Reduced Heart Failure and Mortality in Patients Receiving Statin Therapy Before Initial Acute Coronary Syndrome

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Brief Title: Sex, Statins and Heart Failure

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Suggested tweet: Among patients presenting with #acutecoronarysyndromes as a first manifestation of ASCVD, prior #statin therapy is associated with reduced risk of #acuteheartfailure and improved survival from AHF

Abstract

Background: There is uncertainty regarding the impact of statins on risk of atherosclerotic cardiovascular disease (ASCVD) and its major complication: acute heart failure (AHF).

Objectives: The aim of this study was to investigate whether prior statin therapy translates into lower AHF events and improved survival from AHF among patients presenting with acute coronary syndromes (ACS) as first manifestation of ASCVD.

Methods: Data were drawn from the ISACS Archives. The study population consisted of 14,542 Caucasian patients presenting with ACS without previous ASCVD events. Statin users prior to index event were compared with non-users using inverse probability weighting models. Estimates were compared by test of interaction on the log scale. Main outcome measures were the incidence of AHF according to Killip class classification and the rate of 30-day all-cause mortality in patients presenting with AHF.

Results: Prior statin therapy was associated with a significantly decreased rate of AHF on admission (4.3% absolute risk reduction; risk ratio [RR]: 0.72, 95% CI 0.62 to 0.83) regardless of younger (40 to 75 years) or older age (interaction p: 0.27) and sex (interaction p: 0.22) Moreover, prior statin therapy predicted a lower risk of 30-day mortality in the subset of patients presenting with AHF on admission (5.2 % absolute risk reduction; RR: 0.71; 95% CI: 0.50 to 0.99).

Conclusions: Among adults presenting with ACSs as a first manifestation of ASCVD, prior statin therapy is associated with reduced risk of AHF and improved survival from AHF.

Condensed Abstract:

Despite guideline-based recommendations for atherosclerotic cardiovascular disease (ASCVD), the use of statins in primary prevention is still controversial, owing to the variable risk of events in this population. The present study from the ISACS-Archives registry

suggests that in patients with ACSs as a first manifestation of ASCVD prior use of statins reduces acute heart failure (AHF) events and confers a survival benefit from AHF. Benefits are consistent regardless of age and sex. In the absence of definitive evidence from trials our data provide sufficient grounds for further recommendation of statin therapy in the primary prevention setting.

Clinical registry: clinicaltrials.gov/ct2/show/NCT04008173

Keywords

Statins; atherosclerotic cardiovascular disease; acute heart failure; 30-day mortality

Abbreviations:

ACE= Angiotensin converting enzyme; **ACS=** Acute coronary syndrome; **ARBs=** Angiotensin receptor blockers; **ASCVD**= atherosclerotic cardiovascular disease; **AHF=** Heart failure; **CI=** Confidence interval; **OR=** odds ratio; **RR=** risk ratio; **STEMI=** ST segment elevation myocardial infarction; **USPSTF**=U.S. Preventive Services Task Force

Introduction

In secondary prevention setting, statins reduce the risk of recurrent atherosclerotic cardiovascular disease (ASCVD) events and mortality from ASCVD events, with benefits of comparable magnitude in men and women(1). On the contrary, controversies abound about the role of statins in primary prevention setting (2-4)

It has been argued that prior estimates of statin effects were mainly based on information from both individuals with and without pre-existing ASCVD, which may overestimate the true benefits of statins. Some investigators attempted to quantify the impact of statins on outcomes of women versus men and reported significantly different effect estimates(5,6). Others have questioned the benefits of statins in adults 76 years and older as this age group was poorly represented in the randomized trials for primary prevention of ASCVD. Notably, a large proportion of individuals in early statin trials were taking aspirin and antihypertensive drugs, which may lower the risk of ASCVD development. While this issue is clearly important, there is little or no information on concomitant medications in prior work. Thus, one could reasonably conclude that prior work did not examine the incremental benefit of statin, added to other standard preventive interventions.

The absence of prior convincing data for all-cause mortality has led some researchers to question the benefits of statins among individuals without a history of ASCVD(7,8). Acute coronary events remain the most significant contributors to mortality from ASCVD. However, nobody can predict exactly why one person dies and another does not, as mortality from acute coronary events can be related to multiple factors, the most important being acute heart failure (AHF) on hospital admission(9). Among patients with acute presentation of ASCVD, AHF strongly increases the risk of all-cause death independently of key confounders, including concurrent comorbidities and acute treatment(10). The uncertain relationship between statin use in primary prevention setting and all-cause mortality from

ASCVD probably depends upon the proportion of cases presenting with AHF in the population under scrutiny. In sum, as recognized by both the European Society of Cardiology(11) and the American Heart Association(12), AHF prevention is an urgent public health need.

