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Real-world cardiovascular disease burden in patients with atherosclerotic cardiovascular disease: a comprehensive systematic literature review

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ABSTRACT

Objective: Based on randomized controlled trials (RCTs), non-fatal myocardial infarction (MI) rates range between 9 and 15 events per 1000 person-years, ischemic stroke between 4 and 6 per 1000 person-years, CHD death rates between 5 and 7 events per 1000 person-years, and any major vascular event between 28 and 53 per 1000 person-years in patients with atherosclerotic cardiovascular disease (ASCVD). We reviewed global literature on the topic to determine whether the real-world burden of secondary major adverse cardiovascular events (MACEs) is higher among ASCVD patients.

Methods: We searched PubMed and Embase using MeSH/keywords including cardiovascular disease, secondary prevention and observational studies. Studies published in the last 5 years, in English, with ≥ 50 subjects with elevated low-density lipoprotein cholesterol (LDL-C) or on statins, and reporting secondary MACEs were included. The Newcastle–Ottawa Scale (NOS) was used to assess the quality of each included study.

Results: Of 4663 identified articles, 14 studies that reported MACE incidence rates per 1000 person-years were included in the review (NOS grades ranged from 8 to 9; 2 were prospective and 12 were retrospective studies). Reported incidence rates per 1000 person-years had a range (median) of 12.01–39.9 (26.8) for MI, 13.8–57.2 (41.5) for ischemic stroke, 1.0–94.5 (21.1) for CV-related mortality and 9.7–486 (52.6) for all-cause mortality. Rates were 25.8–211 (81.1) for composite of MACEs. Multiple event rates had a range (median) of 60–391 (183) events per 1000 person-years.

Conclusions: Our review indicates that MACE rates observed in real-world studies are substantially higher than those reported in RCTs, suggesting that the secondary MACE burden and potential benefits of effective CVD management in ASCVD patients may be underestimated if real-world data are not taken into consideration.

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KEYWORDS

Cardiovascular disease; event rates; secondary prevention; hyperlipidemia; hypercholesterolemia; low density lipoprotein; systematic literature review

Introduction

Cardiovascular diseases (CVDs) are the number one cause of death globally, responsible for at least one-third of all deaths in individuals over 35^{1–5}. CVDs, caused by disorders of the heart and blood vessels, include coronary heart disease (e.g. myocardial infarction [MI], angina), cerebrovascular disease (stroke) and peripheral arterial disease. In 2014, up to 11.5% of the adult population in the US was diagnosed with CVD^{4,6}. The American Heart Association has projected that by 2035 up to 45% of the US population will have CVD⁴.

Age-adjusted death rates due to coronary heart disease and stroke have been falling since 1968, although this fall may be lessening⁷. Conversely, a progressive rise in the incidence and prevalence of atherosclerosis and coronary heart disease continues with increasing longevity in both men and women⁸. Atherosclerotic cardiovascular disease (ASCVD), a diffuse condition that involves the build-up of plaque in arterial walls, is directly associated with elevated levels of

low-density lipoprotein cholesterol (LDL-C)^{9,10}. In 2012, about 73.5 million adults in the US had elevated LDL-C levels¹¹.

Although the general improvement in CVD mortality rates has been documented, the real-world burden of secondary CVD events in patients with elevated LDL-C is unclear. It is especially important to examine real-world evidence (RWE) as clinical trials of other conditions typically report lower incident rates¹². In order to understand the current burden of CVD worldwide in people with prior major adverse cardiovascular events (MACEs) and elevated LDL-C, we conducted a systematic literature review of real-world global literature on the topic.

Methods

Data sources and search strategy

Literature searches were conducted in PubMed and Embase (in February and March 2017, respectively) using Medical

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 Supplemental data for this article can be accessed [here](#).

Table 1. PubMed^a search strings.

Search	PubMed Query
(treatments OR outcomes) AND secondary events AND patient population AND study types; Limitations: English, last 5 years	Search (((((((myocardial infarction) OR (cardiovascular death) OR (sudden death) OR (acute coronary syndrome) OR (cardiovascular events) OR (cardiovascular event) OR (ischemic stroke)))))) OR (((percutaneous coronary) OR (coronary artery bypass) OR (revascularization) OR (revascularize) OR (revascularized) OR (angioplasty) OR (stent) OR (CABG)))) AND (((subsequent) OR (prior) OR (recurrent) OR (secondary prevention) OR (first) OR (second) OR (following) OR (preceding) OR (additional) OR (next) OR (after) OR (serial) OR (successive) OR (previous) OR (earlier) OR (consecutive)))) AND (((low density lipoprotein) OR (LDL) OR (hyperlipidemia) OR (lipid lowering) OR (lipid modifying) OR (statin)))) AND (((clinical study) OR (retrospective study) OR (cohort study) OR (cohort analysis) OR (longitudinal study) OR (observational study) OR (case control study) OR (cross sectional study) OR (registry) OR ("real world") OR (claim) OR (claims) OR (cost) OR (Clinical Trial, Phase IV)))) Filters: published in the last 5 years; English
(treatments OR outcomes) AND secondary events AND patient population AND study types	Search (((((((myocardial infarction) OR (cardiovascular death) OR (sudden death) OR (acute coronary syndrome) OR (cardiovascular events) OR (cardiovascular event) OR (ischemic stroke)))))) OR (((percutaneous coronary) OR (coronary artery bypass) OR (revascularization) OR (revascularize) OR (revascularized) OR (angioplasty) OR (stent) OR (CABG)))) AND (((subsequent) OR (prior) OR (recurrent) OR (secondary prevention) OR (first) OR (second) OR (following) OR (preceding) OR (additional) OR (next) OR (after) OR (serial) OR (successive) OR (previous) OR (earlier) OR (consecutive)))) AND (((low density lipoprotein) OR (LDL) OR (hyperlipidemia) OR (lipid lowering) OR (lipid modifying) OR (statin)))) AND (((clinical study) OR (retrospective study) OR (cohort study) OR (cohort analysis) OR (longitudinal study) OR (observational study) OR (case control study) OR (cross sectional study) OR (registry) OR ("real world") OR (claim) OR (claims) OR (cost) OR (Clinical Trial, Phase IV))))
study types	Search (((clinical study) OR (retrospective study) OR (cohort study) OR (cohort analysis) OR (longitudinal study) OR (observational study) OR (case control study) OR (cross sectional study) OR (registry) OR ("real world") OR (claim) OR (claims) OR (cost) OR (Clinical Trial, Phase IV))))
patient population secondary events	Search (((low density lipoprotein) OR (LDL) OR (hyperlipidemia) OR (lipid lowering) OR (lipid modifying) OR (statin))) Search (((subsequent) OR (prior) OR (recurrent) OR (secondary prevention) OR (first) OR (second) OR (following) OR (preceding) OR (additional) OR (next) OR (after) OR (serial) OR (successive) OR (previous) OR (earlier) OR (consecutive))))
treatments	Search (((percutaneous coronary) OR (coronary artery bypass) OR (revascularization) OR (revascularize) OR (revascularized) OR (angioplasty) OR (stent) OR (CABG)))
outcomes	Search (((myocardial infarction) OR (cardiovascular death) OR (sudden death) OR (acute coronary syndrome) OR (cardiovascular events) OR (cardiovascular event) OR (ischemic stroke)))

^aPubMed search string was adapted and reproduced in Embase.

Subject Headings (MeSH) terms and other appropriate keywords (Table 1). The literature review adhered to established guidance as defined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement¹³. The search strategy was limited to the studies published in the last 5 years and limited to the English language. To ensure that the search strategy captured relevant literature, we confirmed that five relevant articles were identified.

