Incidence and Cost of Major Adverse Cardiovascular Events and Major Adverse Limb Events in Patients With Chronic Coronary Artery Disease or Peripheral Artery Disease

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Chronic coronary artery disease (CAD) and peripheral artery disease (PAD) are both associated with elevated risks of major adverse cardiovascular events (MACE) and major adverse limb events (MALE). The frequency of these events in patients with CAD or PAD, and their corresponding costs, are not well understood. Accordingly, we describe the incidence and cost of both MACE and MALE in patients with CAD or PAD. Using a database that included healthcare claims linked to electronic medical records, we identified patients with evidence of chronic CAD and PAD, respectively, between January 1, 2009, and September 30, 2016. We assessed the occurrence of MACE (defined as myocardial infarction, stroke, or cardiovascular-related death) and MALE (critical limb ischemia, amputation, or peripheral artery disease-related revascularization). A total of 99,730 patients met all selection criteria: 86.0% had CAD, 25.8% had PAD, and 11.8% had both. Mean (±standard deviation) age was 67.7 (±11.5) years and 59.8% were male. During follow-up (mean: 1.8 years), 13.6% experienced MACE or MALE (6.3 per 100 person-years [PYs]), predominantly MACE (9.6% [4.3 per 100 PYs]). Adjusted 1-year healthcare costs were $44,495 greater in patients who experienced MACE or MALE (mean [95% confidence interval]: $64,099 [$33,254 to $123,557] vs $19,604 [$10,175 to $37,771]; p < 0.001). In conclusion, approximately 1 in 7 patients with chronic CAD or PAD experiences additional MACE or MALE within approximately 2 years of follow-up; the relatively high risk and cost of these events highlight the need for new secondary prevention therapies that may improve outcomes in these patients. **(Am J Cardiol 2019;123:1893−1899)**

The Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS) trial (n = 27,395 patients with stable coronary artery disease [CAD] or peripheral artery disease [PAD]) demonstrated that rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily) decreased (vs aspirin alone) risk of major adverse coronary events (MACE) and major adverse limb events (MALE).[1,2] While randomized trials like COMPASS are among the highest levels of evidence, generalizability is limited due to their highly controlled, artificial, and environs.[3] Accordingly, clinicians often must translate trial findings to the substantively heterogenous and typically more complex patient mix seen in clinical practice. This can be difficult as >50% of real-world patients do not meet eligibility criteria for trials of cardiovascular therapies.[4] Equally concerning, is that those selected for inclusion in these trials tend to be relatively young and healthy (including fewer co-morbidities).[5,6] An understanding of real-world incidence and associated cost of MACE and MALE, respectively in patients with chronic CAD or PAD is therefore vital to translate learnings from COMPASS to clinical practice. Accordingly, we describe herein incidence and cost of MACE and MALE in approximately 100,000 real-world patients with chronic CAD or PAD.

Methods

We used the Optum Integrated Database, which includes administrative healthcare data (i.e., claims, eligibility for medical and pharmacy benefits, and demographic data) linked to electronic medical records for approximately 5.5 million patients.

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See page 1899 for disclosure information.

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Detailed information for each patient in the database includes: (1) primary and secondary diagnoses (in International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] and ICD-10-CM format); (2) procedures (in ICD-9-CM, ICD-10 CM, Healthcare Common Procedure Coding System, and Current Procedural Terminology, Fourth Edition [CPT-4] format); (3) test and lab results; (4) setting of care (e.g., inpatient, emergency department), and date[s] of service; (5) prescription dispenses from outpatient pharmacies; (6) use of over-the-counter medications, noted in electronic medical records; and (7) total reimbursed amounts for medical care and prescription pharmacotherapies. The database is fully deidentified, compliant with the Health Insurance Portability and Accountability Act 1996, and spanned the period January 1, 2009 to September 30, 2016 (study period).

