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ORIGINAL RESEARCH

Event Rates and Risk Factors for Recurrent Cardiovascular Events and Mortality in a Contemporary Post Acute Coronary Syndrome Population Representing 239 234 Patients During 2005 to 2018 in the United States

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BACKGROUND: Patients with acute coronary syndrome (ACS) are recognized by guidelines as remaining at high risk for adverse outcomes. Evidence from contemporary, representative ACS populations in a clinical practice setting is necessary to identify subgroups and strategies for improving patient outcomes. We aimed to describe event rates and risk factors in an ACS population over prolonged follow-up for cardiovascular end points.

METHODS AND RESULTS: We identified 239 234 patients in the Optum Research Database (57.2% men; mean [standard deviation] age, 69.2 [12.2] years) with evidence of an ACS hospitalization (index ACS) during January 1, 2005 through December 30, 2018. Subgroups were based on index ACS event (myocardial infarction/unstable angina and revascularization status) and the Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention. The 5-year event rate for the primary end point representing nonfatal myocardial infarction, nonfatal ischemic stroke, and cardiovascular death was 33.4% (95% CI, 33.1%–33.7%; *P*<0.001). The risk of experiencing the primary end point was ≈6-fold higher immediately after discharge (≈40.9% annualized risk) as compared with the period 1+ years after hospitalization (≈6.4% annualized risk). Among subgroups, the 5-year primary end point event rate was highest for myocardial infarction without revascularization and a Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention ≥4, at 47.9% (95% CI, 47.3%–48.4%; *P*<0.001) and 56.7% (95% CI, 55.9%–57.4%; *P*<0.001), respectively.

CONCLUSIONS: Patients with ACS remain at very high risk of experiencing recurrent cardiovascular events, particularly early after discharge, with identifiable subgroups at multifold higher risk of specific clinical end points.

Key Words: acute coronary syndrome ■ cardiovascular events ■ risk factor ■ risk stratification

In the current era, health care databases are becoming larger, the coding has become more specific, and increased linkage with other patient-level data has become possible. Better definition of patient populations, subgroups, and outcomes, both over immediate and long-term follow-up now provides greater value from these data. Although new therapies are brought into practice through clinical trials, these observational clinical practice databases provide additional information on existing treatment patterns, patient subgroups

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CLINICAL PERSPECTIVE

What Is New?

- Characteristics, event rates, and predictors of acute coronary syndromes (ACS) were evaluated in a large, contemporary US clinical practice population of 239 234 patients with an ACS hospitalization, from the time of hospital discharge through long-term follow-up.
- Subgroups based on the index ACS type, index revascularization, and the Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention were analyzed separately to identify those who would derive the greatest clinical benefit from guideline-based therapies.
- The Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention was applied to determine its usefulness in risk prognostication in a usual clinical practice population representing patients hospitalized for ACS.

What Are the Clinical Implications?

- This ACS analysis may prove useful to payers, regulatory authorities, clinicians, and clinical guidelines committees.
- Our findings support the claim that patients with ACS remain at very high risk of experiencing recurrent cardiovascular events, particularly early after discharge, with subgroups such as those who experience myocardial infarction without revascularization at index and those with Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention ≥4 at multifold higher risk of specific cardiovascular outcomes.
- The Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention demonstrated usefulness in risk stratification when applied to a large health care administrative claims database, potentially expanding its use to investigators working with similar databases and to inform decision making in clinical practice.

Nonstandard Abbreviations and Acronyms

ACC	American College of Cardiology
AHA	American Heart Association
TRS 2ºP	Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention
UA	unstable angina

not represented in clinical trials, and the potential impact of therapies over extended follow-up.[1]

Patients with an acute coronary syndrome (ACS) are recognized by guidelines as remaining at high risk for future adverse outcomes.[2–7] Numerous medical therapies have not only been validated for secondary cardiovascular prevention, but specifically for patients after ACS. A refined understanding of the characteristics of this population, current treatment patterns, and risk over time is therefore necessary to understand current practice patterns and outcomes, but also which subgroups and strategies are optimal for additional risk mitigation. The primary aim of this study was to evaluate the characteristics, events rates, and risk predictors of ACS in a large and contemporary US clinical practice population, from the time of hospital discharge through long-term follow-up. Specific objectives included: (1) comparison of the characteristics and event rates of the myocardial infarction (MI) versus unstable angina (UA) population and whether these differed by treatment of the index ACS with revascularization; (2) comparison of the characteristics by sex; (3) evaluation of the Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention (TRS 2ºP)[8,9] for risk stratification in a usual clinical practice population with an ACS event; (4) comparison of the similarity (and potential applicability) of our study findings with contemporary randomized controlled trials (RCTs) of ACS populations; and (5) identification of independent risk predictors for trial-related end points, such as cardiovascular death, MI, ischemic stroke, UA, and elective coronary revascularization after discharge.

METHODS

The data underlying the results presented in this study contain proprietary elements owned by Optum Research Database and therefore cannot be broadly disclosed or made publicly available. These underlying data can, however, be made available to a third party via the corresponding author upon reasonable request, assuming certain data security and privacy protocols are in place and that the third party has executed Optum's standard license agreement, which includes restrictive covenants governing the use of the data.

The study cohort was developed from the Optum Research Database, one of the largest anonymized health care research databases in the United States, representing over 70 million patients with data from administrative claims and additional information from enrollment records. In 2018, the Optum Research Database represented 19% of the US population enrolled in commercial health plans and 21% enrolled in Medicare Advantage. Medicare Advantage represents health plans offered by a private company that contracts with Medicare to provide patients with hospital and medical insurance benefits. The study was submitted to the New England Institutional Review Board, received a Waiver of Authorization, and was determined to be exempt from institutional review board review because it did not meet the definition of human subject research (New England Institutional Review Board number 1-9234-1); informed consent was therefore not required.

Cohort Development

Patients with evidence of an ACS hospitalization between January 1, 2005 and December 30, 2018 were identified (Figure S1). For individuals experiencing multiple qualifying ACS hospitalizations, 1 event was randomly selected, which is subsequently referred to as the index ACS. This strategy was used because a patient's characteristics and future risk will differ depending on whether the first, second, or another subsequent ACS event is chosen. Randomly selecting an ACS event helped ensure representativeness (see Data S1 for supporting sensitivity analysis). The index date was the date of hospital discharge and defined the initiation of follow-up. Additional inclusion criteria were age ≥20 years, availability of 1-year baseline data before the index date, and discharge codes indicative of alive status. A 1-year baseline period was chosen because it represented an optimal tradeoff between a more accurate ascertainment of preexisting conditions and sample size (Table S1). To define baseline characteristics, a single claim was sufficient if it was identified from an inpatient stay; otherwise, 2 medical claims on 2 different dates of service were required. Diagnosis and procedure codes for ascertaining clinical conditions were thoroughly reviewed by coauthors, with support provided by subspecialty experts. Patients with a history of heart transplantation were excluded (Figure 1). Medication use at index ACS was determined by medication availability via a filled prescription immediately before the index ACS (Figure S2).[10]

End Points

Patients were followed after index ACS for recurrent cardiovascular events. The primary composite end point was defined as the first occurrence of cardiovascular death, nonfatal MI, or nonfatal ischemic stroke. The secondary end points were defined as the first occurrence of cardiovascular death, nonfatal MI, nonfatal ischemic stroke, nonfatal UA hospitalization, and nonfatal elective coronary revascularization, separately and as a composite. The estimation of event rates for these end points were based on a Kaplan-Meier approach. Separately, we also estimated the event rates for the individual components that contributed to each composite using a competing risk analysis.[11,12] Diagnosis and procedure codes used for identifying these events were based on algorithms used and validated in previous reports (Table S2).[13–20] MI, ischemic stroke, and UA required inpatient hospitalization, whereas criteria for elective coronary revascularization was applied to either the inpatient or outpatient setting. The definition of elective coronary revascularization required that codes for MI, ischemic stroke, or UA not be present on the day of the procedure and included a 30-day lookback period free of other events defined in the composite (eg, MI) to ensure the revascularization procedure was not related to these events. To facilitate an accurate determination of mortality status during follow-up and the subsequent cause of death, the study population was integrated with the National Death Index.[21] Deaths were classified as being cardiovascular-related if the *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) diagnosis codes included I00-I99 in the underlying cause of death field.

Cohort and Subgroup Characteristics

Baseline characteristics included demographics, atherosclerotic cardiovascular disease (ASCVD)-related comorbidities, non-ASCVD comorbidities, revascularization procedures at index ACS, medications, and categories based on the TRS 2ºP, which is a 9-point integer-based risk score derived from clinical trials.[8,9] TRS 2ºP assigns 1 point each (scale 0–9) for heart failure, hypertension, age ≥75 years, diabetes, prior stroke, prior coronary artery bypass grafting, peripheral arterial disease, estimated glomerular filtration rate <60, and smoking. TRS 2ºP categories were: 0 to 1 point (low), 2 to 3 points (intermediate), or ≥4 points (high).

Baseline characteristics for subgroups were also described. These subgroups were: (1) presentations with MI or UA at index ACS; (2) revascularization (coronary artery bypass grafting or percutaneous coronary intervention [PCI]) at or during the 30 days following the index ACS; (3) MI with revascularization, MI without revascularization, UA with revascularization, or UA without revascularization; and (4) sex. Finally, the characteristics of the study cohort were descriptively compared with those of recent RCTs enrolling ACS populations to gain insights into the similarity and potential applicability of trial populations to our cohort(s). An informal search strategy was conducted based on the following criteria to select the trials for comparison: contemporary ACS trials conducted during our cohort identification period from 2005 to 2018 enrolling at least 4000 patients for whom reported baseline characteristics facilitated comparison with our study population (eg, index revascularization status).

Risk Estimation

The proportion of the study cohort defined by guidelines as very high risk for atherosclerotic events was estimated. The first definition used was from the 2018

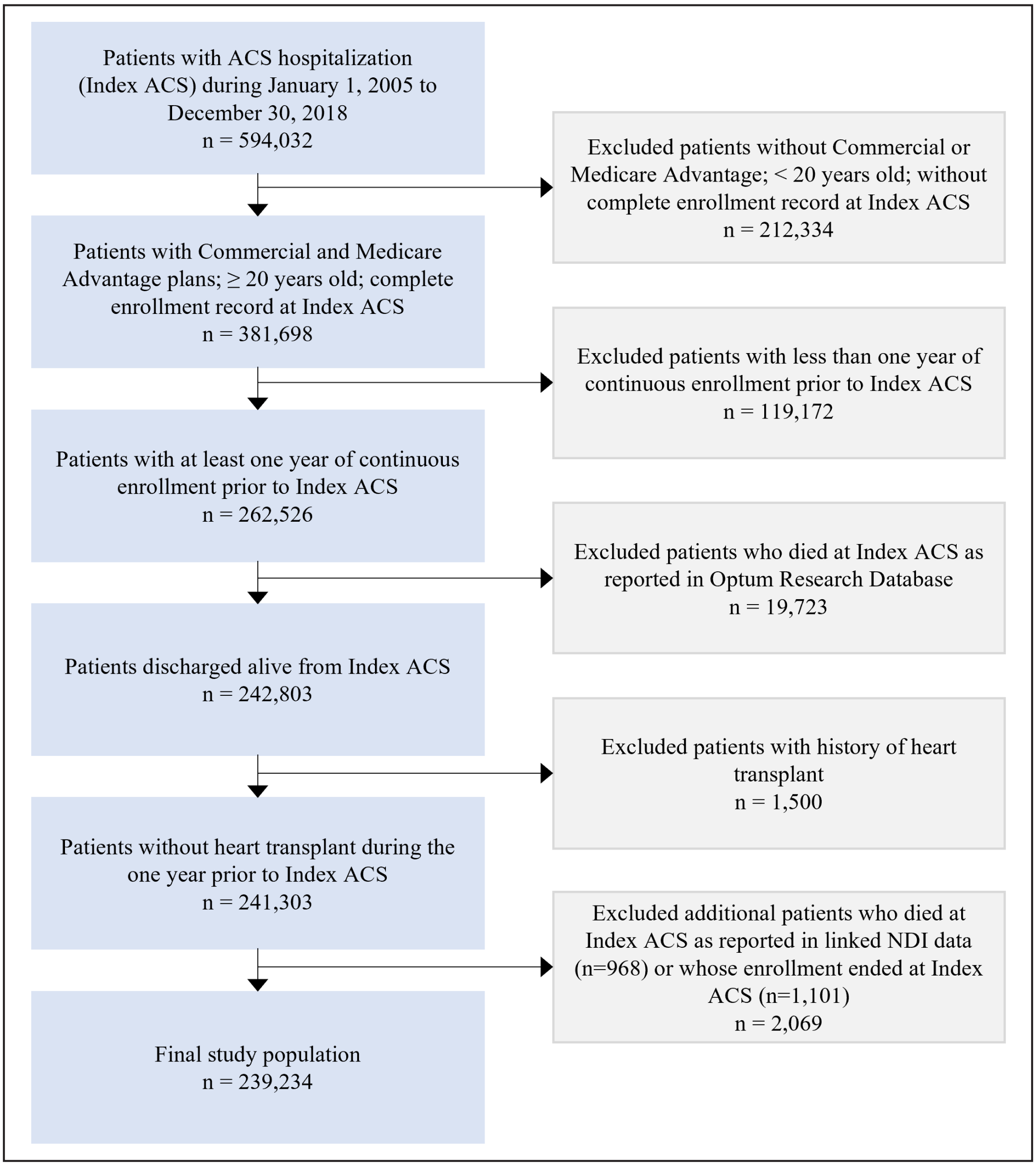

Patients with ACS hospitalization (Index ACS) during January 1, 2005 to December 30, 2018 n = 594,032
Excluded patients without Commercial or Medicare Advantage; < 20 years old; without complete enrollment record at Index ACS n = 212,334
Patients with Commercial and Medicare Advantage plans; ≥ 20 years old; complete enrollment record at Index ACS n = 381,698
Excluded patients with less than one year of continuous enrollment prior to Index ACS n = 119,172
Patients with at least one year of continuous enrollment prior to Index ACS n = 262,526
Excluded patients who died at Index ACS as reported in Optum Research Database n = 19,723
Patients discharged alive from Index ACS n = 242,803
Excluded patients with history of heart transplant n = 1,500
Patients without heart transplant during the one year prior to Index ACS n = 241,303
Excluded additional patients who died at Index ACS as reported in linked NDI data (n=968) or whose enrollment ended at Index ACS (n=1,101) n = 2,069
Final study population n = 239,234

Figure 1. Consort diagram for patient selection.

Patients with an ACS hospitalization during January 1, 2005 to December 30, 2018 were initially selected. Sequential application of the study inclusion and exclusion criteria resulted in a final study population of N=239 234. ACS indicates acute coronary syndrome; and NDI, National Death Index.

American College of Cardiology (ACC)/American Heart Association (AHA) Guidelines for the Management of Blood Cholesterol,[5] which defines patients at very high risk of ASCVD events as those with a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions. In our study cohort, the index ACS qualified as a major ASCVD event, and further assessment for identifying patients at an increased risk of adverse outcomes was conducted by identifying patients presenting with multiple major ASCVD events or additional high-risk factors.

Next, event rates for the composite end points and individual components of the composite were estimated via Kaplan-Meier analyses for the overall cohort and subgroups. For the overall cohort, we also estimated the instantaneous hazard rates over time. In contrast to the more common concept of risk over a specified time horizon (eg, 30 days, 1 year, or 5 years), the instantaneous hazard rate is a measure of risk at a moment in time (see Data S2).[22]

Statistical Analysis

Cox proportional hazards models were used to investigate the association of baseline characteristics with the risk of cardiovascular events during follow-up. Separate models were fitted for each of the composite end points as well as individual components of the composite. Model parameters were estimated via a backward selection strategy with $P>0.05$ as the criteria for filtering nonsignificant variables. We retained index ACS event categories (MI/UA and revascularization status), age, and sex in the model, regardless of statistical significance. For the purpose of qualitative interpretation, we defined a relatively stricter criterion based on hazard ratio (HR) >1.5 (indicating a relatively high impact on risk) together with $P<0.001$ (indicating a high statistical significance) to identify the key factors influencing risk. All statistical analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC).

RESULTS

The overall cohort included 239 234 patients. Median follow-up duration was 1.2 years (interquartile range, 0.4–2.8 years), with follow-up of ≥5 years available for 24 648 patients (10.3%) (Table S3). The mean age was 69 years, 57% were men, and 72% had Medicare Advantage (Table 1). According to the 2018 ACC/AHA guidelines,[5] ≈97% of the cohort was classified as very high risk. Specifically, 87% had a history of at least 2 high-risk conditions, and an additional 10% had a history of 1 of these high-risk conditions.

Demographic and Clinical Characteristics of Subgroups

In Table 1, the subgroup presenting with MI was older, had more comorbidities, but was less likely to have had preexisting coronary heart disease, prior coronary revascularization, or treatment with standard cardiac medications, compared with the subgroup presenting with UA. In both subgroups, 8.6% were hospitalized for ACS within the previous 12 months. The subgroup treated at index ACS with revascularization was younger, more likely to be men, and was less likely to have comorbidities (including prior coronary heart disease), compared with the subgroup not treated with revascularization. Prior ACS within 12 months was lower in the revascularization subgroup, 5.9% versus 10.6%, respectively. Characteristics of the study population stratified by sex are summarized in Table S4.

Event Rates and Instantaneous Risk Over Time

The 5-year rate for the primary end point representing first occurrence of nonfatal MI, nonfatal ischemic stroke, or cardiovascular death was 33.4% (95% CI, 33.1%–33.7%; $P<0.001$) (Figure 2) and for the secondary end point representing first occurrence of nonfatal MI, nonfatal ischemic stroke, cardiovascular death, UA hospitalization, or elective revascularization was 41.8% (95% CI, 41.4%–42.1%; $P<0.001$) (Figure S3). The rates were higher for the individual cardiovascular end points representing nonfatal MI, nonfatal ischemic stroke, and cardiovascular death as compared with UA hospitalization and elective revascularization. The instantaneous risk for the primary end point was highest immediately after discharge at 40.9%. This means that if this rate were to be continued, ≈40.9% would be expected to have had an event at 1 year. The risk gradually declined from discharge to an instantaneous risk of ≈6.7% at 1 year of follow-up. Risk remained stable over time after 1 year (instantaneous risk of ≈6.4%). Table 2 illustrates the event rates for the primary and secondary composite end points and individual components at 5 years.

Next, 4 index ACS subgroups were analyzed (baseline characteristics in Table S5): (1) MI treated with revascularization, (2) MI not treated with revascularization, (3) UA treated with revascularization, and (4) UA not treated with revascularization. Among the subgroups, the rates of the primary and secondary end points were highest for the MI without revascularization subgroup (Figure 3 and Figure S4). Rates of nonfatal MI and UA hospitalization were highest among patients who had already presented with an MI or UA, respectively. Rates for elective revascularization were higher for the subgroup of patients who had already had a revascularization. Finally, higher rates of the primary and secondary composite end points, as well as their individual components, were associated with more points on the TRS 2ºP (Figure 4 and Figure S5).

The current study population was older, more likely to be women, and less likely to be revascularized for an ACS as compared with the RCT populations (Table S6).[23–28] When the current study subgroup with revascularization at index ACS was compared with RCT populations, the baseline characteristics and the 1-year event rates for the primary end point were much more similar (Table S6).

