# Implantable Defibrillator Therapy in Cardiac Arrest Survivors With a Reversible Cause

See Editorial by Patton and Poole

**BACKGROUND:** Current guidelines recommend implantable cardioverter-defibrillator (ICD) therapy in survivors of sudden cardiac arrest (SCA), except in those with completely reversible causes. We sought to examine the impact of ICD therapy on mortality in survivors of SCA associated with reversible causes.

**METHODS AND RESULTS:** We evaluated the records of 1433 patients managed at our institution between 2000 and 2012 who were discharged alive after SCA. A reversible and correctable cause was identified in 792 (55%) patients. Reversible SCA cause was defined as significant electrolyte or metabolic abnormality, evidence of acute myocardial infarction or ischemia, recent initiation of antiarrhythmic drug or illicit drug use, or other reversible circumstances. Of the 792 SCA survivors because of a reversible and correctable cause (age 61±15 years, 40% women), 207 (26%) patients received an ICD after their index SCA. During a mean follow-up of 3.8±3.1 years, 319 (40%) patients died. ICD implantation was highly associated with lower all-cause mortality ($P$<0.001) even after correcting for unbalanced baseline characteristics ($P$<0.001). In subgroup analyses, only patients whose SCA was not associated with myocardial infarction extracted benefit from ICD ($P$<0.001).

**CONCLUSIONS:** In survivors of SCA because of a reversible and correctable cause, ICD therapy is associated with lower all-cause mortality except if the SCA was because of myocardial infarction. These data deserve further investigation in a prospective multicenter randomized controlled trial, as they may have important and immediate clinical implications.

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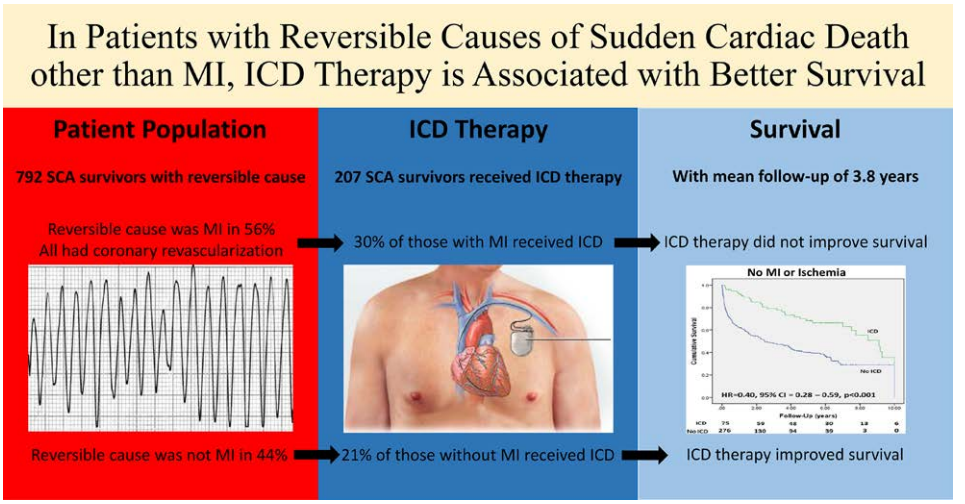


Sudden cardiac arrest (SCA) is the number one cause of death in adults in industrialized countries, with an annual mortality in the United States surpassing 300 000.[1–7] Implantable cardioverter-defibrillators (ICDs) are implanted in high-risk patients to prevent SCA as many of these patients are at risk for subsequent lethal ventricular arrhythmia. Large randomized trials[8–10] have demonstrated benefits of ICD therapy in reducing all-cause mortality in patients with ventricular arrhythmias notably ventricular fibrillation or hemodynamically unstable ventricular tachycardia. On the basis of these trials, published guidelines recommend ICD implantation in survivors of SCA unless the cause of the SCA is deemed reversible and correctible.[11,12] Reversible causes of SCA are reported in 12% to 73% of cases but usually account for ≈50% of SCA.[13,14] In patients with a reversible cause of SCA, an ICD is implanted in ≈40% of survivors[13] without clear evidence to guide this decision.

Determining the exact cause of an SCA and whether it is reversible is fraught with uncertainty. Presumed reversible causes of SCA, such as electrolyte abnormalities, may be consequences of the SCA and associated resuscitation efforts. In addition, reversible causes of SCA, such as myocardial infarction (MI) or ischemia, may not be avoidable in follow-up and may unveil a predisposition, perhaps genetic, to electric instability in certain individuals. In fact, analyses of the AVID (Antiarrhythmics Versus Implantable Defibrillators) registry[14,15] have demonstrated a very high all-cause mortality and SCD during follow-up in survivors of SCA associated with a reversible cause. Thus, although unproven, the presence of an identified reversible cause for SCA may not preclude risk of future ventricular arrhythmias, and ICD therapy may therefore improve survival. The present study examined these questions in a large cohort of SCA survivors.

