Determinants of Antiarrhythmic Drug Efficacy for Ventricular Tachyarrhythmias Using Ambulatory Monitoring and Electrophysiological Techniques

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Sustained ventricular tachycardia and ventricular fibrillation are life-threatening arrhythmias with high rates of recurrence.12 Empiric antiarrhythmic drug therapy has a low success rate for preventing recurrences of these arrhythmias.3 Therefore, the choice of drug therapy has centered around two methodologies to predict drug efficacy: programmed ventricular stimulation with serial drug testing and suppression of asymptomatic ventricular arrhythmias detected by ambulatory monitoring recording and exercise stress testing. There is evidence that both approaches can successfully identify appropriate prophylactic antiarrhythmic drug therapy for sustained ventricular tachyarrhythmias.3-6 The study reported in this issue of Circulation7 was designed to compare the effectiveness of these two methodologies in determining antiarrhythmic drug treatment for such arrhythmias and to identify any clinical characteristic that can help predict drug efficacy in the context of these different methodologies.

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Summary of Findings in the Present Study

The ESVEM investigation patients were either resuscitated from sudden cardiac death events or had electrocardiographically documented sustained ventricular tachycardia or had unmonitored syncope with inducible sustained monomorphic ventricular tachycardia and had more than 480 ventricular premature complexes during 48 hours of ambulatory monitoring. At electrophysiologic study, they all had inducible ventricular tachycardia or ventricular fibrillation. They were randomized, using key clinical characteristics (ejection fraction, ventricular premature complex frequency, presenting arrhythmia, functional class, and type of chronic heart disease) to ensure comparability to other electrophysiologic- or ambulatory monitoring-guided drug therapy.7

A prediction of antiarrhythmic drug efficacy was found in 108 of 242 patients (45%) in the electrophysiological-guided therapy group and in 189 of 244 patients (77%) in the ambulatory monitoring-guided group. By univariate and multivariate analyses, the absence of coronary artery disease, an ejection fraction >0.25, and a mean hourly ventricular premature complex frequency of less than 30 all predicted a determination of drug efficacy in the electrophysiological-guided therapy group. No clinical variable by univariate analysis did so in the ambulatory monitoring-guided therapy group. Via multivariate analysis, only an ejection fraction >0.25 predicted a determination of drug efficacy in the ambulatory monitoring-guided therapy group.

Comparison With Previous Studies

The current study confirms a number of previously noted observations regarding the prevalence and efficiency of achieving predictions of antiarrhythmic drug efficacy as well as the clinical factors that may influence the outcome of drug testing in patients with inducible ventricular tachyarrhythmias by electrophysiological- and ambulatory monitoring-guided modalities.

Kim et al8 reported on the discordance between prediction of drug efficacy for type Ia antiarrhythmic drugs by electrophysiological and ambulatory monitoring modalities. The cumulative prevalence of drug efficacy determined by both modalities and the prevalence for each modality individually found in the current study are similar to but lower than those determined by Mitchell et al9 (overall prevalence of drug efficacy: Mitchell et al, 77%; ESVEM, 61%; prevalence of electrophysiological-guided drug efficacy: Mitchell et al, 54%; ESVEM, 45%; prevalence of ambulatory monitoring-guided drug efficacy: Mitchell et al, 100%; ESVEM, 77%). For the electrophysiologic limb the prevalence of drug efficacy is comparable to those found in other studies.10,11

In the current study the clinical variables of low ejection fraction,10 presence of coronary disease,11 and high ventricular premature complex frequency were found as negative predictors of drug efficacy by electrophysiological-guided modality. Previous investigators demonstrated that the presence of clinical congestive failure,12 a left ventricular aneurysm,13 a large number of prior antiarrhythmic drug trials,11 or arrhythmia episodes,11 sustained ventricular tachycardia as the pre-

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senting or induced arrhythmia,\textsuperscript{15} and male gender\textsuperscript{11} were negative predictive factors for determination of drug efficacy by univariate and multivariate analysis.

The present study did note trends, which did not reach statistical significance, for female gender, absence of coronary disease, and low ventricular premature complex frequency to be univariate correlates of failure of drug efficacy in the ambulatory monitoring limb. Clinical correlates of antiarrhythmic drug efficacy via ambulatory monitoring have not been as extensively studied as those for electrophysiological-guided drug testing. Although these findings in the ambulatory monitoring limb differ from those in the electrophysiological limb, their potential significance should not be disregarded.

Factors That Might Reduce the Prevalence of a Drug Efficacy Prediction in the Electrophysiological Limb of the ESVEM Study Compared With Previous Studies

Differences in inclusion criteria and the prevalence of certain clinical characteristics between the ESVEM study\textsuperscript{7} and previous studies examining antiarrhythmic drug efficacy via electrophysiological testing could account for the apparent reduced predicted drug efficacy rate found in the present study.

In the ESVEM study, a relatively higher proportion of patients had symptomatic congestive heart failure than in previous studies, with 73\% of patients in functional class II–IV by the SAS classification and an overall slightly lower mean ejection fraction of 32±12\%.

In the study by Mitchell et al,\textsuperscript{9} no specific functional classification was given, but the mean ejection fraction was 34±13\%, whereas in the study by Swedlow et al,\textsuperscript{11} only 60\% of the patients were in functional class II–IV by the SAS system.