Risk Factors Associated With the Primary and Individual End Points

The adjusted associations between baseline characteristics and the primary composite end point are shown in Table 3. Age ≥65 years, heart failure, renal disease stages IV to V, ACS hospitalization during the past 12 months, history of ischemic stroke, and an index MI without revascularization were most strongly associated with risk of experiencing the primary end point (HR, >1.5; $P<0.001$). Risks of the individual end points of nonfatal MI and nonfatal ischemic stroke were highly associated with prior events of these types. Key factors most strongly associated with the risk of nonfatal MI

Table 1. Baseline Characteristics: Overall Cohort and Subgroups of Type of Index ACS and Use of Revascularization

	Myocardial infarction, n=169 220	Unstable angina, n=70 014	ACS with revascularization, n=101 476	ACS without revascularization, n=137 758	Total, N=239 234
Demographic characteristics					
Age, y, mean (SD)	70.2 (12.2)	66.9 (11.8)	66.5 (11.3)	71.3 (12.4)	69.2 (12.2)
Age ≥75 y, %	41.6	29.5	26.4	46.6	38.0
Men, %	56.3	59.2	68.7	48.7	57.2
Medicare advantage, %[*]	74.7	64.3	61.2	79.3	71.6
United States region, %					
South	44.1	51.4	47.9	45.0	46.3
Midwest	30.8	27.7	31.5	28.7	29.9
Northeast	16.7	14.7	12.5	18.8	16.1
West/other	8.3	6.1	8.0	7.4	7.7
Atherosclerotic cardiovascular disease characteristics, %					
ACS hospital past 12 mo[†]	8.6	8.6	5.9	10.6	8.6
History of CHD[†]	37.8	54.7	39.9	44.9	42.7
CABG past 12 mo[‡]	1.2	1.5	1.4	1.3	1.3
History of CABG[§]	10.1	14.1	10.2	12.0	11.2
PCI past 12 mo[‡]	4.8	7.7	6.7	4.9	5.7
History of PCI[§]	12.2	19.6	15.7	13.4	14.4
IS hospital past 12 mo[†]	3.3	2.3	1.4	4.2	3.0
History of IS	8.2	4.6	3.6	9.7	7.1
ICBVD without stroke	7.4	8.0	7.4	7.8	7.6
PAD (lower extremities)	3.6	2.8	2.6	3.9	3.4
PAD (aorta)	3.4	2.9	2.7	3.6	3.2
PAD (other, unspecified)[‖]	12.9	11.4	9.8	14.5	12.5
Other comorbidities, %					
Atrial fibrillation/flutter	23.7	18.7	15.0	27.6	22.2
Hypertension	83.8	86.3	81.5	86.8	84.5
Heart failure	39.5	26.4	24.0	44.3	35.7
Renal disease stage III	14.1	10.9	9.4	16.0	13.2
Renal disease stages IV–V[¶]	7.5	4.6	3.7	8.9	6.7
COPD	26.4	22.9	17.9	30.9	25.4
Moderate/severe liver disease	3.4	3.0	2.1	4.1	3.3
Diabetes	41.8	42.9	40.2	43.6	42.1
Diabetes on insulin	15.8	14.9	13.7	17.0	15.6
Treatment status before index ACS (point-in-time), %[#]					
Lipid-lowering therapy[**]	40.2	48.3	41.4	43.5	42.6
ß-Blockers	38.3	46.0	36.5	43.5	40.6
ACEi/ARBs	40.8	44.7	40.5	42.9	41.9
P2Y12 inhibitors[††]	14.4	21.8	16.0	16.9	16.5
Treatment status at 1 y after discharge (point-in-time), %[‡‡]					
Lipid-lowering therapy[**]	63.1	60.1	73.3	52.1	62.1
ß-Blockers	64.2	57.5	69.6	55.2	62.0
ACEi/ARBs	49.4	46.6	53.2	44.3	48.5
P2Y12 inhibitors[††]	42.0	35.5	61.2	20.8	39.9
Treatment status at 1 y after discharge (cumulative), %[‡‡]					
Lipid-lowering therapy[**]	79.5	75.6	90.2	67.5	78.2

(Continued)

Table 1. Continued

	Myocardial infarction, n=169 220	Unstable angina, n=70 014	ACS with revascularization, n=101 476	ACS without revascularization, n=137 758	Total, N=239 234
ß-Blockers	82.3	74.3	88.2	72.0	79.7
ACEi/ARBs	65.7	60.1	69.0	59.3	63.9
P2Y12 inhibitors[††]	55.6	47.8	78.9	30.0	53.0
Procedures at index ACS or 30 d after discharge					
CABG	9.9	18.7	29.4	0.0	12.5
PCI	33.2	27.7	74.5	0.0	31.6
TRS 2ºP categories					
0–1	17.9	22.0	25.0	14.8	19.1
2–3	47.2	52.0	52.7	45.7	48.6
4+	34.8	26.0	22.4	39.5	32.3

Point-in-time assessment indicates medication on hand at 1-year follow-up (see Figure S2), and cumulative assessment indicates medication on hand at any time during the 1-year follow-up. ACEi indicates angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; CABG, coronary artery bypass grafting; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; ICBVD, ischemic cerebrovascular disease; IS, ischemic stroke; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; and TRS 2ºP, Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention.

[*] Represents health plan offered by a private company that contracts with Medicare to provide patients with hospital and medical insurance benefits.

[†] Measured in the 1-year period before the start of the index hospitalization.

[‡] Measured before the start of the index hospitalization using procedure codes only.

[§] Measured 1 year before admission of index hospitalization, during index hospitalization, or in the 30 days after hospitalization, using both diagnosis and procedure codes.

[‖] Includes any type of disease that is noncoronary, noncerebrovascular, or does not involve the lower extremities or aorta.

[¶] Includes dialysis or renal transplant.

[#] Medication on hand at index ACS (see Figure S2).

[**] Includes statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 inhibitors.

[††] Includes clopidogrel, ticagrelor, and prasugrel.

[‡‡] Based on 132 489 patients at 1 year follow-up (myocardial infarction=89 043; unstable angina=43 446; ACS with revascularization=62 508; ACS without revascularization=69 981).

were an ACS within 12 months of the index hospitalization or an MI as the index ACS. The strongest factor associated with risk of nonfatal ischemic stroke was a prior ischemic stroke. The strongest associations with risk of cardiovascular death were age ≥65 years and heart failure. Although statin treatment at baseline was only 41.9% (Table S7), it was associated with lower risk of the primary composite end point and its individual components. Evaluating the individual end points of the secondary composite end point, hospitalization for UA was most strongly associated with an ACS within 12 months of the index hospitalization. The factor most strongly associated with risk of elective revascularization was revascularization for either an index UA or MI (Table S8).

DISCUSSION

We used several approaches to create a large, representative, well-characterized cohort of patients hospitalized with ACS to better understand recurrent risk and risk predictors in a US clinical practice population. According to the 2018 ACC/AHA guidelines,[5] ≈97% of our cohort was classified as very high risk. The 2020 *European Society of Cardiology Guidelines for the Management of ACS in Patients Presenting Without Persistent ST-Segment Elevation*[7] consider all patients with ACS as very high-risk. Consistent with these classifications, we found the 5-year event rate for the primary composite representing first occurrence of nonfatal MI, nonfatal ischemic stroke, or cardiovascular death was 33.4% (95% CI, 33.1%–33.7%; $P<0.001$).

The risk of experiencing the primary end point (Figure 2) was ≈6-fold higher immediately following discharge for the index ACS, as compared with the period ≥1 year after hospital discharge. The extremely high risk immediately after ACS hospitalization underscores the usefulness of risk mitigation strategies when started during, or immediately after, ACS hospitalization.[2–7] Risk during the first year after an ACS was much more pronounced for the nonfatal MI and cardiovascular death end points as compared with the other individual end points. This observation further supports the high expected clinical benefit when guideline-based treatments are initiated during hospitalization for an ACS. The risk of the primary end point was consistently 6.4% after 1 year, illustrating a high residual risk during chronic follow-up.

In general, baseline atherothrombotic disease, index ACS presentation, and use of revascularization were strongly associated with future adverse outcomes (eg, recurrent MI in those with index MI, recurrent UA in

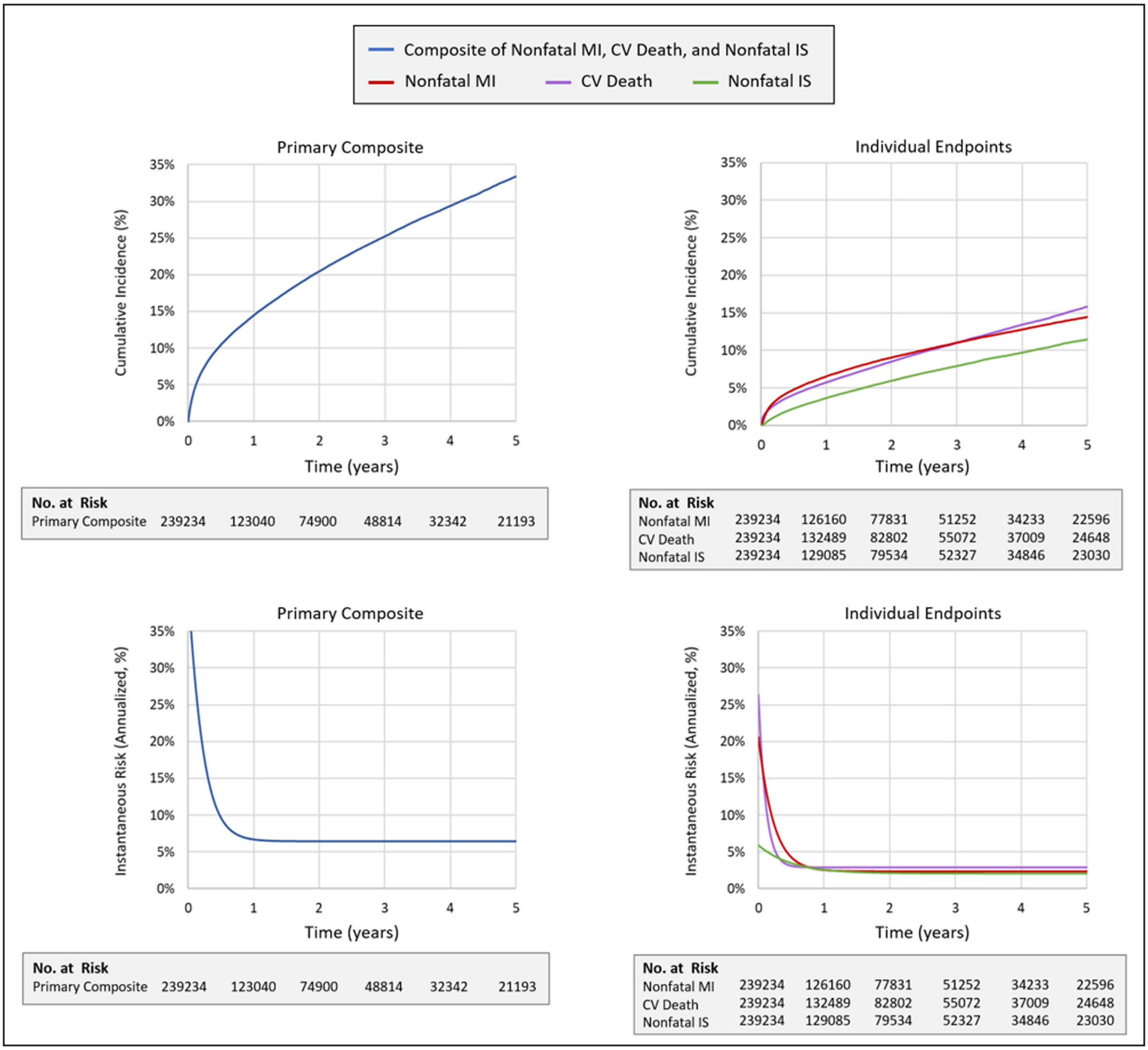


Figure 2. Event rates and instantaneous risk over time for the primary and individual end points.
Shown is the cumulative incidence of the primary end point (first occurrence of nonfatal MI, nonfatal ischemic stroke, or CV death) and individual end points (represented by components of the composite). The KM rates for the primary end point at 1, 3, and 5 years were 14.5% (95% CI, 14.3%–14.6%; *P*<0.001), 25.2% (95% CI, 25.0%–25.5%; *P*<0.001), and 33.4% (95% CI, 33.1%–33.7%; *P*<0.001), respectively. The instantaneous risks (annualized) for the primary end point at 0, 1, and 3 years were 40.9%, 6.7%, and 6.4%, respectively. Below the graphs capturing the cumulative incidence of the primary and individual end points are data on the number of patients at risk of experiencing the corresponding end point. CV indicates cardiovascular; IS, ischemic stroke; KM, Kaplan-Meier; and MI, myocardial infarction.

those with index UA, recurrent ischemic stroke in those with prior stroke, repeat revascularization in those revascularized). Rates of ischemic stroke and cardiovascular death were higher in those not revascularized for index ACS. There are many potential explanations suggested by the data including greater burden of noncardiovascular comorbidities, higher rates of myocardial injury and type 2 MI for which the benefit of revascularization may not be indicated or is less clear, perception of less favorable risk:benefit of revascularization, and greater reluctance of the patient to proceed with revascularization (eg, because of advanced age, renal failure).

Our subgroup analyses yielded further insights. With the increasing use of highly sensitive cardiac biomarkers, separately analyzing MI versus UA subgroups in health care databases will help better separate those who may have an atherothrombotic event

Table 2. Event Rates for the Primary and Secondary Composite End Points and Individual Components at 5 Years

	No. at risk at 5 y	Adjusted cumulative count of events at 5 y[*]	Event rate at 5 y, % (95% CI)
Primary composite end point	21 193	79 923	33.4 (33.1–33.7)
Nonfatal MI[†]	21 193	30 139	12.6 (12.4–12.8)
Nonfatal IS[†]	21 193	22 462	9.4 (9.2–9.6)
Cardiovascular death[†]	21 193	27 323	11.4 (11.2–11.6)
Secondary composite end point	18 604	99 927	41.8 (41.1–42.1)
Nonfatal MI[‡]	18 604	27 061	11.3 (11.1–11.5)
Nonfatal IS[‡]	18 604	20 827	8.7 (8.5–8.9)
Cardiovascular death[‡]	18 604	25 518	10.7 (10.5–10.9)
Nonfatal UA requiring hospitalization[‡]	18 604	10 310	4.3 (4.2–4.4)
Nonfatal elective coronary revascularization[‡]	18 604	16 211	6.8 (6.6–6.9)
Individual end points			
Nonfatal MI[§]	22 596	34 594	14.5 (14.2–14.7)
Nonfatal IS[§]	23 030	27 436	11.5 (11.2–11.7)
Cardiovascular death[§]	24 648	37 888	15.8 (15.6–16.1)
Nonfatal UA requiring hospitalization[§]	23 089	16 251	6.8 (6.6–7.0)
Nonfatal elective coronary revascularization[§]	22 545	21 234	8.9 (8.7–9.1)

IS indicates ischemic stroke; MI, myocardial infarction; and UA, unstable angina.

[*] Estimated by multiplying the 5-year event rate by the initial cohort size. Counts of events for individual components of the composite may not add up to the count of the composite because of rounding.

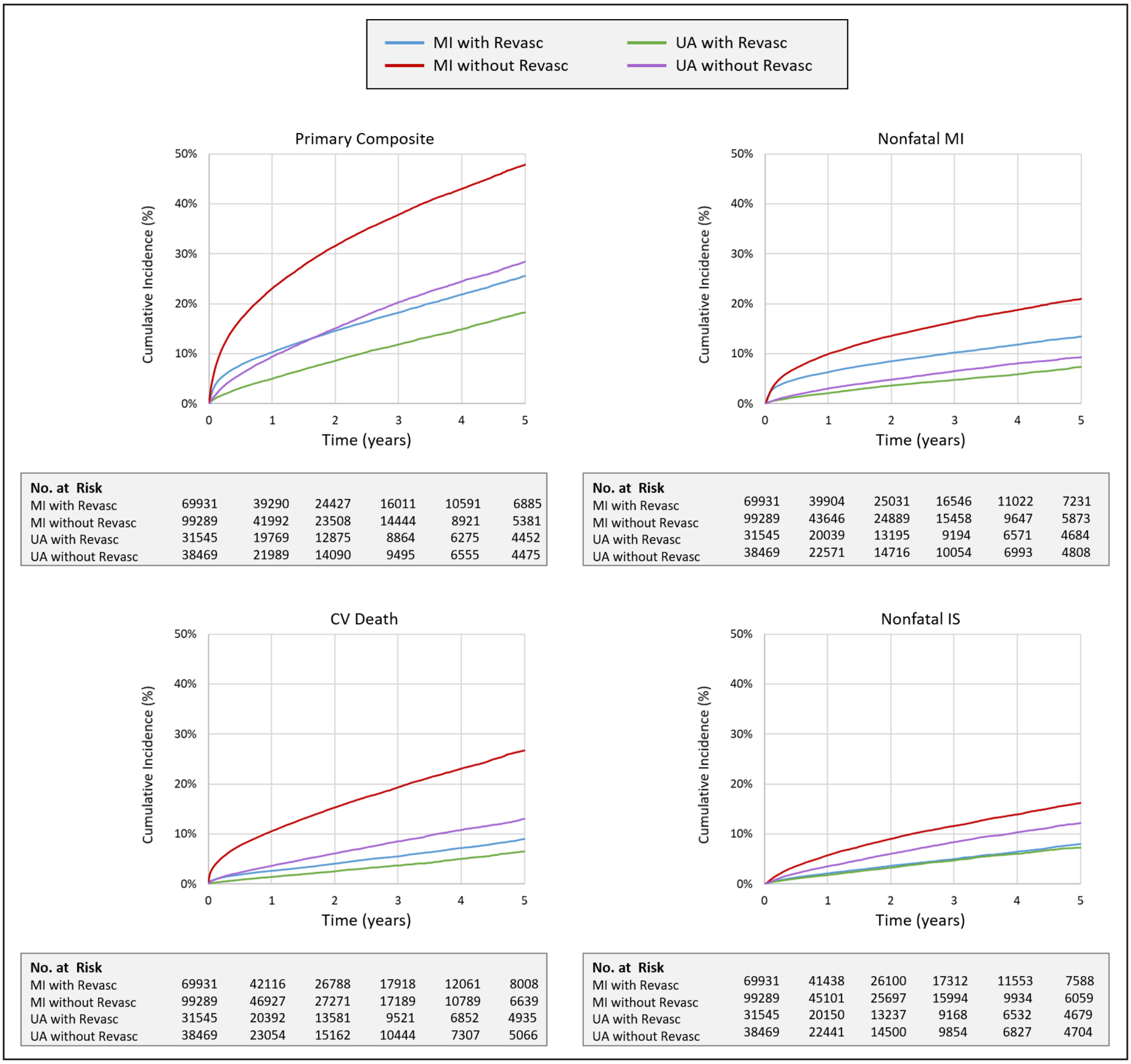
[†] Represent events contributing to the primary composite end point. Estimates are based on competing risk analysis.

[‡] Represent events contributing to the secondary composite end point. Estimates are based on competing risk analysis.

[§] Represent first events regardless of whether they contribute to the primary or the secondary composite end point. Estimates are based on Kaplan-Meier analysis.

versus those who do not. This was apparent in our findings, because the MI subgroups had much higher event rates for the primary composite end point and individual components of the composite when compared with the UA subgroups. In terms of revascularization at index ACS, especially in a US population, our data suggest this criterion may enhance the representation of patients with true acute coronary atherothrombosis (eg, as opposed to type 2 MI). For some patients with ACS presentations, however, a strategy of no angiography nor PCI is also influenced by patients' age and comorbidities. This likely explains the findings in the subgroup without revascularization, which was relatively older, with a greater number of comorbidities, and had a much higher rate for the primary composite end point and individual components of the composite. A much lower proportion of women received revascularization at index ACS (Table S4). In our study population, women were both older and somewhat more comorbid. Older women with ACS have a higher prevalence of age-related functional impairment, which could also have contributed to a lower rate of revascularization.[29] Other studies have indicated a lower likelihood of revascularization in women even after adjusting for other factors, which could also help explain this observation.[30,31] There are, however, no differences in the expected benefit of treatment with revascularization by sex based on evidence from meta-analysis.[32] In regard to the subgroup with revascularization, a comparison of its baseline characteristics with RCTs enrolling patients with ACS revealed these populations to be more similar as compared with the subpopulation without revascularization, which supports the hypothesis that the subpopulation with revascularization more closely represents those experiencing a true acute atherothrombotic event (Table S6).

Application of TRS 2ºP resulted in a substantial stratification of the risk for the primary end point and individual components of the composite (Figure 4). TRS 2ºP was originally developed from a population representing a stable post-MI profile in the TRA 2ºP–TIMI 50 (Thrombin Receptor Antagonist in Secondary Prevention of Atherothrombotic Ischemic Events–Thrombolysis In Myocardial Infarction 50) trial. The TRS 2ºP was demonstrated to effectively stratify the risk of recurrent cardiovascular events in the same trial, as well in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial), an RCT representing a recent ACS population.[8,9] Our study contributes additional evidence on risk stratification via TRS 2ºP in a post-ACS population representing usual clinical practice. For the primary end point, the risk at 5 years for the subgroup with the highest TRS 2ºP category (≥4) was 56.7% (95% CI, 55.9%–57.4%; *P*<0.001) as compared with 12.9% (95% CI, 12.4%–13.4%; *P*<0.001) for the subgroup representing the lowest TRS 2ºP category (0–1), over a 4-fold difference. Because the TRS 2ºP is based on measures commonly available in routine clinical practice (Table S9), our findings support the potential application of the TRS 2ºP for informed decision making on clinical management of patients with ACS, identification of patients at highest risk, and development of future guidelines. TRS 2ºP captured the main risk factors identified in the multivariable Cox model (Table 3) except for the history of coronary heart disease and a prior ACS event, which are not represented in TRS 2ºP, because it was originally developed in a population with a history of MI. An implication of the potential improvement in TRS 2ºP for risk stratification in a post-ACS population could thus be inclusion of the history of coronary heart disease and a prior ACS event.



