Adv Ther (2021) 38:4695–4708
https://doi.org/10.1007/s12325-021-01852-1

ORIGINAL RESEARCH

Cardiovascular Event Rates After Myocardial Infarction or Ischaemic Stroke in Patients with Additional Risk Factors: A Retrospective Population-Based Cohort Study

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Received: April 27, 2021 / Accepted: June 29, 2021 / Published online: July 26, 2021

ABSTRACT

Introduction: The impact of additional risk factors on major cardiovascular event (MACE) rates in patients with a history of myocardial infarction (MI) or ischaemic stroke (IS) treated with statins is not well defined.

Methods: In this retrospective population-based cohort study, patients with a history of MI or IS treated with moderate- or high-intensity statins were identified using Swedish national register data. Patients were incident (index event between July 2006 and December 2014 and followed from diagnosis) or prevalent (MI or IS before July 2006 and followed thereafter). Four subgroups were defined on the basis of additional risk factors associated with increased cardiovascular risk: diabetes mellitus with target organ damage; chronic kidney disease stages 3–4; index event within 2 years after prior MI or IS; and polyvascular disease. First and total MACE rates (i.e. MI, IS, or cardiovascular death) were calculated, and first MACE 10-year risks (prevalent cohort only) were predicted.

Results: Numerically, MACE rates in subgroups were 1.5–3 times higher than in overall populations, and were highest in the 2 years after the index event. First MACE rates in the additional risk factor subgroups were 17.2–33.5 per 100 person-years for the incident cohorts and 9.9–13.2 per 100 person-years for the prevalent cohorts. Total MACE rates per 100 person-years were 20.1–39.8 per 100 person-years and 12.4–17.6 per 100 person-years, respectively.

Conclusion: Despite previous use of moderate- or high-intensity statins, patients with a history of MI or IS, and additional risk factors remain at very high cardiovascular risk.

Keywords: Cardiovascular event rates; Major cardiovascular events; Myocardial infarction; Ischaemic stroke; Lipid-lowering therapy

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12325-021-01852-1.

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Key Summary Points

Why carry out this study?

Evidence on CV event rates in patients with ASCVD comes primarily from clinical trials, so the impact of CV events in clinical practice may be underestimated.

We analysed Swedish national register data to estimate subsequent MACE rates over time in patients with a history of MI or IS, and additional risk factors.

What was learned from this study?

MACE rates after MI or IS were 1.5–3 times higher in patients with additional CV risk factors than in the overall MI and IS populations. Rates were highest in the 2 years after MI or IS and remained stable thereafter.

These results highlight the urgency of secondary prevention interventions early after an MI or IS to reduce the risk of subsequent MACE in these patients.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide, placing a substantial clinical and economic burden on society [1–4]. Management of patients with CVD is based on individual risk, estimated using a combination of well-established risk factors, such as smoking, sedentary lifestyle, dyslipidaemia, hypertension, diabetes mellitus, and chronic kidney disease (CKD) [1]. In particular, elevated low-density lipoprotein cholesterol (LDL-C) is one of the most important modifiable causal factors for atherosclerotic CVD (ASCVD) [5, 6]. High LDL-C levels are directly associated with the development of ASCVD, including coronary, cerebrovascular, and peripheral artery disease (PAD). Patients at higher risk of cardiovascular (CV) events, therefore, require more intensive treatment.

Statin therapy is effective at lowering LDL-C levels for both primary and secondary prevention of ASCVD, and more intensive statin regimens are recommended in high-risk and very high-risk patients [1]. Recent meta-analyses of clinical trial data assessing LDL-C-lowering therapies show that the risk of CV events is reduced in proportion to the absolute reduction in LDL-C [7, 8]. Notably, however, many patients do not achieve LDL-C prevention goals with moderate or high-intensity statins (with or without ezetimibe) [9]. This is particularly important for patients at very high risk of CV events, and even more so in the presence of additional CV risk factors.

The evidence on CV event rates in patients with ASCVD comes primarily from clinical trials, and so the impact of CV events in clinical practice may be underestimated as a result of patient selection bias and a higher quality of care received by participants compared with real-world settings [10–14]. There is, therefore, a need for observational data on CV event rates in very high-risk patients in routine clinical practice. Recent analyses using Swedish national register data have demonstrated that patients with ASCVD have a rate of CV events that is substantially higher than that seen in clinical trials, and that early escalation of treatment to high-intensity statins can reduce the risk of subsequent CV events [15, 16]. Here, we present further analyses of this data set describing subsequent major CV event (MACE) rates over time in populations of patients with a history of myocardial infarction (MI) or ischaemic stroke (IS), and additional risk factors.

