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Prognostic significance of QRS duration and morphology

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Abstract

QRS duration and morphology, evaluated via a standard 12-lead electrocardiogram (ECG), represent an opportunity to derive useful prognostic information regarding the risk of subsequent cardiac events or therapeutic outcomes. Prolonged QRS duration, and the presence of intraventricular conduction abnormalities, usually indicate the presence of changes in the myocardium due to underlying heart disease.

Prolonged QRS duration is often associated with depressed ejection fraction or enlarged left ventricular volumes, but several studies have demonstrated that this simple ECG measure provides independent prognostic value, after adjusting for relevant clinical covariates.

Post-infarction patients with prolonged QRS duration have a significantly increased risk of mortality, although data associating QRS prolongation specifically with sudden death is less supportive. In non-ischemic cardiomyopathy, there is no evidence that QRS duration has prognostic significance in predicting mortality or sudden death. Prolonged QRS duration, and especially presence of left bundle branch block, seems to predict a benefit from cardiac resynchronization therapy in both ischemic and non-ischemic cardiomyopathy patients.

Therefore, QRS duration and morphology should not only be considered a predictor of death or sudden death in patients after myocardial infarction, and in those suspected of coronary artery disease, but also as a predictor of benefit from cardiac resynchronization therapy in patients with heart failure, whether of an ischemic or non-ischemic origin. (Cardiol J 2011; 18, 1: 8–17)

Key words: QRS duration, left bundle branch block, prognosis, mortality

Introduction

QRS duration (QRSd) and morphology, evaluated using a standard 12-lead electrocardiogram (ECG), have always been considered important prognostic markers, even in individuals without structural heart disease.

The Manitoba study [1] consisted of a cohort of 3,983 men with a mean age at entry of 30 years, followed with regular examinations including ECG from 1948. During the 30 year observation period, 70 cases of sudden death occurred in men without previous clinical manifestations of heart disease. Left bundle branch block (LBBB) was found to be associated with a relative 13.8-fold increased risk of sudden death in this cohort of healthy men.

Studies that are more relevant to everyday clinical practice typically involve patients referred for evaluation due to suspected coronary disease. Schinkel et al. [2] analyzed a large cohort of 1,227 patients referred for dobutamine stress echocardiography to evaluate suspected myocardial ischemia.

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During a mean follow-up of more than four years, they found that patients with QRS duration ≥ 120 ms had twice the cardiac mortality as did patients with QRS < 120 ms. Multivariate analysis adjusted for age, gender, smoking, hypertension, diabetes, hypercholesterolemia, ST segment depression, angina, and abnormal stress echocardiogram showed that QRS duration ≥ 120 ms was significantly associated with mortality with a hazard ratio of 1.8.

In another similar study of 4,033 patients with known or suspected coronary artery disease, Elhendy et al. [3] also demonstrated that QRS prolongation was associated with increased mortality after adjusting for relevant clinical covariates. These large studies, and other smaller reports, indicate that QRS duration and morphology is of major prognostic importance even in individuals without organic heart disease. Abnormal QRS duration and morphology frequently identify subjects with clinically undetected cardiac abnormalities and an increased risk of mortality.

Post myocardial infarction population

The standard 12-lead ECG should always be considered when performing risk stratification of patients who have experienced myocardial infarction (MI). Heart rate, atrioventricular conduction, fascicular block, bundle branch block (BBB) and the degree of ST-segment deviation have all been shown to influence survival after MI [4]. Most of the early work (before the era of percutaneous transluminal intervention [PCI]) focused on the relationship between BBB and prognosis post MI. Those early studies consistently associated the presence of BBB with increased short- and long-term mortality with estimates of 20–30% at one year [5–7]. In more recent datasets, it has become clear that specific quantification of the QRSd, and not just the presence or absence of BBB (Table 1), can provide more prognostic information, such as the likelihood of 30 day mortality or sudden cardiac death (SCD) post MI [8].

