Health Care Resource Utilization and Costs Associated with Nonfatal Major Adverse Cardiovascular Events

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ABSTRACT

BACKGROUND: Risk of recurrent cardiovascular events following an initial cardiovascular-related hospitalization remains high despite available interventions. Rates of cardiovascular events as well as associated health care resource utilization and costs are needed to assess the value of treatments.

OBJECTIVE: To quantify, in patients with previous hospitalization for acute coronary syndrome (ACS), rates of nonfatal major adverse cardiovascular events (MACE) and secondary coronary events (SCE), as well as health care utilization and costs associated with a first MACE.

METHODS: Administrative data from a large population of commercial managed care and managed Medicare enrollees in the United States were retrospectively analyzed. Patients with an ACS-related hospitalization from 2006 to 2011 were followed for 12 months to assess subsequent MACE and SCE rates. Patients were aged ≥ 18 years at initial ACS hospitalization (the index episode) and had ≥ 12 months of continuous health plan enrollment before and after the end of the index episode. Resource utilization and costs during a first MACE were assessed. Multivariable analyses were used to assess the associations between cardiovascular risk factors and the occurrence of a MACE, as well as the costs incurred during a first MACE.

RESULTS: Of 75,231 study patients identified, 3.3% had a MACE and 8.3% had an SCE during the 12-month follow-up. Median time to first MACE and SCE from end of the index episode was 4.6 and 3.7 months, respectively. Mean MACE-related cost incurred during the first MACE was \$19,642. Logistic analyses showed that age and diabetes were associated with increased odds of a MACE, while index ACS episodes involving ST-elevation myocardial infarction were associated with reduced odds. Findings from generalized linear models indicated that statin use and age were associated with lower episode-related costs and that MACE occurrence within 3 months of ACS hospitalization was associated with increased episode-related costs.

CONCLUSIONS: MACEs and SCEs represent a common and costly burden in the year following ACS hospitalization. Our findings may inform future economic assessments of new therapies aimed at prevention of MACEs and SCEs.

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What this study adds

- This study adds to what is known about the incidence and cost of major adverse cardiovascular events (MACE) and secondary coronary events (SCE) following hospitalization for acute coronary syndrome (ACS).
- We found that 3.3% of patients had at least 1 MACE, and 8.3% had at least 1 SCE during the 12 months following an ACS hospitalization.
- Mean MACE-related costs incurred during the first MACE was \$19,642, and a MACE occurring within 3 months of an ACS hospitalization was associated with increased costs, whereas age at the time of ACS hospitalization and statin use were associated with decreased costs.

As the leading cause of death in the United States, cardiovascular diseases (CVDs) accounted for approximately 25% of all deaths in 2010.¹ Two of the most common types of CVDs are myocardial infarction (MI) and stroke, which impose considerable clinical and economic burden on society. Annually, approximately 720,000 and 795,000 Americans have an MI or stroke, respectively, and the estimated total cost associated with CVDs was \$315.4 billion in 2010.¹⁻³

Several types of interventions reduce the risk of CVDs, including pharmacological treatments (e.g., antihypertensives, antihyperlipidemics, and antiplatelets); medical devices (e.g., pacemakers, coronary stents, and implantable defibrillators); and surgical coronary revascularization procedures (e.g., coronary artery bypass graft and percutaneous coronary intervention).⁴ However, despite the treatments available, risk of recurrent cardiovascular events remains considerable. Previous trials have shown that even with medication, the risk of a recurrent cardiovascular event could exceed 20% among high-risk populations (e.g., adults with coronary disease, other occlusive arterial disease, or diabetes).^{5,6} This high residual risk highlights the need for new treatments that further reduce the risk of cardiovascular events.⁷

To better understand the economic burden of CVDs and inform future cost and cost-effectiveness assessments of new therapies aimed at cardiovascular event prevention, this study aimed to quantify rates of nonfatal major adverse cardiovascular events (MACE) and secondary coronary events (SCE)

What is already known about this subject

- Despite available treatments, risk of recurrent cardiovascular events remains high, especially in high-risk populations.
- Cardiovascular diseases represent some of the most costly chronic conditions, estimated to cost approximately \$315.4 billion in 2010.

in the 12 months following hospitalization for acute coronary syndrome (ACS) in a large commercially insured population. Among patients with at least 1 subsequent MACE, health care resource utilization, such as hospitalizations, procedures, and outpatient visits, and costs associated with the first MACE were assessed. Within the context of this study, MACE was defined by hospitalization for MI or stroke, and SCE was defined by hospitalization for heart failure, unstable angina, transient ischemic attack, limb amputation due to vascular causes, or coronary revascularization.

