Shocks and increased mortality in implantable cardioverter-defibrillator patients: Impact of shock burden

By

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Abbreviations

ATP=antitachycardia pacing**; AF=**atrial fibrillation**; CAD=**coronary artery disease; **CHF=**congestive heart failure; **CI=**confidence interaval; **DM=**diabetes mellitus; **EF=**ejection fraction; **HTN=**hypertension; **ICD=**implantable cardioverter-defibrillator; **IQR**=interquartile range; **SHFM=**Seattle Heart Failure Model; **SVT=**supraventricular tachycardia; **VA=**ventricular arrhythmia; **VF=**ventricular fibrillation; **VT=**ventricular tachycardia

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Abstract

Background: Implantable cardioverter-defibrillator (ICD) shocks are associated with an increased risk of death. It is unclear whether ICD shocks are detrimental per se, or a marker of higher risk patients.

Objective: We aimed to assess the association between ICD shocks and time to death after correction for baseline mortality based on the Seattle Heart Failure Model (SHFM).

Methods: The primary analysis compared time to death between patients receiving no shocks and patients receiving shocks of any type adjusted for SHFM score at time of implantation and other co-morbidities. Subgroup analyses were performed to further describe the relationship between shocks and mortality risk.

Results: Over a median follow-up of 41 (IQR 23-64) months, ≥1 shock episodes occurred in 59% of 425 patients and 40% of the patients died. Patients receiving shocks of any type had increased risk of death (hazard ratio 1.55; 95% confidence interval 1.07-2.23; P=0.02) versus patients receiving no shocks. While patients with 1-5 days with shock (shockdays) did not show evidence of increased risk of death (1.29 [0.87-1.92]; P=0.20), those with 6-10 shockdays (2.37 [1.31-4.28]; P<0.01) and >10 shockdays (3.66 [1.86-7.20]; P<0.01) had increasingly higher risk. There was no increased hazard for death (0.73 [0.34-1.57]; P=0.42) in patients treated only with antitachycardia pacing (ATP).

Conclusion: ICD shocks were associated with increased mortality risk after adjustment for SHFM predicted mortality and both dose and timing of shocks played a role in this association. ATP did not increase mortality risk suggesting that shocks may be themselves detrimental.

Background and Significance

Heart failure is a prevalent disease, affecting about 5.7 million people in the United States and resulting in about 300,000 deaths each year.[1] There are many causes of heart failure and there are many clinical factors and treatments available that affect mortality. A number of randomized, controlled clinical trials have shown a mortality benefit of implantable cardioverter-defibrillators in the prevention of sudden cardiac death both as primary and secondary prevention in appropriately selected patients.[2,3,4,5,6] Although shocks can be lifesaving, not all shocks save lives and questions have begun to arise as to whether ICD shocks may also predict an increased risk of death and other complications in heart failure patients.

Defibrillator shocks, both appropriate and inappropriate, have recently been found to be associated with increased mortality.[7,8] Appropriate defibrillator shocks have been previously defined as any episode administered for ventricular tachycardia or ventricular fibrillation. Any other reason for shock is considered inappropriate. A retrospective analysis from the Multi-center Automatic Defibrillator Trial (MADIT II) showed that inappropriate ICD shock is a common occurrence and is associated with an increase in all-cause mortality.[7] This analysis found that inappropriate shocks increase the hazard ratio for death in comparison to patients receiving appropriate shocks. This relationship was independent of other covariates that are predictive of the outcome including atrial fibrillation, increased diastolic blood pressure and smoking status and was seen in both patients with ischemic heart disease and non-ischemic heart disease. This same study also found that patients who received inappropriate shocks had a higher hazard ratio for death in comparison to patients that received other forms of inappropriate therapy (anti-

tachycardia pacing). Additional evidence supporting the idea that defibrillator shocks may be detrimental was provided by an analysis of mortality in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT).[8] This analysis showed that among patients with heart failure who receive an ICD for primary prevention, those patients receiving shocks for any arrhythmia had a higher risk of death compared to similar patients who do not receive shocks.

An additional concern is that not all shocks delivered for episodes of ventricular tachycardia or ventricular fibrillation (appropriate shocks) are necessary and that many such rhythms would have spontaneously converted to normal rhythms without therapy. Evidence for this was found in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial, which found that appropriate ICD shocks occurred more frequently than sudden cardiac death in patients with non-ischemic cardiomyopathy, suggesting that ICD shocks do not necessarily serve as a surrogate for sudden cardiac death.[9]

Not only are patients receiving inappropriate or unnecessary ICD shock therapy, which carries with it a certain level of patient discomfort and anxiety, but of even greater concern is that ICD shocks may actually increase the incidence of nonarrythmic deaths as a side effect of therapy.[10,11,12] In a recent review by Tung, et al., it was noted that in the Coronary Artery Bypass Graft-Patch (CABG Patch) trial, although the incidence of arrhythmic death was significantly reduced, there was an unexpected increase in death from other causes in patients randomized to ICD therapy.[12] A similar result was seen in the Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) trial where the prevention of arrhythmic death with ICDs was counterbalanced by excess death from

nonarrythmic etiologies.[12] The leading speculation is that device therapy is reprogramming the mode of death to pump failure. This is further supported by a retrospective analysis of the MADIT II trial that found that patients with chronic ischemic heart disease who were treated with single-chamber or dual-chamber ICDs had improved survival but also an increased risk of heart failure.[13]

Despite the above findings, it is reasonable to question whether patients with progressive heart failure and other factors associated with increased mortality might be more likely to develop arrhythmias resulting in an increased occurrence of both inappropriate and/or appropriate shocks.[14] This begs the question of whether defibrillator shocks are themselves detrimental or are a marker of a sicker patient population. Although the stakes are high given that ICD therapy has been proven to prevent sudden cardiac death, it is also important to consider the benefits of avoiding potential harms of ICD therapy.[12] Given that effective alternative treatments for ventricular tachycardia exist, evidence showing that shocks are indeed detrimental should re-direct efforts to both decrease the number of shocks received by using ATP to terminate ventricular arrythmias as well as direct attention to the prevention and treatment of heart failure in those receiving ICDs.[13,14,15] As such, additional research needs to be done to explore the potential adverse effects of ICD shocks. The primary outcome in this study of all-cause mortality has been previously demonstrated in retrospective analyses of randomized, controlled populations and our goal is to demonstrate the same effect of defibrillator shock in a novel population: veterans seeking care at a Veterans Affairs Medical Center. Overall, we hope to add to the knowledge base regarding the possible detrimental effects of ICD shocks; thereby generating hypotheses and generating research interest in increasing the

use of anti-tachycardia pacing whenever possible to reduce the risk of inappropriate shocks, improving device programming, and optimization of adjunctive medical management for heart failure management.

