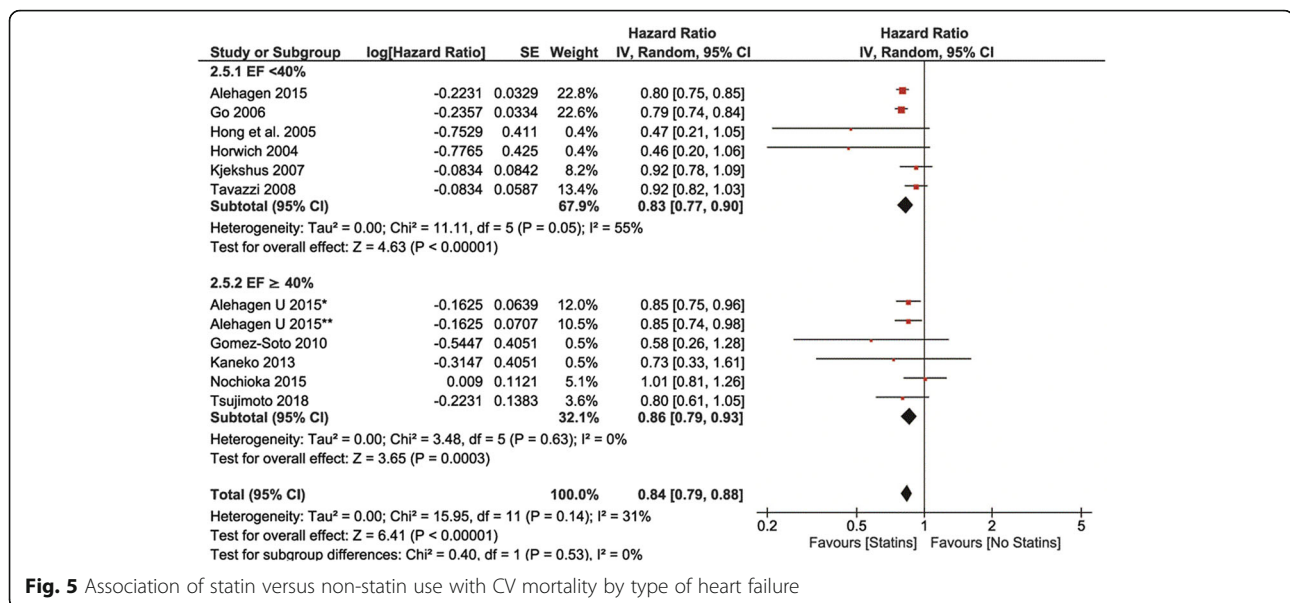**Fig. 3** Association of statin versus non-statin use with **a**) CV mortality, and **b**) CV hospitalizations

Characteristics of included studies

Seventeen studies with a total of 88,100 patients, 42,400 treated with statins and 45,700 without statins, with a mean follow-up 36 months were finally included in the

meta-analysis (Table 1). The mean age of patients was 67 ± 7.2 years, 68% male, 33% had diabetes, 71% had arterial hypertension and 54% were smokers (Table 2). Studies of Sola (2005) [14], Go (2006) [17], Roik (2008)

Fig. 4 Association of statin versus non-statin use with all-cause mortality by type of heart failure

Fig. 5 Association of statin versus non-statin use with CV mortality by type of heart failure

[21], and Hong (2005) [16] evaluated lipophilic statins and studies of Kjekshus [18] (2007), Tavazzi (2008) [22] hydrophilic statins.

Clinical outcomes
Follow-up ranged from 12 to 40 months, with a mean of 36 months. Compared with non-statin users, statin users showed a lower risk of all-cause mortality (HR 0.77, 95% confidence interval [CI], 0.72–0.83, $P < 0.0001$, $I^2 = 63\%$, Fig. 2), CV mortality (HR 0.82, 95% Cl: 0.76–0.88, $P < 0.000$, $I^2 = 63\%$) and CV hospitalization (HR 0.78, 95% Cl: 0.69–0.89, $P = 0.0003$, $I^2 = 36\%$, Fig. 3a and b).