Statins have therapeutic properties that are of potential benefit to patients with AHF of ischemic etiologies, irrespective of lipid levels(13). Statins may improve endothelial function, inhibit inflammatory cytokines, potentiate nitric oxide synthesis, and inhibit the process of apoptosis(14). On the other hand, statin therapy has also the potential to alter plaque composition and reduce the risk of plaque disruption and its thrombotic complications(15). Thus, statin therapy may also decrease the development of AHF by reducing the severity of the first ischemic myocardial event.

In light of the controversy surrounding statin use in primary prevention setting, we undertook the present study to evaluate whether prior use of statins may reduce the prevalence of AHF on hospital admission and its related mortality across age and sex in a large cohort of patients presenting with acute coronary syndromes (ACSs) as first manifestation of ASCVD. In addition, we wished to explore whether reduction in AHF was primarily driven by a reduction in the severity of ACS as documented by its clinical presentation. A requirement of the study was that the outcomes of patients exposed to statins could not be influenced by other potential prevention therapies. This task was achieved by matching concomitant medications using inverse probability of treatment weighting models.

Methods

Derivation cohort

We analyzed data from the International Survey of Acute Coronary Syndromes (ISACS) Archives (NCT04008173) collected from October 2010 to January 2019. The ISACS Archives provides access to de-identified, research cohorts in ACSs(16,17). As the

aim of the current investigation was to investigate the association between cardiovascular outcomes and prior evidence-based medication use, we identified two large clinical registries providing such information, namely the ISACS-TC (NCT01218776) and the EMMACE-3X (Long-term Follow-up of Health-Related Quality of Life in Patients with Acute Coronary Syndrome; NCT01955525) **(Supplemental Table 1)**. In brief, the ISACS-TC registry collected data from 41 centers in 12 European countries: Bosnia and Herzegovina, Croatia, Italy, Kosovo, Lithuania, Macedonia, Hungary, Moldova, Montenegro, Romania, Russian Federation, and Serbia. Among these sites, there were 22 tertiary health care services providing percutaneous coronary intervention (PCI)(18,19). The EMMACE-3X gathered routine clinical information from 47 hospitals in England. Cardiovascular facilities including PCI were available in 33 hospitals(20). Other details of the study design, sampling, and recruitment have been previously published and are summarized in the **Supplemental Material**. The local research ethics committee from each hospital approved the study. Because patient information was collected anonymously, institutional review boards waived the need for individual-informed consent. Both registries had independent source documentation. All data were transferred to the Department of Electrical and Computer Engineering, University of California, Los Angeles, where final statistical analyses were performed.

Patient Population

Patients were eligible for this study if they had clinically confirmed ACS(21). The initial population consisted of 23,567 patients. Patients presenting with prior history of ASCVD events were excluded leaving a final study population of 14,542 patients **(Figure 1).**

Outcome Measures

Key outcome measure was the prevalence of AHF on admission for ACS as index presentation of ASCVD. The diagnosis of AHF was based on clinical symptoms or signs and

radiographic evidence of pulmonary congestion. The presence of AHF at the time of hospital presentation was formally categorized by use of the Killip classification(22). Patients with Killip class ≥2 were defined as presenting with AHF on admission for ACS as index presentation of ASCVD. We also analyzed the association of AHF with all-cause mortality at 30 days from admission. The 30-day window was selected to enrich the data over that acquired during the index hospitalization while mitigating survivor bias. To explore the multifaceted association between AHF after ACS and mortality, we identified ST-segment elevation myocardial infarction (STEMI) as a further predictor of outcome. Reduction in the rates of AHF with ACS might coincide with a decline in the proportion of STEMI in the study population.

Concomitant Care and Definitions

We noted the type of evidence-based medications (aspirin, statins, angiotensin-converting enzyme inhibitors [ACE-inhibitors], angiotensin receptor blockers [ARB] and beta-blockers) given prior to the index event. Mineralocorticoid receptor antagonists have been less widely used in the European clinical practice. As such we have not available data on their use. Medications were determined by the patients' referring physician. Medications received immediately before hospitalization or in the emergency department were not considered prior medication use. Multivessel disease was defined as at least 2 main branches of the epicardial coronary artery with ≥70% stenotic lesions or ≥50% stenosis in the left main coronary artery. All patients with a glomerular filtration rate <60 ml/min/1.73 m^2 for 3 months were defined as having chronic kidney disease. Smoking habits were self-reported. Former smokers were defined as those patients who had a history of smoking tobacco, but were not active smokers at the time of the index event. Hypertension, hypercholesterolemia and diabetes were assessed by designation of medical history prior to admission in the database. Body mass index (BMI) was calculated as weight (kg) divided by height squared

(m^2).The 10-year risk of ASCVD for each patient was calculated by using the Pooled Cohort Equations. We set the cut-off for increased level of ASCVD risk at 10% according to the 2017 final recommendation statement of the USPS Task Force(23).

