



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 $\geq 5\%$ or diabetes); 1025 (32%) as intermediate risk (10-year risk $< 5\%$ but $\geq 1\%$); 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.

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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 $\geq 50\%$ 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 dipyridamole/acetylsalicylic 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 ($LDL = \text{total cholesterol} - HDL - (\text{triglycerides} / 2.2)$). 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 \pm standard deviations (SDs) or medians with interquartile ranges (IQR) were used when appropriate. For our primary analysis a 10-year risk of fatal CVD $\geq 5\%$ 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 $\geq 5\%$) 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

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