Eligibility criteria

The review was conducted using a pre-specified protocol. Eligibility criteria were defined in terms of the population, interventions, comparisons, outcomes and study design (PICOS framework)¹⁴. The population and interventions of interest included patients with a history of ASCVD, elevated LDL-C, hypercholesterolemia or hyperlipidemia, or receiving lipid lowering treatment (e.g. statins). Prior MACEs were defined as: acute coronary syndrome (ACS), MI, non-ST-segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI), ischemic stroke, sudden (cardiac) death, arrhythmias, unstable angina, ischemic (or dilated) cardiomyopathy, heart failure, and treatment interventions (coronary artery revascularization, coronary artery stenting, cerebral artery revascularization, carotid artery revascularization, coronary artery bypass grafting [CABG], and percutaneous coronary intervention [PCI]). Acceptable study designs included retrospective or prospective observational studies. Randomized controlled trials (RCTs) were excluded because a recently published comprehensive systematic review and meta-analysis of RCTs already reported MACE rates¹⁵.

To compare our RWE findings to RCT results, we examined this meta-analysis study in our review.

Study selection

Researchers experienced in literature reviews screened articles in three phases: an initial title/abstract screen and two rounds of full-text screens. Further study inclusion criteria required eligible studies to report outcomes of interest (see *Outcome measures* below) in ≥ 50 human subjects with elevated LDL-C, hypercholesterolemia, hyperlipidemia, or therapy with lipid/cholesterol lowering treatments and prior MACEs. The review was conducted using DistillerSR, a systematic review program (Evidence Partners, Ottawa, Canada).

Outcome measures

The outcomes of interest included quantitative rates of the following: angina, MACEs, coronary heart disease, heart failure, ischemic stroke, mortality (except mortality reported less than 3 months post-operation/hospitalization), MI and stroke. Other outcomes of interest included ACS (e.g. unstable angina, NSTEMI, STEMI), carotid artery revascularization, coronary artery revascularization (e.g. CABG, PCI), peripheral arterial disease, sudden cardiac death and transient ischemic attack (TIA).

Quality assurance

To ensure consistency during screening and abstraction across the multiple reviewers, each reviewer was trained prior

to beginning the literature review. During this training, each reviewer screened the same 30 title/abstracts during the title/abstract screen phase and the same 15 full-text articles during the full-text screen phase. The individual screening decisions were compared against a gold standard, which was developed by a senior researcher with expertise in systematic literature reviews. Reviewers had to achieve $\geq 70\%$ agreement with the gold standard. Disagreements were reviewed and reviewers who did not achieve $\geq 70\%$ agreement with the gold standard were trained further by thoroughly discussing each screening item, response and test study.

Risk of bias assessment

A single reviewer used the Newcastle–Ottawa Scale (NOS) to assess the quality of included studies, with possible grades ranging from zero (lowest quality) to nine (highest quality)^{16,17}. The risk of bias ratings for each study are reported in the [supplementary material \(Supplemental Appendix, Table 5\)](#).

Results

Search and screening overview

PubMed and Embase searches yielded 4663 articles following de-duplication (Figure 1). In the first screening phase, 3057 of 4663 records were excluded. In phase two, 1606 full-length articles were reviewed, of which 1138 were excluded (e.g. 557 due to inappropriate patient population). In the final screening phase, 383 of 468 articles (e.g. 184 did not discuss outcomes of interest) were excluded.

Eighty-five observational studies were abstracted in this review, of which 14 reported outcomes of interest as event rate standardized per patient-years (e.g. per 100, 1000, or

100,000) that allowed for comparison of results across the studies. Although the rest of the studies were relevant to this topic, the outcomes of interest were presented in highly variable formats, such as composite events and a variety of individual rates of MACEs over different follow-up periods, limiting the ability to synthesize results. Thus, these 14 studies are the focus of the current review.

Overview of included studies

Of the 14 included studies, 1 was conducted in Denmark, 1 in Israel, 1 in Spain, 3 in Taiwan, 1 in Thailand, 4 in the UK, and 3 in the US (Table 2). Two of the studies were prospective and 12 were retrospective, with sample sizes ranging from 601 to 273,308 per study. Thirteen studies had an NOS grade of 9 and one a grade of 8, indicating that the evidence was of high quality. Per-patient-year results reported by the 14 studies were standardized to per 1000 patient-years for clearer discussion in this review (Table 3). Studies that reported MI, stroke, death and composite rates are discussed below. Finally, we summarized RCT results based on the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis¹⁵. A comparison of the RWE and RCT results can be found in Table 4 and Figure 2.

Myocardial infarction rate

Four studies reported rates of MI incidence, which ranged from 12.01 to 39.9 (median: 26.8) per 1000 person-years^{22,23,27,28}. All investigated patients on lipid-lowering therapy.

Two large US studies included patients with ASCVD history. Huang *et al.*²² analyzed the HealthCore Integrated Research Database from 2006 to 2014. Study patients had ≥ 1 ASCVD condition (ACS, coronary heart disease, stroke or

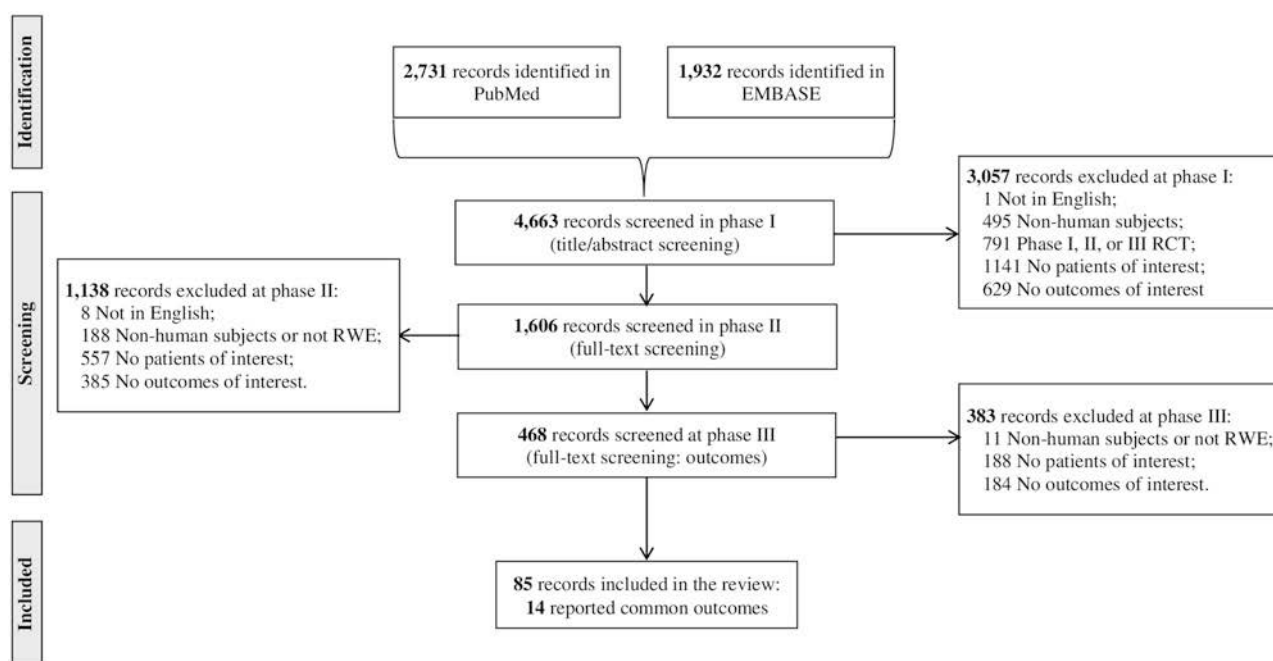


Figure 1. Record search and screening flow chart.

Table 2. Description of studies included in the review.