Statistical analysis

Patient characteristics were stratified according to treatment-group: statin users versus statin nonusers. Our analysis focused solely on the possible interaction between statin therapy and baseline characteristics; no other subgroup analyses on other medications were conducted. Baseline characteristics were reported as percentages for categorical variables and means with standard deviation for continuous variables. We used Multiple Imputation with Chained Equation (MICE) as the imputation method to treat missing data (24). (**Methods in the Supplemental Material)**. To reduce the imbalance of potential confounding factors between statin users and nonusers, we compiled a set of baseline covariates as listed in **Table 1**. Variables included demographics, CV risk factors, medical history and angiographic findings. We used an inverse probability of treatment weighting approach on the basis of propensity scores for confounding adjustment(25) Standardized differences after weighting were calculated to ensure balanced treatment groups with respect to baseline characteristics. Groups were considered balanced when the standardized difference was less than 20%(26) **(Methods in the Supplemental Material)**. The association between AHF on hospital admission and 30-day mortality was also evaluated by logistic regression analyses. We calculated odds ratios (OR) or risk ratios (RR) with their 95% confidence interval (CI) from logistic regression and inverse probability of treatment weighting models, respectively. **(Methods in the Supplemental Material)**. Comparisons of outcomes between groups were assessed by two-sided p-value. To minimize concern about comparison of the treatment effect in subgroups, estimates were compared by test of interaction on the log scale(27). A *P*

value < 0.05 was taken to indicate that the difference between the effects in subgroups was unlikely to have occurred simply by chance **(Methods in the Supplemental Material)**.

Results

Overall, 14,542 patients entered into the study. (**Figure 1**). Patient baseline characteristics are listed in **Supplemental Table 2**. Slightly more than 12% (n = 1,824) of patients reported use of statins. Statin users were more often former smokers and had greater BMI. They had more frequently diabetes, hypertension, hypercholesterolemia compared with statin nonusers. Statin users were more likely to have CKD compared with nonusers, however, there was no statistically significant difference between the two groups. Statin users were also more likely to take concomitant evidence-based medications before admission and showed a numerically, but not significantly higher predicted 10-year ASCVD risk compared with nonusers (**Supplemental Table 3)**. Revascularization procedures by PCI were less common in statin users than nonusers (68.3% vs 73.3%). Fibrinolysis was also less common in statin users (3.7% vs 7.3%), but CABG was notably less common in statin nonusers (2.1% vs 4.1%). None of the reported differences in treatment were significant (**Supplemental Table 4)**

Effect of statins on acute heart failure

After adjustment for inverse probability of treatment weighting, no statistically significant or clinically relevant standardized differences were observed between statin users and nonusers **(Table 1).** Prior statin use was associated with a significantly decreased prevalence of AHF at the time of ACS admission (absolute difference 4.3%; RR: 0.72, 95% CI 0.62 to 0.83) (**Central Illustration**). At the time of ACS admission, reductions in the risk of AHF were not attenuated when controlling for age **(Table 2)** and weight **(Supplemental Table 5)**. The effect of statins was consistent in both patients aged 40 to 75 years (RR: 0.73, 95% CI 0.62 to 0.86) and those aged 76 years and above (RR: 0.66, 95% CI 0.50 to 0.87).

Similar consistence was found for patients with BMI <25 kg/m^2 (RR: 0.80, 95% CI: 0.61 to 1.06) and those with BMI ≥25 kg/m^2. (RR: 0.71, 95% CI: 0.60 to 0.84). There were no interaction effects between statin therapy and age or BMI (**Supplemental Tables 6 and 7**). Statin benefits were also observed when the analysis was restricted to the higher ASCVD risk group (RR: 0.73, 95% CI: 0.63 to 0.85), but were not seen in the lower risk group (RR: 0.85, 95% CI: 0.60 to 1.20) **(Table 3)**. The RR of AHF at the time of ACS admission did not differ significantly when the two subgroups were compared by interaction test **(Supplemental Table 8).**

Effect of statins on prevalence of acute heart failure on admission of ACS analyzed by conventional risk factors

Figure 2 depicts the RRs for clinical outcomes after ACS admission accompanied by AHF when treatment with statins was stratified based on conventional risk factors (**Supplemental Tables 9-13**). Differences were present in all subgroups. Statin use was associated with a substantially lower risk of presenting with AHF on admission for ACS in patients who were current smokers (RR: 0.61; 95% CI 0.46 to 0.80) or former smokers (RR: 0.61; 95% CI 0.43 to 0.87), and for those with hypercholesterolemia (RR: 0.75; 95% CI 0.63 to 0.90), diabetes (RR: 0.58; 95% CI 0.47 to 0.72), and hypertension (RR: 0.71; 95% CI 0.60 to 0.83). Statin therapy produced a higher significant proportional reduction in AHF complicating presentation with ACS in people with diabetes and in those who were current smokers compared with their counterparts (p-values for interaction: 0.03). (**Supplemental Table 14).** In line with these findings, the benefit of statins was observed even in patients with no prior history of hypercholesterolemia (RR: 0.71; 95% CI: 0.54 to 0.92).

