ORIGINAL RESEARCH

Cardiovascular Events and Long-Term Risk of Sudden Death Among Stabilized Patients After Acute Coronary Syndrome: Insights From IMPROVE-IT

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BACKGROUND: Unlike patients with low ejection fraction after an acute coronary syndrome (ACS), little is known about the long-term incidence and influence of cardiovascular events before sudden death among stabilized patients after ACS.

METHODS AND RESULTS: A total of 18 144 patients stabilized within 10 days after ACS in IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) were studied. Cumulative incidence rates (IRs) and IRs per 100 patient-years of sudden death were calculated. Using Cox proportional hazards, the association of ≥1 additional postrandomization cardiovascular events (myocardial infarction, stroke, and hospitalization for unstable angina or heart failure) with sudden death was examined. Early (≤1 year after ACS) and late sudden deaths (>1 year) were compared. Of 2446 total deaths, 402 (16%) were sudden. The median time to sudden death was 2.7 years, with 109 early and 293 late sudden deaths. The cumulative IR was 2.47% (95% CI, 2.23%–2.73%) at 7 years of follow-up. The risk of sudden death following a postrandomization cardiovascular event (150/402 [37%] sudden deaths; median 1.4 years) was greater (IR/100 patient-years, 1.45 [95% CI, 1.23–1.69]) than the risk with no postrandomization cardiovascular event (IR/100 patient-years, 0.27 [95% CI, 0.24–0.30]). Postrandomization myocardial infarction (hazard ratio [HR], 3.64 [95% CI, 2.85–4.66]) and heart failure (HR, 4.55 [95% CI, 3.33–6.22]) significantly increased future risk of sudden death.

CONCLUSIONS: Patients stabilized within 10 days of an ACS remain at long-term risk of sudden death with the greatest risk in those with an additional cardiovascular event. These results refine the long-term risk and risk effectors of sudden death, which may help clinicians identify opportunities to improve care.

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Key Words: long-term outcomes ■ myocardial infarction ■ sudden death

Sudden death is a devastating and unpredictable event that can occur following acute myocardial infarction (MI). It is well known that patients with low ejection fraction or heart failure (HF) following MI are at particularly high risk for sudden death.[1,2] As such, it is a Class I indication to implant an intracardiac defibrillator to reduce sudden death of presumed cardiac etiology for patients with MI complicated by persistent (>3 months) moderate-to-severe left ventricular dysfunction.[3]

In contrast to patients with low ejection fraction, little is known about the incidence of sudden death following an acute coronary syndrome (ACS) in patients without significant left ventricular dysfunction who now make

CLINICAL PERSPECTIVE

What Is New?

- Using adjudicated end point data from the IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) population with 7 years of follow-up, the data show that stable patients with acute coronary syndrome remain at risk of sudden death with a cumulative incidence of 2.47% during follow-up, with >70% of sudden deaths occurring late (>1 year) following acute coronary syndrome.
- Sudden death in these stabilized patients after acute coronary syndrome was 5 times more frequent after a first postrandomization cardiovascular event, particularly myocardial infarction or hospitalization for heart failure.
- The average time interval from a postrandomization cardiovascular event to sudden death was nearly 1.5 years.

What Are the Clinical Implications?

- These results and the length of time between the postrandomization cardiovascular event and sudden death provide novel insights into the long-term risk of sudden death among stable patients with acute coronary syndrome.
- These results highlight potential opportunities for clinicians to improve outcomes of this vulnerable population, including optimization of medical therapy, more consistent care and provider contact, frequent reassessments of left ventricular function when indicated, remote arrhythmia monitoring for concerning symptoms (ie, implantable loop recorder), and reevaluation for intracardiac defibrillator eligibility.

Nonstandard Abbreviations and Acronyms

IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
IR	incidence rate

up approximately half of all patients with MI.[4] These patients may be treated with aggressive measures, such as lifestyle and optimal medical therapy, but they are not eligible for primary prevention intracardiac defibrillator therapy. Recent studies suggest that after ACS, the long-term risk of major adverse cardiac events and readmission persists after hospital discharge.[5,6] A recent analysis from Sweden demonstrated that the incidence of out-of-hospital cardiac arrest within 90 days after MI was <0.3% and that certain clinical parameters

(male sex, diabetes, estimated glomerular filtration rate <30 mL/min/1.73 m^2, Killip Class ≥II, new-onset atrial fibrillation/flutter) in addition to left ventricular ejection fraction (LVEF) predicted out-of-hospital cardiac arrest and non–out-of-hospital cardiac arrest death better than LVEF alone.[7] However, longer term data are sparse with respect to fully understanding the specific risk of sudden death or the influence of postrandomization cardiovascular events on sudden death in this population. Consequently, guidelines do not offer specific recommendations to provide therapies to prevent sudden death in this prevalent and clinically important group.[8] Understanding the influence of postrandomization cardiovascular events may be helpful in identifying patients at greatest risk of sudden death after ACS.

IMPROVE-IT (Improved Reduction of Outcomes: Vytorin Efficacy International Trial) evaluated the long-term effect of ezetimibe combined with simvastatin compared with simvastatin alone among patients stabilized after ACS.[9] It was hypothesized that these patients remain at long-term risk of sudden death and that postrandomization cardiovascular events may predict sudden death. The specific objectives of this analysis were as follows: (1) describe the long-term risk of sudden death in a population of stabilized patients after ACS, including addressing whether the early risk of sudden death seen among patients with low ejection fraction after ACS also occurred in stabilized patients; (2) determine factors associated with the risk of early versus late sudden death; and (3) evaluate any influence of postrandomization cardiovascular events that occurred before sudden death. Our goal was to improve understanding of the relationship between postrandomization cardiovascular events and both early and late sudden death to refine the risk among stabilized patients after ACS.

METHODS

Data to reproduce the results presented herewith can be made available upon reasonable request.

Data Source

IMPROVE-IT was a double-blind, placebo-controlled randomized trial of stabilized patients after ACS with inclusion criteria of ≥50 years of age and hospitalization with an ACS (MI with or without ST-segment elevation or high-risk unstable angina). Their condition had stabilized during the preceding 10 days as previously described.[9] Between October 26, 2005, and July 8, 2010, a total of 18 144 patients underwent randomization at 1147 sites in 39 countries. Patients were randomized to ezetimibe plus simvastatin or simvastatin plus placebo. The primary composite end point was cardiovascular death, nonfatal MI, unstable angina

Table 1. Baseline Clinical Characteristics of Patients Who Experienced Sudden Death or Other Causes of Death or Were Alive by the End of the Follow-Up

