Heart Rhythm Disorders

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).

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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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 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 NIDCM.

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.
Patient counts were summed and the final percentage was calculated directly from raw numbers. Not all studies reported on each of the identified patient characteristics; therefore, different studies are incorporated in the summary for each patient characteristic, and the resulting statistics provide only a rough estimate of the population summarized in this report.

Estimates of 3-year event rates for each study were on the basis of the reported number of events and mean or median follow-up time. Exponential survival (constant mortality rate through time) was assumed in calculating 3-year event rates. Aggregate 3-year event rates for each predictor category were calculated as average study duration weighted by the number of patients in each study.

Data from individual studies were combined to produce aggregated estimates separately for each predictor category using the random-effects model in SAS PROC MIXED (SAS Institute, Cary, North Carolina). Log-odds ratios were used as measures of effect, and their respective variances were specified as known diagonal elements in the R covariance matrix. For studies with no patients in at least 1 of the cells, 0.5 was added to all 4 elements of the 2-by-2 summary tables. Meta-analytic summaries on the basis of ordinary risk ratios were also calculated using the Mantel-Haenszel random-effects method. Finally, the “trim and fill” strategy for estimating the number of studies omitted because of publication bias and adjusting for the latter by symmetrical imputation of the omitted studies was used (7).

**Results**

**Patient characteristics.** Forty-five studies enrolling 6,088 patients with NIDCM were summarized in this meta-analysis (Table 1). Age was 52.8 ± 14.5 years (within-study averages ranged between 39 and 65 years); 77% were male (range 57% to 94%). Average New York Heart Association functional class was 2.3 ± 1.0 (range 1.5 to 3.4). LVEF was 30.6 ± 11.4%; LVEDD was 66.1 ± 8.9 mm.
Performance of individual risk stratification tests. The results for each predictor grouped by category are shown in Figure 2 (8–59), and summarized in Table 2. (A detailed list by predictor is given in Online Table 1).

Raw endpoint rates varied between 4.8% and 79.3%; however, these event rates reflect highly variable follow-up durations (10 months to 8 years) and are not, therefore, directly comparable. Weighted average follow-up duration was 33.6 ± 19.9 months for all studies (median 29, interquartile range 19 to 39 months). The LVEF studies had the longest weighted average follow-up duration (41 months, range 14 to 96 months), and TWA had the shortest (24 months, range 13 to 52 months). Using exponential survival assumption, estimated average 3-year event rate across all studies was 18.9 ± 12.8%. Estimated 3-year event rates for individual studies ranged from 4.5% to 79.3%. When aggregated by predictor, the variability of the 3-year mortality estimate decreased—11.8% to 21.5%.

Table 2 summarizes the sensitivities and specificities for the 12 predictor tests. Sensitivities ranged from 28.8% to 91.0%, and specificities ranged from 36.2% to 87.1%.

Performance of risk stratification tests was compared by estimating the odds ratio (OR) for patients with and without the predictor. The ORs were highest for fragmented QRS (OR: 6.73, 95% confidence interval [CI]: 3.85 to 11.76) and TWA (OR: 4.66, 95% CI: 2.55 to 8.53) and lowest for QRS duration (OR: 1.51, 95% CI: 1.13 to 2.01). All predictors had significant OR for identifying events in the functional, arrhythmia, depolarization, and repolarization categories (p ≤ 0.014 for all). Only 1 study was available for QRS-T angle, which was also a significant predictor of adverse events (p = 0.006). None of the 3 autonomic-based predictors was predictive.
To provide visual evaluation of the potential for publication bias, in Figure 2, the studies are arranged in increasing order of their contribution to the meta-analytic estimate from top to bottom. Because estimates of the predictor effects are more precise when more information is available, one would expect a “funnel” pattern on the plots. As the precision of the estimates increases, the scatter on the horizontal dimension should decrease toward the bottom of the figure.

The OR plot for TWA is representative in this regard. Three of the 4 studies with highest weights report OR estimates that fall below the meta-analytic estimate. The CI for the heaviest weighted study does not even overlap the meta-analytic estimate. Conversely, studies with less precision all report estimates above the meta-analytic estimate. This bias for less precise studies with higher rather than lower estimates of effect to be available in the published literature is often attributed to the tendency for smaller studies with significant p values to be submitted and/or accepted for publication. Consequently, the meta-analytic estimate for the effect of TWA on arrhythmic events should be regarded as optimistic.

