The Effect of Shock Burden on Heart Failure and Mortality

Ciorsti J. MacIntyre, MD, a John L. Sapp, MD, a Amir Abdelwahab, MD, MSc, MB BCH, a Mousa Al-Harbi, MD, a Steve Doucette, MSc, b Chris Gray, MD, a Martin J. Gardner, MD, a and Ratika Parkash, MD, MS c

a Department of Medicine, Division of Cardiology, QEII Health Sciences Centre, Halifax, Nova Scotia, Canada
b Research Methods Unit, Department of Community Health and Epidemiology, Dalhousie University, Halifax, Nova Scotia, Canada

ABSTRACT

Background: Prior studies have demonstrated an association between appropriate implantable cardioverter defibrillator (ICD) shocks and mortality in clinical trials. The effect of shock burden on heart failure and mortality has not been previously studied in a large population-based cohort.

Methods: The cohort was derived using a comprehensive prospective ICD registry in the province of Nova Scotia with a mean follow-up of 4 ± 2.3 years. With the use of time-varying analysis, the relationship among shock burden, mortality, and heart failure hospitalization was determined.

Results: A total of 776 patients (mean age of 64.8 years) were included in the study, of whom 37% received appropriate therapy during follow-up. A single ICD shock did not confer an increased mortality risk compared with no therapy (hazard ratio [HR], 1.23; 95% confidence interval [CI], 0.84-1.79; P = 0.3), but mortality risk was significantly increased with ≥ 2 shocks (HR, 3.23; 95% CI, 2.04-5.09; P < 0.001).

Methods

Study population

This was a prospective cohort study of all patients receiving an ICD in the province of Nova Scotia from January 1, 2004, to December 31, 2013. This study was approved by the institutional ethics board. Data for patients who underwent ICD implantation before 2006 were collected in a retrospective manner. Data on all other patients were collected from a
There was a significant increase in heart failure hospitalization associated with receiving 1 ICD shock (HR, 2.05; 95% CI, 1.46-2.89; \( P < 0.0001 \)) or more than 1 ICD shock (HR, 4.36; CI, 2.53-7.52; \( P < 0.0001 \)) compared with patients receiving no ICD therapy. Patients who received antitachycardia pacing alone showed no difference in heart failure hospitalization (HR, 0.93; CI, 0.67-1.29; \( P = 0.7 \)) and improved survival (HR, 0.69; CI, 0.5-0.96; \( P = 0.03 \)) compared with those receiving no ICD therapy.

**Conclusion:** Ventricular arrhythmia treated with appropriate ICD shocks is associated with an increased risk of heart failure hospitalization, whereas recurrent episodes of ventricular arrhythmia requiring shocks are associated with both higher mortality and higher heart failure hospitalization rates.

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**comprehensive prospective registry. Device follow-up for this cohort was performed as per Canadian guidelines and included remote monitoring follow-up.**\(^{16}\) Device programming was left to physician discretion. Shock reduction programming was adopted uniformly as part of routine programming after the follow-up for this study was completed. All patients who underwent ICD implantation for a primary or secondary prophylactic indication and resided in the province of Nova Scotia were included. Patients with hypertrophic cardiomyopathy, infiltrative cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, ion channelopathies, congenital heart disease, and idiopathic ventricular fibrillation (VF) were excluded from the study. Patient demographics and baseline characteristics including comorbidities were obtained by a trained data abstractor. Implant indication, type of device, ICD therapies, and clinical outcomes including mortality and heart failure hospitalization were collected. Mortality data were obtained through linkage with Vital Statistics of Nova Scotia. Heart failure hospitalization data were obtained through linkage with the Cardiovascular Health Nova Scotia database. The methodology for this study has been described previously.\(^{17,18}\) Cardiovascular Health of Nova Scotia, a branch of the Department of Health, has maintained a registry of all patients who underwent ICD implantation for a primary or secondary prophylactic indication and resided in the province of Nova Scotia. Follow-up for this study was completed. All patients who underwent ICD implantation had a minimum of 1 year of follow-up for this study.

