Atrial Fibrillation in Patients with Implantable Defibrillators

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• Atrial fibrillation • Defibrillator • ICD
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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.[1] 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).[2–4] The number of ICD implants continues to grow; currently, 70,000 ICDs are implanted in the United States on yearly basis.[5] 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, afflicting up to 10% of patients older than the age of 80 years.[1,6,7] 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.[2,3,8–11] Substudies of the Multicenter Automatic

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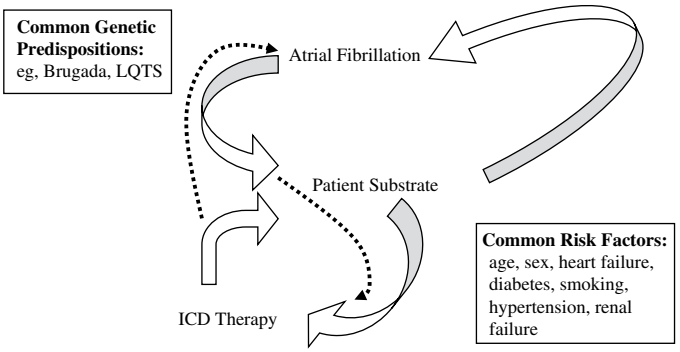

Fig. 1. There is a complex interplay between AF and SCD, with direct effects as well as common risk factors and similar genetic underpinnings.

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.[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.[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).[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.[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.[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.[1,7] Similarly, greater than 99% of ICD recipients have HF attributable to severe LV dysfunction (left ventricular ejection fraction $\leq$35%).[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.[9] Of note, this trend has not been replicated in all the other large RCTs.[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.[1,7] Other cardiovascular risk factors, such as smoking and renal failure, also predispose patients to AF.[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.[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.[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.[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

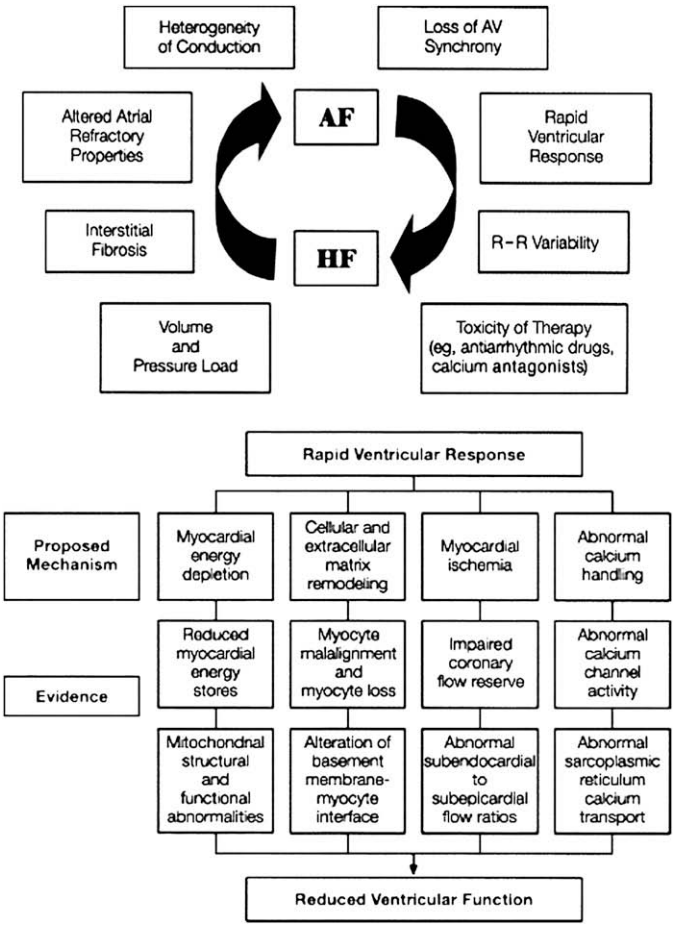

Fig. 2. Mechanisms: AF begets HF, and HF begets AF. This cycle is similar for SCD. (*From* Maisel WH, Stevenson LW. Atrial fibrillation in heart failure: epidemiology, pathophysiology, and rationale for therapy. Am J Cardiol 2003;91(Suppl 1):5D; with permission.)