Subgroup analyses
In comparison to non-statin users, all-cause mortality was reduced in statin users in both EF < 40%and EF ≥40% groups (HR 0.77, 95% Cl: 0.68–0.86, $p < 0.00001$, and HR0.75, 95% Cl: 0.69–0.82, p < 0.00001, respectively, Fig. 4). CV mortality was also reduced in both EF groups using statins (HR 0.86, 95% Cl: 0.79–0.93, $p = 0.0003$, and HR 0.83, 95% Cl: 0.77–0.90, respectively, Fig. 5) with no differences between EF subgroups. Similar reduced were observed for CV hospitalizations – they were reduced in statin users in both EF groups (HR 0.80 95CI: 0.64–0.99, p = 0.04, and HR 0.76 95% CI: 0.61–0.93, $p = 0.009$, respectively, Fig. 6). Statin effects on all primary outcomes were confirmed when only perspective cohort studies were analyzed (after withdrawal of 2 RCTs) (Additional file 1: Figures. S1 to S6).

Effect on all-cause mortality was higher for lipophilic compared to hydrophilic statins (HR 0.59, 95%Cl: 0.37–0.93, $p = 0.02$ and HR 0.97, 95%Cl: 0.88–1.07, p = 0.60, respectively, Fig. 7). Significant decreases of cardiovascular outcomes were also observed only with lipophilic statins- CV mortality (HR 0.79, 95%Cl: 0.74–0.88, $P \le 0.00001$ vs

HR 0.94, 95% Cl: 0.85–1.05,$P = 0.28$, Fig. 8) and CV hospitalizations (HR 0.60, 95%Cl: 0.45–0.86, P = 0.003 vs HR 0.78, 95% Cl: 0.50–1.22, $P = 0.28$, Fig. 9).

Risk of bias assessment.
The two included RCTs had low risk of bias (Additional file 1: Table S1). Many of the cohorts have good quality, about 20% of them that have fair quality (Additional file 1: Table S2).

Discussion
This systematic review evaluated large cohort of HF patients from studies comparing the effect of statin therapy with non-statin therapy on clinical outcomes. Statin treatment decreased all-cause mortality, CV mortality and CV hospitalization in HF with either LVEF ≥40% or LVEF < 40%. Effects of statin use were similar in both EF groups, and also after excluding trials with randomization. Finally, lipophilic (e.g. atorvastatin) and no hydrophilic statins (e.g. rosuvastatin or pravastatin) showed significant reductions in clinical outcomes.

