Arrhythmias in Cardiomyopathy

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Introduction

The morbidity and mortality of patients with most types of cardiomyopathy are related to either pump failure with end-organ dysfunction or arrhythmia-induced death or decompensation. While arrhythmia can complicate the course of a cardiomyopathy with subsequent increase in mortality and morbidity, cardiomyopathy can either be exacerbated or induced by arrhythmias. It can be challenging to quantify the effect of an arrhythmia on left ventricular function or cardiac output or how much the ventricular function will ameliorate after treating an arrhythmia. In our experience, there is usually a component of both a baseline cardiomyopathy and some exacerbation of variable scale caused by the arrhythmia. Treating both ends of this vicious cycle is essential in providing the best chances of recovery. Hence, adequate and prompt therapy of arrhythmias in patients with cardiomyopathy needs to be an essential and initial part in the multidisciplinary approach to these patients.

In this chapter, we are going to review the arrhythmias seen in patients with multiple types of cardiomyopathy and the therapeutic options available. While it is challenging to cover all the cardiomyopathies exhaustively, we are going to discuss the most common and compelling cardiomyopathies known to have a strong association with arrhythmias, while excluding the lone arrhythmic disorders seen without structural heart disease.

Atrial Tachyarrhythmias in Cardiomyopathy

It is well known that atrial arrhythmias often complicate the treatment of patients with cardiomyopathy and heart failure. It is often difficult to determine in a given clinical scenario whether the arrhythmia is the result or the cause of the cardiomyopathy, the classic "chicken or the egg" conundrum. We will first examine the role of atrial arrhythmias complicating or exacerbating cardiomyopathy before turning to an examination of arrhythmia as a cause of cardiomyopathy, the so-called arrhythmia-induced cardiomyopathy (AIC).

Atrial arrhythmias can exacerbate both systolic heart failure or "*h*eart *f*ailure with *r*educed *e*jection *f*raction" (HFrEF) and "*h*eart *f*ailure with *p*reserved *e*jection *f*raction" (HFpEF). We will primarily discuss atrial fibrillation (AF). While less frequent than AF, atrial flutter (AFL), atrial tachycardia (AT), and reentrant supraventricular tachycardia (SVT) may all decompensate or cause a cardiomyopathy.

Atrial Arrhythmias Complicating Treatment of Cardiomyopathy

It can be difficult to determine the primary abnormality in a patient presenting with both an atrial arrhythmia and left ventricular (LV) dysfunction. Even in patients with a previous diagnosis of cardiomyopathy, atrial arrhythmias may result in further deterioration of LV systolic function. In these patients, both atrial arrhythmias and cardiomyopathy must be treated simultaneously.

The ATRIA study found HF to be a more powerful predictor of AF than age, valvular heart disease, hypertension, diabetes, or prior myocardial infarction [1]. There is a direct correlation between the New York Heart Association (NYHA) functional class and the risk of AF [2]. The onset of atrial fibrillation complicates the management of HF and increases the risk of hospital admission for decompensation. Yamada and colleagues found that 20–35 % of patients admitted for decompensated HF were in AF. Of the patients, AF was new in onset in one-third [3].

Atrial Fibrillation and the Risk of Sudden Cardiac Arrest (SCA)

Atrial fibrillation is associated with an increased risk of SCA in a variety of populations [4]. Whether the risk of SCA associated with AF is due to a direct proarrhythmic effect with regard to ventricular arrhythmias or indirectly by worsening HF remains unsettled. If AF is in itself proarrhythmic, this would suggest that therapies to prevent AF (i.e., rhythm-control strategy) might be successful in lowering the risk of SCA. There is evidence to suggest that AF may be proarrhythmic with regard to ventricular arrhythmias. First, the rapid heart rates associated with AF result in a shortening of ventricular refractoriness [5]. Somberg and coauthors reported that programmed stimulation resulted in the induction of ventricular tachycardia in 25 of 26 dogs only during AF but not when the stimulation was performed during sinus rhythm [6]. Finally, the irregular pattern of ventricular activation that occurs with AF increases the risk of "short-long-short" sequences known to be proarrhythmic [7]. In fact, the study by Gronefeld et al. demonstrated that patients with AF had a higher incidence of short-long-short preceding ventricular arrhythmias as compared to patients with sinus rhythm (50 % vs. 16 %, $P = 0.002$) [8].

Atrial Fibrillation Complicating Device Therapy for Heart Failure

A significant number of cardiomyopathy patients will undergo placement of an implantable cardioverter defibrillator (ICD) for either primary or secondary prevention of sudden cardiac arrest (SCA). Studies have shown that patients with AF at the time of ICD placement have a higher rate of inappropriate ICD therapy, appropriate ICD therapy, as well as increased mortality [9, 10]. Aggressive efforts to control the heart rate during AF could conceivably reduce the risk of inappropriate shocks, but it is less clear what effect a heart rate-control strategy would have on mortality or appropriate ICD therapy. However, there is a paucity of data to suggest a rhythm-control strategy is more effective in this regard than a rate-control strategy.

Cardiac resynchronization therapy (CRT) improves symptoms and mortality in patients with HF, beyond the survival improvement seen with ICD therapy alone. There is conflicting data regarding the effects of AF on the efficacy of CRT. Khadjooi and colleagues reported on 295 consecutive NYHA Class III–IV HF patients and AF receiving CRT in a prospective observational study [11]. They found that patients with AF had similar improvement in symptoms, prognosis, and echocardiographic measures of remodeling as did patients in sinus rhythm. It should be noted that although patients in sinus rhythm had a higher percentage of biventricular pacing, the AF patients had a percentage of biventricular pacing of >87%. Linde and MUSTIC investigators reported similar degrees of response to CRT in patients with AF compared to those in sinus rhythm [12]. However, the average heart rate between the two groups at baseline was similar, 75 ± 13 beats per minute (bpm) in the patients in sinus rhythm versus 74 ± 5 for those in AF. Leclercq et al., on behalf of the MUSTIC investigators, reported on CRT in patients with permanent AF [13]. Again, the AF patients in this study had slow ventricular rates that require device placement.

Other investigators reported that patients with AF did not respond as well to CRT. A multicenter prospective observational study, the Cardiac Resynchronization Therapy in Atrial Fibrillation Patients Multinational Registry (CERTIFY), followed 7384 consecutive CRT patients for a median of 37 months. The largest group, 6046 patients, had sinus rhythm. There were 895 patients with AF rate controlled using drug therapy and 443 patients with AF and atrioventricular junction ablation. Patients treated with heart rate-slowing drugs had higher total and cardiac mortality [14]. Given the lack of a control group, the investigators could not comment on the proportional improvement with CRT in each group or determine if, despite poorer outcomes, the AF plus rate control with drug group had a benefit from CRT.

Atrial Flutter and Atrial Tachycardia in Heart Failure

Although AF is the most common arrhythmia seen with HF, atrial flutter (AFL) and atrial tachycardia (AT) are not infrequent. AFL can be difficult to control with antiarrhythmic drugs. Rate control in AFL and AT is also frequently difficult. Ablation of AFL is highly efficacious with a low risk of major complications. Ablation should be considered a first-line therapy for HF patients with either symptomatic AFL or when there is suspicion that AFL is causing a further reduction in systolic function.

There is little data to guide management decisions regarding treatment of AT in cardiomyopathy patients. In selected patients treatment with antiarrhythmic drugs may be successful, although the only approved drugs available for use in this setting are amiodarone or dofetilide [15]. Ablation for AT is also reasonable as a first-line therapy and in patients in whom drug therapy was either unsuccessful or not tolerated.

Arrhythmia-Induced Cardiomyopathy (AIC) and Treatment

Atrial arrhythmias are well known to lead to decompensation of patients with cardiomyopathy. What is less well appreciated is that atrial arrhythmias may in fact be the cause of the cardiomyopathy. This has been referred to as *arrhythmia-induced cardiomyopathy* (AIC). Arrhythmia-induced cardiomyopathy can be induced by ventricular arrhythmias as well as atrial arrhythmias [16].

Atrial Fibrillation as a Cause of AIC

Atrial fibrillation is the most common cause of AIC in adults. In patients with HFrEF, AF may result in a component of AIC. In other patients AF is the cause of the cardiomyopathy. This distinction is not always a simple matter. If the patient has a known underlying cardiomyopathy prior to presenting with AF, the AF is most likely a contributing factor.

However, in a patient who presents with a new dilated cardiomyopathy *and* new AF, the possibility that the AF is the cause of the cardiomyopathy should not be discounted. As in AF patients in general, there continues to be a debate with regard to whether a rate-control or rhythm-control strategy is superior. In patients perceived to have AIC due to AF, there is the added concern that AIC may not be caused by elevated heart rate alone. Other factors such as irregularity of ventricular activation, exacerbation of diastolic failure via loss of active atrial contraction, and worsening of mitral regurgitation may all play a role as well.

The studies reviewed above have demonstrated that ablation therapy for AF in HF is feasible. Most also demonstrate that successful ablation therapy is associated with an improvement in heart function [17–20]. In high-volume centers, with acceptable rates of serious complications, ablation therapy for AF-associated AIC should be considered, especially if the rhythm is not well controlled with antiarrhythmic drug therapy. The data is less clear that this approach is superior to AVJA and CRT pacing. In our practice the approach to treatment of AF in the setting of AIC is highly individualized, taking into account patients' wishes and their overall functional status and comorbidities. It is our practice to, at the least, consider ablation therapy as an option in these patients. In general, unless the patient declines or due to comorbidities there is no reasonable choice of an antiarrhythmic drug, pharmacologic control of the AF is attempted first.

Atrial Flutter as a Cause of AIC

As discussed earlier, AFL is more difficult to rate control. Ablation therapy for AFL is highly efficacious and of low risk. In patients felt to have AIC due to AFL, ablation of the arrhythmia is the treatment of choice.

Supraventricular Tachycardia (SVT) as a Cause of AIC

Ablation therapy is the treatment of choice for any patient with symptomatic reentrant supraventricular tachycardias (atrioventricular nodal reentrant tachycardia or accessory pathway-mediated tachycardias); this is especially true in patients suspected of AIC due to SVT.

Atrial Tachycardia as a Cause of AIC

As with AF, the approach is highly individualized in a given patient. Ablation therapy being the first choice is very dependent on patient preference. In our experience, younger patients, or patients who are not on any prescription medications, tend to gravitated toward an ablation approach.

Management of Atrial Arrhythmias in Cardiomyopathy

Rate Control Versus Rhythm Control in Cardiomyopathy

In 2014 the American Heart Association, the American College of Cardiology, and the Heart Rhythm Society published guidelines for the management of AF [15]. In regard to patients with HF who develop AF, they conclude that "a rhythm control strategy is not superior to a rate control strategy." In reaching this conclusion, the authors reference the work of Roy and colleagues [21]. This randomized multicenter trial compared a rhythm-control strategy versus a rate-control strategy in patients with HF. They followed 1376 patients for a mean of 37 months, 682 patients in the rhythm-control arm and 694 patients in the rate-control arm. There was no statistical difference in cardiovascular death, all-cause death, stroke, or worsening HF between the two arms on an intention-to-treat basis. Ten percent of the rate-control patients crossed over to the rhythm-control strategy due to worsening HF. A higher percentage, 21 %, crossed over from the rhythm-control to the rate-control arm due to an inability to maintain sinus rhythm. Rhythm control was achieved using pharmacologic agents. As with previous studies comparing rhythm- versus rate-control strategies, the adequacy of control of AF is an issue. Fifty-eight percent of the rhythm-control patients had at least one episode of AF during follow-up. The prevalence rate of AF at 4 years of follow-up in the rhythm-control arm was 27 % as compared to prevalence rates of 59–70 % in the rate-control arm [21].

Other studies, however, have demonstrated the benefit of a rhythm-control strategy. The CAFÉ-II trial randomized 61 patients to either rhythm control with amiodarone versus rate control in patients with symptomatic persistent AF and HF [22]. In this study a rhythm-control strategy resulted in significantly more improvement in left ventricular function, quality of life, and N-terminal pro-B-type natriuretic peptide levels when compared to a rate-control strategy.

Moreover, studies have compared atrioventricular junctional ablation (AVJA) versus rate control with drugs, AVHJA versus catheter ablation of AF, as well as catheter ablation of AF versus control patients in the setting of HF. In 2004, Hsu and colleagues reported on a series of 58 consecutive patients with persistent AF and HF treated with catheter ablation compared to 58 matched control patients with persistent AF without HF who underwent ablation therapy [17]. The study showed that ablation therapy for AF in HF patients was feasible and was as likely to be successful compared to patients without HF. They also found that HF patients had significant improvement in left ventricular function, improvement in symptoms, exercise capacity, and quality of life.

Khan et al. compared catheter ablation of AF to AVJA and cardiac resynchronization therapy (CRT) in a multicenter randomized trial [19]. Ablation therapy was found to be superior to AVJA and CRT in patients with drug-resistant persistent AF.

CAMTAF was a single-center, randomized, non-blinded study. The patients in this trial had persistent AF [18]. Twenty-six patients were randomized to ablation therapy and 24 to the rate-control arm. Strict HR control (resting HR < 80 bpm and moderate exercise HR < 110 bpm) was required in the rate-control arm. Freedom from AF after a single ablation procedure was achieved in 10 of 26 patients (38 %). Twenty-one of 26 patients (81 %) were free from AF 6 months after the last ablation therapy. At 1 year 19 of 26 patients (73 %) remained AF free. There were two serious complications (stroke, tamponade) in the ablation arm for a 7.7 % risk of major complication *per patient* or 4.7 % *per procedure*. At 6 months the patients in the ablation arm showed better improvement in ejection fraction, functional capacity, and HF symptoms.

A recent review by Ganesan and colleagues looked at the results of ablation therapy for AF in patients with left ventricular (LV) systolic dysfunction [20]. They identified 19 studies totaling 914 patients with LV systolic dysfunction who underwent ablation therapy for AF. The single procedure success rate was 57 %. The overall success rate (multiple procedures and use of antiarrhythmic drugs) was 82 %. The mean improvement in ejection fraction was 13 %. Seven of the studies demonstrated improvements in exercise capacity and quality of life as well.

In the most recent 2014 guidelines, catheter ablation was considered as "reasonable to treat symptomatic AF in selected patients with significant LV dysfunction and HF." Indications for ablation therapy of AF are given in these guidelines but not specifically for patients with HF.

Concern has been expressed that many of the studies cited may suffer from patient selection bias. The results of the Ablation vs. Amiodarone for Treatment of Atrial Fibrillation in Patients with Congestive Heart Failure and an Implanted ICD/CRT-D (AATAC-AF) should be available soon and may help better define this issue (ClinicalTrials.gov Identifier: NCT00729911).

Summary of Treatment Options for Atrial Arrhythmias in Cardiomyopathy

The following approaches are largely based on the 2014 AF guidelines but include minor modifications based upon the authors' own clinical practice [15].

Treatment of Cardiomyopathy/HF

- All patients should be on guideline-based therapy for their cardiomyopathy.

