Received: 4 May 2022 | Accepted: 23 May 2022

DOI: 10.1111/anec.12985

ORIGINAL ARTICLE

WILEY

QRS fragmentation is associated with increased risk of ventricular arrhythmias in high-risk patients; Data from the SMASH 1 Study

Nur Sourour MD[1,2] | Egil Riveland MD[3,4] | Terje Rømo MD[3] | Patrycja Næsgaard MD, PhD[3] | Harald Kjekshus MD, PhD[1] | Alf Inge Larsen MD, PhD[3,4] | Torbjørn Omland MD, PhD, MPH[1,2] | Helge Røsjø MD, PhD[2,5] | Peder Langeland Myhre MD, PhD[1,2]

[1]Department of Cardiology, Division of Medicine, Akershus University Hospital, Lørenskog, Norway

[2]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

[3]Department of Cardiology, Stavanger University Hospital, Stavanger, Norway

[4]Institute of Clinical Sciences, University of Bergen, Bergen, Norway

[5]Division for Research and Innovation, Akershus University Hospital, Lørenskog, Norway

Correspondence
Peder Langeland. Myhre, MD, PhD, Department of Cardiology, Akershus University Hospital, Sykehusveien 27, 1478 Lørenskog, Norway.
Email: p.l.myhre@medisin.uio.no

Funding information
Western Norway Regional Health Authority; South-Eastern Norway Regional Health Authority

Abstract

Introduction: QRS fragmentation (fQRS), defined as the presence of additional spikes within the QRS complex, has been associated with myocardial conduction abnormalities and arrhythmogenicity.

Objective: We aimed to assess whether fQRS is associated with incident ventricular arrhythmias (VA) in high-risk patients treated with implantable cardioverter-defibrillator (ICD) for primary and secondary prevention.

Methods: In a prospective observational multicenter study, we included 495 patients treated with ICD. fQRS was analyzed according to previously validated criteria, by two physicians blinded for outcome data. Incident VA were obtained from ICD recordings.

Results: ECG recordings interpretable for fQRS were available in 459 patients (93%), aged 66 ± 12 years with left ventricular ejection fraction 40% ± 13%. fQRS was present in 52 patients (11%) with comparable baseline characteristics to patients without fQRS, except higher age, higher prevalence of coronary artery disease (CAD), lower prevalence of cardiomyopathy, and more frequently a secondary prevention ICD indication. Among patients with native QRS, those with fQRS had similar QRS duration and axis to those without fQRS. During 3.1 ± 0.7 years follow-up, 126 patients (28%) had ≥1 VA . fQRS was associated with increased risk of VA (HR 3.41 [95% CI 2.27–5.13], $p < .001$), which persisted after adjusting for age, gender, sex, BMI, CAD, heart failure, renal function, ICD indication, QRS duration, QRS axis, Q waves, and bundle branch block. fQRS was more strongly associated with VA in patients with a primary (HR 6.05 [95% CI 3.16–11.60]) versus secondary (HR 2.39 [95% CI 1.41–4.04]) ICD indication (p-for-interaction = .047).

Conclusions: fQRS is associated with threefold increased risk of VA in high-risk patients, independent of established risk factors.

KEYWORDS
cardiac arrest, implantable cardioverter-defibrillator, QRS fragmentation, risk prediction, ventricular arrhythmia

Study Registration

SMASH 1 Study; ClinicalTrails.gov Identifier: NCT02864771.

1 | INTRODUCTION

Sudden cardiac death (SCD) is a major global health challenge. Currently, the best-known predictor of SCD is either the presence of severe heart failure (HF) or an episode of cardiac arrest. Hence, guidelines recommend treatment with implantable cardioverter-defibrillator (ICD) as primary prevention in patients with symptomatic HF (New York Heart Association [NYHA] classification II-III) and left ventricular ejection fraction (LVEF) ≤35% (Priori et al., 2015). Patients with documented ventricular fibrillation (VF) or sustained ventricular tachycardia (VT) with hemodynamic consequence are also recommended for treatment with ICD (secondary prevention; Priori et al., 2015). However, several studies have found this approach to poorly discriminate patients at high risk of SCD (Buxton, 2003; Pascale et al., 2009).

Ventricular arrhythmias (VA) account for the majority of SCD cases with coronary artery disease (CAD) as the most frequent etiology (Koplan & Stevenson, 2009; Zipes & Wellens, 1998). However, the total burden of less common underlying conditions and arrhythmogenic mechanisms make the prediction of VA challenging. This underlines the need for strategies to identify patients at high risk of VA and SCD. Some electrocardiography (ECG) parameters have been associated with risk of VA, but the results are diverging.

The QRS complex represents ventricular depolarization, and disturbances in the depolarization may cause arrhythmias. QRS fragmentation (fQRS) is a morphological change in the QRS complex and is recognized as additional fractionation or notches within the QRS complex. Presence of fQRS suggests disturbed cardiac depolarization due to myocardial conduction abnormality caused by a non-uniform ventricular activation usually due to myocardial scarring (Das et al., 2006). fQRS has been identified as predictor of VA in patients with Brugada syndrome (Morita et al., 2008) and in patients with CAD and dilated cardiomyopathy (Das et al., 2010; Ratheendran et al., 2020). Accordingly, in the current study we aimed to determine whether fQRS is associated with risk of VA in a heterogeneous population with ICD. We hypothesized that the presence of fQRS in a standard 12-lead ECG is independently associated with risk of VA in patients treated with ICD.

2 | METHODS

2.1 | Study design and study population

The SMASH 1 Study (Scandinavian Multicenter study to Advance risk Stratification in Heart disease—ventricular arrhythmias; NCT#02864771) is a multicenter, observational, prospective study aiming to help identify predictors of VA in patients treated with ICD. Eligible patients were consecutively included during their regular outpatient follow-up visits for ICD control between May 2016 and March 2018 at Akershus University Hospital or Stavanger University Hospital in Norway. All patients treated with ICD, aged ≥18 years, were eligible for enrollment. Inclusion and exclusion criteria are presented in Figure 1. All patients provided informed written consent, and the study was approved by the Regional Ethics Committee (2015/2080) and the local Data Protection Officers at the institutions.