Methods

Data Source

Administrative claims data spanning January 1, 2006, to December 31, 2011, from a large population of commercial managed care and managed Medicare enrollees in the United States were retrospectively analyzed. These data were taken from the MarketScan Commercial Claims and Encounters (CCAE) and Medicare Supplemental Database provided by Truven Health Analytics. The database consists primarily of employer and health plan data containing patient demographics, periods of health plan enrollment, primary and secondary diagnoses, and detailed information about medical and drug utilization and costs. However, information on prescription medications dispensed via hospital pharmacies during inpatient stays was not captured. Patient mortality also was not captured. Because all data were pre-existing and de-identified, an authorized institutional review board, the RTI International Committee for the Protection of Human Subjects (Federal-Wide Assurance #3331), granted approval for study conduct and exemption from requirement of patient-informed consent.

Patient Selection

Patients were selected for inclusion if they had a primary inpatient hospital discharge diagnosis of ACS (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 410.xx [acute myocardial infarction], 411.1 [intermediate coronary syndrome], 411.8x [other acute and subacute forms of ischemic heart disease]) between January 1, 2007, and December 31, 2010. The admission date of the first observed ACS hospitalization defined the index episode start date, and the date 30 days after the hospital discharge was considered the index episode end date. The 30-day extension beyond discharge from the index ACS hospital episode was applied to avoid misidentification of index episode-related resource use as recurring MACEs. The immediate date after completion of the index episode defined the follow-up start date, from which all outcomes were measured for 12 months thereafter. Patients were required to be at least aged 18 years at the index episode date and to have had medical and pharmacy benefits for at least 12 continuous months before the index episode (pre-index period) and after the end of the index episode (post-index period).

Study Measures

Patient characteristics documented in this study included age, sex, geographic region, and health plan type on the hospital admission date for the index episode. The presence of cardiovascular risk factors, including age of at least 60 years at index, pre-index diabetes requiring treatment, pre-index renal disease, and index diagnosis of ST-elevation MI (STEMI) versus non-ST-elevation MI (NSTEMI; Appendix A, available in online article), as well as index statin use and the Charlson Comorbidity Index (CCI) score, were assessed.⁸ We also flagged additional pre-index conditions (Appendix B, available in online article) that have been examined in previous clinical trials in similar populations (e.g., O'Donoghue et al. [2011]⁹ and White et al. [2014],¹⁰ which assessed the efficacy of darapladib in MACE prevention).

In addition to patient characteristics, outcomes of interest included the occurrence of MACEs and SCEs, as well as health care resource utilization and costs associated with first MACEs subsequent to the index ACS hospital episode. MACE was defined in this study as a composite of MI (ICD-9-CM diagnosis code 410.xx [acute myocardial infarction]) and acute ischemic stroke (ICD-9-CM diagnosis codes 433.xx [occlusion and stenosis of precerebral arteries], 434.xx [occlusion of cerebral arteries], and 436.xx [acute, but ill-defined, cerebrovascular disease]). Primary inpatient discharge diagnoses were used to identify the occurrence of a MACE. Nonprimary inpatient discharge diagnoses and outpatient diagnoses for MI and stroke were not used to avoid inclusion of claims likely related to older episodes or history of MACE. Because the study database does not provide complete mortality information, it was not possible to definitively delineate fatal versus nonfatal MACEs for study patients. However, given the study criterion requiring at least 12 months of plan enrollment after the index ACS episode (for provision of adequate follow-up for assessing first and subsequent MACE frequency and MACE costs), any MACE occurring in that time frame, except perhaps a MACE at the end of the 12-month follow-up, was by definition a nonfatal event.

SCE was defined in this study as a composite of hospitalization for heart failure (ICD-9-CM diagnosis code 428.xx), hospitalization for unstable angina (ICD-9-CM diagnosis code 413.xx [angina pectoris]), transient ischemic attack (ICD-9-CM diagnosis code 435.x [transient cerebral ischemia]), limb amputation due to vascular causes (ICD-9-CM procedure code 84.0x-84.1x without any primary or secondary diagnoses for injury from the same confinement [ICD-9-CM diagnosis code 800.xx-999.xx (injury and poisoning)]), and coronary revascularization, including percutaneous coronary intervention (ICD-9-CM procedure codes 36.0x, 00.66; Healthcare Procedure Coding System [HCPCS] codes G0290, G0291; and Current Procedural Terminology [CPT] codes 92973-92975, 92980, 92981, 91984, 92995-92998), and coronary artery bypass graft (ICD-9-CM procedure code 36.1x; HCPCS codes

FIGURE 1 Sample Selection Flowchart

ACS=acute coronary syndrome.

