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FULL RESEARCH PAPER

Eligibility for PCSK9 inhibitors based on the 2019 ESC/EAS and 2018 ACC/AHA guidelines

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Aims The 2018 American College of Cardiology (ACC)/American Heart Association (AHA) and 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) lipid guidelines recently updated their recommendations regarding proprotein convertase subtilisin/kexin-9 inhibitors (PCSK9i). We assessed the potential eligibility for PCSK9i according to the new guidelines in patients with acute coronary syndromes.

Methods and results We analysed a contemporary, prospective Swiss cohort of patients hospitalised for acute coronary syndromes. We modelled a statin intensification effect and an incremental ezetimibe effect on low-density lipoprotein-cholesterol levels among patients who were not on high-intensity statins or ezetimibe. One year after the index acute coronary syndrome event, treatment eligibility for PCSK9i was defined as low-density lipoprotein-cholesterol of 1.4 mmol/l or greater according to ESC/EAS guidelines. For ACC/AHA guidelines, treatment eligibility was defined as low-density lipoprotein-cholesterol of 1.8 mmol/l or greater in the presence of very high-risk atherosclerotic cardiovascular disease, defined by multiple major atherosclerotic cardiovascular disease events and/or high-risk conditions. Of 2521 patients, 93.2% were treated with statins (53% high-intensity statins) and 7.3% with ezetimibe at 1 year, and 54.9% had very high-risk atherosclerotic cardiovascular disease. Low-density lipoprotein-cholesterol levels less than 1.8 mmol/l and less than 1.4 mmol/l at 1 year were observed in 37.5% and 15.7% of patients, respectively. After modelling the statin intensification and ezetimibe effects, these numbers increased to 76.1% and 49%, respectively. The proportion of patients eligible for PCSK9i was 51% according to ESC/EAS criteria versus 14% according to ACC/AHA criteria.

Conclusions In this analysis, the 2019 ESC/EAS guidelines rendered half of all post-acute coronary syndrome patients potentially eligible for PCSK9i treatment, as compared to a three-fold lower eligibility rate based on the 2018 ACC/AHA guidelines.

Keywords Lipids • secondary prevention • PCSK9 inhibitors • statins • ezetimibe

Introduction

Low-density lipoprotein (LDL) cholesterol is a key causal factor of atherosclerotic cardiovascular disease (ASCVD),[1] the leading cause of death worldwide.[2] Lowering of LDL-cholesterol with statins reduces the risk of ASCVD events in primary and secondary prevention.[3] However, a substantial proportion of patients do not achieve adequate reduction in LDL-cholesterol levels despite intensive statin

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treatment, cannot tolerate statins, or remain at high residual risk despite being on statin therapy.[4,5] For high-risk patients in whom statin therapy alone is insufficient, add-on treatment with non-statin medications, ezetimibe and proprotein convertase subtilisin/kexin-9 inhibitors (PCSK9i), is a valuable option.[6]

Following the positive results of cardiovascular outcomes trials of both alirocumab[7] and evolocumab,[8] the 2018 American College of Cardiology (ACC)/American Heart Association (AHA) cholesterol guidelines[9] and 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) dyslipidemia guidelines[10] updated their recommendations regarding the use of PCSK9i in patients with ASCVD. Both guidelines acknowledge the clinical value of intensive LDL-cholesterol lowering in the context of secondary prevention and advocate broader use of PCSK9i compared with earlier consensus documents;[11] however, there are marked differences with respect to risk thresholds and LDL-cholesterol criteria for the use of these medications. To date, the expected impact of these new guidelines on the use of PCSK9i in real-world practice remains largely unknown. Addressing this gap in evidence may have important implications in view of the high prevalence of ASCVD, substantial cholesterol-related residual risk, high cost and associated reimbursement barriers to PCSK9i treatment.

This study sought to evaluate the potential eligibility for PCSK9i according to the recent European versus American guidelines in a contemporary cohort of patients with acute coronary syndromes (ACS) treated by current standards.

Methods

Study population

This analysis was performed within the ELIPS study (NCT01075867), a prospective, multicentre observational cohort study of consecutive ACS patients that aims to assess the quality of care and adherence to recommended preventive treatments at four academic centres in Switzerland.[12,13] In the present analysis we included all ACS patients who were enrolled between 1 January 2009 and 31 December 2017, were alive and had available data on LDL-cholesterol values and lipid-lowering therapies 1 year after the index ACS event. Inclusion criteria were age 18 years and older and index diagnosis of ST-segment elevation myocardial infarction (STEMI), non ST-segment elevation myocardial infarction (NSTEMI) or unstable angina. Exclusion criteria were severe physical disability or dementia, and estimated life expectancy of less than 1 year for non-cardiac reasons. The protocol was approved by local ethical committees, and all patients provided written informed consent.