Characteristic	Sudden death (n=402)	Death from other causes (n=2044)	Alive (n=15 698)	P value*
Age, y				
Mean (SD)	69.1 (10.33)	70.7 (10.00)	63.1 (9.33)	0.001
Median (25th, 75th)	69.6 (60.3, 78.1)	71.8 (63.1, 78.2)	62.3 (56.1, 69.7)	
Sex				
Female	87 (2.0)	545 (12.3)	3784 (85.7)	0.036
Male	315 (2.3)	1499 (10.9)	11 914 (86.8)	
Race or ethnicity				
Asian	27 (3.5)	60 (7.8)	686 (88.7)	<0.001
Black	23 (4.6)	71 (14.2)	405 (81.2)	
Spanish descent	26 (3.2)	82 (10.1)	700 (86.6)	
White	303 (2.0)	1713 (11.3)	13 186 (86.7)	
Other	23 (2.7)	116 (13.8)	704 (83.5)	
Weight, kg				
Mean (SD)	82.6 (18.45)	80.1 (17.74)	83.3 (17.29)	0.003
Median (25th, 75th)	81.0 (70.2, 92.0)	78.8 (68.0, 90.0)	81.8 (71.5, 93.0)	
BMI, kg/m^2				
Mean (SD)	28.8 (6.45)	27.7 (5.61)	28.4 (5.12)	<0.001
Median (25th, 75th)	28.0 (24.8, 31.7)	27.0 (24.1, 30.5)	27.6 (25.0, 30.9)	
Diabetes				
No	211 (1.6)	1294 (9.8)	11 697 (88.6)	<0.001
Yes	190 (3.9)	750 (15.2)	3993 (80.9)	
Hypertension				
No	98 (1.4)	591 (8.4)	6309 (90.2)	0.065
Yes	303 (2.7)	1453 (13.0)	9381 (84.2)	
Heart failure				
No	346 (2.0)	1794 (10.3)	15 205 (87.7)	0.421
Yes	55 (7.0)	250 (31.6)	485 (61.4)	
Peripheral artery disease				
No	347 (2.0)	1792 (10.5)	14 990 (87.5)	0.541
Yes	54 (5.4)	252 (25.1)	699 (69.6)	
Current smoker				
No	278 (2.3)	1400 (11.5)	10 476 (86.2)	0.737
Yes	123 (2.1)	642 (10.7)	5213 (87.2)	
Previous MI				
No	254 (1.8)	1420 (9.9)	12 641 (88.3)	0.013
Yes	145 (3.8)	623 (16.4)	3038 (79.8)	
Previous PCI				
No	298 (2.0)	1536 (10.5)	12 734 (87.4)	0.652
Yes	103 (2.9)	507 (14.2)	2952 (82.9)	
Previous CABG				
No	314 (1.9)	1689 (10.3)	14 447 (87.8)	0.042
Yes	87 (5.2)	355 (21.1)	1242 (73.8)	
Creatinine clearance, mL/min				
Mean (SD)	78.4 (37.66)	73.8 (38.44)	91.2 (33.32)	<0.001
Median (25th, 75th)	69.8 (52.2, 95.8)	66.9 (51.2, 88.5)	86.8 (68.7, 108.7)	

(*Continued*)

Table 1. Continued

Characteristic	Sudden death (n=402)	Death from other causes (n=2044)	Alive (n=15 698)	P value*
Qualifying diagnosis				
STEMI	96 (1.8)	494 (9.5)	4600 (88.6)	0.987
NSTEMI	207 (2.4)	1049 (12.3)	7299 (85.3)	
Unstable angina	98 (2.2)	500 (11.4)	3788 (86.4)	
Diagnostic catheterization				
No	90 (4.1)	384 (17.4)	1730 (78.5)	0.100
Yes	311 (2.0)	1658 (10.4)	13 955 (87.6)	
Prerandomization PCI				
No	174 (3.2)	797 (14.7)	4455 (82.1)	0.093
Yes	226 (1.8)	1246 (9.8)	11 234 (88.4)	
LDL cholesterol, mg/dL				
Mean (SD)	89.3 (19.11)	89.7 (20.68)	94.5 (19.88)	0.628
Median (25th, 75th)	91.0 (75.8, 103.0)	89.4 (74.0, 105.0)	96.0 (80.0, 111.0)	
Killip class				
I	254 (1.9)	1308 (10.0)	11 515 (88.1)	0.424
II	55 (4.9)	227 (20.4)	832 (74.7)	
III	20 (4.7)	83 (19.4)	324 (75.9)	
Heart rate, beats/min				
Mean (SD)	71.4 (11.52)	71.0 (12.49)	68.5 (11.21)	0.592
Median (25th, 75th)	70.0 (64.0, 78.0)	70.0 (62.0, 78.0)	68.0 (60.0, 75.0)	
Region				
United States/Canada	130 (1.9)	797 (11.4)	6046 (86.7)	<0.001
Western Europe	144 (2.0)	848 (11.7)	6282 (86.4)	
Eastern Europe	40 (2.8)	128 (9.0)	1248 (88.1)	
Malaysia/Singapore/Hong Kong	24 (3.9)	43 (7.0)	549 (89.1)	
South America	62 (3.9)	209 (13.2)	1314 (82.9)	
Australia/New Zealand	2 (0.7)	19 (6.8)	259 (92.5)	
Treatment				
Simvastatin	207 (2.3)	1024 (11.3)	7846 (86.4)	0.610
Ezetimibe + simvastatin	195 (2.2)	1020 (11.2)	7852 (86.6)	
Statin at qualifying event				
No	211 (1.8)	1237 (10.4)	10 430 (87.8)	0.105
Yes	189 (3.0)	806 (12.9)	5251 (84.1)	
Baseline aspirin				
No	5 (2.1)	46 (19.6)	184 (78.3)	0.203
Yes	396 (2.2)	1998 (11.2)	15 504 (86.6)	
Baseline thienopyridine				
No	57 (3.4)	245 (14.7)	1370 (81.9)	0.223
Yes	344 (2.1)	1799 (10.9)	14 312 (87.0)	
Baseline β-blocker				
No	48 (3.3)	191 (13.1)	1223 (83.7)	0.110
Yes	353 (2.1)	1853 (11.1)	14 466 (86.8)	
Baseline ACE inhibitor or ARB				
No	56 (1.6)	347 (9.7)	3158 (88.7)	0.133
Yes	345 (2.4)	1696 (11.6)	12 529 (86.0)	

Data are presented as number (percentage) unless otherwise indicated.

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; LDL, low-density lipoprotein; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

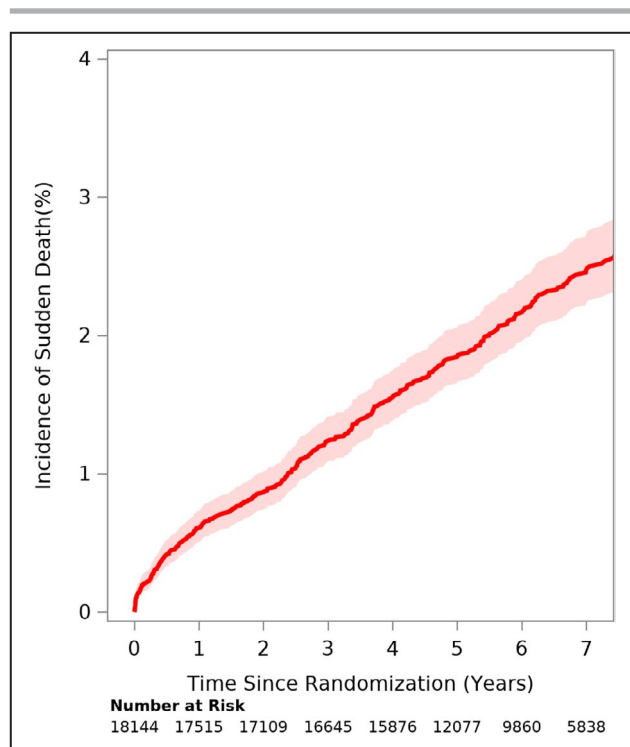*Comparing risk of sudden death vs death from other causes.

