ESC European Society of Cardiology

European Heart Journal - Quality of Care and Clinical Outcomes (2019) **5**, 225–232
doi:10.1093/ehjqcco/qcy058

ORIGINAL ARTICLE

Cardiovascular event rates in a high atherosclerotic cardiovascular disease risk population: estimates from Swedish population-based register data

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Received 2 October 2018; revised 13 December 2018; editorial decision 19 December 2018; accepted 7 January 2019; online publish-ahead-of-print 12 January 2019

Aims This study aimed to estimate the rate of cardiovascular (CV) events in the real world in patients at high risk of recurrent CV events similar to the FOURIER trial population.

Methods and results A retrospective population-based cohort study was conducted using Swedish national registers from 1 July 2001 to 31 December 2015. Patients in the atherosclerotic cardiovascular disease (ASCVD) prevalent cohort met the FOURIER-like inclusion criteria, including treatment with high/moderate-intensity statins, on 1 July 2006. Additionally, two cohorts defined by diagnosis of incident ischaemic stroke (IS) and incident myocardial infarction (MI), meeting the FOURIER-like inclusion criteria were followed from date of diagnosis. Event rates were calculated for the hard major adverse cardiovascular events (MACE) composite: MI, IS, and CV death; and the ASCVD composite: MI, IS, unstable angina, coronary revascularization, and CV death. Approximately half of patients experienced a CV event (ASCVD composite) during follow-up. The MACE composite rates/100 person-years were 6.3, 11.9, and 12.3 in the ASCVD prevalent ($n = 54\,992$), MI incident ($n = 45\,895$), and IS incident ($n = 36\,134$) cohorts, respectively. The ASCVD composite rates/100 person-years were 7.0, 21.7, and 12.9 in the ASCVD prevalent, MI incident, and IS incident cohorts, respectively. The multiple-event MACE composite rates/100 person-years were 8.5 (ASCVD prevalent cohort), 15.4 (MI incident cohort), and 14.4 (IS incident cohort).

Conclusion In this real-world setting, CV event rates were high in all studied cohorts. In particular, the MACE composite rates were two to three times higher than in the FOURIER clinical trial, indicating a substantial disease burden despite treatment with moderate or high-intensity statins.

Keywords Cardiovascular outcomes • Cardiovascular event rates • Secondary prevention • ASCVD

Introduction

Cardiovascular disease (CVD) is the number one cause of death worldwide, accounting for nearly 18 million of global deaths in 2013, of which approximately 7.4 million were related to coronary heart disease (CHD) and 6.7 million were due to stroke.[1,2] Cardiovascular disease burden is rapidly growing due to the increase of major risk factors such as obesity, hypertension, and

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Type 2 diabetes.[3,4] The global economic burden of CVD, including cost of screening, primary prevention, secondary prevention, acute hospital care, and lost productivity, is anticipated to reach 1044 billion US dollar in 2030.[5]

Patients at high-risk of experiencing cardiovascular (CV) events are defined as those with CHD, or other forms of arteriosclerotic disease, diabetes, and multiple risk factors that confer a 10-year risk for CHD >20% (estimated by Framingham risk scores).[6] Elevated levels of low-density lipoprotein cholesterol (LDL-C) has been shown to be a key risk factor of CVD and the treatment of hypercholesterolaemia represents an important strategy to reduce new CV events as well as mortality.[7] The evidence to support the effectiveness of statin therapy in secondary prevention is well proven, where high-risk patients are recommended more intensive statin regimens.[8–11] Recent meta-analyses of data from clinical trials evaluating therapies specifically designed to lower LDL-C, including statins, ezetimibe, and PCSK9 inhibitors, have shown that reducing LDL-C reduces the risk of CV events proportional to the absolute achieved reduction in LDL-C.[12,13]

Established CVD is associated with a higher risk for recurrent CV events following the first event.[14–16] The majority of data informing CV-specific event rates in patients with existing CVD is derived from clinical trial populations. While such data is informative, clinical trials may underestimate event rates for a variety of reasons including disproportionate recruitment from high performing academic centres, higher quality of care received by clinical trial participants, or potential patient selection bias.[17,18] Given the large number of patients who are living with CVD, there is a need to evaluate the CV risk of this patient-group outside of large clinical trials. Further, the availability and future emergence of highly potent therapies that may have clinical value in this population make development of a predictive model in this Subgroup of patients of clinical value. The study 'Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk' (FOURIER) was a double-blinded, randomized, placebo-controlled, multicentre study assessing the impact of additional LDL-C reduction on major CV events when evolocumab is used in combination with statin therapy in patients with clinically evident CVD.[19] The current study aimed to address current gaps in the existing literature by estimating the rate of CV events in the real world among patients meeting FOURIER-like population criteria.