**Statistical analysis**

Baseline variables were summarized as mean ± standard deviation or frequencies with percentage where appropriate. Comparisons for continuous variables were made using Student t tests or the chi-square test for categorical variables. Cox proportional hazards modeling was used to perform multivariable analyses. The variables included in the multivariable analysis for mortality and heart failure were age, sex, ejection fraction, indication for ICD (primary vs secondary prevention), history of heart failure, and creatinine. Results are presented as hazard ratios (HRs) and 95% confidence intervals (CIs). Shocks were modeled as a time-dependent covariate in all analyses with the risk changing after the occurrence of the first shock episode and subsequent shock episodes. ATP was modeled as a time-dependent covariate in the analysis comparing shocks, no therapy, and ATP only. All P values were 2 sided, and values less than 0.05 were considered statistically significant. Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute Inc, Cary, NC).

**Results**

**Baseline clinical characteristics**

Of the 776 patients in the study, 641 (82.6%) were male and mean age at ICD implant was 64.8 ± 11 years. The mean follow-up was 4 ± 2.3 years. Baseline clinical characteristics are shown in Table 1.

**ICD events**

Of the 776 patients included in this study, 157 (20.2%) received a minimum of 1 appropriate ICD shock during the study period, with a mean follow-up of 4 ± 2.3 years. There
were 131 patients (16.9%) who received ATP only and 488 patients (62.9%) who received no appropriate therapy. Of patients receiving appropriate ICD shocks, 58 (36.9%) had improved survival compared with those who received no therapy (HR, 0.69; 95% CI, 0.50-0.96; P = 0.03). Receiving a single appropriate shock was not associated with increased mortality (HR, 1.23; 95% CI, 0.84-1.79; P = 0.3) (Fig. 2).

ICD therapy and heart failure admissions

In unadjusted models, no difference in heart failure admissions was observed in patients with ATP only versus no therapy (HR, 0.93; 95% CI, 0.67-1.29; P = 0.7). Risk of heart failure admission increased significantly with a single ICD shock compared with the no therapy group (HR, 1.9; 95% CI, 1.36-2.67; P = 0.0002). This risk increased further still in patients receiving 2 or more shocks (HR, 3.22; 95% CI, 1.9-5.44; P < 0.0001). On univariate analysis, left ventricular ejection fraction (per unit) (HR, 0.98; 95% CI, 0.97-1; P = 0.01), creatinine (per decile) (HR, 1.01; 95% CI, 1.01-1.01; P < 0.0001), and history of heart failure (HR, 2.26; 95% CI, 1.49-3.43; P = 0.0001) were found to be associated with an increase in mortality. In a multivariate model, receipt of 2 or more appropriate shocks continued to be associated with increased mortality (HR, 3.23; 95% CI, 2.04-5.09; P < 0.0001), but patients experiencing only appropriate ATP had improved survival compared with those who received no therapy (HR, 0.69; 95% CI, 0.50-0.96; P = 0.03). Receiving a single appropriate shock was not associated with increased mortality (HR, 1.23; 95% CI, 0.84-1.79; P = 0.3) (Fig. 2).
risk increased further still in patients receiving 2 or more shocks (HR, 4.36; 95% CI, 2.53-7.52; \( P < 0.0001 \)). Patients who received ATP only showed no increase in heart failure admission compared with those with no ICD therapy (HR, 0.93; 95% CI, 0.67-1.29; \( P = 0.7 \)) (Fig. 2).

**Inappropriate shocks and mortality**

A total of 89 patients (11.5%) experienced inappropriate ICD shocks. Inappropriate shocks were not associated with increased mortality in a time-varying analysis (HR, 0.88; 95% CI, 0.53-1.47; \( P = 0.6 \)), when compared with patients who had not experienced inappropriate ICD shocks in their lifetime. Of the patients receiving inappropriate shocks, 41 received no appropriate therapy (ATP or shocks), 25 received at least 1 appropriate shock, and 23 received appropriate ATP but no appropriate shocks.

**Discussion**

In this population-based cohort of ICD recipients, we demonstrated that increasing shock burden was associated with an increase in both mortality and heart failure hospitalizations. The threshold at which mortality was significantly increased was 2 or more lifetime ICD shocks for ventricular arrhythmia. A single lifetime ICD shock for ventricular arrhythmia increased the risk of heart failure, with incremental risk of heart failure with increasing burden. Patients who had either ATP for VT or no VT at all were at lowest risk for both mortality and heart failure hospitalization. In our cohort, inappropriate shocks alone were not associated with increased mortality risk.