METHODS

Data Sources

This was a retrospective, nationwide, population-based cohort study using Swedish national register data [17–20] from 1 July 2001 to 31 December 2015. Data from three Swedish health registers (the National Patient Register, the Prescribed Drug Register, and the Cause of

Death Register) were linked via unique personal identity numbers, allowing the study to use near-complete data covering the Swedish population. Data collected from the registers included diagnoses and surgical procedures from almost all hospitalisations, outpatient hospital visits and information on drugs filled at pharmacies, and all confirmed dates of death.

The study was performed in accordance with the Helsinki declaration of 1964 and its later amendments. Ethical approval for the present study was obtained from the Regional Ethical Review Board in Stockholm (dnr 2016/456-31/2). The need for individual patient consent was waived as a result of the study design.

Patient Population

The present analysis was based on a pre-existing data set that included patients aged 40–85 years with at least one major or two minor CV risk factors, and who had previously received moderate- or high-intensity statins, with or without ezetimibe. Full details of the overall cohort have been published previously [15] and are summarised in the supplementary material online.

The timeline for patient selection and follow-up is shown in Fig. 1. For the present analysis, four cohorts of patients within the original data set were defined. Two prevalent cohorts included patients with a previously documented MI or IS, respectively, as of 1 July 2006 (index date), and who were followed from that date. Two incident cohorts included patients with a documented MI or IS, respectively, between 1 July 2006 and 31 December 2014, and who were followed from the date of the MI or IS (index date). Within each of these cohorts of patients at very high risk of MACE [1], four subgroups of patients were defined on the basis of the presence of specific additional risk factors: diabetes with target organ damage (i.e. nephropathy, retinopathy, and/or neuropathy); CKD stages 3 or 4; index event (MI or IS) within 2 years after prior MI or IS; and polyvascular disease (previous IS [MI cohort] or MI [IS cohort] and/or known PAD). Selection of these risk factors was based on current clinical guidelines [1] and the existing literature on CV risk equations [21, 22]. Smoking status was not included in the analysis, as this information is not mandatory in the Swedish national registers and is highly under-reported. Hypertension was not included as a risk factor as it is difficult to analyse because of the challenges in creating a robust definition based only on in-hospital diagnosis codes. Similarly, pharmacotherapy use cannot be used to define hypertension, as relevant medications are also used for treating other cardiovascular diseases such as heart failure and CKD.

Endpoints and Analyses

All analyses were descriptive in nature and no formal statistical comparisons were conducted. The main endpoint was MACE, defined as a composite of MI, IS, or CV death. Patients were followed until the first event (or death or end of follow-up) for calculation of first MACE rates, and until death or end of follow-up for calculation of total MACE rates. First and total MACE rates per 100 person-years (both for the prevalent and incident cohorts) and first MACE yearly rates for years 1–6 (for the incident cohorts only) were calculated. Additionally, first MACE 10-year risks were predicted for the prevalent cohorts on the basis of exponential survival functions. A secondary endpoint, a composite of MACE, coronary revascularisation,

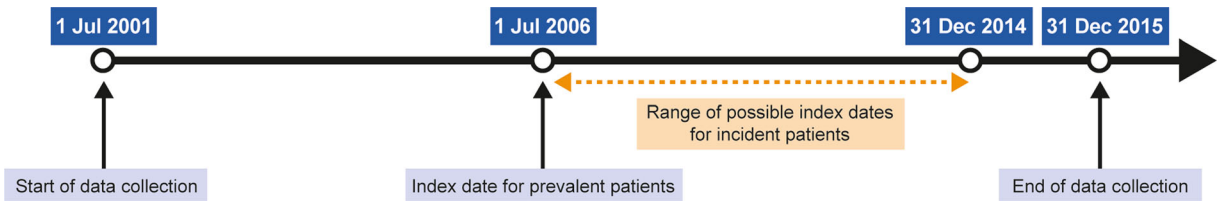

Fig. 1 Timeline of data collection and follow-up

or unstable angina, was also considered. All statistical analyses were performed using Stata 16 (StataCorp LP, College Station, TX, USA).

RESULTS

Study Population

In total, 45,895 incident patients and 37,480 prevalent patients with a history of MI, and 36,134 incident patients and 19,024 prevalent patients with history of IS were included in the analyses (Fig. 2). Baseline characteristics of the incident and prevalent MI and IS cohorts are shown in Tables 1 and 2. As expected, patients in the incident cohorts had a higher prevalence of prior CV events and additional risk factors compared with the prevalent cohorts. The mean time from qualifying MI to index date in the prevalent MI cohort was 2.1 years, and the mean time from qualifying IS to index date in the prevalent IS cohort was 1.9 years.