Reference	Country	Study design and data source	Study time-frame	Study population	Study sample (Subgroups of interest)	Secondary MACEs reported	NOS Rating
Chen <i>et al.</i> 2014 ¹⁸	Taiwan	Retrospective study. National Health Insurance Research Database.	Patient data from 1 January to 31 December 2001. Followed patients as the date of their first statin prescription and through their last medical record before the end of the study period (31 December 2004).	Adult patients with new IS or TIA during 2001 with at least one statin prescription after enrollment.	N = 7243 Statin use groups: In-hospital: 2019 Intermediate: 2266 Late: 2958	Composite endpoints; recurrent IS; hemorrhagic stroke; acute coronary event; all-cause mortality.	9
Chen <i>et al.</i> 2016 ¹⁹	Taiwan	Retrospective study. Taiwan National Health Insurance Research Database.	Patient data from 1 January 2002 to 31 December 2005. Followed patients from the date of first statin prescription through their last medical record before the end of the study period (31 December 2010).	Adult patients who were admitted to hospital for IS or TIA and had initiated statin therapy during hospitalization or within 3 months after discharge.	N = 15,408 Adherence groups: Good: 2274 Intermittent: 3710 Poor: 9424	Composite endpoints; recurrent IS; hemorrhagic stroke; acute coronary event.	9
Chinwong <i>et al.</i> 2015 ²⁰	Thailand	Retrospective study. Medical charts and from the electronic hospital database.	Patient admission data from 1 January 2009 to 31 December 2012. Followed patients for at least 12 months from date of achieving LDL-C goal until the first CVD event, or until end of study period (31 December 2012) whichever came first.	Adult patients hospitalized with a diagnosis of ACS ^a who were treated with statins from 2009 to 2012.	N = 405 (<70 mg/dL, (n = 110); 70–99 mg/dL n = 155; ≥100 mg/dL, n = 140)	Composite endpoints; nonfatal ACS (MI or UA); nonfatal stroke; all-cause death.	9
Danese <i>et al.</i> 2016 ²¹	United Kingdom	Retrospective study. Clinical Practice Research Datalink records.	Patients hospitalized for their first CV event between January 2006 and 31 March 2012. Followed patients for 6 months after index event ("acute period") and 30 months after acute period ("long-term period").	Adult patients with a CV event in the HES data.	N = 24,093 (Second-event cohort: 5274)	MI; UA; IS; PTCA/CABG; HF; TIA.	9
Huang <i>et al.</i> 2016 ²²	USA	Retrospective study. Medical and pharmacy administrative claims and lab results from the HealthCore Integrated Research Database.	Patient data from 1 January 2006 to 30 June 2014.	Patients between 21 and 75 years old with at least one ASCVD ^b condition.	N = 273,308 Statin initiator groups: High-intensity: 23,340 Low-/mod-intensity: 23,340	CV event rates; mortality.	9
Jena <i>et al.</i> 2016 ²³	USA	Retrospective study and economic model; various data sources, including Truven Marketscan insurance claims database.	Enrolled patients with continuous data from 1 January 2005 through 31 December 2006. Followed into the future for an average of 7 years.	Patients with continuous enrollment for 24 months in the Truven Marketscan database with ACC/AHA risk-group criteria.	N = 73,206 (Statin benefit risk group 1 ASCVD ^c patients, n not reported)	MI; IS; UA; revascularization (includes CABG and PCI); CVD mortality.	8
Leibowitz <i>et al.</i> 2016 ²⁴	Israel	Retrospective study. Clalit Health Services comprehensive clinical and	Patient study entry was the date of the first serum LDL-C value in 1 January 2009 to 31	Patients aged 30 to 84 years with pre-existing IHD and	N = 31,619 LDL-C group: Low: 9086	MACEs including MI, UA, stroke, percutaneous coronary	9

(continued)

Table 2. Continued

Reference	Country	Study design and data source	Study time-frame	Study population	Study sample (Subgroups of interest)	Secondary MACEs reported	NOS Rating
Lin <i>et al.</i> 2017 ²⁵	Taiwan	administrative data warehouse. Retrospective study. National Health Insurance Research Database.	December 2013, preceded by ≥ 1 year of adherence to statins. Followed until end of study period. Patient data from 1 January 2005 to 31 December 2010. Followed patients from discharge date of first hospitalization until end of study period (31 December 2011) or the occurrence of the primary outcome, whichever came first.	index LDL-C level < 130 mg/dL. Patients with ACS.	Moderate: 16,782 High: 5751 N = 212,110 Overall: Statins plus ezetimibe: 11,703 Statins alone: 105,914 Ezetimibe alone: 220 Nonusers: 94,273 Propensity-matched: Statins plus ezetimibe: 9137 Statins alone: 9137 N = 4670 (Previous use of cholesterol lowering drugs: 1177)	intervention, coronary artery bypass grafting, or all-cause mortality. Rehospitalization for ACS ⁴ ; rehospitalization for revascularization; rehospitalization for PTCA; rehospitalization for CABG.	9
Ostergaard <i>et al.</i> 2014 ²⁶	Denmark	Retrospective study. Danish National Indicator Project and Odense University Pharmaco-epidemiological Register.	Patients discharged with a stroke diagnosis from hospitals from 1 January 2007 to 30 June 2011. Follow-up began 30 days after discharge and continued until one of the following events, whichever came first: stroke recurrence, death, migration, prescription of an anticoagulant, or end of the study period (30 June 2011). Patient data from January 1993 to December 2007. Followed until end of study period.	Patients discharged with an IS.	Statins alone: 9137 N = 4670 (Previous use of cholesterol lowering drugs: 1177)	Recurrent stroke; death.	9
Sheng <i>et al.</i> 2012 ²⁷	United Kingdom	Prospective study. Medicines Monitoring Unit record-linked database.	Patient data from January 1993 to December 2007. Followed until end of study period.	Patients with a primary diagnosis of diabetes.	N = 6697 (Statin-exposed SP: 514)	TC concentration change from baseline; incident or recurrent APTC events; all-cause mortality.	9
Sheng <i>et al.</i> 2012 ²⁸	United Kingdom	Prospective study. Medicines Monitoring Unit record-linked database.	Patient data from January 1993 to December 2007. Followed until end of study period.	Patients with a primary diagnosis of chronic kidney disease (CKD).	N = 2369 (Statin-exposed SP cohort: 686)	TC concentration change from baseline; incident or recurrent APTC events; all-cause mortality.	9
Sicras-Mainar <i>et al.</i> 2012 ²⁹	Spain	Retrospective study. Badalona Serveis Assistencials database.	Patients with a first stroke episode between January 2003 and December 2005. Followed for 3–6 years.	Patients with a first stroke episode during study period.	N = 601 (Statins: 192)	All cause deaths; recurrent stroke; ACS; any CVE (ischemic heart disease, acute MI). Death; CV hospitalization.	9
Smith <i>et al.</i> 2015 ³⁰	USA	Retrospective study. Healthcare delivery systems participating in the Cardiovascular Research Network (five Kaiser Permanente regions and the Group Health Cooperative in Seattle, Washington).	Patients with hospitalization between January 2000 and December 2008. Follow-up began at 90 days after discharge and followed patients for both 1 year and 2 year time frames.	Adult patients with a primary discharge diagnosis of MI.	N = 21,942 (Statin initiators: n = 5597)	Death; CV hospitalization.	9

(continued)

Table 2. Continued

Reference	Country	Study design and data source	Study time-frame	Study population	Study sample (Subgroups of interest)	Secondary MACEs reported	NOS Rating
Toth <i>et al.</i> 2017 ³¹	United Kingdom	Retrospective study and economic model. Clinical Practice Research Datalink records, Hospital Episode Statistics, Office for National Statistics.	Patient data from 1 January 2004 to 1 January 2011. Followed patients until last available record, death or end of study period (31 December 2011), whichever came first.	Patients with CV event as of 1 January 2005; or patients with CVD diagnosis (ACS, IS, and HF).	N = 2492 High-risk ASCVD ^a : 1448 ACS incident: 602 IS incident: 151 HF incident: 291	Composite of CV events: ACS (MI or UA), IS, coronary revascularization (CABG or PCI), or CV-related death.	9

^aUA, NSTEMI or STEMI.

^bACS, CHD (e.g. MI, angina, and coronary artery stenosis), stroke, or peripheral arterial disease.

^cUA, stable angina, MI, coronary or arterial revascularizations, IS, TIA, peripheral arterial disease, ischemic heart disease, abdominal aortic aneurysm, congestive heart failure, or carotid artery disease.

^dSTEMI, NSTEMI or UA.

^ePatients who had already experienced MI, UA, IS, HF or coronary revascularization.