Methods

Study population

We conducted a historical cohort study using a pre-existing database of patients with implantable cardioverter-defibrillators at the Veterans Affairs Medical Center in Portland, Oregon. The analysis included 425 patients that received ICDs between January 1994 and January 2008 who subsequently received their follow-up at the same hospital. The type of ICD implanted and programming parameters were determined at the discretion of the implanting electrophysiologist according to standard clinical practice.

Data collection

Implant data, ICD programming parameters, ICD follow-up dates and results, records of all ICD therapy events, and date of death were entered prospectively into an independent database maintained by the PVAMC Electrophysiology Department. ICD events were classified by the attending electrophysiologist based on all available clinical and ICD data (including electrograms) as being for ventricular tachycardia (VT), ventricular fibrillation (VF), atrial fibrillation (AF), sinus tachycardia or other supraventricular tachycardia (SVT), or oversensing, and entered prospectively into the independent database. Chart reviews were conducted by trained researchers (JE and GL) in order to obtain baseline clinical characteristics not recorded in the database.

Calculation of the SHFM score

The Seattle Heart Failure Model score was calculated based on the equation described by Levy et al.[8] In order to calculate this score, we required that a participant had no missing variables other than lymphocyte percent or uric acid level. Forty-seven (11%) of 425 patients were excluded for this reason. In the case of missing data for lymphocyte

percent and/or uric acid levels the median values for the complete study population were used.

Study endpoints

The primary analysis compared time to death for all patients receiving shocks to patients receiving no shocks. Patients that received only episodes of antitachycardia pacing (ATP) were included in the no-shock group. The effect of ATP was examined by stratifying the no-shock group into patients receiving ATP only and patients receiving no therapy. Patients with ATP only episodes prior to shock were included in the ATP only group until the time of first shock at which time they became part of the shock group. Shock burden was examined in the entire study population by looking at both cumulative days of shock (shockdays) and cumulative number of shocks stratified into 1-5 shockdays/ total shocks, 6-10 shockdays/ total shocks and >10 shockdays/ total shocks. To further delineate the effects of timing of shocks we looked at patients with ≥5 shocks in a 24-hour period (shock storm) as well as patients that never had an episode of shock storm stratified into those with <5 shockdays/ total shocks and ≥5 shockdays/ total shocks shockdays. We then compared patients with ≥5 shockdays/shocks stratified into shock storm and no-shock storm groups. For all shock burden analyses, the reference group was the no-shock group including both ATP only and no therapy except in the shock storm versus no-shock storm comparison**.**

Statistical analysis

Descriptive statistics on all statistical endpoints and baseline characteristics were performed for the complete study population (n=425) as well as for selected subgroups. Baseline characteristics between the study groups were compared using Wilcoxon rank

sum tests for continuous variables, chi-squared tests for dichotomous variables, or Fisher exact tests as appropriate for dichotomous variables. Follow-up time was calculated as the interval from time of implant to time of death or last-follow-up.

Kaplan-Meier survival curves were constructed for the estimation of unadjusted survival distributions between the shock and no-shock group as well as for subgroup analyses. Log-rank tests were used for the comparison of overall survival between groups. Cox proportional-hazards models were used to examine the relationship between ICD therapies and time to death. Univariate Cox proportional-hazards models were run on baseline characteristics including SHFM score and ejection fraction (EF) as well as presence/absence of chronic kidney disease (CKD), congestive heart failure (CHF), coronary artery disease (CAD), hypertension (HTN), atrial fibrillation (AF), diabetes mellitus (DM), QRS duration (>120ms), and left bundle branch block (LBBB). Multivariate Cox models were run that included covariates with *P*-values of ≤0.20 in univariate analyses and stepwise selection was used to determine the most parsimonious model. Shock was modeled as a time-dependent covariate in all analyses with the risk changing after the occurrence of first shock episode as well as subsequent shock episodes in the shock burden analyses. ATP was modeled as a time-dependent covariate in the subgroup analysis comparing shocks, no therapy, and ATP only. Whether there was an interaction between the SHFM score and shock is also evaluated in the Cox proportional hazard model. All tests were conducted at the two-sided 0.05 significance level. Analysis was performed using SAS version 9.2 (Cary, NC: SAS Institute Inc).

Results

Deaths and ICD event analysis

Of the 425 patients included in the study, 252 (59%) received a shock of any type throughout the study period. There were 190 (45%) patients with 1-5 shockdays, 44 (10%) with 6-10 shockdays and 18 (4%) with >10 shockdays, while 121 (28%) received 1-5 shocks, 51 (12%) received 6-10 shocks and 80 (19%) received >10 shocks. Ninety-six (23%) patients experienced ≥1 episodes of shock storm. In patients without episodes of shock storm 54 (17%) had ≥5 shocks and 34 (8%) had ≥5 shockdays. In the no-shock group, 130 (31%) patients received no therapy and 120 (28%) received ATP only either prior to or without ever receiving a shock. During a median follow-up period of 41 (IQR 23-64) months, 171 (40%) patients died, with 102 (24%) of those receiving shocks. The median time to first shock episode was 8.1 (IQR 2.2-21.7) months and the median number of shocks received was 6 (IQR 2-14).

Clinical characteristics

Baseline characteristics between the shock and no-shock groups are shown in Table 1. Overall, the two groups were similar with the exception of greater percentage furosemide use, primary prevention, and occurrence of diabetes in the no shock group. Baseline characteristics for selected subgroups are shown in Table 2.

ICD shocks and risk death

There was an overall trend toward increased risk of all-cause mortality in the shock versus the no-shock group (hazard ratio [HR] 1.32; 95% confidence interval [CI], 0.97 to 1.81; *P*=0.08) (see appendix for all unadjusted HRs). Univariate Cox proportional hazards analysis (see appendix) indicated that SHFM score (HR 1.99; 95% CI, 1.63-2.42;

P<0.01), CKD (HR 2.04; 95% CI, 1.44-2.89; *P*<0.01) and QRS>120ms (HR 1.48; 95% CI 1.04-2.10; *P*=0.03) where significant predictors of death; however, the SHFM score and CKD were the only covariates that predicted mortality in multivariate analysis. After adjustment, shock was significantly associated with increased risk of death (HR 1.55; 95% CI 1.07-2.23; *P*=0.02). Results for all adjusted Cox hazards models can be found in Table 3. The adjusted survival curves for the shock versus no-shock groups are shown in Figure 1.

