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Abstract	Aims: QRS fragmentation (fQRS) has been proposed as a predictor of sudden cardiac death (SCD) and all-cause mortality in ischemic (ICM) and non-ischemic cardiomyopathy patients. However the value of fQRS in patients with a LVEF b35% is a matter of debate. Methods: All consecutive patients with an indication for an ICD in primary prevention of SCD were included in a retrospective registry from 1996 until 2013. Twelve lead electrocardiograms before implant were analyzed for the presence of fQRS in different regions. Adjusted Cox regression analysis for first appropriate ICD shock (AS) and all-cause mortality was performed. Results: In total 407 patients were included with a mean follow-up of 4.2±3.3 y (age 60.6±11.9 y, 15.7% female and 52.8% ICM). fQRS was present in 46.7% of patients, predominantly inferior (30.7%) followed by anterior (21.4%) and lateral (11.1%) coronary artery territories. fQRSwas significantly more prevalent in ICM(p=0.004). Inferior fQRS was an independent predictor of a first AS within 1 y (HR 2.55, 95%CI 1.28–5.07) and 3 y (HR 1.90, 95%CI 1.14–3.18) after implantation.Whereas, anterior fQRS was an independent predictor of all-cause mortality within 1 y (HR 4.58, 95%CI 1.29–16.19), 3 y (HR 3.92, 95%CI 1.77–8.65) and the complete follow-up (HR 2.22, 95%CI 1.33–3.69). Lateral fQRS was only a predictor of late (N3 y of follow-up) all-cause mortality (HR 2.04,95%CI 1.09–3.81). Conclusions: fQRS in a specific coronary artery territory might be promising to discriminate arrhythmic from mortality risk. Inferior fQRS was a predictor of early arrhythmia, while anterior fQRS was related to mortality.
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Inferior and anterior QRS fragmentation have different prognostic value in patients who received an implantable defibrillator in primary prevention of sudden cardiac death

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ABSTRACT

Aims: QRS fragmentation (fQRS) has been proposed as a predictor of sudden cardiac death (SCD) and all-cause mortality in ischemic (ICM) and non-ischemic cardiomyopathy patients. However the value of fQRS in patients with a LVEF <35% is a matter of debate.
Methods: All consecutive patients with an indication for an ICD in primary prevention of SCD were included in a retrospective registry from 1996 until 2013. Twelve lead electrocardiograms before implant were analyzed for the presence of fQRS in different regions. Adjusted Cox regression analysis for first appropriate ICD shock (AS) and all-cause mortality was performed.
Results: In total 407 patients were included with a mean follow-up of 4.2 ± 3.3 y (age 60.6 ± 11.9 y, 15.7% female and 52.8% ICM). fQRS was present in 46.7% of patients, predominantly inferior (30.7%) followed by anterior (21.4%) and lateral (11.1%) coronary artery territories. fQRS was significantly more prevalent in ICM ($p = 0.004$). Inferior fQRS was an independent predictor of a first AS within 1 y (HR 2.55, 95%CI 1.28–5.07) and 3 y (HR 1.90, 95%CI 1.14–3.18) after implantation. Whereas, anterior fQRS was an independent predictor of all-cause mortality within 1 y (HR 4.58, 95%CI 1.29–16.19), 3 y (HR 3.92, 95%CI 1.77–8.65) and the complete follow-up (HR 2.22, 95%CI 1.33–3.69). Lateral fQRS was only a predictor of late (>3 y of follow-up) all-cause mortality (HR 2.04, 95%CI 1.09–3.81).
Conclusions: fQRS in a specific coronary artery territory might be promising to discriminate arrhythmic from mortality risk. Inferior fQRS was a predictor of early arrhythmia, while anterior fQRS was related to mortality.
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1. Introduction

The indication for an implantable cardioverter-defibrillator (ICD) for primary prevention of sudden cardiac death (SCD) in ischemic (ICM) and non-ischemic cardiomyopathy (NICM) patients is mainly based on left ventricular ejection fraction (LVEF) [1]. There is a continuous search for novel, easy accessible risk stratification tools to improve patient selection, driven by the high costs, possible complications and relatively low intervention rate of ICDs [2].