MACE Rates

First MACE rates per 100 person-years in patients with history of MI were 11.9 in the incident cohort and 6.2 in the prevalent cohort (Table 3). Rates in the subgroups with additional risk factors were numerically 2–3 times higher than in the overall population for the incident MI cohort (21.3–33.5 per 100 person-years) and 1.5–2 times higher for the prevalent MI cohort (10.7–13.2 per 100 person-years). In the prevalent MI cohort, the predicted first MACE 10-year risk in the subgroups with additional risk factors (66–73%) was also substantially higher than in the overall prevalent MI population (46%) (Table 3).

In patients with prior IS, first MACE rates per 100 person-years were 12.3 and 6.9 in the incident and prevalent cohorts, respectively

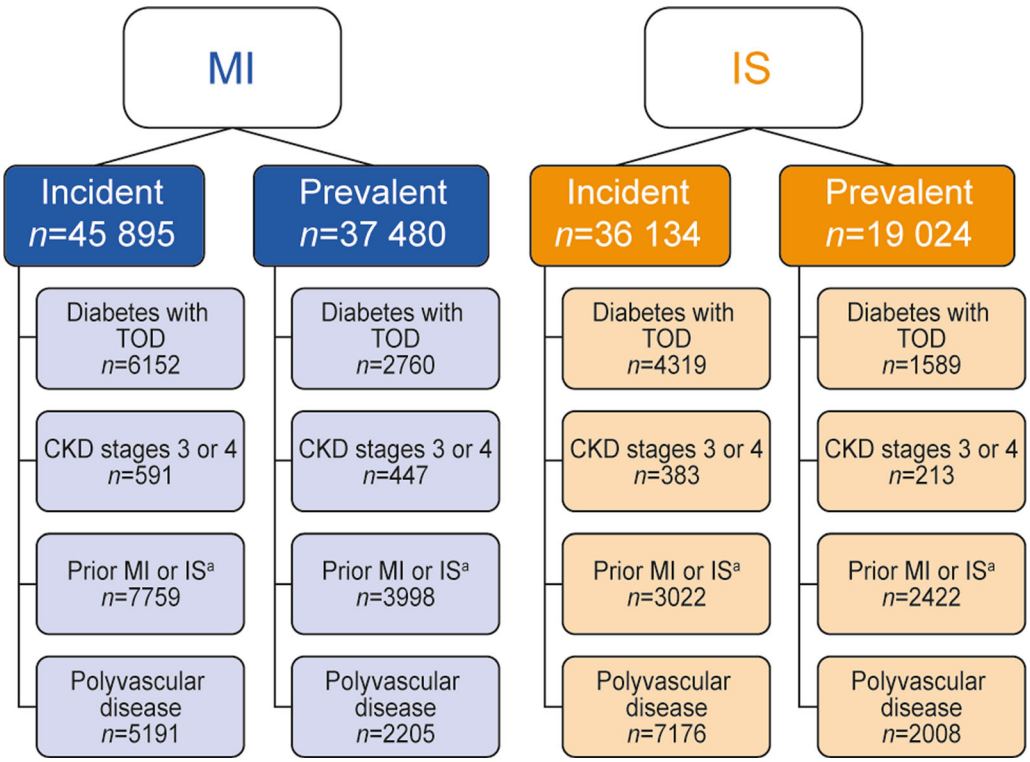

Fig. 2 Study cohorts. [a]Index event within 2 years after prior MI or IS. *CKD* chronic kidney disease, *IS* ischaemic stroke, *MI* myocardial infarction, *TOD* target organ damage

Table 1 Baseline characteristics of patients with a history of MI, overall and subgroups

