The interrelation between implantable cardioverter defibrillators (ICDs) and atrial fibrillation (AF) is becoming increasingly relevant. AF affects more than 2 million Americans and 6 million in Europe. In the United States alone, the prevalence is expected to increase to 5.6 million by 2050. Since the initial US Food and Drug Administration approval in 1985, ICDs have evolved to become standard therapy in patients at high risk for sudden cardiac death (SCD). ICDs have been shown to reduce SCD in patients with ventricular arrhythmias (secondary prevention) and in those at high risk for ventricular arrhythmias (primary prevention). The number of ICD implants continues to grow; currently, 70,000 ICDs are implanted in the United States on yearly basis. The recipients of these devices are generally older adults who have heart disease. It is well known that the incidence and prevalence of AF also increase with age. In addition, given the aging of the population and the adoption of more aggressive approaches to cardiovascular disease, this overlap is likely to continue to increase. AF in the ICD population leads to special problems, such as the delivery of inappropriate ICD therapies, and offers special opportunities for assessing therapy effectiveness because the patient’s AF burden can be assessed more accurately.

OVERLAPPING EPIDEMIOLOGY

Many of the factors that predispose people to AF are the same risk factors that put them at risk for SCD. Therefore, it stands to reason that these subgroups that are most affected by AF are the same groups that might benefit most from ICD therapy. Fig. 1 demonstrates the many associations and overlapping features that connect AF and ICD therapy. In addition to many common risk factors, there are some direct associations, which are discussed elsewhere in this article.

**Age**

Increasing age predisposes patients to AF and SCD. AF clearly increases with advancing age. In fact, AF doubles in incidence with each decade of age, affecting up to 10% of patients older than the age of 80 years. Similarly, subanalyses of major primary and secondary prevention ICD trials in addition to meta-analyses have all shown preserved efficacy of ICDs in the elderly. Substudies of the Multicenter Automatic Implantable Cardiac Defibrillator (MADIT) II trial demonstrated the preservation of efficacy of ICDs in the elderly.

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Defibrillator Implantation Trial (MADIT)-II demonstrated that not only is the efficacy similar in patients older than 75 years of age, but it might even be greater.\textsuperscript{12,13}

**Gender**

Men are generally at higher risk for atrial and ventricular arrhythmias. There is a male predominance in the risk for AF, adjusted for confounders.\textsuperscript{1,7} As of yet, this remains unexplained. Data also suggest that ICDs may be more beneficial in men as compared with women. At baseline, a Multicenter Unsustained Tachycardia Trial (MUSTT) substudy demonstrated that women have less inducibility of sustained ventricular tachycardia (VT).\textsuperscript{14} A meta-analysis investigating the impact of gender on survival among patients with defibrillators for primary prevention also suggested a greater benefit among men.\textsuperscript{15}

**Heart Failure**

Heart failure (HF) is one of the most significant factors for patients at risk for SCD and AF. AF can be found in up to 40% of patients who have symptomatic HF.\textsuperscript{16} Conversely, one quarter of patients with AF have HF. After adjustment, HF was associated with a 4.5- to 6-fold increase risk for AF.\textsuperscript{1,7} Similarly, greater than 99% of ICD recipients have HF attributable to severe LV dysfunction (left ventricular ejection fraction $\leq 35\%$).\textsuperscript{17} In the largest and most recent randomized controlled trial (RCT), patients who had New York Heart Association (NYHA) class IV HF had a 46% reduction in the risk for death with an ICD. This is in contrast to a nonsignificant reduction in risk among NYHA class II patients.\textsuperscript{9} Of note, this trend has not been replicated in all the other large RCTs.\textsuperscript{8,18}

**Fig. 2** demonstrates the cycle in which AF begets HF, which, in turn, increases the burden of AF. This cycle ultimately increases the risk for SCD as well.