The presence of QRS fragmentation (fQRS) on a 12-lead electrocardiogram (ECG) has been shown to reflect inhomogeneous activation of the ventricles by the presence of myocardial infarction or scarring [3–5]. A significant association with myocardial scar and fibrosis has been shown in patients with normal QRS duration (≤120 ms), ventricular conduction defects (QRS >120 ms) and ventricular pacing [6,7]. Recently, Rosengarten et al. performed a meta-analysis evaluating fQRS as risk stratification tool to predict SCD and all-cause mortality [8]. fQRS was significantly associated with ventricular arrhythmia and mortality in both ICM and NICM patients. However, in patients with a LVEF ≤35% fQRS failed to predict ventricular arrhythmia or mortality. These findings indicate that the value of fQRS as risk stratification tool might be limited to certain patient subgroups. We used the long-term database of the University Hospitals of Leuven to assess the predictive value of fQRS in patients with ICM and NICM that received an ICD in the primary prevention of SCD.

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2. Material and methods

2.1. Patient population

All patients who received their first implantation of an ICD for primary prevention of SCD in ICM or NICM conform the current guidelines and were followed in the University Hospitals of Leuven from October 1996 until December 2013 were included in a single-center retrospective registry [1]. Demographic, clinical and electrocardiographic data before the first implantation were collected from the electronic medical record. The patients received routine medical care with clinical visits every 6 months. Device programming and pharmaceutical treatment were according to most recent guidelines. The study was approved by the ethical committee of the University Hospitals of Leuven.

2.2. ECG analysis

Resting 12-lead electrocardiograms (25 mm/s paper speed, 10 mm/mV, filter range 0.05–150 Hz with notch filter at 50/60 Hz) before implantation of the ICD were collected and analyzed by 2 investigators (BV, SVS) for the presence of fQRS. Since all patients received a routine pre-operative 12-lead ECG, a good quality tracing was present in all 12 leads. Analysis was performed blinded for endpoints and without digital magnification of the traces.

Fragmentation criteria differ depending on QRS duration and morphology. ECGs were separated in subgroups: QRS duration ≤120 ms, QRS duration >120 ms and ventricular pacing based on automated analysis by the 'GE Marquette 12SL™ ECG Analysis Program' (GE Medical Systems, Menomonee Falls, WI, USA). Left bundle branch block (LBBB), right bundle branch block (RBBB) and intraventricular conduction delay (IVCD) were assessed according to published criteria [9].

We used the definition of fQRS as recently described (illustrated in Fig. 1). In patients with QRS duration ≤120 ms fQRS was defined as the presence of any RSR′ pattern, ≥1 R prime or notching of R or S wave [6,10]. In case of QRS duration >120 ms, fragmentation was defined as various RSR' patterns with or without a Q wave, with >2 R waves (R′) or >2 notches in the R wave, or >2 notches in the downstroke or upstroke of the S wave [7]. A paced QRS complex was defined as a wide QRS complex (duration >120 ms and without any evidence of QRS fusion) initiated by a paced spike [7]. Fragmentation of paced QRS complexes was defined as the presence of >2 R′ or >2 notches in the S wave [7].

QRS fragmentation was considered to be present when recorded in ≥2 contiguous leads as divided by major coronary artery territory: anterior as V1 to V5, lateral as I, aVL and V6 and inferior as II, III and aVF [6,10]. In case of disagreement between investigators consensus was reached after mutual discussion.

2.3. Endpoints

The primary endpoints of the study were the first appropriate shock (AS) and all-cause mortality. The date and cause of AS was collected, ventricular tachycardia (VT) or ventricular fibrillation (VF), and verified using source documents. AS was selected as surrogate marker for SCD. Mortality was collected with date and cause of death (SCD, cardiac non-sudden, non-cardiac or unknown). In case of heart transplant the date of last follow-up was the date of transplantation. Endpoints were collected until 31-12-2014.

2.4. Statistical analysis

Continuous variables are presented as mean ± standard deviation and categorical variables as number and percentage. Parameters were compared between groups using unpaired Student *t*-test and Chi-square test when appropriate. Inter- and intra-observer variability were investigated using measures of agreement (% and Cohen's kappa). Inter-observer variability was assessed using all digitally available ECGs, whereas intra-observer variability was assessed on a random selection of 100 ECGs which were analyzed a second time blinded for patient information. Endpoints are reported as annual rates (%/y) after 1 y, 3 y or the complete follow-up. Kaplan-Meier analysis with log-rank testing was used to compare endpoint rate. Patients lost to follow-up were censored at the last known follow-up. Cox proportional-hazards regression modeling was used to evaluate the contribution of different baseline parameters to the development of endpoints. Because a single baseline measurement might not predict long-term events, analysis was performed after 1 y, 3 y and complete follow-up respectively to discriminate early from overall predictors. Adjusted Cox regression was performed with a baseline model including: age, gender, etiology of cardiac disease, LVEF, LBBB, renal function, use of beta-blockers, ACE-inhibitors and anti-arrhythmic drugs (amiodarone, digitalis and sotalol). Then, fQRS, both overall and each fQRS region separately, was added to the baseline model and c-statistics were calculated and compared by the methods of DeLong [11]. A p-value <0.05 was considered significant. All statistical analyses were performed using SPSS (IBM Statistics, version 23).