S2205-S2209; CPT codes 33510-33536). Similar to MACEs, SCEs were assessed using primary inpatient discharge diagnoses to avoid capture of claims likely related to older episodes or history of SCEs.

The number and percentage of patients with at least 1 MACE or SCE, as well as those with each of the component conditions during the 12-month follow-up period after the end of the index episode, were reported. Among patients who experienced a MACE or an SCE, time to MACE and SCE were reported. Also among patients who experienced a MACE, resource use and costs associated with the first MACE were reported. A MACE was defined as the period beginning with the hospital admission date of the episode (i.e., MACE onset) until 30 days after the hospital discharge date. A MACE that was censored at the end of follow-up before 30 days after the discharge date was excluded from the cost analysis. The 30-day postdischarge extension of a MACE was imposed to allow for sufficient observation of event-related resource use and to avoid misattribution of these resources to another separate MACE.

For each patient with a MACE, health care utilization and associated costs were aggregated across all MACE-related encounters observed during the first MACE and were reported overall and by the major service setting in which they occurred (i.e., inpatient, emergency department, office visit, pharmacy, other outpatient, or ancillary, identified by place of service on each claim). For each service setting, the number and percent-

age of patients with a visit and the mean (standard deviation [SD]) and median number of visits and costs during the first MACE were reported. The reported costs represented payments made by the submitting plan for services incurred and were adjusted for inflation to 2012 U.S. dollars using the medical care component of the Consumer Price Index. Encounters during the first MACE with primary or nonprimary diagnoses or procedures for a MACE or an SCE or an outpatient prescription for a CVD-related therapy (identified using generic drug names and database-specific therapy class field; see Appendix C, available in online article) were defined as MACE related.

Analytic Strategies

All analyses were conducted using SAS version 9.3 statistical software (SAS Institute, Inc., Cary, NC). Descriptive analyses were conducted for all measures and included means, SDs, and medians for continuous variables and frequency distributions for categorical variables. Logistic regressions were used to assess the relationship between cardiovascular risk factors and the occurrence of MACEs. Generalized linear models (GLMs) with a log-link function and a gamma distribution were estimated to assess the relationship between cardiovascular risk factors and MACE-related costs incurred during the first MACE for the subset of patients with a MACE. The risk factors assessed included at least aged 60 years at index, pre-index diabetes requiring treatment, pre-index renal disease, index STEMI event (compared with index NSTEMI event), and index statin use in the context of logistic regressions and GLMs, as well as having a MACE within 3 months of index (compared with after 3 months) for GLMs. These multivariable models additionally controlled for baseline age, sex, geographic (census) region, health plan type, presence of pre-index flagged conditions, pre-index CCI score, and statin use prior to post-index follow-up. Significance was established at the 0.05 alpha level.

Results

A total of 204,509 patients with an ACS-related hospitalization were initially identified from the study database (Figure 1). After application of the study inclusion criteria, 75,231 ACS patients remained in the study sample. The requirement of at least 12 months of continuous health plan enrollment before and after the index date was the primary reason for sample attrition. All selection criteria combined eliminated 63.2% of the starting sample, resulting in a study sample of 75,231.

Mean [SD] age of the study sample was 64.4 [13.4] years (Table 1). Patients of working age (18-64 years) represented more than half (57.0%) of the patients, and persons aged 65 years and older comprised 43.0% of the sample. Approximately two-thirds of ACS patients were male. Based on the geographic dispersion of employers and health plans captured in the CCAE database, the Midwest and South regions had the largest representation in the study sample (34.9% and 36.1%,

TABLE 1 Baseline Demographic and Clinical Characteristics

Patient Characteristics	N = 75,231	
Age (mean [SD], median)	64.4 [13.4]	62.0
	%	n
Age group		
18-34	0.6	455
35-44	4.7	3,535
45-54	18.6	14,015
55-59	15.7	11,838
60-64	17.3	13,043
65+	43.0	32,345
Male sex	65.8	49,489
Geographic region		
Northeast	12.4	9,330
Midwest	34.9	26,224
South	36.1	27,156
West	16.0	12,002
Unknown	0.7	519
Current statin use ^a	73.1	55,018
Index ACS diagnosis		
STEMI	22.4	16,887
NSTEMI	38.8	29,173
Unstable angina	38.8	29,171
Preindex comorbid conditions of interest		
Diabetes requiring treatment	20.6	15,468
Renal disease	0.1	49
Pre-index CCI score		
0	29.3	22,016
1	25.2	18,989
2	16.8	12,668
3 or greater	28.7	21,558
Mean [SD], median	1.9 [2.2]	1.0

^aStatin prescription that overlaps with the end of the index episode or the start of the follow-up period.