Figure 1. Cumulative incidence of sudden death following randomization among patients with stable acute coronary syndrome.

requiring rehospitalization, coronary revascularization (≥30 days after randomization), or nonfatal stroke. The median follow-up was 6 years.

Patients were excluded if they were considered clinically unstable and defined as displaying any of the following events within 24 hours before screening and randomization: (1) hemodynamic instability, including hypotension defined as sustained systolic blood pressure <90 mm Hg attributed to cardiac failure with associated symptoms, unstable or severe pulmonary edema/decompensated HF, acute mitral regurgitation,

or acute ventricular septal defect; (2) recurrent symptoms of cardiac ischemia; (3) stroke or transient ischemic attack; (4) arrhythmic events, including ventricular fibrillation, ventricular tachycardia lasting >30 seconds or in association with symptoms, complete heart block or high-grade, second-degree heart block; and (5) creatinine clearance <30 mL/min or receiving dialysis. Institutional review boards at participating sites approved the protocol and all patients provided written informed consent.

End Points

An independent clinical events committee whose members were unaware of randomized treatment assignment adjudicated primary end point events and all deaths that were classified according to prespecified criteria. The definition of sudden death was death that occurred suddenly and unexpectedly, and methods for the collection and adjudication of sudden death were performed in a manner similar to prior studies.[10,11] Sudden death must have been documented to have occurred within 24 hours. Postrandomization cardiovascular events before sudden death that were also adjudicated included nonfatal MI, unstable angina requiring hospital admission, and stroke. Definitions for each end point, including sudden death, were described previously in the *Clinical Events Committee Manual of Operations*.[9,12] Hospitalization for HF at least 30 days after randomization was determined by the site investigators.[9,12]

Statistical Analysis

The association between baseline clinical characteristics and the risk of sudden death compared with death from other causes was evaluated using Cox regression with the Lunn-McNeil method.[13] To describe the long-term risk of sudden death in a population of stable patients after ACS, a cumulative incidence

Table 2. Cumulative Incidence Rates (Percentages) of Sudden Death

Time from randomization	Cumulative incidence rate (LCL, UCL)	Number of events	Number remaining
0		0	18 144
30 d	0.15 (0.1, 0.22)	27	18 026
6 mo	0.42 (0.33, 0.52)	75	17 720
1 y	0.6 (0.5, 0.73)	109	17 515
2 y	0.86 (0.74, 1.01)	155	17 109
3 y	1.24 (1.09, 1.41)	222	16 645
4 y	1.55 (1.38, 1.74)	277	15 876
5 y	1.84 (1.65, 2.05)	322	12 077
6 y	2.16 (1.95, 2.4)	361	9860
7 y	2.47 (2.23, 2.73)	390	5838
8 y	2.86 (2.53, 3.23)	402	1402

LCL indicates lower confidence limit; and UCL, upper confidence limit.

Table 3. Baseline Clinical Characteristics of Patients Experiencing a Sudden Death by Postrandomization Cardiovascular Event Status

Characteristic	No postrandomization cardiovascular event (n=252)	Postrandomization cardiovascular event (n=150)	All patients (N=402)
Age, y			
Mean (SD)	68.2 (10.68)	70.4 (9.59)	69.1 (10.33)
Median (25th, 75th)	67.6 (59.5, 77.9)	70.6 (63.4, 78.3)	69.6 (60.3, 78.1)
Sex			
Female	56 (64.4)	31 (35.6)	87 (21.6)
Male	196 (62.2)	119 (37.8)	315 (78.4)
Race or ethnicity			
Asian	19 (70.4)	8 (29.6)	27 (6.7)
Black	14 (60.9)	9 (39.1)	23 (5.7)
Spanish descent	16 (61.5)	10 (38.5)	26 (6.5)
White	188 (62.0)	115 (38.0)	303 (75.4)
Other	15 (65.2)	8 (34.8)	23 (5.7)
Weight, kg			
Mean (SD)	82.3 (18.16)	83.1 (18.98)	82.6 (18.45)
Median (25th, 75th)	80.0 (70.2, 92.0)	81.5 (71.0, 92.0)	81.0 (70.2, 92.0)
BMI, kg/m^2			
Mean (SD)	28.8 (6.83)	28.8 (5.80)	28.8 (6.45)
Median (25th, 75th)	28.2 (24.7, 31.7)	27.7 (25.0, 31.6)	28.0 (24.8, 31.7)
Diabetes			
No	145 (68.7)	66 (31.3)	211 (52.6)
Yes	106 (55.8)	84 (44.2)	190 (47.4)
Hypertension			
No	60 (61.2)	38 (38.8)	98 (24.4)
Yes	191 (63.0)	112 (37.0)	303 (75.6)
Heart failure			
No	220 (63.6)	126 (36.4)	346 (86.3)
Yes	31 (56.4)	24 (43.6)	55 (13.7)
Peripheral artery disease			
No	220 (63.4)	127 (36.6)	347 (86.5)
Yes	31 (57.4)	23 (42.6)	54 (13.5)
Current smoker			
No	162 (58.3)	116 (41.7)	278 (69.3)
Yes	89 (72.4)	34 (27.6)	123 (30.7)
Previous MI			
No	170 (66.9)	84 (33.1)	254 (63.7)
Yes	79 (54.5)	66 (45.5)	145 (36.3)
Previous PCI			
No	196 (65.8)	102 (34.2)	298 (74.3)
Yes	55 (53.4)	48 (46.6)	103 (25.7)
Previous CABG			
No	215 (68.5)	99 (31.5)	314 (78.3)
Yes	36 (41.4)	51 (58.6)	87 (21.7)
Creatinine clearance, mL/min			
Mean (SD)	80.7 (41.04)	74.6 (31.05)	78.4 (37.66)
Median (25th, 75th)	71.1 (51.9, 99.0)	68.0 (52.7, 90.6)	69.8 (52.2, 95.8)

(Continued)