Patients were required to have ≥1 outpatient visits with diagnoses of CAD or PAD and either: (1) evidence of hospital admissions or emergency department visits for CAD (or PAD) >6 months previously (the first outpatient visit >6 months from the date of the last encounter for emergent care (either admission or emergency department visit) was designated the index date) or (2) a second outpatient visit for CAD (or PAD) ≥30 days subsequent to the initial outpatient visit, without evidence of emergent care for CAD (or PAD) between visits (the second outpatient visit was designated the index date) (Figure 1). For patients with multiple index dates, we selected the earliest identified. We focused attention on the period spanning July 1, 2009 to September 29, 2016 so that all selected patients had ≥6 months of baseline information and a minimum of 1 day of follow-up.

We excluded patients with <6 months enrollment before index date (preindex), and those: (1) with preindex evidence of atrial fibrillation (because our focus was on applicability of COMPASS to clinical practice, and rivaroxaban was already indicated for atrial fibrillation at the time the work was conducted); (2) without available preindex claims and electronic medical records data; or (3) aged <18 years at index date.

Follow-up for each patient began on the index date and extended until the earliest of death, disenrollment from health plan, or end of study period. All available information from patients' claims and electronic medical records were compiled for the preindex period and all of follow-up.

Demographic and clinical characteristics were based on information noted during preindex including age, gender, body mass index, geographic region, race, insurance type, selected co-morbidities, Charlson Comorbidity Index,[7] and preindex utilization and cost of healthcare services.

Outcomes of interest during follow-up included: (1) MACE, defined as myocardial infarction, stroke (ischemic or hemorrhagic), or CV-related death (described in detail in the paragraph below); (2) MALE, defined as critical limb ischemia, amputation (except for amputations related to accident/trauma), or PAD-related revascularization (definitions available upon request); and (3) serious bleeding events classified as fatal, related to hospitalization, or other serious bleeding, and defined using the Cunningham et al[8] validated algorithms. Apart from revascularization and CV-related death, patients had to have evidence of a hospital admission or emergency department visit during which a diagnosis specific to MACE/MALE was listed (for admissions, we focused on the primary diagnosis, which represents the reason for hospitalization) (>90% of all identified events resulted in hospital admission). Incidence of revascularization was based on ≥1 relevant procedure codes,