Prevention of Thromboembolic Complications

- The CHA_2DS_2-VASc score should be used to assess the risk of thromboembolic complications, except in patients with valvular AF or patients with HCM.
- With regard to thromboembolic risk, AFL patients are treated the same as AF patients.
- In patients with nonvalvular AF, the newer novel oral anticoagulants should be considered.

Rate Control of AF in Cardiomyopathy Patients

- In patients with HFrEF beta-adrenergic receptor blockers should be used for heart rate control.
- Digoxin, in combination with a beta-blocker, can be helpful, especially in patients with decompensated HF. There continues to be concern that the use of digoxin in AF patients may be associated with increased mortality. If digoxin is used, the serum level should be monitored and kept ≤0.9 ng/ml [23].
- In patients with HFpEF or HCM, non-dihydropyridine calcium channel antagonists are reasonable rate-control agents. Their long-term use should be avoided in patients with HFrEF.
- Intravenous amiodarone is reasonable for heart-rate control when other agents have been unsuccessful or contraindicated.
- Atrioventricular junction ablation for heart-rate control is reasonable. However, the current guidelines state this should only be considered in patients in whom the heart rate could not be controlled with drugs. We recommend attempting a rhythm-control approach before pursuing AVN ablation. In patients with reduced EF, CRT pacing either via a pacing system or ICD should be considered *unless* the cardiomyopathy is felt to be arrhythmia induced.
- It should not be forgotten that, when feasible, a rhythm-control strategy (including ablation therapy of AF) also controls the heart rate.

Rhythm Control of AF in Cardiomyopathy

- In the absence of clearly demonstrable superiority of either rate-control or rhythm-control strategy, patient preference, comorbidities, and goals need to be carefully considered.
- Before embarking on a rhythm-control strategy, any precipitating factors, including HF, should be treated.
- In patients with HFrEF only amiodarone and dofetilide are considered acceptable antiarrhythmic drug choices.
- In patients with ischemic cardiomyopathy but without HF, dronedarone and sotalol are also reasonable.
- In patients with HCM, amiodarone or disopyramide is considered the drug of choice.
- Ablation therapy for AF should be considered for symptomatic patients who do not tolerate antiarrhythmic drug therapy or in whom drug therapy for rhythm control has failed. This is an area of ongoing investigation in which clinical practice patterns may be expected to continue to evolve.

Summary of Treatment Options in Adults with AIC

- Patients with AIC should receive standard guideline-based treatment for LV systolic dysfunction. Whether to continue HF-based therapy after resolution of AIC is a question that remains unresolved.
- Patients with AF or AFL should be treated with oral anticoagulation based on their CHA_2DS_2-VASc score.
- In patients with AIC secondary to AFL or SVT, except in rare circumstances, ablation therapy is the preferred approach.
- In patients with AIC secondary to AF, the superiority of rate control versus rhythm control remains a topic of debate. What is clear is that a lenient approach to heart rate control in AIC is inappropriate. Current guideline recommendations indicate that AVJA should only be done after an attempt at rate control with drugs [15]. There appears to be increasing evidence that rhythm control through ablation therapy may have advantages over both rate-control and pharmacologic rhythm-control strategies. This remains controversial, and clinical practices continue to evolve rapidly.
- In patients with AIC secondary to AT, arrhythmia control with an antiarrhythmic drug and ablation are both reasonable, depending on the individual patient and circumstances.

While it may seem obvious, nonetheless it is important to emphasize that in a patient with AIC, control of the arrhythmia, by the most appropriate means in a given circumstance, is of paramount importance.

Ventricular Tachyarrhythmias in Cardiomyopathy

Premature Ventricular Complexes

Premature ventricular complexes (PVC) are the most common arrhythmia in patients with normal heart function and are often considered benign without structural heart disease. However, in the presence of cardiomyopathy, their prognostic

value becomes dependent on the presence and extent of underlying structural disease in patients with cardiomyopathy [24, 25]. While the presence and decompensation of a cardiomyopathy can cause an increase in PVCs and while most patients with frequent PVCs will not develop cardiomyopathy, frequent PVCs or idiopathic ventricular tachycardia can induce or exacerbate a cardiomyopathy [26]. A PVC can also interfere with cardiac resynchronization therapy and decrease its efficacy.

PVC-Induced Cardiomyopathy

Frequent PVCs can induce a cardiomyopathy in patients without structural heart disease and can exacerbate cardiomyopathy in patients with baseline structural disease [27–29]. This relationship has been confirmed on the basis of reversal of the cardiomyopathy with suppression of the PVCs [30, 31]. The mechanism of PVC-mediated cardiomyopathy is not fully understood. Potential mechanisms include ventricular dyssynchrony, abnormal ventricular filling from the post-PVC pause, and abnormal calcium handling from the short or variable coupling intervals.

The most prominent predictor of cardiomyopathy appears to be a high PVC burden, variably defined as ranging from >10,000 to 25,000 PVCs/day and as >10–24 % of total heartbeats/day [26, 32]. The most accepted cutoff in the 2014 EHRA/HRS/APHRS Expert Consensus on Ventricular Arrhythmias is 10,000 PVCs/day [33]. Decreasing the PVC burden to <5000/day can improve ventricular function [30]. This threshold is helpful when elimination of all PVCs may not be possible in the setting of multiform PVCs. Other PVC characteristics including male sex, increased body mass index, higher PVC coupling interval dispersion, and interpolated PVCs have not been reproducible in all studies.

Therapy for PVC-induced cardiomyopathy should be targeted at suppressing or eliminating the PVCs. It includes antiarrhythmic therapy and catheter ablation. Beta-blockers are frequently considered as first-line therapy because of the low side effect profile, but have limited effectiveness. Dofetilide, mexiletine, sotalol, or amiodarone may be more effective, but with the greater risk of side effects and proarrhythmia. Medical therapy is reserved for patients who fail or are reluctant to undergo catheter ablation.

Catheter ablation has become as the definitive and first-line therapy for PVC-mediated AIC, with success rates ranging from 70 to 90 % [27]. The much better efficacy of ablation therapy over medical therapy is proven in a recent randomized trial [34]. The elimination of a high PVC burden (>10 % or 10,000 PVCs/24 h) in patients with impaired LVEF can be associated with improvement of function, even when structural cardiac abnormalities are present [35].

PVCs Interfering with Cardiac Resynchronization Therapy (CRT)

A high biventricular pacing percentage above 95–98 % of all ventricular beats was associated with a significant reduction in mortality [36]. Frequent PVCs in patients with CRT pacemakers and defibrillators can interfere with biventricular pacing and decrease it below 95 %. Successful ablation of PVCs can improve the efficacy of cardiac resynchronization therapy in nonresponders [37]. In this patient population, a pre-ablation PVC burden of >22 % was associated with a significant improvement in LV function.

Ventricular Tachycardia

Ischemic heart disease is the most common cause of sustained ventricular tachyarrhythmias. In particular, polymorphic ventricular tachycardias (VTs) leading to ventricular fibrillation (VF), or primary VF itself (. Fig. 19.1) due to acute coronary ischemia, are probably the most common causes of sudden cardiac death (SCD). Approximately 20 % of patients with a primary prevention ICD and 45 % of patients with secondary prevention ICD receive an appropriate ICD intervention within the first 2 years following ICD implantation. Additionally, VT storm, defined as 3 or more VT episodes within a 24 h period, may affect 4 % and 20 % of primary and secondary prevention patients, respectively. Moreover, ICD shocks and even appropriate ATP has been linked to increased mortality in this population.

Apart from acute ischemia, ventricular tachyarrhythmias may also occur as a result of structural heart disease that causes localized disturbances of electrical activation in the myocardium or conduction system. In severe disease, left ventricular function may be markedly impaired resulting in an ischemic cardiomyopathy.

The most common structural disturbance leading to tachyarrhythmia susceptibility is scar remaining after a prior myocardial infarction due to obstructive coronary artery disease. However, ventricular scars leading to reentrant VT also occur in nonischemic cardiomyopathies, including idiopathic dilated cardiomyopathy, hypertrophic cardiomyopathy, infiltrative heart disease (e.g., sarcoidosis), right ventricular dysplasia (also now known as right ventricular cardiomyopathy), and postrepair of congenital heart disease or valvular heart disease.

Reentry involving the regions of myocardial scar noted above is the basis for most instances of sustained monomorphic VT in patients with structural heart disease. In such cases, the scar zone contains viable fibers that provide for the slow conduction that is a necessary requirement for sustained reentry. These slow conduction zones and sometimes the coexisting conduction pathways sustaining the arrhythmia can be identified by "electro-anatomic mapping" in the electrophysiology laboratory and subsequently modified by radiofrequency ablation to diminish VT susceptibility.

Bundle branch reentry is an important but less common form of reentry mostly seen in nonischemic dilated cardiomyopathy, but can be occasionally seen in ischemic cardiomyopathy. Typically, bundle branch reentry (■ Fig. 19.2) occurs in the setting of severe cardiomyopathy in which there is usually a combination of both conduction system disease and marked ventricular dilatation. The reentry in these cases uses the bun-

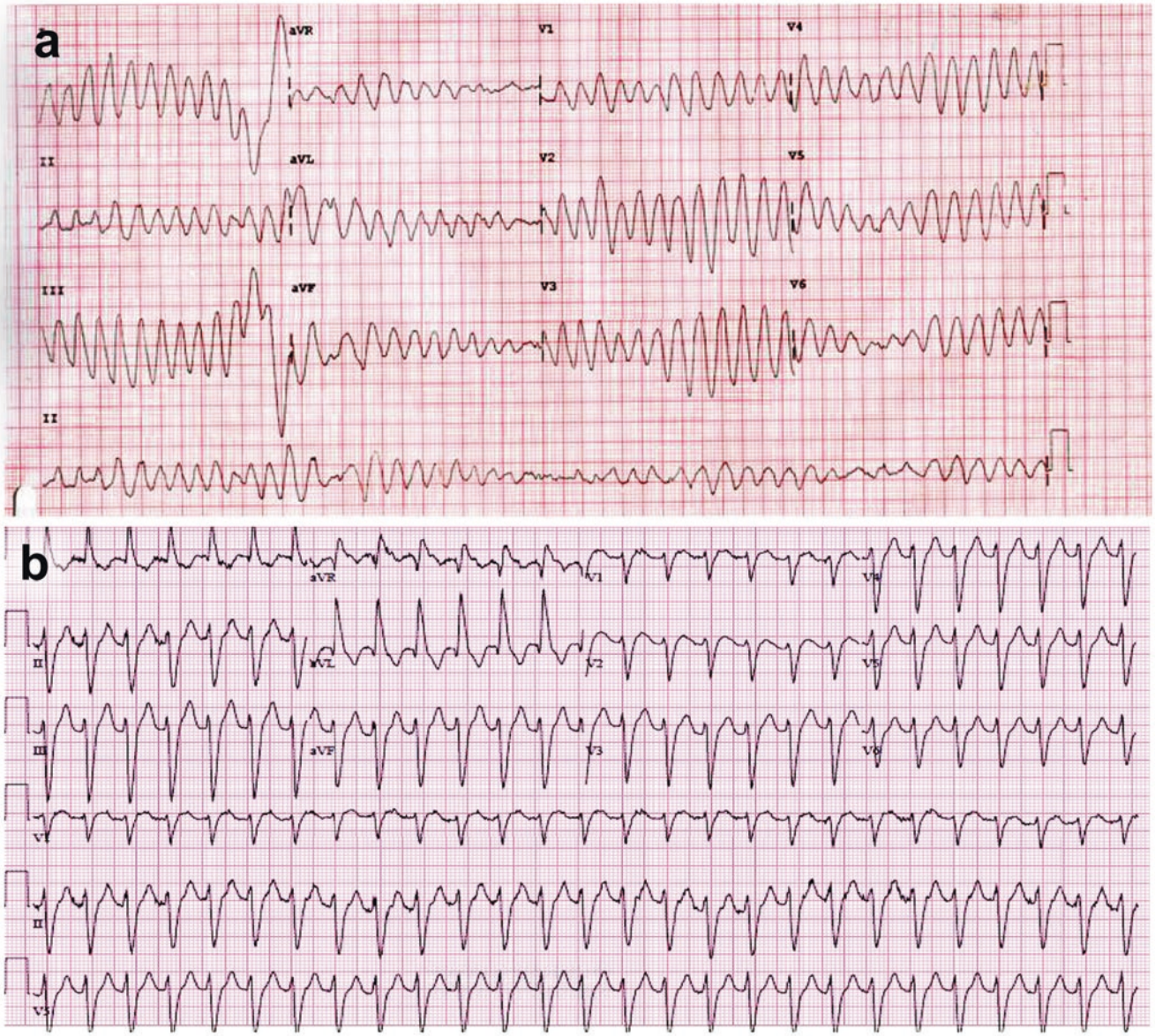

Fig. 19.1 (**a**) ECG exhibiting polymorphous VT that was determined to be torsades de pointes, (**b**) ECG showing sustained scar-related monomorphic VT. *ECG* electrocardiogram, *VT* ventricular tachycardia

dle branches. Most often anterograde ventricular activation occurs over the right bundle branch, with retrograde conduction back over the usually diseased left-sided conduction system. The conduction system disease in conjunction with a dilated ventricle allows for the necessary electrical circuit size that permits sustained reentry. Recognition of this arrhythmia is important because it is amenable to catheter ablation therapy by transecting the bundle branches (usually the right bundle as it is a more discrete target) [38, 39].

Management of VT includes antiarrhythmic therapy and ablation therapy. In the era of defibrillators, VT manifests the most with ICD shocks. Patients who present with an ICD shock should be first evaluated to rule out obvious reversible causes: electrolyte abnormalities, device interrogation to make sure it is an appropriate shock, decomposition of heart failure, ischemic workup especially in patients with ischemic cardiomyopathy, and polymorphic VT. It should be mentioned that ischemia can manifest with monomorphic VT, challenging the old dogma just mentioned. Moreover, beta-blocker therapy needs to be optimized. Once a reversible cause is ruled out and/or treated, medical antiarrhythmic therapy is usually the first-line therapy and needs to be tailored to the type of cardiomyopathy. Antiarrhythmic therapy is detailed in a separate section. Of note, if a patient presents with a single ICD shock with no recurrence, it is reasonable to defer therapy until a significant recurrence since VT burden tends to sometimes wax and wane without intervention.