3. Results

3.1. Demographics

An overview of demographics is shown in Table 1. In total 407 patients received an ICD in primary prevention for ICM ($n = 215$, 52.8%) or NICM ($n = 192$, 47.2%) with a mean follow-up of 4.2 ± 3.3 years.

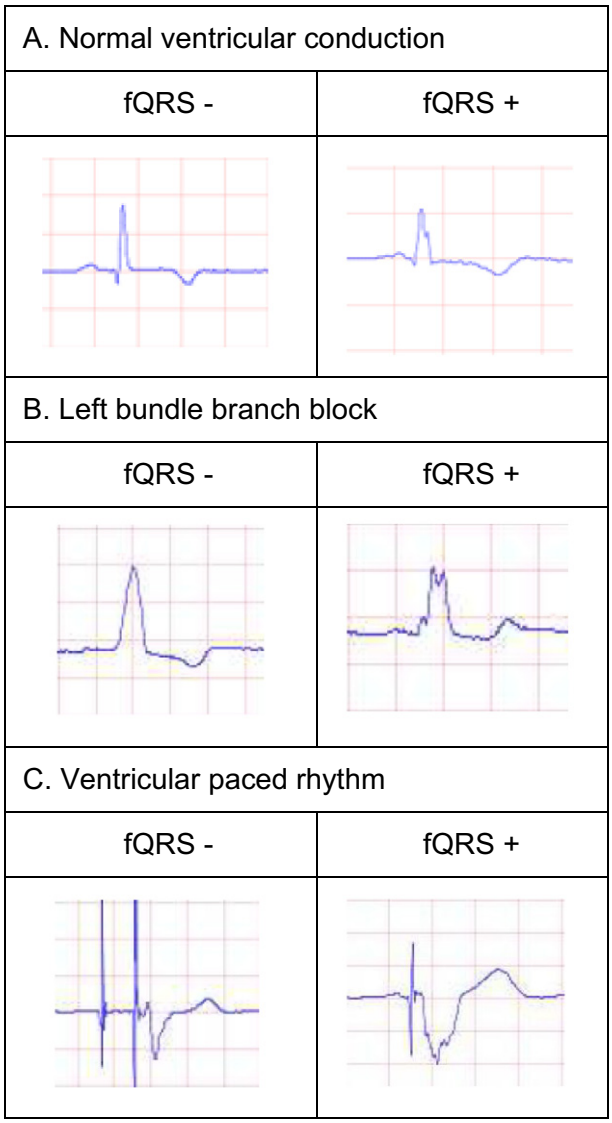


Fig. 1. Examples of fragmented and non-fragmented QRS complexes. Lead V6 is presented for patients with normal ventricular conduction, left bundle branch block and ventricular paced rhythm.

Overall, there were no demographic differences between patients with and without fQRS.

The follow-up was significantly longer in patients with ICM and patients with ICM were significantly older at implantation, had a higher ejection fraction, were less frequently NYHA 3 and were more likely to be male compared to patients with NICM (Supplement 1). Patients with NICM had more often a LBBB and received more frequently CRT-D. Finally, patients with NICM were less often treated with amiodarone, statins and aspirin and more often with beta-blockers prior to implantation, than patients with ICM.

3.2. QRS fragmentation

The results of the fQRS analysis are summarized in Supplement 2. Overall 46.7% of patients had fQRS. Fragmentation was most frequently localized inferior (30.7% of all patients), followed by anterior (21.4%) and lateral leads (11.1%). fQRS was more frequently present in ICM patients ($p = 0.004$).

The inter-observer variability showed a strong agreement between observers with a 91.1% agreement and Cohen's kappa of 0.808 (95% CI 0.790–0.826) when analyzing all leads separately. For regions this was

Table 1
Baseline demographics.