Incident MI cohort	Overall (n = 45,895)	Subgroups			
		Diabetes with TOD (n = 6152)	CKD stages 3 or 4 (n = 591)	MI within 2 years after prior MI or IS (n = 7759)	Polyvascular disease (n = 5191)
Follow-up (years), mean (SD)	3.9 (2.7)	3.1 (2.6)	1.7 (1.5)	3.9 (2.7)	3.0 (2.5)
Age (years), mean (SD)	71.0 (9.6)	70.7 (9.4)	72.9 (8.3)	73.4 (9.0)	74.2 (8.0)
Male sex, n (%)	30,704 (67)	3833 (62)	426 (72)	4840 (62)	3366 (65)
CV history, n (%)					
CABG/PCI	9819 (21)	2313 (38)	245 (41)	3175 (41)	1808 (35)
IS	3981 (9)	756 (12)	68 (12)	2026 (26)	4545 (88)
PAD	2815 (6)	156 (3)	13 (2)	127 (2)	746 (14)
Charlson comorbidity index,[a] mean (SD)	3.2 (2.2)	5.5 (1.8)	6.6 (2.3)	3.5 (2.1)	4.2 (2.1)
Additional risk factors, n (%)					
Hypertension	31,172 (68)	3300 (54)	500 (85)	3958 (51)	3170 (61)
Diabetes	19,699 (43)	6152 (100)	351 (59)	3621 (47)	2219 (43)
CKD	3261 (7)	864 (14)	591 (100)	514 (7)	327 (6)
Lipid-lowering therapy at index date, n (%)					
Moderate- or high-intensity statin	33,664 (73)	4287 (70)	342 (58)	4512 (58)	2616 (50)
Low-intensity statin	2649 (6)	835 (14)	84 (14)	989 (13)	605 (12)
Ezetimibe	931 (2)	148 (2)	26 (4)	185 (2)	98 (2)

Prevalent MI cohort	Overall (n = 37,480)	Subgroups			
		Diabetes with TOD (n = 2760)	CKD stages 3 or 4 (n = 447)	MI within 2 years after prior MI or IS (n = 3998)	Polyvascular disease (n = 2205)
Follow-up (years), mean (SD)	7.3 (3.0)	5.9 (3.4)	3.6 (1.7)	6.2 (3.4)	5.9 (3.3)
Age (years), mean (SD)	72.3 (8.5)	69.3 (9.6)	73.4 (8.8)	72.3 (9.8)	73.6 (8.5)
Male sex, n (%)	24,608 (66)	1753 (64)	317 (71)	2620 (66)	1423 (65)
CV history, n (%)					
CABG/PCI	3977 (11)	947 (34)	234 (52)	1778 (44)	683 (31)

Table 1 continued

Prevalent MI cohort	Overall (n = 37,480)	Subgroups			
		Diabetes with TOD (n = 2760)	CKD stages 3 or 4 (n = 447)	MI within 2 years after prior MI or IS (n = 3998)	Polyvascular disease (n = 2205)
IS	2852 (8)	215 (8)	27 (6)	721 (18)	1913 (87)
PAD	384 (1)	66 (2)	6 (1)	54 (1)	311 (14)
Charlson comorbidity index,[a] mean (SD)	2.6 (1.9)	5.1 (1.6)	5.7 (1.9)	2.9 (1.9)	3.6 (1.8)
Additional risk factors, n (%)					
Hypertension	16,755 (45)	946 (34)	315 (70)	1438 (36)	934 (42)
Diabetes	13,633 (36)	2760 (100)	220 (49)	1234 (31)	757 (34)
CKD	434 (1)	263 (10)	447 (100)	168 (4)	79 (4)
Lipid-lowering therapy at index date, n (%)					
Moderate- or high-intensity statin	36,290 (97)	2450 (89)	321 (72)	2123 (53)	1939 (88)
Low-intensity statin	815 (2)	66 (2)	40 (9)	104 (3)	56 (3)
Ezetimibe	563 (2)	56 (2)	16 (4)	83 (2)	30 (1)

CABG/PCI coronary artery bypass graft/percutaneous coronary intervention, *CKD* chronic kidney disease, *CV* cardiovascular, *IS* ischaemic stroke, *MI* myocardial infarction, *PAD* peripheral artery disease, *SD* standard deviation, *TIA* transient ischemic attack, *TOD* target organ damage

[a] The Charlson comorbidity index is a weighted index that takes into account the number and seriousness of comorbid diseases [29]

(Table 4). Rates in the subgroups with specific additional risk factors were numerically more than 1.5 times higher than in the respective overall population for the incident IS cohorts (17.2–18.8 per 100 person-years) and 1.5–2 times higher in the prevalent IS cohorts (9.9–12.3 per 100 person-years). In the prevalent IS cohort, the predicted first MACE 10-year risk in the subgroups with specific additional risk factors (63–71%) was also substantially higher than in the overall prevalent IS population (50%) (Table 4). Results were similar, but with higher rates, for the secondary endpoint of the composite of MACE, coronary revascularisation, or unstable angina (Table S1 in the supplementary material).

Total MACE rates per 100 person-years were 15.4 and 8.4 in the overall incident and prevalent MI cohorts, respectively (27.2–39.8 per 100 person-years and 15.4–17.6 per 100 person-years, respectively, in the subgroups) (Table 3). Total MACE rates were 14.4 and 7.5 per 100 person-years in the overall incident and prevalent IS cohorts (subgroups: 20.1–23.9 and 12.4–17.0 per 100 person-years, respectively) (Table 4).

