ORIGINAL RESEARCH

Incidence and Predictors of Major Adverse Cardiovascular Events in Patients With Established Atherosclerotic Disease or Multiple Risk Factors

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Background—There is a paucity of contemporary data estimating the incidence of major adverse cardiovascular events (MACE) in patients with established atherosclerotic disease or multiple risk factors managed in routine practice. We estimated 1- and 4-year incidences of MACE and the association between MACE and vascular beds affected in these patients.

Methods and Results—Using US IBM MarketScan data from January 1, 2013 to December 31, 2017, we identified patients ≥45 years old with established coronary artery disease, cerebrovascular disease, peripheral artery disease, or the presence of ≥3 risk factors for atherosclerosis during 2013 with a minimum of 4 years of follow-up. We calculated 1- and 4-year incidences of MACE (cardiovascular death or hospitalization for myocardial infarction or ischemic stroke). A Cox proportional hazards regression model adjusted for age and sex was used to evaluate the association between vascular bed number/location(s) affected and MACE. We identified 1 302 856 patients with established atherosclerotic disease or risk factors for atherosclerosis. Coronary artery disease was present in 16.9% of patients, cerebrovascular disease in 7.6%, peripheral artery disease in 13.6%, and risk factors for atherosclerosis only in 66.0%. The 1- and 4-year incidences of MACE were 1.4% and 6.9%, respectively. At 4 years, MACE was more frequent in patients with atherosclerotic disease in a single (hazard ratio=1.51, 95% CI=1.48–1.55), 2-(hazard ratio=2.35, 95% CI=2.27–2.44), or all 3 vascular beds (hazard ratio=3.30, 95% CI=2.97–3.68) compared with having risk factors for atherosclerosis.

Conclusions—Patients with established atherosclerotic disease or who have multiple risk factors and are treated in contemporary, routine practice carry a substantial risk for MACE at 1- and 4- years of follow-up. MACE risk was shown to vary based on the number and location of vascular beds involved. **(*J Am Heart Assoc*. 2020;9:e014402. DOI: 10.1161/JAHA.119.014402.)**

Key Words: cerebrovascular disease • coronary artery disease • established atherosclerotic disease • major adverse cardiovascular events • peripheral artery disease • risk factors

Cardiovascular disease is one of the leading causes of mortality in the United States.[1] Patients with atherosclerosis are at an elevated risk of major adverse cardiovascular events (MACE). Understanding the incidence rates and comparative risk of MACE based on atherosclerotic disease characteristics may greatly aid efforts to better treat such patients.[2]

The REACH (Reduction of Atherothrombosis for Continued Health) registry provided much–needed insight into clinical event rates of patients at risk of, or with, established atherosclerotic disease. Results from the 1- and 4-year REACH analyses demonstrated that MACE incidence increased over time, with the proportion experiencing MACE surpassing 14% at 4 years of follow-up.[2,3] Several predictors of future atherosclerotic events were also identified in REACH, including polyvascular disease.[3] However, the REACH cohort was enrolled between 2003 and 2004 and followed patients

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An accompanying Table S1 is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.119.014402

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Received August 29, 2019; accepted December 6, 2019.

Clinical Perspective

What Is New?

- Incidences of major adverse cardiovascular events at 1 and 4 years were provided for a contemporary at-risk population.
- Major adverse cardiovascular events incidence increased considerably over time and when multiple vascular beds were involved.

What Are the Clinical Implications?

- These findings may serve as a benchmark for both clinicians and other health professionals when making statements about major adverse cardiovascular events rates in a contemporary population, and when designing future clinical studies.
- There is a need for continued improvement in the prevention and treatment of patients with or at risk of atherosclerosis.

up to 2008. Advances in treatment and prevention of atherosclerotic diseases and changes to evidence-based guidelines over the past decade have had a positive impact on MACE risk.[4] Furthermore, there was likely an important degree of selection bias in the enrollment of REACH patients resulting in a final study cohort not fully representative of the types of atherosclerotic disease seen in daily practice.[3]

This study aimed to provide benchmark estimates for the incidence of MACE in US patients at risk of, or with, established atherosclerotic disease in contemporary routine practice. We also sought to assess the association between the number and type of vascular beds affected and MACE risk.

Methods

Data used in this study were obtained from IBM MarketScan under a license to Bayer AG (and provided to the researchers under a third-party agreement) and cannot be shared.

We performed a retrospective claims database analysis using US IBM MarketScan data from January 1, 2013 through December 31, 2017. IBM MarketScan combines 2 separate databases, a commercial and a Medicare supplemental database, to cover all age groups, and contains claims from 260 contributing employers, 40 health plans, and government and public organizations representing ≈240 million lives.[5] IBM MarketScan captures enrollment records, demographics, *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis codes (and cross-walked *ICD-9* codes), procedure codes, admission and discharge dates, outpatient medical services data, and prescription dispensing records. All MarketScan data are de-identified and are compliant with the Health Insurance Portability and Accountability Act of 1996. This study was determined by our institutional review board to not constitute research involving human subjects according to 45 Code of Federal Regulations 46.102(f) and was deemed exempt from board oversight.

We identified eligible patients according to similar criteria used in the REACH registry by examining claims data in calendar year 2013 (January 1, 2013 through December 31, 2013). All patients ≥45 years of age with established coronary artery disease (CAD) (ie, diagnosis codes suggesting a history of stable[6] or unstable angina,[7] percutaneous coronary intervention,[8,9] coronary artery bypass grafting,[8,10] or myocardial infarction[10]), cerebrovascular disease (CVD) (ie, diagnosis codes suggesting a history of ischemic stroke or transient ischemic attack[11]) or peripheral artery disease (PAD) (ie, diagnosis codes suggesting a history of peripheral arterial disease[9,12] or a prior intervention including angioplasty, stenting, atherectomy, peripheral arterial bypass grafting or amputations[9,10]) or with 3 or more risk factors for atherosclerosis (ie, diagnosis codes suggesting a history of diabetes mellitus,[13] diabetic nephropathy,[9,13] carotid stenosis,[14] hypertension,[13] hypercholesterolemia,[13] smoking,[14] or age ≥65 years for men or ≥70 years for women) were included (Table S1).

Our primary outcome measure was the incidence of MACE (composite of cardiovascular death, myocardial infarction, or ischemic stroke). Secondary outcomes include the incidence of individual MACE components. Myocardial infarction and ischemic stroke were defined as the occurrence of a hospitalization with the appropriate billing codes in the primary position. Cardiovascular death was defined as death occurring in the hospital within 14 days of a myocardial infarction, ischemic stroke, heart failure,[13] acute coronary syndrome,[7] coronary artery bypass grafting, or percutaneous coronary intervention. Baseline data included demographics, vascular disease status, atherothrombotic risk factors, and medications. Patient selection and identification of baseline characteristics were based on the presence of *ICD-10* (or cross-walked *ICD-9*) billing codes from medical and/or prescription claims. Starting on January 1, 2014, patients who met eligibility criteria during calendar year 2013 were followed for 1 and 4 years (patients with at least 9 months of follow-up were included in the 1-year analysis and with at least 3 years and 9 months of follow-up were included in the 4-year analysis) or until MACE occurrence.

Baseline characteristics were analyzed using descriptive statistics. Categorical data were reported as percentages and continuous data as medians with accompanying 25%, 75% ranges. Outcomes were reported as cumulative incidences (proportion of patients experiencing an event) and incidence rates (events/100 person-years [PYs]). A multivariable Cox proportional hazards regression model adjusted for age and sex were utilized to evaluate the association between the number and different vascular bed locations and MACE rates

(model #1). The proportional hazards assumption was tested based on Schoenfeld residuals and was found to be valid for all outcomes. An additional multivariable regression analysis in which we adjusted for age, sex as well as additional risk factors and medications was also performed (model #2). Associations were reported as adjusted hazard ratios with 95% CIs. We performed a sensitivity analysis in which we evaluated an alternative MACE end point that added hospitalization for vascular events or procedures (ie, heart failure, coronary artery bypass graft, percutaneous coronary intervention, acute coronary syndrome, and major adverse limb events). All data management and statistical analysis were performed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY) and SAS 9.4 (SAS Institute Inc, Cary, NC).

Results

Baseline Characteristics

We identified 1 302 856 patients with established atherosclerotic disease or ≥3 risk factors, of whom 1 220 144 (94%) were eligible for inclusion in the 1-year analysis and 625 951 (48%) were eligible for the 4-year analysis (Figure 1). Eligible patients had a median (25%, 75% range) age of 69 years (59, 77) and 46.6% were women (Table 1). Patients with established disease comprised 34.0% of our total eligible population, with the remainder limited to having 3 or more risk factors for atherosclerosis only. Among patients with established atherosclerotic disease, 49.9% had CAD, 22.4% had CVD, and 40.0% had PAD involvement. Most patients had hypertension (95.7%) and hypercholesterolemia (83.0%) and diabetes mellitus was present in >50% of patients. Approximately two thirds of patients received an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, three quarters received a statin, ≈14% a P2Y12, and about half were taking a β-blocker at baseline.

1-Year Outcomes

MACE occurred in 1.4% (1.47 events/100 PYs) of all patients at 1 year with 2.1% (2.12 events/100 PYs) in patients with established disease and 1.1% (1.14 events/100 PYs) in patients with multiple risk factors (Figure 2). MACE events were mainly driven by hospitalization for myocardial infarction (0.8%, 0.77 events/100 PYs), followed by ischemic stroke (0.6%, 0.64 events/100 PYs), and cardiovascular death (0.2%, 0.16 events/100 PYs). Among patients with established disease, MACE incidences were highest in patients with CVD (3.0%), followed by CAD (2.1%) and PAD (2.0%) involvement. Upon sensitivity analysis our alternative MACE end point found higher rates of MACE because of a 2.9% (2.99 events/100 PYs) incidence of hospitalization for additional vascular events or procedures (Figure 3). Cumulative incidence curves for each subgroup by vascular bed are shown in Figure 4.

Multivariable Cox regression analyses adjusted for age and sex (model #1) suggested that compared with patients with risk factors only, established atherosclerotic disease in a single vascular bed was associated with a 68% increased risk of MACE (ranging from 38% for PAD to 121% for CVD) (Figure 5, Table 2). Results of multivariable regression adjusting for age, sex, and additional risk factors and medications (model #2) provided results similar to model #1. Involvement of 2 vascular beds was associated with an increased MACE risk of 186% (ranging from 152% for PAD+CAD to 256% for CAD+CVD). The presence of disease in all 3 vascular beds was associated with a 338% increased risk of MACE risk versus having ≥3 risk factors only. The types of MACE

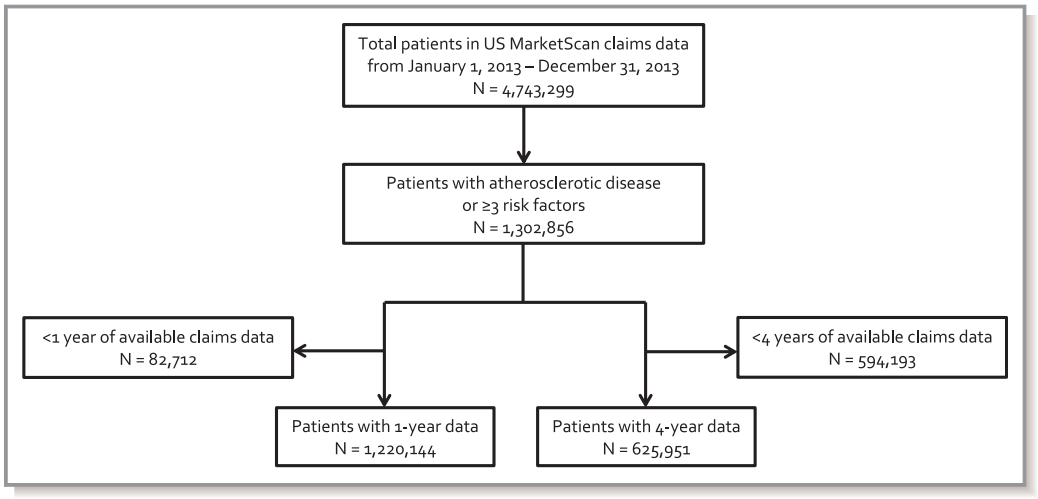

Figure 1. Flow diagram of patient selection.

