ORIGINAL RESEARCH

Predictors of Sudden Cardiac Arrest Among Patients With Post-Myocardial Infarction Ejection Fraction Greater Than 35%

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BACKGROUND: Sudden cardiac arrest (SCA) risk increases after myocardial infarction (MI) in patients with a reduced ejection fraction (EF). However, the risk factors for SCA among patients with a post-MI EF >35% remain poorly understood.

METHODS AND RESULTS: Using the Optum de-identified electronic health record data set from 2008 to 2017, we identified patients with an incident MI diagnosis and troponin elevation who had a post-MI EF >35% and underwent coronary angiography. Primary outcome was SCA within 1 year post-MI. The database was divided into derivation (70%) and validation (30%) cohorts by random selection. Cox proportional hazard regression was used to generate and validate a risk prediction model. Among 31,286 patients with an MI (median age 64.1; 39% female; 87% White), 499 experienced SCA within 1 year post-MI (estimated probability 1.8%). Lack of revascularization at MI, post-MI EF <50%, Black race, renal failure, chronic obstructive pulmonary disease, antiarrhythmic therapy, and absence of beta blocker therapy were independent predictors of SCA. A multivariable model consisting of these variables predicted SCA risk (C-statistic 0.73). Based on this model, the estimated annual probability of SCA was 4.4% (95% CI, 3.9–4.9) in the highest quartile of risk versus 0.6% (95% CI, 0.4–0.8) in the lowest quartile.

CONCLUSIONS: Patients with a post-MI EF >35% have a substantial annual risk of SCA. A risk model consisting of acute coronary revascularization, EF, race, renal failure, chronic obstructive pulmonary disease, antiarrhythmic therapy, and beta blocker therapy can identify patients with higher risk of SCA, who may benefit from further risk stratification and closer monitoring.

Key Words: ejection fraction • myocardial infarction • revascularization • risk prediction • sudden cardiac arrest
primary prevention ICD therapy.14 The objective of the present study was to determine the risk factors for SCA among patients with post-MI EF >35% in a large, contemporary, real-world population.

METHODS

Data Source
We accessed electronic health record data obtained from the Optum de-identified electronic health record data set, which contained de-identified patient data from multiple hospital systems across the United States for roughly 11 million patients from 2007 to 2017.15–17 The Optum de-identified electronic health record data set captures clinical, laboratory, procedural, and pharmacy information recorded by clinicians at the time of in- and outpatient care, using natural language processing, when necessary, to extract and organize data from free-text into semistructured data fields.15,16 To ensure the reliability of the records, we included only data that originated from provider networks listed as “integrated delivery network” and included information through each patient’s date of MI.

This retrospective analysis of a de-identified data set was performed under the permissions granted through an agreement with Optum. The restrictions in the use of the data as governed by this agreement prevent us from sharing these data with other researchers. However, the analysis code will be available upon request from the corresponding author.

Study Population
Patients (age >18-years) with a primary diagnosis of incident MI (International Classification of Diseases, Ninth Revision [ICD-9] diagnostic codes 410.X; International Classification of Diseases, Tenth Revision [ICD-10] diagnostic codes I21.0-4) and concomitant serum troponin elevation consistent with an MI, from January 2008 to March 2017, were included in this study. Concomitant serum troponin level had to show a “rise and fall pattern” with the lowest troponin being ≤80% of the highest.18 The patients included in the cohort needed to have a history of electronic health record records for at least 365 days preceding the qualifying MI, at least 1 in-person follow-up encounter recorded post-MI, and a record of an acute post-MI coronary angiogram. Patients were excluded if they had a previous history of MI or SCA, if the SCA occurred on the day of the incident MI, if they already had a cardiac implantable electronic device at the time of the incident MI, if their post-MI EF was ≤35%, or if there was no recorded post-MI EF measurement (Figure S1). Requirement for a post-MI coronary angiogram was instituted to reduce the number of patients with type II MI or those who are too old, frail, and sick for angiography. These patients are not optimal candidates for further risk stratification if they were deemed not to be appropriate for angiography by their treating physician. Patients who had a cardiac device implanted after MI were censored at the time of the implantation.

Outcome
The outcome variable was time from MI to the first observations of a primary or admitting diagnosis of SCA (ICD-9 diagnostic codes 427.41, 427.5; ICD-10 diagnostic codes I46.X, I49.01) and/or cardiopulmonary resuscitation (current procedural terminology procedure code 92950; ICD-9 procedure code 99.60, ICD-10 procedure codes 5A12012, 5A19054) within 1 year after the incident MI. Patients were censored after their last in-person encounter, or administratively censored at 365 days.

