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# Early statin use and cardiovascular outcomes after myocardial infarction: A population-based case-control study

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ABSTRACT

*Background and aims:* Statin therapy is a cornerstone of secondary prevention after myocardial infarction (MI). However, many patients do not use statins. We studied the association of not using statin early after MI with adverse outcomes.

*Methods:* Consecutive MI patients admitted to 20 Finnish hospitals (n = 64,401; median age 71) were retrospectively studied. Statin was not used by 17.1% within 90 days after MI discharge (exposure). Differences in baseline features, comorbidities, revascularization, and other evidence-based medications were balanced with propensity score matching, resulting in 10,051 pairs of patients with and without statin. Median follow-up was 5.9 years.

*Results:* Patients not using statin early after MI had higher all-cause mortality in 1-year (15.8% *vs.* 11.9%; HR 1.38; CI 1.30–1.46; $p < 0.0001$) and 10-year follow-up (71.1% *vs.* 65.2%; HR 1.34; CI 1.30–1.39; $p < 0.0001$) in the matched cohort. The number needed to harm by not using statin was 24.1 at 1-year and 9.5 at 10-years. The cumulative incidence of major adverse cardiovascular event was higher at 1- and 10-years in matched patients not using statins (sHR 1.15; $p < 0.0001$ for both). Cardiovascular death, new MI, and ischemic stroke were more frequent without early statin. A lack of statin was associated with outcomes regardless of sex, age, atrial fibrillation, dementia, diabetes, heart failure, revascularization, or usage of other evidence-based secondary preventive medications in subgroup analyses.

*Conclusions:* Lack of statin therapy early after MI is associated with adverse outcomes across the spectrum of MI patients. Results underline the importance of timely statin use after MI.

## 1. Introduction

Randomized trials have demonstrated the efficacy of early 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitor (statin) therapy after myocardial infarction (MI) in reducing the risk of cardiovascular events and death [1–3]. Clinical practice guidelines give statins a class IA recommendation after MI [4,5] and recommend their use in all patients irrespective of low-density lipoprotein (LDL) levels. However, a number of patients do not use statins for secondary prevention [6,7], and this is mainly due to suspected adverse events [8,9]. The key role in initiating and advocating secondary preventive statin therapy is held by physicians treating the patient during acute MI admission [6,10]. However, the magnitude of harm caused by not using statins after MI in modern reperfusion era is inadequately known. Placebo controlled statin trials are, due to obvious reasons, not possible in the modern era and evidence is only available from observational data [1]. Furthermore, long-term observational data on the impact of not using statins early after MI is limited. We set out to investigate the real-life outcome association of not using statins early after MI in a longitudinal population-based investigation.

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## 2. Patients and methods

### 2.1. Study patients and design

We studied the association of not using statin therapy early after MI on 1- and 10-year outcomes. The primary outcome of interest was all-cause death. Secondary outcomes were composite major adverse cardiovascular event (MACE; cardiovascular death, new MI, or ischemic stroke [IS]) and MACE components.

Consecutive MI patients aged ≥16 years admitted between Jan 1, 2005–Dec 31, 2017 were retrospectively identified from the Care Register for Healthcare in Finland (CRHF). This nationwide registry includes data on all hospital admissions and major interventional procedures in Finland [11]. All hospitals in Finland that treat MI patients (n = 20; 5 with emergency cardiac surgery) were included in the study. To capture incident MIs, only patients admitted to medical, surgical, or intensive care wards through the emergency department or paramedic services were included [12]. In Finland, cardiovascular medications outside ward treatment are only available from pharmacies by prescription, and all purchases are recorded in the national database used in the study. Medications are dispensed for a maximum of three months. To include only patients with the necessity and possibility of purchasing post-MI medications from a pharmacy, patients not discharged to home or home-like facilities (including nursing homes), patients with prolonged (>60 days) admission, and patients who died within 90 days after MI, were excluded. In addition, patients with missing follow-up data (0.5%) and those treated with aortic or valvular surgery during MI admission were excluded (Supplementary Fig. 1). Index MI was identified with International Classification of Diseases (ICD) version 10 code I21 as the primary discharge diagnosis. The studied outcomes are described in more detail in the Supplementary information. Co-morbidities and treatments were detected as previously described [13].

Prescription medications were detected using Anatomical Therapeutic Chemical Classification (ATC) codes (Supplementary Table 1). Usage of statin and other prescription medication early after MI was defined as a medication purchase within 90 days after hospital discharge. Sequential admissions and hospital transfers after MI admission were combined as a single admission. Follow-up started 90 days after index MI and ended at the latest on Dec 31st' 2018. The median follow-up for survivors was 5.9 (IQR 3.1–9.7) years.