### WHAT IS KNOWN?

- Implantable cardioverter-defibrillators are indicated for survivors of sudden cardiac arrest (SCA), except for those whose SCA occurs in the context of a reversible and correctible cause.
- Reversible and correctible causes of SCA are not clearly defined.
- Patients who survive an SCA in the context of a presumed reversible cause have a high mortality rate.

### WHAT THE STUDY ADDS?

- More than half of the patients who survive an SCA in the context of a reversible and correctable cause have an acute myocardial infarction or myocardial ischemia.
- In patients with reversible cause of SCA, implantable cardioverter-defibrillator therapy is delivered to 26% of patients and is associated with a lower all-cause mortality, even after adjusting for baseline cofounders.
- In subgroup analysis, implantable cardioverter-defibrillator therapy was associated with lower mortality in all survivors of SCA because of a reversible cause, except in those who presented with acute myocardial infarction and underwent complete revascularization.

## METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure.

### Patient Population

Survivors of SCA admitted to the hospitals of the University of Pittsburgh Medical Center between 2000 and 2012 were included in this analysis. The University of Pittsburgh

Institutional Review Board approved this study before initiating any research activities and waived the need to obtain informed consent given the retrospective nature of this analysis. Patients with *International Classification of Disease*, *9th Revision*, Clinical Modification codes for ventricular fibrillation (427.41), ventricular flutter (427.42), ventricular tachycardia (427.1), and cardiac arrest (427.5), who were 18 years of age or older at the time of the index SCA and who did not have an indwelling ICD were identified from the electronic medical record. A total of 3426 patient records with these primary discharge diagnoses were identified. The electronic records of all patients were then manually reviewed to ascertain the actual presence of SCA and the absence of prior ICD implantation. Of the original 3426 records identified, 1375 patients were excluded because the review revealed no actual SCA event and another 618 were excluded because of duplicate entries. The total cohort therefore consisted of 1433 unique patients who were admitted for SCA and were discharged alive from the hospital.

Baseline characteristics, including demographic and clinical data, were obtained on all patients. Details of the SCA including the location (in hospital or out of hospital), the first identified rhythm, admission vital signs, possible reversible causes present on admission, and corrective measures applied during the index hospitalization were obtained from available electronic medical records including notes from emergency medical services, emergency departments, and hospital SCA response team. Reversible causes of SCA were classified according to the AVID registry definition[14,15] and are detailed in Table 1. Our patient classification algorithm was established before initiation of data collection. When no clear cause of SCA could be found after extensive chart review, the SCA was classified as nonreversible. If a reversible cause was identified, it was automatically deemed correctable during the index hospitalization if the cause was thought to be secondary to (1) electrolyte abnormalities (n=160), (2) metabolic abnormalities (n=103), (3) recent initiation of a new antiarrhythmic drug (n=27), (4) illicit drug use (n=61), (5) Wolff–Parkinson–White syndrome (n=0), or (6) other circumstances (n=0) as detailed in Table 1. When SCA was thought to be secondary to myocardial ischemia (n=4) or MI (n=437), it was considered reversed only if the patient underwent coronary revascularization. Using this classification scheme, of the overall cohort of 1433 patients, 375 had no reversible identifiable cause of SCA and 71 had an identifiable reversible cause that could not be corrected. The remaining 792 patients with reversible and corrected causes of SCA constituted our final study population.

Patients were followed from the date of SCA to the primary outcome of all-cause death or until February 20, 2017, through careful review of the electronic medical records. Cases were censored at the date of last follow-up. The cause of death was classified as cardiac or noncardiac by data abstractors and could be identified in 120 out of 319 deaths (38%). ICD implantation during the index hospitalization or in follow-up was recorded for all patients.

## Statistical Analysis

Continuous variables are presented as mean±SD and compared between groups using the Student *t* test, if normally distributed or Mann–Whitney *U* test if non-normally distributed. Discrete variables are presented as frequencies and percentages and were compared using the $\chi^2$ test or Fisher exact test in case of small sample sizes within cells. Time to events (eg, death) was compared between ICD recipients and nonrecipients using Kaplan–Meier survival curves and compared between groups using the log-rank test. After verifying that the proportional hazard assumption was satisfied, independent predictors of mortality were assessed using Cox regression models in which all independent baseline characteristics with *P* value <0.10 on univariate analysis were included. Statistical significance was defined as a 2-sided *P* value <0.05. All statistical analyses were performed on SPSS version 24 software (IBM, Armonk, NY).

