Implantable Cardioverter-Defibrillator Therapy in Patients With Ventricular Fibrillation out of Hospital Cardiac Arrest Secondary to Acute Coronary Syndrome

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Background—Survivors of ventricular fibrillation out of hospital cardiac arrest (VF-OHCA) due to a potentially reversible cause such as acute myocardial infarction (MI) or ischemia are considered to be at low risk of recurrent arrhythmia. Implantable cardioverter defibrillators (ICD) are not routinely recommended in such patients. However, the outcome of these patients in the era of rapid coronary revascularization and ICD therapy is not known.

Methods and Results—We examined the outcome of 114 consecutive survivors of VF OHCA due to acute MI or ischemia in Olmsted County, MN from 1990 to 2011. An ICD was implanted in 45/114 patients. ICD recipients had lower EF [median (IQR) 38 (26 to 54) versus 48 (35 to 58) %; P=0.04]. During a median (IQR) follow-up of 9.9 (4.4 to 14.6) years, ICD implantation was associated with reduced cardiac mortality (HR 0.24 [0.07 to 0.88], P=0.031) and a trend towards reduced all-cause mortality (HR 0.56 [0.30 to 1.02], P=0.059) after adjusting for the first principal component. One or more appropriate ICD therapies were delivered in 19/45, with half of the patients receiving therapy within 1 year. Patients with EF ≤35% at discharge continued to be at long-term risk for ICD therapy compared with those with EF >35% who were at increased risk predominantly in the first 8 months. EF and revascularization were not significantly associated with ICD therapy in the multivariable analysis.

Conclusions—Patients with VF-OHCA in the setting of acute MI or myocardial ischemia remain at high risk of recurrent ventricular arrhythmias, particularly if EF ≤35%. This suggests that ICD implantation may be reasonable if EF ≤35%. (J Am Heart Assoc. 2015;4:e001255 doi: 10.1161/JAHA.114.001255)

Key Words: implantable cardioverter defibrillator • myocardial infarction • out of hospital cardiac arrest • ventricular fibrillation

Ventricular arrhythmias due to coronary artery disease are a leading cause of death in the United States.¹ Patients with ventricular fibrillation (VF) or ventricular tachycardia (VT) without a reversible cause are at high risk of sudden death.²,³ Trials of secondary prevention of sudden death such as the antiarrhythmics versus implantable defibrillator (AVID) trial have shown that implantable cardioverter defibrillators (ICD) reduce the risk of death.⁴⁻⁶ Conversely, it is thought that VT or VF in the setting of a reversible cause such as ischemia or electrolyte abnormalities has a low risk of recurrent arrhythmias and such patients were excluded from the ICD trials. Current guidelines do not recommend ICD implantation in survivors of cardiac arrest due to a potentially reversible cause including the acute phase (24 to 48 hours) of myocardial infarction (MI).⁷⁻⁸ VF in particular is thought to occur as a consequence of ischemia, and thus should be amenable to treatment of ischemia, as opposed to monomorphic VT, which is more common late after myocardial infarction due to reentry around scar. Nonetheless other studies have shown the converse; namely that patients with a potentially reversible cause have a higher mortality in comparison to patients with an established and fixed etiology.⁹ The role of ICD implantation in this population has not been systematically examined in the era of widespread application of rapid coronary revascularization and ICD implantation.¹⁰,¹¹

The aim of this study is to investigate the impact of ICD implantation on long-term outcomes of survivors of VF out-of-hospital cardiac arrest (OHCA) due to acute MI or myocardial ischemia.

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Received July 15, 2014; accepted November 20, 2014.

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DOI: 10.1161/JAHA.114.001255
Methods

Study Population

The study included all patients who received defibrillation by emergency medical personnel for OHCA due to VF with return of spontaneous circulation and survived to discharge in Olmsted County, MN between November 1990 and March 2011. The study was approved by the Institutional Review Boards of Mayo Clinic and Olmsted Medical Center, Rochester, MN. All patients provided consent for the use of medical records for research purposes. Patient demographic data was collected prospectively, while treatment and outcomes were determined retrospectively.

