Chapter from the book *Cardiac Defibrillation - Prediction, Prevention and Management of Cardiovascular Arrhythmic Events*

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1. Introduction

Therapy with implantable cardioverter-defibrillators (ICDs) has been shown to improve survival among several large groups of patients at risk for sudden cardiac death (SCD). Several complicating issues arose from the widespread use of ICDs especially in heart failure (HF) patients. Twenty percent to 35% of HF patients who receive an ICD for primary prevention of SCD will receive an appropriate shock within 1 to 3 years for a life-threatening arrhythmia. Almost half of the HF patients who survive a cardiac arrest and receive an ICD for secondary prevention will receive a shock within 1 year of implant. Implantable cardioverter-defibrillator (ICD) shocks are usually regarded with a sense of relief given that the ventricular tachyarrhythmia was treated, and the SCD was averted. There is, however, accumulating data from the literature showing that patients with ICDs who receive shocks, whether appropriate or spurious, have worse prognosis than similar patients who do not receive shocks. Current guidelines do not provide a clear approach to managing patients presenting with ICD shocks, who clearly represent a high-risk group. However, current data from the literature suggest that ICD shocks should prompt a thorough evaluation to determine the etiology of the shock and to help guide therapeutic interventions.

2. Initial evaluation after ICD discharge

The initial evaluation of the patient who receives an ICD shock begins with interrogation of the device. The timing of the device interrogation depends on the number of shocks and related symptoms. In case of an isolated shock without change in clinical status or symptoms, evaluation should generally occur within a few days. Multiple ICD shocks or shocks associated with worsening HF symptoms, syncope, angina, or electrical storm warrant emergent medical attention. Device interrogation will reveal whether the ICD shock was appropriate or inappropriate. While there is still some debate regarding the definition of an appropriate shock, most authors agree that any shock for ventricular tachycardia (VT) or ventricular fibrillation (VF) is considered appropriate. The acute management strategies depend on the specific etiology of the shock. If the shock was appropriate the next step is to address reversible causes, check and correct electrolytes,
consider antiarrhythmic therapy, optimize betablocker treatment, optimize device therapies including antitachycardia pacing (ATP), and consider intubation and sedation for refractory VT or VF. If the shock was inappropriate the acute strategy is to treat the supraventricular tachycardia, optimize device programming, and assess for possible lead oversensing. In addition to all these acute management strategies it is important to realize that even though the SCD might have been prevented by the ICD shock, the natural history of the disease is now transformed and there is accumulating data suggesting that the prognosis of the group of patients who receive shocks, especially in HF patients, is worse than the rest of the ICD patients.

3. Appropriate ICD shocks

3.1 Prognostic importance of appropriate ICD shocks

Several large trials have shown that therapy with ICDs improves survival among patients who are at risk for SCD. Based on these results the implantation of an ICD for primary prevention has become standard of care for patients who meet the high-risk criteria. One potential result of the broader use of ICDs is that the natural history of the disease in these patients is modified as a consequence of the delivery of ICD therapies. The results of the MADIT II were the first to demonstrate an adverse prognosis associated with ICD therapy used for primary prevention. In this study, among 719 patients with ischemic heart disease, an ICD shock or antitachycardia pacing was reported to be appropriate in 23.5%. The risk of death, was found to be increased by a factor of more than 3 among patients who received ICD shocks or antitachycardia pacing for ventricular tachycardia or ventricular fibrillation.

After an ICD shock for a life-threatening arrhythmia, hospitalizations for HF were more frequent, and mortality was increased 3-fold. Within one year of an ICD shock for ventricular tachycardia (VT) or ventricular fibrillation (VF), the probability of an HF event was 26% and 31%, respectively, while it was 19% for those not having an ICD. The corresponding survival rate one year after initial ICD shock for VT or VF was 80% and the survival curves were related to the rate of the presenting tachycardia. Increased tachycardia rates were associated with lower survival rates. Other clinical factors associated with increased mortality after appropriate ICD discharge, were blood urea nitrogen, lack of beta-blockade, NYHA functional class, presence of atrial fibrillation (AF), and diabetes mellitus. The ICD therapy was associated with a 39% increased risk of a first HF hospitalization and a 58% increase in recurrent admission for HF.

