ORIGINAL ARTICLE

Fragmented QRS and arrhythmic events in patients with implantable cardioverter-defibrillators

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KEY WORDS
arrhythmic events, fragmented QRS, implantable cardioverter--defibrillator

EDITORIAL
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ABSTRACT

BACKGROUND Patients with implantable cardioverter-defibrillators (ICDs) may experience recurrent arrhythmic events (AE). Identification of these patients may help plan further therapy. Fragmented QRS (fQRS) was identified as a risk marker of AE in various populations but its predictive value in patients with ICD has not been established.

AIMS To examine whether fQRS is a risk marker of future AE in patients with ICD.

METHODS We retrospectively analyzed demographic, clinical, electrocardiographic (ECG), procedural, and follow-up data of 367 consecutive patients who received ICD in a single tertiary center. A 12-lead ECG recorded at the time of implantation was analyzed for the presence of fQRS. The analyzed primary endpoint was AE and total mortality was a secondary endpoint.

RESULTS During follow-up lasting mean (SD) 34.5 (18) months, 146 patients (40%) had AE and total mortality was 18% (67 patients). Univariate analysis identified 7 parameters associated with AE of which 2—ICD implantation for secondary prevention (odds ratio [OR], 2.13; 95% CI, 1.13–4.025; $P = 0.02$) and fQRS in inferior ECG leads in patients with QRS duration of less than 120 ms (OR, 4.88; 95% CI, 1.18–20; $P = 0.03$)—remained significant in the multivariable analysis. Total mortality was associated with morbidity but not with fQRS.

CONCLUSIONS Fragmented QRS in inferior ECG leads in patients with QRS duration <120 ms is an independent parameter associated with AE in patients with ICD. Whether it could be helpful in deciding to perform early / prophylactic ablation in these patients needs to be prospectively studied.

INTRODUCTION Although implanted cardioverter-defibrillators (ICDs) significantly decrease arrhythmic and total mortality, recurrences of ventricular tachycardia (VT) or fibrillation (VF) remain a substantial problem. The percentage of appropriate ICD interventions ranges between 8% and 22% (follow-up, 1.9–3.8 years) in patients with ICD implanted for the primary prevention of sudden cardiac death (SCD),[1,2] and between 16% and 32% (follow-up, 3.4–5 years) in those implanted for the secondary prevention.[3,4] It has been shown that recurrent VT / VF and high-energy shocks adversely influence the outcome.[2,5-11] Thus, identification of patients with ICDs who remain at a risk of VT / VF recurrences is important; however, risk stratification in this population is difficult. Parameters such as implantation for the secondary prevention,[12-14] low left ventricular ejection fraction (LVEF),[15-17] and noninvasive programmed ventricular stimulation[18] have been suggested to identify patients at risk, but their predictive value is limited.

Fragmented QRS (fQRS) is a relatively new parameter of unproven prognostic value in various populations. Its presence on surface electrocardiography (ECG) is associated with myocardial scarring and conduction disturbances[19-21]

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WHAT'S NEW?

Fragmented QRS is an easily accessible standard electrocardiography parameter that enables identification of those patients with implantable cardioverter-defibrillators who are at increased risk of arrhythmic events. These patients may require modification of antiarrhythmic therapy or prophylactic catheter ablation.

which may predispose to ventricular arrhythmias (VAs).[22-24] Whether this parameter could be useful for the identification of patients with ICD who are at an increased risk of VT / VF recurrences and ICD shocks has not yet been determined. Therefore, the aim of the study was to assess the value of fQRS in predicting arrhythmic events (AEs) in patients with ICD.

METHODS

Patients The study included consecutive patients who underwent ICD / cardiac resynchronization therapy-defibrillator (CRT-D) implantation between 2006 and 2011 at the Cardiology Department of Saint Vincent a Paulo Hospital in Gdynia, Poland. All patients had either primary or secondary prevention indications according to the current European Society of Cardiology guidelines. All patients signed informed consent to undergo implantation of the device. The study design was approved by the bioethical committee of the Centre of Postgraduate Medical Education (no. 50PB2014). Out of 425 patients, 367 fulfilled the following inclusion criteria: 1) at least 1-year follow-up or arrhythmic death or appropriate ICD intervention occurring within 1 year of follow-up and 2) good-quality preimplantation standard ECG allowing for an accurate QRS assessment.