**Table 1. Definitions of Reversible Causes of SCA**

| Categories of Reversible Causes |
|---|
| 1. Significant electrolyte abnormalities at first blood test after index SCA ($K^+$≤3.0 mEq/L or >5.5 mEq/L or $Mg^{2+}$≤1.2 mEq/L) |
| 2. Significant metabolic abnormalities at first blood test after index SCA ($HCO_3^-$≤16 or ≥32 mmol/L) |
| 3. Evidence of acute MI |
| a. Coronary angiographic diagnosis of acute coronary occlusion |
| b. Elevated cardiac enzymes with ST elevation on surface ECG |
| c. Elevated cardiac enzymes with first documented left bundle branch block on surface ECG |
| d. Elevated cardiac enzymes with ST depression on surface ECG or first documented regional wall motion abnormalities by cardiac imaging |
| 4. Evidence of cardiac ischemia without MI |
| a. Evidence of ischemia on stress cardiac imaging with normal cardiac enzyme levels |
| b. Chest pain preceding SCA and first documented ST-T wave abnormalities on surface ECG with normal cardiac enzyme levels |
| c. Angiographic diagnosis of significant stenosis (>75%) of an epicardial coronary artery and first documented ST-T wave abnormalities on surface ECG with normal cardiac enzyme levels |
| 5. Antiarrhythmic medication reaction: initiation of new antiarrhythmic medication (Vaughan Williams class I or III) within 1 wk of SCA |
| 6. History of or positive blood test for illicit drug use (eg, cocaine) within 24 h of index SCA |
| 7. Other circumstances at the time of SCA (eg, sepsis, trauma, hemorrhage, drowning, electrocution, choking) |
| 8. Evidence of Wolff–Parkinson–White preexcitation pattern on surface ECG |

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

**Table 2. Baseline Characteristics of Cardiac Arrest Patients Associated With a Reversible Cause by Survival Status and ICD Implantation Status**

| | Total (N=792) | Alive (N=473) | Dead (N=319) | *P* Value | ICD (N=207) | No ICD (N=585) | *P* Value |
|---|---|---|---|---|---|---|---|
| Demographics | | | | | | | |
| Age, y | 61±15 | 57±14 | 66±15 | <0.001 | 60±15 | 61±16 | 0.53 |
| Female sex | 40% | 36% | 46% | 0.005 | 33% | 42% | 0.032 |
| Race | | | | 0.020 | | | 0.30 |
| White | 83% | 86% | 79% | | 86% | 82% | |
| Black | 11% | 9% | 13% | | 9% | 11% | |
| Cardiac disease | | | | | | | |
| Any coronary artery disease | 71% | 79% | 65% | 0.001 | 82% | 68% | <0.001 |
| Any myocardial infarction | 62% | 62% | 58% | <0.001 | 71% | 58% | 0.001 |
| Any coronary artery bypass grafting | 25% | 24% | 26% | 0.30 | 29% | 23% | 0.11 |
| Any percutaneous coronary intervention | 47% | 54% | 37% | <0.001 | 54% | 45% | 0.043 |
| Atrial fibrillation | 29% | 22% | 40% | <0.001 | 33% | 28% | 0.21 |
| Ejection fraction (%) | 44±15 | 44±15 | 44±16 | 0.80 | 38±16 | 47±14 | <0.001 |
| New York Heart Association | 21.9±0.9 | 1.6±0.8 | 2.2±0.9 | 0.008 | 1.9±0.9 | 1.9±0.9 | 0.92 |
| New York Heart Association | | | | 0.062 | | | 0.80 |
| Class I | 42% | 58% | 31% | | 40% | 44% | |
| Class II | 23% | 23% | 24% | | 28% | 21% | |
| Class III | 32% | 19% | 40% | | 28% | 33% | |
| Class IV | 3% | 0% | 5% | | 4% | 2% | |
| Comorbidities | | | | | | | |
| Diabetes mellitus | 32% | 24% | 45% | <0.001 | 32% | 32% | 0.93 |
| Hypertension | 60% | 59% | 61% | 0.61 | 63% | 59% | 0.36 |
| Peripheral vascular disease | 10% | 7% | 15% | <0.001 | 14% | 9% | 0.06 |
| Chronic obstructive pulmonary disease | 32% | 24% | 42% | <0.001 | 30% | 32% | 0.54 |
| Chronic kidney disease or dialysis | 12% | 4% | 25% | <0.001 | 9% | 13% | 0.14 |
| Moderate/severe liver disease | 1.1% | 0.4% | 2.2% | 0.034 | 1.0% | 1.2% | 1.00 |
| Dementia | 2.1% | 0.8% | 4.1% | <0.001 | 1.0% | 2.6% | 0.26 |
| Malignancy | 8% | 4% | 15% | <0.001 | 7% | 9% | 0.38 |
| Body mass index, kg/m$^2$ | 30±8 | 30±7 | 30±9 | 0.22 | 30±6 | 30±8 | 0.73 |
| Charlson comorbidity index | 2.53±2.17 | 1.94±1.57 | 3.43±2.60 | <0.001 | 2.52±2.03 | 2.53±2.22 | 0.79 |
| Electrocardiographic parameters | | | | | | | |
| PR interval, ms | 167±40 | 166±40 | 170±42 | 0.20 | 169±40 | 167±41 | 0.52 |
| QRS duration, ms | 101±31 | 102±26 | 110±36 | 0.006 | 111±31 | 103±30 | <0.001 |
| QT interval, ms | 400±68 | 398±66 | 403±71 | 0.48 | 412±77 | 396±64 | 0.050 |
| QTc interval, ms | 471±55 | 468±54 | 477±56 | 0.027 | 479±61 | 469±52 | 0.09 |
| Laboratory values | | | | | | | |
| Serum potassium, mEq/L | 4.3±1.9 | 4.1±1.2 | 4.6±2.6 | 0.001 | 4.2±1.1 | 4.4±2.1 | 0.62 |
| Serum magnesium, mEq/L | 2.0±0.6 | 2.0±0.5 | 2.0±0.6 | 0.68 | 2.0±0.6 | 2.1±0.6 | 0.017 |
| Serum bicarbonate, mmol/L | 24±6 | 23±5 | 24±7 | 0.001 | 24±7 | 23±6 | 0.80 |
| Troponin I, µg/L | 15±53 | 18±60 | 10±40 | <0.001 | 15±64 | 15±48 | 0.63 |
| Creatinine phosphokinase-MB (µg/L) | 74±158 | 85±171 | 57±134 | 0.18 | 41±85 | 91±182 | 0.030 |

