Relation between Total Shock Energy and Mortality in Patients with Implantable Cardioverter-Defibrillator

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Keywords: Total shock energy; Implantable cardioverter-defibrillator; Mortality; Shock accumulation; Low left ventricular ejection fraction; Atrial fibrillation

Abstracts

Background: Implantable Cardioverter-Defibrillator (ICD) shocks have been associated with mortality. However, no study has examined the relation between total shock energy and mortality. The aim of this study is to assess the association of total shock energy with mortality, and to determine the patients who is at risk of this association.

Methods: Data from 316 consecutive patients who underwent initial ICD implantation in our hospital between 2000 and 2011 were retrospectively studied. We collected shock energy for 3 years from the ICD implantation, and determined the relation of shock energy on mortality after adjusting confounding factors.

Results: Eighty-seven ICD recipients experienced shock(s) within 3 years from ICD implantation and 43 patients had died during the follow-up. The amount of shock energy was significantly associated with all-cause death [adjusted hazard ratio (HR) 1.26 (per 100 joule increase), $p < 0.01$] and tended to be associated with cardiac death (adjusted HR 1.30, $p = 0.08$). The survival rate of patients with high shock energy accumulation (≥ 182 joule) was lower ($p < 0.05$), as compared to low shock energy accumulation (< 182 joule), likewise to no shock. Besides, the relation between high shock energy accumulation and all-cause death was remarkable in the patients with low left ventricular ejection fraction (LVEF ≤ 40%) or atrial fibrillation (AF).

Conclusions: Increase of shock energy was related to mortality in ICD recipients. This relation was evident in patients with low LVEF or AF.

Introduction

Implantable Cardioverter-Defibrillator (ICD) is effective for terminating the lethal arrhythmias and decreases mortality in selected patients [1-5]. On the other hand, sub-analysis of those studies reported that ICD shock therapy, regardless of appropriate or inappropriate, was associated with an increased risk of death [6, 7]. Actually, ICD programming to reduce the inappropriate ICD therapies decreased all-cause mortality during the long-term follow-up [8]. However, no study has examined the relation of total shock energy on mortality. In addition, it remains unknown who is likely to receive this relation. Therefore, the present study aimed to assess the association between total shock energy and mortality, and to clarify the subgroup of patients who suffer most from these detrimental consequences. In addition, our findings would help decide the optimal timing for some intervention in ICD recipients after shock.

Methods

Study patients

We performed a retrospective review of 316 consecutive patients who underwent initial ICD implantation at Hokkaido University Hospital from December 2000 to December 2011. Nine patients were excluded for the analysis due to insufficient shock data. Finally, a total of 307 patients were included in the present study (**Supplemental Figure 1**). The study was approved by the Ethics Committee of Hokkaido University Hospital.

Data collection

Baseline data at the time of ICD implantation were collected from the medical records. These included demography, underlying heart diseases, New York Heart Association (NYHA) functional class, echocardiographic data, comorbidities, and medications. Information about ICD therapies [appropriate or inappropriate, therapy type, i.e. shock or anti-tachycardia pacing (ATP), and shock energy] were collected in each patient for 3 years from the ICD implantation. ICD shocks during defibrillation testing were not included for the analysis. The diagnostic classification of ICD therapy events was made by the electrophysiological specialists according to the stored intracardiac electrograms. We obtained the clinical outcomes (all-cause death and cardiac death) until the end of August 2012.

Device programming

Details of device programing had been described previously [9]. Ventricular

fibrillation (VF) zone detected ventricular events faster than 185 – 200 beats / min, and an initial therapy was 30 joule or more (maximum energy of the device). Ventricular tachycardia (VT) zone detected ventricular events faster than 150 – 170 beats / min, and 3 sequences of ATP were initially attempted. If the arrhythmia continued, the first shock with an energy ranging 10 – 20 joule and subsequent shocks with maximal energy were delivered until its termination. The first shock in VT zone was always 10 joule or more in order to prevent possible proarrhythmia induced by low-energy shocks. The device-related detection algorithms such as dual chamber sensing, the stability and sudden-onset criteria were usually employed for the discrimination of supraventricular tachycardia [10]. After October 2006, the morphology-based algorithm for detecting ventricular tachycardia was used as a nominal setting [11]. The ICD devices were manufactured by Boston Scientific (Marlborough, Massachusetts, USA), Medtronic (Minneapolis, Minnesota, USA), or Abbott / St. Jude Medical (Lake Bluff, Illinois, USA).

Study endpoints

The primary endpoint was death from any cause. The cause of death, i.e. cardiac or non-cardiac, was made by attending physicians.

Statistical analysis

Categorical variables were displayed as number (percentage) and continuous variables were expressed as median (first to third quartile). Simple between-group analyses were conducted using Fisher's exact test. Comparison of data among the 3

groups was executed using analysis of variance (ANOVA) for continuous variables and Fisher's exact test for categorical variables (**Table 1**).

The primary analyses for all-cause death and cardiac death were as follows. First, univariate Cox proportional-hazards regression analyses were performed, including all baseline variables except for medications. Among the significant variables (which were *p* value of less than 0.1) in univariate analyses (**Supplemental Table 1**), a stepwise selection was used to determine the most agreeable model. As a result, independent covariates were age, NYHA class III to IV, and cardiac resynchronization therapy (CRT) for all-cause death, and age and NYHA class III to IV for cardiac death. Second, multivariate Cox proportional-hazards regression analyses were performed to estimate the relationship between total shock energy and mortality (**Table 2**). To define the degree of ICD shock accumulation, the cut off value was determined by receiver operating characteristic (ROC) curve analysis. Survival distributions were calculated using Kaplan-Meier method and post-hoc analysis (Holm method) was conducted (**Figure 1**). Additional analyses included univariate Cox proportional-hazards regression for all-cause death to reveal the interaction between high shock energy accumulation and different categorical subgroups in patients with shock (**Figure 2**).

Differences with $p < 0.05$ were considered significant. JMP® Pro (SAS Institute Inc., Cary, NC, USA, version 13) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan, version 1.32), which is a graphical user interface for R (R Foundation for Statistical Computing, Vienna, Austria, version 3.2.2) were used for all statistical analyses.