Using patient's medical records, we retrospectively analyzed baseline demographic and clinical data. There were no differences in the demographic and clinical characteristics between the study group (n = 367) and the group that was excluded from the study due to too short follow-up or poor quality ECG (n = 58).

Electrocardiographic analysis We analyzed 12-lead ECGs (25 mm/s, 10 mm/mV) obtained at the time of ICD implantation. Type of heart rhythm, heart rate, QRS duration including reasons for its prolongation (bundle branch block [BBB] or paced QRS), presence and location of Q wave and fQRS and potential repolarization disturbances (QT, QTc, QTd) were assessed. Locations of both the Q wave and fQRS were defined according to the current guidelines[25] by their presence in at least 2 corresponding ECG leads: V_1 through V_5 for anterior, I, aVL, V_6 for lateral, and II, III, aVF for inferior location.

Because definitions of fQRS are different in patients with narrow (<120 ms) and wide (≥120 ms) QRS complex, fQRS was named f-nQRS in the former group and f-wQRS in the latter group. The f-nQRS was defined as the presence of an additional R wave (R') or notching in the nadir of the S wave, or the presence of more than 1 R' (fragmentation) in 2 contiguous leads corresponding to the major coronary artery territory.[21] In patients with QRS of 120 ms or longer due to BBB, f-wQRS was defined as the presence of more than 2 notches (at least 1 notch more than in typical BBB) or multiple notches of the R wave or more than 2 notches in the nadir of the S wave. A fragmented paced QRS was defined by the presence of more than 2 R' or more than 2 notches in the S wave in 2 contiguous leads.[26]

An example of an original ECG recording with fQRS is presented in FIGURE 1. The analysis of duration and fragmentation of QRS was performed visually. In case of uncertainty, ECG was evaluated by a second investigator (PK) and a consensus was reached. The intra-observer (AK) variability for fQRS detection was calculated by performing the second analysis of random 150 ECG recordings and comparing with the results of the first analysis. The agreement rate reached 89%.

Follow-up All patients after ICD implantation were followed in the outpatient clinic. We analyzed patient status and all events occurring during the follow-up. We also collected data on percentage of ICD / CRT-D pacing, occurrence and number of nonsustained VT, syncope (both associated and not associated with arrhythmia), hospitalizations due to problems with ICD, progression of the disease, and inappropriate ICD interventions. We also evaluated occurrence and number of VTs, VFs, and electrical storms, including VTs below ICD detection window, occurrence and number of appropriate ICD interventions (both antitachycardia pacing and high-energy shocks), time to first ICD intervention, as well as occurrence of death which was classified as arrhythmic, nonarrhythmic, or unknown. In case of incomplete or ambiguous data, the patients or their families were contacted by phone or mail.

Arrhythmic death was defined as death caused by VA recorded by ECG or ICD. In case of sudden death (within 1 hour from the onset of symptoms) when it was impossible to confirm VA on ECG but there were no signs of other potential reasons of death, it was classified as arrhythmic.[27] All uncertain cases of death were consulted with the expert (PK) and joined agreement was obtained as to the type of death. Both the main investigator (AK) and the expert (PK) were blinded to the demographic and clinical data of the patients. If the mode of death remained uncertain, it was classified as unknown and not included in the analysis of the primary endpoint.

The primary endpoint was defined as the first appropriate ICD intervention (antitachycardia