Type of therapy

Given the trend toward decreased survival in the shock group, we conducted further analyses to look at how shocks may be contributing to this finding. To examine whether ATP was associated with increased mortality risk, we stratified the no-shock group into ATP only and no therapy and the adjusted survival curves comparing no therapy, ATP only, and shock are shown in Figure 2. Patients receiving only ATP did not have significantly increased risk of death (HR, 0.73; 95% CI 0.34-1.56; *P*=0.41), while the effect remained in the shock group (HR, 1.55; 95% CI 1.06-2.27; *P*=0.02) in multivariate Cox analysis. Consistent with these findings, when the effects of shock and ATP were combined in an analysis comparing therapy versus no therapy patients receiving therapy of any type did not have significantly decreased survival (HR, 1.35; 95% CI 0.92-1.98; *P*=0.13).

Shock burden

Shock burden was analyzed by looking at cumulative number of days with shocks (shockdays), cumulative number of total shocks (see appendix for unadjusted survival curves), and episodes of shockstorm. In the total patient population used for adjusted

analyses, those patients with 1-5 shockdays did not have significantly increased risk of death (HR 1.29; 95% CI 0.87-1.92; *P*=0.20), while those with 6-10 shockdays (HR 2.37; 95% CI 1.31-4.28; *P*<0.01) and >10 shockdays (HR 3.66; 95% CI 1.86-7.20; *P*<0.01) had increasingly higher risk in multivariate analysis. Likewise, patients that received 1-5 shocks (HR 1.07; 95% CI 0.68-1.69; *P*=0.77) did not have increased risk of death, while those receiving 6-10 shocks (HR 2.05; 95% CI 1.19-3.54; *P*<0.01) or > 10 shocks (HR 2.37; 95% CI 1.47-3.82; *P*<0.01) had a greater than 2-fold increased risk of death as compared to patients that received no shocks.

The effect of timing of shocks was examined by looking at shock burden in patients that did and did not experience episodes of shock storm. First, we looked to see if the increased mortality associated with ≥5 shocks persisted if we eliminated patients with shock storm from the analysis (Table 3). The association remained significant. On the other hand, the analysis comparing patients with and without episodes of shock storm that had ≥5 shockdays (HR 1.20; 95% CI 0.60-2.38; *P*=0.60) or ≥5shocks (HR 1.08; 95% CI 0.63-1.85; *P*=0.78) did not show a significant difference in time to death between these groups.

Discussion

Overall, the results of this study raise concerns that shocks themselves may be associated with increased risk of mortality. This relationship persisted after adjustment for baseline SHFM predicted mortality and other risk factors. The SHFM is a validated model for the prediction of survival in heart failure patients that provided the unique ability to estimate survival forward in time based on a large number of clinical, pharmacological, device and laboratory characteristics.[17] This allowed us to account for the expected changing risk of death in this high-risk population and suggests that differences in predicted survival at baseline are not entirely accounting for the increased mortality associated with shocks. In fact, adjustment for SHFM score strengthened the association between shocks and decreased survival time.

Subsequent subgroup analyses were consistent with the conclusion that shocks may be detrimental *per se*. Our analysis comparing patients receiving no therapy to patients receiving ATP only indicated that ATP is not associated with increased risk of death. This is agreement with the findings reported in previous studies.[7,18]

These strongest associations demonstrated in this study involved the dose and timing of ICD shocks. This is in contrast to the SCD-HeFT and MADIT II analyses which used therapy episodes with ≥1 shocks but did not have data on the total number of shocks.[7,8] Patients in our study that received more shocks or had more days with shocks had significantly increased risk of death as compared to patients receiving no therapy. These results indicate that shock burden in the forms of cumulative days with shock and cumulative number of shocks may play an important role in the relationship between shocks and increased risk of mortality and this effect remains when controlling for

delivery of multiple shocks in one day. Previous studies have found that increased number of shock episodes confer greater risk of death. Sweeney et al reported that patients with episodes of ventricular arrhythmia (VA) and shocks have higher mortality (with ≈20% increased risk per shocked episode) and VA occurrence rates, durations, and electrical therapy burden were highest among patients who were shocked and died.[18] Our analysis comparing patients with ≥5 shockdays/total shocks that experienced episodes of shocks storm to those without shock storm did not indicate an increased risk of death in the shock storm group. Electrical storm, commonly defined as ≥3 ventricular tachyarrythmia detections in 24 h, treated by antitachycardia pacing, shock or eventually untreated is associated with higher mortality than isolated VT/VF.[10,11] Given previous findings along with the limitation of a small sample size in our analysis, this is a question that should be addressed in future studies. It is worth noting that the categories chosen for our dose-response analyses in the entire study population were arbitrary and categories for the subgroup analysis not including shock storm patients were chosen based on the definition of the shock storm variable. Therefore, our results do not imply that five is in any way a hard cut-off for increased mortality risk; however, alternative subgroup category (i.e. quartiles) analyses were consistent with the finding that ~5 shocks/ shockdays and greater were associated with an increased risk of death (data not shown). Overall, the conclusion from the shock burden analysis is that an increasing dose of shocks is detrimental. Whether this is the case when shocks are delivered over different time-frames is a question that remains to be answered.

The underlying mechanism for why shocks may be detrimental is currently unclear; although, there is fairly extensive literature outlining the adverse effects of shocks on

myocardial function. No doubt the mechanism is likely a composite of alterations in electrophysiologic function, hemodynamic function, molecular and neurohumoral changes, and direct myocardial damage interacting with the underlying substrate.[21] For example, Tokano et al have shown that ICD shocks >9J delivered during sinus rhythm or VF resulted in a 10-15% reduction in the cardiac index but shocks of lesser energy did not cause this reduction.[22] This and similar findings may help to explain why shocks, but not ATP, have been associated with increased risk of death.

It is clear that more research is needed to help further elucidate the underlying mechanisms for how shocks are contributing to mortality risk. However, regardless the mechanism, the stakes are high given that ICD therapy has been proven to prevent sudden cardiac death out to as long as 8-years as recently reported by Goldenberg et al.[23] Yet, it is also important to consider the benefits of avoiding potential harms of ICD therapy. Previous studies, such as the DEFINITE trial, found that not all shocks delivered for episodes of ventricular arrhythmias are necessary and that many such rhythms would spontaneously convert to normal rhythms without therapy.[9] Additionally, patient discomfort and anxiety associated with ICD shock therapy deserves mention. Patients with ICD shocks have increased levels of psychological distress, anxiety, anger, post-traumatic stress disorder, and depression as compared to patients that do not receive shocks and these psychological sequelae may be a contributing factor to the increased mortality seen in patients who receive ICD shocks.[24,15]

Analysis of inappropriate versus appropriate shocks has had mixed results in prior studies with MADIT II and SCD-HeFT finding a two-fold increased risk of death while Sweeney et al reporting no increased mortality risk.[7,8,18] The inconsistency among studies may

reflect the fact that this is an inherently difficult analysis to perform as the means to stratify these groups is complicated. Simply stratifying patients into those that only have appropriate shocks or only have inappropriate shocks isolates the type of shock exposure but leaves out a large proportion of patients with both exposures. It may be possible to use a longitudinal design to compare survival in intervals of all appropriate shocks against all inappropriate shocks. The present analysis considered the overall effects of shocks to mortality risk and does not address the risk of appropriate to inappropriate shocks.

