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Low statin use in adults hospitalized with acute coronary syndrome

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ABSTRACT

Objective. To assess recommended and actual use of statins in primary prevention of cardiovascular disease (CVD) based on clinical prediction scores in adults who develop their first acute coronary syndrome (ACS).

Method. Cross-sectional study of 3172 adults without previous CVD hospitalized with ACS at 4 university centers in Switzerland. The number of participants eligible for statins before hospitalization was estimated based on the European Society of Cardiology (ESC) guidelines and compared to the observed number of participants on statins at hospital entry.

Results. Overall, 1171 (37%) participants were classified as high-risk (10-year risk of cardiovascular mortality ≥5% or diabetes); 1025 (32%) as intermediate risk (10-year risk <5% but ≥1%); and 976 (31%) as low risk (10-year risk <1%). Before hospitalization, 516 (16%) were on statins; among high-risk participants, only 236 of 1171 (20%) were on statins. If ESC primary prevention guidelines had been fully implemented, an additional 845 high-risk adults (27% of the whole sample) would have been eligible for statins before hospitalization.

Conclusion. Although statins are recommended for primary prevention in high-risk adults, only one-fifth of them are on statins when hospitalized for a first ACS.

Introduction

The primary prevention of cardiovascular disease (CVD) occurs along two axes: population strategies aimed at the whole community through lifestyle and environmental changes, and targeted strategies, where more intensive preventive measures and medication are aimed at 'high-risk' populations likely to derive the greatest benefit (Nichols et al., 2012; Rose, 2001). One of the major components of the targeted strategy is the prescription of proven medications such as statins to high-risk individuals. Although it has been shown that rates of screening and treatment for hypertension and hypercholesterolemia are increasing (Estoppey et al., 2011; Mann et al., 2008; Walley et al., 2005), adoption of preventive guidelines by physicians and patients is incomplete (Jackevicius et al., 2002; Vashitz et al., 2011). The large discrepancy between recommendations for preventive medications and their actual use in primary prevention could play a significant role in the current burden of CVD. However, the degree of implementation of primary prevention guidelines has been poorly studied in adults who develop a cardiovascular event, and the reasons for inadequate use of preventive medications in primary prevention remain unclear even in high-risk adults (Miedema et al., 2012).

Optimal implementation of guidelines for primary prevention is essential, because statins have also been shown to reduce cardiovascular risk in primary prevention (Cholesterol Treatment Trialists et al., 2012). In this study, we examined the patterns of preventive medication use at the time of hospitalization for acute coronary syndrome (ACS) according to guidelines with a focus on statins, and assessed the clinical factors associated with non-utilization of preventive medication in eligible high-risk adults who develop a first ACS. We hypothesized that a substantial portion of adults presenting with first ACS would not be taking guideline-recommended preventive treatments such as statins before hospitalization.

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Methods

Study population

The SPUM-ACS (Special Programme University Medicine—Acute Coronary Syndrome) research network started enrolling patients hospitalized with ACS at 4 university medical centers in Switzerland from 2009 (Auer et al., 2014; Gencer et al., 2015a,b). Adults with a primary diagnosis of ACS were recruited within 5 days of pain onset. Based on ACS guidelines, criteria for ACS were symptoms compatible with angina pectoris, and at least one of three criteria: (a) changes on electrocardiogram (ECG) such as ST-segment elevation or depression, T-wave inversions, or dynamic repolarization changes on; (b) a positive troponin or elevated creatine kinase; and/or (c) known coronary artery disease specified as status after myocardial infarction, coronary artery bypass graft (CABG), or PCI or newly documented ≥50% stenosis of an epicardial coronary artery during the initial catheterization (Thygesen et al., 2007). Exclusion criteria included language barrier making it impossible to fill out study consent and forms, immediate transfer to another hospital prior to inclusion, or expected inability to complete 1 year of follow-up, either because of shortened life expectancy for non-cardiology-related disease, or expected departure from Switzerland. Among 5378 adults presenting with ACS, 3172 had no previous history of CVD and complete data on cardiovascular risk factors, allowing calculation of risk before hospitalization and were included in this analysis (Appendix Fig. 1). The study protocol was approved by the institutional review board at all participating institutions.