Table 3. Continued

Characteristic	No postrandomization cardiovascular event (n=252)	Postrandomization cardiovascular event (n=150)	All patients (N=402)
Qualifying diagnosis			
STEMI	67 (69.8)	29 (30.2)	96 (23.9)
NSTEMI	127 (61.4)	80 (38.6)	207 (51.6)
Unstable angina	57 (58.2)	41 (41.8)	98 (24.4)
Diagnostic catheterization			
No	51 (56.7)	39 (43.3)	90 (22.4)
Yes	200 (64.3)	111 (35.7)	311 (77.6)
Prerandomization PCI			
No	107 (61.5)	67 (38.5)	174 (43.5)
Yes	144 (63.7)	82 (36.3)	226 (56.5)
LDL cholesterol, mg/dL			
Mean (SD)	91.0 (18.93)	86.5 (19.16)	89.3 (19.11)
Median (25th, 75th)	92.8 (77.7, 106.0)	86.0 (71.0, 99.0)	91.0 (75.8, 103.0)
Killip class			
I	148 (58.3)	106 (41.7)	254 (77.2)
II	37 (67.3)	18 (32.7)	55 (16.7)
III	14 (70.0)	6 (30.0)	20 (6.1)
Heart rate, beats/min			
Mean (SD)	71.4 (11.65)	71.2 (11.33)	71.4 (11.52)
Median (25th, 75th)	70.0 (64.0, 78.0)	70.0 (64.0, 80.0)	70.0 (64.0, 78.0)
Region			
United States/Canada	76 (58.5)	54 (41.5)	130 (32.3)
Western Europe	84 (58.3)	60 (41.7)	144 (35.8)
Eastern Europe	30 (75.0)	10 (25.0)	40 (10.0)
Malaysia/Singapore/Hong Kong	16 (66.7)	8 (33.3)	24 (6.0)
South America	45 (72.6)	17 (27.4)	62 (15.4)
Australia/New Zealand	1 (50.0)	1 (50.0)	2 (0.5)
Treatment			
Simvastatin	140 (67.6)	67 (32.4)	207 (51.5)
Ezetimibe + simvastatin	112 (57.4)	83 (42.6)	195 (48.5)
Statin at qualifying event			
No	145 (68.7)	66 (31.3)	211 (52.8)
Yes	105 (55.6)	84 (44.4)	189 (47.3)
Baseline aspirin			
No	3 (60.0)	2 (40.0)	5 (1.2)
Yes	248 (62.6)	148 (37.4)	396 (98.8)
Baseline thienopyridine			
No	34 (59.6)	23 (40.4)	57 (14.2)
Yes	217 (63.1)	127 (36.9)	344 (85.8)
Baseline β-blocker			
No	27 (56.3)	21 (43.8)	48 (12.0)
Yes	224 (63.5)	129 (36.5)	353 (88.0)
Baseline ACE inhibitor or ARB			
No	37 (66.1)	19 (33.9)	56 (14.0)
Yes	214 (62.0)	131 (38.0)	345 (86.0)

Data are presented as number (percentage) unless otherwise indicated. Categorical variables are represented as number (row percentage) for columns 1 and 2. Categorical variables for column 3 are represented as number (column percentage).

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; LDL, low-density lipoprotein; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; and STEMI, ST-segment–elevation myocardial infarction.

Table 4. Time From First Postrandomization Cardiovascular Event to Sudden Death

Time from first postrandomization cardiovascular event to sudden death, y	Number of patients	Percentage
0–1	65	43.3
1–2	32	21.3
2–3	20	13.3
3–4	13	8.7
4–5	11	7.3
5–6	7	4.7
>6	2	1.3

curve was created for sudden death accounting for other deaths as competing risks. The number of deaths was analyzed, and the cumulative incidence rates (IRs) of sudden death at 30 days, 6 months, and yearly throughout follow-up were calculated while accounting for competing risk of death from other causes. Early sudden death was defined as sudden death within 1 year of hospitalization for ACS (a qualifying event for inclusion into IMPROVE-IT) based on prior studies demonstrating that the majority of events occur during this time period.[14]

To compare the risk of early versus late sudden death associated with each postrandomization event, cause-specific Cox regression models with time-dependent indicators for each postrandomization cardiovascular event in the early period (randomization through 1 year of follow-up) and the late period (>1 year after randomization) were used. Deaths from other causes were censored.

To determine the independent association between baseline clinical characteristics and the risk of sudden death, a cause-specific Cox regression model (an "overall" model) was fit. Candidate variables included age, sex, body mass index, race or ethnicity, smoking status, diabetes, hypertension, HF, peripheral arterial disease, MI, percutaneous coronary intervention, coronary artery bypass grafting, creatinine clearance, type of index event (unstable angina/ST-segment–elevation MI/non–ST-segment–elevation MI), diagnostic catheterization, Killip class, heart rate, region, and qualifying low-density lipoprotein. LVEF before discharge was not included in the model because of the high rates of missingness (19.8%) and also may be potentially misleading given the lack of LVEF captured after discharge during the long period of follow-up. Killip class was also missing (19.4%). All of the other variables were missing in <10% of patients. Variables were selected for the model using stepwise selection with an entry P value of 0.10 and a retained P value of 0.05. The nonlinearity of the relationship between continuous candidate predictors and sudden death was evaluated using

restricted cubic splines. Piecewise linear spline transformations were applied for the following (cut points): age (70 years), body mass index (25 kg/m^2), creatinine clearance (75 mL/min), baseline heart rate (80 beats/min). Proportional hazards assumption was assessed using Schoenfeld residuals plots. Prior coronary artery bypass grafting and prior HF violated the proportional hazards assumption and were addressed by adding interaction terms with time. To determine whether study group (ezetimibe + simvastatin versus simvastatin) was associated with sudden death, a cause-specific Cox regression model for sudden death was created with study group and randomization stratification factors (prior use of lipid-lowering therapy, type of ACS, and status with respect to enrollment in the concurrent Early Glycoprotein IIb/IIIa Inhibition in Non–ST-Segment Elevation Acute Coronary Syndrome Trial) as covariates, as previously described.[9]

To assess the clinical characteristics associated with early versus late sudden death, a cause-specific Cox regression model censoring all events at 1 year ("early" model) and a landmark model using a subset of patients still at risk at 1 year ("late" model) were fit. Candidate covariates included all variables previously mentioned, with the same piecewise linear spline transformations for the continuous variables.

