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Statin therapy and clinical outcomes in myocardial infarction patients complicated by acute heart failure: insights from the EPHESUS trial

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Aims Several clinical trials have shown that in patients with acute myocardial infarction (MI), statin therapy improves cardiovascular (CV) outcomes, but in these trials patients with acute heart failure (HF) were excluded or only a few were included. In patients with chronic HF, statin therapy does not reduce all-cause or CV mortality. We aimed to assess the association between statin therapy and clinical outcomes in the setting of acute HF with systolic dysfunction complicating acute MI.

Methods and results We performed a post-hoc analysis in 6632 patients included in the EPHESUS trial. The mean age of patients was 64 years and 71% were male. Overall, 47% of patients had a statin prescribed at baseline. Cox regression models and a secondary analysis using propensity score matching were fit to assess the association between statin prescription and clinical outcomes. During a mean follow-up of 16 $\pm$ 7 months, all-cause death occurred in 385 (12%) patients with and in 647 (18%) patients without a statin ($P < 0.001$). After extensive adjustment, the risk of all-cause death was 20% lower in patients on statin [hazard ratio (HR) 0.80, 95% confidence interval (CI) 0.69–0.92, $P = 0.001$]. This positive association was mostly due to a lower risk of CV death (HR 0.76, 95% CI 0.65–0.88, $P = 0.0002$). In contrast, statin use was associated with a higher risk of non-CV hospitalizations (HR 1.16, 95% CI 1.02–1.33, $P = 0.02$).

Conclusion Our results suggest that patients with acute HF complicating acute MI may benefit from being on statin therapy. Prospective clinical trials are required to validate these findings.

Keywords Acute heart failure • Statin therapy • Acute myocardial infarction • EPHESUS trial

Introduction

Several clinical trials have shown that in acute and post-acute myocardial infarction (MI) statin therapy improves cardiovascular (CV) morbidity and mortality as well as all-cause mortality.[1–4] Based on this evidence, statin treatment is a cornerstone therapy in patients with acute and post-acute coronary artery disease (CAD) and in patients at high risk of developing CAD. However, in previous trials of acute and post-acute MI, patients with acute heart failure (HF) were excluded or only a few were included.[4–8] Thus, the effect of statin therapy in this particular subgroup of patients is not clearly established.

Patients with chronic heart failure (CHF) frequently have a history of CAD as well as a pathophysiology of inflammation, fibrosis, and hypertrophy.[9] Thus, it was hypothesized and also suggested by retrospective analysis of major clinical trials that statin

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treatment may also have a prognostic benefit in patients with established CHF.[10,11] However, the prospective CORONA as well as GISSI-HF trials have shown that treatment with rosuvastatin does not reduce all-cause mortality in patients with systolic CHF, although the drug did reduce the number of CV hospitalizations in the CORONA trial.[12,13] However, these trials did not investigate whether patients who evolve to CHF while receiveing a statin benefit from the therapy. Thus, whether statin therapy may exert a protective effect when prescribed at initial stages of HF development is an important and unsolved clinical question.

The EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival study) trial assessed the effects of the mineralocorticoid receptor antagonist eplerenone in patients with acute MI complicated by clinical signs and symptoms of HF and left ventricular dysfunction.[14] About half of the patients had a statin prescribed at baseline. In this study, we aimed to assess the association between statin prescription at baseline and clinical outcomes in patients with acute systolic HF included in the EPHESUS trial.

Methods

The study design and results of the EPHESUS trial have been published previously.[14,15] In brief, EPHESUS was a multicentre, randomized, double-blind trial including 6632 patients with acute MI complicated by clinical signs and symptoms of HF and a left ventricular ejection fraction (LVEF) $\leq 40\%$. In patients with diabetes who met the criteria of left ventricular dysfunction after acute MI, clinical signs and symptoms of HF did not have to be demonstrated. Eligible patients were randomized to either treatment with eplerenone ($n = 3319$) or placebo ($n = 3313$) between 3 and 14 days after acute MI, and were followed for up to 33 months (mean follow-up 16 months).

We performed a post-hoc analysis in all 6632 patients included in the EPHESUS trial. We assessed the association between statin prescription at baseline and clinical outcomes. The baseline represented the entire period of hospital stay, including the period before and after randomization to eplerenone, and hospital discharge. There were missing values at baseline for a few clinical variables used for adjustment; therefore, the final multivariate Cox analysis was performed in 6213 patients.