ACS=acute coronary syndrome; CCI=Charlson Comorbidity Index; NSTEMI=non-ST-elevation myocardial infarction; SD=standard deviation; STEMI=ST-elevation myocardial infarction.

TABLE 2 Major Adverse Cardiovascular Events and Secondary Coronary Events During the 12-Month Follow-up Period

Event	N = 75,231	
Patients with Event	%	n
MACE^a		
First MACE	3.3	2,503
Second MACE	0.2	137
Third MACE	<0.1	9
Type of MACE (not mutually exclusive)		
MI	2.5	1,880
Stroke	0.9	642
SCE^a		
First SCE	8.3	6,259
Second SCE	0.9	688
Third SCE	0.1	107
Type of SCE (not mutually exclusive)		
Heart failure	2.7	2,025
Unstable angina	0.1	62
Transient ischemic attack	0.2	188
Limb amputation due to vascular causes	0.1	85
Coronary revascularization	5.5	4,129
Days to Event from End of Prior Episode^b		
	Mean [SD]	Median
MACE		
First MACE	149.8 [93.9]	139.0
Second MACE	92.4 [66.1]	78.0
Third MACE	50.6 [40.9]	44.0
SCE		
First SCE	129.1 [94.0]	112.0
Second SCE	90.0 [64.7]	79.0
Third SCE	59.3 [47.6]	48.0
Timing of First MACE Among Those with a MACE		
	%	n
Within 3 months following index episode	33.4	835
After 3 months following index episode	66.6	1,668

^aEach event type is counted once per episode; however, multiple event types are allowed per episode.

^bEach episode is given 30 days from hospital discharge.

MACE= major adverse cardiovascular event; MI=myocardial infarction; SCE=secondary coronary event; SD=standard deviation.

respectively). Compared with the general U.S. population, the Northeast was underrepresented in this study (12.4%). A substantial proportion of patients were receiving statin treatment at the index episode date (73.1%). Patients had an index diagnosis of NSTEMI as frequently as unstable angina (38.8% of patients, each), whereas an index diagnosis of STEMI was less frequently observed (22.4% of patients). Examining specific comorbid conditions and clinical events of interest, we observed that diabetes requiring treatment was relatively common (20.6% of patients), whereas renal disease was not (0.1% of patients). The mean [SD] and median CCI score, assessed during 12 months prior to the index ACS hospital admission date, were relatively low at 1.9 [2.2] and 1.0, respectively, based upon previously established indices.¹¹

Overall, 2,503 ACS patients (3.3%) had at least 1 MACE during the 12-month follow-up period (Table 2). However, the study inclusion criteria requiring a minimum 12-month follow-up period eliminated fatal MACEs, except for those experienced at the end of the follow-up period. Furthermore, mortality was not reported in the MarketScan CCAE database and hence not captured in this analysis. Among patients with at least 1 follow-up MACE, MI was the most common event type (1,880 patients: 75.1% of patients with MACEs, 2.5% of patients overall). Stroke was a relatively uncommon MACE in the post-ACS setting (642 patients, or 0.9% of patients) but was seen in a quarter (25.6%) of all patients with MACEs. Among patients with a follow-up MACE, mean [SD] and median times to the first MACE from the end of the index episode were 149.8

TABLE 3 Logistic Regressions Evaluating Association Between Occurrence of MACEs and Measures of Interest

Measures of Interest, Each from a Separate Model ^a	Odds Ratio	95% CI	P Value ^b	Sample Size	Number of Cases
At least aged 60 years at index (reference = under 60)	1.233	(1.119-1.359)	<0.001	75,231	2,503
Pre-index diabetes requiring treatment (reference = no diabetes)	1.476	(1.340-1.625)	<0.001	75,231	2,503
Pre-index renal disease (reference = no renal disease)	0.764	(0.185-3.156)	0.710	75,231	2,503
Statin use at end of index episode (reference = no statin use)	0.865	(0.793-0.943)	0.001	75,231	2,503
STEMI index MI event (reference = NSTEMI)	0.782	(0.698-0.875)	<0.001	46,060	1,610

^aEach model additionally controls for baseline age, sex, geographic (census) region, health plan type, presence of pre-index flagged conditions, pre-index CCI score, and statin use prior to post-index follow-up unless collinear with independent variable of interest.

^bNot adjusted for multiple comparisons.

CCI = Charlson Comorbidity Index; CI = confidence interval; MACE = major adverse cardiovascular event; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.

[93.9] and 139.0 days, respectively. Approximately one-third of patients with at least 1 MACE experienced the event within 3 months after the index episode. Among patients with at least 1 MACE, 137 patients (5.5% of those with an event) experienced a second event during the 12-month follow-up period. Mean [SD] and median times to the second MACE from the end of the prior MACE were 92.4 [66.1] and 78.0 days for patients with a second event, respectively. Only 9 patients experienced a third MACE during the 12-month follow-up period.