### 2.2. Data sources and permissions

Study data were formed by combining data in the following national level, mandatory-by-law registries; the CRHF, the Finnish cancer registry, the prescription medication purchase registry, the reimbursement registry of prescription medications, and causes of death registry that have the full coverage of the Finnish population (Supplementary). This was a retrospective register study; therefore, the requirement for informed consent was waived, and the participants were not contacted. The study was approved by the national authorities (Findata; permission THL/164/14.02.00/2021 and Statistics Finland; permission TK-53-484-20).

### 2.3. Statistical analysis

Differences between study groups were analyzed with *t*-test, Wilcoxon rank-sum test, chi square tests (non-matched groups) or paired *t*-test, and McNemar's test (matched groups). The Cochran-Armitage test was used to study the trends of early statin usage. Effect sizes in baseline characteristics between groups were evaluated by standardized mean differences (SMD). Propensity scores based on age, sex, alcohol abuse, anemia, atrial fibrillation, cerebrovascular disease, chronic pulmonary disease, coagulopathy, dementia, depression, insulin dependent diabetes, non-insulin dependent diabetes, heart failure, hypertension, hypothyroidism, liver disease, malignancy, paralysis, peripheral vascular disease, psychotic disorder, rheumatic disease, renal failure, valvular disease, revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG), type of MI, pharmacotherapy after MI ($P2Y_{12}$-inhibitor, angiotensin-converting-enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB), aldosterone antagonist, antiarrhythmic, beta-blocker, digitalis, ezetimibe, or oral anticoagulant), treatment in university hospital, and year of MI, were created with logistic regression. Propensity scores were used for local optimal 1:1 caliper matching using a 0.05 caliper width of the logit of the standard deviation without replacing. Potential residual confounding was estimated by calculating the E-value [14]. Potential association modifications by ezetimibe were studied with interaction-term analyses. Due to limited patient numbers, multivariable regression was used for studying subgroups in the overall cohort.

Outcomes were studied using a cumulative incidence function and Cox regression (primary outcome) or Fine-Gray regression accounting for competing risk due to non-endpoint specific death (secondary outcomes) [15]. Matched cohort was analyzed with matching stratified regression. Multivariable regression models were adjusted with the same variables as used for propensity scoring (except for the year of MI). Schoenfeld residuals were used for the confirmation of proportional hazard assumptions. The number needed to harm (NNH) for not using early statin therapy was calculated with a hazard ratio (HR) as previously described [16]. The results were given as the mean, median, percentage, SMD, HR, or sub distribution HR (sHR), with 95% CI, IQR, or ±SD. Statistical significance was inferred at $p$ value $< 0.05$. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for analyses.

## 3. Results

A total of 64,401 patients were included in the study (mean age 69.7 SD 12.4 years). Of all patients, 17.1% did not use statins early after MI. Atorvastatin or rosuvastatin were used by 43.3% of statin users (Supplementary Table 2). Patients not on early statins were older, more often female, had higher comorbidity burden, and were less frequently revascularized (Table 1). Notably, patients with diabetes, cerebrovascular disease, or peripheral vascular disease used statins less frequently after MI. The usage of digitalis or aldosterone antagonists were more prevalent in the non-statin group. $P2Y_{12}$-inhibitors, ACEi/ARBs, beta-blockers, and ezetimibe were used with notable lower frequencies by non-statin users in the non-matched cohort after MI (Table 1). The proportion of patients without early statins decreased from 24.8% in 2005 to 13.2% in 2016 ($p < 0.0001$ for trend) (Fig. 1). Differences in baseline features, treatments, and usage of other secondary preventive measures were balanced by propensity score matching, identifying 10,051 patient pairs with and without early statin therapy after MI (Table 1).

### 3.1. All-cause mortality

During the 10-year follow-up, 10,802 of the matched patients died (Fig. 2). All-cause mortality at 1-year was 15.8% in the non-statin group *vs.* 11.9% in the statin group (HR 1.38; CI 1.30–1.46; $p < 0.0001$) in the matched cohort. At the end of the 10-year follow-up, the cumulative all-cause mortality was 71.1% *vs.* 65.2%, respectively (HR 1.34; CI 1.30–1.39; $p < 0.0001$). The NNH by not using early statins after MI was

**Table 1**
Baseline features of all and propensity matched myocardial infarction (MI) patients with and without statin therapy after MI.