Statins are able to decrease vascular and myocardial oxidative stress [30, 31] and possess anti-inflammatory properties [32, 33]. A lot of available studies have shown that they limit signal transmission from membrane receptors and slow down pathologic heart and vessels remodeling, inhibit the action of angiotensin II, and process of apoptosis [31]. Statins might also change myocardial action potential plateau by modulation of Kv1.5 and Kv4.3 channels activity and inhibition of sympathetic nerve activity and in the consequence suppress arrhythmogenesis [34]. Those beneficial effects of statin therapy might be negated by increases in collagen
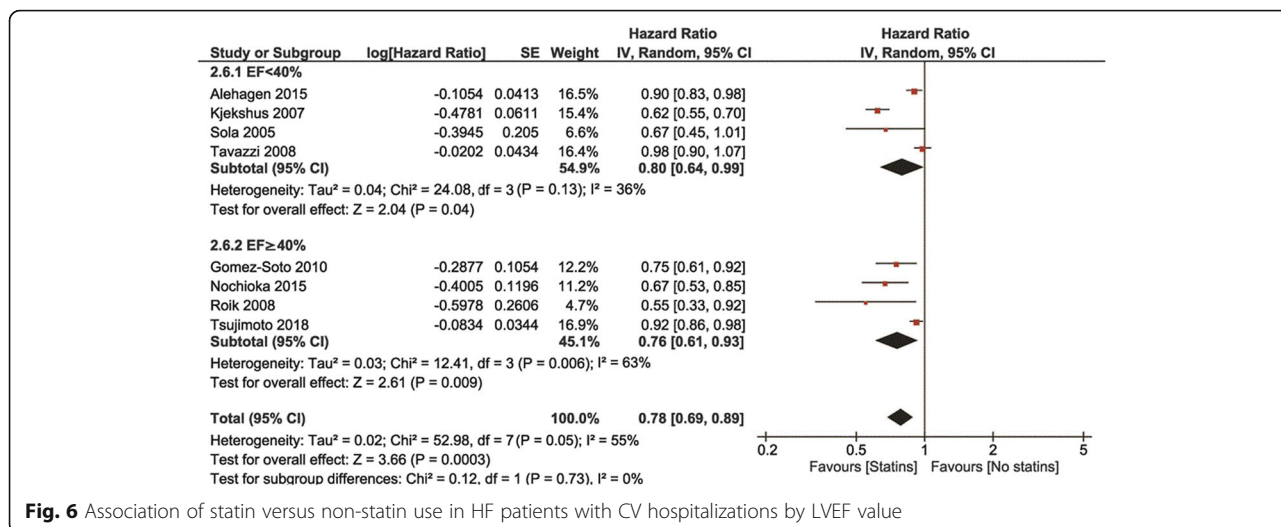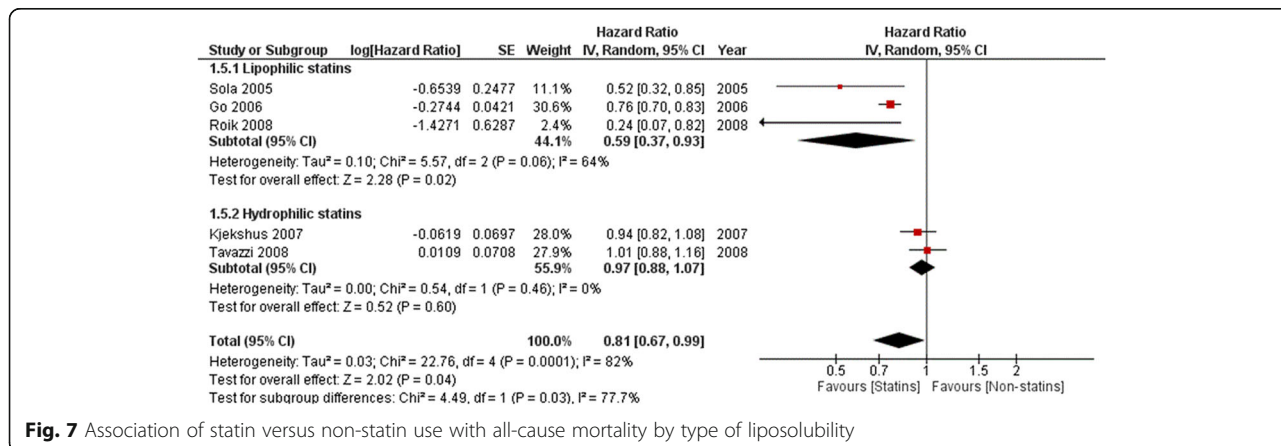
Fig. 6 Association of statin versus non-statin use in HF patients with CV hospitalizations by LVEF value

turnover markers as well as a reduction in plasma co-enzyme Q10 (CoQ10) levels in chronic heart failure (CHF) patients [35–37].

There has been a large discussion on the role of lipid-lowering therapy in HF patients. Available knowledge has indicated that statins might be potentially harmful in HF due to decreased endotoxin defense, diminishing thereby the potentially beneficial pleiotropic effects. There is some suggestive evidence that statins might reduce muscle strength and alter energy metabolism during aerobic exercise [38]. Based on our recent hypothesis this pro-sarcopenic effect of statins might be responsible of their limited efficacy in HF patients [38]. On the other hand, some available data indicate that statins may even have beneficial effects by preserving or even increasing lean mass and exercise performance [38]. Large trials with hydrophilic rosuvastatin did not indicate a significant role for statins in patients with chronic HF, although the drug did reduce the number of CV hospitalizations in the CORONA trial [39, 40]. Although the abovementioned RCTs using hydrophilic rosuvastatin showed no beneficial effect

on all-cause mortality, other studies like Anker et al. [41] reported that patients with chronic HF in the Evaluation of Losastan In The Elderly-2 (ELITE 2) study who received statin therapy at baseline had lower mortality. The authors drew the conclusion that in chronic HF, treatment with statins was related to lower mortality, independent of cholesterol levels, disease etiology and clinical status [41, 42]. The results of our meta-analysis are in line with the above conclusions, as we also clearly showed significantly lower mortality in HF patients on statin therapy.