Table 1. Baseline Characteristics of Individuals Evaluated at 1 Year of Follow-Up

	All	Total Established Disease	Any CAD*	Any CVD*	Any PAD*	Multiple Risk Factors Only
	N=1 220 144	N=414 718	N=206 804	N=92 695	N=165 967	N=805 426
Demographics, n (%)						
Age, y (median, 25%, 75% range)	69 (59, 77)	68 (58, 77)	66 (57, 76)	70 (60, 79)	70 (60, 79)	69 (59, 77)
45–64	482 682 (39.6)	177 817 (42.9)	97 413 (47.1)	33 921 (36.6)	61 874 (37.3)	304 865 (37.9)
65–74	347 443 (28.5)	102 711 (24.8)	51 626 (25.0)	22 772 (24.6)	42 786 (25.8)	244 732 (30.4)
75–84	301 033 (24.7)	98 639 (23.8)	44 877 (21.7)	25 978 (28.0)	43 528 (26.2)	202 394 (25.1)
≥85	88 986 (7.3)	35 551 (8.6)	12 888 (6.2)	10 024 (10.8)	17 779 (10.7)	53 435 (6.6)
Females	568 449 (46.6)	182 121 (43.9)	75 582 (36.5)	48 838 (52.7)	78 008 (47.0)	386 328 (48.0)
Vascular disease status, n (%)						
CAD	206 804 (16.9)	206 804 (49.9)	206 804 (100)	14 372 (15.5)	26 593 (16.0)	0 (0)
CVD	92 695 (7.6)	92 695 (22.4)	14 372 (6.9)	92 695 (100)	12 892 (7.8)	0 (0)
PAD	165 967 (13.6)	165 967 (40.0)	26 593 (12.9)	12 892 (13.9)	165 967 (100)	0 (0)
Polyvascular disease	47 639 (11.5)	47 639 (11.5)	37 856 (18.3)	24 155 (26.1)	36 376 (21.9)	0 (0)
Risk factors only	805 426 (66.0)	0 (0)	0 (0)	0 (0)	0 (0)	805 426 (100)
CAD alone	168 948 (13.8)	168 948 (40.7)	168 948 (81.7)	0 (0)	0 (0)	0 (0)
CVD alone	68 540 (5.6)	68 540 (16.5)	0 (0)	68 540 (73.9)	0 (0)	0 (0)
PAD alone	129 591 (10.6)	129 591 (31.2)	0 (0)	0 (0)	129 591 (78.1)	0 (0)
CAD+CVD	11 263 (0.9)	11 263 (2.7)	11 263 (5.4)	11 263 (12.2)	0 (0)	0 (0)
CAD+PAD	23 484 (1.9)	23 484 (5.7)	23 484 (11.4)	0 (0)	23 484 (14.1)	0 (0)
CVD+PAD	9783 (0.8)	9783 (2.4)	0 (0)	9783 (10.6)	9783 (5.9)	0 (0)
CAD+CVD+PAD	3109 (0.3)	3109 (0.7)	3109 (1.5)	3109 (3.4)	3109 (1.9)	0 (0)
Risk factors, n (%)						
Diabetes mellitus	664 852 (54.5)	158 985 (38.3)	78 617 (38.0)	34 435 (37.1)	70 941 (42.7)	505 867 (62.8)
Diabetic nephropathy	35 461 (2.9)	8745 (2.1)	4353 (2.1)	1847 (2.0)	4258 (2.6)	26 716 (3.3)
Carotid stenosis	119 502 (9.8)	61 549 (14.8)	25 793 (12.5)	22 576 (24.4)	28 499 (17.2)	57 953 (7.2)
Hypertension with treatment	1 167 903 (95.7)	372 716 (89.9)	193 102 (93.4)	83 534 (90.1)	144 929 (87.3)	795 187 (98.7)
Hypercholesterolemia with treatment	1 012 856 (83.0)	287 540 (69.3)	159 801 (77.3)	62 524 (67.5)	104 989 (63.3)	725 316 (90.1)
Smoker	82 309 (6.7)	30 172 (7.3)	15 909 (7.7)	6246 (6.7)	13 131 (7.9)	52 137 (6.5)
Age ≥70 y in females or ≥65 y in males	692 709 (56.8)	217 950 (52.6)	101 416 (49.0)	53 959 (58.2)	95 744 (57.7)	474 759 (58.9)
Medication use, n (%)						
ACE/ARB	819 305 (67.1)	238 925 (57.6)	126 245 (61.0)	52 377 (56.5)	92 405 (55.7)	580 380 (72.1)
β-blockers	603 103 (49.4)	229 397 (46.4)	140 479 (67.9)	45 618 (49.2)	78 324 (47.2)	373 706 (46.4)
Calcium channel blockers	388 394 (31.8)	125 793 (30.3)	60 270 (29.1)	31 832 (34.3)	52 535 (31.7)	262 601 (32.6)
Diuretics	541 473 (44.4)	167 789 (40.5)	83 814 (40.5)	37 480 (40.4)	71 110 (42.8)	373 684 (48.4)
Antidiabetic agents	502 417 (41.2)	112 629 (27.2)	56 698 (27.4)	22 981 (24.8)	50 095 (30.2)	389 788 (48.4)
Statin	958 703 (78.6)	275 428 (66.4)	154 072 (74.5)	59 954 (64.7)	99 705 (60.1)	683 275 (84.8)
P2Y12 inhibitors	172 802 (14.2)	111 640 (26.9)	75 184 (36.4)	24 181 (26.1)	33 998 (20.5)	61 162 (7.6)
Oral anticoagulants	137 180 (11.2)	58 432 (14.1)	29 058 (14.1)	17 521 (18.9)	22 271 (13.4)	78 748 (9.8)
NSAIDs including COX-2 inhibitors	261 459 (21.4)	84 030 (20.3)	41 413 (20.0)	18 492 (19.9)	33 427 (20.1)	177 429 (22.0)

ACE/ARB indicates angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; CAD, coronary artery disease; COX-2, cyclo-oxygenase-2; CVD, cerebrovascular disease; NSAIDs, nonsteroidal anti-inflammatory drugs; PAD, peripheral artery disease.
*These cohorts overlap each other.

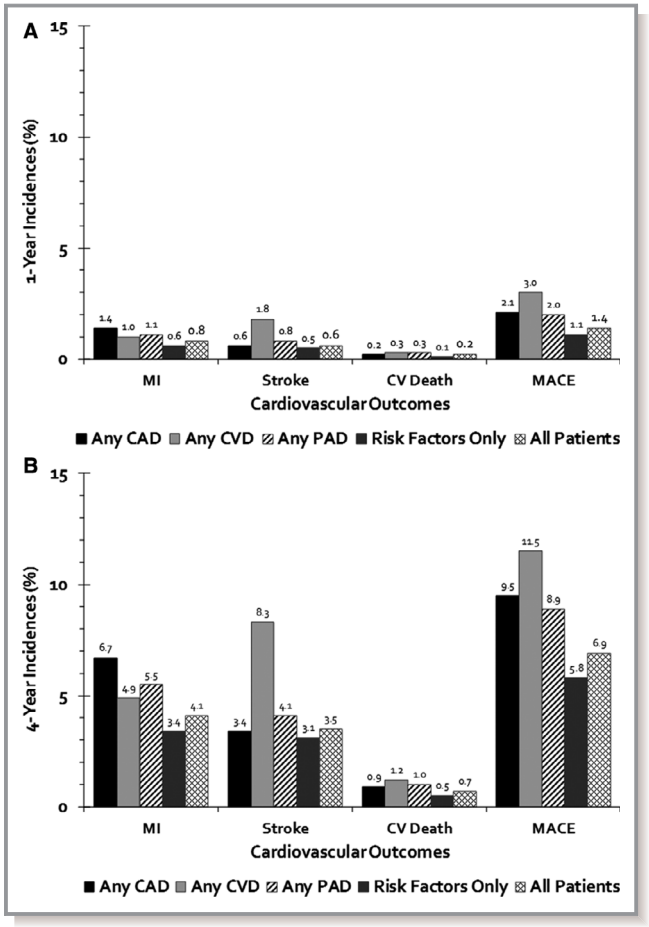

Figure 2. Incidence of MACE of individuals evaluated at 1 (**A**) and 4 years (**B**) of follow-up. CAD indicates coronary artery disease; CV, cardiovascular; CVD, cerebrovascular disease; MACE, major adverse cardiovascular event; MI, myocardial infarction; PAD, peripheral artery disease.

experienced in the CAD, CVD, PAD, and multiple risk factor cohorts are shown in Table 3.

4-Year Outcomes

At 4 years, MACE was 6.9% (1.89 events/100 PYs) overall with 9.1% (2.58 events/100 PYs) in patients with established disease and 5.8% (1.54 events/100 PYs) in patients with multiple risk factors (Figure 2). Incidence rates for MACE outcomes increased at 4 years compared with that of 1 year. Events remained highest in CVD (11.5%), followed by CAD (9.5%) and PAD (8.9%). Myocardial infarction, ischemic stroke, and cardiovascular death occurred in 4.1% (1.11 events/100 PYs), 3.5% (0.95 events/100 PYs), and 0.7% (0.17 events/100 PYs) of all patients, respectively. Upon sensitivity analysis, our alternative MACE end point again found higher rates of MACE because of a 14.4% (4.02 events/100 PYs) incidence of hospitalization for additional vascular events or procedures.

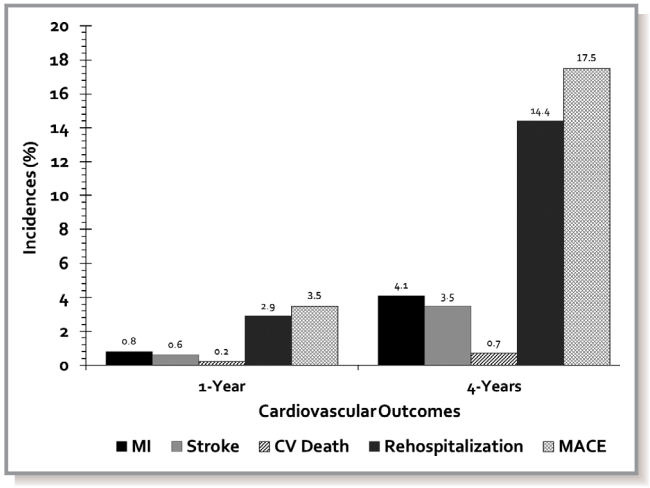

Figure 3. Incidence of major adverse cardiovascular events including hospitalization for vascular events or procedures at 1 and 4 years of follow-up. CV indicates cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.

Upon multivariable Cox regression adjusted for age and sex (model #1), there was a 51% increase in MACE risk in single vascular disease (ranging from 31% for PAD to 79% for CVD) compared with patients with risk factors only. Cox regression adjusting for age, sex, and additional risk factors and medications (model #2) yielded results that were overall

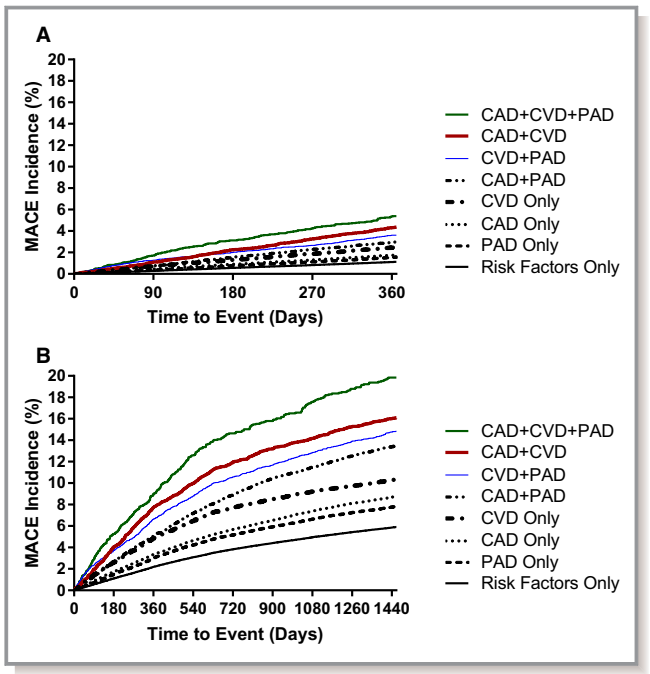

Figure 4. Cumulative incidence of MACE of individuals evaluated at 1 (**A**) and 4 years (**B**) of follow-up by vascular beds. CAD indicates coronary artery disease; CVD, cerebrovascular disease; MACE, major adverse cardiovascular event; PAD, peripheral artery disease.

