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Prognostic Importance of Defibrillator Shocks in Survivors of Sudden Cardiac Death

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Abstract

Implantable cardioverter-defibrillator (ICD) implantation is standard of care for patients who have survived life threatening ventricular tachyarrhythmias (LTVA). ICD shocks predict future adverse events in patients with ICD implantation for primary prevention. However, the role of ICD shocks in prediction of adverse events in a secondary prevention population is unknown.

The Antiarrhythmics Versus ICDs (AVID) Trial (n=1016) was a randomized controlled trial comparing ICD (n=507) and antiarrhythmic drugs (n=509) in the treatment of patients with LTVA. Mean follow-up duration was 916 ± 471 days. We analyzed the ICD arm of the AVID trial using the NHLBI limited access dataset. ICD shocks were categorized as appropriate if underlying rhythm triggering the shock was ventricular tachycardia or ventricular fibrillation. All other ICD shocks were considered as inappropriate. Data on ICD therapy was available for 420 patients. Any shock (n=380), any appropriate (n=296) or any inappropriate (n=72) shock was not associated with increased all cause, cardiac or arrhythmic mortality. However any appropriate shock was associated with increased LTVA.

In conclusion, ICD shocks do not confer increased risk of death on follow up in LTVA survivors. Use of ICD shocks as surrogate marker for adverse outcomes is not viable in secondary prevention patients.

Keywords: Implantable cardioverter-defibrillator; Ventricular tachycardia; Ventricular fibrillation

Introduction

Heart failure patients with decreased ejection fraction are at increased risk of sudden death due to ventricular arrhythmias. Since its introduction in 1980 [1], use of implantable cardioverter-defibrillator (ICD) as a therapeutic modality has been effective in heart failure patients treating malignant arrhythmias for both primary [2,3] and secondary prevention [4,5]. Device therapy can be classified as appropriate and inappropriate shocks. Appropriate shock includes shock therapy for LTVA like ventricular tachycardia (VT) and ventricular fibrillation (VF). Inappropriate shock includes shock therapy for supra ventricular arrhythmias including atrial fibrillation (AF), atrial flutter etc or any other inappropriate sensing.

Prior studies have reported that appropriate and inappropriate shock therapy identifies ICD recipients at increased risk of mortality as compared to those who received no shocks in a primary prevention cohort [6-8]. No prior studies have detailed the risk of mortality after ICD shock therapy in a secondary prevention population. We hypothesized that similar effect of ICD shocks could also be observed in a secondary prevention population. For this purpose we decided to investigate the Anti-arrhythmics Versus Implantable Defibrillators (AVID) trial, 4 which is the largest secondary prevention trial.

Methods

AVID trial evaluated the efficacy of ICD therapy for secondary prevention by randomizing patients to an ICD arm (n = 507) and anti-arrhythmic arm (n = 509). A post-hoc analysis was performed in the ICD arm using the National Heart, Lung, and Blood Institute (NHLBI) limited access AVID dataset. The trial had a randomized and observational phase of follow-up. For our study we also included the data from the observational phase of follow-up. Appropriate institutional review board approval was obtained from Wayne State University. Of note, none of the authors of the present paper are affiliated with the NHLBI.

Study population

Detailed study design, inclusion and exclusion criteria for the patients in AVID study have been described previously [9,10]. Briefly, patients were eligible if they had suffered LTVA such as VT/VF or had syncope with an inducible ventricular arrhythmia on electrophysiological study. Of the 507 patients in the ICD arm, 492 patients had ICD implanted at the time of hospital discharge. Out of these, data regarding ICD therapy was available for 425 patients. Patients for whom the cause of ICD therapy was classified as 'unknown' by the principal investigator (n=5) were also removed from the final study cohort. Thus, a total of 420 patients were included in the final analyses.

ICD devices and therapy

During the course of the AVID trial, various ICD devices were used, all of which were advanced-generation units with tiered therapy capable of anti-tachycardia pacing (ATP), cardioversion, defibrillation and bradycardia pacing with recommended biphasic shock capability and electrocardiographic memory [10]. Devices were programmed for a 10 joule safety margin for energy levels needed for defibrillation. Appropriate and inappropriate shocks were based on the definitions mentioned earlier. Therapy due to device malfunction was also termed as inappropriate.

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Follow-up and outcomes

The ICD's were interrogated quarterly and also after any ICD shock. The ICD therapy events committee reviewed the ICD interrogation printouts including the available clinical data and electrocardiograms. Details of arrhythmia responsible of ICD therapy were recorded. An episode was defined as a therapy or series of therapies used to treat the same arrhythmia. Therapies occurring less than 5 minutes apart were considered to be a part of the same arrhythmic episode. The type of therapy (shocks and ATP), number of attempts at ATP, outcomes of ATP, number of shocks, type of shocks (low-energy and/or high-energy) and the result of shocks (effective, ineffective, inappropriate) were recorded in detail [11].