| | All patients | | | | Matched patients | | | |
|---|---|---|---|---|---|---|---|---|
| | No statin | Statin | | | No statin | Statin | | |
| Variable | N = 11,027 | N = 53,374 | *p*-value | \|SMD\| | N = 10,051 | N = 10,051 | *p*-value | \|SMD\| |
| Age, years (SD) | 75.9 (12.3) | 68.3 (12.1) | <0.0001 | 0.638 | 75.2 (12.3) | 75.3 (10.8) | 0.261 | 0.028 |
| Women | 48.9% | 33.3% | <0.0001 | 0.320 | 47.5% | 47.6% | 0.929 | 0.001 |
| Co-morbidities | | | | | | | | |
| Alcohol abuse | 3.5% | 2.9% | 0.001 | 0.034 | 3.5% | 3.4% | 0.758 | 0.004 |
| Anemia | 6.3% | 2.7% | <0.0001 | 0.173 | 6.0% | 5.7% | 0.346 | 0.013 |
| Atrial fibrillation | 24.8% | 12.7% | <0.0001 | 0.315 | 23.3% | 24.2% | 0.107 | 0.022 |
| Cerebrovascular disease | 16.8% | 10.3% | <0.0001 | 0.193 | 16.4% | 17.1% | 0.190 | 0.018 |
| Chronic pulmonary disease | 17.3% | 12.7% | <0.0001 | 0.128 | 16.9% | 17.0% | 0.792 | 0.004 |
| Coagulopathy | 0.5% | 0.4% | 0.017 | 0.024 | 0.5% | 0.6% | 0.632 | 0.007 |
| Dementia | 10.8% | 3.3% | <0.0001 | 0.297 | 9.3% | 9.3% | 0.919 | 0.001 |
| Depression | 13.5% | 8.8% | <0.0001 | 0.147 | 13.0% | 12.7% | 0.494 | 0.010 |
| Diabetes | 29.6% | 24.8% | <0.0001 | 0.109 | 30.1% | 30.7% | 0.341 | 0.013 |
| Insulin dependent | 10.5% | 8.4% | <0.0001 | 0.072 | 10.8% | 11.0% | 0.538 | 0.009 |
| Non-insulin dependent | 19.1% | 16.4% | <0.0001 | 0.071 | 19.3% | 19.7% | 0.538 | 0.009 |
| Heart failure | 35.8% | 17.0% | <0.0001 | 0.435 | 33.4% | 33.8% | 0.455 | 0.010 |
| Hypertension | 58.6% | 50.2% | <0.0001 | 0.169 | 58.7% | 59.8% | 0.079 | 0.030 |
| Hypothyroidism | 6.4% | 4.6% | <0.0001 | 0.082 | 6.3% | 6.4% | 0.817 | 0.003 |
| Liver disease | 1.9% | 0.8% | <0.0001 | 0.089 | 1.7% | 1.5% | 0.430 | 0.011 |
| Malignancy | 16.3% | 11.1% | <0.0001 | 0.151 | 16.0% | 16.0% | 1.000 | <0.0001 |
| Paralysis | 0.6% | 0.4% | 0.0002 | 0.035 | 0.6% | 0.5% | 0.454 | 0.011 |
| Peripheral vascular disease | 10.9% | 6.6% | <0.0001 | 0.152 | 10.8% | 11.3% | 0.194 | 0.018 |
| Prior CABG | 4.9% | 3.5% | <0.0001 | 0.070 | 5.0% | 5.6% | 0.093 | 0.024 |
| Prior myocardial infarction | 18.4% | 12.7% | <0.0001 | 0.157 | 17.9% | 18.5% | 0.094 | 0.022 |
| Psychotic disorder | 4.6% | 3.0% | <0.0001 | 0.086 | 4.5% | 4.1% | 0.208 | 0.018 |
| Rheumatic disease | 8.4% | 6.0% | <0.0001 | 0.094 | 8.2% | 8.0% | 0.584 | 0.008 |
| Renal failure | 5.6% | 2.5% | <0.0001 | 0.158 | 5.2% | 5.5% | 0.311 | 0.014 |
| Valvular disease | 8.2% | 4.7% | <0.0001 | 0.143 | 8.0% | 8.6% | 0.135 | 0.021 |
| Revascularization | 28.5% | 65.6% | <0.0001 | 0.801 | 31.0% | 30.4% | 0.196 | 0.014 |
| PCI | 25.0% | 57.9% | <0.0001 | 0.709 | 27.1% | 26.8% | 0.490 | 0.008 |
| CABG | 3.8% | 8.4% | <0.0001 | 0.194 | 4.2% | 3.8% | 0.153 | 0.019 |
| MI type | | | <0.0001 | 0.353 | | | 0.138 | 0.031 |
| Anterior ST-elevation MI | 12.2% | 19.2% | | | 12.6% | 12.4% | | |
| Other ST-elevation MI | 10.6% | 19.9% | | | 11.2% | 10.8% | | |
| Non-ST-elevation MI | 77.2% | 61.0% | | | 76.2% | 76.8% | | |
| Pharmacotherapy after MI | | | | | | | | |
| ACEi or ARB | 50.8% | 72.0% | <0.0001 | 0.447 | 54.1% | 54.7% | 0.372 | 0.012 |
| Aldosterone antagonist | 4.8% | 3.5% | <0.0001 | 0.061 | 4.7% | 4.5% | 0.635 | 0.007 |
| Antiarrhythmic | 1.1% | 1.2% | 0.317 | 0.011 | 1.1% | 1.3% | 0.221 | 0.017 |
| Beta-blocker | 71.7% | 88.0% | <0.0001 | 0.415 | 75.1% | 75.6% | 0.329 | 0.013 |
| Digoxin | 5.6% | 2.6% | <0.0001 | 0.150 | 5.3% | 5.0% | 0.366 | 0.013 |
| Ezetimibe | 2.5% | 3.4% | <0.0001 | 0.056 | 2.6% | 2.7% | 0.507 | 0.009 |
| Oral anticoagulant | 17.4% | 14.0% | <0.0001 | 0.095 | 17.8% | 18.2% | 0.486 | 0.010 |
| $P2Y_{12}$-inhibitor | 36.6% | 74.4% | <0.0001 | 0.821 | 40.0% | 40.6% | 0.231 | 0.012 |
| Treatment in university hospital | 33.8% | 43.4% | <0.0001 | 0.194 | 34.8% | 34.5% | 0.649 | 0.006 |
| Year of MI | | | <0.0001 | 0.228 | | | 0.756 | 0.229 |