Abnormal intraventricular conduction has been extensively examined as a risk stratification tool in diverse cardiovascular disease (CVD) populations, including patients with abnormal left ventricular (LV) function, dyssynchrony and those at increased risk of SCD. Most of this work has focused on patients with chronic CVD and will be discussed in detail below. The prognostic significance of quantitative QRS conduction post acute MI has been relatively under-studied in comparison with these more chronic forms of CVD. Existing data is mainly derived from *post-hoc* analysis of multi-center registries focusing on revascularization, with 30 day all-cause mortality as a common endpoint.

Recently, Wong et al. [9] examined the relationship between QRSd and 30 day mortality post MI in a prespecified *post hoc* analysis of the Hirulog and Early Reperfusion or Occlusion (HERO)-2 trial. They examined QRSd at baseline and 60 minutes after fibrinolysis in over 12,000 patients. Only patients with normal QRSd (< 125 ms) or RBBB at both time points were included in the analysis. Patients who developed LBBB or QRS delay not meeting the criteria for RBBB were excluded. Any prolongation of the QRS within this studied population was associated with increased 30 day mortality, but only in patients with anterior MI, and not with inferior MI. In the anterior MI population, the authors noted a 30–40% increase in 30 day mortality for every 20 ms increase in the QRSd from baseline. A similar relationship was found in the GUSTO-1 [8] population with QRS prolongation within the normal range (100 *vs* 80 ms) post anterior MI carrying the strongest association and greatest prognostic significance for 30 day mortality (OR 1.55; 95% CI 1.43–1.68).

Shortcomings of this robust dataset include its compilation prior to the current PCI era, and the lack of data regarding the actual cause of death. Recent efforts have sought to overcome these limitations and describe the prognostic weight of QRS prolongation, as well as specify the cause of death, with particular attention paid to SCD. Bauer et al. [10] prospectively analyzed 1,455 survivors of acute MI aged 75 or under with a dichotomized QRS variable cutoff of 120 ms, and found a strong association of QRS prolongation with total mortality (HR 4.0; 95% CI 2.3–6.9 after multivariate analysis). However, the authors did not find a significant association with SCD. A decreased incidence of BBB was found in patients in this population when compared to studies performed in the pre-PCI era (6 *vs* 10–20%) but with similar one year all-cause mortality (18.6 *vs* 20.8%) [5]. The study pointed towards patients with abnormal QRSd carrying higher post MI mortality, but not from SCD. In another study by Guerrero et al. [11], analyses of 3,053 post-infarction patients who underwent primary angioplasty showed that LBBB was associated with five-fold higher in-hospital mortality; the authors did not report prognostic value of QRS duration.

In an effort to assess the efficacy of treatment with valsartan and captopril, and their combination, in high-risk patients after MI (The Valsartan In Acute Myocardial Infarction [VALIANT] trial [12])

Table 1. Prognostic significance of QRS duration in post-infarction randomized clinical trials.