The Principal Investigator (PI) determined the distinction between rapidly occurring multiple arrhythmias and repeated shocks from single episode. Arrhythmias responsible for shocks were adjudicated by the local PI as well as an events committee reviewer. For the purpose of current study, PI's adjudication was used. The arrhythmia diagnosis made by the PI was generally correct on review by an Events Committee. Patients having received a shock therapy but having no data on PI's adjudication for causal arrhythmia (n=12) were not classified into either category.

Outcomes of our analysis were all cause mortality and cardiac death. According to AVID protocol, 'death' was considered as the time when the respiration and circulation (pulse) stopped without recovery. An independent review committee classified death as cardiac or noncardiac after reviewing the clinical data on the event extensively. They classified cardiac death when there was evidence of congestive heart failure or shock, myocardial infarction or recent invasive cardiac procedures. Arrhythmic death was termed as a cardiac death due to life-threatening arrhythmias which were recorded in the electrocardiograms, rhythm strips and/or hospital monitors [12].

Baseline parameters of the patients who did and who did not receive ICD therapy were compared with the Chi-square or the ANOVA. Cox proportional-hazards models [13] were used to estimate the association between ICD shocks to death. All analyses were carried out using the SAS Statistical software version 9.1 (SAS Institute, Cary, North Carolina). All clinical variables (beta-blocker, ACE inhibitor, aspirin, warfarin use, history of MI, smoking, age, sex, diabetes

Characteristics	**Patients who received any shock (n = 380)**	**Patients who received any appropriate shock (n = 296)**	**Patients who received any Inappropriate shock (n=72)**	**Patients who received no shock (n = 40)**
Age-Group in years	60-64	60-64	60-64	65-69
Ejection Fraction (%)	31±13	30.2 ± 12	33±14	28.4±10.4
NYHA Class -III	6.1 (23)	6.1 (18)	5.6 (4)	7.5 (3)
Male Gender	78.7 (299)	78.4 (232)	80.6 (58)	85 (34)
Congestive Heart Failure	49.2 (187)	49.3 (146)	50 (36)	55 (22)
Diabetes	21.8 (83)	22 (65)	16.7 (12)	37.5 (15)
Hypertension	53.4 (203)	56.7 (168)	40.3 (29)	57.5 (23)
Atrial Fibrillation/Flutter	24.7 (94)	22.6 (67)	31.9 (23)	15 (6)
History of Myocardial Infarction	70 (266)	70.2 (208)	69.4 (50)	85 (34)
History of CABG*	28.9 (110)	29.7 (88)	30.6 (22)	45 (18)
Smoking	22.6 (86)	21.3 (63)	29.2 (21)	27.5 (11)
ACE Inhibitor therapy	74.9 (285)	74.6 (221)	72.2 (52)	75 (30)
Aspirin therapy	60 (228)	60.1 (178)	61.1 (44)	65 (26)
Lipid lowering therapy	12.9 (49)	13.2 (39)	12.5 (9)	30 (12)
Beta Blocker therapy	35 (133)	33.5 (99)	40.3 (29)	40 (16)

[All values are % or n (mean ± SD)]
NYHA – New York Heart Association
*CABG – Coronary Artery Bypass Grafting

Table 1: Baseline clinical characteristics of study groups.

Type of Shock	**All patients**	**Patients who died**	**Cause of Death**		
			Arrhythmic Cause	Non-arrhythmic Cardiac cause *number of patients*	Noncardiac causes
Any shock	380	74	17	34	23
Any appropriate	296	62	11	30	21
Any inappropriate	72	8	2	4	2
No shock	40	9	3	4	2

ICD = Implantable Cardioverter-Defibrillator

Table 2: ICD Shock and Cause of Death.

	Any Shock vs. no shock	Any Appropriate shock vs. no appropriate shock	Any Inappropriate shock vs. no inappropriate shock	Any Appropriate vs. no shock	Any inappropriate shock vs. no shock
Total mortality	0.81, 0.19-3.34	1.36,0.41-4.49	0.75, 0.38-1.48	1.06, 0.50-2.23	1.63, 0.48-5.46
Arrhythmic death	0.23, 0.01-3.55	2.73, 0.26-28.74	1.49, 0.43-5.17	0.68, 0.17-2.65	1.29, 0.14-11.98
Cardiac death	0.42, 0.06-2.67	2.4, 0.48-11.84	0.98, 0.45-2.12	1.04, 0.42-2.56	2.23, 0.47-10.56
Recurrent VT/VF	0.93,0.25-3.42	3.41, 1.15-10.08*	0.47, 0.29-0.76*	2.68,1.35-5.33*	0.81,0.31-2.12

(Beta-blocker, angiotensin converting enzyme inhibitor, aspirin, warfarin use, history of MI, smoking, age, sex, diabetes mellitus, hypertension, left ventricular ejection fraction, renal disease and lipid lowering therapy. All data represented as HR, 95% CI. All p=NS unless mentioned.*p value <0.05)

Table 3: Final Multivariate Hazard Ratios for Cardiovascular outcomes.