ACEi = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blocker, CABG = coronary artery bypass graft, SMD = standardized mean difference, MI = myocardial infarction, PCI = percutaneous coronary intervention.

24.1 (CI 20.0–30.4) at 1-year and 9.5 (CI 8.5–10.6) at 10-years. The E-value was 2.01 (CI 1.94–2.13) for 10-year mortality. The results of the matched study population were consistent in the subgroup analyses in the overall cohort. The lack of early statin therapy after MI was associated with an increased risk of death in patients sub-grouped by sex, age, atrial fibrillation, dementia, diabetes, heart failure, revascularization, ST-elevation, usage of $P2Y_{12}$-inhibitors, ACEi/ARBs, or betablockers, and prior usage of statins both at 1-year and 10-year follow-up in the overall cohort (Table 2).

### 3.2. Major adverse cardiovascular events

Of the matched patients, 9621 had MACE; 7451 died due to cardiovascular causes; 4712 had new MI; and 2075 had IS during the 10-year follow-up. The cumulative incidence of MACE was 18.7% among patients without early statin therapy *vs.* 16.6% among patients with early statin therapy (sHR 1.15; CI 1.09–1.21; $p < 0.0001$) at 1-year in the matched cohort. At 10-years, the cumulative incidence of MACE was 58.0% without early statin therapy *vs.* 56.0% with statin therapy (sHR 1.15; CI 1.11–1.19; $p < 0.0001$) (Fig. 3). No significant interactions between early statin and early ezetimibe therapies after MI were observed regarding 10-year all-cause mortality (interaction $p = 0.252$)

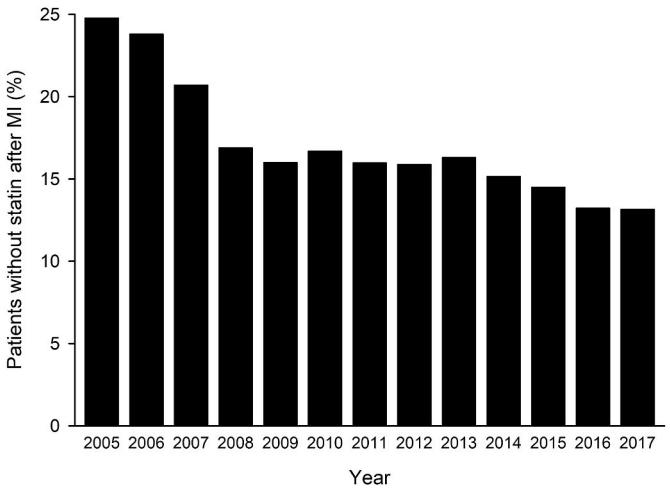


**Fig. 1.** Proportion of patients without statin therapy early after myocardial infarction (MI).

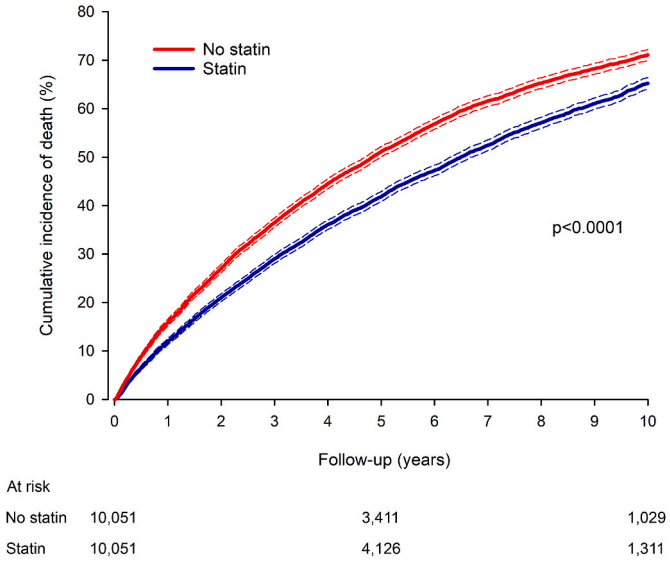


**Fig. 2.** All-cause mortality of propensity matched patients with and without statin therapy early after myocardial infarction.
The dashed lines represent a 95% confidence interval.

