ORIGINAL RESEARCH

Competing Risks of Cardiovascular Versus Noncardiovascular Death During Long-Term Follow-Up After Acute Coronary Syndromes

Alexander C. Fanaroff, MD; Matthew T. Roe, MD, MHS; Robert M. Clare, MS; Yuliya Lokhnygina, PhD; Ann Marie Navar, MD, PhD; Robert P. Giugliano, MD, SM; Stephen D. Wiviott, MD; Andrew M. Tershakovec, MD, MPH; Eugene Braunwald, MD; Michael A. Blazing, MD

***Background*—**Understanding the relative risk of cardiovascular versus noncardiovascular death is important for designing clinical trials. These risks may differ depending on patient age, sex, and type of acute coronary syndrome (ACS).

***Methods and Results*—**IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) was a randomized controlled trial of simvastatin plus either ezetimibe or placebo following stabilized ACS. Cause of death was adjudicated by an independent committee. We compared the cumulative incidence of cardiovascular and noncardiovascular death for patients with unstable angina/non-ST-segment elevation myocardial infarction (UA/NSTEMI) and ST-segment elevation myocardial infarction (STEMI), in those <65 and ≥65 years old, and males and females, over 7 years of follow-up. Of 18 131 patients, the presenting event was STEMI for 5190 (29%) and UA/NSTEMI for 12 941 (71%); 10 173 (56%) patients were <65 years old and 7971 (44%) were ≥65 years old at presentation. UA/NSTEMI patients were older than STEMI patients, with more cardiovascular and noncardiovascular risk factors. In STEMI patients, the cumulative incidence of cardiovascular death was higher for ~4 years following the index event, after which noncardiovascular death predominated. In UA/NSTEMI patients, the cumulative incidence of cardiovascular death remained higher than noncardiovascular death over the full follow-up period. Patients ≥65 years old and <65 years old had a higher incidence of cardiovascular death than noncardiovascular death over the entirety of follow-up. Female patients had a higher incidence of cardiovascular death than noncardiovascular death for ~6 years following the index event; male patients had a higher incidence of cardiovascular death than noncardiovascular death over the entirety of follow-up.

***Conclusions*—**Among post-ACS patients enrolled in a long-term clinical trial, the relative incidence of cardiovascular and noncardiovascular death differed based on type of ACS presentation and sex, but not age. These findings further delineate long-term prognosis after ACS and should inform the design of future cardiovascular outcomes trials. **(*J Am Heart Assoc*. 2017;6: e005840. DOI: 10.1161/JAHA.117.005840.)**

Key Words: acute coronary syndrome • clinical trial • death

Patients with unstable angina (UA) and non-ST-segment elevation myocardial infarction (NSTEMI) differ from those with ST-segment elevation myocardial infarction (STEMI) in important ways; as a group, they are older and more likely to have both cardiovascular and other comorbidities, including diabetes mellitus, chronic lung disease, and chronic kidney disease.[1–5] Epidemiologic studies and clinical trials have mostly demonstrated that all-cause mortality is greater for patients with STEMI than for those with UA/NSTEMI over the first 2 to 3 months after the event, but over long-term follow-up, all-cause mortality is higher for patients with UA/NSTEMI compared with STEMI and for older patients compared with younger patients.[6–16] However, these studies were unable to reliably capture cause of death and, as such, are unable to determine the contributions of cardiovascular and noncardiovascular mortality to overall mortality in post–acute coronary syndrome (ACS) patients.

The relative incidence of cardiovascular and noncardiovascular death is of particular interest in the design and interpretation of cardiovascular clinical trials. Failure to account for the competing risk of noncardiovascular death can lead to overestimates of event rates observed, and

From the Duke Clinical Research Institute, Durham, NC (A.C.F., M.T.R., R.M.C., Y.L., A.M.N., M.A.B.); Division of Cardiology, Duke University, Durham, NC (A.C.F., M.T.R., A.M.N., M.A.B.); Thrombolysis in Myocardial Infarction (TIMI) Study Group, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (R.P.G., S.D.W., E.B.); Merck & Co. Inc., Kenilworth, NJ (A.M.T.).

Accompanying Tables S1, S2 and Figures S1 through S6 are available at http://jaha.ahajournals.org/content/6/9/e005840/DC1/embed/inline-supplementary-material-1.pdf

Correspondence to: Alexander C. Fanaroff, MD, Duke Clinical Research Institute, 2400 Pratt St, Durham, NC. E-mail: alexander.fanaroff@duke.edu

Received May 1, 2017; accepted July 25, 2017.

Clinical Perspective

What Is New?

- This analysis of IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) demonstrated that the relative incidence of cardiovascular and noncardiovascular death differed based on type of acute coronary syndrome presentation, but not age.
- In patients with ST-segment elevation myocardial infarction, the cumulative incidence of cardiovascular death was higher for 4 years following the index event, after which noncardiovascular death predominated; however, patients with non-ST-segment elevation myocardial infarction or unstable angina had a higher incidence of cardiovascular death over the full follow-up period.
- Patients ≥65 years old and <65 years old had a higher incidence of cardiovascular death than noncardiovascular death over the entirety of follow-up.

What Are the Clinical Implications?

- Patients with unstable angina or non-ST-segment elevation myocardial infarction remain at higher risk for cardiovascular death than noncardiovascular death over long-term follow-up, and their comorbidities should be targeted appropriately.
- The long-term incidence of cardiovascular death following admission for unstable angina or non-ST-segment elevation myocardial infarction remains high, despite advancements in pharmacotherapy and invasive management.

noncardiovascular death rates affect sample size as patients are effectively "censored" at the time of death.[17,18] The relative likelihood of cardiovascular versus noncardiovascular death after initial presentation with ACS is likely to change over time and to differ among patients who present with STEMI and UA/NSTEMI, given differences in baseline characteristics, but this has not been well defined over a prolonged follow-up period. Further delineation of the long-term frequencies of cardiovascular versus noncardiovascular death following ACS may inform the design and conduct of future cardiovascular outcomes trials that commonly incorporate cardiovascular death into the composite primary outcome and may help patients and physicians prioritize multiple competing comorbidities.

The strict adjudication of end points and long duration of follow-up of contemporary post-ACS patients in the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) allow for an in-depth exploration of the relative incidence of cardiovascular and noncardiovascular mortality in a large cohort of patients with ACS. Specifically, the goals of this analysis were to (1) compare the cumulative incidence of cardiovascular and noncardiovascular death over time in patients after ACS, and (2) determine whether the relative contributions of cardiovascular and noncardiovascular mortality varied by presenting diagnosis or patient age.

Methods

The IMPROVE-IT trial design and primary results have been previously published.[19–21] Briefly, IMPROVE-IT was a randomized, double-blind, placebo-controlled clinical trial testing the efficacy and safety of ezetimibe compared with placebo on a background of simvastatin therapy for the prevention of cardiovascular events in patients stabilized after hospitalization for ACS. Patients were enrolled within 10 days of hospitalization for ACS, and received simvastatin 40 mg daily with either ezetimibe or matching placebo. All patients with acute MI ≥50 years of age; patients with anterior STEMI of any age; and patients with UA who were ≥50 years old and had either diabetes mellitus, prior myocardial infarction (MI), a history of peripheral arterial disease or cerebrovascular disease, coronary artery bypass grafting within at least 3 years, or known multivessel coronary artery disease were eligible for inclusion. All patients were required to be hospitalized with symptoms of acute cardiac ischemia. Key exclusion criteria included planned coronary artery bypass grafting surgery, creatinine clearance <30 mL/min, active liver disease, or ongoing treatment with statin therapy with greater potency than simvastatin 40 mg daily.

The trial was designed so that the minimum follow-up for each patient was 30 months; because of prolonged enrollment, the median follow-up was 6 years. The trial began enrolling patients on October 26, 2005; because of high enrollment of patients with STEMI in the first phase of the trial, and concern that the lower long-term risk of these patients would require lengthening of follow-up, enrollment of these patients was phased out beginning in September 2007 and was nearly complete by April 2008.[21] Total enrollment was completed on July 8, 2010. Though 42% of patients discontinued the study drug by 6 years, an average of 7% per year, only 653 patients (3.5%) had unknown vital status at the conclusion of the trial. This analysis includes all randomized patients except those with missing MI type (n=13).

Outcomes and Key Covariates

The co-primary outcomes for this analysis were cardiovascular and noncardiovascular death. Cardiovascular death was classified as death caused by coronary heart disease (fatal MI, sudden death, nonsudden cardiac death, unwitnessed death, or procedural death), other atherosclerotic disease (cerebrovascular disease and other), and other nonatherosclerotic cardiovascular disease. Noncardiovascular death was

classified as death caused by diabetes mellitus, malignancy, renal disease, accident, suicide, and other. Clinical end points, including cause of death, were adjudicated using standardized definitions by a clinical events committee blinded to treatment assignment.