Outcomes

We assessed the association between statin prescription at baseline and all clinical outcomes measured in the EPHESUS trial. This includes the two primary outcomes [all-cause death, and the combined outcome of CV death or first CV hospitalization (including HF, recurrent MI, stroke, and ventricular arrhythmia hospitalization]. The secondary outcomes were CV death, and all components of CV death, including sudden death. Further, we assessed the impact of statin use on CV and non-CV hospitalizations. All outcomes were adjudicated by the blinded critical event committee and hard recorded in the database.

Statistical methods

At baseline, continuous variables were described as means $\pm$ standard deviation (SD), and categorical variables as frequencies (percentages). Variables were compared by using a *t*-test or a χ^2 test, as required.

We assessed the association between baseline statin prescription and clinical outcomes using a multivariate Cox proportional hazard regression models. We adjusted for the significantly different baseline variables and those considered clinically important. The following variables were tested in the final multivariate model for primary and secondary outcomes: age, gender, race, smoking status, body mass index (BMI), total cholesterol, mean arterial pressure, LVEF, estimated glomerular filtration rate (eGFR), reperfusion or revascularization, history of angina, MI, hypertension, diabetes, previous HF hospitalization, and concomitant medication with angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs), beta-blockers, other lipid-lowering drugs, aspirin, other antiplatelet agents, anticoagulants, antiarrhythmics, diuretics, and the study drug.

We checked the log-linearity of the continuous variables and the Cox proportionality assumptions of all variables. The log-linearity was assessed by generating one dummy variable per quintile of each variable, entering these in the Cox model, and plotting the resulting Cox estimators against the mean values of the quintiles. Based on the log-linearity criteria, we reclassified the continuous variables ejection fraction and heart rate from continuous to categorical variables (EF $>35\%$ and HR >80 b.p.m.). Assumption of risk proportionality was assessed statistically by testing the cofactor $\times$ time interaction and visually by plotting the log[$-$log(survival)] curves.

We also checked the model for multicollinearity, and, because we found a high correlation between total cholesterol and LDL cholesterol ($r = 0.5$), we included in the final model only total cholesterol. We excluded HDL from the final model because 635 patients had missing values on this variable.

We checked for interactions between statin use and all significant variables from the final model—age, ejection fraction, GFR, angina, previous MI, diabetes, revascularization, stroke, beta-blocker, anticoagulant, and antiplatelet agents, and none was significant ($P < 0.05$).

All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA). Results were estimated as hazard ratios (HRs) with 95% confidence intervals (CIs). The two-tailed significance level was set at $P < 0.05$.

Sensitivity analysis:propensity score analysis (pseudo-randomization)

A secondary analysis using propensity score matching was performed to validate the findings of the Cox analysis. Propensity scores were constructed using logistic regression with statin use as predicted event and baseline covariates as predictors. All variables shown in *Table 1* were used as covariates. The efficacy of propensity score matching (covariant balance) was assessed by evaluating the standard difference in covariates between patients with and without a statin. The standard difference measures the degree of bias in covariate means across exposure. All Cox analyses were performed on the subsample of propensity score-matched patients.

Results

Overall, 3095 patients (47%) had a statin prescribed at baseline. From the 47% of patients who had a statin at baseline, $\sim 10\%$ had a statin prescribed before hospital admission for acute MI, and 90% had a statin initiated during hospital stay. Patient characteristics at baseline are presented in *Table 1*. The mean age of the patients was 64 ± 11 years and 71% were male. Patients who received a statin prescription were younger, more often smokers, and had a higher BMI, a lower LVEF, but a better kidney function on average. Furthermore, they had a higher total cholesterol level and more frequently a history of reperfusion or revascularization. Patients on statins also had a higher prescription