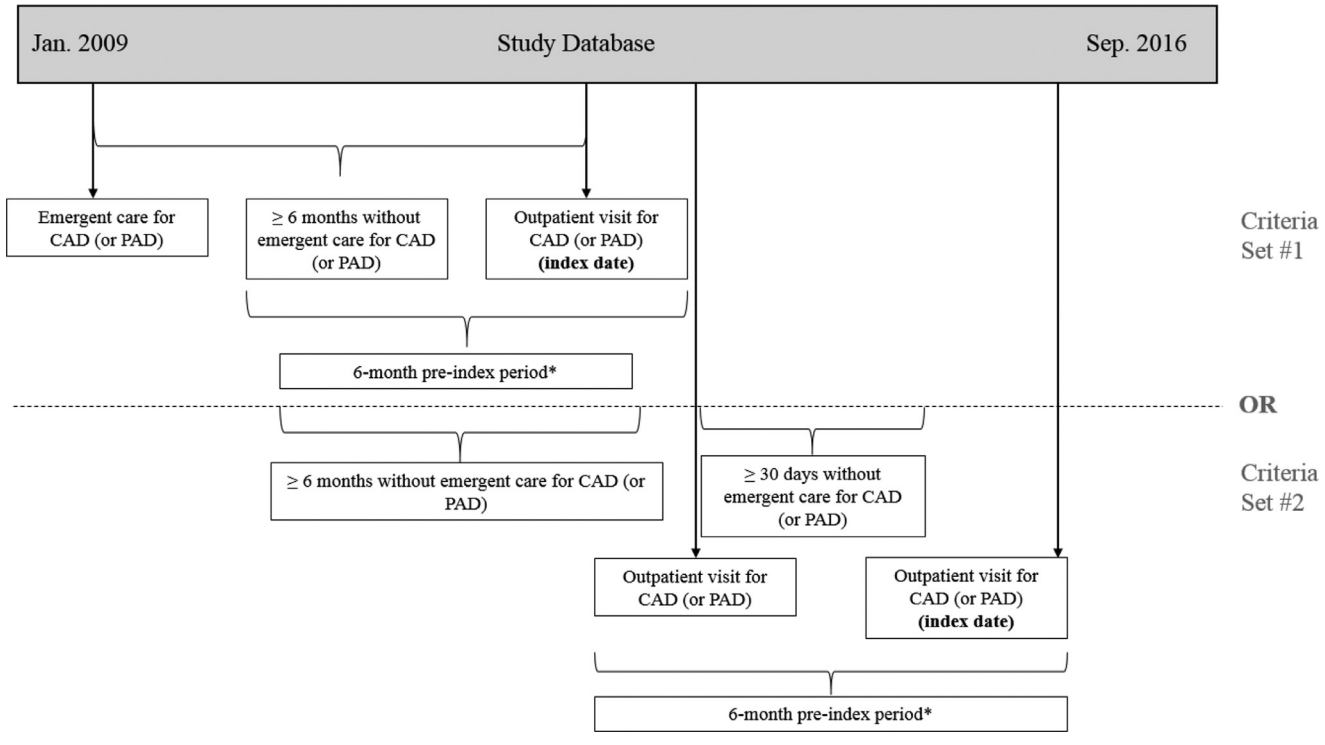

Figure 1. Illustration of sample selection.

irrespective of setting of care. Bleeds could occur in hospital or emergency department settings.

Mortality was assessed using specific information within the database (e.g., hospital discharge disposition, evidence of death recorded in the electronic medical record, diagnosis of death [e.g., ICD-9-CM 348.82, ICD-10 G93.82]), augmented by methods described by Paramore et al.[9] Specifically, death was assumed to have occurred if there was: (1) evidence during follow-up of a serious event (e.g., metastatic cancer, trauma, aortic dissection, and pulmonary embolism) resulting in ambulance service or emergent care (as defined above); (2) no subsequent claims for medical care or pharmacotherapy; and (3) disenrollment the next month. For all patients with evidence of death as defined above, those with CV-related diagnoses on the last date for which data were available (or during the admission where applicable) were assumed to have experienced CV-related death.

Total healthcare costs were assessed over the first year of follow-up and were defined as the sum of inpatient and outpatient care and prescription pharmacotherapy. In all instances, reimbursed amounts (i.e., insurance reimbursement plus patient liability [e.g., co-pay and co-insurance]) served as a proxy for costs. All costs were updated to reflect 2016 dollars using the medical-care component of the United States consumer price index.[10]

The incidence of MACE, MALE, and serious bleeds, respectively, during follow-up was assessed, along with corresponding incidence rates, expressed per 100 person-years (PYs). We stratified patients based on whether they experienced an event of interest during the first year and developed multivariate linear regression models to compare total 1-year healthcare costs between the 2 groups. Covariates used in these models included age, gender, race, payer type, smoking status, body mass index, preindex coronary artery bypass graft or percutaneous coronary intervention, limb ischemia, dyslipidemia, hypertension, and Charlson Comorbidity Index.

All analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina), and were run on the aggregate population as well as for the subgroups with CAD and PAD, respectively.

Results

A total of 99,730 patients were identified who met all selection criteria; 85,754 (86.0%) had CAD and 25,695 (25.8%) had PAD. Approximately 12% (n = 11,719) had both conditions.

Mean (±SD) age was 67.7 (±11.5) years; 59.8% were men, 71.8% were white, and 56.3% had Medicare insurance (Table 1). Co-morbidities were common—65.8% had hypertension and 61.5% had dyslipidemia. Most (74.3%) received CV-related prescription medications during preindex. Sixty-three percent of patients with CAD were male; the corresponding value for patients with PAD was 49.8%. The prevalence of co-morbidities was generally similar in the 2 subgroups, although PAD patients tended to be nominally more likely to have these conditions.