Methods

Study design

A retrospective population-based cohort study was conducted using Swedish national-based population registers. The study included adult patients, 40–85 years of age, at high risk of CV events receiving statin therapy who were followed for the occurrence of subsequent CV events. The study period ranged from 1 January 2001 to 31 December 2015. Patients were followed until either CV event, death, or end of the study period.

Data sources

Patient-level data from the (i) National Patient Register, (ii) Cause of Death Register, and (iii) Prescription Drug Register, were linked together by the Swedish National Board of Health and Welfare using unique personal identifiers.[20–23] The three national registers are mandatory to report to and are associated with a high degree of completeness.[20,21] Therefore, the registers enable complete nation-wide coverage of the Swedish population. The Prescription Drug Register includes data on all prescriptions filled at pharmacies, including drug type, dispensing date, dose and pack size. Information on diagnoses, hospitalizations, surgical and non-surgical procedures, and outpatient specialist visits were collected from the National Patient Register for the complete observable period for each patient. The Cause of Death Register provided confirmed dates of death together with cause of death, allowing for removing patients from the analyses when they were no longer under observation and for identifying deaths as either CV-related or non-CV-related. Ethical approval was obtained from the regional ethical review board in Stockholm on 3 March 2016; reference number 2016/456-31/2. Individual patient informed consent is not required for register studies on retrospective data in Sweden and was therefore not collected.

Patient population

Three study cohorts were identified and followed separately for outcomes; (i) the atherosclerotic cardiovascular disease (ASCVD) prevalent cohort which included patients with myocardial infarction (MI), ischaemic stroke (IS), or peripheral artery disease (PAD) who met the FOURIER-like criteria as of 1 July 2006 (index date); (ii) the MI incident cohort which included patients with an incident MI who met the FOURIER-like criteria at the time of the MI event (variable index dates from 1 July 2006 to 31 December 2014); (iii) the IS incident cohort which included patients with an incident IS who met the FOURIER-like criteria at the time of the IS event (variable index dates from 1 July 2006 to 31 December 2014).

The three study cohorts were identified in the Swedish dataset by applying the FOURIER-like inclusion criteria within a real-world clinical practice setting. All three cohorts needed to fulfil the FOURIER-like criteria at index date, including; age between 40 and 85 at index date; one or more (≥1) filled statin prescriptions of moderate and/or high-intensity during the 1-year period prior to the index date; at least one (≥1) major risk factor or two (≥2) minor risk factors, as defined in *Table 1*. Statin dose intensity was defined in accordance with the American College of Cardiology and the American Heart Association (ACC/AHA) guidelines for cholesterol treatment (*Table 2*).[7] While not included in the ACC/AHA guidelines, simvastatin 80 mg was defined as high-intensity based on its expected LDL-C reduction of nearly 50%.[24]

Patients were excluded if they had a new MI or IS event within 4 weeks after the index date, had a known history of haemorrhagic stroke, or were recipient of any major organ transplant. Data used in the FOURIER trial criteria, which were not available in Swedish registers included LDL-C, high-density lipoprotein cholesterol (HDL-C), triglycerides, smoking information, New York Heart Association (NYHA) class, and other lab data such as blood pressure, estimated glomerular filtration rate, and creatinine kinase levels.

The study cohorts were not mutually exclusive. Patients could thus be included in both the prevalent and an incident cohort. In addition, patients could be included in both incident cohorts if they had a MI and an IS during follow-up, if the FOURIER-like criteria were fulfilled at the time of the index event. Each new CV event during follow-up, i.e. each outcome event, was counted in the appropriate cohort.

Study outcomes

The study outcomes were composites of CV events occurring during follow-up. The hard major adverse cardiovascular events (MACE) composite was defined as MI, IS, or CV death; the ASCVD composite was defined as MI, IS, unstable angina (UA), coronary revascularization (coronary artery bypass grafting or percutaneous coronary intervention), or CV death. CV events were defined as hospitalizations with a primary ICD-10 diagnosis for the included outcome events: MI, UA, IS, or CV death, or as coronary revascularization using procedure codes.

