ESC European Society of Cardiology

European Heart Journal - Cardiovascular Pharmacotherapy (2023) **9**, 156–164
https://doi.org/10.1093/ehjcvp/pvac064

ORIGINAL ARTICLE
Acute Coronary Syndromes

Initial statin dose after myocardial infarction and long-term cardiovascular outcomes

Ville Kytö [1,2,*], Päivi Rautava [2,3] and Aleksi Tornio [4,5]

[1]Heart Center and Center for Population Health Research, Turku University Hospital and University of Turku, Turku, Finland; [2]Turku Clinical Research Center, Turku University Hospital, Turku, Finland; [3]Department of Public Health, University of Turku, Turku, Finland; [4]Integrative Physiology and Pharmacology, Institute of Biomedicine, University of Turku, Turku, Finland; and [5]Unit of Clinical Pharmacology, Turku University Hospital, Turku, Finland

Received 2 September 2022; revised 19 October 2022; accepted 14 November 2022; online publish-ahead-of-print 16 November 2022

Aims Effective statin therapy is a cornerstone of secondary prevention after myocardial infarction (MI). Real-life statin dosing is nevertheless suboptimal and largely determined early after MI. We studied long-term outcome impact of initial statin dose after MI.

Methods and results Consecutive MI patients treated in Finland who used statins early after index event were retrospectively studied (N = 72 401; 67% men; mean age 68 years) using national registries. High-dose statin therapy was used by 26.3%, moderate dose by 69.2%, and low dose by 4.5%. Differences in baseline features, comorbidities, revascularisation, and usage of other evidence-based medications were adjusted for with multivariable regression. The primary outcome was major adverse cardiovascular or cerebrovascular event (MACCE) within 10 years. Median follow-up was 4.9 years. MACCE was less frequent in high-dose group compared with moderate dose [adjusted hazard ratio (HR) 0.92; $P < 0.0001$; number needed to treat (NNT) 34.1] and to low dose [adj.HR 0.81; $P < 0.001$; NNT 13.4] as well as in moderate-dose group compared with low dose (adj.HR 0.88; $P < 0.0001$; NNT 23.4). Death (adj.HR 0.87; $P < 0.0001$; NNT 23.6), recurrent MI (adj.sHR 0.91; $P = 0.0001$), and stroke (adj.sHR 0.86; $P < 0.0001$) were less frequent with a high- vs. moderate-dose statin. Higher initial statin dose after MI was associated with better long-term outcomes in subgroups by age, sex, atrial fibrillation, dementia, diabetes, heart failure, revascularisation, prior statin usage, or usage of other evidence-based medications.

Conclusion Higher initial statin dose after MI is dose-dependently associated with better long-term cardiovascular outcomes. These results underline the importance of using a high statin dose early after MI.

Keywords Coronary artery disease • Myocardial infarction • Statin • Outcomes

Introduction

Intensive low-density lipoprotein (LDL) cholesterol lowering via effective pharmacotherapy plays a crucial role in secondary prevention after myocardial infarction (MI).[1–3] Although novel and highly effective therapies are emerging, such as PCSK9 inhibitors and siRNAs, 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (statins) are currently the mainstay and first-line therapy after ischaemic events.[4,5] Higher statin doses were shown to be more effective at reducing adverse outcomes in an earlier clinical trial,[6] and the extent of LDL reduction has been linked to better outcomes in observational data after MI.[3] In real life, dosing of statins is, however, known to be suboptimal, with moderate- and low-dose statins frequently used in secondary prevention.[7,8] The benefits of higher statin doses after MI in the modern reperfusion and pharmacotherapy era are currently inadequately known. Therefore, we set out to investigate the real-life, long-term outcome impact of initial statin dose after MI using a population-based design.

Methods

Study design

We studied the impact of first statin dose after MI on long-term outcomes. The primary outcome was composite major adverse cardiovascular and cerebrovascular event (MACCE; all-cause death, recurrent MI, or stroke) within ten years of index event. Secondary outcomes were all-cause death, recurrent MI, and stroke. Studied outcomes are described in more detail in the Supplement. Consecutive adult MI patients admitted between 1 July 2004 and 30 June 2018 were retrospectively identified from the Care Register for Healthcare in Finland (CRHF). Only the first MI admission during the study period was included. The CRHF includes data on all hospital admissions and major interventional procedures in Finland.[9] All

* Corresponding author. Tel: +358 2 3130000, Email: ville.kyto@utu.fi

Table 1 Classification of statin intensity and Anatomical Therapeutic Classification codes used for statin detection.

	Intensity			
	High	Moderate	Low	ATC codes
Atorvastatin	40–80 mg	10–20 mg	-	C10AA05, C10BA05, C10BX03, C10BX08, C10BX11, C10BX12, C10BX15
Fluvastatin	-	80 mg	20–40 mg	C10AA04
Lovastatin	-	40 mg	20 mg	C10AA02, C10BA01
Pitavastatin*				C10AA08
Pravastatin	-	40–80 mg	10–20 mg	C10AA03, C10BA03, C10BX02
Cerivastatin*				C10AA06
Simvastatin	80 mg	20–60 mg	10 mg	C10AA01, C10BA02, C10BA04, C10BX01, C10BX04
Rosuvastatin	20–40 mg	10 mg	-	C10AA07, C10BA06, C10BX05, C10BX07, C10BX09, C10BX10, C10BX13, C10BX14

* Not used by study patients

Finnish hospitals that treat MI patients (N = 20, of which five university hospitals have emergency cardiac surgery available) were included in the study. Index MI was identified with ICD-10 code I21 as the primary discharge diagnosis. To capture only incident MIs, patients admitted to medical, surgical, or intensive care wards through paramedic services or emergency departments were included.[10] Patients who purchased a statin within 90 days after hospital discharge from the index MI were included (N = 72 780). In Finland, out-of-hospital cardiovascular medications are available only from pharmacies with a prescription and are dispensed for a maximum of three-month usage. All purchases are recorded in the national database that was used in the study.[11] Patients with missing follow-up data (N = 2), usage of a PCSK9 inhibitor (N = 2), and those treated with aortic or valvular surgery (N = 375) during the index admission were excluded (Supplementary material online, *Figure S1*). Co-morbidities, treatments, and prescription medications were detected using a combination of national registries as previously defined.[12] Initial usage of statins and other prescription medications after MI was defined as medication purchase within 90 days after hospital discharge.[13] Statin usage before MI was defined as a purchase within 90 days prior to MI. Adherence to statin therapy during follow-up was studied at yearly intervals (Supplement Methods). Statin intensity was classified as high, moderate, or low[14] (*Table 1*). Follow-up data were available up to 31 December, 2018. Median follow-up was 4.9 (IQR 2.3–8.5; maximum 10.0) years.