Results

Baseline characteristics of the patients

Baseline characteristics of the patients were given in **Table 1**. Most of patients were male (78%) and received ICD for secondary prevention (73%). Almost half of patients had non-ischemic heart disease. Atrial fibrillation was found in about a quarter of patients.

ICD events

Within 3 years from ICD implantation, 87 out of 307 patients (28%) received at least a shock of any type. They consisted of 40 patients (46%) with only appropriate shock(s), 36 patients (41%) with only inappropriate shock(s) and 11 patients (13%) with both shocks. In the patients without shock (N = 220), 24 patients (11%) experienced only ATP(s) (**Supplemental Figure 2A**). Among 51 patients with appropriate shock, 32 (63%), 16 (31%), and 3(6%) patients received shock(s) for VT, VF, and both VT and VF event(s), respectively. On the other hand, ATP(s) were delivered for VT in all 24 patients with ATP(s) as appropriate ICD therapy (**Supplemental Figure 2B**). Electrical storm (ES) occurred in 21 out of 307 patients (7%), and 3 patients out of 21 ES patients had only ATPs. Five patients out of 51 appropriate shock patients (10%) had more than one shock per VT or VF event.

ICD shock energy

In the patients with shock (N = 87), the median number of ICD shocks was 2

(interquartile range [IQR] 1 – 6), and the median total shock energy was 60 joule (IQR 31 – 175). Depending on the types of shock, it was 60 joule (IQR 31 – 60) in patients with appropriate shock, 36 joule (IQR 31 – 86) in those with inappropriate shock, and 267 joule (IQR 123 – 443) in those with both shocks. The summary of patients with 1, 2, 3 or more VT / VF events and delivered shock energy for appropriate and inappropriate ICD shocks is given in **Supplemental Table 2**.

Mortality

Of the 307 patients, 43 patients (14%) died during the follow-up. Twenty-one patients (49%) had cardiac death and 22 patients (51%) had non-cardiac death. The cause of cardiac death was heart failure in 20 patients and arrhythmia in 1 patient. With regard to non-cardiac death, there were 8 patients (36%) with malignancy, 4 patients (18%) with infection, 3 patients (14%) with frailty, 2 patients (9%) with stroke, one patient (5%) with hepatic disease, and 4 patients (18%) with unknown cause. In relation to ICD shocks, death occurred in 20 out of 87 patients (23%) with any shock and in 23 out of 220 patients (10%) without shock, respectively (with vs. without any shock, $p < 0.01$). Twelve of 87 patients (14%) with any shock and 9 of 220 patients (4%) without any shock died of cardiac cause (with vs. without any shock, $p < 0.01$).

The association between total shock energy and mortality

In an adjusted (multivariate) Cox proportional-hazards regression analysis by appropriate covariates, the increase of total shock energy (per 100 joule) was related to the risk of all-cause death and tended to be associated with cardiac death (**Table 2**). For

defining the categorical subgroups, the ROC analysis among the patients with any shock determined that the cut off value of total shock energy for predicting all-cause death was 182 joule. The sensitivity was 0.40, specificity 0.82, and area under the curve 0.58. Based on this analysis, the patients were divided into 3 groups: no shock (N = 220), low shock accumulation (< 182 joule) (N = 67), and high shock accumulation (≥ 182 joule) (N = 20) (**Supplemental Figure 1**). Baseline characteristics among the 3 groups were given in **Table 1**. The incidences of all-cause death and cardiac death were 10% (23 / 220) and 4% (9 / 220) in no shock, 18% (12 / 67) and 12% (8 / 67) in low shock accumulation, and 40% (8 / 20) and 20% (4 / 20) in high shock accumulation, respectively. Kaplan-Meyer curves for survival-free from all-cause death and cardiac death for each group were depicted in **Figures 1A and 1B**, respectively. The cumulative incidence of all-cause death was significantly greater in patients with high shock accumulation, as compared to those with no shock or those with low shock accumulation (**Figure 1A**). Similarly, the rate of cardiac death was higher in high shock accumulation group than in no shock group (**Figure 1B**).

Interaction between total shock energy on death and subgroups of patients in shock patients

The relation between high shock accumulation and all-cause death in different subgroups are presented in **Figure 2**. Two interaction effects between subgroup and high shock accumulation on death were identified: low LVEF (≤ 40%) and AF [p = 0.04 (low LVEF) and 0.04 (AF) for interaction]. On the other hand, type of shock, i.e. appropriate shock(s), inappropriate shock(s), and both shocks, had little influence on the

association between shock accumulation and all-cause death (p = 0.94 for interaction).

Shock interval and death

In the patients with shock (N = 87), 51 patients (59%) had experienced the ICD shocks twice or more. In these patients, 26 patients (51%) received only appropriate shocks, 14 patients (27%) received only inappropriate shocks, and 11 patients (22%) received both shocks. The median of shock interval, which was calculated as an average time interval between shocks in each patient, was 12 days (IQR 0 – 81). There was no association between mortality and shock interval (**Supplemental Table 3**). Median time interval from the last shock to death for patients who received any types of shock was 648 days (IQR 158 – 1342). Time intervals from the last shock delivery to death based on the total shock energy (TSE) and types of shock are shown in **Supplemental Table 4**.

Discussion

The present study has shown two major findings. First, the increase of shock energy was related to mortality in patients with ICD. Second, there were significant interactions in two distinct subgroups, i.e. patients with low LVEF (≤ 40 %) or those with AF had the higher risk of all-cause death in case of high shock accumulation. Because of the small number of death events, further evidences are required to prove the direct linking cumulative shock energy with mortality.