Effect of statins on acute heart failure prevalence on admission for ACS: data sorted by sex.

Women **(Table 4)** benefited from statin therapy with a 6.3 % absolute risk reduction in AHF following ACS (RR: 0.66; 95% CI, 0.53- 0.83) over non-statin therapy, whereas men had a 3.6% reduction (RR: 0.74; 95% CI, 0.62 to 0.89.) The effect of sex did not vary across treatment groups (p-value for interaction, 0.22). The interaction test is reported in **Supplemental Table 15**.

Effect of statins on 30-day all-cause mortality after admission with ACS and prevalent acute HF.

AHF on admission for ACS was predictive of mortality at 30 days among women and men (ORs in log scale: 1.74; 95% CI, 1.49 – 1.99 and 2.17; 95% CI, 1.96 – 2.39, respectively). **(Supplemental Figure 1).** To investigate the relationships among statin therapy, AHF following ACS and death at an individual level, we restricted our analysis to 2,431 ACS patients (16.7%) presenting with AHF on admission.

Prior statin therapy predicted a lower risk of 30-day mortality in statin users compared with statin nonusers (15.5% vs. 20.7%; RR: 0.71; 95% CI: 0.50 to 0.99) **(Table 5).** This benefit was not observed in patients without AHF on hospital admission (**Supplemental Table 16, Central Illustration).** The median time (q1, q3) from admission with AHF to the occurrence of death was 2 (1-5) days.

Effects of statins on prevalence of STEMI in subjects with acute HF on admission with ACS

Clinical presentation with STEMI as index event was strongly related to prevalence of AHF on hospital admission for ACS (OR in log scale: 0.66; 95%CI: 0.56–0.77). **(Supplemental Figure 2).** We, therefore, investigated whether the use of statins before index event may have affected the risk of presenting with STEMI (**Figure 3).** Overall, previous use of statins was associated with substantially lower risk of presenting with STEMI (RR: 0.64; 95%CI 0.58 to 0.71). Effects were consistent for men (RR: 0.61; 95% CI, 0.54-

0.69) and women (RR: 0.76; 95% CI, 0.64-0.90) and for the groups aged 40 to 75 years (RR: 0.70, 95% CI 0.62 to 0.78) and 76 years and above (RR: 0.59, 95% CI 0.46 to 0.75) with suggestion of interaction effects by sex (p-value: 0.02), but not by age (p-value: 0.11). (**Supplemental Tables 17-21.).** Only 23% of AHF events were accompanied by a NSTE-ACS. There was no demonstrable difference between the effect of statin therapy on risk of a first HF event preceded by STEMI or NSTE-ACS (**Supplemental Table 22).** The RRs of statin-users versus non-users for AHF prevalence on admission were 0.82 (95% CI 0.69–0.98) and 0.67 (95% CI 0.52–0.86) respectively (interaction p-value: 0.0983) (**Supplemental Table 23**).

Discussion

The current study demonstrates that statin therapy given in a primary prevention setting led to a reduction in the number of patients suffering AHF after an ACS as a first manifestation of ASCVD. The absolute risk of developing AHF on admission for ACS was reduced by approximately 4%. While the RR reductions were similar in STEMI and non-STEMI-ACS patients, the absolute risk reduction was considerably greater in STEMI patients, whose AHF event rates were substantially higher. Remarkably, this study also found that statin use predicted a lower risk of 30-day mortality in patients presenting with AHF on hospital admission following ACS (5.2% absolute risk reduction and a 29% RR reduction). This finding is of special note as it provides further information on the mechanistic process linking statin therapy to reduced mortality from ASCVD. In sum, the advantage of statin therapy was 2-fold: a lower percentage of people had AHF on hospital admission, and statin users with AHF on presentation with ACS had lower mortality than statin nonusers with AHF on presentation with ACS.