All patients received advanced cardiac life support and early defibrillation by emergency medical personnel. Mayo Clinic, Rochester receives all patients resuscitated for OHCA in Olmsted County. Data regarding baseline characteristics and inpatient management were obtained from Mayo Clinic medical records. The etiology of VF was divided into (1) acute MI, (2) acute myocardial ischemia, and (3) nonischemic etiology. In all cases the rhythm was confirmed by review by an experienced physician who established the Olmsted County resuscitation program (RDW). Acute MI was diagnosed based on elevation of cardiac enzymes (CK-MB or troponin T) and electrocardiographic changes (new ST segment–T wave changes, new left bundle branch block or new pathologic q waves) or angiographic evidence of plaque rupture or thrombosis as per the Universal definition of Myocardial Infarction. Elevation of cardiac enzymes less than 2 times the upper limit of normal was not considered to be evidence of MI since such elevation can also be seen in the setting of cardiac resuscitation without an acute coronary event. Patients without evidence for acute MI who had symptoms of myocardial ischemia prior to the arrest and angiographic evidence of significant coronary artery disease (CAD) (>70% stenosis of 1 or more epicardial coronary arteries) were considered to have acute myocardial ischemia without infarct. One hundred and nine patients (96%) underwent echocardiographic assessment of left ventricular ejection fraction during the hospitalization and repeat assessment was performed in 60 (52%) at a median of 137 (interquartile range 49 to 445) days following discharge. The ejection fraction during index hospitalization was used for analysis. The cerebral performance category (CPC) score was determined prospectively at the time of hospital discharge. CPC score of ≥3 was defined as poor neurologic outcome at discharge.

The outcomes of interest were all-cause mortality, cardiac mortality, and appropriate ICD therapy. Variables related to ICD implantation and subsequent device therapies were obtained from the Mayo Clinic ICD database. All stored device therapy episodes were examined by an electrophysiologist or a specially trained electrophysiology device nurse prospectively to classify them as appropriate or inappropriate. Appropriate ICD therapy was defined as termination of a ventricular arrhythmia with antitachycardia pacing or shock therapy. The ventricular rate prior to the first ICD therapy following implantation was noted when available. All patients were primarily followed in the Mayo device clinic for ICD management and ICD follow-up was considered to have terminated for the purposes of this study if they transferred care to another institution. Data on mortality and cause of death was obtained from the Minnesota Death Index. Cardiac mortality was defined as death primarily due to coronary artery disease, heart failure, cardiac arrhythmias, or sudden death.

Statistical Methods

Categorical variables are summarized as N (%) and compared using the chi-square test. Continuous variables are summarized using mean (SD) or median (interquartile range, IQR) as appropriate and compared using t test or rank sum test. A temporal trend for ICD implantation was analyzed by forming 6 groups of 19 subjects according to date of arrest and plotting the percent of ICD device use versus the mean date of arrest. For mortality analyses, date of arrest was used as time zero. A time-dependent variable was used to model the effect of ICD implantation (in both unadjusted and multivariable models), since implantation may have occurred up to 8 weeks post arrest. For Kaplan-Meier survival plots, a landmark approach was used, with landmark time at 8 weeks, so that any events prior to that time were excluded. For analysis of ICD events in those implanted with the device, time zero was the date of implantation. Cox proportional hazards models were used to estimate both unadjusted and adjusted hazard ratios (95% confidence interval). Covariates for adjustment were chosen from among risk factors that were significant (P<0.05) in the age-adjusted analysis. To avoid estimation problems due to too many variables in the model for cardiac death, we collapsed covariates into a single measure using principal components analysis. After principal components were estimated, the first principal component was used as the covariate for risk adjustment. Principal component analysis is also presented for all-cause mortality. The increased risk of subsequent ICD therapy after 8 months due to early (within first 8 months) ICD therapy was estimated using Poisson regression on the number of events and with the log of follow-up time included as an offset variable. A 2-tailed P<0.05 was considered statistically significant. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC).