Relation between ICD shock and mortality

Previous studies suggested that ICD shock therapy, regardless appropriate or inappropriate shock, was associated with the increased risk of death [6, 7]. MADIT-RIT trial demonstrated that programming of ICD therapies, which were high-rate or delayed therapy, was associated with reductions in inappropriate therapy and all-cause mortality [8]. Larsen et al reported that the shock burden, especially the cumulative number of days with shocks (shock days), was related to the risk of death when it became more than 5 days [12]. On the other hand, the recent ALTITUDE study proposed that the adverse prognosis after first shock appears to be more related to the underlying arrhythmia than to an adverse effect from the shock itself [13]. This study evaluated the association between first shock episode rhythms and survival in patients with an ICD, and found that patients with first inappropriate shocks for atrial fibrillation had an increased risk of death, whereas those for sinus tachycardia or noise / artifact / oversensing showed a similar survival to patients with no shock. The causes (i.e. noise /

artifact / oversensing) of first inappropriate shock may have been corrected immediately. In contrast, as a history of atrial fibrillation is one of the major causes for inappropriate shocks [6, 7, 9], the shock episode would have been recurrent, thereby resulting in high accumulation of the shocks and worse outcomes. Aktas et al also reported that increasing number of ICD shocks during defibrillation threshold (DFT) testing was not associated with increased risk for heart failure or death in the sub-analysis of MADIT-CRT [14]. Therefore, our findings that high shock accumulation was associated with increased mortality should be interpreted with caution, because ventricular arrhythmias are highly prevalent in patients with advanced heart failure [15], and the ICD shock could be an epi-phenomenon of more advanced disease.

Possible mechanism of worse outcomes by ICD shock

We think that the mechanism of the increased risk of death by ICD shock is related to the adverse effects of electrical shocks on myocardial function. This is because that electrical shocks were significantly associated with depressed cardiac function, lower mean arterial pressure, and impaired cardiac output in experimental studies [16, 17], and also in a clinical study [18]. In addition, Tereshchenko et al reported that the local injury current on bipolar near-field right ventricular electrograms, which occurred by excessive large shock-induced changes in transmembrane potential due to electroporation, was associated with the increased risk of congestive heart failure progression [19]. In experimental studies, shock-induced electroporation changed the membrane integrity and produced the intracellular uptake of membrane impermeable molecules, thereby resulting in cellular injury [20, 21]. Therefore, we consider that

cellular electroporation injury leads to irreversible myocardial dysfunction.

Effect of shock energy on patients with low LVEF or AF

Cardiac function and its performance reserve are reduced in patients with low LVEF. In these patients, ICD shock may be an epi-phenomenon of more advanced disease. The prevalence of AF increases in association with the severity of heart failure status [22]. And vice versa, AF precipitates left ventricular dysfunction via the loss of atrial contraction and irregular rapid ventricular rhythm. Thus, AF and heart failure frequently coexist up to 30% of patients [23]. Due to some physiological mechanisms in common, patients with these factors can be under the influence of detrimental relationship between shock energy and death.

Clinical implications

The present study showed that patients with high shock accumulation were significantly related to the mortality compared to those with low shock accumulation (**Figure 1**). Moreover, we revealed the remarkable interaction between shock energy and death in the specific patients who had low LVEF or AF. These novel findings suggest that shock reduction in patients after shock is important for not only quality of life but also prognosis. For this purpose, catheter ablation for VT and even VF may be promising [24-28]. The VANISH trial demonstrated that catheter ablation was superior to escalated antiarrhythmic drug therapy in terms of decrease in the primary composite outcome of death, VT storm, or appropriate ICD shock among patients with ischemic cardiomyopathy and an ICD who had VT despite the use of antiarrhythmic drugs [29].

However, no randomized clinical trials have demonstrated that catheter ablation reduce the risk of death in patients receiving an ICD [29-32]. A future prospective study is necessary whether the shock reduction by catheter ablation for the selected ICD patients (e.g., those with low LVEF or AF) improves the prognosis.

Study limitations

This study has several limitations to be acknowledged. The present study was retrospective and conducted in a single center. Therefore, the present findings need to be confirmed in a multicenter prospective study to be generalized. We assessed total shock energy in each patient based on ICD therapy for 3 years from the ICD implantation. The ICD shock which occurred after 3 years might also influence on mortality. The type and settings of the ICD devices were determined by the attending electrophysiological specialist based on patient background such as heart failure status, which might affect the shock burden and mortality. We calculated the shock energy based on the stored values from the ICD. The amount of true electrical energy discharged on the heart may vary from each patient, even with the same amount of delivered shock energy. Finally, the present analyses were underpowered by the limited number of death events, that is, total 20 deaths in 87 patients receiving any ICD shock (**Figure 2 and Supplemental Table 4**).

Conclusions

The present study showed that the cumulative ICD shock energy was associated with mortality. This association increased in the patients with low LVEF (≤ 40%) or AF. Our observations should be interpreted with caution, because the close relationship exists between ventricular arrhythmias requiring ICD shocks and the progression of heart failure [15].

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References

[1] Goldberger Z, Lampert R. Implantable cardioverter-defibrillators: expanding indications and technologies. JAMA : the journal of the American Medical Association. 2006;295:809-18.

[2] AVID Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. The Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators. The New England journal of medicine. 1997;337:1576-83.

[3] Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, 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. The New England journal of medicine. 1996;335:1933-40.

[4] Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. The New England journal of medicine. 2002;346:877-83.

[5] Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. The New England journal of medicine. 2005;352:225-37.

[6] Poole JE, Johnson GW, Hellkamp AS, Anderson J, Callans DJ, Raitt MH, et al. Prognostic importance of defibrillator shocks in patients with heart failure. The New England journal of medicine. 2008;359:1009-17.

[7] Daubert JP, Zareba W, Cannom DS, McNitt S, Rosero SZ, Wang P, et al. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms,

predictors, and survival impact. Journal of the American College of Cardiology. 2008;51:1357-65.

[8] Moss AJ, Schuger C, Beck CA, Brown MW, Cannom DS, Daubert JP, et al. Reduction in inappropriate therapy and mortality through ICD programming. The New England journal of medicine. 2012;367:2275-83.

[9] Tenma T, Yokoshiki H, Mizukami K, Mitsuyama H, Watanabe M, Sasaki R, et al. Predictors and Proarrhythmic Consequences of Inappropriate Implantable Cardioverter-Defibrillator Therapy. Circulation journal : official journal of the Japanese Circulation Society. 2015;79:1920-7.

[10] Swerdlow CD. Supraventricular tachycardia-ventricular tachycardia discrimination algorithms in implantable cardioverter defibrillators: state-of-the-art review. Journal of cardiovascular electrophysiology. 2001;12:606-12.