Data sources and permissions

Data on hospital admissions, major operations, malignancies, prescription medication purchases, medication reimbursements, and mortality of the included patients were obtained from national registries and combined. The data in the CRHF registry, the Finnish cancer registry, prescription medication purchase registry, and reimbursement registry of prescription medication were obtained from the Findata/National Institute for Health and Welfare of Finland (permission no: THL/164/14.02.00/2021). Mortality data were obtained from the nationwide cause of death registry maintained by Statistics Finland (permission no: TK-53–484-20). The included registries are mandatory by law and offer full coverage of the Finnish population (Supplement methods).

The requirement for informed consent was waived by law due to the study design. The participants were not contacted. The legal basis for the processing of personal data was public interest and scientific research (EU General Data Protection Regulation 2016/679 (GDPR), Article 6(1) (e) and Article 9(2) (j); Data Protection Act, Sections 4 and 6).

Statistical analysis

Differences between study groups were analysed with x^2 test, *t*-test, and Wilcoxon rank-sum test. The Cochran–Armitage test was used to study trends. Outcomes were studied using cumulative incidence function and Cox regression (MACCE and all-cause death) or Fine-Gray regression accounting for competing risk of non-endpoint specific death (recurrent MI and stroke).[15] Schoenfeld residuals were used for confirmation of proportional (sub distribution) hazard assumptions. Multivariable regression models were adjusted with the predetermined baseline features listed in *Table 2*. Potential residual confounding was estimated by calculating the E-value.[16] Number needed to treat (NNT) for long-term outcomes was calculated with hazard ratio (HR) as previously described.[17] Results were given as the mean, median, percentage, standardized mean difference (SMD), HR, or sub distribution HR (sHR) with 95% confidence interval (CI), IQR, or ± standard deviation (SD). Statistical significance was detected at P value < 0.05. SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used for the analyses.

Results

A total of 72 401 patients were included in the study, of whom 26.4% had high, 69.1% had moderate, and 4.5% had low statin doses as the first-line statin therapy after MI. Therapy intensity decreased with increasing age (*Table 2*). Simvastatin was the most frequently used initial statin overall and atorvastatin most frequently used high-dose statin (Supplementary material online, *Table S1*). A high-dose statin was used more frequently by patients with the fewest co-morbidities, and a low dose was used by patients with the highest co-morbidity burden (*Table 2*). Revascularization was associated with higher statin dosing. Usage of an adenosine diphosphate (ADP) inhibitor or angiotensin-convertase-enzyme inhibitor (ACEi)/antiotensin receptor blocker (ARB) after MI was also associated with a higher statin dose. Atrial fibrillation and usage of oral anticoagulation were associated with lower initial statin dose. The proportion of patients with a high-dose statin after MI increased substantially during the study period, while usage of moderate- and low-dose statins decreased (trend $P < 0.0001$) (*Figure 1*a). Of the post-MI patients who used statin therapy prior to MI, 24.3% were prescribed a high dose, 25.2% were prescribed a moderate dose, and 50.5% were prescribe a low dose after MI ($P < 0.0001$). Statin dose was increased after MI in 18.6% of patients with a moderate dose and in 89.8% of patients with a low-dose statin before MI (*Figure 1*b). Adherence to statin therapy decreased during follow-up with 24.1% of patients classified

Table 2 Baseline features of myocardial infarction patients by intensity of statin therapy after myocardial infarction.

Variable	Statin dose N = 19 078 High	N = 50 082 Moderate	N = 3241 Low	*P*-value Between group
Age, years (SD)	64.8 (11.6)	68.9 (12.1)	76.2 (10.5)	<0.0001
Women	26.6%	34.4%	48.8%	<0.0001
Medical history				
Alcohol abuse	3.6%	2.8%	1.9%	<0.0001
Anaemia	2.2%	2.9%	4.9%	<0.0001
Atrial fibrillation	9.8%	13.2%	22.4%	<0.0001
Cerebrovascular disease	9.4%	10.1%	15.8%	<0.0001
Chronic pulmonary disease	11.4%	12.9%	14.6%	<0.0001
Coagulopathy	0.4%	0.4%	0.7%	0.005
Dementia	2.0%	3.4%	7.4%	<0.0001
Depression	9.4%	8.6%	11.0%	<0.0001
Diabetes	24.7%	24.3%	34.6%	<0.0001
Insulin dependent	8.2%	8.2%	12.9%	<0.0001
Non-insulin dependent	16.5%	16.1%	21.6%	<0.0001
Heart failure	12.2%	17.9%	31.1%	<0.0001
Hypertension	47.6%	49.8%	61.3%	<0.0001
Liver disease	1.0%	0.8%	1.1%	0.026
Malignancy	11.1%	11.3%	14.0%	<0.0001
Paralysis	0.5%	0.3%	0.3%	0.045
Peripheral vascular disease	6.4%	6.8%	9.9%	<0.0001
Prior CABG	3.7%	3.1%	5.2%	<0.0001
Prior myocardial infarction	12.6%	13.5%	20.4%	<0.0001
Psychotic disorder	2.7%	3.0%	3.2%	0.027
Rheumatic disease	5.3%	7.4%	6.1%	<0.0001
Renal failure	2.1%	2.7%	5.5%	<0.0001
Valvular disease	4.0%	4.7%	8.7%	<0.0001
Revascularization	79.7%	62.7%	38.9%	<0.0001
PCI	72.7%	54.9%	33.6%	<0.0001
CABG	7.9%	8.5%	6.1%	<0.0001
ST-elevation MI	45.8%	38.4%	24.6%	<0.0001
Pharmacotherapy after MI				
ADP-inhibitor	85.8%	71.5%	51.9%	<0.0001
ACEi or ARB	78.0%	70.8%	64.5%	<0.0001
Aldosterone antagonist	4.4%	3.7%	4.7%	<0.0001
Antiarrhythmic	1.2%	1.2%	1.6%	0.075
Beta-blocker	86.5%	88.2%	85.5%	<0.0001
Digoxin	1.0%	2.9%	6.1%	<0.0001
Ezetimibe	5.0%	2.4%	3.2%	<0.0001
Oral anticoagulant	11.2%	14.3%	18.1%	<0.0001
Treatment in university hospital	60.6%	49.6%	41.8%	<0.0001
Admission > 30 days	2.0%	3.7%	6.9%	<0.0001