(*Continued*)

**Table 2. Continued**

| | Total (N=792) | Alive (N=473) | Dead (N=319) | *P* Value | ICD (N=207) | No ICD (N=585) | *P* Value |
|---|---|---|---|---|---|---|---|
| Vital signs at admission | | | | | | | |
| Heart rate (beats per minute) | 88±25 | 88±24 | 90±27 | 0.51 | 87±23 | 89±27 | 0.42 |
| Systolic blood pressure, mm Hg | 128±30 | 128±30 | 127±31 | 0.81 | 131±27 | 126±31 | 0.054 |
| Diastolic blood pressure, mm Hg | 72±30 | 74±34 | 69±21 | 0.003 | 74±22 | 72±32 | 0.07 |
| Cardiac arrest | | | | | | | |
| Location (out of hospital) | 45% | 47% | 42% | 0.014 | 60% | 40% | <0.001 |
| Initial rhythm of cardiac arrest | | | | <0.001 | | | <0.001 |
| Ventricular tachycardia | 13% | 13% | 13% | | 20% | 11% | |
| Ventricular fibrillation | 49% | 58% | 36% | | 69% | 42% | |
| Asystole | 10% | 7% | 14% | | 2% | 13% | |
| Pulseless electric activity | 10% | 8% | 14% | | 2% | 13% | |
| Unspecified | 18% | 15% | 22% | | 7% | 21% | |
| Index hospitalization | | | | | | | |
| Length of stay, d | 14±14 | 12±12 | 18±17 | <0.001 | 13±12 | 15±15 | 0.26 |

ICD indicates implantable cardioverter-defibrillator.

## RESULTS

Baseline characteristics of SCA survivors from a reversible and corrected cause are detailed in Table 2. Our study cohort consisted mainly of white men with high prevalence of medical comorbidities, including coronary artery disease, diabetes mellitus, hypertension, chronic obstructive pulmonary disease, and atrial fibrillation. The mean left ventricular systolic function for the overall cohort was mildly reduced. About half of all SCA events occurred outside of the hospital, whereas the other half occurred during in-hospital care. The presenting rhythm of SCA could be determined in 652 patients (82%) and consisted primarily of ventricular fibrillation (49%). Of the overall cohort, 207 patients (26%) received an ICD after the index SCA.