Plasma lipid measurements and clinical follow-up

At baseline (i.e. during hospitalisation for the index ACS event), plasma levels of total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured from the first available fasting sample within 24 hours of hospital admission. LDL-cholesterol was calculated using the Friedewald equation when triglycerides were less than 4.5 mmol/l. Fasting lipid levels were measured at the scheduled follow-up visit after 1 year. Medical treatment was recorded at baseline (i.e. patient-reported treatment prior to the index ACS event), at discharge after hospitalisation and after 1 year. The intensity of statin therapy was classified as low, moderate or high according to current definitions[9,10] (Supplementary *Table 1*). Physicians were encouraged to prescribe guideline-directed statin treatment at discharge; that is, high-intensity statins except for patients in whom such regimens were not deemed appropriate (e.g. due to a history of intolerance, patient characteristics or concomitant medications that increased the risk of developing statin-related adverse events). Treating physicians were encouraged not to discontinue or change to a lower-intensity statin regimen during the follow-up period, unless clinically indicated. Patients were systematically followed throughout 1 year to assess adverse cardiac and cerebrovascular events, and clinical endpoints were adjudicated by a panel of independent experts.

Eligibility for PCSK9i

Eligibility for PCSK9i treatment was assessed at 1 year after the index ACS event. Treatment eligibility (Supplementary *Table 2*) was defined according to the ESC/EAS criteria[10] based solely on LDL-cholesterol levels; that is LDL-cholesterol 1.4 mmol/l or greater (55 mg/dl) while on maximally tolerated statin in combination with ezetimibe. Eligibility according to ACC/AHA criteria[9] was based on a combination of LDL-cholesterol levels and clinical criteria; that is, LDL-cholesterol 1.8 mmol/l or greater (70 mg/dl) while on maximally tolerated statin and ezetimibe treatment in patients with very high-risk ASCVD, defined by a combination of multiple major ASCVD events and/or multiple high-risk conditions (Supplementary *Figure 1*). Major ASCVD events included the index ACS event (all patients by definition), and in addition, reported events prior to baseline assessment (history of myocardial infarction (MI), history of stroke, history of peripheral arterial disease) as well as adjudicated events that occurred during 1-year follow-up after the index ACS event (non-fatal MI or cerebrovascular event) (Supplementary *Figure 1*).

Because not all patients were on high-intensity statins at 1 year, and similar to previous analyses,[14,15] for both guideline criteria we modelled a statin intensification effect based on the average LDL-cholesterol-lowering potency of statins. This included modelling a 50% reduction on the observed LDL-cholesterol levels in all patients who were on no statin treatment, and a 20% reduction in patients who were on low or moderate-intensity statin treatment at 1 year.[10,16] In addition, we modelled the effect of ezetimibe by applying an incremental 24% reduction on LDL-cholesterol levels[17] (either on the observed levels in patients on high-intensity statins, or on levels after modelling of the statin intensification effect, if applicable) in all patients who were not receiving ezetimibe.

Study assessments

The study's primary objective was to assess the proportion of patients meeting the criteria for PCSK9i treatment 1 year after the index ACS event according to the ESC/EAS versus ACC/AHA guidelines.[9,10] We compared treatment eligibility after modelling the effect of high-intensity statins as well as ezetimibe in patients who were not on such treatment at 1 year. In ancillary analyses, we assessed treatment eligibility based on the observed LDL-cholesterol values (i.e. without any modelling); and after modelling only the statin intensification effect or only the ezetimibe effect in patients not receiving the respective treatment at 1 year.

Statistical analyses

Continuous variables are summarised as mean (standard deviation), categorical variables as actual numbers and percentages. Baseline characteristics, medications and plasma lipid levels were compared using Fisher's test for binary variables, chi-square test for more than two categories, or unpaired *t*-tests for continuous variables. All analyses were conducted using Stata version 16.1 (Stata Corporation, College Station, TX, USA) and R version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). The statistical significance was set at the 0.05 level.