Over an average follow-up of 1.8 years, 13.6% of patients experienced ≥1 MACE or MALE (predominantly MACE), resulting in a rate of 6.3 events per 100 PYs (Table 2). The most common MACE was myocardial infarction and stroke; for MALE, they were critical limb ischemia and revascularization. Incidence and corresponding rates of MACE and MALE differed by subgroup, ranging from 12.4% (5.7 per 100 PYs) of patients with CAD to 22.9% (12.2 per 100 PYs) of patients with PAD. (It was 31.8% [11.6 per 100 PYs] in patients with both conditions [data not shown]). CAD patients were more likely to experience MACE than MALE; PAD patients were more likely to experience MALE than MACE.

Patients with MACE and/or MALE averaged $44,495 more in 1-year multivariate-adjusted total healthcare costs than those without these events ($p < 0.001$); patients with MACE averaged $51,779 more in total healthcare costs ($p < 0.001$); and for patients with MALE, it was $37,440 more ($p < 0.001$) (Table 3). In patients with CAD, those with MACE or MALE averaged $48,457 more in multivariate-adjusted total healthcare costs than those without, including $49,968 more in those with MACE and $42,962 more in those with MALE (all comparisons $p < 0.001$). In those with PAD, patients with MACE or MALE averaged $34,216 more in total healthcare costs than those without, including $44,659 more in those with MACE and $30,305 more in those with MALE (all $p < 0.001$).

A total of 7.0% of patients experienced a serious bleeding event during follow-up, at a rate of 3.1 per 100 PYs, with PAD patients more likely than CAD patients to experience these events (Table 2). In multivariate analyses, patients who experienced bleeds averaged $43,988 more in 1-year costs than those who did not; the subgroup with bleeds associated with hospitalization averaged $54,947 more in total 1-year healthcare cost (Table 3).

Discussion

Approximately 1-in-7 patients with chronic and stable CV disease in our study experienced a MACE or MALE within 2 years, including 1-in-8 patients with CAD, 1-in-5 patients with PAD, and 1-in-3 patients with CAD and PAD. Total 1-year healthcare costs associated with these events were $44,495 for all patients, $48,457 for those with CAD and $34,216 for those with PAD (the corresponding estimate for a person aged 65 years was $21,752 in 2017 dollars.[11])

Accordingly, within our sample, MACE and MALE may have increased total healthcare costs by about $603 million (i.e., 13.6% × 99,730 × $44,495). This however, is likely an underestimate, as we focused on incident events only; our use of a 1-year period over which to assess healthcare costs also likely limited the impact of these events, particularly for those with expected long-term sequelae, such as stroke. Given the proved efficacy noted in the COMPASS trial, use of rivaroxaban (in combination with low-dose aspirin) as secondary prevention for patients with CAD and/or PAD may reduce costs of care for MACE and/or MALE, albeit at an elevated risk of bleeding. We note that in COMPASS the net clinical benefit of rivaroxaban (plus low-dose aspirin) was found to be positive in the subgroup deemed treatment adherent, with a 20% lower risk of developing the relevant composite outcome (i.e., CV death, stroke, myocardial infarction,