At the baseline visit, patients underwent a standardized interview to obtain information regarding medical history, symptoms, and medication use. Diabetes mellitus (DM), HF, cardiomyopathy, and CAD were defined by review of medical records and patient interviews. Measurements of heart rate and blood pressure (three measurements, where the average of the 2nd and 3rd measurement was used) were performed after 5-min rest. Standard 10-s 12-lead ECG recording was obtained upon inclusion using Mortara 350/380 (filter 150 Hz, AC filter 50 Hz, 50 mm/s, 10 mm/mV) or Schiller AT-110 (filter 150 Hz, AC Filter 50 Hz, 50 mm/s, 10 mm/mv). Blood samples were collected by venipuncture and analyzed by the core laboratory at each hospital.

2.2 | Outcome measures

The primary outcome of the SMASH 1 Study was defined a priori as episodes of ventricular fibrillation (VF) or ventricular tachycardia (VT) that were sustained (>100 beats per minute >30 s) or resulting in appropriately delivered ICD therapy (electrical shock or anti-tachycardia pacing [ATP]). Secondary outcome was defined as death from any cause. Arrhythmic events were obtained from ICD interrogations and/or hospital records during follow-up and include ICD-recorded (monitored and treated events) and clinically recorded events (including sustained VT episodes outside programmed monitor/treatment zones) and were conducted by experienced cardiac electrophysiologists. Study investigators reviewed the ICD recordings and reports in the electronic healthcare record and performed validation to ensure that only real events and appropriate ICD therapies were included as outcomes in this analysis. Adjudicators did not have knowledge of fQRS in the baseline ECG. In a sensitivity analysis accounting for death as a competing risk, we combined incident VA or appropriate ICD therapy with all-cause death. Clinical events were recorded by reports in the electronic healthcare records and by obtaining data from the Norwegian Cause of Death Registry (follow-up until 01.09.2020).

2.3 | ECG criteria for fQRS

Adjudication of fQRS on ECG was based on the following criteria as defined by Das et al. (2006), Das et al. (2008), Das et al. (2010): fQRS was defined as the presence of an additional R wave (R′), the