The frequency of patients experiencing at least 1 event before early and late sudden death and point estimates for the IR/100 patient-years of sudden death following a cardiovascular event and the IR/100 patient-years of sudden death without a postrandomization cardiovascular event were determined to describe cardiovascular events occurring before sudden death. IR/100 patient-years were calculated by dividing the number of sudden deaths by the number of years "at risk"; for example, IR/100 patient-years of sudden death following a cardiovascular event was calculated by dividing the total number of patients who experienced sudden death after a cardiovascular event by the total follow-up (until death or the end of follow-up) after a cardiovascular event in patients who had a cardiovascular event during the study. CIs for IR/100 patient-years were computed using the method for calculating CI for the hazard rate of an exponential distribution. The following events were individually added to the final overall model previously described: (1) MI; (2) HF; (3) a composite of MI, stroke, or hospitalization for unstable angina; and (4) a composite of MI, stroke, hospitalization for angina, or HF. Only the first postrandomization cardiovascular event was considered in each model. The relationship between the number of postrandomization cardiovascular events before sudden death was explored using the overall model.
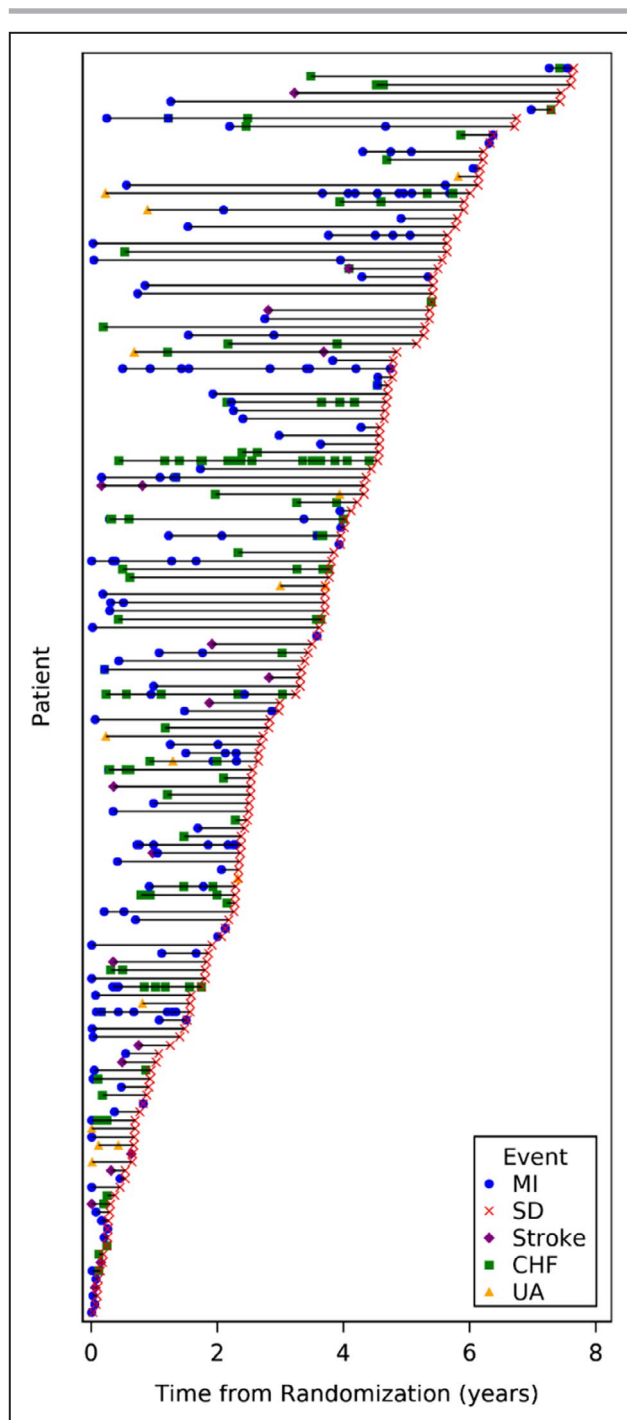
Figure 2. Time from first postrandomization cardiovascular event to sudden death among patients with a postrandomization cardiovascular event.
Each line represents a unique patient. CHF indicates congestive heart failure; MI, myocardial infarction; SD, sudden death; and UA, unstable angina.

RESULTS

Study Population

A total of 18 144 patients with ACS were enrolled in IMPROVE-IT. The baseline clinical characteristics of

patients with sudden death (n=402), those with other causes of death (n=2044), and those alive at the end of the trial (n=15 698) are shown in Table 1. Compared with patients who were alive at the end of the trial, patients who died (sudden death and nonsudden death) were older; had greater comorbidities, including cardiac risk factors; were more likely to sustain a non–ST-segment–elevation MI; and were less likely to receive percutaneous coronary intervention. Overall, 54.3% of study participants had a normal predischarge LVEF. In addition, 23.5% had mild or moderate dysfunction (LVEF ≥30%–49%), whereas only 2.4% had severe dysfunction (LVEF <30%). However, 19.7% did not have LVEF assessed before discharge.

Incidence of Long-Term Sudden Death and Influence of Postrandomization Cardiovascular Events

Of 2446 total deaths, 402 (16%) were sudden death in nature (median 2.7 years of follow-up; 109 early [≤1 year after discharge], 293 late [>1 year after discharge]). The cumulative IR of sudden death was 2.47% (lower confidence limit, upper confidence limit: 2.23, 2.73) at 7 years of follow-up (Figure 1, Table 2). Of 402 patients with sudden death, 150 (37% [30 early, 120 late]) had ≥1 postrandomization cardiovascular event, and 252 (63% [79 early, 173 late]) had no postrandomization cardiovascular events. Compared with patients who experienced sudden death and had a postrandomization cardiovascular event, those who experienced sudden death with no cardiovascular event were generally younger, had fewer comorbidities, and presented more often with ST-segment–elevation MI (Table 3). Among the 150 patients who experienced sudden death and had a postrandomization cardiovascular event, the majority of the cardiovascular events comprised MI and hospitalization for HF. This was the case for both the early and late cohorts of patients who died suddenly and had a postrandomization cardiovascular event. The risk of sudden death was greater in patients following a postrandomization cardiovascular event (IR/100 patient-years, 1.45 [95% CI, 1.23–1.69]) compared with those with no postrandomization cardiovascular event (IR/100 patient-years, 0.27 [95% CI, 0.24–0.30]).

Time From First Postrandomization Cardiovascular Event to Sudden Death

Among patients with a postrandomization cardiovascular event before sudden death, the distribution of time from the first postrandomization cardiovascular event to sudden death is shown in Table 4. The majority of sudden deaths occurred within 2 years after the first postrandomization cardiovascular event (median

Table 5. Association of Postrandomization Cardiovascular Events and Sudden Death

Variable	Patients with ≥1 event			Multivariable HR (95% CI)*	P value
	Sudden death (n=402), n (%)	Death from other causes (n=2044), n (%)	Alive (n=15 698), n (%)		
MI	97 (24.1)	352 (17.2)	1579 (10.1)	3.64 (2.85–4.66)	<0.001
HF	54 (13.4)	267 (13.1)	388 (2.5)	4.55 (3.33–6.22)	<0.001
Composite postrandomization cardiovascular event of MI, UA, or stroke	123 (30.6)	462 (22.6)	2097 (13.4)	3.76 (2.99–4.73)	<0.001
Composite postrandomization cardiovascular event of MI, UA, stroke, or HF	150 (37.3)	609 (29.8)	2331 (14.9)	4.32 (3.46–5.39)	<0.001

HF indicates heart failure; HR, hazard ratio; MI, myocardial infarction; and UA, unstable angina.

*Multivariable HR (95% CI) for association with risk of sudden death.

time 1.4 years). A timeline of the first postrandomization cardiovascular event and sudden death for each individual patient is shown in Figure 2. The median time from the first postrandomization cardiovascular event to sudden death was longer for MI or hospitalization for HF (1.4 and 1.6 years, respectively) compared with hospitalization for unstable angina or stroke (0.7 and 0.8 years, respectively). A timeline of sudden death among patients without a cardiovascular event is shown in Figure S1.