Table 1
Baseline demographic and clinical characteristics by study cohort*

Variable	Any CAD (N = 85,754)	Any PAD (N = 25,695)	Aggregate (N = 99,730)
Mean (SD) age (years)	67.4 (11.4)	70.9 (11.2)	67.7 (11.5)
Men	53,654 (62.6%)	12,806 (49.8%)	59,596 (59.8%)
Race			
White	62,404 (72.8%)	17,397 (67.7%)	71,636 (71.8%)
Black	5,477 (6.4%)	2,611 (10.2%)	7,048 (7.1%)
Asian	1,190 (1.4%)	362 (1.4%)	1,348 (1.4%)
All other	16,683 (19.5%)	5,325 (20.7%)	19,698 (19.8%)
Payer type			
Commercial	38,795 (45.2%)	8,251 (32.1%)	43,555 (43.7%)
Medicare	46,958 (54.8%)	17,444 (67.9%)	56,174 (56.3%)
All other	1 (0.0%)	0 (0.0%)	1 (0.0%)
Geographic region			
Northeast	14,432 (16.8%)	5,343 (20.8%)	17,339 (17.4%)
Midwest	32,462 (37.9%)	9,314 (36.2%)	37,643 (37.7%)
South	31,943 (37.2%)	8,781 (34.2%)	36,528 (36.6%)
West	4,803 (5.6%)	1,547 (6.0%)	5,714 (5.7%)
Body mass index (kg/m^2)			
<18.5	257 (0.3%)	149 (0.6%)	356 (0.4%)
18.5−24.9	3,854 (4.5%)	1,580 (6.1%)	4,736 (4.7%)
25−29.9	6,929 (8.1%)	2,045 (8.0%)	7,919 (7.9%)
>30	8,947 (10.4%)	2,283 (8.9%)	10,047 (10.1%)
Missing/unknown	65,767 (76.7%)	19,638 (76.4%)	76,672 (76.9%)
Smoking status			
Current	7,984 (9.3%)	3,541 (13.8%)	9,820 (9.8%)
Former	7,518 (8.8%)	2,249 (8.8%)	8,539 (8.6%)
Never	5,364 (6.3%)	1,416 (5.5%)	6,178 (6.2%)
Missing/unknown	64,888 (75.7%)	18,489 (72.0%)	75,193 (75.4%)
Comorbidities			
Hypertension	56,549 (65.9%)	18,483 (71.9%)	65,608 (65.8%)
Dyslipidemia	54,137 (63.1%)	15,562 (60.6%)	61,371 (61.5%)
Diabetes mellitus	27,311 (31.8%)	10,136 (39.4%)	32,032 (32.1%)
Malignancy	18,264 (21.3%)	5,780 (22.5%)	21,287 (21.3%)
Chronic pulmonary disease	14,427 (16.8%)	5,504 (21.4%)	16,981 (17.0%)
Congestive heart failure	10,831 (12.6%)	2,832 (11.0%)	11,562 (11.6%)
Prior stroke	1,774 (2.1%)	802 (3.1%)	2,163 (2.2%)
Coronary bypass	1,123 (1.3%)	446 (1.7%)	1,315 (1.3%)
Percutaneous coronary intervention	2,047 (2.4%)	496 (1.9%)	2,179 (2.2%)
≥1 Cardiovascular-related prescription medications			
Anticoagulants	3,028 (3.5%)	1,088 (4.2%)	3,624 (3.6%)
Antiplatelets	19,739 (23.0%)	5,194 (20.2%)	21,230 (21.3%)
Antihypertensives	58,136 (67.8%)	16,025 (62.4%)	65,762 (65.9%)
Cholesterol-modifying agents	51,451 (60.0%)	12,982 (50.5%)	57,166 (57.3%)
Nitroglycerin	2,250 (2.6%)	332 (1.3%)	2,312 (2.3%)
Pentoxifylline	152 (0.2%)	248 (1.0%)	292 (0.3%)
Any of the above	64,910 (75.7%)	18,256 (71.0%)	74,055 (74.3%)
Mean (SD) total healthcare cost during the 6-month preindex period ($)	$11,549 ($25,233)	$14,492 ($31,009)	$11,659 ($25,279)

CAD = coronary artery disease; PAD = peripheral artery disease; SD = standard deviation.
* Unless otherwise noted, all variables are n (%).

fatal bleeding, and symptomatic bleeding) as compared with those randomized to aspirin only (hazard ratio: 0.80; 95% confidence interval: 0.70 to 0.90). However, it is important to note that available estimates of the reduction in risk of MACE and MALE, the increase in risk of bleeds, and the overall net clinical benefit of rivaroxaban (plus low-dose aspirin) are based on a highly selected population who demonstrated relatively high adherence to such therapy within the "artificial" environs of a randomized clinical trial. In clinical practice, the decision to use rivaroxaban will likely be dependent on the characteristics of a particular patient, including both risks for MACE and MALE and risk of bleeds. We note that clinicians already have some guidance with respect to the former, including the Thrombolysis In Myocardial Infarction risk score[12] and the Global Registry of Acute Coronary Events risk score[13] (although both focus on patients with acute coronary syndrome). Accordingly, corresponding estimates of the real-world clinical and economic consequences