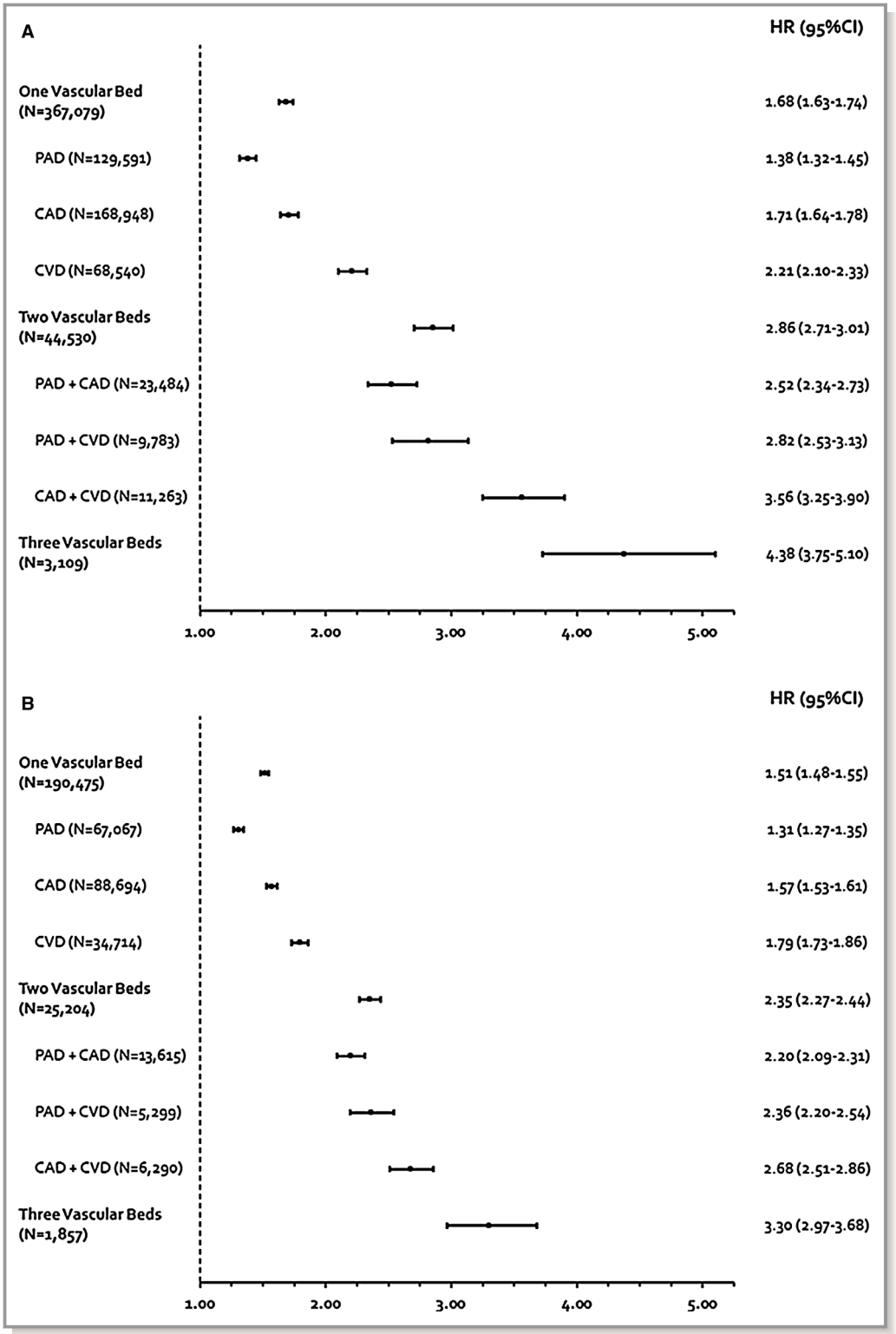

Figure 5. Relative hazard of MACE of individuals evaluated at 1 (**A**) and 4 years (**B**) of follow-up by vascular beds. CAD indicates coronary artery disease; CVD, cerebrovascular disease; HR, hazard ratio; PAD, peripheral artery disease.

consistent with model #1. Involvement of 2 vascular beds was associated with a 135% increase in risk (ranging from 120% for PAD+CAD to 168% for CAD+CVD). When 3 vascular beds were involved, MACE risk was increased by 230%. Rates for the overall and each MACE outcome separately are listed in Table 4.

Table 2. Cox Regression Models of MACE at 1- and 4 Years of Follow-Up

Variables	1-Year of Follow-Up		4 Years of Follow-Up	
	Model #1 HR (95% CI)	Model #2 HR (95% CI)	Model #1 HR (95% CI)	Model #2 HR (95% CI)
Age, y				
45–64	1.44 (1.38–1.50)	1.47 (1.41–1.54)	1.32 (1.28–1.35)	1.35 (1.31–1.38)
75–84	2.17 (2.08–2.25)	2.26 (2.16–2.35)	2.15 (2.10–2.21)	2.24 (2.18–2.30)
≥85	3.50 (3.33–3.67)	3.71 (3.53–3.91)	3.71 (3.59–3.83)	3.92 (3.79–4.06)
Female	0.80 (0.78–0.83)	0.81 (0.79–0.84)	0.79 (0.78–0.81)	0.80 (0.79–0.82)
Vascular beds (RFO as referent)				
CAD only	1.71 (1.64–1.78)	1.50 (1.43–1.57)	1.57 (1.53–1.61)	1.36 (1.33–1.40)
CVD only	2.21 (2.10–2.33)	2.05 (1.95–2.17)	1.79 (1.73–1.85)	1.66 (1.60–1.72)
PAD only	1.38 (1.32–1.45)	1.28 (1.22–1.35)	1.31 (1.27–1.35)	1.21 (1.17–1.24)
CAD+CVD	3.56 (3.25–3.90)	2.68 (2.44–2.94)	2.68 (2.51–2.86)	2.01 (1.88–2.15)
CAD+PAD	2.52 (2.34–2.73)	1.83 (1.69–1.98)	2.20 (2.09–2.31)	1.61 (1.53–1.70)
CVD+PAD	2.82 (2.53–3.13)	2.29 (2.05–2.55)	2.36 (2.20–2.54)	1.94 (1.80–2.09)
CAD+CVD+PAD	4.38 (3.75–5.10)	2.82 (2.41–3.29)	3.30 (2.97–3.68)	2.16 (1.94–2.41)
Risk factors				
Diabetes mellitus	…	1.25 (1.20–1.30)	…	1.17 (1.14–1.20)
Diabetic nephropathy	…	1.27 (1.17–1.37)	…	1.25 (1.19–1.31)
Carotid stenosis	…	1.13 (1.08–1.18)	…	1.09 (1.06–1.12)
Hypertension with treatment	…	1.16 (1.06–1.26)	…	1.16 (1.09–1.22)
Hypercholesterolemia	…	0.88 (0.81–0.95)	…	0.91 (0.87–0.96)
Smoker	…	1.56 (1.47–1.65)	…	1.47 (1.42–1.53)
Medications				
ACEI or ARB	…	0.94 (0.91–0.97)	…	0.93 (0.91–0.95)
β-blocker	…	1.29 (1.25–1.33)	…	1.24 (1.22–1.27)
Calcium channel blocker	…	1.13 (1.10–1.17)	…	1.14 (1.12–1.17)
Diuretics	…	1.07 (1.04–1.10)	…	1.05 (1.03–1.08)
Statin	…	0.87 (0.80–0.93)	…	0.84 (0.80–0.88)
P2Y12 inhibitor	…	1.49 (1.43–1.54)	…	1.51 (1.48–1.55)
Oral anticoagulant	…	1.04 (0.99–1.08)	…	1.05 (1.02–1.08)
Metformin	…	0.88 (0.84–0.91)	…	0.91 (0.89–0.94)
α-glucosidase inhibitor	…	1.37 (1.06–1.79)	…	1.10 (0.91–1.32)
DPP4 inhibitors	…	0.97 (0.91–1.03)	…	0.98 (0.94–1.02)
GLP1 agonists	…	0.76 (0.68–0.85)	…	0.80 (0.75–0.86)
SGLT2 inhibitors	…	1.00 (0.78–1.28)	…	0.95 (0.81–1.11)
Sulphonylureas or glinides	…	1.24 (1.18–1.29)	…	1.21 (1.18–1.25)
Thiazolidinediones	…	0.89 (0.82–0.98)	…	0.92 (0.87–0.98)
Insulin	…	1.74 (1.67–1.82)	…	1.76 (1.71–1.81)

ACEI or ARB indicates angiotensin-converting enzyme inhibitor or angiotensin receptor blocker; CAD, coronary artery disease; CVD, cerebrovascular disease; DPP4, dipeptidyl peptidase IV; GLP-1, glucagon-like peptide-1; HR, hazard ratio; MACE, major adverse cardiovascular event; PAD, peripheral artery disease; RFO, risk factors only; SGLT2, sodium/glucose cotransporter member 2.

Table 3. Incidences and Rates of MACE at 1-Year of Follow-Up

	All	Total Established Disease	Any CAD*	Any CVD*	Any PAD*	Multiple Risk Factors Only
	N=1 220 144 Events/100 PY (95% CI) n (%)	N=414 718 Events/100 PY (95% CI) n (%)	N=206 804 Events/100 PY (95% CI) n (%)	N=92 695 Events/100 PY (95% CI) n (%)	N=165 967 Events/100 PY (95% CI) n (%)	N=805 426 Events/100 PY (95% CI) n (%)
MACE	1.47 (1.45–1.49)	2.12 (2.07–2.16)	2.19 (2.12–2.25)	3.04 (2.93–3.16)	2.04 (1.97–2.11)	1.14 (1.11–1.16)
	17 671 (1.4)	8620 (2.1)	4437 (2.1)	2749 (3.0)	3322 (2.0)	9051 (1.1)
Myocardial infarction	0.77 (0.76–0.79)	1.14 (1.11–1.17)	1.44 (1.39–1.49)	1.07 (1.00–1.13)	1.11 (1.06–1.16)	0.59 (0.57–0.60)
	9320 (0.8)	4648 (1.1)	2922 (1.4)	971 (1)	1812 (1.1)	4672 (0.6)
Ischemic stroke	0.64 (0.62–0.65)	0.88 (0.86–0.91)	0.65 (0.61–0.68)	1.89 (1.80–1.98)	0.81 (0.77–0.86)	0.51 (0.49–0.52)
	7669 (0.6)	3616 (0.9)	1325 (0.6)	1713 (1.8)	1333 (0.8)	4053 (0.5)
Cardiovascular death	0.16 (0.15–0.17)	0.23 (0.22–0.25)	0.23 (0.21–0.25)	0.31 (0.27–0.35)	0.26 (0.24–0.29)	0.12 (0.11–0.13)
	1914 (0.2)	955 (0.2)	475 (0.2)	283 (0.3)	426 (0.3)	959 (0.1)

CAD indicates coronary artery disease; CVD, cerebrovascular disease; MACE, major adverse cardiovascular event; PAD, peripheral artery disease; PY, person-years.
*These cohorts overlap each other.

