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

Agata Bielecka-Dabrowa 1,2†, Ibadete Bytyçi 3,4†, Stephan Von Haehling 5, Stefan Anker 6, Jacek Jozwiak 7, Jacek Rysz 8, Adrian V. Hernandez 9,10, Gani Bajraktari 3,4, Dimitri P. Mikhailidis 11 and Maciej Banach 1,2*

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, I² = 63%), CV mortality (HR 0.82, 95% CI: 0.76–0.88, P < 0.0001, I² = 36%), and CV hospitalization (HR 0.78, 95% CI: 0.69–0.89, P = 0.0003, I² = 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

* Correspondence: maciej.banach@icloud.com
† Agata Bielecka-Dabrowa & Ibadete Bytyçi contributed equally to this paper
1Department of Hypertension, Medical University of Lodz, Rzgowska, 281/289; 93-338 Lodz, Poland
2Department of Cardiology and Congenital Diseases of Adults, Polish Mother’s Memorial Hospital Research Institute (PMMHRI), Lodz, Poland

Full list of author information is available at the end of the article

© The Author(s). 2019 Open Access This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.
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 (HFrEF) and preserved LVEF (HFpEF) and mortality and morbidity of patients with these types of HF are also high [3, 4]. The pathophysiology of HFrEF 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 \( \geq 40\% \)) 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
| 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 | HFrEF | 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; mortality mortality | 12 mo     |
| Go et al. 2006      | Prospective cohort | HFrEF | HF patients | previous statin-induced myopathy or hypersensitivity decompensated HF | Statins: Control | Rosuvastatin | CV death Non-fatal MI Stroke | 28 mo     |
| Kjekshus et al. 2007 CORONA | RCTs | HFrEF | HF patients, EF < 40%, NYHA II-IV | | Statins: Control | Rosuvastatin | All-cause mortality; All-cause mortality; Hospitalizations | 36 mo     |
| Coleman et al. 2008 | Prospective cohort | HFrEF | HF patients EF < 40% und--ergoing ICD | HF patients with LVDD | Statins: Control | Not specified | All-cause mortality; VT/VF incidence | 31 mo     |
| Roik et al. 2008    | Prospective cohort | HFrEF | 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 | 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 | HFrEF | 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 | HFrEF | 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 | HFrEF | HF patients with EF ≥50% | Incomplete follow-up Non-documented EF | Statins: Control | Not specified | All-cause mortality; Hospitalization | 2 y       |
| Nochioka et al. 2015| Prospective cohort | HFrEF | HF patients with stages B-D | NR | Statins: Control | Not specified | All-cause mortality; Hospitalization | 3 y       |
| Alehagen U et al. 2015 | Prospective cohort | HFrEF | HF patients with EF ≥50% | HF patients with EF < 50% | Statins: Control | Not specified | All-cause mortality; Hospitalization | 12 mo     |
| Alehagen et al. 2015| Prospective cohort | HFrEF | HF patients | HF patients with EF ≥50% | Statins: Control | Not specified | All-cause mortality; Hospitalization | 24 mo     |
| Tsujimoto et al. 2018 | Prospective cohort | HFrEF | HF patients with preserved EF | HOCMP systemic illness with 1 Life expectancy < 3 y | Statins: Control | Not specified | All-cause mortality; CV and Non-CV mortality; | 3.3 y     |

Abbreviations: HF: heart failure; HFrEF: heart failure with reduced ejection fraction; HFrEF: 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 ± 0.3 |
|                    | C    | 191 | ≤35% | 53.8 ± 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 | NR         | NR       |
|                    | C    | 68  | ≥50% | 65 ± 16  | NR       | 45 | 12 | 72 | NR | NR         | NR       |
| 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 | 79 | 89 | NR         | NR       |
|                    | C    | 11,950 | ≤40% | 72.9 ± 11.4| NR | 60 | 41 | 83 | 54 | NR         | NR       |
| Kjekshus et al. 2007 | S | 2814  | ≤40% | 73 ± 7.1  | 27 ± 4.5 | 76 | 30 | 63 | 9  | 5.36 ± 1.1 | 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 | 27.1 ± 4.6 | 78.6 | 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 | NR | NR | NR | NR | 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 | NR | NR | NR | NR         | NR       |
| Nochioka et al. 2015 | S | 1163 | ≥50% | 69.0 ± 11.0| 67.5 | 45 | 33.8 | 85 | 85 | 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 |
| Tsumimoto et al. 2018 | S | 1765 | ≥50% | 69 ± 9.6 | 55 | 42 | 29 | 93.1 | 10.5 | NR | NR |
|                    | C    | 1613 | ≥50% | 68.1 ± 9.6| 53 | 28 | 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
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).

Fig. 3 Association of statin versus non-statin use with a) CV mortality, and b) Hospitalization
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, I² = 63%, Fig. 2), CV mortality (HR 0.82, 95% CI: 0.76–0.88, P < 0.0001, I² = 63%) and CV hospitalization (HR 0.78, 95% CI: 0.69–0.89, P = 0.0003, I² = 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% CI: 0.68–0.86, p < 0.0001, and HR 0.75, 95% CI: 0.69–0.82, p < 0.0001, respectively, Fig. 4). CV mortality was also reduced in both EF groups using statins (HR 0.86, 95% CI: 0.79–0.93, p = 0.0003, and HR 0.83, 95% CI: 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).