Overall, 6,259 patients (8.3%) had at least 1 SCE during the 12-month follow-up period (Table 2). Among patients with at least 1 follow-up SCE, the most common type was coronary revascularization, observed in 66.0% of patients with an SCE and 5.5% of patients overall. The next most common SCE was heart failure, observed in 32.4% of patients with an SCE and 2.7% of patients overall. Unstable angina or noncoronary ischemic events, as well as limb amputations due to vascular causes, were infrequently observed SCEs.

From the logistic regression results (Table 3), being aged 60 years or older at the index episode date was associated with a 23.3% increase in the odds of a MACE. Pre-index diabetes was associated with a 47.6% increase in the odds of experiencing a MACE. For patients whose index ACS episode involved an MI, having a STEMI diagnosis was associated with a 21.8% reduction in the odds of a MACE as compared with an NSTEMI diagnosis. Statin use at the end of the index ACS episode was associated with a 13.5% reduction in the odds of a MACE. Since only 49 patients had renal disease in the pre-index period, there was virtually no power to assess its relationship with events.

Among study patients with at least 1 MACE during the 12-month follow-up period, by definition, all had an inpatient hospital admission. Mean [SD] and median costs of \$18,576 [\$38,027] and \$5,973, respectively, were observed for all MACE-related inpatient care during the first MACE (Table 4). Patients had an average of 1 MACE-related hospital admission during the first MACE. The majority of patients with MACEs (82.3%) had a CVD-related outpatient prescription, with mean [SD] and median outpatient prescription costs during the first

MACE of \$228 [\$294] and \$146 per patient, respectively. We observed less than a quarter of patients visiting the emergency department or a physician's office during the first MACE for a MACE-related reason. Mean [SD] and median total episode-related costs per patient for the first MACE were \$19,642 [\$38,690] and \$6,563, respectively. During the first MACE, we found that MI-related costs accounted for 85.0% of total mean episode costs.

The multivariable GLM results (Table 5) indicate that being aged 60 years or older at the index episode date was associated with significantly lower cost (63.4% lower) of the first MACE episode. Having a MACE within the first 3 months of follow-up was associated with a significant 35.5% increase in episode costs. Statin use at the end of the index episode was associated with a significant 9.2% reduction in the cost of the first MACE. We observed no significant association between episode costs and pre-index diabetes, pre-index renal disease, or index STEMI (for those with an index MI event).

Discussion

In this large-scale observational study, we assessed rates and costs of nonfatal MACEs in patients with a prior history (within the preceding year) of an ACS-related hospitalization to address current literature gaps and to provide supporting information for future economic assessments of therapies aimed at MACE prevention. A review of published reports also assessing population-based cardiovascular event rates may provide additional context to our findings. One recent claims-based study by Chapman et al. (2011) found an overall cardiovascular hospitalization event rate (MACEs and SCEs combined, defined by MI, heart failure, unstable angina, angina pectoris, other ischemic heart disease, ischemic stroke, transient ischemic attack, and peripheral vascular disease) of 16.1% over a variable follow-up period of up to 3 years after a previous cardiovascular-related hospitalization.¹² Although the Chapman et al. study did not assess specific event rates separately, the reported composite rate of 16.1% falls moderately above the range of event rates we observed for MACEs and SCEs combined (11.6%) during 12

TABLE 4 MACE-Related^a Health Care Resource Utilization and Costs Incurred During the First MACE^b

Resources	N = 2,503	
Patients with At Least 1 Service	%	n
Hospitalizations	100.0	2,503
Emergency department	18.1	452
Physician's office	22.0	550
Pharmacy (outpatient)	82.3	2,059
Ancillary outpatient	47.9	1,200
MI-related	76.6	1,918
Stroke-related	31.1	778
Total	100.0	2,503
Number of Services	Mean [SD]	Median
Hospitalizations	1.1 [0.4]	1.0
Emergency department	0.2 [0.4]	0.0
Physician's office	0.3 [0.8]	0.0
Pharmacy (outpatient)	3.7 [2.9]	3.0
Ancillary outpatient	1.3 [2.6]	0.0
MI-related	6.6 [7.7]	5.0
Stroke-related	2.5 [5.4]	0.0
Total	6.6 [4.1]	6.0
Costs per Patient	Mean [SD] (\$)	Median (\$)
Hospitalizations	18,576 [38,027]	5,973
Emergency department	34 [138]	0
Physician's office	57 [1,234]	0
Pharmacy (outpatient)	228 [294]	146
Ancillary outpatient	748 [3,917]	0
MI-related	16,698 [38,016]	2,099
Stroke-related	5,043 [25,689]	0
Total	19,642 [38,690]	6,563

^aMACE-related services were identified as those with a MACE diagnosis, an SCE diagnosis or procedure, or a CVD drug prescription.