Discussion

In this large, contemporary real-world study of patients with established atherosclerosis or at high risk for atherosclerotic complications, the proportion of patients experiencing MACE increased by nearly 5-fold from year 1 to 4 of follow-up. Sensitivity analysis in which hospitalizations for additional vascular events and procedures were included in the definition of MACE showed an even higher incidence of events that were driven largely by rehospitalizations. The development of MACE appeared to vary depending on the number and location of vascular bed(s) affected. Atherosclerotic disease in a single vascular bed increased risk for MACE by up to 68%, whereas disease in 3 beds was associated with an ≈4-fold increase in MACE. Patients with any CVD involvement experienced the highest rates of MACE followed by patients with any CAD then any PAD, regardless of the number of vascular beds affected. Our findings may serve as a benchmark for both clinicians and other health professionals when making statements about MACE rates in a contemporary population, and when designing future clinical trials.

Although our inclusion criteria were similar to that of REACH and most of our findings were consistent with those observed in the prospective studies, there are key differences in findings worth mentioning. After 4 years of follow-up, MACE risk in patients with established disease increased both in REACH and our study by a substantial degree (3.4-fold in REACH and 4.3-fold in our study). Absolute incidences for MACE were, however, different. At 1 year, 4.2% of patients in REACH experienced MACE versus only 1.4% in our evaluation.

Table 4. Incidences and Rates of MACE at 4 Years of Follow-Up

	All	Total Established Disease	Any CAD*	Any CVD*	Any PAD*	Multiple Risk Factors Only
	N=625 951 Events/100 PY (95% CI) n (%)	N=217 536 Events/100 PY (95% CI) n (%)	N=110 456 Events/100 PY (95% CI) n (%)	N=48 160 Events/100 PY (95% CI) n (%)	N=87 838 Events/100 PY (95% CI) n (%)	N=408 415 Events/100 PY (95% CI) n (%)
MACE	1.89 (1.87–1.91)	2.58 (2.54–2.61)	2.70 (2.65–2.76)	3.34 (3.26–3.43)	2.54 (2.49–2.60)	1.54 (1.53–1.56)
	43 428 (6.9)	19 859 (9.1)	10 542 (9.5)	5539 (11.5)	7853 (8.9)	23 569 (5.8)
Myocardial infarction	1.11 (1.10–1.13)	1.54 (1.52–1.57)	1.89 (1.84–1.93)	1.37 (1.31–1.42)	1.53 (1.49–1.58)	0.90 (0.88–0.91)
	25 918 (4.1)	12 088 (5.6)	7443 (6.7)	2337 (4.9)	4810 (5.5)	13 830 (3.4)
Ischemic stroke	0.95 (0.93–0.96)	1.21 (1.18–1.23)	0.95 (0.92–0.98)	2.36 (2.28–2.43)	1.15 (1.12–1.19)	0.81 (0.80–0.83)
	22 051 (3.5)	9487 (4.4)	3800 (3.4)	3975 (8.3)	3631 (4.1)	12 564 (3.1)
Cardiovascular death	0.17 (0.17–0.18)	0.25 (0.24–0.26)	0.23 (0.22–0.25)	0.33 (0.31–0.36)	0.28 (0.26–0.30)	0.14 (0.13–0.14)
	4123 (0.7)	1985 (0.9)	949 (0.9)	580 (1.2)	904 (1.0)	2138 (0.5)

CAD indicates coronary artery disease; CVD, cerebrovascular disease; MACE, major adverse cardiovascular event; PAD, peripheral artery disease; PY, person-years.
*These cohorts overlap each other.

Similarly, the absolute risk of MACE varied when focusing solely on patients with established atherosclerotic disease (15.8% in REACH versus 9.1% in our study at 4 years).[2,3] These inconsistencies in absolute MACE risk evaluations are likely a consequence of important differences in patients' relative involvement of various vascular beds. Selection of patients in the REACH registry may not have resulted in a cohort that is entirely representative of those with established or at high risk for atherosclerotic disease. In particular, this selection bias in REACH appears to have resulted in patients with established PAD or risk factors only being substantially under-represented. The 2019 heart disease statistics report from the American Heart Association[15] suggest that in contrast to the relative prevalence of established CAD, there should be about one third as many patients with CVD and nearly twice as many with PAD. In REACH, the ratio of CAD to PAD patients was only 1 to 0.22, while the ratio in our study (1–0.80) was closer to that reported by the American Heart Association. The investigators of REACH have acknowledged the limited external validity of their findings resulting from their non-population-based registry.[3]

Moreover, REACH patients with established PAD had a high MACE risk in comparison to patients with disease in other vascular beds. Findings from the 1-year analysis of REACH concluded that PAD patients suffered from the highest MACE and cardiovascular death rates,[3] whereas we found PAD patients had the lowest rates of MACE and second lowest rates of cardiovascular death among patients with atherosclerotic disease at both 1 and 4 years. Prior research[16] suggests that fewer than 50% of patients with PAD are aware of the condition, while physicians are unaware of the presence of PAD in 70% of those with the condition. Classic claudication symptoms are found in only a minority of patients (11%),[17] and the US Preventive Services Task Force has stated there is insufficient evidence to support the use of the ankle–brachial index in screening for PAD among asymptomatic individuals (likely impeding the diagnosis of patients with less severe disease).[18] It is therefore possible that the patients with established PAD who were selected for enrollment into the REACH registry had more severe disease (presence of acute limb ischemia/Fontaine class 3 or higher) compared with PAD patients included in our analysis. Such differences in patient selection/inclusion could certainly explain some of the difference in MACE rates observed between the 2 studies.

Advances in the prevention and treatment of atherosclerotic disease have contributed substantially to reductions in the incidence of MACE.[4] Since the REACH registry completed its patient follow-up in 2008, notable changes have been made to standards of care for the management of atherosclerotic disease patients. These included several updates to American College of Cardiology/American Heart Association guidelines, which have recommended more intensive blood pressure control, increased use of high-intensity statins, and an increased scope and duration of treatment with dual antiplatelet therapy.[19–21] As a result, over the past decade, age-adjusted death rates for cardiovascular disease patients dropped by 22.1% in the United States,[15] with data suggesting that ≈47% of the decline in cardiovascular death was because of evidence-based medical and surgical treatments, including secondary preventive therapies after myocardial infarction or revascularization (11%), initial treatments for acute myocardial infarction or unstable angina (10%), treatments for heart failure (9%), revascularization for chronic angina (5%), and other therapies (12%). Another 44% of the decline in cardiovascular death was attributed to greater reductions in key risk factors, such as total cholesterol (24%), systolic blood pressure (20%), smoking prevalence (12%), and physical inactivity (5%).[4,22] As our study cohort consisted of patients identified during calendar year 2013 and treated/followed through 2017, it provides data on patients with established or at high risk for atherosclerotic disease managed under these new standards of care. Our study suggests that patients with established or at high risk for atherosclerotic disease still have a substantial residual risk for MACE when treated in routine practice (and that patients with polyvascular disease have the highest residual risk) even when being treated in the era of updated guidelines that call for more aggressive medical management. This study therefore emphasizes the need for continued improvement in the prevention and treatment of patients with or at risk of atherosclerosis. Importantly, while our study can assess the proportion of patients using preventative strategies such as medications (statins, antihypertensives, antidiabetic agents), we could not assess whether the intensity of treatment prescribed was optimal.

Our study has limitations worth discussing. First, misclassification bias must always be considered in claims database analyses and, when present, can detrimentally impact a study's internal validity.[23] Second, clinical adjudication of events was not possible within our claims database analysis. Of note, the REACH registry, while performed prospectively, also did not independently adjudicate outcomes. Third, our MarketScan claims data only allowed the capture of in-hospital death outcomes and, therefore, absolute cardiovascular death rates in our study may be underestimated (though relative rates across atherosclerotic disease types are likely accurate). Fourth, because of the methods used to select our established atherosclerotic disease and risk-factors-only cohorts, some degree of selection bias was likely present in our study. As an example, to be included in the risk-factor-only cohort, patients had to have ≥3 risk factors for atherosclerotic disease including diabetes mellitus, diabetic nephropathy, hypercholesterolemia with treatment, hypertension with treatment, carotid stenosis, smoking, or advanced

age (males ≥65 or females ≥70). The requirement for hypercholesterolemia to be "treated" for the risk-factor-only cohort, while patients with established disease could have untreated or no history of hypercholesterolemia likely explains why the risk-factor-only patients had the highest utilization of statins (88.4% versus 66.4% for established disease patients). Of note, a similar finding of higher statin use in the risk-factor-only cohort compared with many established disease groups was also seen in the REACH registry.[24] Next, we used US commercial and Medicare supplemental plan claims data. As a consequence, our results are most generalizable to an insured US population with established or at high risk for atherosclerotic disease.[5] Finally, while we highlight some similarities and contrasts between our findings and that of the REACH registry, because of differences in methodology and types of patients included, direct comparison of results is not recommended.

Conclusions

This large, contemporary study identified a substantial risk for MACE in patients with established atherosclerotic disease or with multiple risk factors treated in routine clinical practice. We also showed that the number and specific location of vascular bed involvement were associated with MACE risk. Our findings may serve as a benchmark for both clinicians and other health professionals when making statements about MACE rates in a contemporary population, and when designing future clinical trials. Moreover, they emphasize the need for continued improvement in the prevention and treatment of patients with or at risk of atherosclerosis.

Sources of Funding

Funding was provided by Bayer AG, Berlin, Germany and a Medical Staff Internal Grant from Hartford Hospital, Hartford, CT. MarketScan data used in this study were obtained from IBM under a third-party license agreement with Bayer AG, Berlin, Germany. The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors have approved the final manuscript.

Disclosures

Coleman has received research funding and honoraria from Bayer AG (significant), Janssen Scientific Affairs LLC (significant), and Portola Pharmaceuticals, Inc (modest). Alberts reports consultancy or speaker fees and honoraria from Genentech (modest), Janssen Pharmaceuticals (significant), Boehringer Ingelheim (modest), Pfizer (significant), Bristol-Myers Squibb (significant), Medscape (modest), Portola (significant), and patents/royalties from Duke University (modest). The remaining authors have no disclosures to report.

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SUPPLEMENTAL MATERIAL

Table S1. List of Baseline and Outcome Variable Codes*.