Effect on all-cause mortality was higher for lipophilic compared to hydrophilic statins (HR 0.59, 95%CI: 0.37–0.93, p = 0.02 and HR 0.97, 95%CI: 0.88–1.07, p = 0.60, respectively, Fig. 7).

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.
turnover markers as well as a reduction in plasma coenzyme 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].

Large trials with hydrophilic rosuvastatin did not indicate a significant role for statins in chronic HF, although the drug did reduce the number of CV hospitalizations in the CORONA trial [39, 40]. Although the above-mentioned 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 associated 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. 6](image)

**Fig. 6** Association of statin versus non-statin use in HF patients with CV hospitalizations by LVEF value

![Fig. 7](image)

**Fig. 7** Association of statin versus non-statin use with all-cause 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 available 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, raising the 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 beneficial 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
the risk of HF hospitalizations. These results raise
the possibility that statins might have exerted benefi-
cial 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 set-
ing of HF, and we should expect different effects
for hydrophilic and lipophilic 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 con-
sequence protecting them from life-threatening arrhyth-
mias. The lipophilic statins (e.g. atorvastatin and
simvastatin) become easily embedded in the cell mem-
brane, 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 hydro-
philic 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 re-
sults 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 sig-
nificant reduction in risk of all-cause mortality, CV mor-
tality 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 sys-
tem, 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 hyper-
trophy, 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 re-
sults of Fukuta et al. and Liu et al. [56, 57].

There are some obvious limitations associated with
this systematic review. First, there was limited informa-
tion available on patient characteristics such as
compliance with statin therapy or statin dosage. In-
cluded 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 infor-
mation and hydrophilic statin arm included only two
RCT studies while the other included only observa-
tional studies [59–61]. Most studies included in our
meta-analysis were performed before 2016 when there
was no fixed LVEF cut-off points for HFrEF and
HFmrEF; that is why we combined HFrEF and
HFmrEF patients in one group of patients with LVEF
≥40%. The HFmrEF patients, as a new and distinct
group, had many intermediate characteristics com-
pared with HFrEF and HFpEF subjects.

Conclusions
Statins may have beneficial effect on main CV out-
comes in HF patients irrespective of the different eti-
ologies 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 random-
ized study of the effect of statins, in particular lipo-
philic, 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.

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; HR: hazard ratio; HTN: arterial hypertension; IBD: 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

Acknowledgements

Not applicable.

Authors’ contributions

AB-D, SH, SA and MB are responsible 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.

Funding

Nothing to declare.

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

AB-D, IB, JR, JJ, SvH, and AVH have no conflicts of interest to disclose; DPM has given talks and attended conferences sponsored by MSD, AstaZeneca 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, Daichi Sankyo, Esperion, Lilly, MSD, Resverlogix, Sanofi-Aventis; Grants from Sanofi and Valeant.

Author details

1Department of Hypertension, Medical University of Lodz, Rogowska, 281/289; 93-338 Łódź, Poland. 2Department of Cardiology and Congenital Diseases of Adults, Polish Mother’s Memorial Hospital Research Institute (PWMMHR), Łódz, Poland. 3Clinic of Cardiology, University Clinical Centre of Kosovo, Prishtina, Republic of Kosovo. 4Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden. 5Department of Cardiology and Pneumology, University Medical Center Gottingen (UMG), Gottingen, Germany. 6Charité-Universitätsmedizin Berlin, Berlin, Germany. 7Department of Family Medicine and Public Health, Institute of Medicine, University of Opole, Opole, Poland. 8Department of Nephrology, Hypertension and Family Medicine, Medical University of Lodz, Łódz, Poland. 9Health Outcomes, Policy, and Evidence Synthesis (HOPES) Group, University of Connecticut School of Pharmacy, Storrs, CT, USA. 10School of Medicine, Universidad Peruana de Ciencias Aplicadas (UPC), Lima, Peru. 11Department of Clinical Biochemistry, Royal Free Campus, University College London Medical School, University College London (UCL), London, UK.