Ablation therapy for VT related to cardiomyopathy is slowly gaining momentum and is currently considered in patients with recurrent VT resistant to antiarrhythmic medical therapy [40]. Although the occurrence of VT increases mortality in patients with structural heart disease, there is

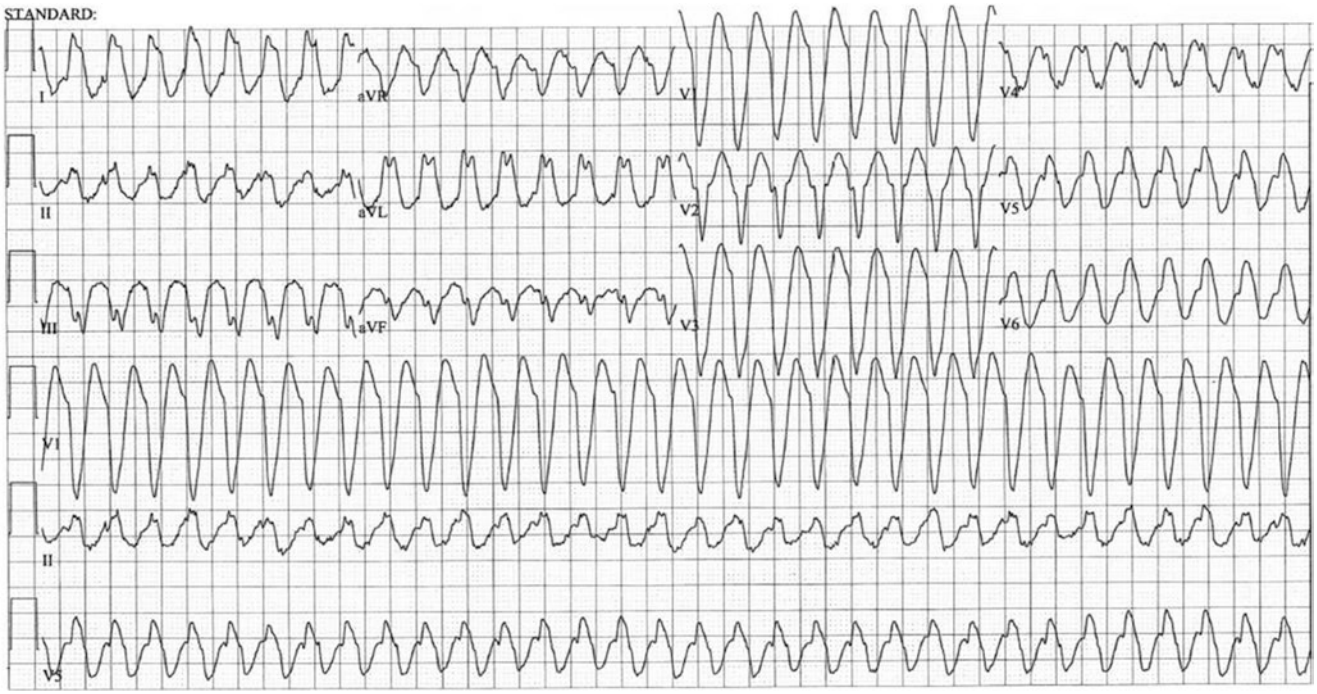

Fig. 19.2 ECG showing bundle branch reentry VT in a patient with conduction system disease. *VT* ventricular tachycardia

still debate whether VT suppression, especially with VT ablation, affects mortality.

There are two main approaches to VT ablation with ramifications of each. The first is based on activation mapping, which includes inducing the clinical VT and using 3D and conventional mapping techniques to define the circuit and ablate the area responsible for sustaining the tachycardia. This is limited by the fact that only about 10 % of the VTs are hemodynamically stable enough to have time for mapping while in VT. The percentage of VTs amenable to this approach increased with the advent of hemodynamic support such as an intra-aortic balloon pump, the CARDIOHELP system (Maquet Cardiopulmonary AG, Hirrlingen, Germany), and IMPELLA (Abiomed, Danvers, MA). This method is limited by the potential vascular complications with hemodynamic support and the potential of stunning the myocardium with subsequent severe decompensation of heart failure from prolonged times in VT during the ablation. The second method consists of substrate modification, with the advantage of performing ablation in sinus rhythm without prolonged time in VT. The goal is to homogenize the scarred area in order to eliminate potential slow conduction channels responsible for sustaining VT. There are a multitude of approaches within substrate modification, which is out of the scope of this chapter. Overall, most operators use a hybrid approach between the two methods that permits targeting of the clinical VT and prevents future potential circuits.

We will review the efficacy of VT ablation with each of the most common clinical scenarios.

Ablation Therapy for VT in Ischemic Cardiomyopathy (ICM)

Two main relatively large prospective randomized clinical trials examine the outcomes after VT ablation in patients with ICM [41, 42].

SMASH-VT included 128 patients with recently implanted ICDs for secondary prevention and with primary prevention ICDs who had received a single appropriate therapy [41]. Freedom from recurrent VT/VF resulting in appropriate ICD therapy after 2 years of follow-up was significantly higher in the ablation arm (88 % versus 67 %; HR 0.35; 95 % CI 0.15–0.78; $P = 0.007$) compared with controls.

The second landmark trial was the Ventricular Tachycardia Ablation in Coronary Heart Disease (VTACH) study that enrolled 110 patients with hemodynamically stable VT, prior MI, and reduced left ventricular ejection fraction (LVEF), who were randomly assigned to catheter ablation and ICD versus ICD alone [42]. After 2 years, the ablation arm had less VT/VF (47 % versus 29 %; HR 0.61; 95 % CI 0.37–0.99; $P = 0.045$) and fewer appropriate ICD shocks per patient year (mean 0.6 ± 2.1 versus 3.4 ± 9.2 shocks; $P = 0.018$).

There are a multitude of retrospective studies with various success rates and effects on mortality. The main limitation is the largely heterogeneous ablation techniques adopted. There are two ongoing VT ablation studies for ICM patients, the VANISH and BERLIN trials, that will also study mortality [43, 44]. Two other trials, STAR-VT and PARTITA, will include both ICM and NICM patients [45, 46].

Ablation Therapy for VT in Nonischemic Cardiomyopathy (NICM)

Unlike ICM, where the underlying substrate is relatively well defined based on the affected coronary artery, patients with NICM have heterogeneous substrates that include different degrees of involvement of the mid-myocardium and epicardium, usually in the perivalvular regions.

To date, there are no prospective randomized trials describing outcomes of VT ablation in patients with NICM. In general, patients with NICM have higher rates of acute procedural failure and long-term VT recurrence after ablation therapy compared to patients with ICM. The HELP-VT study was a prospective observational European single-center study that enrolled 63 patients with NICM and 164 patients with ICM treated with VT ablation [47]. VT-free survival rates at 1-year follow-up were 40.5 % for NICM and 57 % for ICM. One large single-center retrospective observational study included 226 patients with NICM treated with VT ablation. The composite endpoint of death, heart transplantation, or hospitalization for VT recurrence at 1 year (after the last ablation) was 31 % [48].

Role of the Implantable Cardioverter Defibrillator

Patients with either ischemic or nonischemic cardiomyopathy have an increased risk of SCD due to ventricular tachyarrhythmias. SCD is also the leading cause of mortality in patients with heart failure (HF) and occurs at a rate six to nine times that seen in the general population.

The Role of Implantable Cardioverter Defibrillator (ICD) Therapy in Cardiomyopathy

In general, a systolic dysfunction worsens (i.e., the left ventricular [LV] ejection fraction becomes lower), and the severity of HF becomes more marked. In LV dysfunction of NYHA Class I and II and moderate III severity, SCD is most often due to VF, and ICD therapy has proved highly effective. However, as LV function deteriorates further (severe NYHA Class III and Class IV), the propensity for bradyarrhythmic deaths increases (particularly pulseless electrical activity). Inasmuch as the most prominent bradyarrhythmias in this setting are associated with pulseless electrical activity (PEA), they are not amenable to ICD therapy. Prevention of the latter scenario requires that both medical therapy to slow deterioration of LV function and ICD therapy to terminate VF events be employed in concert at an early stage of patient care.

Given the worrisome susceptibility to SCD in patients with diminished LV ejection fraction (particularly <35 %) and heart failure, the ICD has emerged as an important life-saving treatment option. Randomized trials have consistently shown that ICD implantation reduces mortality in HF patients with reduced left ventricular function, as well as in patients who have suffered a cardiac arrest [49–51] (Tables 19.1 and 19.2). Further, ICD therapy has always proved superior to antiarrhythmic drug therapy. Two broad categories of patients are candidates for ICD therapy: (a) secondary SCD prevention and (b) primary SCD prevention.

Secondary SCD Prevention

Secondary prevention refers to the prevention of SCD in patients who have survived a prior cardiac arrest or sustained VT. If the initial arrhythmic event was not due to a clearly reversible or temporary cause (such as an electrolyte disturbance, a transient hypoxia due to respiratory failure, or an acute coronary ischemia episode that can be addressed), then there is a high risk (>40 %) of experiencing a recurrent episode of VT or VF in the next 2 years [52]. In such cases, several clinical trials have shown that ICD use results in improved survival compared with antiarrhythmic agents. By way of summarizing these observations, a meta-analysis of secondary prevention trials (*AVID* [Antiarrhythmics Versus Implantable Defibrillators], *CASH* [Cardiac Arrest Study Hamburg], and *CIDS* [Canadian Implantable Defibrillator Study] [51, 53, 54]) demonstrated that ICD use was associated with a 50 % relative risk reduction for arrhythmic death and a 25 % relative risk reduction for all-cause mortality [55] (Table 19.1).

Primary SCD Prevention

Primary SCD prevention refers to the use of ICDs in individuals who are at risk for, but have not yet experienced, an episode of sustained VT, VF, or resuscitated cardiac arrest. Early primary prevention trials focused on patients with ischemic cardiomyopathy (*MADIT-I* [Multicenter Automatic Defibrillator Implantation Trial], *MUSTT* [Multicenter Unsustained Tachycardia Trial], *MADIT-II* [Multicenter Automatic Defibrillator Implantation Trial-II], *CABG-Patch* [Coronary Artery Bypass Graft Patch Trial]) [49, 56–58]. These prospective, randomized, multicenter studies showed benefit of ICD therapy for primary SCD prevention and improved total survival in patients with ischemic cardiomyopathy (Table 19.2). Initial trials of ICD therapy for primary prevention in patients with nonischemic cardiomyopathy (*CAT*, the Cardiomyopathy Trial) and *AMIOVIRT* (amiodarone versus implantable cardioverter defibrillator) showed no survival benefit, but were limited by small sample size [59, 60]. However, subsequent larger trials (*DEFINITE*, Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation, and *SCD-HeFT*, Sudden Cardiac Death in Heart Failure Trial) have extended the evidence of ICD benefit to patients with nonischemic cardiomyopathy and have demonstrated decreased mortality from prophylactic ICD implantation in this patient group [50, 61] (Table 19.2).

Given the high risk of SCD in the early post-myocardial infarction (MI) period (e.g., in the Valsartan in Acute Myocardial Infarction Trial [*VALIANT*], the risk of sudden

Table 19.1 Major randomized clinical ICD trials (secondary prevention)

Study	Year	Inclusion criteria	Patients, *n*	ICD, *n*	Mean follow-up (month)	Main result
AVID [5]	1997	Any of (1) VF, (2) VT with syncope, or (3) VT with severe symptoms and EF ≤ 40 %	1016	507	18	ICD therapy resulted in 31 % RR reduction in mortality (CI 10–52 %), $P = 0.002$
CASH [7]	2000	Cardiac arrest secondary to ventricular arrhythmia	288	99	57	ICD therapy resulted in nonsignificant 23 % RR reduction in mortality (CI lower bound–11 %), $P = 0.08$
CIDS [8]	2000	Any of (1) VF, (2) out-of-hospital cardiac arrest requiring defibrillation or cardioversion, (3) VT with syncope, (4) VT ≥ 150 bpm with symptoms and EF ≤ 35 %, or (5) unmonitored syncope with subsequent VT	659	328	36	ICD therapy resulted in nonsignificant 20 % RR reduction in mortality (CI—8–40 %) $P = 0.142$

Table 19.2 Major randomized clinical ICD trials

Primary prevention in ischemic cardiomyopathy						
Study	Year	Inclusion criteria	Patients, *n*	ICD, *n*	Follow-up (mo)	Main result
MADIT [10]	1996	EF ≤ 35 %, MI ≥ 3 weeks before entry, NSVT, inducible sustained VT on EPS, NYHA I–III	196	95	27	ICD therapy resulted in 54 % RR reduction in mortality (CI 18–74 %), $P = 0.009$
CABG [12] Patch	1997	EF ≤ 35 %, abnormal SAECG, epicardial ICD during CABG	900	446	32	ICD therapy did not reduce mortality, $P = 0.64$
MUSTT [11]	1999	EF ≤ 40 %, MI 1 month before entry, asymptomatic NSVT	704	161	39 (median)	ICD therapy resulted in 55 % RR reduction in mortality (CI 37–68 %), $P = 0.001$
MADIT-II [4]	2002	EF ≤ 30 %, MI 1 month before entry, NYHA I–III	1232	742	20	ICD therapy resulted in 31 % RR reduction in mortality (CI 7–49 %), $P = 0.016$
SCD-HeFT [3]	2005	EF ≤ 35 %, 3 months of optimal medical therapy, NYHA II–III	2521 total, 1310 ischemic	829 total, 431 ischemic	45.5 (median)	Overall, ICD therapy resulted in 23 % RR reduction in mortality (CI 4–38 %), $P = 0.007$; in ischemic patients, ICD therapy resulted in nonsignificant 21 % RR reduction in mortality (CI—4–40 %), $P = 0.05$. No evidence of effect modification by etiology
Primary prevention in ischemic cardiomyopathy: early after MI						
DINAMIT [16]	2004	EF ≤ 35 %, within 6–40 days of MI, depressed HRV, or average Holter HR ≥ 80 bpm, NYHA I–III	674	332	33	ICD group had a significant decrease in risk of death due to arrhythmia, $P = 0.009$ but a significant increase in risk of non-arrhythmic death, $P = 0.02$. ICD therapy did not reduce all-cause mortality, $P = 0.66$

IRIS [17]	2009	EF ≤ 40 %, within 5–31, HR—90 bpm or NSVT ≥ 150 bpm, NYHA I–III	898	445	37	ICD group had a significant decrease in sudden cardiac death, $P = 0.049$ but a significant increase in risk of non-sudden cardiac death, $P = 0.001$. ICD therapy did not reduce mortality, $P = 0.78$
Primary prevention in nonischemic cardiomyopathy						
CAT [13]	2002	EF ≤ 30 %, new-onset DCM, NYHA II–III	104	50	66	ICD therapy did not reduce mortality, $P = 0.55$
AMIOVIRT [14]	2003	EF ≤ 35 %, DCM, asymptomatic NSVT, NYHA I–III	103	51	36	ICD therapy did not reduce mortality, $P = 0.80$
DEFINITE [15]	2004	EF ≤ 35 %, NSVT, NYHA I–III	458	229	29	ICD therapy resulted in nonsignificant 35 % RR reduction in mortality (CI—6–60 %), $P = 0.08$
SCD-HeFT [3]	2005	EF ≤ 35 %, 3 months optimal medical therapy, NYHA II–III	2521 total, 1310 ischemic	829 total, 431 ischemic	45.5 (median)	Overall, ICD therapy resulted in 23 % RR reduction in mortality (CI 4–38 %), $P = 0.007$; in ischemic patients, ICD therapy resulted in nonsignificant 21 % RR reduction in mortality (CI—4–40 %), $P = 0.05$. No evidence of effect modification by etiology