ADP, adenosine diphosphate; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; PCI, percutanous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction.

as non-adherent 10 years after index MI (*Figure 2*). The dosage of used statins remained similar during the follow-up (27.7% high, 68.3% moderate, and 4.0% low dose at 10 years) (*Figure 2*)

During the 10-year follow-up, 27 647 patients experienced MACCE. Occurrence of MACCE was 43.3% in the high-dose group, 53.3% in the moderate-dose group, and 76.4% in the low-dose group during the follow-up after index MI (*Figure 3*). After adjustments for baseline features, treatments, and other post-MI pharmacotherapies, higher statin dose was dose-dependently associated with lower risk of MACCE (*Table 3*). Risk of MACCE was lower in the high-dose group

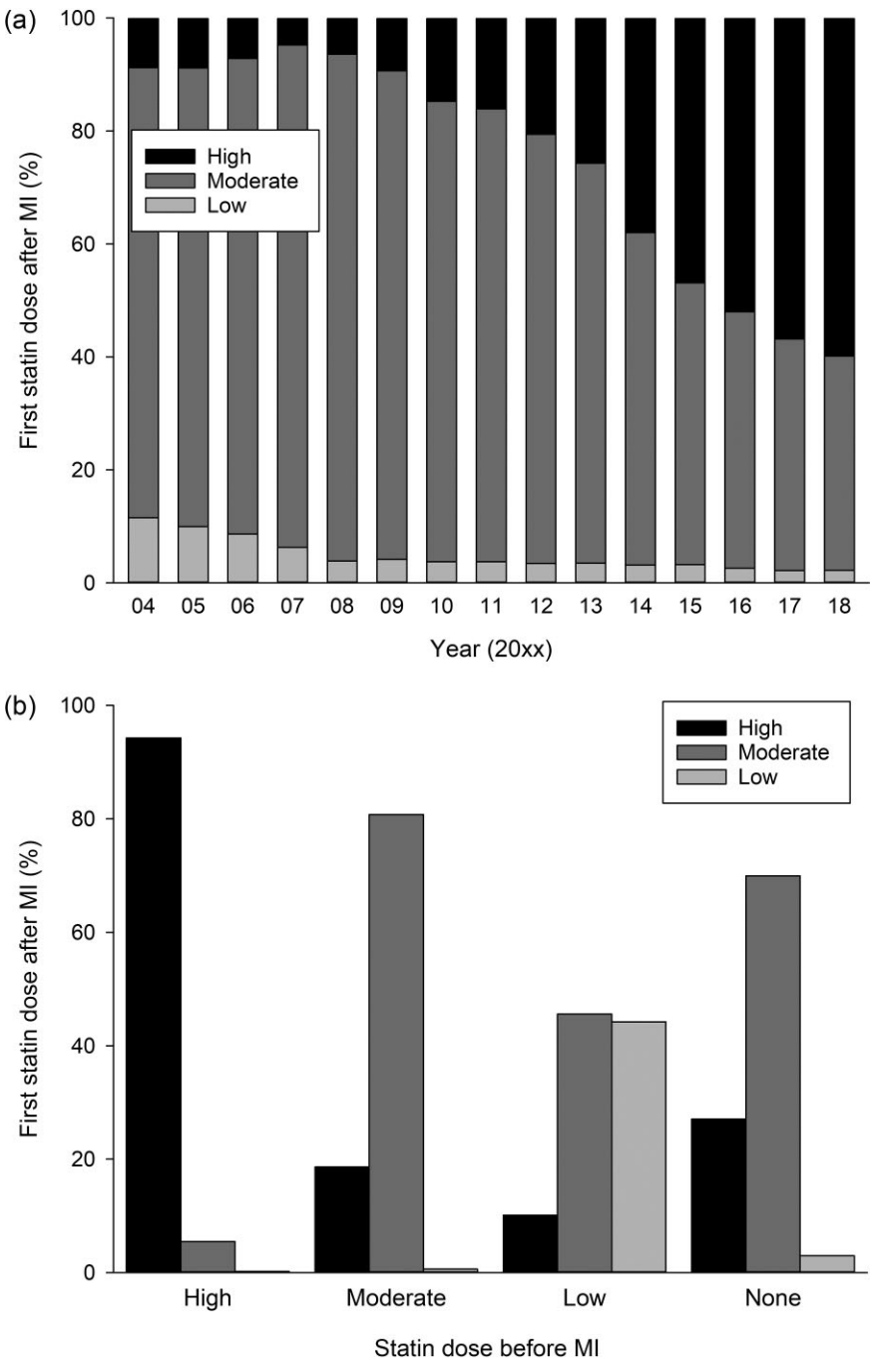

Figure 1 (a) Trends for first statin dose after myocardial infarction during the study period. (b) Association of statin dose used before and after myocardial infarction.