Trial	n	Population	QRS variable	Primary endpoint	Results (95% CI)
GUSTO-1	34,166	STEMI and no confounding ECG factors at entry (paced rhythms, ventricular rhythms, or LBBB)	Continuous 100 *vs* 80 ms	30 day all-cause mortality	OR 1.55 (1.43–1.68); $p < 0.001$ for death with anterior MI and 1.08 (1.03–1.13); $p < 0.001$ for any other infarct location
Bauer et al.*	1,455	Survivors of AMI under 76 years of age without a paced rhythm	Dichotomous with 120 ms cut point	All-cause mortality at two years	HR for primary endpoint 4.0 (2.3–6.9); $p < 0.001$; HR for cardiac mortality 3.9 (1.9–7.8); $p < 0.001$; HR for SCD not significant
Elhendy et al.	4,033	Patients with known or suspected CAD	Continuous without defined increment	All-cause mortality at five years	QRS duration of > 105 ms highest risk for mortality; HR 8.49 (4.4–16.34); $p < 0.0001$
DINAMIT*	674	Patients 6–40 days post AMI randomized to ICD *vs* standard therapy	Dichotomous with 120 ms cut point	All-cause mortality at 2.5 years with SCD as a secondary endpoint	No association between QRS duration and risk of all-cause mortality or SCD
VALIANT*	403	Post AMI with LV dysfunction ± symptomatic HF	Continuous with quartiles starting at < 75 to > 108 ms	Combined endpoint of HF, SCD, CD, stroke and MI at two year follow-up	HR for primary endpoint of 1.31 (1.06–1.64); 1.57 (1.03–2.4) and 1.31 (1.03–2.4) for each QRS duration quartile
DIAMOND	1,510	Post AMI with LV dysfunction and without HF	Continuous 20 ms increments starting at 80 ms	All-cause mortality with ten year follow up	6% increase in death for each 10 ms increase in QRS duration; HR 1.06 (1.04–1.09); $p < 0.0001$
HERO 2	12,456	STEMI with normal QRS duration (80–120 ms) or RBBB at baseline	Continuous 20 ms increments starting at 80 ms	30 day all-cause mortality	30–40% increase in death in anterior MI only for every 20 ms increase in QRS duration; OR 1.42 (1.33–1.51); $p < 0.0001$

*Only trials to assess sudden cardiac death incidence and QRS duration post acute myocardial infarction; STEMI — ST segment elevation myocardial infarction; ECG — electrocardiogram; LBBB — left bundle branch block; AMI — acute myocardial infarction; CAD — coronary artery disease; ICD — implantable cardioverter-defibrillator; LV — left ventricle; HF — heart failure; RBBB — right bundle branch block; SCD — sudden cardiac death; CD — cardiac death; CI — confidence interval; OR — odds ratio; HR — hazard ratio

the authors included QRS duration as a prespecified subgroup. The primary outcomes included all-cause and cardiovascular mortality as well as SCD events. Patients with QRS prolongation were found to have increased ventricular volumes, decreased left ventricular ejection fraction (LVEF), and a higher incidence of heart failure (HF), cardiovascular death and SCD. As observed in the HERO-2 and GUSTO-1 trials, the increased risk was seen even with QRS prolongation within the normal range. Subsequent work by Solomon et al. [13] with the VALIANT cohort found that risk of sudden death within 30 days of MI was highest in patients with an abnormal LVEF, which in the primary study correlated strongly with QRSd. This conclusion reinforces the belief that QRSd is an indicator of the burden of CVD and probably carries with it an increased risk of SCD post MI.

There is some inconsistency in the conclusions of the aforementioned studies examining the risk of SCD post MI with abnormal QRSd. Most of the literature supports an increased risk of all-cause mortality at 30 days, and at longer follow-up, regardless of the method of revascularization used to treat the acute infarction. Why, then, should different conclusions be drawn about the prognostic value of QRSd for SCD events? The probable reason is that there is a good deal of inconsistency between these studies, particularly when the patient population is considered. VALIANT enrolled patients who were post MI with abnormal LVEF, while Bauer's study [10] took all comers with MI who were in normal sinus rhythm. The population with abnormal QRSd in the Bauer study [10], felt to be disproportionably sicker than the population with normal intraventricular conduction, had baseline characteristics almost identical to the entire VALIANT population. This suggests that the VALIANT patients with abnormal QRSd have an increased burden of cardiovascular illness and worse ventricular function when compared to Bauer's population with abnormal QRSd. This is, in fact, the case and probably serves to identify a population within the VALIANT cohort that is at a higher baseline risk of SCD than the Bauer population. These study population differences act to explain the prognostic value for abnormal QRSd within the VALIANT population and not the Bauer population. Abnormal QRSd is, at least, a risk for all-cause mortality at both 30 days and later, and is also probably prognostic of SCD events, although the data is currently inconclusive.