RR = relative risk, CI = 95 % confidence interval, EF = left ventricular ejection fraction, NYHA = New York Heart Association Class, DCM = dilated cardiomyopathy, Mo = month, SAECG = signal-averaged ECG, HRV = heart rate variability

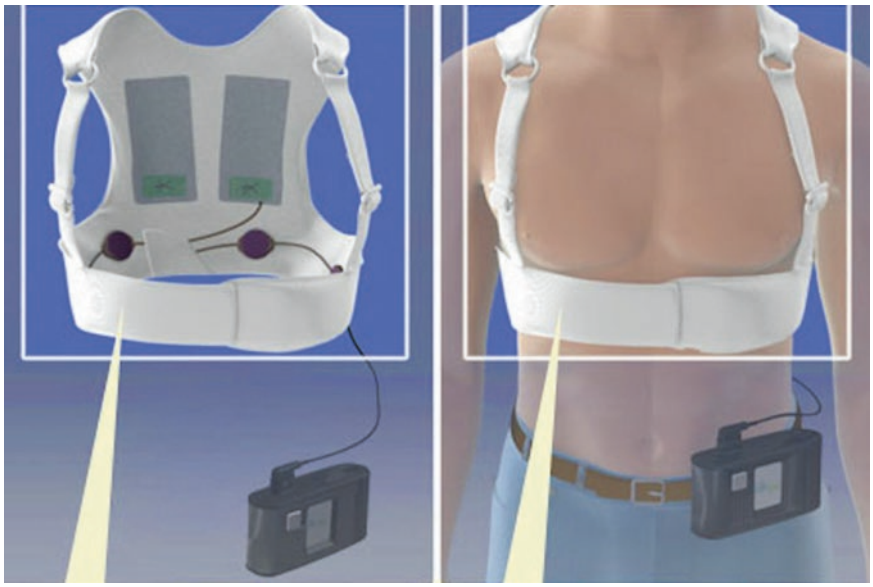

Fig. 19.3 Life Vest, wearable cardiac defibrillator (WCD), ZOLL Medical Corporation, Pittsburgh, PA, USA

death was highest in the first 30 days after an MI) and the benefits of ICD therapy in patients with cardiac dysfunction due to MI, the consideration arose that ICD implantation would be beneficial early after MI [52]. However, two separate randomized trials have failed to show the benefit of ICD implantation within 30–40 days after MI (*DINAMIT*, *IRIS*) [62, 63] (Table 19.2). Subsequent analysis of *VALIANT* and *DINAMIT* has demonstrated a possible pathophysiologic mechanism for the absence of benefit of ICD implantation in the early period after MI [52, 62]. In *DINAMIT*, only 50 % of the sudden deaths were attributable to arrhythmia, whereas mechanical causes of SCD (e.g., LV rupture, acute mitral regurgitation) were common in the other half of patients. Similarly in *VALIANT*, in the first month after MI, 80 % of sudden cardiac deaths appeared to be due to recurrent MI or myocardial rupture, and presumed arrhythmia-induced SCD only accounted for 20 %. By 1 year, the proportions of sudden deaths due to non-arrhythmia versus arrhythmia causes were equal, and over time there appeared to be a very gradual increase in the proportion of sudden deaths due to arrhythmia (approximately 60 % at 30 months). Therefore, early implantation of an ICD in this patient population would not be expected to significantly impact deaths. These observations have led to specific recommendations regarding "waiting periods" between the occurrence of an acute event and the placement of an ICD. In fact, after these studies, CMS (Center for Medicare & Medicaid Services) ruled that there should be at least 40 days of waiting period after MI before ICD implantation. In addition, due to the possibility of EF improvement in patients who underwent revascularization or in whom there were reversible causes of NICM (myocarditis, postpartum cardiomyopathy, etc.), CMS requirements demand at least 90 days waiting period after revascularization and/or newly diagnosed and medically treated NICM before ICD implantation [64].

Not infrequently, the waiting time rules and exposure to risk that they necessitate cause patients and physicians to be very uncomfortable. The introduction of more widespread use of wearable ICDs (WCD) (Fig. 19.3) has substantially reduced risk of SCD in these waiting periods. Recently Epstein et al. reported findings in 8453 patients who had a WCD prescribed in the first 3 months post-MI [65]. A total of 133 patients (1.6 %) received 309 appropriate shocks from their WCD. Of these patients, 91 % were resuscitated from a ventricular arrhythmia. With 40-day and 3-month waiting periods in patients post-MI, the WCD successfully treated SCD in 1.4 %, and the risk was highest in the first month of WCD use.

Recommendations for Implantable Cardioverter Defibrillators (Tables 19.3 and 19.4)

Recommendations on the use of the ICD in clinical practice have been provided in four important guideline documents sponsored by the American College of Cardiology (ACC), the American Heart Association (AHA), Heart Rhythm Society (HRS), and the European Society of Cardiology (ESC) [66–68]. Current ICD indications and recommendations are summarized in Tables 19.3 and 19.4 [69].

Recommendations for Wearable ICD (WCD)

WCDs are recommended for patients with accepted indications for ICD implantation but who also have (usually temporary) contraindications for such a procedure [65, 70]. The most common are those in the CMS mandated "waiting periods" after acute MI or revascularization. Other temporary contraindications include an infected ICD system that requires explanation with the need for long-term antibiotic treatment. A second group of WCD candidates comprises

Table 19.3 Recommendations for implantable cardioverter defibrillators (2012 ACCF/AHA/HRS Focused Update Incorporated into the ACCF/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities) [24]

Class I	Level of evidence
• ICD therapy is indicated in patients who are survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes.	A
• ICD therapy is indicated in patients with structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable.	B
• ICD therapy is indicated in patients with syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study.	B
• ICD therapy is indicated in patients with LVEF less than or equal to 35 % due to prior MI who are at least 40 days post-MI and are in NYHA functional Class II or III.	A
• ICD therapy is indicated in patients with nonischemic DCM who have an LVEF less than or equal to 35 % and who are in NYHA functional Class II or III.	B
• ICD therapy is indicated in patients with LV dysfunction due to prior MI who are at least 40 days post-MI, have an LVEF less than or equal to 30 %, and are in NYHA functional Class I.	A
• ICD therapy is indicated in patients with non-sustained VT due to prior MI, LVEF less than or equal to 40 %, and inducible VF or sustained VT at electrophysiological study.	B
Class IIa	Level of evidence
• ICD implantation is reasonable for patients with unexplained syncope, significant LV dysfunction, and nonischemic DCM.	C
• ICD implantation is reasonable for patients with sustained VT and normal or near-normal ventricular function.	C
• ICD implantation is reasonable for patients with HCM who have 1 or more major† risk factors for SCD.	C
• ICD implantation is reasonable for the prevention of SCD in patients with ARVD/C who have 1 or more risk factors for SCD.	C
• ICD implantation is reasonable to reduce SCD in patients with long-QT syndrome who are experiencing syncope and/or VT while receiving beta-blockers.	B
• ICD implantation is reasonable for non-hospitalized patients awaiting transplantation.	C
• ICD implantation is reasonable for patients with Brugada syndrome who have had syncope.	C
• ICD implantation is reasonable for patients with Brugada syndrome who have documented VT that has not resulted in cardiac arrest.	C
• ICD implantation is reasonable for patients with catecholaminergic polymorphic VT who have syncope and/or documented sustained VT while receiving beta-blockers.	C
• ICD implantation is reasonable for patients with cardiac sarcoidosis, giant cell myocarditis, or Chagas disease.	C

(continued)

Table 19.3 (continued)

Class IIb	Level of evidence
• ICD therapy may be considered in patients with nonischemic heart disease who have an LVEF of less than or equal to 35 % and who are in NYHA functional Class I.	C
• ICD therapy may be considered for patients with long-QT syndrome and risk factors for SCD.	B
• ICD therapy may be considered in patients with syncope and advanced structural heart disease in whom thorough invasive and non-invasive investigations have failed to define a cause.	C
• ICD therapy may be considered in patients with a familial cardiomyopathy associated with sudden death.	C
• ICD therapy may be considered in patients with LV non-compaction cardiomyopathy.	C
Class III	Level of evidence
• ICD therapy is not indicated for patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 year, even if they meet ICD implantation criteria specified in the Class I, IIa, and IIb recommendations above.	C
• ICD therapy is not indicated for patients with incessant VT or VF.	C
• ICD therapy is not indicated in patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up.	C
• ICD therapy is not indicated for NYHA Class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or CRT-D.	C
• ICD therapy is not indicated for syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias and without structural heart disease.	C
• ICD therapy is not indicated when VF or VT is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, RV or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease).	C
• ICD therapy is not indicated for patients with ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma).	B

Table 19.4 HRS/ACC/AHA expert consensus statement on the use of implantable cardioverter defibrillator therapy in patients who are not included or not well represented in clinical trials (2013) [25]

• In patients with abnormal cardiac biomarkers that are not thought to be due to an MI and who otherwise would be candidates for implantation on the basis of primary prevention or secondary prevention criteria, implantation of an ICD *is recommended*.
• Implantation of an ICD within the first 40 days following acute MI in patients with preexisting systolic ventricular dysfunction (who would have qualified for a primary prevention ICD) is *not recommended*.
• In patients who, within 40 days of an MI, develop sustained (or hemodynamically significant) ventricular tachyarrhythmias >48 h after an MI and in the absence of ongoing ischemia, implantation of an ICD *is recommended*.
• Implantation of an ICD for primary prevention is *not recommended* with in the first 3 months after initial diagnosis of NICM.
• If recovery of left ventricular function is unlikely, implantation of an ICD for primary prevention can be useful between 3 and 9 months after initial diagnosis of NICM.

patients under investigation for a disease with a high risk of arrhythmic death or pending definitive diagnosis (e.g., those with inheritable arrhythmic disorder who are awaiting results of confirmatory testing or survivors of a cardiac arrest of unclear (and potentially treatable or reversible) origin). The third group consists of patients with severe heart failure awaiting cardiac transplantation and, finally, patients having a condition that temporarily places them at high risk of an arrhythmic death (e.g., patients with a low LVEF resulting from potentially reversible condition such as a newly diagnosed dilated cardiomyopathy (that could be due to transient myocarditis) or an ischemic cardiomyopathy in the early period after revascularization or in the early period after a MI).

Antiarrhythmic Drug Therapy for Atrial and Ventricular Tachyarrhythmias in Cardiomyopathy

The apparent antiarrhythmic effects of certain compounds have been recognized for well over 250 years. Cardiac glycosides and quinine are perhaps the earliest examples. However, most of the antiarrhythmic drugs (AADs) currently in use have been introduced in only the last 35–40 years. Currently, AADs remain a mainstay for termination and prevention of atrial fibrillation (AF) and provide useful adjunctive therapy for certain forms of ventricular tachycardia (VT). Few, however, have proved effective for ventricular fibrillation prevention (with the possible exception of amiodarone and perhaps bretylium).

The primary goals of current AAD therapy have been the reduction of frequency, duration, and severity of arrhythmia episodes. Unfortunately, on the negative side, most AADs have cardiac and noncardiac adverse effects that limit their clinical utility in important segments of the patient population, particularly those with more than minimal left ventricular (LV) dysfunction and/or heart failure.

Overview of Current Antiarrhythmic Drugs

Table 19.5 summarizes the most widely available antiarrhythmic drugs using the Vaughan Williams classification which focuses on each drug's principal cardiac channel effects. However, it is recognized that drug actions are much more complex than the Vaughan Williams approach allows and that actual drug effects on arrhythmias are not readily predicted by the classification. Given this important limitation, an attempt has been made to provide a more comprehensive and precise classification of drug effects [71, 72]. This effort (the so-called Sicilian gambit), while scientifically robust, is necessarily complex and as a result has largely been neglected in recent years.

Excluding beta-adrenergic blockers, calcium channel blockers, and cardiac glycosides, the majority of available "membrane-active" antiarrhythmic drugs exert predominant effects on cardiac sodium or potassium currents. The first of the orally available membrane-active agents to have a prominent place in therapeutics was quinidine and its congeners (derived from quinine). Procainamide became available in the early 1950s. Thereafter, at least in the USA, there was a long delay before the emergence of disopyramide in the late 1970s. Flecainide, encainide (the latter now withdrawn from the US market), ethmozine, mexiletine, tocainide (also withdrawn), imipramine, bretylium/bethanidine (not used to any extent), and amiodarone appeared in the 1980s. Propafenone, sotalol, dofetilide, dronedarone, and ivabradine followed.

Encainide, like flecainide, is a Vaughan Williams Class 1C agent (Table 19.5), but its use was discontinued in many countries (but not all) after CAST (Cardiac Arrhythmia Suppression Trial) revealed increased death rate in the treatment group [73]. Flecainide remains available due to additional studies showing benefit in supraventricular tachycardias, particularly atrial fibrillation (AF).

Tocainide is an orally available lidocaine "look-alike," but its use was undermined by an excessive number of adverse effects (especially hematologic). Imipramine (a long-used QT-prolonging tricyclic antidepressant) was, surprisingly to many, incorporated in the pre-CAST pilot study (CAPS), but was never a serious antiarrhythmic drug contender, and reasonably dropped by the wayside as far as cardiac arrhythmia therapy was concerned in the mid-1980s [74]. Bretylium was developed in the 1970s and proved to be an interesting antifibrillatory drug and was commercially available for parenteral use in the USA. The principal indication for bretylium was termination of refractory VF and VF prevention during acute care scenarios. However, while bretylium has an excellent inotropic profile, it induced profound postural hypotension and was difficult to use; in addition, it was not available for oral administration. Bethanidine (which had been widely used as an antihypertensive drug for many years and may still be used in some countries) has bretylium-like antifibrillatory properties [75]. However, although orally absorbable, very cheap, and widely available in the world, it is also difficult to use due to induction of postural hypotension. Techniques were devised to minimize the postural hypotension limitation, but given the emergence of amiodarone, the impetus to use bethanidine largely evaporated.

Sodium channel-blocking drugs (Table 19.5) are often called membrane-stabilizing agents because they decrease the excitability of cardiac tissue. Typically, these drugs exhibit use dependence. This means that the predominant effect on conduction (sodium channel blockade) is seen at rapid heart rates. On the ECG, QRS widening due to conduction slowing is often observed.