		All		fQRS −		fQRS +		*p*-Value
n		407		217	53.3%	190	46.7%	
Follow-up	(y)	4.2 ± 3.3		4.2 ± 3.3		4.2 ± 3.4		0.946
Age	(y)	60.6 ± 11.9		61.5 ± 10.0		59.5 ± 13.8		0.098
Gender	Male	343	84.3%	184	84.8%	159	83.7%	0.759
	Female	64	15.7%	33	15.2%	31	16.3%	
Etiology	ICM	215	52.8%	100	46.1%	115	60.5%	0.004
	NICM	192	47.2%	117	53.9%	75	39.5%	
NYHA	1	95	23.4%	49	22.6%	46	24.2%	0.904
	2	156	38.3%	83	38.2%	73	38.4%	
	3	156	38.3%	85	39.2%	71	37.4%	
BMI	(kg/m^2)	26.3 ± 4.4		26.7 ± 4.4		25.9 ± 4.5		0.062
EF	(%)	28.3 ± 10.3		28.6 ± 10.4		28.0 ± 10.2		0.525
Creatinine	(mg/dl)	1.34 ± 1.01		1.27 ± 0.54		1.42 ± 1.36		0.120
Device	VVI	156	38.3%	75	34.6%	81	42.6%	0.108
	DDD	80	19.7%	50	23.0%	30	15.8%	
	CRT-D	171	42.0%	92	42.4%	79	41.6%	
ECG	HR (bpm)	67.1 ± 13.4		67.5 ± 12.5		66.6 ± 14.5		0.499
	QRS (ms)	136.0 ± 34.6		134.5 ± 32.6		137.7 ± 36.8		0.357
	QTcF (ms)	456.6 ± 43.3		456.0 ± 40.3		457.4 ± 46.6		0.742
BBB	No	236	68.0%	121	55.8%	115	60.5%	0.240
	LBBB	142	34.9%	79	36.4%	63	33.2%	
	RBBB	29	7.1%	17	7.8%	12	6.3%	
Rhythm	SR	354	87.0%	183	84.3%	171	90.0%	0.216
	AF	37	9.1%	23	10.6%	14	7.4%	
	PM	16	3.9%	11	5.1%	5	2.6%	
History	Stroke	40	9.8%	19	8.8%	21	11.1%	0.437
	Diabetes	75	18.4%	40	18.4%	35	18.4%	0.997
	AF	102	25.1%	61	28.1%	41	21.6%	0.129
Medication	BB	347	85.3%	192	88.5%	155	81.6%	0.051
	ACE-I/ARB	370	90.9%	196	90.3%	174	91.6%	0.660
	Aspirin	234	57.7%	127	58.5%	108	56.8%	0.732
	Loopdiuretics	247	60.7%	123	56.7%	124	65.3%	0.077
	Digitalis	47	11.5%	20	9.2%	27	14.2%	0.116
	Amiodarone	137	33.7%	67	30.9%	70	36.8%	0.204
	Sotalol	7	1.7%	3	1.4%	4	2.1%	0.576
	Statin	241	59.2%	129	59.4%	112	58.9%	0.918

Abbreviations.
ACE-I/ARB: Angiotensin converting enzyme inhibitor/angiotensin receptor blocker; AF: atrial fibrillation; BB: beta-blocker; BBB: bundle branch block; BMI: body mass index; bpm: beats per minute; EF: left ventricular ejection fraction; ICM: ischemic cardiomyopathy; HR: heart rate; LBBB: left bundle branch block; ms: milliseconds; NICM: non-ischemic cardiomyopathy; PM: pacemaker; RBBB: right bundle branch block; SR: sinus rhythm; y: years

90.1% agreement with a kappa of 0.795 (95% CI 0.760–0.830). The intra-observer variability after a second read of 100 randomly selected ECGs showed a very strong agreement of 95.0% and a kappa of 0.880 (95% CI 0.849–0.911) for the first observer and 93.5% agreement and a kappa of 0.850 (95% CI 0.883–0.817). More detailed analysis is available as Supplement 3.

3.3. Appropriate shocks

Appropriate shock rates are shown in Supplement 4. A total of 97 patients (23.8%) received at least one AS during follow-up with an annual first AS rate of 8.3%/y after 3 years, 7.8%/y for VT and 1.6%/y for VF. Patients with ICM had their first AS significantly earlier, but after 3 years and at the end of follow-up there was no difference between ICM and NICM.