Considerations on U. S. Preventive Services Task Force guidelines

The U. S. Preventive Services Task Force (USPSTF) recommends the use of statins in primary prevention to substantially reduce the probability of ASCVD events and mortality in adults aged 40 to 75 years who have one or more conventional cardiovascular risk factors and a calculated 10-year ASCVD event risk of 10% or greater. USPSTF statements on statins were released along with a systematic review on which the recommendations are based(28). Notably, the systematic review did not exclude studies that included patients taking statins for secondary prevention, who have a higher baseline risk of cardiac events and death and thus are more likely to benefit from therapy. This approach may have enlarged the benefit attributed to a primary prevention population. Nevertheless, this guideline is unique. Recommendations have now shifted away from the practice of treating lipid targets moving to a specific goal: prevention of ASCVD morbidity and mortality even in patients with normal cholesterol levels. In fact, persons may meet the 10-year risk level above 10% only because of age or other concomitant conventional risk factors. However, so far, there are no clinical studies of statins that investigated patients based on a specific risk threshold calculated using the USPSTF risk prediction guidelines. Thus, research evidence could be at odds with expert opinions.

Benefits of statins according to U. S. Preventive Services Task Force algorithm

Framing our questions around the current USPSTF algorithm for the primary prevention of ASCVD in adults, the current study aimed to determine whether initiation of statin therapy in primary prevention setting may lead to a reduction in one of the most severe cardiovascular outcomes: ischemic AHF. Patients were eligible for this study if they had clinically confirmed ACS as a first manifestation of ASCVD. The 10-year ASCVD risk for each patient was calculated by using the ACC/AHA Pooled Cohort Equations. The cut-off for increased level of ASCVD risk was set at 10% according to the 2017 final recommendation statement of the USPS Task Force(23). Patient characteristics were stratified according to

treatment-group: statin users versus statin nonusers. Results of such analysis showed that prior statin use was associated with a significantly decreased rate of AHF on hospital admission. Reductions in the risk of presenting with AHF complicating ACS were not attenuated when controlling for older age. Benefits of statins were observed when the analysis was restricted to the higher ASCVD risk group 10%), but were not seen in the lower risk group. When statin treatment was stratified based on conventional risk factors, statin use was associated with a substantially lower risk of presenting with AHF on admission in patients who were current smokers or former smokers, and for those with hypercholesterolemia, diabetes and hypertension. In line with these findings, the benefit of statins was seen even in patients with no history of hypercholesterolemia. As regards sex, the current study suggests that the benefit might be more pronounced in women and, therefore, reinforces the value of treating women with statins to reduce the burden of CV mortality. On this background, people with an ASCVD risk threshold exceeding 10% would be advised to start taking a statin unless there is a clear medical reason why they could not do it. Ongoing trials will give more information about primary prevention in older persons.

Severity of ACS presentation accompanied by acute HF

Early studies found that the use of statins and betablockers in adults with first clinical presentation of ASCVD was associated with lower odds of presenting with myocardial infarction than with stable angina, suggesting that these agents may stabilize the underlying coronary

plaque(29). The same mechanisms potentially apply in STEMI versus NSTE-ACS. Typically, STEMI results from a total and prolonged occlusion of a major coronary artery. By contrast, non-STEMI ACS is usually associated with incomplete coronary occlusion. Conceptually, early-onset HF after ACSs reflects extensive myocardial damage, and AHF on admission is common after STEMI, but much less after NSTE-ACS(30). In our study, statin

users versus nonusers had a similar pattern of exposure to concomitant evidence-based medications including betablockers. Patients presenting with ACS who received statins before admission were significantly less likely to have STEMI (RR, 0.64; 95% CI, 0.58 – 0.71) compared with patients not taking statins. Consistent with prior observations, we also found that patients with STEMI were more likely to present with AHF than those with NSTE-ACS. Accordingly, the absolute risk reduction in AHF was considerably greater in STEMI patients whose AHF event rates were substantially higher than in NSTE- ACS patients. Our findings, therefore, suggest that use of statins may reduce the risk of developing AHF by increasing the likelihood of a more stable and lower-risk first clinical presentation of ASCVD.

Benefits of statins on early mortality from acute HF associated with ACS as first presentation of ASCVD

Although it is not possible to know exactly why one person dies from AHF after ACS and another does not, as mortality from AHF can be related to multiple factors including STEMI vs NSTE-ACS, and time delay to treatment with PCI or thrombolytics, the presence of AHF denotes a high risk of mortality at population-level. In the cohort analyzed herein, the mortality rate of ACS complicated by AHF on hospital admission was more than 5-fold higher than the mortality rate of ACS without AHF on hospital admission. Much more importantly, the present study demonstrates a strong association between use of statins prior to the index event and reduced mortality in patients with AHF on hospital admission (5.2 % absolute risk reduction and a 29% RR reduction). This finding suggests that the anti-ischemic effects of statins in ACS may extend beyond plaque stabilization, subsequent less severity of the disease and succeeding reduction of AHF events