Factors Associated With Sudden Death

In a multivariable model, several factors were associated with the risk of sudden death, including region, older age, history of diabetes, body mass index, and prior coronary artery bypass grafting (c-index, 0.78; Table S1). The results of the early (c-index, 0.74) and late (c-index, 0.79) models are shown in Tables S2 and S3, respectively. Among postrandomization cardiovascular events in the overall population, postrandomization MI (hazard ratio [HR], 3.64; 95% CI, 2.85–4.66) and HF ≥30 days after randomization (HR, 4.55; 95% CI, 3.33–6.22) were strongly associated with future risk of sudden death after adjusting for baseline factors (Table 5). The risk of sudden death increased with the number of postrandomization cardiovascular events compared with no events: 1-event HR, 3.89 (95% CI, 3.19–4.76); versus 2-event HR, 6.22 (95% CI, 4.61–8.38); versus ≥3-event HR, 17.56 (95% CI, 13.61–22.66) (Table 6). There was no significant difference in sudden death between simvastatin + ezetimibe versus ezetimibe (HR, 0.94 [95% CI, 0.78–1.15]; P=0.56).

DISCUSSION

Prior work has demonstrated that the risk of sudden death following MI is greatest among those with significant left ventricular dysfunction[2] for whom intracardiac defibrillators for primary prevention are indicated if there is no significant improvement within 3 months of optimization of medical management.[3] Using adjudicated end point data from the IMPROVE-IT population with 7 years of follow-up, the data show that stable patients with ACS remain at risk of sudden death with a cumulative incidence of 2.47% during follow-up, with >70% of sudden deaths occurring late (>1 year) following ACS. Clinical variables associated with sudden death included a higher cardiac risk factor burden and prior revascularization. Sudden death in these stabilized patients after ACS was 5 times more frequent after a first postrandomization cardiovascular event, but the average time interval from a postrandomization cardiovascular event to sudden death was nearly 1.5 years. These results and the length of time between the postrandomization cardiovascular event and sudden death provide novel insights into the long-term risk of sudden death among stable patients with ACS.

The incidence of sudden death in this stabilized cohort of patients with ACS should first be placed into context. In this study, the overall cumulative incidence of postrandomization sudden death was 0.6% at 1 year and 2.5% at up to 8 years, which is greater than expected compared with the age-matched general population.[15] In contrast, the rate of sudden death in the

Table 6. Association of the Number of Postrandomization Cardiovascular Events With Sudden Death

Number of events*	Sudden death (n=402), n (%)	Death from other causes (n=2044), n (%)	Alive (n=15 698), n (%)	HR (95% CI)†
1 event	92 (22.9)	362 (17.7)	1751 (11.2)	3.89 (3.19–4.76)
2 events	30 (7.5)	141 (6.9)	342 (2.2)	6.22 (4.61–8.38)
≥3 events	28 (7.0)	106 (5.2)	238 (1.5)	17.56 (13.61–22.66)

HR indicates hazard ratio.

*Events included myocardial infarction, hospitalization for unstable angina, stroke, or hospitalization for heart failure.

†HR (95% CI) for risk of sudden death compared with no events.

current analysis is lower than that in individuals with HF with reduced ejection fraction.[16] In the PARADIGM-HF (Prospective Comparison of angiotensin receptor-neprilysin inhibitor with angiotensin-converting enzyme inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial,[17] the annual incidence of sudden death was 3.7%.[18] However, in the current analysis, patients who experienced a postrandomization hospitalization for HF or MI had a ≥5 times increased risk for future sudden death, particularly when multiple postrandomization cardiovascular events occurred (17 times increased risk for future sudden death with ≥3 postrandomization cardiovascular events). This is consistent with evaluations of worsening prognosis in patients with HF following HF admissions.[19]

This analysis has important implications for stabilized patients after ACS and after discharge. First, these patients remain at risk for sudden death, which is greatest in the first year but appears to persist in the long term. This is despite a high proportion of patients receiving optimal medical therapy at randomization and their frequent follow-up (every 4 months)[9] and salient given the underestimation of perceived risk in both patients with cardiovascular disease and their treating physicians.[20,21] Second, this is 1 of the first studies to describe both the increased risk of sudden death associated with a postrandomization cardiovascular event (5 times increased risk of sudden death versus index ACS event only) and to define the time interval (1.5 years between the first postrandomization cardiovascular event and sudden death), a potentially sufficient period in which key interventions could be performed to abrogate sudden death in some patients. These interventions include optimization of medical therapy,[22] more consistent care and provider contact, frequent reassessments of left ventricular function when indicated, remote arrhythmia monitoring for concerning symptoms (ie, implantable loop recorder), and reevaluation for intracardiac defibrillator eligibility.[23]

The current analysis does have some limitations. First, approximately 1 in 5 patients did not have LVEF documented, and even among those with LVEF documented, detailed information was unavailable on postdischarge LVEF recovery after ACS. However, the estimated percentage is likely low because the inclusion criteria for IMPROVE-IT required clinical stability after MI for enrollment, with the subsequent absence of any patients with cardiogenic shock (Killip Class IV) in the trial. Second, despite frequent postdischarge visits to evaluate lipid lowering (previously discussed), concomitant therapies (including dosages) surrounding other aspects of patient care after discharge were not systematically documented, including the rates of intracardiac defibrillator use. Third, this analysis focused on specific postrandomization cardiovascular events to predict future sudden death, and it is possible that

other events may also identify patients at risk of a cardiac event. However, these cardiovascular events are both easily recognizable as markers of risk in clinical practice and adjudicated (except hospitalization for HF), adding both to the practicality and robustness of this analysis.

In conclusion, stabilized patients after ACS remain at long-term risk of sudden death. The incidence of sudden death is greatest among those with a cardiovascular event, particularly MI or hospitalization for HF. These results identify those stabilized patients after ACS at the greatest long-term risk of sudden death and highlight potential opportunities for clinicians to improve the care and outcomes of this vulnerable population.