Variable	Code(s)	Code Description
Coronary artery disease		
Stable or unstable angina	I200, I2109, I2111, I2119, I2129, I213, I214, I240	ICD-10 Diagnosis
Percutaneous coronary intervention	Z98.61, Z95.5	ICD-10 Diagnosis
	92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 02700D6, 02700DZ, 02700T6, 02700TZ, 02700Z6, 02700ZZ, 02703D6, 02703DZ, 02703T6, 02703TZ, 02703Z6, 02703ZZ, 02704D6, 02704DZ, 02704T6, 02704TZ, 02704Z6, 02704ZZ, 02710D6, 02710DZ, 02710T6, 02710TZ, 02710Z6, 02710ZZ, 02713D6, 02713DZ, 02713T6, 02713TZ, 02713Z6, 02713ZZ, 02714D6, 02714DZ, 02714T6, 02714TZ, 02714Z6, 02714ZZ, 02720D6, 02720DZ, 02720T6, 02720TZ, 02720Z6, 02720ZZ, 02723D6, 02723DZ, 02723T6, 02723TZ, 02723Z6, 02723ZZ, 02724D6, 02724DZ, 02724T6, 02724TZ, 02724Z6, 02724ZZ, 02730D6, 02730DZ, 02730T6, 02730TZ, 02730Z6, 02730ZZ, 02733D6, 02733DZ, 02733T6, 02733TZ, 02733Z6, 02733ZZ, 02734D6, 02734DZ, 02734T6, 02734TZ, 02734Z6, 02734ZZ, C9600, C9601, C9602, C9603, C9604, C9605, C9606, C9607, C9608, 0270046, 027004Z, 0270346, 027034Z, 0270446, 027044Z, 0271046, 027104Z, 0271346, 027134Z, 0271446, 027144Z, 0272046, 027204Z, 0272346, 027234Z, 0272446, 027244Z, 0273046, 027304Z, 0273346, 027334Z, 0273446, 027344Z	CPT-4 Procedure
Coronary artery bypass graft	566, 567, 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33520, 33521, 33522, 33523, 33525, 33528, 33530, 33533, 33534, 33535, 33536, 35600, 4110F, 75762, 75764, 75766, 75767, 93551, C9604, C9605, G8158, G8159, G8160, G8161, G8162, G8163, G8164, G8165, G8166, G8167, G8170, G8171, G8172, G8497, G8544, G8573, G8574, I2570, I25700, I25701, I25708, I25709, I2571, I25710, I25711, I25718, I25719, I2572, I25720, I25721, I25728, I25729, I2573, I25730, I25731, I25738, I25739, I2579, I25790, I25791, I25798, I25799, I25810, T82211, T82211A, T82211D, T82211S, T82212, T82212A, T82212D, T82212S, T82213, T82213A, T82213D, T82213S, T82218, T82218A, T82218D, T82218S, Z951, 0210093, 0210098, 0210099, 021009C, 021009F, 021009W, 02100A3, 02100A8, 02100A9, 02100AC, 02100AF, 02100AW, 02100J3, 02100J8, 02100J9, 02100JC, 02100JF, 02100JW, 02100K3, 02100K8, 02100K9, 02100KC, 02100KF, 02100KW, 02100Z3, 02100Z8, 02100Z9, 02100ZC, 02100ZF, 0210344, 02103D4, 0210444, 0210493, 0210499, 0210499, 021049F, 021049W, 02104A3, 02104A8, 02104A9, 02104AC, 02104AF, 02104AW, 02104D4, 02104J3, 02104J8, 02104J9, 02104JC, 02104JF, 02104JW, 02104K3, 02104K8, 02104K9, 02104KC, 02104KF, 02104KW, 02104Z3, 02104Z8, 02104Z9, 02104ZC, 02104ZF, 0211093, 0211098, 0211099, 021109C, 021109F, 021109W, 02110A3, 02110A8, 02110A9, 02110AC, 02110AF, 02110AW, 02110J3, 02110J8, 02110J9, 02110JC, 02110JF, 02110JW, 02110K3, 02110K8, 02110K9, 02110KC, 02110KF, 02110KW, 02110Z3, 02110Z8, 02110Z9, 02110ZC, 02110ZF, 0211344, 02113D4,	CPT-4 Procedure

	211444, 0211493, 0211498, 0211499, 021149C, 021149F, 021149W, 02114A3, 02114A8, 02114A9, 02114AC, 02114AF, 02114AW, 02114D4, 02114J3, 02114J8, 02114J9, 02114JC, 02114JF, 02114JW, 02114K3, 02114K8, 02114K9, 02114KC, 02114KF, 02114KW, 02114Z3, 02114Z8, 02114Z9, 02114ZC, 02114ZF, 0212093, 0212098, 0212099, 021209C, 021209F, 021209W, 02120A3, 02120A8, 02120A9, 02120AC, 02120AF, 02120AW, 02120J3, 02120J8, 02120J9, 02120JC, 02120JF, 02120JW, 02120K3, 02120K8, 02120K9, 02120KC, 02120KF, 02120KW, 02120Z3, 02120Z8, 02120Z9, 02120ZC, 02120ZF, 0212344, 02123D4, 0212444, 0212493, 0212498, 0212499, 021249C, 021249F, 021249W, 02124A3, 02124A8, 02124A9, 02124AC, 02124AF, 02124AW, 02124D4, 02124J3, 02124J8, 02124J9, 02124JC, 02124JF, 02124JW, 02124K3, 02124K8, 02124K9, 02124KC, 02124KF, 02124KW, 02124Z3, 02124Z8, 02124Z9, 02124ZC, 02124ZF, 0213093, 0213098, 0213099, 021309C, 021309F, 021309W, 02130A3, 02130A8, 02130A9, 02130AC, 02130AF, 02130AW, 02130J3, 02130J8, 02130J9, 02130JC, 02130JF, 02130JW, 02130K3, 02130K8, 02130K9, 02130KC, 02130KF, 02130KW, 02130Z3, 02130Z8, 02130Z9, 02130ZC, 02130ZF, 213344, 02133D4, 0213444, 0213493, 0213498, 0213499, 021349C, 021349F, 021349W, 02134A3, 02134A8, 02134A9, 02134AC, 02134AF, 02134AW, 02134D4, 02134J3, 02134J8, 02134J9, 02134JC, 02134JF, 02134JW, 02134K3, 02134K8, 02134K9, 02134KC, 02134KF, 02134KW, 02134Z3, 02134Z8, 02134Z9, 02134ZC, 02134ZF, 0210498, B2020ZZ, B2021ZZ, B202YZZ, B2030ZZ, B2031ZZ, B203YZZ, B212010, B2120ZZ, B212110, B2121ZZ, B212Y10, B212YZZ, B213010, B2130ZZ, B213110, B2131ZZ, B213Y10, B213YZZ, B22300Z, B2230ZZ, B22310Z, B2231ZZ, B223Y0Z, B223YZZ, B223Z2Z, B223ZZZ, B233Y0Z, B233YZZ, B233ZZZ	
Myocardial infarction	I21, I21.0, I21.01, I21.02, I21.09, I21.1, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3, I21.4, I22, I22.0, I22.1, I22.2, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8, I25.2	ICD-10 Diagnosis
Cerebrovascular disease		
Ischemic stroke	I63	ICD-10 Diagnosis
Transient ischemic attack	G45.0, G45.1, G45.2, G45.4, G45.8, G45.9	ICD-10 Diagnosis
Peripheral artery disease		
History of peripheral artery disease	I70201, I70202, I70203, I70208, I70209, I70211, I70212, I70213, I70218, I70219, I70221, I70222, I70223, I70228, I70229, I70231, I70231, I70232, I70232, I70233, I70233, I70234, I70234, I70235, I70235, I70238, I70238, I70239, I70239, I70241, I70241, I70242, I70242, I70243, I70243, I70244, I70244, I70245, I70245, I70248, I70248, I70249, I70249, I7025, I7025, I70261, I70262, I70263, I70268, I70269, I70291, I70292, I70293, I70298, I70299	ICD-10 Diagnosis
Angioplasty	39.50	ICD-9 Procedure†
Stenting	00.55, 39.90,	ICD-9 Procedure†
Atherectomy	17.56	ICD-9 Procedure†

Peripheral arterial bypass grafting	39.25, 39.26, 39.29	ICD-9 Procedure†
Amputations	0Y6C0Z1, 0Y6C0Z2, 0Y6C0Z3, 0Y6D0Z1, 0Y6D0Z2, 0Y6D0Z3, 0Y6H0Z1, 0Y6H0Z2, 0Y6H0Z3, 0Y6J0Z1, 0Y6J0Z2, 0Y6J0Z3, 0Y6M0Z0, 0Y6N0Z0, 0Y6H0Z3, 0Y6J0Z3, 0Y6H0Z1, 0Y6H0Z2, 0Y6H0Z3, 0Y6J0Z1, 0Y6J0Z2, 0Y6J0Z3, 0Y6F0ZZ, 0Y6G0ZZ, 0Y6C0Z1, 0Y6C0Z2, 0Y6C0Z3, 0Y6D0Z1, 0Y6D0Z2, 0Y6D0Z3, 0HQBXZZ, 0HQCXZZ, 0HQDXZZ, 0HQEXZZ, 0HQFXZZ, 0HQGXZZ, 0HQHXZZ, 0HQJXZZ, 0HQKXZZ, 0HQLXZZ, 0HQMXZZ, 0HQNXZZ, 0X600ZZ, 0X610ZZ, 0X620ZZ, 0X630ZZ, 0X680Z1, 0X680Z2, 0X680Z3, 0X690Z1, 0X690Z2, 0X690Z3, 0X6B0ZZ, 0X6C0ZZ, 0X6D0Z1, 0X6D0Z2, 0X6D0Z3, 0X6F0Z1, 0X6F0Z2, 0X6F0Z3, 0X6J0Z0, 0X6J0Z4, 0X6J0Z5, 0X6J0Z6, 0X6J0Z7, 0X6J0Z8, 0X6J0Z9, 0X6J0ZB, 0X6J0ZC, 0X6J0ZD, 0X6J0ZF, 0X6K0Z0, 0X6K0Z4, 0X6K0Z5, 0X6K0Z6, 0X6K0Z7, 0X6K0Z8, 0X6K0Z9, 0X6K0ZB, 0X6K0ZC, 0X6K0ZD, 0X6K0ZF, 0X6L0Z0, 0X6L0Z1, 0X6L0Z2, 0X6L0Z3, 0X6M0Z0, 0X6M0Z1, 0X6M0Z2, 0X6M0Z3, 0X6N0Z0, 0X6N0Z1, 0X6N0Z2, 0X6N0Z3, 0X6P0Z0, 0X6P0Z1, 0X6P0Z2, 0X6P0Z3, 0X6Q0Z0, 0X6Q0Z1, 0X6Q0Z2, 0X6Q0Z3, 0X6R0Z0, 0X6R0Z1, 0X6R0Z2, 0X6R0Z3, 0X6S0Z0, 0X6S0Z1, 0X6S0Z2, 0X6S0Z3, 0X6T0Z0, 0X6T0Z1, 0X6T0Z2, 0X6T0Z3, 0X6V0Z0, 0X6V0Z1, 0X6V0Z2, 0X6V0Z3, 0X6W0Z0, 0X6W0Z1, 0X6W0Z2, 0X6W0Z3, 0XQ60ZZ, 0XQ63ZZ, 0XQ64ZZ, 0XQ6XZZ, 0XQ70ZZ, 0XQ73ZZ, 0XQ74ZZ, 0XQ7XZZ, 0XQ80ZZ, 0XQ83ZZ, 0XQ84ZZ, 0XQ8XZZ, 0XQ90ZZ, 0XQ93ZZ, 0XQ94ZZ, 0XQ9XZZ, 0XQB0ZZ, 0XQB3ZZ, 0XQB4ZZ, 0XQBXZZ, 0XQC0ZZ, 0XQC3ZZ, 0XQC4ZZ, 0XQCXZZ, 0XQD0ZZ, 0XQD3ZZ, 0XQD4ZZ, 0XQDXZZ, 0XQF0ZZ, 0XQF3ZZ, 0XQF4ZZ, 0XQFXZZ, 0XQG0ZZ, 0XQG3ZZ, 0XQG4ZZ, 0XQGXZZ, 0XQH0ZZ, 0XQH3ZZ, 0XQH4ZZ, 0XQHXZZ, 0XQJ0ZZ, 0XQJ3ZZ, 0XQJ4ZZ, 0XQJXZZ, 0XQK0ZZ, 0XQK3ZZ, 0XQK4ZZ, 0XQKXZZ, 0XQL0ZZ, 0XQL3ZZ, 0XQL4ZZ, 0XQLXZZ, 0XQM0ZZ, 0XQM3ZZ, 0XQM4ZZ, 0XQMXZZ, 0XQN0ZZ, 0XQN3ZZ, 0XQN4ZZ, 0XQNXZZ, 0XQP0ZZ, 0XQP3ZZ, 0XQP4ZZ, 0XQPXZZ, 0XQQ0ZZ, 0XQQ3ZZ, 0XQQ4ZZ, 0XQQXZZ, 0XQR0ZZ, 0XQR3ZZ, 0XQR4ZZ, 0XQRXZZ, 0XQS0ZZ, 0XQS3ZZ, 0XQS4ZZ, 0XQSXZZ, 0XQT0ZZ, 0XQT3ZZ, 0XQT4ZZ, 0XQTXZZ, 0XQV0ZZ, 0XQV3ZZ, 0XQV4ZZ, 0XQVXZZ, 0XQW0ZZ, 0XQW3ZZ, 0XQW4ZZ, 0XQWXZZ, 0Y620ZZ, 0Y630ZZ, 0Y640ZZ, 0Y670ZZ, 0Y680ZZ, 0Y6C0Z1, 0Y6C0Z2, 0Y6C0Z3, 0Y6D0Z1, 0Y6D0Z2, 0Y6D0Z3, 0Y6F0ZZ, 0Y6G0ZZ, 0Y6H0Z1, 0Y6H0Z2, 0Y6H0Z3, 0Y6J0Z1, 0Y6J0Z2, 0Y6J0Z3, 0Y6M0Z0, 0Y6M0Z4, 0Y6M0Z5, 0Y6M0Z6, 0Y6M0Z7, 0Y6M0Z8, 0Y6M0Z9, 0Y6M0ZB, 0Y6M0ZC, 0Y6M0ZD, 0Y6M0ZF, 0Y6N0Z0, 0Y6N0Z4, 0Y6N0Z5, 0Y6N0Z6, 0Y6N0Z7, 0Y6N0Z8, 0Y6N0Z9, 0Y6N0ZB, 0Y6N0ZC, 0Y6N0ZD, 0Y6N0ZF, 0Y6P0Z0, 0Y6P0Z1, 0Y6P0Z2, 0Y6P0Z3, 0Y6Q0Z0, 0Y6Q0Z1, 0Y6Q0Z2, 0Y6Q0Z3, 0Y6R0Z0,	CPT-4 Procedure