Results

Outcomes of VF Out of Hospital Cardiac Arrest

Of the 333 patients treated by emergency medical personnel for VF OHCA, 68 (20%), 19 (6%) and 90 (27%) patients died
pre-hospital, in the emergency room and in the hospital, respectively. One hundred and fifty-six (47%) patients survived to hospital discharge, of whom 114 (73%) were determined to have acute myocardial infarction (AMI) or ischemia as the etiology of the arrest. The etiology of the arrest in the other 42 (27%) patients included dilated cardiomyopathy (n=12), idiopathic VF (8), channelopathy (3), Torsades de pointes (3), myocarditis (2), flail mitral leaflet with severe mitral regurgitation (2), drug induced coronary vasospasm (2), amyloid heart disease (1), hypokalemia (1), and was unknown in 8 patients. Our investigation focuses on the outcomes of 114 survivors of VF arrest due to AMI or ischemia.

Characteristics of Patients With VF Arrest due to Acute Myocardial Infarction or Ischemia

The mean age of survivors of VF OHCA due to AMI or ischemia was 63.5 (11.5) years and 93 (82%) were males. Ninety-one (80%) were diagnosed with AMI (STEMI in 48 and NSTEMI in 43) at the time of the OHCA. Myocardial ischemia related to significant CAD was the likely etiology of VF arrest in 23 (20%). Coronary angiography was performed in 105 (92%) patients during the same admission. Angiography was not performed in the remaining due to known CAD with anatomy unsuitable for revascularization (n=4), significant hypoxic encephalopathy (n=3), and patient’s refusal to undergo angiography (n=2). Coronary revascularization was successfully performed in 67 (59%) patients (percutaneous coronary intervention in 42 and coronary artery bypass surgery in 25) prior to discharge.

An ICD was implanted in 45 (39%) patients within 8 weeks of the index event. The median (IQR) time interval to ICD implantation was 9 (7, 14) days. One patient underwent ICD implantation 1.3 years after the OHCA due to a persistently low EF and was included in the group with no ICD for the purposes of this analysis. The characteristics of patients with and without ICD implantation are presented in Table 1. Figure 1 presents the temporal trends in ICD implantation. A steady increase in the proportion of patients receiving an ICD is noted until 2002 followed by a plateau. Patients who received an ICD were more likely to have coronary ischemia without acute MI (44 versus 4%, P<0.001), but had similar rates of revascularization of the culprit coronary artery (53 versus 62%, P=0.3) and complete coronary revascularization (47 versus 51%, P=0.7) compared with those without ICD. The median (IQR) ejection fraction (EF) was lower in ICD recipients at hospital discharge (38 [26 to 54] versus 48 [35 to 58]%, P=0.04) and at follow-up (35 [29 to 49] versus 48 [36 to 58]%, P=0.06). The CPC score was 1 in 105 (92.1%), 2 in 2 (1.7%), 3 in 6 (5.3%), and 4 in 1 (0.9%) patient. Amiodarone was the most common anti-arrhythmic drug prescribed at discharge and was more likely to be prescribed to patients without an ICD (7 versus 21%, P=0.04).

Risk Factors for Mortality

Fifty-one (45%) patients died over a median follow-up of 9.9 (4.4 to 14.6) years. Survival at 1, 3, and 5 years was 94%, 86%, and 74%, respectively. The majority of patients died of non-cardiovascular illnesses (50%) including malignancy (n=13), anoxic brain injury secondary to the cardiac arrest (n=6), chronic obstructive lung disease (n=3), sepsis (n=2), Alzheimer’s dementia (n=1), and presumptive diagnosis of dehydrated in a 97-year-old (n=1). Cardiovascular mortality occurred in 18/114 (16%) patients. The etiology of cardiovascular death included heart failure (n=9), sudden death in patients without ICD (n=5), acute myocardial infarction (n=3), and stroke secondary to atrial fibrillation (n=1). The cause of death could not be adjudicated in 7 patients.