background incidence of lone AF in the same, often young, age group (**Fig. 3**).[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.[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.[26] AF was an important cause of inappropriate

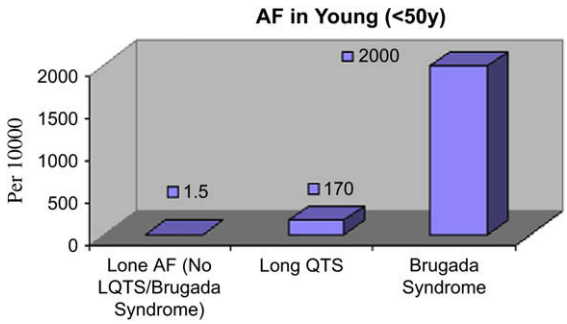

Fig. 3. Prevalence of atrial fibrillation (AFib) in young patients with and without LQTS and Brugada syndrome.

ICD shocks in these patients. One study reported that the number of inappropriate shocks exceeded the number of appropriate shocks (14.5% vs 10%).[27]

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.[23]

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.[23] 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.[28]

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.[29,30]

Atrial Fibrillation as an Independent Risk Factor for Mortality in Patients who have Implantable Cardioverter Defibrillators

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.[31] 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.[32] 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).[33] Furthermore, additional smaller studies did not identify AF as an independent predictor of mortality.[34,35]

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.[29] A substudy of predictors of VT or ventricular fibrillation (VF) occurrence in patients who had ICDs also confirmed this association.[36]

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 (58 patients [6%]), multivariate regression analysis demonstrated an increased risk for combined HF hospitalization and death in comparison to patients with sinus rhythm.[30] 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.[37–42]

Supraventricular tachyarrhythmia is the most common independent predictor of inappropriate shocks, and of these, AF is the most frequent type (44%–51%).[37–42] Sinus tachycardia is the second most common cause of inappropriate shocks, which occur more commonly in patients