Received: 28 June 2019 Accepted: 16 October 2019

Published online: 31 October 2019

References

1. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. Circulation. 2014;129:50–54.
2. Ponikowski P, Voors AA, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016;37(27):2129–2177.
3. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006;355(25):251–9.
4. Steinberg BA, Zhao X, Heidenreich PA, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: prevalence, therapies, and outcomes. Circulation. 2012;126(5–55).
5. Liao J, Oesterle A. The Pleiotropic Effects of Statins - From Coronary Artery Disease and Stroke to Atrial Fibrillation and Ventricular Tachyarrhythmia. Curr Vasc Pharmacol. 2019;17(3):222–32.
6. Mohler D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
7. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Rev Esp Cardiol. 2016;69(12):1517–47.
8. Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: https://www-handbook.cochrane.org.
9. Zeng X, Zhang Y, Kwong JS, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med. 2015;8(2):10–10.
10. Cooper HM, Hedges LV. The handbook of research synthesis. New York: Russell Sage Foundation; 1994.
11. Hojo SP, Djulbegovic B, Hojo I. Estimating the mean and variance from the median, range, and the size of a sample. BMJ Med Res Methodol. 2005;5:13.
12. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
13. Horwich TB, MacLeann WR, Fonarow GC. Statin therapy is associated with improved survival in ischemic and non-ischemic heart failure. J Am Coll Cardiol. 2004;43:642–8.
14. Sola S, Mir MO, Rajagopalan S, Helmy T, Tandon N, Khan BV. Statin therapy is associated with improved cardiovascular outcomes and levels of inflammatory markers in patients with heart failure. J Card Fail. 2005;1:607–12.
15. Fukuta H, Sane DC, Brucks S, Little WC. Statin therapy may be associated with lower mortality in patients with diastolic heart failure: a preliminary report. Circulation. 2005;112:557–63.
16. Hong YJ, Jeong MH, Hyun DW, et al. Prognostic significance of simvastatin therapy in patients with ischemic heart disease who underwent percutaneous coronary intervention for acute myocardial infarction. Am J Cardiol. 2005;95:619–22.

17. Go AS, Lee WJ, Yangs J, Lo JC, Gurwitz JH. Statin therapy and risks for death and hospitalization in chronic heart failure. JAMA. 2006;296:2015–11.

18. Kjekshus J, Apetrei E, Barrios V, et al. Rosuvastatin in older patients with systolic heart failure. N Engl J Med. 2007;357:2248–61.

19. HuanLoh P, Windram JD, Tin L, et al. The effects of initiation or continuation of statin therapy on cholesterol level and all-cause mortality after the diagnosis of left ventricular systolic dysfunction. Am Heart J. 2007;153:337–44.

20. Coleman CI, Kluger J, Bhavnani S, et al. Association between statin use and mortality in patients with implantable cardioverter-defibrillators and left ventricular systolic dysfunction. Heart Rhythm. 2008;5:507–10.

21. Roik M, Starczewska MH, Huczek Z, Kochanowski J, Opolski G. Statin therapy and mortality among patients hospitalized with heart failure and preserved left ventricular function—a preliminary report. Acta Cardiol. 2008;63:683–92.

22. Tavazzi L, Maggioni AP, Marchioli R, et al. Effect of rosuvastatin in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet. 2008;372:1231–9.

23. Gomez-Soto FM, Romero SP, Bernal JA, et al. Mortality and morbidity of newly diagnosed heart failure treated with statins: a propensity-adjusted cohort study. Int J Cardiol. 2010;140:210–8.

24. Kaneko H, Suzuki S, Yajima J, et al. Clinical characteristics and long-term outcomes of Japanese heart failure patients with preserved versus reduced left ventricular ejection fraction: a prospective cohort of Shinken database 2004-2011. J Cardiovasc Med. 2013;62:102–9.

25. Yap J, Sim D, Lim CP, et al. Predictors of two-year mortality in Asian patients with heart failure and preserved ejection fraction. Int J Cardiol. 2015;183:33–8.

26. Nachholt K, Sakata Y, Miyata S, et al. Prognostic impact of statin use in patients with heart failure and preserved ejection fraction. Circ J. 2015;79:574–82.

27. Alehagen U, Bengtsson L, Edner M, et al. Association between use of statins and mortality in patients with heart failure and ejection fraction of ≤50%. Circ Heart Fail. 2015;8:682–70.

28. Alehagen U, Bengtsson L, Edner M, et al. Association between use of statins and outcomes in heart failure with reduced ejection fraction: prospective propensity score matched cohort study of 21 864 patients in the Swedish heart failure registry. Circ Heart Fail. 2015;8:252–60.

29. Tsujimoto T, Kajio H. Favorable effects of statins in the treatment of heart failure with preserved ejection fraction in patients without ischemic heart disease. Int J Cardiol. 2018;255:111–7.

30. Brown JH, Del RE DP, Sussman MA. The Rac and rho hall of fame: a decade

31. Banach M, Serban C, Ursoniu S, et al. Lipid and blood pressure Meta-analysis controlled trials. Pharmacol Res. 2015;99:329–36.

32. Bielecka-Dabrowa A, Fabis J, Mikhailidis DP, et al. Proscopnic effects of statins may limit their effectiveness in patients with heart failure. Trends Pharmacol Sci. 2018;39:331–53.
systematic review and meta-analysis of randomized controlled trials.
Pharmacol Res. 2017;122:105–17.
60. Schachter M. Chemical, pharmacokinetic and pharmacodynamic properties
of statins: an update. Fundam Clin Pharmacol. 2005;19(1):117–25.
61. Henninger C, Huelsenbeck S, Wenzel P, Brand M, Huelsenbeck J, Schad A,
Fritz G. Chronic heart damage following doxorubicin treatment is alleviated
by lovastatin. Pharmacol Res. 2015;91:47–56.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in
published maps and institutional affiliations.