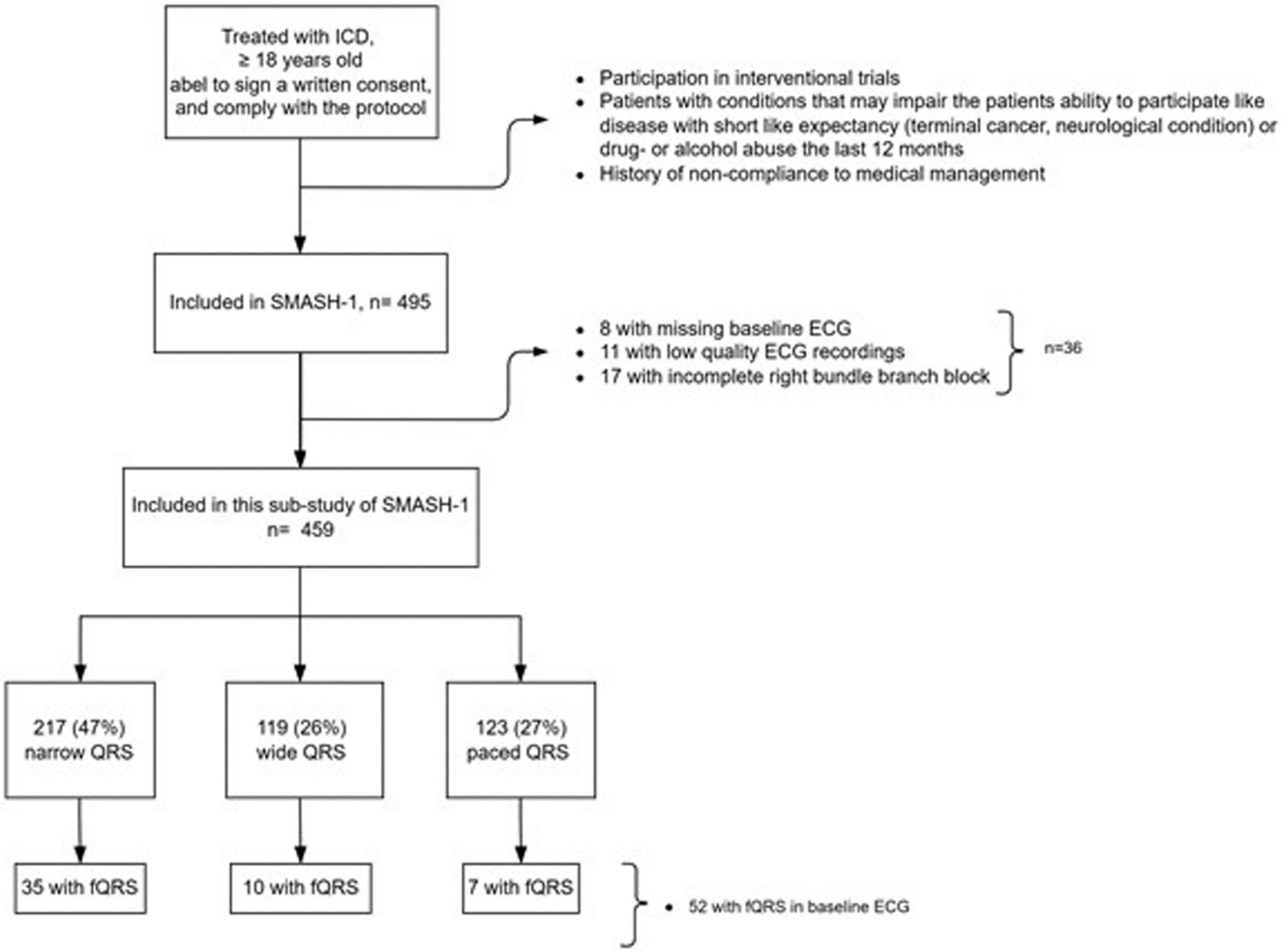

FIGURE 1 Flow diagram of the SMASH 1 Study

presence of >1 R′ (fragmentation) or notching in the downslope of the S wave (Figure 2a). For ECGs with wide QRS complexes (>120 ms), including bundle branch block (BBB), fQRS was defined as various RSR′ patterns, with >2 R waves or >2 notches in the R wave or S wave (Figure 2b). In case of paced QRS, fQRS was defined as the presence of >2 R′ or >2 notches in the S waves. fQRS was only classified if observed in two contiguous leads: Lateral leads (I, aVL, and V6) corresponding to left circumflex artery territory, anterior leads (V1–V5) corresponding to the left anterior descending artery territory or inferior leads (II, III, and aVF) corresponding to right coronary artery territory (Das et al., 2006). Patients with incomplete right bundle branch block (iRBBB) were excluded, as there is risk of over-interpretation of fQRS in these ECGs (Das et al., 2006; Das et al., 2008).

Two independent experienced physicians evaluated all ECGs blinded to outcome and adjudicated the presence of fQRS. If the two reviewers disagreed on the adjudication, this was solved by consensus, involving a third adjudicator if needed.

2.4 | Statistical analysis

Baseline characteristics are expressed as N (%) for categorical variables, median [Q1, Q3] for skewed continuous variables, and mean ± SD for normally distributed continuous variables. Patients with and without fQRS in baseline ECG were compared using ANOVA or *t*-test for continuous variables and Chi-square test for categorical variables. To assess independent predictors of fQRS, we performed a multivariable logistic regression analysis with fQRS as the dependent variable and age, sex, body mass index (BMI), CAD, HF, estimated glomerular filtration rate (eGFR), and ICD indication

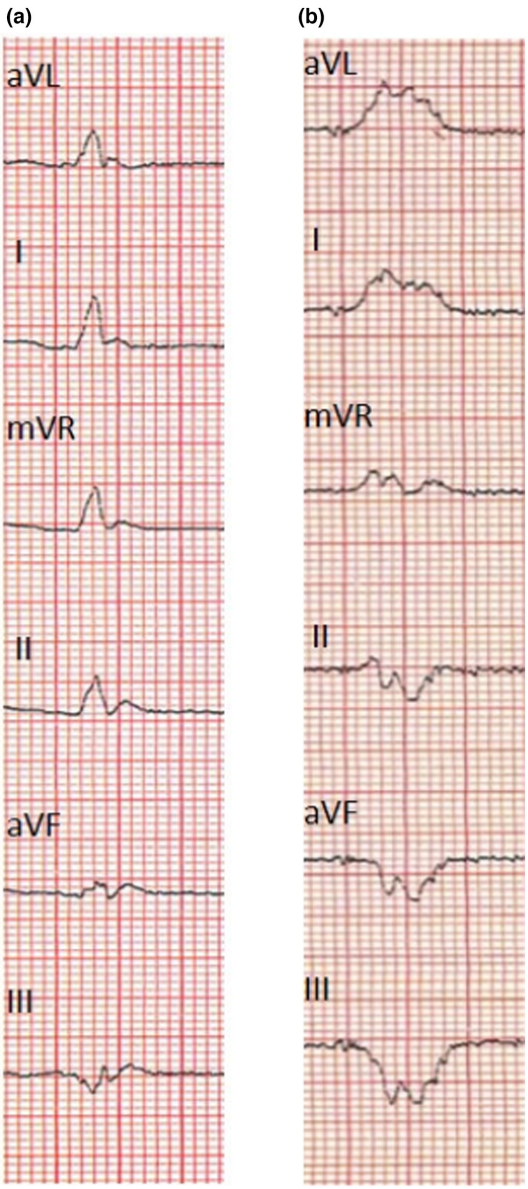

FIGURE 2 Example of fragmented QRS in a patient with narrow QRS (panel a) and wide QRS (panel b), with paper speed 50 mm/s. (a) Patient with QRS fragmentation in narrow QRS in both lateral and inferior wall (i.e., additional R wave). (b) Patient with QRS fragmentation in wide QRS in lateral wall (i.e., >2 notches in R waves) and also in inferior wall to some extent (i.e., >2 notches in S waves).

as independent variables. In patients with native QRS (without ventricular PM rhythm) on the baseline ECG, we performed an extended multivariable regression analysis also including baseline ECG parameters: QRS duration, QRS axis, presence of Q wave, and BBB. We examined the association between the presence of fQRS on baseline ECG and time to the first event of incident ventricular arrhythmias using Cox proportional hazards regression analyses. The models were adjusted for a priori determined covariates based on established risk factors for VA and used in three separate models: Model 1 was adjusted for age, sex, and BMI, and Model 2 was additionally adjusted for CAD, HF, eGFR, and ICD indication. In Model 3, we additionally adjusted for QRS duration, QRS axis, presence of Q wave, and BBB in patients with native QRS on ECG. Sensitivity, specificity, and likelihood ratios were calculated for the ability of fQRS to predict VA. Kaplan–Meier plots were used to visualize the proportion of patients with events over time. Stata software (version 16, Statacorp.) was used to perform all analyses. For all statistical tests, p-value of less than 0.05 was considered significant.

TABLE 1 Baseline characteristics of the study population

Age	66.1 ± 12.0
Sex (male)	378 (82.5%)
Body mass index, kg/m^2	27.8 ± 4.7
Systolic blood pressure, mm Hg	126 ± 21
Diabetes mellitus	91 (19.8%)
Estimated glomerular filtration rate, ml/min/1.73 m^2	74 ± 23.4
Coronary artery disease	291 (64.4%)
History of acute myocardial infarction	260 (57.0%)
History of heart failure	370 (80.8%)
Left ventricular ejection fraction, %	40 ± 13
New York Heart Association class III-IV	49 (10.7%)
Cardiomyopathy	30 (6.6%)
Previous ventricular arrhythmias[a]	257 (56.2%)
History of atrial fibrillation	188 (41.2%)
ICD indication (secondary)	223 (48.6%)
Baseline ECG Parameters[b]	
Bundle branch block	80 (23.8%)
QRS duration (ms)	106 [94, 126]
QRS axis (degrees)	7 [−24, 38]
QTc duration (ms)	433 ± 34

Note: Data is shown as n (%), mean ± SD or median [Q1, Q3].
[a]Including episodes registered before ICD implantation.
[b]In patients with native QRS on baseline ECG (n = 336).