Table 1 Baseline characteristics of patients according to statin use

Characteristics	Statin (n = 3095)	No statin (n = 3537)	P-value
General characteristics			
Age, years, mean (SD)	62.2 ± 11.6	65.4 ± 11.2	<0.001
Female sex, n (%)	820 (26.5)	1098 (31.0)	<0.001
Race, n (%)			0.004
Caucasian	2779 (89.8)	3205 (90.6)	
Black	44 (1.4)	30 (0.8)	
Other	33 (1.1)	35 (1)	
Clinical presentation			
Smoking, n (%)	2075 (67)	1965 (56)	<0.001
Body mass index, kg/m^2	27.7 ± 4.6	27.1 ± 4.4	<0.001
Total cholesterol, mg/dL	5.1 ± 1.3	4.9 ± 1.3	<0.001
LDL cholesterol, mg/dL	3.0 ± 1.1	3.3 ± 1.5	0.1
HDL cholesterol, mg/dL	1.1 ± 2.4	1.2 ± 2.9	0.3
Heart rate >80 b.p.m., n (%)	1046 (33.8)	1190 (33.7)	0.8
MAP, mean (SD)	86.2 ± 11.2	89.1 ± 11.4	<0.001
LVEF >35%, n (%)	1650 (53.5)	1996 (56.5)	<0.001
eGFR, mL/min/1.73 m^2, mean (SD)	71.8 ± 21.5	68.2 ± 21.5	<0.001
Reperfusion or revascularization, n (%)	1764 (57)	1242 (35)	<0.001
Clinical history, n (%)			
Angina pectoris	1203 (38.9)	1532 (43.3)	<0.001
Myocardial infarction	871 (28.1)	932 (26.4)	0.1
Hypertension	1771 (57.2)	2236 (63.2)	<0.001
Diabetes	1034 (33.4)	1108 (31.3)	0.07
Atrial fibrillation or flutter	80 (2.6)	107 (3.0)	0.3
Previous hospitalization for HF	219 (7.1)	293 (8.2)	0.06
Medications, n (%)			
Other lipid-lowering drugs	38 (1.2)	69 (1.9)	0.02
ACE inhibitor or angiotensin receptor blocker	2806 (90.7)	2945 (83.3)	<0.001
Beta-blockers	2495 (80.6)	2466 (69.7)	<0.001
Aspirin	2786 (90.0)	3084 (87.2)	<0.001
Other antiplatelet agents	1277 (41.3)	633 (17.9)	<0.001
Anticoagulant	424 (13.7)	684 (19.3)	<0.001
Antiarrhythmic	307 (9.9)	475 (13.4)	<0.001
Diuretics	1754 (56.7)	2230 (63.1)	<0.001
Eplerenone	1550 (50.1)	1679 (50.0)	0.9

ACE, angiotensin-converting enzyme; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection faction; MAP, mean arterial pressure.

rate of most HF classes of medication, except for anticoagulants, other lipid-lowering drugs, antiarrhythmics, and diuretics, which were more often prescribed in patients without a statin.

Univariate Cox survival analysis

During a mean follow-up of 16 ± 7 months, all-cause death occurred in 385 (12%) patients with and in 647 (18%) patients without a statin (*Table 2*). Death from CV causes accounted for the majority of all-cause death events in both statin and non-statin patients (326 events, 85% in the statin group; and 564 events, 87% in the non-statin group). Sudden death accounted for the majority of deaths from CV causes (~40%).

In univariate survival analysis, the risk of all-cause death was 34% lower in statin vs. non-statin users (HR 0.66, 95% CI 0.59–0.75, $P < 0.001$). Kaplan–Meier survival curves clearly show a benefit of statin use on all-cause death, with the two curves differentiating immediately after baseline (*Figure 1*).

Statin prescription was also univariately associated with a significant benefit on the composite outcome of CV death or CV hospitalization (HR 0.86, 95% CI 0.78–0.94, $P < 0.001$), on CV death (HR 0.65, 95% CI 0.56–0.74; $P < 0.001$), and on all causes of CV death (*Table 2*).

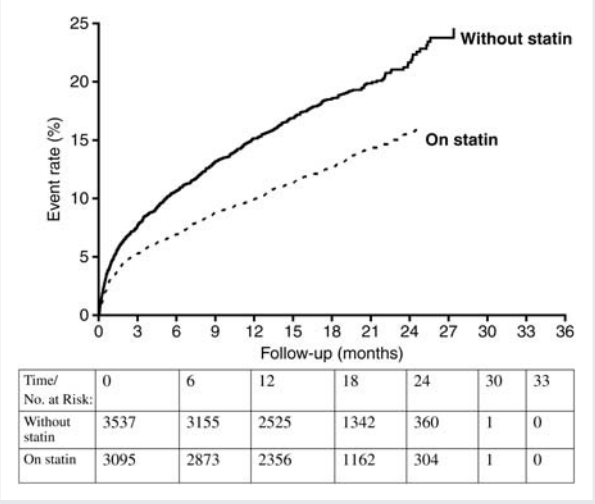
Further, statin use was associated with a lower risk for a first hospitalization for non-fatal stroke as well as both fatal and non-fatal stroke (*Tables 2* and *3*).