During a mean follow-up of 3.8±3.1 years, 319 (40%) patients died. Table 2 details the baseline characteristics of patients who died during follow-up compared with those who survived. Table 2 details the baseline characteristics of patients who received an ICD after the index SCA compared with those who did not. Patients who died were older, were more likely to be women, and had a higher prevalence of certain comorbidities, including atrial fibrillation, chronic obstructive pulmonary disease, peripheral vascular disease, and chronic kidney disease, reflected in a significantly higher Charlson comorbidity index. Patients who died during follow-up also had a wider QRS complex on the surface ECG and had more advanced symptoms of heart failure compared with patients who survived despite comparable left ventricular ejection fraction. Interestingly, patients who died were less likely to have MI or ischemia as a reversible cause of SCA at presentation compared with patients whose SCA was associated with other reversible causes (39% versus 67%; *P*<0.00; Table 3). Baseline characteristics of patients with MI or ischemia versus those with other reversible causes of SCA are shown in Table 4. As expected, those presenting with SCA in the context of MI or ischemia were more likely to undergo coronary

**Table 3. Frequency of Reversible Causes of SCA in the Overall Cohort and by Survival Status and ICD Implantation Status**

| Reversible Cause of SCA | Total (N=792) | Survival Status | | ICD Status | |
|---|---|---|---|---|---|
| | | Dead (N=319) | Alive (N=473) | ICD (N=207) | No ICD (N=585) |
| Myocardial infarction | 437 (55%) | 123 (38%) | 314 (66%) | 130 (63%) | 307 (52%) |
| Myocardial ischemia | 4 (1%) | 3 (1%) | 1 (1%) | 2 (1%) | 2 (1%) |
| Electrolyte abnormalities | 160 (20%) | 88 (27%) | 72 (15%) | 40 (19%) | 120 (20%) |
| Metabolic abnormalities | 103 (13%) | 69 (22%) | 34 (7%) | 14 (7%) | 89 (15%) |
| Illicit drug abuse | 61 (8%) | 24 (8%) | 37 (8%) | 10 (5%) | 51 (9%) |
| New antiarrhythmic drug | 27 (3%) | 12 (4%) | 15 (3%) | 11 (5%) | 16 (3%) |

ICD indicates implantable cardioverter-defibrillator; and SCA, sudden cardiac arrest.

**Table 4. Baseline Characteristics of Patients With Cardiac Arrest Associated With Myocardial Infarction or Ischemia Versus Other Causes**

| | MI/ Ischemia (N=441) | Other Causes (N=351) | *P* Value |
|---|---|---|---|
| Demographics | | | |
| Age, y | 62±12 | 59±18 | 0.002 |
| Female sex | 31% | 50% | <0.001 |
| Race | | | 0.024 |
| White | 88% | 78% | |
| Black | 6% | 17% | |
| Cardiac disease | | | |
| Any coronary artery disease | 99% | 36% | <0.001 |
| Any myocardial infarction | 99% | 14% | <0.001 |
| Any coronary artery bypass grafting | 35% | 12% | <0.001 |
| Any percutaneous coronary intervention | 79% | 8% | <0.001 |
| Atrial fibrillation | 16% | 14% | 0.039 |
| Ejection fraction (%) | 42±15 | 49±16 | <0.001 |
| New York Heart Association | 1.7±0.9 | 2.2±0.9 | 0.024 |
| New York Heart Association | | | 0.097 |
| Class I | 54% | 29% | |
| Class II | 20% | 27% | |
| Class III | 26% | 38% | |
| Class IV | 0% | 6% | |
| Comorbidities | | | |
| Diabetes mellitus | 29% | 37% | 0.018 |
| Hypertension | 62% | 57% | 0.13 |
| Peripheral vascular disease | 13% | 8% | 0.026 |
| Chronic obstructive pulmonary disease | 25% | 40% | <0.001 |
| Chronic kidney disease or dialysis | 7% | 18% | <0.001 |
| Moderate/severe liver disease | 0.0% | 2.6% | 0.001 |
| Dementia | 0.9% | 3.7% | 0.011 |
| Malignancy | 6% | 11% | 0.020 |
| Body mass index, kg/m$^2$ | 30±6 | 30±9 | 0.047 |
| Charlson comorbidity index | 2.52±1.91 | 2.54±2.46 | 0.12 |
| Electrocardiographic parameters | | | |
| PR interval, ms | 172±43 | 161±36 | <0.001 |
| QRS duration, ms | 105±27 | 106±35 | 0.22 |
| QT interval, ms | 402±59 | 397±77 | 0.06 |
| QTc interval, ms | 465±33 | 479±62 | 0.002 |
| Laboratory values | | | |
| Serum potassium, mEq/L | 4.1±1.0 | 4.6±2.7 | 0.08 |
| Serum magnesium, mEq/L | 2.1±0.5 | 2.0±0.6 | 0.006 |
| Serum bicarbonate, mmol/L | 23±4 | 24±8 | 0.005 |
| Troponin I, μg/L | 25±67 | 2±7 | <0.001 |
| Creatinine phosphokinase-MB, μg/L | 109±190 | 21±63 | <0.001 |
| Vital signs at admission | | | |
| Heart rate (beats per minute) | 84±22 | 94±28 | <0.001 |
| Systolic blood pressure, mm Hg | 128±31 | 127±30 | 0.65 |
| Diastolic blood pressure, mm Hg | 72±21 | 73±38 | 0.70 |
| Cardiac arrest | | | |
| Location (out of hospital) | 47% | 42% | 0.13 |
| Initial rhythm of cardiac arrest | | | <0.001 |
| Ventricular tachycardia | 15% | 11% | |
| Ventricular fibrillation | 67% | 28% | |
| Asystole | 5% | 15% | |
| Pulseless electric activity | 2% | 21% | |
| Unspecified | 11% | 25% | |
| Index hospitalization | | | |
| Length of stay, d | 13±14 | 17±15 | <0.001 |