**Other Cardiovascular Risk Factors**

Many of the cardiovascular risk factors for AF are also risk factors for ventricular arrhythmias and SCD. Of the major cardiovascular risk factors, diabetes is a significant predictor of AF.\textsuperscript{1,7} Other cardiovascular risk factors, such as smoking and renal failure, also predispose patients to AF.\textsuperscript{1,7} Although there are few published data on the relationship between these cardiovascular risk factors and the efficacy of ICDs, the data available suggest that these same risk factors increase the risk for SCD. For instance, suboptimal glycemic control, smoking, and renal failure have all been associated with increased risk for ventricular arrhythmias.\textsuperscript{19-21} Therefore, in patients who already have an indication for ICD, these subgroups (eg, smokers, diabetics, patients who have renal failure) may derive greater benefit from ICDs. Quantifying the extent of benefit derived from ICD therapy in these populations is an area in which further investigation is required, however.

The role of hypertension in the overlapping epidemiology is more complex. Although hypertension is clearly a strong independent risk factor for AF, its influence on the effectiveness of ICDs is less straightforward.\textsuperscript{1,7} A subanalysis of MADIT-II demonstrated an inverse relation between systolic and diastolic blood pressure and ICD efficacy. That is, among patients with “higher” blood pressures (systolic blood pressures of $\geq 130$ mm Hg or diastolic blood pressures of $\geq 80$ mm Hg), with a higher risk for SCD, the efficacy of an ICD is attenuated.\textsuperscript{22}

**Patients with Channelopathies (Long QT Syndrome, Brugada Syndrome)**

The association between repolarization channelopathies of the ventricular myocardium and AF has recently become more clear. The prevalence of AF in patients with long QT syndrome (LQTS) and Brugada syndrome is significantly higher than the
background incidence of lone AF in the same, often young, age group (Fig. 3).\textsuperscript{23,24}

Brugada syndrome is classically characterized in relation to its propensity for SCD attributable to ventricular arrhythmias. Therefore, ICDs are indicated for patients who have Brugada syndrome.\textsuperscript{25} The arrhythmogenic substrate may not be restricted to the ventricles, however, and may also be present in the atria. Atrial arrhythmias are being increasingly recognized in patients who have Brugada syndrome, the most common of which is AF. One of the largest studies is a retrospective evaluation from 14 centers of 220 patients with ICDs who had Brugada syndrome. In this study, 10% (23 of 220) of patients had AF.\textsuperscript{26} AF was an important cause of inappropriate

![AF in Patients with ICDs](image)

Fig. 2. Mechanisms: AF begets HF, and HF begets AF. This cycle is similar for SCD. (From Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003;91(Suppl 1):5D; with permission.)

![AF in Young (<50y)](image)

Fig. 3. Prevalence of atrial fibrillation (AFib) in young patients with and without LQTS and Brugada syndrome.
ICD shocks in these patients. One study reported that the number of inappropriate shocks exceeded the number of appropriate shocks (14.5% vs 10%).

Similarly, patients who have LQTS are at considerable risk for SCD, with indication for an ICD. In LQTS, the potassium and sodium channels are thought to be defective in the atria and ventricles. A recent study reported an incidence of AF of 1.7% among patients who are gene-positive for LQTS. This is significantly greater than the baseline risk of 0.1% in an otherwise similar comparison group.

Although the excess burden of AF in these patients who have channelopathies is quite clear, the therapeutic options are less so. Most cardiac ion channel disorders, which predispose to familial AF, shorten the action potential duration (APD). Sotalol may prolong the APD through potassium channel blockade, which would be particularly unsafe in patients who have LQTS. Reports of harm with amiodarone may further limit medical management in these subsets of patients. Therefore, catheter ablation targeting pulmonary venous triggers might have a more prominent role in these subsets of patients and may even be considered primary therapy. One study showed that AF ablation in patients with paroxysmal AF and electrocardiograms consistent with Brugada syndrome was safe and effective.