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Table 1 Risk factors included in the FOURIER-like inclusion criteria

Major risk factors—one or more (≥1) required	Diabetes (Type 1 or Type 2)
	Age ≥65 years and ≤85 years at time of index date
	If qualifying with MI; the MI event occurred during 6 months prior to the index date, or the patient has a history of IS and/or PAD in the baseline period
	If qualifying with IS; the IS event occurred during 6 months prior to index date, or the patient has a history of MI and/or PAD in the baseline period
Minor risk factors—two or more (≥2) required	Coronary revascularization with no history of MI
	Coronary artery disease
	Metabolic syndrome

MI, myocardial infarction; IS, ischaemic stroke; PAD, peripheral artery disease.

Table 2 Statin dose intensity

Intensity	Statin type and strength for daily doses
Moderate-intensity statin	Fluvastatin 40 mg twice daily
	Fluvastatin XL 80 mg
	Lovastatin 40 mg
	Pravastatin 40 mg and 80 mg
	Simvastatin 20–40 mg
	Atorvastatin 10 mg and 20 mg
	Rosuvastatin 5 mg and 10 mg
	Pitavastatin 2–4 mg
High-intensity statin	Atorvastatin 40–80 mg
	Rosuvastatin 20 mg and 40 mg
	Simvastatin 80 mg

Demographics and clinical characteristics, including age at index, gender, follow-up time, diabetes, hypertension, medication use, Charlson comorbidity index, and history of CV, was assessed during the baseline period. CV history during baseline included MI, UA, IS, transient ischaemic attack (TIA), heart failure (HF), and coronary revascularization.

A minimum of 30 days was required between outcome events of the same type to be considered as separate events. If a MI or UA was followed by a coronary revascularization, a minimum of 30 days was required to have passed for the revascularization procedure to be considered as a separate event. CV death was defined as death from any CV-related cause (ICD-10-CM codes I00 to I78), or as death within 30 days of hospitalization due to a CV event. Non-CV death was defined as death from any other cause than CV-related one.

Statistical analysis

The baseline period was defined as the 5-year period prior to the index date and was used to observe demographic and clinical characteristics as well as the patient selection criteria. Statin-use was observed during the 1-year period prior to index date and patients were followed until either CV event, lost to follow-up, or end of study. Patient characteristics were assessed during the baseline period and presented as mean and standard deviation for continuous variables, and absolute numbers (*n*) or proportions (%) for categorical variables. Rates of incident CV events were calculated by dividing the number of first events by the person-years of follow-up until the event, death, or end of follow-up, expressed per 100 person-years. Cardiovascular event rates for multiple events were calculated as the total number of events divided by the total follow-up time, until either death or end of follow-up (31 December 2015).

All conditions in the register data were identified based on the ICD-10 coding system, which includes diagnoses, and the KVÅ coding system, which includes medical procedures. All data management and statistical analysis was performed using MySQL and Stata 14 (StataCorp LP, College Station, TX, USA).

Results

The number of patients meeting the study inclusion criteria was 54 992 for the ASCVD prevalent cohort, 45 895 for the MI incident cohort, and 36 134 for the IS incident cohort (*Table 3*). The overall high ASCVD risk study population had a mean age of >70 years, at least 60% were men, and the majority of all patients had hypertension. Few patients (3–10%) were receiving high-intensity statin therapy at baseline, while 25% of patients in the MI incident cohort and 11% of patients in the IS incident cohort received a high-intensity statin on the first filled prescription date following index event. Approximately half of patients (ASCVD prevalent cohort: 43.8%; MI incident cohort: 54.0%; IS incident cohort: 40.0%) experienced a CV event of either MI, UA, IS, coronary revascularization, or CV death, during a mean follow-up of 7.3 years, 3.9 years, and 3.7 years in the ASCVD prevalent cohort, the MI incident cohort, and the IS incident cohort, respectively (*Table 4*). A large proportion of patients had more than one (≥2) CV event during follow-up; the hard MACE composite: 13.8% (ASCVD prevalent cohort), 12.2% (MI incident cohort), 10.1% (IS incident cohort); the ASCVD composite: 16.1% (ASCVD prevalent cohort), 19.2% (MI incident cohort), and 10.9% (IS incident cohort). The most frequent CV event within both outcome composites was CV death (*Table 5*).