Potential mechanisms of benefits associated with statin use in acute HF associated with ACS

Although there are a variety of potential mechanisms that could account for this observation, our data suggest that some hypotheses can be rejected. The association is not attributable to age, diabetes or impaired renal function(31,32), as we created a sample in which treatment was independent of the above measured baseline covariates. The interaction does not reflect a proxy for more unrecognized coronary artery disease and worse outcomes in statin nonusers, since in our study, the angiographic severity of coronary artery disease was similar in statin users and nonusers. Contributors to the favorable AHF outcomes in statin users may include some still poorly explored pathophysiologic mechanisms, such as the potential pleiotropic actions of these medications (33-35). These mechanisms may lead to restoration of microvascular tone, which may potentially enhance ventricular function(36). Statins may mitigate the progression of ischemic injury and prevent left ventricular dilation after myocardial infarction (37,38). There are no available data in humans to support or refute these hypotheses. In this regard, discovering novel biomarkers reflecting pro-inflammatory and pro-fibrotic processes in HF will be of paramount importance to identify which AHF patients most benefit from statin therapy(39-41).

Benefits and harms of statins

No medication comes without risks, and statins are no different. The most commonly reported side effect is muscle pain and fatigability(42). Statins can also somewhat increase the risk of diabetes (43), and kidney disease(44,45), but these side effects are rare and poorly documented. Our study was addressed to search benefits, not harms. Nevertheless, our findings may inform the potential role of ASCVD risk in decision making. We found no reduction in total serious CV events for patients with a 10-year ASCVD risk below 10%, thus the net benefit-harm equation has zero overall benefit in this population. Broadening the USPSTF recommendations to include statin therapy for low-risk individuals

unnecessarily exposes these people to the incidence of adverse effects without providing clear benefit.

Study limitations

The current study has some potential limitations. First, residual confounding might exist even if mitigated by matching using propensity-based methods. Second, all patients in our cohort are Caucasians. To what degree the findings can be applied to diverse populations with different geographic locations, differing socioeconomic backgrounds, and different public health expenditures remains uncertain. Third, the type, duration and dosing of statins were not analyzed. Although some studies have described possible pathophysiological mechanisms that could favor hydrophilic or lipophilic statins regarding HF outcomes, these mechanisms have not been further confirmed. Fourth, we calculated ASCVD risk at the time of the index event. We do not know what the risk was at time of statin initiation. ASCVD risk is not static but can vary significantly over time. However, we may speculate that statin users with ASCVD risk below 10% on hospital admission have been positively influenced by previous treatment and as so they presented with a less harmful initial manifestation of ASCVD. Finally, patients' baseline risk was categorized using the current USPSTF algorithm. The risk scores used by the other guidelines cannot be used in the current study because we investigated areas outside the limits of these guidelines, specifically the role of lipid modification therapy in the clinical management of other conditions considered to be risk factors for ASCVD such as hypertension, diabetes, smoking, and overweight (46-48).

Conclusions

In conclusion, although treatment effect in observational studies should be interpreted with caution, the results of the current study underline the importance of treatment with statins to reduce the risk of acute ischemic HF events and early mortality from AHF events in adults at high risk of ASCD events. Our results support USPSTF guidelines and suggest

using higher 10-year ASCVD risk thresholds when recommending statins for primary prevention of ASCVD, but also support the use of statins in the older populations, an issue that is still unsettled.

Clinical Perspective

Competency in Patient Care: In patients with acute coronary syndromes as a first manifestation of cardiovascular disease, prior statin therapy is associated with a lower risk of acute heart failure (HF) and improved survival from HF.

Translational Outlook: Prospective studies are needed to assess the efficacy of statin therapy for prevention of adverse outcomes related to HF in patients with ischemic heart disease.

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FIGURE LEGEND

Figure 1: Flow Chart of the Study Cohort

The aim of the figure is to illustrate the patient inclusion and exclusion criteria from the ISACS-Archives registry. Patients were considered eligible if they had clinically confirmed acute coronary syndromes. The initial population consisted of 23,567 patients. Patients presenting with prior history of cardiovascular disease events (history of stroke, angina, MI, heart failure, prior revascularization, PAD) were excluded leaving a final study population of 14,542 patients. Figure created with BioRender.

Abbreviations: MI= myocardial infarction, PAD= peripheral artery disease

Figure 2: Statin effect on AHF following ACS by cardiovascular RFs

Horizontal lines indicate corresponding 95% confidence intervals around risk ratios in log scale. All models were balanced for age, female sex, major CV risk factors, chronic obstructive pulmonary disease, chronic kidney disease, medications before admission [aspirin, ACE-inhibitors/angiotensin receptor blockers, beta-blockers] and multivessel disease. Created with Biorender.com

Abbreviations: ACS, acute coronary syndrome; AHF, acute heart failure; CI, Confidence Interval; RF, Risk Factors; lnRR, Risk Ratio in log scale.