Analysis of data from the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) showed findings consistent with those of the MADIT-II study. In the SCD-HeFT study, 33% of HF patients received an ICD shock. Among these patients treated with ICD discharges the most common cause of death was progressive HF. Patients receiving an appropriate shock had a 5-fold increase in risk of death, whereas patients receiving an inappropriate shock had a 2-fold increase in risk of death. Multiple shocks increased the risk of death more than single shocks. The median time from shock to death was 168 days among patients receiving appropriate shocks and 294 days among patients receiving inappropriate shocks. The risk of death with appropriate ICD shocks was higher in the study by Poole et al. increased by a factor of more than 5. The higher risk of death associated with appropriate ICD shocks found by Poole and colleagues in comparison to the MADIT II study may be
related to the longer follow-up and the exclusion of patients with NYHA class I disease (selection of patients with higher risk than those in MADIT II). In addition these results reflect the use of primarily single-lead ICDs, a single zone of therapy, and shock-only programming for high-rate arrhythmias that were most likely to be life-threatening. Similar to MADIT-II patients, SCD-HeFT patients with NYHA functional class III and ischemic cardiomyopathy had a shorter duration between initial shock and death. Subgroup analyses from MADIT-II trial confirm that ICD shocks increase the risk for first and recurrent HF events.

One of the most important questions generated by these results is why ICD patients tend to have worsening prognosis and more frequent HF after an ICD shock. Myocardial damage induced by ICD shocks may contribute to worsening HF. This is suggested by the adverse impact on prognosis of inappropriate shocks. In the MADIT-II study, however, inappropriate shocks did not increase the risk of adverse outcomes. In the study by Poole and colleagues, mortality after an inappropriate shock was approximately 3-fold less than after appropriate therapy, thus downplaying the role of shock-induced myocardial damage contributing to HF risk, and suggesting that arrhythmia may simply be a marker of worsening HF.

In an editorial comment on the study of Poole et al., Healey and Connolly surmised the situation as follows: “Although it is plausible that shocks somehow have an adverse effect on myocardial function, this is unlikely to be a major factor. What is much more likely is that the occurrence of a ventricular arrhythmia that causes a shock is signaling a meaningful change in the patient’s clinical status….occurrence of shocks is not a random event in an otherwise stable clinical course but a sign of clinical deterioration in the underlying disease process.” We concur with this opinion. Furthermore, inappropriate ICD discharges, which largely result from atrial fibrillation or other rapidly conducting supraventricular tachycardias may be associated with higher subsequent mortality because they too, though to a lesser degree than ventricular tachyarrhythmias, signify underlying electrical and/or structural abnormalities that negatively impact the prognosis of those patients who experience them compared to those who do not.

Another interesting hypothesis is that right ventricular pacing with a dual-chamber ICD may contribute to increased HF risk after ICD implant. In the MADIT-II study, however, the risk of HF events was similar whether patients received a single- or dual-chamber ICD despite differences in right ventricular pacing (92% of patients with single-lead ICDs had no pacing, whereas 66% of patients with dual-chamber ICDs had cumulative RV pacing exceeding 50%). Even if right ventricular pacing has a certain contribution to the adverse outcomes, the increased risk of HF after ICD implantation cannot be solely due to right ventricular pacing.

These findings suggest that, in HF patients, an ICD shock is associated with a 2-to 5-fold increase in mortality, most commonly due to progressive HF. It is not known whether the arrhythmia leading to ICD shock is a marker for worsening HF or whether the shock itself leads to worsening HF. Regardless of the individual factors causing greater HF events in current ICD populations, there appear to be multiple triggers that, when combined with high-risk patients, cause an increased HF risk. Heart failure patients with high-risk features such as NYHA functional class III, atrial fibrillation (AF), and ischemic cardiomyopathy require closer observation and management after ICD shock as sudden death risk is now transformed to an increased HF event risk.