The significant decrease in CV hospitalization seen with rosuvastatin in the CORONA trial should not be overlooked [39, 40]. Based on the data of 5000 patients with ischemic HF, the authors concluded that the lack of statin benefits in the treatment of HF patients could have been associated with some specific patients' characteristics [40]. Some criticism was associeted to the fact that the study participants were too old (mean age: 73 years); moreover, a large majority was in advanced HF stages [40]. In another important trial - the Effect of n-3 polyunsaturated

Fig. 7 Association of statin versus non-statin use with all-cause mortality by type of liposolubility
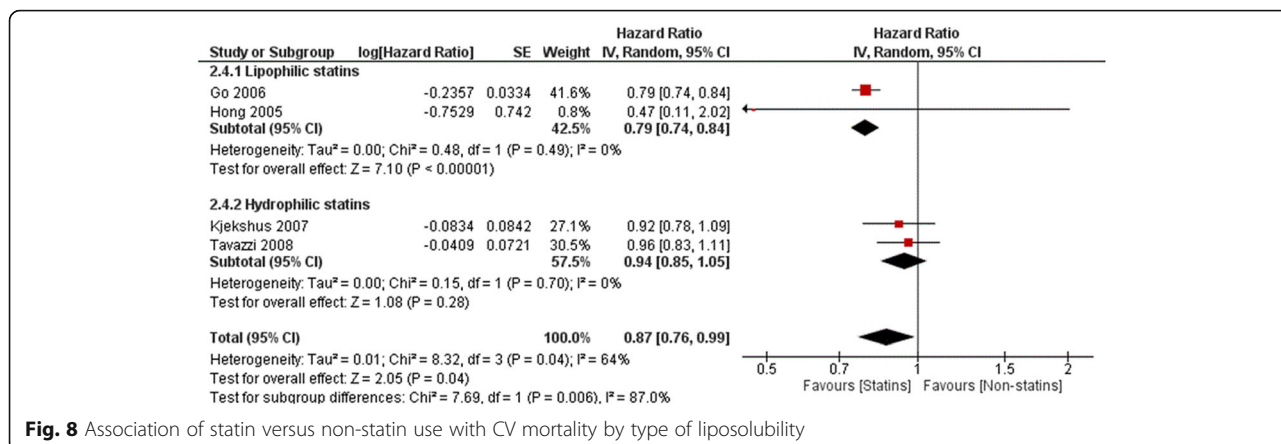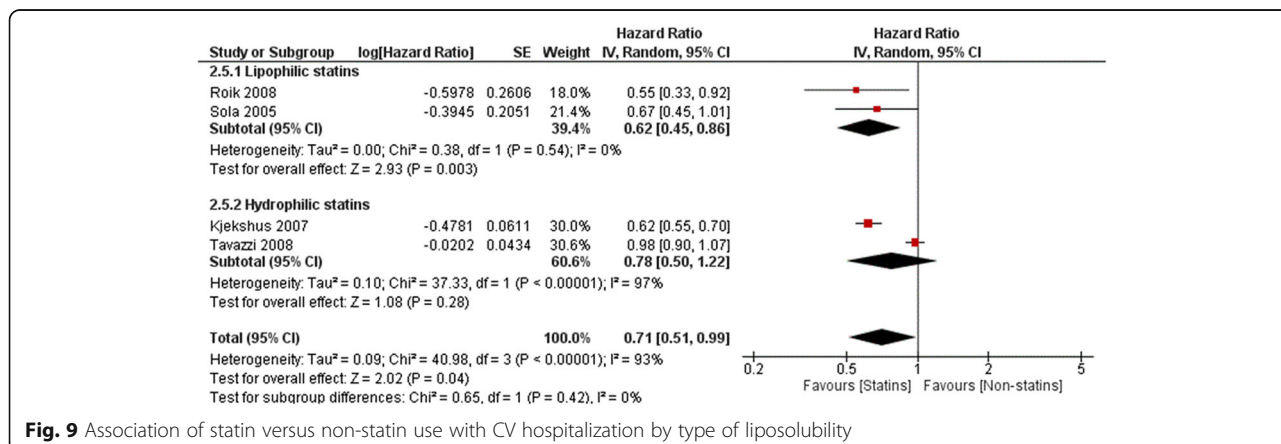
Fig. 8 Association of statin versus non-statin use with CV mortality by type of liposolubility

fatty acids in patients with chronic heart failure (GISSI-HF), patients on statins were not included, which may have resulted in more patients with severe ischemia being excluded (individuals with ischemic HF represented only 40% of patients). Finally, patients receiving cardiac resynchronization therapy were either excluded or represented a small percentage of the studied population. It is important as there are some avaiable data, including a retrospective analysis of the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial, suggesting that statin therapy might be associated with improved survival in HF patients receiving resynchronization therapy [43]. The GISSI-HF trial also had a relatively large number of patients who discontinued therapy for reasons other than adverse drug reactions (31%) compared with only 10% in the CORONA trial, raisingthe question of whether this might have impacted the final results of the study. The investigators of GISSI-HF also suggested that there were too few acute ischemic events in heart failure patients for a statin to show a benefit [39]. An alternative theory to explain the

controversial results between real-life cohorts and the large RCTs was based on observation that in the CORONA trial the lowest N-terminal pro-B-type natriuretic peptide tertile did benefit from rosuvastatin therapy, with a significant reduction in the primary outcome. It has been suggested that in patients with less advanced HF, statin therapy might be benefitial in reduction of coronary events, whereas in severe HF, it is too late to for the potential benefits from statin therapy due to progressive loss of pump function [44].