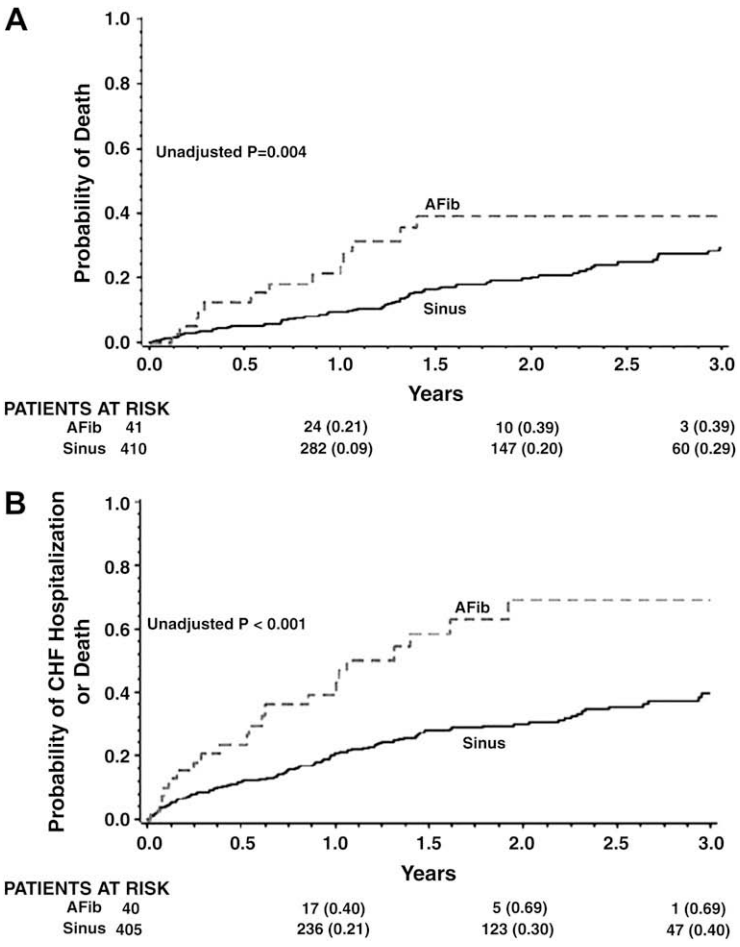

Fig. 4. In a MADIT-II substudy, AF significantly increased mortality (*A*) and the cumulative probability of congestive heart failure (CHF) hospitalization or death compared to patients in sinus rhythm at baseline (*B*). Difference in mortality abated after controlling for age, NYHA class, blood urea nitrogen (BUN) level, and use of beta-blockers, however. (*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; 3:633; with permission.)

with primary prevention ICDs.[39] Smoking and diastolic hypertension have been implicated as risk factors for inappropriate shocks as well.[40–42] Rare causes include device malfunction, lead failure, and oversensing of myopotentials or T waves.[37]

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."[43,44] In addition, ICD shocks can incite dangerous arrhythmias. Finally, inappropriate ICD shocks cause premature battery depletion, which may render devices less cost-effective.[45] Ultimately, in the MADIT-II study, inappropriate therapies were associated with an increased probability of death.[30,46] 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.[47] 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.[48–51]

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.[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.[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.[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%; **Fig. 5**).[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.[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.[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.[57] Also, epicardial leads may predispose patients to AF more so than endocardial leads, although the data are sparse.[58]

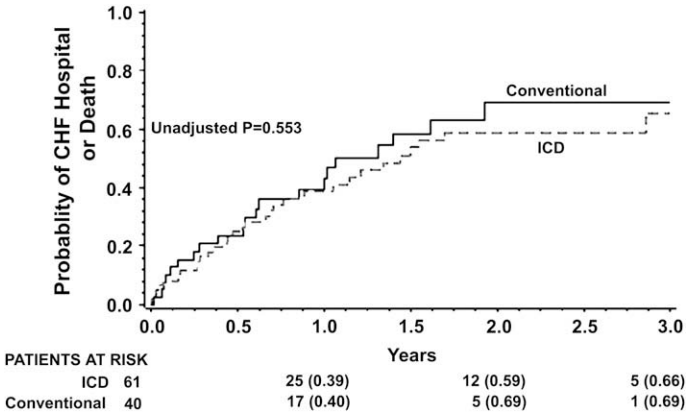

Fig. 5. Cumulative probability of combined end point of congestive heart failure (CHF) hospitalization or death in MADIT-II patients with AF by: implantable ICD versus conventional therapy. (*From* Zareba W et al. Implantable cardioverter-defibrillator therapy and risk of congestive heart failure or death in MADIT II patients with atrial fibrillation. Heart Rhythm 2006;3:634; with permission.)

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.[59,60] 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 ($\geq$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 $CHADS_2$ 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.

REFERENCES

1. Kannel WB, Benjamin EJ. The status of the epidemiology of atrial fibrillation. Med Clin North Am 2008; 92(1):17–40.
2. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002;346:877–83.
3. Buxton AE, Lee KL, Fisher JD, et al. A randomized study of the prevention of sudden death in patients with coronary artery disease. N Engl J Med 1999; 341:1882–90.
4. The Antiarrhythmic versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable cardioverter defibrillators in patients resuscitated from near-fatal