MACE Rates Over Time

Across all subgroups within the incident MI and IS cohorts, MACE rates were highest in the first year after the index event, declining during year 2 and remaining stable thereafter (Fig. 3).

Table 2 Baseline characteristics of patients with a history of IS, overall and subgroups

Incident IS cohort	Overall (n = 36,134)	Subgroups			
		Diabetes with TOD (n = 4319)	CKD stages 3 or 4 (n = 383)	MI within 2 years after prior MI or IS (n = 3022)	Polyvascular disease (n = 7176)
Follow-up (years), mean (SD)	3.7 (2.6)	3.2 (2.5)	1.5 (2.0)	3.8 (2.8)	3.2 (2.5)
Age (years), mean (SD)	72.9 (8.7)	71.7 (8.9)	73.7 (8.4)	73.8 (8.7)	74.5 (8.1)
Male sex, n (%)	27,719 (60)	2743 (64)	269 (70)	1839 (61)	4741 (66)
CV history, n (%)					
TIA	4048 (11)	466 (11)	47 (12)	400 (13)	754 (11)
MI	5321 (15)	844 (20)	52 (14)	2145 (71)	6822 (95)
PAD	1624 (5)	85 (2)	7 (2)	31 (1)	306 (4)
Charlson comorbidity index,[a] mean (SD)	3.0 (2.1)	5.4 (1.9)	6.4 (2.3)	3.5 (2.1)	4.1 (2.1)
Additional risk factors, n (%)					
Hypertension	26,535 (73)	2433 (56)	320 (84)	1731 (57)	4121 (57)
Diabetes	14,140 (39)	4319 (100)	203 (53)	1027 (34)	2584 (36)
CKD	1772 (5)	434 (10)	383 (100)	119 (4)	341 (5)
Lipid-lowering therapy at index date, n (%)					
Moderate- or high-intensity statin	31,386 (87)	3795 (88)	336 (88)	2559 (85)	6457 (90)
Low-intensity statin	2113 (6)	647 (15)	61 (16)	271 (9)	670 (9)
Ezetimibe	448 (1)	61 (1)	7 (2)	39 (1)	124 (2)

Prevalent IS cohort	Overall (n = 19,024)	Subgroups			
		Diabetes with TOD (n = 1589)	CKD stages 3 or 4 (n = 213)	MI within 2 years after prior MI or IS (n = 2422)	Polyvascular disease (n = 2008)
Follow-up (years), mean (SD)	7.0 (3.1)	6.0 (3.3)	3.5 (1.8)	6.6 (3.2)	5.9 (3.3)
Age (years), mean (SD)	73.0 (7.7)	69.7 (8.8)	73.3 (8.3)	71.9 (9.0)	73.8 (8.3)
Male sex, n (%)	11 201 (59)	1008 (63)	170 (80)	1540 (64)	1297 (65)
CV history, n (%)					
TIA	1894 (10)	150 (9)	24 (11)	316 (13)	193 (10)

Table 2 continued

Prevalent IS cohort	Overall (n = 19,024)	Subgroups			
		Diabetes with TOD (n = 1589)	CKD stages 3 or 4 (n = 213)	MI within 2 years after prior MI or IS (n = 2422)	Polyvascular disease (n = 2008)
MI	2852 (15)	228 (14)	28 (13)	770 (32)	1913 (95)
PAD	131 (1)	17 (1)	–[b]	22 (1)	114 (6)
Charlson comorbidity index,[a] mean (SD)	2.5 (1.8)	4.7 (1.5)	5.4 (2.2)	2.6 (1.7)	3.6 (1.7)
Additional risk factors, n (%)					
Hypertension	8120 (43)	632 (40)	165 (78)	1106 (46)	861 (43)
Diabetes	7026 (37)	1589 (100)	98 (46)	723 (30)	674 (34)
CKD	436 (2)	121 (8)	213 (100)	44 (2)	68 (3)
Lipid-lowering therapy at index date, n (%)					
Moderate- or high-intensity statin	13,880 (73)	1383 (87)	86 (40)	2140 (88)	1757 (88)
Low-intensity statin	981 (5)	44 (3)	18 (8)	69 (3)	54 (3)
Ezetimibe	142 (1)	23 (1)	–[b]	31 (1)	31 (2)

CABG/PCI coronary artery bypass graft/percutaneous coronary intervention, *CKD* chronic kidney disease, *CV* cardiovascular, *IS* ischaemic stroke, *MI* myocardial infarction, *PAD* peripheral artery disease, *SD* standard deviation, *TIA* transient ischemic attack, *TOD* target organ damage

[a] The Charlson comorbidity index is a weighted index that takes into account the number and seriousness of comorbid diseases [29]

[b] $n < 5$, data not shown

DISCUSSION

This large study with nationwide coverage of Swedish register data shows that patients with a history of MI or IS, and additional risk factors have a very high risk of suffering subsequent MACE despite previous use of standard-of-care lipid-lowering therapy (i.e. moderate- or high-intensity statins, with or without ezetimibe). This is particularly true for patients with specific additional risk factors, such as diabetes, CKD, subsequent events within 2 years, and polyvascular disease.