Definitions
Post-MI EF was measured within 0 to 7 days after the incident MI. This time point was chosen to mimic the
circumstances of the clinicians who are frequently put in the position to perform risk stratification for SCA based on the information available during the index hospitalization. Indeed, SCA risk is highest early after MI, requiring risk stratification to be considered during the index hospitalization. Serum troponin was considered elevated if the patient had a laboratory record of troponin T or troponin I that was greater than the upper bound of normal range in that laboratory (or if a positive result indicator was present, in cases where no upper bound was listed) and was collected within 7 days before or after the date of the MI diagnosis. Cardiac catheterization or coronary revascularization procedures performed within 7 days after the incident MI, and before a patient’s SCA or censoring time, were considered as acute. Diabetes mellitus was determined from diagnostic codes, fasting glucose measurements, hemoglobin A1c levels, or use of diabetes mellitus medications. Chronic kidney disease was defined as having an estimated glomerular filtration rate <60 mL/min on 2 separate days at least 14 days apart. Previous heart failure event was defined as inpatient hospitalization with a diagnosis of heart failure and documented administration of intravenous diuretics or an inotrope before the incident MI.

Statistical Analysis
Continuous variables were shown as median (25th–75th percentile) and categorical variables as percentages. The database was divided into derivation (70%) and validation (30%) cohorts by random selection. All potential risk factors shown in Table 1 were included in the initial regression model using the derivation cohort. The final predictive model was determined using the Lasso Cox regression for variable selection. Then, a standard Cox regression model using only risk factors with nonzero coefficients in the Lasso regression was fit in the validation cohort. Estimated hazard ratios (HRs), CIs, and \( P \) values are provided based on this standard Cox regression model.

The calibration of the Cox model fit to the validation cohort was examined by estimating the risk of post-MI SCA for all patients in the derivation and validation cohorts together, separating them into quartiles based on this estimated risk, and then separately calculating the cumulative probability of post-MI SCA within 1 year for each stratum using Kaplan-Meier estimation.

Post hoc analyses focused on the impact of post-MI EF and revascularization or coronary angiogram were conducted by updating the Cox model fit to the validation cohort to analyze more precisely defined versions of these predictors. Other predictors were left in the Cox model for analyses.

Analyses were performed using R Version 3.6.0\(^2\) with the survival\(^3,4\) and glmnet\(^5\) packages. A \( P \) value <0.05 was considered significant.

### Table 1. Baseline Characteristics of the Patients With Incident MI

| Variables                                           | Patients (n=31286) |
|-----------------------------------------------------|-------------------|
| Age at MI, y                                        | 64.1 (54.9–74)    |
| Sex (Female)                                        | 12338 (39%)       |
| Race                                                |                   |
| Black                                               | 2642 (8%)         |
| White                                               | 27293 (87%)       |
| Other/Unknown                                       | 1351 (4%)         |
| Smoking                                             |                   |
| Never                                               | 6081 (19%)        |
| Previous                                            | 13126 (42%)       |
| Current                                             | 10804 (35%)       |
| Not observed                                        | 1275 (4%)         |
| Diabetes mellitus                                   | 10940 (35%)       |
| Renal dysfunction                                   | 9513 (30%)        |
| Coronary artery disease                             | 29545 (94%)       |
| Coronary artery bypass graft or percutaneous coronary intervention | 23236 (74%) |
| Chronic obstructive pulmonary disease               | 6581 (21%)        |
| Prior heart failure hospitalization                 | 840 (30%)         |
| Hypertension                                        | 27415 (88%)       |
| Left ventricular ejection fraction                  | 55 (45, 60)       |
| Left BBB                                            | 1377 (4%)         |
| Right BBB                                           | 1513 (5%)         |
| Troponin level ng/mL                                | 2.8 (0.7, 12.4)   |
| Angiotensinogen-converting enzyme inhibitor/angiotensin receptor blocker | 19374 (62%) |
| Beta blocker                                        | 25265 (81%)       |
| Antiarrhythmic                                      | 2741 (9%)         |

Continuous variables are presented as median (25th, 75th percentile). Binary variables are presented as count (percentage), BBB indicates bundle branch block, and MI, myocardial infarction.