MI indicates myocardial infarction.

revascularization. They were also more likely to be men and to have ventricular tachycardia or fibrillation as a presenting SCA rhythm. Although the 2 groups had comparable Charlson comorbidity indices, those presenting with SCA in the context of MI or ischemia had a shorter length of stay for their index hospitalization.

During the period of follow-up, 207 patients (26%) received an ICD. The device implantation was in the context of the index hospitalization for SCA in 83% of patients. Patients who received an ICD were more likely to be men with coronary artery disease and MI and had lower left ventricular ejection fraction and longer QRS and QTc intervals on the surface ECG. Importantly, they were also more likely to have ventricular tachycardia or fibrillation as their initial documented cardiac rhythm (Table 2). Compared with patients who were not implanted with a defibrillator, ICD recipients had significantly lower mortality (hazard ratio, 0.61; 95% CI, 0.47–0.80; *P*<0.001; Figure 1A) even after correcting for unbalanced baseline characteristics (hazard ratio, 0.10; 95% CI, 0.03–0.33; *P*<0.001; Table 5), and survival in ICD recipients remained superior compared with patients with no ICD when examining several patient subgroups by age, sex, race, left ventricular ejection fraction, and location of SCA (Figure 2). However, when separating patients by type of reversible cause of SCA, the ICD survival benefit was not present in patients whose SCA was associated with MI or cardiac ischemia (hazard ratio, 1.04; 95% CI, 0.72–1.51; *P*=0.83; Figure 1B) but was demonstrated exclusively in those patients whose SCA was not associated with MI or car-

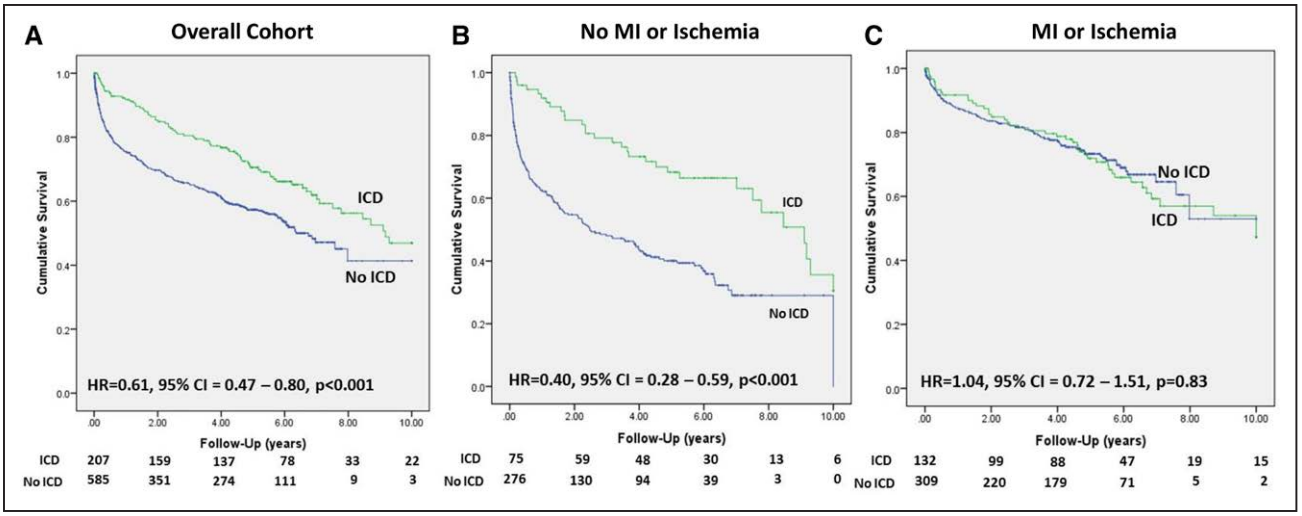


**Figure 1. Survival of patients with versus without implantable cardioverter-defibrillator (ICD) by reversible cause of sudden cardiac arrest (SCA).**
Kaplan–Meier survival curves for the cohort of patients with reversible and corrected cause of SCA, stratified by ICD therapy status for the overall cohort (**A**), for patients whose SCA was associated with myocardial infarction (MI) or cardiac ischemia (**B**), and for patients whose SCA was not associated with MI or ischemia (**C**).

diac ischemia group (hazard ratio, 0.40; 95% CI, 0.28–0.59; *P*<0.001; Figures 1C and 2). After correcting for unbalanced baseline characteristics between patients who died and those who did not, including age, sex, location of SCA, and presenting rhythm among other covariates, the presence of an ICD remained highly associated with lower all-cause mortality in patients who did not have evidence of MI or cardiac ischemia at presentation (hazard ratio, 0.01; 95% CI, 0.01–0.02; *P*<0.001).