3 | RESULTS

3.1 | Baseline characteristics

Of 495 patients enrolled in the SMASH 1 Study, 36 (7%) patients were excluded from the current analysis due to missing baseline ECG, low-quality ECG recordings, and the presence of iRBBB (Figure 1). The 459 patients included in this analysis were aged 66 ± 12 years, 8% were male, and BMI was 28 ± 5 kg/m^2 (Table 1). Moreover, 20% had DM and 64% had established CAD, including 57% of the total population having a prior myocardial infarction (MI). In total, 12 patients had underlying arrhythmogenic right ventricular cardiomyopathy, 12 patients had hypertrophic cardiomyopathy, and 6 patients had channelopathy. Mean LVEF was 40% ± 13% in the total study cohort with LVEF 38% ± 13% in patients with primary ICD indication. In total, 81% of the population reported a diagnosis of HF and 11% were classified in NYHA functional class 3 or 4. The indication for ICD was primary prevention in 51% of

the population, 27% had CRT-D, and the time from implantation to study inclusion in the SMASH 1 Study was 5.0 ± 6.7 years.

3.2 | Predictors of fQRS

In the baseline ECG, 217 (47%) patients had narrow QRS, 119 (26%) had wide QRS, and 123 (27%) had paced QRS, among whom 100 (81%) had biventricular pacing. fQRS was present in 52 patients (11%), and of these 35 (67%) had narrow QRS, 10 (19%) had wide QRS, and 7 (13%) had paced QRS. The adjudicators agreed on the ECG interpretation of fQRS in 99% of the cases. Patients with fQRS were older (69 ± 11 vs 66 ± 12 years, $p = .04$), had higher prevalence of CAD (86% vs 62%, $p < .001$), and were more likely to have established CAD (86% vs 62%, $p < .001$) than patients without fQRS (Table 2). Patients with fQRS had more frequently ICD implantation for secondary prevention (65% vs. 46%, $p = .01$) and more frequently experienced an episode of VT or VF prior to study enrollment (83% vs. 53%, $p < .001$). Other baseline characteristics, like gender, prevalence of HF, and LVEF, were comparable between patients with fQRS and without fQRS. Among patients with native QRS ($n = 336$), there were no significant differences in measurements of established ECG parameters between patients with versus without fQRS, including QRS duration, QRS axis, QTc, prevalence of BBB, and heart rate.

In a multivariable prediction model with all patients, history of CAD and a secondary prevention ICD indication remained independently associated with the presence of fQRS (Table S1).

3.3 | fQRS in association with incident ventricular arrhythmias and appropriate ICD therapy

During a mean follow-up of 3.1 ± 0.7 years, 126 patients (28%) had at least one registered episode of VA, including 115 patients with sustained VT, 40 with VF, and 110 with appropriate ICD therapy. The presence of fQRS in the baseline ECG was associated with a higher risk of time to the first event of incident VA or appropriate ICD therapy: HR 3.41 (95% CI 2.27–5.13), $p < .001$ (Table 3, Figure 3). fQRS remained associated with the primary endpoint after adjusting for age, sex, and BMI (Model 1; HR 3.28 [95% CI 2.18–4.94], $p < .001$) and after additionally adjusting for CAD, HF, eGFR, and ICD indication (Model 2; HR 2.60 [95% CI 1.69–4.01], $p < .001$). fQRS also remained associated with the primary endpoint after additionally adjusting for established ECG parameters in patients with native QRS, including QRS duration, QRS axis, presence of Q wave, and BBB on baseline ECG (Model 3; HR 2.79 [95% CI 1.71–4.54], $p < .001$). The association between fQRS and the primary endpoint was consistent between the two study sites (HR 3.37 [95% CI 1.98–5.73] and HR 3.63 [95% CI 1.89–6.98],

TABLE 2 Baseline characteristics of patients with and without fQRS

	fQRS not present $n = 407$	fQRS present $n = 52$	*p*-value
Age	65.7 ± 12.1	69.3 ± 11.4	.04
Sex (female)	73 (17.9%)	7 (13.7%)	.46
Body mass index, kg/m^2	27.8 ± 4.7	27.9 ± 4.9	.82
Systolic blood pressure, mmHg	125 ± 20	127 ± 22	.50
Diabetes mellitus	80 (19.7%)	11 (21.2%)	.80
Estimated glomerular filtration rate, ml/min/1.73m^2	74 ± 23	71 ± 25	.42
Coronary artery disease	247 (61.6%)	44 (86.3%)	<.001
History of acute myocardial infarction	218 (54.0%)	42 (80.8%)	<.001
History of heart failure	325 (80.0%)	45 (86.5%)	.26
History of atrial fibrillation	162 (40.1%)	26 (50.0%)	.17
Left ventricular ejection fraction, %	41 ± 13	38 ± 12	.21
New York Heart Association class III-IV	44 (10.8%)	5 (9.6%)	.79
Cardiomyopathy	30 (7.4%)	0 (0.0%)	.04
Previous ventricular arrhythmias[a]	214 (52.8%)	43 (82.7%)	<.001
ICD indication (secondary)	189 (46.4%)	34 (65.4%)	.01
Baseline ECG Parameters[b]			
Bundle branch block	72 (24.7%)	8 (17.8%)	.31
QRS duration (ms)	106 [94, 130]	112 [100, 118]	.70
QRS axis (degrees)	7 [−24, 38]	12.0 [−21, 44]	.59
QTc duration (ms)	432 ± 35	433 ± 28	.91

Note: Data is shown as n (%) or mean ± SD.

[a]Including episodes registered before ICD implantation.

[b]In patients with native QRS on baseline ECG ($n = 336$).