### Ethical Approval
All data used in this study have been statistically de-identified according to the Health Insurance Portability and Accountability Act of 1996 164.514 Privacy Rule. As this study is analyzing preexisting, de-identified data that was accessed in a manner compliant with the Health Insurance Portability and Accountability Act, it is exempt from institutional review board approval.

### RESULTS

#### Patient Characteristics
Baseline characteristics of the 31286 patients with incident MI and post-MI EF >35% are shown in Table 1. The median age (25th–75th percentile) of the patients was 64.1 (54.9–74.0) and 39% were female. At the time of the MI, 94% had a history of coronary artery...
disease and 35% had diabetes mellitus. The median post-MI EF was 55% (45%–60%), and 10 106 (32%) patients had EF 35% to 50%. All patients were required to have undergone coronary angiogram, 19 171 (61%) had percutaneous coronary intervention and 4065 (13%) had coronary artery bypass graft surgery (Table 1). Post-MI beta blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers were prescribed in 81% and 62% of the patients, respectively. Over half the patients (n=20 076, 64%) were administratively censored at 12 months, and the first quartile of the time to censoring was 7.0 months.

Sudden Cardiac Arrest

Of the 31 286 patients, a total of 499 had SCA and 1673 died within 1 year post-MI. The estimated cumulative probability of SCA within 1 year post-MI was 1.8%. The median time from MI to cardiac arrest was 28 (6–116) days (Figure 1). Of the 499 patients who had SCA, 40% were alive at 1 year post-MI.

The risk factors identified in the derivation cohort were absence of coronary revascularization at the time of the incident MI, revascularization with coronary artery bypass graft (as opposed to percutaneous coronary intervention) at the time of incident MI, post-MI EF 35% to –50%, Black race, history of heart failure, history of chronic obstructive pulmonary disease, history of renal failure, history of diabetes mellitus, antiarrhythmic therapy, absence of beta blocker therapy, and markedly elevated serum troponin (>7.5 ng/mL). Estimated HRs and regression coefficients of the risk factors based on the Cox model fit to the validation cohort are displayed in Table 2. Among the set of risk factors identified in the derivation cohort, lack of coronary revascularization, post-MI EF 35% to 50%, Black race, history of chronic obstructive pulmonary disease, history of renal failure, antiarrhythmic therapy, and absence of beta blocker therapy were independently associated with SCA in the model fit to the validation cohort (Figure 2). The Cox model fit to the validation cohort had a C-statistic of 0.73 for discriminating SCA. The estimated probability of SCA in 1 year was 4.4% (95% CI, 3.9–4.9) in the highest quartile of risk versus 0.6% (95% CI, 0.4–0.8) in the lowest quartile (Figure 3 and Table 3).

![Figure 1](https://example.com/images/figure1.png)

**Figure 1.** Cumulative probability of SCA after MI in patients with EF >35%. Probability of SCA (y-axis) is shown vs months since MI (x-axis). Point estimates are represented by the solid black line with the CIs represented as the space confined within the 2 black dotted lines. EF indicates ejection fraction; MI, myocardial infarction; and SCA, sudden cardiac arrest.
Adabag et al Post- MI Cardiac Arrest

Ejection Fraction

EF was measured within 7 days post-MI. There was an inverse association between post-MI EF and the risk of SCA within 1 year (Figure 4). After adjusting for other risk factors, the SCA risk was highest in those with an EF between 36% and 39%, gradually declining until the EF was ≥45%. In comparison to patients with EF 36% to 39%, the risk was 18% lower (HR, 0.82; 95% CI, 0.43–1.55) in those with EF 40% to 44%, 59% lower (HR, 0.41; 95% CI, 0.20–0.88) in patients with EF 45% to 49%, 51% lower (HR, 0.49; 95% CI, 0.25–0.97) in patients with EF 50% to 54% and 63% lower (HR, 0.37; 95% CI, 0.19–0.74) in patients with EF 55% to 59% (Figure 4).

DISCUSSION

In this large, contemporary, real-world data set of patients with a post-MI EF >35% who underwent a coronary angiography, we found that lack of coronary revascularization, post-MI EF 35% to 50%, Black race, history of chronic obstructive pulmonary disease, history of renal failure, antiarrhythmic therapy, and absence of beta blocker therapy were independent predictors of SCA within 1 year. A multivariable model consisting of these variables predicted SCA with a C-statistic of 0.73. Patients who score high on this risk model may benefit from further risk stratification, and closer monitoring, to prevent SCA.