ventricular arrhythmias. N Engl J Med 1997;337: 1576–83.
5. Zhan C, Baine WB, Sedrakyan A, et al. Cardiac device implantation in the United States from 1997 through 2004: a population-based analysis. J Gen Intern Med 2008;23(Suppl 1):13–19.
6. Go AS, Hylek EM, Phillips KA, et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. JAMA 2001; 285(18):2370–5.
7. Benjamin EJ, Levy D, Vaziri SM, et al. Independent risk factors for atrial fibrillation in a population-based cohort: the Framingham Heart study. JAMA 1994; 271:840–4.
8. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary artery disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators (MADIT). N Engl J Med 1996;335:1933–40.
9. Kadish A, Dyer A, Daubert JP, et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy (DEFINITE). N Engl J Med 2004;350:2151–8.
10. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. N Engl J Med 2005;352:225–37.
11. Lee DS, Green LD, Liu PP, et al. Effectiveness of implantable defibrillators for preventing arrhythmic events and death: a meta-analysis. J Am Coll Cardiol 2003;41(9):1573–82.
12. Huang DT, Sesselberg HW, McNitt S, et al. Improved survival associated with prophylactic implantable defibrillators in elderly patients with prior myocardial infarction and depressed ventricular function: a MADIT-II substudy. J Cardiovasc Electrophysiol 2007;18(8):833–8.
13. Goldenberg I, Moss AJ. Treatment of arrhythmias and use of implantable cardioverter-defibrillators to improve survival in elderly patients with cardiac disease. Clin Geriatr Med 2007;23(1):205–19.
14. Russo AM, Stamato NJ, Lehmann MH, et al. Influence of gender on arrhythmia characteristics and outcome in the Multicenter Unsustained Tachycardia Trial. J Cardiovasc Electrophysiol 2004;15(9):993–8.
15. Henyan NN, White CM, Gillespie EL, et al. The impact of gender on survival amongst patients with implantable cardioverter defibrillators for primary prevention against sudden cardiac death. J Intern Med 2006;260(5):467–73.
16. Stevenson WG, Stevenson LW. Atrial fibrillation in heart failure. N Engl J Med 1999;341:910–1.
17. Goldberger Z, Lampert R. Implantable cardioverter-defibrillators: expanding indications and technologies. JAMA 2006;295(7):809–18.
18. Zareba W, Piotrowicz K, McNitt S, et al. Implantable cardioverter-defibrillator efficacy in patients with heart failure and left ventricular dysfunction. Am J Cardiol 2005;95(12):1487–91.
19. Chen-Scarabelli C, Scarabelli TM. Suboptimal glycemic control, independently of QT interval duration, is associated with increased risk of ventricular arrhythmias in a high-risk population. PACE 2006;29(1):9–14.
20. Goldenberg I, Moss AJ, McNitt S, et al. Cigarette smoking and the risk of supraventricular and ventricular tachyarrhythmias in high risk cardiac patients with implantable cardioverter defibrillators. J Cardiovasc Electrophysiol 2006;17(9):937–9.
21. Herzog CA, Li Shuling, Weinhandl ED, et al. Survival of dialysis patients after cardiac arrest and the impact of cardioverter defibrillators. Kidney Int 2005; 68:818–25.
22. Goldenberg I, Moss AJ, McNitt S, et al. Inverse relationship of blood pressure levels to sudden cardiac mortality and benefit of the implantable cardioverter-defibrillator in patients with ischemic left ventricular dysfunction. J Am Coll Cardiol 2007;49(13): 1427–33.
23. Johnson JN, Tester DJ, Perry J, et al. Prevalence of early-onset atrial fibrillation in congenital long QT syndrome. Heart Rhythm 2008;5:704–9.
24. Babai Bigi MA, Aslani A, Shahrzad S. Clinical predictors of atrial fibrillation in Brugada syndrome. Europace 2007;9:947–50.
25. Francis J, Antzelevich C. Atrial fibrillation and Brugada syndrome. J Am Coll Cardiol 2008;51:1149–53.
26. Sacher F, Probst V, Iesaka Y, et al. Outcome after implantation of a cardioverter-defibrillator in patients with Brugada syndrome: a multi-centre study. Circulation 2006;114(22):2317–24.
27. Park DW, Nam GB, Rhee KS, et al. Clinical characteristics of Brugada syndrome in a Korean population. J Am Coll Cardiol 2002;40:1437–44.
28. Yamada T, Yoshida Y, Tsuboi N, et al. Efficacy of pulmonary vein isolation in paroxysmal atrial fibrillation patients with a Brugada electrocardiogram. Circ J 2008;72(2):281–6.
29. Wyse DG, Love JC, Yao Q, et al. Atrial fibrillation: a risk factor for increased mortality—an AVID registry analysis. J Interv Card Electrophysiol 2001;5: 267–73.
30. Zareba W, Steinberg JS, McNitt S, et al. Implantable cardioverter-defibrillator therapy and risk of congestive heart failure or death in MADIT II patients with atrial fibrillation. Heart Rhythm 2006;3:631–7.
31. Benjamin EJ, Wolf PA, D'Agostino RB, et al. Impact of atrial fibrillation on the risk of death: the Framingham Heart study. Circulation 1998;98:946–52.
32. Dries DL, Exner DV, Gersh BJ, et al. Atrial fibrillation is associated with an increased risk for mortality and heart failure progression in patients with asymptomatic and symptomatic left ventricular systolic