Patients in the prevalent cohorts may have had their qualifying MI or IS event up to 5 years before the index date, while patients in the incident cohorts were followed from the time of the qualifying event. This led to differences in MACE rates between the two cohorts, as the risk of a second event is highest in the first years after the initial event and decreases thereafter. The risk of a subsequent CV event has been reported to be higher in the first year post-MI and remain high in the following years [1], and this study aimed to describe the change in CV risk over time by producing MACE yearly rates for the incident cohorts.

In patients with an incident MI or IS, first MACE rates were highest in the first 2 years after the index event, decreasing during year 2 and remaining stable in year 3 and beyond. At 1 year after the index event, the rates were more than three times that seen after year 3 across all subgroups. Moreover, in the first year after MI or IS, the MACE yearly rates in the subgroups of

Table 3 First and total MACE rates of patients with a history of MI, overall and subgroups

	First MACE					Total MACE		
	n	Events (*n*)	Follow-up (person-years)	MACE rate per 100 person-years	10-year risk (%)	Events (*n*)	Follow-up (person-years)	MACE rate per 100 person-years
Incident MI cohort								
Overall	45,895	18,021	151,317	11.9	–	27,255	177,057	15.4
Subgroups					–			
Diabetes with TOD	6152	3179	14,910	21.3		5209	19,172	27.2
CKD stages 3 or 4	591	281	839	33.5		397	998	39.8
Prior MI or IS[a]	7759	2065	9467	21.8		3545	12,711	27.9
Polyvascular disease	5191	842	3301	25.5		4291	15,757	27.2
Prevalent MI cohort								
Overall	37,480	15,100	245,177	6.2	46	23,102	275,117	8.4
Subgroups								
Diabetes with TOD	2760	1465	13,654	10.7	66	2848	16,241	17.5
CKD stages 3 or 4	447	189	1431	13.2	73	281	1597	17.6
Prior MI or IS[a]	3998	2218	20,511	10.8	66	3806	24,762	15.4
Polyvascular disease	2205	1279	10,947	11.7	69	2037	13,017	15.6

CKD chronic kidney disease, *IS* ischaemic stroke, *MACE* major cardiovascular events, *MI* myocardial infarction, *TOD* target organ damage

[a] Index event within 2 years after prior MI or IS

patients with specific additional risk factors were almost double those of the overall incident MI or IS cohorts.

As expected, first MACE rates in the present study based on real-world clinical practice data were considerably higher than those seen in recent clinical trials. Notably, this data set was designed to have almost identical inclusion criteria to the FOURIER study [23]. To allow a comparison of real-world and clinical trial data, we conducted an ad hoc analysis of data from the FOURIER study, showing that first MACE rates in the placebo arm in patients with a history of MI were 3.4 per 100 person-years overall, and 3.8–6.3 per 100 person-years in the subgroups with additional risk factors (Table S2 in the supplementary material) (Amgen, data on file), compared with 6.2 per 100 person-years

Table 4 First and total MACE rates of patients with a history of IS, overall and subgroups

	n	First MACE				Total MACE		
		Events (*n*)	Follow-up (person-years)	MACE rate per 100 person-years	10-year risk (%)	Events (*n*)	Follow-up (person-years)	MACE rate per 100 person-years
Incident IS cohort								
Overall	36,134	14,039	113,982	12.3	–	19,058	132,189	14.4
Subgroups								
Diabetes with TOD	4319	1969	11,448	17.2	–	2778	13,850	20.1
CKD stages 3 or 4	383	259	1423	18.2	–	392	1798	21.8
Prior MI or IS[a]	3022	1672	8888	18.8	–	2736	11,455	23.9
Polyvascular disease	7176	3440	19,046	18.1	–	4816	22,775	21.1
Prevalent IS cohort								
Overall	19,024	8124	118,272	6.9	50	9990	132,849	7.5
Subgroups								
Diabetes with TOD	1589	796	8036	9.9	63	1282	9512	13.5
CKD stages 3 or 4	213	81	661	12.3	71	118	745	15.8
Prior MI or IS[a]	2422	1227	12,386	9.9	63	1865	14,990	12.4
Polyvascular disease	2008	1175	9850	11.9	70	2000	11,739	17.0