The cause of death could be determined from the electronic health records in 120 out of 319 (38%) deaths. It was classified as a cardiac death in 53 of 120 (44%) of deaths (54% of deaths in the ICD group and 38% in the no ICD group, *P*=0.13). Unfortunately, further classification of cardiac deaths as arrhythmic versus

**Table 5. Independent Predictors of Mortality in Cardiac Arrest Survivors**

| | *P* Value | Hazard Ratio | 95.0% CI |
|---|---|---|---|
| | | | Lower –Upper |
| ICD placement | <0.001 | 0.10 | 0.03–0.33 |
| Out-of-hospital cardiac arrest | 0.21 | 1.91 | 0.69–5.32 |
| Presenting rhythm asystole or PEA* | 0.93 | 1.05 | 0.34–3.29 |
| Age (per 1 y increase) | 0.007 | 0.94 | 0.91–0.98 |
| Female sex | 0.61 | 0.81 | 0.36–1.82 |
| Black patients (compared with whites) | 0.66 | 0.75 | 0.21–2.71 |
| Atrial fibrillation | 0.007 | 4.12 | 1.46–11.58 |
| NYHA class (per 1 U increase) | 0.25 | 0.73 | 0.43–1.24 |
| Charleston comorbidity index (per 1 U increase) | <0.001 | 1.49 | 1.20–1.85 |
| QRS duration | 0.016 | 1.02 | 1.00–1.03 |
| QTc duration | 0.99 | 1.00 | 0.99–1.01 |
| Troponin I serum level | 0.92 | 1.00 | 0.99–1.01 |
| Potassium serum level | 0.31 | 1.23 | 0.82–1.83 |
| Bicarbonate serum level | 0.16 | 1.00 | 0.98–1.02 |
| Diastolic blood pressure | 0.92 | 0.99 | 0.98–1.01 |
| Reversible cause of other than MI/ischemia† | 0.001 | 0.13 | 0.04–0.44 |

ICD indicates implantable cardioverter-defibrillator; MI, myocardial infarction; NYHA, New York Heart Association; and PEA, pulseless electric activity.

*Compared with patients presenting with a shockable rhythm (ventricular fibrillation or tachycardia).

†Compared with patients presenting with sudden cardiac arrest in the context of MI or ischemia.

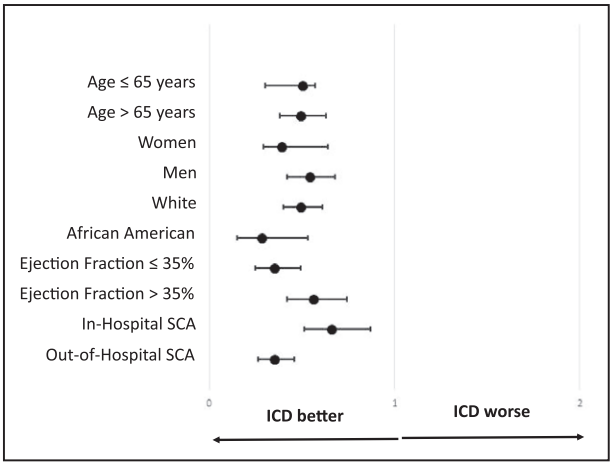


**Figure 2. Forest plot of the hazard ratio of overall survival between implantable cardioverter-defibrillator (ICD) recipients and nonrecipients in demographic and clinical subgroups of the cohort of patients with reversible and corrected causes of sudden cardiac arrest (SCA).**

nonarrhythmic could not be reliably ascertained from available data.

Of the 207 patients who received an ICD, 32 patients (15%) received appropriate ICD therapy for ventricular arrhythmias over a mean follow-up of 3.6±3.2 years. Of note, the rate of appropriate ICD therapy was lower in patients whose SCA was in the context of MI or cardiac ischemia compared with other reversible SCA causes (12% versus 21%; *P*=0.08).

## DISCUSSION

Our data demonstrate that ICD therapy is associated with lower all-cause mortality than no ICD therapy in survivors of SCA because of a reversible and correctable cause except in those patients whose SCA was associated with MI. These data are important because they suggest that the current guidelines[11] for ICD therapy in secondary prevention of SCA, which have not been recently updated, may need to be revised. Our present data, if confirmed in a multicenter prospective randomized controlled trial, would have significant implications on the clinical management of SCA survivors.