dysfunction: a retrospective analysis of the SOLVD trials. J Am Coll Cardiol 1998;32:695–703.
33. Mathew J, Hunsberger S, Fleg J, et al. Incidence, predictive factors, and prognostic significance of supraventricular tachyarrhythmias in congestive heart failure. Chest 2000;118:914–22.
34. Crijns HJ, Tjeerdsma G, de Kam PJ, et al. Prognostic value of the presence and development of atrial fibrillation in patients with advanced chronic heart failure. Eur Heart J 2000;21:1238–45.
35. Carson PE, Johnson GR, Dunkman WB, et al. The influence of atrial fibrillation on prognosis in mild to moderate heart failure: the V-HeFT studies. Circulation 1993;87(Suppl VI):VI102–10.
36. Klein G, Lissel C, Fuchs AC, et al. Predictors or VT/VF-occurrence in ICD patients: results from the PROFIT-study. Europace 2006;8(8):618–24.
37. Klein RC, Raitt MH, Wilkoff BL, et al. Analysis of implantable cardioverter defibrillator therapy in the Antiarrhythmics Versus Implantable Defibrillators (AVID) trial. J Cardiovasc Electrophysiol 2003;14:940–8.
38. Sweeney MO, Wathen MS, Volosin K, et al. Appropriate and inappropriate ventricular therapies, quality of life, and mortality among primary and secondary prevention implantable cardioverter defibrillator patients: results from the Pacing Fast VT Reduces Shock Therapies (PainFREE Rx II) trial. Circulation 2005;111:2898–905.
39. Daubert JP, Zareba W, Cannom DS, et al. Inappropriate implantable cardioverter-defibrillator shocks in MADIT II: frequency, mechanisms, predictors, and survival impact. J Am Coll Cardiol 2008;51:1357–65.
40. Theuns DAMJ, Klootwijk AP, Simoons ML, et al. Clinical variables predicting inappropriate use of implantable cardioverter-defibrillator in patients with coronary heart disease or nonischemic dilated cardiomyopathy. Am J Cardiol 2005;95:271–4.
41. Alter P, Waldhans S, Plachta E, et al. Complications of implantable cardioverter defibrillator therapy in 440 consecutive patients. Pacing Clin Electrophysiol 2005;28:926–32.
42. Wilkoff BL, Hess M, Young J, et al. Differences in tachyarrhythmia detection and implantable cardioverter defibrillator therapy by primary or secondary prevention indication in cardiac resynchronization therapy patients. J Cardiovasc Electrophysiol 2004;15:1002–9.
43. Larsen G, Hallstrom A, McAnulty J, et al. Cost-effectiveness of the implantable cardioverter-defibrillator versus antiarrhythmic drugs in survivors of serious ventricular arrhythmias: results of the Antiarrhythmics Versus Implantable Defibrillators (AVID) economic analysis study. Circulation 2002;105(17):2049–57.
44. Mark DB, Anstrom KJ, Sun JL, et al. Quality of Life with Defibrillator Therapy or Amiodarone in Heart Failure. N Eng J Med 2008;359:999–1008.