Drugs with major effects on blocking potassium currents prolong the action potential duration and refractory periods. Quinidine, procainamide, disopyramide, sotalol, and dofetilide are primarily potassium channel-blocking drugs that display reverse use dependence such that repolarization is prolonged at slow heart rates. The latter effect predisposes these drugs to lengthen the QT interval most dramatically

Table 19.5 Vaughan Williams classification

Class	Drugs	Channel(s) blocked	Mechanism(s)
Ia	Quinidine	I_{Na}, I_{Kr}, acetylcholine	(Na^+) channel block (intermediate association/dissociation) and K^+ channel-blocking effect
	Procainamide		
	Disopyramide		
Ib	Lidocaine	I_{Na}	(Na^+) channel block (fast association/dissociation)
	Phenytoin		
	Mexiletine		
	Tocainide		
Ic	Encainide	I_{Na}, β	(Na^+) channel block (slow association/dissociation)
	Flecainide		
	Propafenone		
	Moricizine		
II	Carvedilol		Beta-adrenergic blockers
	Propranolol		
	Esmolol		
	Timolol		
	Metoprolol		
	Atenolol		
	Bisoprolol		
III	Amiodarone	I_{Kr}, I_{Na}, I_{Ca}, β, α, acetylcholine	K^+ channel blocker
	Sotalol	I_{Kr}, β	Sotalol is also a beta-blocker
	Ibutilide	I_{Kr}, I_{Na} agonist	Amiodarone has Class I, II, III, and IV activity
	Dofetilide	I_{Kr}	
	Dronedarone	I_{Kr}, I_{Na}, I_{Ca}, β, α, acetylcholine	

(continued)

Table 19.5 (continued)

Class	Drugs	Channel(s) blocked	Mechanism(s)
IV	Verapamil		Ca^{2+} channel blockers
	Diltiazem		
	Ivabradine	I_f	Inhibition of the funny channel

Sodium channels (I_{Na}): fast Na^+, phase 0 depolarization of non-pacemaker cardiac action potentials
Potassium channels
Transient outward (I_{to}): contributes to phase 1 of non-pacemaker cardiac action potentials
Delayed rectifier (I_{Kr}): phase 3 repolarization of cardiac action potentials
Calcium channels (I_{Ca}): slow inward, long-lasting current; phase 2 non-pacemaker cardiac action potentials and late phase 4 and phase 0 of SA and AV nodal cells; important in vascular smooth muscle contraction
β beta antagonist; α alpha antagonist
I_f: funny current

during bradyarrhythmias and increase susceptibility to triggering torsade-de-pointes (TdP) ventricular tachycardia.

Apart from their electrophysiological effects, most available antiarrhythmic drugs also exhibit negative inotropic effects, thereby limiting their applicability in patients with diminished LV function (i.e., most patients with structural heart disease) and/or heart failure. Disopyramide and procainamide are perhaps the most negatively inotropic agents. On the other hand, quinidine, dofetilide, bethanidine (not used), and amiodarone are perhaps the most innocent agents in this regard.

Due to their negative inotropic effects, Class 1C agents and dronedarone are generally not used in LV dysfunction/heart failure patients. On the other hand, quinidine (not often used these days), dofetilide, sotalol, and amiodarone are generally acceptable in heart failure, but patient response must be carefully monitored. Other factors limiting AAD use in individual patients include the mechanism of clearance of the agent and how that might be affected by systemic disease (◘ Table 19.6). By way of example, elimination of both sotalol and dofetilide is highly dependent on renal function status, and their dosages must be adjusted accordingly. Similarly, AAD plasma concentrations may be altered by the presence of other AADs. Perhaps the quinidine-digoxin interaction was the earliest important AAD-AAD interaction to be identified, and it may have contributed to many cases of the so-called quinidine syncope (see later).

Role of Specific Antiarrhythmic Drugs

Treatment of most paroxysmal supraventricular tachycardias (SVTs) is now focused predominantly on mapping and ablation, since ablation offers a cure, whereas AADs offer only palliation. Currently, AADs are primarily used for AF and to some extent for other primary atrial tachycardias (AT).

Quinidine, procainamide, and disopyramide are no longer widely used for the treatment or prevention of AF or ATs in developed countries. Although these drugs can be useful, their adverse effects and the presence of better tolerated alternatives have undermined their use; consequently, they are not discussed further in this section. Amiodarone, despite its multiple numerous side effects and lack of supportive US Food and Drug Administration labeling, has become ubiquitous in the AF population, but careful follow-up is mandatory to assess for development of adverse effects (◘ Table 19.6). Amiodarone is discussed in more detail below.

Flecainide

Flecainide, in addition to its prominent conduction slowing effect due to sodium channel-blocking activity (which may widen the QRS complex), also has mild IKr (rapid component of the delayed rectifier potassium channel) blocking effects, but is not generally associated with significant QT prolongation.

Flecainide is contraindicated in individuals with prior myocardial infarction and reduced LV function because of increased ventricular proarrhythmia risk [15]. It is also potentially hazardous in patients with conduction system disease, as it may predispose to aggravating the severity of atrioventricular (AV) block or sinus node dysfunction. Consequently, flecainide is rarely used for VT, since VT patients often have underlying LV dysfunction and/or conduction system disease. However, flecainide may be useful for prevention of AF in patients without severe structural heart disease. In this circumstance, flecainide may reduce recurrences and/or slow atrial rate in ongoing AF or AT.

On a cautionary note, it is important to recognize that flecainide-induced conduction slowing in AF patients may have unexpected adverse consequences. Flecainide (as well as other AADs, such as propafenone) can slow and regularize AF resulting in new-onset atrial flutter (so-called Type 1C flutter) [76]. The occurrence of "1C flutter," which typically exhibits a slower atrial rate than does conventional atrial flutter, can result in a paradoxical increase of ventricular rate due to lesser block at the AV node level. The outcome may be substantial clinical distress. Thus, flecainide must be used in conjunction with a beta-blocker or calcium channel blocker to slow AV nodal conduction in the event 1C flutter develops.

In AF, flecainide may be used as first-line therapy in patients without structural heart disease. Oral flecainide (200–300 mg) has been used as a "pill-in-the-pocket" approach in patients who have infrequent AF and are capable of recognizing onset of an episode so they know to take the medication (preferably within an average of 30 min of arrhythmia onset).

Class IC antiarrhythmic agents such as flecainide are no longer recommended as therapy for VT in patients with ischemic heart disease or LV dysfunction from any cause. This limitation arose as a result of the CAST trial findings which showed that both all-cause mortality and arrhythmic death were increased with both encainide and flecainide. This exclusion of flecainide has been extended to nonischemic cardiomyopathy patients as well, despite the fact that they were not evaluated in CAST.

As a rule, flecainide tends to be well tolerated. However, common non-cardiovascular side effects include dizziness and visual disturbance in 5–10 % of patients [77].

Propafenone

Propafenone has beta-adrenergic blocking properties in addition to its 1C sodium channel-blocking activity. It also has mild negative inotropic and chronotropic effects.

In AF and AT, propafenone may be used as first-line therapy in patients without structural heart disease (typically 150 mg BID). High-dose oral propafenone (450–600 mg) has also been used as a "pill-in-the-pocket" approach in paroxysmal AF patients. As with flecainide, propafenone should be partnered with an AV nodal-blocking drug. Propafenone is not recommended for most VT patients with LV dysfunction.

Table 19.6 Antiarrhythmic drug dosing and side effects

Antiarrhythmic drug	Metabolism/dose	Major non-cardiovascular toxicity	Major cardiovascular toxicity
Quinidine	• Hepatic CYP3A4 (70 %), renal (30 %) • Sulfate, 600 three times a day • Gluconate, 324–648 every 8 h	Thrombocytopenia, cinchonism, pruritus, rash	QRS prolongation with toxic doses, torsades de pointes (not dose related)
Propafenone	• Hepatic • 150–300 every 8 h • Sustained release 225–425 twice a day	Metallic taste, dizziness	Atrial flutter with 1:1 conduction; ventricular tachycardia; may unmask Brugada-type ST elevation; contraindicated with coronary disease
Flecainide	• Renal/hepatic CYP2D6 • 50–100 mg twice a day	Dizziness, headache, visual blurring	Atrial flutter with 1:1 conduction; ventricular tachycardia; may unmask Brugada-type ST elevation; contraindicated with coronary disease
Sotalol	• Renal: 80–120 mg twice a day • Maximum dose 240 mg twice a day	Bronchospasm	Bradycardia, torsades de pointes
Dofetilide	• Renal/hepatic CYP3A4 • 500 μg twice a day • Renally dose adjusted	None	Torsades de pointes
Amiodarone	• Hepatic; half-life 50 days • Oral load 10 g over 7–10 days, then 400 mg for 3 weeks, then 200 mg/day • Intravenous: 150–300 mg bolus, then 1 mg/min infusion for 6 h followed by 0.5 mg/min thereafter	Pulmonary (acute hypersensitivity pneumonitis, chronic interstitial infiltrates); hepatitis; thyroid (hypothyroidism or hyperthyroidism); photosensitivity; blue-gray skin discoloration with chronic high dose; nausea; ataxia; tremor; alopecia	Sinus bradycardia
Ibutilide (intravenous)	• Hepatic CYP3A4 • 1 mg intravenous over 10 min; repeat after 10 min if necessary	Nausea	Torsades de pointes
Dronedarone	• Renal, hepatic, gastrointestinal • 400 mg twice a day	Anorexia; nausea; hepatotoxicity	Bradycardia
Mexiletine	• Hepatic • 200 mg three time a day	Dizziness, heartburn, nausea, nervousness, trembling, unsteadiness	Bradycardia
Disopyramide	• Hepatic • 125 mg four times a day	Dry mouth, constipation, Urinary retention, blurred vision	Negative inotrope Hypotension

The major non-cardiovascular adverse effects of propafenone include a metallic taste as well as dizziness and visual disturbances. High-dose oral propafenone (450–600 mg) has been used as a "pill-in-the-pocket" approach in patients who have infrequent AF and are capable of recognizing onset of an episode, preferably within an average of 30 min of arrhythmia onset.

Sotalol

Sotalol is a potassium channel (IKr) blocker and beta-blocker with minimal non-cardiovascular side effects and a high rate of utilization. Sotalol is cleared by the kidneys and is prescribed twice daily unless the creatinine clearance is low (between 30 and 60 mL/min) when single daily dosage is used. It is often started as an inpatient at a dose of 80 mg twice daily and up-titrated with attention to QT prolongation. The potassium channel-blocking effect increases with increasing dosage, and, as a result, the risk of torsade-de-pointes ventricular proarrhythmia (TdP) increases at a higher dosage.

Initially, sotalol was approved for treatment of AF with a recommendation for inpatient initiation. However, most recent guidelines allow for it to be started as an outpatient [15]. The Sotalol Amiodarone Atrial Fibrillation Efficacy Trial (SAFE-T) initiated either sotalol or amiodarone in the outpatient setting during AF without adverse effect and with an equivalent rate of restoring sinus rhythm [76]. In the OPTIC trial examining the potential to reduce shock frequency in secondary prevention ICD recipients, amiodarone plus beta-blockers was shown to be superior to monotherapy with sotalol or beta-blockers [78].

Sotalol is considered reasonable as first-line therapy for patients with coronary artery disease and relatively preserved left ventricular function. Sotalol may also be considered as an option for first-line therapy in VT, particularly in patients in whom beta-blockade is tolerated. The principal sotalol side effects parallel those of most beta-blockers and include fatigue, bronchospasm, and dyspnea. Sotalol can also exacerbate sinus node dysfunction (◘ Table 19.6).

Dofetilide

Dofetilide is also primarily an IKr blocker, without other clinically significant electrophysiological effects. It is cleared by the kidneys and must be dosed according to creatinine clearance (◘ Tables 19.1 and 19.2). It was approved for use in the USA in 2000 with a 3-day mandatory in-hospital loading period. ◘ Figure 19.4 shows an onset of TdP during inpatient dofetilide loading. Dofetilide is more effective for the maintenance of sinus rhythm in AF patients than it is for restoring sinus rhythm [79].

Dofetilide is a reasonable first-line therapy choice in AF/AT patients in whom coronary artery disease is present and especially if associated with LV dysfunction. It has been demonstrated to be relatively safe in the settings of heart failure and post-myocardial infarction populations [80, 81]. Dofetilide is not recommended for use in VT; however, it has been used off-label when other more conventional options are contraindicated.

The principal risk factors for dofetilide adverse effects (particularly TdeP) include hypokalemia, hypomagnesemia, female gender, baseline prolonged QT interval, or congenital long-QT syndrome and concomitant use of other QT-prolonging therapies. It is one of the few antiarrhythmics that have little if no effect on sinus node function.

Amiodarone

Amiodarone is the most commonly prescribed antiarrhythmic drug for AF/AT, despite not having been approved by the US FDA for that indication. Amiodarone is a complex iodinated compound that acts on multiple channels including antagonism of α- and β-adrenergic receptors (◘ Fig. 19.2). It is the most effective antiarrhythmic drug currently available, but its ease of use is limited by a myriad of non-cardiovascular side effects [82]. The major cardiovascular side effect of amiodarone is sinus bradycardia, with a higher risk of pacemaker requirement in women [83].

QT prolongation is common with amiodarone but fortunately is very rarely associated with TdP (<0.5 %) [84]. The combination of amiodarone with the CYP3A4 substrate simvastatin has been associated with an increased risk of myositis [85]. Conversely, this risk seems to be smaller when amiodarone is combined with pravastatin, which does not use the cytochrome P450 system for metabolism. The most important drug-drug interaction with amiodarone occurs with potentiation of the anticoagulant effect of warfarin through inhibition of CYP2C9. In addition, amiodarone can reduce digoxin clearance.

Amiodarone is orally well absorbed with high bioavailability, but it may also be administered as an intravenous agent; the parenteral form has been used for terminating AF, but in reality it is only weakly effective for this purpose [86]. On the other hand parenteral amiodarone is a very effective agent for slowing ventricular response in AF.

A major limitation of amiodarone is its exceedingly long half-life, 58 days (range 15–142 days). As a result, it takes a long time to "load" amiodarone and also a long time to eliminate it if side effects become an issue. As rule, amiodarone can be loaded orally over the course of 3–4 weeks. A day or two of parenteral loading (0.5–1 mg/min IV) may help accelerate loading and is generally well tolerated.