TABLE 3 Cox regression analyses for the association between fQRS and incident ventricular arrhythmia (N = 126); univariate and multivariate models

	Unadjusted model			Model 1[a] (*n* = 450)			Model 2[b] (*n* = 439)			Model 3[c] (patients with native QRS; *n* = 293)		
	Hazard ratio [95% CI]	*Z*-value	*p*-value	Hazard ratio [95% CI]	*Z*-value	*p*-value	Hazard ratio [95% CI]	*Z*-value	*p*-value	Hazard ratio [95% CI]	*Z*-value	*p*-value
QRS fragmentation	3.41 [2.27–5.13]	5.9	<.001	3.28 [2.18–4.94]	5.7	<.001	2.60 [1.69–4.01]	4.3	<.001	2.79 [1.71–4.54]	4.1	<.001
Age				1.18 [1.00–1.40]	2.0	.046	1.08 [0.88–1.31]	0.7	.46	1.23 [0.97–1.56]	1.7	.08
Sex				1.08 [0.68–1.73]	0.3	.75	1.37 [0.85–2.20]	1.3	.19	1.05 [0.61–1.82]	0.2	.85
Body mass index, kg/m^2				1.02 [0.69–1.50]	0.1	.94	1.01 [0.69–1.50]	0.1	.94	0.95 [0.60–1.51]	−0.2	.82
Coronary artery disease							1.55 [0.97–2.47]	1.8	.07	1.32 [0.72–2.41]	0.9	.37
History of heart failure							1.46 [1.17–1.81]	3.4	.001	1.66 [1.29–2.12]	4.0	<.001
eGFR, ml/min/1.73 m^2							1.04 [0.96–1.13]	1.0	.34	1.10 [0.99–1.21]	1.8	.08
ICD indication (secondary)							1.41 [0.96–2.06]	1.8	.08	1.63 [1.02–2.61]	2.0	.04
QRS duration										0.90 [0.79–1.02]	−1.7	.09
QRS axis										0.99 [0.95–1.02]	−0.7	.47
Q wave presence										1.08 [0.67–1.72]	0.3	.76
Bundle branch block										1.41 [0.70–2.84]	1.0	.33

[a]Model 1: adjusted for age, sex, and body mass index.

[b]Model 2: adjusted for Model 1 + coronary artery disease, heart failure, estimated glomerular filtration rate, and ICD indication.

[c]Model 3: adjusted for Model 2 + QRS duration, QRS axis, presence of Q wave, and bundle branch block in patients with native QRS on baseline ECG.

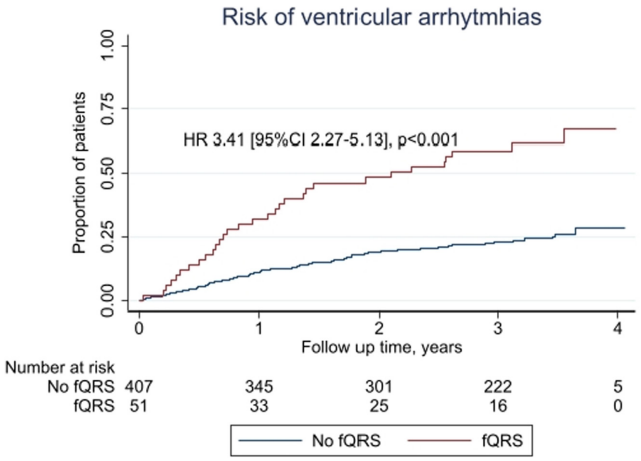

FIGURE 3 Survival analysis of time to ventricular arrhythmia and appropriate ICD therapy in patients with and without QRS fragmentation present in the baseline ECG

p-for-interaction = .93; Table S2). The association between fQRS and the primary endpoint was independent of the presence of BBB on baseline ECG (among patients with native QRS, *p*-for-interaction = .76). The presence of fQRS had specificity 94% and sensitivity 25% with a positive likelihood ratio of 4.2 for incident VA or appropriate ICD therapy.

In a sensitivity analysis including all-cause death ($N = 68$) in a combined outcome with incident VA or appropriate ICD therapy, fQRS was associated with the risk of incident VA or death: HR 2.65 [95% CI 1.82–3.87], $p < .001$, and this persisted in the adjusted models.

3.4 | fQRS and outcome according to ICD indication

fQRS was associated with the primary endpoint irrespective of ICD indication, but there was a stronger association among patients with a primary prevention ICD indication than patients with a secondary prevention ICD indication (HR 6.05 [95% CI 3.16–11.60] versus HR 2.39, [95% CI 1.41–4.04], respectively, *p*-for-interaction = .047). Among patients with a primary ICD indication, the presence of fQRS was associated with established CAD ($p = .048$) andprior MI ($p = .02$). fQRS and pathological Q waves were the only variables associated with the primary endpoint in multivariable models in these patients (Table S3). The association between fQRS and the primary endpoint in primary prevention was not modified by the presence or absence of CAD (p-for-interaction 0.39): HR 4.78 [95% CI 2.33–9.84], $p < .001$ and HR 8.63 [95% CI 1.85–40.3], $p = .006$, respectively.

3.5 | fQRS in association with ventricular tachycardia and ventricular fibrillation

When assessing the association between fQRS and components of the primary endpoint, we found an association between fQRS and incident VT (HR 3.04 [95% CI 1.96–4.71], $p < .001$), which persisted in the adjusted Model 3 ($p = .003$). fQRS was also associated with incident VF (HR 2.56, [95% CI 1.18–5.57], $p = .02$), which persisted after adjustments ($p = .03$). Among patients with incident VT or VF, 88% were appropriately treated with ATP or DC shock, and fQRS also predicted appropriate ICD therapy: HR 3.56, [95% CI 2.31–5.48], $p < .001$), which persisted after adjustments ($p < .001$).

In patients with primary ICD indication, fQRS was strongly associated with incident VT (HR 4.79 [95% CI 2.30–9.98], $p < .001$) and VF (HR 6.85 [95% CI 2.18–21.53], $p = .001$), and these associations persisted in the adjusted Model 3 ($p < .001$ for VT and $p = .004$ for VF).