Results

Patients

Out of 3762 patients hospitalised for ACS between 2009 and 2017, 97 died within 1-year follow-up, 1142 had missing data for calculated LDL-cholesterol levels and two for statin therapy, yielding a final sample of 2521 patients for the present analysis (Supplementary *Figure 2*). The baseline characteristics are summarised in *Table 1*. Mean age was 61.7±11.9 years, 80.7% of patients were men, 14.8% had diabetes mellitus and 12.2% had a history of previous MI. Most patients were hospitalised for STEMI (54.8%), and 92.7% were treated for the index ACS event by means of percutaneous coronary intervention.

Lipid-lowering medications

The use of statins was 25.4% at baseline, 98.5% at discharge and 93.2% at 1-year follow-up. The proportion of patients receiving high, moderate and low-intensity statin treatment at discharge was 62.1%, 35.6% and 0.8%, respectively; the proportions at 1-year follow-up were 53%, 38.2% and 1.9% (Supplementary *Table 3*). Ezetimibe was used by 2.5% of patients at discharge and 7.3% of patients at one year.

Lipid levels at 1 year

Mean LDL-cholesterol levels decreased from 3.27±1.10 mmol/l at baseline to 2.16±0.87 mmol/l at 1 year. The proportion of patients with LDL-cholesterol less than 1.8 mmol/l and less than 1.4 mmol/l at 1 year was 37.5% versus 15.7%, respectively; 549 patients (21.8%) had LDL-cholesterol levels between 1.4 and 1.8 mmol/l (Supplementary *Table 4*). After modelling the effect of high-intensity statins, 48.9% of patients had LDL-cholesterol levels less than 1.8 mmol/l and 24% had LDL-cholesterol levels less than 1.4 mmol/l. After additional modelling of the ezetimibe effect, where applicable,

Table 1 Baseline characteristics of patients.

Characteristics	All patients	Eligibility for PCSK9 inhibitor at 1 year according to guidelines	
		ESC/EAS	ACC/AHA
Number of patients	2521	1286	354
Age (years)	61.7 (11.9)	60.3 (11.6)	63.0 (11.8)
Women	486 (19.3%)	265 (20.6%)	88 (24.9%)
Premature coronary artery disease[a]	832 (33.0%)	473 (36.8%)	103 (29.1%)
Cardiovascular risk factors			
Diabetes mellitus	372 (14.8%)	147 (11.4%)	67 (18.9%)
Arterial hypertension	1274 (50.6%)	636 (49.5%)	240 (67.8%)
Current smoker	1008 (40.0%)	567 (44.1%)	148 (41.8%)
Family history of coronary artery disease	687 (27.3%)	364 (28.4%)	108 (30.7%)
Previous myocardial infarction	307 (12.2%)	190 (14.8%)	104 (29.5%)
Previous PCI	348 (13.8%)	208 (16.2%)	116 (32.8%)
Previous CABG	80 (3.2%)	49 (3.8%)	22 (6.2%)
Peripheral arterial disease	104 (4.1%)	49 (3.8%)	26 (7.3%)
History of stroke/TIA	87 (3.5%)	38 (3.0%)	19 (5.4%)
Renal dysfunction[b]	277 (11.2%)	128 (10.1%)	52 (15.1%)
Familial hypercholesterolemia			
Possible	488 (22.2%)	319 (29.1%)	83 (28.2%)
Probable	69 (3.1%)	61 (5.6%)	41 (13.9%)
Definite	9 (0.4%)	9 (0.8%)	6 (2.0%)
Statin treatment at baseline	639 (25.4%)	376 (29.3%)	171 (48.3%)
Type of index acute coronary syndrome			
Unstable angina	99 (3.9%)	55 (4.3%)	16 (4.5%)
NSTEMI	1040 (41.3%)	522 (40.6%)	171 (48.3%)
STEMI	1381 (54.8%)	708 (55.1%)	167 (47.2%)
Treatment of index event			
PCI	2338 (92.7%)	1181 (91.8%)	316 (89.3%)
CABG	8 (0.3%)	6 (0.5%)	1 (0.3%)
Medical therapy	175 (6.9%)	99 (7.7%)	37 (10.5%)

PCSK9: proprotein convertase subtilisin/kexin-9; ACC: American College of Cardiology; AHA: American Heart Association; ESC: European Society of Cardiology; EAS: European Atherosclerosis Society; STEMI: ST-segment elevation myocardial infarction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass grafting; TIA: transient ischaemic attack.
Data are presented as number (%) or mean (standard deviation).
[a]Age under 55 years for men and under 60 years for women at baseline.
[b]Estimated glomerular filtration rate less than 60 ml/min/1.73m^2.