[11] Swerdlow CD, Brown ML, Lurie K, Zhang J, Wood NM, Olson WH, et al. Discrimination of ventricular tachycardia from supraventricular tachycardia by a downloaded wavelet-transform morphology algorithm: a paradigm for development of implantable cardioverter defibrillator detection algorithms. Journal of cardiovascular electrophysiology. 2002;13:432-41.

[12] Larsen GK, Evans J, Lambert WE, Chen Y, Raitt MH. Shocks burden and increased mortality in implantable cardioverter-defibrillator patients. Heart rhythm : the official journal of the Heart Rhythm Society. 2011;8:1881-6.

[13] Powell BD, Saxon LA, Boehmer JP, Day JD, Gilliam FR, 3rd, Heidenreich PA, et al. Survival after shock therapy in implantable cardioverter-defibrillator and cardiac resynchronization therapy-defibrillator recipients according to rhythm shocked. The

ALTITUDE survival by rhythm study. Journal of the American College of Cardiology. 2013;62:1674-9.

[14] Aktas MK, Huang DT, Daubert JP, Schuger CD, McNitt S, Goldenberg I, et al. Effect of defibrillation threshold testing on heart failure hospitalization or death in the Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy (MADIT-CRT). Heart rhythm : the official journal of the Heart Rhythm Society. 2013;10:193-9.

[15] Santangeli P, Rame JE, Birati EY, Marchlinski FE. Management of Ventricular Arrhythmias in Patients With Advanced Heart Failure. Journal of the American College of Cardiology. 2017;69:1842-60.

[16] Xie J, Weil MH, Sun S, Tang W, Sato Y, Jin X, et al. High-energy defibrillation increases the severity of postresuscitation myocardial dysfunction. Circulation. 1997;96:683-8.

[17] Osswald S, Trouton TG, O'Nunain SS, Holden HB, Ruskin JN, Garan H. Relation between shock-related myocardial injury and defibrillation efficacy of monophasic and biphasic shocks in a canine model. Circulation. 1994;90:2501-9.

[18] Tokano T, Bach D, Chang J, Davis J, Souza JJ, Zivin A, et al. Effect of ventricular shock strength on cardiac hemodynamics. Journal of cardiovascular electrophysiology. 1998;9:791-7.

[19] Tereshchenko LG, Faddis MN, Fetics BJ, Zelik KE, Efimov IR, Berger RD. Transient local injury current in right ventricular electrogram after implantable cardioverter-defibrillator shock predicts heart failure progression. Journal of the American College of Cardiology. 2009;54:822-8.

[20] Nikolski VP, Sambelashvili AT, Krinsky VI, Efimov IR. Effects of electroporation on

optically recorded transmembrane potential responses to high-intensity electrical shocks. American journal of physiology Heart and circulatory physiology. 2004;286:H412-8.

[21] Nikolski VP, Efimov IR. Electroporation of the heart. Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology. 2005;7 Suppl 2:146-54.

[22] Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. The American journal of cardiology. 2003;91:2d-8d.

[23] Prabhu S, Voskoboinik A, Kaye DM, Kistler PM. Atrial Fibrillation and Heart Failure - Cause or Effect? Heart, lung & circulation. 2017;26:967-74.

[24] Stevenson WG, Khan H, Sager P, Saxon LA, Middlekauff HR, Natterson PD, et al. Identification of reentry circuit sites during catheter mapping and radiofrequency ablation of ventricular tachycardia late after myocardial infarction. Circulation. 1993;88:1647-70.

[25] Arenal A, Glez-Torrecilla E, Ortiz M, Villacastin J, Fdez-Portales J, Sousa E, et al. Ablation of electrograms with an isolated, delayed component as treatment of unmappable monomorphic ventricular tachycardias in patients with structural heart disease. Journal of the American College of Cardiology. 2003;41:81-92.

[26] Haissaguerre M, Shoda M, Jais P, Nogami A, Shah DC, Kautzner J, et al. Mapping and ablation of idiopathic ventricular fibrillation. Circulation. 2002;106:962-7.

[27] Yokoshiki H, Mitsuyama H, Watanabe M, Mizukami K, Tsutsui H. Suppression of ventricular fibrillation by electrical modification of the Purkinje system in hypertrophic cardiomyopathy. Heart and vessels. 2014;29:709-17.

[28] Nogami A, Sugiyasu A, Kubota S, Kato K. Mapping and ablation of idiopathic ventricular fibrillation from the Purkinje system. Heart rhythm : the official journal of the Heart Rhythm Society. 2005;2:646-9.

[29] Sapp JL, Wells GA, Parkash R, Stevenson WG, Blier L, Sarrazin JF, et al. Ventricular Tachycardia Ablation versus Escalation of Antiarrhythmic Drugs. The New England journal of medicine. 2016.

[30] Reddy VY, Reynolds MR, Neuzil P, Richardson AW, Taborsky M, Jongnarangsin K, et al. Prophylactic catheter ablation for the prevention of defibrillator therapy. The New England journal of medicine. 2007;357:2657-65.

[31] Kuck KH, Schaumann A, Eckardt L, Willems S, Ventura R, Delacretaz E, et al. Catheter ablation of stable ventricular tachycardia before defibrillator implantation in patients with coronary heart disease (VTACH): a multicentre randomised controlled trial. Lancet. 2010;375:31-40.

[32] Kuck KH, Tilz RR, Deneke T, Hoffmann BA, Ventura R, Hansen PS, et al. Impact of Substrate Modification by Catheter Ablation on Implantable Cardioverter-Defibrillator Interventions in Patients With Unstable Ventricular Arrhythmias and Coronary Artery Disease: Results From the Multicenter Randomized Controlled SMS (Substrate Modification Study). Circulation Arrhythmia and electrophysiology. 2017;10.

Figure captions

Figure 1. Survival curves for each total shock energy group

A. Kaplan-Meyer curves for survival-free from all-cause death. **B**. Kaplan-Meyer curves for survival-free from cardiac death. The *p* values are taken from log-rank test.