compared with the moderate-dose group (adj.HR 0.92; $P < 0.0001$) and the low-dose group (adj.HR 0.81; $P < 0.0001$), as well as in the moderate-dose group compared with the low-dose group (adj.HR 0.88; $P < 0.0001$) (*Table 3*). The NNTs for 10-year MACCE were 34.1 (CI 24.5–55.2) for high dose vs. moderate dose, 13.4 (CI 10.8–18.9) for high dose vs. low dose, and 23.4 (CI 18.5–35.6) for moderate dose vs. low-dose statin. The E-value was 1.39 (CI 1.28–1.49) for high dose vs. moderate dose, 1.77 (CI 1.60–1.92) for high dose vs. low dose, and 1.53 (CI 1.39–1.63) for moderate dose vs. low dose in terms of ten-year MACCE. Higher initial statin dose after MI was associated with a lower risk of MACCE in patients sub-grouped by age, sex, atrial fibrillation, dementia, diabetes, heart failure, revascularization, ST-elevation, usage of ADP inhibitors, ACEi/ARBs, or beta-blockers, and prior usage of a statin (Supplementary material online, *Table S2*).

Of all patients, 13 154 had recurrent MI, 5055 experienced stroke, and 19 483 died during the follow-up period. All-cause 10-year mortality was 28.9% in the high-dose group, 41.6% in the moderate-dose group, and 68.0% in the low-dose group (*Figure 4*). Mortality was

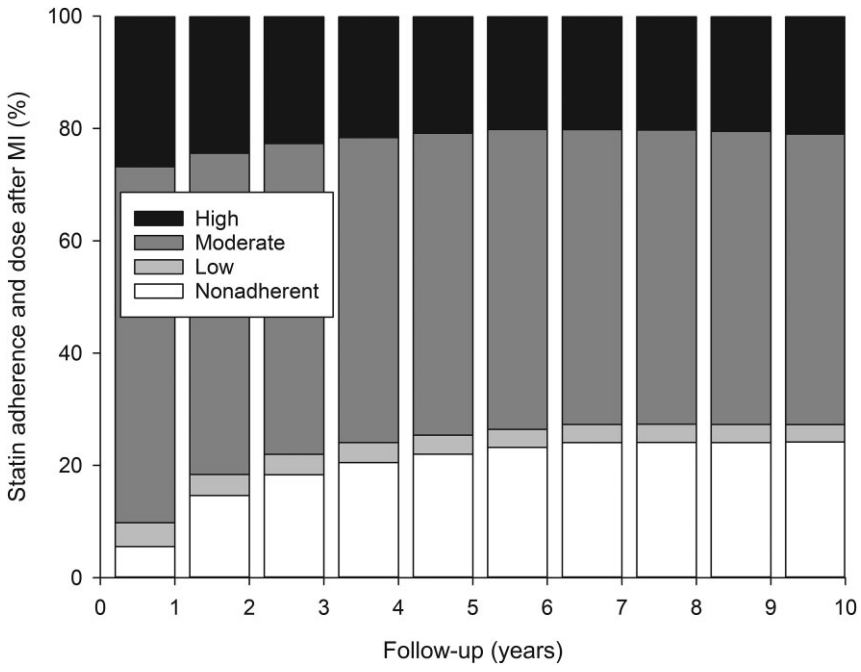

Figure 2 Adherence to statin use and used dose during the follow-up after index myocardial infarction.

dose-dependently lower with a higher statin dose after adjustments (*Table 3*). The NNT was 23.6 (CI 17.9–34.5) for high dose vs. moderate dose, 9.9 (CI 8.0–12.9) for high dose vs. low dose, and 23.4 (CI 16.3–35.6) for moderate dose vs. low-dose statin to ten-year mortality. Cumulative incidence of recurrent MI at ten years was 21.4% in the high-dose group, 23.2% in the moderate-dose group, and 34.2% in the low-dose statin group (*Figure 5*). Sub-distribution hazard of recurrent MI was lower with a higher statin dose (*Table 3*). Cumulative ten-year incidence of stroke (9.9% in the high-dose group, 11.7% in the moderate-dose group, and 14.5% in the low-dose group) (*Figure 5*) was lower in the high-dose statin group vs. the moderate- and low-dose groups, but not in the moderate vs. the low-dose group after adjustments (*Table 3*).

Discussion

This observational, population-based study investigated the impact of initial statin dose after MI on long-term adverse outcomes. Higher initial statin dose was independently associated with lower risk of MACCE and all-cause mortality after MI. The NNT for using a high dose vs. a moderate-dose statin early after MI was 34.1 for MACCE and 23.6 for all-cause mortality at 10 years.

Earlier randomized trials have shown the benefits of early higher intensity statin therapy in terms of secondary prevention after MI.[6,18] These trials were, however, from an era with higher population risk factors[19] and prior to the current percutaneous coronary interventions and dual antiplatelet therapies. To the best of our knowledge, there have been no current-era trials on the effects of statin dose after MI. A recent Swedish registry study found early LDL reduction after MI to be linearly associated with reduction of major cardiovascular events and death.[3] In agreement with this study, in a French registry study of patients with a history of previous MI, the intensity of statin therapy was associated with a lower risk of major cardiovascular events.[8] We studied a clinically straightforward question regarding the potential long-term benefit of using different statin doses initially after MI. Our results showed a robust association of a more intensive initial early statin dose with lower risk of MACCE, death, recurrent MI, and stroke over the long-term follow-up after MI.

Notably, the association of statin dose and the cardiovascular outcome was present across a wide spectrum of patients sub-grouped by age, sex, comorbidities, and usage of other evidence-based secondary preventive medications. Our results were in line with previous observations on beneficial statin influence regardless of sex[20] or comorbidities.[21] In agreement with previous results,[3] the association of statin dose with outcomes was less prominent in patients already using a statin before MI. Although there was no observable difference in MACCE between high vs. moderate doses in previous statin users, high and moderate doses were associated with better outcomes vs. a low dose, which indicated that intense statin therapy is also beneficial in these patients.