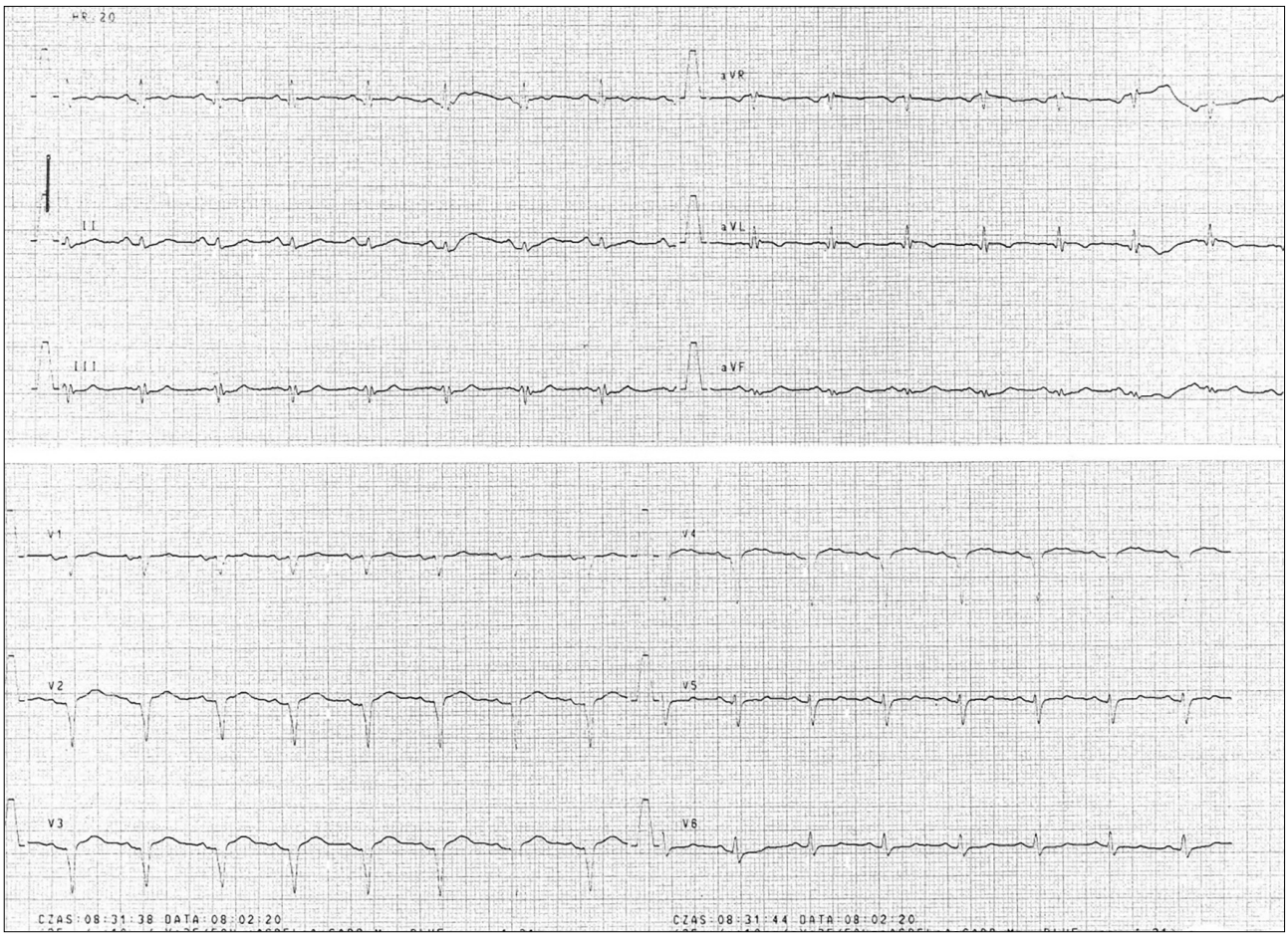

FIGURE 1 Original example of a fragmented QRS in inferior electrographic leads in a patient with QRS duration of less than 120 ms

pacing and/or ICD shock) and/or arrhythmic death. The secondary endpoint was total mortality.

Statistical analysis All calculations were performed with Statistica, version 12.0 statistical package (StatSoft Inc, Palo Alto, California, United States). The results are presented as mean (SD) or median (interquartile range) when the data distribution was not normal. In order to compare groups in pairs for quantitative data, the *t* test or the Mann–Whitney test were used with respect to the type of distribution of the variables tested. Qualitative data were compared according to the number of cases in each compared category and/or their expected values using the χ^2 test with Yates correction, or the Fisher exact test. Univariate analyses by means of logistic regressions were carried out in order to evaluate the risk factors associated with each of considered endpoints. Subsequently, the multivariable logistic regression analyses were carried out, including all variables that were significant in the respective univariate analyses (either performed by comparisons of groups or univariate logistic regressions). The proportions of patient survival were estimated with the Kaplan–Meier curves. The log-rank test was used to examine the significance of differences in survival between compared groups. In order to determine the optimal cutoff threshold values, receiver operating characteristic analysis was used with the determination of the course of the curves and the area under the curve (AUC) calculation. In all calculations, the significance level was set at a *P* value of less than 0.05.