Figure 2. Hazard ratios for all-cause death in high shock accumulation, according to selected subgroups

Hazard ratio indicates the risk of all-cause death in patients with high shock accumulation (≥ 182 joule) versus those with low shock accumulation (< 182 joule) . The squares represent hazard ratios and the horizontal lines indicate corresponding 95% confidence intervals. The vertical dotted line shows no effect point. Two subgroup interactions were identified, for low LVEF (≤ 40%) and AF. On the other hand, significant interaction was not observed for the type of shock.

Supplemental Figure captions

Supplemental Figure 1. Study flow diagram

Three hudred seven out of 316 consecutive patients who underwent initial ICD implantation included in the present study. We divided these 307 patients into 2 groups which were with shock (N =87) or without shock (N = 220). The 87 patients with shock were categorized as the following 2 groups: those with low shock accumulation (< 182 joule) (N = 67) and with high shock accumulation (≥ 182 joule) (N = 20)

Supplemental Figure 2. ICD events

A. Eighty-seven out of 307 patients (28%) received at least a shock of any type. They consisted of 37 patients (42%) with only appropriate shock(s), 33 patients (38%) with only inappropriate shock(s) and 17 patients (20%) with both shocks. In patients without shock (N = 220), 24 patients (11%) experienced only ATP(s). **B.** Twenty-four patients without any shock received appropriate ATP(s) therapy, which was delivered for VT events (100%) (left column). Regarding shock therapy, 32 (63%), 16 (31%), and 3(6%) out of 51 patients received appropriate shock(s) for VT, VF, and both VT and VF event(s), respectively (right column).