^bEach episode was given 30 days from hospital discharge.

CVD = cardiovascular disease; MACE = major adverse cardiovascular event; MI = myocardial infarction; SCE = secondary coronary event; SD = standard deviation.

months of follow-up. The difference observed may be due to the inclusion of fatal events, peripheral vascular disease overall (rather than limb amputations due to peripheral vascular disease), and angina pectoris (in addition to unstable angina), as well as a longer follow-up period.

Additional studies have assessed cardiovascular event rates in patients with prior cardiac history using large-scale, prospective patient registries. A notable example is the Reduction of Atherothrombosis for Continued Health (REACH) Registry, which is a contemporary international outpatient study of patients with either stable symptomatic vascular disease (coronary heart disease, stroke, transient ischemic attack, or peripheral artery disease) or multiple risk factors for vascular disease (e.g., hypertension, diabetes, hyperlipidemia, carotid stenosis, and smoking).¹³ One study based on REACH data by Mahoney et al. (2008) reported 1-year cardiovascular event rates for patients in the United States with a prior history of coronary

heart disease and other high-risk vascular conditions.¹⁴ In the Mahoney et al. study, the overall percentage of patients with at least 1 composite cardiovascular event (i.e., cardiovascular death, MI, or stroke) after 1 year of follow-up was 4%. Although our study could not assess fatal events, our estimate of the proportion of patients with at least 1 MI (2.5%) and 1 stroke (0.9%), when combined, approached the 1-year composite rate reported by Mahoney et al.

As confirmed in other studies,^{15,16} older age and diabetes were associated with increased risk of a MACE, whereas statin use was associated with a decreased risk of a MACE.¹⁷ We also found that patients with a STEMI index event were at somewhat lower risk of a MACE than patients with an NSTEMI index event, among the subset of patients who had 1 of these types of index events, although the mechanism behind this association is unclear and warrants further exploration. One previous study in a Korean population also found a lower 12-month risk of nonfatal MI and coronary artery bypass graft following a previous STEMI than following a previous NSTEMI.¹⁸ One possible explanation for lower subsequent MACE risk in STEMI patients is that these patients may have received more extensive disease intervention (coronary stenting, catheterization, revascularization, and other procedures often emergently needed in STEMI cases) as compared with NSTEMI patients during the index ACS hospitalization. If true, this finding may suggest that more aggressive intervention for NSTEMI may decrease subsequent MACE risk.

The large mean health care costs observed for the first MACE during the 12-month follow-up period were consistent with previous findings from similar studies. Closely matching estimations of cardiovascular events were reported by Chapman et al., with an average hospitalization cost for a subsequent cardiovascular event following an index cardiovascular event of \$17,709.¹² These estimates were slightly lower than those observed in this study (\$18,576). The differences observed between these studies may be attributed to our inclusion of the 30-day episode extension following discharge from the hospital versus their restriction to the inpatient stay associated with the event, as well as to different conditions and procedures designated as disease related. Based upon the multivariable analyses, we observed a significant reduction in the cost of the first MACE among patients aged 60 years or older, possibly due to differing health plan payment representation within the database among retired patients.

Since previous research has shown an association between statin use and reduced health care costs,¹⁹ we also found that patients with statin use at the end of the index episode had reduced first MACE costs, which may indicate a reduction in cardiovascular complications associated with statin use.²⁰ Furthermore, the increased first MACE costs found among patients with an early MACE (within 3 months of the index ACS hospital discharge) warrant further exploration, with an emphasis on characterizing the event severity and treatment profile of the index ACS and subsequent MACE episodes.

TABLE 5 Generalized Linear Models Evaluating Association Between MACE-Related^a Health Care Costs of First MACE and Measures of Interest Among Patients with a MACE

Measures of Interest, Each from a Separate Model ^b	Rate Ratio ^c	95% CI	P Value	Sample Size
At least aged 60 years at index (reference = under 60)	0.366	(0.328-0.408)	<0.001	2,503
Pre-index diabetes (reference = no diabetes)	0.960	(0.866-1.064)	0.437	2,503
Pre-index renal disease (reference = no renal disease)	2.684	(0.588-12.247)	0.203	2,503
Statin use at end of index episode (reference = no statin use)	0.908	(0.828-0.996)	0.041	2,503
Early MACE within 3 months (reference = after 3 months)	1.355	(1.237-1.484)	<0.001	2,503
STEMI index MI event (reference = NSTEMI)	0.994	(0.876-1.129)	0.931	1,610

^aMACE-related services were identified as those with a MACE diagnosis, an SCE diagnosis or procedure, or a CVD drug prescription.