Supplemental Material

Tables S1–S3
Figure S1

REFERENCES

1. Adabag AS, Therneau TM, Gersh BJ, Weston SA, Roger VL. Sudden death after myocardial infarction. *JAMA*. 2008;300:2022–2029. doi: 10.1001/jama.2008.553
2. Solomon SD, Zelenkofske S, McMurray JJV, Finn PV, Velazquez E, Ertl G, Harsanyi A, Rouleau JL, Maggioni A, Kober L, et al. Sudden death in patients with myocardial infarction and left ventricular dysfunction, heart failure, or both. *N Engl J Med*. 2005;352:2581–2588. doi: 10.1056/NEJMoa043938
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128:e240–327. doi: 10.1161/CIR.0b013e31829e8776
4. Miller AL, Dib C, Li L, Chen AY, Amsterdam E, Funk M, Saucedo JF, Wang TY. Left ventricular ejection fraction assessment among patients with acute myocardial infarction and its association with hospital quality of care and evidence-based therapy use. *Circ Cardiovasc Qual Outcomes*. 2012;5:662–671. doi: 10.1161/CIRCOUTCOMES.112.965012
5. Fordyce CB, Wang TY, Chen AY, Thomas L, Granger CB, Scirica BM, Henry TD, Wong GC, Ramanathan K, Hansen CM, et al. Long-term post-discharge risks in older survivors of myocardial infarction with and without out-of-hospital cardiac arrest. *J Am Coll Cardiol*. 2016;67:1981–1990. doi: 10.1016/j.jacc.2016.02.044
6. Hess PL, Wojdyla DM, Al-Khatib SM, Lokhnygina Y, Wallentin L, Armstrong PW, Roe MT, Ohman EM, Harrington RA, Alexander JH, et al. Sudden cardiac death after non-ST-segment elevation acute coronary syndrome. *JAMA Cardiol*. 2016;1:73–79. doi: 10.1001/jamacardio.2015.0359
7. Faxén J, Jernberg T, Hollenberg J, Gadler F, Herlitz J, Szummer K. Incidence and predictors of out-of-hospital cardiac arrest within 90 days after myocardial infarction. *J Am Coll Cardiol*. 2020;76:2926–2936. doi: 10.1016/j.jacc.2020.10.033
8. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, Deal BJ, Dickfeld T, Field ME, Fonarow GC, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2018;138:e272–e391. doi: 10.1161/CIR.0000000000000549
9. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, Darius H, Lewis BS, Ophuis TO, Jukema JW, et al. Ezetimibe added to statin therapy after acute coronary syndromes. *N Engl J Med*. 2015;372:2387–2397. doi: 10.1056/NEJMoa1410489
10. Deo R, Norby FL, Katz R, Sotoodehnia N, Adabag S, DeFilippi CR, Kestenbaum B, Chen LY, Heckbert SR, Folsom AR, et al. Development and validation of a sudden cardiac death prediction model for the general population. *Circulation*. 2016;134:806–816. doi: 10.1161/CIRCULATIONAHA.116.023042
11. O'Connor CM, Carson PE, Miller AB, Pressler ML, Belkin RN, Neuberg GW, Frid DJ, Cropp AB, Anderson S, Wertheimer JH, et al. Effect of amlodipine on mode of death among patients with advanced heart failure in the PRAISE trial. Prospective Randomized Amlodipine Survival Evaluation. *Am J Cardiol*. 1998;82:881–887. doi: 10.1016/s0002-9149(98)00496-2
12. 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;168:205–12.e1. doi: 10.1016/j.ahj.2014.05.004
13. Lunn M, McNeil D. Applying Cox regression to competing risks. *Biometrics*. 1995;51:524–532. doi: 10.2307/2532940
14. Zaman S, Kovoor P. Sudden cardiac death early after myocardial infarction: pathogenesis, risk stratification, and primary prevention. *Circulation*. 2014;129:2426–2435. doi: 10.1161/CIRCULATIONAHA.113.007497
15. Bogle BM, Ning H, Mehrotra S, Goldberger JJ, Lloyd-Jones DM. Lifetime risk for sudden cardiac death in the community. *J Am Heart Assoc*. 2016;5:e002398. doi: 10.1161/JAHA.115.002398
16. Shen LI, Jhund PS, Petrie MC, Claggett BL, Barlera S, Cleland JGF, Dargie HJ, Granger CB, Kjekshus J, Køber L, et al. Declining risk of sudden death in heart failure. *N Engl J Med*. 2017;377:41–51. doi: 10.1056/NEJMoa1609758
17. McMurray JJV, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med*. 2014;371:993–1004. doi: 10.1056/NEJMoa1409077
18. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341:709–717. doi: 10.1056/NEJM199909023411001
19. Solomon SD, Dobson J, Pocock S, Skali H, McMurray JJV, Granger CB, Yusuf S, Swedberg K, Young JB, Michelson EL, et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation*. 2007;116:1482–1487. doi: 10.1161/CIRCULATIONAHA.107.696906
20. Leifheit-Limson EC, D'Onofrio G, Daneshvar M, Geda M, Bueno H, Spertus JA, Krumholz HM, Lichtman JH. Sex differences in cardiac risk factors, perceived risk, and health care provider discussion of risk and risk modification among young patients with acute myocardial infarction: The VIRGO study. *J Am Coll Cardiol*. 2015;66:1949–1957. doi: 10.1016/j.jacc.2015.08.859
21. Everett B, Salamonson Y, Rolley JX, Davidson PM. Underestimation of risk perception in patients at risk of heart disease. *Eur J Cardiovasc Nurs*. 2016;15:e2–9. doi: 10.1177/1474515114556712
22. Bahit MC, Kochar A, Granger CB. Post-myocardial infarction heart failure. *JACC Heart Fail*. 2018;6:179–186. doi: 10.1016/j.jchf.2017.09.015
23. Pokorney SD, Miller AL, Chen AY, Thomas L, Fonarow GC, de Lemos JA, Al-Khatib SM, Velazquez EJ, Peterson ED, Wang TY. Reassessment of cardiac function and implantable cardioverter-defibrillator use among medicare patients with low ejection fraction after myocardial infarction. *Circulation*. 2017;135:38–47. doi: 10.1161/CIRCULATIONAHA.116.022359

SUPPLEMENTAL MATERIAL

Table S1. Predictors of sudden death: Overall model.

Variable	Multivariable HR (95% CI)	Multivariable Chi-Square	Multivariable P value
Overall effect of region		57.1	<.001
Australia/New Zealand vs United States/Canada	0.53 (0.13–2.15)		
Eastern Europe vs United States/Canada	1.84 (1.28–2.66)		
Malaysia/Singapore/Hong Kong vs United States/Canada	2.73 (1.7–4.39)		
South America vs United States/Canada	2.73 (1.98–3.77)		
Western Europe vs United States/Canada	1.09 (0.85–1.39)		
Overall effect of age		54.5	<.001
Age in 5 yrs up to 70	1.16 (1.05–1.28)		
Age in 5 yrs above 70	1.42 (1.25–1.60)		
History of diabetes	1.94 (1.57–2.39)	38.8	<.001
BMI per 2 kg/m^2 above 25	1.11 (1.07–1.16)	26.8	<.001
Overall effect of prior CABG		20.5	<.001
Prior CABG, follow-up time ≤1 yr	0.91 (0.52–1.60)		
Prior CABG, follow-up time ≥1 yr	1.97 (1.46–2.66)		
Male sex	1.73 (1.35–2.23)	18.4	<.001
Current smoker	1.68 (1.32–2.13)	18.2	<.001
Creatinine clearance per 10 mL/min up to 75	0.82 (0.74–0.90)	17.4	<.001
Overall effect of prior HF		16.4	<.001
Prior HF, follow-up time ≤1.5 yr	1.13 (0.64–2.02)		
Prior HF, follow-up time >1.5 yr	2.1 (1.47–3.01)		
Overall effect of Killip class		15.4	<.001
Killip class II vs Class I	1.6 (1.21–2.12)		
Killip class III vs Class I	1.71 (1.13–2.59)		

Variable	Multivariable HR (95% CI)	Multivariable Chi-Square	Multivariable P value
Baseline heart rate per 10 bpm up to 80	1.25 (1.12–1.41)	14.6	<.001
Overall effect of QE		14.2	<.001
NSTEMI vs Unstable angina	1.6 (1.24–2.06)		
STEMI vs Unstable angina	1.63 (1.18–2.25)		
Previous myocardial infarction	1.53 (1.21–1.92)	13.1	<.001
PCI after QE and prior to randomization	0.68 (0.55–0.85)	11.8	<.001
Previous peripheral artery disease	1.63 (1.21–2.20)	10.2	0.001
Baseline beta blockers	0.69 (0.51–0.94)	5.7	0.017
History of hypertension	1.29 (1.01–1.65)	4.2	0.041

C index: 0.78

BMI indicates body mass index; bpm, beats per minute; CABG, coronary artery bypass grafting; CI, confidence interval; HF, heart failure; HR, hazard ratio; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; QE, qualifying event; STEMI, ST-elevation myocardial infarction.