STEMI was defined as symptoms of cardiac ischemia, persistent ST-segment elevation ≥0.1 mV in at least 2 contiguous ECG leads, and elevation in troponin I, troponin T, or creatine kinase MB fraction above the upper limit of normal. NSTEMI was defined as symptoms of cardiac ischemia plus elevation in troponin I, troponin T, or creatine kinase MB fraction above the upper limit of normal without persistent ST-segment elevation. Any other patient meeting inclusion criteria for the study was diagnosed with UA.

Statistical Analysis

Baseline characteristics stratified by diagnosis (STEMI and UA/NSTEMI), age (<65 and ≥65 years old), and sex (male and female) were reported as frequencies with percentages for categorical variables and as medians (25th, 75th percentiles) for continuous variables. Categorical variables were compared using χ^2 tests, and continuous variables were compared using analysis of variance; where distributional assumptions were violated, we used Fisher exact and Kruskal–Wallis tests, respectively.

We evaluated the cumulative incidence of cardiovascular and noncardiovascular death over 7 years of follow-up by presenting diagnosis (UA/NSTEMI versus STEMI), age (<65 and ≥65 years old), and sex (female versus male); we also evaluated the cumulative incidence of noncardiovascular death and the trial's primary end point (cardiovascular death, nonfatal MI, nonfatal stroke, UA requiring hospital admission, or coronary revascularization occurring at least 30 days after randomization) by presenting diagnosis and age. Since these results were similar for patients randomized to simvastatin and those randomized to simvastatin plus ezetimibe, pooled data are presented. Scaled Schoenfeld residuals were used to evaluate the proportional hazards assumption for STEMI versus UA/NSTEMI and for age <65 versus ≥65 years old for the outcomes of cardiovascular and noncardiovascular death over the 7-year follow-up. Because proportional hazards were not met for the comparison of cardiovascular death in patients with STEMI versus UA/NSTEMI, we produced a curve depicting the estimated hazard ratio of cardiovascular death for patients with STEMI versus UA/NSTEMI at any given point over the follow-up interval using the methods described by Lunn and McNeil.[22] We also tested whether hazard ratios for STEMI versus UA/NSTEMI and age <65 versus ≥65 years old were different for cardiovascular as compared with noncardiovascular death.[22]

Since the trial stopped enrollment of patients with STEMI earlier than those with UA/NSTEMI, median duration of follow-up was different for patients with STEMI compared with those with UA/NSTEMI. Therefore, as a sensitivity analysis, we repeated the above analyses including only patients enrolled from October 26, 2005 through April 1, 2008, the time period when the trial enrolled both STEMI and UA/NSTEMI patients.

To account for the fact that the trial inclusion criteria for patients with UA enriched for patients with more severe vascular disease, we performed a second sensitivity analysis that attempted to minimize the effect of the trial inclusion criteria. For this analysis, we included only patients ≥50 years old with elevated cardiac biomarkers; in effect, this analysis compared patients ≥50 years old with STEMI to those with NSTEMI, independent of enrichment factors.

All participants in IMPROVE-IT provided written informed consent to participate. The investigators had full access to all of the data. The Duke Clinical Research Institute performed all analyses using SAS software, version 9.3.

Results

Baseline Clinical Characteristics

Of 18 144 patients enrolled in IMPROVE-IT, 18 131 had data for ACS type, and all had data for age. The qualifying ACS event was STEMI for 5190 patients (28.6%), and UA/NSTEMI for 12 941 (71.4%), of whom 8555 had NSTEMI and 4386 had UA. Compared with patients with STEMI, patients with UA/NSTEMI were older and had a higher burden of risk factors, but were less likely to have undergone percutaneous coronary intervention (PCI) during hospitalization for their index event and to have been discharged on guideline-directed secondary prevention medications (P<0.001 for all comparisons, Table). Limiting this analysis to the time period during which both STEMI and UA/NSTEMI were being enrolled resulted in 5033 presenting with STEMI and 6099 with UA/NSTEMI.

A total of 10 173 patients were <65 years old, and 7971 were ≥65 years old. Compared with younger patients, older patients more often presented with UA/NSTEMI and had a higher burden of cardiac risk factors (P<0.001 for all comparisons). They had less frequently undergone PCI during hospitalization for their index event, but were taking guideline-directed medical therapy at a similar rate to younger patients. Overall, 13 728 patients were male, compared with 4416 patients who were female. Compared with male patients, female patients were older and had a higher incidence of hypertension and diabetes mellitus, but a lower incidence of coronary artery bypass grafting and multivessel coronary artery disease. Their index event was less likely to be a STEMI, and they were less likely to have undergone PCI for this index event than male patients (Table S1).

Table. Baseline Characteristics by ACS Type and Age

	Overall (N=18 144)	ACS Type			Age		
		STEMI (N=5190)	UA/NSTEMI (N=12 941)	*P* Value	<65 Y (N=10 173)	≥ 65 Y (N=7971)	*P* Value
Demographic characteristics							
Age, y	63 (56, 71)	60 (54, 68)	64 (57, 72)	<0.001	57 (53, 61)	72 (68, 77)	<0.001
Male sex	13 728 (75.7%)	4154 (80.0%)	9566 (73.9%)	<0.001	8105 (79.7%)	5623 (70.5%)	<0.001
White	15 202 (83.8%)	4458 (85.9%)	10 734 (82.9%)	<0.001	8316 (81.8%)	6886 (86.4%)	<0.001
Body mass index, kg/m^2	28 (25, 31)	27 (25, 30)	28 (25, 31)	<0.001	28 (25, 32)	27 (25, 30)	<0.001
Prior medical history							
History of hypertension	11 137 (61.4%)	2499 (48.2%)	8636 (66.7%)	<0.001	5622 (55.3%)	5515 (69.2%)	<0.001
History of diabetes mellitus	4933 (27.2%)	1013 (19.5%)	3917 (30.3%)	<0.001	2506 (24.6%)	2427 (30.5%)	<0.001
Prior CHF	790 (4.4%)	70 (1.3%)	720 (5.6%)	<0.001	296 (2.9%)	494 (6.2%)	<0.001
Prior atrial fibrillation	948 (5.2%)	119 (2.3%)	829 (6.4%)	<0.001	250 (2.5%)	698 (8.8%)	<0.001
Previous PAD	1005 (5.5%)	156 (3.0%)	848 (6.6%)	<0.001	391 (3.8%)	614 (7.7%)	<0.001
Prior PCI	3562 (19.6%)	453 (8.7%)	3106 (24.0%)	<0.001	1786 (17.6%)	1776 (22.3%)	<0.001
Prior CABG	1684 (9.3%)	96 (1.9%)	1588 (12.3%)	<0.001	611 (6.0%)	1073 (13.5%)	<0.001
History of angina	7449 (41.1%)	1011 (19.5%)	6437 (49.7%)	<0.001	3658 (36.0%)	3791 (47.6%)	<0.001
Prior multivessel CAD	2706 (15.4%)	217 (4.3%)	2488 (20.0%)	<0.001	1177 (11.9%)	1529 (20.0%)	<0.001
Previous MI	3806 (21.0%)	487 (9.4%)	3316 (25.6%)	<0.001	1864 (18.3%)	1942 (24.4%)	<0.001
History of stroke	682 (3.8%)	104 (2.0%)	578 (4.5%)	<0.001	254 (2.5%)	428 (5.4%)	<0.001
Current smoker	5978 (33.0%)	2338 (45.1%)	12 939 (28.1%)	<0.001	4614 (45.4%)	1364 (17.1%)	<0.001
Details of qualifying event							
STEMI	5190 (28.6%)	5190 (100.0%)	. . .	. . .	3432 (33.8%)	1758 (22.1%)	<0.001
NSTEMI	8555 (47.2)	. . .	8555 (66.1%)	. . .	4516 (44.4%)	4039 (50.7%)	<0.001
UA	4386 (24.2%)	. . .	4386 (33.9%)	. . .	2217 (21.8%)	2169 (27.2%)	<0.001
Killip class				<0.001			
1	13 077 (72.3%)	3737 (72.0%)	9338 (72.4%)		7434 (73.3%)	5643 (71.0%)	<0.001
2	1114 (6.2%)	348 (6.7%)	766 (5.9%)		494 (4.9%)	620 (7.8%)	
3	301 (1.7%)	71 (1.4%)	230 (1.8%)		132 (1.3%)	169 (2.1%)	
4	126 (0.4%)	62 (1.2%)	64 (0.5%)		67 (0.7%)	59 (0.7%)	
Unknown	3474 (19.2%	972 (18.7%)	2501 (19.4%)		2014 (19.9%)	1460 (18.4%)	
Creatinine clearance	85 (66, 107)	88 (69, 110)	83 (64, 106)	<0.001	99 (81, 120)	68 (55, 84)	<0.001