4 | DISCUSSION

In this study, we found a strong and independent association between the presence of fQRS and incident VA and appropriate ICD therapy. Patients with fQRS had a threefold increased risk for developing VA irrespective of established risk factors and ECG parameters. These results suggest that interpreting ECGs for fragmentation of the QRS complex may improve risk stratification for SCD.

4.1 | Pathophysiology reflected by QRS fragmentation

In our study of unselected patients treated with ICD, fQRS was present in 11%, which is lower than in previous populations by Das: 23% in patients with ischemic and nonischemic cardiomyopathy, excluding patients with paced rhythm and inherited channelopathies (Das et al., 2010) and 35% in patients with CAD (Das et al., 2006). As these populations were selected for by the etiology of the cardiomyopathy or by the presence of CAD, this is not surprising and highlights the additional value provided by our study of non-selected patients with ICD. The presence of fQRS in our study was associated with established CAD, prior MI and a primary indication for ICD. There were limited associations to demographics and other comorbidities. The underlying mechanism causing the QRS complex to fragment is not completely understood. Early studies have focused on fQRS as a marker of myocardial scar. In agreement with our findings, Das et al. reported that fQRS represents myocardial scar, as indicated by regional perfusion abnormalities detected by nuclear stress test (Das et al., 2006). fQRS was superior to Q waves in detecting myocardial scars with significantly higher sensitivity and negative predictive value: 86% and 93%, respectively, for fQRS and 36% and 71%, respectively, for Q waves. Ratheendran et al. also reported an association between fQRS and myocardial scar in patients with hypertrophic cardiomyopathy (HCM; Ratheendran et al., 2020). They reported a higher incidence of delayed gadolinium enhancement on cardiac magnetic resonance imaging (CMR), indicating the presence of myocardial scar, in patients with fQRS compared with patients without fQRS (85% vs. 10%, respectively). The presence of fQRS had an 85% sensitivity and 90% specificity in detecting myocardial scar on CMR.

The criteria for fQRS are different for patients with narrow and wide QRS. Both increased QRS duration and presence of fQRS represent a conduction delay and a depolarization abnormality in the left ventricle. Interestingly, we found no association between presence of fQRS and QRS duration or axis among patients with native QRS, suggesting that this phenomenon is independent of other electrophysiological measures of ventricular depolarization. Hence, the exact pathophysiology behind fQRS remains unknown and is an area for future studies to investigate.

4.2 | QRS fragmentation as a predictor for ventricular arrhythmias

There is an unmet need to identify patients at risk of SCD. The current patient selection for treatment with ICD has major limitations and suffers from both poor sensitivity and specificity. Novel approaches to identify patients at risk are typically complicated and involve advanced imaging and deep phenotyping (de Haan et al., 2011; Lee Daniel & Goldberger, 2013). In this study, we found fQRS, which is an easily available parameter from standard 12-lead ECG, to be associated with a threefold increased risk of VA, with a specificity of 94%. In agreement with previous studies (Igarashi et al., 2017; Kucharz & Kułakowski, 2020; Ozcan et al., 2014), fQRS was superior to, and independent of, established clinical risk factors and ECG parameters with respect to VA. Our results, however, demonstrate a stronger association between fQRS and VA, which may relate to our sample size being larger and more heterogeneous. Furthermore, our outcome measure was specific for ventricular arrhythmias, as opposed to broader composite endpoints used in other studies (Engstrom et al., 2022).

In our study, fQRS was significantly associated with both incident VT and VF separately, although the number of events was lower and confidence intervals wider for VF. Importantly, the association between fQRS and VA was independent of QRS duration and the presence of BBB, which may suggest that the arrhythmogenicity reflected by fQRS is a result of heterogeneous ventricular depolarization rather than a conduction delay per se.

The incidence of sudden death has declined in heart failure with reduced ejection fraction (HFrEF) as a result from the cumulative benefit of evidence-based treatment (Shen et al., 2017). The effect of ICD treatment as primary prevention in patients with nonischemic HFrEF was investigated in the Danish trial (Køber et al., 2016). In this trial, ICD therapy was not superior to usual clinical care with respect to long-term rate of all-cause death, although there was a reduction in SCD. This demonstrates the importance of developing better risk stratification tools in patients considered for primary prevention ICD. A previous study of patients with primary prevention ICD indication did not find an association between fQRS and risk of either all-cause mortality or arrhythmic mortality (Cheema et al., 2010). However, this study did not investigate the association with incident VT or VF. In our study, fQRS was strongly predictive of VA in patients with a primary prevention indication for ICD, and this association was stronger than among secondary prevention patients. Moreover, the association between fQRS and VA in primary prevention was irrespective of the presence of CAD, suggesting that in nonischemic HFrEF, where the effect of ICD therapy is more uncertain, there may be a role for fQRS in identifying patients with increased risk of cardiac arrest (Maheshwari et al., 2013).

4.3 | Strengths

This was a large, investigator-initiated multicenter study with long follow-up. The main finding of the study was consistent across the study sites. Reporting SCD and whether it is caused by malignant VA can be challenging and inaccurate. Several studies have defined SCD according to guidelines as a sudden, unexpected, and nontraumatic death of healthy individuals occurring within one hour after onset of symptoms (Priori et al., 2015; Zipes et al., 2006). If it is unwitnessed, it is still defined as SCD if the individual was healthy 24 h before the death occurred (Priori et al., 2015). In our study, we have more accurate definitions of VA beyond clinical observations, as our arhythmical events are actual events documented and interrogated by experienced cardiac electrophysiologists. As ICD treatment prevents SCD caused by VA (Bardy et al., 2005; Buxton et al., 1999), we believe the association between fQRS and incident VA in our study is likely to translate to an association between fQRS and SCD. This is supported by the fact that 88% of the patients with VA also were treated with ATP or DC shock as programmed in the ICD algorithms.