In the context of SCA associated with a reversible cause, ICD implantation rates are highly variable.[13] This may reflect the state of uncertainty in the medical community over this issue, driven in large part by significant ambiguity in the published guidelines, where the secondary prevention indications have not been updated for the past 2 decades.[11,12] For instance, in survivors of SCA associated with acute coronary syndrome, the rate of ICD implantation was 15% in 1994, increased to 60% in 2002, and fell to 47% in 2010.[13] In addition, clinical characteristics are comparable between SCA survivors receiving ICDs compared with those not receiving ICD therapy,[13] indicating that the management strategy is less dependent on clinical criteria and is driven more by patient and physician preferences, absent strong evidence for or against ICD therapy in this setting.

Reversible causes of SCA are reported in 12% to 73% of cases but usually account for ≈50% of SCA,[13,14] which is consistent with the findings in our present study. With a reversible cause, ICDs are implanted in ≈40% of SCA survivors[13] without clear evidence to guide this decision. The key source of uncertainty leading to disparate practices is the lack of a clear definition of what constitutes a reversible cause of SCA. In addition, determining the exact cause of a SCA and whether it is reversible is often fraught with uncertainty. Reversible causes such as electrolyte abnormalities documented after a cardiac arrest may be a consequence of the SCA and resuscitation efforts rather than causal. Also, reversible causes may not be avoidable in future follow-up. Moreover, the occurrence of SCA in the presence of a presumed reversible cause may reveal a predisposition to electric cardiac instability in certain individuals, whereas arrhythmic triggers such metabolic disturbances or exposure to certain medications vary over time.

In our study, patients with SCA in the context of MI had a significantly better survival than patients whose SCA was not associated with acute coronary syndrome and did not seem to extract a mortality benefit from ICD implantation. This result is not surprising because all these patients had undergone coronary revascularization before being classified as having a reversible and corrected cause of SCA. After coronary revascularization, the benefit of ICD therapy may be significantly diluted as previously demonstrated in a randomized trial,[16] particularly that the rates of target vessel reocclusion or revascularization have significantly improved over the years and are below 10% for both percutaneous coronary interventions and coronary bypass surgery.[17] Metabolic derangements and exposure to illicit drugs or antiarrhythmic medications are not as readily avoidable in future follow-up which is why ICD therapy may have more of an impact on survival in that setting.

Our present data are consistent with analyses of the AVID registry.[14,15] These data have demonstrated high all-cause mortality and sudden death during follow-up in survivors of SCA associated with a reversible cause, which is comparable to the control arm of the AVID trial,[10] that is, comparable to the patients whose SCA was not associated with a reversible cause and who did not receive an ICD. Thus, the mere correction of an identifiable reversible cause for SCA may not portend protection against future ventricular arrhythmias, and ICD therapy may therefore improve survival. This hypothesis, however, remains unproven in a prospective study. One important difference from the AVID registry[14,15] is that the incidence of acute MI in association with SCA was higher in our patient population. This is likely to be because of the higher sensitivity of troponin I testing used in our study compared with creatinine phosphokinase-MB essays used in AVID.

The present study has limitations. It is a single-center, retrospective analysis and therefore may be subject to bias. We have tried to mitigate this concern by adjusting for unbalanced covariates that could influence the primary outcome of all-cause mortality. In addition, we have included all survivors of SCA over the study period from all 25 hospitals in the University of Pittsburgh Medical Center network, which spans a large geographical area over western Pennsylvania and represents a spectrum of institutions ranging from urban tertiary centers to rural community hospitals. Despite these efforts, remaining unaccounted bias cannot be completely excluded. There are known factors that can influence mortality which we unfortunately did not measure (eg, patients' frailty index or cognitive status) and other factors that are suspected to impact

mortality (eg, patients' socioeconomic status, personal preferences and beliefs, and physicians' implicit biases) which could not be accounted for from reviewing the electronic health records. Also, although there is no established definition for a reversible cause of SCA, we have clearly outlined our definitions in this study, which were adapted from the AVID trial and registry.[14,15] Finally, despite our efforts to adjudicate the cause of death in this cohort, this could only be done in a subset of patients where the cause of death could be classified as cardiac or noncardiac but not reliably as arrhythmic or not.

## CONCLUSIONS

In conclusion, our data suggest that ICD therapy is associated with lower all-cause mortality in survivors of SCA in the context of a reversible and correctable cause except in those with MI. These results deserve further confirmation in a multicenter, prospective randomized controlled trial, as they have important and immediate clinical implications to patient care.

## DISCLOSURES

None.

## AFFILIATIONS

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## FOOTNOTES

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