Continued

DOI: 10.1161/JAHA.117.005840

Table. Continued

	Overall (N=18 144)	ACS Type		P Value	Age		P Value
		STEMI (N=5190)	UA/NSTEMI (N=12 941)		<65 Y (N=10 173)	≥ 65 Y (N=7971)	
Treatment for qualifying event							
PCI during index hospitalization	12 641 (69.7%)	4633 (89.3%)	8007 (61.9%)	<0.001	7447 (73.2%)	5194 (65.2%)	<0.001
CABG within 30 days of randomization	167 (0.9%)	28 (0.5%)	139 (1.1%)	<0.001	81 (0.8%)	86 (1.1%)	0.05
Concomitant medications at randomization							
Aspirin	17 898 (98.7%)	5161 (99.4%)	12 733 (98.4%)	<0.001	10 069 (99.0%)	7829 (98.3%)	<0.001
β-Blocker	16 672 (91.9%)	4944 (95.3%)	11 724 (90.6%)	<0.001	9454 (93.0%)	7218 (90.6%)	<0.001
$P2Y_{12}$ inhibitor	16 455 (90.8%)	4963 (95.7%)	11 490 (88.8%)	<0.001	9328 (91.8%)	7127 (89.5%)	<0.001
ACE inhibitor	12 743 (70.3%)	4051 (78.1%)	8690 (67.2%)	<0.001	7264 (71.5%)	5479 (68.8%)	<0.001
Nitrates	13 418 (74.0%)	3893 (75.1%)	9524 (73.6%)	0.05	7524 (74.0%)	5894 (74.0%)	0.95

Continuous data presented as median (25th, 75th percentile); categorical data presented as count (percentage). ACE indicates angiotensin-converting enzyme; ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHF, congestive heart failure; MI, myocardial infarction; NSTEMI, non-STEMI; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

Cumulative Incidence of Cardiovascular Versus Noncardiovascular Death by ACS Type

Among patients with UA/NSTEMI, 842 patients (7-year cumulative incidence 7.7%, 95% confidence interval [CI], 7.2–8.3%) died of cardiovascular causes over the 7-year follow-up and 730 (7.0%, 95% CI, 6.5–7.5%) died of noncardiovascular causes. For patients with STEMI, 232 (4.4%, 95% CI, 3.9–5.0%) died of cardiovascular causes and 275 (5.2%, 95% CI, 4.6–5.8%) died of noncardiovascular causes. The majority of cardiovascular deaths in both groups were caused by coronary heart disease; specific causes of death can be found in Table S2. Noncardiovascular death was most often caused by malignancy in both groups of patients.

For patients with UA/NSTEMI, the cumulative incidence of cardiovascular death remained higher than noncardiovascular death over the entirety of the 7-year follow-up; however, for patients with STEMI, noncardiovascular deaths outnumbered cardiovascular deaths after ~4 years of follow-up (Figure 1). Patients with STEMI had a greater hazard of cardiovascular death compared with patients with UA/NSTEMI for 1 month, after which patients with UA/NSTEMI had a greater hazard of cardiovascular death (Figure 2). Patients with STEMI had a smaller risk of noncardiovascular death than patients with UA/NSTEMI throughout the entirety of follow-up (hazard ratio 0.73, 95% CI, 0.63–0.84). Hazard ratios for patients with STEMI compared with UA/NSTEMI were significantly different for cardiovascular and noncardiovascular death over 7 years of follow-up (P=0.02). For both STEMI and UA/NSTEMI patients, the cumulative incidence of the primary composite outcome was greater than that of noncardiovascular death alone over the entirety of follow-up (Figure S1).

In a sensitivity analysis performed to account for the fact that IMPROVE-IT's inclusion criteria limited enrollment of patients with UA to those with more severe atherosclerotic disease or diabetes mellitus, we repeated the above analyses for patients ≥50 years old with either STEMI or NSTEMI as their qualifying diagnosis. Patients with these qualifying diagnoses were included in the trial regardless of the presence or absence of other risk factors. Overall, the results were similar to the primary analysis; patients with NSTEMI had a higher cumulative incidence of cardiovascular death than noncardiovascular death over the entirety of follow-up, whereas noncardiovascular deaths predominated in patients with STEMI after the first 4 years of follow-up (Figure S2). Similarly, patients with STEMI were more likely to die of cardiovascular causes over the first month of follow-up, after which point patients with NSTEMI were more likely to die of cardiovascular causes, and patients with NSTEMI were more likely than patients with STEMI to die of

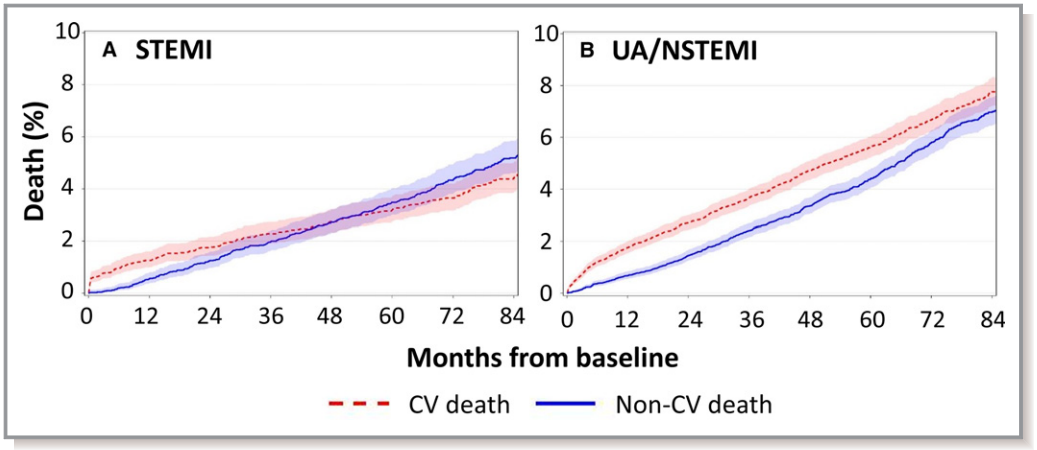


Figure 1. Cumulative incidence of cardiovascular and noncardiovascular death for patients with (A) STEMI and (B) UA/NSTEMI. Seven-year Kaplan–Meier mortality rates: cardiovascular death: STEMI, 4.5%; UA/NSTEMI, 6.5%; noncardiovascular death: STEMI, 5.3%; UA/NSTEMI, 5.6%. CV indicates cardiovascular; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

noncardiovascular causes for the duration of follow-up (Figure S3).

In a second sensitivity analysis that accounted for the different lengths of follow-up for STEMI and UA/NSTEMI patients, we limited our population to patients enrolled while the trial was enrolling both categories of patients, with findings again similar to the primary analysis (Figure S4).

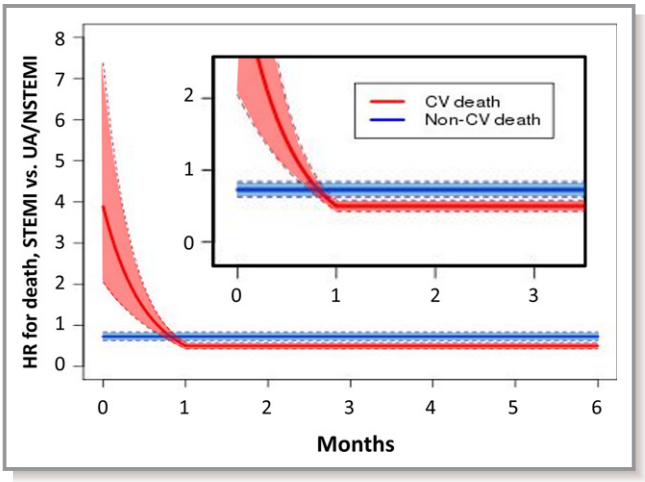


Figure 2. Hazard ratio (HR) for death over time for STEMI compared with UA/NSTEMI. HR curves are truncated at 6 months, but HRs for cardiovascular and noncardiovascular death remained constant through the end of follow-up. Solid lines represent HR curves; dashed lines represent 95% confidence limits with confidence interval denoted by shading. CV indicates cardiovascular; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

Cumulative Incidence of Cardiovascular Versus Noncardiovascular Death By Age and Sex

Among patients <65 years old, 350 patients (7-year cumulative incidence 3.8%, 95% CI, 3.4–4.3%) died of cardiovascular causes over 7 years of follow-up, compared with 321 (3.5%, 95% CI, 3.1–4.0%) who died of noncardiovascular causes. In patients ≥65 years old, 725 patients (10.3%, 95% CI, 9.5–11.0%) died of cardiovascular causes over 7-year follow-up, and 685 (10.0%, 95% CI, 9.3–10.8%) died of noncardiovascular causes. In both groups, the most common cause of cardiovascular death was death attributable to coronary heart disease and the most common cause of noncardiovascular death was malignancy (Table S1). Both patients <65 and those ≥65 years old had a higher cumulative incidence of cardiovascular compared with noncardiovascular death over the entirety of follow-up (Figure 3). Compared with patients <65 years old, patients ≥65 years old were roughly 3-fold more likely than patients <65 years old to die because of either cardiovascular (hazard ratio 2.89; 95% CI, 2.54–3.28) or noncardiovascular causes (hazard ratio 3.06; 95% CI, 2.68–3.50) over the 7-year follow-up. Hazard ratios for patients <65 compared with those ≥65 years old were not significantly different between cardiovascular and noncardiovascular death (P=0.53). For patients <65 years old and those ≥65 years old, the cumulative incidence of the primary composite outcome was greater than that of noncardiovascular death alone over the entirety of follow-up (Figure S5).