It is unknown whether the increase in risk in association to the appropriate ICD shocks is due to the ventricular arrhythmia (VA) or shocks and whether anti-tachycardia pacing
(ATP) termination can reduce this risk. To determine whether mortality in ICD patients is influenced by the type of therapy (shocks or ATP) delivered, Sweeney et al. evaluated the effects of baseline characteristics, VT, fast VT (FVT, 188–250 bpm), VF, and therapy type (shocks or ATP) on mortality among 2135 patients in four trials of ATP to reduce shocks. The results revealed that patients with VA episodes and shocks have higher mortality (20% increased risk per shocked episode) than patients with neither or patients with VA treated only with ATP. In addition patients with more VA episodes and more shocks have higher mortality than patients with less of both. Interestingly, in this study, inappropriate shocked episodes were not associated with increased mortality risk. There are three potential explanations for these findings: (a) electrical trauma from shocks, but not ATP, increases risk; (b) VA episodes increase mortality risk irrespective of terminating therapy; (c) VA episodes and the shocks, but not ATP, increase mortality risk. Interactions between adverse shock effects are possible for scenarios (a) and (c) such that patients with more VA episodes may be more susceptible to harm from shocks. When electrical therapy type was included in the statistical analysis, ATP-terminated VT and shocked VF remained significant predictors of death. However, the risk in either case was indistinguishable from the risk unqualified for therapy (4% for VT vs. 3% for VT ATP; 15% for VF vs. 16% for VF shocks) and uncoupling the mortality effect of therapy type from episode type was impossible. Therefore, it was not possible to conclude that shocks for VT are harmful and that ATP is harmless or that shocks for VF increase episode risk. However, since 1/3 of FVT episodes were shocked and 2/3 ATP terminated, episode and therapy type mortality effects could be statistically uncoupled. FVT treated with ATP only was not associated with increased risk of death, whereas similar FVT episodes that were shocked increased the risk of death by 32% suggesting that shocks are associated with increased risk and ATP is not. The majority of shocks (60%) were for FVT, and 72% of shocked patients had at least one shock for FVT, making shocked FVT the most prevalent type of shocked episode and the dominant shock effect in the mortality models. Most shocks that were delivered in this study were for FVT and occurred at a 12 times higher rate among patients who died, whereas shocks for VF occurred at a 8 times higher rate.

Time spent in VA was 7 times higher per month among patients who died, and episode durations were higher for all episode/therapy combinations and greatest for shocked episodes preceded by failed ATP (22-fold increase). In addition to receiving more shocks, patients who died had longer duration shocked episodes (including failed ATP) and spent more time in shocked episodes compared with survivors. It is possible that longer episode durations after failed ATP magnify the adverse effect of shocks. In summary, the results from the study of Sweeney et al. confirm that shocks are associated with increased risk of adverse outcomes while ATP is not. This is consistent with data from MADIT II where ATP, unlike shocks, was not associated with increased risk of death.

3.2 Possible mechanisms for increased risk of negative outcomes associated with appropriate ICD shocks

The idea that shocks are associated with risk of death and HF in ICD patients is not new. A commonly held interpretation is that VA is a marker for clinical deterioration, shocks are harmless, and the increased risk reflects progression of the myocardial disease. An alternative explanation is that shocks may causally increase risks of HF and death. In MADIT II, the risk of first and recurrent HF hospitalization increased by 90% and 74%, respectively, after appropriate shocks. Survival after the first appropriate shock was 80% at
1 year. This was significantly less than the survival before the first shock, and the nonsudden cardiac death rate increased 17%. Shock-related myocardial injury has been investigated extensively. Large shock field strengths destroy cardiac myocytes causing biomarker release, which increases with shock strength and proximity to recent MI. The severity of post-resuscitation myocardial depression increases with shock strength, and is inversely related to survival. Repetitive shocks may cause cardiovascular collapse and death due to electromechanical dissociation.

One reasonable hypothesis would be that the specific type of the arrhythmia episode may precondition the myocardium to the adverse effects of shocks and that factors unique to spontaneous ventricular arrhythmias magnify these effects, particularly in ATP-unresponsive ventricular episodes.