	0Y6R0Z1, 0Y6R0Z2, 0Y6R0Z3, 0Y6S0Z0, 0Y6S0Z1, 0Y6S0Z2, 0Y6S0Z3, 0Y6T0Z0, 0Y6T0Z1, 0Y6T0Z2, 0Y6T0Z3, 0Y6U0Z0, 0Y6U0Z1, 0Y6U0Z2, 0Y6U0Z3, 0Y6V0Z0, 0Y6V0Z1, 0Y6V0Z2, 0Y6V0Z3, 0Y6W0Z0, 0Y6W0Z1, 0Y6W0Z2, 0Y6W0Z3, 0Y6X0Z0, 0Y6X0Z1, 0Y6X0Z2, 0Y6X0Z3, 0Y6Y0Z0, 0Y6Y0Z1, 0Y6Y0Z2, 0Y6Y0Z3, 0YQ90ZZ, 0YQ93ZZ, 0YQ94ZZ, 0YQ9XZZ, 0YQB0ZZ, 0YQB3ZZ, 0YQB4ZZ, 0YQBXZZ, 0YQC0ZZ, 0YQC3ZZ, 0YQC4ZZ, 0YQCXZZ, 0YQD0ZZ, 0YQD3ZZ, 0YQD4ZZ, 0YQDXZZ, 0YQF0ZZ, 0YQF3ZZ, 0YQF4ZZ, 0YQFXZZ, 0YQG0ZZ, 0YQG3ZZ, 0YQG4ZZ, 0YQGXZZ, 0YQH0ZZ, 0YQH3ZZ, 0YQH4ZZ, 0YQHXZZ, 0YQJ0ZZ, 0YQJ3ZZ, 0YQJ4ZZ, 0YQJXZZ, 0YQK0ZZ, 0YQK3ZZ, 0YQK4ZZ, 0YQKXZZ, 0YQL0ZZ, 0YQL3ZZ, 0YQL4ZZ, 0YQLXZZ, 0YQM0ZZ, 0YQM3ZZ, 0YQM4ZZ, 0YQMXZZ, 0YQN0ZZ, 0YQN3ZZ, 0YQN4ZZ, 0YQNXZZ, 0YQP0ZZ, 0YQP3ZZ, 0YQP4ZZ, 0YQPXZZ, 0YQQ0ZZ, 0YQQ3ZZ, 0YQQ4ZZ, 0YQQXZZ, 0YQR0ZZ, 0YQR3ZZ, 0YQR4ZZ, 0YQRXZZ, 0YQS0ZZ, 0YQS3ZZ, 0YQS4ZZ, 0YQSXZZ, 0YQT0ZZ, 0YQT3ZZ, 0YQT4ZZ, 0YQTXZZ, 0YQU0ZZ, 0YQU3ZZ, 0YQU4ZZ, 0YQUXZZ, 0YQV0ZZ, 0YQV3ZZ, 0YQV4ZZ, 0YQVXZZ, 0YQW0ZZ, 0YQW3ZZ, 0YQW4ZZ, 0YQWXZZ, 0YQX0ZZ, 0YQX3ZZ, 0YQX4ZZ, 0YQXXZZ, 0YQY0ZZ, 0YQY3ZZ, 0YQY4ZZ, 0YQYXZZ, F0DZ8UZ, F0DZ8ZZ, F0DZ8UZ, F0DZ8UZ, F0DZ8UZ, 0XH80YZ, 0XH83YZ, 0XH84YZ, 0XH90YZ, 0XH93YZ, 0XH94YZ, 0XHB0YZ, 0XHB3YZ, 0XHB4YZ, 0XHC0YZ, 0XHC3YZ, 0XHC4YZ, 0XHD0YZ, 0XHD3YZ, 0XHD4YZ, 0XHF0YZ, 0XHF3YZ, 0XHF4YZ, 0XHG0YZ, 0XHG3YZ, 0XHG4YZ, 0XHH0YZ, 0XHH3YZ, 0XHH4YZ, F0DZ8UZ, F0DZ8UZ, F0DZ8UZ, 0YHC0YZ, 0YHC3YZ, 0YHC4YZ, 0YHD0YZ, 0YHD3YZ, 0YHD4YZ, 0YHF0YZ, 0YHF3YZ, 0YHF4YZ, 0YHG0YZ, 0YHG3YZ, 0YHG4YZ, 0YHH0YZ, 0YHH3YZ, 0YHH4YZ, 0YHJ0YZ, 0YHJ3YZ, 0YHJ4YZ, N0PCS, 3E0U0GB, 3E0U3GB, 3E0V0GB, 3E0V3GB, 0PHC08Z, 0PHC38Z, 0PHC48Z, 0PHD08Z, 0PHD38Z, 0PHD48Z, 0PHF08Z, 0PHF38Z, 0PHF48Z, 0PHG08Z, 0PHG38Z, 0PHG48Z, 0PHH08Z, 0PHH38Z, 0PHH48Z, 0PHJ08Z, 0PHJ38Z, 0PHJ48Z, 0PHK08Z, 0PHK38Z, 0PHK48Z, 0PHL08Z, 0PHL38Z, 0PHL48Z, 0QH608Z, 0QH638Z, 0QH648Z, 0QH708Z, 0QH738Z, 0QH748Z, 0QH808Z, 0QH838Z, 0QH848Z, 0QH908Z, 0QH938Z, 0QH948Z, 0QHB08Z, 0QHB38Z, 0QHB48Z, 0QHC08Z, 0QHC38Z, 0QHC48Z, 0QHG08Z, 0QHG38Z, 0QHG48Z, 0QHH08Z, 0QHH38Z, 0QHH48Z, 0QHJ08Z, 0QHJ38Z, 0QHJ48Z, 0QHK08Z, 0QHK38Z, 0QHK48Z, 0Y6C0Z1, 0Y6C0Z2, 0Y6C0Z3, 0Y6D0Z1, 0Y6D0Z2, 0Y6D0Z3, 0Y6H0Z1, 0Y6H0Z2, 0Y6H0Z3, 0Y6J0Z1, 0Y6J0Z2, 0Y6J0Z3, 0Y6M0Z0, 0Y6N0Z0, 0Y6H0Z3, 0Y6J0Z3, 0Y6H0Z1, 0Y6H0Z2, 0Y6H0Z3, 0Y6J0Z1, 0Y6J0Z2, 0Y6J0Z3, 0Y6F0ZZ, 0Y6G0ZZ, 0Y6C0Z1, 0Y6C0Z2, 0Y6C0Z3, 0Y6D0Z1, 0Y6D0Z2, 0Y6D0Z3, 0HQBXZZ, 0HQCXZZ, 0HQDXZZ, 0HQEXZZ, 0HQFXZZ, 0HQGXZZ, 0HQHXZZ, 0HQJXZZ, 0HQKXZZ, 0HQLXZZ, 0HQMXZZ, 0HQNXZZ,	

	0X600ZZ, 0X610ZZ, 0X620ZZ, 0X630ZZ, 0X680Z1, 0X680Z2, 0X680Z3, 0X690Z1, 0X690Z2, 0X690Z3, 0X6B0ZZ, 0X6C0ZZ, 0X6D0Z1, 0X6D0Z2, 0X6D0Z3, 0X6F0Z1, 0X6F0Z2, 0X6F0Z3, 0X6J0Z0, 0X6J0Z4, 0X6J0Z5, 0X6J0Z6, 0X6J0Z7, 0X6J0Z8, 0X6J0Z9, 0X6J0ZB, 0X6J0ZC, 0X6J0ZD, 0X6J0ZF, 0X6K0Z0, 0X6K0Z4, 0X6K0Z5, 0X6K0Z6, 0X6K0Z7, 0X6K0Z8, 0X6K0Z9, 0X6K0ZB, 0X6K0ZC, 0X6K0ZD, 0X6K0ZF, 0X6L0Z0, 0X6L0Z1, 0X6L0Z2, 0X6L0Z3, 0X6M0Z0, 0X6M0Z1, 0X6M0Z2, 0X6M0Z3, 0X6N0Z0, 0X6N0Z1, 0X6N0Z2, 0X6N0Z3, 0X6P0Z0, 0X6P0Z1, 0X6P0Z2, 0X6P0Z3, 0X6Q0Z0, 0X6Q0Z1, 0X6Q0Z2, 0X6Q0Z3, 0X6R0Z0, 0X6R0Z1, 0X6R0Z2, 0X6R0Z3, 0X6S0Z0, 0X6S0Z1, 0X6S0Z2, 0X6S0Z3, 0X6T0Z0, 0X6T0Z1, 0X6T0Z2, 0X6T0Z3, 0X6V0Z0, 0X6V0Z1, 0X6V0Z2, 0X6V0Z3, 0X6W0Z0, 0X6W0Z1, 0X6W0Z2, 0X6W0Z3, 0XQ60ZZ, 0XQ63ZZ, 0XQ64ZZ, 0XQ6XZZ, 0XQ70ZZ, 0XQ73ZZ, 0XQ74ZZ, 0XQ7XZZ, 0XQ80ZZ, 0XQ83ZZ, 0XQ84ZZ, 0XQ8XZZ, 0XQ90ZZ, 0XQ93ZZ, 0XQ94ZZ, 0XQ9XZZ, 0XQB0ZZ, 0XQB3ZZ, 0XQB4ZZ, 0XQBXZZ, 0XQC0ZZ, 0XQC3ZZ, 0XQC4ZZ, 0XQCXZZ, 0XQD0ZZ, 0XQD3ZZ, 0XQD4ZZ, 0XQDXZZ, 0XQF0ZZ, 0XQF3ZZ, 0XQF4ZZ, 0XQFXZZ, 0XQG0ZZ, 0XQG3ZZ, 0XQG4ZZ, 0XQGXZZ, 0XQH0ZZ, 0XQH3ZZ, 0XQH4ZZ, 0XQHXZZ, 0XQJ0ZZ, 0XQJ3ZZ, 0XQJ4ZZ, 0XQJXZZ, 0XQK0ZZ, 0XQK3ZZ, 0XQK4ZZ, 0XQKXZZ, 0XQL0ZZ, 0XQL3ZZ, 0XQL4ZZ, 0XQLXZZ, 0XQM0ZZ, 0XQM3ZZ, 0XQM4ZZ, 0XQMXZZ, 0XQN0ZZ, 0XQN3ZZ, 0XQN4ZZ, 0XQNXZZ, 0XQP0ZZ, 0XQP3ZZ, 0XQP4ZZ, 0XQPXZZ, 0XQQ0ZZ, 0XQQ3ZZ, 0XQQ4ZZ, 0XQQXZZ, 0XQR0ZZ, 0XQR3ZZ, 0XQR4ZZ, 0XQRXZZ, 0XQS0ZZ, 0XQS3ZZ, 0XQS4ZZ, 0XQSXZZ, 0XQT0ZZ, 0XQT3ZZ, 0XQT4ZZ, 0XQTXZZ, 0XQV0ZZ, 0XQV3ZZ, 0XQV4ZZ, 0XQVXZZ, 0XQW0ZZ, 0XQW3ZZ, 0XQW4ZZ, 0XQWXZZ, 0Y620ZZ, 0Y630ZZ, 0Y640ZZ, 0Y670ZZ, 0Y680ZZ, 0Y6C0Z1, 0Y6C0Z2, 0Y6C0Z3, 0Y6D0Z1, 0Y6D0Z2, 0Y6D0Z3, 0Y6F0ZZ, 0Y6G0ZZ, 0Y6H0Z1, 0Y6H0Z2, 0Y6H0Z3, 0Y6J0Z1, 0Y6J0Z2, 0Y6J0Z3, 0Y6M0Z0, 0Y6M0Z4, 0Y6M0Z5, 0Y6M0Z6, 0Y6M0Z7, 0Y6M0Z8, 0Y6M0Z9, 0Y6M0ZB, 0Y6M0ZC, 0Y6M0ZD, 0Y6M0ZF, 0Y6N0Z0, 0Y6N0Z4, 0Y6N0Z5, 0Y6N0Z6, 0Y6N0Z7, 0Y6N0Z8, 0Y6N0Z9, 0Y6N0ZB, 0Y6N0ZC, 0Y6N0ZD, 0Y6N0ZF, 0Y6P0Z0, 0Y6P0Z1, 0Y6P0Z2, 0Y6P0Z3, 0Y6Q0Z0, 0Y6Q0Z1, 0Y6Q0Z2, 0Y6Q0Z3, 0Y6R0Z0, 0Y6R0Z1, 0Y6R0Z2, 0Y6R0Z3, 0Y6S0Z0, 0Y6S0Z1, 0Y6S0Z2, 0Y6S0Z3, 0Y6T0Z0, 0Y6T0Z1, 0Y6T0Z2, 0Y6T0Z3, 0Y6U0Z0, 0Y6U0Z1, 0Y6U0Z2, 0Y6U0Z3, 0Y6V0Z0, 0Y6V0Z1, 0Y6V0Z2, 0Y6V0Z3, 0Y6W0Z0, 0Y6W0Z1, 0Y6W0Z2, 0Y6W0Z3, 0Y6X0Z0, 0Y6X0Z1, 0Y6X0Z2, 0Y6X0Z3, 0Y6Y0Z0, 0Y6Y0Z1, 0Y6Y0Z2, 0Y6Y0Z3, 0YQ90ZZ, 0YQ93ZZ, 0YQ94ZZ, 0YQ9XZZ, 0YQB0ZZ, 0YQB3ZZ, 0YQB4ZZ, 0YQBXZZ, 0YQC0ZZ, 0YQC3ZZ, 0YQC4ZZ, 0YQCXZZ, 0YQD0ZZ, 0YQD3ZZ, 0YQD4ZZ, 0YQDXZZ, 0YQF0ZZ, 0YQF3ZZ, 0YQF4ZZ, 0YQFXZZ, 0YQG0ZZ, 0YQG3ZZ, 0YQG4ZZ, 0YQGXZZ, 0YQH0ZZ, 0YQH3ZZ,	