Among male patients, 816 died of cardiovascular causes over 7 years of follow-up (7-year cumulative incidence 6.6%, 95% CI, 6.2–7.1%), compared with 759 (6.3%, 95% CI, 5.8–6.7%) who died of noncardiovascular causes. Among female

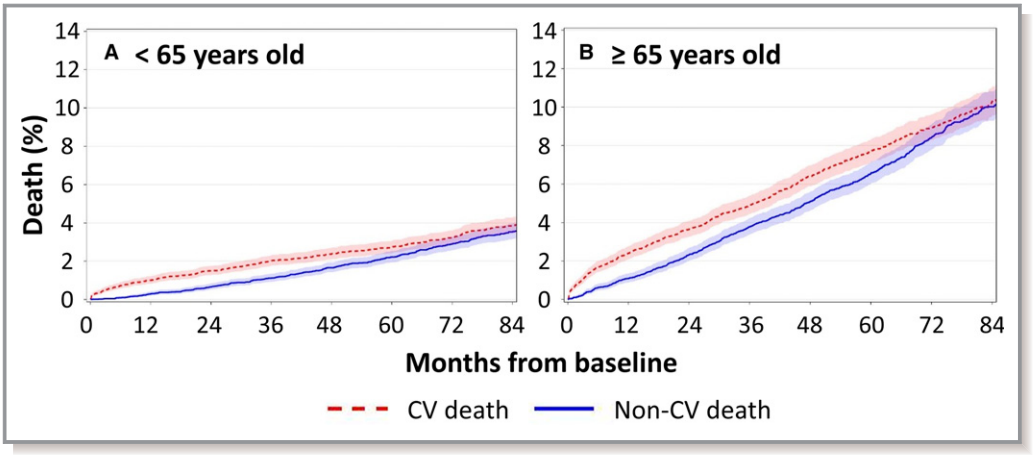


Figure 3. Cumulative incidence of cardiovascular and noncardiovascular death for patients (A) <65 years old and (B) ≥65 years old. Seven-year Kaplan–Meier mortality rates: cardiovascular death: <65 years old, 3.4%; ≥65, 9.1%; noncardiovascular death: <65, 3.2%; ≥65, 8.6%). CV indicates cardiovascular.

patients, 259 (6.6%, 95% CI, 5.8–7.4%) died of cardiovascular causes over the 7-year follow-up and 247 (6.5%, 95% CI, 5.7–7.4%) died of noncardiovascular causes. In both groups, the most common cause of cardiovascular death was death caused by coronary heart disease, and the most common specific cause of noncardiovascular death was malignancy (Table S2). Male patients had a higher cumulative incidence of cardiovascular death than noncardiovascular death over the entirety of follow-up; whereas among female patients, the cumulative incidence of noncardiovascular death equaled that of cardiovascular death after 6 years of follow-up (Figure S6).

Discussion

In this analysis of IMPROVE-IT, we demonstrate that, among patients stabilized after ACS, the relative contributions of cardiovascular and noncardiovascular death to overall mortality over long-term follow-up differ by type of presenting diagnosis. Although older patients were 3-fold more likely than younger patients to die of either cardiovascular or noncardiovascular causes over the duration of follow-up, the relative contributions of cardiovascular and noncardiovascular death were not affected by age. Similarly, both men and women were more likely to die of cardiovascular causes over the entirety of follow-up. By contrast, patients with UA/NSTEMI were more likely to die of cardiovascular versus noncardiovascular causes for the entirety of follow-up; however, in patients with STEMI, cardiovascular death was more common than noncardiovascular death only for ~4 years, after which noncardiovascular death predominated. The sensitivity analyses suggest that the larger contribution of cardiovascular death to mortality in patients with NSTEMI was not because of trial inclusion parameters or differential follow-up length specific to IMPROVE-IT, but rather because of patient factors.

In IMPROVE-IT, patients presenting with STEMI had higher mortality than those presenting with UA/NSTEMI for the first month, after which mortality rates in those with UA/NSTEMI were higher. This crossover is similar to what has been shown elsewhere, where patients with STEMI have higher in-hospital and short-term all-cause mortality rates than those with UA/NSTEMI; but over longer-term follow-up, cumulative mortality for patients with UA/NSTEMI catches up with or surpasses that of STEMI patients.[8,9,13,23,24] Our finding of that crossover occurring within 1 month is earlier than has been shown in other studies, and likely reflects the enrollment criteria of stabilization required before randomization. Long-term higher cardiovascular and noncardiovascular mortality among UA/NSTEMI patients has been attributed to a higher baseline prevalence of multiple comorbidities, including multivessel coronary artery disease, heart failure, diabetes mellitus, chronic kidney disease, and chronic lung disease, a finding we also demonstrated in patients in IMPROVE-IT.[1,2,5,7,9,10] Thus, it is important for clinicians and patients to understand that patients with UA/NSTEMI remain at higher risk for cardiovascular than noncardiovascular death over long-term follow-up, and that care of their multiple comorbidities should be targeted appropriately. Moreover, despite numerous pharmacologic, interventional, and surgical improvements, long-term cardiovascular mortality following NSTEMI remains high.

In IMPROVE-IT, patients with UA/NSTEMI had a higher cumulative incidence of cardiovascular death than noncardiovascular death throughout the follow-up period. By contrast, for patients with STEMI, the cumulative incidence of cardiovascular death was higher than noncardiovascular death for the first 4 years, after which noncardiovascular death predominated. These findings are similar to those seen in an analysis of a registry of Japanese patients undergoing

primary PCI: when patients with death within 6 months after PCI were excluded, the cumulative incidence of noncardiovascular death was greater than that of cardiovascular death after 2 to 3 years.[25] We demonstrated, through our sensitivity analyses, that the likeliest explanation for these findings is that UA/NSTEMI patients' cardiovascular comorbidities were more extensive than those of STEMI patients, and continued to outweigh noncardiovascular comorbidities throughout follow-up. The sensitivity analysis limited to patients enrolled while the trial was enrolling both STEMI and UA/NSTEMI patients was similar to the primary analysis, suggesting that differential follow-up does not explain our findings. The second sensitivity analysis, limited to patients with positive cardiac biomarkers, controlled for differences in enrollment criteria between the STEMI and UA/NSTEMI cohorts of IMPROVE-IT. IMPROVE-IT limited enrollment of patients with UA/NSTEMI to those with positive cardiac biomarkers (ie, patients with NSTEMI) or UA with comorbidities that increase the likelihood of cardiovascular death.[26–28] This analysis was also similar to the primary analysis, suggesting that IMPROVE-IT's differential inclusion criteria did not drive our results. Thus, the relative impact of noncardiovascular death on event rates will vary both over time and by presenting diagnosis. Although death rates were higher in older adults, there was no difference in the relative incidence of cardiovascular compared with noncardiovascular death in older and younger adults.

Understanding the relative incidence of cardiovascular and noncardiovascular death has important implications for clinical trial design. Most clinical trials in cardiovascular disease utilize Kaplan–Meier or Cox proportional hazards analyses to compare rates of composite end points, usually including cardiovascular mortality, between treatment arms.[20,29,30] Noncardiovascular death acts as a competing risk, as patients who die are unable to subsequently experience a cardiovascular end point. Assuming that neither treatment arm has an effect on noncardiovascular mortality, failure to account for noncardiovascular death is unlikely to affect the point estimate for the treatment effect.[31,32] However, whether using traditional or a competing events framework, noncardiovascular deaths will reduce statistical power to identify a difference between groups as patients experiencing noncardiovascular death are censored at the time of death. This requires the recruitment of more patients or longer-term follow-up to accrue sufficient events. For trials that use all-cause mortality as an end point, a treatment targeted to a cardiovascular pathway should have no effect on noncardiovascular death, and noncardiovascular deaths will not add to the power to identify a difference between groups. Indeed, if 1 group has a lower proportion of cardiovascular deaths than a comparator because of treatment efficacy, but a higher proportion of noncardiovascular deaths by random chance, then using all-cause mortality as a component of the primary end point may obscure the true treatment effect. Though we found that the cumulative incidence of composite primary outcome events remains substantially higher than that of noncardiovascular death over the entirety of follow-up in all groups studied, our findings suggest that following patients with STEMI past 4 years may yield diminishing returns as noncardiovascular deaths accrue faster than cardiovascular deaths, but that patients with UA/NSTEMI will continue to accrue cardiovascular deaths faster than noncardiovascular deaths for at least 7 years after their initial event. By contrast, neither sex nor older age appeared to have any effect on the relative incidence of cardiovascular compared with noncardiovascular death, though patients >65 years old had a 3-fold higher incidence of both cardiovascular and noncardiovascular mortality. Any statistical power lost from noncardiovascular death among patients >65 years old should be offset by a higher rate of cardiovascular death in this population.