Clinical Implications

If, in fact, shocks are detrimental the observed clinical efficacy of ICD therapy may be the result of competing influences with shocks terminating potentially fatal arrhythmias but also increasing the risk of death though other mechanisms. It follows that if the same number of life threatening arrhythmias could be terminated with fewer shocks and shocks could be used less often for self terminating or non life threatening arrhythmias then perhaps the overall efficacy of ICD therapy could be improved. What is needed are prospective randomized trials looking at different programming options that would reduce the number of shock such as: 1) increased use of ATP 2) employing more aggressive use of discriminators designed to prevent inappropriate therapy 3) increasing the heart rate that will trigger therapy and 4) delaying therapy to give more rhythms a chance to self terminate so that less therapy of any kind including shocks is required. Each potential fix carries potential risks related to delaying therapy with an increased risk of hemodynamic compromise before definitive therapy is delivered or by preventing therapy all together for potentially life threatening arrhythmias. Randomized trials are

required to determine whether the net effect of these interventions actually reduces shocks and prolongs survival.

Limitations

Our sample consisted of a diverse ICD population from a single VA medical center including both primary and secondary prevention with a long follow-up period. The heterogeneity of our population may be considered a strength for evaluating ICD shocks in a real-world clinical practice; however, our results may not be generalizable to other populations. The nature of data collection, namely chart review, is subject to missing data and misclassification that may have affected study results. Calculation of the SHFM score required imputation of certain variables and all calculations where made assuming implantation of a standard ICD (no BiV ICD). Survival is difficult to predict in heart failure patients and the ability to accommodate for a patient's changing risk over time is a challenge in any analysis involving this patient population. The use of the SHFM was an attempt to capture this changing risk. While repeat measurements of baseline risk factors may have added to our ability to control for changing mortality risk, when to re-measure such factors to capture changing risk is a complex question. Given that this is a retrospective analysis, nothing can be said about whether ICD shocks are truly causative of increased risk of death.

Conclusion

The results of our study indicate that shocks may contribute to increased total mortality. Patients receiving cumulatively more shocks or more days with shocks are at increased risk for death. Further prospective research, in the form of a randomized clinical trial, is needed to look at optimizing ICD therapy as well as risk stratification.

Public Health Implications

Knowledge is an unending adventure at the edge of uncertainty.

--Jacob Bronowski

Sudden cardiac death accounts for 250-300,000 deaths per year in the United States and remains a major contributor to morbidity and mortality and a significant public health issue.[25] Initial studies showed a clear survival benefit for ICD implantation for secondary prevention while ICD therapy for primary prevention showed a survival benefit in the majority of, but not all, studies. Furthermore, there is mounting evidence that shocks delivered by ICDs may be detrimental; however, the nature of this relationship is yet to be entirely elucidated and the causal nature of this association is yet to be established. What remains to be tested is the hypothesis that the overall mortality benefit derived from ICD therapy is competing with the adverse effects of ICD shocks.

There are currently a number of programming parameters that may be used to reduce the number of shocks delivered for cardiac arrhythmias including: 1) the use of antitachycardia pacing to terminate specific forms of ventricular tachycardia 2) the use of more aggressive discriminators to decrease sensing of atrial arrhythmias and the resulting inappropriate therapy and 3) delaying shock therapy to allow runs of ventricular tachycardia to potentially self-terminate. However, each of these methods of shock reduction may be associated with potential risks such as hemodynamic compromise from delayed therapy and missed therapy for life-threatening ventricular arrhythmias. The potential risks involved in shock reduction strategies coupled with the uncertainty surrounding the causal association of ICD shocks and increased risk of death provide a

clear case for the development of randomized controlled trials evaluating ICD programming strategies to reduce shocks. If the mortality benefit of shock reduction outweighs the risk of the tested programming characteristics, the benefit of ICD implantation may be greatly enhanced. Alternatively, a lack of risk reduction will provide insight and drive further research. Until studies provide insight to the above questions, there is simply not enough information to safely recommend changes to guidelines regarding ICD implantation.

For the time being, a second course of action is to concentrate on the adequate dissemination of current implantation guidelines throughout the medical community. ICD implantation has increased dramatically in the last decade and the concern has recently been raised that not all ICDs are implanted according to evidence-based criteria. A recent study in JAMA by Al-Khatib et al concluded that in the National Cardiovascular Data Registry-ICD Registry, 22.5% of ICD implantations between January 2006 and June 2009 did not meet evidence-based criteria. [26] This rate was significantly lower for electrophysiologists than other physician types. This study was not without its own limitations; however, these findings suggest that physicians may require further education regarding current implantation guidelines. Furthermore, these findings along with the findings from other studies suggest patients thought to require ICD implantation best be referred to physicians with formal training.[26,27] Not only are there improved rates of appropriate implantation and decreased rates of complications in the setting of formal training but there is the additional benefit of enrolling patients in future ICD studies that will hopefully soon be developed.

Overall, there remains a large area of uncertainty regarding ICD therapy. While uncertainty is uncomfortable, it also affords the opportunity to further our understanding of optimal ICD therapy delivery and more importantly to improve patient survival.

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Table 1. Selected baseline clinical characteristics for primary study groups