Abbreviations. ACS, acute coronary syndrome; APTC, Antiplatelet Trialist's Collaboration; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass surgery; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular event; HES, Hospital Episode Statistics; HF, heart failure; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MACEs, major adverse cardiac events; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; PP, primary prevention; PTCA, percutaneous transluminal coronary angioplasty; SP, secondary prevention; STEMI, ST-elevation myocardial infarction; TC, total cholesterol; TIA, transient ischemic attack; UA, unstable angina.

TIA, and peripheral arterial disease) and initiated high-intensity statins, low-/moderate-intensity statins, or no statins. MI incidence rates were 39.9 and 32.7 per 1000 person-years in high- and low-/moderate-intensity statin initiators, respectively. Another US study reported MACE rates based on the Truven MarketScan insurance claims database, estimated for ASCVD patients with ≥ 1 inpatient claim or ≥ 2 outpatient claims between 2005 and 2006 for unstable angina, stable angina, MI, coronary or arterial revascularizations, ischemic stroke, TIA, peripheral arterial disease, ischemic heart disease, abdominal aortic aneurysm, congestive heart failure, and carotid artery disease. Among patients with ASCVD, treated with lipid-lowering therapy and uncontrolled with LDL-C ≥ 70 mg/dL, incidence rates of MI were 23.26 per 1000 person-years and 26.70 per 1000 person-years in patients with LDL-C ≥ 100 mg/dL²³.

Sheng *et al.* performed two cohort studies in Tayside, Scotland, UK using the Medicines Monitoring (MEMO) unit record-linked database^{27,28}. In one study, among patients with diabetes, the statin-exposed secondary prevention (SP) cohort ($n = 514$) had a nonfatal MI incidence rate of 12.01 per 1000 person-years (95% CI: 8.34–17.28)²⁷. In the study among patients with chronic kidney disease (CKD), the nonfatal MI incidence rate was 26.8 per 1000 person-years (95% CI: 20.6–34.9) among the statin-exposed secondary prevention cohort²⁸.

Ischemic stroke/transient ischemic attack rates

Of the six studies that reported incidence rates of stroke, four specifically reported rates of ischemic or TIA stroke^{18,19,22,23}. All studies included patients on lipid-lowering therapy, while one additionally included patients with elevated LDL-C. Reported incidence of ischemic stroke ranged from 13.8 to 57.2 (median: 41.5) per 1000 person-years^{18,19,22,23}, while TIA incidence rates ranged from 7.2 to 13.2 per 1000 person-years^{18,22}.

Huang *et al.*²² reported ischemic stroke rates of 16.1 in the high-intensity statin patients and 13.8 in the low-/moderate-intensity statin patients and TIA rates of 12.1 and 10.1 in the high-intensity and low-/moderate-intensity statin patients, respectively. In ASCVD patients with lipid-lowering therapy, Jena *et al.*²³ reported rates of ischemic stroke of 20.69 and 22.47 in patients with LDL-C ≥ 70 mg/dL and LDL-C ≥ 100 mg/dL, respectively. In a large Taiwanese study using the National Health Insurance Research Database (NHIRD), Chen *et al.*¹⁸ examined 7243 adult patients with a first TIA or stroke in 2001 and ≥ 1 statin prescription. Incidence rate for ischemic stroke for in-hospital (initiated during index hospitalization, $n = 2019$), "intermediate" (initiated within 1 year of discharge, $n = 2266$), and "late" (initiated 1 year or later after discharge, $n = 2958$) statin use groups were 39.7, 43.3, and 55.9, respectively. TIA rates among in-hospital, intermediate, and late statin use groups were 7.2, 11.5, and 13.2, respectively. Also using the NHIRD, Chen *et al.*¹⁹ included patients with ischemic stroke or TIA between 2002 and 2005 who initiated statin therapy during hospitalization or within 3 months of discharge. Ischemic stroke rates among good,

Table 3. Description of results reported in the reviewed studies.

Reference	MI	Stroke	Death	Other	Composite
Chen <i>et al.</i> 2014 ¹⁸	n/a	In-hospital, intermediate, late statin exposure status, <i>n</i> (%): IS: 227 (11.2), 252 (11.1), 198 (6.7) TIA: 41 (2.0), 67 (3.0), 47 (1.6) In-hospital, intermediate, late statin exposure status, crude incidence rate per 1000 person-years: IS: 39.7, 43.3, 55.9 TIA: 7.2, 11.5, 13.2 Good, intermittent, poor statin adherence, <i>n</i> (%): IS: 524 (23.0), 887 (23.9), 2110 (22.4) Good, intermittent and poor statin adherence, crude incidence rate per 1000 person-years: IS: 47.0, 53.6, 57.2	n/a	In-hospital, intermediate, late statin exposure status, <i>n</i> (%): Acute coronary event: 62 (3.1), 44 (1.9), 37 (1.3) In-hospital, intermediate, late statin exposure status, crude incidence rate per 1000 person-years: Acute coronary event: 10.9, 7.6, 10.5	In-hospital, intermediate, late statin exposure status, <i>n</i> (%): Composite endpoints: 369 (18.3), 396 (17.5), 304 (10.3) In-hospital, intermediate, late statin exposure status, crude rate per 1000 person-years: Composite endpoints: 64.6, 68.1, 85.9
Chen <i>et al.</i> 2016 ¹⁹	n/a	Good, intermittent, poor statin adherence, <i>n</i> (%): IS: 524 (23.0), 887 (23.9), 2110 (22.4) Good, intermittent and poor statin adherence, crude incidence rate per 1000 person-years: IS: 47.0, 53.6, 57.2	n/a	Good, intermittent, poor statin adherence, <i>n</i> (%): Acute coronary event: 78 (3.4), 139 (3.7), 300 (3.2) Good, intermittent and poor statin adherence, crude incidence rate per 1000 person-years: Acute coronary event: 7.0, 8.4, 8.1	Good, intermittent, poor statin adherence, <i>n</i> (%): Composite endpoints: 798 (35.1), 1338 (36.1), 3218 (34.1) Good, intermittent and poor statin adherence, crude rate per 1000 person-years: Composite endpoints: 71.6, 80.9, 87.3 LCL-C: <70, 70–99, ≥100 groups, <i>n</i> : 9, 17, 20 LCL-C: <70, 70–99, ≥100 groups, rate per 1000 person-years: Composite first events of nonfatal ACS, nonfatal stroke, death: 43, 66, 88
Chinwong <i>et al.</i> 2015 ²⁰	n/a	LCL-C: <70, 70–99, ≥100 groups, <i>n</i> : Nonfatal stroke: 0, 1, 0 LCL-C: <70, 70–99, ≥100 groups, incidence rate per 1000 person-years: Nonfatal stroke: 0, 4, 0	LCL-C: <70, 70–99, ≥100 groups, <i>n</i> : All-cause death: 5, 3, 5 LCL-C: <70, 70–99, ≥100 groups, incidence rate per 1000 person-years: All-cause death: 22, 12, 22	LCL-C: <70, 70–99, ≥100 groups, <i>n</i> : Nonfatal ACS: 7, 13, 15 LCL-C: <70, 70–99, ≥100 groups, incidence rate per 1000 person-years: Nonfatal ACS: 33, 51, 66	LCL-C: <70, 70–99, ≥100 groups, <i>n</i> : First event cohort, rate per 1000 person-years: PTCA/CABG: 5082 Acute (long-term) CV event rate by Charlson comorbidity score 0, 1, 2+ 2+ 234 (60), 234 (95), 288 (122) Second event cohort, rate per 1000 person-years: Acute (long-term) CV event rate by Charlson comorbidity score 0, 1, 2+ 255 (111), 380 (126), 391 (196)
Danese <i>et al.</i> 2016 ²¹	First event cohort, <i>n</i> : MI: 4468 Second event cohort, <i>n</i> : MI: 769	First event cohort, <i>n</i> : IS: 3489 TIA: 1657 Second event cohort, <i>n</i> : IS: 532 TIA: 266	First event cohort, rate per 1000 person-years: Acute (long-term) all-cause mortality: 285 (54) Acute (long-term) all-cause mortality by Charlson comorbidity score 0, 1, 2+ 135 (24), 227 (48), 420 (84) Second event cohort, rate per 1000 person-years: Acute (long-term) all-cause mortality: 365 (62) Acute (long-term) all-cause mortality by Charlson comorbidity score 0, 1, 2+ 87 (14), 243 (33), 486 (92)	First event cohort, rate per 1000 person-years: PTCA/CABG: 5082 Acute (long-term) CV event rate by Charlson comorbidity score 0, 1, 2+ 234 (60), 234 (95), 288 (122) Second event cohort, rate per 1000 person-years: Acute (long-term) CV event rate by Charlson comorbidity score 0, 1, 2+ 255 (111), 380 (126), 391 (196)	First event cohort, rate per 1000 person-years: PTCA/CABG: 5082 Acute (long-term) CV event rate by Charlson comorbidity score 0, 1, 2+ 234 (60), 234 (95), 288 (122) Second event cohort, rate per 1000 person-years: Acute (long-term) CV event rate by Charlson comorbidity score 0, 1, 2+ 255 (111), 380 (126), 391 (196)
Huang <i>et al.</i> 2016 ²²	Patients with ≥1 events, <i>n</i> (%): high-intensity statin initiators, low/moderate intensity statin initiators: MI: 2044 (8.8), 1722 (7.4) Incidence rate per 1000 person-years: high-intensity statin initiators, low/moderate intensity statin	Patients with ≥1 events, <i>n</i> (%): high-intensity statin initiators, low/moderate intensity statin initiators: IS: 870 (3.7), 758 (3.2) TIA: 655 (2.8), 556 (2.4) Incidence rate per 1000 person-years: high-intensity statin initiators, low/moderate intensity statin	Patients with ≥1 events, <i>n</i> (%): high-intensity statin initiators, low/moderate intensity statin initiators: CV-related mortality: 83 (0.4), 54 (0.2) All-cause mortality: 621 (2.7), 544 (2.3) Incidence rate per 1000	Patients with ≥1 events, <i>n</i> (%): high-intensity statin initiators, low/moderate intensity statin initiators: Coronary revascularization, including CABG and PCI: 1765 (7.6), 1610 (6.9) UA in the inpatient/emergency department setting: 1992 (8.5),	Patients with ≥1 events, <i>n</i> (%): high-intensity statin initiators, low/moderate intensity statin initiators: Composite CV outcome (ACS, stroke, coronary revascularization, and CVD related mortality): 4777 (20.55), 4205 (18.0) Rate per 1000 person-years: high-