76.1% of patients had LDL-cholesterol less than 1.8 mmol/l and 49% of patients had LDL-cholesterol less than 1.4 mmol/l (*Figure 1(a)*). *Figure 1(b)* shows the distribution of LDL-cholesterol levels at 1 year, indicating observed levels as well as levels after modelling the statin intensification and ezetimibe effects.

Eligibility for PCSK9i at 1 year

At 1 year, 51% of all patients ($n = 1286$) would be eligible for treatment with a PCSK9i according to ESC/EAS guidelines based on a modelled LDL-cholesterol level of 1.4 mmol/l or greater on high-intensity statins and ezetimibe (*Figure 1(a)*).

Regarding ACC/AHA eligibility criteria, 1384 patients (54.9%) met the criteria of very high-risk ASCVD at 1 year: 511 (20.3%) had multiple ASCVD events, 1297 (51.4%) had one major ASCVD event and multiple high-risk conditions and 424 (16.8%) had a combination of both features (mutually non-exclusive conditions; *Figure 2(a)*). After modelling the high-intensity statin and ezetimibe effects, the proportion of patients who had very high-risk ASCVD and LDL-cholesterol of 1.8 mmol/l or greater at 1 year and would thereby be eligible for PCSK9i according to ACC/AHA criteria was 14% ($n = 354$). The respective number was 997 patients (39.5%) without modelling the statin-intensification and ezetimibe effects; 779 (30.9%) after modelling only the statin intensification effect; and 548 (21.7%) after modelling only the ezetimibe effect.

Comparing the two guidelines, all 354 patients eligible by ACC/AHA criteria were also eligible for the ESC/EAS criteria, and in addition 932 patients were eligible only by ESC/EAS criteria. There were no patients meeting only ACC/AHA criteria but not the ESC/EAS criteria. The results are summarised in the Venn diagram in *Figure 2(b)*.

Discussion

To our knowledge, this is the first study comparing the expected impact of the recent European and American lipid guidelines on the

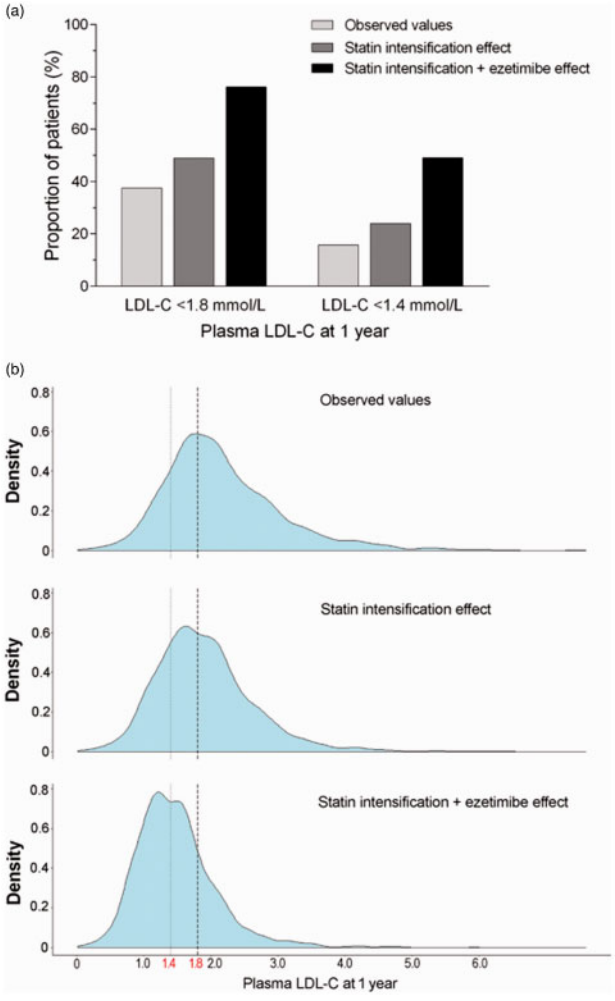

Figure 1 (a) Proportion of patients with plasma low-density lipoprotein (LDL) cholesterol levels less than 1.8 mmol/l (<70 mg/dl) and less than 1.4 mmol/l (<55 mg/dl) at 1 year. (b) Distribution of LDL-cholesterol levels at 1 year. Shown are observed LDL-cholesterol levels at 1 year (upper graph), as well as levels after modelling a statin intensification effect (middle graph) and an incremental ezetimibe effect (lower graph).