The largest proportion of patients experiencing an incident MI during follow-up was seen in the MI incident cohort. Similarly, the largest proportion of patients that had an incident IS during follow-up was seen in the IS incident cohort. The CV death rate per 100 person-years were 4.7, 5.3, and 7.2 in patients with one prior CV event (MI, UA, IS, TIA, coronary revascularization, HF) vs. 6.7, 8.7, and 8.0 in patients with two or more (≥2) prior events in the ASCVD prevalent, the MI incident and the IS incident cohort, respectively (*Table 6*). Cardiovascular event rates for incident events and multiple events are presented in *Table 7*. The rates of incident CV events per 100 person-years for the hard MACE composite were 6.3 (ASCVD prevalent cohort), 11.9 (MI incident cohort), and 12.3 (IS incident cohort). Within the ASCVD prevalent cohort, the hard MACE composite rate was found to be higher (7.3 per 100-person years) for the subgroup of patients with a diabetes mellitus (type 1 or 2) diagnosis, compared with the overall study cohort. The rates of incident CV events for the ASCVD composite were 7.0 (ASCVD prevalent cohort), 21.7 (MI incident cohort), and 12.9 (IS incident cohort). The

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Table 3 Patient characteristics at baseline

	ASCVD prevalent cohort ($n = 54\,992$)		MI incident cohort ($n = 45\,895$)		IS incident cohort ($n = 36\,134$)	
	Mean or proportion	SD or count	Mean or proportion	SD or count	Mean or proportion	SD or count
Age (years)	72.5	8.3	71.0	9.6	72.9	8.7
Gender, male (%)	63.2	34 754	66.9	30 704	60.1	21 719
CV history (%)						
History of MI	68.2	37 480	100[a]	45 895	14.7	5321
History of UA	17.9	9841	12.1	5546	5.3	1903
History of IS	34.6	19 024	8.7	3981	100[a]	36 134
History of HF	20.8	11 445	27.1	12 413	17.5	6331
History of TIA	5.1	2827	4.5	2052	11.2	4048
History of CABG/PCI	8.9	4884	21.4	9819	3.4	1230
Charlson comorbidity index	2.5	1.8	3.2	2.2	3.00	2.1
Follow-up length (years)	7.3	3.0	3.9	2.7	3.7	2.6
Diabetes (%)	36.4	20 014	42.9	19 699	39.1	14 140
Hypertension (%)	98.0	53 916	99.6	45 724	96.8	34 961
Chronic kidney disease (%)	2.6	1447	7.1	3261	4.9	1772
High-intensity statin at index (%)	3.3	1814	10.6	4847	7.7	2792
High-intensity statin as first filled prescription following index event (%)	—	—	25.1	11 516	10.9	3947
Anti-thrombotic medication (%)	48.1	26 438	51.5	23 640	59.1	21 365
Anti-hypertensive medication (%)	47.2	25 976	51.9	23 823	57.4	20 726

ASCVD, atherosclerotic cardiovascular disease; CABG/PCI, coronary artery bypass grafting/percutaneous coronary intervention; IS, ischaemic stroke; MI, myocardial infarction; SD, standard deviation; UA, unstable angina.
[a]Including the index event (myocardial infarction/ischaemic stroke).

multiple-event MACE composite rates were 8.5, 15.4, and 14.4, respectively, in the ASCVD prevalent, MI incident, and IS incident cohorts. The multiple-event ASCVD composite rate was 9.6, 22.5, and 15.2, in the ASCVD prevalent cohort, the MI incident cohort, and the IS incident cohort, respectively.

Discussion

Existing data informing rates of incident CV events are mainly derived from clinical trial populations which may underestimate event rates due to potential patient selection bias from trial recruitment, or to the stringent clinical care received by clinical trial participants. Real-world evidence from this retrospective cohort study demonstrates that CVD burden among high-risk patients with clinically evident ASCVD being treated with moderate or high-intensity statin therapy is substantial, especially in close proximity to an incident CV event.