Use of drugs for primary prevention

Preventive drugs that were taken prior to hospitalization were self-reported and systematically collected by trained study nurses. Anti-platelet medications were acetylsalicylic acid (Aspirin), clopidogrel (Plavix®), prasugrel (Efient®), ticagrelor (Brilique®) and dipiridamole/actetylsalicyclic acid (Asasantine®). Lipid lowering agents included HMG-CoA reductase inhibitors (statins), fibrates, niacin, ezetimibe and bile acid resins. Anti-hypertensives included all medications in the classes ACE inhibitors, angiotensin II receptor blockers, beta blockers, calcium-channel blockers and diuretics. Oral anti-diabetic medications and insulin were also recorded.

Eligibility for statins

Indications for preventive drug initiation in primary prevention according to different guidelines are shown in Appendix Table 1. Eligibility for statins and cardiovascular risk estimates are based on the three sets of recommendations that are principally used in mainland Europe: (1) the European Society of Cardiology (ESC) guidelines with the SCORE calculator (Perk et al., 2012); (2) the American Heart Association guidelines (Stone et al., 2013), with the Atherosclerotic Cardiovascular Disease (ASCVD) calculator (Goff et al., 2013); and (3) the International Atherosclerosis Society guidelines, adopted by the Swiss Atherosclerosis Association (AGLA), with the PROCAM score modified for Switzerland (Expert Dyslipidemia and Grundy, 2013). The ESC guidelines, used for our primary analysis given their dominance in Europe, differentiate between patients for whom they recommend "immediate drug intervention" and those whom physicians can "consider drug" (Perk et al., 2012). When reference is made to an individual being "statin eligible", they are in the category recommending "immediate drug intervention". Similarly, with the AHA/ACC guidelines, we differentiate between those with a clear indication for immediate statin therapy (i.e. diabetics and high-risk), and those with a 10-year risk between 5 and 7.5% and those above age 75, for whom it is "reasonable to offer treatment"; for ease of comparison, we classify these intermediate categories as "consider drug" (Appendix Table 1) (Goff et al., 2013).

Cardiovascular risk equations — Algorithms

For ESC guidelines, we used the SCORE algorithm for low-risk countries, calibrated for Switzerland (Marques-Vidal et al., 2008). The ASCVD algorithm was taken from the publicly available Pooled Cohort Equations from the ACC/AHA guidelines (Goff et al., 2013). The PROCAM score used was the one modified for Switzerland and recommended by AGLA (Assmann et al., 2002).

Covariates

Previous cardiovascular disease (CVD) was defined as previous coronary heart disease (MI, percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG)), cerebrovascular accident, transient ischemic attack, or peripheral arterial disease. Baseline diabetes was defined based on patient report, taking anti-diabetic medication or insulin, or an admission hemoglobin A1c of 6.5% or greater. History of smoking was defined as those who had smoked >20 packs of cigarettes per year, at least one cigarette per day or one cigar per week, or at least 360 g of tobacco per year. Current smokers were those with a history of smoking who had smoked within the last month (Ryan et al., 2012). Family history of CVD was based on patient report of a major cardiovascular event in a brother or father younger than 55 years of age, or a mother or sister younger than 65. Systolic blood pressure was taken from the inpatient records. Values for total cholesterol, HDL-cholesterol and triglycerides were taken from the first blood draw of the hospitalization, typically taken in the emergency department, in order to minimize acute-phase changes in lipid levels, and analyzed at each center (Pitt et al., 2008). LDL cholesterol was calculated using the Friedewald formula (LDL = total cholesterol − HDL − (triglycerides / 2.2)). Education status was dichotomized as having followed an apprenticeship, vocational school or less, or having a high school or university graduation.