Kaplan Meier analyses with log-rank comparison are shown in Fig. 2. Results of univariate Cox regression of the variables included in the baseline model and fQRS variables are shown in Supplement 5A. The results of the adjusted Cox regression analysis for the association of fQRS with AS are summarized in Table 2A. The presence of fQRS, more specifically in the inferior leads, was an independent predictor of receiving a first AS early during follow-up (1- and 3-y; Fig. 2C). The models including inferior fQRS had the largest increase in c-statistics, however the increase did not reach significancy. Although the Kaplan Meier graph for AS and anterior fQRS showed significant divergence, this was not significant in Cox regression analysis (Fig. 2B).

3.4. Mortality

Mortality rates are shown in Supplement 4. Overall 82 (20.1%) of patients died during follow-up. Kaplan-Meier analysis showed no significant difference in survival between ICM and NICM.

Kaplan Meier analyses with log-rank comparison are shown in Fig. 2 (2D, 2E and 2F). Results of univariate Cox regression of the variables included in the baseline model and fQRS variables are shown in Supplement 5B. Adjusted Cox regression analysis results for mortality are summarized in Table 2B. The presence of fQRS in the anterior region was an independent predictor of early mortality and the models including anterior fQRS showed significant increase of C-statistic values. For mortality occurring more than 3 years after implant both anterior and lateral fQRS were independent predictors, although with only very limited changes in c-statistics.

4. Discussion

In this long-term registry of patient with an ICD for primary prevention of SCD, QRS fragmentation was present in 46.7% of patients prior to ICD implantation and was significantly more prevalent in ICM patients. fQRS in different regions had a different prognostic significance. Inferior fQRS was an independent predictor of an early anti-arrhythmic high voltage intervention, while anterior fQRS was an independent predictor of mortality.

4.1. Prevalence

The observed prevalence of fQRS in our study is remarkably higher than in previously reported trials. In MADIT II patients, the prevalence was 33% and in a study by Cheema et al. on ICM and NICM patients the prevalence was 32.5% [12,13]. Both trials also analyzed ECGs of patients eligible for receiving an ICD in primary prevention. Comparing demographics, our registry included more patients with QRS duration ≥120 ms and patients with more pronounced heart failure as the NYHA class was higher and patients received more beta-blockers and ACE-I/ARB. There is also a difference in the use of amiodarone. This probably can be explained by the fact that reimbursement of ICDs in primary prevention in Belgium was limited to patients who fulfilled classic MADIT 1 and MUST criteria until 2006, i.e. a decreased EF, presence of nsVT on monitoring and inducibility of VT on EPS during antiarrhythmic treatment [14–17]. Although the ECGs were evaluated using the same criteria at routine clinical ECG device settings and without magnifying the traces, we cannot rule out a different scoring by the investigators, since the evaluation remains somewhat subjective.

4.2. Endpoints

Current knowledge on fQRS has mainly focused on its presence regardless of its location. Only a few studies have reported risk analysis categorized by major coronary artery territory. Overall results are inconsistent. In the prospective study by Cheema et al. there was no association between fQRS in any territory and all-cause and arrhythmic mortality, neither for ICD shocks in ICD patients after a mean follow-up 40 ± 17 months [13].

We report a significant association between inferior fQRS and appropriate high voltage therapy early after implantation. This is in line with the findings in the MADIT II study population [12]. They identified inferior fQRS as a significant predictor of a combined endpoint of SCD and ICD shocks (HR 1.46, $p = 0.032$). However, inferior fQRS was also an independent predictor of all-cause mortality (HR 1.44, $p = 0.036$). The presence of fQRS in the anterior or lateral leads showed no significant relation with therapy or mortality in their analysis. Keeping in mind