According to the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) guidelines for the management of dyslipidaemias, patients with either documented CVD, very high levels of individual risk factors (such as increased lipid or blood pressure levels), or chronic kidney disease are at very high or high total CV risk.[25] The population in this study is similar to the very high-risk population defined in the ESC/EAS guidelines, which advocate for active management of all risk factors. Despite treatment with moderate or high-intensity statins, almost 44% of the patients in the ASCVD prevalent cohort experienced a new event (MI, UA, IS, coronary revascularization, or CV-related death) during a mean follow-up of 7.3 years. In the two incident cohorts CV burden was even higher, with approximately 54% in the MI incident cohort and 40% in the IS incident cohort experiencing at least one new CV event within the ASCVD composite during a mean follow-up of almost 4 years.

These findings are in line with previous real-world data showing a high burden of CVD among high-risk patients. Toth *et al.*[26] applied the FOURIER eligibility criteria to identify patients in UK medical records and showed that approximately 33% of patients in the high-risk ASCVD cohort (similar to the ASCVD prevalent cohort) experienced at least one (≥1) new event (MI, IS, UA, coronary revascularization, or CV death) during a mean follow-up of 5.4 years. The corresponding proportions in UK incident cohorts were 27% and 40% over 2.8 years, defined by diagnosis of IS or acute coronary syndrome (ACS) (MI or UA), respectively. The rates of incident CV events per 100 person-years based on UK data were 7.5, 21.1, and 11.9, respectively, for the high-risk ASCVD cohort, the ACS incident cohort, and the IS incident cohort. In addition, Punekar *et al.*[27] showed that 33.9% of high-risk patients experienced at least one new event (MI, IS, coronary revascularization, UA, TIA, or HF) over 2 years follow-up, based on US administrative claims data. The relatively large share of patients (ASCVD prevalent cohort: 16.2%; MI incident cohort: 19.2%; IS incident cohort: 10.9%) who experienced

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Table 4 Frequency of cardiovascular events during follow-up within the ASCVD composite and the hard MACE composite

Event count	ASCVD prevalent cohort				MI incident cohort				IS incident cohort			
	ASCVD composite		Hard MACE composite		ASCVD composite		Hard MACE composite		ASCVD composite		Hard MACE composite	
	N	Percentage	*N*	Percentage	*N*	Percentage	*N*	Percentage	*N*	Percentage	*N*	Percentage
Total with ≥1 incident CV event	24 100	43.8	22 427	40.8	24 806	54.0	18 021	39.3	14 470	40.0	14 039	38.9
1	15 222	27.7	14 825	27.0	15 997	34.9	12 414	27.0	10 546	29.2	10 401	28.8
2	5756	10.5	5197	9.5	5415	11.8	3562	7.8	2840	7.9	2686	7.4
3	1892	3.4	1563	2.8	1942	4.2	1230	2.7	755	2.1	683	1.9
≥4	1230	2.2	842	1.5	1452	3.2	815	1.8	329	0.9	269	0.7

The ASCVD composite includes myocardial infarction, unstable angina, ischaemic stroke, revascularization procedures (coronary artery bypass grafting/percutaneous coronary intervention), and cardiovascular death.
The hard MACE composite includes myocardial infarction, ischaemic stroke, and cardiovascular death.
ASCVD, atherosclerotic cardiovascular disease; IS, ischaemic stroke; MACE, major adverse cardiovascular event; MI, myocardial infarction; *N*, number of patients.

two or more recurrent CV events (≥2 events) in the current study is in line with the results found by Punekar *et al.* where 12.9% of high-risk patients had three or more (≥3) CV events.

For the two incident cohorts, survivors of MI and IS are at immediate risk of having an additional CV event where in most cases, subsequent events are of the same type as previously experienced by the patient. A significant proportion of patients (37.4% in the ASCVD prevalent cohort, 28.6% in the MI incident cohort, and 46.3% in the IS incident cohort) died due to CVD despite moderate or high-intensity statin use. Cardiovascular death rates increased with the number of events, showing that patients who experienced two or more recurrent CV events are at greater risk of dying due to CVD.

Most clinical trials examining CV event rates often present results focusing on the first CV event after the index date. However, to fully understand the CV burden and its impact on patients and the healthcare system, it is important to also evaluate subsequent CV events experienced by patients. In addition to the first CV event, this study quantified and captured both the occurrence of multiple and of recurrent events, by also following patients with established CVD past their first outcome event until either death or end of follow-up.