No. at Risk						
MI with Revasc	69931	39290	24427	16011	10591	6885
MI without Revasc	99289	41992	23508	14444	8921	5381
UA with Revasc	31545	19769	12875	8864	6275	4452
UA without Revasc	38469	21989	14090	9495	6555	4475

No. at Risk						
MI with Revasc	69931	39904	25031	16546	11022	7231
MI without Revasc	99289	43646	24889	15458	9647	5873
UA with Revasc	31545	20039	13195	9194	6571	4684
UA without Revasc	38469	22571	14716	10054	6993	4808

No. at Risk						
MI with Revasc	69931	42116	26788	17918	12061	8008
MI without Revasc	99289	46927	27271	17189	10789	6639
UA with Revasc	31545	20392	13581	9521	6852	4935
UA without Revasc	38469	23054	15162	10444	7307	5066

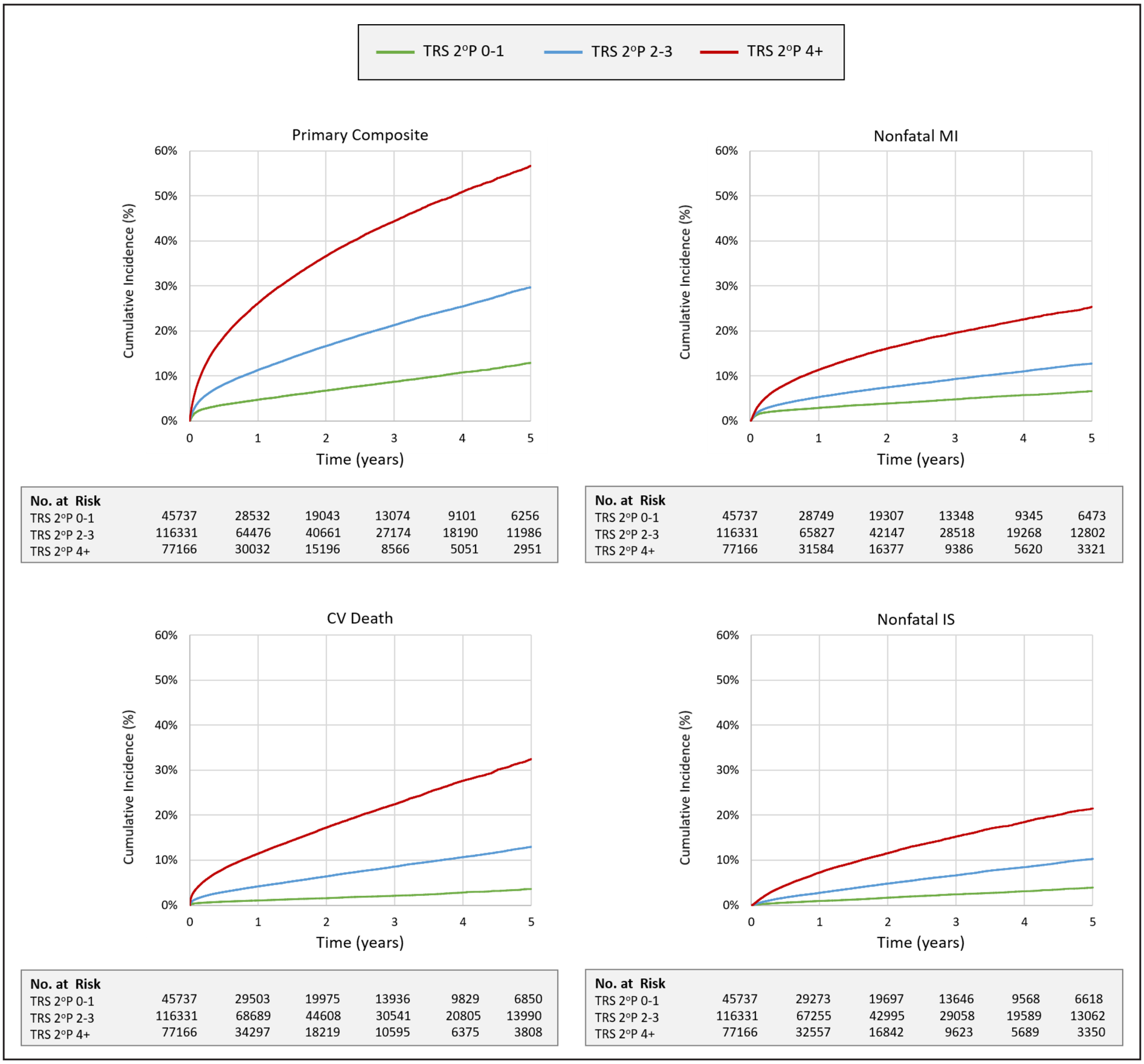
No. at Risk						
MI with Revasc	69931	41438	26100	17312	11553	7588
MI without Revasc	99289	45101	25697	15994	9934	6059
UA with Revasc	31545	20150	13237	9168	6532	4679
UA without Revasc	38469	22441	14500	9854	6827	4704

Figure 3. Event rates for the primary and individual end points by type of index acute coronary syndrome and use of revascularization.

Shown is the cumulative incidence of the primary end point (first occurrence of nonfatal MI, nonfatal ischemic stroke, or CV death) and individual end points (represented by components of the composite) by index ACS (MI/UA and revascularization status). Below each graph are data on the number of patients in each index ACS subgroup who are at risk of experiencing the corresponding end point. ACS indicates acute coronary syndrome; CV, cardiovascular; IS, ischemic stroke; MI, myocardial infarction; Revasc, revascularization; and UA, unstable angina.

Our study indicated absence of treatment with revascularization at index ACS is an independent predictor of risk after adjustment of other patient characteristics and comorbidities, including those represented in TRS 2ºP. Evidence suggests improved outcomes with routine invasive as compared with medical therapy alone in a population with ACS.[32] This observation combined with our study findings indicate that though revascularization may improve patient outcomes, it could be a less viable option in clinical practice for patients presenting with multiple comorbidities and/or advanced age. In Figure 5 and Figure S6, we presented an analysis that combines TRS 2ºP categories and revascularization status, which offers further improvement on a framework for identifying those at a higher risk and indicates that individuals with TRS 2ºP ≥4 without revascularization have a 5-fold higher risk as compared with those with TRS 2ºP ≤1 and revascularization.

The proportion of patients receiving PCI at index ACS was only 33.2% and 27.7% for the MI and UA



Primary Composite

No. at Risk						
TRS 2ºP 0-1	45737	28532	19043	13074	9101	6256
TRS 2ºP 2-3	116331	64476	40661	27174	18190	11986
TRS 2ºP 4+	77166	30032	15196	8566	5051	2951

Nonfatal MI

No. at Risk						
TRS 2ºP 0-1	45737	28749	19307	13348	9345	6473
TRS 2ºP 2-3	116331	65827	42147	28518	19268	12802
TRS 2ºP 4+	77166	31584	16377	9386	5620	3321

CV Death

No. at Risk						
TRS 2ºP 0-1	45737	29503	19975	13936	9829	6850
TRS 2ºP 2-3	116331	68689	44608	30541	20805	13990
TRS 2ºP 4+	77166	34297	18219	10595	6375	3808

Nonfatal IS

No. at Risk						
TRS 2ºP 0-1	45737	29273	19697	13646	9568	6618
TRS 2ºP 2-3	116331	67255	42995	29058	19589	13062
TRS 2ºP 4+	77166	32557	16842	9623	5689	3350

Figure 4. Event rates for the primary and individual end points by categories of TIMI risk score for secondary prevention. Shown is the cumulative incidence of the primary end point (first occurrence of nonfatal MI, nonfatal ischemic stroke, or CV death) and individual end points (represented by components of the composite) by TRS 2ºP categories. Below each graph are data on the number of patients in each TRS 2ºP category who are at risk of experiencing the corresponding end point. CV indicates cardiovascular; IS, ischemic stroke; MI, myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; and TRS 2ºP, Thrombolysis in Myocardial Infarction Risk Score for Secondary Prevention.

subgroups, respectively, which is lower than the rates typically reported in RCTs (Table S6). The 2021 *ACC/AHA Guidelines for Coronary Artery Revascularization*[33] recommends the decision to treat with revascularization be based on clinical indications, regardless of sex, race, or ethnicity. In our study, the following factors were more prevalent in the subgroup with ACS without revascularization (Table 1): age ≥75 years, women, atrial fibrillation, heart failure, renal disease, chronic obstructive pulmonary disease, and diabetes. In contrast, prior ASCVD comorbidities generally were numerically higher in the ACS with revascularization subgroup, which indicates that non-ASCVD comorbidities and patient suitability for PCI procedure likely contributed to the lower rates of PCI. Other criteria mentioned in the 2021 ACC/AHA guidelines for consideration of revascularization are disease complexity, technical feasibility, and patient preference, all of which could also have influenced rates of PCI, especially in those with comorbidities and advanced age. In addition, in typical clinical practice, chest pain caused by acute myocardial injury (eg, pulmonary embolism) or chronic

Table 3. Patient Characteristics Associated With the Primary and Individual End Points: Cox Proportional Hazard Model

	Primary end point[*]	Nonfatal myocardial infarction[†]	Nonfatal ischemic stroke[‡]	Cardiovascular death[§]
	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Index ACS type and revascularization status				
MI with revascularization	1.16 (1.13–1.20)	2.08 (1.97–2.19)	0.74 (0.70–0.79)	0.85 (0.81–0.89)
MI without revascularization	1.81 (1.76–1.86)	2.46 (2.34–2.59)	1.15 (1.10–1.21)	1.86 (1.78–1.94)
UA with revascularization	0.69 (0.66–0.72)	0.85 (0.79–0.92)	0.65 (0.61–0.70)	0.59 (0.55–0.63)
UA without revascularization	Reference	Reference	Reference	Reference
Demographics				
Age, y				
20–44	0.68 (0.62–0.75)	0.79 (0.70–0.89)	0.61 (0.51–0.74)	0.52 (0.42–0.64)
45–64	Reference	Reference	Reference	Reference
≥65	1.62 (1.58–1.66)	1.28 (1.23–1.32)	1.47 (1.41–1.55)	2.56 (2.44–2.69)
Men	1.00 (0.98–1.02)	1.00 (0.97–1.03)	0.87 (0.84–0.90)	1.09 (1.06–1.12)
Cardiovascular comorbidities and risk factors				
Atrial fibrillation/flutter	1.21 (1.18–1.23)	…	1.23 (1.19–1.28)	1.40 (1.36–1.44)
Hypertension	1.21 (1.17–1.25)	1.19 (1.14–1.26)	1.45 (1.36–1.56)	1.08 (1.03–1.14)
Heart failure	1.74 (1.70–1.77)	1.49 (1.44–1.54)	1.26 (1.21–1.31)	2.51 (2.43–2.60)
Renal disease				
Stage III	1.25 (1.22–1.29)	1.22 (1.17–1.27)	1.19 (1.14–1.25)	1.33 (1.28–1.38)
Stage IV	1.61 (1.54–1.68)	1.51 (1.40–1.62)	1.36 (1.24–1.49)	1.87 (1.76–1.98)
Stage V	1.58 (1.52–1.64)	1.58 (1.49–1.68)	1.63 (1.52–1.76)	1.59 (1.50–1.68)
Stage ≤II	Reference	Reference	Reference	Reference
COPD	1.20 (1.17–1.22)	1.23 (1.19–1.28)	1.16 (1.11–1.20)	1.20 (1.16–1.24)
Moderate/severe liver disease	…	1.13 (1.05–1.22)	…	0.87 (0.80–0.95)
Diabetes				
Not receiving insulin	1.11 (1.09–1.14)	1.19 (1.15–1.23)	1.28 (1.23–1.33)	0.96 (0.92–0.99)
Receiving insulin	1.33 (1.29–1.36)	1.49 (1.44–1.55)	1.64 (1.57–1.72)	1.04 (1.00–1.09)
No diabetes	reference	Reference	Reference	Reference
Tobacco use	0.91 (0.89–0.93)	1.07 (1.04–1.11)	…	0.70 (0.68–0.72)
Baseline atherosclerotic cardiovascular disease				
History of CHD				
ACS hospitalization past 12 mo	1.58 (1.53–1.63)	2.33 (2.23–2.44)	1.10 (1.03–1.17)	1.31 (1.25–1.37)
No ACS hospitalization past 12 mo	1.24 (1.21–1.26)	1.34 (1.29–1.38)	1.12 (1.07–1.16)	1.23 (1.19–1.27)
No history of CHD	Reference	Reference	Reference	Reference
History of ICBVD				
IS hospitalization past 12 mo	1.81 (1.74–1.89)	1.05 (0.98–1.13)	4.70 (4.43–4.99)	1.45 (1.36–1.54)
IS without hospitalization past 12 mo	2.00 (1.94–2.07)	0.89 (0.83–0.96)	4.75 (4.52–4.99)	1.78 (1.69–1.87)
ICBVD without stroke	1.11 (1.07–1.15)	1.01 (0.95–1.07)	1.44 (1.35–1.55)	1.07 (1.01–1.13)
No history of ICBVD	Reference	Reference	Reference	Reference
PAD, lower extremities	1.12 (1.07–1.17)	1.15 (1.08–1.23)	…	1.16 (1.08–1.24)
PAD, aorta	1.11 (1.06–1.16)	1.09 (1.01–1.17)	1.16 (1.06–1.27)	1.13 (1.05–1.21)
Concurrent cardiovascular medications				
Any statin	0.86 (0.84–0.87)	0.90 (0.87–0.93)	0.89 (0.86–0.92)	0.79 (0.77–0.81)
β-Blockers	…	…	…	1.05 (1.01–1.08)
ACEi/ARB	0.94 (0.92–0.96)	0.96 (0.93–0.99)	0.94 (0.91–0.98)	0.92 (0.89–0.95)

(Continued)

Table 3. Continued

	Primary end point*	Nonfatal myocardial infarction†	Nonfatal ischemic stroke‡	Cardiovascular death§
	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Antiplatelets	1.16 (1.14–1.19)	1.20 (1.16–1.25)	1.18 (1.13–1.24)	1.11 (1.07–1.15)

Ellipses (…) indicate the covariate was determined to be nonsignificant in the model for that end point. ACEi indicates angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; ICBVD, ischemic cerebrovascular disease; *ICD-9/ICD-10*, *International Classification of Diseases, Ninth Revision and Tenth Revision*; IS, ischemic stroke; MI, myocardial infarction; NDI, National Death Index; PAD, peripheral arterial disease; and UA, unstable angina.

*A major cardiovascular event for the primary end point is the NDI-based date of cardiovascular death or the last date of an inpatient encounter with at least 1 *ICD-9/ICD-10* code diagnosis for acute myocardial infarction or ischemic cerebrovascular disease with stroke.

†A nonfatal myocardial infarction is defined as the last date of an inpatient encounter with at least 1 *ICD-9/ICD-10* diagnosis for acute myocardial infarction.

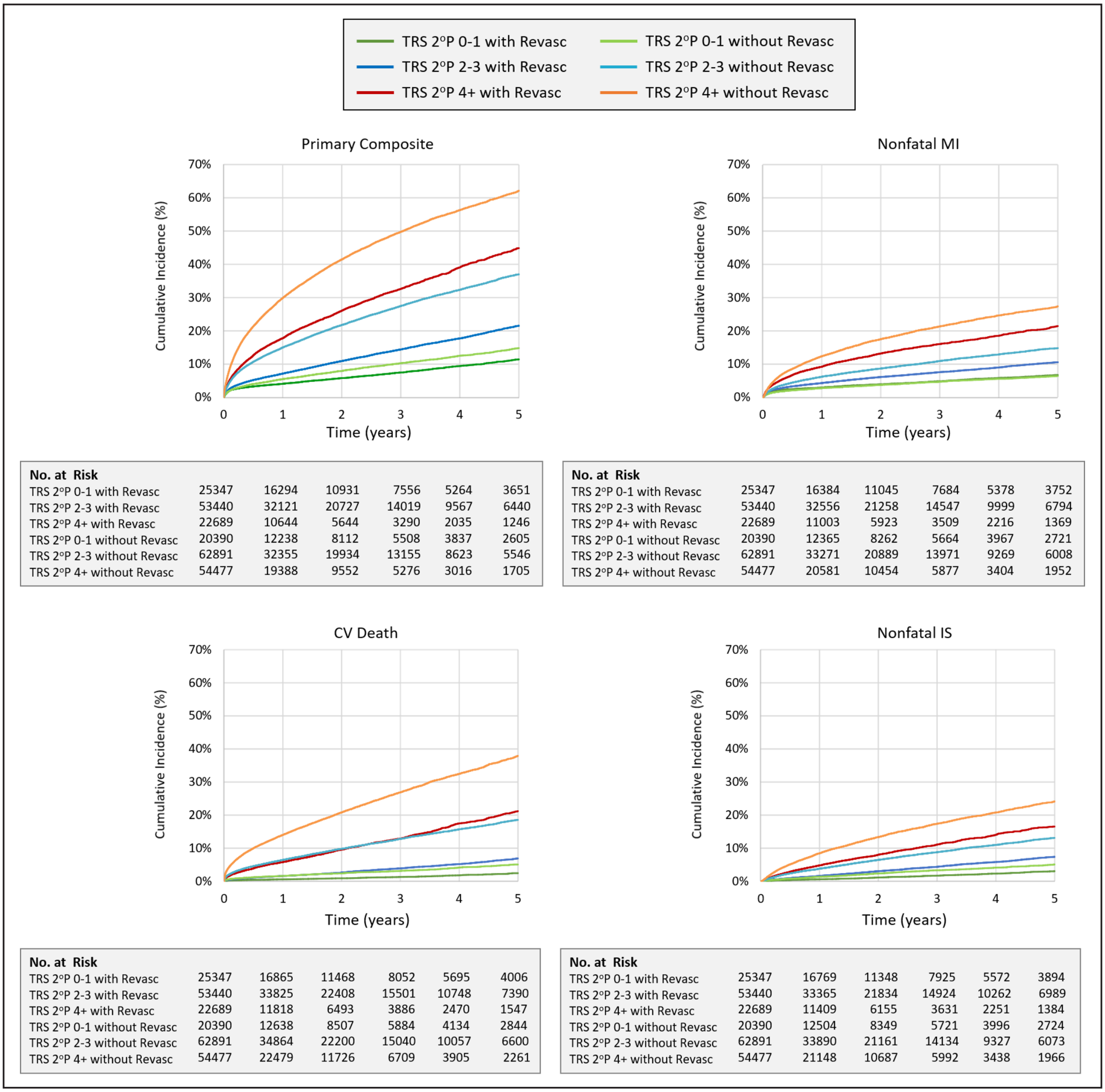
‡A nonfatal ischemic stroke is defined as the last date of an inpatient encounter with at least 1 *ICD-9/ICD-10* diagnosis for ischemic cerebrovascular disease with stroke.

§A cardiovascular-related death is defined as the NDI-based date of cardiovascular death.

myocardial injury (eg, renal failure) can be coded as myocardial infarction, because of symptoms and elevated biomarkers. Because such patients with myocardial injury (in contrast to acute MI) and type 2 MI less frequently meet an indication for revascularization, the category of ACS without revascularization was enriched with these patients. Of note, this subgroup also had greater rates of noncardiovascular comorbidities, which may have altered the risk:benefit assessment, thus contributing to the lower rate of revascularization. An important avenue for additional research on this topic could be investigating disparities in treatment with revascularization, representing factors such as sex, race, and ethnicity.

The goal of guideline-based therapies in a population with ASCVD or an ACS event is to reduce the risk of recurrent cardiovascular events.[34,35] The absolute risk reduction with treatment depends on the patient's baseline risk representing characteristics before treatment (ie, presentation at index ACS in the current study) and the choice of treatment, meaning patients at higher predicted risk at index ACS are expected to derive greater absolute benefit from a given treatment.[22] In our study, the use of guideline-based therapies was relatively low at baseline, which could be because of low prescription rates, nonadherence, or that many patients experiencing an ACS event may not have prior clinical ASCVD or other treatment indications. The use of guideline-based therapies increased during 1 year after index ACS (Tables S10 and S11). The use of lipid-lowering therapies, for example, was 41.4% and 43.5%, before index ACS in subgroups with and without revascularization, respectively (based on a point-in-time evaluation), increasing to 73.3% and 52.1%, respectively, at 1 year (the same measure being 90.2% and 67.5%, respectively, based on cumulative evaluation) (Table 1). The pattern was similar for P2Y12 inhibitors, where before the index ACS, ≈16.0% and 16.9% were receiving a P2Y12 inhibitor in subgroups with and without revascularization, respectively. At 1 year after discharge, the rate increased to ≈61.2% and 20.8%, respectively (78.9% and 30.0%, respectively, based on cumulative evaluation). The potential explanations noted previously about the differences in the subgroups with and without revascularization, likely also explains the marked difference in the rates of treatment with lipid-lowering therapies and P2Y12 inhibitors in these subgroups, with the subgroup without revascularization heavily influencing the low overall use of guideline-recommended medical therapy at 1 year after discharge. Because the guidelines strongly endorse medical therapies such as lipid-lowering therapies[5] and P2Y12 inhibitors[36] after ACS (the latter at least for 1 year in most patients), it is apparent that the guideline-recommended use of these therapies can be improved. Thus, a broad implication from our study on improving patient outcomes in clinical practice is to identify patients at higher risk (eg, based on combination of TRS 2ºP and revascularization status) and permit timely initiation, appropriate intensification, and continuation of guideline-based therapies.