or MACE (interaction $p = 0.419$). The cumulative incidence of cardiovascular death was 10.6% in the non-statin group *vs.* 9.1% in the statin group (sHR 1.19; CI 1.11–1.27; $p < 0.0001$) at 1-year and 46.9% *vs.* 44.8%, respectively, at 10-year follow-up (sHR 1.19; CI 1.15–1.24; $p < 0.0001$). The cumulative incidence of new MI was 10.1% in the non-statin group *vs.* 9.8% in the statin group (sHR 1.03; CI 0.97–1.10; $p = 0.380$) at the 1-year follow-up. During the 10-year follow-up, the cumulative incidence of new MI was 27.7% in the non-statin group and 27.0% in the statin group (sHR 1.05; CI 1.01–1.10; $p = 0.039$). The cumulative IS incidence was 3.8% in the non-statin group *vs.* 3.1% in the statin group (sHR 1.25; CI 1.12–1.39; $p < 0.0001$) at 1-year, and 12.9% *vs.* 12.4%, respectively, at the 10-year follow-up (sHR 1.08; CI 1.02–1.16; $p = 0.016$).

## 4. Discussion

This observational, longitudinal, population-based study investigated the association of not using statins early after MI with outcomes. Not using statins early after MI was independently associated with an increased all-cause mortality rate and MACE. The NNH by omitting early statin use was 24.1 at 1- and 9.5 at 10-years for mortality after MI. The risk of death was higher in patients not using early statins, regardless of sex, age, major comorbidities, revascularization, or other evidence-based secondary preventive medications.

Reduction of LDL cholesterol by effective lipid-lowering therapy reduces cardiovascular risk and mortality [2]. Although other high-intensity lipid-lowering therapies such as PCSK9 inhibitors are emerging [17], statins are currently the first-line medications for lipid-lowering therapy in secondary prevention [4,5]. Statins act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is an early, rate-limiting step in cholesterol biosynthesis [18]. In addition, statins may also have additionally beneficial effects of plaque composition and pleiotropic effects on the endothelium, immune system, myocardium, platelets, and vascular smooth muscles that cannot be explained by cholesterol reduction [19]. Large-scale randomized trials and observational studies have demonstrated the effect of statins in reducing the risk of major cardiovascular events [1–3,20]. The benefits are most evident in secondary prevention after ischemic events [2,3].

Placebo controlled statin trials are however not fully representative of the current MI population and treatment modalities [1] and recent observational outcome studies have focused on differences among statin users [20,21]. Revascularization by percutaneous coronary intervention and usage of dual antiplatelet therapies have dramatically increased while prevalence of smoking, high blood pressure, and high cholesterol-levels have decreased since early statin trials [22]. Notably, we found that statin use starting within the first 90-days after discharge was associated with lower all-cause mortality and MACE at 1-year follow-up. This finding is consistent with previous studies showing the benefits of timely lipid lowering after MI [1,20]. However, long-term follow-up studies of non-statin users are limited. Our long-term results of early statin support the previous randomized trials and underline the importance of timely statin therapy in secondary prevention after MI. Our study originated from the clinically straightforward question of what impact the lack of early statin use has after MI in relation to long-term outcomes. Therefore, the definition of statin use was limited to the first three months after MI, which is the maximum period that reimbursed prescription medications like statins are dispensed by pharmacies in Finland [23]. In clinical reality, statins are initiated already during MI admission. The concept of in-hospital initiation of higher intensity lipid-lowering therapy (PCSK9 inhibitor) after MI will be addressed by the ongoing EVOLVE-MI trial.

The extent of statin underuse early after MI found in the current study is in agreement with the EUROASPIRE V survey, which reports 16% of patients not using lipid lowering medication after coronary artery disease related hospitalization, with national variability from 25% to 2% within 27 European countries [7]. Correspondingly, a recent US study found that 19% of US adults did not use statins within 90 days after MI during 2007–2016 [24]. Reasons for not using life-saving statin therapy, despite solid evidence of its benefits, are complex and inadequately understood, regardless of the fact that the safety of statins has been extensively demonstrated [8]. Serious adverse events caused by statins are rare; muscle symptoms associated with elevation in creatine kinase levels occur in <1% of patients and severe liver toxicity in 0.001% of patients [8,25]. Statins are not associated with an increased risk of cancer or non-vascular related death [26]. There is a modestly increased risk of newly diagnosed diabetes in clinical trials with an HR of 1.1–1.2, yet this is associated with a predisposing risk of diabetes [8]. The benefits of statins far outweigh any safety concerns in secondary prevention [8]. Suspicion of side-effects is the major cause of discontinuing statin use [9] and is likely a major determinant for patients' hesitation in starting treatment in the first place. Interestingly, previous investigations found that 20% of statin users stopped therapy due to suspected side-effects; however, 35% restarted treatment and over 90% tolerated re-started therapy, indicating that true statin intolerance is rare [9]. Additionally, exaggerated claims about side-effects and