(continued)

Table 3. Continued

Reference	MI	Stroke	Death	Other	Composite
Jena <i>et al.</i> 2016 ²³	<p>initiators: MI: 39.9, 32.7</p> <p>Incidence rates per 1000 person-years: patients with ASCVD^a treated with lipid lowering therapy and uncontrolled: with LDL-C ≥ 70 mg/dL goal, with LDL-C ≥ 100 mg/dL goal: MI: 23.26, 26.70 n/a</p>	<p>statin initiators: IS: 16.1, 13.8; TIA: 12.1, 10.1</p> <p>Incidence rates per 1000 person-years: patients with ASCVD treated with lipid lowering therapy and uncontrolled: with LDL-C ≥ 70 mg/dL goal, with LDL-C ≥ 100 mg/dL goal: IS: 20.69, 22.47 n/a</p>	<p>person-years: high-intensity statin initiators, low/moderate intensity statin initiators: CV-related mortality: 1.5, 1.0 All-cause mortality: 11.2, 9.7</p> <p>Incidence rates per 1000 person-years: patients with ASCVD treated with lipid lowering therapy and uncontrolled: with LDL-C ≥ 70 mg/dL goal, with LDL-C ≥ 100 mg/dL goal: CVD mortality: 20.03, 22.12 n/a</p>	<p>1816 (7.8)</p> <p>Incidence rate per 1000 person-years: high-intensity statin initiators, low/moderate intensity statin initiators: Coronary revascularization, including CABG and PCI: 34.2, 30.6 UA in the inpatient/emergency department setting: 39.0, 34.8 Incidence rates per 1000 person-years: patients with ASCVDa treated with lipid lowering therapy and uncontrolled: with LDL-C ≥ 70 mg/dL goal, with LDL-C ≥ 100 mg/dL goal: Revascularization: 32.50, 35.45 UA: 41.57, 46.01 n/a</p>	<p>intensity statin initiators, low/moderate intensity statin initiators: Composite CV outcome (ACS, stroke, coronary revascularization, and CVD related mortality): 103.1, 87.0</p> <p>n/a</p> <p>Low, moderate, high LDL-C groups, n: MACEs: 2681, 4595, 1759 Age <75 years (≥ 75 years) patients in low, moderate, high LDL-C groups, n: MACEs: 1708 (953), 3022 (1573), 1183 (576) Unadjusted (adjusted) rates per 1000 person-years in low, moderate, high LDL-C groups: MACEs: 78.1 (78.1), 71.0 (71.0), 81.3 (81.3) Age <75 years (≥ 75 years) rates per 1000 person-years in low, moderate, high LDL-C groups: MACEs: 68.8 (101.7), 63.8 (90.7), 72.4 (108.2) n/a</p>
Lin <i>et al.</i> 2017 ²⁵	n/a	n/a	n/a	<p>Statins alone, statins plus ezetimibe, n: Rehospitalization for ACS: 1779, 1265 Rehospitalization for revascularization: 1172, 845 Rehospitalization for PTCA: 1059, 775 Rehospitalization for CABG: 149, 95 Incidence rates per 1000 person-years, statins alone, statins plus ezetimibe: Rehospitalization for ACS: 62.0, 41.4 Rehospitalization for revascularization: 38.8, 26.9 Rehospitalization for PTCA: 34.3, 24.4 Rehospitalization for CABG: 4.6, 2.9</p>	n/a

(continued)

Table 3. Continued

Reference	MI	Stroke	Death	Other	Composite
Ostergaard <i>et al.</i> 2014 ²⁶	n/a	Among patients with prior use of cholesterol lowering drugs, <i>n</i> (%): Recurrent stroke: 64 (5.4) Rate per 1000 patient-years, antiplatelet use group (current, recent, non-use) in patients with current statin use: Recurrent stroke: 26.3, 32.8, 32.3	Among patients with prior use of cholesterol lowering drugs, <i>n</i> (%): All-cause death: 127 (10.8) Rate per 1000 patient-years, antiplatelet use group (current, recent, non-use) in patients with current statin use: All-cause death: 38.2, 36.9, 50.7	n/a	n/a
Sheng <i>et al.</i> 2012 ²⁷	Rates per 1000 person-years statin-exposed SP cohort: Non-fatal MI: 12.01	Rates per 1000 person-years statin-exposed SP cohort: Non-fatal stroke: 12.05	Rates per 1000 person-years statin-exposed SP cohort: CV death: 35.28 All-cause mortality: 51.16	n/a	Rates per 1000 person-years statin-exposed SP cohort: APTC end point: 44.63
Sheng <i>et al.</i> 2012 ²⁸	Rates per 1000 person-years, statin-exposed SP cohort: Non-fatal MI: 26.8	Rates per 1000 person-years, statin-exposed SP cohort: Non-fatal stroke: 15.5	Rates per 1000 person-years, statin-exposed SP cohort: CV death: 94.5 All-cause mortality: 151.1	n/a	Rates per 1000 person-years statin-exposed SP cohort: APTC end point: 114.2
Sicras-Mainar <i>et al.</i> 2012 ²⁹	n/a	Patients with statins during 6 year follow up, <i>n</i> (%): Recurrence of fatal/non-fatal stroke 14 (7.3) Incidence rate per 1000 patient-years, patients with statins during 6 year follow up: Recurrence of fatal/non-fatal stroke: 16.78 n/a	Patients with statins during 6 year follow up, <i>n</i> (%): All-case death: 22 (11.5) Incidence rate per 1000 patient-years, patients with statins during 6 year follow up: All-case death: 26.09	Patients with statins during 6 year follow up, <i>n</i> (%): Any CVE: 21 (10.9) Rate per 1000 person-years, patients with statins during 6 year follow up: Any CVE: 25.76	Patients with statins during 6 year follow up, <i>n</i> (%): Any CVE: 21 (10.9) Rate per 1000 person-years, patients with statins during 6 year follow up: Any CVE: 25.76
Smith <i>et al.</i> 2015 ³⁰	n/a	n/a	Statin initiators, <i>n</i> (%): All-cause deaths over 1 year: 614 (11.0) Rates per 1000 person-years, statin initiators: All-cause deaths: 119.3 n/a	n/a	Statin initiators, <i>n</i> (%): CV hospitalizations over 1 year, 805 (14.4) Rates per 1000 person-years, statin initiators: CV hospitalizations: 168.4 Composite outcome, high-risk ASCVD ^b , ACS incident, IS incident, HF incident cohorts, <i>n</i> (%): ≥1 event: 482 (33.3), 241 (40.0), 41 (27.2), 96 (33.0) ≥2 events: 203 (14.0), 111 (18.4), 15 (9.9), 27 (9.3) ≥3 events: 89 (6.1), 50 (8.3), 2 (1.3), 9 (3.1) ≥4 events: 42 (2.9), 19 (3.2) ≥5 events: 20 (1.4), 12 (2.0) Composite outcome (excluding revascularization), high-risk ASCVD, ACS incident, IS incident, HF incident cohorts, <i>n</i> (%): ≥1 event: 417 (28.8), 189 (31.4), 37 (24.5), 81 (27.8) ≥2 events: 142 (9.8), 66 (11.0), 12 (7.9), 17 (5.8)
Toth <i>et al.</i> 2017 ³¹	n/a	n/a	n/a	n/a	n/a