The frequent use of low- and moderate-dose statin therapy during the first half of the study period can partly be explained by higher prices and reimbursement restrictions of atorvastatin and rosuvastatin.[22]

Importantly, we found that patients in the highest risk groups for adverse outcomes used the lowest intensity of statins. The same paradoxical phenomenon was observed in previous studies.[7] In people aged > 75 years, the beneficial effect of statins on secondary prevention has been clearly demonstrated.[7] However, older patients and those with multiple morbidities and polypharmacy may be perceived as more likely to suffer from adverse effects and drug/drug interactions, thus reducing the intensity of used statin therapy. Taken together, the current and previous results strongly underline the importance of using high statin dosing early after MI whenever possible.

Current guidelines advocate high-dose statins and intensive LDL reduction after MI. High-dose statins have class IA guideline recommendations for all patients after MI in the US lipid guidelines[2] and European STEMI guidelines.[4] More recent European lipid[1] and NSTEMI[5] guidelines give IA recommendations for lowering LDL-C

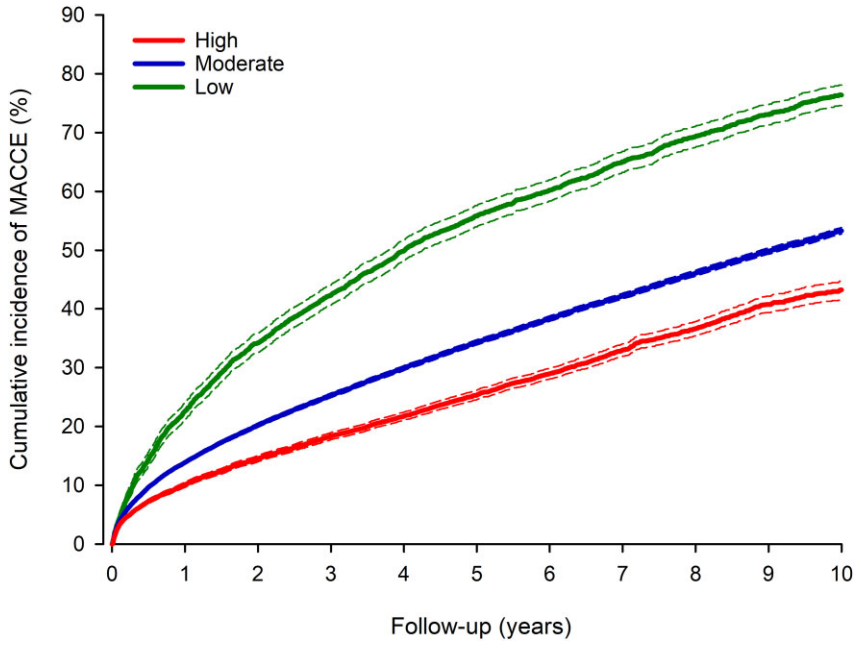

Figure 3 Cumulative incidence of major adverse cardiovascular or cerebrovascular event after myocardial infarction by first statin dose after index event. Dashed lines represent 95% confidence intervals.

Table 3 Results of multivariable adjusted regression models comparing 10-year outcomes between patients with different initial statin dose after myocardial infarction. Models are adjusted for age, sex, comorbidities (listed in Table 2), revascularization (PCI or CABG), ST-elevation, pharmacotherapy after MI (listed in Table 1), treating hospital, and index admission duration of > 30 days.

	High vs. Moderate		High vs. Low		Moderate vs. Low	
Outcome	**adj.HR (95%CI)**	***P*-value**	**adj.HR (95%CI)**	***P*-value**	**adj.HR (95%CI)**	***P*-value**
MACCE	0.92 (0.89–0.95)	<0.0001	0.81 (0.77–0.86)	<0.0001	0.88 (0.85–0.92)	<0.0001
Death	0.87 (0.83–0.91)	<0.0001	0.76 (0.71–0.81)	<0.0001	0.88 (0.83–0.92)	<0.0001
Outcome	**adj.sHR (95%CI)**	***P*-value**	**adj.sHR (95%CI)**	***P*-value**	**adj.sHR (95%CI)**	***P*-value**
Recurrent MI	0.91 (0.87–0.96)	0.0001	0.79 (0.73–0.85)	<0.0001	0.86 (0.81–0.92)	<0.0001
Stroke	0.86 (0.80–0.92)	<0.0001	0.88 (0.78–1.00)	0.049	1.03 (0.93–1.15)	0.570

MACCE = Major adverse cardiovascular or cerebrovascular event. MI = myocardial infarction. sHR = Subdistribution HR.

below < 1.4 mmol/l, which is very rarely achieved by non-high-dose statins. Interestingly, the addition of a PCSK9 inhibitor to a high-dose statin further reduces coronary plaque burden,[23] which suggests potential benefits of even more intensive LDL lowering in the future, albeit outcome studies are still in progress. The proportion of patients with high-dose statins after MI is, however, notably low in real life, as shown by our data and previous observational studies.[7,8,24,25] Importantly, the initial statin dose after MI is a strong determinant of later dosing, as shown by a US study that found only 4% of patients discharged on low- or moderate-dose statins were up-titrated to high intensity within one year after MI.[26] Post-MI lipid testing influenced the usage of high intensity statins only slightly,[26] further underlining the importance of initial statin dose and undermining potential reliance on future dose increases after discharge. Luckily, our results and recent data from the US[7] demonstrate an increasing trend for high-dose statin use after MI.

