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Running title: SCD Risk Stratification in NIDCM

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ABSTRACT

Objectives – To provide a meta-analysis to estimate the performance of 12 commonly reported risk stratification tests as predictors of arrhythmic events in patients with NIDCM.

Background – Multiple techniques have been assessed as predictors of death due to ventricular tachyarrhythmias/sudden death in patients with non-ischemic dilated cardiomyopathy (NIDCM).

Methods - Forty-five studies enrolling 6088 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, non-sustained 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 trim-and-fill method to estimate the influence of missing studies on the results.

Results – Patients were 52.8±14.5 years old and 77% were male. LVEF was 30.6±11.4%. Test sensitivities ranged from 28.8% to 91.0%; specificities from 36.2% to 87.1%; odds ratios from 1.5 to 6.7. OR was highest for fragmented QRS and TWA (OR=6.73 and 4.66, 95% confidence interval 3.85-11.76 and 2.55-8.53, respectively) and lowest for QRS duration (OR=1.51, 1.13-2.01). None of the autonomic tests (HRV, HRT, BRS) 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 SCD in patients with NIDCM. It is likely that combinations of tests will be required to optimize risk stratification in this population.

Key words: cardiomyopathy, sudden death, arrhythmia

Abbreviations

BRS - baroreflex sensitivity
CI – confidence interval
EPS - electrophysiology study
HRT - heart rate turbulence
HRV - heart rate variability
LVEDD - left ventricular end diastolic dimension
LVEF - left ventricular ejection fraction
NIDCM - nonischemic dilated cardiomyopathy
NSVT – nonsustained ventricular tachycardia
QRST - QRS-T angle
SAECG - signal averaged ECG
SCD – sudden cardiac death
TWA - T-wave alternans

INTRODUCTION

SCD occurs in 184,000-462,000 people annually in the US.(1) Although the majority have ischemic heart disease, a substantial fraction have NIDCM. Primary prevention of SCD focuses on identifying high risk subpopulations that could benefit from more intensive therapies, such as the 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 12-20% estimated mortality at three 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 VT/VF accounts for a substantial proportion of the mortality in this disease, though the ICD may also prevent SCD secondary to bradyarrhythmias in some patients.

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 in this population.(1) Most studies that have addressed this issue are either small, non-randomized, 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: BRS, EPS, HRT, HRV, LVEDD, LVEF, NSVT, QRS duration, fragmented QRS, QRST, SAECG, and TWA.

Only English language articles in 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 DEFINITE(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 end-points. 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 two 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 (Figure 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 based on survival analyses rather than 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 based on survival curves rather than raw numbers in many reports.

In addition to raw counts, we extracted baseline patient characteristics, medical covariates, medications, end-points 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 non-uniform 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, though five 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 64-70mm, for LVEF between 25-35%. Abnormal QRS duration was defined by a cut-off of 110-120 msec. The cut-offs for abnormal HRV varied between 50 and 120 msec for SDNN. Abnormal BRS was defined by >3 or >6 msec/mmHg. Two studies used both slope and onset criteria to define abnormal HRT, while the third only used slope.

End-Points. When available, arrhythmic end-points were utilized: sudden or arrhythmic death, cardiac arrest, appropriate ICD therapy, and documented VT/VF. If arrhythmic end-points were not reported, total mortality was included. Finally, studies in which non-arrhythmic 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 three-year event rates for each study were based on the reported number of events and mean or median follow-up time. Exponential survival (constant mortality rate through time) was assumed in calculating three-year event rates. Aggregate three-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, NC). 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 one of the cells, 0.5 was added to all four elements of the 2 by 2 summary tables. Meta-analytic summaries based on ordinary risk ratios were also calculated using the Mantel-Haenszel random-effects method. Finally, ‘trim and fill’ strategy for estimating the number of studies omitted due to 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 39-65 years); 77% were male (range 57-94%). Average NYHA class was 2.3±1.0 (range 1.5-3.4). LVEF was 30.6±11.4%; LVEDD was 66.1±8.9mm.

Performance of Individual Risk Stratification Tests. The results for each predictor grouped by category are shown in figure 2, and summarized in table 2 (detailed list by predictor is in the online appendix).

Raw end-point rates varied between 4.8-46.6%; 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, inter-quartile range 19-39 months). LVEF studies had the longest weighted average follow-up duration (41 months,range 14-96) and TWA had the shortest (24 months,range 13-52). Using exponential survival assumption, estimated average three-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—11.8-21.5%.

Table 2 summarizes the sensitivities and specificities for the twelve predictor tests. Sensitivities ranged from 28.8-91.0% and specificities ranged from 36.2-87.1%.

Performance of risk stratification tests was compared by estimating the odds ratios (OR) for patients with and without the predictor. OR were highest for fragmented QRS (OR=6.73,95%CI 3.85-11.76) and TWA (OR=4.66,95%CI 2.55-8.53) and lowest for QRS duration (OR=1.51,95%CI 1.13-2.01). All predictors had significant OR for identifying events in the functional, arrhythmia, depolarization and repolarization categories ($p \leq 0.014$ for all). Only one

study was available for QRS-T angle, which was also a significant predictor of adverse events (p=0.006). None of the three autonomic-based predictors was predictive.

In order 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. Since 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 four studies with highest weights report OR estimates that fall below the meta-analytical estimate. The confidence interval 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 of OR. 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, 0.72-2.05, p=0.25; LVEF:OR=2.73, 1.99-3.76, p<0.001; NSVT:OR=2.06, 1.48-2.96, p<0.001; QRS duration:OR=1.46, 1.10-1.94, p=0.013;

TWA:OR=2.03, 1.25-3.29, 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. These techniques incorporate functional parameters, depolarization and repolarization abnormalities, and arrhythmic markers. Based on 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 one predictor is generally in the range of 2-4, precluding their usefulness in isolation for individual patient decisions.(8-10) 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 dilatation as well as 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 PVCs and NSVT that originate in the subendocardium.(11) However, when sustained monomorphic VT occurs in NIDCM, reentry within the myocardium is the most common mechanism.(12-14) Similar to ischemic cardiomyopathy, the substrate for reentry in NIDCM is probably scar-based.(15,16) Recent MRI data confirm that the presence and extent of myocardial

fibrosis correlate with risk of adverse outcomes, including appropriate ICD therapy.(17,18) Another finding is the presence of low-voltage electrograms along the reentry circuit, consistent with scar.(15,16) 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 pathophysiologic processes in NIDCM.

The present analysis consolidates the best available literature on risk stratification for SCD in NIDCM. This population has been less studied than those with ischemic cardiomyopathy. The cumulative number of patients included for each technique in the present report ranges from 359-2,692, while a similar analysis from 2001 in patients with coronary artery disease included a range of 4,022-9,883 for each technique.(19) Similarly, among the five largest primary prevention ICD trials, there were 3,596 patients with ischemic cardiomyopathy versus 1,262 patients with NIDCM.(20) This reflects, in part, the lower prevalence of NIDCM; the annual incidence has been reported to be 5-8 cases/100,000 people with a prevalence of 36-40/100,000 individuals.(4) In contrast, ischemic heart disease is thought to be responsible for 60-75% of heart failure incidence and prevalence in the United States. As patients with NIDCM are younger,(4,21) 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 NYHA functional class, criteria that are neither specific nor sensitive enough to adequately capture the highest risk individuals. Indeed, in the present

analysis, the odds ratio for LVEF was 2.86, with sensitivity and specificity of 71.1% and 50.5%, respectively. This is consistent with epidemiologic observations that many SCDs occur in patients with LVEF>35%(22-24). 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 one or two 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 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 above.

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 demonstrated that a multi-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 two-year predicted major arrhythmic event rates of 41% or 3%, respectively.(19) Similarly, a risk score comprising five clinical variables, each of which had a hazard ratio<2, performed well for intermediate-term risk stratification in patients enrolled in MADIT-II.(25) Other reports also highlight the utility of combining predictors for risk stratification.(26,27) In order to achieve adequate risk stratification for clinical decision making with a high level of discrimination, odds ratios>15-20 are likely necessary.(9,28) Clearly, this cannot be achieved with the currently available techniques when used individually.

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–i.e. only Asians in the two studies evaluating fragmented QRS. Some important studies were undoubtedly excluded, such as the TWA substudy from SCD-HeFT(29) due to 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 1.25-3.29, 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 non-arrhythmic 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. While 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.

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 specificity. Based on the available literature, there are promising risk assessment tools which 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 this 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 in 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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Figure Legends:

Figure 1: **Flow chart of study selection process**

Figure 2: Raw and meta-analytic odds ratios with 95% confidence intervals by study and predictor category.
For autonomic parameters, data are shown for BRS ((30), (31)), HRT ((32), (33), (34)), and HRV ((35), (30), (31), (36)).
For functional parameters, data are shown for LVEDD ((37), (38), (39), (40)), LVEF ((37), (3), (38), (41), (31), (42), (43), (39), (44), (40), (45), (46)).
For arrhythmia parameters, data shown for EPS ((47), (48), (49), (50), (51), (52), (53), (44), (54), (40), (56), (55), (56), (57), (58)) and NSVT ((37), (47), (35), (48), (59), (3), (60), (61), (31), (62), (42), (39), (40), (55), (45), (58), (63), (46)).
For depolarization parameters, data are shown for QRS duration/LBBB ((48), (3), (60), (30), (31), (78), (42), (80), (40), (45)), SAECG ((37), (3), (64), (31), (65), (39), (66), (40), (67), (57)), and fragmented QRS ((68), (69)).
For repolarization parameters, data are shown for TWA ((37), (70), (71), (72), (73), (64), (31), (39), (74), (75), (76), (77)).

Table 1: Summaries of patient characteristics for studies included in meta-analysis

Variable	Studies	N	Summary	Range
STUDY CHARACTERISTICS				
Duration of Follow-up (months)—Mean±SD	45	6,088	33.6±19.9	10-96
Estimated 3-yr Event Rate (%)—Mean±SD			18.9±12.8	4.5-79.3
PATIENT CHARACTERISTICS				
N—(Mean±SD)	45	6,088	135.3±125.4	15-572
Age (years)—Mean±SD	36	4,953	52.8±14.5	38.9-64.5
Male—(%)	38	5,089	76.7	57-94
NYHA class—Mean±SD	27	4,277	2.3±1.0	1.5-3.4
Diabetes—(%)	8	1,912	16.5	0-23
Hypertension—(%)	5	1,721	27.8	10.5-39
Duration of CHF (months)—Mean±SD	4	867	10.4±17.5	4-25
Left Bundle Branch Block—(%)	11	2,247	30.1	19-42.6
Right Bundle Branch Block—(%)	7	1,244	2.7	0-9
Non-Sustained Ventricular Tachycardia—(%)	15	2,239	42.7	14.5-100
Syncope—(%)	11	1,206	6.8	0-54
Implantable Cardioverter Defibrillator—(%)	11	2,315	15.6	0-100
History of Atrial Fibrillation—(%)	20	3,185	17.1	0-41

Heart Rate (bpm)—Mean±SD	3	805	72.8±12.1	70-81
Systolic Blood Pressure (mm/Hg)—Mean±SD	4	747	123.5±15.9	120-127
Diastolic Blood Pressure (mm/Hg)—Mean±SD	3	568	75.9±12.2	74-78
LVEDV (mm)—Mean±SD	2	486	205.6±76.6	171.0-208.7
LVESV (mm)—Mean±SD	2	486	146.9±64.7	121.0-149.2
LVEF (%)—Mean±SD	28	4,098	30.6±11.4	17-45
LVEDD (mm)—Mean±SD	17	2,657	66.1±8.9	61-73
LVESD (mm)—Mean±SD	1	446	55.1±9.6	N/A
Peak Oxygen Uptake (ml/kg/min)—Mean±SD	2	560	16.4±5.8	14.8-16.8
PCWP (mm/Hg)—Mean±SD	6	390	16.4±10.0	14-22
Cardiac Index (l/min/m^2)—Mean±SD	5	369	2.6±0.77	2.1-2.9
MEDICATIONS				
ACE Inhibitor—(%)	18	3,445	62.4	8.5-100
Amiodarone—(%)	21	3,753	80.4	38.8-100.0
Beta Blockers—(%)	19	3,604	71	0.0-98.8
Digoxin—(%)	18	3,408	58.6	19-97
Diuretics—(%)	4	733	35.3	16.0-74.5
Spironolactone—(%)	16	2,792	12.3	0-22