Previous work by Sweeney et al.\(^9\) reported that patients with shock-terminated episodes of ventricular arrhythmia have a higher mortality risk, but did not examine the effect of shock burden on the outcomes of mortality and heart failure. Likewise, in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), a single appropriate shock increased the risk of death 5-fold. Additional shocks were associated with a 3-fold increased risk of death.\(^8\) Our data represent a contemporary cohort than either of these studies, albeit with conventional programming, rather than shock reduction programming, which was adopted after this study was completed.

Myocardial injury due to both transthoracic and intracardiac shocks is well established.\(^16,19-21\) Increasing shock strength causes cardiac biomarker release, and detrimental effects on ventricular function have been demonstrated.\(^15\) Tokano et al.\(^19\) showed that ICD shocks greater than 9 J result in a 10% to 15% reduction in the cardiac index, whereas lower-energy shocks did not result in objective hemodynamic compromise. Therefore, the absence of a relationship between ATP therapy and mortality is not surprising. This has also been borne out in the literature with multiple studies observing that ATP is not associated with increased mortality risk.\(^9\) The association between shocks and objective impairment in ventricular function as well as cardiac biomarker release supports the hypothesis that the shock itself may be harmful, at least in the short term. The association between ICD shocks for ventricular arrhythmia and increased mortality also supports the hypothesis of harm. This does not, however, exclude the possibility that the presence of more advanced myocardial disease, unresponsive to pacing termination, results in a worse prognosis. Therefore, it is difficult to ascertain whether it is the shock itself that is harmful versus the properties of the disease substrate and consequently the ventricular arrhythmia itself.

The effect of shock reduction programming could not be evaluated in this study, because it was not in effect at the time the study was performed. Inappropriate shocks were associated with a 2-fold increased risk of death in both the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).\(^7,8\) In these prior studies, the majority of inappropriate shocks were due to atrial fibrillation, which may be a marker of worse prognosis in a heart failure population.\(^22\) In our study, the majority of inappropriate shocks were due to sinus tachycardia, which may partially explain the discrepancy between our study and others that have demonstrated an
The association between inappropriate shocks and mortality. Likewise, Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RT) showed that inappropriate ICD therapy and ICD shocks were independently associated with increased mortality. Randomization to high-rate detection was associated with a reduced risk of mortality in this primary prevention ICD population. Patients in the conventional programming arm received a higher frequency of both appropriate and inappropriate therapies with almost twice the number of shocks seen in the high-rate and delayed treatment arms. Conversely, neither this analysis nor that by Sweeney et al. showed this relationship. The Avoid Delivering Therapies for Non-sustained Arrhythmias in ICD Patients III (ADVANCE III) trial, which randomized patients to ICD programming with long detection intervals versus standard detection intervals, showed a significant decrease in the rate of total ICD therapies and of inappropriate shocks and hospitalizations, without a statistically significant difference in mortality. Similar results were seen in a secondary prevention population in the PainFree SST Substudy. Prolonged VF detection intervals were associated with lower rates of treated VF episodes and were not associated with increased syncope or mortality. Although the absence of a relationship between inappropriate shocks and mortality may argue against a direct detrimental effect of shocks, it has been hypothesized that the type of arrhythmia episode may precondition the myocardium to the adverse effect of a shock.

Although the link between risk of heart failure and death in the ICD patient population is well established, the association between increasing risk of heart failure admission with increasing shock burden has not previously been described. Our study demonstrates a clear, incremental risk of heart failure hospitalization with increasing shock burden for ventricular arrhythmia. In MADIT II, the risk of first heart failure hospitalization increased by 90% after appropriate shocks. The risk of recurrent heart failure hospitalization increased by 74% after appropriate ICD shocks. Again, what remains unclear is whether shocks and increasing ventricular arrhythmia burden are a marker for disease progression or if there is a causal link. Although these associations are not proof of causation, they do support an underlying mechanism of direct myocardial injury in an already compromised myocardium increasing the subsequent risk of heart failure and subsequent ventricular arrhythmias as previously described.

