Antiarrhythmic Drug Therapy for New-Onset Ventricular Arrhythmia (VT/VF) in ICD Patients

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Implantable cardioverter-defibrillators (ICD) have been firmly established as the most effective treatment for primary and secondary prevention of sudden cardiac death (SCD) in a variety of conditions such as ischemic cardiomyopathy, nonischemic dilated cardiomyopathy, and other inherited genetic conditions affecting the heart (arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, the ion channelopathies, and so forth).[1–4] The use of ICD for prevention of SCD has increased exponentially over the past decade, and this has resulted in a large population of patients living with ICDs.[5–7] ICD patients and physicians treating them have to contend with the prospect of recurrent ventricular arrhythmia (ventricular tachycardia [VT] and ventricular fibrillation [VF]) resulting in therapy, including both shocks and antitachycardia pacing (ATP). Multiple randomized controlled trials (RCTs) have shown that about 20% of patients receiving ICDs will need adjunctive antiarrhythmic therapy to prevent ventricular arrhythmia and resultant ICD therapy.[8–14] There is growing evidence to suggest that ventricular arrhythmia resulting in ICD therapy is associated with a higher risk of morbidity and mortality.[15–17] Patients with symptomatic ventricular arrhythmia and ICD shocks may have restrictions imposed on them (eg, driving restrictions, inability to operate heavy machinery) that may result in loss of employment. In addition, frequent ICD therapy results in increased use of health care resources.[18–21] The purpose of this review is to understand the role of antiarrhythmic therapy in management of ICD patients with new-onset ventricular arrhythmia.

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INCIDENCE OF VENTRICULAR ARRHYTHMIA IN PATIENTS WITH ICD AND PROGNOSTIC SIGNIFICANCE

Data from large, randomized ICD trials have shown that by 4 years after implantation of an ICD 30% to 35% patients have experienced at least one shock. Further analysis revealed that two-thirds (16%–20%) of the shocks resulted from ventricular arrhythmia and one-third resulted from supraventricular arrhythmia, inappropriate sensing, or patient-related and device-related issues. This result translates to a 6% to 10% annual incidence of ventricular arrhythmia in ICD patients.[13–15,22] Data from trials incorporating ICD programming strategies to reduce shocks have shown that 85% of ventricular arrhythmias occurring in ICD patients were secondary to monomorphic VT (rates ranging from 188 to 250 beats/min) with VF accounting for the remaining 15%.[23–25]

Long-term follow-up data from large ICD trials, including the Multicenter Automatic Defibrillator Implantation Trial-II (MADIT-II) and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), have shown that new-onset ventricular arrhythmia in ICD patients conferred a threefold increase in the risk of death. The most common cause of death in these patients was progressive heart failure and nonsudden cardiac death. Recent trials evaluating optimal programming of ICD antitachycardia therapy parameters have shown that both appropriate and inappropriate shocks resulted in increased risk of death. Patients without any ventricular arrhythmia and patients treated with ATP alone fared better than patients receiving shocks (survival rates at 1 year were 5% lower).[11–14] Another interesting observation was that patients receiving ICD shocks were likely to have a high rate of recurrent ventricular arrhythmia, and in about 10% to 20% of cases the initial presentation was in the form of an electrical storm (ES; $\geq$3 episodes of VT separated by >5 minutes during a 24-h period, each resulting in an appropriate shock by the ICD). Electrical storms were associated with a very poor prognosis and resulted in a twofold to threefold increase in all-cause and cardiac mortality.[26–28] Lastly, in 8% to 10% of patients supraventricular arrhythmias, especially atrial fibrillation (AF), may be responsible for triggering ventricular arrhythmia, resulting in ICD shocks.[29] Multivariate analyses of pooled data from primary and secondary prevention ICD trials have identified risk factors for ventricular arrhythmia and ICD shocks (summarized in **Box 1**).[12,15]

Patients receiving frequent ICD shocks have poor health-related quality of life and psychological distress ranging from posttraumatic stress disorder to depression. Such patients require frequent emergency department and hospital visits, and may have accelerated battery depletion resulting in increased use of health care resources.[18–20,30]

Box 1
Clinical predictors of recurrent ventricular arrhythmia and ICD therapy

- Secondary prevention indication and/or appropriate therapy after ICD implantation
- Congestive heart failure
- Severe left ventricular systolic dysfunction (left ventricular ejection fraction <25%)
- Associated acute coronary syndrome
- Associated supraventricular tachycardia (especially atrial fibrillation)

The trials quoted have exclusively included patients with ischemic or nonischemic dilated cardiomyopathy. Patients receiving ICD for other indications such as arrhythmogenic right ventricular cardiomyopathy, hypertrophic cardiomyopathy, cardiac valve disease, and ion channelopathies are underrepresented in these studies. Information regarding incidence of ventricular arrhythmia and ICD shocks in these patients is based on anecdotal reports and small cohort studies. A French cohort study including more than 2000 patients reported that the incidence of ventricular arrhythmia in the group of ICD patients, without ischemic or nonischemic dilated cardiomyopathy, was similar to that observed in the large, randomized ICD trials quoted previously. However, the incidence of appropriate ICD shocks was noted to be lower in this cohort of patients.[31]

It is clear that most patients will develop ventricular arrhythmia at some point in time after ICD implantation and that this is a poor prognostic indicator, contributing to morbidity and mortality. Therefore, there is growing interest in prevention of ventricular arrhythmia and ICD shocks in these patients. However, it is as yet not clear if ventricular arrhythmia in this situation is causative of death or simply a marker for poor prognosis resulting from progressive ventricular systolic dysfunction and other comorbid conditions. The available data seem to suggest that both factors may be responsible for the poor prognosis noted in ICD patients developing ventricular arrhythmia. The final question that is yet to be answered is: will prevention and treatment of ventricular arrhythmia translate to improved survival in ICD patients?