The main finding from the meta-analysis of Preiss et al. [45] was a significant reduction in non-fatal MI and a modest (however still significant) reduction in first non-fatal HF hospitalizations [45]. The composite outcome of HF death and HF hospitalizations was also significantly reduced in the statin groups, but was driven exclusively by a reduction in HF hospitalizations. A noteworthy finding from the Preiss et al. study [45] concerns the mechanisms, by which statin therapy reduced the risk of HF hospitalizations. Interestingly, neither a reduced risk of non-fatal MI nor a decrease in LDL-C correlated with

Fig. 9 Association of statin versus non-statin use with CV hospitalization by type of liposolubility

the risk of HF hospitalizations. These results raise the possibility that statins might have exerted beneficial effects on HF hospitalizations through their pleiotropic properties [45]. The results of our meta-analysis are consistent with the referred meta-analysis [45] and support a positive influence of the pleiotropic properties of statins on HF outcomes. What is worth emphasizing, recent evidence suggests that there is no class effect for statin use in the setting of HF, and we should expect different effects for hydrophilic and lipophylic statins [46].

It seems that one of the most important mechanisms of statins in this group of patients could be to rapidly affect signaling pathways in myocardial cell membranes and/or the autonomic nervous system, and in the consequence protecting them from life-threatening arrhythmias. The lipophilic statins (e.g. atorvastatin and simvastatin) become easily embedded in the cell membrane, having overlapping locations in the hydrocarbon core adjacent to the phospholipid head groups [47–49]. Evidence from a meta-analysis of RCTs by Lipinski et al. of statins in HF showed a significant benefit of hydrophilic atorvastatin on all-cause mortality, LVEF, and hospitalization due to HF, whereas similar effects were not observed in patients randomized to the hydrophilic rosuvastatin [50]. We have recently seen the same results for statin types as per our pro-sarcopenic hypothesis [38]. Our findings also support the findings by Liu et al. in patients with HF, which indicated a significant reduction in risk of all-cause mortality, CV mortality and hospitalization for worsening HF using lipophilic statins [50, 51]. Based on the available data it is known that lipophilic statins are to be much more susceptible to oxidative metabolism by the CYP450 system, and those metabolized by this system are more likely to produce muscle toxicity because of the risk of drug interactions with many drugs that inhibit CYP450 [38]. However based on the results of our study lipophilic statins revealed better outcomes in HF patients.

Recent ESC guidelines on HF have introduced a new phenotype based on LVEF, mid-range HF (HFmrEF) that falls between the classical HFrEF and HFpEF phenotypes [2, 7]. Therefore, statins might improve outcomes in these types of HF [53] through exerting beneficial effects on inflammation, LV hypertrophy, interstitial fibrosis, endothelial dysfunction and arterial stiffness, all of which contribute to the pathophysiology of HF with LVEF ≥40% [52, 54]. In the study of Alehagen et al. [55], 9140 patients in the prospective Swedish Heart Failure Registry with HF and EF ≥50% were divided into those treated with statins ($n = 3427$) and untreated with statins (n = 5713). Statins were associated with better one-year

survival (85% vs 80%; $p < 0.001$), reduced CV death and composite all-cause mortality or CV hospitalization [55]. In a meta-analysis, Fukuta et al. [56] assessing the effect of statin therapy on mortality in patients with HF with LVEF≥45% with the use of propensity score analysis, showed that investigated therapy was associated with reduced mortality, which suggests the potential mortality benefit of statins in HFpEF [56]. Another meta-analysis included a total of 11 eligible studies with 17,985 patients with HF and EF > 45% [6]. Statin use was associated with a 40% lower risk of mortality (RR 0.60, 0.49–0.74, p < 0.001). Finally, cumulative meta-analysis by Liu et al. showed an obvious trend of reduction in mortality with statins [57, 58]. The results of our analysis in patients with HF and LVEF ≥40% are consistent with the results of Fukuta et al. and Liu et al. [56, 57].