When adjusted for age, the risk factors for all-cause mortality were: (1) history of peripheral vascular disease (HR 2.84 [1.32 to 6.08], P=0.007), (2) history of chronic obstructive pulmonary disease (HR 2.23 [1.02 to 4.83], P=0.04), (3) higher creatinine at discharge (HR 2.98 [1.73 to 5.14] per 1 mg/dL increase in creatinine, P<0.001), (4) heart failure at discharge (HR 3.02 [1.61 to 5.67], P<0.001), and (5) abnormal CPC score (HR 2.88 [1.21 to 6.82], P=0.016). EF at discharge was not predictive of all-cause mortality (HR 0.99 [0.98 to 1.01] per 1% increase in EF, P=0.5). ICD implantation was not significantly correlated with all-cause mortality in the univariate (HR 0.85 [0.47 to 1.5], P=0.58) analysis. In unadjusted landmark Kaplan-Meier analysis, patients with an ICD had similar survival when compared with those without ICD despite having significantly lower ejection fraction (mean 37.5 versus 49%) (Figure 2A). In the multivariable model, age, peripheral vascular disease, creatinine at discharge, CPC score ≥3, and heart failure independently predicted greater all-cause mortality (Table 2). After adjusting for confounders in the multivariable model, ICD implantation was not associated with a statistically significant reduction in risk of death (HR 0.60 [0.30 to 1.20], P=0.15). When adjusting only for the first principal component of the risk factors a trend towards reduced mortality was seen in ICD recipients (HR 0.56 [0.30 to 1.02], P=0.059), although this did not reach statistical significance (Table 3). When considering only the cohort who were discharged “neurologically intact” (CPC score <3, n=107), ICD implantation showed a trend towards reduced all-cause mortality in the multivariable analysis (HR 0.52 [0.25 to 1.05], P=0.07).

Significant risk factors for cardiac mortality after adjusting for age were: (1) prior history of CAD (HR 2.99 [1.04 to 8.63], P=0.042), (2) shock in hospital (HR 3.9 [1.47 to 10.3], P=0.006), (3) heart failure at discharge (6.86 [2.54 to 18.5], P<0.001), (4) creatinine at discharge (HR 3.39 [1.54 to 7.46] per 1 mg/dL increase, P=0.002) and (5) abnormal CPC score (HR 4.42 [1.25 to 15.6], P=0.021). Complete coronary
revascularization prior to discharge (HR 0.24 [0.07 to 0.85], P=0.027) and higher EF at discharge (HR 0.93 [0.89 to 0.97] per 1% increase in EF, P<0.001) were protective of death from cardiac causes. The unadjusted landmark Kaplan-Meier analysis of cardiac mortality stratified by the presence or absence of ICD is shown in Figure 2B. ICD implantation was

Table 1. Clinical Characteristics of Survivors of Ventricular Fibrillation Out of Hospital Cardiac Arrest due to Myocardial Ischemia: A Comparison of Patients With and Without ICD Implantation Within 8 weeks

| Clinical Characteristic                  | No Implantable Cardioverter Defibrillator (N=69) | Implantable Cardioverter Defibrillator Implanted (N=45) | P Value |
|-----------------------------------------|-------------------------------------------------|--------------------------------------------------------|---------|
| Age, y                                   | 64.2 (11.6)                                     | 62.5 (11.4)                                             | 0.43    |
| Male gender, n (%)                       | 55 (80%)                                        | 38 (84%)                                               | 0.52    |
| Cardiovascular risk factors              |                                                 |                                                        |         |
| Diabetes mellitus, n (%)                 | 11 (16%)                                        | 13 (29%)                                               | 0.11    |
| Hypertension, n (%)                      | 32 (47%)                                        | 28 (62%)                                               | 0.11    |
| Hypercholesterolemia, n (%)              | 35 (51%)                                        | 26 (59%)                                               | 0.43    |
| History of smoking, n (%)                | 45 (70%)                                        | 36 (82%)                                               | 0.39    |
| Past medical history                     |                                                 |                                                        |         |
| Coronary artery disease, n (%)           | 32 (46%)                                        | 26 (58%)                                               | 0.23    |
| Myocardial infarction, n (%)             | 25 (36%)                                        | 24 (53%)                                               | 0.07    |
| Coronary artery bypass surgery, n (%)    | 11 (16%)                                        | 11 (24%)                                               | 0.26    |
| Congestive heart failure, n (%)          | 11 (16%)                                        | 13 (29%)                                               | 0.10    |
| Peripheral vascular disease, n (%)       | 10 (14%)                                        | 6 (13%)                                                | 0.86    |
| Stroke/TIA, n (%)                        | 11 (16%)                                        | 7 (16%)                                                | 0.96    |
| Chronic obstructive pulmonary disease, n (%) | 5 (7%)                                           | 6 (13%)                                                | 0.28    |
| Cause of VF arrest                       | <0.001                                          |                                                        |         |
| ST elevation myocardial infarction, n (%) | 38 (55%)                                        | 10 (22%)                                               |         |
| Non-ST elevation myocardial infarction, n (%) | 28 (41%)                                        | 15 (33%)                                               |         |
| Myocardial ischemia, n (%)               | 3 (4%)                                          | 20 (44%)                                               |         |
| Multivessel disease, n (%)               | 40 (66%)                                        | 31 (72%)                                               | 0.48    |
| Revascularization following VF arrest    |                                                 |                                                        |         |
| Any revascularization                    | 43 (62%)                                        | 24 (53%)                                               | 0.3     |
| Percutaneous coronary intervention       | 34 (49%)                                        | 8 (18%)                                                | 0.001   |
| Coronary artery bypass surgery           | 9 (13%)                                         | 16 (36%)                                               |         |
| Complete coronary revascularization, n (%)| 35 (51%)                                        | 21 (47%)                                               | 0.67    |