EMIAT and CAMIAT evaluated amiodarone use in patients recovering from myocardial infarction (MI) [87, 88]. EMIAT was a European randomized double-blind placebo-controlled trial to assess whether amiodarone reduced all-cause mortality (primary endpoint) and cardiac mortality and arrhythmic death (secondary endpoints) in survivors of myocardial infarction with a LV ejection fraction (LVEF) of 40 % or less. CAMIAT was a Canadian randomized double-blind placebo-controlled trial designed to assess the effect of amiodarone on the risk of resuscitated ventricular fibrillation or arrhythmic death among survivors of myocardial infarction with frequent or repetitive PVCs. Both reports found that incidences of cardiovascular death and arrhythmic death or resuscitated cardiac arrest were significantly lower in patients receiving both beta-blockers and amiodarone than in those not receiving beta-blockers, with or without amiod-

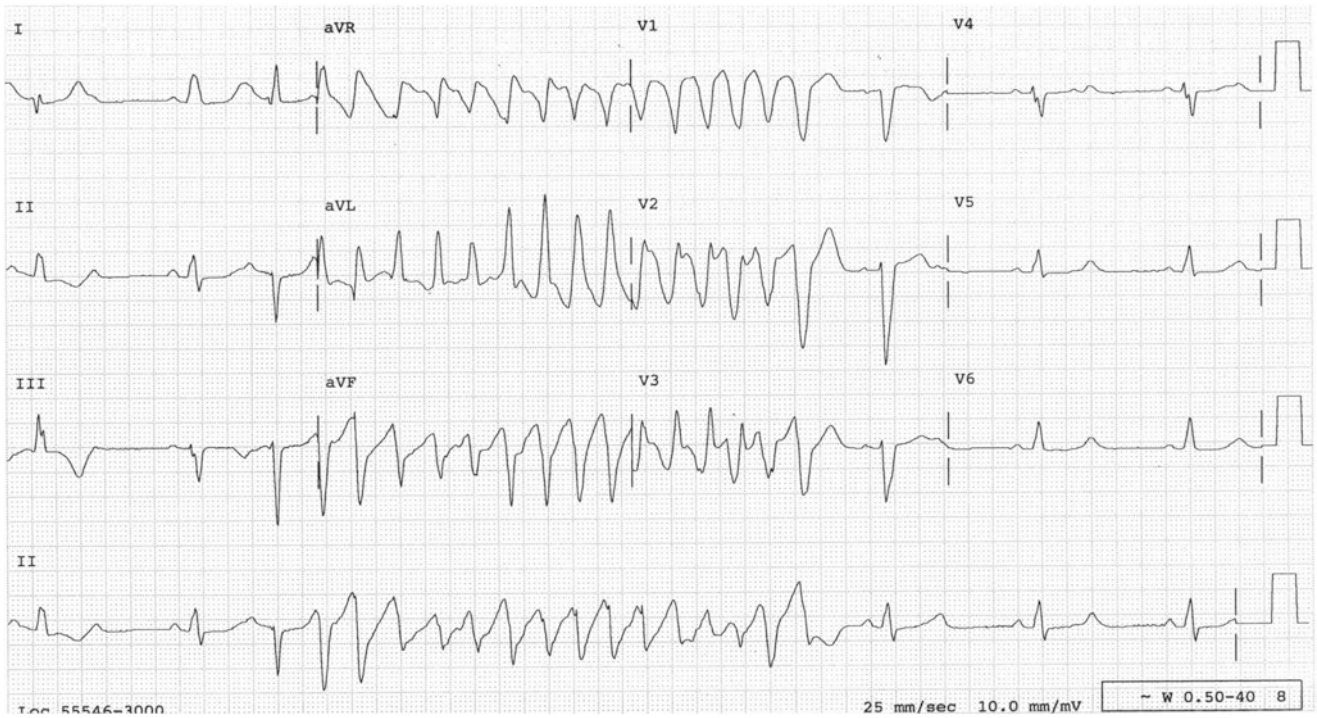

Fig. 19.4 50-year-old male with a history of ischemic cardiomyopathy with EF 20–25 % with a single-chamber ICD and difficult-to-control AF who presented as an elective admission for attempted chemical cardioversion with dofetilide. Two hours after his second dose of dofetilide, the patient developed torsades de pointes and received a shock from his ICD. Note the long-short sequence prior to initiation of tachycardia

arone. TdP occurred in less than 1 % of patients in the EMIAT and CAMIAT trials.

In the case of AF treatment, amiodarone should be reserved as second-line therapy if coronary artery disease is associated with LV dysfunction because of the severity of potential adverse effects. However, despite this admonition, in clinical practice amiodarone seems to have become the first choice AAD for AF prevention. Oral amiodarone can also be used to convert AF to sinus rhythm, but effectiveness is unpredictable.

In VT amiodarone should be a second-line agent for patients who are intolerant or not candidates for sotalol. However, amiodarone is often used as a first-line agent, especially in patients with an excessive ICD shock burden. Increasingly, however, ablation may be preferred to drug therapy in this situation.

Dronedarone

Dronedarone is the first of a group of drugs that have been designed to resemble amiodarone but with fewer non-cardiovascular side effects. It is similar in structure to amiodarone with the addition of a Methanesulfonamide group and the absence of iodine moieties (Fig. 19.2). An initial study, ANDROMEDA, which was designed to assess the effect of dronedarone on mortality in patients with advanced congestive heart failure, disappointingly revealed increased mortality in the dronedarone-treated group [89]. The drug is therefore contraindicated in patients with decompensated congestive heart failure. Subsequent efficacy studies and a major safety study in healthier patients with AF and without decompensated heart failure have shown no significant extra-cardiovascular toxicities and a reduction in hospitalizations and cardiovascular mortality associated with this drug [90]. However, the PALLAS study indicated that dronedarone may be less desirable in patients with permanent AF [91].

In AF patients, dronedarone may reasonably be considered as first-line therapy in patients with intermittent AF but without structural heart disease. With regard to VT, dronedarone has been shown to be effective in suppressing ventricular tachyarrhythmias in animal studies and in case reports of patients with refractory VT/VF episodes. However, the results of ANDROMEDA and PALLAS have raised doubts about the safety of this medication in patients with more than modest severity structural heart disease.

Other Drugs Used in VT

Beta-adrenergic blockers are almost a routine part of VT preventive treatment as they are deemed first-line therapy for their established survival benefit in patients with systolic heart failure or those who have recently suffered an acute MI [92]. In addition, beta-blockers are indicated in the treatment of certain ion channelopathies, such as congenital long-QT syndrome and catecholaminergic polymorphous VT (CPVT) [93].

Mexiletine

Currently, mexiletine is the most commonly used Class I antiarrhythmic agent, but is only rarely used as a stand-alone AAD. It was used in 20 % of patients who received adjuvant antiarrhythmic treatment in the ICD arm of the AVID trial [94]. As a Class IB antiarrhythmic agent (lidocaine-like), it does not seem to carry the increased mortality risk associated with the Class IC drugs. This mortality aspect is based on observational data with the Class IB drug lidocaine from the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO-I and GUSTO-IIb) trials [95]. On the other hand, mexiletine is often poorly tolerated due to gastrointestinal side effects.

Ethmozine (Moricizine)

In the Cardiac Arrhythmia Suppression Trial (CAST), ethmozine showed only a nonsignificant increase of mortality from 5.4 to 7.2 %. This is in line with other class IC antiarrhythmics [73]. Ethmozine is only rarely used in current US clinical practice.

Drugs Less Often Used or Under Development

Quinidine

Originally, quinidine was derived from the bark of the cinchona plant and was identified as a potential antiarrhythmic drug more than a century ago. It has important vagolytic and α-blocking effects with an intermediate sodium channel-blocking action at rapid heart rates and higher concentrations. It has a prominent potassium channel-blocking effect at slower heart rates and normal concentrations resulting in QT interval prolongation and increased TdP susceptibility (the basis for what was once called "quinidine syncope" although the concomitant use of cardiac glycosides may have contributed).

Quinidine has a long history for termination and prevention of AF, but is only rarely used for that purpose these days as other more readily tolerated agents are available. Similarly, quinidine is no longer used for VT due to the risk of torsade de pointes. However, quinidine's blocking effect on the Ito current (cardiac transient outward potassium current) has generated interest as a potential therapy for Brugada syndrome and idiopathic ventricular fibrillation [96]. Its non-cardiovascular adverse effects include diarrhea as well as cinchonism (tinnitus and headache) and thrombocytopenia.

Disopyramide

Disopyramide is a sodium channel-blocking drug with potent anticholinergic and negative inotropic effects. The anticholinergic effects have led to its recommendation for patients with vagally induced AF despite little supporting evidence [15]. However, because of its negative inotropic effects, disopyramide should be avoided in patients with left ventricular dysfunction as it can aggravate heart failure. In addition, given its powerful anticholinergic side effects, it should be avoided in the setting of narrow-angle glaucoma, prostatic hypertrophy, or myasthenia gravis.

Disopyramide is not recommended due to the risk of TdP in patients with structural heart disease. On the other hand, it may have a particular niche application in hypertrophic cardiomyopathy (HCM) in which its negative inotropic properties may act to diminish outflow obstruction [97].

Ibutilide

Ibutilide is an intravenous IKr blocker that also enhances the late inward sodium current [98]. Ibutilide is ≈50 % effective at restoring sinus rhythm in recent onset AF patients. It is slightly more effective for atrial flutter than for AF. Patients must be monitored closely for QT prolongation and TdP for at least 2 h after infusion.

Procainamide

Procainamide (◘ Table 19.5) is a Class 1A agent which is available for both oral and parenteral administration. Although not often used for this purpose, it remains a reasonable alternative, when administered intravenously, for pharmacological termination of new-onset atrial fibrillation. Long-term procainamide use is now rare as the drug is associated with many adverse effects, including hypotension, QT prolongation with TdP, and a lupus-like syndrome. As a result, procainamide's use has declined substantially in recent years.

Ivabradine

Ivabradine is a so-called "funny current" (I_f) blocker that has the effect of slowing the heart rate. It has been approved for heart failure but also finds "off-label" use for reducing heart rate in the syndrome of inappropriate sinus tachycardia and may also have some benefit in postural orthostatic tachycardia syndrome (POTS) [99].

Ranolazine

Ranolazine is a novel antianginal drug with multiple ion channel-blocking antiarrhythmic activities. It is a piperazine derivative with a chemical structure similar to lidocaine; its most potent ion channel-blocking effect is on late sodium currents, and it has modest capacity to prolong the QT interval on ECG.

In the MERLIN-TIMI 36 trial, despite causing modest QT prolongation, ranolazine was shown clinically to reduce arrhythmia episodes, including non-sustained VT, by ambulatory cardiac monitoring in patients presenting with acute coronary syndrome [100]. Based on limited but positive clinical experiences with ranolazine, it appears to be beneficial as add-on therapy in patients with recurrent VT events while on a Class III antiarrhythmic agent. Currently, an ongoing trial is examining the utility of ranolazine for reducing the risk of ventricular tachyarrhythmia and death in patients with implantable cardioverter defibrillators (ICDs).

Azimilide

Azimilide has been undergoing clinical study for many years and remains an investigational Class III antiarrhythmic agent that blocks both the rapid (IKr) and slow (IKs) components of the delayed rectifier cardiac potassium current. In the SHIELD trial, both symptomatic tachyarrhythmias terminated by antitachycardia pacing and appropriate ICD therapies for VT/VF episodes were reduced in patients receiving azimilide [101]. However, the ALIVE trial did not reveal significant differences in all-cause, cardiac, or arrhythmic mortality [102].

Upstream Therapies

Upstream therapies are primarily focused on AF prevention. The concept is to prevent the development of atrial electrical and mechanical remodeling and thereby reduce AF susceptibility. Data support use of ACE inhibitors (ACEI) or angiotensin-receptor blocker (ARB) for primary prevention of new-onset AF in patients with heart failure HF with reduced LVEF [103]. However, this application of these agents is already implied given the Class I indication for use of ACEI/ARB for the treatment of systolic dysfunction assuming no apparent contraindication (e.g., poor renal function) [104].

ACEIs and ARBs have been studied for both primary and secondary prevention of AF. In particular, angiotensin-receptor blockers have been studied for the reduction of new-onset AF in patients with hypertension but without significant structural heart disease [105]. On the other hand, there are not as yet conclusive data to support the use of aldosterone inhibitors for the primary or secondary prevention of AF.

The impact of statins as upstream therapy has been the subject of several systematic reviews [106]. The outcomes for the primary or secondary prevention of AF have been conflicting. Administration of statins may reduce postoperative AF in patients undergoing coronary artery bypass graft surgery [107].

Overall therapy with an ACE inhibitor, ARB, or statin is not proven beneficial for primary prevention of AF in patients without cardiovascular disease [108]. Nonetheless, these drugs are commonly indicated as concomitant treatment for associated comorbidities (e.g., hypertension) in patients with or without structural heart disease.

Arrhythmias in Specific Conditions

Valvular Cardiomyopathies

The 2014 AHA/ACC/HRS Guideline defined *nonvalvular* AF as AF in the absence of any of the following: rheumatic mitral stenosis, mechanical or bioprosthetic heart valve or mitral valve repair [15]. This aligns closely with the definition used by Lip and colleagues in their development of what would become the CHA_2DS_2-Vasc score. In that investigation, patients were selected from the Euro Heart Survey on AF populations who were "without mitral stenosis or previous heart valve surgery" [109].

Most readers will be aware that the trials of the so-called novel oral anticoagulants or NOACs excluded patients with valvular AF. For that reason, NOACs were only approved by the US Food and Drug Administration for use in patients with nonvalvular AF. Unfortunately, the trials for these agents defined "valvular AF" in different ways, so that, for example, a patient with severe aortic stenosis would have been excluded from the dabigatran trial, whereas in the rivaroxaban trail, only hemodynamically significant mitral stenosis or prosthetic heart valves were excluded. These differences were recently discussed in detail in a review by De Caterina and Camm [110]. This review also highlights the fact that the highest risk of thromboembolic complications in AF and concomitant valvular heart disease occurs in mitral stenosis. There is little evidence that other types of valvular heart disease increases the risk of thromboembolic complications related to AF. In fact, there is evidence that mitral regurgitation may confer protection from thromboembolic complications in AF [110].

While far from settled, from a practical standpoint, in patients with AF, *valvular heart disease* refers primarily to (a) mitral stenosis, (b) prosthetic heart valves, or (c) mitral valve repair. It should be noted that only the North American guidelines define valve repair as "valvular AF."

Arrhythmias Associated with Disorders of the Atrioventricular (AV) Valves

Any disorder of the AV valves, either regurgitant or stenosis, that results in an increase in atrial strain and size will result in an increased risk of atrial arrhythmias. Not surprisingly, the primary arrhythmia seen in disorders of one, or both, of the AV valves is AF. Typical and atypical atrial flutters, as well as ectopic atrial tachycardia, can also be seen. Of note, it is also possible that AF may, itself, result in AV valve regurgitation [111].

Management of AF in the setting of AV valve diseases is not fundamentally different than in any other population with AF besides thromboembolic prophylaxis reviewed above.

Patients with AV valve disease are usually not at increased risk of ventricular arrhythmias, unless the valvular heart disease has resulted in a cardiomyopathy. Ventricle incisions are unusual in modern AV valve surgery, but in older patients with a history of AV valve surgery, if a ventriculotomy was performed, the resulting ventricular scar can predispose to ventricular arrhythmias.

Arrhythmias Associated with Ebstein's Abnormality

Ebstein's abnormality of the tricuspid valve is uniquely associated with an increased risk of AV accessory pathways (AP). Patients with Ebstein's anomaly frequently have multiple accessory pathways. They may have AV reentrant using the AP in both the retrograde direction resulting in a narrow-complex supraventricular tachycardia (SVT) or in the antegrade direction resulting in a wide-complex tachycardia. The latter can be difficult to distinguish from ventricular tachycardia [112].

Treatment of AP-mediated tachycardia is primarily catheter ablation. In infants and small children, antiarrhythmic drug therapy should be used to delay catheter ablation until the child has an opportunity to grow.

Surgical Treatment of AF During Valve Surgery

Roughly 40–50 % of patients undergoing mitral valve surgery have a history of AF. Atrial fibrillation after mitral valve surgery is associated with worse outcomes. In centers with experienced operators, the Cox-Maze procedure can be performed in mitral valve or mitral valve plus tricuspid valve surgery with no increase in operative mortality or morbidity [113].