With the prognostic relationship of QRSd post MI probably carrying an increased risk of death and SCD post MI, the next question is whether or not it should be used in guiding antiarrhythmic therapy during this vulnerable time. The DINAMIT [14] trial primarily examined the efficacy of implantable cardioverter-defibrillator (ICD) placement in patients 6–40 days post MI with abnormal LVEF, along with impaired cardiac autonomic function (depressed HR variability or elevated 24-hour HR on Holter monitoring), but also stratified the patients by QRSd as a prespecified subgroup. On the whole, the trial did not show any mortality benefit for ICD placement, but it did display a non-significant trend towards benefit for ICD placement in patients with prolongation of the QRS beyond 120 ms. The authors noted that arrhythmic death was significantly decreased, with a similar increase in nonarrhythmic death, resulting in no all-cause mortality benefit for ICD implantation within this population.

It is as yet unclear whether prolongation of the QRS complex post acute MI poses an independent risk for SCD. Abnormal QRS duration is prognostic of increased short-term [8, 9] and long-term [5, 10] all-cause mortality probably secondary to the higher burden of CVD within this population. The question of what to do with this information beyond standard post MI aggressive medical therapy remains unanswered.

Ischemic cardiomyopathy

Abnormal intraventricular conduction has been examined extensively as a risk factor for overall mortality, as well as SCD, in patients with ischemic cardiomyopathy (ICM) (Table 2). Earlier studies such as the CASS trial [15] established abnormal intraventricular conduction in patients with ICM as an independent risk factor for all-cause mortality, particularly for LBBB. The limitations of this data are that it was compiled prior to the current revascularization era and did not specifically address arrhythmic death.

Current understanding of the relationship between QRS prolongation and risk of SCD in the ICM population has resulted from secondary analyses of multi-center defibrillator databases such as MUSTT and MADIT-II. Although this data is robust, the magnitude of the relationship between abnormal intraventricular conduction and SCD in the ICM population, along with its clinical utility, remains unclear.

In their analysis of the MUSTT population, Zimetbaum et al. [16] examined the relationship between numerous ECG abnormalities and all-cause mortality/SCD in patients who were not treated with antiarrhythmic therapy (antiarrhythmic

Table 2. Prognostic significance of QRS duration and morphology in ischemic cardiomyopathy randomized clinical trials.

Trial	n	Population	QRS variable	Primary endpoint	Results (95% CI)
MADIT II	1,232	LVEF < 30 one month or more from AMI and three months from revascularization	Dichotomous with 120 ms cut-point	SCD in medically treated patients and SCD or VT/VF in ICD group	HR of 2.12 (1.2–3.76); p = 0.01 in the medical arm and HR of 0.77 (0.47–1.24); p = 0.28 in the ICD arm
SCD-HeFT*	2,521 total 1,400 ICM	NYHA class II or III CHF randomized to placebo, amiodarone or ICD	Dichotomous with 120 ms cut-point	All-cause mortality; median follow-up of 45 months	HR 0.67 (0.49–0.93) for ≥ 120 ms and 0.84 (0.62–1.14) for < 120 ms *vs* placebo in ICD arm
Stecker et al.*†	562	Single-centre cohort of ICD recipients for both 1° and 2° prevention	Continuous ≥ 100 ms, ≥ 120 ms, ≥ 140 ms thresholds	Arrhythmic events in patients followed for more than one year	Adjusted OR 2.32 (1.37–5.51) QRS ≥ 100 ms; 1.77 (0.97–3.23) QRS ≥ 120 ms; 1.24 (0.65–2.38) QRS ≥ 140 ms
MUSTT	1,638	LVEF ≤ 40, no ICD or antiarrhythmic medication and no VT/VF during EPS	Descriptive IVCD, LBBB, RBBB	Arrhythmic death	IVCD HR 1.44 (1.11–1.88); p = 0.0069; LBBB HR 1.49 (1.02–2.17); p = 0.04; RBBB HR 1.05 (0.65–1.71); p = 0.8383
COMPANION*	1,520	NYHA class III or IV CHF randomized to medical therapy, CRT, CRT-ICD	Continuous ≤ 147 ms, 148–168 ms, ≥ 169 ms	All-cause mortality at 12 months	HR 0.6 (0.3–0.9) QRS ≥ 169 ms; 0.65 (0.35–0.95) QRS 148–168 ms; 0.75 (0.4–1.25) ≤ 147 ms
PROFIT*†	250	Consecutive patients meeting ACC/AHA criteria for ICD placement (1° and 2° prevention)	Dichotomous with 150 ms cut-point	VT/VF treated by ICD *in situ*	Log-rank p = 0.016 for QRS ≥ 150 ms at two year follow-up
PainFREE II†	431	CAD ICD for 1° or 2° prevention randomized to ATP *vs* shock for ventricular arrhythmia	Continuous with 120 ms cut-point analysis reported	VT/VF requiring therapy	OR 1.072 (0.66–1.74) QRS ≥ 120 ms; no QRS duration threshold displayed significant association with arrhythmic events