^bEach model additionally controls for baseline age, sex, geographic (census) region, health plan type, presence of pre-index flagged conditions, pre-index CCI score, and statin use prior to post-index follow-up unless collinear with independent variable of interest.

^cThe rate ratio is the exponentiated parameter estimate, denoting the multiplicative effect of the reported level versus the reference level.

CCI = Charlson Comorbidity Index; CI = confidence interval; CVD = cardiovascular disease; MACE = major adverse cardiovascular event; MI = myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; SCE = secondary coronary event; STEMI = ST-elevation myocardial infarction.

A study on the use of secondary prevention drug therapy among ACS patients suggests that patients are not commonly prescribed guideline medication therapies during the first 3 months following an ACS hospitalization, which may lead to more complicated cardiovascular events during this time.²¹

Limitations

Our study was subject to several limitations that should be considered in the interpretation of our findings. First, patients were identified and costs were designated on the basis of ICD-9-CM diagnosis codes and HCPCS, CPT, and ICD-9-CM procedure codes, with no access to patient charts for confirmation of events. The extent to which coding errors may have led to misclassification of patients is unclear, but it is likely small.^{22,23} Second, due to the lack of clinical and comprehensive mortality information in the MarketScan CCAE database, we could not further validate the occurrence of outcomes of interest and could not include death due to CVD as a component of MACEs. Detection of MACEs from primary discharge diagnoses and the designation of 30 days after MACE discharge as the episode duration may have led to an underestimation of the number of outcomes observed during the follow-up period. Third, due to our requirement of continuous health plan enrollment for 12 months following the index episode, we may have introduced selection bias toward healthier patients in these data. On a related note, due to the requirement of a 12-month pre-index period, we cannot be certain that the index ACS episode was a patient's first experience of an ACS episode. Fourth, treatment assessment was based upon outpatient prescription claims data, which reflect medications prescribed, not necessarily medications taken. Fifth, the MarketScan CCAE database does not provide details on prescription drug use during hospitalization, thereby underestimating the use of pharmacotherapy. Sixth, we assessed only the direct medical costs associated with cardiovascular episodes and did not have data to examine the overall burden of these conditions to include indirect costs (e.g., lost workplace productivity and caregiver burden). Finally, this

study was limited to managed care enrollees; thus, the results may not be generalizable to the entire U.S. population or to individuals covered by other federal insurance programs (e.g., Medicaid or Veterans Affairs). The Northeast's underrepresentation in our study sample further reduces generalizability; to the extent that per capita health care costs are higher in the Northeast as compared with other regions, our overall cost estimates for MACEs may be somewhat conservative.

Conclusions

Findings from this study provide current information on the characteristics, event rates, and episode-based health care resource use and costs of MACEs in a commercial population with previous history of ACS. The recurrence of cardiovascular events in the year following hospitalization for ACS, including MACEs and SCEs, represents a common and costly burden for patients in the United States. The data presented here may be useful in future evaluations of the cost-effectiveness of new cardiovascular treatments.

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DISCLOSURES

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Study concept and design were contributed by Ariely, Bell, and Mitra, along with Korsnes and Davis. Korsnes was primarily responsible for data collection, assisted by the rest of the authors. Analysis was performed by Korsnes, Davis, Ariely, and Bell, assisted by Mitra. The manuscript was written and revised by Korsnes, Davis, and Ariely, along with Bell and assisted by Mitra.

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APPENDIX A Cardiovascular Risk Factors

Risk Factor	Identification Codes and Methods
At least aged 60 years at index	
Pre-index diagnosis of diabetes requiring treatment	ICD-9-CM diagnosis codes: 250.xx with prescription for antidiabetic drug
Pre-index renal disease (diagnosis of stage 3 or higher chronic kidney disease, kidney transplant, or nephrectomy)	ICD-9-CM diagnosis codes: 584.xx, 585.3-585.6, 586.xx, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93 HCPCS codes: 50220, 50225, 50230, 50234, 50236, 50240, 50340, 50360, 50365, 50370, 50543, 50545, 50546, 50548
Index myocardial infarction	
STEMI	ICD-9-CM diagnosis codes: 410.0x-410.6x, 410.8x
NSTEMI	ICD-9-CM diagnosis codes: 410.7x

HCPCS = Healthcare Common Procedure Coding System; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-elevation myocardial infarction.