Figure 3: Statin effect on STEMI risk: distribution by sex and age

Horizontal lines indicate corresponding 95% confidence intervals around risk ratios in log scale. All models were balanced for age, major CV risk factors, chronic obstructive pulmonary disease, chronic kidney disease, medications before admission [aspirin, ACE-inhibitors/angiotensin receptor blockers, beta-blockers] and multivessel disease. Created with Biorender.com

Abbreviations: CI, Confidence Interval; lnRR, Risk Ratio in log scale; STEMI, ST elevation myocardial infarction;

Central Illustration: Statin use and improved survival in ischemic heart failure

Among adults presenting with ACSs as a first manifestation of ASCVD, prior statin therapy is associated with reduced risk of AHF and improved survival from AHF. Created with Biorender.com

Abbreviations: ACS, Acute coronary syndrome; AHF, Acute Heart Failure; ASCVD, Atherosclerotic Cardiovascular Disease; CI, Confidence Interval

Table 1. IPTW: outcomes sorted by statin use before index event.

Characteristics	Statin users N=1,824	Statin nonusers N=12,718	Standardized difference
Age, years	63.2±11.2	61.8±12.2	0.12
Female sex	31.2	29.8	0.03
Cardiovascular risk factors			
Diabetes	23.2	21.1	0.05
History of hypertension	67.5	61.4	0.13
History of hypercholesterolemia	40.6	36.9	0.08
Current smokers	42.9	43.5	-0.01
Former smokers	13.5	11.1	0.07
Clinical history			
COPD	5.4	5.6	-0.009
Chronic kidney disease	5.3	4.3	0.05
Medications before admission			
Aspirin	19.2	16.6	0.07
ACE inhibitors/ ARBs	35.8	32.6	0.07
Beta blockers	23.7	20.1	0.09
Angiographic findings			
Multivessel disease	43.1	43.8	-0.01
Outcome			***P* value**
AHF on admission following ACS	13.4	17.7	<0.0001
Risk Ratio (95%CI)	0.72 (0.62 – 0.83)		<0.0001

Data are percentages or means ± Standard deviation unless stated otherwise.

Abbreviations: ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; AHF, acute heart failure; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; IPTW, inverse probability of treatment weighting

Table 2. IPTW: outcomes sorted by age and statin use before index event.

Characteristics	40 to 75 years			76 years or older		
	Statin users N=1,483	**Statin nonusers N=10,559**	**Standardized difference**	**Statin users N=320**	**Statin nonusers N=1,731**	**Standardized difference**
Age, years	60.2±8.6	59.5±8.9	0.080	80.2±3.4	80.7±4.2	-0.14
Female sex	29.7	27.6	0.008	46.0	46.2	-0.003
Cardiovascular risk factors						
Diabetes	23.0	20.8	0.05	28.5	26.3	0.05
History of hypertension	66.6	60.4	0.13	76.3	73.5	0.06
History of hypercholesterolemia	41.1	38.1	0.06	35.5	31.1	0.10
Current smokers	48.2	47.9	0.006	15.4	12.9	0.07
Former smokers	12.8	10.8	0.06	16.7	14.5	0.06
Clinical history						
COPD	5.2	5.3	-0.007	6.8	7.9	-0.04
Chronic kidney disease	3.2	3.2	-0.004	15.9	11.0	0.14
Medications before admission						
Aspirin	17.7	15.7	0.05	27.9	24.2	0.08
ACE inhibitors/ ARBs	34.7	31.5	0.07	43.9	43.8	0.001
Beta blockers	21.8	19.1	0.07	35.8	29.3	0.14

Angiographic findings						
Multivessel disease	39.7	41.6	-0.04	57.2	60.4	-0.06
Outcome			***P*-value**			***P*-value**
AHF on admission following ACS	11.8	15.6	<0.0001	23.9	32.3	0.0016
Risk Ratio (95%CI)	0.73 (0.62 – 0.86)		<0.0001	0.66 (0.50 – 0.87)		0.003

Data are percentages or means ± Standard deviation unless stated otherwise.

Abbreviations: ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; AHF, acute heart failure; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; IPTW, inverse probability of treatment weighting

Table 3· IPTW: outcomes sorted by 10-year ASCVD risk* and prior statin use.