ACE indicates angiotensin converting enzyme; ICD, implantable cardioverter defibrillators; TIA, transient ischemic attack; VF, ventricular fibrillation.

Figure 1. Temporal trends in ICD implantation following VF out of hospital cardiac arrest in the setting of MI or acute myocardial ischemia. The ICD implantation status for each patient is provided at the bottom as a function of time. ICD indicates implantable cardioverter defibrillators; VF, ventricular fibrillation.
not a significant predictor of cardiac mortality in the univariate analysis (HR 1.05 [0.39 to 2.78], P = 0.93). Due to the small number of events, we do not present a model for cardiac death adjusted for all covariates. However, after converting the risk factors into a single measure with principal components, ICD was independently associated with lower cardiac mortality (HR 0.24 [0.07 to 0.88], P = 0.031) (Table 3).

Survival was examined in the subgroup of 91 patients with “acute MI” as the etiology of the VF arrest, of whom 25 received an ICD. Subjects with acute MI (n=91) were similar to those with ischemia in terms of age (63 [±12] versus 64 [±10] years, P = 0.8), gender (male 81 versus 83%), and presenting EF (46 [30 to 58] versus 42 [22 to 53] %, P = 0.2), but were more likely to be revascularized (67 versus 26%, P = 0.003). Survival at 1, 3, and 5 years was 94%, 85%, and 77%, respectively, similar to that seen in the overall cohort. In landmark unadjusted Kaplan-Meier analysis, survival in patients with and without an ICD was not significantly different (P = 0.5). In multivariable analysis, ICD implantation was not a significant predictor of survival in this subgroup (HR 1.20 [0.53 to 2.75], P = 0.65).

Appropriate ICD Therapy in Survivors of VF Arrest

One or more appropriate therapies were delivered by the ICD in 19 (42%) of the 45 ICD recipients over a median follow-up of 4.6 (2.7 to 12.3) years. Figure 3 shows the Kaplan-Meier analysis of time to first appropriate ICD therapy stratified by EF. The cumulative incidence of first ICD therapy at 1, 2, and 4 years was 24%, 29%, and 38%, respectively. Two patients received appropriate therapy within 40 days of the OHCA. The risk for first ICD therapy was highest in the first year after implantation. Of the patients who received an appropriate therapy, 53% did so in the first year. In patients with EF >35%, 4 of 22 patients received 1 or more ICD therapies, the risk being the highest in the first 8 months following which no first-time ICD discharges were seen. In contrast, patients with EF ≤35% continued to experience first appropriate ICD therapy throughout the period of follow-up. An appropriate ICD therapy in the first 8 months increased the risk of subsequent therapies, (risk ratio 8.8, 95% CI 6.2 to 12.5). The rate of appropriate ICD therapy in the subgroup with acute MI was similar to the overall cohort: 29 and 33% at 1 and 2 years, respectively.

In univariate analysis, appropriate ICD discharge was associated with advanced age (66.4 [8.6] versus 59.7 [12.2] years, P = 0.02), lower EF (24 [18 to 35] versus 51 [35 to 58]%, P = 0.004), and peripheral vascular disease (21 versus 7%, P = 0.02). Patients who received ICD therapy were less likely to be revascularized (32% versus 67%, P = 0.02) and had a trend towards higher rates of heart failure after OHCA (47 versus 15%, P = 0.06) and history of MI prior to OHCA (68 versus 44%.