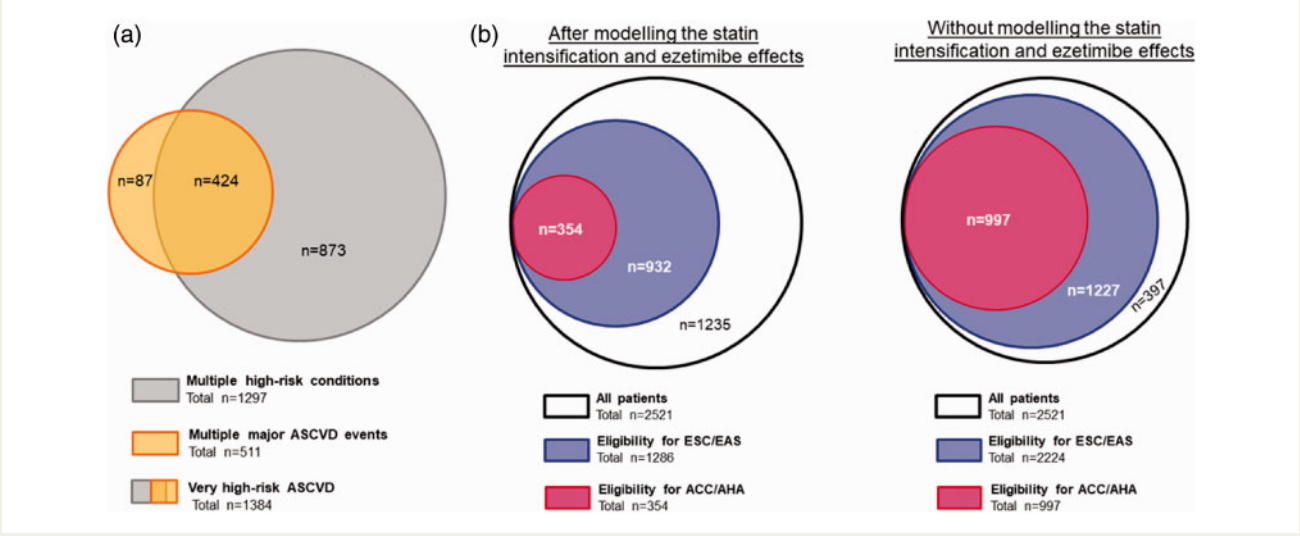

Figure 2. (a) Venn diagram showing the number of patients with multiple major atherosclerotic cardiovascular disease (ASCVD) events, multiple high-risk conditions and overall patients with very high-risk ASCVD at 1 year according to the American College of Cardiology (ACC)/American Heart Association (AHA) definition. (b) Venn diagram showing the number of patients eligible for proprotein convertase subtilisin/kexin-9 inhibitor (PCSK9i) treatment at 1 year according to the European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) and ACC/AHA guidelines after modelling (left) and without modelling (right) the statin intensification and ezetimibe effects.

proportion of secondary prevention patients considered potentially eligible for treatment with PCSK9i in real-world practice. In this large, prospective cohort of ACS patients receiving contemporary treatment, the 2019 ESC/EAS guidelines were found to be far more liberal, rendering half of all post-ACS patients eligible for PCSK9i despite optimised oral lipid-lowering therapy, as compared to one of seven patients according to 2018 ACC/AHA criteria. Only a few patients were on ezetimibe treatment 1 year after the index ACS event; modelling the incremental effect of ezetimibe on top of optimised statin therapy reduced the number of PCSK9i-eligible patients substantially – a relative reduction by one-third for ESC/EAS criteria and about 50% for ACC/AHA criteria. These findings provide novel insights regarding the eligibility patterns for PCSK9i treatment in clinical practice and may be informative for clinicians, payers and health systems in defining the appropriate use and value of lipid-lowering therapies in patients with ASCVD.