Investigations of shock-related myocardial injury have focused on acute effects that may be insufficient to account for reduced survival after appropriate shocks. Other mechanisms may be important. Shocks may activate signaling pathways in the molecular cascade of HF. The clinical consequence may manifest months after shocks.

In contrast to the data on ICD shocks, there is no evidence that ATP has adverse cardiac effects. ATP termination of VT or FVT, unlike shocks, does not cause biomarker release or reduce ventricular pump function.

3.3 Clinical implications

Twenty-two percent to 35% of patients will receive appropriate ICD therapy for VT or VF within 3 years of implant, with an annual ICD shock rate of 5%. Despite the possible increase risk of death and HF with shocks, ICDs prolong survival. Near total reliance on shocks may have underestimated the ICD survival benefit in the above-mentioned clinical trials. The SCD-HeFT study was designed to provide ICD therapy that consisted of shock-only, single lead therapy for rapid, sustained VT or VF. No dual chamber or ATP therapy was allowed. The incidence of appropriate shock for VT or VF was 22.4%. Sixty-seven percent of patients received no ICD therapy. In the MADIT-II study, dual-chamber devices were used with the capability of ATP or shock therapy.

Since VF can only be terminated with shocks, uncoupling therapy from episode risk could be indirectly addressed with graded shock energies. Strategies to minimize shocks by using ATP as first line device therapy when possible, decrease shock energies, and reduce the burden of ventricular arrhythmias by using antiarrhythmic drugs and substrate modification may further improve survival in ICD patients. There are several other strategies that were proven effective in reducing device shocks. In a recent study by Desai and colleagues in the present study of 549 patients with heart failure and ICDs, smoking significantly increased the incidence of appropriate ICD shocks 3.7 times, and the use of statins significantly reduced appropriate ICD shocks by 46%. This is consistent with previous results from the MADIT II trial.

4. Inappropriate ICD shocks

Inappropriate ICD discharges result from the inability to distinguish supraventricular from ventricular arrhythmias, abnormal arrhythmia sensing or mechanical problems such as lead fracture, insulation break, and lead dislodgement. The shocks are painful, psychologically disturbing, potentially arhythmogenic and possibly associated with worse survival.
4.1 Incidence, mechanisms, and predictors of inappropriate shocks

An important contribution to the literature on the epidemiology of inappropriate ICD therapy was provided by the investigators of the MADIT II trial.\textsuperscript{16} The authors reported an incidence of inappropriate shocks of 11.5\% with a cumulative 1 and 2 year event rate of 10\% and 13\% respectively.\textsuperscript{16} In other studies such as AVID, PainFREE Rx, SCD-HeFT the incidence of inappropriate shocks was reported to be 20\%, 15\% and 32\% respectively.\textsuperscript{1, 26} The MIRACLE ICD study reported an incidence of inappropriate detection of 32\% but not all detections resulted in an ICD discharge. Although the incidence of inappropriate ICD shocks was found to be somewhere between 10\% and 35\% in all the studies available in literature, the ratio of inappropriate ICD shocks over the appropriate shocks varies widely depending on the population that was studied. The highest ratio is expected to occur in patients who receive ICDs for primary prevention where the incidence of appropriate ICD shocks is relatively low. The majority of these patients experience the first inappropriate shock after a mean period of 17±15 months from the device implantation. The cumulative percent rate was found to be around 7\% at 1 year, 13\% at 3 years and 18\% at 5 years. Approximately a third of the patients who receive one inappropriate shock typically receive the second one after a mean period of 11±11 months with the cumulative event rate of 28\%, 49\%, and 55\% at 1 year, 3 years and 5 years respectively after the first shock.\textsuperscript{27}

The most common causes of inappropriate ICD shocks are supraventricular tachycardia episodes and inappropriate sensing. Of all supraventricular tachycardias, AF with rapid ventricular response is the most common cause of an inappropriate ICD shock. This occurs because most ICDs are programmed to recognize VT when the heart rate exceeds a threshold value and SVTs may do so. Device companies have developed algorithms by which ICDs may differentiate VT from SVT using such parameters as sudden onset, rhythm stability and electrogram template matching. These strategies have demonstrated little impact in reducing discharges for SVT in part due to limited rhythm discrimination, because VT and SVT can mimic each other, and in greater part because they are probably little utilized by programming physicians.