(continued)

Table 3. Continued

Reference	MI	Stroke	Death	Other	Composite
					≥3 events: 58 (4.0), 34 (5.6), 2 (1.3), 6 (2.1) ≥4 events: 26 (1.8), 11 (1.8) ≥5 events: 14 (1.0), 6 (1.0) Composite outcome rates per 1000 patient-years in high-risk ASCVD, ACS incident, IS incident, HF incident cohorts: Rate: 75, 211, 119, 163 Multiple-event rate: 123, 257, 133, 233 Composite outcome (excluding revascularization) rates per 1000 patient-years in high-risk ASCVD, ACS incident, IS incident, HF incident cohorts: Rate: 64, 148, 112, 131 Multiple-event rate: 100, 183, 121, 191

^aUA, stable angina, MI, coronary or arterial revascularizations, IS, TIA, peripheral arterial disease, ischemic heart disease, abdominal aortic aneurysm, congestive heart failure, or carotid artery disease.

^bPatients who had already experienced MI, UA, IS, HF or coronary revascularization.

Abbreviations: ACS, acute coronary syndrome; APTC, Antiplatelet Trialist's Collaboration (non-fatal MI, non-fatal stroke or CV death); CABG, coronary artery bypass surgery; CV, cardiovascular; CVD, cardiovascular event; HF, heart failure; IS, ischemic stroke; LDL-C, low-density lipoprotein cholesterol; MACEs, major adverse cardiac events; MI, myocardial infarction; n/a, not available; PCI, percutaneous coronary intervention; PP, primary prevention; PTCA, percutaneous transluminal coronary angioplasty; SP, secondary prevention; TIA, transient ischemic attack; UA, unstable angina.

intermittent and poor statin adherence groups were 47.0, 53.6 and 57.2, respectively¹⁹.

The remainder of included studies reported incidence rates of unspecified stroke or definitions of stroke that included hemorrhagic stroke. The two Sheng *et al.* studies reported an incidence rate per 1000 person-years of nonfatal ischemic or hemorrhagic stroke of 12.05 (95% CI: 8.42–17.23) in diabetic statin-exposed patients²⁷, and an incidence rate of 15.5 (95% CI: 11.0–21.9) in statin-exposed secondary prevention CKD patients²⁸. In Thai patients with angina pectoris or MI discharges, Chinwong *et al.*²⁰ reported incidence rates for unspecified nonfatal stroke of 0, 4 and 0 per 1000 person-years in those with LDL-C <70 mg/dL, LDL-C 70–99 mg/dL and LDL-C ≥100 mg/dL, respectively. In currently statin-treated ischemic stroke patients in Denmark, Ostergaard *et al.*²⁶ reported rates of recurrent ischemic, hemorrhagic or unspecified stroke per 1000 person-years of 26.3 in current antiplatelet-treated patients, 32.8 in the recently treated antiplatelet patients, and 32.3 in the non-antiplatelet-treated patients. Among patients with prior stroke episode and with LDL-C of 100–190 mg/dL from six primary care centers and two hospitals in Spain, Sicras-Mainar *et al.*²⁹ reported cumulative incidence rates per 1000 person-years for fatal and non-fatal ischemic and hemorrhagic stroke of 45.22 in non-statin users and 16.78 in statin users.

Mortality

Among the nine included studies reporting mortality rates, all evaluated patients on lipid-lowering therapy^{20–23,26–30}. Incidence of CV-related mortality was reported in four studies, ranging from 1.0 to 94.5 (median: 21.1) per 1000 person-years^{22,23,27,28}. Incidence of all-cause mortality was reported in eight studies, ranging from 9.7 to 486 (median: 52.6) per 1000 person-years^{19–22,26–30}.

Three studies included ASCVD patients. Danese *et al.*²¹ examined UK patients treated with lipid-modifying therapy prior to their first MACE; cohorts were stratified by Charlson Comorbidity Score (0, 1 or 2+). Reported death rates per 1000 person-years 6 months post MACE were 285 for the entire cohort, and 135, 227 and 420 by 0, 1 and 2+ scores, respectively. In the subsequent 30 months period, rates were 54 for the entire cohort, and 24 for score 0, 48 for score 1 and 84 for score 2+. In patients with a subsequent event, death rates in a 6 month period were 365 for the entire cohort, and 87, 243 and 486 for 0, 1 and 2+ score subgroups, respectively. In the subsequent period, death rate was 62 per 1000 person-years for the entire cohort, with 14, 33 and 92 deaths per 1000 person-years for scores 0, 1 and 2+, respectively. In Huang *et al.*²², all-cause mortality incidence rates per 1000 person-years in ASCVD patients on high-intensity statins or low-/moderate-intensity statins were 11.2 and 9.7, respectively, while CV-related mortality was 1.5 in the high-intensity statin group and 1.0 in the low-/moderate-intensity statin group. In another US study, patients with ASCVD treated with lipid-lowering therapy and LDL-C ≥70 mg/dL and ≥100 mg/dL had CVD mortality rates of 20.03 and 22.12 per 1000 person-years, respectively²³.

In Sheng *et al.*²⁷, statin-exposed patients with history of CVD and diabetes had a CV death incidence rate per 1000

Table 4. Comparison of real-world evidence (RWE) versus randomized controlled clinical trial (RCT) results.

MACE Rate	Range (median)	
	RWE	RCT results ^a
MI incidence rate	12.01–39.9 (26.8) per 1000 person-years ^{22,23,27,28}	Non-fatal MI: 9–15 (13) events per 1000 person-years
Ischemic stroke incidence rate	13.8–57.2 (41.5) per 1000 person-years ^{18,19,22,23}	4–6 (5) per 1000 person-years
Revascularization incidence rate	Any coronary revascularization (CABG, PTCA): 30.6 or 34.2 events per 1000 person-years ²²	Any coronary revascularization (CABG, PTCA, unspecified): 12–32 (26) events per 1000 person-years
	Rehospitalization for CABG: 2.9 or 4.6 events per 1000 person-years ²⁵	CABG: 3–9 (7) events per 1000 person-years
	Rehospitalization for PTCA: 24.4 or 34.3 events per 1000 person-years ²⁵	PTCA: 2–18 (13) events per 1000 person-years
	Unspecified: 26.9–38.8 (34.0) per 1000 person-years ^{23,25}	Unspecified: 5–6 (6) events per 1000 person-year
CVD related death incidence rate	1.0–94.5 (21.1) per 1000 person-years ^{22,23,27,28}	5–7 (7) events per 1000 person-years
All-cause mortality incidence rate	9.7–486 (52.6) per 1000 person-years ^{20–22,26–30}	21 events per 1000 person-years
Composite CVD event rate	25.8–211 (81.1) per 1000 person-years ^{18–20,22,24,27–29,31}	28–53 (45) per 1000 person-years
Multiple event rate	60 to 391 (183) events per 1000 person-years ^{21,30,31}	

^aCTTC 2010¹⁵ (ranges and medians reported here are based on the point estimates among statin treated comparator cohorts from the 26 trials reported in this publication).