The relatively higher percentage of patients with coronary artery disease in the ESVEM could also contribute to a reduced prevalence of predicted drug efficacy. In the ESVEM study, 83\% of patients in the electrophysiological limb had coronary disease, whereas in the study by Mitchell et al,\textsuperscript{9} 75\% of the patients had coronary disease.

A third difference in inclusion criteria prevalence is the relatively higher percentage of patients (97\%) with inducible sustained monomorphic ventricular tachycardia. In previous studies, with higher prevalences of predicted drug efficacy, the percentage of patients with sustained ventricular tachycardia varied between 35\% and 82\%.\textsuperscript{8–10,14,15}

Finally, in the ESVEM trial, the use of exercise testing to modify the efficacy prediction in the electrophysiological limb may have contributed to reducing the prevalence of predicted drug efficacy compared with all previous studies in which exercise testing was never so employed. In the ESVEM trial, 16 patients with predicted drug efficacy by electrophysiological testing were ultimately classified as drug failure because of a positive exercise test. If these patients were reclassified as drug efficacy by electrophysiological testing alone, the prevalence of predicted drug efficacy in the electrophysiological limb would be increased from 45\% to 51\%.

Factors That Might Bias the ESVEM Study Toward a Higher Prevalence of Predicted Drug Efficacy in the Ambulatory Monitoring Limb

The criteria for predicted drug efficacy via ambulatory monitoring used in the ESVEM study are less stringent than those used previously. Prior studies generally required a 70\% reduction in isolated ventricular premature complex frequency, a 90\% reduction in ventricular couplet frequency, and complete eradication of nonsustained ventricular tachycardia during 24-hour ambulatory monitoring to determine drug efficacy and minimize the influence of spontaneous variability.\textsuperscript{16–18} Some of the differences in the ambulatory monitoring criteria are related to the use of 48 hours of ambulatory monitoring in the ESVEM trial. Under these circumstances, a lower suppression rate will still indicate a drug effect rather than spontaneous variability. However, when subgroup analysis is applied, despite the use of a longer duration of ambulatory monitoring in the ESVEM trial, the criteria used are still too lenient and could result in an artifactual determination of drug efficacy.

Specifically, previous studies by Pratt et al\textsuperscript{19} showed that spontaneous variability in ventricular ectopy is increased in coronary disease patients such that for 48 hours of ambulatory monitoring a 73\% reduction in mean ventricular premature complex frequency is necessary to ensure a drug effect. Since 86\% of patients in the ambulatory monitoring limb of the ESVEM study had coronary disease, the higher percentage of reduction in mean ventricular premature complex frequency should have been used as the criteria for predicted drug efficacy.

Furthermore, the degree of spontaneous variability in ambient ventricular ectopy in coronary disease patients within 60 days of an acute infarct is also increased and would require an 87\% reduction in mean ventricular premature complex frequency for the ESVEM study to ensure a drug effect.\textsuperscript{20} In the ESVEM trial, the exclusion criteria for recent infarct is ≤21 days. Thus, for patients included in the study who had had their infarction 22–60 days previously, a higher percent suppression of mean ventricular premature complex frequency should have been used to avoid an artifactually increased prevalence of predicted drug efficacy.

Finally, Pratt et al\textsuperscript{20} demonstrated that for high-frequency nonsustained ventricular tachycardia (i.e., ≥10 episodes per 24 hours), only a 74\% reduction in episodes of nonsustained ventricular tachycardia for 48 hours of ambulatory monitoring is required to ensure a drug effect. However, for low-frequency nonsustained ventricular tachycardia (five or fewer episodes per 24 hours), complete eradication of nonsustained ventricular tachycardia is required. Although in the ESVEM trial no specifics are given about the number of patients in the ambulatory monitoring limb with low-frequency nonsustained ventricular tachycardia, previous reports indicate that the majority of such patients (≥70\%) have low-frequency nonsustained ventricular tachycardia (i.e., less than five episodes per 24 hours). Thus, it can be contended that the more stringent and commonly used criteria of complete eradication of nonsustained
ventricular tachycardia should have been used in the ESVEM trial.

Implications of the ESVEM Study for Therapeutic Approaches to the Sustained Ventricular Tachyarrhythmias

As documented in the ESVEM study and previous studies, determination of drug efficacy by the ambulatory monitoring approach requires less time than the electrophysiological approach, thereby potentially shortening hospitalization and reducing overall costs of treatment. However, as the authors indicate, this observation may be of little value for cost savings if the ambulatory monitoring approach is not at least equally successful as the electrophysiological approach in determining effective long-term antiarrhythmic drug therapy. So far, at least one previous comparative study that directly examined this question showed that electrophysiological-guided therapy was definitely superior. Finally, although it would still be of value academically to know which of the two approaches is more accurate in choosing effective antiarrhythmic drug therapy for sustained ventricular tachyarrhythmias, it may become a moot point, clinically. Implanted pacemaker defibrillators have the highest efficacy in preventing sudden cardiac death or syncope due to recurrent ventricular tachyarrhythmia (i.e., 0.5–1.0% annual sudden death rate versus a 3–10% annual sudden death rate with predicted effective antiarrhythmic drug therapy via electrophysiological approach). Currently, antiarrhythmic drug therapy is still particularly useful for patients who are not candidates for surgical intervention. However, as technological advances allow miniaturization of the pacemaker defibrillators so they can be implanted in an infraclavicular pocket and the nonthoracotomy lead systems become FDA approved and more widely available, antiarrhythmic drug therapy for life-threatening ventricular tachyarrhythmias may be relegated to a second-line approach.

References

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