Table 2
Incidence of MACE or MALE during all follow-up by cohort

	Any CAD (N = 85,754)				Any PAD (N = 25,695)				Aggregate (N = 99,730)			
	Events				Events				Events			
Event	N	%	Follow-up, years	Rate per##### 100 PYs	N	%	Follow-up, years	Rate per##### 100 PYs	N	%	Follow-up, years	Rate per##### 100 PYs
MACE												
Myocardial infarction	3818	4.5%	196,146.0	1.95	1150	4.5%	56,369.1	2.04	4270	4.3%	228,126.2	1.87
Stroke	3538	4.1%	197,093.7	1.80	1428	5.6%	55,915.6	2.55	4262	4.3%	228,620.3	1.86
Cardiovascular death	2398	2.8%	202,225.7	1.19	891	3.4%	57,966.7	1.54	2722	2.7%	234,845.1	1.16
Any MACE	8318	9.7%	191,567.3	4.34	2900	11.3%	54,527.6	5.32	9578	9.6%	222,533.5	4.30
MALE												
Critical limb ischemia	1832	2.1%	199,090.3	0.92	2880	11.2%	52,763.1	5.46	3459	3.5%	228,685.8	1.51
Amputation	353	0.4%	201,722.8	0.17	434	1.7%	57,315.1	0.76	574	0.6%	234,012.6	0.25
Revascularization	1951	2.3%	198,422.6	0.98	1664	6.5%	54,847.5	3.03	2782	2.8%	229,477.5	1.21
Any MALE	3323	3.9%	196,033.1	1.70	3788	14.7%	50,923.1	7.44	5,385	5.4%	224,748.7	2.40
Any MACE or MALE	10,609	12.4%	186,677.9	5.68	5887	22.9%	48,394.4	12.16	13,585	13.6%	214,178.4	6.34
Bleeding												
Associated with hospitalization	4,312	5.0%	195,533.7	2.2	1,684	6.6%	55,562.7	3.03	5,122	5.1%	226,975.4	2.36
Resulting in death	254	0.3%	202,155.9	0.13	94	0.4%	57,951.2	0.16	302	0.3%	234,224.5	0.13
Any bleeding event	5,874	6.8%	192,753.5	3.05	2,214	8.6%	54,709.1	4.05	6,956	7.0%	223,757.2	3.11

CAD = coronary artery disease; MACE = major adverse cardiac event; MALE = major adverse limb event; PAD = peripheral artery disease; PY = person-year.

associated using rivaroxaban (plus low-dose aspirin) as secondary prevention—along with its net clinical benefit—must remain conjectural until sufficient experience has been accumulated by practicing clinicians to undertake such an examination.

Incidence of the primary outcome in COMPASS (i.e., myocardial infarction, stroke, or CV-related death) observed in our real-world patients was nearly twice that of the aspirin-only arm of COMPASS (9.6% vs 5.4%), and the incidence of bleeds was more than triple (7.0% vs 1.9%).[2] This difference in MACE and MALE persisted for both MACE in CAD (9.7% vs 5.6%)[14] and MALE in PAD (10.7% vs 2.3%).[1] The rate of MACE observed in our study was approximately 50% higher than that reported by COMPASS (4.3 per 100 PYs vs 2.9 per 100 PYs).[15] One reason for this difference may be the difference in risk of the study populations; the current population (vs the COMPASS population) were less likely to have various co-morbidities (e.g., diabetes [32% vs 38%] and hypertension [66% vs 75%]); and less likely to have received lipid-lowering drugs (57% vs 89%).[2]