In contrast, statin use was associated with a small increase in the composite outcome of all-cause death or all-cause hospitalization (HR 1.08, 95% CI 1.01–1.15, $P = 0.02$) (*Table 2*). When we

Table 2 The association between statin prescription and clinical outcomes in univariate and multivariate Cox analysis

Outcome	Statin, *n* (%) (*n* = 3095)	No statin, *n* (%) (*n* = 3537)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Primary						
All cause death	385 (12%)	647 (18%)	0.66 (0.59–0.75)	<0.001	0.80 (0.69–0.92)	0.001
CV death or CV hospitalization	813 (26%)	1065 (30%)	0.86 (0.78–0.94)	0.0008	0.97 (0.88–1.06)	0.3
Secondary						
All-cause death or hospitalization	1703 (55%)	1856 (52%)	1.08 (1.01–1.15)	0.02	1.09 (1.01–1.17)	0.02
CV death	326 (11%)	564 (16%)	0.65 (0.56–0.74)	<0.001	0.76 (0.65–0.88)	0.0002
Sudden death (CV)	135 (4%)	228 (6%)	0.66 (0.53–0.82)	0.0001	0.77 (0.61–0.96)	0.02
Death from acute MI	63 (2.04)	109 (3.08)	0.65 (0.48–0.89)	0.006	0.74 (0.54–1.02)	0.07
Death from worsening HF	86 (2.8)	145 (4.1)	0.66 (0.51–0.86)	0.002	0.75 (0.56–1.01)	0.06
Death from stroke	15 (0.5)	39 (1.1)	0.43 (0.24–0.77)	0.005	0.53 (0.28–0.96)	0.04
CV hospitalizations (non-fatal)						
CV hospitalizations overall	589 (19%)	666 (18.8%)	0.9 (0.88–1.1)	0.9	–	–
Myocardial infarction	230 (6.5%)	223 (7.2)	1.09 (0.90–1.30)	0.4	–	–
Heart failure	341 (11%)	395 (11.2%)	0.97 (0.84–1.12)	0.6	–	–
Ventricular arrhythmias	53 (1.7)	53 (1.5)	1.12 (0.77–1.64)	0.5	–	–
Stroke	46 (1.5)	75 (2.1)	0.68 (0.47–0.99)	0.04	0.81 (0.56–1.19)	0.3

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.



Time/ No. at Risk:	0	6	12	18	24	30	33
Without statin	3537	3155	2525	1342	360	1	0
On statin	3095	2873	2356	1162	304	1	0

Figure 1 Kaplan-Meier survival curves (all-cause death) in patients who receive or not a statin at baseline.

assessed individually the cause of hospitalization, we found no significant association with the risk of CV hospitalizations, but a significant association with the risk of non-CV hospitalizations (HR 1.20, 95% CI 1.06–1.36, $P = 0.004$) (*Table 3*).

Multivariate Cox analysis

After extensive adjustment, the risk of all-cause death remained 20% lower in patients with vs. those without a statin (HR 0.80, 95% CI 0.69–0.92, $P = 0.001$) (*Table 2*). This positive association was mostly due to a lower risk of CV death (HR 0.76, 95% CI 0.65–0.88, $P = 0.0002$). The reduction of CV death was mainly due to a lower rate of sudden death (HR 0.77, 95% CI 0.61–0.96, $P = 0.02$) and death from stroke (HR 0.53, 95% CI 0.28–0.96, $P = 0.04$), but was also due a lower rate of death from worsening HF and from recurrent acute MI (*Table 2*).

After adjustment, statin use was not associated with a positive effect on the composite outcome of CV death or CV hospitalization; this was probably due to a non-significant effect on non-fatal CV hospitalizations (*Table 2*).

Statin use was not associated with the overall risk of a first (fatal and non-fatal) CV hospitalization, or a first hospitalization for HF, but appeared to be associated with a lower risk of hospitalization for stroke (HR 0.72, 95% CI 0.51–1.00, $P = 0.05$) (*Table 3*). In contrast, statin use remained associated with a higher risk of non-CV hospitalizations (HR 1.16, 95% CI 1.02–1.33, $P = 0.02$) (*Table 3*).

Propensity score analysis

After matching, 4322 patients were subdivided into statin and no statin intake groups. The Cox analysis performed in this subsample of patients showed results similar to those obtained in the multivariate Cox model performed in the full sample of patients. This included: (i) a small increase in the risk of all-cause death or hospitalization (HR 1.14, 95% CI 1.05–1.23, $P = 0.002$); and (ii) an increase in non-CV hospitalizations (HR 1.17, 95% CI 1.01–1.35, $P = 0.04$) in statin users vs. non-statin users (*Table 4*).