**Table 2**
Statin use, crude cumulative all-cause mortality at 1- and 10-years after myocardial infarction (MI), and results of multivariable adjusted regression models comparing patients without *vs.* with statin therapy early after MI, in the subgroups of the overall cohort.

| | | | One-year | | | | Ten-year | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | No statin after MI | | Mortality | | Multivariable adjusted | | Mortality | | Multivariable adjusted | |
| Patient group | % | *p*-value | No statin | Statin | HR (95% CI) | *p*-value | No statin | Statin | HR (95% CI) | *p*-value |
| **All patients** | 17.1% | | 17.0% | 5.1% | 1.45 (1.35–1.55) | <0.0001 | 73.1% | 42.1% | 1.35 (1.30–1.39) | <0.0001 |
| **Sex** | | <0.0001 | | | | | | | | |
| Men | 13.7% | | 16.9% | 4.7% | 1.53 (1.40–1.68) | <0.0001 | 68.5% | 37.4% | 1.42 (1.36–1.49) | <0.0001 |
| Women | 23.3% | | 17.1% | 6.1% | 1.35 (1.22–1.49) | <0.0001 | 78.1% | 51.1% | 1.26 (1.20–1.32) | <0.0001 |
| **Age (years)** | | <0.0001 | | | | | | | | |
| <60 | 8.8% | | 4.3% | 1.1% | 1.86 (1.28–2.69) | 0.001 | 23.5% | 13.3% | 1.46 (1.24–1.73) | <0.0001 |
| 60–69 | 10.8% | | 9.4% | 2.6% | 1.71 (1.38–2.11) | <0.0001 | 47.7% | 27.5% | 1.51 (1.36–1.67) | <0.0001 |
| 70–79 | 16.0% | | 14.2% | 5.6% | 1.51 (1.32–1.71) | <0.0001 | 72.3% | 52.0% | 1.41 (1.32–1.50) | <0.0001 |
| ≥80 | 32.2% | | 24.2% | 12.6% | 1.36 (1.24–1.48) | <0.0001 | 94.1% | 83.5% | 1.27 (1.21–1.33) | <0.0001 |
| **Atrial fibrillation** | | <0.0001 | | | | | | | | |
| Yes | 28.8% | | 22.9% | 10.8% | 1.38 (1.23–1.56) | <0.0001 | 85.7% | 69.5% | 1.26 (1.18–1.34) | <0.0001 |
| No | 15.1% | | 15.0% | 4.3% | 1.47 (1.35–1.59) | <0.0001 | 69.3% | 38.3% | 1.38 (1.33–1.44) | <0.0001 |
| **Dementia** | | <0.0001 | | | | | | | | |
| Yes | 40.6% | | 26.3% | 15.4% | 1.42 (1.18–1.71) | 0.0002 | 97.0% | 87.7% | 1.38 (1.26–1.52) | <0.0001 |
| No | 16.0% | | 15.9% | 4.8% | 1.45 (1.35–1.56) | <0.0001 | 70.3% | 40.7% | 1.34 (1.29–1.39) | <0.0001 |
| **Diabetes** | | <0.0001 | | | | | | | | |
| Yes | 19.8% | | 19.4% | 8.2% | 1.33 (1.19–1.48) | <0.0001 | 80.8% | 58.4% | 1.27 (1.20–1.34) | <0.0001 |
| No | 16.2% | | 16.0% | 4.1% | 1.51 (1.38–1.64) | <0.0001 | 70.3% | 37.0% | 1.37 (1.32–1.43) | <0.0001 |
| **Heart failure** | | <0.0001 | | | | | | | | |
| Yes | 30.3% | | 25.7% | 14.0% | 1.27 (1.16–1.39) | <0.0001 | 90.0% | 74.2% | 1.24 (1.18–1.30) | <0.0001 |
| No | 13.8% | | 12.2% | 3.3% | 1.67 (1.52–1.84) | <0.0001 | 63.5% | 35.1% | 1.44 (1.37–1.50) | <0.0001 |
| **Revascularization** | | <0.0001 | | | | | | | | |
| Yes | 8.2% | | 6.8% | 2.6% | 1.40 (1.19–1.65) | <0.0001 | 48.6% | 31.3% | 1.30 (1.22–1.40) | <0.0001 |
| No | 30.1% | | 21.5% | 10.0% | 1.45 (1.35–1.56) | <0.0001 | 82.1% | 59.4% | 1.34 (1.29–1.39) | <0.0001 |
| **ST-elevation MI** | | <0.0001 | | | | | | | | |
| Yes | 10.8% | | 12.6% | 3.2% | 1.55 (1.32–1.82) | <0.0001 | 63.6% | 33.6% | 1.40 (1.30–1.50) | <0.0001 |
| No | 20.7% | | 18.3% | 6.4% | 1.42 (1.32–1.53) | <0.0001 | 76.1% | 47.5% | 1.33 (1.28–1.38) | <0.0001 |
| **$P2Y_{12}$-inhibitor**[a] | | <0.0001 | | | | | | | | |
| Yes | 9.2% | | 11.8% | 3.5% | 1.51 (1.33–1.69) | <0.0001 | 62.0% | 34.8% | 1.39 (1.31–1.47) | <0.0001 |
| No | 33.8% | | 20.0% | 9.8% | 1.41 (1.30–1.52) | <0.0001 | 78.7% | 59.2% | 1.31 (1.25–1.36) | <0.0001 |
| **ACEi/ARB**[a] | | <0.0001 | | | | | | | | |
| Yes | 12.7% | | 14.8% | 4.6% | 1.41 (1.28–1.54) | <0.0001 | 72.3% | 41.5% | 1.28 (1.22–1.34) | <0.0001 |
| No | 26.7% | | 19.2% | 6.6% | 1.50 (1.36–1.65) | <0.0001 | 73.2% | 43.4% | 1.43 (1.36–1.50) | <0.0001 |
| **Beta-blocker** [a] | | <0.0001 | | | | | | | | |
| Yes | 14.4% | | 16.6% | 4.9% | 1.45 (1.35–1.57) | <0.0001 | 74.7% | 41.4% | 1.35 (1.30–1.40) | <0.0001 |
| No | 32.7% | | 17.9% | 7.2% | 1.43 (1.25–1.65) | <0.0001 | 68.9% | 50.0% | 1.33 (1.23–1.43) | <0.0001 |
| **Prior statin** | | <0.0001 | | | | | | | | |
| Yes | 15.8% | | 14.7% | 8.0% | 1.35 (1.20–1.53) | <0.0001 | 67.8% | 55.2% | 1.19 (1.12–1.27) | <0.0001 |
| No | 17.6% | | 17.7% | 4.1% | 1.50 (1.38–1.64) | <0.0001 | 74.7% | 37.1% | 1.41 (1.35–1.47) | <0.0001 |