Figure 1

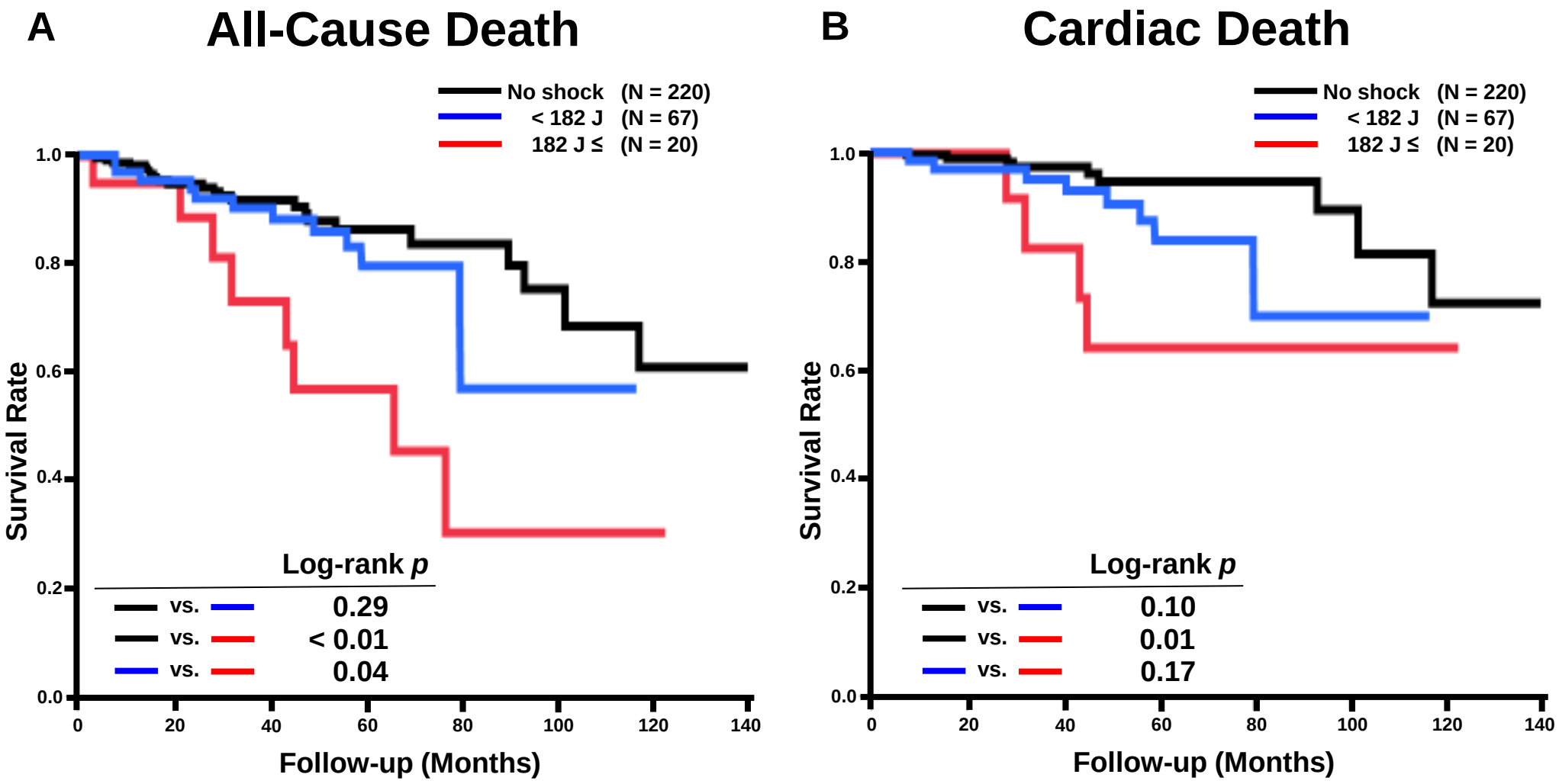
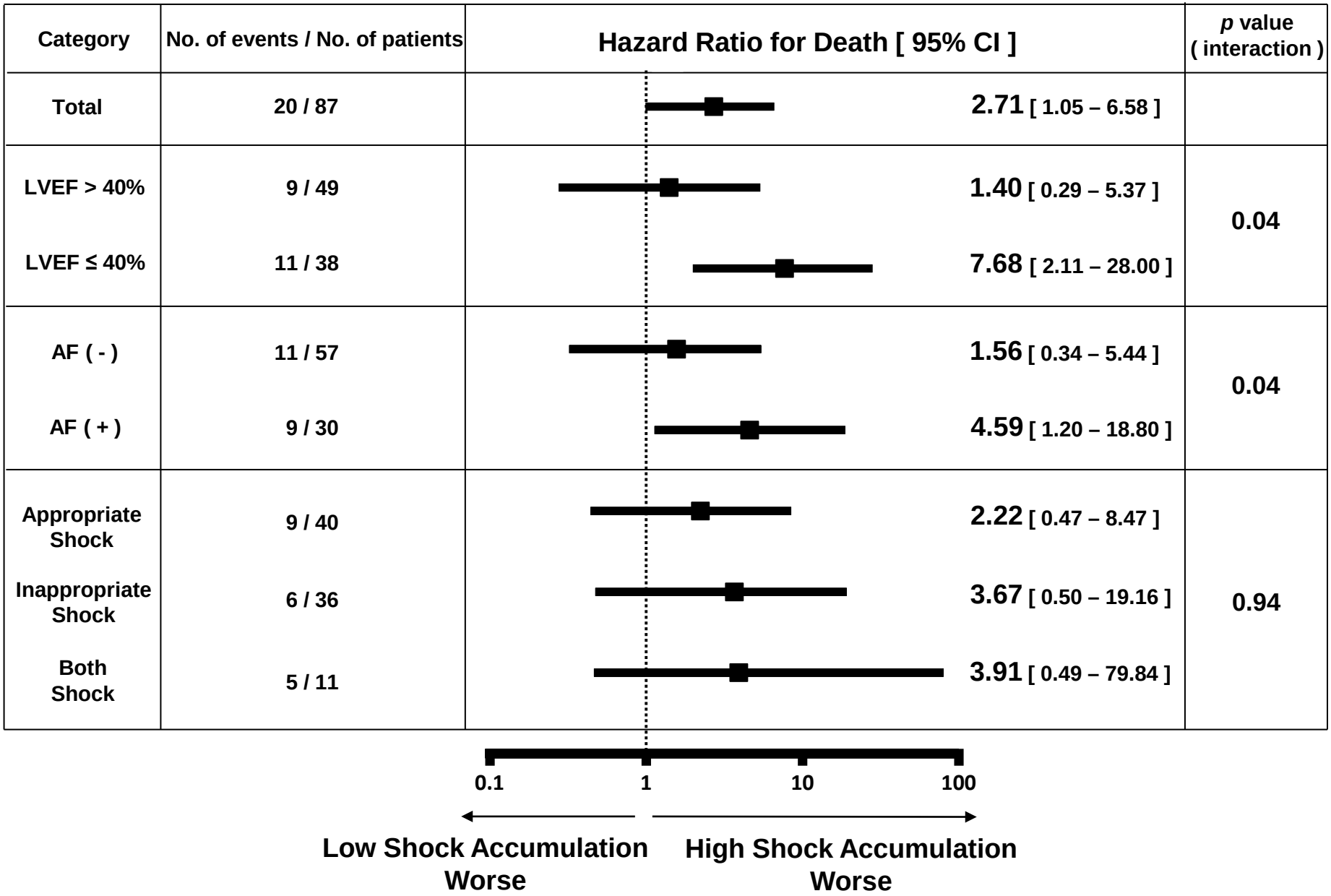
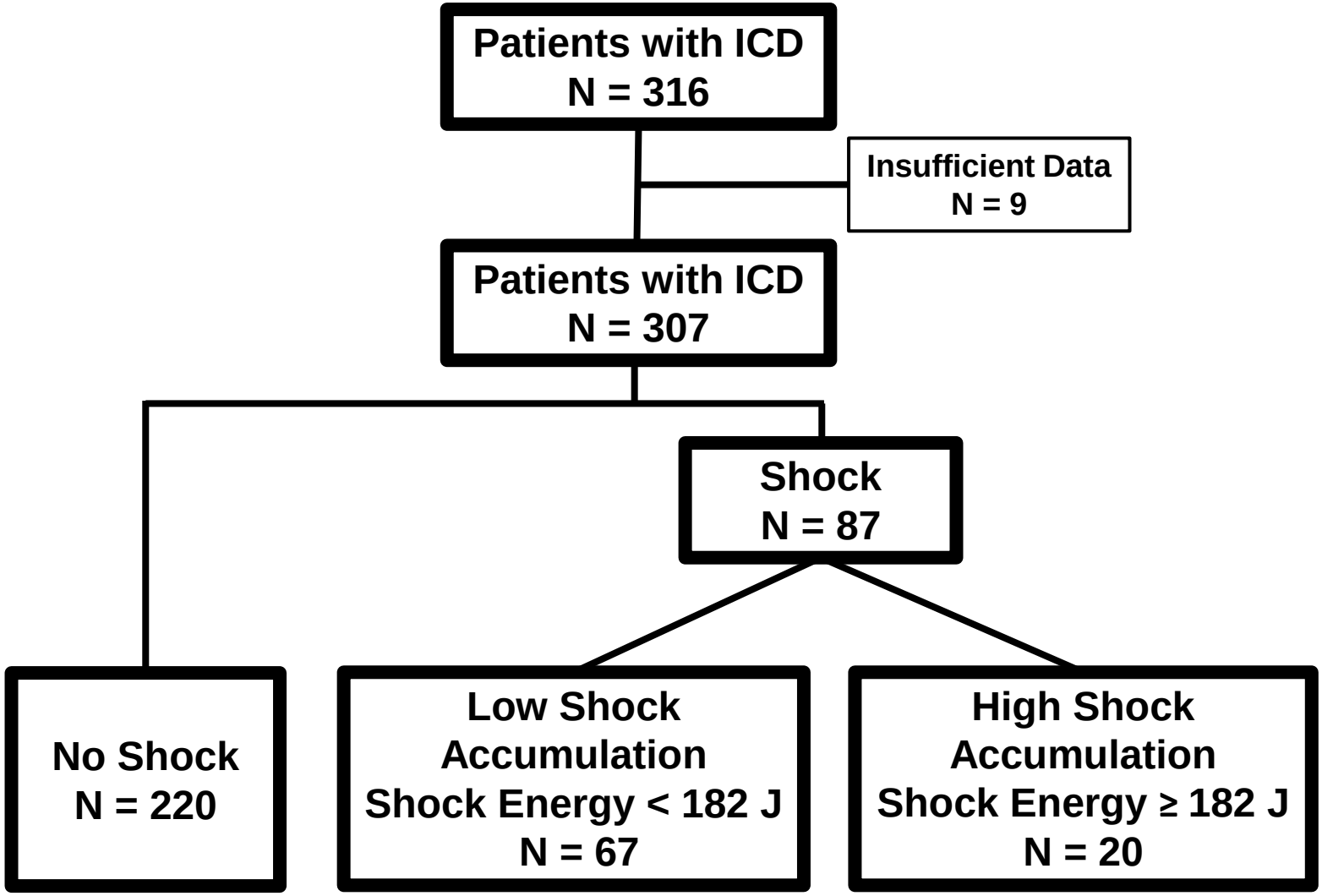