**IMPACT OF ATRIAL FIBRILLATION ON PATIENTS WITH IMPLANTABLE CARdioverter DEFibrillators**

Although there is clear overlap in risk factors that predispose patients to AF and SCD, whether AF is independently associated with an increased risk for death in patients at risk for SCD is debated. It does not appear, however, that the presence of AF reduces the efficacy of ICDs. Among patients who have congestive HF in general, AF has not been consistently shown to increase mortality. In the Framingham cohort, AF is an independent marker of increased mortality in patients who have structurally diseased hearts.

In addition, data from large studies suggest that patients who have HF and supraventricular tachyarrhythmias in general, and AF in particular, have an increased rate of HF exacerbation, an increased rate of hospitalization for HF, and an increased rate of death. Other large studies confirmed these findings however, the survival benefits from restoration and maintenance of sinus rhythm were offset by adverse effects of antiarrhythmic drugs (ie digoxin). Furthermore, additional smaller studies did not identify AF as an independent predictor of mortality.

Specific data on the additional risk for AF in patients with ICDs are limited and similarly conflicting. From the Antiarrhythmic Versus Implantable Defibrillators (AVID) registry, patients who present initially with life-threatening ventricular arrhythmias and have a history of AF or atrial flutter are at increased risk for death (HR = 1.20; 95% confidence interval [CI] = 1.03–1.40). Of note, given that the patients were not randomized, there were many significant differences in baseline characteristics between the patient groups. Insofar as such an analysis can adequately adjust for these differences, the data suggest that a history of AF or atrial flutter is an independent risk factor for mortality.

A substudy of predictors of VT or ventricular fibrillation (VF) occurrence in patients who had ICDs also confirmed this association. In a substudy of MADIT-II, 102 (8%) of the patients who had AF at baseline were evaluated for the combined risk for HF hospitalization and death. First, there was no significant difference in the incidence of inducible VT between patients with AF and sinus rhythm at study baseline. Second, after adjustment, mortality was no longer significantly higher in patients with AF at baseline (hazard ratio [HR] = 1.54, 95% CI: 0.85–2.87). The combined end point of HF hospitalization and death, however, occurred significantly more frequently in patients with AF even after adjustment (HR = 1.68, 95% CI: 1.02–2.75; Fig. 4). Of the patients with newly detected AF (68 patients [6%]), multivariate regression analysis demonstrated an increased risk for combined HF hospitalization and death in comparison to patients with sinus rhythm. Further study, such as a meta-analysis, might clarify the effect of AF on mortality in patients with ICDs.

**Inappropriate Shocks and Atrial Fibrillation**

Despite the proven benefit of ICDs, inappropriate shocks remain a problem in a significant number of patients. Inappropriate shocks are shock therapies delivered by an ICD for the treatment of nonventricular arrhythmias. Inappropriate shocks comprise 12% to 30% of all shock therapies delivered. Supraventricular tachyarrhythmia is the most common independent predictor of inappropriate shocks, and of these, AF is the most frequent type (44%–51%). Sinus tachycardia is the second most common cause of inappropriate shocks, which occur more commonly in patients...
with primary prevention ICDs. Smoking and diastolic hypertension have been implicated as risk factors for inappropriate shocks as well. Rare causes include device malfunction, lead failure, and oversensing of myopotentials or T waves.

Ultimately, inappropriate shocks have all the adverse consequences of ICD shocks without any of the proven benefit. Moreover, patients who receive multiple inappropriate therapies experience a diminished quality of life. Some even experience psychologic symptoms, including “phantom shocks.” In addition, ICD shocks can incite dangerous arrhythmias. Finally, inappropriate ICD shocks cause premature battery depletion, which may render devices less cost-effective. Ultimately, in the MADIT-II study, inappropriate therapies were associated with an increased probability of death. These data stress the importance of reducing inappropriate shocks.

