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Sudden Cardiac Death Risk Stratification in Patients With Nonischemic Dilated Cardiomyopathy

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Objectives The purpose of this study was to provide a meta-analysis to estimate the performance of 12 commonly reported risk stratification tests as predictors of arrhythmic events in patients with nonischemic dilated cardiomyopathy.

Background Multiple techniques have been assessed as predictors of death due to ventricular tachyarrhythmias/sudden death in patients with nonischemic dilated cardiomyopathy.

Methods Forty-five studies enrolling 6,088 patients evaluating the association between arrhythmic events and predictive tests (baroreflex sensitivity, heart rate turbulence, heart rate variability, left ventricular end-diastolic dimension, left ventricular ejection fraction, electrophysiology study, nonsustained ventricular tachycardia, left bundle branch block, signal-averaged electrocardiogram, fragmented QRS, QRS-T angle, and T-wave alternans) were included. Raw event rates were extracted, and meta-analysis was performed using mixed effects methodology. We also used the trim-and-fill method to estimate the influence of missing studies on the results.

Results Patients were 52.8 ± 14.5 years of age, and 77% were male. Left ventricular ejection fraction was 30.6 ± 11.4%. Test sensitivities ranged from 28.8% to 91.0%, specificities from 36.2% to 87.1%, and odds ratios from 1.5 to 6.7. Odds ratio was highest for fragmented QRS and TWA (odds ratios: 6.73 and 4.66, 95% confidence intervals: 3.85 to 11.76 and 2.55 to 8.53, respectively) and lowest for QRS duration (odds ratio: 1.51, 95% confidence interval: 1.13 to 2.01). None of the autonomic tests (heart rate variability, heart rate turbulence, baroreflex sensitivity) were significant predictors of arrhythmic outcomes. Accounting for publication bias reduced the odds ratios for the various predictors but did not eliminate the predictive association.

Conclusions Techniques incorporating functional parameters, depolarization abnormalities, repolarization abnormalities, and arrhythmic markers provide only modest risk stratification for sudden cardiac death in patients with nonischemic dilated cardiomyopathy. It is likely that combinations of tests will be required to optimize risk stratification in this population. (J Am Coll Cardiol 2014;63:1879–89) © 2014 by the American College of Cardiology Foundation

Sudden cardiac death (SCD) occurs in 184,000 to 462,000 people annually in the United States (1). Although the majority have ischemic heart disease, a substantial fraction have nonischemic dilated cardiomyopathy (NIDCM). Primary prevention of SCD focuses on identifying high-risk subpopulations of patients who could benefit from more intensive therapies, such as the implantable cardioverter-defibrillator (ICD), which reduces mortality in selected subgroups of patients (2,3).

See page 1890

NIDCM is the second leading cause of left ventricular systolic dysfunction (4) with a 12% to 20% estimated mortality at 3 years (2,3,5). Death occurs from both advanced heart failure and SCD. In a meta-analysis of ICD trials in patients with NIDCM, there was a 31% mortality reduction with ICD therapy (6), indicating that SCD due to ventricular tachycardia (VT)/ventricular fibrillation (VF) accounts for a substantial proportion of the mortality in this disease, although the ICD may also prevent SCD secondary to bradyarrhythmias in some patients.

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Abbreviations and Acronyms

BRS = baroreflex sensitivity
CI = confidence interval
EPS = electrophysiology study
HRT = heart rate turbulence
HRV = heart rate variability
ICD = implantable cardioverter-defibrillator
LVEDD = left ventricular end-diastolic dimension
LVEF = left ventricular ejection fraction
NIDCM = nonischemic dilated cardiomyopathy
NSVT = nonsustained ventricular tachycardia
SAECG = signal-averaged electrocardiogram
SCD = sudden cardiac death
TWA = T-wave alternans
VF = ventricular fibrillation
VT = ventricular tachycardia

Both the potential for improved survival with the ICD and the challenge of optimally deploying this therapy to the patients who will benefit from it highlight the importance of risk stratification in NIDCM. Despite the plethora of available techniques, no definitive test or set of tests is recommended for this population (1). Most studies that have addressed this issue are either small and nonrandomized or are challenged by the use of a variety of endpoints. The aim of this analysis was to aggregate the results of available studies in an attempt to provide a platform for future development of a risk stratification algorithm.