Table S2. Predictors of sudden death: Early model.

Variable	Multivariable HR (95% CI)	Multivariable Chi-Square	Multivariable P value
Creatinine clearance per 10 mL/min up to 75	0.65 (0.55–0.77)	25.6	<.001
History of diabetes	2.18 (1.48–3.22)	15.5	<.001
BMI per 2 kg/m^2 above 25	1.13 (1.06–1.21)	14.5	<.001
Catheterization after QE prior to randomization	0.48 (0.31–0.74)	11.1	<.001
Age in 5 yrs above 70	1.4 (1.13–1.72)	9.7	0.002
Male sex	2.17 (1.32–3.55)	9.4	0.002
Current smoker	1.72 (1.11–2.66)	5.9	0.015
Previous myocardial infarction	1.64 (1.1–2.44)	5.9	0.015

C-index: 0.74
BMI indicates body mass index; CI, confidence interval; HR, hazard ratio; QE, qualifying event.
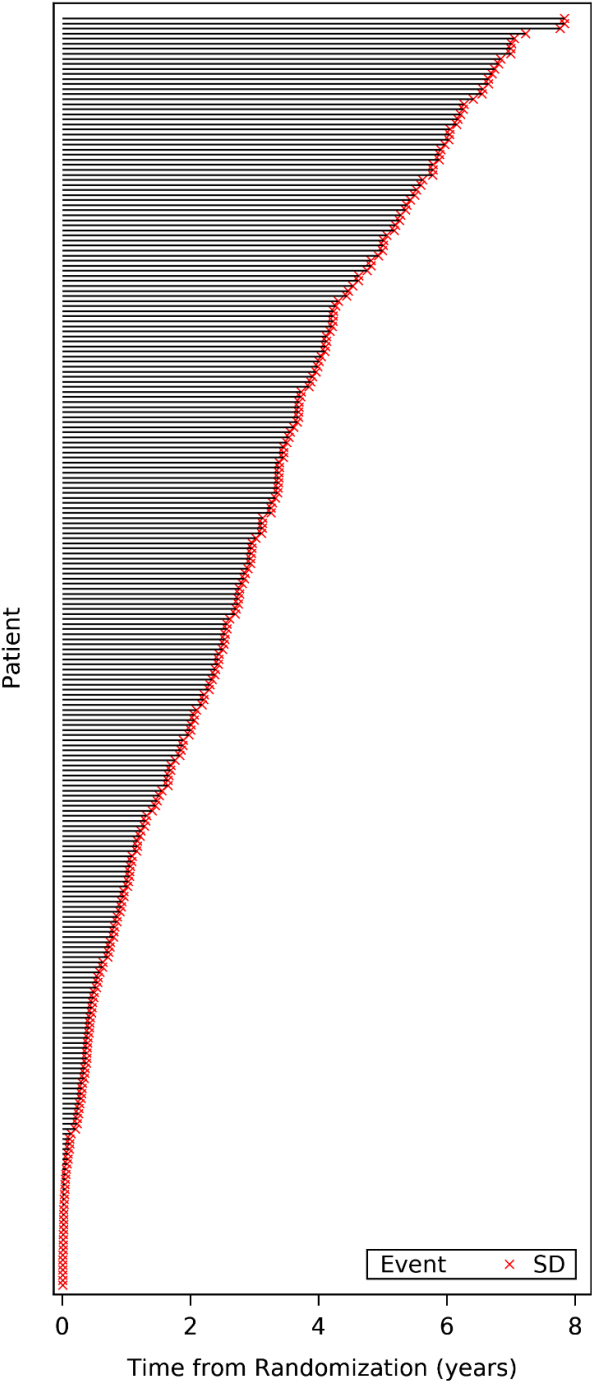
Table S3. Predictors of sudden death: Late model.

Variable	Multivariable HR (95% CI)	Multivariable Chi-Square	Multivariable P value
Overall effect of region		47.2	<.001
Australia/New Zealand vs United States/Canada	0.71 (0.17, 2.9)		
Eastern Europe vs United States/Canada	2.17 (1.44, 3.28)		
Malaysia/Singapore/Hong Kong vs United States/Canada	3.1 (1.79, 5.36)		
South America vs United States/Canada	2.6 (1.77, 3.83)		
Western Europe vs United States/Canada	1.01 (0.75, 1.34)		
Overall effect of age		41.3	<.001
Age in 5 yrs up to 70	1.2 (1.06, 1.34)		
Age in 5 yrs above 70	1.4 (1.21, 1.63)		
History of diabetes	1.95 (1.53, 2.48)	29.0	<.001
Previous CABG (≥3 years prior to entry)	2.08 (1.52, 2.83)	21.5	<.001
BMI per 2 kg/m^2 above 25	1.1 (1.05, 1.16)	15.8	<.001
Overall effect of Killip class		14.6	<.001
Killip class II vs Class I	1.7 (1.23, 2.36)		
Killip class ≥III vs Class I	1.86 (1.14, 3.02)		
Prior CHF	1.98 (1.38, 2.83)	13.9	<.001
Baseline heart rate per 10 bpm up to 80	1.29 (1.13, 1.48)	13.5	<.001
Overall effect of QE		11.9	0.003
NSTEMI vs Unstable angina	1.69 (1.25, 2.27)		
STEMI vs Unstable angina	1.49 (1.02, 2.18)		
Current smoker	1.62 (1.23, 2.15)	11.6	<.001
Previous peripheral artery disease	1.78 (1.26, 2.51)	10.9	<.001
Male sex	1.53 (1.14, 2.04)	8.2	0.004
Previous myocardial infarction	1.47 (1.12, 1.94)	7.8	0.005

Variable	Multivariable HR (95% CI)	Multivariable Chi-Square	Multivariable P value
Creatinine clearance per 10 mL/min up to 75	0.86 (0.77, 0.96)	7.2	0.007
Baseline beta blockers	0.65 (0.45, 0.92)	5.8	0.016
PCI after QE and prior to randomization	0.74 (0.57, 0.95)	5.4	0.020

C-index: 0.79
BMI indicates body mass index; CABG, coronary artery bypass grafting; CHF, congestive heart failure; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; QE, qualifying event; STEMI, ST-elevation myocardial infarction.

Figure S1. Time from first post-randomization cardiovascular event to sudden death among patients without a post-randomization cardiovascular event. Each line represents a unique patient.

SD indicates sudden death.