In this study, ATP therapy was associated with improved survival but not with increased admission for heart failure. Although the mechanism underlying this observation was not addressed in this study, it may reflect changes in medical therapy secondary to this intervention, thereby improving both heart failure and mortality outcomes. Alternatively, the underlying substrate responsive to ATP termination may be intrinsically different than that requiring a shock for arrhythmia termination.

Given our findings, it is important to improve understanding of whether suppression of ventricular arrhythmia using medical or ablation therapy may improve outcomes in this population. In the Ventricular Tachycardia Ablation vs Enhanced Drug Therapy In Structural Heart Disease (VANISH) trial, high rates of recurrent appropriate ICD shocks, VT storm, and mortality were observed among patients with VT that occurred despite antiarrhythmic drugs. In the group randomized to catheter ablation, there was a significant reduction in the composite outcome of death, VT storm, or appropriate ICD shock, largely driven by reductions in rates of appropriate shocks and episodes of VT storm. Further exploration of whether earlier intervention in patients who have ventricular arrhythmia to improve heart failure and mortality is warranted.

**Study limitations**

Certain limitations do apply to this analysis. This is a single-center cohort study in which data collection was limited to predetermined fields; thus, there is the possibility that other information that was not collected may have an impact on the outcomes studied, such as medication compliance, optimization of heart failure therapies, dynamic change in heart failure status, and cause of death. On the basis of the observational nature of the data, this study cannot imply causation, but only an association among shocks.
mortality, and heart failure hospitalization. The burden of inappropriate shocks on mortality was not explored in this analysis. Further, these data were derived from a cohort treated before data demonstrating programming could markedly reduce inappropriate shocks; nevertheless, there was no effect of inappropriate shocks on mortality in our cohort. Device programming was not standardized in this real-world cohort, but one would not expect this to exert a significant effect on our findings as the major effect in MADIT-RIT was on ATP and inappropriate shocks, neither of which increased mortality in our study.

Further research is needed to better characterize the pathophysiologic mechanism underlying the effect of shocks on mortality and heart failure. Although shocks will continue to be an important component of sudden death prevention, it is important moving forward to continue to study and refine ICD programming strategies to minimize potential harms. It is also important for clinicians to be aware of the association between ICD shocks and risk of heart failure decompensation. Further studies of shock avoidance in the prevention of heart failure decompensation are warranted.

**Conclusion**

Patients who experience more than a single ICD shock have an increased risk of both mortality and heart failure hospitalization, whereas ATP alone does not increase the risk of mortality or heart failure hospitalization. Likewise, inappropriate shocks are not associated with increased mortality risk. This suggests that reduction of ventricular arrhythmia requiring shocks may alter the progression of both heart failure and mortality. This study provides important insight into the management of patients with ICDs and recurrent ventricular arrhythmia. Heart failure progression may be halted by early and aggressive treatment of ventricular arrhythmia with catheter ablation or antiarrhythmic drugs. The optimal modality of treatment remains to be determined; however, it remains crucial to institute early therapy with the potential to improve prognosis. Testing of this hypothesis in clinical trials is important to determine the true magnitude of effect. Whether ventricular arrhythmia worsens progression of heart failure or vice versa remains to be determined.