Principle strategies for inappropriate shock reduction include antiarrhythmic drugs and several different device-based detection or discrimination enhancements. Earlier generation devices were hindered by atrial undersensing during long blanking periods and atrial oversensing of R waves during short blanking periods. This led to difficulty in diagnosing ventricular tachyarrhythmias in the setting of AF with rapid ventricular rates. To minimize inappropriate shocks from AF, newer single-chamber devices use enhanced detection criteria, such as R-R interval stability, abrupt onset of tachyarrhythmia, QRS morphology, and sustained duration. In addition to these technical advancements, dual-chamber devices also include comparisons of atrial and ventricular rates. Earlier clinical reports differ on the additional benefit of a dual-chamber device. A meta-analysis comparing single-chamber with dual-chamber arrhythmia discrimination algorithms suggests that dual-chamber arrhythmia discrimination is associated with a further reduction of inappropriately treated episodes. Other reports also support this finding.
Nevertheless, despite device improvements, inappropriate ICD therapy continues to be a problem and there is room for further improvement. For instance, among all episodes of VT, 3% occur during underlying AF. In patients with known paroxysmal AF, 18% of ventricular arrhythmias in the VF zone occur during AF.\textsuperscript{52} Disabling discrimination of supraventricular from ventricular arrhythmias in the VF zone avoids undersensing of true VT or VF at the cost of an increased likelihood of inappropriate shocks. Enabling discrimination in the VF zone may delay or disable appropriate treatment, which is unacceptable. More work is needed to improve on current strategies.

Recent strategies to reduce the burden of inappropriate shocks include home-based monitoring and catheter ablation. Home-based monitoring of devices elucidates silent episodes of AF, breakthrough AF episodes on drugs, and previously unobserved atrial undersensing and VT. With easy and frequent availability of updates from the device’s memory, allowing for early device reprogramming and appropriate medication adjustment can help to reduce the incidence of inappropriate shocks.\textsuperscript{53} Atrioventricular node ablation in patients with drug refractory AF can eliminate rapid ventricular response-generated inappropriate shocks. Loss of atrial kick may not be desirable in some patients, however, specifically those with hypertrophic cardiomyopathy and severe diastolic dysfunction. If drug therapy is not effective in preventing recurrences of atrial fibrillation, and recurrent shocks and AV node ablation are deemed undesirable, left atrial catheter ablation (pulmonary vein isolation with or without linear lesions) might be considered as an alternative. While such a strategy has not been proven effective in ICD patients with recurrent shocks, the benefit of left atrial catheter ablation recently has been demonstrated in a randomized trial of patients who have drug-resistant atrial fibrillation and congestive heart failure.\textsuperscript{54}

**IMPACT OF IMPLANTABLE CARDIOVERTER DEFIBRILLATORS ON PATIENTS WITH ATRIAL FIBRILLATION**

Data are limited on the efficacy of ICDs in patients with AF. In the MADIT-II substudy, the cumulative 2-year probability of AF was 7%. Among patients with AF, ICD therapy reduced the 2-year mortality rate from 39% in 41 conventionally treated patients to 22% in 61 ICD-treated patients (HR = 0.51), which was not statistically significant (\( P = .079 \)). In this study, there was also no difference in the combined end point of HF hospitalization or death at 2 years among patients with AF treated with ICD therapy versus conventional therapy (69% versus 59%; \textbf{Fig. 5}).\textsuperscript{30}