Discussion

In this post-hoc analysis of the EPHESUS trial, we found that initiation of statin therapy mainly during hospital stay for acute HF

Table 3 The association between statin prescription and the first cardiovascular and non-cardiovascular hospitalization (fatal and non-fatal)

Outcome	Statin, *n* (%) (*n* = 3095)	No statin, *n* (%) (*n* = 3537)	Univariate analysis		Multivariate analysis	
			HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
CV hospitalization overall	651 (21.3%)	777 (22%)	0.97 (0.89–1.63)	0.5	–	–
Heart failure	378 (12.2%)	453 (12.8%)	0.94 (0.82–1.07)	0.4	–	–
Acute MI	252 (7.9%)	281 (8.1%)	1.00 (0.85–1.19)	0.9	–	–
Ventricular arrhythmias	53 (1.7)	53 (1.5)	1.12 (0.77- 1.64)	0.5	–	–
Unstable angina	302 (9.8)	326 (9.2)	1.0 (0.89–1.2)	0.7	–	–
Stable angina	89 (2.9)	87 (2.5)	1.14 (0.85–1.53)	0.4	–	–
Stroke	56 (1.8)	105 (3)	0.59 (0.43–0.82)	0.002	0.72 (0.51–1.00)	0.05
Non-CV hospitalizations	550 (17.8 %)	527 (14.9)	1.20 (1.06–1.36)	0.004	1.16 (1.02–1.33)	0.02

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

Table 4 The association between statin prescription and clinical outcomes in propensity score analysis

Outcome	All, *n* (%) (*n* = 4322)	Statin, *n* (%) (*n* = 2161)	No statin, *n* (%) (*n* = 2161)	Cox analysis	
				HR (95% CI)	*P*-value
All-cause death	639 (15)	292 (46)	347 (54)	0.84 (0.72–0.98)	0.03
CV death or CV hospitalization	1255 (29)	628 (50)	627 (50)	1.01 (0.90–1.13)	0.87
All-cause death or hospitalization	2364 (54.7)	1228 (52)	1136 (48)	1.14 (1.05–1.23)	0.002
CV death	549 (13)	248 (45)	301 (55)	0.82 (0.69–0.97)	0.02
CV hospitalizations (fatal and non-fatal)	1314 (30)	664 (51)	650 (49)	1.03 (0.92–1.15)	0.62
Non CV hospitalizations (fatal and non-fatal)	724 (17)	388 (54)	336 (46)	1.17 (1.01–1.35)	0.04

CI, confidence interval; CV, cardiovascular; HR, hazard ratio.

complicating acute MI is associated with a lower risk of all-cause death. This positive association was mostly due to a reduction in CV death. Statin use was not significantly associated with the overall risk of CV hospitalization, including HF and MI, but was associated with a lower risk of stroke hospitalization. In contrast, statin use was associated with a moderately higher rate of non-CV hospitalizations.

While statin therapy has been shown to have a benefit in a broad range of patients with acute and post-acute CAD, its benefit in the subgroup of patients with acute systolic HF complicating acute MI has not been specifically studied. Only 8% of patients with HF were enrolled in the MIRACL trial (patients with unstable angina and non-Q-wave acute MI),[4] and only 6% of them were enrolled in the IDEAL trial (post-acute MI patients).[8] In the PROVE-IT trial (acute MI or high-risk unstable angina), the proportion of HF patients included is not clear, but at the time of enrolment patients had to be in a stable condition.[5] Furthermore, in trials enrolling patients undergoing angioplasty or cardiac surgery, only 4% of patients had HF.[6,7] Our positive findings in acute HF patients are in contrast to findings reported in CHF patients. Indeed, in both CORONA[12] and GISSI-HF trials,[13] treatment with rosuvastatin did not reduce all-cause or CV mortality.