Limitations

In sensitivity analysis, we did not find that our results were impacted by trial inclusion parameters or differential follow-up length in different subgroups. However, patient populations that enroll in clinical trials are different from those that do not,[33,34] and our findings regarding the relative risk of cardiovascular and noncardiovascular death for patients enrolled in IMPROVE-IT may not apply more generally to the broader population with ACS. Furthermore, IMPROVE-IT enrolled patients following discharge after an index ACS presentation, and these stabilized patients are likely to differ substantially from the full population of patients admitted to the hospital with ACS. However, our results were broadly consistent with a similar analysis performed in a registry population, but mortality rates were lower.[25] Regardless, our findings are applicable to the population of stabilized ACS patients likely to be enrolled in clinical trials, and thus provide important information to guide design of future clinical trials.

Conclusion

In this analysis of IMPROVE-IT, we demonstrate that, among patients stabilized after ACS, the relative contribution of cardiovascular and noncardiovascular death to overall mortality varies depending on type of ACS presentation and duration elapsed since the index event, but not depending on age at presentation. Noncardiovascular death competes with cardiovascular outcomes, effectively reducing sample size. Efficient design of long-term cardiovascular outcome trials requires that sample size and power calculations include careful consideration of the competing risks of cardiovascular and noncardiovascular deaths when determining the desired

proportions of patients with STEMI versus UA/NSTEMI. Our analysis specifically informs these considerations, and thus should be valuable and informative for future post-ACS clinical trial design.

Sources of Funding

The IMPROVE-IT trial was supported by Merck & Co., Inc. Fanaroff is supported by NIH grant 5T32HL069749-13 and American Heart Association grant 17FTF33661087. Navar is supported by NHLBI grant K01HL133416.

Disclosures

Fanaroff reports research funding through DCRI from Gilead Sciences. Roe reports research support from AstraZeneca, Eli Lilly & Co., Janssen Pharmaceuticals, Sanofi-Aventis, Daiichi-Sankyo, Familial Hypercholesterolemia Foundation, Ferring Pharmaceuticals; educational activities for Amgen and Bristol-Myers Squibb; and consulting for Eli Lilly & Co, Daiichi-Sankyo, Elsevier Publishers, Boehringer-Ingelheim, PriMed, Myokardia, AstraZeneca, Merck & Co, and Amgen. Navar reports research support from Amgen, Regeneron and Sanofi; and consulting for Amgen and Sanofi. Giugliano reports executive committee membership for the FOURIER and EBBINGHAUS studies, supported by a research grant from Amgen; research grant support to the Brigham and Women's Hospital from Amgen and Merck; honoraria for CME lectures and/or consulting from Amgen, Daiichi-Sankyo, and Merck; and honoraria for CME lectures and/or consulting from the American College of Cardiology, Bristol-Myers Squibb, CVS Caremark, and Pfizer. Wiviott reports grant support from Merck and Sanofi-Aventis; grant support and personal fees from AstraZeneca, Bristol-Myers Squibb, Eisai, Arena, and Eli Lilly/Daiichi-Sankyo; personal fees from Aegerion, Angelmed, Janssen, Xoma, ICON Clinical, and Boston Clinical Research Institute outside the submitted work. Tershakovec reports employment by & ownership interest in Merck & Co., Inc. Braunwald reports membership of the TIMI Study Group, which has received research grant support from Amgen, Bristol-Myers Squibb, and Merck to conduct clinical trials related to lipid therapy; grant support from GlaxoSmithKline, Bristol-Myers Squibb, Duke University, AstraZeneca, and Johnson & Johnson; grant support and personal fees from Daiichi-Sankyo and Sanofi Aventis; personal fees from The Medicines Company, Menarini International, Bayer, and Medscape; and other support from Novartis. Blazing reports research support from Merck & Co and Sanofi-Aventis; educational activities for Amgen, Inc. and AstraZeneca; and consulting for Amgen, AstraZeneca, Pfizer; Merck & Co., Novartis Pharmaceutical Company, and Sanofi-Aventis. Others: The remaining authors have nothing to disclose.

References

1. Steg PG, Goldberg RJ, Gore JM, Fox KA, Eagle KA, Flather MD, Sadiq I, Kasper R, Rushton-Mellor SK, Anderson FA. Baseline characteristics, management practices, and in-hospital outcomes of patients hospitalized with acute coronary syndromes in the Global Registry of Acute Coronary Events (GRACE). *Am J Cardiol*. 2002;90:358–363.
2. Enriquez JR, de Lemos JA, Parikh SV, Peng SA, Spertus JA, Holper EM, Roe MT, Rohatgi A, Das SR. Association of chronic lung disease with treatments and outcomes patients with acute myocardial infarction. *Am Heart J*. 2013;165:43–49.
3. Montalescot G, Dallongeville J, Van Belle E, Rouanet S, Baulac C, Degrandsart A, Vicaut E. STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial infarction as defined by the ESC/ACC definition (the OPERA registry). *Eur Heart J*. 2007;28:1409–1417.
4. Shroff GR, Frederick PD, Herzog CA. Renal failure and acute myocardial infarction: clinical characteristics in patients with advanced chronic kidney disease, on dialysis, and without chronic kidney disease. A collaborative project of the United States Renal Data System/National Institutes of Health and the National Registry of Myocardial Infarction. *Am Heart J*. 2012;163:399–406.
5. Fox CS, Muntner P, Chen AY, Alexander KP, Roe MT, Cannon CP, Saucedo JF, Kontos MC, Wiviott SD. Use of evidence-based therapies in short-term outcomes of ST-segment elevation myocardial infarction and non-ST-segment elevation myocardial infarction in patients with chronic kidney disease a report from the National Cardiovascular Data Acute Coronary Treatment and Intervention Outcomes Network Registry. *Circulation*. 2010;121:357–365.
6. García-García C, Subirana I, Sala J, Bruguera J, Sanz G, Valle V, Arós F, Fiol M, Molina L, Serra J. Long-term prognosis of first myocardial infarction according to the electrocardiographic pattern (ST elevation myocardial infarction, non-ST elevation myocardial infarction and non-classified myocardial infarction) and revascularization procedures. *Am J Cardiol*. 2011;108:1061–1067.
7. Polonski L, Gasior M, Gierlotka M, Osadnik T, Kalarus Z, Trusz-Gluza M, Zembala M, Wilczek K, Lekston A, Zdrojewski T. A comparison of ST elevation versus non-ST elevation myocardial infarction outcomes in a large registry database: are non-ST myocardial infarctions associated with worse long-term prognoses? *Int J Cardiol*. 2011;152:70–77.
8. Chan MY, Sun JL, Newby LK, Shaw LK, Lin M, Peterson ED, Califf RM, Kong DF, Roe MT. Long-term mortality of patients undergoing cardiac catheterization for ST-elevation and non-ST-elevation myocardial infarction. *Circulation*. 2009;119:3110–3117.
9. Abbott JD, Ahmed HN, Vlachos HA, Selzer F, Williams DO. Comparison of outcome in patients with ST-elevation versus non-ST-elevation acute myocardial infarction treated with percutaneous coronary intervention (from the National Heart, Lung, and Blood Institute Dynamic Registry). *Am J Cardiol*. 2007;100:190–195.
10. Allen LA, O'Donnell CJ, Camargo CA, Giugliano RP, Lloyd-Jones DM. Comparison of long-term mortality across the spectrum of acute coronary syndromes. *Am Heart J*. 2006;151:1065–1071.
11. Terkelsen CJ, Lassen JF, Nørgaard BL, Gerdes JC, Jensen T, Gøtzsche LBH, Nielsen TT, Andersen HR. Mortality rates in patients with ST-elevation vs. non-ST-elevation acute myocardial infarction: observations from an unselected cohort. *Eur Heart J*. 2005;26:18–26.
12. Agarwal SK, Singla I, Hreybe H, Saba S. Clinical predictors of late death in survivors of acute myocardial infarction. *Tex Heart Inst J*. 2009;36:24–30.
13. Vora AN, Wang TY, Hellkamp AS, Thomas L, Henry TD, Goyal A, Roe MT. Differences in short-and long-term outcomes among older patients with ST-elevation verses non-ST-elevation myocardial infarction with angiographically proven coronary artery disease. *Circ Cardiovasc Qual Outcomes*. 2016;9:513–522.
14. Cox DA, Stone GW, Grines CL, Stuckey T, Zimetbaum PJ, Tcheng JE, Turco M, Garcia E, Guagliumi G, Iwaoka RS. Comparative early and late outcomes after primary percutaneous coronary intervention in ST-segment elevation and non-ST-segment elevation acute myocardial infarction (from the CADILLAC trial). *Am J Cardiol*. 2006;98:331–337.
15. Aguirre FV, Younis LT, Chaitman BR, Ross AM, McMahon RP, Kern MJ, Berger PB, Sopko G, Rogers WJ, Shaw L. Early and 1-year clinical outcome of patients' evolving non-Q-wave versus Q-wave myocardial infarction after thrombolysis results from the TIMI II study. *Circulation*. 1995;91:2541–2548.
16. Goodman SG, Langer A, Ross AM, Wildermann NM, Barbagelata A, Sgarbossa EB, Wagner GS, Granger CB, Califf RM, Topol EJ. Non-Q-wave versus Q-wave myocardial infarction after thrombolytic therapy angiographic and prognostic insights from the global utilization of streptokinase and tissue plasminogen activator for occluded coronary arteries-I angiographic substudy. *Circulation*. 1998;97:444–450.
17. Maki E. Power and sample size considerations in clinical trials with competing risk endpoints. *Pharm Stat*. 2006;5:159–171.