Quantitative evaluation of publication bias using the trim-and-fill method (R and L estimators were used) suggested that missing studies may exist in the HRV, LVEF, NSVT, QRS, and TWA predictor categories. The L estimator indicated that for the 12 reports in the TWA section, 11 unreported counterparts are likely. After imputing the missing studies with symmetrical mirror images of the published reports, the meta-analytic estimates of the OR were reduced in each of these categories (HRV OR: 1.21, 95% CI: 0.72 to 2.05, p = 0.25; LVEF OR: 2.73, 95% CI: 1.99 to 3.76, p < 0.001; NSVT OR: 2.06, 95% CI: 1.48 to 2.96, p < 0.001; QRS duration OR: 1.46, 95% CI: 1.10 to 1.94, p = 0.013; TWA OR: 2.03, 95% CI: 1.25 to 3.29, p = 0.004). These findings show that the effect for the variables evaluated in this report could be as small as half the size estimated from the published reports as a result of publication bias. It is noteworthy, however, that the p values remained relatively unchanged, and the overall qualitative conclusions about the effectiveness of the predictors were not affected by trim-and-fill imputation.

Discussion

The present study demonstrates that a variety of risk stratification techniques are useful in identifying SCD risk in NIDCM patients. These techniques incorporate functional parameters, depolarization and repolarization abnormalities, and arrhythmogenic markers. On the basis of the available data, disturbances in autonomic function do not appear promising at this point for SCD risk stratification in NIDCM. At best, the odds ratio for any 1 predictor is generally in the range of 2 to 4, precluding their usefulness in isolation for individual patient decisions (60–62). Still, given the fact that there are so many predictors along different pathophysiological pathways, these findings provide a platform upon which multidimensional risk assessment can be further developed.

In contrast to ischemic cardiomyopathy, the pathophysiology of ventricular arrhythmias in NIDCM is less well understood. Arrhythmogenesis is likely multifactorial and may be related to structural changes such as fibrosis and left ventricular dilation as well as to primary and secondary electrophysiological changes; these may result in ventricular tachyarrhythmias due to reentry, abnormal automaticity, and triggered activity. Focal mechanisms seem to underlie the isolated premature ventricular complexes (PVCs) and NSVT that originate in the subendocardium (63). However, when sustained monomorphic VT occurs in NIDCM, reentry within the myocardium is the most common mechanism (64–66). Similar to ischemic cardiomyopathy, the substrate for reentry in NIDCM is probably scar-based (67,68). Recent magnetic resonance imaging data confirm that the presence and extent of myocardial fibrosis correlate with risk of adverse outcomes, including appropriate ICD therapy (69,70). Another finding is the presence of low-voltage electrograms along the reentry circuit, consistent with scar (67,68). The pathogenesis of polymorphic VT/VF in NIDCM is less understood. The overarching theme is that arrhythmogenesis in NIDCM may be due to the interplay of several variables and that no single abnormality can fully explain the process. This idea is consistent with the findings of the present report, which highlights the potential utility of risk markers representing a wide range of pathophysiological processes in NIDCM.

The present analysis consolidates the best available literature on risk stratification for SCD in NIDCM. This population of patients has been less studied than patients with ischemic cardiomyopathy. The cumulative number of patients included for each technique in the present report ranges from 359 to 2,692, whereas a similar analysis from 2001 involving patients with coronary artery disease included a range of 4,022 to 9,883 for each technique (71). Similarly, among the 5 largest primary prevention ICD trials, there were 3,596 patients with ischemic cardiomyopathy versus 1,262 patients with NIDCM (72). That reflects, in part, the lower prevalence of NIDCM; the annual incidence has been reported to be 5 to 8 cases per 100,000 persons, with a prevalence of 36 to 40 per 100,000 persons (4). In contrast, ischemic heart disease is thought to be responsible for 60% to 75% of heart failure incidence and prevalence in the United States. As patients with NIDCM are younger (4,73), appear to have a better prognosis, and receive less overall benefit from the ICD (6) than patients with ischemic cardiomyopathy, the potential role for risk stratification is even greater.

Current guidelines for ICD implantation in patients with NIDCM rely solely on the imprecise parameters of depressed LVEF and New York Heart Association functional class, criteria that are neither specific nor sensitive enough to adequately capture the highest risk patients. Indeed, in the present analysis, the OR for LVEF was 2.86, with sensitivity and specificity of 71.1% and 50.5%, respectively. This finding is consistent with epidemiologic observations that...
many SCDs occur in patients with LVEF >35% (74–76). In fact, no technique has yet emerged as precise enough to affect clinical decision making. The best predictors of adverse outcomes include TWA, LVEDD, EPS, SAECG, LVEF, QRS duration, and NSVT. Fragmented QRS and QRS-T angle were also significant, but were only addressed in 1 or 2 studies. Notably, TWA was the most sensitive predictor in the group, and EPS was the most specific. In contrast, HRV, HRT, and BRS were not statistically significant predictors. This finding suggests that autonomic dysfunction may be a less important or variable factor in the pathophysiology of ventricular arrhythmias in NIDCM than the other processes described in the preceding text.