*Includes non-ischemic cardiomyopathy patients in analysis; †includes secondary arrhythmia prevention patients in analysis; ICM — ischemic cardiomyopathy; LVEF — left ventricular ejection fraction; VT — ventricular tachycardia; VF — ventricular fibrillation; EPS — electrophysiological study; CRT — cardiac resynchronization therapy; other abbreviations as in Table 1

medication or ICD implantation). The ECG abnormalities included: intraventricular conduction delay (IVCD), LBBB, RBBB, left ventricular hypertrophy, and left atrial hypertrophy, with the relevant endpoints being arrhythmic death and all-cause mortality. After multivariate adjustment, only IVCD (HR 1.44), and LBBB (HR 1.49) were associated with arrhythmic death and all-cause mortality. The increase in total mortality associated with LBBB or IVCD, however, outweighed the increase in arrhythmic death risk, suggesting a lack of cause and effect between conduction abnormalities and death. The authors noted that patients with LBBB or IVCD had lower ejection fractions and a higher incidence of symptomatic HF than those without, suggesting that the increase in overall mortality was probably due to a sicker LBBB and IVCD population. These results seem to mesh well with previous data from the CASS registry that displayed increased all-cause mortality associated with LBBB, but not with RBBB, in patients with ischemic heart disease [15].

While the sub-analysis of CASS and MUSTT dealt primarily with medically managed patients with HF, the question of whether or not patients with ICM and abnormal intraventricular conduction were more likely to benefit from ICD placement due to aborted SCD remained. In an initial analysis of both SCD-HEFT and MADIT-II, a greater baseline prolongation of QRS was associated with a trend toward increased benefit from ICD implantation [17, 18]. This association, although present, was not significant in either study.

A subsequent analysis of 431 patients in the PainFREE II study did not display any association between QRS duration and ventricular tachycardia (VT)/ventricular fibrillation (VF) in ICD treated patients [19]. Dhar et al. [20] performed an analysis of 731 patients from the MADIT-II cohort with prolonged QRSd, and found it to be an independent predictor of SCD in medically managed patients (HR 2.12) but not in ICD-treated patients (HR 0.77). This is not surprising, because the ICD-treated MADIT II patients died predominantly of non-sudden HF, and QRSd would not be expected to predict HF mortality. At the same time, VT/VF is much more common than SCD, indicating that many ventricular arrhythmias terminate spontaneously. The MADIT-II substudy treated QRSd as a continuous variable, while other studies have utilized an inconsistent cutoff value to determine if QRSd is abnormal. This difference, along with the near identical patient populations (ICD and non-ICD groups), allowed the authors to display a consistent association of lengthened QRSd and SCD across the spectrum of QRSd, as well as determining the prognostic significance of abnormal intraventricular conduction within these two groups.