Statistical analysis

Frequencies, means ± standard deviations (SDs) or medians with interquartile ranges (IQR) were used when appropriate. For our primary analysis a 10-year risk of fatal CVD ≥5% based on ESC algorithm was considered high-risk (Perk et al., 2012). In order to compare between risk algorithms, the threshold for high-risk was defined as a 10-year risk of fatal or non-fatal CHD of 20% using the PROCAM calculator and a 10-year risk of first CVD event of 7.5% using the ASCVD calculator, similar to previous trials, as these are the thresholds above which the majority of patients are recommend to initiate statin therapy (Appendix Table 2) (Kavousi et al., 2014). Adults with diabetes and evidence of complications (nephropathy) or concurrent risk factors (smoking or hypertension) were considered high-risk. To assess factors associated with optimal compliance to primary prevention guidelines before hospitalization for first ACS, we examined the associations between baseline clinical characteristics and statin usage, using logistic models, and reported results as odds ratios (OR) and 95% confidence intervals (CI). Those taking statins prior to hospitalization (reference group) were compared to those eligible for statins. Sensitivity analyses were performed for two potential sources of bias: (a) excluding those presenting 24 h after the onset of symptoms and those with acute heart failure; and (b) excluding those already taking statins. Statistical significance was set at 0.05. All analyses were performed using STATA version 13 (StataCorp, College Station, Texas, USA).

Results

Among 3172 adults with first ACS and no previous CVD, 1321 (42%) were current smokers and 463 (15%) had diabetes. Anti-hypertensive drugs were the most commonly used preventive drugs before hospitalization for ACS, with 1128 (36%) taking at least one medication, along with 516 (16%) taking statins and 463 (15%) Aspirin. Table 1 reports baseline characteristics stratified by statin use at the time of hospital admission. Adults taking statins were older, more obese, had a lower level of education, were less likely to be current smokers, and were more frequently hypertensive or diabetic as compared to adults not taking statins. Mean LDL levels were 2.7 (±1.0) for those taking statins and 3.5 (±1.0) for those not taking statins ($p < 0.001$). Adults taking statins were also less likely to present with a STEMI (44% vs. 62%), but had higher rates of NSTEMI (50% vs. 36%) and unstable angina (6% vs. 2%) than those not taking statins.

The cardiovascular risk classification at the time of hospitalization using the three risk scores most commonly used in Switzerland is shown in Fig. 1. Using the SCORE calculator, 37% of adults were classified as high-risk (estimated 10-year CVD mortality ≥5%) and 32% were at intermediate risk (estimated 10-year CVD mortality below 5%). The number of adults at high-risk was 51% with the ASCVD calculator and 35% with the PROCAM calculator. Sensitivity analyses excluding those

Table 1
Characteristics of study population, stratified by statin use at the time of admission for acute coronary syndrome (n = 3172).

	Taking statins (n = 516)	Not taking statins (n = 2656)	p-Value
Demographic characteristics			
Age, years	65 ± 12	61 ± 12	<0.001
Female	113 (22%)	577 (22%)	0.93
Caucasian	486 (94%)	2505 (94%)	0.91
Education, post-secondary	102 (24%)	701 (30%)	0.027
Alcohol consumption			
<1 serving/month	138 (31%)	637 (26%)	0.006
1 serving/month to 2 servings/week	135 (30%)	919 (38%)	
>2 servings/week	173 (39%)	853 (35%)	
Cardiovascular risk factors			
Current smoker	167 (32%)	1154 (43%)	<0.001
Former smoker	169 (33%)	643 (24%)	
Non-smokers	180 (35%)	859 (32%)	
Hypertension	394 (76%)	1208 (45%)	<0.001
Diabetes	143 (28%)	320 (12%)	<0.001
Family history	140 (27%)	655 (25%)	0.24
BMI, kg/m^2	27.6 ± 4.5	26.9 ± 4.3	0.002
Obesity[a]	126 (25%)	544 (21%)	0.049
GFR <60 mL/min/1.73 m^2	64 (13%)	248 (9%)	0.024
Total cholesterol, mmol/l	4.5 ± 1.2	5.3 ± 1.2	<0.001
LDL-cholesterol, mmol/l	2.7 ± 1.0	3.5 ± 1.0	<0.001
HDL-cholesterol, mmol/l	1.2 ± 0.4	1.2 ± 0.4	0.75
Triglyceride, mmol/	1.4 ± 1.1	1.4 ± 1.3	0.30
Type of acute coronary syndrome[b]			
STEMI	218 (44%)	1591 (62%)	<0.001
NSTEMI	250 (50%)	923 (36%)	
Unstable angina	28 (6%)	56 (2%)	