RESULTS

Baseline characteristics Baseline clinical characteristics are shown in TABLE 1. The majority of patients were men and the mean (SD) age was 65.2 (11) years. Implantable cardioverter-defibrillators were mostly implanted for primary prevention. The prevailing heart disease was coronary artery disease (CAD), followed by dilated cardiomyopathy (DCM). The majority of patients had a history of at least one myocardial infarction (MI) and were treated invasively with PCI and/or CABG. The mean LVEF was 27.7% and New York Health Association class III was the most common stage of heart failure. Over one-third of patients had atrial fibrillation. Almost all patients (92%) were treated with a β-blocker and 31%, with amiodarone. The majority (52%) of patients had a single-chamber ICD, and around

TABLE 1 **Baseline patient characteristics (continued on the next page)**

Parameter		Value (n = 367)
Male sex		306 (83.4)
Age, y, mean (SD)		65.2 (10.6)
Primary prevention		259 (70.6)
CAD		273 (74.6)
History of MI		221 (60.2)
Number of MI	0	146 (40.1)
	1	127 (34.9)
	2	67 (18.4)
	≥3	24 (6.6)
History of CABG / PCI		184 (50.4)
Complete revascularization		188 (64.6)
DCM		102 (27.9)
HCM		10 (2.7)
ARVC		3 (0.8)
LVEF, %, mean (SD)		27.7 (9.5)
LVEDD, cm, mean (SD)		6.5 (3.4)
NYHA class	I	10 (6)
	II	68 (41)
	III	84 (50.6)
	IV	4 (2.4)
Comorbidities		
Supraventricular tachyarrhythmia (mainly AF)		137 (37.3)
COPD		41 (11.2)
DM		107 (29.1)
AH		212 (57.8)
PAD		33 (9)
Stroke/TIA		32 (8.7)
Hypothyroidism		14 (3.8)
Hyperthyroidism		18 (4.9)
Creatinine, mg/dl, mean (SD)		1.1 (0.4)
GFR, ml/min, mean (SD)		74.7 (24)
BMI, kg/m^2, mean (SD)		27.6 (4.5)
Drugs influencing QRS		
β-Blocker		335 (91.8)
Amiodaron		113 (31)
Sotalol		8 (2.2)
CCB		35 (9.6)
Digoxin		62 (17)

TABLE 1 Baseline patient characteristics (continued from the previous page)

Parameter	Value (n = 367)
Device	
ICD VR	191 (52)
ICD DR	124 (33.8)
CRT-D	52 (14.2)
Single-coil lead	188 (52.8)
Double-coil lead	175 (48.2)

Data are presented as number (percentage) of patients unless otherwise indicated.

Abbreviations: AH, arterial hypertension; AF, atrial fibrillation; ARVC, arrhythmogenic right ventricular cardiomyopathy; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CCB, calcium channel blockers; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy-defibrillator; DCM, dilated cardiomyopathy; DM, diabetes mellitus; GFR, glomerular filtration ratio; HCM, hypertrophic cardiomyopathy; ICD DR, dual-chamber implantable cardioverter defibrillator; ICD VR, single-chamber implantable cardioverter defibrillator; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack

one-third (34%), a dual-chamber device. The remaining patients had ICDs with resynchronization capabilities (CRT-D).

In the whole study group (n = 367) fQRS was present in 161 patients (44%). In the subgroup of patients with QRS of less than 120 ms (n = 165), this number was 41 (25%) whereas in the subgroup with QRS of 120 ms or greater (n = 202), it was 120 (59%).

Events during follow-up The mean (SD) duration of follow-up was 34.5 (17.9) months. Episodes of VT in the ICD detection zone occurred in 128 patients, below this zone, in 12, VF, in 34, and electrical storm, in 20. Arrhythmic death was noted in 10 patients and total mortality was 18.3% (67 patients). The median (interquartile range) time to first appropriate ICD intervention was 9 (3–18) months. Appropriate ICD interventions occurred in 141 patients, ICD shock, in 75, and ATP, in 122. Inappropriate interventions were recorded in 69 cases. In summary, the primary endpoint occurred in 146 patients whereas the secondary, in 67 patients.