Key strengths of our study include a large (N=239 234) and contemporary (2005–2018) population, with ACS hospitalization representing a usual clinical practice setting, from the time of hospital discharge through long-term follow-up (N=24 648 patients with ≥5 years follow-up). Another key strength of this study as compared with prior investigations was that determination of mortality status was supplemented with National Death Index data to provide a more reliable ascertainment of cardiovascular mortality.[37] The ACS population characterization, subgroup analyses, event rate patterns, and risk predictor analyses may prove useful to multiple stakeholders including payers, regulatory authorities, clinicians, and clinical guidelines committees for the purpose of identifying those at highest risk of adverse events and who would derive the highest clinical benefit from evidence-based therapies. In addition, these data may help inform academic and governmental organizations that track data on heart disease and stroke.



Primary Composite

No. at Risk						
TRS 2ºP 0-1 with Revasc	25347	16294	10931	7556	5264	3651
TRS 2ºP 2-3 with Revasc	53440	32121	20727	14019	9567	6440
TRS 2ºP 4+ with Revasc	22689	10644	5644	3290	2035	1246
TRS 2ºP 0-1 without Revasc	20390	12238	8112	5508	3837	2605
TRS 2ºP 2-3 without Revasc	62891	32355	19934	13155	8623	5546
TRS 2ºP 4+ without Revasc	54477	19388	9552	5276	3016	1705

Nonfatal MI

No. at Risk						
TRS 2ºP 0-1 with Revasc	25347	16384	11045	7684	5378	3752
TRS 2ºP 2-3 with Revasc	53440	32556	21258	14547	9999	6794
TRS 2ºP 4+ with Revasc	22689	11003	5923	3509	2216	1369
TRS 2ºP 0-1 without Revasc	20390	12365	8262	5664	3967	2721
TRS 2ºP 2-3 without Revasc	62891	33271	20889	13971	9269	6008
TRS 2ºP 4+ without Revasc	54477	20581	10454	5877	3404	1952

CV Death

No. at Risk						
TRS 2ºP 0-1 with Revasc	25347	16865	11468	8052	5695	4006
TRS 2ºP 2-3 with Revasc	53440	33825	22408	15501	10748	7390
TRS 2ºP 4+ with Revasc	22689	11818	6493	3886	2470	1547
TRS 2ºP 0-1 without Revasc	20390	12638	8507	5884	4134	2844
TRS 2ºP 2-3 without Revasc	62891	34864	22200	15040	10057	6600
TRS 2ºP 4+ without Revasc	54477	22479	11726	6709	3905	2261

Nonfatal IS

No. at Risk						
TRS 2ºP 0-1 with Revasc	25347	16769	11348	7925	5572	3894
TRS 2ºP 2-3 with Revasc	53440	33365	21834	14924	10262	6989
TRS 2ºP 4+ with Revasc	22689	11409	6155	3631	2251	1384
TRS 2ºP 0-1 without Revasc	20390	12504	8349	5721	3996	2724
TRS 2ºP 2-3 without Revasc	62891	33890	21161	14134	9327	6073
TRS 2ºP 4+ without Revasc	54477	21148	10687	5992	3438	1966

Figure 5. Event rates for the primary and individual end points by categories of TIMI risk score for secondary prevention and use of revascularization.

Shown is the cumulative incidence of the primary end point (first occurrence of nonfatal MI, nonfatal ischemic stroke, or CV death) and individual end points (represented by components of the composite) by TRS 2ºP categories and use of revascularization. Below each graph are data on the number of patients in each TRS 2ºP category with or without revascularization who are at risk of experiencing the corresponding end point. CV indicates cardiovascular; IS, ischemic stroke; MI, myocardial infarction; Revasc, revascularization; TIMI, Thrombolysis In Myocardial Infarction; and TRS 2ºP, Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention.

Limitations

The Optum Research Database represents individuals enrolled in commercial and Medicare Advantage health plans in the United States. Thus, the analysis may not be representative of the noninsured population, those covered under a public insurance program other than Medicare Advantage (eg, Medicaid and other Medicare plans), or international populations. Evidence suggests that patients with ACS without insurance or with Medicaid are less likely to receive evidence-based therapies and have worse outcomes compared with those with private insurance.[38–40] Claims databases capture medications received via coverage under a health plan. As such, medications obtained over the counter (eg, aspirin) or those that are paid entirely out of pocket (eg, statin medication paid at list price) will not be captured. Studies investigating concordance between claims databases and patient self-report or medication inventory have reported an agreement of ≈87.5% for statins,[41] indicating a possibility for a slight underestimation of treatment with statins in our study. We used claims-based discharge diagnoses from inpatient hospitalizations for defining nonfatal cardiovascular events. Studies evaluating validation of this methodology as adjudicated by investigators have concluded positive predictive values for MI within the range of 88.4% to 96.9%.[13–17] Similar studies have reported the range of positive predictive values for ischemic stroke as 80.4% to 91.1%.[15,16,18–20] A recent study that evaluated this methodology for trial end points adjudicated by a clinical events committee using standardized end point definitions concluded a positive predictive value of 85.7% for MI but only 47.1% for stroke (authors recommended caution in interpretation because of the low number of stroke events).[42] In addition, unlike clinical trials, which typically classify patients into ST versus non–ST-segment–elevation MI by electrocardiographic review, this cannot be reliably done using claims data. Our study mainly focused on the demographic, clinical, and treatment-related factors as predictors of recurrent cardiovascular event risk in a population with ACS. Though biomarkers including high-sensitivity troponin T, N-terminal pro-B-type natriuretic peptide, growth-differentiation factor-15, and high-sensitivity C-reactive protein have shown to offer useful prognostication on top of clinical risk predictors (eg, TRS 2ºP),[43] these biomarkers are not typically collected in a manner that enables their incorporation in our analysis. Furthermore, during the identification period, 2005 to 2018, the United States moved from MI definitions based on less-sensitive biomarkers to highly sensitive biomarkers (high-sensitivity troponin), which likely affected the classification of MI versus UA in clinical practice over this period. Although tobacco use was captured for the study, assessment was limited to instances where it is recorded in relation to patient care and does not adequately measure frequency and amount of tobacco use. Our reported measures of tobacco use are thus likely to be underestimated. Finally, the RCTs used for comparing our study population with trial populations represented global trials, whereas our study population represents only patients in the United States.

CONCLUSIONS

In a large, representative, and well-characterized US population followed after discharge from ACS hospitalization, the 5-year event rate for the primary composite end point representing nonfatal MI, nonfatal ischemic stroke, or cardiovascular death was 33.4% (95% CI, 33.1%–33.7%; $P<0.001$). The risk of experiencing the primary end point was ≈6-fold higher immediately following the index ACS, as compared with ≥1 year after hospital discharge. For health care stakeholders interested in understanding the applicability of RCT data to clinical practice populations, the subgroup and risk predictor analysis identified a methodology to better identify a trial-like population and characteristics that predict specific clinical end points. In addition to these new insights, the TRS 2ºP demonstrated use in risk stratification when applied to a large health care administrative claims database, potentially expanding its use to investigators working with similar databases.

ARTICLE INFORMATION

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Supplemental Material

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SUPPLEMENTAL MATERIAL

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Figure S1. Schematic of the Study and Patient Identification Period

Figure S2. Determination of Treatment Status as of the Index Date (reproduced from Cannon et al. 2017)[10]

Figure S3. Event Rates and Instantaneous Risk Over Time for the Secondary and Individual Endpoints

Figure S4. Event Rates for the Secondary and Individual Endpoints by Type of Index Acute Coronary Syndrome and Use of Revascularization

Figure S5. Event Rates for the Secondary and Individual Endpoints by Categories of TIMI Risk Score for Secondary Prevention

Figure S6. Event Rates for the Secondary and Individual Endpoints by Categories of TIMI Risk Score for Secondary Prevention and Use of Revascularization

Supplemental Methods

Estimation of Instantaneous Hazard Rate Over Time

Let $S(t)$ denote the survivor function defined as the probability of not experiencing an event of interest by time t. Equivalently, the cumulative incidence of events is $E(t) = 1 - S(t)$. Let $dS(t)$ denote the size of population that experiences an event of interest during a small time-interval from t to $t + dt$. The instantaneous hazard rate, $\lambda(t)$, is defined as the instantaneous rate of events in the population that has survived to time t. Thus:[11]

$$\lambda(t) = \frac{1}{S(t)} \frac{dS(t)}{dt}$$

The implied cumulative incidence of events, $E(t)$, from this expression is:

$$E(t) = 1 - \exp\left(- \int_{0}^{t} \lambda(\tau) d\tau \right)$$

If the hazard rate over time is constant with $\lambda(t) = \lambda$, the expression reduces to $E(t) = 1 - \exp(-\lambda t)$. If it is time dependent, functional forms representing its time dependence can be utilized. A useful functional form for this purpose is:

$$\lambda(t) = A + B \exp(-Ct)$$

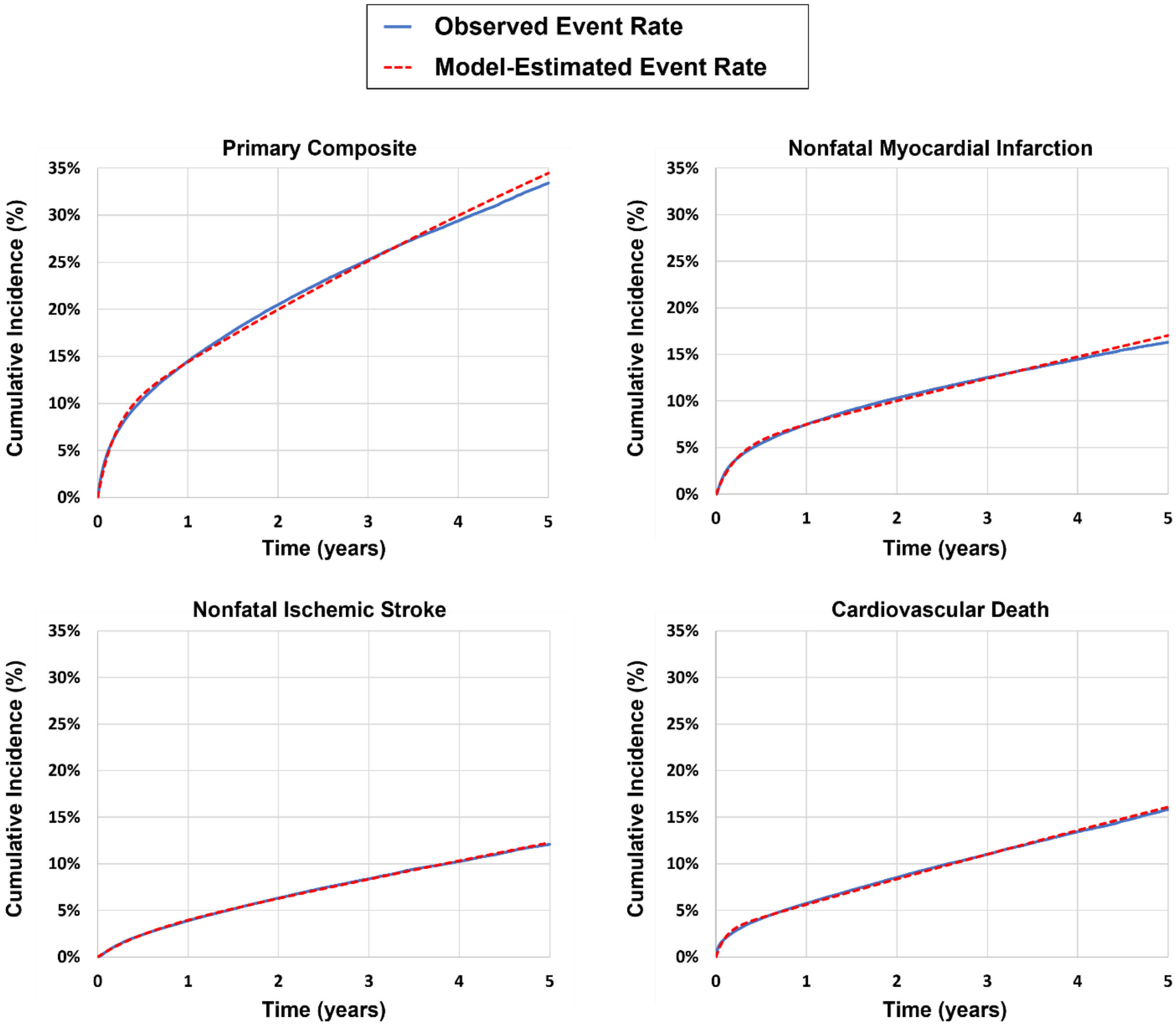
Where A, B, and C are parameters in the above expression for instantaneous hazard rate. This functional was found to adequately describe the patterns of cardiovascular event rates over time in 22 randomized controlled trials (RCTs) for lipid-lowering therapies.[22] It captures a pattern of an initial elevation of risk (e.g., close to the Index ACS event) that gradually declines over time to a more constant risk (e.g., > 2 years after Index ACS). It also has the flexibility to model a constant risk over time (i.e., B = 0). With this functional form, $E(t)$ can be expressed as:

$$E(t) = 1 - \exp\left(-\left(At + \frac{B}{C}(1 - \exp\,(-Ct)\right)\right)$$

From the SciPy.Optimize package in Python 3.0[44], we used the minimize function to fit this expression to the observed event rates over time for the primary and individual endpoints which resulted in following estimates of A, B, and C:

	A	B	C
Primary Composite	0.07	0.46	5.15
Nonfatal Myocardial Infarction	0.03	0.23	4.43
Nonfatal Ischemic Stroke	0.02	0.04	1.95
Cardiovascular Death	0.03	0.28	9.69

The following Figure represents a comparison of the observed and model-estimated event rates over time:



The hazard rates over time in Figure 2 of the manuscript represent the curve defined by $\lambda(t) = A + B\exp(-Ct)$ obtained via the model-estimated values of A, B, and C.

Sensitivity Analysis of Selecting the First or Last Qualifying ACS as Index

For patients with multiple qualifying ACS events, we randomly selected one as the Index ACS. Patients were followed from that point onwards for CV events. This was done to minimize the potential of bias and to better align the findings with how the risk needed to be interpreted from the study findings.

Here we describe a sensitivity analysis estimating the impact on the primary endpoint of selecting either the first or the last qualifying ACS as the Index ACS. We stratified the study population (N = 239,234) into six mutually exclusive subgroups based on the number of qualifying ACS events and whether the first or last was chosen as the Index ACS. The following table summarizes the percent of patients and 5-year event rate for the primary endpoint for each subgroup.

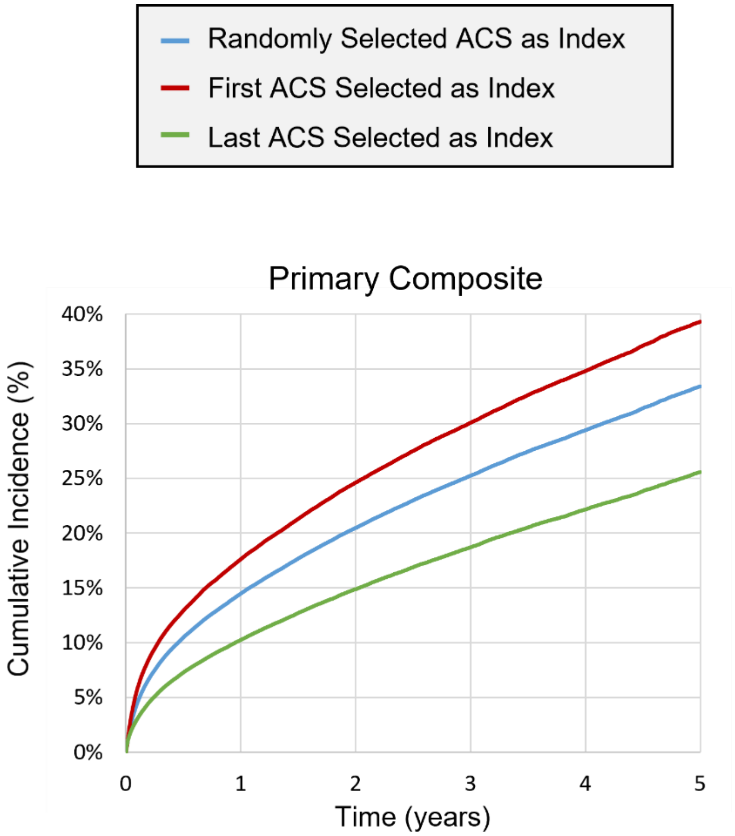
Subgroup	Number of Qualifying ACS Events	Randomly Selected ACS as Index was …	Percent of Patients	5-Year Event Rate for the Primary Endpoint*
1	1	—	82.1	22.7%
2	2	First	6.4	81.3%
3	2	Last	6.4	36.8%
4	≥ 3	First	1.5	87.8%
5	≥ 3	Last	1.5	50.5%
6	≥ 3	Other[†]	2.1	87.1%
Total Study Population (N = 239,234)			100.0	33.4%

* Via Kaplan-Meier Estimation

[†] The randomly selected ACS event as Index was neither first nor last

The subgroup with only one qualifying ACS was more likely to be less comorbid (as these patients had a smaller number of ACS events) than other subgroups and hence relatively lower risk. Also, these patients did not have another ACS event (i.e., nonfatal MI) during the follow-up and were only at risk for nonfatal ischemic stroke or CV death when considering the primary composite endpoint. Together, these factors resulted in a relatively lower 5-year event rate of 22.7% in this subgroup. Subgroups 2 and 4 represent patients with more than one qualifying ACS in which the first event was chosen as the Index ACS. In these subgroups, the patients had at least one additional ACS event during follow-up, which explains the relatively high 5-year event rate of 81.3% and 87.8%, respectively. Compared to subgroups 2 and 4, the opposite was true for subgroups 3 and 5. These subgroups, in which the last qualifying ACS event was chosen as the Index ACS, had relatively lower 5-year event rates of 36.8% and 50.5%, respectively. This finding is intuitive since patients in subgroups 3 and 5 did not have another ACS event (i.e., nonfatal MI) during the follow-up (by definition). The monotonic increase in risk in subgroups 1, 3, and 5 is reflective of the history of a progressively larger number of prior ACS events.

To determine the potential range of 5-year event rates depending on the ACS event selected, we performed two additional weighted Kaplan-Meier (KM) analyses where the subgroups described above were used to construct weights to estimate the outcome if the first or last qualifying ACS event during the identification period was selected as the Index ACS event. Results are summarized in the figure below.



- Subgroups 2 and 3 in the previous table are comparable as they were divided into these groups randomly. This means that a counterfactual situation where in both subgroups 2 and 3 the first qualifying ACS event was selected as the Index ACS can be estimated by reweighing the observations such that the weight of subgroup 3 is transferred to subgroup 2. In other words, by reweighing observations in subgroup 3 as 0, and subgroups 2 as 2 (= (6.4 + 6.4) / 6.4).
- Similarly, a counterfactual situation where in subgroups 4, 5, and 6 the first qualifying ACS event was selected as the Index ACS can be estimated by reweighing the observations such that the weight of subgroups 5 and 6 is transferred to subgroup 4. In other words, by reweighing observations in subgroups 5 and 6 as 0, and subgroup 4 as 3.4 (= (1.5 + 1.5 + 2.1) / 1.5).

Thus, the KM event rate for the primary composite endpoint over time for a scenario representing selection of the first qualifying ACS event as the Index ACS for all patients can be estimated by reweighing the observations in subgroups 1, 2, and 4 as 1, 2, and 3.4, respectively, and reweighting the observations in remaining subgroups as 0. The estimated KM event rate for the primary composite endpoint over time for the scenario representing selection of the last qualifying ACS event as the Index ACS for all patients can be generated in a similar manner.