Results are provided as mean ± standard deviation or as number of participants (percentage). Statistical analysis by Chi-square or Student's t-test.
BMI: body mass index; GFR: glomerular filtration rate; STEMI: ST segment elevation myocardial infarction; NSTEMI: non-ST segment elevation myocardial infarction.
[a] Defined as a BMI ≥30 kg/m^2.
[b] Data regarding type of acute coronary syndrome is missing for 20 subjects taking statins and 86 not taking statins.

presenting 24 h after the onset of symptoms, those with acute heart failure, or those already taking statins did not have a significant impact on the distribution of participants by risk score.

Current statin use and statin eligibility, stratified by risk level using the SCORE calculator from ESC guidelines, is reported in Table 2. In addition to 516 (16%) adults with current statins use, ESC guidelines would recommend statins prescription to 845 adults (27%), and would consider statins for a further 843 (27%) adults. Among 1171 high-risk adults with a 10-year risk for CVD-related mortality of 5% or above, and/or diabetes with other risk factors, only 236 (20%) were taking statins at baseline, whereas another 845 (72%) were eligible for statins prescription following ESC guidelines. Fig. 2 and Appendix Table 3 show similar figures using new ACC/AHA guidelines or Swiss AGLA recommendations.

The comparison between 516 adults taking statins before hospitalization for first ACS to the 843 adults with an indication for immediate statins in primary prevention but without use is shown in Table 3. Smoking was associated with lower odds of taking statins when primary prevention guidelines would recommend them (OR 0.69, 95% CI 0.55–0.87). Already taking an anti-hypertensive medication was strongly associated with taking statins (OR 3.36, 95% CI 2.67–4.22), while having a family history of premature CVD was of borderline significance (OR 1.28, 95% CI 1.00–1.65).

Discussion

In this large study of adults without previous CVD, only 37% of those presenting with their first ACS were classified as high-risk at the time of their event by ESC guidelines (with a 10-year risk of cardiovascular mortality ≥5% or diabetes). Further, only 16% were taking statins, including only 20% of those classified as high-risk by ESC guidelines. Comparison of those currently on statins and those who were eligible but not taking statins showed that current smoking was negatively associated with statin use.

With only 37% identified as high-risk using the SCORE calculator, a large portion of adults presenting with first ACS are potentially missed by targeted strategies for primary prevention. This result was not significantly improved using the ASCVD or PROCAM calculators. Other cohorts have shown similarly poor performance of CVD risk calculators among ACS patients without previous CVD, particularly among young STEMI patients (Collins and Altman, 2010; Mortensen et al., 2013). A smaller cohort from Denmark of adults presenting with a first MI obtained similar results, with the SCORE calculator identifying 148 of 393 (38%) as high-risk (5-year risk ≥5%) (Mortensen et al., 2013). A large British study found that the recommended QRISK2 calculator could identify 40% of those with first cardiovascular events as high-risk in men, but only 26% of women with CV events, again similar to our findings with the SCORE calculator (Collins and Altman, 2010).