The 2014 Guideline document gives surgical ablation of AF in selected patients undergoing cardiac surgery (not just mitral valve surgery), for other reasons a consensus Class IIa indication [15].

Conduction Abnormalities After Aortic Valve Replacement/Intervention

Surgical replacement of the aortic valve is associated with a significant risk of postoperative conduction abnormalities including complete heart block (CHB). In one single-center study, 8.5 % of patients undergoing isolated aortic valve required permanent pacemaker placement (PPM) [114]. Transcatheter aortic valve replacement (TAVR) has also been found to carry a significant risk of post-intervention conduction system disease and CHB, influenced by a variety of factors including type of valve used, depth of implantation, degree of calcification, and pre-procedure conduction system disease, among others. The need for PPM after TAVR is higher than after surgical valve replacement [115].

In the AHA/ACC/HRS 2008 Guidelines for Device-Based Therapy, CHB or high-degree second-degree postoperative AV block, when not expected to improve, was considered a Class I indication for PPM [66]. TAVR is not specifically mentioned in the 2008 AHA/ACC/HRS guidelines. The European Society of Cardiology published Guidelines on Cardiac Pacing in 2013 that included TAVR in its recommendations for pacing after cardiac surgery [116]. Pacing for high-degree or complete AV block after cardiac surgery or TAVR was given a Class I indication. A 7-day period of observation for recovery of AV conduction was suggested, but in patients with poor escape rhythms, shortening of the observation period was deemed acceptable.

Whether the appearance of new LBBB post-TAVR is an indication for PPM remains a subject of debate. In our experience the decision to pace in this situation is often dependent on the operator, the institution, and the wishes of the patient.

Hypertrophic Cardiomyopathy

Atrial Arrhythmia in Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is reviewed elsewhere in this chapter. However, a few salient points should be emphasized. Patients with HCM who develop AF (or AFL) should be started on oral anticoagulation, assuming no contraindication to such, regardless of their CHA_2DS_2-VASc score. This is a Class I (LOE: B) recommendation in the 2014 guidelines. Antiarrhythmic drug therapy with amiodarone or disopyramide with a beta-adrenergic receptor blocker or a non-dihydropyridine calcium antagonist was given a Class IIa (LOE: C) indication [15]. Catheter ablation for AF in HCM when drugs fail or are not tolerated was given a similar indication.

Ventricular Arrhythmia and Sudden Cardiac Death in Hypertrophic Cardiomyopathy

The substrate for ventricular arrhythmias in HCM lies in the disorganized, chaotic architecture of myocardial cells and the connective tissue. Management of VT begins with avoidance of potential triggers for VT and sudden cardiac death (SCD). Patients with unequivocal or probable HCM should not participate in most competitive sports [117]. While beta-adrenergic blockers and non-dihydropyridine calcium channel blockers are often used to improve symptoms, primarily angina or dyspnea [118], available data does not support a significant role for these drugs in the prevention of VT or SCD [119]. The implantable cardioverter defibrillator (ICD) is the current mainstay for SCD protection. Antiarrhythmic drugs, such as sotalol and amiodarone, may be added empirically as adjunctive therapy to manage VT causing ICD shocks.

Early descriptions of HCM from tertiary care centers estimated the annual mortality to be as high as 6 % [120], but larger, community-based studies suggest that most patients have a more benign course with an annual mortality of 1 % or less [120, 121]. Risk factors have been identified from observational studies and registries. Not surprisingly, HCM patients at highest risk for SCD are survivors of a prior SCD or sustained ventricular tachyarrhythmia [118]. These patients are candidates for ICD implant for secondary prevention [65].

Nearly 90 % of HCM patients will have premature ventricular contractions (PVCs), and 30 % will have non-sustained ventricular tachycardia (NSVT) on ambulatory monitoring [122]. There arrhythmias pose a management dilemma to physicians. NSVT has a high negative predictive value (95 %) but low positive predictive value (10–20 %) for SCD [122, 123]. The significance of ventricular arrhythmias

may be age-dependent, with younger patients being at higher risk. In one study of 531 HCM patients, the odds ratio of SCD in patients ≤30 years of age with NSVT was 4.35 (95 % CI: 1.54–12.28, $P = 0.006$) compared with 2.16 (95 % CI: 0.82–5.69, $P = 0.1$) in patients >30 years of age [124]. An electrophysiologic study (EPS) to test for inducibility of VT is of little value in risk stratification: polymorphic VT and ventricular fibrillation (VF) are often induced, which are considered nonspecific endpoints [120, 125, 126].

Expert consensus has identified major risk factors for SCD in HCM patients [65, 118]. In general, these seem to be more significant in younger patients and include NSVT, family history of SCD, syncope, massive LVH (wall thickness is ≥30 mm), and a hypotensive or flat blood pressure response to exercise. Other factors that have been proposed or considered include young age at diagnosis, degree of late gadolinium enhancement on cardiac MRI, and degree of left ventricular outflow tract obstruction [118]. Genetic testing is of limited value for risk stratification because of the large number of mutations, many of which may be novel to a given family [118].

While there is general consensus on the identity of the major risk factors, their positive predictive value is low. Although the annual risk of SCD in a community-based HCM population may be 1 % or less, at least one risk factor may be found in nearly 50 % of HCM patients [119]. Even a single major risk factor can be significant, however. In one retrospective ICD study, 35 % of HCM patients with an ICD implanted for primary prevention on the basis of a single identified risk factor received an appropriate ICD therapy [127].

US Guidelines provide broad latitude for ICD therapy in HCM patients. ICD implantation is considered "reasonable for patients with HCM who have 1 or more major risk factors for SCD" [65]. A European Task Force on SCD reserves their strongest recommendation for a primary prevention ICD in HCM patients to those with two or more risk factors but still provides that a single risk factor may be sufficient to decide to place an ICD [126]. The new HCM Risk-SCD calculator, which could be accessed at http://doc2do.com/hcm/web-HCM.html, was based on recommendation of the 2014 European guidelines for ICD. The ICD should be considered if the annual risk is >6 %, may be considered between 4 and 6 %, and should generally not be indicated if <4 % [128, 129]. Although this risk score performed better than the 2003 and 2011 guidelines, it still missed some high-risk patients in one cohort and overestimated the risk in another [130, 131].

There are no randomized trials of ICD therapy specific to HCM patients. In one retrospective study of 506 HCM patients with ICDs, 20 % had appropriate therapies with an intervention rate of 10.6 % and 3.6 % per year in secondary and primary prevention patients, respectively [127]. While appropriate ICD therapy does not equate to lives saved, it is argued that the discrepancy in HCM may be less than in ischemic heart disease. Due to the disorganized and thick myocardium, VT is poorly tolerated; moreover, polymorphic VT or VF may be unlikely to terminate spontaneously [119]. A meta-analysis of 2190 HCM patients with ICDs (mean age, 42 years; 83 % for primary prevention) across 16 studies showed a low annualized rate of cardiac and noncardiac mortality (0.6 % and 0.4 %, respectively). The rate of appropriate and inappropriate ICD intervention was 3.3 % and 4.8 % per year, respectively [132].

Ultimately, the decision to implant an ICD is an endeavor that requires discussion of the potential risks and benefits with each individual patient. The difficulty of these decisions is evident in an international registry of HCM patients under 20 years of age. Of 224 ICD patients (188 primary prevention), appropriate therapy was frequent (43 patients, 19 %), as were complications (91 patients, 41 %). A single risk facture identified some primary prevention patients at risk and the number of risk factors (1, 2, or 3) did not predict the likelihood of ICD therapy [133].

Catheter ablation of VT currently has only a very limited role in HCM patients. Polymorphic VT and VF, as opposed to monomorphic VT, are frequent and are not amenable to current mapping techniques. During EPS, polymorphic VT and VF were induced more than three times more frequently than monomorphic VT [134]. Stored electrograms in ICDs show that approximately half of the appropriate ventricular therapies are for VF [127]. In addition to mapping challenges, the thick, hypertrophic myocardium limits the effective delivery of radiofrequency energy to potentially critical myocardial sites. Nevertheless, a combination of epicardial and endocardial approaches may offer an option for the control of monomorphic VT in highly selected patients [135].

Arrhythmogenic Right Ventricular Cardiomyopathy

ARVC (also referred to as arrhythmogenic right ventricular dysplasia (ARVD), ARVD/C, or ARVC/D) is an inherited cardiomyopathy characterized by fibro-fatty replacement of portions of the myocardium, usually most evident in the right ventricle (RV). Patients may develop VT and SCD, particularly in association with exercise. Patients with ARVC may have multiple morphologies of VT, typically of "left bundle branch block morphology" reflective of RV origin [136, 137]. ARVC is inherited as an autosomal dominant trait caused by mutations in a variety of genes predominantly encoding proteins composing desmosomes. Given their role in cell-cell connection, defects in desmosomes may become clinically relevant at an earlier time in the thin-walled RV than the left ventricle (LV) [138]. Early pathologic studies showed a predilection for myocardial thinning, scarring, and aneurysm formation in the RV infundibulum, apex, and inflow regions [136, 139]. Electroanatomical mapping of the RV demonstrates areas of low voltage consistent with scar and correlating with myocardial scaring that may be identified by cardiac MRI [137, 139, 140].

Although VT and sudden death may occur at rest in patients with ARVC, there is a clear association with exertion. Athletes with a "definite," "borderline," or "possible"

diagnosis of ARVC are recommended not to participate in most competitive sports [117]. Beta-blockers are often used to attenuate sympathetic stimulation, although there is currently no evidence that they reduce mortality or ventricular arrhythmias [141]. Surprisingly, the clinical significance of VT in a given ARVC patient is uncertain. Mortality was low in early series of ARVC patients with VT who were treated primarily with antiarrhythmic drugs and very few ICDs [142, 143]. ARVC patients frequently have preserved LV function so VT may be better tolerated and may be less likely to degenerate into VF. Nevertheless, there is general consensus that ARVC patients with prior cardiac arrest, sustained VT, or VF should undergo ICD implant [65, 126]. Antitachycardia pacing is highly effective in terminating VT in ARVC patients and may reduce ICD shocks [144]. Available data from small studies of ARVC patients support the use of ICDs in such secondary prevention patients [144–147].

Guidelines support ICD implantation for primary prevention of sudden cardiac death in ARVC patients felt to be at high risk but, as opposed to HCM, consensus is lacking on the specific factors that identify high-risk individuals [65]. Retrospective ICD studies have variously identified predictors of subsequent ICD therapies that include a history of syncope [148] and NSVT and inducibility of sustained VT or VF [149] or spontaneous VT [144]. Interestingly, although considered a potential risk factor [126], a family history of SCD due to ARVC was not found to be a predictor of risk in multivariate analysis in several studies [144, 148, 149].

A meta-analysis of 610 primary and secondary prevention patients in 24 studies showed an annualized rate of appropriate and inappropriate ICD therapies of 9.5 % and 3.7 %, respectively. ICD-related complications were frequent (20.3 %), such as largely difficult lead placement and lead malfunction [150]. ICD implantation may be challenging in ARVC patients. Lead placement may be difficult due to low-voltage electrograms in the RV. Fatty infiltration and inflammatory changes in the RV may increase the risk of perforation [145, 148–150].

Although ablation is not considered a primary therapy for VT, it is an important adjunctive therapy to reduce ICD shocks. In contrast to HCM, in ARVC patients, VT is frequently monomorphic, sustained, and inducible with PES and may be hemodynamically stable. These features render VT more amenable to catheter ablation. Large and/or multiple regions of ventricular scarring, however, provide substrate for multiple forms of ventricular tachycardia. In more challenging cases such as these, "substrate modification" may successfully ablate VT. In these techniques mapping is performed during sinus rhythm to identify and target "potential" reentrant circuits [151].

The acute success rate of VT ablation may be increased with the addition of epicardial ablation techniques to the more traditional endocardial approach [152, 153]. The potential value of this approach is suggested by early morphologic studies of ARVC that showed that the pathologic process appears to begin, or is at least more extensive, in the epicardium and then extends toward the endocardium [137, 139]. Although ablation techniques may acutely reduce VT occurrence in ARVC, the continued progression of the pathologic process may still limit long-term VT-free survival.

Antiarrhythmic drugs alone have not been shown to reduce the risk of sudden death but are often used as adjunctive therapy to reduce shocks from ICDs. A report from the North American ARVC Registry showed that neither beta-blockers nor sotalol reduced the risk of ventricular arrhythmias, while amiodarone (used in only ten patients) had superior efficacy in preventing ventricular arrhythmias [141].

Arrhythmia-Induced Cardiomyopathy in Children

Children are not shrunken adults. They neither present with the same arrhythmias as adults nor is the approach to management necessarily the same as in adult patients. While we have a large number of adults with congenital heart disease and arrhythmias in our practice, we do not hesitate to refer to a pediatric electrophysiologist when appropriate.

Outcomes in children or infants with dilated cardiomyopathy are poor [154]. The search for reversal causes, such as AIC, must be rigorous. Supraventricular tachyarrhythmias are more common than ventricular arrhythmias in children. Consequently, in the pediatric population, AIC is more commonly caused by atrial.

Atrial Tachycardia (AT) as a Cause of Pediatric AIC

Ectopic atrial tachycardia is an uncommon arrhythmia in infants and children, but it is associated with AIC. Koike et al. reported on a small series of nine patients in 1988 with what they referred to as "atrial automatic tachycardia." Over half the patients in that series had dilated cardiomyopathy. They also noted that 33 % of the patients had spontaneous resolution of their arrhythmia [155].

A more recent multicenter retrospective review of 249 patients with focal atrial tachycardia (FAT) reported a 28 % incidence of dilated cardiomyopathy [156]. They found an overall rate of resolution of the FAT in 89 %. Antiarrhythmic drug therapy was utilized in 154 patients. The most common agent used was a β-blocker in 53 %, with an efficacy rate of 42 %. Antiarrhythmic drug therapy controlled the FAT in 72 %. Catheter ablation controlled the FAT in 80 % of the patients. The authors highlight the wide variation in approaches. Similar to the study by Koike, this study also found that the FAT resolved spontaneously in approximately one-third of the patients [156].

Permanent Junctional Reciprocating Tachycardia (PJRT) as a Cause of Pediatric AIC

PJRT is a reentrant tachycardia mediated by an unusual accessory pathway. This is a "long RP" tachycardia seen in infants and children. PJRT is often incessant. Because PJRT

can occur in infants, the first manifestation may be AIC and HF. In a recent review, 7 % of the case presented as hydrops in neonates. The rhythm rarely resolves spontaneously. Fortunately, it is amenable to catheter ablation, thought control with an antiarrhythmic may be used initially to allow for growth of the child prior to catheter ablation [157].

Junctional Ectopic Tachycardia (JET) as a Cause of Pediatric AIC

Junctional ectopic tachycardia is most often seen after surgery for congenital heart disease [158]. Less commonly it occurs in the absence of surgery. The nonsurgical form of JET is associated with high morbidity and mortality [159]. JET is often incessant and has been associated with AIC. Although the focus is often near the atrioventricular junction, catheter ablation is effective and can be performed with an acceptably low risk of inadvertent high-degree or complete AV block [159]. As in PJRT, medical control may be attempted in order to delay catheter ablation and allow the child to grow.