The present analysis can help guide future efforts at improving risk stratification in NIDCM by providing a starting point for which techniques to consider. Bailey et al (71) demonstrated that a multiple-tier risk stratification approach in patients with coronary artery disease can, in theory, be highly discriminative with 92% of the population stratified into either a high- or low-risk group with 2-year predicted major arrhythmic event rates of 41% or 3%, respectively. Similarly, a risk score comprising 5 clinical

Figure 2 Raw and Meta-Analytic Odds Ratios With 95% Confidence Intervals by Study and Predictor Category

(A) For autonomic parameters, data are shown for baroreflex sensitivity (BRS) (8,9), heart rate turbulence (HRT) (10–12), and heart rate variability (HRV) (8,9,13,14). (B) For functional parameters, data are shown for left ventricular end-diastolic diameter (LVEDD) (15–18) and left ventricular ejection fraction (LVEF) (3,9,15–24). (C) For arrhythmia parameters, data are shown for electrophysiology (EP) study (18,22,25–37) and nonsustained ventricular tachycardia (NSVT) (3,9,13,15,17,18,20,23–26,34–42). (D) For depolarization parameters, data are shown for fragmented QRS (43,44), QRS duration/left bundle branch block (LBBB) (3,8,9,18,20,23,26,39,45,46), and signal-averaged electrocardiogram (3,9,15,17,18,35,47–50). (E) For repolarization parameters, data are shown for T-wave alternans (9,15,17,47,51–58). Continued on the next page.
variables, each of which had a hazard ratio <2, performed well for intermediate-term risk stratification in patients enrolled in the MADIT-II (Multicenter Automatic Defibrillator Implantation Trial-II) trial (77). Other reports also highlight the utility of combining predictors for risk stratification (78, 79). To achieve adequate risk stratification for clinical decision making with a high level of discrimination, ORs of >15 to 20 are likely necessary (61, 80). Clearly, that cannot be achieved with the currently available techniques when used individually.

**Study limitations.** Several limitations need to be acknowledged. Foremost, the majority of the studies included were small, with sample sizes <100. Evidence of publication bias of reporting only positive studies with small sample sizes was detected in several categories. Skewed patient populations were also noted; namely, only Asians were included in the 2 studies evaluating fragmented QRS. Some important studies were undoubtedly excluded, such as the TWA substudy from the SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial) (81) because of the inability to obtain raw data from the information provided. It is notable that after accounting for “missing studies” by the imputation technique, the OR for TWA was 2.03 with 95% CI of 1.25 to 3.29, a range that certainly encompasses this report that was not included in the present analysis. In addition, a variety of endpoints were used in these studies. Many were arrhythmia specific, but several included all-cause mortality, cardiovascular mortality, worsening heart failure, or heart transplantation. While every attempt was made to focus on arrhythmic endpoints, some endpoints in this analysis may represent nonarrhythmic events, which may reduce the specificity of the parameters. Even the arrhythmic endpoints are not equivalent as appropriate ICD shocks are not a surrogate for arrhythmic SCD. In addition to the various endpoints, there was heterogeneity in the definition of abnormal test results among the included studies. Although
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<th>Spec. (%)</th>
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<td>24.0</td>
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<td>85.5</td>
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<td>2.01* (1.22–3.31)</td>
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<td>4.66 (2.55–8.53)</td>
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*1 study available; raw rather than meta-analytical value is reported.

BRS = measure of baroreflex sensitivity; HRV = heart rate variability; LBBB = left bundle branch block; NPA = negative predictive accuracy; NSVT = nonsustained ventricular tachycardia; OR = odds ratio; PPA = positive predictive accuracy; Prev. = prevalence; RR = risk ratio; SAECG = signal-averaged electrocardiogram; Sens. = sensitivity; Spec. = specificity; TWA = T-wave alternans.
these limitations preclude precise quantitative conclusions about the predictive value of each test, the qualitative results are consistent and informative. Furthermore, this analysis highlights the need for more uniform definitions and reporting of studies evaluating factors predicting SCD risk. Finally, a range of medical therapy was used in these studies and the interaction of medical therapy with the prognostic value of these tests may be a significant factor.

Conclusions

The present analysis provides important insights into risk stratification in NIDCM. The current model for risk stratification in NIDCM is handicapped by both limited sensitivity and limited specificity. On the basis of available literature, there are promising risk assessment tools that are both widely available and easily measurable. Going forward, each of these tools will have to be studied in a coordinated fashion prospectively in larger trials. There are tremendous opportunities to ameliorate the public health problem of SCD and simultaneously improve cost effectiveness. As most SCDs occur in patients who do not meet current criteria for an ICD, broadening the criteria will certainly bring more of the at-risk population under the safety net, but if that is not done using a method with high discrimination, it will create a tremendous burden on the health care system. Similarly, if a significant number of patients receiving ICDs with the current criteria can be risk stratified to a low-risk group for whom there is no survival benefit from the device, these patients can avoid the risk of device implantation and eliminate an unnecessary cost to the health care system. Using these data to develop successful risk stratification approaches should, therefore, be a high priority.

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REFERENCES


Key Words: arrhythmia • cardiomyopathy • sudden death.

For a supplemental table, please see the online version of this article.