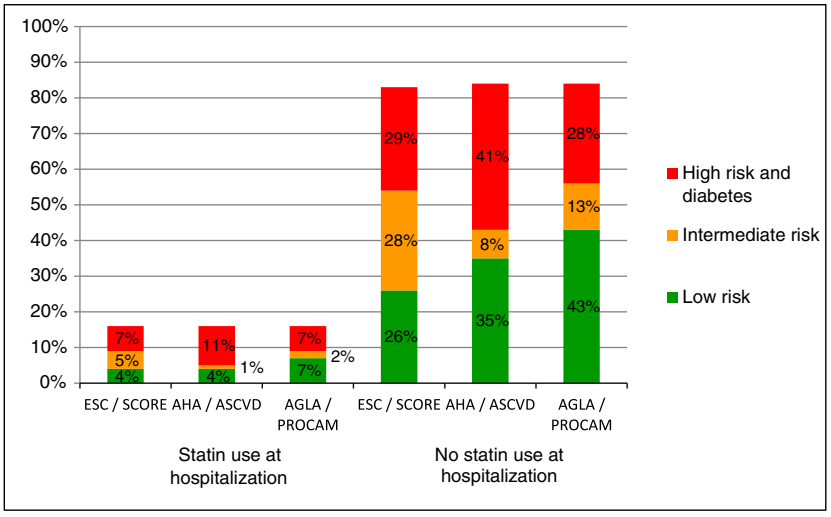

Fig. 1. Cardiovascular risk classification at the time of hospitalization for ACS among adults without a history of CVD, stratified by guidelines (n = 3172). ESC: European Society of Cardiology. SCORE: Systemic COronary Risk Evaluation. AHA: American Heart Association. ASCVD: AtheroSclerotic CardioVascular Disease risk score. AGLA: Swiss Atherosclerosis Working Group. PROCAM: Munster Heart Study risk score.

Table 2
Eligibility for statins before an acute coronary syndrome using the European Society of Cardiology (ESC) guidelines (n = 3172).

Risk level with SCORE calculator	Taking statins at baseline	Not at target LDL, per ESC	Eligible but not using statins	Consider statin therapy	No indication for statins
Low (<1%) (n = 976)	136 (14%)	0 (0%)	0 (0%)	0 (0%)	840 (86%)
Intermediate (≥1% to <5%) (n = 1025)	144 (14%)	645 (63%)	0 (0%)	753 (73%)	128 (12%)
High (≥5% and/or diabetes) (n = 1171)	236 (20%)	1002 (86%)	845 (72%)	90 (8%)	0 (0%)
Total (n = 3172)	516 (16%)	1647 (52%)	845 (27%)	843 (27%)	968 (31%)

SCORE: Systematic COronary Risk Evaluation.

Taken together, these results remind us of the limits to the discriminatory power of existing risk calculators, and suggest that our results can be applied to other countries. The prevention paradox is frequently invoked to explain the fact that the majority of adults who experience cardiovascular events are seen as low risk based on clinical risk factors (Weinberg, 1993); because low and intermediate individuals make up the vast majority of the population, even if they have a low event rate they will end up being the majority of adults presenting with clinical CVD. Hence, to continue downward trends in the incidence of CVD, population-based strategies are needed. Nonetheless, further research should seek to improve risk stratification in order to improve the accuracy of targeted prevention strategies (Polonsky and Greenland, 2012).

Overall, 16% were using statins before hospitalization for ACS. Similar results have been reported in patients with STEMI in the US (Miedema et al., 2012). The authors of that study attributed the low statin usage to the poor performance of complex targeted strategies and risk scores in younger populations. However that study was limited by the lack of baseline laboratory values, preventing calculation of risk scores. We found that among adults identified as high-risk based on cardiovascular risk scores, with either a 10-year risk of mortality over 5% or diabetes, only 20% were taking statins. Thus, even among adults with a high burden of traditional risk factors, statins were not being taken prior to a first ACS. Among adults at intermediate risk (a 5-year risk of CV mortality between 1 and 5%), 14% were taking statins and 73% could consider statins after efforts to improve diet and exercise. It is important to note that with the mean LDL level in those not taking statins at 3.5 mmol/L, it is critical that other risk factors be incorporated to determine the global risk and statin eligibility (Perk et al., 2012).