CKD chronic kidney disease, *IS* ischaemic stroke, *MACE* major cardiovascular events, *MI* myocardial infarction, *TOD* target organ damage

[a] Index event within 2 years after prior MI or IS

overall and 10.7–13.2 per 100 person-years in the subgroups for prevalent patients in the present study. In patients with a recent MI (within less than 1 year) in the placebo arm of FOURIER, the first MACE rate was 3.8 per 100 person-years, compared with 11.9 per 100 person-years in the incident MI cohort in the present study. Similarly, in the ODYSSEY study, 1126 MACE events (but also including non-CV mortality) were reported in 9462 patients with a recent acute coronary syndrome followed for 2.8 years, meaning an event rate of 4.3 per 100 person-years for the placebo arm [14]. First MACE rates in patients with a history of IS in the placebo arm of FOURIER were 4.0 per 100 person-years overall and 4.7–6.7 per 100 person-years in the subgroups, compared with 6.9 and 9.9–12.3 per 100 person-years, respectively, in prevalent patients in the present analysis (Table S2 in the supplementary material)

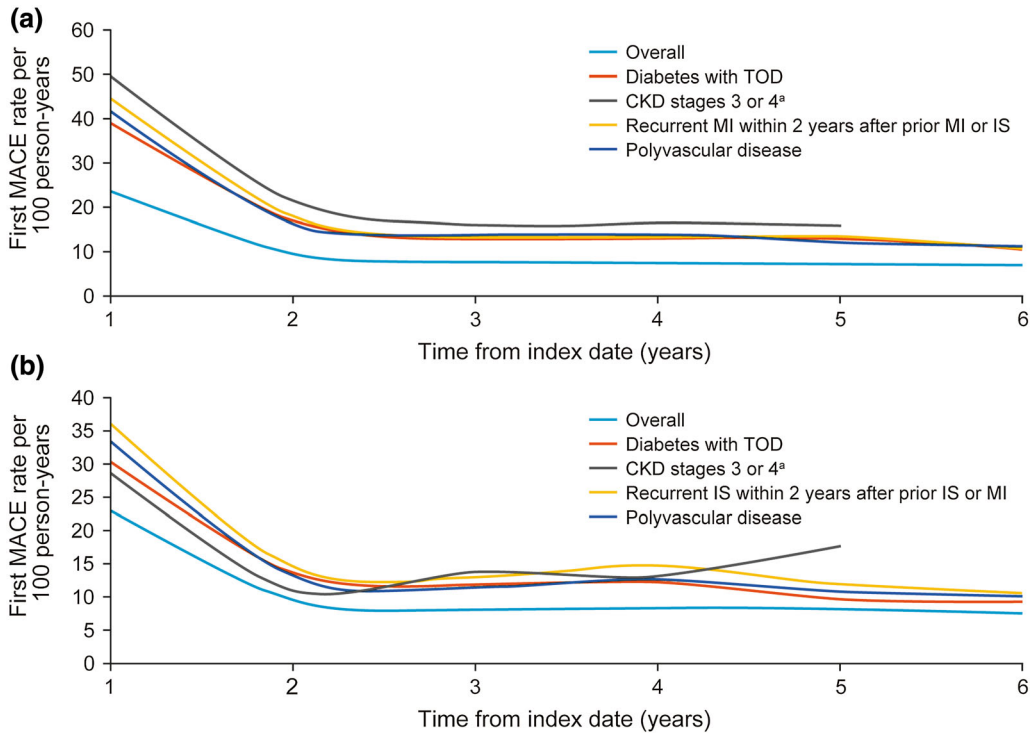

Fig. 3 First MACE yearly rates, overall and subgroups. **a** Patients with incident MI. **b** Patients with incident IS. [a]Patient numbers in the CKD subgroup were too small for analysis after year 5. *CKD* chronic kidney disease, *IS* ischaemic stroke, *MACE* major cardiovascular events, *MI* myocardial infarction, *TOD* target organ damage

(Amgen, data on file). The first MACE rate in patients with a recent IS in the placebo arm of FOURIER was 4.3 per 100 person-years, compared with 12.3 per 100 person-years in the incident IS cohort in the present study.