Recently, Gatzoulis et al used a multistep risk stratification scheme in a multicenter prospective cohort study of patients post-MI with preserved EF. They screened 575 consecutive patients with EF >40% post-MI for noninvasive arrhythmic risk markers and referred those with a positive risk factor (n=204; 35.5% of the cohort) for electrophysiologic study. Sustained ventricular tachycardia or ventricular fibrillation was

Table 2. Multivariable Predictors of Post-MI SCA Within 1 Year

| Risk Factor                                      | No. (%) of Patients With Risk Factor | Regression Coefficients* | Hazard Ratio | 95% CI | P Value |
|------------------------------------------------|-------------------------------------|--------------------------|-------------|--------|---------|
| Renal dysfunction                               | 9513 (30%)                          | 0.857                    | 2.36        | 1.67–3.33 | <0.0001 |
| No beta blockers                                | 6021 (19%)                          | 0.673                    | 1.96        | 1.39–2.78 | 0.0001  |
| Angiogram only, no revascularization            | 8050 (26%)                          | 0.689                    | 1.99        | 1.39–2.86 | 0.0002  |
| Ejection fraction <50%                          | 10 106 (32%)                        | 0.586                    | 1.80        | 1.30–2.48 | 0.0003  |
| Race, Black                                     | 2642 (8%)                           | 0.704                    | 2.02        | 1.33–3.08 | 0.001   |
| Antiarhythmic                                   | 2741 (9%)                           | 0.615                    | 1.85        | 1.20–2.84 | 0.005   |
| Chronic obstructive pulmonary disease           | 6581 (21%)                          | 0.395                    | 1.48        | 1.05–2.09 | 0.024   |
| Troponin >7.5 ng/mL                              | 10 217 (32%)                        | 0.299                    | 1.35        | 0.96–1.90 | 0.090   |
| Diabetes mellitus                               | 10 940 (35%)                        | 0.264                    | 1.30        | 0.93–1.82 | 0.120   |
| Coronary artery bypass graft                    | 4065 (13%)                          | 0.384                    | 1.47        | 0.90–2.41 | 0.127   |
| Heart failure history                           | 840 (3%)                            | 0.232                    | 1.26        | 0.65–2.45 | 0.495   |

MI indicates myocardial infarction; and SCA, sudden cardiac arrest.

*Regression coefficients are provided to allow calculation of predicted risk score for a new patient.
inducible in 41 (7%) patients, who were referred for ICD implantation. After 32 months, 9 patients (1.6% of the study population) had appropriate ICD therapies, resulting in an annual event rate 8.2% but no arrhythmic events occurred in patients without any noninvasive risk factors or in those with noninvasive risk factors but a negative electrophysiology study. Although this cohort study does not provide definitive evidence, it is an example of how a risk model, such as the one presented here, could be used as a screening tool in clinical practice.

Left ventricular EF is an important predictor of SCD after MI but there are few data among patients with EF >35%. In the VALIANT (Valsartan in Acute Myocardial Infarction) trial, post-MI SCD risk in patients whose EF was 30% to 40% was not significantly different from those with EF >40%. The present analysis, with a larger number of patients, shows a lower risk of SCA as the EF improves from 35% to 45% (Figure 4). However, the SCA risk flattened after the EF >45%. These results complement the observations from ICD cohorts where the risk of appropriate ICD therapy is still present, albeit lower, after improvement of EF and minimal in those with normalized EF.

Further, significant recovery in EF may occur post-MI after the resolution of early myocardial stunning. This phenomenon is particularly significant among patients who had been revascularized. In PREDICTS (Prediction of ICD Treatment Study) 57% of the patients with an early post-MI EF <35% had EF recovery to >35% by 3 months, including 26% who had EF >50%. In the YOUNG-MI registry, patients with recovery of EF had 8x reduction in mortality. In the present analysis, we used the EF measurement within 7 days post-MI to match the circumstances of the clinicians who frequently find themselves put in position to risk stratify using the clinical variables measured during the index hospitalization. Indeed, the risk of SCA is highest early after MI and this approach most closely reflects real-world clinical practice.
This investigation showed that absence of revascularization after MI increased SCA risk, which is consistent with prior studies. In the CASS (Coronary Artery Surgery) study coronary artery bypass surgery reduced SCD. In an analysis of the MADIT II (Multicenter Automatic Defibrillator Implantation Trial II) study, patients who were revascularized within the preceding 18 months did not accrue benefit from ICD therapy. Finally, in the CABG-Patch (Coronary Artery Bypass Graft-Patch) trial, ICD implantation at the time of coronary artery bypass graft surgery failed to reduce mortality among patients with EF <35% likely because of effective revascularization. Our results align with these observations even in an era of more aggressive post-MI pharmacotherapy and early access to cardiac catheterization after SCA.