ACEi = angiotensin-converting-enzyme inhibitor, ARB = angiotensin receptor blocker.
[a] After MI.

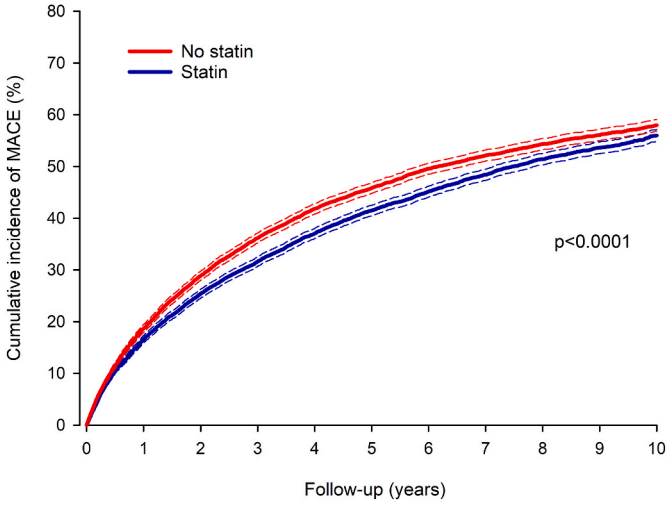


**Fig. 3.** Cumulative incidence of major adverse cardiovascular event (MACE) in propensity matched patients with and without statin therapy early after myocardial infarction.
The dashed lines represent a 95% confidence interval.

negative media coverage are linked to statin underuse [3,27]. In a randomized crossover trial, side effects were similar between statin and placebo after re-starting therapy in patients who had abandoned statins due to side-effect [28]. Patients' self-perception of cardiovascular risk after MI is also limited as shown by previous study finding only 53% of young MI patients to considered themselves at risk for heart disease [29]. Alarmingly, an even lower proportion (46%) of patients reported being told that they were at risk by healthcare personnel [29]. Although the proportion of patients using statins after MI is increasing, there is still significant room for improvement in supporting statin use after MI.