Characteristic	Patients with shock episodes (N = 252)	Patients without shock episodes (N = 173)	*P*-value
Age, y	65 (57-72)	64 (58-72)	0.755
Male, % (n)	99 (250)	99 (172)	0.999
Current smokers			
Hemoglobin, g/dL	13.7 (12.7-14.8)	13.5 (12.3-14.6)	0.058
Lymphocyte, %	21.7 (15.7-26.5)	20.3 (15.9-25.8)	0.098
Uric acid, mg/dL	7.1 (5.7-8.8)	6.9 (5.6-9.2)	0.937
Total cholesterol, mg/dL	163 (139-192)	162 (135-197)	0.697
Sodium, mEq/L	138 (136-140)	137 (135-139)	0.192
Ejection fraction, %	30 (25-41)	30 (21-40)	0.478
QRS duration, ms	120 (102-152)	116 (102-140)	0.247
QRS>120ms, % (n)	43 (109)	46 (79)	0.623
LBBB, % (n)	34 (81)	34 (55)	0.964
Systolic BP, mm Hg	123 (112-136)	122 (111-136)	0.531
Ischemic, % (n)	81 (204)	77 (134)	0.648
Primary prevention, % (n)	35 (88)	51 (87)	<0.001
ACE-Inhibitor, % (n)	71 (178)	73 (124)	0.651
Beta-blocker, % (n)	86 (217)	82 (139)	0.191
ARB, % (n)	10 (26)	11 (18)	0.940
Statin, % (n)	70 (176)	68 (116)	0.681
Allopurinol**,** % (n)	7 (18)	6 (11)	0.781
Aldosterone antagonist,% (n)	20 (49)	22 (37)	0.576
Diuretics,% (n)			
Furosemide	49 (123)	61 (103)	0.019
HCTZ	7 (17)	3 (5)	0.117
Bumex	1 (3)	3 (5)	0.278
NYHA Class			0.146
I	24 (61)	25 (45)	
I-II	9 (22)	5 (6)	
II	39 (98)	38 (65)	
II-III	6 (14)	2 (4)	
III	19 (48)	24 (42)	
III-IV	2 (5)	4 (6)	
IV	2 (4)	2 (4)	
Congestive Heart Failure,% (n)	90 (223)	89 (152)	0.871
Coronary Artery Disease,% (n)	92 (230)	88 (152)	0.175
Atrial Fibrillation,% (n)	47 (117)	38 (65)	0.063
Hypertension,% (n)	86 (213)	81 (137)	0.149
Diabetes Mellitus,% (n)	42 (104)	52 (90)	0.030
Chronic Kidney Disease,% (n)	33 (78)	33 (56)	0.855
SHFM 1-yr survival, %	96.4 (93.4-97.8)	95.9 (93.0-97.6)	0.196
SHFM 5-yr survival, %	83.4 (71.4-89.4)	81.1 (69.4-88.7)	0.106

*BP indicates blood pressure; ARB, angiotensin receptor blocker; HCTZ, Hydrochlorothiazide; NYHA, New York Heart Association. Continuous variables are shown as median (25^{th}, 75^{th} percentiles).

Table 2. Selected baseline clinical characteristics for study subgroups

Characteristic	No Therapy (N=130)	ATP Only (N=120)	<5 Shocks (N=102)	≥5 Shocks (N=54)	<5 Shockdays (N=122)	≥5 Shockdays (N=34)	Shock storm (N=96)
Age, y	63 (58-71)	65 (58-73)	64 (58-71)	66 (56-71)	65 (58-72)	64 (55-70)	65 (57-72)
QRS>120ms, % (n)	48 (62)	40 (48)	47 (45)	47 (24)	48 (59)	44 (15)	36 (35)
LBBB, % (n)	35 (44)	28 (34)	30 (28)	50 (24)	31 (37)	19 (59)	26 (20)
CHF,% (n)	88 (113)	88 (105)	92 (88)	94 (48)	89 (109)	94 (32)	86 (82)
CAD,% (n)	88 (114)	89 (107)	88 (84)	94 (48)	88 (107)	94 (32)	91 (96)
AF,% (n)	38 (48)	40 (48)	48 (46)	61 (31)	51 (62)	62 (21)	34 (36)
HTN,% (n)	79 (100)	88 (105)	88 (84)	84 (43)	84 (103)	85 (29)	81 (85)
DM,% (n)	52 (67)	46 (55)	39 (37)	53 (27)	40 (49)	53 (18)	37 (39)
CKD,% (n)	35 (45)	28 (34)	30 (29)	31 (16)	32 (39)	29 (10)	29 (29)
EF, %	30 (22-41)	30 (25-41)	30 (23-40)	28 (20-36)	30 (23-40)	27 (20-36)	32 (26-45)
SHFM 1-yr survival, %	95.8 (91.8-97.4)	96.5 (93.9-98.1)	96.1 (92.8-97.4)	96.1 (93.5-97.5)	96.2 (94.1-97.4)	95. (92.4-97.7)	97.0 (93.4-98.3)
SHFM 5-yr survival, %	80.8 (65.3-87.9)	83.6 (73.1-91.0)	82.3 (68.9-87.7)	82.1 (71.6-88.3)	82.6 (73.4-87.8)	80.4 (67.5-88.8)	85.7 (71.2-91.7)

Continuous variables are shown as median (25^{th}, 75^{th} percentiles).

Table 3. Adjusted Hazard Ratios for Primary and Subgroup Analyses

Analysis	Hazard Ratio	95% Confidence Interval	*P*-value
Shock			
Shock vs. no shocks	1.55	1.07-2.23	0.02
1-5 shockdays vs. no shocks	1.29	0.87-1.92	0.20
6-10 shockdays vs. no shocks	2.37	1.31-4.28	<0.01
>10 shockdays vs. no shocks	3.66	1.86-7.20	<0.01
1-5 shocks vs. no shocks	1.07	0.68-1.69	0.75
6-10 shocks vs. no shocks	2.05	1.19-3.54	<0.01
>10 shocks vs. no shocks	2.37	1.47-3.82	<0.01
Therapy type			
Any therapy vs. no therapy	1.35	0.92-1.98	0.13
Shock vs. no therapy	1.55	1.06-2.28	0.02
ATP only vs. no therapy	0.73	0.34-1.56	0.41
No Shock storm			
< 5 shockdays vs. no shocks	1.20	0.76-1.89	0.44
≥ 5 shockdays vs. no shocks	3.51	1.83-6.75	<0.01
< 5 shocks vs. no shocks	1.06	0.65-1.73	0.83
≥ 5 shocks vs. no shocks	2.87	1.65-4.98	<0.01
≥ 5 Shockdays			
Shock storm vs. no shock storm	1.20	0.60-2.38	0.60
≥ 5 Shocks			
Shock storm vs. no shock storm	1.08	0.63-1.85	0.78

The no-shock group includes ATP only and no therapy. The therapy group includes all therapy episodes of any type. Shock storm is defined at ≥5 shocks in a 24-hour period. Covariates include the Seattle Heart Failure Model score and chronic kidney disease. Other covariates tested included congestive heart failure, coronary artery disease, QRS duration >120ms, LBBB, ejection fraction, smoking status, diabetes mellitus, hypertension, atrial fibrillation and primary prevention.