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**References**

1. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. N Engl J Med 1997;337:1576-83.
2. Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. N Engl J Med 1999;341:1882-90.
3. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. Circulation 2000;101:1297-302.
4. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. N Engl J Med 1996;335:1933-40.
5. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877-83.
6. Bandy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225-37.
7. Daubert JP, Zareba W, Cannom DS, et al. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. J Am Coll Cardiol 2008;51:1357-65.
8. Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. N Engl J Med 2008;359:1009-17.
9. Sweeney MO, Sherfesee L, DeGroot PJ, Warthen MS, Wilkoff BL. Differences in effects of electrical therapy type for ventricular arrhythmias on mortality in implantable cardioverter-defibrillator patients. Heart Rhythm 2010;7:353-60.
10. Hurst TM, Hinrichs M, Breidenbach C, Katz N, Waldecker B. Detection of myocardial injury during transvenous implantation of automatic cardioverter-defibrillators. J Am Coll Cardiol 1999;34:402-8.
11. Epstein AE, Kay GN, Plumb VJ, Dailey SM, Anderson PG, Gross and microscopic pathological changes associated with nonthoracotomy implantable defibrillator leads. Circulation 1998;98:1517-24.
12. Tereshchenko LG, Faddis MN, Fetics BJ, et al. Transient local injury current in right ventricular electrogram after implantable cardioverter-defibrillator shock predicts heart failure progression. J Am Coll Cardiol 2009;54:822-8.
13. Schron EB, Exner DV, Yaq Q, et al. Quality of life in the antiarrhythmics versus implantable defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks. Circulation 2002;105:589-94.
14. Herbst JH, Goodman M, Feldstein S, Reilly JM. Health-related quality-of-life assessment of patients with life-threatening ventricular arrhythmias. Pacing Clin Electrophysiol 1999;22:915-26.
15. Irvine J, Dorian P, Baker B, et al. Quality of life in the Canadian Implantable Defibrillator Study (CIDS). Am Heart J 2002;144:282-9.
16. Yee R, Verma A, Beardsall M, et al. Canadian Cardiovascular Society/Canadian Heart Rhythm Society joint position statement on the use of remote monitoring for cardiovascular implantable electronic device follow-up. Can J Cardiol 2013;29:644-51.
17. Cox JL. Optimizing disease management at a health care system level: the rationale and methods of the improving cardiovascular outcomes in Nova Scotia (ICONS) study. Can J Cardiol 1999;15:787-96.

18. Parkash R, Sapp JI, Basta M, et al. Use of primary prevention implantable cardioverter-defibrillators in a population-based cohort is associated with a significant survival benefit. Circ Arrhythm Electrophysiol 2012;5:706-13.

19. Tokano T, Bach D, Chang J, et al. Effect of ventricular shock strength on cardiac hemodynamics. J Cardiovasc Electrophysiol 1998;9:791-7.

20. Runsio M, Kallner A, Kallner G, Rosenqvist M, Bergfeldt L. Myocardial injury after electrical therapy for cardiac arrhythmias assessed by troponin-T release. Am J Cardiol 1997;79:1241-5.

21. Stoddard MF, Labovitz AJ, Stevens LL, et al. Effects of electrophysiologic studies resulting in electrical countershock or burst pacing on left ventricular systolic and diastolic function. Am Heart J 1988;116:364-70.

22. Dries DL, Exner DV, Gersh BJ, et al. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic dysfunction: a retrospective analysis of the SOLVD trials. Studies of Left Ventricular Dysfunction. J Am Coll Cardiol 1998;32:695-703.

23. Ruwald AC, Schuger C, Moss AJ, et al. Mortality reduction in relation to implantable cardioverter defibrillator programming in the Multicenter Automatic Defibrillator Implantation Trial-Reduce Inappropriate Therapy (MADIT-RIT). Circ Arrhythm Electrophysiol 2014;7:785-92.

24. Moss AJ, Schuger C, Beck CA, et al. Reduction in inappropriate therapy and mortality through ICD programming. N Engl J Med 2012;367:2275-83.

25. Gasparini M, Proceder A, Klersy C, et al. Effect of long-detection interval vs standard-detection interval for implantable cardioverter-defibrillators on antitachycardia pacing and shock delivery: the ADVANCE III randomized clinical trial. JAMA 2013;309:1903-11.

26. Sterns LD, Meine M, Kurita T, et al. Extended detection time to reduce shocks is safe in secondary prevention patients: the secondary prevention substudy of PainFree SST. Heart Rhythm 2016;13:1489-96.

27. Goldenberg I, Moss AJ, Hall WJ, et al. Causes and consequences of heart failure after prophylactic implantation of a defibrillator in the multicenter automatic defibrillator implantation trial II. Circulation 2006;113:2810-7.

28. Sapp JI, Wells GA, Parkash R, et al. Ventricular tachycardia ablation versus escalation of antiarrhythmic drugs. N Engl J Med 2016;375:111-21.