4.4 | Limitations

We included patients treated with ICD, who are a high-risk population for VA. Our results can, therefore, not directly be applied to other patient populations or the general population who are at much lower risk. We had an uneven distribution of sex across our cohort with 83% males, although this typically represents the population with ICD. ECGs were obtained upon study enrollment, which was mean 5.0 ± 6.7 years after ICD implantation. Our patients were included at two centers, and all ECGs were analyzed by two independent adjudicators with the risk of observer bias; however, there was 99% agreement in the adjudication of fQRS. ECG recordings were done at paper speed 50 mm/s, as opposed to standard 25 mm/s, due to local routines. We excluded 19 (4%) patients because of missing, or non-interpretable ECG due to artifacts. However, this exclusion was random and not likely to influence our results. ICD programming was not standardized and may thus infer some variations in the sensitivity of VT detections. However, physicians were blinded to the fQRS status and any variations are not likely to bias the results. Patients who died from an unknown cause and who did not have their ICD interrogated post-mortem could potentially have died from VA. However, we demonstrate similar results when adding all-cause death to the primary outcome measure.

5 | CONCLUSIONS

fQRS is a highly feasible and easily available tool that can aid in assessing the risk for subsequent VA. Our study demonstrates that the presence of fQRS in ECG is associated with a threefold higher risk of developing VA, beyond established risk factors. The association appeared strongest in patients with a primary prevention ICD indication where there is an unmet need for novel risk assessment tools. Evaluating fQRS may prove to become such a tool. Automated detection of fQRS as a part of the computer algorithm interpretation of ECG, to reduce the risk of misinterpreting normal variant such as iRBBB, is a potential way forward. This could aid clinicians in detecting fQRS easily and potentially support decision-making regarding ICD implantation in high-risk patients.

ACKNOWLEDGMENTS

We are grateful for the substantial contributions from the study nurses Sanna Johannesson, Lisa Frødin, Anne Gro Larsen, and Jorunn Nilsen for invaluable help in organizing and executing the study visits. We also want to thank the cardiac electrophysiologists Dr. Arne Strand, Dr. Trude Berget, Dr. Huy Pham, and Dr. Gabor Kuntz for reading the ICDs and recording the events.

FUNDING INFORMATION

Drs. Sourour and Myhre were supported by grants from the South-Eastern Norway Regional Health Authority. Dr. Riveland is supported by a grant from the Western Norway Regional Health Authority.

CONFLICT OF INTEREST

Dr. Røsjø has received personal fees from Thermo Fischer BRAHMS, CardiNor and SpinChip Diagnostics. Dr Kjekshus has served on advisory boards and received speaker fees from Bayer and Pfizer. Dr. Omland has served on advisory boards for Abbott Diagnostics, Roche Diagnostics, and Bayer and has received research support from Abbott Diagnostics, Novartis, Roche Diagnostics, Singulex, and SomaLogic via Akershus University Hospital, and speaker's or consulting honoraria from Roche Diagnostics, Siemens Healthineers, and CardiNor. Dr. Myhre has served on advisory boards and received speaker fees from AmGen, AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, and Novo Nordisk. All other authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ETHICAL APPROVAL

The study was conducted in accordance with the Declaration of Helsinki. All patients provided informedwritten consent, and the study was approved by the Regional Ethics Committee (2015/2080) and the local DataProtection Officers at the institutions.

ORCID

Nur Sourour https://orcid.org/0000-0003-1068-8753
Egil Riveland https://orcid.org/0000-0001-7068-2631
Terje Rømo https://orcid.org/0000-0003-1747-6710
Patrycja Næsgaard https://orcid.org/0000-0002-4407-9887
Harald Kjekshus https://orcid.org/0000-0003-3695-8950
Alf Inge Larsen https://orcid.org/0000-0002-9141-0499
Torbjørn Omland https://orcid.org/0000-0002-6452-0369
Helge Røsjø https://orcid.org/0000-0003-2114-3134
Peder Langeland Myhre https://orcid.org/0000-0002-5871-1804

REFERENCES

Bardy, G. H., Lee, K. L., Mark, D. B., Poole, J. E., Packer, D. L., Boineau, R., Domanski, M., Troutman, C., Anderson, J., Johnson, G., McNulty, S. E., Clapp-Channing, N., Davidson-Ray, L. D., Fraulo, E. S., Fishbein, D. P., Luceri, R. M., & Ip, J. H. (2005). Amiodarone or an implantable cardioverter–defibrillator for congestive heart failure. *The New England Journal of Medicine*, *352*, 225–237.

Buxton, A. E. (2003). Risk stratification for sudden death: Do we need anything more than ejection fraction? *Cardiac Electrophysiology Review*, *7*, 434–437.

Buxton, A. E., Lee, K. L., Fisher, J. D., Josephson, M. E., Prystowsky, E. N., & Hafley, G. (1999). A randomized study of the prevention of sudden death in patients with coronary artery disease. *The New England Journal of Medicine*, *341*, 1882–1890.

Cheema, A., Khalid, A., Wimmer, A., Bartone, C., Chow, T., Spertus, J. A., & Chan, P. S. (2010). Fragmented QRS and mortality risk in patients with left ventricular dysfunction. *Circulation. Arrhythmia and Electrophysiology*, *3*, 339–344.

Das, M. K., Khan, B., Jacob, S., Kumar, A., & Mahenthiran, J. (2006). Significance of a fragmented QRS complex versus a Q wave in patients with coronary artery disease. *Circulation*, *113*, 2495–2501.

Das, M. K., Maskoun, W., Shen, C., Michael, M. A., Suradi, H., Desai, M., Subbarao, R., & Bhakta, D. (2010). Fragmented QRS on twelve-lead electrocardiogram predicts arrhythmic events in patients with ischemic and nonischemic cardiomyopathy. *Heart Rhythm*, *7*, 74–80.