	0YQH4ZZ, 0YQHXZZ, 0YQJ0ZZ, 0YQJ3ZZ, 0YQJ4ZZ, 0YQJXZZ, 0YQK0ZZ, 0YQK3ZZ, 0YQK4ZZ, 0YQKXZZ, 0YQL0ZZ, 0YQL3ZZ, 0YQL4ZZ, 0YQLXZZ, 0YQM0ZZ, 0YQM3ZZ, 0YQM4ZZ, 0YQMXZZ, 0YQN0ZZ, 0YQN3ZZ, 0YQN4ZZ, 0YQNXZZ, 0YQP0ZZ, 0YQP3ZZ, 0YQP4ZZ, 0YQPXZZ, 0YQQ0ZZ, 0YQQ3ZZ, 0YQQ4ZZ, 0YQQXZZ, 0YQR0ZZ, 0YQR3ZZ, 0YQR4ZZ, 0YQRXZZ, 0YQS0ZZ, 0YQS3ZZ, 0YQS4ZZ, 0YQSXZZ, 0YQT0ZZ, 0YQT3ZZ, 0YQT4ZZ, 0YQTXZZ, 0YQU0ZZ, 0YQU3ZZ, 0YQU4ZZ, 0YQUXZZ, 0YQV0ZZ, 0YQV3ZZ, 0YQV4ZZ, 0YQVXZZ, 0YQW0ZZ, 0YQW3ZZ, 0YQW4ZZ, 0YQWXZZ, 0YQX0ZZ, 0YQX3ZZ, 0YQX4ZZ, 0YQXXZZ, 0YQY0ZZ, 0YQY3ZZ, 0YQY4ZZ, 0YQYXZZ, F0DZ8UZ, F0DZ8ZZ, F0DZ8UZ, F0DZ8UZ, F0DZ8UZ, 0XH80YZ, 0XH83YZ, 0XH84YZ, 0XH90YZ, 0XH93YZ, 0XH94YZ, 0XHB0YZ, 0XHB3YZ, 0XHB4YZ, 0XHC0YZ, 0XHC3YZ, 0XHC4YZ, 0XHD0YZ, 0XHD3YZ, 0XHD4YZ, 0XHF0YZ, 0XHF3YZ, 0XHF4YZ, 0XHG0YZ, 0XHG3YZ, 0XHG4YZ, 0XHH0YZ, 0XHH3YZ, 0XHH4YZ, F0DZ8UZ, F0DZ8UZ, F0DZ8UZ, 0YHC0YZ, 0YHC3YZ, 0YHC4YZ, 0YHD0YZ, 0YHD3YZ, 0YHD4YZ, 0YHF0YZ, 0YHF3YZ, 0YHF4YZ, 0YHG0YZ, 0YHG3YZ, 0YHG4YZ, 0YHH0YZ, 0YHH3YZ, 0YHH4YZ, 0YHJ0YZ, 0YHJ3YZ, 0YHJ4YZ, N0PCS, 3E0U0GB, 3E0U3GB, 3E0V0GB, 3E0V3GB, 0PHC08Z, 0PHC38Z, 0PHC48Z, 0PHD08Z, 0PHD38Z, 0PHD48Z, 0PHF08Z, 0PHF38Z, 0PHF48Z, 0PHG08Z, 0PHG38Z, 0PHG48Z, 0PHH08Z, 0PHH38Z, 0PHH48Z, 0PHJ08Z, 0PHJ38Z, 0PHJ48Z, 0PHK08Z, 0PHK38Z, 0PHK48Z, 0PHL08Z, 0PHL38Z, 0PHL48Z, 0QH608Z, 0QH638Z, 0QH648Z, 0QH708Z, 0QH738Z, 0QH748Z, 0QH808Z, 0QH838Z, 0QH848Z, 0QH908Z, 0QH938Z, 0QH948Z, 0QHB08Z, 0QHB38Z, 0QHB48Z, 0QHC08Z, 0QHC38Z, 0QHC48Z, 0QHG08Z, 0QHG38Z, 0QHG48Z, 0QHH08Z, 0QHH38Z, 0QHH48Z, 0QHJ08Z, 0QHJ38Z, 0QHJ48Z, 0QHK08Z, 0QHK38Z, 0QHK48Z, 0Y6P0Z0, 0Y6P0Z1, 0Y6P0Z2, 0Y6P0Z3, 0Y6Q0Z0, 0Y6Q0Z1, 0Y6Q0Z2, 0Y6Q0Z3, 0Y6R0Z0, 0Y6R0Z1, 0Y6R0Z2, 0Y6R0Z3, 0Y6S0Z0, 0Y6S0Z1, 0Y6S0Z2, 0Y6S0Z3, 0Y6T0Z0, 0Y6T0Z1, 0Y6T0Z2, 0Y6T0Z3, 0Y6U0Z0, 0Y6U0Z1, 0Y6U0Z2, 0Y6U0Z3, 0Y6V0Z0, 0Y6V0Z1, 0Y6V0Z2, 0Y6V0Z3, 0Y6W0Z0, 0Y6W0Z1, 0Y6W0Z2, 0Y6W0Z3, 0Y6X0Z0, 0Y6X0Z1, 0Y6X0Z2, 0Y6X0Z3, 0Y6Y0Z0, 0Y6Y0Z1, 0Y6Y0Z2, 0Y6Y0Z3, 0Y6M0Z4, 0Y6M0Z5, 0Y6M0Z6, 0Y6M0Z7, 0Y6M0Z8, 0Y6M0Z9, 0Y6M0ZB, 0Y6M0ZC, 0Y6M0ZD, 0Y6M0ZF, 0Y6N0Z4, 0Y6N0Z5, 0Y6N0Z6, 0Y6N0Z7, 0Y6N0Z8, 0Y6N0Z9, 0Y6N0ZB, 0Y6N0ZC, 0Y6N0ZD, 0Y6N0ZF, 0Y6P0Z0, 0Y6P0Z1, 0Y6P0Z2, 0Y6P0Z3, 0Y6Q0Z0, 0Y6Q0Z1, 0Y6Q0Z2, 0Y6Q0Z3, 0Y6R0Z0, 0Y6R0Z1, 0Y6R0Z2, 0Y6R0Z3, 0Y6S0Z0, 0Y6S0Z1, 0Y6S0Z2, 0Y6S0Z3, 0Y6T0Z0, 0Y6T0Z1, 0Y6T0Z2, 0Y6T0Z3, 0Y6U0Z0, 0Y6U0Z1, 0Y6U0Z2, 0Y6U0Z3, 0Y6V0Z0, 0Y6V0Z1, 0Y6V0Z2, 0Y6V0Z3, 0Y6W0Z0, 0Y6W0Z1, 0Y6W0Z2, 0Y6W0Z3, 0Y6X0Z0, 0Y6X0Z1, 0Y6X0Z2, 0Y6X0Z3, 0Y6Y0Z0,	