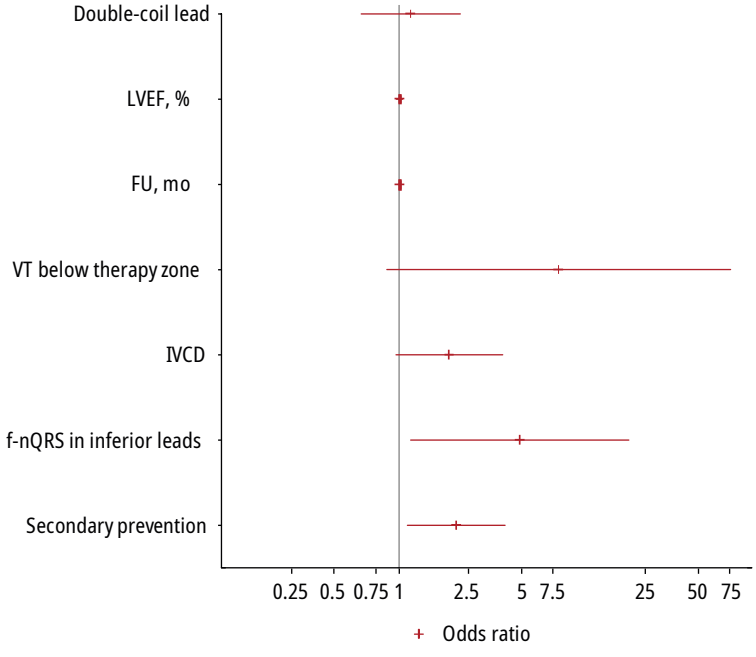

FIGURE 2 Odds ratios with 95% CI for the primary endpoint
Abbreviations: f-nQRS, fragmented QRS in patients with a narrow QRS complex; FU, follow-up; IVCD, interventricular conduction delay; VT, ventricular tachycardia; others, see TABLE 1

Predictors of arrhythmic events (primary endpoint) Parameters associated with the primary endpoint in the univariate analysis included ICD implanted for secondary prevention, f-nQRS in inferior ECG leads, occurrence of VT below arrhythmia detection zone, lower LVEF, longer follow-up, double-coil defibrillation lead, and interventricular conduction delay. Detailed results are shown in FIGURE 2.

In the multivariable analysis, 2 parameters remained independently associated with higher risk: ICD implantation for secondary prevention (odds ratio [OR], 2.13; 95% CI, 1.13–4.025; $P = 0.02$) and f-nQRS in inferior ECG leads (OR, 4.88; 95% CI, 1.18–20; $P = 0.03$). Detailed results are shown in FIGURES 2, 3, and 4.

When the subgroups with ischemic (273 patients [74.6%]) and nonischemic etiology were analyzed separately, f-nQRS in inferior leads was not present more often in patients with AE in any of the groups ($P = 0.13$ in the ischemic group and $P = 0.35$ in the nonischemic group).

Predictors of total mortality (secondary endpoint) Parameters associated with total mortality in the univariate analysis were older age, significant right coronary artery narrowing, higher number of MI, altered renal function, supraventricular tachyarrhythmias, atrial fibrillation, diabetes, increased LV end-diastolic diameter, diuretic therapy, and shorter follow-up.