Although clinical reports of AF in patients who have ICDs are common, reports of ICD shocks inducing AF are rare. These reports suggest that defibrillation shocks within a threshold of “atrial vulnerability” are more likely to induce AF. It seems that defibrillations at greater than this threshold of vulnerability, which are now more common, are less likely to induce AF.\textsuperscript{55} This might explain why there have been fewer reports of inducing AF with the more recent generations of ICDs. Timing shock delivery to the atrial cycle seems to be of marginal or no benefit in the prevention of shock-induced AF.\textsuperscript{56} Notably, external cardioversion (ECV) can induce AF with high recurrence rates in patients with an established history of AF, but it bears no prognostic significance.\textsuperscript{57} Also, epicardial leads may predispose patients to AF more so than endocardial leads, although the data are sparse.\textsuperscript{58}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{fig5.png}
\caption{Cumulative probability of combined end point of congestive heart failure (CHF) hospitalization or death in MADIT-II patients with AF by: implantable ICD versus conventional therapy. (From Zareba W et al. Implantable cardioverter-defibrillator therapy and risk of congestive heart failure or death in MADIT II patients with atrial fibrillation. Heart Rhythm 2006;3:634; with permission.)}
\end{figure}
Conversely, AF is sometimes considered as a trigger for ventricular arrhythmia. Multiple reports have consistently identified an association between AF and appropriate ICD therapy, however, suggesting such a relation. Mechanistically, irregular ventricular excitation with AF in diseased hearts leads to inhomogeneous repolarization, and thus to a higher vulnerability predisposing to sustained ventricular arrhythmias. In fact, short-long-short sequences could be proarrhythmic irrespective of underlying rhythm. The electrophysiologic mechanism seems to be irregular rather than rapid ventricular activation, with a high incidence of short-long-short sequences preceding ventricular tachyarrhythmias.61

Finally, these devices can also be used to record and follow the incidence and burden of AF. Using these devices for treatment on the other hand, atrial overdrive pacing to reduce the incidence of AF, has not yet been proven.62

DRUGS IN PATIENTS WITH ATRIAL FIBRILLATION AND IMPLANTABLE CARdioverter DEFibrillators

To reduce the burden of inappropriate shocks and the need for appropriate therapies, many medical regimens have been tried. Up to 70% of patients with ICDs are also maintained on antiarrhythmic drugs for atrial or ventricular arrhythmia suppression.63

Antiarrhythmic Drugs and Implantable Cardioverter Defibrillator Shocks

Despite beta-blockade, up to 40% of patients still experience shocks in their first year.63 Amiodarone and sotalol are most commonly used to suppress shocks. Amiodarone significantly reduces inappropriate and appropriate shocks relative to class I antiarrhythmics and beta-blockade alone.64,65 Although sotalol significantly reduced the risk for a first shock compared with placebo, the risk reduction was not significant when compared with beta-blockers (HR = 0.61, 95% CI: 0.37–1.01).64,66 All these drugs have relatively high discontinuation rates (~20%), however. Amiodarone, in particular, is associated with adverse pulmonary and thyroid events.64,67

A recent prospective observational study investigated the association between statin therapy and inappropriate shocks in patients with AF or atrial flutter. Of the 1445 patients treated with statins and ICDs, there was a significant reduction in inappropriate shocks (HR 0.47, 95% CI: 0.35–0.64).68 This finding must be interpreted within the limitations of a nonrandomized study. A randomized controlled study to evaluate the effects of statin therapy is needed.

Antiarrhythmic Drugs and Defibrillation Threshold

The efficacy of ICDs for terminating ventricular tachyarrhythmias is contingent on an adequate safety margin for defibrillation energy, commonly referred to as the defibrillation threshold (DFT). Antiarrhythmic drugs used to suppress AF, namely amiodarone and sotalol, have variable effects on DFTs. Amiodarone, the most effective anti-AF drug raises the DFT with chronic use (≥6 weeks) by virtue of its Na+ channel-blocking property (although acute intravenous loading can reduce the DFT), Sotalol, dofetilide, ibutilide, and class II beta-blockers reduce the DFT.69 The proarrhythmic nature of class IC drugs in patients with LV dysfunction limits their use; except for propafenone, these drugs raise the DFT in nonrandomized studies.70

The Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) substudy is one of the few RCTs looking at clinical outcomes in relation to the effects of antiarrhythmic drugs on DFTs. This study demonstrated that patients on beta-blockade had a decrease in mean DFT over time, which is often seen independent of beta-blockade. Consistent with prior studies, amiodarone increased the DFT and sotalol decreased the DFT. Importantly, this study demonstrated that in the era of modern device systems, the magnitude of the increase in the DFT with amiodarone is unlikely to be clinically significant.71 Currently, the need for routine DFT reassessment after instituting antiarrhythmic drug therapy remains debated.