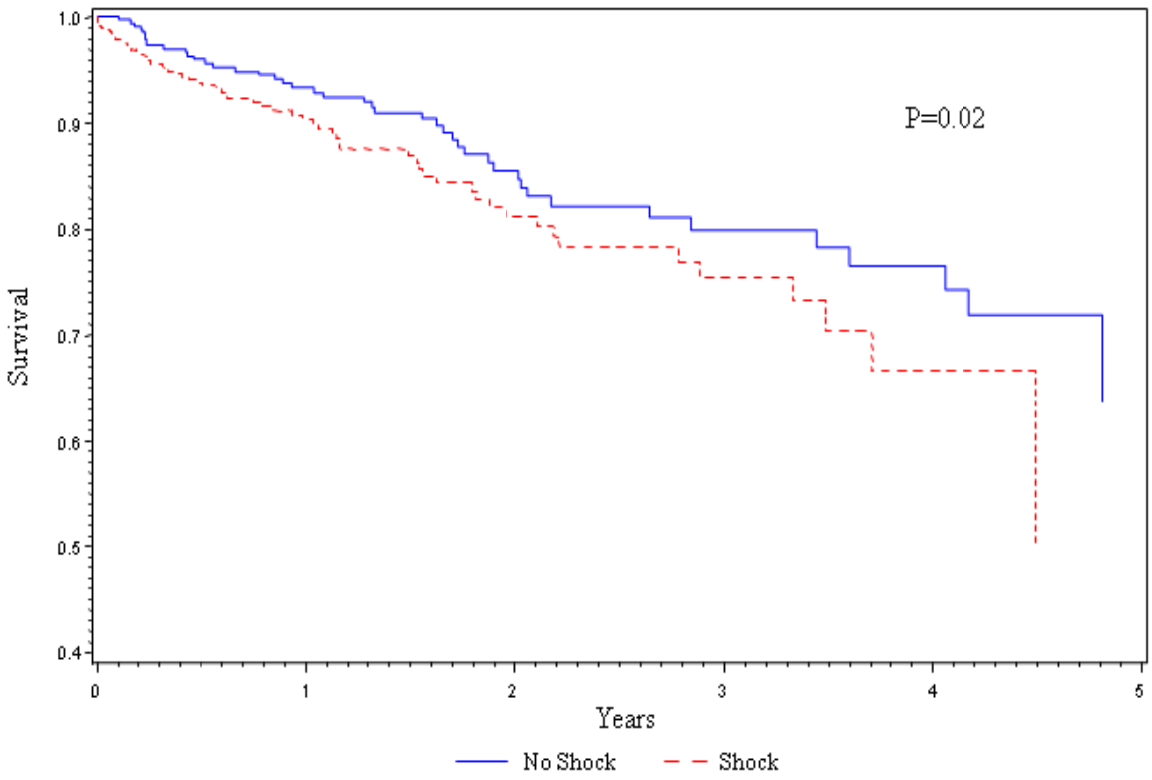


Figure 1. Survival curves adjusted for SHFM score and presence of CKD differed between the shock and the no-shock groups, with decreased survival in the shock group. While the graph is limited to 5-years of follow-up, the *P*-value displayed is calculated based on the total study duration.

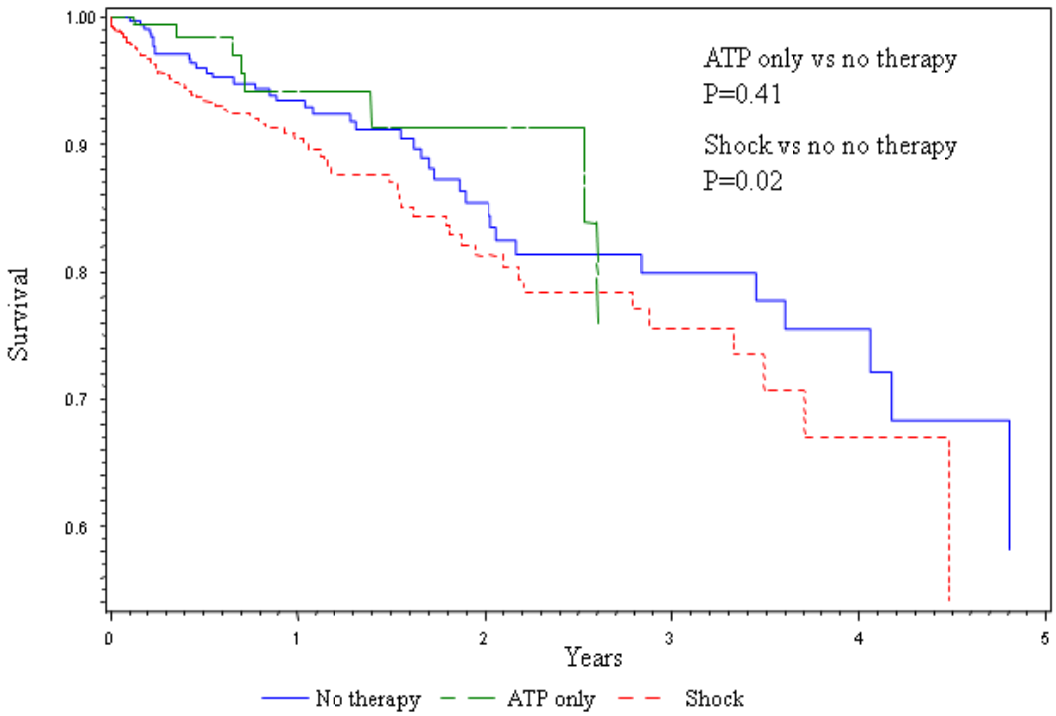


Figure 2. Survival curves adjusted for SHFM score and presence of CKD differed between the shock, ATP only, and no-therapy groups, with decreased survival in the shock group but not in the ATP only group as compared to no-therapy. While the graph is limited to 5-years of follow-up, the *P*-values displayed are calculated based on the total study duration.

Appendices

Appendix A. Predictors of All-Cause Mortality by Cox Proportional Hazards Regression Analysis

