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RESEARCH ARTICLE

Prevalence and incidence of intra-ventricular conduction delays and outcomes in patients with heart failure and reduced ejection fraction: insights from PARADIGM-HF and ATMOSPHERE

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Aims The importance of intra-ventricular conduction delay (IVCD), the incidence of new IVCD and its relationship to outcomes in heart failure and reduced ejection fraction (HFrEF) are not well studied. We addressed these questions in the PARADIGM-HF and ATMOSPHERE trials.

Methods and results The risk of the primary composite outcome of cardiovascular death or heart failure hospitalization and all-cause mortality were estimated by use of Cox regression according to baseline QRS duration and morphology in 11 861 patients without an intracardiac device. At baseline, 1789 (15.1%) patients had left bundle branch block (LBBB), 524 (4.4%) right bundle branch block (RBBB), 454 (3.8%) non-specific IVCD, 2588 (21.8%) 'mildly abnormal' QRS (110–129 ms) and 6506 (54.9%) QRS <110 ms. During a median follow-up of 2.5 years, the risk of the primary composite endpoint was higher among those with a wide QRS, irrespective of morphology: hazard ratios (95% confidence interval) LBBB 1.36 (1.23–1.50), RBBB 1.54 (1.31–1.79), non-specific IVCD 1.65 (1.40–1.94) and QRS 110–129 ms 1.35 (1.23–1.47), compared with QRS duration <110 ms. A total of 1234 (15.6%) patients developed new-onset QRS widening ≥130 ms (6.1 per 100 patient-years). Incident LBBB occurred in 495 (6.3%) patients (2.4 per 100 patient-years) and was associated with a higher risk of the primary composite outcome [hazard ratio 1.42 (1.12–1.82)].

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Conclusion In patients with HFrEF, a wide QRS was associated with worse clinical outcomes irrespective of morphology. The annual incidence of new-onset LBBB was around 2.5%, and associated with a higher risk of adverse outcomes, highlighting the importance of repeat electrocardiogram review.
Trial Registration: ClinicalTrials.gov Identifier NCT0083658 (ATMOSPHERE) and NCT01035255 (PARADIGM-HF).

Keywords Heart failure • Left bundle branch block • Prognosis • Cardiac resynchronization therapy • Electrocardiography

Introduction

Intra-ventricular conduction delay (IVCD), particularly with a left bundle branch block (LBBB) morphology, results in a dyssynchronous electrical activation sequence of the heart.[1] LBBB is known to be associated with worse outcomes in patients with heart failure (HF) and reduced ejection fraction (HFrEF), and cardiac resynchronization therapy (CRT) reduces the risk of worsening heart failure and improves survival in such patients with a QRS duration ≥130 ms.[2–7] Less is known about the prevalence and prognostic significance of right bundle branch block (RBBB) and non-specific IVCD (nsIVCD) in HFrEF. More importantly, very little is known about the incidence and clinical consequences of new-onset QRS widening in patients with HFrEF.[8,9] This information is important as a new diagnosis of IVCD may be of prognostic importance and may identify an indication for CRT.

In the present study we examined the prognostic importance of prevalent and incident QRS widening to a duration of ≥130 ms using data from two HFrEF trials which included a broad spectrum of ambulatory patients receiving contemporary therapy. The trials had nearly identical enrolment criteria.

Methods

The design, baseline characteristics and primary results of the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) and the Aliskiren Trial to Minimize OutcomeS in Patients with HEart FailuRE trial (ATMOSPHERE) are published.[10–14] Both trials were approved by the ethics committee at each study centre. All patients provided written informed consent.

Study patients

For the present study we included patients without a device (pacemaker, CRT or implantable cardioverter-defibrillator) and a baseline QRS duration between 60 and 240 ms (*Figure 1*). For analyses of incident IVCD, we excluded all patients with QRS ≥130 ms at baseline and identified those who developed QRS widening (QRS ≥130 ms) at annual follow-up electrocardiograms (ECGs) and subsequently grouped these patients according to QRS morphology: LBBB, RBBB or nsIVCD with the hierarchy of LBBB > RBBB > nsIVCD if several different morphologies were reported.

The inclusion criteria for PARADIGM-HF and ATMOSPHERE were similar and included: New York Heart Association (NYHA) functional class II–IV status, left ventricular ejection fraction (LVEF) ≤35% (initially ≤40% for PARADIGM-HF but changed to ≤35% by amendment), and a plasma B-type natriuretic peptide (BNP) ≥150 pg/mL or N-terminal proBNP (NT-proBNP) ≥600 pg/mL. In both trials, patients who had been hospitalized for HF within the preceding 12 months could be enrolled with a lower natriuretic peptide concentration (BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL). Plasma NT-proBNP was measured in a core laboratory with the Roche Elecsys proBNP assay (Roche Diagnostics GmbH, Mannheim, Germany), with a coefficient of variation <2.5% at all levels tested.