Good adherence to statin therapy has been linked with a lower risk of cardiovascular events.[8,27-29] Yet, real-life, long-term statin adherence is inadequate as shown by our results and previous findings,[8,30] and, paradoxically, high-risk patients are most likely to discontinue statins.[31] Interestingly, we found the distribution of used statin doses to remain virtually equal during the long-term secondary prevention after MI underlining the real-life importance of initial statin dosing. The reasons for non-adherence are complex and inadequately understood, regardless of the fact that the safety of statins has been extensively demonstrated.[32] Even though serious adverse effects caused by statins are rare, a large proportion of patients have mild muscle symptoms.[32-34] Except for autoimmune-mediated necrotizing

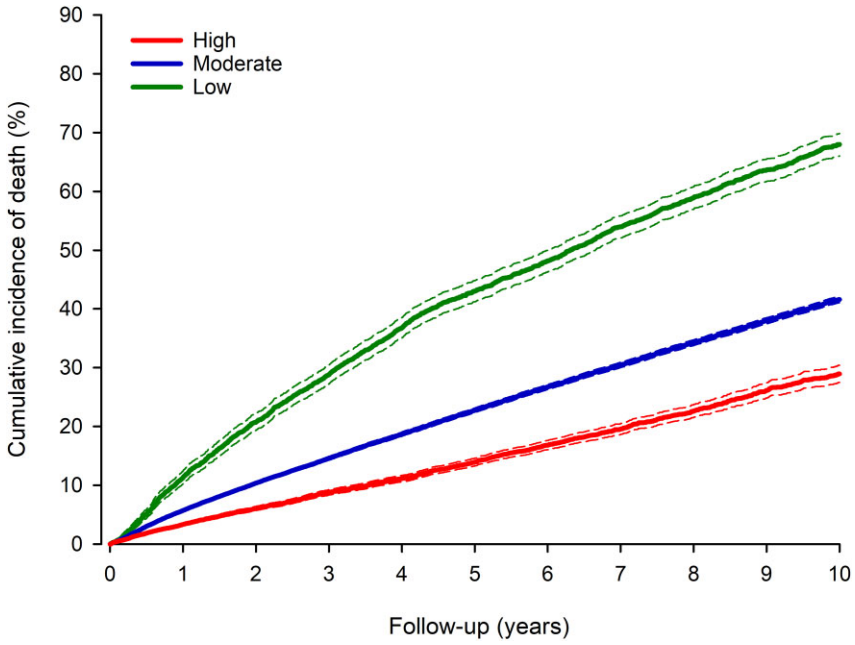

Figure 4 All-cause mortality after myocardial infarction by first statin dose after index event. Dashed lines represent 95% confidence intervals.

myositis, the muscle toxicity of statins is a concentration-dependent phenomenon. High-dose statin therapy is associated with a higher frequency of muscle symptoms, with up to 10% of patients reporting muscle complaints during high-dose statin therapy.[35,36] These muscle symptoms—and the fear of them—is a major factor that limits adherence to statin therapy.[32]

Notably, we found that moderate-dose statins yield better outcomes than low-dose statins. This reflects an important notion that, although a low-dose statin is better than no statin,[37] the dose should be kept as high as possible even if high doses are not tolerated. Moreover, ezetimibe added to a statin reduces adverse outcomes after acute coronary syndrome.[38] Our analyses were adjusted for ezetimibe to emphasize the fact that ezetimibe should not be used as a replacement for a higher statin dose but rather as a complementary therapy with a maximally tolerated statin.[1]

There are strengths and limitations in our study. We used an all-comer, population-based study design with combined nationwide registries to avoid selection and lost-to-follow-up biases. The results were adjusted with broad coverage of potential confounders, but residual confounding by non-recognized factors was, nevertheless, possible, and may have influenced the results of the study. As we did not have access to dosing instructions, statin dose was assumed to be unit per day, which is the case in 95% of prescriptions, based on a previous study in Finland.[39] Furthermore, we did not have access to detailed information on LDL levels or other laboratory measures, angiographical data, other imaging data, socioeconomic status, or lifestyle features. It is also possible that potential non-adjusted changes in MI care over time may influence the results. Based on the E-value, the observed risk reduction in long-term MACCE by high- vs. moderate-dose statin could be explained by an unmeasured confounding associated with a higher statin dose and MACCE by a risk ratio of 1.4 for each, above and beyond the measured confounders, but weaker confounding could not accomplish this.[16] The ethnic backgrounds of the patients were not available, but, because the Finnish population is predominantly white, the generalizability of our results to more diverse populations may be limited. Incomplete and erroneous coding are inherent limitations of observational registries, but it is unlikely that these potential errors would have influenced study groups significantly differently. Our study was designed as an intention-to-treat type analysis. Therefore, our results may differ from the on-treatment results in long-term follow-up.

In conclusion, a higher initial statin dose after MI is dose-dependently associated with better long-term cardiovascular outcomes. Association was present across the spectrum of MI patients. Paradoxically, however, patients with the highest risk for adverse outcomes used the lowest intensity of statins. These results underline the importance of using high statin dosing early after MI.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

Acknowledgment

This work was supported by grant funding from the Paavo Nurmi Foundation, the Finnish Foundation for Cardiovascular Research, and the Finnish State research funding.

Conflict of interests: None.

Data availability

The data underlying this article were provided by the Findata and the Statistics Finland by permission. Data requests should be directed to the Findata (www.findata.fi).