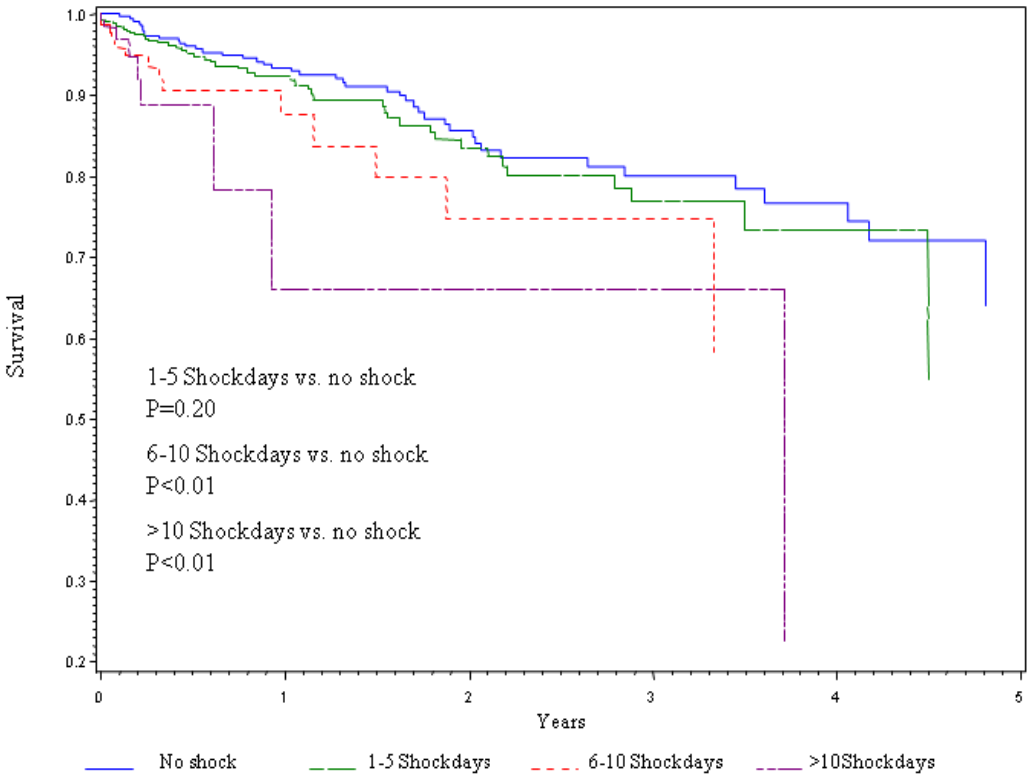
Variable	Hazard Ratio	95% Confidence Interval	*p*-value
SHFM score	1.99	1.63-2.42	<0.01
Chronic kidney disease	2.04	1.44-2.89	<0.01
Congestive heart failure	1.85	0.94-3.64	0.08
Coronary artery disease	1.65	0.77-3.55	0.20
Atrial fibrillation	1.02	0.72-1.45	0.91
Hypertension	0.62	0.55-1.43	0.62
Diabetes mellitus	1.08	0.76-1.53	0.68
Current smoking	0.96	0.71-1.44	0.96
Primary prevention	1.18	0.81-1.70	0.39
QRS>120	1.48	1.04-2.10	0.03
Left bundle branch block	1.24	0.88-1.80	0.20
EF	0.99	0.97-1.00	0.05

Univariate analysis of covariates. SHFM score, chronic kidney disease, congestive heart failure, coronary artery disease, QRS>120 ms, and left bundle branch block were included in the multivariate analysis for inclusion criteria $P \leq 0.20$. SHFM score and CKD were the only predictive variables included in the final multivariate model.

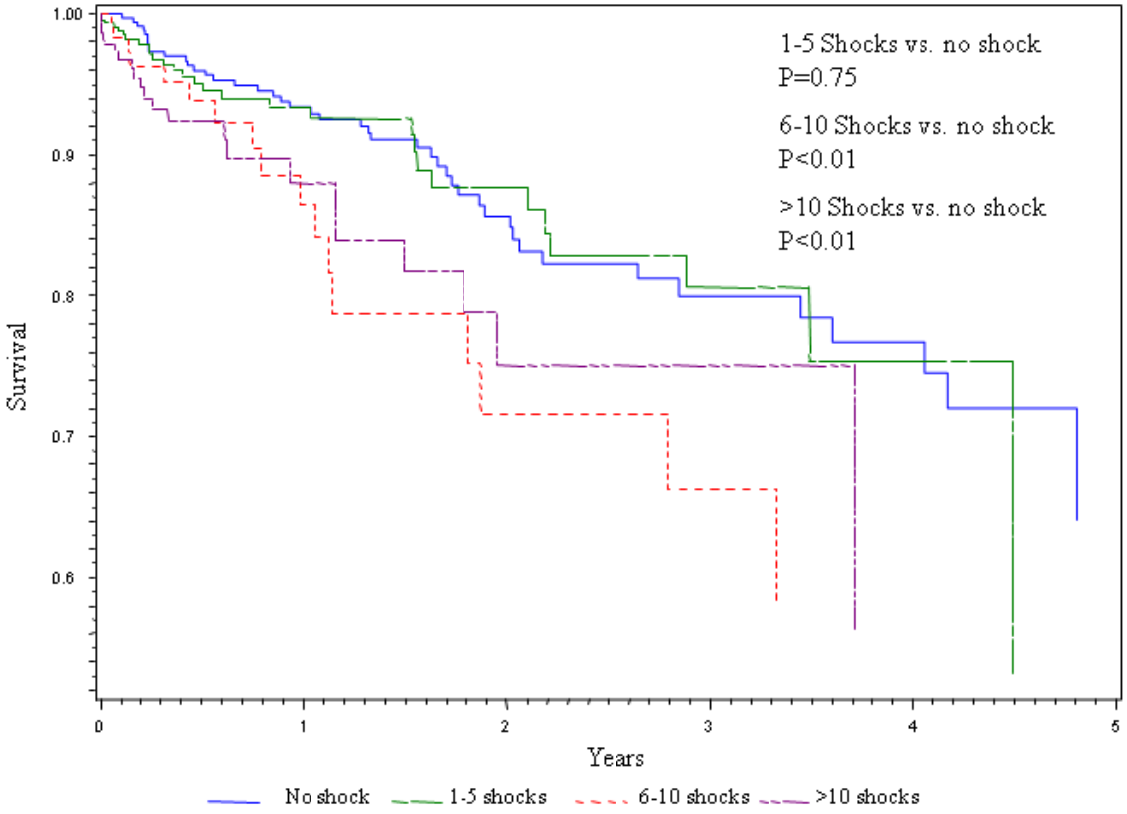
Appendix B. Unadjusted hazard ratios for primary and subgroup analyses

Variable	Hazard Ratio	95% Confidence Interval	*P*-value
Shock			
Shock vs. no shocks	1.32	0.97-1.81	0.08
1-5 shocks vs no shocks	1.01	0.68-1.48	0.98
6-10 shocks vs. no shocks	1.64	1.01-2.66	0.05
>10 shocks vs. no shocks	1.75	1.17-2.62	<0.01
>5 shocks vs. ≤ 5shocks	1.70	1.24-2.34	<0.01
1-5 shockdays vs. no shocks	1.15	0.82-1.62	0.41
6-10 shockdays vs. no shocks	1.57	0.94-2.63	0.08
>10 shockdays vs. no shocks	3.21	1.78-5.81	<0.01
Therapy type			
Therapy vs. no therapy	1.24	0.89-1.73	0.20
Shock vs. no therapy	1.37	0.98-1.90	0.06
ATP only vs. no therapy	0.85	0.47-1.54	0.60
No shock storm			
<5 Shockdays vs. no shocks	1.03	0.70-1.52	0.88
≥5 Shockdays vs. no shocks	2.42	1.39-4.22	<0.01
<5 Shocks vs. no shocks	0.91	0.59-1.38	0.65
≥5 Shocks vs. no shocks	2.14	1.35-3.39	<0.01
≥5 Shockdays			
Shock storm vs. no shock storm	1.14	0.60-2.16	0.69
≥5 Shocks			
Shock storm vs. no shock storm	1.00	0.60-1.66	0.99