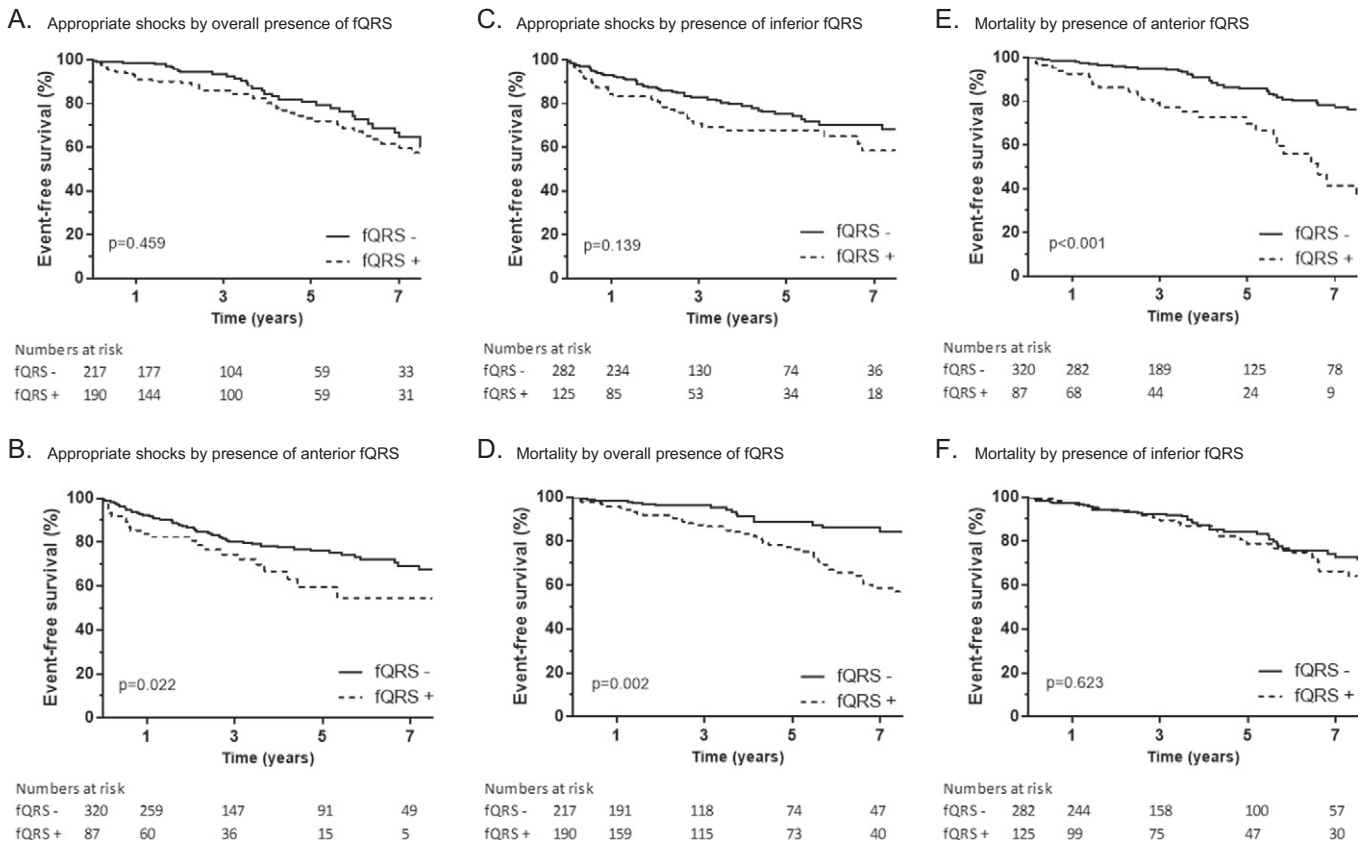


Fig. 2. Kaplan-Meier graphs comparing patients with and without fQRS on 12 lead ECG taken before ICD implant for appropriate shocks and mortality.

that the median follow-up in MADIT II was only 19 months, these findings are in line with the results in our ICM subgroup after 1 and 3 years of follow-up. We hypothesize that the significant findings in Kaplan Meier analysis for the association of anterior fQRS and AS are influenced by competing risks as anterior fQRS was a powerfull predictor of early mortality.

A larger study by Pei et al. in patients with ICM or NICM, also including patients with LVEF >35%, studied multiple ECG parameters [18]. In NICM patients inferior fQRS was associated with all-cause mortality (HR1.43, $p = 0.038$), but in ICM patients inferior fQRS was associated with all-cause mortality (HR1.89, $p < 0.001$), non-sudden cardiac death (HR1.44, $p = 0.049$) and SCD (HR 2.71, $p < 0.001$). There was no predictive value for anterior or lateral fQRS. A population study by Terho et al., with a mean follow-up of 30 ± 11 years, showed a significant association of the presence of lateral fQRS in patients with cardiac disease and all-cause (HR 1.9, $p = 0.001$), cardiac (HR 2.5, $p = 0.001$) and arrhythmic (HR 3.0, $p = 0.004$) mortality [19]. Due to the different categorization of myocardial territories, comparison with our results is difficult.