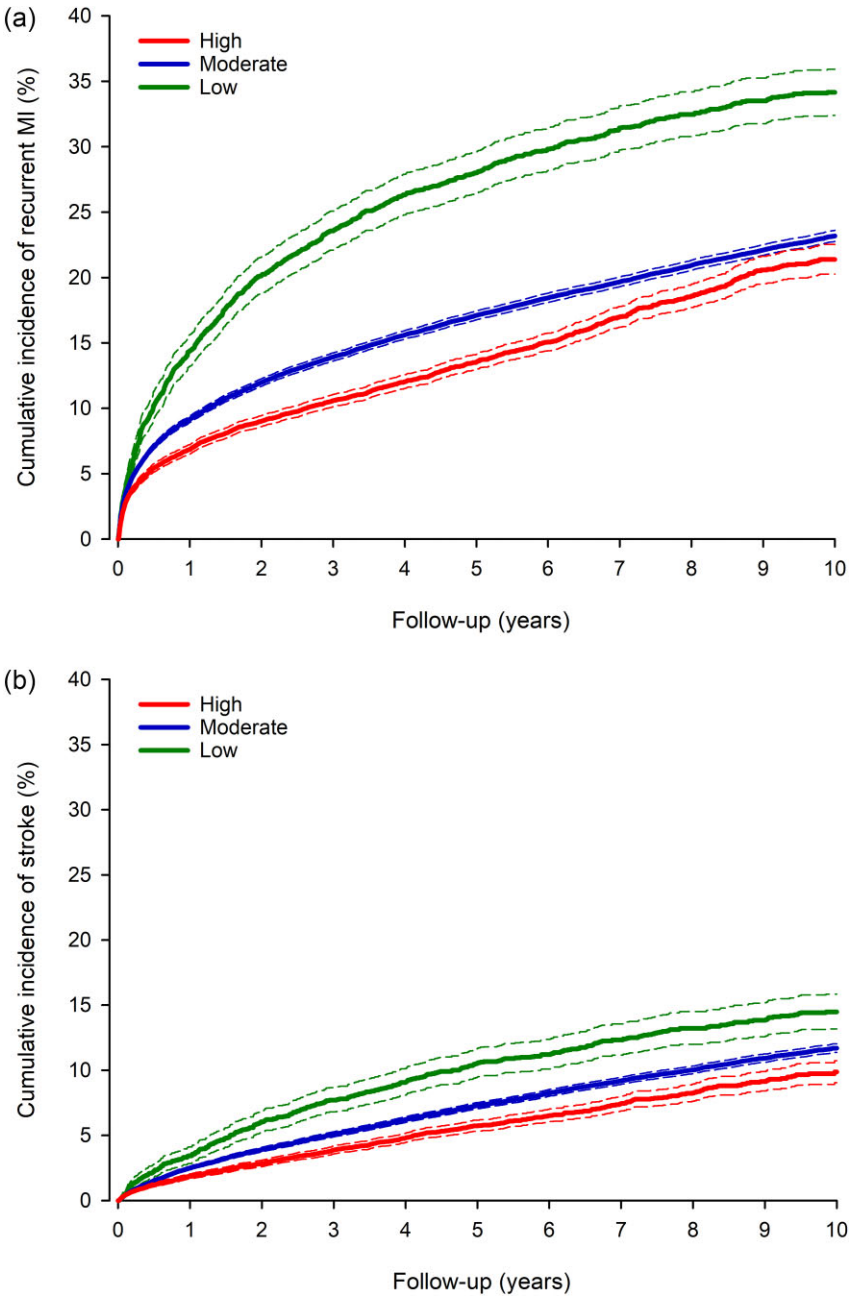

Figure 5 Cumulative incidence of (a) recurrent myocardial infarction and (b) stroke after MI by first statin dose after index event. Competing risk curves. Dashed lines represent 95% confidence intervals.

References

1. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O,Group ESCSD. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–188.
2. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, Goldberg R, Heidenreich PA, Hlatky MA, Jones DW, Lloyd-Jones D, Lopez-Pajares N, Ndumele CE, Orringer CE, Peralta CA, Saseen JJ, Smith SC Jr., Sperling L, Virani SS, Yeboah J. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *Circulation* 2019;**139**:e1082–e1143.
3. Schubert J, Lindahl B, Melhus H, Renlund H, Leosdottir M, Yari A, Ueda P, James S, Reading SR, Dluzniewski PJ, Hamer AW, Jernberg T, Hagstrom E. Low-density lipoprotein cholesterol reduction and statin intensity in myocardial infarction patients and major adverse outcomes: a Swedish nationwide cohort study. *Eur Heart J* 2021;**42**:243–252.
4. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio ALP, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimsky P, Group ESCSD. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting

with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
5. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Juni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM, Group ESCSD. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;**42**:1289–1367.
6. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004;**350**:1495–1504.
7. Yao X, Shah ND, Gersh BJ, Lopez-Jimenez F, Noseworthy PA. Assessment of trends in statin therapy for secondary prevention of atherosclerotic cardiovascular disease in US adults from 2007 to 2016. *JAMA Network Open* 2020;**3**:e2025505.
8. Schiele F, Quignot N, Khachatryan A, Gusto G, Villa G, Kahangire D, Chauny JV, Ricci L, Desamericq G. Clinical impact and room for improvement of intensity and adherence to lipid lowering therapy: five years of clinical follow-up from 164,565 post-myocardial infarction patients. *Int J Cardiol* 2021;**332**: 22–28.
9. Kyto V, Myllykangas ME, Sipila J, Niiranen TJ, Rautava P, Gunn J. Long-term outcomes of mechanical vs. biologic aortic valve prosthesis in patients older than 70 years. *Ann Thorac Surg* 2019;**108**:1354–1360.
10. Kerola AM, Juonala M, Palomaki A, Semb AG, Rautava P, Kyto V. Case fatality of patients with type 1 diabetes after myocardial infarction. *Diabetes Care* 2022;**45**:1657–1665.
11. Posti JP, Ruuskanen JO, Sipila JOT, Luoto TM, Rautava P, Kyto V. Effect of oral anticoagulation and adenosine diphosphate inhibitor therapies on short-term outcome of traumatic brain injury. *Neurology* 2022;**99**:e1122–e1130.
12. Kerola AM, Palomaki A, Rautava P, Kyto V. Less revascularization in young women but impaired long-term outcomes in young men after myocardial infarction. *Eur J Prev Cardiol*.2022;**29**:1437–1445.
13. Kyto V, Saraste A, Tornio A. Early statin use and cardiovascular outcomes after myocardial infarction: a population-based case-control study. *Atherosclerosis* 2022;**354**: 8–14.
14. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, Goldberg AC, Gordon D, Levy D, Lloyd-Jones DM, McBride P, Schwartz JS, Shero ST, Smith SC Jr., Watson K, Wilson PW, Eddleman KM, Jarrett NM, LaBresh K, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr., Tomaselli GF. 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. *Circulation* 2014;**129**:S1–45.
15. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. *Circulation* 2016;**133**:601–609.
16. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-Value. *Ann Intern Med* 2017;**167**:268–274.
17. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;**319**:1492–1495.
18. Cholesterol Treatment Trialists C, Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, Peto R, Barnes EH, Keech A, Simes J, Collins R. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;**376**: 1670–1681.
19. Borodulin K, Vartiainen E, Peltonen M, Jousilahti P, Juolevi A, Laatikainen T, Mannisto S, Salomaa V, Sundvall J, Puska P. Forty-year trends in cardiovascular risk factors in Finland. *Eur J Public Health* 2015;**25**:539–546.
20. Cholesterol Treatment Trialists C, Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, Mihaylova B, Simes J, Collins R, Kirby A, Colhoun H, Braunwald E, La Rosa J, Pedersen TR, Tonkin A, Davis B, Sleight P, Franzosi MG, Baigent C, Keech A. Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015;**385**:1397–1405.
21. Cholesterol Treatment Trialists C, Kearney PM, Blackwell L, Collins R, Keech A, Simes J, Peto R, Armitage J, Baigent C. Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis. *Lancet* 2008;**371**:117–125.
22. Martikainen JE, Saastamoinen LK, Korhonen MJ, Enlund H, Helin-Salmivaara A. Impact of restricted reimbursement on the use of statins in Finland: a register-based study. *Med Care* 2010;**48**:761–766.
23. Raber L, Ueki Y, Otsuka T, Losdat S, Haner JD, Lonborg J, Fahrni G, Iglesias JF, van Geuns RJ, Ondracek AS, Radu Juul Jensen MD, Zanchin C, Stortecky S, Spirk D, Siontis GCM, Saleh L, Matter CM, Daemen J, Mach F, Heg D, Windecker S, Engstrom T, Lang IM, Koskinas KC. Effect of alirocumab added to high-intensity statin therapy on coronary atherosclerosis in patients with acute myocardial infarction: the PACMAN-AMI randomized clinical trial. *JAMA* 2022;**327**:1771–1781.
24. De Backer G, Jankowski P, Kotseva K, Mirrakhimov E, Reiner Z, Ryden L, Tokgozoglu L, Wood D, De Bacquer D. Management of dyslipidaemia in patients with coronary heart disease: results from the ESC-EORP EUROASPIRE V survey in 27 countries. *Atherosclerosis* 2019;**285**:135–146.
25. Lassenius MI, Toppila I, Bergius S, Perttila J, Airaksinen KEJ, Pietila M. Cardiovascular event rates increase after each recurrence and associate with poor statin adherence. *Eur J Prev Cardiol*. 2021;**28**:884–892.
26. Wang WT, Hellkamp A, Doll JA, Thomas L, Navar AM, Fonarow GC, Julien HM, Peterson ED, Wang TY. Lipid testing and statin dosing after acute myocardial infarction. *J Am Heart Assoc* 2018;**7**:e006460.
27. Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. *JAMA* 2007;**297**:177–186.
28. Mazhar F, Hjemdahl P, Clase CM, Johnell K, Jernberg T, Sjolander A, Carrero JJ. Intensity of and adherence to lipid-lowering therapy as predictors of major adverse cardiovascular outcomes in patients with coronary heart disease. *J Am Heart Assoc* 2022;**11**:e025813.
29. Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Di Angelantonio E, Franco OH, Halvorsen S, Hobbs FDR, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoglu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B, Group ESCSD. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;**42**:3227–3337.
30. Loiveke P, Marandi T, Ainla T, Fischer K, Eha J. Adherence to recommendations for secondary prevention medications after myocardial infarction in Estonia: comparison of real-world data from 2004 to 2005 and 2017 to 2018. *BMC Cardiovasc Disord* 2021;**21**:505.
31. Shore S, Jones PG, Maddox TM, Bradley SM, Stolker JM, Arnold SV, Parashar S, Peterson P, Bhatt DL, Spertus J, Ho PM. Longitudinal persistence with secondary prevention therapies relative to patient risk after myocardial infarction. *Heart* 2015;**101**:800–807.
32. Newman CB, Preiss D, Tobert JA, Jacobson TA, Page RL 2nd, Goldstein LB, Chin C, Tannock LR, Miller M, Raghuveer G, Duell PB, Brinton EA, Pollak A, Braun LT, Welty FK. Statin safety and associated adverse events: a scientific statement from the american heart association. *Arterioscler Thromb Vasc Biol* 2019;**39**:e38–e81.
33. Alfirevic A, Neely D, Armitage J, Chinoy H, Cooper RG, Laaksonen R, Carr DF, Bloch KM, Fahy J, Hanson A, Yue QY, Wadelius M, Maitland-van Der Zee AH, Voora D, Psaty BM, Palmer CN, Pirmohamed M. Phenotype standardization for statin-induced myotoxicity. *Clin Pharmacol Ther* 2014;**96**:470–476.
34. Casula M, Gazzotti M, Bonaiti F, Arca M, Averna M, Zambon A, Catapano AL, Group PS. Reported muscle symptoms during statin treatment amongst Italian dyslipidaemic patients in the real-life setting: the PROSISA study. *J Intern Med* 2021;**290**:116–128.
35. Parker BA, Capizzi JA, Grimaldi AS, Clarkson PM, Cole SM, Keadle J, Chipkin S, Pescatello LS, Simpson K, White CM, Thompson PD. Effect of statins on skeletal muscle function. *Circulation* 2013;**127**:96–103. 1
36. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. *Cardiovasc Drugs Ther* 2005;**19**:403–414.
37. Heart Protection Study Collaborative G. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20,536 high-risk individuals: a randomised controlled trial. *Lancet North Am Ed* 2011;**378**:2013–2020.
38. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, De Ferrari GM, Ruzyllo W, De Lucca P, Im K, Bohula EA, Reist C, Wiviott SD, Tershakovec AM, Musliner TA, Braunwald E, Califf RM,Investigators I-I. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med* 2015;**372**:2387–2397.
39. Romppainen T, Rikala M, Aarnio E, Korhonen MJ, Saastamoinen LK, Huupponen R. Measurement of statin exposure in the absence of information on prescribed doses. *Eur J Clin Pharmacol* 2014;**70**:1275–1276.