Methods

Literature search. We sought to identify all published reports evaluating predictors of arrhythmic events in patients with NIDCM. A primary prevention population was targeted, but studies that included a small proportion of secondary prevention patients (<20%) were also included.

The search was performed with the MEDLINE electronic database and was supplemented with manual searches through the reference lists of the publications. Key words used were "nonischemic cardiomyopathy" and "idiopathic dilated cardiomyopathy." The scope of the database search was further defined by the following predictors: baroreflex sensitivity (BRS), electrophysiology study (EPS), heart rate turbulence (HRT), heart rate variability (HRV), left ventricular end-diastolic dimension (LVEDD), left ventricular ejection fraction (LVEF), nonsustained ventricular tachycardia (NSVT), QRS duration, fragmented QRS, QRS-T angle, signal-averaged electrocardiogram (SAECG), and T-wave alternans (TWA).

Only English language studies involving human subjects published from inception to 2012 were considered. If multiple publications from the same patient cohort were discovered, we used the data from the latest reports with the largest numbers of appropriate subjects and outcomes. Unpublished data from the DEFINITE (DEFIbrillators in Non-Ischemic cardiomyopathy Treatment Evaluation) trial (3) were available to the investigators and were also included in the summary results.

The initial list of candidate publications was constructed by crossing all studies including NIDCM populations with each of the predictor categories. The abstracts of the identified reports were examined for presence of arrhythmic outcomes and follow-up endpoints. Studies that did not report follow-up data or did not use predictors of interest were excluded from further consideration. Full texts of the publications identified at this stage were independently examined by 2 investigators, raw data were extracted where possible, and the results were independently verified by a third author. Studies in which outcomes for NIDCM patients were not reported separately from ischemic cardiomyopathy patients were excluded (Fig. 1).

Data extraction. Raw counts of true positives, false positives, false negatives, and true negatives were extracted from each study whenever possible. When raw data were not reported, proportions of positive cases, event rates, risk ratios, sensitivity, and specificity were used to calculate the raw numbers. Some of these statistics were on the basis of survival analyses rather than on contingency tables; therefore, derived estimates were included in this report when they matched the reported data to within 10%. This margin of error was deemed acceptable as predictor effectiveness was on the basis of survival curves rather than raw numbers in many reports.

In addition to raw counts, we extracted baseline patient characteristics, medical covariates, medications, endpoints used, and length of follow-up from each report. In studies that included both NIDCM and ischemic cardiomyopathy patients, baseline demographic characteristics were used only if reported separately for NICDM.

Evaluation of test results. Several of the studied parameters had nonuniform definitions of abnormal results, examples of which are noted below. Patients with positive and indeterminate TWA findings were generally analyzed in the same group and compared against patients with negative TWA in the majority of the reports, although 5 studies excluded patients with indeterminate TWA. Positive EPS was variably defined and included inducible monomorphic and polymorphic VT as well as VF. Cut-offs for abnormal LVEDD varied between 64 mm and 70 mm, and for LVEF, between 25% and 35%. Abnormal QRS duration was defined by a cut-off of 110 ms to 120 ms. The cut-offs for abnormal HRV varied between 50 ms and 120 ms for SDNN (standard deviation of NN [normal RR] intervals). Abnormal BRS was defined by >3 or >6 ms/mm Hg. Two studies used both slope and onset criteria to define abnormal HRT, whereas the third only used slope.

Endpoints. When available, arrhythmic endpoints were utilized: sudden or arrhythmic death, cardiac arrest, appropriate ICD therapy, and documented VT/VF. If arrhythmic endpoints were not reported, total mortality was included. Finally, studies in which nonarrhythmic events (i.e., cardiac or heart failure mortality, heart transplantation) were included in composite endpoints with arrhythmic events were also accepted, but in the vast majority of studies a primary arrhythmic endpoint was noted.

Data analysis. Baseline characteristics from the included studies were summarized by using weighted averages of means and standard deviations for continuous variables.