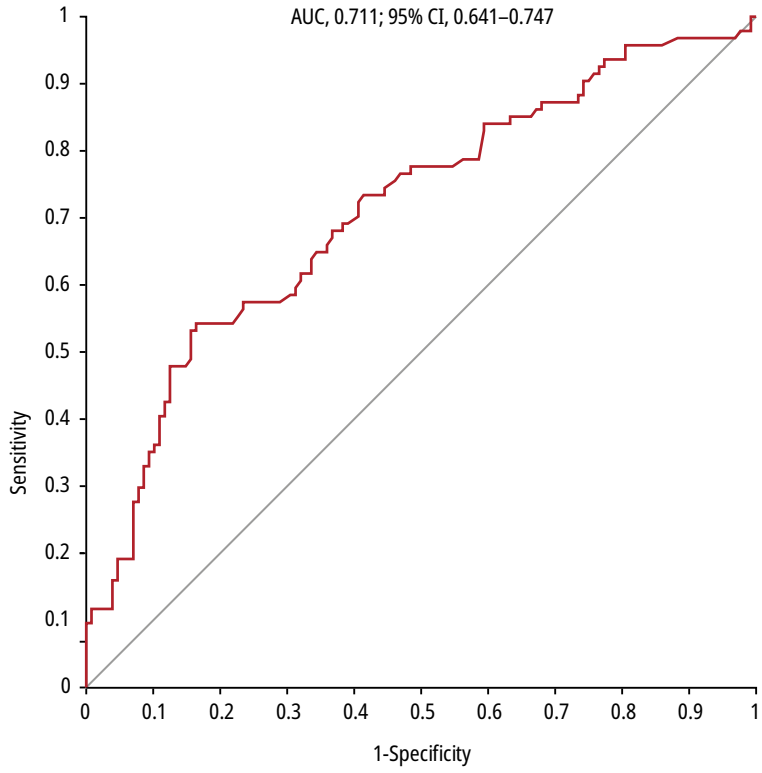

FIGURE 3 Receiver operating characteristic curve for 2 independent parameters for identification of patients with the primary endpoint
Abbreviations: AUC, area under the curve

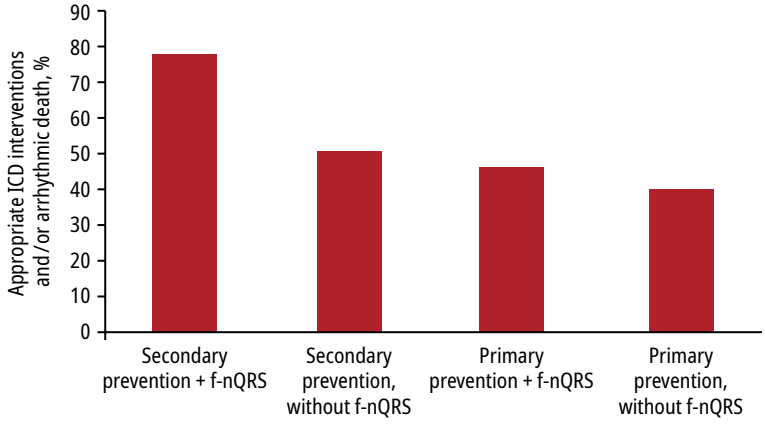

FIGURE 4 Percentage of patients who reached the primary endpoint depending on the presence of fragmented QRS in inferior electrographic leads in patients with QRS of less than 120 ms and the type of prevention of sudden cardiac death
Abbreviations: ICD, implantable cardioverter-defibrillator; others, see FIGURE 2

The ECG parameters associated with total mortality included prolonged QRS, QT, and QTc durations as well as f-wQRS in inferior and lateral ECG leads, fragmented R wave, Q wave, and Q wave in BBB / paced QRS. Total mortality was higher in patients with lower detection and therapy zone and in those who experienced VF, electrical storm, and syncope during follow-up.

Multivariable analysis showed that independent parameters associated with higher total mortality risk were: VF during follow-up (OR, 12.82; 95% CI, 2.288–71.429; P = 0.004), lower VT detection and therapy zone (OR, 0.868; 95% CI, 0.805–0.937; P <0.001), diuretic therapy (OR, 6.060; 95% CI, 1.225–29.412; P = 0.03), and shorter follow-up (OR, 0.918; 95% CI, 0.881–0.956; P <0.001). These results are shown in FIGURES 5 and 6.

DISCUSSION

The main finding of our study is that f-nQRS in inferior ECG leads as well as secondary prevention for ICD implantation are independent factors associated with higher risk of AEs in patients with ICD.