The main strength of our study is the long mean follow-up of 4.2 ± 3.3 years together with the endpoint analysis at separate intervals. Risk stratification in primary prevention of SCD should focus on discriminating a high arrhythmic risk from a high early non-arrhythmic mortality risk. We present findings that fQRS in different myocardial territories might be helpful in this discrimination. This possibility has been suggested before in ICM. Patients with a known MI presenting with ventricular arrhythmia were more likely to have inferior MI localization [20]. The pathophysiology of this 'inferior-arrhythmia and anterior-mortality' hypothesis is complex. First, larger infarcts may have a more pronounced hemodynamic impact associated with a lower LVEF and increased risk of non-sudden cardiovascular death. In the DINAMIT trial a lower LVEF was a predictor of both arrhythmic and non-arrhythmic mortality, hence creating a competing risk [21]. Anterior infarcts were associated with larger MI sizes, a lower LVEF, more overt heart failure, a higher complication rate and higher in-hospital and long-term mortality [22–24]. A second part of the explanation could be related to the anatomy of the autonomic nervous system. The afferent vagal fibers are mainly located in the inferoposterior wall, while the sympathetic nerve fibers are distributed equally over the inferoposterior and anterior left ventricular wall [25]. As such an anterior MI could reduce sympathetic activity and abolish its arrhythmogenic consequences, especially since the inferoposterior located vagal fibers remain preserved, and vice versa for inferior MI. A third hypothesis involves the potential damage to the papillary muscles, which could cause ventricular arrhythmia based on a re-entry mechanism [25]. It is estimated that the posteromedial papillary muscle is up to 10 times more frequently involved in an inferior MI compared to the anterolateral papillary muscle and an anterior MI, which is related to the blood supply of the papillary muscles. How and whether these hypotheses in post-MI scarring can be translated to progressive fibrosis and scarring in NICM remains uninvestigated and warrants further investigation.

5. Limitations

This study suffers from all the inherent limitations of its single center retrospective nature. The true clinical value of fQRS needs confirmation in large prospective trials.

The number of females included in the registry was only 15.7%, hence there was insufficient statistical power for gender analysis. Also, subgroups based on QRS-width were too small with only a limited number of endpoints to perform reliable analysis in patients with or without LBBB.

In the last decades ICD indication guidelines have changed significantly with consequences on clinical practice like expansion towards NICM and the introduction of CRT-D [26]. Also, ICD programming changed with more conservative ICD treatment as delayed-therapy

Table 2
Adjusted Cox regression analysis including C-statistics.