Summary of Treatment of Pediatric AIC

- As in adults with AIC, pediatric patients with AIC should also be treated with standard therapies for LV systolic dysfunction.
- Medical management is often required in order to allow for growth of the patient prior to catheter ablation.
- In atrial tachycardia, spontaneous resolution is seen in a substantial portion of patients, making medical control and delay in catheter ablation reasonable.
- Junctional ectopic tachycardia and PJRT rarely resolve spontaneously. Catheter ablation is frequently required.

Arrhythmias Related to Cardiac Sarcoid (CS)

Symptomatic cardiac involvement in patient with systemic sarcoidosis occurs in about 55 of patient; however, asymptomatic involvement can be 25 % based on autopsy or up to 55 % based on cardiac imaging. The main arrhythmic disorders observed are conduction abnormalities and ventricular tachycardia. CS may be difficult to differentiate from other forms of NICM, such as ARVC. Unlike ARVC, CS typically presents with more extensive LV scar and can have septal involvement. A full review of arrhythmia management in patients with CS was recently published in the 2014 HRS Expert Consensus Statement on the Diagnosis and Management of Arrhythmias Associated with Cardiac Sarcoidosis [160].

Conduction Abnormalities

Atrioventricular nodal (AV) block at various degrees is a common presentation of patients with CS. The most recent 2013 guidelines for device-based therapy included three CS-specific recommendations, all class IIa: a pacemaker is useful even if the AV block is transient, immunosuppression can be useful for Mobitz II and complete AV bloc, and ICD can be considered in patients with an indication for a permanent pacemaker [69]. Immunosuppression with corticosteroids reversed AV conduction in an average of 47 % of patients. When implanting a pacemaker, it is prudent to implant the device first and wait for the incision to heal before starting on immunosuppressants to decrease the risk of device infection.

Management of Ventricular Arrhythmias

In general, two main mechanisms are implicated in VT in patients with CS. VT can reentry around fixed scar in burned-out areas of myocardium and is typically monomorphic. The second mechanism is inflammation causing either monomorphic or polymorphic VT. The role of immunosuppression is controversial, with some studies showing decrease in arrhythmia burden, while others failed to benefit. Moreover, there are reports showing corticosteroids can exacerbate VT initially and can be linked to aneurysm formation. Theoretically, corticosteroids would be beneficial for arrhythmias in the initial inflammatory phase of the disease. The initial therapy of VT also includes antiarrhythmics including amiodarone and sotalol.

The largest published study of ablation therapy for VT in patients with CS included 21 patients [161]. The rate of complete acute procedural success was relatively poor, and freedom from VT after 1 year after a single ablation was only 25 % (37 % after multiple procedures). Ablation was effective, however, in acutely terminating VT storm in 78 %. Currently, VT ablation is considered for VT storms and high VT burden refractory to immunosuppressive and antiarrhythmic medical therapy.

Risk of SCD and Role of ICD

There is a paucity of data and factors to risk stratify patients with CS. For patients with an LVEF <35 % or history of VT/VF arrest, the need for an ICD is clear based on the major primary and secondary prevention trials. Most studies show that patients with normal RV and LV function have very low event rate. However, mild LV dysfunction does not seem to be benign. In the biggest cohort of patient with CS and ICDs reported, most of the patients who received appropriate shocks had an LVEF >35 % [162]. Hence, ICD implant may be considered (Class IIb) in patients with EF between 35 and 50 % despite immunosuppressive therapy. Otherwise, an CID can be useful (Class IIa) in patients with CS and an indication for a pacemaker implantation, history of unexplained syncope, or inducible sustained VT, irrespective of LVEF. The value of EP study is controversial (Class IIb), although an inducible VT is accepted as a Class IIa indication [160].

Arrhythmias in Patients with Left Ventricular Assist Devices (LVAD)

LVADs have been used increasingly in the management of medically refractory end-stage heart failure after the Randomized Evaluation of Mechanical Assistance for the

Treatment of Congestive Heart Failure trial (REMATCH) demonstrated a survival benefit from LVADs in patients with advanced end-stage heart failure [163]. These currently serve as a bridge to recovery in fulminate myocarditis or massive MI, as bridge to transplant, or as destination therapy. Patients with LAD still experience a significant burden of arrhythmias both in the postoperative period and later after recovery. Since most of the hemodynamic load is carried by the LVAD, one would suspect that the impact of arrhythmias would be minimal. However, both atrial and ventricular arrhythmias continue to impact these patient symptoms and quality of life.

Atrial Arrhythmias in Patients with LVAD

Atrial arrhythmias in LVAD patients comprise mostly of AFL and AFib. AFL can be a classic cavo-tricuspid isthmus-dependent flutter but may also be scar related from atriotomies performed during LVAD implantation or earlier cardiac surgeries. AFib is present in close to 50 % of the patients with LVAD in a study of 106 patients [164]. While paroxysmal AFib was not found to be associated with increased mortality, HF hospitalizations, bleeding, or thromboembolism, persistent AFib was an independent predictor of the composite endpoint of death or HF hospitalization, driven mostly by an increased risk of HF hospitalizations [164]. This suggests that the immediate hemodynamic impact of AFib on LVAD patients is likely to be minimal, but the more chronic presence of AFib and its burden might either affect the RV function or have a primary chronic hemodynamic impact in this patient population. There was no increase in bleeding or thromboembolism with persistent AFib, but thromboembolic events happened at higher INR in patients with AF [164]. Another study of 389 patients with LVAD showed that the presence of preoperative AFib was associated with an increased risk of thromboembolism after LVAD implant [165]. Both studies favor using a higher INR target of 2–3 rather than 2–2.5 in patients with LVAD. The latter study did not show a mortality impact from AFib but did not dichotomize patients into paroxysmal or persistent AFib.

In our experience, even paroxysmal AFib still impacts the quality of life in a limited number of patients, in which a rhythm-control approach with medical or ablation therapy should be considered. Intervention on AFib or AFL with ablation can positively impact their quality of life and RV function [166, 167].

Ventricular Arrhythmias in Patients with LVAD

Sustained ventricular arrhythmias (VA) are still frequent in up to 52 % of the LVAD population. They are often well tolerated but can still cause hemodynamic collapse and thromboembolism [168, 169]. The presence of preexisting VAs, cause of cardiomyopathy, device type, indication for support, and duration of follow-up have been found to be associated with the risk of post-LVAD VAs [170–173]. VAs are generally divided into two main categories that have different etiology distribution and different priorities for management options.

Early arrhythmias occur in the first 2–4 weeks after LVAD implant. They are mostly due to suck-down events, altered early repolarization, mechanical trauma and apical irritation caused by LVAD cannula, perioperative adrenergic stimulation and the use of adrenergic agonists, or simply recurrence of ventricular arrhythmias recorded before the LVAD implant. These arrhythmias tend to decrease in frequency in the initial recovery period. There is growing evidence that LVAD-induced unloading of the left ventricle may reduce the risk of VA through reverse electrophysiological remodeling and reduction of QRS and QT intervals [174]. The management of the early VAs consists of targeting their mechanism: fluid management with focus on the right ventricular function, reinitiating and advancing beta-blocker therapy as soon as deemed tolerable, antiarrhythmic therapy, and autonomic modulation like left stellate ganglion blockade in order to temporize VAs through the postoperative recovery period [175]. In select cases where the above measures are ineffective and the patient cannot tolerate frequent VAs that are hindering his recovery, ablation therapy can be considered (Fig. 19.5).

Late VAs occur after the first month post-LVAD implant. Only a minority (less than 15 %) of VAs are related to the inflow cannula. The majority of VAs are related to intrinsic myocardial scar present before the LVAD implant [176]. This agrees with the fact that the recurrence of post-LVAD VAs is higher in patients with secondary prevention ICDs compared to patients with primary prevention ICDs [177]. Management still includes ruling out suck-down events by interrogating the LVAD; manage the fluid status and RV function first before considering more invasive approaches. Antiarrhythmic medications can be tried as a first-line therapy. However, most of these patients are already on some

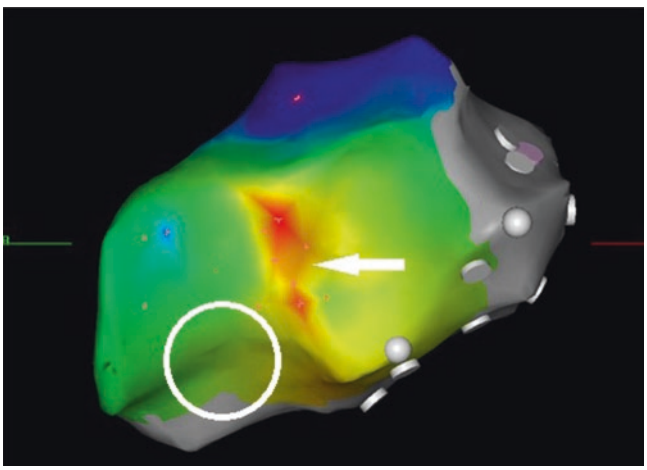

Fig. 19.5 Activation map of a pleomorphic VT induced by mechanical irritation of the cannula on the mid to distal lateral wall of the left ventricle. VT was refractory to beta-blockers and antiarrhythmics. The mechanism was confirmed with intracardiac echocardiography. Cannula location is illustrated with the *white circle*. Ablation at that level (*arrow*) inhibited VT. Patient had no recurrences, and we avoided revising the cannula because of cannula-induced VT

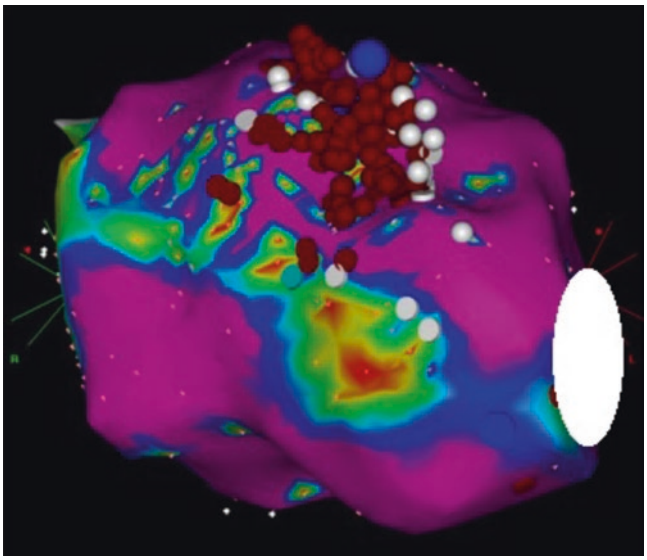

Fig. 19.6 Patient with ischemic cardiomyopathy with VT storm more than 1 month after LVAD implant, refractory to multiple antiarrhythmic medications, and beta-blockers. The LVAD cannula is represented by a *white circle*. The location of the VT (*blue dot*) was away from the cannula in a scar area located in the mid-anterior wall of the LV. Ablation at that location terminated VT storm and provided a more stable recovery

kind of antiarrhythmic medication before their implant and ablation therapy should be considered in refractory patients and especially in patient with hemodynamic compromise, high VA burden, and subsequent ICD shocks. Consideration should be given to increasing the threshold for therapy on the ICD by elevating the heart rate on the VT or VF detection zones and increasing detection times. VT ablation has a good acute success rate of 86 % for the first procedure, a recurrence rate of 33 % with limited follow-up [176, 178] (Fig. 19.6).

The association of VAs to mortality after LVAD implant is controversial, so is the utility of ICDs in increasing survival [179–181]. A recent meta-analysis of observational studies including 1179 patients found that post-LVAD VAs were associated with increased all-cause mortality at 60, 120, and 180 days, but only pre-LVAD VAs were independent risk factors of post-LVAD all-cause mortality [182]. This suggests that, while post-LVAD VAs are an indicator of worse outcomes, it might not be a direct cause. Studies are ongoing to assess the utility of ICD in patients with LVAD.

It is also important to recognize the potential for LVAD and ICD interaction. There have been several reports on electromagnetic interference of the HeartMate II LVAD with the ICD telemetry inhibiting communication between the ICD and its programmer in select ICD models [183]. The ICD lead characteristics can also be affected with a decrease in R-wave amplitude, a decrease in impedance, and an increase in capture threshold [183, 184]. This can lead to failure to sense VAs, failure to capture, and inappropriate pacing caused by undersensing. ICD interrogation should be performed after LVAD implant to detect these changes. The ICD can be tested to make sure it can detect VA and deliver therapy, and the lead should be revised if needed. However, the risks or revision should be weighed against the risks of infection in a patient population where the efficacy of the ICD is questioned, especially in patients with biventricular VADs and in patient close to being transplanted.

Autonomic Modulation for Arrhythmia Control

Several studies have shown that imbalance in the cardiac autonomous system and sympathetic nerve sprouting around the myocardium play a significant role in the genesis of VT/VF [185]. Sympathetic hyperactivity outside the heart has also been associated with increased incidence of VA [186]. Neuromodulation, designed to either increase the parasympathetic tone or decrease the sympathetic tone, is emerging as a viable therapy to treat refractory arrhythmias. It includes spinal cord stimulation, thoracic epidural anesthesia, renal denervation, and cardiac sympathetic denervation.

The effect of spinal cord stimulation in suppressing ventricular arrhythmias has been shown in animal models and in case reports in humans [187, 188]. This method has not shown a significant effect on cardiac remodeling in heart failure in a randomized feasibility study [189]. Although this study is not definitive, it is unclear whether this method is going to be studied further.

Renal denervation has shown additional benefits on top of AFib ablation in patients with persistent AFib and severe hypertension. The benefit of renal denervation for VT/VF was shown only in case studies [190, 191]. Ongoing studies include evaluation of renal sympathetic denervation (Renal Sympathetic Denervation to Suppress Ventricular Tachyarrhythmias [RESCUE-VT] and Renal Sympathetic Denervation as an Adjunct to Catheter-based VT Ablation [RESET-VT]) as adjuvant therapy to prevent recurrent VA [192, 193].

Cardiac sympathetic denervation was studied in left or bilateral stellate ganglia blockage (alcohol or RF ablation of ganglia or injection of anesthetic) or resection. Left and bilateral cardiac sympathetic denervation has been shown to acutely reduce the burden of ICD shocks and control VT storm in a small number of patients [194, 195]. Left versus bilateral stellate ganglia surgical resection was compared in a retrospective study of 41 patients [196]. There was a more decrease in ICD shock and VT burden in the bilateral resection arm. The risks of the procedure included change in sweating pattern in 10 %, ptosis in 2 %, and skin sensitivity in 12 % of the patients. The randomized PREVENT VT study (Cardiac Denervation Surgery for Prevention of Ventricular Tachyarrhythmias) is analyzing bilateral cardiac sympathectomy for the control of refractory VAs [197].

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