Abbreviations. CABG, coronary artery bypass surgery; CVD, cardiovascular disease; CVE, cardiovascular event; MACEs, major adverse cardiac events; MI, myocardial infarction; n/a, not available; PTCA, percutaneous transluminal coronary angioplasty.

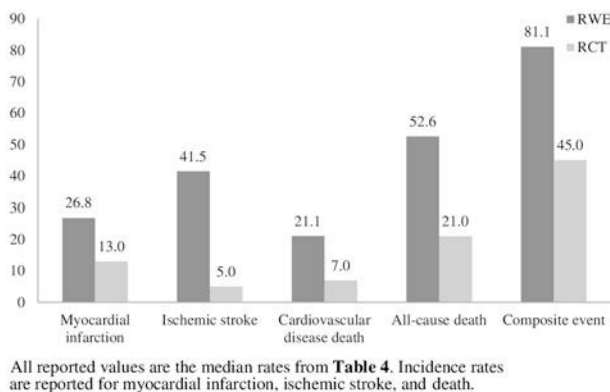


Figure 2. Comparisons of real-world evidence (RWE) versus randomized controlled clinical trial (RCT) rates.

person-years of 35.28 (95% CI: 28.05–44.38). All-cause mortality rate was 51.16 (95% CI: 42.29–61.89). In another study, the same group reported an incidence rate per 1000 person-years of CV death among statin-exposed secondary prevention CKD patients of 94.5 (95% CI: 80.4–111.0), with an all-cause mortality rate of 151.1 (95% CI: 133.3–171.3)²⁸. A Thai study of statin-treated ACS patients reported all-cause death rates of 22 (LDL-C <70 mg/dL group), 12 (70–99 mg/dL group) and 22 (≥100 mg/dL group) per 1000 person-years²⁰. Smith *et al.*³⁰ reported an all-cause death rate of 119.3 per 1000 person-years in MI patients that initiated statins, based on data from the Cardiovascular Research Network.

Two studies focused on stroke cohorts. In Sicras-Mainar *et al.*²⁹, all-cause mortality rates per 1000 person-years in stroke patients with elevated LDL-C were 36.25 and 26.09 in the no statins and statins groups, respectively. Among ischemic stroke patients stratified by antiplatelet and statin use in Ostergaard *et al.*²⁶, all-cause death rates per 1000 person-years were 38.2 (current antiplatelet), 36.9 (recent antiplatelet) and 50.7 (non-use antiplatelet).

Composite major adverse cardiovascular event rate

Eleven studies reported composite MACE rates, although definitions of the composite varied between studies^{18–22,24,27–31}.

Of these, nine studies reported composite event rates, which ranged from 25.8 to 211 (median: 81.1) events per 1000 person-years^{18–20,22,24,27–29,31}. Danese *et al.*, Smith *et al.* and Toth *et al.* reported multiple event rates, which ranged from 60 to 391 (median: 183) events per 1000 person-years^{21,30,31}.

Four studies included patients with ASCVD. In the first event cohort in the acute 6 month period, Danese *et al.*²¹ reported multiple MACE rates of 234, 234 and 288 per 1000 person-years for Charlson Comorbidity Scores 0, 1 and 2+, respectively. In the subsequent 30 months, the multiple rates per 1000 person-years were 60 for score 0, 95 for score 1 and 122 for score 2+. In the second event cohort, subsequent MACE rates per 1000 person-years in the acute period were 255, 380 and 391 for 0, 1 and 2+ score groups. For the long-term period, patients with score 0 had 111, score 1 had 126, and score 2+ had 196 multiple MACEs per 1000 person-years. Toth *et al.*³¹ assessed UK data from CPRD, HES and the Office for National Statistics from 2004 to 2011. High-intensity statin treated patients with LDL-C ≥70 mg/dL or other dyslipidemias were categorized into high-risk ASCVD, incident ACS, incident ischemic stroke, and incident heart failure cohorts. The composite MACE rates per 1000 patient-years were 75 in the high-risk ASCVD cohort, 211 in the incident ACS cohort, 119 in the ischemic stroke and 163 in the heart failure cohorts; multiple event rates were 123, 257, 133 and 233, respectively. Excluding revascularization, the composite MACE rates were 64 in high-risk ASCVD, 148 in ACS, 112 in ischemic stroke and 131 in heart failure cohorts, while multiple event rates were 100, 183, 121 and 191, respectively. Leibowitz *et al.*²⁴ reported that the first occurrence of MACE (MI, unstable angina, stroke, PCI, CABG or all-cause mortality) per 1000 person-years was 78.1, 71.0, and 81.3 in patients with LDL-C ≤70 mg/dL, LDL-C 70.1–100.0 mg/dL, and LDL-C 100.1–130.0 mg/dL, respectively, among Israeli patients with prior MACEs and statin therapy. In Huang *et al.*²², composite rates (of ACS, stroke, coronary revascularization and CV-related mortality) in ASCVD patients on high-intensity statins or low-/moderate-intensity statins were 103.1 and 87.0 per 1000 person-years, respectively.

Sheng *et al.*²⁷ reported recurrent Antiplatelet Trialist's Collaboration (APTCL) events, including nonfatal MI, nonfatal

stroke or death from vascular causes in statin-exposed patients with CVD and diabetes: 44.63 per 1000 person-years (95% CI: 36.65–54.35). The APTC event rate in a statin-exposed secondary prevention CKD population was 114.2 (95% CI: 99.7–130.8)²⁸.

Chinwong *et al.*²⁰ reported composite event rates (non-fatal ACS, stroke and all-cause death) which were 43, 66 and 88 per 1000 person-years in patients that achieved LDL-C <70 mg/dL, LDL-C 70–99 mg/dL, and LDL-C \geq 100 mg/dL, respectively.

In a multicenter US study of over 5000 patients initiated on statins post-MI, the multiple event rate per 1000 person-years of CV hospitalization was 168.4³⁰.

Three studies evaluated stroke patients. Chen *et al.*¹⁸ reported rate per 1000 person-years of a composite endpoint of recurrent ischemic stroke, hemorrhagic stroke, acute coronary event and all-cause mortality. Rates in the in-hospital, intermediate and late statin use groups were 64.6, 68.1 and 85.9, respectively. In Chen *et al.*¹⁹, the composite rates (recurrent ischemic stroke, hemorrhagic stroke or acute coronary event) were 71.6, 80.9 and 87.3 per 1000 person-years in the good, intermittent and poor statin adherence groups, respectively. Sicras-Mainar *et al.*²⁹ reported rates of MACEs (ischemic heart disease, acute MI, fatal or non-fatal ischemic or hemorrhagic stroke) of 25.76 per 1000 person-years in statin-treated patients.