For further comparison, a recent population-based Swiss cohort of healthy adults without CVD found that 8.3% were taking statins, compared to a further 13.5% who were statin-eligible according to ESC guidelines, all of whom were at high-risk (Nanchen et al., 2009). That study had a much younger population and 54% women, however it supports our finding that full implementation of ESC guidelines could significantly improve coverage of high-risk adults in Switzerland. While full coverage with statins would not reduce the risk of treated patients to zero, it has been shown to significantly decrease the risk of ACS in primary prevention (Cholesterol Treatment Trialists et al., 2012).

When exploring factors associated underuse of statins among adults eligible for statins who were not receiving therapy, we found that smokers were less likely to be taking statins, whereas those taking anti-hypertensives were more likely to be taking statins. Other studies have similarly found that former smokers are particularly adherent to statin therapy while smokers have lower rates of long-term statin use, possibly due to multiple confounders such as socioeconomic status (Halava et al., 2014; Warren et al., 2013). Conversely, because current smoking is a strong cardiovascular risk factor, current smokers are more likely to have a statin indication. Thus, our exploration of factors

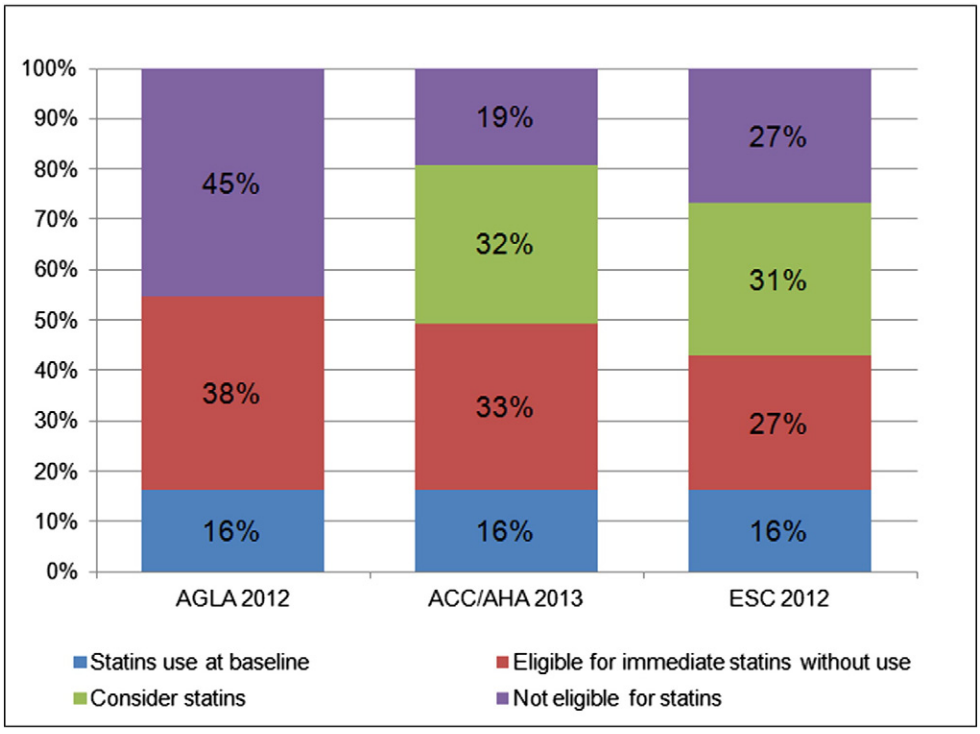

Fig. 2. Eligibility for statins before hospitalization in adults presenting with first acute coronary syndrome, stratified by guidelines (n = 3172). ESC: European Society of Cardiology. ACC: American College of Cardiology. AHA: American Heart Association. AGLA: Swiss Atherosclerosis Working Group.