Table S1. Comparison of Baseline Characteristics for Pre-Existing Conditions by Selection of the Duration of Baseline Period

Baseline period	**6 months**	**1 year**	**2 years**
N	239,234*	239,234	157,950
Atherosclerotic Cardiovascular Disease Characteristics, %			
History of CHD	33.9	42.7	48.9
History of CABG	8.6	11.2	13.6
History of PCI	10.8	14.4	17.6
History of IS	6.0	7.1	9.2
ICBVD without stroke	5.5	7.6	10.9
PAD (lower)	2.5	3.4	4.5
PAD (aorta)	2.4	3.2	4.6
PAD (other; unspecified)[†]	9.8	12.5	16.0
Other Comorbidities, %			
Atrial fibrillation/flutter	21.1	22.2	24.9
Hypertension	80.7	84.5	87.9
Heart failure	33.7	35.7	38.8
Renal Disease Stage III	11.0	13.2	16.5
Renal Disease Stages IV–V[††]	6.4	6.7	7.2
COPD	23.0	25.4	28.3
Moderate/severe liver disease	2.6	3.3	4.0
Diabetes	40.1	42.1	44.0
Diabetes on insulin	14.1	15.6	16.4

[*] The overall number of patients with availability of 6-month baseline is greater than 239,234, the number of patients with availability of 1-year baseline. However, in order to facilitate a

comparison that is driven purely by the incremental information collected during a 1-year versus a 6-month baseline for same patients, this group was kept as the same 239,234 patients with a 1-year baseline; [†]Includes any type of disease that is non-coronary, non-cerebrovascular, or does not involve the lower extremities or aorta; [††]Includes dialysis or renal transplant.

CABG, coronary artery bypass grafting; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; hosp., hospitalization; ICBVD, ischemic cerebrovascular disease; IS, ischemic stroke; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

Table S2. Diagnosis and Procedure Codes for Identifying Clinical Conditions and Endpoints

Acute Coronary Syndrome Event

These codes are utilized together with the evidence of an inpatient hospitalization.

Code Type	Codes
ICD-9 Dx	410.*, 411.1, 411.81
ICD-10 Dx	I21.0*, I21.1*, I21.2*, I21.3*, I21.4*, I21.9*, I22.*, I20.0*, I20.1*, I25.110, I25.111, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790, I25.701, I25.711, I25.721, I25.731, I25.751, I25.761, I25.791

Myocardial Infarction Endpoint

These codes are utilized together with the evidence of an inpatient hospitalization.

Code Type	Codes
ICD-9 Dx	410.*
ICD-10 Dx	I21.0*, I21.1*, I21.2*, I21.3*, I21.4*, I21.9*, I22.*, I21.A*

Coronary Artery Bypass Graft

Code Type	Codes
ICD-9 Dx	V45.81, 414.02, 414.03, 414.04, 414.05, 414.07, 996.03
ICD-10 Dx	Z951, I25.700, I25.710, I25.720, I25.730, I25.750, I25.760, I25.790, I25.701, I25.711, I25.721, I25.731, I25.751, I25.761, I25.791, I25.810, I25.812, I25.708, I25.709, I25.718, I25.719, I25.728, I25.729, I25.738, I25.739, I25.758, I25.759, I25.768, I25.769, I25.798, I25.799, I25.811, T82.211*, T82.212*, T82.213*, T82.218*
CPT	33510-33529, 33531-33536
HCPCS	S2205-S2209
ICD-10 Proc	0210093, 0210098, 0210099, 0210493, 0210498, 0210499, 0211093, 0211098, 0211099, 0211493, 0211498, 0211499, 0212093, 0212098, 0212099, 0212493, 0212498, 0212499, 0213093, 0213098, 0213099, 0213493, 0213498, 0213499, 021009C, 021009W, 02100A3, 02100A8, 02100A9, 02100AC, 02100AW, 02100Z3, 02100Z8, 02100Z9, 02100ZC, 021049C, 021049W, 02104A3, 02104A8, 02104A9, 02104AC, 02104AW, 02104Z3, 02104Z8, 02104Z9, 02104ZC, 021109C, 021109W, 02110A3, 02110A8, 02110A9, 02110AC, 02110AW, 02110Z3, 02110Z8, 02110Z9, 02110ZC, 021149C, 021149W, 02114A3, 02114A8, 02114A9, 02114AC, 02114AW, 02114Z3, 02114Z8, 02114Z9, 02114ZC, 021209C, 021209W, 02120A3, 02120A8, 02120A9, 02120AC, 02120AW, 02120J3, 02120J8, 02120JW, 02120Z3, 02120Z8, 02120Z9, 02120ZC, 021249C, 021249W, 02124A3, 02124A8, 02124A9,

	02124AC, 02124AW, 02124Z3, 02124Z8, 02124Z9, 02124ZC, 021309C, 021309W, 02130A3, 02130A8, 02130A9, 02130AC, 02130AW, 02130Z3, 02130Z8, 02130Z9, 02130ZC, 021349C, 021349W, 02134A3, 02134A8, 02134A9, 02134AC, 02134AW, 02134Z3, 02134Z8, 02134Z9, 02134ZC, B212010, B2120ZZ, B212110, B2121ZZ, B212Y10, B212YZZ, B213010, B2130ZZ, B213110, B2131ZZ, B213Y10, B213YZZ, B22300Z, B2230ZZ, B22310Z, B2231ZZ, B223Y0Z, B223YZZ, B223Z2Z, B223ZZZ
ICD-9 Proc	36.1*, 36.2

Percutaneous Coronary Intervention

Code Type	Codes
ICD-9 Dx	V45.82
ICD-10 Dx	T82855A, T82855D, T82855S, Z955, Z9861
CPT	92929, 92933, 92934, 92937, 92938, 92941, 92943, 92944, 92980, 92981, 92982, 92984, 92995, 92996
HCPCS	C9600, C9601, C9602, C9603, C9604, C9605, C9606, C9607, C9608, G0290, G0291
ICD-9 Proc	0.66, 36.0*
ICD-10 Proc	0270346, 0270356, 0270366, 0270376, 0271346, 0271356, 0271366, 0271376, 0272346, 0272356, 0272366, 0272376, 0273346, 0273356, 0273366, 0273376, 0370346, 0370356, 0370366, 0370376, 0371346, 0371356, 0371366, 0371376, 02703E6, 02713E6, 02723E6, 02733E6, 03703E6, 03713E6, 027034Z, 027035Z, 027036Z, 027037Z, 02703D6, 02703DZ, 02703EZ, 02703F6, 02703FZ, 02703G6, 02703GZ, 02703T6, 02703TZ, 02703Z6, 02703ZZ, 027134Z, 027135Z, 027136Z, 027137Z, 02713D6, 02713DZ, 02713EZ, 02713F6, 02713FZ, 02713G6, 02713GZ, 02713T6, 02713TZ, 02713Z6, 02713ZZ, 027234Z, 027235Z, 027236Z, 027237Z, 02723D6, 02723DZ, 02723EZ, 02723F6, 02723FZ, 02723G6, 02723GZ, 02723T6, 02723TZ, 02723Z6, 02723ZZ, 027334Z, 027335Z, 027336Z, 027337Z, 02733D6, 02733DZ, 02733EZ, 02733F6, 02733FZ, 02733G6, 02733GZ, 02733T6, 02733TZ, 02733Z6, 02733ZZ, 02C03Z6, 02C03ZZ, 02C13Z6, 02C13ZZ, 02C23Z6, 02C23ZZ, 02C33Z6, 02C33ZZ, 037034Z, 037035Z, 037036Z, 037037Z, 03703D6, 03703DZ, 03703EZ, 03703F6, 03703FZ, 03703G6, 03703GZ, 03703Z6, 03703ZZ, 037134Z, 037135Z, 037136Z, 037137Z, 03713D6, 03713DZ, 03713EZ, 03713F6, 03713FZ, 03713G6, 03713GZ, 03713Z6, 03713ZZ, 03C03Z6, 03C03ZZ, 03C13Z6, 03C13ZZ, X2C0361, X2C1361, X2C2361, X2C3361

Coronary Heart Disease

Code Type	Codes
ICD-9 Dx	410.*, 411.1, 411.81, 412., 414.00, 414.01, 414.1*, 414.2*, 414.3*, 414.4*, 414.8*, 414.9*, 413.*
ICD-10 Dx	I20.0*, I20.1*, I21.0*, I21.1*, I21.2*, I21.3*, I21.4*, I21.9*, I22.*, I25.110, I25.111, I23.*, I24.*, I25.10, I25.118, I25.119, I25.2*, I25.3*, I25.4*, I25.5*, I25.6*, I25.82, I25.83, I25.84, I25.89, I25.9*, I20., I20.8*, I20.9*

Ischemic Cerebrovascular Disease with Stroke History

Code Type	Codes
ICD-9 Dx	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91
ICD-10 Dx	I63, I63.0*, I63.2*, I63.3*, I63.5*, I63.6*, I63.8*, I63.9*, I69.3*

Ischemic Cerebrovascular Disease with Stroke Event

These codes are utilized together with the evidence of an inpatient hospitalization.

Code Type	Codes
ICD-9 Dx	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91
ICD-10 Dx	I63, I63.0*, I63.2*, I63.3*, I63.5*, I63.6*, I63.8*, I63.9*

Ischemic Cerebrovascular Disease without Stroke

Code Type	Codes
ICD-9 Dx	433.00, 433.10, 433.20, 433.30, 433.80, 433.90, 434.00, 434.10, 434.90
ICD-10 Dx	I6501, I6502, I6503, I6509, I651, I6521, I6522, I6523, I6529, I658, I659, I6601, I6602, I6603, I6609, I6611, I6612, I6613, I6619, I6621, I6622, I6623, I6629, I663, I668, I669, I67.2, I72.0, I72.5, I72.6, T82.311*, T82.321*, T82.331*, T82.391*
CPT	37215, 37216, 35301, 35501, 35506, 35507, 35508, 35509, 35510, 35601, 35606, 35642, 35645, 37218
ICD-9 Proc	00.63, 39.72, 39.74, 00.61, 00.64
ICD-10 Proc	031209J, 031209K, 03120AJ, 03120AK, 03120JJ, 03120JK, 03120KJ, 03120KK, 03120ZJ, 03120ZK, 031309J, 031309K, 03130AJ, 03130AK, 03130JJ, 03130JK, 03130KJ, 03130KK, 03130ZJ, 03130ZK, 031409J, 031409K, 03140AJ, 03140AK, 03140JJ, 03140JK, 03140KJ, 03140KK, 03140ZJ, 03140ZK, 031509J, 031509K, 03150AJ, 03150AK, 03150JJ, 03150JK, 03150KJ, 03150KK, 03150ZJ, 03150ZK, 031609J, 031609K, 03160AJ, 03160AK, 03160JJ, 03160JK, 03160KJ, 03160KK, 03160ZJ, 03160ZK, 031H09G, 031H09J, 031H0AG, 031H0AJ, 031H0JG, 031H0JJ, 031H0KG, 031H0KJ, 031H0ZG, 031H0ZJ, 031J09G, 031J09K, 031J0AG, 031J0AK, 031J0JG, 031J0JK, 031J0KG, 031J0KK, 031J0ZG, 031J0ZK, 031K0KJ, 031L0KK, 031M0KJ, 031N0KK, 037G046, 037G04Z, 037G056, 037G05Z, 037G066, 037G06Z, 037G076, 037G07Z, 037G0D6, 037G0DZ, 037G0E6, 037G0EZ, 037G0F6, 037G0FZ, 037G0G6, 037G0GZ, 037G0Z6, 037G0ZZ, 037G346, 037G34Z, 037G356, 037G35Z, 037G366, 037G36Z, 037G376, 037G37Z, 037G3D6, 037G3DZ, 037G3E6, 037G3EZ, 037G3F6, 037G3FZ, 037G3G6, 037G3GZ, 037G3Z6, 037G3ZZ, 037G446, 037G44Z, 037G456, 037G45Z, 037G466, 037G46Z, 037G476, 037G47Z, 037G4D6, 037G4DZ, 037G4E6, 037G4EZ, 037G4F6, 037G4FZ, 037G4G6, 037G4GZ, 037G4Z6, 037G4ZZ, 037H046, 037H04Z, 037H056, 037H05Z, 037H066, 037H06Z, 037H076, 037H07Z, 037H0D6, 037H0DZ, 037H0E6, 037H0EZ, 037H0F6, 037H0FZ, 037H0G6, 037H0GZ, 037H0Z6, 037H0ZZ, 037H346, 037H34Z, 037H356, 037H35Z, 037H366, 037H36Z, 037H376, 037H37Z, 037H3D6, 037H3DZ, 037H3E6, 037H3EZ, 037H3F6, 037H3FZ, 037H3G6, 037H3GZ, 037H3Z6, 037H3ZZ, 037H446, 037H44Z, 037H456, 037H45Z, 037H466, 037H46Z, 037H476, 037H47Z, 037H4D6, 037H4DZ, 037H4E6, 037H4EZ, 037H4F6, 037H4FZ, 037H4G6, 037H4GZ, 037H4Z6, 037H4ZZ, 037J046, 037J04Z, 037J056, 037J05Z, 037J066, 037J06Z, 037J076, 037J07Z,

	037J0D6, 037J0DZ, 037J0E6, 037J0EZ, 037J0F6, 037J0FZ, 037J0G6, 037J0GZ, 037J0Z6, 037J0ZZ, 037J346, 037J34Z, 037J356, 037J35Z, 037J366, 037J36Z, 037J376, 037J37Z, 037J3D6, 037J3DZ, 037J3E6, 037J3EZ, 037J3F6, 037J3FZ, 037J3G6, 037J3GZ, 037J3Z6, 037J3ZZ, 037J446, 037J44Z, 037J456, 037J45Z, 037J466, 037J46Z, 037J476, 037J47Z, 037J4D6, 037J4DZ, 037J4E6, 037J4EZ, 037J4F6, 037J4FZ, 037J4G6, 037J4GZ, 037J4Z6, 037J4ZZ, 037K046, 037K04Z, 037K056, 037K05Z, 037K066, 037K06Z, 037K076, 037K07Z, 037K0D6, 037K0DZ, 037K0E6, 037K0EZ, 037K0F6, 037K0FZ, 037K0G6, 037K0GZ, 037K0Z6, 037K0ZZ, 037K346, 037K34Z, 037K356, 037K35Z, 037K366, 037K36Z, 037K376, 037K37Z, 037K3D6, 037K3DZ, 037K3E6, 037K3EZ, 037K3F6, 037K3FZ, 037K3G6, 037K3GZ, 037K3Z6, 037K3ZZ, 037K446, 037K44Z, 037K456, 037K45Z, 037K466, 037K46Z, 037K476, 037K47Z, 037K4D6, 037K4DZ, 037K4E6, 037K4EZ, 037K4F6, 037K4FZ, 037K4G6, 037K4GZ, 037K4Z6, 037K4ZZ, 037L046, 037L04Z, 037L056, 037L05Z, 037L066, 037L06Z, 037L076, 037L07Z, 037L0D6, 037L0DZ, 037L0E6, 037L0EZ, 037L0F6, 037L0FZ, 037L0G6, 037L0GZ, 037L0Z6, 037L0ZZ, 037L346, 037L34Z, 037L356, 037L35Z, 037L366, 037L36Z, 037L376, 037L37Z, 037L3D6, 037L3DZ, 037L3E6, 037L3EZ, 037L3F6, 037L3FZ, 037L3G6, 037L3GZ, 037L3Z6, 037L3ZZ, 037L446, 037L44Z, 037L456, 037L45Z, 037L466, 037L46Z, 037L476, 037L47Z, 037L4D6, 037L4DZ, 037L4E6, 037L4EZ, 037L4F6, 037L4FZ, 037L4G6, 037L4GZ, 037L4Z6, 037L4ZZ, 037P046, 037P04Z, 037P056, 037P05Z, 037P066, 037P06Z, 037P076, 037P07Z, 037P0D6, 037P0DZ, 037P0E6, 037P0EZ, 037P0F6, 037P0FZ, 037P0G6, 037P0GZ, 037P0Z6, 037P0ZZ, 037P346, 037P34Z, 037P356, 037P35Z, 037P366, 037P36Z, 037P376, 037P37Z, 037P3D6, 037P3DZ, 037P3E6, 037P3EZ, 037P3F6, 037P3FZ, 037P3G6, 037P3GZ, 037P3Z6, 037P3ZZ, 037P446, 037P44Z, 037P456, 037P45Z, 037P466, 037P46Z, 037P476, 037P47Z, 037P4D6, 037P4DZ, 037P4E6, 037P4EZ, 037P4F6, 037P4FZ, 037P4G6, 037P4GZ, 037P4Z6, 037P4ZZ, 037Q046, 037Q04Z, 037Q056, 037Q05Z, 037Q066, 037Q06Z, 037Q076, 037Q07Z, 037Q0D6, 037Q0DZ, 037Q0E6, 037Q0EZ, 037Q0F6, 037Q0FZ, 037Q0G6, 037Q0GZ, 037Q0Z6, 037Q0ZZ, 037Q346, 037Q34Z, 037Q356, 037Q35Z, 037Q366, 037Q36Z, 037Q376, 037Q37Z, 037Q3D6, 037Q3DZ, 037Q3E6, 037Q3EZ, 037Q3F6, 037Q3FZ, 037Q3G6, 037Q3GZ, 037Q3Z6, 037Q3ZZ, 037Q446, 037Q44Z, 037Q456, 037Q45Z, 037Q466, 037Q46Z, 037Q476, 037Q47Z, 037Q4D6, 037Q4DZ, 037Q4E6, 037Q4EZ, 037Q4F6, 037Q4FZ, 037Q4G6, 037Q4GZ, 037Q4Z6, 037Q4ZZ, 03CG0Z6, 03CG0ZZ, 03CG3Z6, 03CG3ZZ, 03CG4Z6, 03CG4ZZ, 03CH0Z6, 03CH0ZZ, 03CH3Z6, 03CH3ZZ, 03CH4Z6, 03CH4ZZ, 03CJ0Z6, 03CJ0ZZ, 03CJ3Z6, 03CJ3ZZ, 03CJ4Z6, 03CJ4ZZ, 03CK0Z6, 03CK0ZZ, 03CK3Z6, 03CK3ZZ, 03CK4Z6, 03CK4ZZ, 03CL0Z6, 03CL0ZZ, 03CL3Z6, 03CL3ZZ, 03CL4Z6, 03CL4ZZ, 03CP0Z6, 03CP0ZZ, 03CP3Z6, 03CP3ZZ, 03CP4Z6, 03CP4ZZ, 03CQ0Z6, 03CQ0ZZ, 03CQ3Z6, 03CQ3ZZ, 03CQ4Z6, 03CQ4ZZ

Peripheral Arterial Disease, Leg

Code Type	Codes
ICD-9 Dx	445.02
ICD-10 Dx	I70201, I70202, I70203, I70211, I70212, I70213, I70221, I70222, I70223, I70231, I70232, I70233, I70234, I70235, I70238, I70239, I70241, I70242, I70243, I70244, I70245, I70248, I70249, I70261, I70262, I70263, I70291, I70292, I70293, I70301, I70302, I70303, I70311, I70312, I70313, I70321, I70322, I70331, I70332, I70333, I70334, I70335, I70338, I70339, I70341,

	I70342, I70343, I70344, I70345, I70348, I70349, I70361, I70362, I70363, I70391, I70392, I70393, I70401, I70402, I70403, I70411, I70412, I70413, I70421, I70422, I70423, I70431, I70432, I70433, I70434, I70435, I70438, I70439, I70441, I70442, I70443, I70444, I70445, I70448, I70449, I70461, I70462, I70463, I70491, I70492, I70493, I70501, I70502, I70503, I70511, I70512, I70513, I70521, I70522, I70523, I70531, I70532, I70533, I70534, I70535, I70538, I70539, I70541, I70542, I70543, I70544, I70545, I70548, I70549, I70561, I70562, I70563, I70591, I70592, I70593, I70601, I70602, I70603, I70611, I70612, I70613, I70621, I70622, I70623, I70631, I70632, I70633, I70634, I70635, I70638, I70639, I70641, I70642, I70643, I70644, I70645, I70648, I70649, I70661, I70662, I70663, I70691, I70692, I70693, I70701, I70702, I70703, I70711, I70712, I70713, I70721, I70722, I70723, I70731, I70732, I70733, I70734, I70735, I70738, I70739, I70741, I70742, I70743, I70744, I70745, I70748, I70749, I70761, I70762, I70763, I70791, I70792, I70793, I72.3, I72.4, I743, I745, I75021, I75022, I75023, I75029, T82.312*, T82.322*, T82.332*, T82.392*
CPT	35454, 35456, 35459, 35470, 35473, 35474, 35482, 35483, 35485, 35521, 35533, 35537, 35538, 35539, 35540, 35541, 35546, 35548, 35549, 35551, 35556, 35558, 35563, 35565, 35566, 35570, 35571, 35583, 35585, 35587, 35621, 35623, 35637, 35638, 35641, 35646, 35647, 35651, 35654, 35656, 35661, 35663, 35665, 35666, 35671, 93668, 37220, 37221, 37222, 37223, 37224, 37225, 37226, 37227, 37228, 37229, 37230, 37231, 37232, 37233, 37234, 37235
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Peripheral Arterial Disease, Aorta