More recently, QRSd has been used as a stratification tool for arrhythmic risk in patients post ICD placement within the MADIT II cohort [21]. Amongst other basic clinical factors, it was found to have a significant association with events, carrying a HR of 1.56. The model already has been validated, indicating the importance of QRSd among other variables composing MADIT II score [22].

Non-ischemic cardiomyopathy

Compared to the ICM population, there is little data examining the relationship between QRSd and SCD/VF events in the non-ischemic cardiomyopathy (NICM) population (Table 3). Our current understanding of the prognostic implications of abnormal QRSd within the NICM population is the result of subgroup analyses of large multi-center defibrillator efficacy trials, similar to the ICM population. The major exception to this is the Marburg Cardiomyopathy study (MACAS), a kind of 'natural history' cohort study of NICM patients that examined the prognostic implications of baseline patient characteristics in relation to outcomes. Previous small studies had shown that an abnormal signal averaged ECG has prognostic value in predicting ventricular arrhythmias and sudden deaths within the NICM population [23, 24]. However, standard 12-lead ECG is the principal source of information regarding QRS duration and morphology.

In MACAS [25], a cohort of 343 NICM patients were followed clinically for the development of arrhythmic events with baseline variables obtained including QRSd and morphology. Neither LBBB nor RBBB predicted arrhythmic events within this cohort. The only baseline characteristic that was predictive of VF/SCD events was enrollment LVEF (RR of 2.3 for every 10% decrease in ejection fraction). Although MACAS was observational in nature, it provided excellent information regarding the natural history of NICM and cast doubt upon the predictive utility of QRSd for VF/SCD events.

Subsequent to the findings of MACAS, the DEFINITE trial [26] enrolled patients with idiopathic dilated cardiomyopathy and either premature ventricular complexes or non-sustained ventricular tachycardia on 24-hour Holter monitoring and randomized them to either ICD placement or standard medical therapy. Within this population, they found that ICD treatment resulted in an absolute decrease in mortality over standard therapy of 7%

Table 3. Prognostic significance of QRS duration in non-ischemic cardiomyopathy randomized clinical trials.

Trial	n	Population	QRS variable	Primary endpoint	Results (95% CI)
DEFINITE	458	NICM with EF < 36% and PVCs or NSVT on 24-h Holter monitoring	Dichotomous with 120 ms cut-point	SCD with mean follow-up of 29 months	HR for death QRS ≥ 120 ms of 0.5 (0.1–1.1) favoring ICD therapy; HR for QRS < 120 ms of 0.7 (0.3–1.5) favoring ICD; difference not significant
MACAS	343	NICM with EF < 45% and EDD of > 56 mm and no prior sustained VT, VF or class IV HF	Descriptive LBBB, RBBB	SCD with mean follow-up of 52 months	HR for SCD of 1.36 for LBBB; p = 0.19 and 1.6 for RBBB; p = 0.57
SCD-HeFT*	2,521 total 1,100 NICM	NYHA class II or III CHF randomized to placebo, amiodarone or ICD	Dichotomous with 120 ms cut-point	All-cause mortality; median follow-up of 45 months	HR 0.67 (0.49–0.93) for ≥ 120 ms and 0.84 (0.62–1.14) for < 120 ms *vs* placebo in ICD arm
Amiya et al.	78	Consecutive patients with NICM meeting WHO criteria	Dichotomous with 120 ms cut-point	Cardiac death or hospitalization for HF	Multivariate HR for primary end-point of 1.02 (1.003–1.038); p = 0.0008
Hombach et al.	141	Consecutive patients with NICM meeting WHO criteria who underwent cardiac MR	Dichotomous with 110 ms cut-point	Cardiac death or SCD with median follow-up of four years	Multivariate HR of 3.19 (1.4–7.29); p = 0.045 for QRS > 110 ms