18. Berry SD, Ngo L, Samelson EJ, Kiel DP. Competing risk of death: an important consideration in studies of older adults. *J Am Geriatr Soc*. 2010;58:783–787.
19. Cannon CP, Giugliano RP, Blazing MA, Harrington RA, Peterson JL, Sisk CM, Strony J, Musliner TA, McCabe CH, Veltri E. Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimbe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes. *Am Heart J*. 2008;156:826–832.
20. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397.
21. Blazing MA, Giugliano RP, Cannon CP, Musliner TA, Tershakovec AM, White JA, Reist C, McCagg A, Braunwald E, Califf RM. Evaluating cardiovascular event reduction with ezetimibe as an adjunct to simvastatin in 18 144 patients after acute coronary syndromes: final baseline characteristics of the IMPROVE-IT study population. *Am Heart J*. 2014;168:205–212.e1.
22. Lunn M, McNeil D. Applying Cox regression to competing risks. *Biometrics*. 1995;51:524–532.
23. Armstrong PW, Fu Y, Chang WC, Topol EJ, Granger CB, Betriu A, Van de Werf F, Lee KL, Califf RM. Acute coronary syndromes in the GUSTO-IIb trial: prognostic insights and impact of recurrent ischemia. *Circulation*. 1998;98:1860–1868.
24. Yan AT, Tan M, Fitchett D, Chow CM, Fowlis RA, McAvinue TG, Roe MT, Peterson ED, Tu JV, Langer A. One-year outcome of patients after acute coronary syndromes (from the Canadian Acute Coronary Syndromes Registry). *Am J Cardiol*. 2004;94:25–29.
25. Yamashita Y, Shiomi H, Morimoto T, Yaku H, Furukawa Y, Nakagawa Y, Ando K, Kadota K, Abe M, Nagao K, Shizuta S, Ono K, Kimura T; CREDO-Kyoto AMI Registry Investigators. Cardiac and noncardiac causes of long-term mortality in ST-segment-elevation acute myocardial infarction patients who underwent primary percutaneous coronary intervention. *Circ Cardiovasc Qual Outcomes*. 2017;10: e002790.
26. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, Browner D. Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med*. 1992;326:381–386.
27. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA*. 2002;287:2570–2581.
28. Califf R, Armstrong P, Carver J, D'agostino R, Strauss W. 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary disease events. Task Force 5. Stratification of patients into high, medium and low risk subgroups for purposes of risk factor management. *J Am Coll Cardiol*. 1996;27:1007–1019.
29. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001–2015.
30. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.
31. Prentice RL, Kalbfleisch JD, Peterson AV Jr, Flournoy N, Farewell V, Breslow N. The analysis of failure times in the presence of competing risks. *Biometrics*. 1978;34:541–554.
32. Haneuse S, Lee KH. Semi-competing risks data analysis accounting for death as a competing risk when the outcome of interest is nonterminal. *Circ Cardiovasc Qual Outcomes*. 2016;9:322–331.
33. Martin SS, Ou FS, Newby LK, Sutton V, Adams P, Felker GM, Wang TY. Patient- and trial-specific barriers to participation in cardiovascular randomized clinical trials. *J Am Coll Cardiol*. 2013;61:762–769.
34. Hutchinson-Jaffe AB, Goodman SG, Yan RT, Wald R, Elbarouni B, Rose B, Eagle KA, Lai CC, Baer C, Langer A. Comparison of baseline characteristics, management and outcome of patients with non-ST-segment elevation acute coronary syndrome in versus not in clinical trials. *Am J Cardiol*. 2010;106:1389–1396.

SUPPLEMENTAL MATERIAL

Table S1. Baseline characteristics by sex

	Overall (N=18,144)	Sex		
		Male (N=13,728)	Female (N=4416)	P value
Demographic characteristics				
Age, yrs	63 (56, 71)	62 (56, 70)	65 (58, 73)	< 0.001
White	15,202 (83.8%)	11,615 (84.6%)	3587 (81.2%)	< 0.001
Body mass index, kg/m^2	28 (25, 31)	28 (25,31)	28 (24, 32)	0.10
Prior medical history				
History of hypertension	11,137 (61.4%)	8044 (58.6%)	3093 (70.1%)	< 0.001
History of diabetes	4933 (27.2%)	3526 (25.7%)	1407 (31.9%)	< 0.001
Prior CHF	790 (4.4%)	552 (4.0%)	238 (5.4%)	< 0.001
Prior atrial fibrillation	948 (5.2%)	700 (5.1%)	248 (5.6%)	0.18
Previous PAD	1005 (5.5%)	737 (5.4%)	268 (6.1%)	0.08
Prior PCI	3562 (19.6%)	2830 (20.6%)	732 (16.6%)	< 0.001
Prior CABG	1684 (9.3%)	1385 (10.1%)	299 (6.8%)	< 0.001
History of angina	7449 (41.1%)	5585 (40.7%)	1864 (42.3%)	< 0.001
Prior multivessel CAD	2706 (15.4%)	2168 (16.4%)	538 (12.5%)	< 0.001
Previous MI	3806 (21.0%)	3051 (22.3%)	755 (17.1%)	< 0.001
History of stroke	682 (3.8%)	486 (3.5%)	196 (4.4%)	0.006
Current smoker	5978 (33.0%)	4688 (34.2%)	1290 (29.2%)	< 0.001
Details of qualifying event				
STEMI	5190 (28.6%)	4154 (30.3%)	1036 (23.5%)	< 0.001
NSTEMI	8555 (47.2)	6419 (46.8%)	2136 (48.4%)	0.06
UA	4386 (24.2%)	3147 (22.9%)	1239 (28.1%)	< 0.001
Killip class				< 0.001
1	13,077 (72.3%)	10,004 (73.0%)	3073 (69.9%)	
2	1114 (6.2%)	792 (5.8%)	322 (7.3%)	
3	301 (1.7%)	216 (1.6%)	85 (1.9%)	
4	126 (0.4%)	89 (0.6%)	37 (0.8%)	
Unknown	3474 (19.2%	2597 (19.0%)	877 (20.0%)	
Creatinine clearance	85 (66, 107)	88 (69, 110)	74 (56, 95)	< 0.001

	Overall (N=18,144)	Sex		
		Male (N=13,728)	Female (N=4416)	P value
Treatment for qualifying event				
PCI during index hospitalization	12,641 (69.7%)	9934 (72.4%)	2707 (61.3%)	< 0.001
CABG within 30 days of randomization	167 (0.9%)	141 (1.0%)	26 (0.6%)	0.008
Concomitant medications at randomization				
Asprin	17,898 (98.7%)	13,568 (98.9%)	4330 (98.2%)	< 0.001
Beta-blocker	16,672 (91.9%)	12,644 (92.1%)	4028 (91.3%)	0.07
$P2Y_{12}$ inhibitor	16,455 (90.8%)	12,605 (91.9%)	3850 (87.3%)	< 0.001
ACE inhibitor	12,743 (70.3%)	9820 (71.6%)	2923 (66.3%)	< 0.001
Nitrates	13,418 (74.0%)	10,119 (73.8%)	3299 (74.8%)	0.18

Continuous data presented as median (25^{th}, 75^{th} percentile); categorical data presented as count (percentage).