Code Type	Codes
ICD-9 Dx	441.3, 441.4
ICD-10 Dx	I70.0, I71.3*, I71.4*, I71.5*, I71.6*, I7401, I7409
CPT	35452, 35472, 35481, 34800, 34802, 34803, 34804, 34805, 35081, 35082, 35091, 35092, 35102, 35103
ICD-10 Proc	0410090, 0410490, 0470046, 0470056, 0470066, 0470076, 0470346, 0470356, 0470366, 0470376, 0470446, 0470456, 0470466, 0470476, 0471046, 04700E6, 04703E6, 04704E6, 04100A0, 04100J0, 04100K0, 04100Z0, 04104A0, 04104J0, 04104K0, 04104Z0, 047004Z, 047005Z, 047006Z, 047007Z, 04700D6, 04700DZ, 04700EZ, 04700F6, 04700FZ, 04700G6, 04700GZ, 04700Z6, 04700ZZ, 047034Z, 047035Z, 047036Z, 047037Z, 04703D6, 04703DZ, 04703EZ, 04703F6, 04703FZ, 04703G6, 04703GZ, 04703Z6, 04703ZZ, 047044Z, 047045Z, 047046Z, 047047Z, 04704D6, 04704DZ, 04704EZ, 04704F6, 04704FZ, 04704G6, 04704GZ, 04704Z6, 04704ZZ, 04C00Z6, 04C00ZZ, 04C03Z6, 04C03ZZ, 04C04Z6, 04C04ZZ, 04R007Z, 04R00JZ, 04R00KZ, 04R047Z, 04R04JZ, 04R04KZ, 04U007Z, 04U00JZ, 04U00KZ, 04U037Z, 04U03JZ, 04U03KZ, 04U047Z, 04U04JZ, 04U04KZ

Peripheral Arterial Disease, Other

Code Type	Codes
ICD-9 Dx	445.01, 443.9
ICD-10 Dx	I70.1*, I70208, I70209, I70218, I70219, I70228, I70229, I7025, I70268, I70269, I70298, I70299, I70308, I70309, I70318, I70319, I70323, I70328, I70329, I7035, I70368, I70369, I70398, I70399, I70408, I70409, I70418, I70419, I70428, I70429, I7045, I70468, I70469, I70498, I70499, I70508, I70509, I70518, I70519, I70528, I70529, I7055, I70568, I70569, I70598, I70599, I70608, I70609, I70618, I70619, I70628, I70629, I7065, I70668, I70669, I70698, I70699, I70708, I70709, I70718, I70719, I70728, I70729, I7075, I70768, I70769, I70798, I70799, I70.8*, I70.92, I72.1, I72.2, I742, I744, I748, I749, I75011, I75012, I75013, I75019, I7581, I7589, I73.8, I73.89, I73.9, I73

CPT	35450, 35458, 35471, 35475, 35480, 35484, 35511, 35512, 35515, 35516, 35518, 35522, 35523, 35525, 35526, 35531, 35535, 35536, 35560, 35612, 35616, 35626, 35631, 35632, 35633, 35634, 35636, 35650, 37205, 37206, 37207, 37208
ICD-9 Proc	38.13, 39.50
ICD-10 Proc	0312090, 0312091, 0312092, 0312093, 0312094, 0312095, 0313090, 0313091, 0313092, 0313093, 0313094, 0313095, 0314090, 0314091, 0314092, 0314093, 0314094, 0314095, 0315090, 0315091, 0315092, 0315094, 0315095, 0316090, 0316091, 0316092, 0316093, 0316095, 0372046, 0372056, 0372066, 0372076, 0372346, 0372356, 0372366, 0372376, 0372446, 0372456, 0372466, 0372476, 0373046, 0373056, 0373066, 0373076, 0373346, 0373356, 0373366, 0373376, 0373446, 0373456, 0373466, 0373476, 0374046, 0374056, 0374066, 0374076, 0374346, 0374356, 0374366, 0374376, 0374446, 0374456, 0374466, 0374476, 0410091, 0410092, 0410093, 0410094, 0410095, 0410491, 0410492, 0410493, 0410494, 0410495, 0471056, 0471066, 0471076, 0471346, 0471356, 0471366, 0471376, 0471446, 0471456, 0471466, 0471476, 0475046, 0475056, 0475066, 0475076, 0475346, 0475356, 0475366, 0475376, 0475446, 0475456, 0475466, 0475476, 0479046, 0479056, 0479066, 0479076, 0479346, 0479356, 0479366, 0479376, 0479446, 0479456, 0479466, 0479476, 03720E6, 03723E6, 03724E6, 03730E6, 03733E6, 03734E6, 03740E6, 03743E6, 03744E6, 04710E6, 04713E6, 04714E6, 04750E6, 04753E6, 04754E6, 04790E6, 04793E6, 04794E6, 047E046, 047E056, 047E066, 047E076, 041E099, 03120A0, 03120A1, 03120A2, 03120A3, 03120A4, 03120A5, 03120J0, 03120J1, 03120J2, 03120J3, 03120J4, 03120J5, 03120K0, 03120K1, 03120K2, 03120K3, 03120K4, 03120K5, 03120Z0, 03120Z1, 03120Z2, 03120Z3, 03120Z4, 03120Z5, 03130A0, 03130A1, 03130A2, 03130A3, 03130A4, 03130A5, 03130J0, 03130J1, 03130J2, 03130J3, 03130J4, 03130J5, 03130K0, 03130K1, 03130K2, 03130K3, 03130K4, 03130K5, 03130Z0, 03130Z1, 03130Z2, 03130Z3, 03130Z4, 03130Z5, 03140A0, 03140A1, 03140A2, 03140A3, 03140A4, 03140A5, 03140J0, 03140J1, 03140J2, 03140J3, 03140J4, 03140J5, 03140K0, 03140K1, 03140K2, 03140K3, 03140K4, 03140K5, 03140Z0, 03140Z1, 03140Z2, 03140Z3, 03140Z4, 03140Z5, 03150A0, 03150A1, 03150A2, 03150A4, 03150A5, 03150J0, 03150J1, 03150J2, 03150J4, 03150J5, 03150K0, 03150K1, 03150K2, 03150K3, 03150K4, 03150K5, 03150Z0, 03150Z1, 03150Z2, 03150Z4, 03150Z5, 03160A0, 03160A1, 03160A2, 03160A3, 03160A5, 03160J0, 03160J1, 03160J2, 03160J3, 03160J5, 03160K0, 03160K1, 03160K2, 03160K3, 03160K4, 03160K5, 03160Z0, 03160Z1, 03160Z2, 03160Z3, 03160Z5, 03170K0, 03170K3, 03180K1, 03180K4, 037204Z, 037205Z, 037206Z, 037207Z, 03720D6, 03720DZ, 03720EZ, 03720F6, 03720FZ, 03720G6, 03720GZ, 03720Z6, 03720ZZ, 037234Z, 037235Z, 037236Z, 037237Z, 03723D6, 03723DZ, 03723EZ, 03723F6, 03723FZ, 03723G6, 03723GZ, 03723Z6, 03723ZZ, 037244Z, 037245Z, 037246Z, 037247Z, 03724D6, 03724DZ, 03724EZ, 03724F6, 03724FZ, 03724G6, 03724GZ, 03724Z6, 03724ZZ, 037304Z, 037305Z, 037306Z, 037307Z, 03730D6, 03730DZ, 03730EZ, 03730F6, 03730FZ, 03730G6, 03730GZ, 03730Z6, 03730ZZ, 037334Z, 037335Z, 037336Z, 037337Z, 03733D6, 03733DZ, 03733EZ, 03733F6, 03733FZ, 03733G6, 03733GZ, 03733Z6, 03733ZZ, 037344Z, 037345Z, 037346Z, 037347Z, 03734D6, 03734DZ, 03734EZ, 03734F6, 03734FZ, 03734G6, 03734GZ, 03734Z6, 03734ZZ, 037404Z, 037405Z, 037406Z, 037407Z, 03740D6, 03740DZ, 03740EZ, 03740F6, 03740FZ, 03740G6, 03740GZ, 03740Z6, 03740ZZ, 037434Z, 037435Z, 037436Z, 037437Z, 03743D6, 03743DZ, 03743EZ, 03743F6, 03743FZ, 03743G6, 03743GZ, 03743Z6, 03743ZZ, 037444Z, 037445Z, 037446Z, 037447Z, 03744D6, 03744DZ, 03744EZ, 03744F6, 03744FZ, 03744G6, 03744GZ, 03744Z6, 03744ZZ, 03C20Z6, 03C20ZZ,

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Table S3. Length of Study Follow-up: By Overall Cohort and Subgroups of Type of Index Acute Coronary Syndrome Combined with Use of Revascularization

		MI with Revascularization n = 69,931	**MI without Revascularization n = 99,289**	**UA with Revascularization n = 31,545**	**UA without Revascularization n = 38,469**	**Total N = 239,234**
Follow-up (Years)*	Mean (SD)	2.2 (2.3)	1.6 (1.9)	2.6 (2.6)	2.3 (2.5)	2.0 (2.2)
	Median	1.4	0.9	1.6	1.4	1.2
	IQR	0.6 – 3.1	0.3 – 2.2	0.7 – 3.6	0.5 – 3.2	0.4 – 2.8
Distribution of patients during follow-up, %						
< 30 days		4.7	12.5	3.3	4.9	7.7
30 days to < 180 days		17.7	23.0	15.5	18.1	19.7
180 days to < 365 days		17.4	17.2	16.6	17.1	17.2
1 year to < 2 years		21.9	19.8	21.6	20.5	20.8
2 years to < 3 years		12.7	10.2	12.9	12.3	11.6
3 years to < 4 years		8.4	6.4	8.5	8.2	7.6
4 years to < 5 years		5.8	4.2	6.1	5.8	5.2
≥ 5 years		11.5	6.7	15.6	13.2	10.3

*Number of days, measured in years, from the day after discharge from Index ACS hospitalization to the earliest of disenrollment, death, or study end date (December 31st, 2018). A total of 2,069 patients were dropped from follow-up analyses because of end of enrollment on date of discharge from the Index ACS hospitalization (n = 1,101); or National Death Index (NDI)-based death on the date of discharge from the Index ACS hospitalization (n = 968).

ACS, acute coronary syndrome; IQR, inter-quartile range; MI, myocardial infarction; SD, standard deviation; UA, unstable angina.

Table S4. Baseline Characteristics: Overall Cohort and Subgroups of Sex

	Male **n=136,755**	**Female** **n=102,479**	**Total** **N=239,234**
Index ACS Type and Revascularization Status			
MI with Revascularization, %	34.9	21.6	29.2
MI without Revascularization, %	34.8	50.5	41.5
UA with Revascularization, %	16.0	9.4	13.2
UA without Revascularization, %	14.3	18.5	16.1
Demographic Characteristics			
Age, mean (SD), years	67.4 (12.2)	71.7 (11.6)	69.2 (12.2)
Age ≥ 75 years, %	31.5	46.7	38.0
Age ≥ 80 years, %	17.8	29.7	22.9
Male, %	100.0	0.0	57.1
Medicare Advantage, %[*]	64.9	80.6	71.6
United States region, %			
South	46.9	45.4	46.3
Midwest	29.7	30.3	29.9
Northeast	15.4	17.1	16.1
West/other	8.1	7.2	7.7
Atherosclerotic Cardiovascular Disease Characteristics, %			
ACS hosp. past 12 months[†]	8.4	8.9	8.6
History of CHD[†]	44.8	40.0	42.7
CABG past 12 months[‡]	1.6	1.0	1.3
History of CABG[§]	13.4	8.4	11.2
PCI past 12 months[‡]	6.3	4.8	5.7
History of PCI[§]	15.9	12.4	14.4
IS hosp. past 12 months[†]	2.6	3.6	3.0
History of IS	6.2	8.4	7.1
ICBVD without stroke	7.3	8.0	7.6
PAD (lower extremities)	3.3	3.5	3.4
PAD (aorta)	3.5	2.8	3.2
PAD (other; unspecified)[‖]	12.0	13.2	12.5
Other Comorbidities, %			
Atrial fibrillation/flutter	21.7	23.0	22.2
Hypertension	82.3	87.6	84.5

Heart failure	32.6	39.8	35.7
Renal Disease Stage III	12.4	14.2	13.2
Renal Disease Stages IV-V[#]	6.3	7.2	6.7
COPD	23.3	28.2	25.4
Moderate/severe liver disease	3.4	3.0	3.3
Diabetes mellitus	41.0	43.7	42.1
Diabetes mellitus on insulin	14.1	17.5	15.6
Treatment Status Prior to Index ACS (Point-In-Time), %[**]			
Lipid-lowering therapy[††]	42.5	42.7	42.6
ß-blockers	38.5	43.2	40.6
ACEi/ARBs	39.9	44.6	41.9
P2Y12 Inhibitors[‡‡]	16.9	16.1	16.5
Treatment Status at 1-Year Post-Discharge (Point-In-Time), %[**]			
Lipid-lowering therapy[††]	64.5	58.8	62.1
ß-blockers	62.1	61.9	62.0
ACEi/ARBs	48.3	48.7	48.5
P2Y12 Inhibitors[‡‡]	43.5	35.0	39.9
Treatment Status at 1-Year Post-Discharge (Cumulative), %[§§]			
Lipid-lowering therapy[††]	80.8	74.7	78.2
ß-blockers	81.0	77.9	79.7
ACEi/ARBs	63.9	63.8	63.9
P2Y12 Inhibitors[‡‡]	57.8	46.6	53.0
Procedures at Index ACS or 30-Days Post-Discharge			
CABG	16.0	7.8	12.5
PCI	37.1	24.2	31.6
TRS 2ºP Categories			
0 to 1	21.6	15.8	19.1
2 to 3	47.9	49.6	48.6
4+	30.5	34.6	32.3

[*] Represents health plan offered by a private company that contracts with Medicare to provide patients with hospital and medical insurance benefits; [†] Measured in the 1-year period prior to the start of the index hospitalization; [‡] Measured prior to the start of the index hospitalization using procedure codes only; [§] Measured 1-year prior to admission of index hospitalization, during index

hospitalization, or in the 30-days post-hospitalization, using both diagnosis and procedure codes; [‖]Includes any type of disease that is non-coronary, non-cerebrovascular, or does not involve the lower extremities or aorta; [#]Includes dialysis or renal transplant; [**]Medication on hand at Index ACS (see Figure S2); [††]Includes statins, ezetimibe and/or proprotein convertase subtilisin/kexin type 9 inhibitors; [‡‡]Includes clopidogrel, ticagrelor, and prasugrel; [§§]Based on 132,489 patients at 1-year follow-up (Male = 76,320; Female = 56,169). Point-in-time assessment indicates medication on hand at 1-year follow-up (see Figure S2) and cumulative assessment indicates medication on hand at any time during the 1-year follow-up.

ACEi, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; CABG, coronary artery bypass grafting; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; hosp., hospitalization; ICBVD, ischemic cerebrovascular disease; IS, ischemic stroke; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; TRS 2°P, Thrombolysis In Myocardial Infarction (TIMI) Risk Score for Secondary Prevention; UA, unstable angina.

Table S5. Baseline Characteristics: Overall Cohort and Subgroups of Type of Index Acute Coronary Syndrome Combined with Use of Revascularization

	MI with Revasculari-zation n=69,931	MI without Revasculari-zation n=99,289	UA with Revasculari-zation n=31,545	UA without Revasculari-zation n=38,469	Total N=239,234
Demographic Characteristics					
Age, mean (SD), years	66.4 (11.6)	72.9 (11.9)	66.5 (10.5)	67.2 (12.7)	69.2 (12.2)
Age ≥ 75 years, %	27.1	51.8	24.8	33.3	38.0
Male, %	68.3	47.9	69.5	50.7	57.2
Medicare Advantage, %[*]	61.6	83.9	60.3	67.5	71.6
United States region, %					
South	46.9	42.2	50.1	52.4	46.3
Midwest	31.9	30.1	30.7	25.3	29.9
Northeast	12.4	19.7	12.7	16.4	16.1
West/other	8.7	8.1	6.5	5.9	7.7
Atherosclerotic Cardiovascular Disease Characteristics, %					
ACS hosp. past 12 months[†]	5.3	10.9	7.3	9.6	8.6
History of CHD[†]	30.8	42.7	59.8	50.5	42.7
CABG past 12 months[‡]	1.2	1.2	1.7	1.3	1.3
History of CABG[§]	8.4	11.2	14.0	14.1	11.2
PCI past 12 months[‡]	5.7	4.2	9.0	6.6	5.7
History of PCI[§]	12.9	11.8	21.9	17.7	14.4
IS hosp. past 12 months[†]	1.4	4.7	1.4	3.0	3.0
History of IS	3.8	11.3	3.2	5.8	7.1
ICBVD without stroke	6.4	8.2	9.6	6.7	7.6
PAD (lower extremities)	2.6	4.3	2.6	2.9	3.4
PAD (aorta)	2.6	3.9	2.9	2.9	3.2
PAD (other; unspecified)[‖]	9.3	15.5	11.0	11.7	12.5
Other Comorbidities, %					
Atrial fibrillation/flutter	14.7	30.0	15.5	21.3	22.2
Hypertension	79.0	87.2	86.9	85.8	84.5
Heart failure	25.9	49.1	19.9	31.8	35.7
Renal Disease Stage III	9.4	17.4	9.3	12.3	13.2
Renal Disease Stages IV-V[#]	3.9	10.0	3.0	6.0	6.7

COPD	17.7	32.6	18.4	26.6	25.4
Moderate/severe liver disease	2.1	4.2	2.2	3.7	3.3
Diabetes mellitus	38.6	44.1	43.7	42.2	42.1
Diabetes mellitus on insulin	13.3	17.7	14.6	15.1	15.6
Treatment Status Prior to Index ACS (Point-In-Time), %[**]					
Lipid-lowering therapy[††]	36.5	42.8	52.2	45.1	42.6
ß-blockers	31.3	43.2	48.1	44.3	40.6
ACEi/ARBs	37.5	43.0	47.3	42.7	41.9
P2Y12 Inhibitors[‡‡]	12.5	15.7	23.8	20.1	16.5
Treatment Status at 1-Year Post-Discharge (Point-In-Time), %[**]					
Lipid-lowering therapy[††]	74.2	53.1	71.4	50.0	62.1
ß-blockers	71.5	57.6	65.6	50.4	62.0
ACEi/ARBs	54.8	44.5	49.7	43.8	48.5
P2Y12 Inhibitors[‡‡]	65.1	21.3	53.3	19.8	39.9
Treatment Status at 1-Year Post-Discharge (Cumulative), %[§§]					
Lipid-lowering therapy[††]	91.4	68.7	87.6	65.0	78.2
ß-blockers	90.4	75.0	83.7	66.0	79.7
ACEi/ARBs	71.7	60.2	63.2	57.4	63.9
P2Y12 Inhibitors[‡‡]	82.7	31.2	70.9	27.5	53.0
Procedures at Index ACS or 30-Days Post-Discharge					
CABG	24.0	0.0	41.4	0.0	12.5
PCI	80.3	0.0	61.5	0.0	31.6
TRS 2ºP Categories					
0 to 1	26.0	12.2	22.7	21.5	19.1
2 to 3	51.4	44.3	55.6	49.0	48.6
4+	22.6	43.4	21.8	29.5	32.3

[*]Represents health plan offered by a private company that contracts with Medicare to provide patients with hospital and medical insurance benefits; [†]Measured in the 1-year period prior to the start of the index hospitalization; [‡]Measured prior to the start of the index hospitalization using procedure codes only; [§]Measured 1-year prior to admission of index hospitalization, during index hospitalization, or in the 30-days post-hospitalization, using both diagnosis and procedure codes; [‖]Includes any type of disease that is non-coronary, non-cerebrovascular, or does not involve the

lower extremities or aorta; [#]Includes dialysis or renal transplant; [**]Medication on hand at Index ACS (see Figure S2); [††]Includes statins, ezetimibe and/or proprotein convertase subtilisin/kexin type 9 inhibitors; [‡‡]Includes clopidogrel, ticagrelor, and prasugrel. [§§]Based on 132,489 patients at 1-year follow-up (MI with revascularization = 42,116; MI without revascularization = 46,927; UA with Revascularization = 20,392; UA without Revascularization = 23,054). Point-in-time assessment indicates medication on hand at 1-year follow-up (see Figure S2) and cumulative assessment indicates medication on hand at any time during the 1-year follow-up.

ACEi, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARBs, angiotensin receptor blockers; CABG, coronary artery bypass grafting; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; hosp., hospitalization; ICBVD, ischemic cerebrovascular disease; IS, ischemic stroke; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; TRS 2°P, Thrombolysis In Myocardial Infarction (TIMI) Risk Score for Secondary Prevention; UA, unstable angina.