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**Table 2. Multivariable Analysis of Risk Factors for All-Cause Mortality Following Out of Hospital Cardiac Arrest**

| Risk Factor                        | Hazard Ratio (95% CI) | P Value |
|------------------------------------|-----------------------|---------|
| ICD implantation                   | 0.60 (0.30 to 1.20)   | 0.15    |
| Age (per 10 year increment)        | 1.73 (1.27 to 2.36)   | <.001   |
| Peripheral vascular disease        | 2.66 (1.19 to 5.93)   | 0.017   |
| Discharge creatinine (per 1 mg/dL increment) | 2.74 (1.42 to 5.28) | 0.003   |
| Congestive heart failure           | 2.87 (1.27, 6.48)     | 0.011   |
| Chronic obstructive pulmonary disease | 1.10 (0.42 to 2.86) | 0.85    |
| Abnormal CPC score                 | 2.55 (1.00 to 6.53)   | 0.050   |

All variables included in the model are presented above. CPC indicates cerebral performance category; ICD, implantable cardioverter defibrillators.

DOI: 10.1161/JAHA.114.001255

**Figure 2.** A, Unadjusted landmark Kaplan-Meier analysis of all-cause mortality stratified by ICD implantation status, beginning 8 weeks after index event. Mortality in patients with an ICD was similar to that of those without an ICD despite significantly lower ejection fraction (inset). B, Unadjusted landmark Kaplan-Meier analysis of cardiac mortality stratified by ICD implantation status. ICD indicates implantable cardioverter defibrillators.
Recurrent VT/VF or Sudden Death in Patients Without ICD Implantation

Of the 63 patients who did not undergo ICD implantation, 5 experienced sudden death and 1 had syncope with documented ventricular arrhythmia a median of 530 (interquartile range 272 to 1828) days after the index event. This included 2 patients who declined ICD, 1 patient with hypoxic encephalopathy, and 2 patients with and without revascularization with EF >35%. Patients who experienced recurrent arrhythmia or sudden death were significantly older (75 [14] versus 63 [11]%, P=0.02). All 6 patients had the index OHCA event in the setting of an AMI but only 2 were revascularized. The median EF of the 6 patients was 27 (range 20 to 47.5)%. Only 1 patient who experienced subsequent sudden death was revascularized and had an ejection fraction >35% at the time of the index OHCA.

Discussion

We present the long-term outcomes following ICD implantation for out-of-hospital cardiac arrest due to VF in the setting of acute myocardial infarction or ischemia in a population-based cohort. The main findings of the study are: (1) ICD implantation may be associated with reduced cardiac mortality after adjusting for other risk factors, (2) risk factors for all-cause mortality include advanced age, higher serum creatinine levels, peripheral vascular disease, cardiogenic shock during hospitalization, complete revascularization, ejection fraction at discharge, congestive heart failure, and abnormal CPC score. The first principal component accounted for 31% of the variance of the risk factors.

When grouped by revascularization status and EF dichotomized at 35%, no subgroup free of ICD therapy could be identified. However, only 4/19 patients with ICD therapy had EF >35%. In multivariable analysis, advanced age (HR per 10 year increment 1.82 [1.02 to 3.23], P=0.04), but not EF or revascularization status, was significantly associated with ICD therapies. The rate of ventricular arrhythmia leading to the first appropriate ICD therapy was available in 18 patients. Ventricular rate of tachyarrhythmias was <180 bpm in 2 patients, 180 to 220 bpm in 8 patients, and >220 bpm in 8 patients.

![Figure 3. Kaplan-Meier analysis of time to first appropriate ICD therapy stratified by discharge ejection fraction. ICD indicates implantable cardioverter defibrillators.](image)

P=0.07). When grouped by revascularization status and EF dichotomized at 35%, no subgroup free of ICD therapy could be identified. However, only 4/19 patients with ICD therapy had EF >35%. In multivariable analysis, advanced age (HR per 10 year increment 1.82 [1.02 to 3.23], P=0.04), but not EF or revascularization status, was significantly associated with ICD therapies.