Atrial fibrillation (AF) is a common finding in patients with low left ventricular ejection fraction and HF symptoms. Among HF patients, AF can occur with a prevalence of as high as 50\% in patients with New York Heart Association (NYHA) functional class IV. Patients with HF and ICDs who also have AF have a significantly higher risk of experiencing inappropriate ICD shocks than patients without AF. Furthermore, patients with permanent AF seem to have doubled risk of developing an inappropriate shock, and patients with paroxysmal or persistent AF are exposed to a tripled risk of developing inappropriate ICD shocks when compared with the patients without any history of AF.

There are other risk factors for inappropriate shocks in addition to supraventricular tachyarrhythmias. Age younger than 70 years, nonischemic cardiomyopathy, non-use of statins, smoking, and interim appropriate ICD shocks were reported to be independent predictors of inappropriate ICD shocks.\textsuperscript{16, 24, 29}

The MADIT II trial data analysis as well as other recent studies shows a significant 3-fold increase in the risk of inappropriate ICD shocks among current smokers. The overall risk of inappropriate ICD therapy was significantly increased among current smokers (20\%) compared to past smokers (14\%) and patients who never smoked (11\%). This difference was mainly due to the increased numbers of ICD shocks in the current smokers group. The main causes of the ICD shocks in these groups were supraventricular tachycardia and sinus tachycardia, which were more frequent in current smokers than in past and never-smokers.
Tobacco smoke causes sympathetic stimulation as well as increased platelet reactivity and endothelial dysfunction, tachycardia and high blood pressure, all of these leading to supraventricular tachycardia which could potentially induce inappropriate ICD shocks.\(^1\), \(^2\), \(^4\)

In some cases the treatment for ventricular arrhythmias can precipitate AF and initiate an inappropriate ICD discharge. An inappropriate therapy itself causing VT can lead to an appropriate ICD discharge as well. Most of the patients who received an ICD for VT or VF have predisposing factors that are common for VT and AF, which also makes them more prone in developing AF and increases their risk of inappropriate discharge.\(^3\), \(^3\)

Recent studies have demonstrated that patients younger than seventy years old are at increased risk for experiencing inappropriate ICD shocks\(^2\) due chiefly to sinus tachycardia episodes.\(^2\)

One study has demonstrated that the cause of inappropriate shocks is partly dependent on the number of ICD leads. Patients with single chamber devices received more shocks for sinus tachycardia compared to those with dual chamber units (28\% vs 8\%), whereas patients with CRT devices received more shocks due to abnormal sensing compared to patients with single chamber ICDs (15\% vs. 8\%).\(^2\)

### 4.2 Prognostic importance of inappropriate ICD shocks

Data from ICD trials have demonstrated that inappropriate ICD discharges may compound the prognostic risk of appropriate shocks. Poole et al. found that among patients who received ICDs for primary prevention of SCD the risk of death doubled when inappropriate shocks were delivered in comparison to patients who did not receive shocks at all.\(^1\) A patient who received an appropriate shock and an inappropriate shock has a risk of death increased by a factor of 11 when compared with a patient who received no shock at all. The patients who received at least two previous appropriate shocks and have received an inappropriate shock have a risk of death increased by 15 and additional inappropriate shocks do not result in further increase in the risk of death. Similar findings were reported in the MADIT II trial. Although previous studies reported appropriate shocks to be predictors of future CHF hospitalizations, in the MADIT II trial the inappropriate shocks did not predict future hospitalizations.\(^1\)

It is uncertain why an inappropriate shock is associated with an increase in mortality. One possible explanation could be the fact that the development of AF, the most common cause of an inappropriate shock, in a patient with heart failure carries a worse prognosis.\(^3\) Benjamin et al. showed that the occurrence of AF was associated with a 1.5 to 1.9-fold risk of all-cause mortality.\(^3\) These findings were confirmed also in an ICD population by Borleffs and colleagues who found a 1.7 times increased risk of mortality in patients with permanent AF when compared with non-AF population. The highest mortality is shown by the patients who have permanent atrial fibrillation followed by those with persistent atrial fibrillation and then by patients with paroxysmal atrial fibrillation.\(^2\)

