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 2,446 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
Fordyce et al. Sudden Death Following Stable ACS

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 m², 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 (8.8)       | <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/m²**                         |                      |                                 |                 |          |
| 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 (88.2)   | 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 (87.6)   | 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)
| 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)                      | 11 516 (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.
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.8,12

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

| 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/m²                  | 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 (74.5)           |
|                             | Yes 55 (53.4)                                    | 48 (46.6)                                     | 103 (25.7)           |
| Previous CABG               | No 215 (88.5)                                    | 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 postrandomization           | 51 (56.7)                                        | 39 (43.3)                                     | 90 (22.4)            |
| Yes                            | 200 (64.3)                                       | 111 (35.7)                                    | 311 (77.6)           |
| Prerandomization PCI           |                                                  |                                               |                      |
| No postrandomization           | 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 (67.4)                                       | 83 (32.6)                                     | 195 (48.5)           |
| Statin at qualifying event     |                                                  |                                               |                      |
| No postrandomization           | 145 (68.7)                                       | 66 (31.3)                                     | 211 (62.6)           |
| Yes                            | 105 (55.6)                                       | 84 (44.4)                                     | 189 (47.3)           |
| Baseline aspirin               |                                                  |                                               |                      |
| No postrandomization           | 3 (60.0)                                         | 2 (40.0)                                      | 5 (1.2)              |
| Yes                            | 248 (62.6)                                       | 148 (37.4)                                    | 396 (98.8)           |
| Baseline thienopyridine        |                                                  |                                               |                      |
| No postrandomization           | 34 (59.6)                                        | 23 (40.4)                                     | 57 (14.2)            |
| Yes                            | 217 (63.1)                                       | 127 (36.9)                                    | 344 (85.8)           |
| Baseline β-blocker             |                                                  |                                               |                      |
| No postrandomization           | 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 postrandomization           | 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.
curvature 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 non-linearity 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/m2), 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.

### 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 |

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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
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 for whom intracardiac defibrillators for primary prevention are indicated if there is no significant improvement within 3 months of optimization of medical management. 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. In contrast, the rate of sudden death in the

### Table 5. Association of Postrandomization Cardiovascular Events and Sudden Death

| Variable | Patients with ≥1 event |   |   |   |
|----------|------------------------|---|---|---|
|          | Sudden death (n=402), n (%) | Death from other causes (n=2044), n (%) | Alive (n=15,698), n (%) | Multivariable HR (95% CI)* | P value |
| 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.

### 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.
current analysis is lower than that in individuals with HF with reduced ejection fraction. 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, the annual incidence of sudden death was 3.7%. 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.

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) and salient given the underestimation of perceived risk in both patients with cardiovascular disease and their treating physicians. 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, 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.

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.

ARTICLE INFORMATION
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**Supplemental Material**

**Tables S1–S3**

**Figure S1**

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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)     |                          |                       |
| 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/m² 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)           |                          | <.001                 |
| STEMI vs Unstable angina                      | 1.63 (1.18–2.25)          |                          | <.001                 |
| 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/m² 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/m² 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.