The rate of ventricular arrhythmia leading to the first appropriate ICD therapy was available in 18 patients. Ventricular rate of tachyarrhythmias was <180 bpm in 2 patients, 180 to 220 bpm in 8 patients, and >220 bpm in 8 patients.

Table 3. Risk Adjusted Estimates for Mortality Based on the First Principal Component of the Covariates

| Endpoint                  | Hazard Ratio (95% CI) | P Value |
|---------------------------|-----------------------|---------|
| All-cause mortality       |                       |         |
| ICD implantation          | 0.56 (0.30 to 1.02)   | 0.059   |
| Risk factors (first principal component*) | 1.86 (1.54 to 2.26) | <0.001 |
| Cardiac mortality         |                       |         |
| ICD implantation          | 0.24 (0.07 to 0.88)   | 0.031   |
| Risk factors (first principal component*) | 3.81 (2.16 to 6.73) | <0.001 |

CPC indicates cerebral performance category; ICD, implantable cardioverter defibrillators.

*Based on age, peripheral vascular disease, chronic obstructive pulmonary disease, creatinine at discharge, congestive heart failure, and abnormal CPC score. The first principal component accounted for 27% of the variance of the risk factors.

**Based on age, prior coronary artery disease, cardiogenic shock during hospitalization, complete revascularization, ejection fraction at discharge, congestive heart failure, and abnormal CPC score. The first principal component accounted for 31% of the variance of the risk factors.
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reduced mortality (associated with all-cause mortality, although a trend towards lower mortality was noted in those with CPC ≤3). When the subgroup with acute MI alone was considered, ICD implantation again was not significantly predictive of all-cause mortality. The mortality rate of survivors of OHCA in our study is comparable to that reported by Borleffs et al in the Leiden out-of-hospital cardiac arrest study. The predictors of death in the current study included higher age, poor renal function, poor neurological recovery following OHCA, peripheral artery disease, and heart failure. The majority of deaths were, however, due to non-cardiac illness or heart failure, with arrhythmic death being uncommon even among patients without an ICD.

Over a median follow-up of 4.6 years, 40% of ICD recipients received at least 1 appropriate therapy. This was also true of the subgroup with acute MI as the etiology of VF arrest. The high risk despite a reversible cause as the presumed trigger likely reflects the substantial residual substrate abnormalities in many patients. The rate of ICD therapy in this study (35% at 3 years) is lower than that observed in trials of secondary prevention of sudden death due to a non-reversible cause such as AVID (69% at 3 years) and higher than that noted in primary prevention trials (21% at 3.8y in SCDHeFT). Our findings are, however, comparable to the rate of appropriate ICD therapy noted in the Leiden out-of-hospital cardiac arrest study, which included patients with an "irreversible cause." The higher rate of ICD therapy noted in the AVID trial could be explained by the limited capability in the trial to differentiate appropriate from inappropriate therapy. These results should also be interpreted in light of the fact that differences in ICD programming significantly influence ICD therapy rate.

Patients with EF ≤35% at the time of discharge were at higher risk of recurrent ventricular arrhythmia. This suggests that the magnitude of myocardial injury at the time of the index event and potentially LV function prior to OHCA modulates the risk of subsequent VT/VF. This is consistent with observations from randomized controlled trials of secondary prevention in which patients with EF <35% benefit the most from ICD implantation. A retrospective analysis of the AVID trial and a meta-analysis of 3 secondary prevention trials noted that while ICD improved survival in patients with EF <35%, survival of those with EF ≥35% was similar to that of patients treated with antiarrhythmic drug.

Despite the overall lower risk of ICD therapy, patients with EF >35% were at risk of ICD therapy in the first 8 months after OHCA. Absence of arrhythmia recurrence in the first 8 months predicted continued arrhythmia-free survival in the long term. Heart failure and myocardial remodeling soon after an MI may explain increased risk for early recurrence of arrhythmia. However, the continued long-term risk for recurrent VT/VF in patients with early recurrence could suggest the persistence of an underlying arrhythmic substrate in these patients. Epstein et al reported the feasibility and efficacy of use of a wearable cardiac defibrillator in high risk patients following AMI. Our results suggest that temporary defibrillator support such as the wearable cardiac defibrillator may be reasonable in OHCA survivors with EF >35%, with no further escalation to ICD implantation in the absence of a relatively early recurrence of ventricular arrhythmia.