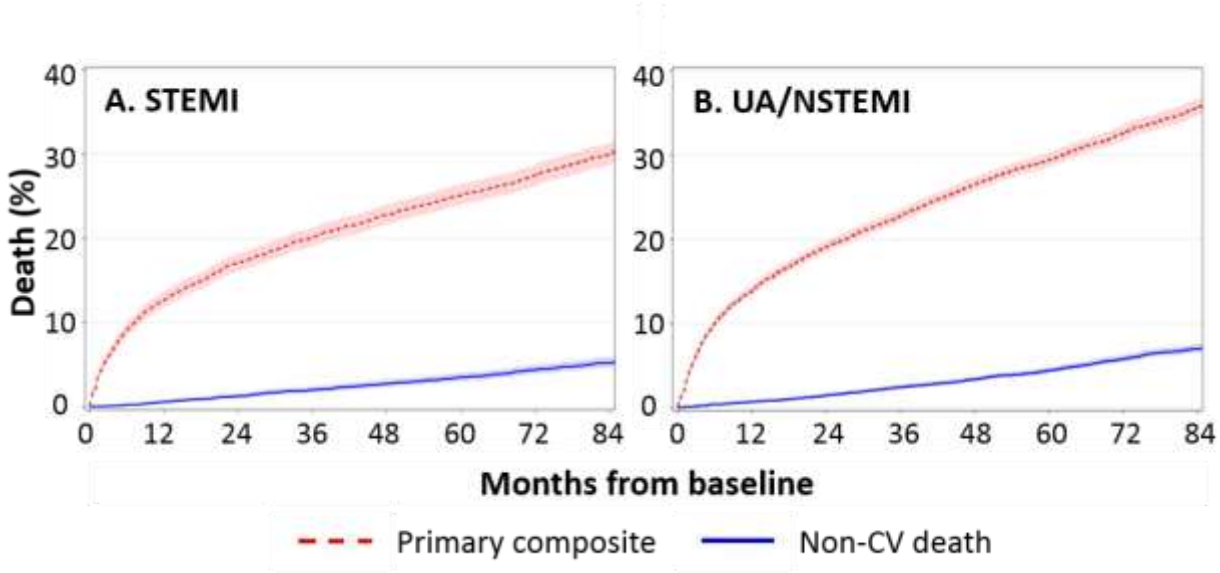
STEMI, ST segment elevation myocardial infarction; NSTEMI, non-STEMI; UA, unstable angina; CHF, congestive heart failure; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; ACE, angiotensin-converting enzyme.

Table S2. Causes of death for patients with STEMI, UA/NSTEMI, < 65 years old, ≥ 65 years old, male, and female

	ACS Type		Age		Sex	
	STEMI (N=5190)	**UA/NSTEMI (N=12,941)**	**< 65 years (N=10,173)**	**≥ 65 years (N=7971)**	**Male (N = 13,728)**	**Female (N = 4,416)**
CV death						
Coronary heart disease	232 (4.5%)	842 (6.5%)	350 (3.4%)	725 (9.1%)	816 (5.9%)	259 (5.9%)
Acute MI	195 (3.8%)	705 (5.5%)	311 (3.1%)	590 (7.4%)	691 (5.0%)	210 (4.8%)
Sudden death	35 (0.7%)	84 (0.7%)	50 (0.5%)	69 (0.9%)	89 (0.7%)	30 (0.7%)
Non-sudden death	96 (1.9%)	305 (2.4%)	158 (1.6%)	244 (3.1%)	315 (2.3%)	87 (2.0%)
Unwitnessed death	31 (0.7%)	224 (1.7%)	51 (0.5%)	204 (2.6%)	197 (1.4%)	58 (1.3%)
Procedural death	29 (0.6%)	66 (0.5%)	39 (0.4%)	56 (0.7%)	67 (0.5%)	28 (0.6%)
Atherosclerotic vascular disease	4 (0.1%)	26 (0.2%)	13 (0.1%)	17 (0.2%)	23 (0.2%)	7 (0.2%)
Cerebrovascular disease	30 (0.6%)	104 (0.8%)	29 (0.3%)	105 (1.3%)	97 (0.7%)	37 (0.8%)
Other atherosclerotic disease	25 (0.5%)	78 (0.6%)	23 (0.2%)	80 (1.0%)	76 (0.6%)	27 (0.6%)
Other cardiovascular disease	5 (0.1%)	26 (0.2%)	6 (0.1%)	25 (0.3%)	21 (0.2%)	10 (0.2%)
Non-CV death	7 (0.1%)	33 (0.3%)	10 (0.1%)	30 (0.4%)	28 (0.2%)	12 (0.3%)
Accidental	275 (5.3%)	730 (5.6%)	321 (3.2%)	685 (8.6%)	759 (5.5%)	247 (5.6%)
Diabetes	6 (0.1%)	28 (0.2%)	14 (0.1%)	20 (0.3%)	28 (0.2%)	6 (0.1 %)
Malignancy	0 (0%)	1 (0.01%)	0 (0%)	1 (0.01%)	1 (0.01%)	0 (0%)
Renal	163 (3.1%)	389 (3.0%)	210 (2.1%)	342 (4.3%)	442 (3.2%)	110 (2.5%)
Suicide	5 (0.1%)	19 (0.2%)	6 (0.1%)	18 (0.2%)	14 (0.1%)	10 (0.2%)
Other	2 (0.04%)	7 (0.1%)	5 (0.1%)	4 (0.1%)	8 (0.1%)	1 (0.02%)
Unknown cause	99 (1.9%)	286 (2.2%)	86 (0.9%)	300 (3.8%)	266 (1.9%)	120 (2.7%)

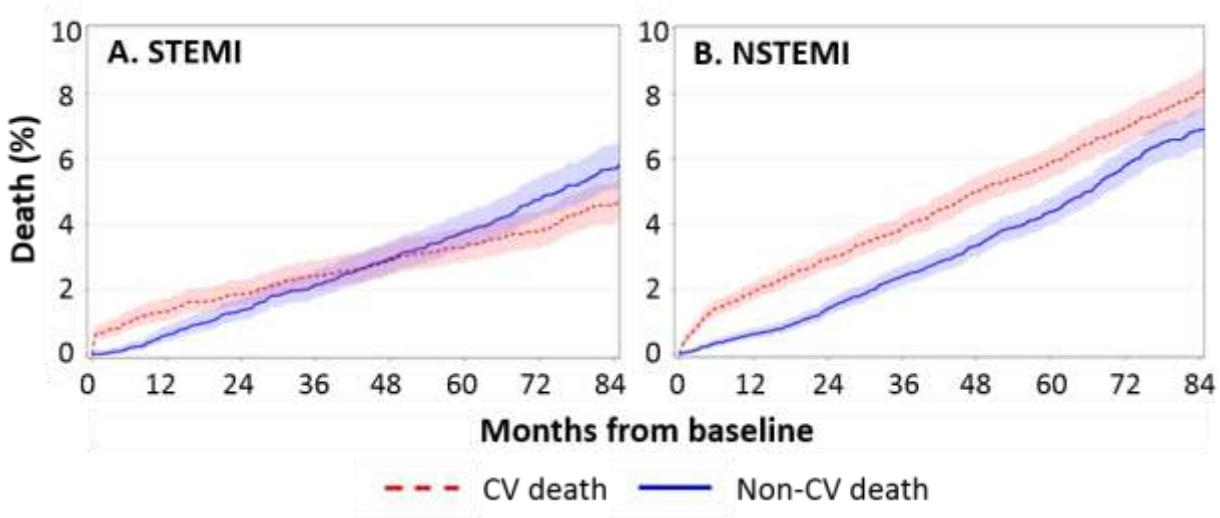
CV, cardiovascular; MI, myocardial infarction. Sudden death defined as unexpected death in which the time is known, with or without preceding angina symptoms. Non-sudden coronary heart disease death defined as death occurring in a patient with cardiovascular symptoms and gradual deterioration prior to death. Unwitnessed death defined as unexpected death with unknown time or alternative cause of death. Procedural death was adjudicated when a patient died within 7 days or during the same hospitalization as cardiac surgery, percutaneous intervention, or angiography. Cerebrovascular death defined as death occurring secondary to stroke, intracranial hemorrhage, or peri-cerebrovascular procedure. Other atherosclerotic disease death defined as death secondary to aortic, mesenteric, renal, or peripheral vascular disease, or procedures related to these vascular beds. Other cardiovascular disease death included death due to endocarditis, valvular heart disease, or endocarditis. Non-cardiovascular causes were not strictly defined; other non-cardiovascular death required a cause of death to be specified. If cause of death was not known, it was adjudicated as unknown.