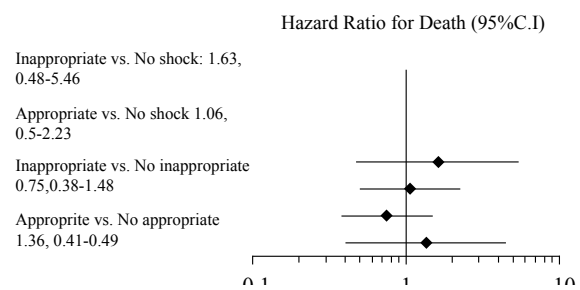

Figure 1:

mellitus, hypertension, left ventricular ejection fraction, renal disease and lipid lowering therapy) which could potentially confound or interact with the dependent variables were also included into the model, irrespective of their univariate p value. Age was considered as an interval variable. Further variable selection in the model was conducted using stepwise selection. A two-tailed probability < 0.05 was used for declaring statistical significance.

Results

Characteristics of the study groups

Baseline characteristics of each group are shown in Table 1. Patients who received any shock (appropriate or inappropriate) had a higher ejection fraction (EF), were younger, were less likely to develop CHF and were more likely to have atrial fibrillation. Patients who did not receive any shock were more likely to have diabetes, hypertension, history of MI and coronary artery bypass grafting (CABG) (Table 1).

380 patients received shocks, 296 patients received appropriate shocks and 72 patients received inappropriate shocks. 40 patients did not receive any shocks at all. 12 patients did not have any information on PI's adjudication on the type of shock and remained unclassified. It is noteworthy that the majority (72%) of the ventricular arrhythmias was VT, and 9 percent of all arrhythmias were VF. Of the 72 deaths in ICD recipients with any shock, 17 (22.9%) were due to arrhythmia (Table 2).

Impact of ICD shocks on outcomes

Over a mean follow-up duration was 18.2 ± 12.2 months, a total of 80 patients died and the crude mortality rates were 15.8 ± 3.2 percent in the ICD group. Arrhythmic death constituted less than 1 percent of all ICD episodes[11]. On multivariate analysis, the relative risk of all cause mortality (HR, 95% C.I, p) associated with an appropriate (1.06, 0.38 to 1.48, NS) or an inappropriate shock (1.63, 0.48 to 5.46, NS) did not differ significantly from that in patients who have not received any shocks (Table 3). Similarly, neither appropriate nor inappropriate shocks were not a significant predictor of cardiac and arrhythmic death (Figure 1).

Also, any appropriate shock was associated with an increased risk of recurrent VT/VF as compared to patients who received no shock (2.68, 1.35 to 5.33, p= 0.004) or no appropriate shock (3.41, 1.15 to 10.08, p= 0.02). However, the occurrence of any inappropriate shock was associated with a decreased risk of recurrent VT/VF (0.47, 0.29 to 0.76, p= 0.002) as compared to patients who received no inappropriate shocks. There were no differences in mortality between patients who received inappropriate shocks and no shocks.

Discussion

The current study showed that the occurrence of an appropriate or an inappropriate ICD shock in survivors of SCD does not predict mortality. Hence, use of ICD shocks as a surrogate marker for mortality in secondary prevention population is not plausible. This is in contrast to prior studies done in primary prevention population which have shown that ICD shocks predict mortality. Our study also identified increased risk of recurrent VT/VF in ICD recipients who have received any appropriate shock.

The first analysis addressing these findings was from the Multicenter Automatic Defibrillator Trial II (MADIT-II) [3]. This was a primary prevention ICD trial on patients with ischemic cardiomyopathy with EF $< 30\%$, randomly assigned to ICD arm or standard medical therapy arm. Patients in the ICD group have a better survival compared to patient in the standard arm. In a subgroup analysis, MADIT-II investigators showed that among the 720 ICD recipients the risk of death was more than 3 times greater in patients who received appropriate ICD shock therapy compared to patients without any shock therapy. Also, inappropriate shock therapy for arrhythmias like SVT, AF doubled the patient's risk of all-cause mortality. The investigators reasoned that ICD shock therapy would have caused myocardial damage contributing to subsequent cardiac death.

SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) [2] is also a multicenter primary prevention ICD trial including heart failure patients (EF $\leq 35\%$) of ischemic and non-ischemic etiology in almost equal proportions, randomly assigned to ICD, amiodarone or placebo. Further analyses on the ICD arm ($n = 811$) showed that patients receiving appropriate shock therapy are at even more risk (> 5 times) of mortality compared to more than 3-fold increase in MADIT-II trial. Also, they supported the findings of MADIT-II trial that the risk of death was two times more in patients receiving inappropriate shock therapy.

Our study differs from the prior analysis in that we analyzed a predominantly secondary prevention population, in whom association between ICD shocks and all cause mortality has not been studied in detail. It may be postulated that the ICD therapy was very efficient in terminating malignant arrhythmias, thereby decreasing the mortality rates. This finding is consistent with previous reports of low mortality rates observed in secondary prevention population [14] suggesting the effectiveness of ICD therapy. In addition, the mean EF in the AVID trial is approx 33%, which is much higher compared to the mean EF of 25% and 23% in SCD-HeFT [2] and MADIT-II [3] trials respectively. As there are robust data to suggest that survival correlates with EF [15], patients in the AVID trial could have had better prognosis compared to the ICD recipients with lower EF in the other primary prevention trials. The other interesting possibility to explore will be the fact that the increased mortality noted in association with shocks by earlier studies may in fact be due to natural progression of the disease and deterioration of clinical status of the patients. It is plausible that the delivery of shock was a surrogate indicator for deteriorating clinical status which in turn predisposed the patient to LTVAs and increased mortality.

Several possibilities may be considered for the finding of increased risk of recurrent VT/VF in patients who received appropriate shock therapy. In particular, the mechanical stress due to the electrical conversion therapy received before, would have caused an additional insult to the underlying myocardium. This could act as a potential substrate predisposing the patient for further serious ventricular tachyarrhythmia [16]. Despite this increased risk of malignant arrhythmias, there was no increased mortality in ICD recipients who

had appropriate and inappropriate shocks compared with those who had no shocks. This emphasizes the effectiveness of ICD shock therapy in aborting LTVA.

Prior case series have shown that many SVT can progress to VT/VF causing SCD [17]. It could be hypothesized that abortion of these malignant SVT prematurely by inappropriate shock therapy could decrease the incidence of malignant ventricular arrhythmias significantly. Despite the possible myocardial damage that might occur during these shock therapies, this could partially explain the decreased risk of VT/VF in patients receiving inappropriate shock therapy.

Another explanation for our findings is that not all ventricular arrhythmias are life threatening [18]. Few of the ventricular arrhythmias including monomorphic VT will not require ICD therapy. In the Pain FREE Rx II trial [19], majority of the monomorphic VT terminated spontaneously before ATP, confirming the fact that not all ventricular arrhythmias require electrical conversion therapy. Also, the number of shocks – whether appropriate or inappropriate – may not be correlated with rates of mortality [20]. Therefore mere counting of shocks does not indicate a life saved. A recent analysis also introduced the prospect of the interaction between the arrhythmia type (VT, Fast VT, VF) and electrical therapy type (shocks vs. ATP) in predicting mortality, and attempted to uncouple it. Among patients with Fast VT, ATP terminated episode was not associated with increased mortality, where as shock terminated episode was [21].

However it should be noted that the patient population for AVID trial was accrued more than a decade ago which brings up the question of applicability of the results to the present day scenario. Although the study included patients with new generation ICDs of that era, there have been improvements in ICD technology in terms of sensing and discriminatory properties of devices. One could only speculate that these advances would have reduced the burden of inappropriate or pseudo-inappropriate shocks so as to correlate true clinical deterioration and ICD therapies. Newer and more focused prospective trials will be needed with improving technology and changing indications for ICD implantation.

Limitations

The present study suffers the drawbacks of a post-hoc analysis of the randomized controlled trial. The study was not originally designed to evaluate the prognostic importance of ICD shock therapy. Also, the power of the study is limited precluding the interpretation of the results. Additionally we did not have access to the details of the rhythm type and electrical therapy type, obviating a comparative analysis. However the AVID trial is the largest trial of secondary prevention to date and therefore we believe that our results deserve merit pending further investigation into similar observations.

In conclusion, both appropriate and inappropriate shock therapies in ICD recipients do not predict long term mortality in secondary prevention population. As reported previously [11], ICD therapy cannot be used as a surrogate marker for mortality in clinical trials involving secondary population.

Disclosures

Part of the study results were presented at the 58th annual scientific sessions of the American College of Cardiology 2009 at Orlando, FL. None of the authors are affiliated with the NHLBI or the AVID trial or have any financial disclosures.

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