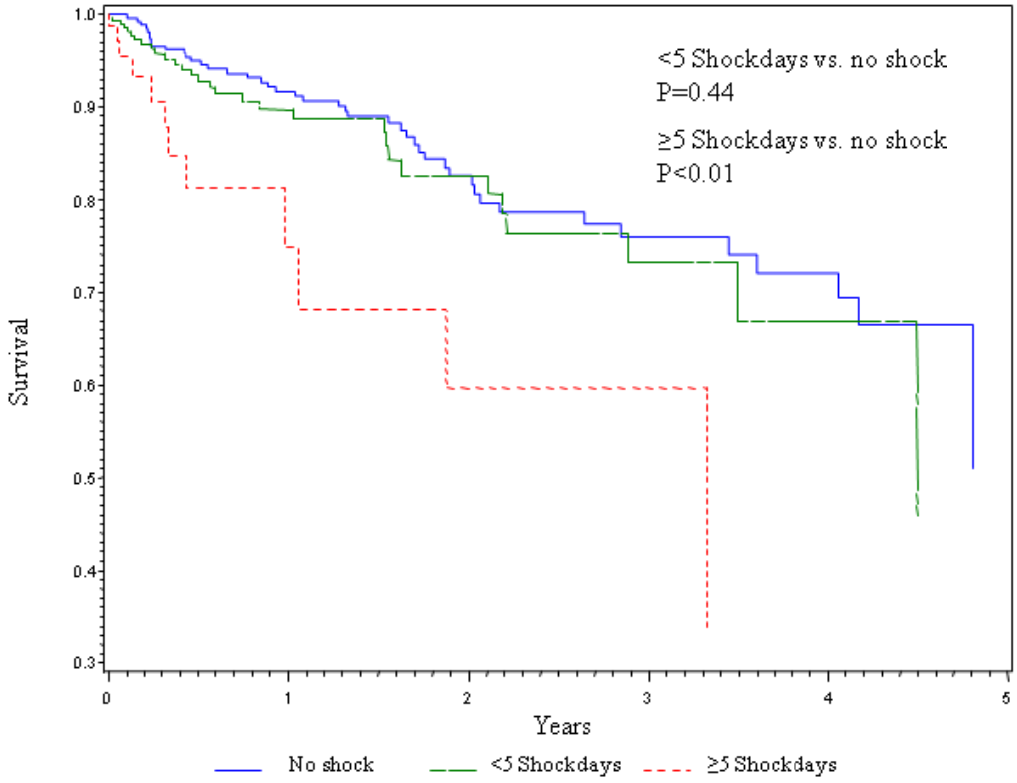
The no-shock group includes ATP only and no therapy. The therapy group includes all therapy episodes of any type. Shock storm is defined at ≥5 shocks in a 24-hour period.
ATP=antitachycardia pacing



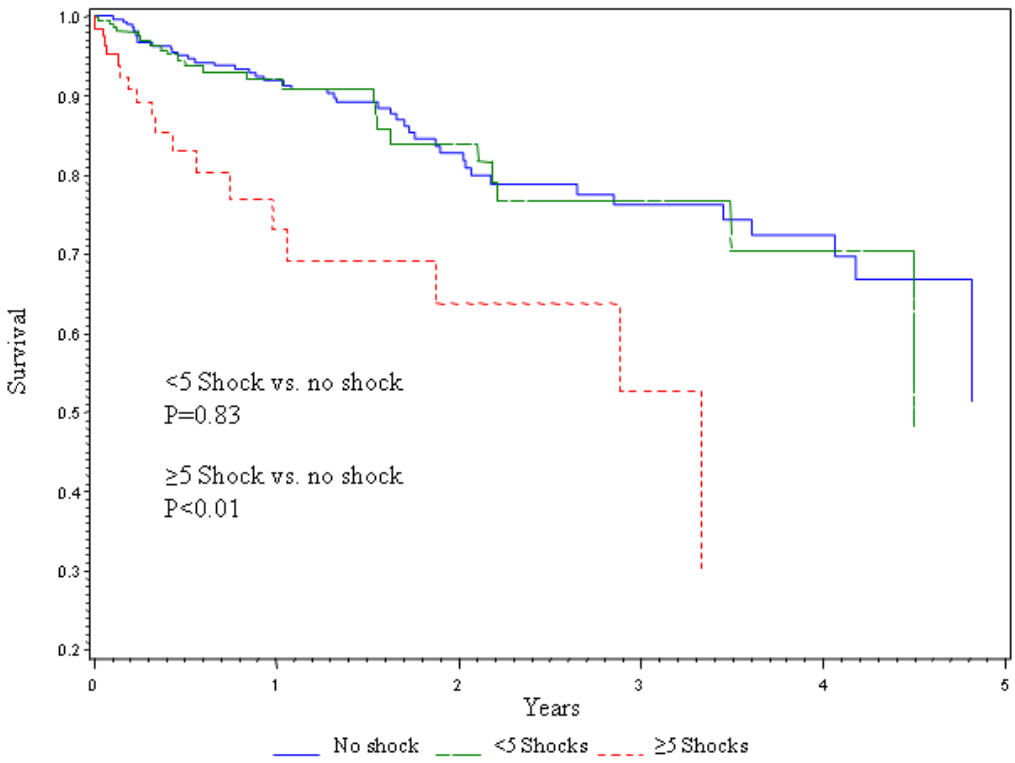
Appendix C. Survival curves comparing patients with increasing number of days (Shockdays) with shocks to the no-shock group adjusted for SHFM score and presence of CKD. While the graph is limited to 5-years of follow-up, the *P*-values displayed are calculated for the entire study duration.



Appendix D. Survival curves comparing patients with increasing number of shocks to the no-shock group adjusted for SHFM score and presence of CKD. While the graph is limited to 5-years of follow-up, the *P*-values displayed are calculated for the entire study duration.



Appendix E. Survival curves comparing patients that never experienced episodes of shock storm stratified into <5 days with shocks (Shockdays) and ≥5 days with shocks (Shockdays) as compared to the no-shock group adjusted for SHFM score and presence of CKD. While the graph is limited to 5-years of follow-up, the *P*-values displayed are calculated for the entire study duration.



Appendix F. Survival curves comparing patients that never experienced episodes of shock storm stratified into <5 shocks and ≥5 shocks as compared to the no-shock group adjusted for SHFM score and presence of CKD. While the graph is limited to 5-years of follow-up, the *P*-values displayed are calculated for the entire study duration.