This study analysed a large study population combined with long follow-up to study CV outcomes. Mean follow-up was longer in all three study cohorts compared with the 2.2 years of follow-up in the FOURIER clinical trial. The primary outcome in the FOURIER clinical trial, incidence of CV death, MI, IS, hospitalization for UA, or coronary revascularization (corresponding to the ASCVD composite), occurred in 14.6% of participants in the placebo group. The key secondary endpoint, a composite of MI, IS, or CV related death (corresponding to the hard MACE composite), occurred in 7.4% of patients. The multiple-events MACE composite rates in this study were more than two to three times higher compared with the placebo plus standard background therapy arm in the FOURIER trial (4.2 per 100 person-years).[28] Several differences may account for the discrepancies between the clinical trial rates and the rates reported from this real-world study. The majority of the high ASCVD risk patients in this study were on moderate-intensity statin treatment at the time of index. As for the FOURIER clinical trial, most participants were high-intensity statin users; the placebo group included 69.1% patients on high-intensity statin therapy, 30.7% on moderate-intensity statin therapy, and 0.2% of patients were classified as low-intensity statin users, unknown intensity, or no data. In addition, the quality of care may differ between the real-world setting and a clinical trial for a variety of reasons including disproportionate recruitment from high performing academic centres, whereas this study comprised patients from nationwide population-based registers with complete coverage. Further, the proportion of women in the current study (ASCVD prevalent cohort: 36.8%; the MI incident cohort: 33.1%; the IS incident cohort: 39.9%) was larger than in the FOURIER outcomes trial (25.0%).

Strengths of this study include the high degree of validity, completeness and data quality in the Swedish national registers,[20,21,23] which enable reliable real-world estimates. The National Patient Register contains more than 99% of hospitalizations, while The Prescription Drug Register covers all prescriptions distributed via pharmacies. Using ICD-10 codes when identifying CV events can be seen as a limitation in the study. Ludvigsson *et al.*[21] have found that positive predictive values of the recorded diagnoses were 85–95%

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Table 5 Distribution of events (%) within the ASCVD composite and the hard MACE composite for multiple events

	ASCVD prevalent cohort		MI incident cohort		IS incident cohort	
	ASCVD composite	Hard MACE composite	ASCVD composite	Hard MACE composite	ASCVD composite	Hard MACE composite
MI (%)	30.0	34.0	32.0	46.9	13.7	14.4
IS (%)	20.8	23.5	7.6	11.1	35.2	37.0
CV death (%)	37.4	42.4	28.6	42.0	46.3	48.7
UA (%)	6.9	—	13.8	—	2.4	—
CABG/PCI (%)	4.9	—	18.0	—	2.5	—

The ASCVD composite includes myocardial infarction, unstable angina, ischaemic stroke, revascularization procedures (coronary artery bypass grafting/percutaneous coronary intervention), and cardiovascular death.
The hard MACE composite includes myocardial infarction, ischaemic stroke, and cardiovascular death.
ASCVD, atherosclerotic cardiovascular disease; CABG/PCI, coronary artery bypass grafting/percutaneous coronary intervention; CV death, cardiovascular death; IS, ischaemic stroke; MACE, major adverse cardiovascular event; MI, myocardial infarction; UA, unstable angina.

Table 6 Cardiovascular death rates by event count

	ASCVD prevalent cohort				MI incident cohort				IS incident cohort			
Event count[a]	*N*	P-Y	Rate per 100 P-Y	SE per 100 P-Y	*N*	P-Y	Rate per 100 P-Y	SE per 100 P-Y	*N*	P-Y	Rate per 100 P-Y	SE per 100 P-Y
1	4010	85 321	4.7	1.5	2709	51 349	5.3	1.9	2046	28 444	7.2	2.1
≥2	4721	70 068	6.7	1.4	3938	45 321	8.7	1.5	1574	19 727	8.0	2.4

ASCVD, atherosclerotic cardiovascular disease; IS, ischaemic stroke; MI, myocardial infarction; *N*, number of patients; P-Y, person-year; SE, standard error.
aEvent count includes myocardial infarction, ischaemic stroke, unstable angina, transient ischaemic attack, and heart failure.