To the best of our knowledge, only 1 other study estimated incidence of MACE or MALE in real-world patients with chronic CAD/PAD based on definitions employed in COMPASS. Darmon et al implemented selection criteria from COMPASS on patients enrolled in the Reduction of Atherothrombosis for Continued Health registry, which is a large (n = 65,531) prospective international observational registry that included patients aged >45 years with established atherosclerotic arterial disease or ≥3 risk factors for atherothrombosis between December 2003 and June 2004. Only 52.9% of evaluable REACH enrollees met selection criteria for COMPASS.[15] Relative to our study, COMPASS-like subjects identified within the REACH registry were nominally older (mean age = 71.1 vs 67.7 years in our study), more likely to be men (64.5% vs 59.8%), and more likely to have various co-morbidities, including congestive heart failure (13.5% vs 11.6%), hypertension (86.0% vs 65.8%), hypercholesterolemia (78.0% vs 61.5%), and diabetes (41.0% vs 32.1%). Darmon et al also reported higher rates of MACE or MALE, including any MACE (4.2 per 100 PYs vs 2.9 per 100 PYs in COMPASS). Interestingly, while somewhat younger and less likely to have co-morbidities, the rate of MACE in the COMPASS-like patients in our study was comparable to that reported by Darmon et al. We believe that our study more closely reflects the current risk of MACE and MALE in patients with chronic CAD or PAD because: (1) it represents the experience of almost 100,000 patients with chronic CAD/PAD seen in clinical practices across the United States; (2) it captures a more recent time period; and (3) the use of insurance claims likely resulted in fairly comprehensive estimates of emergent MACE and MALE.

Our study has several potential limitations. First, it was based on analyses of electronic healthcare data, which may suffer from errors of omission and/or commission. Without access to patients or their physicians, the magnitude of such errors is unknowable. Second, while all patients had chronic disease and were precluded from experiencing MACE or MALE for at least 6 months before index date, they varied with respect to time with disease, number of previous MACE or MALE experienced, and underlying disease stability/severity. While this relatively heterogenous sample likely captured real-world patients and their event rates accurately, the impact of various factors such as time with disease on the outcomes of interest could not be ascertained. Third, we focused on the first MACE or MALE identified during follow-up; our findings therefore underrepresent the true rate of MACE or MALE and costs thereof. Fourth, assessment of mortality and the reason thereof was based on algorithms (where mortality was unavailable directly from medical

Table 3
Multivariate-adjusted healthcare costs of MACE or MALE during first year of follow-up by cohort

	Any CAD (N = 85,754)			Any PAD (N = 25,695)			Aggregate (N = 99,730)		
Costs ($)*	Event	No event	Difference†	Event	No event	Difference†	Event	No event	Difference†
MACE									
Myocardial infarction	$78,367 ($40,581-$151,338)	$21,219 ($11,010-$40,895)	$57,148	$74,985 ($65,024-$86,470)	$21,075 ($18,932-$23,460)	$53,910	$79,756 ($41,320-$153,943)	$21,816 ($11,323-$42,033)	$57,940
Stroke	$67,084 ($34,728-$129,584)	$20,846 ($10,816-$40,176)	$46,238	$61,322 ($53,505-$70,280)	$20,442 ($18,363-$22,756)	$40,880	$69,483 ($35,995-$134,127)	$21,357 ($11,085-$41,149)	$48,126
Cardiovascular death	$54,049 ($27,937-$104,567)	$21,102 ($10,949-$40,670)	$32,947	$52,909 ($45,225-$61,900)	$21,205 ($19,049-$23,605)	$31,704	$59,336 ($30,689-$114,724)	$21,741 ($11,284-$41,888)	$37,595
Any MACE	$70,602 ($36,598-$136,197)	$20,634 ($10,706-$39,768)	$49,968	$64,595 ($57,186-$72,964)	$19,936 ($17,908-$22,192)	$44,659	$73,068 ($37,892-$140,896)	$21,289 ($11,049-$41,017)	$51,779
MALE									
Critical limb ischemia	$59,678 ($30,851-$115,440)	$21,070 ($10,932-$40,609)	$38,608	$46,025 ($40,991-$51,678)	$19,285 ($17,323-$21,469)	$26,740	$52,449 ($27,180-$101,209)	$20,608 ($10,696-$39,706)	$31,841
Amputation	$82,113 ($41,718-$161,621)	$21,261 ($11,031-$40,976)	$60,852	$91,335 ($77,439-$107,725)	$20,918 ($18,791-$23,285)	$70,417	$96,773 ($49,666-$188,561)	$21,571 ($11,196-$41,561)	$75,202
PAD revascularization	$68,568 ($35,468-$132,557)	$21,115 ($10,955-$40,694)	$47,453	$62,822 ($55,586-$71,000)	$19,093 ($17,151-$21,254)	$43,729	$68,952 ($35,719-$133,105)	$20,746 ($10,768-$39,971)	$48,206
Any MALE	$63,987 ($33,137-$123,556)	$21,025 ($10,909-$40,521)	$42,962	$48,438 ($43,238-$54,263)	$18,133 ($16,288-$20,187)	$30,305	$57,541 ($29,836-$110,973)	$20,101 ($10,433-$38,729)	$37,440
Any MACE or MALE	$68,868 ($35,709-$132,819)	$20,403 ($10,586-$39,324)	$48,457	$51,384 ($45,948-$57,463)	$17,168 ($15,421-$19,113)	$34,216	$64,099 ($33,254-$123,557)	$19,604 ($10,175-$37,771)	$44,495
Bleeding									
Associated with hospitalization	$73,137 ($37,877-$141,219)	$21,031 ($10,912-$40,534)	$52,106	$70,408 ($61,671-$80,383)	$20,548 ($18,458-$22,873)	$49,860	$76,494 ($39,639- $147,615)	$21,547 ($11,183- $41,515)	$54,947
Resulting in death	$66,633 ($33,360-$133,091)	$21,295 ($11,049-$41,042)	$45,338	$60,728 ($41,785-$88,257)	$21,428 ($19,250-$23,853)	$39,300	$72,014 ($36,205- $143,241)	$21,849 ($11,340- $42,096)	$50,165
Any bleeding event	$62,136 ($32,198-$119,912)	$20,989 ($10,890-$40,452)	$41,147	$60,395 ($53,233-$68,522)	$20,496 ($18,412-$22,815)	$39,899	$65,516 ($33,966- $126,373)	$21,528 ($11,174- $41,478)	$43,988