Characteristics	<10% of risk			≥10% of risk		
	Statin users N=334	Statin nonusers N=3,258	Standardized difference	Statin users N=1,490	Statin nonusers N=9,460	Standardized difference
Cardiovascular risk factors						
History of hypertension	52.7	48.4	0.09	72.0	65.6	0.14
History of hypercholesterolemia	35.0	30.9	0.09	41.5	38.8	0.06
Former smokers	13.4	10.4	0.09	13.7	11.4	0.07
Clinical history						
COPD	4.0	3.6	0.02	6.1	6.2	-0.005
Chronic kidney disease	1.6	2.0	-0.03	6.0	5.1	0.04
Medications before admission						
Aspirin	13.5	11.8	0.05	20.8	18.0	0.07
ACE inhibitors/ ARBs	26.6	23.6	0.07	38.8	35.4	0.07
Beta blockers	18.5	16.0	0.07	25.0	21.4	0.09
Angiographic findings						
Multivessel disease	32.2	33.0	-0.02	46.7	47.2	-0.01
Outcome			***P*-value**			***P*-value**
AHF on admission following ACS	11.9	13.7	0.3379	14.4	18.7	0.0001

Risk Ratio (95% CI)	0.85 (0.60 – 1.20)	0.3608	0.73 (0.63 – 0.85)	0.0001

Data are percentages unless stated otherwise. Age, sex, diabetes and current smokers were not included in the model as they were represented in the Pooled Cohort Equation·

Abbreviations: ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; AHF, acute heart failure; ARBs, angiotensin receptor blockers; ASCVD, atherosclerotic cardiovascular disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; IPTW, inverse probability of treatment weighting·

*10-year ASCVD risk calculated using the simplified Pooled Cohort Equations·

Table 4. IPTW: outcomes sorted by sex and statin use before index event.

Characteristics	Women			Men		
	Statin users N=646	Statin nonusers N=3,674	Standardized difference	Statin users N=1,178	Statin nonusers N=9,044	Standardized difference
Age, years	67.0±11.2	65.4±12.0	0.14	61.5±10.7	60.2±11.9	0.11
Cardiovascular risk factors						
Diabetes	25.2	25.3	-0.002	22.7	19.3	0.08
History of hypertension	74.3	69.1	0.11	64.5	58.1	0.13
History of hypercholesterolemia	43.0	38.3	0.10	39.3	36.4	0.06
Current smokers	30.2	32.4	-0.05	48.3	48.1	0.003
Former smokers	8.2	7.6	0.02	16.3	12.7	0.10
Clinical history						
COPD	5.7	6.7	-0.04	5.4	5.2	0.008
Chronic kidney disease	6.6	5.6	0.04	4.7	3.7	0.05
Medications before admission						
Aspirin	22.2	19.0	0.08	17.6	15.5	0.06
ACE inhibitors/ ARBs	48.2	41.9	0.13	30.3	28.7	0.03
Beta blockers	29.3	26.2	0.07	20.8	17.6	0.08
Angiographic findings						

Multivessel disease	39.1	40.7	-0.03	45.1	45.1	-0.0007
Outcome			***P* value**			***P* value**
AHF on admission following ACS	15.9	22.2	0.0001	12.2	15.8	0.0005
Risk Ratio (95%CI)	0.66 (0.53 – 0.83)		0.0003	0.74 (0.62 – 0.89)		0.0014

Data are percentages or means ± Standard deviation unless stated otherwise.

Abbreviations: ACE, angiotensin converting enzyme; ACS, acute coronary syndrome; AHF, acute heart failure; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease; IPTW, inverse probability of treatment weighting

Table 5. IPTW in patients with AHF on admission: outcomes sorted by prior statin use			
Characteristics	**Statin users N=285**	**Statin nonusers N=2,146**	**Standardized difference**
Age, years	67.4±10.8	66.6±12.0	0.08
Female sex	40.3	36.7	0.07
Cardiovascular risk factors			
Diabetes	31.0	31.8	-0.02
History of hypertension	66.2	63.8	0.05
History of hypercholesterolemia	42.0	34.7	0.15
Current smokers	31.0	34.3	-0.07
Former smokers	13.3	11.0	0.07
Clinical history			
COPD	10.0	9.2	0.03
Chronic kidney disease	11.8	6.0	0.20
Medications before admission			
Aspirin	24.3	19.8	0.11
ACE inhibitors/ ARBs	37.5	34.4	0.07
Beta blockers	22.2	22.3	-0.003
Angiographic findings			
Multivessel disease	55.2	58.7	-0.07
Outcome			***P*- value**
30-day mortality	15.5	20.7	0.03
Risk Ratio (95%CI)	0.71 (0.50 – 0.99)		0.04

Data are percentages or means ± Standard deviation unless stated otherwise.

Abbreviations: ACE, angiotensin converting enzyme; AHF, acute heart failure; ARBs, angiotensin receptor blockers; COPD, chronic obstructive pulmonary disease, IPTW, inverse probability of treatment weighting