Half of the ICD recipients who had recurrent arrhythmia died so in the first year and early recurrence increased the risk for subsequent arrhythmia by 8-fold. Prior studies have shown a similar high risk of death from arrhythmias in the first 6 to 12 months after an AMI in patients without OHCA. However, the randomized controlled DINAMIT and IRIS trials did not show improved overall survival with ICD implantation following recent MI despite a reduction in arrhythmic death. Of note, patients with a primary VF arrest were excluded from randomization in these trials. The findings of the current study parallel these findings and suggest that the reduced cardiac mortality due to early ICD implantation after VF OHCA may be offset by increased mortality due to non-cardiac causes.

We could not identify a clinically relevant subgroup of patients completely free of ICD therapy. EF was not significantly associated with subsequent ICD therapy in the multivariable analysis, although effect of the small sample size cannot be ruled out. While patients who presented with coronary ischemia without infarction were more likely to receive an ICD compared with those who presented with AMI, the initial presentation did not significantly predict subsequent ICD therapies. Furthermore, while revascularization was protective of recurrent VT/VF in the univariate analysis, this was not the case after adjusting for age and EF. These findings underscore the difficulty in clinically identifying patients who are truly at low risk even in the presence of a so-called "reversible cause."

Limitations
The current study has the limitations of a retrospective non-randomized, single-center study. The decision to implant an ICD was likely biased by multiple factors and only known confounders were adjusted for using multivariable analysis. There may be unknown confounders for which we could not adjust. Furthermore, the small sample size limited our ability to adjust for confounders. Our finding of significant association between ICD implantation and reduced cardiac mortality was based on adjusting for the first principal component of the risk factors, which is not the same as adjusting for the risk factors themselves and certainly involves some loss of information. The sample size also limited our power to detect small differences in the outcomes of interest as was noted with the impact of ICD implantation on all-cause mortality.
This highlights the need for a prospective large, multicenter, randomized study of the utility of ICD implantation in this population. Distinguishing myocardial ischemia as the primary etiology of VF from ischemia secondary to the arrest can be challenging. We restricted our analysis to patients who had documented symptoms of ischemia prior to the arrest and significant CAD. Further subgroup analysis of patients with acute MI only showed trends similar to the overall cohort, ie, no significant association between ICD implantation and survival. Therapy delivered by an ICD does not always equate to aborted sudden death and device programming can significantly affect the number of therapies delivered. The majority of ICD-treated VT/VF had rate >180 bpm and was highly likely to be clinically relevant. Moreover, the occurrence of appropriate therapies does indicate the continued presence of a substrate for recurrent ventricular arrhythmias in this population. The risk analysis in this study was based on events at the time of the index OHCA and subsequent outcomes could have been affected by dynamic changes in the disease process. Finally, the use of administrative data to ascertain cause of death could potentially lead to misclassification.

Conclusions
We report outcomes following VF OHCA in the setting of acute MI or acute ischemia in a population-based sample. Patients with VF OHCA in the setting of acute MI or myocardial ischemia remain at high risk of recurrent ventricular arrhythmias and ICD implantation may be associated with reduced risk of cardiac mortality and a statistically non-significant trend towards reduction in all-cause mortality. The role of ICD implantation in VF OHCA due to a “potentially reversible cause” warrants further investigation in a large prospective multicenter registry and a randomized controlled trial. In the absence of such data, patients with pre-discharge EF ≤35% could reasonably be considered for ICD implantation due to significant long-term risk of recurrent arrhythmias and ICD therapy. Our findings in general support the recommendations for appropriate use of ICD published by the American Heart Association.25 Patients with EF >35% have a significant early risk, which then stabilizes; the use of a temporary defibrillator such as a wearable cardiac defibrillator and the role of ICD implantation should be further investigated.

Sources of Funding
This publication was made possible by Center for Translational Sciences Activities Grant Number UL1 TR000135 from the National Center for Advancing Translational Sciences (NCATS), a component of the National Institutes of Health (NIH). Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NIH.

Disclosures
None.

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