There are a number of differences between our study and the previous CHF trials that may explain the different findings. The CORONA trial included elderly patients, with a mean age of 73 years, while the EPHESUS trial included patients 10 years younger, i.e. mean age 64 years. In the elderly HF population, an effect on all-cause death is difficult to achieve with any drug given the age competitive factor.[16,17] On the other hand, it may very well be that the pathophysiology of the disease is different in CHF compared with initial disease stages. Several studies have shown that while high cholesterol levels are associated with higher risk in patients with CAD,[18] they seem to be protective in established CHF,[19] and in the elderly population in general.[20] This phenomenon of 'reverse epidemiology' in CHF has also been observed with regard to BMI.[21] Nevertheless, the concept of 'reverse epidemiology' was refuted several times given the confounding factor of the underlying sickness of CHF patients. However, it seems rather that the first hypothesis is more plausible as in the CORONA trial rosuvastatin did reduce the number of CV

hospitalizations.[12] Interestingly, in the GISSI-HF trial, prescription of rosuvastatin was not associated with any clinical benefit.[13] In this trial, however, only 40% of patients had a history of ischaemic disease and 33% an acute MI, as opposed to 60% and 100% of patients with an acute MI in the CORONA and the EPHESUS trial, respectively. From the perspective of these trials, one may speculate that statin therapy could be more beneficial in ischaemic/post- acute MI HF patients. Nevertheless, more prospective studies are necessary to confirm this hypothesis.

Statin therapy may have beneficial effects in patients with acute HF not only by lowering cholesterol, but also by a plethora of pleiotropic effects, including reduction of inflammation and improvement of endothelial function,[22–24] as well as by a protective effect on renal function.[25] The lack of a significant effect of statin use on the first CV hospitalization observed in our study is difficult to interpret, and could probably be explained by the fact that by living longer, patients on statin therapy have a higher chance of being hospitalized. However, we found a borderline beneficial effect on stroke hospitalization, and also a considerable reduction in the risk of death from stroke with statin use (50% risk reduction). Given the positive effects of statins on vascular function and capillary density,[26,27] one would expect a reduction of stroke events, but also a more pronounced effect on recurrent acute MI or worsening HF events. Whether this lower effect on acute MI/HF hospitalizations is due to specific HF disease characteristics or due to adverse effects of statins on ubiquinone (coenzyme Q10) production, which may affect cardiac metabolism,[28,29] or both, has to be further explored.

In contrast to the beneficial or neutral effects of statin use on CV death and CV hospitalizations, we found a higher risk with drug use on the combined outcome of all-cause death or hospitalizations, which was mostly attributable to non-CV hospitalizations. Although this effect may be a chance finding, it remained significant in various models, including propensity score analysis. One may speculate that by living longer, patients on statin are at higher risk for non-CV hospitalizations. However, this does appear to be the case for CV hospitalizations. Our database did not allow a detailed analysis of the cause of non-CV hospitalizations as these events have not been adjudicated by an expert committee in the EPHESUS trial. However, previous meta-analyses have pointed out that statin therapy may be associated with adverse events, such as myopathy, new-onset diabetes, and an increase in hepatic enzymes.[30–32] The risk of adverse events may be particularly elevated with high doses of statins, but unfortunately we do not have data on the dose of statin prescribed in this study.

There are several strengths and limitations of our study. The study was performed in a very large trial database of acute post-MI acute HF patients. This very large number of patients (6300 patients) and events (1032 death events) are usually seen in meta-analytic studies. The main limitation is the post-hoc nature of the study, i.e. patients were not prospectively randomized to statin or placebo. To address the issue of confounding by indication, we applied two different statistical methods which showed similar results. First, we adjusted for an extensive number of clinical variables (23 clinical covariates) in a multivariate Cox model, and, secondly, we performed a matched propensity score analysis. However, there may be unknown or unmeasured confounding variables which were not adjusted for, and which could have affected some or all of the observed relationships. This bias may apply especially for non-CV hospitalizations as adjusting for all possible risk factors is particularly difficult in a post-hoc analysis. Secondly, we assumed that patients who did not initiate statin therapy during hospitalization will not initiate it during follow-up, and those who initiated the therapy at baseline would not stop it. Previous studies have shown that patients discharged without a drug prescription are unlikely to be started on these therapies as outpatients.[33,34] Indeed, in our study, 70% of patients on a statin at baseline were still taking a statin at the last visit, and in patients not on a statin at baseline, 18% were taking a statin at the last visit, and as such we assume that the effect size did not change to a great extent.

In conclusion, in patients with acute HF post-MI, statin therapy was associated with a lower risk of all-cause death. The reduction of all-cause death appears to be mainly attributable to a lower rate of CV death, especially sudden death and stroke. Prospective clinical trials are required to validate these findings.

Conflict of interest: H.K. conducted research for, and acted as a steering committee member for EPHESUS (Pfizer).

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