	0Y6Y0Z1, 0Y6Y0Z2, 0Y6Y0Z3, 0Y6M0Z4, 0Y6M0Z5, 0Y6M0Z6, 0Y6M0Z7, 0Y6M0Z8, 0Y6M0Z9, 0Y6M0ZB, 0Y6M0ZC, 0Y6M0ZD, 0Y6M0ZF, 0Y6N0Z4, 0Y6N0Z5, 0Y6N0Z6, 0Y6N0Z7, 0Y6N0Z8, 0Y6N0Z9, 0Y6N0ZB, 0Y6N0ZC, 0Y6N0ZD, 0Y6N0ZF	
Risk Factors		
History of diabetes	Per the Elixhauser algorithm for comorbidity measures	ICD-10 Diagnosis
Diabetic nephropathy	Has a history of diabetes + R80, R80.0, R80.1, R80.2, R80.3, R80.8, R80.9	ICD-10 Diagnosis
Carotid stenosis	I62.2, I65.21, I65.22, I65.23, I65.29	ICD-10 Diagnosis
Hypertension despite treatment	Per the Elixhauser algorithm for comorbidity measures	ICD-10 Diagnosis
	Amlodipine Besylate/Benazepril Hydrochloride, Amlodipine Besylate/HCTZ/Olmesartan Medoxomil, Amlodipine Besylate/Hydrochlorothiazide/Valsartan, Amlodipine Besylate/Olmesartan Medoxomil, Amlodipine Besylate/Telmisartan, Amlodipine Besylate/Valsartan, Azilsartan Medoxomil, Azilsartan Medoxomil/Chlorthalidone, Benazepril Hydrochloride, Benazepril Hydrochloride/Hydrochlorothiazide, Candesartan Cilexetil, Candesartan Cilexetil/Hydrochlorothiazide, Captopril, Captopril/Hydrochlorothiazide, Enalapril Maleate, Enalapril Maleate/Hydrochlorothiazide, Eprosartan Mesylate, Eprosartan Mesylate/Hydrochlorothiazide, Fosinopril Sodium, Fosinopril Sodium/Hydrochlorothiazide, Hydrochlorothiazide/Irbesartan, Hydrochlorothiazide/Lisinopril, Hydrochlorothiazide/Losartan Potassium, Hydrochlorothiazide/Moexipril Hydrochloride, Hydrochlorothiazide/Olmesartan Medoxomil, Hydrochlorothiazide/Quinapril Hydrochloride, Hydrochlorothiazide/Telmisartan, Hydrochlorothiazide/Valsartan, Irbesartan, Lisinopril, Losartan Potassium, Moexipril Hydrochloride, Olmesartan Medoxomil, Perindopril Erbumine, Quinapril Hydrochloride, Ramipril, Telmisartan, Trandolapril, Trandolapril/Verapamil Hydrochloride, Valsartan, Eplerenone, Hydrochlorothiazide/Spironolactone, Spironolactone, Acebutolol Hydrochloride, Atenolol, Atenolol/Chlorthalidone, Bendroflumethiazide/Nadolol, Betaxolol Hydrochloride, Bisoprolol Fumarate, Bisoprolol Fumarate/Hydrochlorothiazide, Carvedilol, Hydrochlorothiazide/Metoprolol Succinate, Hydrochlorothiazide/Metoprolol Tartrate, Hydrochlorothiazide/Propranolol Hydrochloride, Labetalol Hydrochloride, Metoprolol Succinate, Metoprolol Tartrate, Nadolol, Nebivolol Hydrochloride, Penbutolol Sulfate, Pindolol, Propranolol Hydrochloride, Sotalol Hydrochloride, Timolol, Aliskiren/Amlodipine Besylate, Aliskiren/Amlodipine Besylate/Hydrochlorothiazide, Amlodipine Besylate, Amlodipine Besylate/Atorvastatin Calcium, Amlodipine Besylate/Benazepril Hydrochloride, Amlodipine Besylate/HCTZ/Olmesartan Medoxomil, Amlodipine	Medication Billing Code

	Besylate/Hydrochlorothiazide/Valsartan, Amlodipine Besylate/Olmesartan Medoxomil, Amlodipine Besylate/Telmisartan, Amlodipine Besylate/Valsartan, Felodipine, Isradipine, Nifedipine, Nisoldipine, Diltiazem Hydrochloride, Aliskiren/Amlodipine Besylate/Hydrochlorothiazide, Aliskiren/Hydrochlorothiazide, Amiloride Hydrochloride/Hydrochlorothiazide, Amlodipine Besylate/Hydrochlorothiazide/Valsartan, Atenolol/Chlorthalidone, Azilsartan Medoxomil/Chlorthalidone, Benazepril Hydrochloride/Hydrochlorothiazide, Bisoprolol Fumarate/Hydrochlorothiazide, Candesartan Cilexetil/Hydrochlorothiazide, Captopril/Hydrochlorothiazide, Chlorothiazide, Chlorothiazide Sodium, Chlorothiazide/Methyldopa, Chlorothiazide/Reserpine, Chlorthalidone, Chlorthalidone/Clonidine Hydrochloride, Cryptenamine/Methyclothiazide, Cryptenamine/Methyclothiazide, Deserpidine/Hydrochlorothiazide, Enalapril Maleate/Hydrochlorothiazide, Eprosartan Mesylate/Hydrochlorothiazide, Fosinopril Sodium/Hydrochlorothiazide, Guanethidine Monosulfate/Hydrochlorothiazide, Hydralazine Hydrochloride/Hydrochlorothiazide, Hydrochlorothiazide, Hydrochlorothiazide/Lisinopril, Hydrochlorothiazide/Losartan Potassium, Hydrochlorothiazide/Methyldopa, Hydrochlorothiazide/Metoprolol Succinate, Hydrochlorothiazide/Metoprolol Tartrate, Hydrochlorothiazide/Moexipril Hydrochloride, Hydrochlorothiazide/Olmesartan Medoxomil, Hydrochlorothiazide/Propranolol Hydrochloride, Hydrochlorothiazide/Quinapril Hydrochloride, Hydrochlorothiazide/Reserpine, Hydrochlorothiazide/Spironolactone, Hydrochlorothiazide/Telmisartan, Hydrochlorothiazide/Triamterene, Hydrochlorothiazide/Valsartan, Indapamide, Methyclothiazide, Metolazone, Trandolapril/Verapamil Hydrochloride, Verapamil Hydrochloride	
Hypercholesterolemia treated with medication	Amlodipine Besylate/Atorvastatin Calcium, Atorvastatin Calcium, Atorvastatin Calcium/Ezetimibe, Ezetimibe/Simvastatin, Fluvastatin Sodium, Lovastatin, Lovastatin/Niacin, Niacin/Simvastatin, Pitavastatin Calcium, Pravastatin Sodium, Rosuvastatin Calcium, Simvastatin, Simvastatin/Sitagliptin Phosphate, Cholestyramine, Colesevelam, Colestipol Hydrochloride, Ezetimibe, Fenofibrate, Gemfibrozil, Lomitapide Mesylate, Niacin, Omega-3-Acid Ethyl Esters	Medication Billing Code
Smoker	F17.20, F17.200, F17.201, F17.203, F17.208, F17.209, F17.21, F17.210, F17.211, F17.213, F17.218, F17.219, F17.29, F17.290, F17.291, F17.293, F17.298, F17.299, Z72.0	ICD-10 Diagnosis

Major adverse cardiovascular events		
Myocardial infarction	I21, I21.0, I21.01, I21.02, I21.09, I21.1, I21.11, I21.19, I21.2, I21.21, I21.29, I21.3, I21.4, I22, I22.0, I22.1, I22.2, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.7, I23.8, I25.2	ICD-10 Diagnosis
Ischemic stroke	I63	ICD-10 Diagnosis
Heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, 142.5-I42.9, I43.x, I50.x, P29.0	ICD-10 Diagnosis
Acute coronary syndrome	I200, I2109, I2111, I2119, I2129, I213, I214, I240	ICD-10 Diagnosis
Coronary artery bypass grafting	566, 567, 33510, 33511, 33512, 33513, 33514, 33516, 33517, 33518, 33519, 33520, 33521, 33522, 33523, 33525, 33528, 33530, 33533, 33534, 33535, 33536, 35600, 4110F, 75762, 75764, 75766, 75767, 93551, C9604, C9605, G8158, G8159, G8160, G8161, G8162, G8163, G8164, G8165, G8166, G8167, G8170, G8171, G8172, G8497, G8544, G8573, G8574, I2570, I25700, I25701, I25708, I25709, I2571, I25710, I25711, I25718, I25719, I2572, I25720, I25721, I25728, I25729, I2573, I25730, I25731, I25738, I25739, I2579, I25790, I25791, I25798, I25799, I25810, T82211, T82211A, T82211D, T82211S, T82212, T82212A, T82212D, T82212S, T82213, T82213A, T82213D, T82213S, T82218, T82218A, T82218D, T82218S, Z951, 0210093, 0210098, 0210099, 021009C, 021009F, 021009W, 02100A3, 02100A8, 02100A9, 02100AC, 02100AF, 02100AW, 02100J3, 02100J8, 02100J9, 02100JC, 02100JF, 02100JW, 02100K3, 02100K8, 02100K9, 02100KC, 02100KF, 02100KW, 02100Z3, 02100Z8, 02100Z9, 02100ZC, 02100ZF, 0210344, 02103D4, 0210444, 0210493, 0210499, 0210499, 021049F, 021049W, 02104A3, 02104A8, 02104A9, 02104AC, 02104AF, 02104AW, 02104D4, 02104J3, 02104J8, 02104J9, 02104JC, 02104JF, 02104JW, 02104K3, 02104K8, 02104K9, 02104KC, 02104KF, 02104KW, 02104Z3, 02104Z8, 02104Z9, 02104ZC, 02104ZF, 0211093, 0211098, 0211099, 021109C, 021109F, 021109W, 02110A3, 02110A8, 02110A9, 02110AC, 02110AF, 02110AW, 02110J3, 02110J8, 02110J9, 02110JC, 02110JF, 02110JW, 02110K3, 02110K8, 02110K9, 02110KC, 02110KF, 02110KW, 02110Z3, 02110Z8, 02110Z9, 02110ZC, 02110ZF, 0211344, 02113D4, 211444, 0211493, 0211498, 0211499, 021149C, 021149F, 021149W, 02114A3, 02114A8, 02114A9, 02114AC, 02114AF, 02114AW, 02114D4, 02114J3, 02114J8, 02114J9, 02114JC, 02114JF, 02114JW, 02114K3, 02114K8, 02114K9, 02114KC, 02114KF, 02114KW, 02114Z3, 02114Z8, 02114Z9, 02114ZC, 02114ZF, 0212093, 0212098, 0212099, 021209C, 021209F, 021209W, 02120A3, 02120A8, 02120A9, 02120AC, 02120AF, 02120AW, 02120J3, 02120J8, 02120J9, 02120JC, 02120JF, 02120JW, 02120K3, 02120K8, 02120K9, 02120KC, 02120KF, 02120KW, 02120Z3, 02120Z8, 02120Z9, 02120ZC, 02120ZF, 0212344, 02123D4, 0212444, 0212493, 0212498, 0212499, 021249C, 021249F, 021249W, 02124A3, 02124A8, 02124A9, 02124AC, 02124AF, 02124AW, 02124D4, 02124J3, 02124J8, 02124J9, 02124JC, 02124JF, 02124JW, 02124K3, 02124K8,	CPT-4 Procedure

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Percutaneous coronary intervention	92920, 92921, 92924, 92925, 92928, 92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 02700D6, 02700DZ, 02700T6, 02700TZ, 02700Z6, 02700ZZ, 02703D6, 02703DZ, 02703T6, 02703TZ, 02703Z6, 02703ZZ, 02704D6, 02704DZ, 02704T6, 02704TZ, 02704Z6, 02704ZZ, 02710D6, 02710DZ, 02710T6, 02710TZ, 02710Z6, 02710ZZ, 02713D6, 02713DZ, 02713T6, 02713TZ, 02713Z6, 02713ZZ, 02714D6, 02714DZ, 02714T6, 02714TZ, 02714Z6, 02714ZZ, 02720D6, 02720DZ, 02720T6, 02720TZ, 02720Z6, 02720ZZ, 02723D6, 02723DZ, 02723T6, 02723TZ, 02723Z6, 02723ZZ, 02724D6, 02724DZ, 02724T6, 02724TZ, 02724Z6, 02724ZZ, 02730D6, 02730DZ, 02730T6, 02730TZ, 02730Z6, 02730ZZ, 02733D6, 02733DZ, 02733T6, 02733TZ, 02733Z6, 02733ZZ, 02734D6, 02734DZ, 02734T6, 02734TZ, 02734Z6, 02734ZZ, C9600, C9601, C9602, C9603, C9604, C9605, C9606, C9607, C9608, 0270046, 027004Z, 0270346, 027034Z, 0270446, 027044Z, 0271046, 027104Z, 0271346, 027134Z, 0271446, 027144Z, 0272046, 027204Z, 0272346, 027234Z, 0272446, 027244Z, 0273046, 027304Z, 0273346, 027334Z, 0273446, 027344Z	CPT-4 Procedure
Major adverse limb event	00.55, 17.56, 39.50, or 39.90, 39.25, 39.26, 39.39, 84.13, 84.14, 84.15, 84.16, 84.17	ICD-9 Procedure†

*Code position and associated healthcare encounter for endpoints-of-interest are described further in the main publication text.

†Any ICD-9 codes were converted to ICD-10 using the Centers for Medicare and Medicaid Services (CMS) General Equivalence Mappings (GEMs) files available at: https://www.cms.gov/Medicare/Coding/ICD10/2018-ICD-10-CM-and-GEMs.html (Last accessed on November 21, 2019).