Some of the risk variables associated with SCA in this post-MI cohort with EF >35% were also identified as markers of SCD previously in other populations. Docherty et al reported the post-MI risk factors for SCD from 3 large clinical trials performed 20 years ago. They identified age >70 years, heart rate ≥70 beats/min, smoking, Killip class III/IV, left ventricular EF ≤30%, atrial fibrillation, history of prior MI, heart failure, diabetes mellitus, renal dysfunction, and no coronary reperfusion or revascularization at index MI. Compared with theirs, the current study population includes only patients with EF >35% and is more contemporary. It is also notable 39% of the current study population were female.

Our results confirm previous studies, which also showed that Blacks have a 2 times higher risk of SCA and SCD than Whites. Although investigating the factors for the increased risk was beyond the scope of the current study, previous studies have identified income,

Table 3. Kaplan-Meier Estimates of SCA Probability at 1 Year

| Number of Patients in Risk Quartile | Cumulative Probability of SCA at 1 Year (95% CI) | Risk Score Cutoff* |
|-----------------------------------|---------------------------------|-------------------|
| 7813 | 0.58% (0.40%–0.76%) | <0.65 |
| 7669 | 0.80% (0.59%–1.00%) | <1.11 |
| 7884 | 1.49% (1.20%–1.77%) | <1.79 |
| 7920 | 4.37% (3.88%–4.86%) | >=1.79 |

SCA indicates sudden cardiac arrest.

*Risk score cutoffs are provided so that the coefficients from Table 2 can be used to predict the risk quartile of a new patient.

Figure 3. Estimated probability of SCA in quartiles of risk predicted by the model. Probability of SCA (y-axis) is shown vs months since MI (x-axis). Point estimates are represented by the solid colored lines with the CIs represented as the corresponding shaded colored area surrounding the solid lines. MI indicates myocardial infarction; and SCA, sudden cardiac arrest.
education, hypertension, diabetes mellitus, and renal failure. Our results also support previous studies that have identified chronic obstructive pulmonary disease as a risk factor for SCD and ICD shocks.

Limitations
Several limitations should be considered when interpreting the results of this retrospective analysis. First, patients experiencing SCA who did not survive to be taken to a hospital would not have been captured in this data set, which may be responsible for the relatively large proportion of patients surviving SCA in our sample. However, the annual SCA incidence in this cohort is similar to the annual SCD risk from other post-MI cohorts. Second, a substantial number of patients were excluded because they did not have EF measurements within 7 days of an MI or did not have an encounter recorded at least 365 days before the MI, which may have reduced the representativeness of our sample. However, these exclusion criteria were necessary to identify a cohort with EF >35%, to confirm that the MI was incident and to increase the accuracy of comorbidity detection. Third, although SCA was not validated in the Optum database per se, prior studies have validated SCA in large administrative data sets like Optum. Finally, the mechanism of SCA cannot be determined from this study. Although arrhythmic SCA can be prevented by ICD therapy, events due to nonarrhythmic causes would not be affected.

CONCLUSIONS
Patients with post-MI EF >35% have a substantial risk of SCA within 1 year post-MI. The multivariable risk model of clinical variables presented in this study can be used as a screening tool to identify patients with the highest risk who may benefit from further risk stratification. Our findings build on the increased interest in risk stratification soon after MI and add to recent evidence affording benefit of ICDs early in the post-MI period.

ARTICLE INFORMATION
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SUPPLEMENTAL MATERIAL
Figure S1. Cohort selection.

Patients with MI and concomitant serum elevated troponin
(n = 196,770)

Exclusions:
- Missing EF (n = 86,110)
- No encounter record at least one year before MI (n = 32,373)
- Reduced EF (n = 20,435)
- Previous MI (n = 9,536)
- Provider network non-integrated delivery network (n = 2,566)
- Existing or early implant CIED (n = 1,706)
- No in-person encounter after MI (n = 1,374)
- Previous SCA (n = 1,153)
- Under 18 at time of MI (n = 11)
- Did not undergo angiogram (n = 10,130)

Analysis Cohort
(n = 31,286)

CIED = cardiovascular implantable electronic device; EF = ejection fraction; MI = myocardial infarction;
SCA = sudden cardiac arrest