Fragmented QRS on surface ECG is one of the markers of myocardial scarring[28] and also depicts the size of the scar.[29,30] Thus, fQRS is a noninvasive marker of potential arrhythmogenic substrate. In our study, f-nQRS in inferior ECG leads was independently associated with higher risk of appropriate ICD interventions and / or arrhythmic death. Similar results but in different patient populations and without specification of ECG leads with fQRS presence have been reported by others. Among patients with idiopathic DCM (LVEF ≤40%, majority without ICD), f-nQRS was associated with a combined endpoint consisting of all-cause mortality and VA.[17] Some authors reported that in the group with ICD (both primary and secondary prevention, CAD and DCM patients) presence of f-nQRS was associated with lower VA-free survival, regardless of ECG lead location, compared with patients without fQRS and with those with wide QRS.[24] However, these results have not been confirmed in a study which aimed to improve patients' selection for ICD implantation for primary prevention.[31]

Also, a subanalysis of the MADIT II (Multicenter Automatic Defibrillator Implantation Trial-II) revealed strong correlation between fQRS in inferior leads and ICD shock, SCD, and total mortality.[22] However, contrary to our study, this association was driven primarily by the increase in events found in patients with LBBB. Reasons for such results remain unclear.

Higher arrhythmogenicity of scars depicted by fQRS in inferior rather than in other locations can be explained by the fact that majority of endings of the vagal nerve are located in the inferior and posterior ventricular wall. Thus, necrosis in this area minimizes protective vagal effects on the heart. According to another hypothesis, impairment of the papillary muscle predisposes to re-entrant VA. Because damage to the posteromedial papillary muscle occurs during inferior MI 10-fold more often than damage to the anterolateral papillary muscle due to anterior MI, fQRS in inferior leads, depicting this damage, may have higher prognostic value than fQRS in other leads.[32]

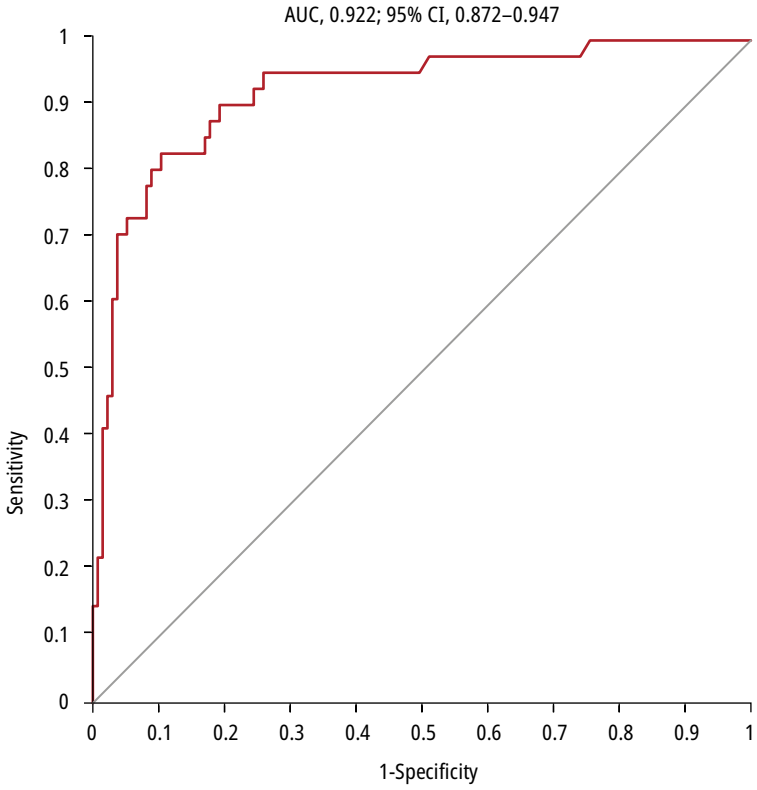

FIGURE 5 Receiver operating characteristic curve for 4 independent parameters for identification of patients with a secondary endpoint
Abbreviations: see FIGURE 3