Das, M. K., Suradi, H., Maskoun, W., Michael, M. A., Shen, C., Peng, J., Dandamudi, G., & Mahenthiran, J. (2008). Fragmented wide QRS on a 12-lead ECG: a sign of myocardial scar and poor prognosis. *Circulation. Arrhythmia and Electrophysiology*, *1*, 258–268.

de Haan, S., Meijers, T. A., Knaapen, P., Beek, A. M., van Rossum, A. C., & Allaart, C. P. (2011). Scar size and characteristics assessed by CMR predict ventricular arrhythmias in ischaemic cardiomyopathy: Comparison of previously validated models. *Heart*, *97*, 1951–1956.

Engstrom, N., Dobson, G., Ng, K., & Letson, H. (2022). Fragmented QRS is associated with ventricular arrhythmias in heart failure patients: A systematic review and meta-analysis. *Annals of Noninvasive Electrocardiology*, *27*, e12910.

Igarashi, M., Tada, H., Yamasaki, H., Kuroki, K., Ishizu, T., Seo, Y., Machino, T., Murakoshi, N., Sekiguchi, Y., Noguchi, Y., & Nogami, A. (2017). Fragmented QRS is a novel risk factor for ventricular arrhythmic events after receiving cardiac resynchronization therapy in nonischemic cardiomyopathy. *Journal of Cardiovascular Electrophysiology*, *28*, 327–335.

Køber, L., Thune, J. J., Nielsen, J. C., Haarbo, J., Videbæk, L., Korup, E., Jensen, G., Hildebrandt, P., Steffensen, F. H., Bruun, N. E., Eiskjær, H., Brandes, A., Thøgersen, A. M., Gustafsson, F., Egstrup, K., Videbæk, R., Hassager, C., Svendsen, J. H., Høfsten, D. E., … DANISH Investigators. (2016). Defibrillator implantation in patients with nonischemic systolic heart failure. *The New England Journal of Medicine*, *375*, 1221–1230.

Koplan, B. A., & Stevenson, W. G. (2009). Ventricular tachycardia and sudden cardiac death. *Mayo Clinic Proceedings*, *84*, 289–297.

Kucharz, A., & Kułakowski, P. (2020). Fragmented QRS and arrhythmic events in patients with implantable cardioverter-defibrillators. *Kardiologia Polska*, *78*, 1107–1114.

Lee Daniel, C., & Goldberger, J. J. (2013). CMR for sudden cardiac death risk stratification. *JACC: Cardiovascular Imaging*, *6*, 345–348.

Maheshwari, S., Acharyya, A., Puddu, P. E., Mazomenos, E. B., Leekha, G., Maharatna, K., & Schiariti, M. (2013). An automated algorithm for online detection of fragmented QRS and identification of its various morphologies. *Journal of the Royal Society Interface*, *10*, 20130761.

Morita, H., Kusano, K. F., Miura, D., Nagase, S., Nakamura, K., Morita, S. T., Ohe, T., Zipes, D. P., & Wu, J. (2008). Fragmented QRS as a marker of conduction abnormality and a predictor of prognosis of Brugada syndrome. *Circulation*, *118*, 1697–1704.

Ozcan, F., Turak, O., Canpolat, U., Avci, S., Tok, D., Isleyen, A., Cebeci, M., Yuzgeçer, H., Gurel, O. M., Topaloglu, S., & Aras, D. (2014). Fragmented QRS predicts the arrhythmic events in patients with heart failure undergoing ICD implantation for primary prophylaxis: More fragments more appropriate ICD shocks. *Annals of Noninvasive Electrocardiology*, *19*, 351–357.

Pascale, P., Schlaepfer, J., Oddo, M., Schaller, M. D., Vogt, P., & Fromer, M. (2009). Ventricular arrhythmia in coronary artery disease: Limits of a risk stratification strategy based on the ejection fraction alone and impact of infarct localization. *Europace*, *11*, 1639–1646.

Priori, S. G., Blomstrom-Lundqvist, C., Mazzanti, A., Blom, N., Borggrefe, M., Camm, J., Elliott, P. M., Fitzsimons, D., Hatala, R., Hindricks, G., et al. (2015). 2015 ESC Guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *European Heart Journal*, *36*, 2793–2867.

Ratheendran, A. C., Subramanian, M., Bhanu, D. K., Prabhu, M. A., Kannan, R., Natarajan, K. U., Saritha Sekhar, S., Thachathodiyil, R., Harikrishnan, M. S., & Pai, P. G. (2020). Fragmented QRS on electrocardiography as a predictor of myocardial scar in patients with hypertrophic cardiomyopathy. [Abstract]. *Acta Cardiologica*, *75*, 42–46.

Shen, L., Jhund, P. S., Petrie, M. C., Claggett, B. L., Barlera, S., Cleland, J. G. F., Dargie, H. J., Granger, C. B., Kjekshus, J., Køber, L., Latini, R., Maggioni, A. P., Packer, M., Pitt, B., Solomon, S. D., Swedberg, K., Tavazzi, L., Wikstrand, J., Zannad, F., … McMurray, J. J. V. (2017). Declining risk of sudden death in heart failure. *The New England Journal of Medicine*, *377*, 41–51.

Zipes, D. P., Camm, A. J., Borggrefe, M., Buxton, A. E., Chaitman, B., Fromer, M., Gregoratos, G., Klein, G., Moss, A. J., Myerburg, R. J., Priori, S. G., Quinones, M. A., Roden, D. M., Silka, M. J., Tracy, C., Priori, S. G., Blanc, J. J., Budaj, A., Camm, A. J., … Heart Rhythm Society. (2006). ACC/AHA/ESC 2006 guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: a report of the American College of Cardiology/American Heart Association Task Force and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Develop guidelines for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death) developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Europace*, *8*, 746–837.

Zipes, D. P., & Wellens, H. J. J. (1998). Sudden cardiac death. *Circulation*, *98*, 2334–2351.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Sourour, N., Riveland, E., Rømo, T., Næsgaard, P., Kjekshus, H., Larsen, A. I., Omland, T., Røsjø, H., & Myhre, P. L. (2022). QRS fragmentation is associated with increased risk of ventricular arrhythmias in high-risk patients; Data from the SMASH 1 Study. *Annals of Noninvasive Electrocardiology*, *27*, e12985. https://doi.org/10.1111/anec.12985