A
All-Cause Death
No shock (N = 220)
< 182 J (N = 67)
182 J ≤ (N = 20)
Survival Rate
1.0
0.8
0.6
0.4
0.2
0.0
0
20
40
60
80
100
120
140
Follow-up (Months)
Log-rank p
vs. 0.29
vs. < 0.01
vs. 0.04
B
Cardiac Death
No shock (N = 220)
< 182 J (N = 67)
182 J ≤ (N = 20)
Survival Rate
Follow-up (Months)
Log-rank p
vs. 0.10
vs. 0.01
vs. 0.17

Figure 2


Category
No. of events / No. of patients
Hazard Ratio for Death [95% CI]
p value (interaction)
Total
20 / 87
2.71 [1.05 – 6.58]
LVEF > 40%
9 / 49
1.40 [0.29 – 5.37]
0.04
LVEF ≤ 40%
11 / 38
7.68 [2.11 – 28.00]
AF (-)
11 / 57
1.56 [0.34 – 5.44]
0.04
AF (+)
9 / 30
4.59 [1.20 – 18.80]
Appropriate Shock
9 / 40
2.22 [0.47 – 8.47]
Inappropriate Shock
6 / 36
3.67 [0.50 – 19.16]
0.94
Both Shock
5 / 11
3.91 [0.49 – 79.84]
0.1
1
10
100
Low Shock Accumulation Worse
High Shock Accumulation Worse