Table S6. Comparison of Baseline Characteristics and Event Rates for the Current Study with Selected Clinical Trials Involving a Post-Acute Coronary Syndrome Population

	Current Study			**Clinical Trials**					
	Overall ACS Cohort N=239234	**ACS with Revascul-arization n=101476**	**MI with Revascul-arization n=69931**	**ISAR – REACT 5 N=4018**	**ODYSSEY OUTCO-MES N=18294**	**IMPROVE – IT N=18144**	**ATLAS ACS 2 – TIMI 51 N=15526**	**TRACER N=12944**	**PLATO N=18624**
Year Published	NA	NA	NA	2019	2018	2015	2012	2012	2009
Treatment	NA	NA	NA	Ticagrelor	Alirocumab	Simvastatin + Ezetimibe	Rivaroxaban	Vorapaxar	Ticagrelor
Comparator	NA	NA	NA	Prasugrel	Placebo	Simvastatin Only	Placebo	Placebo	Clopidogrel
Age, mean, years	69.2	66.5	66.4	64.6	58.6	63.6	61.5	64.0*	62.0*
Time from Index ACS to follow-up initiation, median, days	0.0	0.0	0.0	0.0	79.1	5.0	4.7	0.9	0.2
Female, %	42.8	31.3	31.7	23.8	25.1	24.1	25.0	28.2	28.3
Diabetes, %	42.1	40.2	38.6	21.4	29.1	27.3	31.8	31.4	25.1
Heart Failure, %	35.7	24.0	25.9	—	15.3	4.1	—	—	5.8

PAD, %	19.1	15.1	14.5	—	4.1	5.7	—	7.2	6.2
History of MI, %	—	—	—	16.0	19.5	20.7	27.3	29.2	20.7
History of PCI, %	14.4	15.7	12.9	23.1	17.1	19.8	—	23.7	13.1
History of CABG, %	11.2	10.2	8.4	6.5	5.6	9.3	—	11.8	6.2
History of Stroke, %	7.1	3.6	3.8	—	3.2	—	Excluded	4.1	4.0[†]
Index ACS Type, %									
MI	70.7	68.9	100.0	87.0	82.8	75.6	76.4	—	80.5
UA	29.3	31.1	0.0	13.0	17.1	24.4	23.6	—	16.8
PCI	31.6	74.5	80.3	84.8	—	69.7	—	57.4	61.1
CABG	12.5	29.4	24.0	1.8	—	—	—	10.4	4.7[‡]
PCI/CABG	44.1	100.0	100.0	86.6	72.7	—	60.4	—	65.8
1-year event rate, %	14.5[§]	8.6[§]	10.3[§]	7.0[‖]	5.0[#]	13.4[**]	6.9[††]	15.7[‡‡]	9.7[††]

Characteristics represent the comparator arm. A hyphen **(**—) indicates the data was not reported.

*Median; [†]Non-hemorrhagic stroke; [‡]Any cardiac surgery; [§]Cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke; [‖]All-cause death, myocardial infarction, stroke; [#]Coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, unstable angina hospitalization; [**]Cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, unstable angina hospitalization, coronary revascularization; ††Cardiovascular death, myocardial infarction, stroke; ‡‡Cardiovascular death, myocardial infarction, stroke, recurrent ischemia with rehospitalization, urgent coronary revascularization.

ACS, acute coronary syndrome; ATLAS ACS2-TIMI 51, Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome-Thrombolysis in Myocardial Infarction[26]; CABG, coronary artery bypass graft surgery; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial[25]; ISAR-REACT 5, The Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment[23]; MI, myocardial infarction; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment with Alirocumab[24]; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes[28]; TRACER, Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome[27]; UA, unstable angina.

Table S7. Lipid-Lowering Therapy at Baseline: Point-In-Time Evaluation[*]

	MI with Revasculariz-ation n = 69,931	**MI without Revasculariz-ation n = 99,289**	**UA with Revasculariz-ation n = 31,545**	**UA without Revasculariz-ation n = 38,469**	**Total N = 239,234**
Any LLT therapy, %	36.5	42.8	52.2	45.1	42.6
Statin Therapy, %	35.8	42.3	51.2	44.1	41.9
Low to Moderate-Intensity Statin, %	24.1	29.8	32.8	29.8	28.5
High-Intensity Statin, %	11.7	12.5	18.4	14.3	13.3
Ezetimibe, %	2.3	2.0	4.9	3.8	2.8
PCSK9 Inhibitor, %	0.0	0.0	0.1	0.0	0.0
No Concurrent LLT, %	63.5	57.2	47.8	54.9	57.4

*Medication supply within 30 days of the Index ACS

ACS, acute coronary syndrome; LLT, lipid-lowering therapy; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; UA, unstable angina.

Table S8. Patient Characteristics Associated with the Secondary and Individual Endpoints: Cox Proportional Hazard Model

	Secondary Endpoint[*]	**Nonfatal Myocardial Infarction**[†]	**Nonfatal Ischemic Stroke**[‡]	**Cardiovascular Death**[§]	**Nonfatal Unstable Angina Hospitalization**[‖]	**Nonfatal Elective Coronary Revasculari-zation**[#]
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Index ACS Event and Revascularization Status						
MI with Revascularization	1.18 (1.15, 1.21)	2.08 (1.97, 2.19)	0.74 (0.70, 0.79)	0.85 (0.81, 0.89)	0.64 (0.60, 0.68)	1.96 (1.84, 2.09)
MI without Revascularization	1.45 (1.41, 1.48)	2.46 (2.34, 2.59)	1.15 (1.10, 1.21)	1.86 (1.78, 1.94)	0.39 (0.37, 0.42)	0.84 (0.79, 0.90)
UA with Revascularization	0.96 (0.93, 1.00)	0.85 (0.79, 0.92)	0.65 (0.61, 0.70)	0.59 (0.55, 0.63)	1.00 (0.94, 1.06)	1.95 (1.82, 2.09)
UA without Revascularization	reference	reference	reference	reference	reference	reference
Demographics						
Age						
20 – 44	0.75 (0.70, 0.81)	0.79 (0.70, 0.89)	0.61 (0.51, 0.74)	0.52 (0.42, 0.64)	0.97 (0.85, 1.12)	0.87 (0.78, 0.98)
45 – 64	reference	reference	reference	reference	reference	reference
≥ 65	1.31 (1.29, 1.34)	1.28 (1.23, 1.32)	1.47 (1.41, 1.55)	2.56 (2.44, 2.69)	0.81 (0.77, 0.85)	0.82 (0.79, 0.86)
Male	1.04 (1.03, 1.06)	1.00 (0.97, 1.03)	0.87 (0.84, 0.90)	1.09 (1.06, 1.12)	0.99 (0.94, 1.03)	1.30 (1.25, 1.36)
Cardiovascular Comorbidities & Risk Factors						
Atrial fibrillation/ flutter	1.12 (1.10, 1.14)	—	1.23 (1.19, 1.28)	1.40 (1.36, 1.44)	0.88 (0.83, 0.93)	0.73 (0.69, 0.77)
Hypertension	1.19 (1.16, 1.23)	1.19 (1.14, 1.26)	1.45 (1.36, 1.56)	1.08 (1.03, 1.14)	1.33 (1.23, 1.44)	1.10 (1.04, 1.16)

Heart failure	1.54 (1.51, 1.56)	1.49 (1.44, 1.54)	1.26 (1.21, 1.31)	2.51 (2.43, 2.60)	1.24 (1.17, 1.30)	—
Renal Disease						
Stage III	1.19 (1.17, 1.22)	1.22 (1.17, 1.27)	1.19 (1.14, 1.25)	1.33 (1.28, 1.38)	1.09 (1.02, 1.17)	0.89 (0.83, 0.95)
Stage IV	1.51 (1.45, 1.57)	1.51 (1.40, 1.62)	1.36 (1.24, 1.49)	1.87 (1.76, 1.98)	1.34 (1.17, 1.52)	0.89 (0.76, 1.04)
Stage V	1.47 (1.41, 1.52)	1.58 (1.49, 1.68)	1.63 (1.52, 1.76)	1.59 (1.50, 1.68)	1.40 (1.27, 1.55)	1.03 (0.91, 1.15)
Stage ≤ II	reference	reference	reference	reference	reference	reference
COPD	1.15 (1.13, 1.17)	1.23 (1.19, 1.28)	1.16 (1.11, 1.20)	1.20 (1.16, 1.24)	1.25 (1.19, 1.32)	0.93 (0.88, 0.97)
Moderate/severe liver disease	—	1.13 (1.05, 1.22)	—	0.87 (0.80, 0.95)	—	—
Diabetes						
Not receiving insulin	1.12 (1.10, 1.14)	1.19 (1.15, 1.23)	1.28 (1.23, 1.33)	0.95 (0.92, 0.98)	1.23 (1.17, 1.29)	1.17 (1.12, 1.23)
Receiving insulin	1.32 (1.29, 1.35)	1.50 (1.44, 1.56)	1.65 (1.57, 1.73)	1.04 (1.00, 1.08)	1.53 (1.44, 1.62)	1.37 (1.29, 1.45)
No Diabetes	reference	reference	reference	reference	reference	reference
Tobacco Use	0.94 (0.92, 0.95)	1.08 (1.04, 1.11)	—	0.70 (0.68, 0.72)	—	—
Baseline Atherosclerotic Cardiovascular Disease						
History of CHD						
ACS hosp. past 12 months	1.69 (1.64, 1.74)	2.33 (2.23, 2.44)	1.10 (1.03, 1.17)	1.31 (1.25, 1.37)	3.61 (3.37, 3.87)	1.49 (1.38, 1.61)
No ACS hosp. past 12 months	1.27 (1.25, 1.30)	1.34 (1.29, 1.38)	1.12 (1.07, 1.16)	1.23 (1.19, 1.27)	1.74 (1.65, 1.84)	1.29 (1.23, 1.35)
No history of CHD	reference	reference	reference	reference	reference	reference
History of ICBVD						
IS hosp. past 12 months	1.61 (1.55, 1.67)	1.05 (0.98, 1.13)	4.70 (4.43, 4.99)	1.45 (1.36, 1.54)	—	0.72 (0.62, 0.85)

IS without hosp. past 12 months	1.77 (1.72, 1.83)	0.89 (0.83, 0.96)	4.75 (4.52, 4.99)	1.78 (1.69, 1.87)	—	0.80 (0.70, 0.90)
ICBVD without stroke	1.08 (1.04, 1.12)	1.01 (0.95, 1.07)	1.44 (1.35, 1.55)	1.07 (1.01, 1.13)	—	1.08 (1.00, 1.17)
No history of ICBVD	reference	reference	reference	reference	reference	reference
PAD, lower extremities	1.13 (1.08, 1.17)	1.15 (1.08, 1.23)	—	1.16 (1.08, 1.24)	—	1.27 (1.14, 1.42)
PAD, aorta	1.10 (1.05, 1.14)	1.09 (1.01, 1.17)	1.16 (1.06, 1.27)	1.13 (1.05, 1.21)	1.19 (1.06, 1.34)	—
Concurrent Cardiovascular Medications						
Any statin	0.88 (0.86, 0.89)	0.90 (0.87, 0.93)	0.89 (0.86, 0.92)	0.79 (0.77, 0.81)	0.86 (0.82, 0.90)	0.96 (0.92, 1.00)
Beta-blockers	—	—	—	1.05 (1.01, 1.08)	—	—
ACEi/ARB	0.94 (0.93, 0.96)	0.96 (0.93, 0.99)	0.94 (0.91, 0.98)	0.92 (0.89, 0.95)	0.95 (0.90, 0.99)	—
Antiplatelets	1.21 (1.18, 1.24)	1.20 (1.16, 1.25)	1.18 (1.13, 1.24)	1.11 (1.07, 1.15)	1.40 (1.32, 1.47)	1.37 (1.30, 1.45)

A hyphen (—) indicates the covariate was determined to be non-significant in the model for that endpoint.

[*] A major cardiovascular event for the secondary endpoint is the NDI-based date of cardiovascular death or the last date of an inpatient encounter with at least one ICD-9/ICD-10 code diagnosis for acute myocardial infarction or ischemic cerebrovascular disease with stroke; or date associated with a procedural code for coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention) at least 30 days after the end of an inpatient encounter for an ACS event or ischemic cerebrovascular disease with stroke. [†] A nonfatal myocardial infarction is defined as the last date of an inpatient encounter with at least one ICD-9/ICD-10 diagnosis for acute myocardial infarction. [‡] A nonfatal ischemic stroke is defined as the last date of an inpatient encounter with at least one ICD-9/ICD-10 diagnosis for ischemic cerebrovascular disease with stroke. [§] A cardiovascular death is defined as the NDI-based

date of cardiovascular death. [‖]Nonfatal unstable angina hospitalization is defined as the last date of an inpatient encounter with at least one ICD-9/ICD-10 diagnosis for unstable angina. [#]Nonfatal elective coronary revascularization is defined as the date associated with a procedural code for coronary revascularization (coronary artery bypass graft or percutaneous coronary intervention) at least 30 days after the end of an inpatient encounter for an ACS event or ischemic cerebrovascular disease with stroke.

ACEi, angiotensin converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; CHD, coronary heart disease; COPD, chronic obstructive pulmonary disease; hosp., hospitalization; ICBVD, ischemic cerebrovascular disease; ICD, International Classification of Diseases; IS, ischemic stroke; MI, myocardial infarction; NDI, National Death Index; PAD, peripheral arterial disease; UA, unstable angina.

Table S9. Presence of Risk Factors in the TIMI Risk Score for Secondary Prevention

	TRS 2°P Cohort			
	TRS 2°P 0-1 n = 45,737	**TRS 2°P 2-3 n = 116,331**	**TRS 2°P 4+ n = 77,166**	**Total N = 239,234**
Inputs to TRS 2°P*, %				
Heart failure	2.8	23.5	73.5	35.7
Hypertension	42.2	91.6	99.0	84.5
Age ≥ 75	6.4	35.0	61.4	38.0
Diabetes Mellitus	3.7	37.5	71.9	42.1
Ischemic Stroke	0.3	3.7	16.4	7.1
Coronary Artery Bypass Graft[†]	0.5	5.8	25.8	11.2
Peripheral Artery Disease[‡]	0.1	2.4	15.4	6.2
Renal Disease[§]	0.3	7.4	50.3	19.9
Tobacco Use	21.8	42.1	55.4	42.5

[*] Estimated based on medical claims data for all 9 inputs. [†] History measured prior to index hospitalization using both diagnosis and procedure codes. [‡] History based on codes indicating peripheral artery disease of the lower extremities or aorta. [§] Based on an estimated glomerular filtration rate value < 60 within 365 days of index or a diagnosis code associated with renal disease stage 3, 4, or 5.

TIMI, Thrombolysis in Myocardial Infarction; TRS 2°P, Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention.

Table S10. Lipid-Lowering Therapy at 1-Year Follow-up: Point-In-Time Evaluation*

	MI with Revasculariz-ation n = 42,116	MI without Revasculariz-ation n = 46,927	UA with Revasculariz-ation n = 20,392	UA without Revasculariz-ation n = 23,054	Total N = 132,489
Any LLT therapy, %	74.2	53.1	71.4	50.0	62.1
Statin Therapy, %	73.3	52.5	70.2	49.1	61.3
Low to Moderate-Intensity Statin, %	34.2	34.3	39.5	33.0	34.9
High-Intensity Statin, %	39.1	18.2	30.8	16.1	26.4
Ezetimibe, %	4.4	2.2	7.0	4.4	4.0
PCSK9 Inhibitor, %	0.1	0.0	0.1	0.0	0.1
No Concurrent LLT, %	25.8	46.9	28.6	50.0	37.9

* Medication supply within 30 days of 1-year follow-up post-Index ACS

ACS, acute coronary syndrome; LLT, lipid-lowering therapy; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; UA, unstable angina.

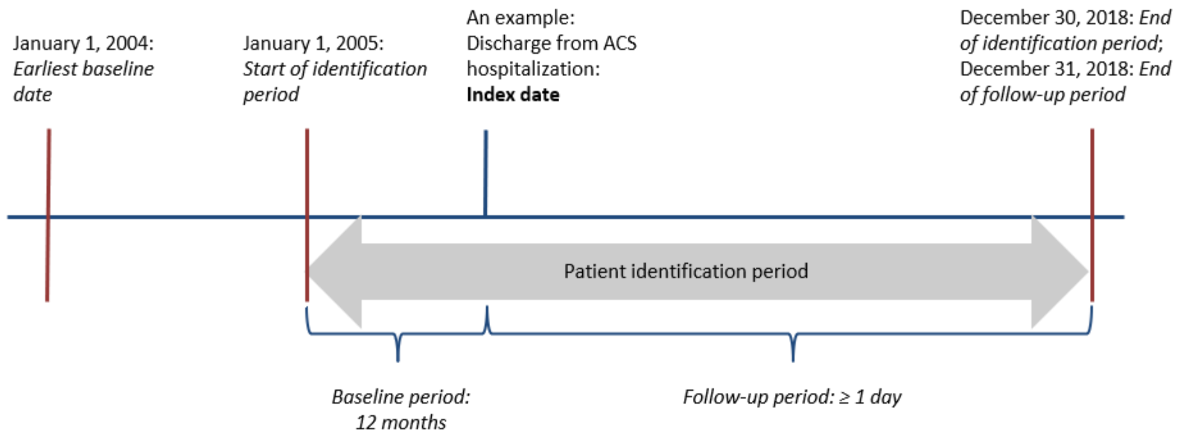
Table S11. Lipid-Lowering Therapy at 1-Year Follow-up: Cumulative Evaluation*

	MI with Revasculariz-ation n = 42,116	MI without Revasculariz-ation n = 46,927	UA with Revasculariz-ation n = 20,392	UA without Revasculariz-ation n = 23,054	Total N = 132,489
Any LLT therapy, %	91.4	68.7	87.6	65.0	78.2
Statin Therapy, %	90.8	68.1	86.6	64.0	77.5
Low to Moderate-Intensity Statin, %	43.2	44.4	49.5	43.4	44.6
High-Intensity Statin, %	47.6	23.8	37.1	20.6	32.8
Ezetimibe, %	6.3	3.2	9.7	6.3	5.7
PCSK9 Inhibitor, %	0.2	0.1	0.2	0.1	0.1
No Concurrent LLT, %	8.6	31.3	12.4	35.0	21.8

* Medication supply at any time from discharge to 1-year follow-up post-Index ACS

ACS, acute coronary syndrome; LLT, lipid-lowering therapy; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; UA, unstable angina.

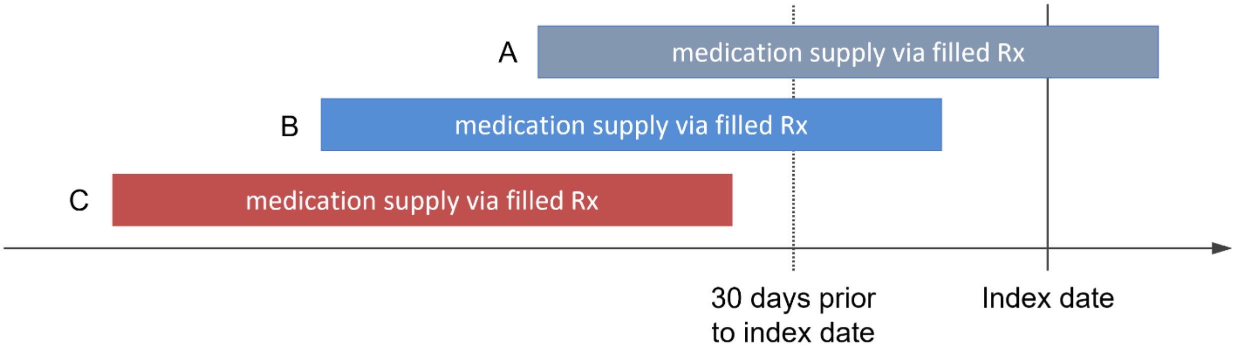
Figure S1. Schematic of the Study and Patient Identification Period


January 1, 2004:
Earliest baseline date
January 1, 2005:
Start of identification period
An example:
Discharge from ACS hospitalization:
Index date
December 30, 2018: *End of identification period*;
December 31, 2018: *End of follow-up period*
Patient identification period
Baseline period: 12 months
Follow-up period: ≥ 1 day

Shown is a schematic of the study and patient identification period utilized to identify patients with an ACS hospitalization between January 1, 2005 and December 30, 2018 in the Optum Research Database. For individuals experiencing multiple qualifying ACS hospitalizations, one event was randomly selected (subsequently referred to as "Index ACS") which helped ensure representativeness. The index date was the date of hospital discharge from Index ACS and defined the initiation of follow-up. The twelve months immediately prior to the index date were defined as the baseline period and utilized to identify pre-existing cardiovascular and non-cardiovascular conditions using medical claims.

