Empiric Antiarrhythmic Drug Therapy in Patients With Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Pragmatism or Anachronism?*

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In this issue of the *Journal*, Marcus et al. (1) present an observational study of ventricular tachycardia (VT)/ventricular fibrillation (VF) outcomes associated with use of specific empiric antiarrhythmic drug (AAD) therapies in a well-documented population of patients with arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) from the prospectively collected North American ARVC Registry. The ARVC/D patients from this registry who had received an implantable cardioverter-defibrillator (ICD) were followed up for the subsequent occurrence of VT/VF. For each analysis, outcomes during periods of time patients received a specific AAD therapy were compared with periods of time that patients did not receive that AAD therapy and with periods of time that patients did not receive any AAD therapy using time-dependent covariate analyses. The results suggest that empiric standard beta-blockers neither increased nor decreased follow-up VT/VF (with weak evidence of a decrease in some analyses), that empiric sotalol did not decrease follow-up VT/VF (with more convincing evidence of an increase in some analyses), and that empiric amiodarone decreased follow-up VT/VF.

The major strengths of the report are the extent to which the patients were investigated to define the presence of ARVC/D, the relatively large size of the ARVC/D population studied, and the use of prospectively collected data. Furthermore, this is the first rigorous evaluation of empiric AAD therapy in this setting, and ascertainment of VT/VF outcomes was maximized by studying patients with ICDs.

The major weaknesses of the report are those inherent to observational trials, the small numbers of patients with ARVC/D who received each AAD therapy, and the substantial number of comparisons that increase the probability that an apparently statistically significant difference resulted from chance alone. The observational nature of the study indicates that use of specific AAD therapies was uncontrolled, raising the possibility that therapy selection was based on unmeasured factors that may have impacted outcomes. For a trial of patients with ARVC/D, the study by Marcus et al. (1) is large. Nevertheless, the numbers of patients who received each AAD therapy were small (n = 58 for standard beta-blockers, n = 38 for sotalol, and n = 10 for amiodarone). The multiple statistical comparisons question the veracity of any apparent statistically significant differences. The study population is simply too small to use the standard statistical corrections for these multiple comparisons.

Drawing inferences from these results requires consideration of the goals of AAD therapy and previously published data from this and other clinical settings.

As with any therapy, use of AAD therapy demands a clear formulation of the goals of therapy. Relative to AAD therapies, the dominant goals are prevention of sudden death, expecting that achieving this goal will decrease all-cause mortality, and prevention of VT/VF. Although frequently concurrent, these 2 goals are not necessarily synonymous. There are frequent instances when the achievement of both goals is impossible, unnecessary, or inadvisable. When AAD therapy for prevention of VT/VF was first attempted in patients resuscitated from sustained VT/VF, most of whom had coronary artery disease (CAD) and prior myocardial infarction (MI), empiric AAD therapy (that chosen without objective evidence of a beneficial antiarrhythmic effect) was not associated with reductions in VT/VF or sudden death (2). Alternatively, AAD therapy individualized for a specific patient by demonstration of an apparent beneficial effect by either suppression of frequent/complex ventricular ectopy or suppression of VT/VF induced by programmed stimulation was suggested to reduce VT/VF occurrences (3,4). However, this advantage has not been shown to translate into a reduction of sudden death or all-cause mortality (5). Empiric amiodarone therapy was an exception because it was found to decrease both VT/VF and sudden death, although the latter translated only weakly to a reduction in all-cause mortality (6). When the ICD was shown to be effective for the purpose, ICD implantation became the dominant approach to the prevention of sudden death and all-cause mortality in patients with a propensity to VT/VF and AAD therapies were largely abandoned for this purpose. However, because current ICDs do not

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prevent VT/VF and because ICD therapies for VT/VF may be both harmful and hurtful, AAD therapy for the goal of preventing VT/VF and their ICD treatments has had a resurgence. Empiric AAD therapies are usually used in this setting. In patient populations dominated by those with CAD and prior MI, evidence of a reduction in ICD therapies for VT/VF has been reported for empiric treatment with standard beta-blockers (7), sotalol (8), and amiodarone (9). In the study by Marcus et al. (1), only empiric amiodarone was effective in patients with ARVC/D. Of course, these differences may relate to differences in the patients’ structural heart disease. Nevertheless, these apparent differences may be caused by artifacts. With respect to standard beta-blockers, some of the analyses by Marcus et al. (1) suggest a decrease in follow-up VT/VF, and at least 1 study, in a population dominated by patients with CAD and prior MI, suggested that compared with empiric standard beta-blockers, empiric sotalol therapy may increase subsequent VT/VF (10). Nevertheless, 2 other trials found that empiric sotalol therapy neither increased nor decreased subsequent VT/VF (9,11). In this regard, it is notable that, as in patients with CAD and prior MI (12), sotalol therapy individualized by suppression of inducible VT/VF by programmed stimulation is the single most frequently predicted-effective AAD therapy and is also effective in preventing follow-up VT/VF in patients with ARVC/D (13). When sotalol is to be used in this setting with the strong intent to prevent VT/VF, consideration should be given to first predicting its efficacy by the programmed stimulation approach.

In conclusion, Marcus et al. (1) provide us with important data regarding the empiric use of AAD therapy in patients with ARVC/D. In distinction to patients with CAD and prior MI, the finding that standard beta-blockers may not reduce the probability of VT/VF in patients with ARVC/D argues against its use in all patients. Nevertheless, the simplicity and safety of empiric beta-blocker therapy coupled with the suggestion of benefit in some of the analyses of Marcus et al. (1) recommends that beta-blockers be used first when the goal of prevention of VT/VF is established unless permitting additional episodes of VT/VF is highly undesirable. Empiric sotalol therapy is now more difficult to recommend, especially when permitting additional episodes of VT/VF is highly undesirable. It appears that, as in other settings, the most effective empiric AAD therapy in patients with ARVC/D is amiodarone.

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