Table 3
Clinical factors associated with compliance to guidelines for statin use in primary prevention (n = 1361).

	Currently on statins (n = 516)	Eligible but not on statins (n = 845)	OR (95% CI)
Age, years	64.8 ± 12	64.1 ± 11	1.00 (1.00–1.01)
Female	113 (22%)	182 (22%)	1.02 (0.80–1.41)
Education, post-secondary	102 (24%)	210 (28%)	0.82 (0.62–1.08)
More than 2 alcoholic beverages per week	173 (39%)	285 (37%)	1.06 (0.83–1.35)
Current smoker relative to never and former smokers	167 (32%)	345 (41%)	0.69 (0.55–0.87)
BMI ≥ 30	167 (25%)	205 (25%)	1.00 (0.78–1.30)
Diabetes	143 (28%)	267 (32%)	0.83 (0.65–1.06)
Hypertension	394 (76%)	478 (57%)	2.48 (1.94–3.17)
Taking anti-hypertensive drugs	339 (66%)	307 (36%)	3.36 (2.67–4.22)
Family history of premature CVD	140 (27%)	190 (22%)	1.28 (1.00–1.65)

Results are provided as mean ± standard deviation, as number of participants (percentage) or as odds ratio and (95% confidence interval). Statistical analysis using Student's t-test, Chi-square or logistic regression.

associated with optimal statin use requires validation through the analysis of other primary prevention cohorts.

Limitations

Measurements of lipids and blood pressure were taken during the hospital admission for ACS; as a result they could be modified during the acute phase and may not be the same as lipid levels prior to hospitalization when treatment decisions were made (Pitt et al., 2008; Burnier, 2012). However, exclusion of the small number of participants presenting 24 h or more after the onset of their symptoms and those with acute heart failure did not have a significant impact on the results. Medication use was based on patient reporting rather than physician records (Staroselsky et al., 2008). Also, as the use of statins lowers the risk score of treated adults, those taking statins could increase the number of participants classified as low risk. However, the exclusion of those taking statins at the time of hospitalization did not have a significant effect on the distribution of participants between risk categories. Finally, while patients taking statins at the time of hospitalization had proportionally fewer STEMIs, this was likely due to confounding by indication (McManus et al., 2011); that those taking statins were also older and more likely to have hypertension and diabetes.

Conclusion

In conclusion, few adults presenting with first ACS were taking statins at the time of hospitalization, including only 20% of high-risk adults identified by cardiovascular risk scores. Efforts should be made to improve the identification of adults at highest risk for acute coronary syndromes and improve uptake of statins for primary prevention among those identified as high risk by the current SCORE calculator.

Conflicts of interest statement

RK received lecture fees from EliLilly, Servier and Bayer. FM has received research grants to the institution from Amgen, AstraZeneca, Boston Scientific, Biotronik, Medtronic, MSD, EliLilly and St. Jude Medical including speaker or consultant fees. SW has received research grants to the institution from Abbott, Biotronik, Boston Scientific, Edwards Lifesciences, Medtronic, Medicines Company and St Jude, and speaker fees from Astra Zeneca, Eli Lilly, Abbott, Biotronik, Boston Scientific, Bayer and Biosensors. TFL received research grants to the institution from AstraZeneca, Bayer, Biosensors, Biotronik, Boston Scientific, Daichi Sankyo, Eli Lilly, Medtronic, MSD, Roche and Servier, including lecture fees. CMM received research grants to the institution from EliLilly, AstraZeneca, Roche and MSD including speaker or consultant fees. All other authors have no conflict of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ypmed.2015.05.012.

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