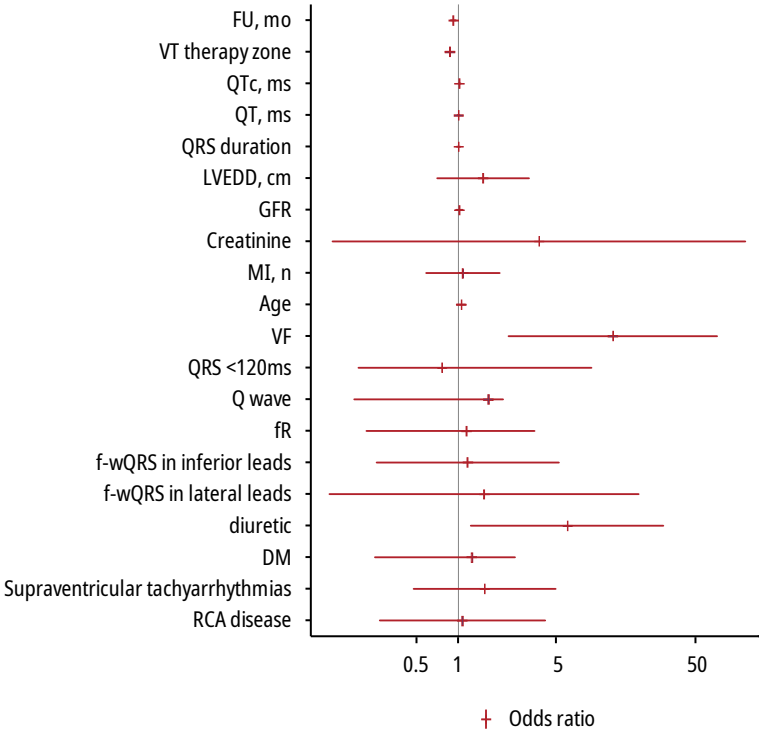

FIGURE 6 Odds ratios with 95% CI for secondary endpoints
Abbreviations: f-wQRS, fragmented QRS in patients with a wide QRS complex; RCA, right coronary artery; VF, ventricular fibrillation; others, see TABLE 1 and FIGURE 2

Inferior ECG leads are the most common location for fQRS both in healthy populations[33] and patients with heart failure.[22] It remains unclear why only in the presence of organic heart disease this parameter is associated with AE. Currently, a survey is underway that aims to differentiate mild variants of fQRS from malignant ones, corresponding to myocardial scarring.[33]

The primary endpoint occurred more often in patients with ICDs implanted for secondary prevention than in those with ICDs for primary prevention. However, total mortality between these groups did not differ. These results are similar to those presented in other studies. Patients with a history of SCD are at a higher risk of arrhythmia recurrence while those with ICDs implanted for primary prevention often never benefit from the device. Nevertheless, primary prevention patients usually have lower LVEF and more comorbidities, which makes total mortality similar (as in our study) or higher than in the secondary prevention group.[3,13]

The clinical utility of detecting fQRS (primarily f-nQRS) in ICD recipients is not known. It may be speculated that these patients should be offered earlier ablation or antiarrhythmic drug modification because they are at an increased risk of serious AEs. However, this has to be tested in a prospective study. Although f-nQRS in inferior ECG leads and secondary prevention occurred to be the only 2 independent parameters predicting AEs, the value of AUC of 0.711 is rather moderate. The model for predicting total mortality occurred more accurate (AUC of 0.992); however, it did not include any type of QRS fragmentation which suggests that in ICD recipients, fQRS (mainly f-nQRS) is more a marker of arrhythmic substrate than of cardiac impairment.

The prognosis in ICD recipients may differ according to underlying disease. Recently, it has been shown that prognosis is better in nonischemic than ischemic etiology.[34] Also, the fQRS prognostic performance may be associated with etiology. However, in our study, the fQRS did not remain an independent predictor of AE in the subgroups with ischemic and nonischemic etiology, probably due to reduced number of patients when the subgroups were analyzed.

The present study has several limitations. First, this is a retrospective analysis with all its limitations. However, follow-up data were prospectively collected during outpatient visits which should minimize inaccuracies. Second, visual inspection of ECG tracings in order to identify fQRS is always subjective and reproducibility is not 100%. However, the intraobserver agreement was moderately good and every effort was undertaken to correctly identify fQRS.

Conclusion Fragmented QRS in inferior ECG leads in patients with a narrow QRS complex is an independent risk factor for appropriate ICD interventions and / or arrhythmic death.

ARTICLE INFORMATION

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CONFLICT OF INTEREST None declared.

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