ACS, acute coronary syndrome.

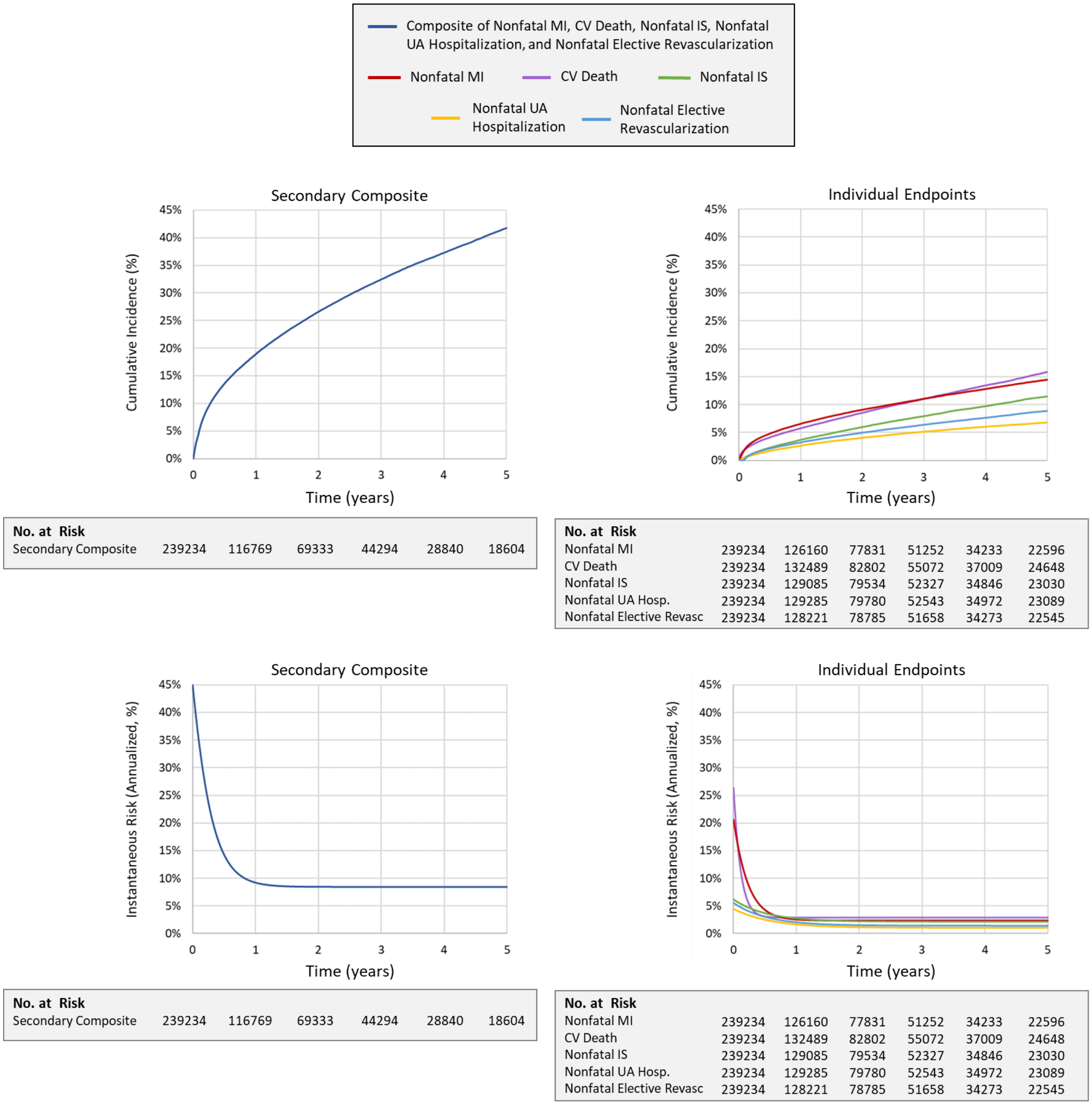
Figure S2. Determination of Treatment Status as of the Index Date (reproduced from Cannon et al. 2017)[10]


A
medication supply via filled Rx
B
medication supply via filled Rx
C
medication supply via filled Rx
30 days prior to index date
Index date

Blue bars representing scenarios A and B (medication supply via filled prescription (Rx) on or within 30 days prior to the index date) define the patient as being treated as of the index date. The red bar representing scenario C (medication supply via filled Rx more than 30 days prior to the index date) defines the patient as not being treated as of the index date.

Rx, prescription.

Figure S3. Event Rates and Instantaneous Risk Over Time for the Secondary and Individual Endpoints



No. at Risk						
Secondary Composite	239234	116769	69333	44294	28840	18604

No. at Risk						
Nonfatal MI	239234	126160	77831	51252	34233	22596
CV Death	239234	132489	82802	55072	37009	24648
Nonfatal IS	239234	129085	79534	52327	34846	23030
Nonfatal UA Hosp.	239234	129285	79780	52543	34972	23089
Nonfatal Elective Revasc	239234	128221	78785	51658	34273	22545

No. at Risk						
Secondary Composite	239234	116769	69333	44294	28840	18604

No. at Risk						
Nonfatal MI	239234	126160	77831	51252	34233	22596
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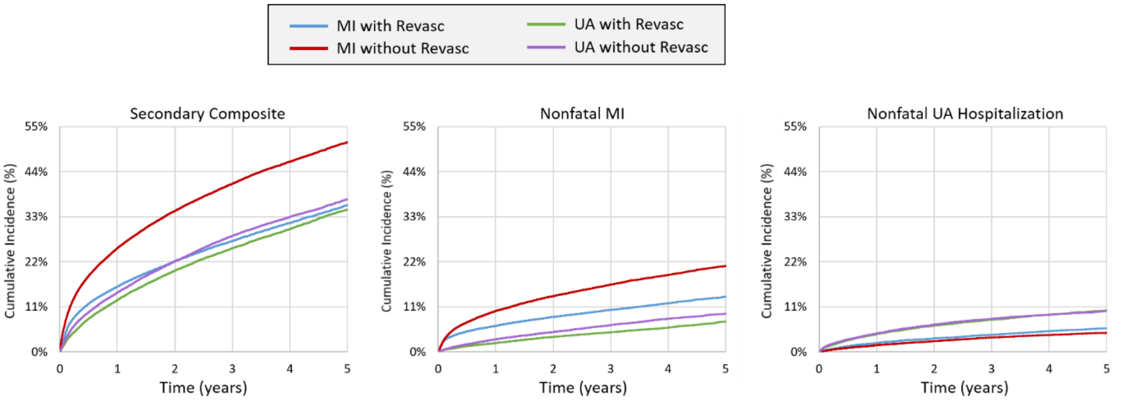
Nonfatal Elective Revasc	239234	128221	78785	51658	34273	22545

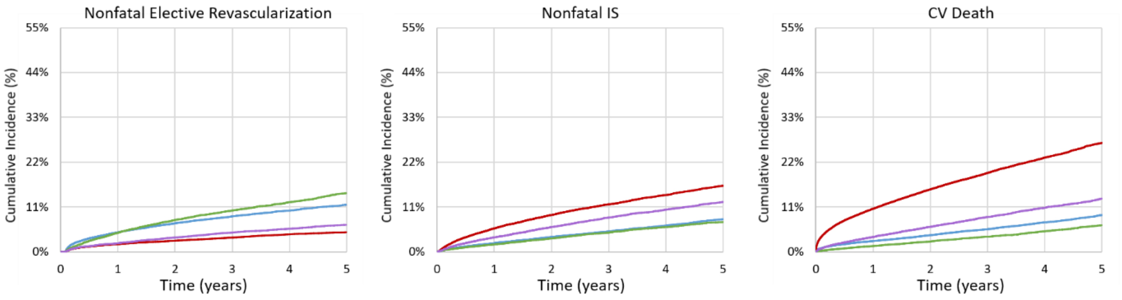
Shown is the cumulative incidence of the secondary endpoint (first occurrence of: nonfatal MI, nonfatal ischemic stroke, CV death, nonfatal UA requiring hospitalization, or nonfatal elective coronary revascularization) and individual endpoints (represented by components of the composite). The Kaplan-Meier rates for the secondary endpoint at 1, 3, and 5 years were 19.0% (95% CI 18.8% to 19.1%; $p < 0.001$), 32.5% (95% CI 32.2% to 32.7%; $p < 0.001$), and 41.8% 95% CI 41.4% to 42.1%; $p < 0.001$), respectively. The instantaneous risks (annualized) for the secondary endpoint at 0-, 1-, and 3-years were 45.0%, 9.2%, and 8.4%, respectively. Below the graphs capturing the cumulative incidence of the secondary and individual endpoints is data on the number of patients at risk of experiencing the corresponding endpoint.

CV, cardiovascular; hosp., hospitalization; IS, ischemic stroke; MI, myocardial infarction; Revasc, revascularization; UA, unstable angina.

Figure S4. Event Rates for the Secondary and Individual Endpoints: By Type of Index Acute Coronary Syndrome and Use of Revascularization



No. at Risk																		
MI with Revasc	69931	36880	22342	14353	9316	5968	69931	39904	25031	16546	11022	7231	69931	41269	25987	17252	11483	7581
MI without Revasc	99289	40816	22629	13743	8423	5059	99289	43646	24889	15458	9647	5873	99289	46278	26708	16709	10440	6395
UA with Revasc	31545	18220	11301	7541	5204	3586	31545	20039	13195	9194	6571	4684	31545	19573	12739	8808	6285	4456
UA without Revasc	38469	20853	13061	8657	5897	3991	38469	22571	14716	10054	6993	4808	38469	22165	14346	9774	6764	4657

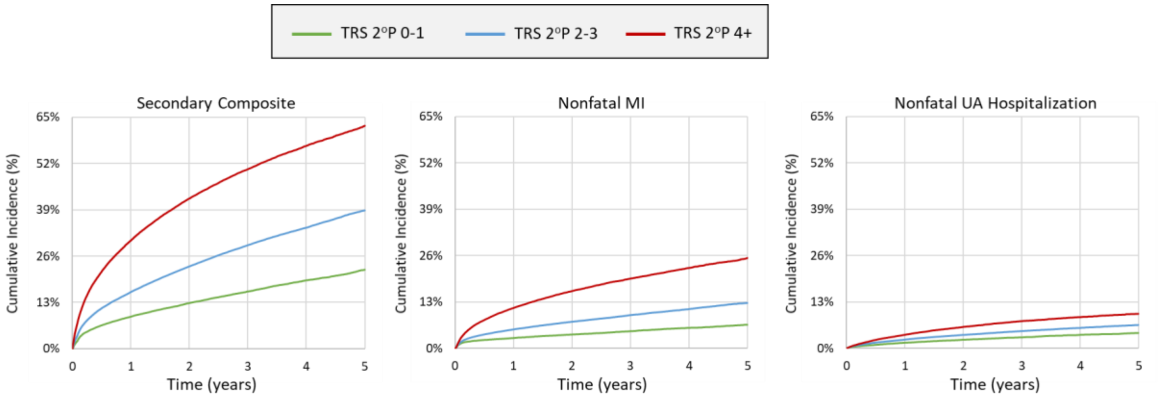


No. at Risk																		
MI with Revasc	69931	40113	24991	16439	10915	7147	69931	41438	26100	17312	11553	7588	69931	42116	26788	17918	12061	8008
MI without Revasc	99289	46066	26584	16608	10352	6345	99289	45101	25697	15994	9934	6059	99289	46927	27271	17189	10789	6639
UA with Revasc	31545	19455	12536	8607	6065	4269	31545	20150	13237	9168	6532	4679	31545	20392	13581	9521	6852	4935
UA without Revasc	38469	22587	14674	10004	6941	4784	38469	22441	14500	9854	6827	4704	38469	23054	15162	10444	7307	5066

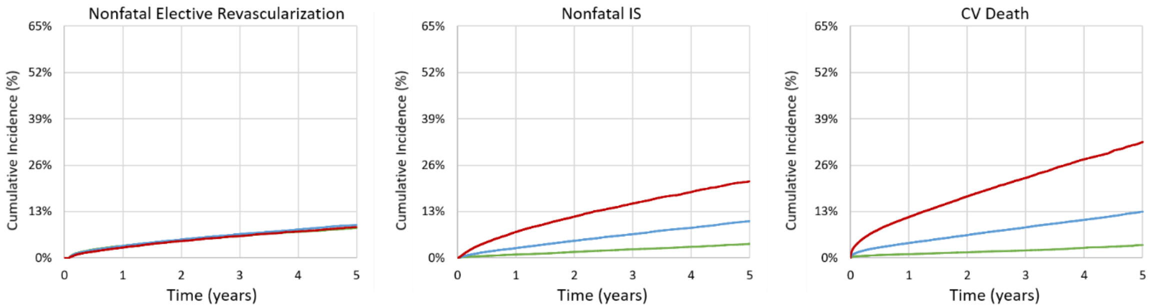
Shown is the cumulative incidence of the secondary endpoint (first occurrence of: nonfatal MI, nonfatal ischemic stroke, CV death, nonfatal UA requiring hospitalization, or nonfatal elective coronary revascularization) and individual endpoints (represented by components of the composite) by Index ACS (MI/UA and revascularization status). Below each graph is the number of patients in each Index ACS subgroup who are at risk of experiencing the corresponding endpoint.

ACS, acute coronary syndrome; CV, cardiovascular; IS, ischemic stroke; MI, myocardial infarction; Revasc, coronary revascularization; UA, unstable angina.

Figure S5. Event Rates for the Secondary and Individual Endpoints by Categories of TIMI Risk Score for Secondary Prevention



No. at Risk																		
TRS 2ºP 0-1	45737	27213	17771	11973	8209	5568	45737	28749	19307	13348	9345	6473	45737	29057	19497	13503	9451	6543
TRS 2ºP 2-3	116331	61195	37613	24600	16180	10489	116331	65827	42147	28518	19268	12802	116331	67097	43012	29112	19622	13068
TRS 2ºP 4+	77166	28361	13949	7721	4451	2547	77166	31584	16377	9386	5620	3321	77166	33131	17271	9928	5899	3478

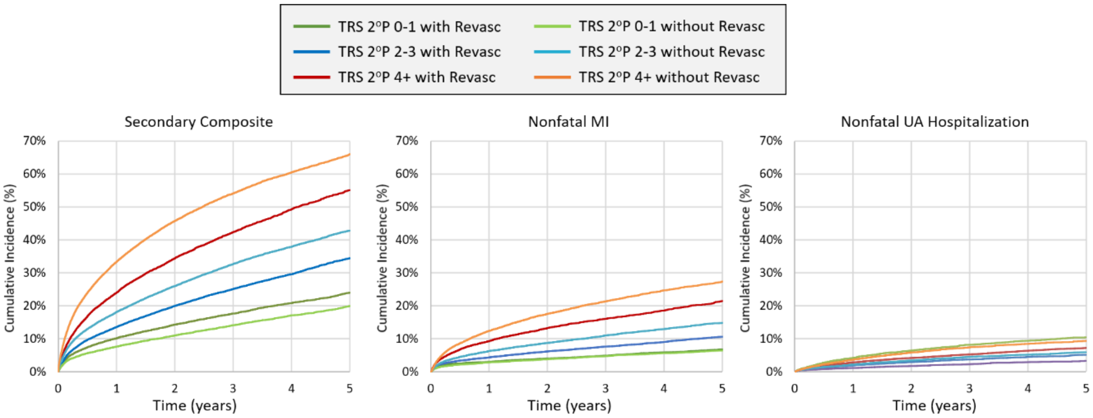


No. at Risk																		
TRS 2ºP 0-1	45737	28472	18974	13050	9091	6272	45737	29273	19697	13646	9568	6618	45737	29503	19975	13936	9829	6850
TRS 2ºP 2-3	116331	66443	42421	28628	19261	12801	116331	67255	42995	29058	19589	13062	116331	68689	44608	30541	20805	13990
TRS 2ºP 4+	77166	33306	17390	9980	5921	3472	77166	32557	16842	9623	5689	3350	77166	34297	18219	10595	6375	3808

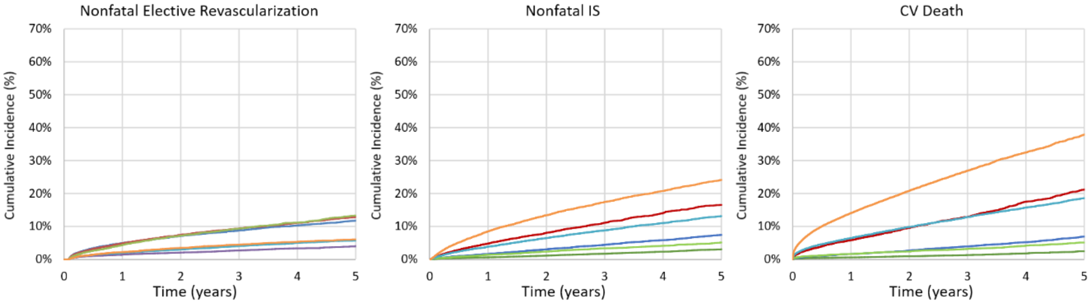
Shown is the cumulative incidence of the secondary endpoint (first occurrence of: nonfatal MI, nonfatal ischemic stroke, CV death, nonfatal UA hospitalization, or nonfatal elective coronary revascularization) and individual endpoints (represented by components of the composite) by TRS 2ºP categories. Below each graph is the number of patients in each TRS 2ºP category who are at risk of experiencing the corresponding endpoint.

CV, cardiovascular; IS, ischemic stroke; MI, myocardial infarction; Revasc, revascularization; TIMI, Thrombolysis in Myocardial Infarction; TRS 2°P, Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention; UA, unstable angina.

Figure S6. Event Rates for the Secondary and Individual Endpoints by Categories of TIMI Risk Score for Secondary Prevention and Use of Revascularization



No. at Risk																		
TRS 2°P 0-1 with Revasc	25347	15254	9926	6716	4585	3120	25347	16384	11045	7684	5378	3752	25347	16553	11128	7753	5441	3797
TRS 2°P 2-3 with Revasc	53440	29962	18689	12336	8249	5437	53440	32556	21258	14547	9999	6794	53440	32912	21484	14691	10066	6846
TRS 2°P 4+ with Revasc	22689	9884	5028	2842	1686	997	22689	11003	5923	3509	2216	1369	22689	11377	6114	3616	2261	1394
TRS 2°P 0-1 without Revasc	20390	11959	7845	5257	3624	2448	20390	12365	8262	5664	3967	2721	20390	12504	8369	5750	4010	2746
TRS 2°P 2-3 without Revasc	62891	31233	18924	12264	7931	5052	62891	33271	20889	13971	9269	6008	62891	34185	21528	14421	9556	6222
TRS 2°P 4+ without Revasc	54477	18477	8921	4879	2765	1550	54477	20581	10454	5877	3404	1952	54477	21754	11157	6312	3638	2084



No. at Risk																		
TRS 2°P 0-1 with Revasc	25347	16020	10647	7336	5106	3540	25347	16769	11348	7925	5572	3894	25347	16865	11468	8052	5695	4006
TRS 2°P 2-3 with Revasc	53440	32231	20841	14167	9675	6547	53440	33365	21834	14924	10262	6989	53440	33825	22408	15501	10748	7390
TRS 2°P 4+ with Revasc	22689	11317	6039	3543	2199	1329	22689	11409	6155	3631	2251	1384	22689	11818	6493	3886	2470	1547
TRS 2°P 0-1 without Revasc	20390	12452	8327	5714	3985	2732	20390	12504	8349	5721	3996	2724	20390	12638	8507	5884	4134	2844
TRS 2°P 2-3 without Revasc	62891	34212	21580	14461	9586	6254	62891	33890	21161	14134	9327	6073	62891	34864	22200	15040	10057	6600
TRS 2°P 4+ without Revasc	54477	21989	11351	6437	3722	2143	54477	21148	10687	5992	3438	1966	54477	22479	11726	6709	3905	2261

Shown is the cumulative incidence of the secondary endpoint (first occurrence of: nonfatal MI, nonfatal ischemic stroke, CV death, nonfatal UA requiring hospitalization, or nonfatal elective coronary revascularization) and individual endpoints (represented by components of the composite) by TRS 2°P categories and use of revascularization. Below each graph is the number of patients in each TRS 2°P category with or without revascularization who are at risk of experiencing the corresponding endpoint.

CV, cardiovascular; IS, ischemic stroke; MI, myocardial infarction; Revasc, revascularization; TIMI, Thrombolysis in Myocardial Infarction; TRS 2°P, Thrombolysis In Myocardial Infarction Risk Score for Secondary Prevention; UA, unstable angina.