*Includes ischemic cardiomyopathy patients in analysis; NICM — non-ischemic cardiomyopathy; EF — ejection fraction; PVC — premature ventricular complexes; NSVT — non-sustained ventricular tachycardia; EDD — end-diastolic diameter; WHO — Word Health Organization; MR — magnetic resonanse; other abbreviations as in Table 1

at two years (14.1 *vs* 7.9%). This difference was not, however, found to be statistically significant. QRSd was a prespecified subgroup within the study with a QRSd of 120 ms as their dichotomous cutoff point. A trend toward benefit of ICD therapy in patients with a QRSd longer than 120 ms was seen, but again did not reach statistical significance. This should not cause surprise, because the overall DEFINITE trial had limited statistical power and so subgroup analyses were even further underpowered. The shortcomings of this data include the fact that QRSd was treated as a dichotomous variable without specification for morphology or BBB. Previous studies in an ischemic population showed that LBBB patients are at higher risk of arrhythmic death than those with RBBB [15]. Regardless of the shortcomings of this data, it indicates that QRS duration does not have prognostic significance in predicting SCD/VF in the NICM population.

SCD-HEFT [17] is the largest randomized clinical trial so far to assess the efficacy of ICD treatment in the NICM population. Its design randomized 1,100 NICM and 1,400 ICM patients to receive amiodarone, ICD or placebo treatment. As a predefined subgroup of this population, the patients were stratified based upon a dichotomous QRS cutoff of 120 ms, but without further stratification into ischemic *vs* non-ischemic etiologies of LV dysfunction. The group as a whole did display a non-significant trend towards benefit of ICD placement if the QRSd was longer than 120 ms, with the specificity of this result for the NICM population still in question. This finding is consistent with the results of MACAS and the DEFINITE subgroup that did not support abnormal QRSd as having a prognostic role for SCD events.

With our current shortcomings regarding risk stratification for SCD in both the ICM and NICM populations, imaging, or more specifically cardiac magnetic resonanse imaging (MRI), has been seen as a possible tool to better identify patients at risk. Hombach et al. [27] examined the utility of cardiac MRI in conjunction with QRSd and QTc in predicting SCD and cardiac death. Of the 149 patients enrolled, 94 had a QRSd of > 110 ms with a statistically significant HR of 5.43 for the primary endpoint. QRSd, along with diabetes, cardiac index and right ventricular end-diastolic volume index on cardiac MRI, was significantly associated with the primary endpoint in Hombach's NICM cohort.

Overall, the current data indicates a lack of predictive value of QRSd for SCD events in the NICM population. This conclusion rests on subgroup analysis of ICD efficacy trials either specifically designed for, or that just happened to include,

patients with NICM. These trials are smaller than those that have examined the same question in the ICM population. No trial involving a NICM population has treated QRSd as a continuous variable, or differentiated patients with QRS prolongation into BBB subgroups.

QRSd appears to be a better indicator of the overall burden of CVD, and less of an independent predictor of SCD, within the NICM population.

QRS duration and morphology in cardiac resynchronization therapy patients

Cardiac resynchronization therapy (CRT) is indicated in HF patients with prolonged QRSd (≥ 120 ms) [28–32]. The criterion of wide QRS complex, qualifying HF patients for CRT, indicates that a delay in intraventricular conduction is associated with delayed activation of certain regions of the heart and impaired dysynchronous contraction. Applying LV or biventricular pacing in such patients improves electrical activation of the ventricles and improves contractility by synchronizing movements of the LV free wall and interventricular septum. Previous studies have documented that prolonged QRSd, especially if associated with a LBBB, is associated with more advanced LV dysfunction in HF patients. However, the prognostic significance of BBB in HF patients remains controversial. Baldasseroni et al. [33] evaluated the prognostic significance of QRS morphology in 5,517 HF outpatients, with LBBB proving to be predictive of all-cause mortality when compared to patients without LBBB. Barsheshet et al. [34] evaluated 4,102 hospitalized HF patients. RBBB, but not LBBB, was found to be predictive for mortality. Differences in clinical characteristics of studied patients probably contribute to these differences.