The absolute effectiveness of statin therapy is linked to overall cardiovascular risk [4]. Paradoxically, we found early statin underuse to be more common in patients with the highest risk. Patients with higher age, atrial fibrillation, diabetes, heart failure, those without revascularization, and those without other evidence-based secondary preventive medications used statins less frequently. In addition, statin use was less common in women after MI. These results agree with previous observations [30,31]. Notably, the risk of death after MI was attenuated by statins regardless of age, sex, the abovementioned comorbidities, revascularization, MI type, or other evidence-based medications. Post-MI statin use was associated with lower all-cause mortality in patients aged ≥80 and those with dementia, wherein the evidence for statin use is more limited [32]. Due to high-risk patients who are more

likely to discontinue statin therapy [30], it is possible that our results underestimate the relative beneficence of early statins in high-risk patient groups.

It is well established that high-dose statins reduce post-MI risk more than low- or moderate dose statins [4,21,33], and guidelines recommend that high-doses should be the first line therapy after MI [4,5]. Additionally, low- or moderate dose statin therapy reduces vascular outcomes in the long-run [34]. We found atorvastatin or rosuvastatin being used by 43% of statin users early after MI. In agreement, a previous Finnish study found that high-dose statins are used by 33% of statin users at 6-months after MI, with the proportion of high-dose declining thereafter [6]. Luckily, however, the trend of high-dose statin use is increasing [24].

Adherence to statin therapy is unequivocally associated with a lower risk of death and cardiovascular outcomes [21,35]. Nonadherence to statin use is highly prevalent even in secondary prevention and presents a major barrier to reduce mortality and morbidity [36–39]. For example, in previous studies in Germany and France, the statin discontinuation rate was about 20% during a 4 to 5-year follow-up after recent MI [21]. Medication nonadherence may occur at different times, namely at the start of therapy if the patient does not fill the initial prescription (primary nonadherence) or at a later stage wherein the patient initiates the therapy but does not follow dosing instructions or discontinues therapy (secondary nonadherence) [40]. Unlike to our study of early statin use, the majority of research in the context of secondary prevention after MI has focused on long-term adherence to statins [37,41]. In a previous study in Canada, primary statin nonadherence in patients discharged after MI was 11.1% and 5.2% at 7 days and 120 days post discharge, respectively [41]. In contrast to our study, however, nonadherence was calculated against pharmacy fulfillment of given prescriptions. Consequently, a lack of discharge prescriptions arising from medical practices during the acute setting of MI might partly explain the somewhat higher primary non-adherence to statin therapy in our study [42]. Of all MI patients, 17% did not initiate statin therapy after MI in our data. A previous study showed that 13% of MI patients never purchased statins within the first 1000 days after the index event in Finland [6]. Taken together, these findings suggest that lack of statin in the early phase after MI is a strong proxy for lacking statin also in the long-term as well as to poor adherence. The underlying causes of both statin omission and nonadherence remain however to be further studied.

The current study has strengths and limitations. We used a combination of nationwide registries to avoid selection bias and adjusted the results with a broad coverage of confounders with propensity matching. Residual confounding by non-recognized factors is nevertheless possible and may influence the results of the study. One potential residual confounder that was not directly measured in our data is socioeconomical status, which is inversely associated with statin usage [43]. In addition, we did not have access to information on laboratory analyses (e.g. cholesterol levels, creatine kinase, or liver enzymes), smoking status, body mass index, dietary habits, angiographical data on extent of coronary disease, or other imaging data. Based on the E-value, the observed HR of 1.34 for death could be explained by an unmeasured confounding associated with early statin usage and death by a risk ratio of 2.0-fold each, above and beyond the measured confounders, but weaker confounding could not do so [14]. However, given the extent of variable studies, we consider existence of such confounding unlikely. An inherent limitation to registries is incomplete coding and coding errors. It is likely that these errors occur at a similar rate in both study groups, and thus it is unlikely that they would significantly bias our main findings. Our study was designed as intention to treat type analysis and we did not study adherence or later statin initiations. Therefore, our results may differ from the on-treatment impact of statins in long-term follow-up. Also, we were unable to study potential statin side-effects. We did not have data on the ethnic backgrounds of studied patients, but since the Finnish population is predominantly white, the generalizability of our results to more diverse populations may be limited.

In conclusion, approximately one sixth of patients in this population-based study did not use statin early after discharge for MI. Paradoxically, statin use was less frequent in patients at highest risk. Lack of statin therapy early after MI was strongly associated with the risk of death and major cardiovascular outcomes. Risk of death was increased by not using early statin regardless of age, sex, relevant comorbidities, revascularization, or other evidence-based secondary preventive medications. These results underline the importance of increasing awareness of the benefits of statin use among patients and healthcare personnel alike to improve timely statin use in secondary prevention after MI.

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## CRediT authorship contribution statement

**Ville Kytö:** Study design, acquisition, analysis, and interpretation of the data, and drafting of the manuscript. **Antti Saraste:** Interpretation of the data and critical revision of the manuscript. **Aleksi Tornio:** Study desing, interpretation of the data, and critical revision of the manuscript.

## Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2022.06.1019.

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