Other causes that could explain the increase in mortality could be explained by the direct effect of the shocks on the myocardium. The presence of positive cardiac markers after inappropriate discharge suggests that the shock causes myocardial damage leading to ventricular dysfunction.\(^2\), \(^3\) Shocks with higher energy delivered are more likely to cause more myocardial damage. Tokano and colleagues demonstrated that shocks with energy greater than 9 J cause a 10\% to 15\% transient reduction of the cardiac index. The duration and the extent of the effect are proportional to the shock strength. The detrimental...
The homodynamic effect of a ventricular defibrillator shock appears to be due to the shock itself, and not to ventricular fibrillation. The latest conclusion was drawn from the observation that a similar degree of ventricular stunning was noted after shocks delivered during the baseline rhythm as with shocks that terminated ventricular fibrillation.

4.3 Impact on psychology and lifestyle

Delivery of an ICD shock, is often associated with increased psychological distress in patients and their families. The AVID trial extended these findings by demonstrating that patients who received more than one ICD shock within the initial year of implantation reported significant declines in physical functioning and mental well-being. Increased sadness, anxiety, fatigue, and nervousness were also found to be associated with more ICD discharges. Other studies reported that overall psychological distress was significantly correlated with the total number of ICD shocks a patient receives.

4.4 Clinical implications

Ever since ICD therapy was developed technology improved constantly including the ability to differentiate supraventricular from ventricular tachyarrhythmias and to prevent inappropriate discharges. In spite of all the progress been made, recent research that assessed the incidence of inappropriate shocks in the ICDs implanted recently in comparison to those implanted a while ago did not show any improvement even more than that it appeared that the patients who received the ICDs more recently are exposed to a greater risk of developing an inappropriate shock. This phenomenon is mostly explained by the fact that guidelines for ICD implantation keep changing, shifting more towards primary prevention. The primary prevention group is represented by patients who usually have a more advanced underlying cardiac disease, which exposes them to a higher risk of developing AF, which is the number one cause of inappropriate discharge. Criteria incorporated in the modern ICD algorithms used to discriminate ventricular from supraventricular tachycardia include rapidity of onset of the arrhythmia and QRS morphology. Discriminating algorithms typically increase the specificity but at the same time they decrease the sensitivity for VT recognition. Despite widespread use of antiarrhythmic medications in patients with ICDs there are only a few studies documenting the efficacy of these therapies in this patient population. Sotalol and dofetilide when used as antiarrhythmic agents in patients with ICDs were found to reduce the risk of inappropriate shocks. Amiodarone was also found to be effective in preventing inappropriate shocks in patients with ICDs but it has a significant number of side effects and can lead to elevation of the defibrillation threshold (DFT).

In addition, the β-adrenergic blocking agents are efficacious antiarrhythmic drug therapies and can be effective in reducing the incidence of both supraventricular and ventricular arrhythmias in ICD patients. Finally, trying to address other identifiable predictors of inappropriate shocks might be beneficial in terms of reducing both appropriate and inappropriate shocks: smoking cessation, treating illnesses that can cause sinus tachycardia, starting the patient on a statin if appropriate.

5. References


Millions of people throughout the world currently depend on appropriate, timely shocks from implantable cardioverter defibrillators (ICDs) to avoid sudden death due to cardiovascular malfunctions. Therefore, information regarding the use, applications, and clinical relevance of ICDs is imperative for expanding the body of knowledge used to prevent and manage fatal cardiovascular behavior. As such, the apt and timely research contained in this book will prove both relevant to current ICD usage and valuable in helping advance ICD technology. This book is divided into three comprehensive sections in order to cover several areas of ICD research. The first section introduces defibrillator technology, discusses determinants for successful defibrillation, and explores assessments of patients who receive defibrillation. The next section talks about predicting, preventing, and managing near catastrophic cardiovascular events, and research presented in the final section examine special cases in ICD patients and explore information that can be learned through clinical trial examinations of patients with defibrillators. Each chapter of this book will help answer critical questions about ICDs.

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