The prognostic significance of QRS morphology has been evaluated in several CRT trials. In the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial [28] enrolling class III and IV HF patients, there was no significant difference in the risk of primary or secondary endpoints between patients with LBBB and patients with RBBB or IVCD. In the study by Iler et al. [35] of 337 CRT patients, LBBB was not predictive of death or heart transplant outcome. In another cohort of 636 CRT patients [36], three-year average survival was significantly better in LBBB than in RBBB patients. In a study by Wokhlu et al. [37] of 505 CRT patients, survival over a median 2.6 years of follow-up was significantly better in LBBB than in RBBB patients receiving CRT. These observations indicate that a therapy, in this case CRT, might modify the prognostic significance of QRS morphology: LBBB patients seem to benefit more from CRT than RBBB patients, and therefore have better survival.

The MADIT-CRT [38] (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy) evaluated the effects of CRT-D *vs* ICD-only therapy in 1,820 mild to moderate HF patients with ischemic (NYHA class I or II) and non-ischemic (class II) cardiomyopathy with ejection fraction ≤ 30% and QRS ≥ 130 ms. The CRT-D therapy was associated with a 34% reduction in the risk of primary endpoint, defined as death from any cause or a non-fatal HF event (whichever came first). Patients with QRS duration ≥ 150 ms derived significantly more benefit from CRT-D than did patients with QRS < 150 ms. The LBBB patients demonstrated the most significant effect of resynchronization therapy in terms of reduction of HF progression, whereas no such benefit was observed in the RBBB and IVCD patients [39].

The MADIT-CRT trial provided evidence that CRT very dramatically reduces the progression of HF in relatively asymptomatic or mildly symptomatic patients with a low ejection fraction and wide QRS complex. Similarly, in recently reported results of extended follow-up from the REVERSE trial [40] that studied patients with HF in NYHA class I or II with QRS ≥ 120 ms, the authors found that patients with QRSd ≥ 152 ms tended to derive more benefit from CRT (measured by composite HF status) than patients with a QRS shorter than 152 ms.

The results of the Resynchronization/Defibrillation in Advance Heart Failure Trial (RAFT) provide further evidence for the importance of wide QRS complex and LBBB morphology [41]. RAFT enrolled 1,798 NYHA class II or III HF patients with an ejection fraction ≤ 30% and an intrinsic QRS ≥ 120 ms or a paced QRS ≥ 200 ms, and randomized them to an ICD or CRT-D. The risk of primary endpoint (HF hospitalization or death) was significantly reduced, by 25% (HR 0.75; $p < 0.001$). Patients with wide QRS benefited from CRT-D therapy significantly more than patients with QRS < 150 ms and patients with LBBB benefited more from CRT-D than patients with RBBB, IVCD or paced QRS. RAFT also showed a significant decrease in mortality, which was significantly higher than in MADIT-CRT [42].

Summary

QRS duration and morphology should be considered as important prognostic information indicating more advanced cardiac pathology secondary to underlying heart disease, whether that heart disease is known about or not. Post-infarction patients with prolonged QRSd have a significantly increased risk of mortality, although data associating QRS prolongation specifically with sudden death is less supportive. In NICM, there is no evidence that QRSd carries prognostic significance for predicting mortality or sudden death. However, cohorts of patients with HF and low ejection fraction usually include about 50% of patients with NICM; in such studies, a significantly prolonged QRSd, and especially the presence of LBBB, seem to predict benefit from CRT-D therapy in both ICM and NICM patients [43]. Therefore, QRS duration and morphology should not only be considered as a predictor of death or sudden death, but also as a predictor of benefit from CRT in patients with HF, whether of ischemic or non-ischemic origin.

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