45. Schron EB, Exner DV, Yao Q, et al. Quality of life in the Antiarrhythmics Versus Implantable Defibrillators trial: impact of therapy and influence of adverse symptoms and defibrillator shocks. Circulation 2002;105(5):589–94.
46. Poole JE, Johnson GW, Hellkamp AS, et al. Prognostic importance of defibrillator shocks in patients with heart failure. N Eng J Med 2008;359:1009–17.
47. Theuns DAMJ, Klootwijk AP, Goedhart DM, et al. Prevention of inappropriate therapy in implantable cardioverter-defibrillators: results of a prospective, randomized study of tachyarrhythmia detection algorithms. J Am Coll Cardiol 2004;44:2362–7.
48. Theuns DAMJ, Rivero-Ayerza M, Boersma E, et al. Prevention of inappropriate therapy in implantable defibrillators: a meta-analysis of clinical trials comparing single-chamber and dual-chamber arrhythmia discrimination algorithms. Int J Cardiol 2008;125:352–7.
49. Swerdlow CD, Cannom DS. Supraventricular tachycardia–ventricular tachycardia discrimination algorithms in implantable cardioverter defibrillators: state-of-the-art review. J Cardiovasc Electrophysiol 2001;12:606–12.
50. Friedman PA, McClelland RL, Bamlet WR, et al. Dual-chamber versus single-chamber detection enhancements for implantable defibrillator rhythm diagnosis: the Detect Supraventricular Tachycardia study. Circulation 2006;112(25):2871–9.
51. Wilkoff BL, Williamson BD, Stern RS, et al. Strategic programming of detection and therapy parameters in implantable cardioverter-defibrillators reduces shocks in primary prevention patients: results from the PREPARE study. J Am Coll Cardiol 2008;52(7):541–50.
52. Stein K, Hess M, Hannon C, et al. Simultaneous atrial and ventricular tachyarrhythmias in defibrillator recipients: does AF beget VF?. [abstract]. J Am Coll Cardiol 1999;22:115A.
53. Schoenfeld MH, Compton SJ, Mead RH, et al. Remote monitoring of implantable cardioverter defibrillators: a prospective analysis. Pacing Clin Electrophysiol 2004;27:757–63.
54. Khan MN, Jais PJ, Cummings J, et al. Pulmonary-vein isolation for atrial fibrillation in patients with heart failure. NEJM 2008;359:1778–85.
55. Florin TJ, Weiss DN, Peters RW, et al. Induction of atrial fibrillation with low-energy defibrillator shocks in patients with implantable cardioverter defibrillators. Am J Cardiol 1997;80(7):960–2.
56. Jones GK, Johnson G, Troutman C, et al. Incidence of atrial fibrillation following ventricular defibrillation with transvenous lead system in man. J Cardiovasc Electrophysiol 1992;3(5):411–7.
57. Brembilla-Perrot B, Beurrier D, Houriez P, et al. Significance of external cardioversion induced atrial