This very high risk of subsequent MACE in patients with MI or IS and additional risk factors indicates that there is a large unmet need with current disease management, and that additional interventions may be warranted, particularly early after an MI or IS. Indeed, this issue has been raised in European treatment guidelines, which recommend the use of aggressive secondary prevention interventions, including intense LDL-C-lowering treatment [1, 24]. This is also consistent with a recent Swedish study that compared LDL-C levels achieved 6–10 weeks after an MI to the 2019 European Society for Cardiology/European Atherosclerosis Society guidelines LDL-C goal (below 1.4 mmol/L and at least a 50% reduction in LDL-C [1]) and found that more than 80% of patients were eligible for escalated lipid-lowering therapy [25]. Ensuring that patients with ASCVD and additional risk factors are offered intensified treatment known to decrease CV risk is crucial to avoiding a recurrence of CV events. In addition, a range of other preventive measures should be considered alongside lipid control, including encouraging adherence to lipid-lowering therapy, smoking cessation, diet and lifestyle advice, and, where relevant, control of hypertension and hyperglycaemia [1, 24].

Strengths of the present study include the long follow-up period, the large sample size, and the robustness of the data sets used, which cover all inpatient and specialised outpatient visits occurring in Sweden between 2006 and 2015. The National Patient Register contains more than 99% of hospitalisations, while the Prescribed Drug Register covers all prescriptions dispensed at pharmacies. This study, therefore, provides good estimates on event rates in patients in real-world clinical practice, rather

than being based on highly selected clinical trial populations. As a result, our data could serve as a valuable source for populating health economic models evaluating interventions reducing CV risk.

Limitations of the study include the small sample size of some subgroups, and the lack of data on LDL-C levels, meaning that changes in CV risk could not be linked to the level of control of hyperlipidaemia. It is, however, well documented that the use of intensive lipid-lowering therapy is associated with CV risk reduction in very high-risk patients in clinical practice [26–28]. It should be noted that patients were included on the basis of the use of moderate- or high-intensity statins during the 1 year before the index date, but may have stopped or changed therapy by the index date. In addition, statin use, including adherence, and other concomitant therapies and interventions were not studied during follow-up, so potential treatment discontinuations and changes in type or intensity of treatment were not accounted for. It should also be noted that some very high-risk patients may reside in secondary care, such as rehabilitation facilities, and their statin use may not appear in a register of prescriptions. Furthermore, at the beginning of the study period, secondary prevention with high-intensity statins was not standard clinical practice in Sweden but became standard of care in 2012. This study was descriptive in nature. No statistical comparison of differences in rates between the subgroups was conducted, and further research to assess the statistical significance of the differences in rates might be of interest, in line with existing studies [21, 22]. It might also be of interest to investigate the relevance of other risk factors that were not included in the present analysis, such as smoking or hypertension, because of the limitations of the data. Finally, it is important to note that, as this study was conducted in Sweden, the results might not be generalisable to other countries.

CONCLUSION

In conclusion, patients with very high CV risk with a history of MI or IS, and additional risk factors showed very high MACE rates despite previous use of lipid-lowering therapy with moderate- or high-intensity statins. Overall and in all subgroups, MACE rates were highest in the first 2 years following the index event and stable thereafter, highlighting the urgency of secondary prevention interventions early after an MI or IS to reduce the risk of subsequent MACE in these patient populations.

ACKNOWLEDGEMENTS

Funding. Open access funding provided by Uppsala University. This work, including payment of the journal's Rapid Service fee, was supported by Amgen.

Medical Writing, Editorial, and Other Assistance. Medical writing assistance was provided by Dan Booth PhD (Bioscript Medical Ltd, Macclesfield, UK) and funded by Amgen.

Author Contributions. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. ES and GV were responsible for data acquisition and analysis. All authors were involved in the study design, interpretation of results, and the drafting and critical review of the manuscript, and gave their approval for submission.

Disclosures. Emil Hagström acted as an expert committee member for and received lecture fees and institutional research grants from Sanofi and Amgen, and lecture fees from AstraZeneca, Bayer, and Novo Nordisk. Francesc Sorio Vilela and Guillermo Villa are employees and stockholders of Amgen. Maria K. Svensson was an employee and stockholder of Amgen when the study was performed. Sara Hallberg and Emma Söreskog are employees of Quantify Research, which was contracted and paid by Amgen to conduct the study.

Compliance with Ethics Guidelines. The study was performed in accordance with the

Helsinki declaration of 1964 and its later amendments. Ethical approval for the present study was obtained from the Regional Ethical Review Board in Stockholm (dnr 2016/456-31/2). The need for individual patient consent was waived as a result of the study design.

Data Availability. All data generated or analysed during this study are included in this published article and as supplementary material online.

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