PCSK9 monoclonal antibodies decrease LDL-cholesterol levels by about 60% on top of statins and significantly reduce the risk of MI, stroke and coronary revascularisation, while maintaining a favourable safety profile.[7,8,18] Although the recent guidelines[9,10] are based on the same evidence of randomised clinical trials of PCSK9i, they provide distinctly different answers to the question of which patients should receive these medications. First, the addition of a PCSK9i on top of maximally tolerated statins and ezetimibe is recommended for all secondary prevention patients with LDL-cholesterol levels above a certain threshold in the European guidelines versus only for patients with the combination of elevated LDL-cholesterol levels and certain very high-risk clinical characteristics according to the American guidelines. Second, the ACC/AHA document is more conservative regarding the LDL-cholesterol threshold compared with the lower threshold in the ESC/EAS guidelines. Notably, about one in five patients had LDL-cholesterol levels between 1.4 and 1.8 mmol/l at 1 year in this study. Third, for the given criteria, the ESC/EAS guidelines recommend using PCSK9i with a class I indication ('is recommended') as opposed to a class IIa indication ('is reasonable') for the ACC/AHA guidelines. While the American approach is by definition more restrictive (even if only the LDL-cholesterol thresholds were to be considered), this study provides novel quantitative evidence indicating that the differing recommendations translate into three-fold more post-ACS patients fulfilling the ESC/EAS eligibility criteria compared with those meeting the ACC/AHA criteria for PCSK9i treatment.

A key finding of this study is that eligibility rates according to both guidelines fell more markedly when modelling the incremental effect of ezetimibe than with the modelled intensification of statin treatment (*Figure 1*). The eligibility rate of almost 85% by ESC/EAS criteria based on the observed LDL-cholesterol levels at 1 year fell to about 75% with statin intensification and to 51% with the additional ezetimibe effect. For ACC/AHA criteria, the respective figures were about 40%, 31% and 14%. These findings are likely linked to two factors: first, the relatively greater incremental LDL-cholesterol-lowering effect of adding ezetimibe compared with increasing statin dose (about 6% LDL-cholesterol reduction per doubling of statin dose);[16] and second, the very small numbers of patients (7.5% of all) who were receiving ezetimibe at 1 year as compared to the much larger number of patients (more than half) taking a high-intensity statin. Other contemporary studies also point to the very low uptake of ezetimibe in patients with ASCVD.[19,20] Taken together, these findings indicate that the broader use of ezetimibe – a safe, low-cost, generically available drug – may enable many patients attain (or get closer to) currently recommended treatment goals.

While PCSK9i improve clinical prognosis in secondary prevention, high market prices have limited their widespread adoption. As

previously experienced with statins,[21] evidence of clinical benefit along with population-based estimations of treatment eligibility is required to assess whether healthcare savings accrued from the reduction of cardiovascular events might counterbalance treatment costs. A recent analysis applying current ACC/AHA guideline criteria in a US cohort of patients with very high-risk ASCVD found that at its current list price (reduced in October 2018 in the US) evolocumab added to standard background therapy met accepted cost-effectiveness thresholds across a range of risk profiles.[22] The present study provides new insights on treatment eligibility that will be useful to inform cost-effectiveness analyses according to transatlantic guideline criteria, also taking into account different drug prices and reimbursement policies in different countries.

Limitations

This study has several limitations. As we included patients with ACS known to be at particularly high risk of recurrent ischaemic events, our findings may not be directly generalisable to patients with more stable clinical manifestations of ASCVD or patients in primary prevention. While there is substantial inter-individual variability in treatment responses to LDL-cholesterol-lowering therapies,[23] we used assumptions of average responses to statins and ezetimibe – an approach also applied in previous similar analyses.[14,15,24] The number of candidates for PCSK9i is likely to be underestimated in our main analyses that assumed 100% tolerability of high-intensity statins, a limitation common to all similar studies.[14,15,24] The present findings from a high-income European country may not be directly applicable to other countries with different ethnicity and socioeconomic environments. Although ACC/AHA guideline criteria are based on either LDL-cholesterol or non-HDL-cholesterol cut-offs, only LDL-cholesterol levels were used in the present analysis. Finally, it should be noted that potential eligibility according to any of the guidelines would not necessarily result in the prescription of PCSK9i in clinical practice for several reasons including individual patient preferences, reimbursement barriers, possible contraindications, or LDL-cholesterol levels only slightly exceeding the respective eligibility thresholds.

Author contribution

KCK contributed to the conception and design of the work. BG, DN, DC, RK, MRB, SC, OM, CMM, NR, MW, LR and FM contributed to the acquisition and interpretation of data for the work. MB and DH contributed to the analysis of data for the work. KCK drafted the manuscript. SW, TFL, MW and LR critically revised the manuscript. All authors gave final approval and agree to be accountable for all aspects of the work ensuring integrity and accuracy.

Declaration of conflicting interests

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Supplemental material

Supplemental material for this article is available online.

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