There are some obvious limitations associated with this systematic review. First, there was limited information available on patient characteristics such as compliance with statin therapy or statin dosage. Included studies did not have enough data to check the correlations with cholesterol level and other variables like body mass index (BMI). The solubility of statins was a variable that was also not available in most of the trials, despite the fact the authors of this analysis asked all investigators of included studies about this; therefore, analyses by solubility was performed only based on limited number of studies with that information and hydrophilic statin arm included only two RCT studies while the other included only observational studies [59–61]. Most studies included in our meta-analysis were performed before 2016 when there was no fixed LVEF cut-off points for HFpEF and HFmrEF; that is why we combined HFpEF and HFmrEF patients in one group of patients with LVEF ≥40%. The HFmrEF patients, as a new and distinct group, had many intermediate characteristics compared with HFrEF and HFpEF subjects.

Conclusions

Statins may have beneficial effect on main CV outcomes in HF patients irrespective of the different etiologies and EF levels. Lipophilic statins, and not hydrophilic statins might be favorable for patients with heart failure independently from their postulated prosarcopenic effects [38]. The present meta-analysis emphasizes the need for a new, well-design randomized study of the effect of statins, in particular lipophilic, in HF patients. There will also be a need for additional analyses assessing the impact of cholesterol levels, BMI, type and doses of statin, and body mass compartments on outcomes. This information could establish a target group of patients with HF who will

benefit the most from statin therapy as well as the type and dose of statins that are optimal in these patients.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12944-019-1135-z.

Additional file 1: Appendix 1. Assessment of risk of bias in the included studies using Cochrane criteria for RCTs. **Appendix 2.** Assessment of risk of bias in the included studies using Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies. **Figure S1.** Association of statin versus non-statin use with all-cause mortality in heart failure only in cohort studies. **Figure. S2**. Association of statin versus non-statin use with CV mortality in heart failure only in cohort studies. **Figure S3.** Association of statin versus non-statin use hospitalization in heart failure only in cohort studies. **Figure S4.** Association of statin versus non-statin use with all-cause mortality by type of heart failure only in cohort studies. **Figure S5.** Association of statin versus non-statin use with CV mortality by type of heart failure only in cohort studies. **Figure S6.** Association of statin versus non-statin use with hospitalization by type of heart failure only in cohort studies. **Table S1.** Assessment of risk of bias in the included studies using Cochrane criteria for RCTs. **Table S2.** Assessment of risk of bias in the included studies using Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort studies.

Abbreviations

ACC/AHA: American College of Cardiology/American Heart Association; BMI: body mass index; CAD: coronary artery disease; CHF: chronic heart failure; CI: confidence interval; CoQ10: coenzyme Q10; CV: cardiovascular; DM: diabetes mellitus; EAS: European Society of Atherosclerosis; HF: heart failure; HFmrEF: heart failure with mid-range left ventricular ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced left ventricular ejection fraction; HR: hazard ratio; HTN: arterial hypertension; IRB: Institutional Review Board; LDL: low density cholesterol; LVEF: left ventricular ejection fraction; MI: myocardial infarction,; NLA: National Lipid Association; RCTs: randomized controlled trials; SD: standard deviation; SElogHR: standard errors of the log HR; TC: total cholesterol; TGs: triglycerides

Authors' contributions

AB-D, SH, SA and MB are resposible for the concept of all manuscript. AB-D, IB, JJ independently evaluated each article separately. Disagreements were resolved by discussion with a third party (MB). IB, GB, JR performed statistical analysis. AB-D, IB, AH, MB, DM analyzed and interpreted data and were major contributor in writing the manuscript. All authors read, improved and approved the final manuscript.

Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

ABD, IB, JR, JJ, SvH, and AVH have no conflicts of interest to disclose; DPM has given talks and attended conferences sponsored by MSD, AstraZeneca and Libytec; SDA reports personal fees from Bayer, Boehringer Ingelheim, Vifor, Servier and Novartis, outside the submitted work; MB has served on the speakers bureau of Abbott/Mylan, Abbott Vascular, Actavis, Akcea, Amgen, Biofarm, KRKA, MSD, Sanofi-Aventis, Servier and Valeant, and has served as a consultant to Abbott Vascular, Akcea, Amgen, Daichii Sankyo, Esperion, Lilly, MSD, Resverlogix, Sanofi-Aventis; Grants from Sanofi and Valeant.

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