Table 7 Cardiovascular event rates per 100 person-years: incident and multiple-event rates, by outcome

	ASCVD prevalent cohort				MI incident cohort				IS incident cohort			
Endpoint	Events	P-Y	Rate per 100 P-Y	SE per 100 P-Y	Events	P-Y	Rate per 100 P-Y	SE per 100 P-Y	Events	P-Y	Rate per 100 P-Y	SE per 100 P-Y
Hard MACE composite	22 427	356 308	6.3	0.7	18 021	151 317	11.9	0.7	14 039	113 982	12.3	0.8
ASCVD composite	24 100	345 113	7.0	0.6	24 806	114 472	21.7	0.6	14 470	112 351	12.9	0.8
Hard MACE composite—multiple events	33 886	400 685	8.5	0.5	27 255	177 057	15.4	0.6	19 058	132 189	14.4	0.7
ASCVD composite—multiple events	38 406	400 685	9.6	0.4	39 917	177 057	22.5	0.4	20 031	132 189	15.2	0.7

The ASCVD composite includes myocardial infarction, unstable angina, ischaemic stroke, revascularization procedures (coronary artery bypass grafting/percutaneous coronary intervention), and cardiovascular death.
The hard MACE composite includes MI, IS, and cardiovascular death.
ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; IS, ischaemic stroke; MACE, major adverse cardiovascular events; MI, myocardial infarction; P-Y, person-years; SE, standard error.

for most diagnoses in the Swedish National Patient Register, when comparing to information in medical records. Further, approximately 90% of patients with a primary diagnosis of MI, had MI as the underlying cause of death according to medical records. Another limitation to the study is that laboratory values, including LDL-C and other lipid values (HDL-C, triglycerides), are not available in the Swedish national registers. The study population's LDL-C level was thus unknown. The lack of lipid values is anticipated to have limited impact since the patients will be of similar CV risk as the FOURIER trial population based on the inclusion criteria of history of CV events (MI, IS, PAD) as well as statin treatment for elevated LDL-C and other CV risk factors (e.g. diabetes). According to Swedish treatment guidelines, high-risk patients (based on the SCORE-model, ≥10%) and patients with a cholesterol level >4.9 mmol/L, are recommended moderate or high-

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intensity statin treatment.[29,30] Thus, filled prescriptions of moderate and/or high-intensity statins are considered an appropriate proxy for LDL-C. Other risk factors include familial hypercholesterolaemia status and lifestyle conditions such as smoking which were not possible to account for in this real-world data, nor was it the focus of the study to investigate their impact on the risk of CV events. Another limitation is that statin use was not studied during follow-up, meaning that patients may have discontinued their statin treatment several years before experiencing an event. In fact, findings from the EUROASPIRE IV survey, showed that 11.6% of patients discontinued their statin therapy during the one-year period after hospital discharged after a coronary event.[31] However, statin adherence is difficult to study in a retrospective dataset based on national registers, compared with a clinical setting such as the FOURIER trial where patients are assumed to receive optimal lipid lowering treatment with statins.

The study findings highlight the unmet need and clinical burden among high-risk patients treated with high or moderate-intensity statin therapy and indicate the need for additional and alternative therapeutic options. Evidence from the FOURIER trial indicates that evolocumab, a PCSK9 inhibitor, may provide additional benefit for CV event reduction as add-on compared with moderate or high-intensity statin therapy alone. Furthermore, more recent AHA/ACC recommendations state that in very high-risk patients with multiple high-risk clinical factors, and if LDL-C levels remain ≥70 mg/dL (≥1.8 mmol/L), adding a PCSK9 inhibitor is reasonable if the cost/benefit ratio is favourable.[32]

Conclusions

Despite treatment with moderate- or high-intensity statins, the population with clinically evident ASCVD experiences high CV event rates, especially in close proximity to an earlier event. A large proportion of patients experience recurrent CV events and CV death rates show that patients who have recurrent CV events are at greater risk of dying. In this real-world setting, the multiple-event MACE composite rates were more than two to three times higher than in the FOURIER clinical trial, indicating a substantial burden for patients and health care system.

Funding

This study was funded by Amgen, Inc.

Conflict of interest: M.L., J.B., and S.H. are employed by Quantify Research, a contract research organization that provides consultancy services for the pharmaceutical industry. K.M.F. has received consulting fees from Amgen, Inc. M.E. has no conflicts of interest to disclose. M.T., Y.Q. are employed by Amgen, Inc., and own Amgen stock/stock options. G.V. is employed by Amgen (Europe) GmbH, and owns Amgen stock/stock options. M.K.S. is employed by Amgen AB, and owns Amgen stock/stock options.

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