Randomized controlled trial results review

The CTTC conducted an extensive literature review and meta-analysis of 26 randomized clinical trials to assess the safety and efficacy of lowering of LDL-C with statin therapy¹⁵. Findings from these analyses indicate that further reductions in LDL-C safely lead to further reductions in the incidence of MACEs, including heart attack, revascularization and ischemic stroke¹⁵. Based on the point estimates among statin treated comparator cohorts from the 26 trials reported by the CTTC, the occurrence of a non-fatal MI per annum ranged from 0.9% to 1.5% (9–15 events per 1000 person-years), CHD death per annum ranged from 0.5% to 0.7% (5–7 events per 1000 person-years), any coronary revascularization (CABG, PTCA, unspecified) from 1.2% to 3.2% (12–32 events per 1000 person-years), any ischemic stroke from 0.4% to 0.6% (4–6 per 1000 person-years) and any major vascular event from 2.8% to 5.3% (28–53 per 1000 person-years) in statin users¹⁵. All-cause mortality was reported as 21 events per 1000 person-years. Table 4 and Figure 2 summarize MACE rates based on RWE and RCTs.

Discussion

Our comprehensive literature review summarizes the global real-world CVD burden in patients with prior MACEs and elevated LDL-C. We found that the MACE rates in RCTs were typically lower than the rates we identified in real-world studies. We compared the MACE rates observed in real-world studies with those reported in a recent comprehensive meta-analysis of 26 clinical trials¹⁵. According to the CTTC,

non-fatal MI rates range from 9 to 15 events per 1000 person-years, while we found that MI rates range from 12.01 to 39.9 per 1000 person-years based on RWE. Further, RCT findings show ischemic stroke rates range from 4 to 6 per 1000 person-years versus from 13.8 to 57.2 per 1000 person-years in RWE studies. Similarly, CVD-related death rates were generally lower in RCTs than in real-world studies, with MACE rates ranging from 5 to 7 and 1.0 to 94.5 per 1000 person-years, respectively. Based on RCT data all-cause mortality is 21 events per 1000 person-years, while RWE indicates rates range from 9.7 to 486 in patients of interest. RCTs also report lower rates for coronary revascularization versus RWE, particularly for unspecified revascularization: 5–6 events versus 26.9–38.8 per 1000 person-years, respectively. Composite event rates are also higher in RWE studies versus RCTs: ranging from 25.8 to 211 versus 28 to 53 per 1000 person-years. Moreover, real-world data indicates multiple event rates ranging from 60 to 391 events per 1000 person-years. These findings indicate that the burden of secondary MACEs in clinical practice may be considerably higher than reported in clinical trials.

The importance of considering RWE has been discussed in prior studies^{12,32–34}. Although RCTs are considered the “gold standard” for establishing the efficacy of specific interventions, this methodological approach is probably not sufficient for describing the epidemiology and real-world disease burden in the general population. This is demonstrated by the stringent patient selection criteria (e.g. exclusion of high risk patients) and highly controlled clinical settings typically employed by RCTs, leading to limited generalizability of disease burden to the general population and routine clinical practices^{12,32–34}. Elliot *et al.*¹² found that rates of hypoglycemia were consistently higher in real-world studies compared to RCTs in patients with type 1 or type 2 diabetes. Toth *et al.*³⁴ found that cost-effectiveness analyses based on real-world rather than RCT data are more likely to conclude that a treatment is cost-effective, because RCTs are more likely to underestimate the true benefit of lipid-lowering therapies. Because of this, several national and international clinical and research organizations endorse the use of RWE in the evaluation of new technologies³⁴. Together with prior research and evidence generated in this study, this data underscores the importance of conducting and considering observational population studies in CVD to produce generalizable disease burden estimates in a real-world setting.

Differences in results observed in RCTs versus observational studies are primarily associated with differences in the study populations, settings and outcomes^{34,35}. RCTs typically examine highly selected patient populations in tightly controlled and monitored settings and often focus on time-to-first-event outcomes, while observational studies include patients that may be excluded from RCTs and focus on real-world conditions with greater variation in practice and patient settings and examine all relevant events^{34,35}. Specifically, prior research has examined potential key drivers of the differences in MACE results generated by RCTs and RWE. The differences primarily stem from the variations in definitions of CVD risk or CVD events, and dissimilarities in the composition of the study patient samples³⁴.

The definitions of composite, multiple event and mortality rates in particular vary across studies. For example, RCTs typically report incident event rates, while RWE studies commonly report multiple event rates^{21,30,31}. It is important to be aware whether an incident or a multiple event rate is reported since not only are the fundamental interpretations of the two values different but the absolute values resulting from these measures are also dramatically different. Further, individual events included in the composite tend to differ across studies. For example, the Antiplatelet Trialist's Collaboration event endpoint in Sheng *et al.*^{27,28} included non-fatal MI, non-fatal stroke and CV death, while the composite in Chen *et al.*¹⁸ included ischemic stroke, TIA, hemorrhagic stroke and acute coronary event. Additionally, MACE rate estimates may vary due to database limitations. Administrative health insurance claims databases, often examined in RWE studies, lack mortality data and prevent direct linking to official death records due to de-identification of the analytic datasets²². Even if linkage is possible, assessment of mortality is poor since patients can disappear from a claims database due to disenrollment from a health plan or claims may be missing due to coding errors. These may be the reasons for the substantially low mortality rates observed by Huang *et al.*²², particularly since the CV-related mortality algorithm included a requirement of ≥ 1 inpatient stay or emergency department visit with a MACE as a primary diagnosis within 30 days of death²². Yet, a lack of a relevant claim in the database does not guarantee absence of an event of interest; thus, the mortality rates in Huang *et al.*²² were likely underestimated.

The growing burden of CVD and the changing landscape of CVD management have also been well documented worldwide^{4,8,36–44}. Most recent projections indicate that up to 45% of the US population will have CVD by 2035, with costs skyrocketing from \$555 billion in 2016 to \$1.1 trillion by 2035⁴. Similarly, increased CVD burden projections have been shown for the UK and China^{38,39}. Several recent large scale cross-sectional surveys in European countries revealed that, despite lipid-lowering drugs, 30%–80% of the surveyed patients with coronary heart disease remained above the recommended lipid targets, depending on the LDL cholesterol target^{43,44}. Fleg *et al.*⁸ explains that there is a progressive rise in the incidence and prevalence of CHD with increasing longevity in both men and women. The aging and growth of the world's population have led to rising numbers of CVD deaths and, moreover, low- and middle-income countries are confronted by an increasing number of people experiencing CVD at younger ages^{36,42}. Our findings further underscore the global burden of CVD and the importance of generating RWE to better understand the true burden of this disease.

Limitations

The strength of this review lies in its comprehensive search, review and synthesis of global literature on secondary MACE rates in patients with ASCVD. NOS grades for the 14 studies included in the review were all 9, with the exception of one which had a grade of 8. This study also has limitations. By design this review only examined observational studies.

The studies included in this review varied in design, patient population, treatments and definitions of outcomes, and the data were reported in several ways across the reviewed studies. Thus, the heterogeneity of the data made it difficult to compare directly between studies and prevented us from conducting a meta-analysis. In addition, although this was a rigorous systematic literature review on multiple broad research topics using PubMed and Embase, a search of different literature databases and implementation of a different variety of search terms and search strings may have yielded somewhat different results. We present all-cause mortality results in this review; however, these findings should be considered with caution since it has been previously argued that interventions should not be withheld until they have been proven to reduce all-cause mortality⁴⁵. It should also be noted that health insurance claims databases, examined by several of the studies in this review, are designed for administrative purposes, not for research; as with any coded data, under- or over-coding may have occurred. Finally, despite the observational nature of the studies in this review, some MACE outcomes of interest, such as CV-related mortality, may have been underestimated for various reasons, e.g. due to limited study follow-up periods, event identification algorithms, coding errors or limited availability of relevant information in the databases.

Conclusions

Our review indicates that MACE rates observed in real-world settings are substantially higher than those rates reported in RCTs. These results suggest that the true secondary MACE burden and potential benefits of effective CVD management among ASCVD patients may be underestimated if real-world data is not considered.

Transparency

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Declaration of financial/other relationships

P.X., F.O'N., Y.Q. and N.Y. have disclosed that they are employees and shareholders of Amgen Inc. D.C., T.B. and D.B. have disclosed that they are employees of the Partnership for Health Analytic Research (PHAR) LLC, a health services research company paid by Amgen to conduct this research. W.Hs. has disclosed that she is a former employee of PHAR and was paid by PHAR to support this research.

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