Anticoagulation in Patients with Implantable Cardioverter Defibrillators

Anticoagulation is advocated in patients who have AF with major predictors of stroke based on the CHADS2 scoring system. Implantable cardioverter-defibrillators do not alter the decision to anticoagulate a patient or not. Moreover, anticoagulation protocols are not specific for patients with AF who have ICDs.

Anticoagulation for the evaluation of the DFT in patients with AF should be treated analogously to direct-current cardioversion in patients with AF. The risk for thromboembolism is assumed to be the same. There is even a potential for stroke from spontaneous (device-mediated) appropriate and inappropriate shocks in patients with subtherapeutic anticoagulation. Therefore, patients with ICDs and AF need to be anticoagulated as per...
the guidelines before and after undertaking DFT testing.72

With regard to anticoagulation at the time of implantation, it remains common practice to postpone device implantation until the international normalized ratio (INR) has normalized. Data are mixed regarding the benefit of reversing anticoagulation even at the time of implantation. The largest study is an observational study of 1025 patients followed prospectively over a 4-year period. Nearly 50% of the patients underwent device implantation (pacemakers and ICDs) without reversal of anticoagulation (mean INR = 2.6, range: 1.5–6.9). There was no significant difference in complication rates between the two groups (13 of 470 patients in the anticoagulated group, 21 of 555 patients in the “nonanticoagulated” group).73 Another widely cited, small study revealed that there were significantly more pocket hematomas among patients who received warfarin plus intravenous heparin. There was no difference in outcome or complication rate among a subset of 49 patients randomized to receive heparin 6 versus 24 hours post-implant. The only stroke occurred in a patient on warfarin alone.74

CARDIOVERSION

As shown, the increasing rate of ICD implantation and AF is occurring in similar patient populations. One approach to management has been maintenance of sinus rhythm because of concern for higher morbidity and possible mortality in this population. Moreso in patients with CRT-Ds, AF may reduce the efficacy of the device.75 External and internal cardioversion are alternatives to pharmacotherapy to restore sinus rhythm in these high-risk patients.

External Cardioversion

The use of ECV has long been a cause for concern in patients with ICDs because of the potential for adverse effects on the device generator or leads. These concerns are mainly based on reports before the 1990s.76 More recently, a prospective randomized comparison of biphasic versus monophasic shock energy application in a group of 44 patients with implanted devices demonstrated that cardioversion was safe after excluding patients with known sensing abnormalities. There was no difference in response to biphasic versus monophasic shock energy. Currently, the guidelines suggest that ECV is safe in patients with ICDs. The recommendation remains to check devices before and after cardioversion. Studies suggesting that this may not be necessary are small and inconclusive.77

Implantable Atrial Defibrillators

Implantable dual-chamber cardioverter defibrillators, with the capacity for atrial sensing and cardioversion for atrial arrhythmias, continue to be an active area of research. Several devices have been developed with atrial cardioversion and ventricular defibrillation capacity and are being tested in the United States and abroad. Results of their overall efficacy are mixed.78,79 Of note, some data suggest that when episodes are treated quickly with an atrial defibrillator, the time between episodes is lengthened and the burden is reduced.80 An important limitation of atrial defibrillators, however, is that few patients can tolerate the therapy. The pain threshold for defibrillation shocks is quite low. An internal shock less than 1 J is similarly uncomfortable to those of higher energy.81 Further technical improvements and appropriate patient selection are still required to improve the potential benefits of such devices.

SUMMARY

AF is common in patients who have implantable defibrillators and presents some unique challenges and opportunities. AF burden can be assessed more accurately, allowing for evaluation of therapy efficacy (drugs or ablation). It remains to be shown whether home monitoring of defibrillators to detect and treat AF more quickly can reduce cardiovascular and stroke end points. The goals of therapy remain the same—reduction of symptoms (including HF exacerbation and inappropriate ICD therapies) by controlling rate or rhythm and anticoagulation for stroke prophylaxis.

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