APPENDIX B Flagged Conditions of Interest

Condition	Identification Codes
Liver disease, cirrhosis, or disorders of the biliary tract	ICD-9-CM diagnosis code: 570-573.x, 576.x, 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, V42.7
Stage 4 or higher chronic kidney disease, kidney transplant, or nephrectomy	ICD-9-CM diagnosis code: 584.xx, 585.4-585.6, 586.xx, 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, V42.0 HCPCS code: 50220, 50225, 50230, 50234, 50236, 50240, 50340, 50360, 50365, 50370, 50543, 50545, 50546, 50548
Hospitalization or emergency department visit due to heart failure, hypertension, asthma, or chronic obstructive pulmonary disease	ICD-9-CM diagnosis code: 428.xx, 401.x, 997.91, 491.xx-494.x, 496, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4, 425.5, 425.7-425.9
Any life-threatening condition including HIV/AIDS and cancer (other than nonmelanoma skin cancer) and excluding vascular disease	ICD-9-CM diagnosis code: 042-044, 140.x-172.x, 174.x-208.xx, 238.6
Pregnancy	ICD-9-CM diagnosis code: V22.x, V23.x, V24.0, V24.1, V27.x, V28.x
Anaphylaxis	ICD-9-CM diagnosis code: 995.0, 995.27, 995.3, 995.6x, 999.4x, V13.81
Alcohol abuse, drug abuse, or mental health disorders	ICD-9-CM diagnosis code: 290.xx-301.xx, 303.xx-305.xx, 306.xx-319

HCPCS = Healthcare Common Procedure Coding System; HIV/AIDS = human immunodeficiency virus/acquired immunodeficiency syndrome; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

APPENDIX C Cardiovascular Disease-Related Therapies

Drug Class	Generic Names
Alpha beta blockers	carvedilol, labetalol
Angiotensin receptor blockers	candesartan, irbesartan, losartan, telmisartan, valsartan
Angiotensin converting enzyme inhibitors	benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, trandolapril
Antiarrhythmic agents	amiodarone, flecainide, procainamide, sotalol
Antihyperlipidemics	colestilan, dextran, elastase, fenofibrate, fenofibric acid, gemfibrozil, niaspan, nicomol, polyene phosphatidyl, probucol, soy sterol
Antihypertensives, hypotensives, and vasodilators	alacepril, aliskiren, benazepril, benzyhydrochlorothiazide, budralazine, bunazosin, cadralazine, candesartan cilexetil, captopril, carbazochrome, cilazapril hydrate, clonidine, delapril, doxazosin, enalapril maleate, guanabenz, hydralazine, imidapril, irbesartan, lisinopril, losartan, methyldopa, olmesartan medoxomil, perindopril erbumine, prazosin, quinapril, reserpine, sodium nitroprusside, telmisartan, temocapril, terazosin, trandolapril, urapidil, valsartan
Antithrombotics	acenocoumarol, acetylsalicylate, acetylsalicylic, alteplase, carbasalate, eicosapentaenoic, eptifibatide, ethyl icosapentate, fondaparinux, nadroparin, phenprocoumon, prasugrel, reteplase, streptokinase, sulodexide, tenecteplase, tissue plasminogen activator, triflusal, urokinase
Antithrombotics: anticoagulants	argatroban, dabigatran etexilate, dalteparin, enoxaparin, heparin, parnaparin, reviparin, warfarin
Antithrombotics: antiplatelets	abciximab, beraprost, cilostazol, clopidogrel, dipyridamole, epoprostenol, eptifibatide, limaprost, alfadex, nifedipine, ozagrel, sarpogrelate, ticlopidine, tirofiban
Beta blockers	acebutolol, alprenolol, amosulalol, arotinolol atenolol, betaxolol, bevantolol, bisoprolol, bopindolol, bufetolol, carteolol, carvedilol, celiprolol, esmolol, labetalol, landiolol, metoprolol, nadolol, nipradilol, oxprenolol, penbutolol, pindolol, propranolol, sotalol
Calcium channel blockers	amlodipine, aranidipine, azelnidipine, barnidipine, benidipine, bepridil, cilnidipine, diltiazem, efonidipine, felodipine, manidipine, nicardipine, nifedipine, nilvadipine, nisoldipine, nitrendipine, verapamil
Cardiac glycosides	deslanoside, digitoxin, digoxin
Diuretics	amiloride, azosemide, benzyhydrochlorothiazide, bumetanide, chlorthalidone, eplerenone, ethacrynic acid, furosemide, hydrochlorothiazide, indapamide, isosorbide, mefruside, meticrane, piretanide, potassium canrenoate, spironolactone, tolaptan, torasemide, torsemide, triamterene, trichlormethiazide, triparamide
Niacin	nicotinic
Statins	atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin