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VV' alternans triplets on near-field ICD intracardiac electrogram is associated with mortality

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Abstract

Background—In heart failure (HF) patients with implantable cardioverter-defibrillator (ICD) the risk of death from causes other than tachyarrhythmia is substantial. Benefit from ICD is determined by 2 competing risks: appropriate ICD shock or non-arrhythmic death. The goal of the study was to test predictors of competing outcomes.

Methods—Patients with structural heart disease (N= 234, mean age 58.5±15.1; 71% men, 80% whites, 61% ischemic cardiomyopathy) and primary (75%) or secondary prevention ICD, underwent a 5 min baseline near-field electrogram (NF EGM) recording. VV' alternans triplets were quantified as a percentage of three sinus VV' cycles sequences of “short-long-short” or “long-short-long” order. Appropriate ICD shock for fast ventricular tachycardia (FVT, cycle length 240ms)/ventricular fibrillation (VF) and composite non-arrhythmic death (pump failure death or heart transplant) served as competing outcomes.

Results—Over a median follow-up of 2.4 years, 26 patients (4.6% per person-year of follow-up) developed FVT/VF with ICD shock, and 35 (6.3% per person-year of follow-up) had non-arrhythmic death. In competing risk analysis, after adjustment for demographics, LVEF, NYHA class, cardiomyopathy type, use of class I antiarrhythmics, and diabetes, increased percentage of VV' alternans triplets (>69%) was associated with non-arrhythmic death (SHR 2.09; 95%CI 1.03–4.23; P=0.041), rather than with FVT/VF (SHR 1.05; 95%CI 0.45–2.46; P=0.901). Risk of non-arrhythmic death was especially high in diabetics with VV' alternans triplets in the highest quartile (SHR 3.46; 95%CI 1.41–8.50; P=0.007).

Conclusion—In ICD patients with structural heart disease sinus VV' alternans triplets on NF EGM is independently associated with non-arrhythmic death, rather than with FVT/VF.

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Keywords

Implantable Cardioverter-Defibrillator; ventricular arrhythmia; mortality; competing risk

Introduction

As ventricular tachycardia (VT)/ventricular fibrillation (VF) may be reverted to sinus rhythm via defibrillation, implantable cardioverter defibrillators (ICD) are used to prevent sudden cardiac death (SCD). Initially used as a therapeutic device for secondary prevention of SCD in patients, who survived cardiac arrest or VT/VF, ICDs are now widely used for primary SCD prevention. However, competing risks of mortality significantly impact the survival gain of ICD therapy. ICDs are effective at reducing the number of deaths due to VT/VF, but this gain may be outweighed by parallel rise of non-arrhythmic mode of death. Up to 23% of ICD patients die without using their devices(1). In patients alive and free of appropriate ICD therapy in the first 5–6 years after ICD implantation the decision about device replacement could be difficult. Currently, there is no validated approach to guide device replacement decision, which ought to take into account competing risks of sustained VT/VF and death before appropriate device therapy. Non-cardiac comorbidities are associated with higher mortality after ICD generator replacement(2) and might reduce survival benefit from ICD. At the same time, some ICD patients whose LVEF improves to above 35% remain at risk for VT/VF and appropriate ICD shocks(3). There is currently a paucity of data to identify populations that are unlikely to benefit from ICD generator replacement, and additional studies are needed.

We recently showed that mechanical alternans (but not repolarization alternans) is associated with the risk of heart failure (HF) progression and non-arrhythmic pump failure death(4) in acute hospitalized HF. However, association of mechanical alternans with outcomes in stable HF patients has not been explored. Previous studies showed that in HF patients, mechanical alternans, and alternans of inter-beat intervals are interdependent(5). The aim of this study was to investigate the association between alternans of inter-beat intervals and competing outcomes in patients with structural heart disease and ICD implanted for primary or secondary prevention of SCD.

Methods

We retrospectively analyzed prospectively collected data of the ICD-EGMs study(6) (NCT00916435). The study protocol was approved by the Johns Hopkins University and Washington University Human Studies Committees. All patients gave written informed consent before entering the study.

Study Population

Inclusion and exclusion criteria of ICD-EGMs study were previously described(6). Patients with structural heart disease older than 18 years were enrolled if they had a transvenous ICD device implanted for primary or secondary prevention of SCD. Pregnant women, and patients with inherited channelopathies, or concomitant conditions other than cardiac

diseases that were associated with a high likelihood of death during 1 year after enrollment were excluded. In this study, we applied additional exclusion criteria and excluded participants if they (1) presented at baseline EGM in any rhythm other than sinus; or (2) had more than 15% of non-sinus beats on baseline EGM; or (3) were paced either from right atrium or ventricle more than 5% during the preceding 3 months.

Intracardiac EGM recording

As previously described(6), baseline near-field (NF) right ventricular (RV) intracardiac electrograms (EGMs) were recorded at rest during 5–15 min simultaneously with one-lead (lead II) surface ECG via Medtronic programmer 2090 using the NI USB-9215A portable data acquisition system, with customized LabVIEW (National Instruments, Austin, TX) software application. A right atrial EGM was simultaneously recorded in patients with dual chamber ICD devices. All study patients had a dedicated bipolar ICD lead implanted with 8 mm distance from tip to ring. Bipolar endocardial NF RV EGM was recorded as the difference of potentials between the tip and the ring of the dedicated bipolar ICD lead implanted in the RV apex. Baseline EGM recording was performed about 7 days after device implantation (6). In a subset of patients EGM recording was repeated at subsequent office visits(7).

All analyzed recordings were in sinus rhythm. Premature ventricular complexes with one subsequent beat were excluded from the analysis, as previously described(6). In this study we included series of VV' intervals measured on NF RV EGM during median three minutes. VV' intervals were measured automatically between dominant (positive or negative) deflection on NF RV EGM by custom Matlab software at the Johns Hopkins Hospital. Appropriateness of NF RV EGM R peak detection was confirmed by visual inspection of recordings (LGT). AA' intervals were measured on atrial EGM. AV intervals were measured as time intervals between major NF deflections on atrial and RV EGMs.

VV', AA' and AV alternans triplet analysis

VV' alternans triplets (VValt) were measured by the computer software, developed at the University of Adelaide (MB). For alternans measurement, the first normal sinus 60 VV' intervals were considered. VV' changes of consecutive beats were analyzed using the symbolic transformation rule below – an *increase* in VV' was represented by '+1', *decrease* by '-1' while no change was denoted by '0'. A threshold was not applied when comparing the values of VV' intervals.

$$+1:VV'_{i+1} - VV'_i > 0 \quad 0:VV'_{i+1} - VV'_i = 0 \quad -1:VV'_{i+1} - VV'_i < 0$$

Sequences of three consecutive symbols of VV' series was used to measure VValt. VV' alternans triplets were defined as “short-long-short” sequences, i.e. increase followed by decrease (with symbolic sequence '-1', '+1', '-1') or “long-short-long” sequences, decrease followed by increase (with symbolic sequence '+1', '-1', '+1'), respectively. VValt was defined as the percentage of VV' alternans triplets contained within 60 VV'. In a subgroup of patients with dual-chamber ICD AA' alternans (AAalt) and AV alternans (AValt) was similarly calculated from the sequence of AA' and AV intervals, respectively. In order to

answer a question whether VV' intervals sequence was driven by AA' and AV intervals sequences, and whether AV intervals sequence was driven by AA' sequence, linear regression coefficients were calculated.

The magnitude of VV' alternans triplets (VValtmagn) was defined as $VValtmagn = 0.5(|VV'_{i+1} - VV'_i| + |VV'_{i+2} - VV'_{i+1}|)$, i.e the average absolute change in VV'. For further comparison, we calculated basic time domain heart rate variability (HRV) metrics: mean NN (the average VV' interval of normal sinus beats), SDNN (the standard deviation of normal VV' intervals) and rMSSD (the root-mean-square of normal VV' intervals).

Study outcomes

ICD-EGMs study participants were followed-up prospectively as previously described(6). Two competing end-points were considered in this study: sustained fast VT (FVT)/VF vs. non-arrhythmic death. Sustained FVT/VF event was diagnosed if ICD shock was delivered to terminate FVT/VF event with cycle length (CL) ≥ 240 msec. Competing outcome of non-arrhythmic death was defined as all-cause death or heart transplant, whichever came first. Time to event was measured from the day of study enrollment, when intracardiac EGMs were recorded.

Statistical analysis

Results are presented as mean $\pm$ standard deviation (SD) after confirmation of normal distribution. Continuous variables were compared using the independent samples *t* test. The Pearson chi-square test was used to compare categorical variables. One-way ANOVA with Bonferroni correction was used to compare clinical characteristics of patients with different outcomes. The percentage of VV' alternans was considered as a continuous variable and was also categorized in quartiles. In a subset of patients, reproducibility of VV' alternans between 2 consecutive visits was studied using a paired *t*-test. The univariable and multivariable Fine and Gray competing risk regression analysis(8) was performed to determine if the VV' alternans triplets in the highest quartile is associated with the risk of FVT/VF, or the risk of non-arrhythmic death. First, unadjusted competing risks were estimated. Then competing risks models were adjusted by demographics: age, sex, and race (Model 1). For further adjustment, the clinical and demographic variables that were associated with end-points as shown previously(6; 9) were considered. Sample size dictated necessity to create multiple models, to avoid overfitting. Model 2 is adjusted by demographics and NYHA class ≥ 3 (dichotomized) and LVEF (continuous); Model 3 is adjusted by demographics and cardiomyopathy type (ischemic vs. non-ischemic); Model 4 is adjusted by demographics and use of class I antiarrhythmics; Model 5 is adjusted by demographics and use of class III antiarrhythmics; Model 6 is adjusted by demographics and diabetes mellitus; Model 7 is adjusted by demographics, LVEF, NYHA class ≥ 3 , cardiomyopathy type, use of class I antiarrhythmics, and diabetes. In order to test impact of autonomic neuropathy and baroreflex sensitivity, interaction of VV' alternans triplets with diabetes was tested; and competing risk analysis was stratified by the presence of diabetes. Analysis was also stratified by the use of class III antiarrhythmics. The multivariate-adjusted sub-hazard ratios (SHRs) for outcomes were also calculated for the VV' alternans triplets modeled as a continuous variable using quadratic splines with 4 knots. Schoenfeld-like

residuals were evaluated to test the assumption of the subhazards proportionality. A *P*-value of <0.05 was considered significant. Data were analyzed using STATA 13 (StataCorp LP, College Station, TX).

Results

Patient population

This study population included 234 patients (mean age 58.5 ± 15.1 ; 67 [28.6%] female; 45 [19.2%] blacks). Most of participants ($n=163$, 70%) had single-chamber ICD implanted for primary prevention of SCD ($n=176$, 75%). Ischemic cardiomyopathy was diagnosed in 142 (61%) patients; New York Heart Association (NYHA) heart failure class I in 56 (24%), class II in 103 (44%), class III in 31 (13%), and class IV in 2 (1%) patients. Most of ischemic cardiomyopathy patients ($n=111$, 78%) have had a history of revascularization: percutaneous transluminal coronary angioplasty, or coronary artery bypass grafting. Mean left ventricular ejection fraction was 33.3 ± 12.2 %.

Competing outcomes: FVT/VF vs. non-arrhythmic death combined end-point

During a median follow-up of 2.4 years, 26 patients (11.1% or 4.6% per person-year of follow-up) developed FVT/VF and received appropriate rescue ICD shock. Non-arrhythmic death combined end-point was more frequent ($n=35$; 15.0% or 6.3% per person-year of follow-up). Non-arrhythmic death was confirmed in 32 patients, and additional 3 patients had successful heart transplant. Patients in non-arrhythmic death group were older, with higher probability of having ischemic cardiomyopathy, advanced HF, and diabetes mellitus (Table 1).

VV' alternans triplets and heart rate variability

Representative example of VV' alternans triplets pattern is shown on Figure 1. VV' alternans triplets were present on average in more than half of VV' intervals (63.2 ± 8.7 %; range 31% to 85%). Patients with non-arrhythmic death outcome exhibited a significantly higher percentage VV' alternans triplets compared to patients with FVT/VF (Table 1), and outcome-free participants, although absolute numerical difference between groups was small. The average magnitude of VV' alternans triplets, on the other hand, was comparable between survivors and non-survivors. Neither meanNN nor SDNN or rMSSD was significantly different between both groups. The percentage of *VValt* was not correlated with *meanNN* ($r = 0.04$, $p = 0.52$), *SDNN* ($r = 0.06$, $p = 0.38$) and showed only weak correlation with *rMSSD* ($r = 0.18$, $p = 0.006$). Amongst patients with VV' interval triplets in a highest quartile, there were more diabetics (Table 2). A trend towards higher percentage of VV' alternans was seen in patients on class I antiarrhythmics (70.0 ± 8.0 vs. 63.0 ± 8.6 %, $P=0.137$). The paired *t*-test did not find a significant difference in the percentage of VV' alternans at 2 consecutive office visits 3–4 months apart ($n=67$; $P=0.271$).

Relationships between AA' alternans, AV alternans, and VV' alternans

In all patients with dual-chamber ICDs, VV' intervals strongly depended on AA' intervals (mean regression coefficient 0.81 ± 0.17 ; $P<0.0001$). In paired analysis there was no difference in a percentage of *VValt* vs *AAalt* (58.3 ± 12.8 vs. 60.2 ± 11.9 %; $P=0.092$). In

paired analysis AValt was less frequent as compared to VValt (52.2 ± 18.1 vs. $58.3 \pm 12.8\%$; $P=0.001$) and AAalt (52.2 ± 18.1 vs. $60.2 \pm 11.9\%$; $P=0.0001$). In most of patients (74.6%) VV' intervals sequence was determined by both AA' and AV' sequences, whereas in 25.4% of patients VV' intervals sequence was determined by AA' intervals only, without significant impact of AV intervals sequence. In Cox regression analysis strength of association between AA' and VV' intervals was associated with mortality: the steeper AA'-VV' regression slope the higher risk of death (HR 0.027; 95%CI 0.001–0.699; $P=0.03$).

Competing risks of FVT/VF and non-arrhythmic death

LVEF was not associated with outcomes in this study population. Advanced HF was associated with increased risk of both FVT/VF and non-arrhythmic death (Table 3). Besides NYHA HF class, only the use of antiarrhythmics was associated with the competing risk of FVT/VF. In contrast, age ≥ 65 y, ischemic cardiomyopathy, and diabetes mellitus predicted competing risk of non-arrhythmic death.

In univariable competing risk analysis continuous variable VV' alternans triplets were associated with the risk of non-arrhythmic death (SHR 1.10; 95%CI 1.04–1.14; $P<0.0001$), but not with FVT/VF (SHR 1.00; 95%CI 0.95–1.05; $P=0.962$). Patients with VV' alternans triplets in the highest quartile ($>69\%$) had 2.5-fold increased risk of non-arrhythmic death (Table 4), but not of FVT/VF (Figure 2). Competing risk of non-arrhythmic death was only slightly attenuated after further adjustment for LVEF, NYHA class and other clinical characteristics. Antiarrhythmics functioned as mediators of non-arrhythmic death: a sub-hazard ratio in models 4 and 5 increased, as compared to model 1. Importantly, VV' alternans triplets provided additional predictive value, above NYHA HF class (Figure 2). Competing sub-hazard curves showed that participants with a large percentage of VV' alternans triplets had a larger chance of dying from non-arrhythmic death (Supplemental Figure 1).

Because of the observed mediator effect of class III antiarrhythmics on a non-arrhythmic death, we stratified Cox regression by the use of class III antiarrhythmics. Remarkably, risk of non-arrhythmic death was 3.5-times higher for ICD patients with high ($>69\%$) percentage of VV' alternans on class III anti-arrhythmic drugs [SHR 3.52; (95%CI 1.03–12.06); $P=0.045$], while no significant association was seen in patients who did not take class III antiarrhythmics [HR 2.00; (95%CI 0.85–4.65); $P=0.111$; $P_{\text{interaction}}=0.593$].

Diabetes mellitus in this study is an important confounder of the risk of non-arrhythmic death, associated with increased VV' alternans triplets. Adjustment for diabetes significantly attenuated the risk of non-arrhythmic death (Table 4). Interaction with diabetes was borderline ($P=0.107$). Interestingly however, when stratified by diabetes, competing analysis (Table 5) revealed that VV' alternans triplets carried dissimilar risks in diabetics vs. non-diabetics. While diabetic patients with VV' alternans triplets in the highest quartile experienced tripled competing risk of non-arrhythmic death, non-diabetic patients, on the contrary, demonstrated a trend towards doubled competing risk of FVT/VF (Figure 3).

Discussion

The major finding of this study is the demonstration of the independent association of increased percentage of sinus intracardiac RV NF EGM VV' alternans triplets with elevated competing risk of non-sudden death, which persisted after adjustment for LVEF, NYHA class, type of cardiomyopathy, and use of class I and III antiarrhythmics. In contrast, intracardiac VV' alternates triplets did not associate with competing risk of FVT/VF. Association of a high percentage of VV' alternans with non-arrhythmic death was especially strong in ICD patients on class III antiarrhythmic drugs and in diabetics. In this study of primary and secondary prevention ICD patients with structural heart disease, rate of non-arrhythmic death (6.3% per person-year) exceeded the rate of FVT/VF events with ICD shock (4.6% per person-year). Monitoring of the percentage of VV' alternans triplets on NF EGM could be easily incorporated into ICD device follow-up, and could possibly guide medical management of ICD patients, including use of anti-arrhythmic medications. Further studies of AA', AV and VV' alternans are needed.

Gordon Moe in 1968 described two mechanisms(10), which explain intracardiac VV' alternans observed in this study: (1) alternation between dissociated intra-AV-nodal transmission pathways, and (2) ventriculophasic modulation of sinus node and/or AV-nodal conduction.

Alternation between dissociated intra-AV-nodal transmission pathways

When AV-nodal conduction is stressed (as at fast heart rates), or depressed (as with the use of AV-nodal agents, such as beta-blockers, calcium channel blockers, digitalis, and anti-arrhythmic medications), dissociation may occur. It is unlikely that the conductivity of the two AV nodal pathways will be equally depressed. If the conduction intervals in the two pathways are not equal, alternation of the conduction time must occur(10). In accordance with this finding, we observed a trend towards higher percentage of VV' alternans in patients on class I antiarrhythmics. In this study, we measured alternans of RV activation timing on RV NF EGM, and thus were able to capture differences due to the beat-to-beat change in AV conduction. Most of the participants used AV-nodal agents, and therefore dissociated intra-AV-nodal transmission mechanism might be plausible in this patient population and might explain observed high rate (mean 63%) of NF EGM VV' alternans triplets. At the same time, our study suggests that AV node could mitigate effect of sympathetic tone on the ventricle of the heart and decrease percentage of alternans.

Ventriculophasic modulation of sinus node and/or AV-nodal conduction

The ventriculophasic phenomenon was first described in AV block by Parsonnet and Miller(11) in 1944, Roth and Kisch(12) in 1948, Rosenbaum and Lepeschkin(13) in 1955, and explained by Moe(10) in 1968. Each pressure pulse (stroke volume) triggers vagal discharge. Alternating with each pressure pulse sympathetic nerve activity(14) was shown in HF patients. Cholinergic activity in the sinoatrial (SA) pacemaker and the AV node is at a minimum just prior to each vagal burst, providing less depressed SA activation (AV conductivity, accordingly). Therefore, in patients with slightly depressed SA pacemaker or AV conductivity (as with the use of AV-nodal agents) SA activation (AV interval) of the

beat following a relatively long VV' interval will be slightly shorter, which might result in a slightly shorter VV' interval. In turn, after a slightly shorter VV' interval SA and AV node will experience a larger cholinergic effect, which results in a slightly longer VV' interval. Such alternation of VV' intervals is inevitably manifested by mechanical alternans, as well(5),(15). Low-gain feedback control of the vicious cycle results in persisting mechanical and VV' alternans. This mechanism is consistent with our recently reported observation of nearly persistent mechanical alternans in some MAS study participants(4). Importantly, in this study VV' alternans predicted non-arrhythmic death, but not FVT/VF, which is consistent with the MAS study results.

Very few studies evaluated clinical significance of VV' alternans, and yielded conflicting results. While Guzzetti et al(16) observed increased percentage of non-variable symbolic patterns before VT/VF in ICD patients, Huikuri et al(17) reported VV' alternans on surface ECG before VT on Holter. The interaction with diabetes observed in this study adds to this controversy. We observed two contradictory patterns of associations: VV' alternans in non-diabetics trended towards association with FVT/VF, whereas in diabetics VV' alternans was strongly associated with non-arrhythmic death. A novel holistic approach is needed to understand the complexity of interactions between VV' alternans, mechanical alternans, and repolarization alternans, and their associations with outcomes.

Method of VV' alternans detection: VV' alternans triplets

Standard methods for VV' alternans analysis such as power-spectral density appear to be inadequate to study complex and short-term instabilities in VV' that may occur after arrhythmic events(16). The concept of symbolic dynamics employs a coarse-graining procedure in which some of the detailed information is lost, but the robust properties of the dynamics are preserved, and therefore provides an easy interpretation of physiological data through a simplified description by means of a few symbols, and have been widely used to study RR dynamics(18; 19). The symbolic approach used in this study provides high flexibility in VV' alternans analysis by taking into account short and relevant patterns of VV' dynamics – thus capturing any brief and transient instability.

Study limitations

Small sample size is an important limitation of this study. While intriguing, the borderline findings of the study (interaction with diabetes) should be considered hypothesis-generating, and require confirmation in future studies. In this study, we arbitrarily chose the duration of 60 normal VV' intervals to measure alternans. Optimum data length was not investigated and reproducibility of the VV'(RR') alternans measure has yet to be established. In studies on T wave alternans, frequency domain and moving average methods were employed to obtain average values, improving the signal to noise ratio (20). In contrast to microvolt alternans in the T wave, VV'(RR') intervals can be delineated with comparably high precision. This enabled us to measure alternans in a true beat-to-beat fashion. Since we observed alternans for more than 50% of beats, our finding cannot be solely attributed to random effects and deterministic origins of VV' alternans have to be considered.

Clinical implications

Monitoring of the percentage of VV' alternans could help to manage ICD patients, especially those on antiarrhythmic medications. ICD patients with high percentage of VV' alternans are at a high risk of non-arrhythmic death and therefore will likely benefit from additional careful medical management of HF. Importantly, the association of VV' alternans with non-arrhythmic death was particularly strong in patients on class III antiarrhythmic medications. In the future, monitoring of the percentage of VV' alternans may help to guide a safe regimen of anti-arrhythmic therapy. However, a prospective study of VV' alternans is needed before its implementation in clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Representative example of AA' and VV' alternans triplets on ICD EGM. Upper panel shows atrial EGM. Lower panel shows simultaneously recorded right ventricular near-field EGM.

Figure 2.

Adjusted by demographics cumulative incidence functions for the FVT/VF (**A**), and non-arrhythmic death (**B**), in patients with the highest VV' alternans triplets quartile, and those with the lower 3 VV' alternans triplets quartiles. Adjusted by demographics cumulative incidence functions for the FVT/VF (**C**), and non-arrhythmic death (**D**) in 4 categories of patients: those with the highest VV' alternans triplets quartile and NYHA class I–II, patients with the highest VV' alternans triplets quartile and NYHA class III–IV, those with the lower 3 VV' alternans triplets quartiles and NYHA class III–IV, patients with the lower 3 VV' alternans triplets quartiles and NYHA class I–II.

Figure 3.

Unadjusted cumulative incidence functions for the FVT/VF (**A, C**), and non-arrhythmic death (**B, D**), in diabetic (**A, B**) and non-diabetic (**C, D**) patients with the highest VV' alternans triplets quartile, and those with the lower 3 VV' alternans triplets quartiles.

Table 1

Clinical and ECG characteristics of patients with competing outcomes

Characteristic	Outcome-Free (n=173)	FVT/VF (n=26)	Non-arrhythmic death (n=35)	ANOVA or χ^2 P
Age(SD), y	57.6(14.8)	55.4(14.4)	65.3(15.4)	0.011
Men, n(%)	119(68.8)	19(73.0)	29(82.9)	0.239
Whites, n(%)	139(80.4)	22(82.6)	28(80.0)	0.869
LVEF(SD), %	33.7(12.8)	33.0(11.4)	31.5(9.8)	0.624
Primary prevention ICD, n(%)	135(78.0)	18(69.2)	23(65.7)	0.231
Ischemic CM, n(%)	96(55.5)	18(69.2)	28(80.0)	0.016
NYHA class III–IV, n(%)	15(8.7)	8(30.8)	10(28.6)	<0.0001
Revascularization, n(%)	76(79.2)	13(72.2)	22(78.6)	0.806
Diabetes, n(%)	36(37.5)	10(55.6)	18(64.3)	0.027
Hypertension, n(%)	85(88.5)	17(94.4)	24(85.7)	0.655
Single-chamber ICD, n(%)	69(71.9)	11(61.1)	29(71.4)	0.276
ACEI or ARBs, n(%)	130(75.1)	21(80.8)	29(82.9)	0.544
Beta-blockers, n(%)	141(81.5)	22(84.6)	30(85.7)	0.799
Aldosterone antagonists, n(%)	63(36.4)	9(34.6)	11(31.4)	0.850
Statins, n(%)	110(63.6)	14(53.9)	23(65.7)	0.587
Class I antiarrhythmics, n(%)	1(0.58)	4(15.4)	0	<0.0001
Class III antiarrhythmics, n(%)	41(23.7)	11(42.3)	12(34.3)	0.085
Atrial fibrillation Hx, n(%)	42(24.3)	5(19.2)	13(37.1)	0.206
meanNN (SD), ms	851.3(209.8)	802.7(137.9)	853.3(191.6)	0.503
SDNN (SD), ms	55.5(38.8)	50.7(32.5)	52.9(46.7)	0.814
rMSSD (SD), ms	66.7(52.5)	61.3(43.4)	70.1(64.0)	0.814
VValt (SD), %	62.3(8.5)	63.2(9.7)	67.7(7.2)	0.003
VValt_Magn (SD), ms	55.2(43.9)	52.3(38.0)	59.7(55.4)	0.800

Table 2

Clinical characteristics of patients with VV' alternans triplets in the fourth quartile compared to patients with alternans triplets in the lower three quartiles.

	Q1–Q3 VV'alt (58.6% – 69%), n=188	Q4 VV'alt (69.1%–84.5%), n=46	P
Age (SD), y	57.9(15.0)	61.0(15.1)	0.205
Men, n(%)	135(71.8)	32(69.6)	0.763
White, n(%)	151(80.3)	38(82.6)	0.724
Ischemic cardiomyopathy, n(%)	111(59.0)	31(67.4)	0.299
Primary prevention ICD, n(%)	144(76.6)	32(69.6)	0.322
NYHA class III–IV, n(%)	23(12.2)	10(21.7)	0.097
LVEF (SD), %	33.3(12.1)	33.4(12.9)	0.951
Hx of atrial fibrillation, n(%)	50(26.6)	10(21.7)	0.499
Diabetes mellitus, n(%)	52(27.7)	27(58.7)	<0.0001
Hypertension, n(%)	142(75.5)	35(76.1)	0.937
Use of Nitrates, n(%)	36(19.2)	16(34.8)	0.022
Use of beta-blockers, n(%)	154(81.9)	39(84.8)	0.647
Use of class III antiarrhythmics, n(%)	52(27.7)	12(26.1)	0.830
Single-chamber ICD, n(%)	134(71.3)	29(63.0)	0.460

Table 3

Unadjusted competing risks of FVT/VF vs. non-arrhythmic death

Predictor	FVT/VF (n=26)		Non-arrhythmic death (n=35)	
	SHR (95%CI)	P	SHR (95%CI)	P
Age > 65y	0.45(0.17–1.20)	0.109	2.60(1.33–5.07)	0.005
LVEF ≤ 25%	0.77(0.29–2.06)	0.598	0.79(0.34–1.82)	0.574
NYHA class III	3.02(1.34–6.81)	0.008	3.03(1.43–6.42)	0.004
Non-ischemic cardiomyopathy	0.66(0.28–1.52)	0.328	0.35(0.15–0.80)	0.013
Secondary prevention	1.43(0.62–3.30)	0.403	1.62(0.83–3.18)	0.160
Diabetes mellitus	1.28(0.58–2.79)	0.542	2.63(1.35–5.11)	0.004
Use of class 1 antiarrhythmic	13.6(5.05–36.33)	<0.0001	-	
Use of class 3 antiarrhythmic	2.16(0.99–4.71)	0.053	1.51(0.75–3.30)	0.250
Use of Nitrates	1.59(0.70–3.62)	0.269	1.43(0.69–2.96)	0.331
History of Atrial fibrillation	0.70(0.26–1.85)	0.466	1.96(0.98–3.94)	0.057

Table 4

Competing risks subhazard ratios for ICD-EGMs study participants with the VV' alternans triplets in the highest quartile (> 69%)

	FVT/VF (n=26)		Non-arrhythmic death (n=35)	
Model	SHR (95%CI)	P	SHR (95%CI)	P
Unadjusted	1.57(0.67–3.70)	0.299	2.54(1.26–5.13)	0.009
Model 1	1.70(0.71–4.04)	0.232	2.38(1.19–4.78)	0.015
Model 2	1.64(0.68–3.95)	0.274	2.30(1.17–4.53)	0.016
Model 3	1.64(0.68–3.95)	0.274	2.32(1.15–4.66)	0.018
Model 4	1.29(0.56–2.95)	0.548	2.64(1.31–5.32)	0.007
Model 5	1.29(0.56–2.95)	0.548	2.45(1.20–4.97)	0.013
Model 6	1.59(0.63–4.01)	0.330	1.87(0.92–3.80)	0.085
Model 7	1.05(0.45–2.46)	0.901	2.09(1.03–4.23)	0.041

Model 1 is adjusted by age, sex, race. Model 2 is adjusted by demographics and NYHA class 3 and LVEF; Model 3 is adjusted by demographics and cardiomyopathy type; Model 4 is adjusted by demographics and use of class I antiarrhythmics; Model 5 is adjusted by demographics and use of class III antiarrhythmics; Model 6 is adjusted by demographics and diabetes mellitus; Model 7 is adjusted by demographics, LVEF, NYHA class 3, cardiomyopathy type, use of class I antiarrhythmics, and diabetes.

Table 5

Unadjusted competing risks subhazard ratios for diabetics and non-diabetic participants with the VV' alternans triplets in the highest quartile (> 69%)

FVT/VF (n=26)			Non-arrhythmic death (n=35)	
Subgroup	SHR (95%CI)	P	SHR (95%CI)	P
Diabetics	0.86(0.22–3.29)	0.822	3.46(1.41–8.50)	0.007
Non-diabetics	2.42(0.81–7.23)	0.113	0.52(0.07–4.13)	0.540