A. Appropriate shocks				
	Adjusted Cox regression		C-statistics	
AS 1 y	*p*-Value	Hazard ratio (95% CI)	C (95% CI)	*p*-Value vs. baseline
Baseline model			0.663 (0.573–0.752)	
fQRS	0.007	2.695 (1.314–5.527)	0.702 (0.618–0.786)	0.252
fQRS anterior	0.083	1.876 (0.922–3.815)	0.678 (0.591–0.766)	0.497
fQRS inferior	0.008	2.552 (1.284–5.072)	0.690 (0.606–0.775)	0.386
fQRS lateral	0.384	1.507 (0.598–3.793)	0.671 (0.581–0.761)	0.451
fQRS anterior + inferior	0.151 + 0.012	1.710 (0.822–3.560) + 2.438 (1.213–4.899)	0.697 (0.615–0.779)	0.337
fQRS anterior + lateral	0.085 + 0.397	1.871 (0.918–3.813) + 1.485 (0.595–3.704)	0.681 (0.594–0.769)	0.434
AS 3 y				
Baseline model			0.647 (0.576–0.718)	
fQRS	0.086	1.547 (0.940–2.548)	0.644 (0.571–0.716)	0.847
fQRS anterior	0.449	1.224 (0.707–2.189)	0.634 (0.563–0.705)	0.089
fQRS inferior	0.014	1.904 (1.141–3.175)	0.656 (0.587–0.726)	0.680
fQRS lateral	0.625	1.204 (0.572–2.531)	0.650 (0.579–0.722)	0.564
fQRS anterior + inferior	0.677 + 0.017	1.131 (0.634–2.017) + 1.876 (1.119 - 3.147)	0.652 (0.582–0.722)	0.841
fQRS anterior + lateral	0.453 + 0.633	1.242 (0.705–2.187) + 1.197 (0.571–2.510)	0.639 (0.567–0.710)	0.347
AS complete fu				
Baseline model			0.640 (0.582–0.699)	
fQRS	0.294	1.252 (0.823–1.904)	0.639 (0.579–0.698)	0.864
fQRS anterior	0.187	1.384 (0.854–2.245)	0.632 (0.573–0.692)	0.412
fQRS inferior	0.245	1.300 (0.836–2.021)	0.641 (0.582–0.699)	0.989
fQRS lateral	0.725	0.884 (0.446–1.754)	0.640 (0.582–0.698)	0.920
fQRS anterior + inferior	0.226 + 0.296	1.351 (0.830–2.198) + 1.268 (0.813–1.978)	0.635 (0.575–0.694)	0.652
fQRS anterior + lateral	0.182 + 0.686	1.390 (0.857–2.254) + 0.869 (0.440–1.717)	0.632 (0.572–0.691)	0.411
B. Mortality				
	Adjusted Cox regression		C-statistics	
Mortality 1 y	*p*-Value	Hazard ratio (95% CI)	C (95% CI)	*p*-Value vs. baseline
Baseline model			0.810 (0.707–0.914)	
fQRS	0.136	2.856 (0.719–11.336)	0.838 (0.758–0.919)	0.261
fQRS anterior	0.018	4.575 (1.293–16.190)	0.871 (0.808–0.933)	0.057
fQRS inferior	0.822	0.849 (0.204–3.359)	0.809 (0.703–0.916)	0.767
fQRS lateral	0.599	1.609 (0.273–9.471)	0.809 (0.702–0.915)	0.791
fQRS anterior + inferior	0.016 + 0.611	4.726 (1.324–16.642) + 0.672 (0.146–3.106)	0.872 (0.810–0.934)	0.032
fQRS anterior + lateral	0.015 + 0.398	4.940 (1.360–19.947) + 2.151 (0.365–12.690)	0.876 (0.812–0.940)	0.028
Mortality 3 y				
Baseline model			0.764 (0.684–0.844)	
fQRS	0.008	3.301 (1.359–8.021)	0.802 (0.730–0.874)	0.188
fQRS anterior	0.001	3.915 (1.772–8.652)	0.816 (0.746–0.887)	0.114
fQRS inferior	0.956	1.024 (0.445–2.357)	0.765 (0.685–0.844)	0.676
fQRS lateral	0.199	1.936 (0.706–5.309)	0.775 (0.692–0.857)	0.462
fQRS anterior + inferior	0.001 + 0.676	3.991 (1.805–8.826) + 0.826 (0.336–2.027)	0.815 (0.743–0.886)	0.120
fQRS anterior + lateral	0.001 + 0.111	4.203 (1.867–9.462) + 2.270 (0.828–6.220)	0.825 (0.758–0.892)	0.048
Mortality complete fu				
Baseline model			0.716 (0.656–0.777)	
fQRS	0.011	1.865 (1.154–3.014)	0.722 (0.662–0.781)	0.701
fQRS anterior	0.002	2.216 (1.333–3.686)	0.713 (0.652–0.774)	0.814
fQRS inferior	0.626	1.125 (0.701–1.806)	0.717 (0.657–0.777)	0.924
fQRS lateral	0.025	2.040 (1.092–3.811)	0.717 (0.657–0.777)	0.990
fQRS anterior + inferior	0.002 + 0.651	2.217 (1.331–3.691) 1.118 (0.690–1.811)	0.713 (0.652–0.774)	0.802
fQRS anterior + lateral	0.002 + 0.020	2.253 (1.352–3.756) + 2.058 (1.118 - 3.786)	0.722 (0.661–0.783)	0.730

and high-rate therapy zones. These changes, together with changes in pharmacological treatment, might have influenced the ICD therapy rates and therefore endpoint analysis.

The cause of death was not available in 45.1% of patients. Therefore, subgroup analysis for cardiac death versus non-cardiac death was not possible.

Currently the technique to detect fQRS is based on a visual interpretation of routine clinical ECGs, hence inexpensive and easy accessible. Although there was a strong agreement between the observers, inter- and intra-observer variability remains a possible issue. The question rises whether a novel mathematical approach to quantify the presence and different patterns of fQRS could resolve the variable findings on the specific location of fQRS [27].

6. Conclusion

The presence of fQRS in a specific coronary artery territory is a promising risk stratification tool for discriminating arrhythmic from total mortality risk. Inferior fQRS was an early predictor of arrhythmia, while anterior fQRS was related to mortality in our population.

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