CAD = coronary artery disease; MACE = major adverse cardiac event; MALE = major adverse limb event; PAD = peripheral artery disease.

* All costs are adjusted to 2016 dollars.

† All differences are significant, that is, p value <0.001.

records), the sensitivity and specificity of which are unknown. Fifth, while findings represent the total paid to providers for services and prescription pharmacotherapies, they do not include the cost of over-the-counter therapies or indirect costs. As the latter are believed to comprise approximately 40% of total costs of CV disease in the United States,[16] our findings represent a conservative estimate of the impact of MACE and MALE in patients with chronic and stable CAD or PAD. Similarly, our focus on 1-year costs likely underestimate total cost of MACE and MALE, particularly stroke, as most patients require substantial and long-term care (i.e., >12 months) following such an event. Finally, while large and geographically diverse, ours was a convenience—not a random—sample. Consequently, the generalizability of our findings to all patients with chronic and stable CAD or PAD is unknown.

In conclusion, approximately 1 in 7 patients with chronic and stable CAD or PAD in clinical practice experience MACE or MALE within approximately 2 years. Total healthcare costs in patients with MACE or MALE are about 3-fold higher than in those without. Further study is needed to better understand how the benefits of medications demonstrated in recent clinical trials translate to clinical practice.

Conflict of Interest Disclosure

AB, AS, TB, BM, and BN are employed by Evidera, a research and consulting company to the biopharma industry. In their salaried positions, they work with a variety of companies and organizations and are precluded from receiving payment or honoraria directly from these organizations for services rendered. NL reports an involvement with Bayer and Janssen, WT with Janssen as a consultant and speaker, and JB reports involvement with Janssen and AstraZeneca as a researcher. At the time the research was conducted, QZ was an employee of Janssen and TB was an employee of Evidera.

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Author Contributions: AB acted as principal investigator and conceptualized the study. AS and TB performed background research and interpretations of the data. AB and BM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. BM was responsible for data management and conducting the analysis. All authors contributed to the drafting and revision of the manuscript, and all gave their final approval of the final version to be published.

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