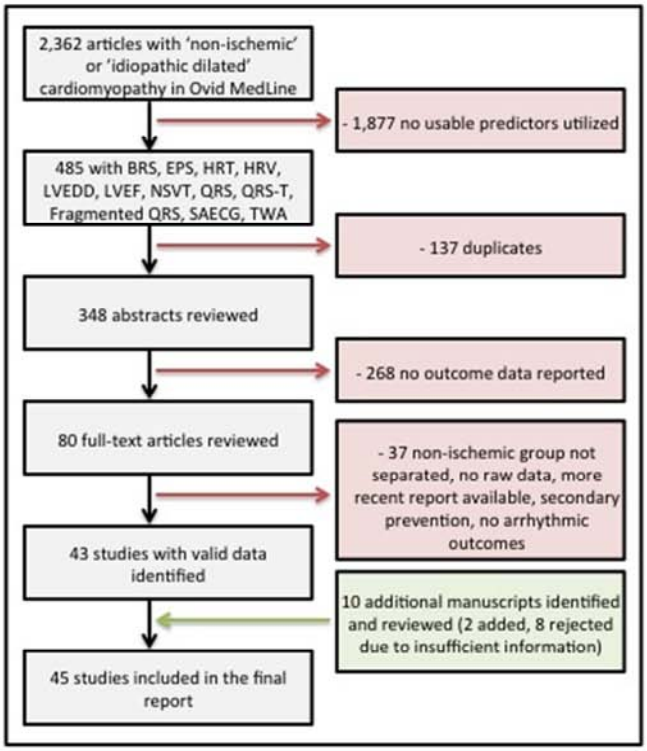
NYHA – New York Heart Association; **CHF** – congestive heart failure; **LVEDV** – left ventricular end diastolic volume; **LVESV** – left ventricular end systolic volume; **LVEF** – left ventricular ejection fraction; **LVEDD** – left ventricular end diastolic dimension; **LVESD** – left

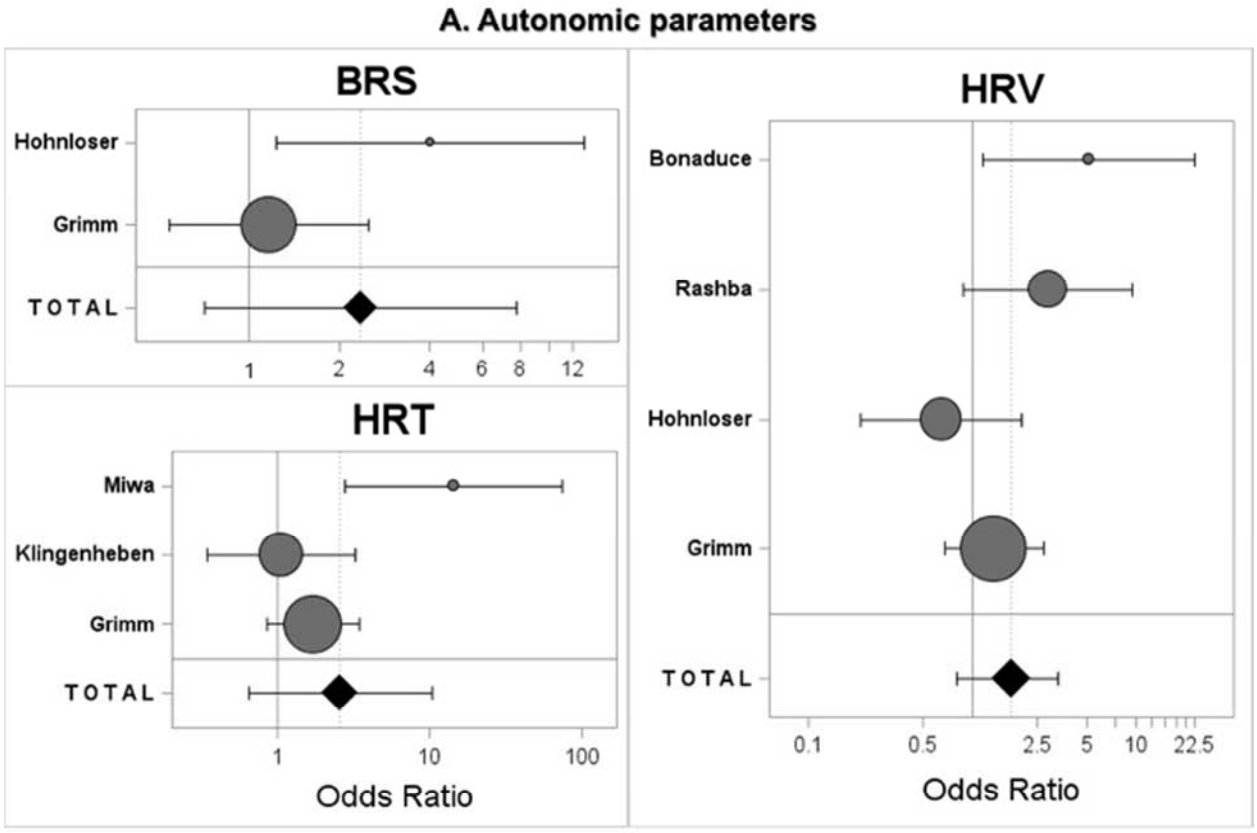
ventricular end systolic dimension; **PCWP** – pulmonary capillary Wedge pressure; **ACEI** – angiotensin-converting-enzyme inhibitor

Table 2. Meta-analytic summaries of test performance by predictor category

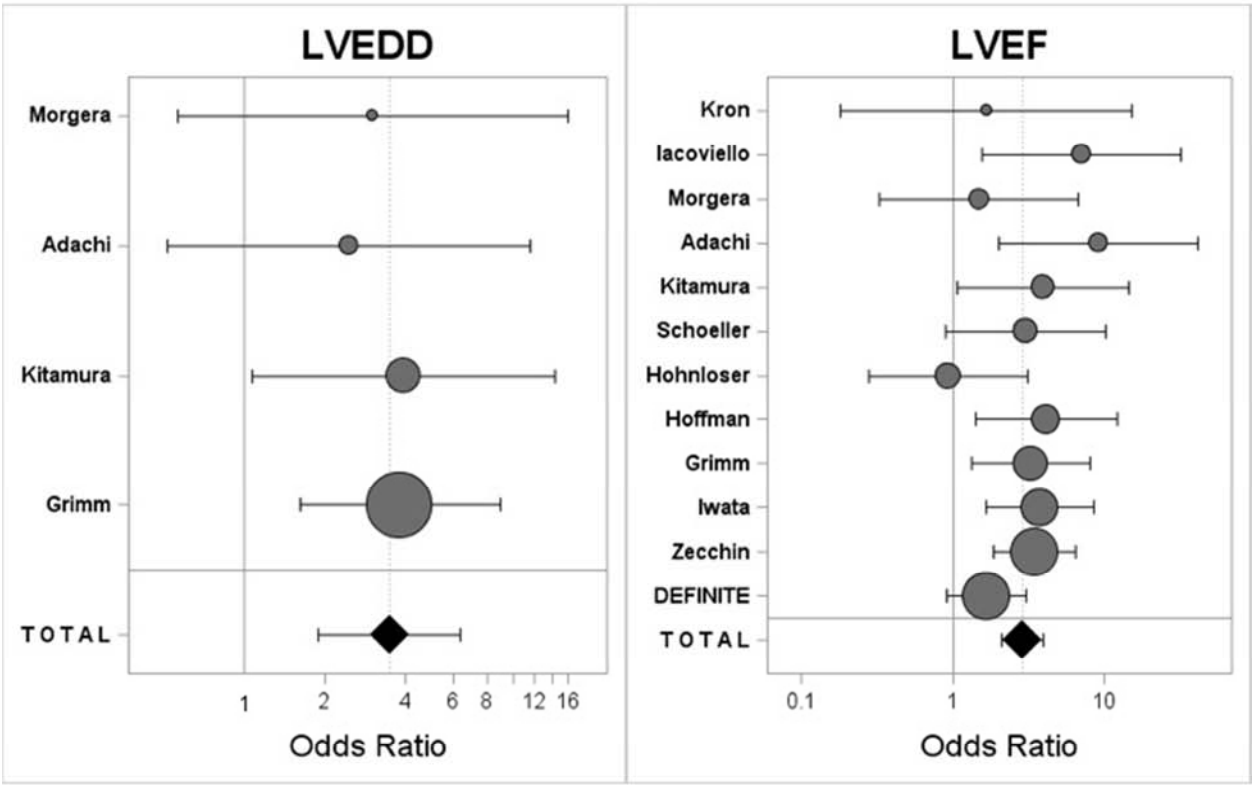
Predictor	Studies	Events/N (%)	Calculated 3-year Event Rate	Prevalence	Sensitivity	Specificity	PPA	NPA	RR (95% CI)	OR (95% CI)	p-value
AUTONOMIC											
BRS	2	48/359 (13.4)	17.0%	52.9	64.6	48.9	16.3	89.9	1.80 [0.63-	1.98 [0.60-	0.23
HRT	3	66/434 (15.2)	18.6%	32.3	47.0	70.4	22.1	88.1	2.12 [0.77-	2.57 [0.64-	0.16
HRV	4	83/630 (13.2)	15.6%	43.1	55.4	58.8	16.9	89.7	1.52 [0.84-	1.72 [0.80-	0.13
FUNCTIONAL											
LVEDD	4	62/427 (14.5)	17.1%	42.9	66.1	61.1	22.4	91.4	2.85 [1.70-	3.47 [1.90-	0.014
LVEF	12	293/1,804	16.9%	53.1	71.7	50.5	21.9	90.2	2.34 [1.85-	2.87 [2.09-	<0.001
ARRHYTHMIA											
EPS	15	146/936 (15.6)	21.5%	15.4	28.8	87.1	29.2	86.9	2.09 [1.30-	2.49 [1.40-	0.004
NSVT	18	403/2,746	15.7%	45.5	64.0	57.7	20.7	90.3	2.45 [1.90,	2.92 [2.17,	<0.001
DEPOLARIZATION											
QRS/LB	10	262/1,797	14.7%	35.7	45.4	65.9	18.5	87.6	1.43 [1.11-	1.51 [1.13-	0.010
SAECG	10	152/1,119	19.9%	36.9	51.3	65.4	18.9	89.5	1.84 [1.18-	2.11 [1.18-	0.017
Fragmented QRS	2	65/652 (10.0)	11.8%	25.6 %	61.5 %	78.4 %	24.0 %	94.8 %	5.16 [3.17, 8.41]	6.73 [3.85, 11.76]	<0.001
REPOLARIZATION											
QRS-T	1	97/455 (21.3)	25.0%	62.2	74.2	41.1	25.4	85.5	1.75* [1.16-	2.01* [1.22-	0.006*
TWA	12	177/1,631	15.8%	66.8	91.0	36.2	14.8	97.0	3.25 [2.04,	4.66 [2.55,	<0.001

* One study available, raw rather than meta-analytical value is reported **PPA**=positive predictive accuracy; **NPA**=negative predictive accuracy; **RR**=risk ratio; **OR**=odds ratio

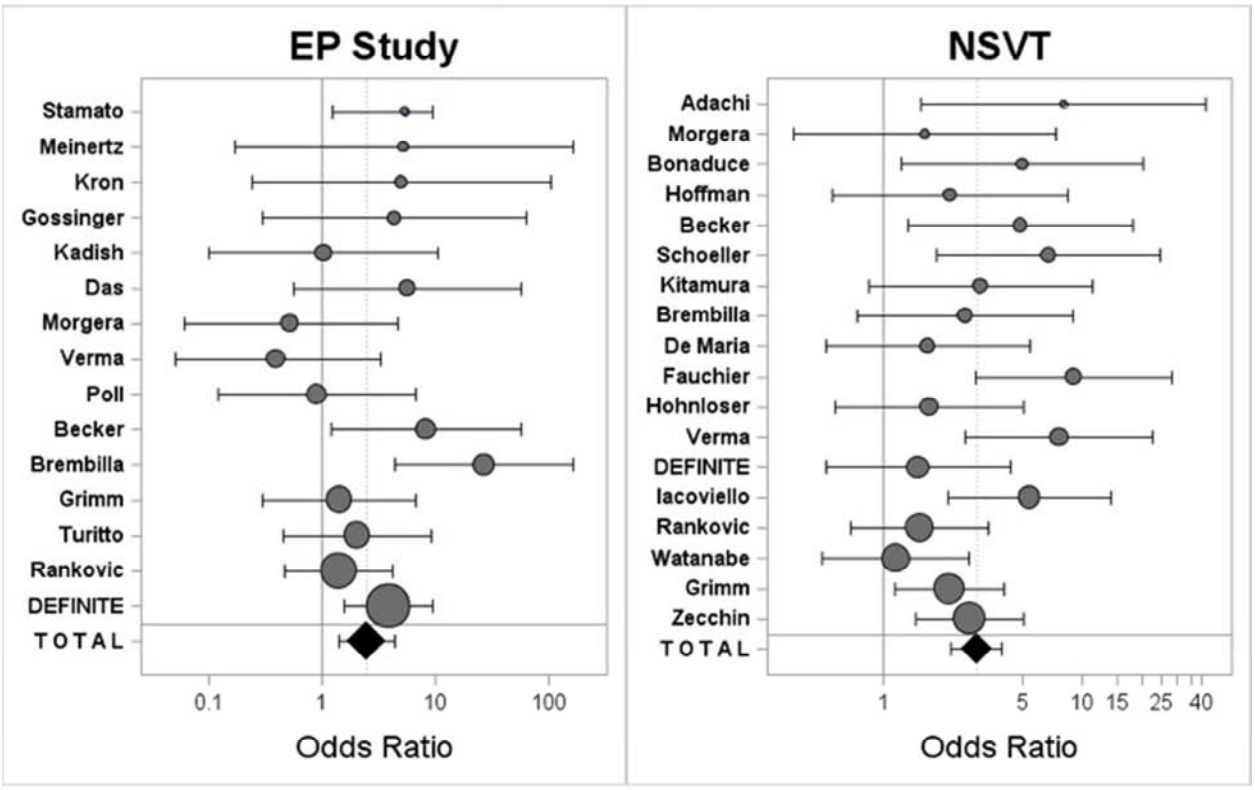



A. Autonomic parameters
BRS
Hohnloser
Grimm
TOTAL
1
2
4
6
8
12
HRT
Miwa
Klingenheben
Grimm
TOTAL
1
10
100
Odds Ratio
HRV
Bonaduce
Rashba
Hohnloser
Grimm
TOTAL
0.1
0.5
2.5
5
10
22.5
Odds Ratio

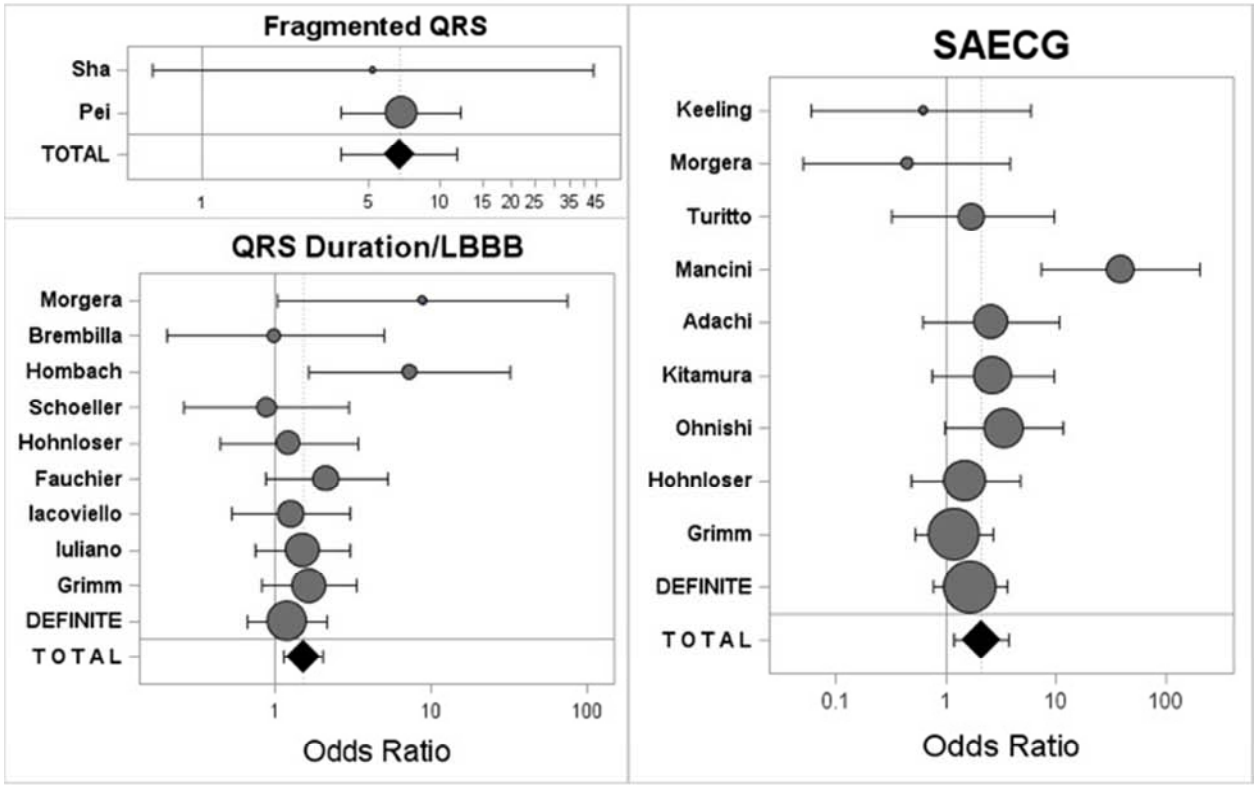
B. Functional parameters



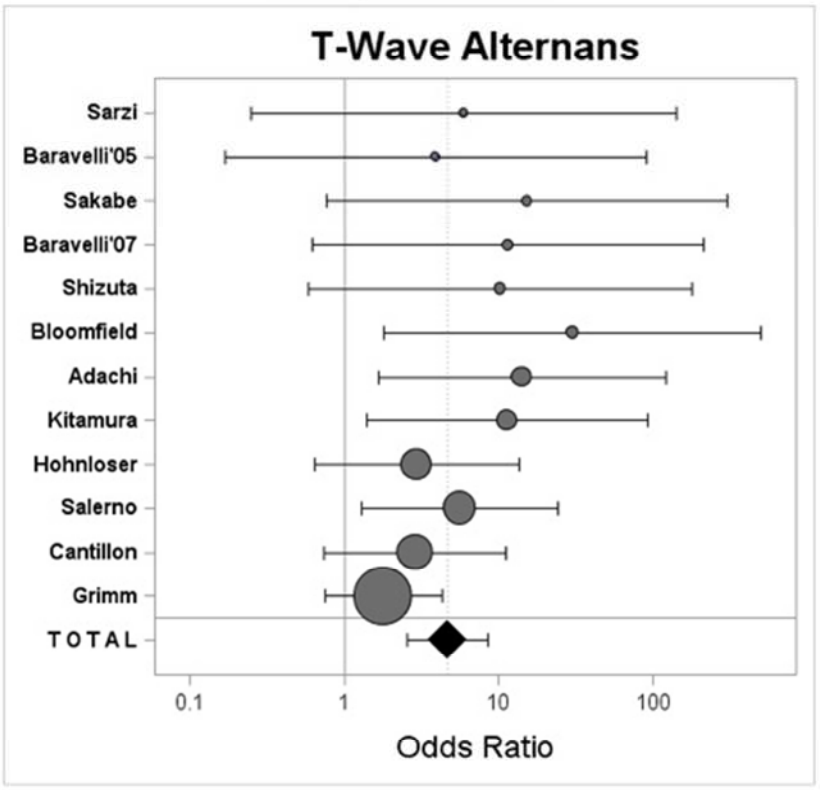
C. Arrhythmia-based parameters



D. Depolarization parameters



E. Repolarization



Appendix Table

a: Raw data summaries by study and predictor category—Autonomic predictors

Study	Observed Event Rate	N	F/U (mo)	End-Point(s)	TP	FP	FN	TN	Sens	Spec	PPA	NPA	RR	OR
AUTONOMIC														
BRS														
Grimm (2005)(30)	13.08%	237	52	SCD+VTVF	18	112	13	94	58.1%	45.6%	13.8%	87.9%	1.14	1.16
Hohnloser (2003)(31)	13.93%	122	14	SCD+CA+VTVF	13	47	4	58	76.5%	55.2%	21.7%	93.5%	3.36	4.01
TOTAL		**359**	**33.0**		**31**	**159**	**17**	**152**	**64.6%**	**48.9%**	**16.3%**	**89.9%**	**1.62**	**1.74**
HRT														
Grimm (2003)(32)	17.36%	24	41	SCD+VTVF	16	53	26	14	38.1	73.5	23.2	85.0	1.5	1.7

		2						7	%	%	%	%	4	1
Klingenheben (2008)(33)	17.44%	86	22	SCD+VTVF+rCA	8	37	7	34	53.3 %	47.9 %	17.8 %	82.9 %	1.04	1.05
Miwa (2009)(34)	8.49%	106	15	SCD+CVD+AS+VT	7	19	2	78	77.8 %	80.4 %	26.9 %	97.5 %	10.8	14.4
TOTAL		**434**	**26.0**		**31**	**109**	**35**	**259**	**47.0 %**	**70.4 %**	**22.1 %**	**88.1 %**	**1.86**	**2.10**
HRV														
Bonaduce (1999)(35)	40.00%	40	39	CVD	12	9	4	15	75.0 %	62.5 %	57.1 %	78.9 %	2.71	5.00
Grimm (2005)(30)	14.45%	263	52	SCD+VTVF	22	113	16	112	57.9 %	49.8 %	16.3 %	87.5 %	1.30	1.36
Hohnloser (2003)(31)	14.53%	117	14	SCD+CA+VTVF	5	39	12	61	29.4 %	61.0 %	11.4 %	83.6 %	0.69	0.65
Rashba (2006)(36)	5.69%	211	24	ACM	7	65	5	134	58.3 %	67.3 %	9.7%	96.4 %	2.70	2.89

TOTAL		**631**	**32.3**		**46**	**226**	**37**	**322**	**55.4 %**	**58.8 %**	**16.9 %**	**89.7 %**	**1.64**	**1.77**

F/U=follow-up duration; **TP**=true positive count; **FP**=false positive count; **FN**=false negative count; **TN**=true negative count; **Sens**=sensitivity; **Spec**=specificity; **PPA**=positive predictive accuracy; **NPA**=negative predictive accuracy; **RR**=risk ratio; **OR**=odds ratio;

BRS=baroreflex sensitivity; **HRT**=heart rate turbulence; **HRV**=heart rate variability; **LVEDD**=left ventricular end diastolic dimension; **LVEF**=left ventricular ejection fraction; **EPS**=electrophysiology study; **NSVT**=non-sustained ventricular tachycardia; **LBBB**=left bundle branch block; **SAECG**=signal-averaged electrocardiogram; **TWA**=T-wave alternans

SCD=sudden cardiac death; **VT**=ventricular tachycardia; **VTVF**=ventricular tachycardia/fibrillation; **CA**=cardiac arrest; **rCA**=resuscitated cardiac arrest; **AS**=appropriate shock; **ACM**=all-cause mortality; **ArrD**=arrhythmic death; **CHFD**=chronic heart failure death; **HTx**=heart transplant; **CVD**=cardiovascular death;

b: Raw data summaries by study and predictor category—Functional predictors

Study	**Observed**	**N**	**FU Months**	**End-Point(s)**	**TP**	**FP**	**FN**	**TN**	**Sens**	**Spec**	**PPA**	**NPA**	**RR**	**OR**

	Event Rate													
FUNCTIONAL														
LVEDD														
Adachi (2001)(37)	15.63%	64	24	SCD+VTVF	3	8	7	46	30.0 %	85.2 %	27.3 %	86.8 %	2.06	2.46
Grimm (2000)(38)	15.84%	202	32	SCD+ArrD+VT +AS	24	75	8	95	75.0 %	55.9 %	24.2 %	92.2 %	3.12	3.80
Kitamura (2002)(39)	14.46%	83	21	SCD+VTVF	8	24	4	47	66.7 %	66.2 %	25.0 %	92.2 %	3.19	3.92
Morgera (2004)(40)	10.26%	78	85	SCD+VTVF+AS	6	35	2	35	75.0 %	50.0 %	14.6 %	94.6 %	2.71	3.00
TOTAL		**427**	**40.5**		**41**	**142**	**21**	**223**	**66.1 %**	**61.1 %**	**22.4 %**	**91.4 %**	**2.60**	**3.07**
LVEF														
Adachi	15.63%	64	24	SCD+VTVF	7	11	3	43	70.0	79.6	38.9	93.5	5.9	9.1

(2001)(37)									%	%	%	%	6	2
DEFINITE (2004)(3)	12.88%	458	29	SCD+rCA+AS	43	246	16	153	72.9%	38.3%	14.9%	90.5%	1.57	1.67
Grimm (2000)(38)	15.84%	202	32	SCD+ArrD+VT+AS	25	89	7	81	78.1%	47.6%	21.9%	92.0%	2.76	3.25
Hoffman (1988)(41)	24.04%	104	53	SCD	20	39	5	40	80.0%	50.6%	33.9%	88.9%	3.05	4.10
Hohnloser (2003)(31)	13.14%	137	14	SCD+CA+VTVF	14	94	4	25	77.8%	21.0%	13.0%	86.2%	0.94	0.93
Iacoviello (2007)(42)	12.86%	140	39	SCD+VTVF	16	65	2	57	88.9%	46.7%	19.8%	96.6%	5.83	7.02
Iwata (2001)(43)	37.72%	114	31	VT	31	29	12	42	72.1%	59.2%	51.7%	77.8%	2.33	3.74
Kitamura (2002)(39)	14.46%	83	21	SCD+VTVF	8	24	4	47	66.7%	66.2%	25.0%	92.2%	3.19	3.92
Kron (1988)(44)	20.00%	20	23	SCD+VTVF	2	6	2	10	50.0	62.5	25.0	83.3	1.5	1.6

									%	%	%	%	0	7
Morgera (2004)(40)	10.26%	78	85	SCD+VTVF+AS	5	37	3	33	62.5 %	47.1 %	11.9 %	91.7 %	1.43	1.49
Schoeller (1993)(45)	15.29%	85	49	SCD	8	25	5	47	61.5 %	65.3 %	24.2 %	90.4 %	2.52	3.01
Zecchin (2008)(46)	15.99%	319	96	SCD+VTVF+AS	31	83	20	185	60.8 %	69.0 %	27.2 %	90.2 %	2.79	3.45
TOTAL		**1,804**	**41.3**		**210**	**748**	**83**	**763**	**71.7 %**	**50.5 %**	**21.9 %**	**90.2 %**	**2.23**	**2.58**

c: Raw data summaries by study and predictor category—Arrhythmia-based predictors

Study	Observed Event Rate	N	FU Months	End-Point(s)	TP	FP	FN	TN	Sens	Spec	PPA	NPA	RR	OR
ARRHYTHMIA														
EPS														
Becker (2003)(47)	6.38%	94	22	SCD+VTVF	2	5	4	83	33.3 %	94.3%	28.6 %	95.4 %	6.21	8.30
Brembilla (1991)(48)	7.61%	92	24	SCD+VTVF	4	4	3	81	57.1 %	95.3%	50.0 %	96.4 %	14.0	27.0
Das (1986)(49)	16.67%	24	12	SCD+VT	2	3	2	17	50.0 %	85.0%	40.0 %	89.5 %	3.80	5.67
Daubert (2009)(50)	15.20%	204	29	VTVF+AS	10	19	21	154	32.3 %	89.0%	34.5 %	88.0 %	2.87	3.86
Gossinger	9.38%	32	21	SCD	1	3	2	26	33.3	89.7%	25.0	92.9	3.5	4.3

(1990)(51)									%		%	%	0	3
Grimm (1998)(52)	26.47%	34	24	SCD+VTVF+AS	4	9	5	16	44.4%	64.0%	30.8%	76.2%	1.29	1.42
Kadish (1993)(53)	16.28%	43	20	SCD+VT	1	5	6	31	14.3%	86.1%	16.7%	83.8%	1.03	1.03
Kron (1988)(44)	20.00%	20	23	SCD+VTVF	1	1	3	15	25.0%	93.8%	50.0%	83.3%	3.00	5.00
Meinertz (1985)(54)	4.76%	42	16	CHFD+SCD	0	1	2	39	0.0%	97.5%	0.0%	95.1%	4.20	5.21
Morgera (2004)(40)	10.26%	78	85	SCD+VTVF+AS	1	15	7	55	12.5%	78.6%	6.3%	88.7%	0.55	0.52
Poll (1986)(56)	35.00%	20	17	CA+SCD+VT	2	4	5	9	28.6%	69.2%	33.3%	64.3%	0.93	0.90
Rankovic (2002)(55)	42.59%	54	27	APS	10	11	13	20	43.5%	64.5%	47.6%	60.6%	1.21	1.40
Stamato	13.33%	15	19	SCD	0	0	2	13	0.0%	100.0	N/A	86.7	3.2	5.2

(1986)(56)										%		%	0	2
Turitto (1994)(57)	11.25%	80	22	SCD+VTVF	3	14	6	57	33.3 %	80.3%	17.6 %	90.5 %	1.9 1	2.1 2
Verma (2010)(58)	23.08%	104	25	AS	1	8	23	72	4.2%	90.0%	11.1 %	75.8 %	0.4 6	0.3 9
TOTAL		**936**	**25.7**		**42**	**10 2**	**10 4**	**688**	**28.8 %**	**87.1 %**	**29.2 %**	**86.9 %**	**2.2 2**	**2.7 2**
NSVT														
Adachi (2001)(37)	15.63%	64	24	SCD+VTVF	8	18	2	36	80.0 %	66.7%	30.8 %	94.7 %	5.8 5	8.0 0
Becker (2003)(47)	9.55%	157	22	SCD+VTVF	12	64	3	78	80.0 %	54.9%	15.8 %	96.3 %	4.2 6	4.8 8
Bonaduce (1999)(35)	40.00%	40	39	ACM	12	9	4	15	75.0 %	62.5%	57.1 %	78.9 %	2.7 1	5.0 0
Brembilla (1991)(48)	12.62%	103	24	SCD+VTVF	9	42	4	48	69.2 %	53.3%	17.6 %	92.3 %	2.2 9	2.5 7

De Maria (1992)(59)	5.50%	218	29	SCD	5	62	7	144	41.7 %	69.9%	7.5%	95.4 %	1.61	1.66
DEFINITE (2004)(3)	12.88%	458	29	SCD+rCA+AS	55	360	4	39	93.2 %	9.8%	13.3 %	90.7 %	1.42	1.49
Fauchier (2004)(60)	14.20%	162	53	SCD+VTVF	19	48	4	91	82.6 %	65.5%	28.4 %	95.8 %	6.74	9.01
Grimm (2005)(61)	13.41%	343	52	SCD+VTVF	22	89	24	208	47.8 %	70.0%	19.8 %	89.7 %	1.92	2.14
Hohnloser (2003)(31)	12.71%	118	14	SCD+CA+VTVF	7	35	8	68	46.7 %	66.0%	16.7 %	89.5 %	1.58	1.70
Hoffman (1996)(62)	14.08%	71	15	SCD+VTVF	6	25	4	36	60.0 %	59.0%	19.4 %	90.0 %	1.94	2.16
Iacoviello (2007)(42)	13.41%	179	39	SCD+VTVF	17	48	7	107	70.8 %	69.0%	26.2 %	93.9 %	4.26	5.41
Kitamura (2002)(39)	14.46%	83	21	SCD+VTVF	8	28	4	43	66.7 %	60.6%	22.2 %	91.5 %	2.61	3.07

Morgera (2004)(40)	10.26%	78	85	SCD+VTVF+ AS	3	19	5	51	37.5 %	72.9%	13.6 %	91.1 %	1.5 3	1.6 1
Rankovic (2002)(55)	42.59%	54	27	APS	18	20	5	11	78.3 %	35.5%	47.4 %	68.8 %	1.5 2	1.9 8
Schoeller (1993)(45)	15.29%	85	49	SCD	9	18	4	54	69.2 %	75.0%	33.3 %	93.1 %	4.8 3	6.7 5
Verma (2010)(58)	23.08%	104	25	AS	11	8	13	72	45.8 %	90.0%	57.9 %	84.7 %	3.7 9	7.6 2
Watanabe (1992)(63)	26.36%	110	34	ACM	15	39	14	42	51.7 %	51.9%	27.8 %	75.0 %	1.1 1	1.1 5
Zecchin (2008)(46)	15.99%	319	96	SCD+VTVF+ AS	22	59	29	209	43.1 %	78.0%	27.2 %	87.8 %	2.2 3	2.6 9
TOTAL		**2,746**	**37.6**		**258**	**991**	**145**	**1,352**	**64.0 %**	**57.7 %**	**20.7 %**	**90.3 %**	**2.13**	**2.43**

d: Raw data summaries by study and predictor category—Depolarization predictors

Study	Observed Event Rate	N	FU Months	End-Point(s)	TP	FP	FN	TN	Sens	Spec	PPA	NPA	RR	OR
DEPOLARIZATION														
QRS Duration/LBBB														
Brembilla (1991)(48)	12.62%	103	24	SCD+VTVF	2	14	11	76	15.4 %	84.4 %	12.5 %	87.4 %	0.99	0.99
DEFINITE (2004)(3)	12.88%	458	29	SCD+rCA+AS	19	114	40	285	32.2 %	71.4 %	14.3 %	87.7 %	1.16	1.19
Fauchier (2004)(60)	14.20%	162	53	SCD+VTVF	10	37	13	102	43.5 %	73.4 %	21.3 %	88.7 %	1.88	2.12
Grimm (2005)(30)	14.45%	263	52	SCD+VTVF	17	74	21	151	44.7 %	67.1 %	18.7 %	87.8 %	1.53	1.65
Hohnloser	13.14%	137	14	SCD+CA+VTV	7	41	11	78	38.9	65.5	14.6	87.6	1.1	1.2

(2003)(31)				F					%	%	%	%	8	1
Hombach (2009)(78)	17.73%	141	47	CVD+SCD+AS	23	71	2	45	92.0 %	38.8 %	24.5 %	95.7 %	5.7 5	7.2 9
Iacoviello (2007)(42)	13.41%	179	39	SCD+VTVF	10	56	14	99	41.7 %	63.9 %	15.2 %	87.6 %	1.2 2	1.2 6
Iuliano (2002) (80)	21.47%	191	45	SCD	19	55	22	95	46.3 %	63.3 %	25.7 %	81.2 %	1.3 7	1.4 9
Morgera (2004)(40)	10.26%	78	85	SCD+VTVF+AS	7	31	1	39	87.5 %	55.7 %	18.4 %	97.5 %	7.3 7	8.8 1
Schoeller (1993)(45)	15.29%	85	49	SCD	5	30	8	42	38.5 %	58.3 %	14.3 %	84.0 %	0.8 9	0.8 8
TOTAL		**1,797**	**43.7**		**119**	**523**	**143**	**1012**	**45.4 %**	**65.9 %**	**18.5 %**	**87.6 %**	**1.5 0**	**1.6 1**
SAECG														
Adachi (2001)(37)	15.63%	64	24	SCD+VTVF	4	11	6	43	40.0 %	79.6 %	26.7 %	87.8 %	2.1 8	2.6 1

DEFINITE (2004)(3)	15.51%	245	32	SCD+rCA+AS	28	130	10	77	73.7%	37.2%	17.7%	88.5%	1.54	1.66
Grimm (2003)(64)	10.97%	237	52	SCD+VTVF	12	88	14	123	46.2%	58.3%	12.0%	89.8%	1.17	1.20
Hohnloser (2003)(31)	12.50%	128	14	SCD+CA+VTVF	5	26	11	86	31.3%	76.8%	16.1%	88.7%	1.42	1.50
Keeling (1993)(65)	7.81%	64	18	SCD+VTVF	1	17	4	42	20.0%	71.2%	5.6%	91.3%	0.64	0.62
Kitamura (2002)(39)	14.46%	83	21	SCD+VTVF	5	15	7	56	41.7%	78.9%	25.0%	88.9%	2.25	2.67
Mancini (1993)(66)	15.12%	86	10	ACM+VTVF+HTx	11	9	2	64	84.6%	87.7%	55.0%	97.0%	18.2	39.1
Morgera (2004)(40)	10.26%	78	85	SCD+VTVF	1	17	7	53	12.5%	75.7%	5.6%	88.3%	0.48	0.45
Ohnishi (1990)(67)	27.78%	54	18	ACM	9	12	6	27	60.0%	69.2%	42.9%	81.8%	2.36	3.38

Turitto (1994)(57)	11.25%	80	22	SCD+VTVF	2	10	7	61	22.2 %	85.9 %	16.7 %	89.7 %	1.6 2	1.7 4
TOTAL		**1,119**	**29.6**		**78**	**335**	**74**	**632**	**51.3 %**	**65.4 %**	**18.9 %**	**89.5 %**	**1.80**	**1.99**
Fragmented QRS														
Pei (2012) (68)	9.79%	572	36		32	84	24	432	57.1 %	83.7 %	27.6 %	94.7 %	5.1 8	6.7 9
Sha (2011) (69)	11.25%	80	14		8	43	1	28	88.9 %	39.4 %	15.7 %	96.6 %	3.2 7	3.7 1
TOTAL		**652**	**25**		**40**	**127**	**25**	**460**	**61.5 %**	**78.4 %**	**24.0 %**	**94.8 %**	**4.65**	**5.80**

e: Raw data summaries by study and predictor category—Repolarization predictors

Study	Observed Event Rate	N	FU Months	End-Point(s)	TP	FP	FN	TN	Sens	Spec	PPA	NPA	RR	OR
REPOLARIZATION														
QRS-T Angle														
Pavri (2008)(79)	21.32%	455	30	ACM+AS+rCA	72	211	25	147	74.2%	41.1%	25.4%	85.5%	1.75	2.01
TWA														
Adachi (2001)(37)	15.63%	64	24	SCD+VTVF	9	21	1	33	90.0%	61.1%	30.0%	97.1%	10.2	14.1
Baravelli (2005)(70)	8.00%	25	17	SCD+VTVF+AS	2	13	0	10	100.0%	43.5%	13.3%	100.0%	3.44	3.72
Baravelli (2007)(71)	8.57%	70	19	CVD+VTVF+AS	6	34	0	30	100.0%	46.9%	15.0%	100.0%	9.83	11.32

Bloomfield (2006)(72)	8.87%	282	20	ACM+AS	25	162	0	95	100.0%	37.0%	13.4%	100.0%	26.0	29.8
Cantillon (2007)(73)	23.61%	72	38	ACM+VTVF	14	34	3	21	82.4%	38.2%	29.2%	87.5%	2.33	2.88
Grimm (2003)(64)	14.45%	263	52	SCD+VTVF	31	160	7	65	81.6%	28.9%	16.2%	90.3%	1.67	1.80
Hohnloser (2003)(31)	13.14%	137	14	SCD+CA+VTVF	16	87	2	32	88.9%	26.9%	15.5%	94.1%	2.64	2.94
Kitamura (2002)(39)	14.46%	83	21	SCD+VTVF	11	35	1	36	91.7%	50.7%	23.9%	97.3%	8.85	11.31
Sakabe (2001)(74)	43.33%	30	13	VTVF	13	11	0	6	100.0%	35.3%	54.2%	100.0%	7.56	14.2
Salerno (2007)(75)	7.40%	446	19	CVD+VTVF+rCA	20	272	2	152	90.9%	35.8%	6.8%	98.7%	5.27	5.59
Sarzi Braga (2004)(76)	21.43%	14	19	CVD+SCD+AS	3	6	0	5	100.0%	45.5%	33.3%	100.0%	4.20	5.44

Shizuta (2011)(77)	7.59%	145	36	SCD+VTVF+ AS	11	93	0	41	100.0 %	30.6 %	10.6 %	100.0 %	9.2 0	10.1
TOTAL		**1,631**	**24.3**		**161**	**928**	**16**	**526**	**91.0 %**	**36.2 %**	**14.8 %**	**97.0 %**	**5.01**	**5.70**