tachyarrhythmias. Pacing Clin Electrophysiol 2003; 26(11):2111–5.
58. Katz A, Evans JJ, Fogel RI, et al. Atrial fibrillation/flutter induced by implantable ventricular shocks: difference between epicardial and endocardial energy delivery. J Cardiovasc Electrophysiol 1997;8(1):35–41.
59. Rienstra M, Smit MD, Nieuwland W, et al. Persistent atrial fibrillation is associated with appropriate shocks and heart failure in patients with left ventricular dysfunction treated with an implantable cardioverter defibrillator. Am Heart J 2007;153:120–6.
60. Stein KM, Euler DE, Meher R, et al. Do atrial tachyarrhythmias beget ventricular tachyarrhythmias in defibrillator patients? J Am Coll Cardiol 2002;40(2): 335–40.
61. Gronefeld GC, Mauss O, Li YG, et al. Association between atrial fibrillation and appropriate implantable cardioverter defibrillator therapy: results from a prospective study. J Cardiovasc Electrophysiol 2000;11(11):1208–14.
62. Padeletti L, Muto C, Maounis T, et al. Atrial fibrillation in recipients of cardiac resynchronization therapy devices: 1-year results of the randomized MASCOT trial. Am Heart J 2008;156(3):520–6.
63. Bollmann A, Husser D, Cannom DS. Antiarrhythmic drugs in patients with implantable cardioverter-defibrillators. Am J Cardiovasc Drugs 2005;5(6):371–8.
64. Connolly SJ, Dorian P, Roberts RS, et al. Optimal pharmacological therapy in cardioverter defibrillator patients. I. Comparison of beta-blockers, amiodarone plus beta-blockers, or sotalol for prevention of shocks from implantable cardioverter defibrillators: the OPTIC study: a randomized trial. JAMA 2006; 295:165–71.
65. The CASCADE Investigators. Cardiac arrest in Seattle: conventional versus amiodarone drug evaluation (CASCADE study). Am J Cardiol 1991;67(7):578–84.
66. Pacifico A, Hohnloser SH, Williams JH, et al. Prevention of implantable-defibrillator shocks by treatment with sotalol: d,l-Sotalol Implantable Cardioverter-Defibrillator Study Group. N Engl J Med 1999;340(24): 1855–62.
67. Lee CH, Nam GB, Park HG, et al. Effects of antiarrhythmic drugs on inappropriate shocks in patients with implantable defibrillators. Circ J 2008;72: 102–5.
68. Bhavnani SP, Coleman CI, White CM, et al. Association between statin therapy and reductions in atrial fibrillation or flutter and inappropriate shock therapy. Europace 2008;10:854–9.
69. Page RL. Effects of antiarrhythmic medication on implantable cardioverter-defibrillator function. Am J Cardiol 2000;85:1481–5.
70. Stevens SK, Haffajee CI, Naccarelli GV, et al. Effects of oral propafenone on defibrillation and pacing thresholds in patients receiving implantable cardioverter-defibrillators. Propafenone Defibrillation Threshold Investigators. J Am Coll Cardiol 1996; 28(2):418–22.
71. Hohnloser SH, Dorian P, Roberts R, et al. Effect of amiodarone and sotalol on ventricular defibrillation threshold: the Optimal Pharmacological Therapy in Cardioverter Defibrillator Patients (OPTIC) trial. Circulation 2006;114:104–9.
72. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the European Society of Cardiology Committee for practice guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Atrial Fibrillation) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. J Am Coll Cardiol 2006;48:149–246.
73. Giudici MC, Barold SS, Paul DL, et al. Pacemaker and implantable cardioverter defibrillator implantation without reversal of warfarin therapy. PACE 2004;27:358–60.
74. Michaud GF, Pelosi F, Noble MD, et al. A randomized trial comparing heparin initiation 6 h or 24 h after pacemaker or defibrillator implantation. J Am Coll Cardiol 2000;35(7):1915–8.
75. Gasparini M, Auricchio A, Regoli F, et al. Four-year efficacy of cardiac resynchronization therapy on exercise tolerance and disease progression: the importance of performing atrioventricular junction ablation in patients with atrial fibrillation. J Am Coll Cardiol 2006;48:734–43.
76. Levine PA. Effect of cardioversion and defibrillation on implanted cardiac pacemakers. In: Barold SS, editor. Modern cardiac pacing. Mount Kisco (NY): Futura Publ. Co; 1985. p. 875–86.
77. Manegold JC, Israel CW, Ehrlich JR, et al. External cardioversion of atrial fibrillation in patients with implanted pacemaker or cardioverter-defibrillator systems: a randomized comparison of monophasic and biphasic shock energy application. Eur Heart J 2007;28:1731–8.
78. Gradaus R, Seidl K, Korte T, et al. Reduction of ventricular tachyarrhythmia by treatment of atrial fibrillation in ICD patients with dual-chamber implantable cardioverter/defibrillators capable of atrial therapy delivery: the REVERT-AF study. Europace 2007; 9(7):534–9.
79. Geller JC, Reek S, Timmermans C, et al. Treatment of atrial fibrillation with an implantable atrial defibrillator—long term results. Eur Heart J 2003;24:2083–9.
80. Levy S, Ricard P, Lau CP, et al. Multicenter low energy transvenous atrial defibrillation (XAD) trial results in different subsets of atrial fibrillation. J Am Coll Cardiol 1997;29(4):750–5.
81. Dosdall DJ, Ideker RE. Intracardiac atrial defibrillation. Heart Rhythm 2007;4:S51–56.