Figure S1. Cumulative incidence of the primary composite outcome and non-CV death for patients with A) STEMI and B) UA/NSTEMI



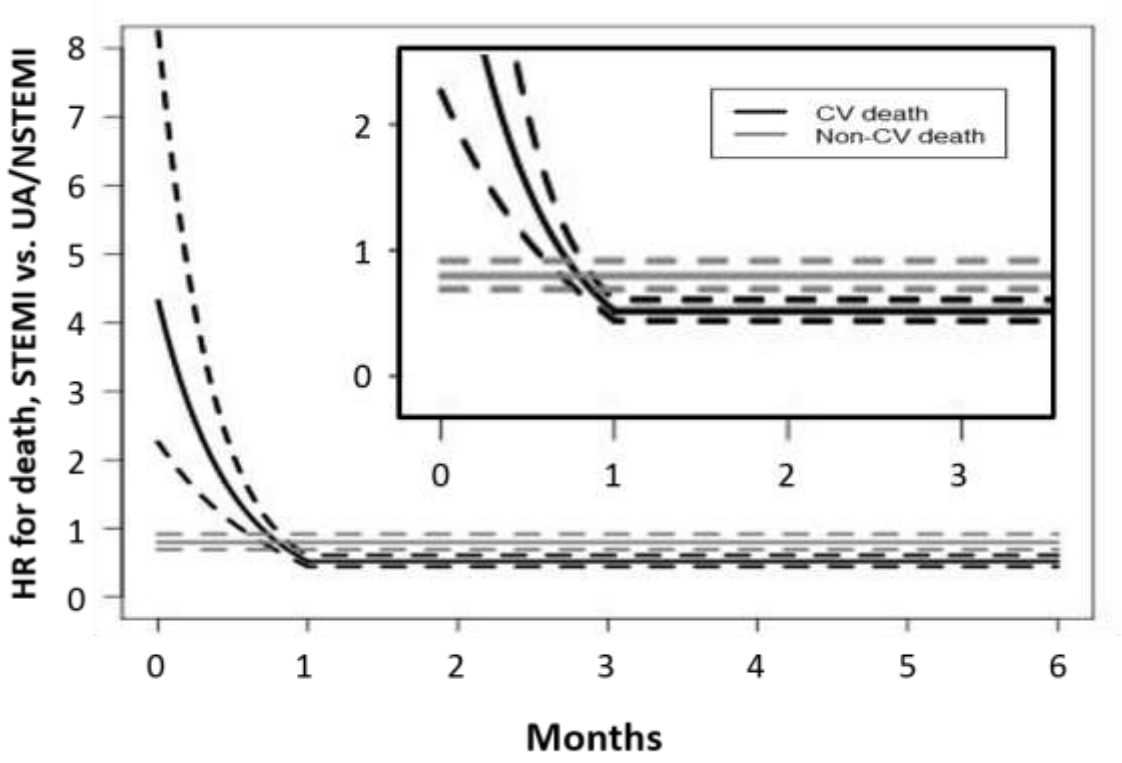
Shading around each curve represents the 95% confidence interval

Figure S2. Cumulative incidence of CV and non-CV death for patients > 50 years old with A) STEMI and B) NSTEMI



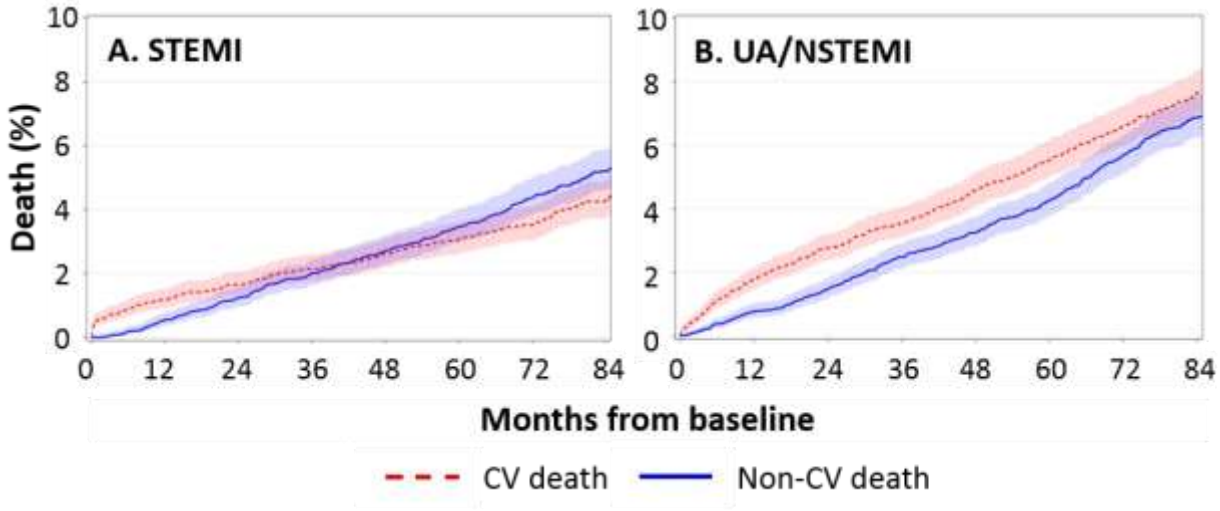
Shading around each curve represents the 95% confidence interval

Figure S3. Hazard ratio for death over time for STEMI compared to NSTEMI among patients > 50 years old



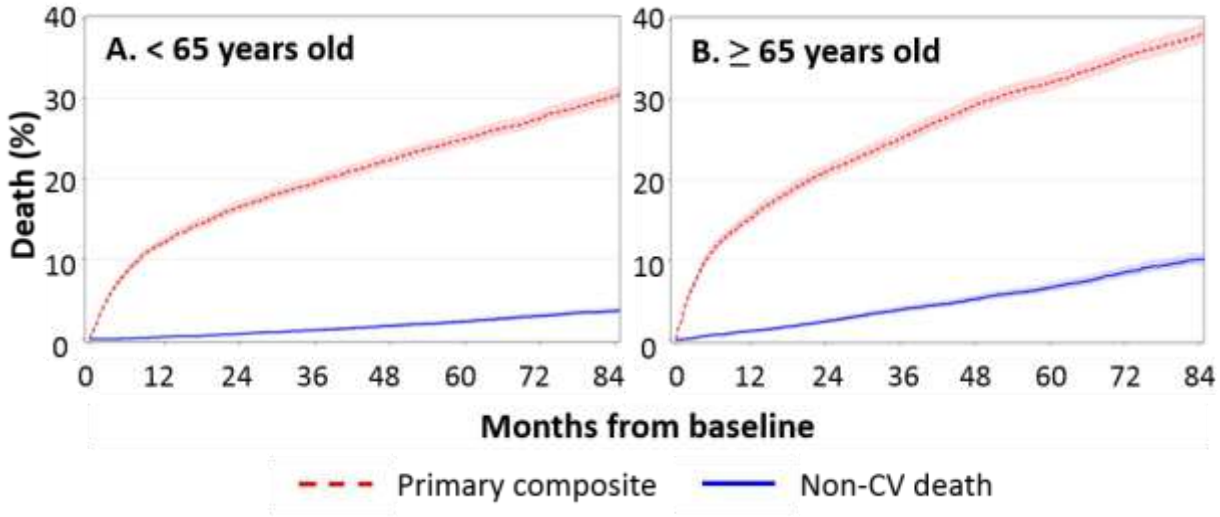
HR curves are truncated at 6 months, but HRs for CV and non-CV death remained constant through the end of follow-up.

Figure S4. Cumulative incidence of CV and non-CV death for patients with A) STEMI and B) UA/NSTEMI enrolled before April 1, 2008



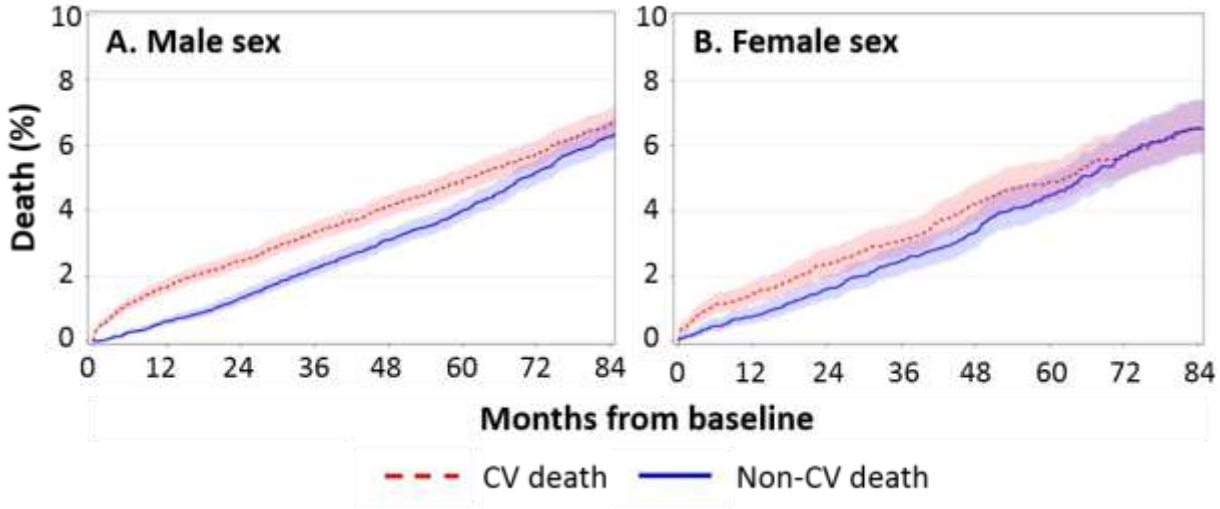
Shading around each curve represents the 95% confidence interval

Figure S5. Cumulative incidence of the primary composite outcome and non-CV death for patients with A) < 65 years old and B) ≥ 65 years old



Shading around each curve represents the 95% confidence interval

Figure S6. Cumulative incidence of CV and non-CV death for A) male and B) female patients



Shading around each curve represents the 95% confidence interval