Supplemental Figure 1



Supplemental Figure 2

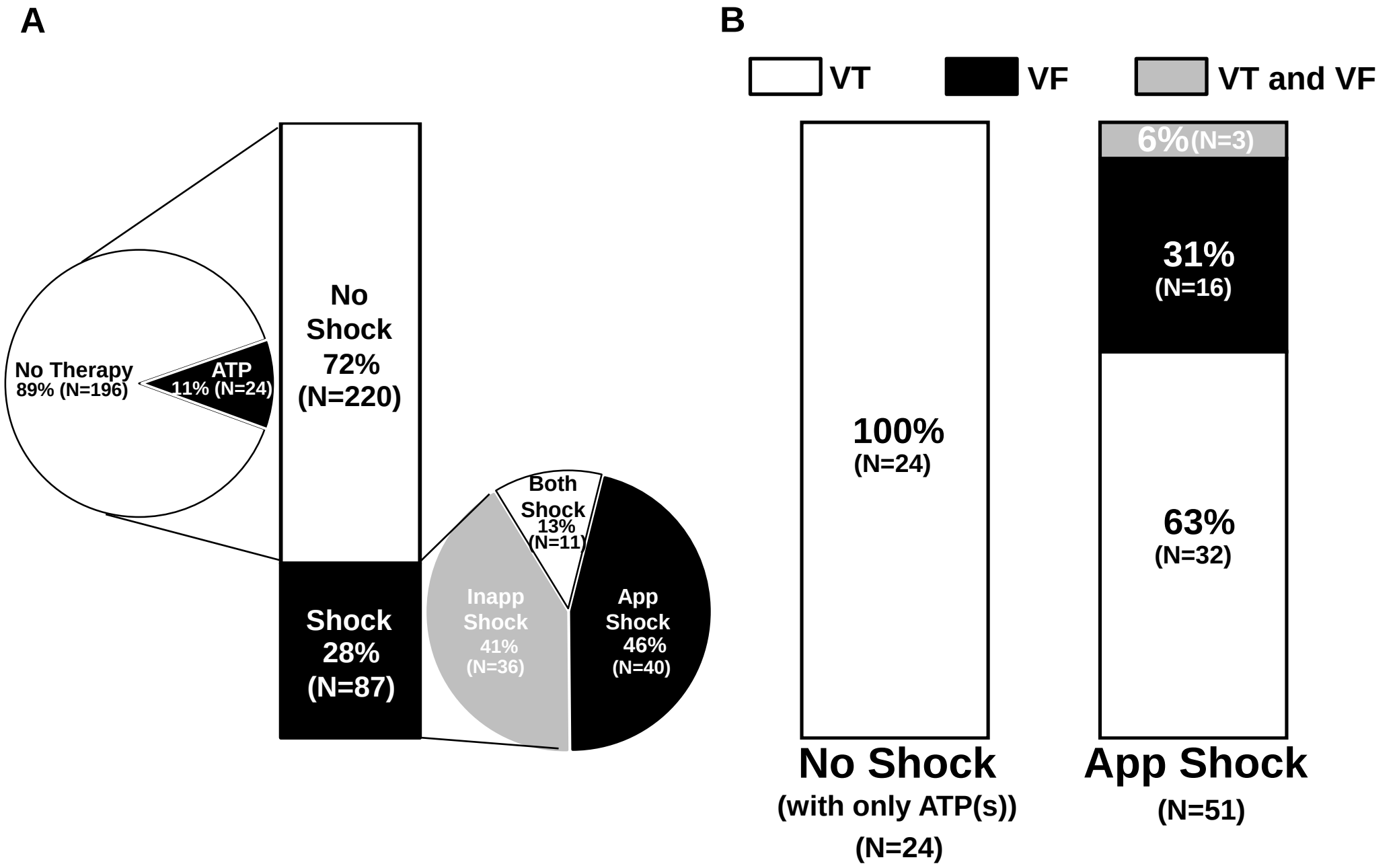


Table 1. Characteristics of the Patients

	Total Patients (N = 307)	No Shock Patients (N = 220)	Shock Patients (N = 87)		*p* value
			TSE < 182 J (N = 67)	TSE ≥ 182 J (N = 20)	
Age (years)	60 (49 - 70)	62 (52 - 71)	56 (45 - 67)	54 (29 - 69)	< 0.01
Male	239 (78)	171 (78)	53 (79)	15 (75)	0.92
NYHA class III - IV	76 (25)	55 (25)	16 (24)	5 (25)	0.98
LVEF (%)	43 (29 - 60)	42 (29 - 59)	42 (29 - 58)	54 (33 - 64)	0.19
Underlying Heart diseases					0.17
Ischemic	86 (28)	67 (30)	17 (25)	2 (10)	
Nonischemic	162 (53)	112 (51)	39 (58)	11 (55)	
PED	59 (19)	41 (19)	11 (17)	7 (35)	
Devices					0.98
Single chamber	94 (31)	67 (31)	20 (30)	7 (35)	
Dual chamber	141 (46)	102 (46)	31 (46)	8 (40)	
CRT	72 (23)	51 (23)	16 (24)	5 (25)	
Indication					0.02
Primary prevention	82 (27)	67 (30)	14 (21)	1 (5)	
Secondary prevention	225 (73)	153 (70)	53 (79)	19 (95)	
Comorbidities					
Atrial fibrillation	79 (26)	49 (22)	22 (33)	8 (40)	0.07
Paroxysmal	46 (58)	29 (59)	11 (50)	6 (75)	
Persistent	33 (42)	20 (41)	11 (50)	2 (25)	
Diabetes mellitus	68 (22)	56 (25)	9 (13)	3 (15)	0.08
Hypertension	69 (22)	52 (24)	15 (22)	2 (10)	0.38
Medications					
Na channel blockers	28 (9)	16 (7)	10 (15)	2 (10)	0.16
β blockers	214 (70)	151 (69)	50 (75)	13 (65)	0.58
Amiodarone	143 (47)	103 (47)	31 (46)	9 (45)	0.97
ACEI / ARB	198 (64)	141 (64)	48 (72)	10 (45)	0.09
Diuretics	148 (48)	108 (49)	32 (48)	8 (40)	0.74

Note: Data are n (%) or shown as median (first to third quatile). ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers; CRT, cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association functional class; PED, primary electrical disease. TSE, total shock

energy. The *p* values are results of the comparisons among three groups (no shock, TSE < 182 J, and TSE ≥ 182 J).

Table 2. Adjusted Hazard Ratios for the Association between Total Shock Energy and Mortality

	Adjusted HR	95% CI	*p* value
Total shock energy (per 100 joule increase)			
All-cause death	1.26	1.04 - 1.46	< 0.01
Cardiac death	1.30	0.91 - 1.65	0.08

Note: The covariates for multivariate analyses included the following: Age, NYHA class III to IV, and CRT for all-cause death, age and NYHA class III to IV for cardiac death. See details in Statistical analysis of the text. CI, confidence interval; HR, hazard ratio.

Supplemental Table 1. The Risk of Death in All Patients

	HR (univariate)	95% CI	P value
All-cause death			
Age (per 1 year-old increase)	1.06	1.03 - 1.09	< 0.01
NYHA III - IV	3.72	2.01 - 6.86	< 0.01
LVEF (per 1% increase)	0.96	0.94 - 0.98	< 0.01
Undelying heart diseases			< 0.01
Ischemic vs. Nonischemic	1.20	0.63 - 2.22	0.57
Ischemic vs. PED	11.34	2.31 - 204.65	< 0.01
Nonischemic vs. PED	9.44	2.01 - 168.54	< 0.01
CRT	2.20	1.08 - 4.33	0.03
Atrial fibrillation	2.46	1.31 - 4.53	< 0.01
Hypertension	2.03	1.02 - 3.82	0.04
Cardiac death			
Age (per 1 year-old increase)	1.05	1.01 - 1.09	< 0.01
NYHA III - IV	10.87	4.36 - 30.83	< 0.01
LVEF (per 1% increase)	0.94	0.90 - 0.97	< 0.01
Underlying heart disease			< 0.01
Ischemic vs. Nonischemic	0.62	0.20 - 1.59	0.33
Ischemic vs. PED	> 100	Not Calculated	0.02
Nonischemic vs. PED	> 100	Not Calculated	< 0.01
CRT	7.00	2.65 - 20.40	< 0.01
Atrial fibrillation	3.35	1.36 - 8.27	< 0.01

Note: Abbreviations as in Table 1 and Table 2.

Supplemental Table 2. The Number of VT/VF Events and Shock Energy

	Appropriate shock (N = 40)			
VT/VF event	**1**	**2**	**3**	**more**
N	16 (40)	6 (15)	3 (7.5)	15 (37.5)
Shock Energy, joule				
Appropriate	31 (21 - 31)	58 (45 - 68)	111 (76 - 147)	155 (111 - 450)
Inappropriate	—	—	—	—

	Both shock (N = 11)			
VT/VF event	**1**	**2**	**3**	**more**
N	2 (18)	2 (18)	1 (9)	6 (55)
Shock Energy, joule				
Appropriate	20 (15 - 26)	65 (63 - 68)	123 (123 - 123)	298 (177 - 392)
Inappropriate	216 (110 - 321)	45 (40 - 50)	123 (123 - 123)	46 (37 - 65)

Note: Data are n (%) or shown as median (first to third quatile). VF, ventricular fibrillation; VT, ventricular tachycardia.

Supplemental Table 3. Relation between Shock Interval and Death

	Adjusted HR	95% CI	*p* value
Shock interval (per 10 days increase)			
All-cause death	0.98	0.93 - 1.02	0.44
Cardiac death	1.00	0.94 - 1.04	0.85

Note: Abbreviations as in Table 2.

Supplemental Table 4. Time Intervals from the Last Shock to Death

	All patients	Patients who died	Time from last shock to death (day)	
			median	IQR
Total	87	20	648	158 - 1342
Shock energy				
TSE < 182 J	67	12	801	159 - 1452
TSE ≥ 182 J	20	8	564	155 - 1305
Types of shock				
Appropriate	40	9	182	151 - 1306
Inappropriate	36	6	547	146 - 1097
Both	11	5	1305	667 - 1773

Note: IQR, interquartile range. Other abbreviations as in Table 1.