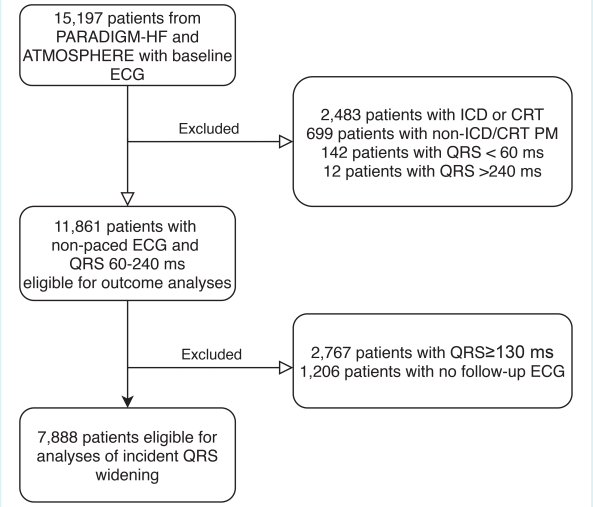

Figure 1 Flowchart of the study population. CRT, cardiac resynchronization therapy; ECG, electrocardiogram; ICD, implantable cardioverter-defibrillator; PM, pacemaker.

Patients were required to be taking an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) at a dose equivalent to enalapril 10 mg daily for at least 4 weeks before screening, along with a stable dose of a beta-blocker (unless contraindicated or not tolerated) and a mineralocorticoid receptor antagonist, if indicated. The exclusion criteria included history of intolerance of an ACE inhibitor or ARB, symptomatic hypotension (or a systolic blood pressure <100 mmHg at screening/<95 mmHg at randomization), an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (<40 mL/min/1.73 m^2 for ATMOSPHERE), a serum potassium concentration >5.2 mmol/L at screening (>5.4 mmol/L at randomization) (<5.0 mmol/L and <5.2 mmol/L, respectively in ATMOSPHERE) or a history of angioedema.

Study procedures

In both PARADIGM-HF and ATMOSPHERE, patients first received enalapril (5 or) 10 mg twice daily (single-blind)[15] and then

sacubitril/valsartan (single-blind) for an additional 4 to 6 weeks in PARADIGM-HF and aliskiren plus enalapril in ATMOSPHERE. In PARADIGM-HF, patients tolerating both drugs at target doses were randomly assigned to enalapril 10 mg twice daily or sacubitril/valsartan 200 mg twice daily, and in ATMOSPHERE, patients who tolerated both drugs were randomized in a 1:1:1 ratio to receive: (i) combination of 5 or 10 mg enalapril twice daily and aliskiren 150 mg once daily (combination group); (ii) aliskiren 150 mg once daily; (iii) enalapril 5 or 10 mg twice daily.

Categorization of patients according to baseline electrocardiographic findings

The case report form in each study asked investigators to report QRS duration (in ms) and there was an additional question about QRS morphology (specifically whether there was RBBB or LBBB). The information collected was used to categorize patients by baseline QRS duration: QRS <110 ms (normal), QRS 110–129 ms (mildly abnormal) and ≥130 ms (prolonged). Individuals with QRS ≥130 ms were additionally categorized by QRS morphology (i.e. LBBB, RBBB, nsIVCD subcategories). This resulted in the following five groups overall: (1) normal QRS duration: <110 ms (irrespective of reported QRS morphology), (2) mildly abnormal IVCD: QRS duration 110–129 ms (irrespective of reported QRS morphology), (3) LBBB: QRS ≥130 ms + LBBB morphology, (4) RBBB: QRS ≥130 ms + RBBB morphology, and (5) nsIVCD: QRS ≥130 ms without either LBBB or RBBB reported.

Outcomes

In the present manuscript we focused on the primary endpoint of both trials which was the first occurrence of cardiovascular death or HF hospitalization, as well as each of the components separately. We also report death from any cause, which was a secondary endpoint in PARADIGM-HF and a pre-specified exploratory outcome in ATMOSPHERE, as well as the two major modes of cardiovascular death, i.e. death due to worsening HF ('pump failure') and sudden cardiac death. All suspected HF hospitalizations and deaths in each trial were adjudicated by the same endpoint committee.

Statistical analysis

Baseline characteristics are presented as means with standard deviations for continuous variables and frequencies and percentages for categorical variables. Event rates are reported per 100 patient-years of follow-up according to QRS duration and for those with QRS duration ≥130 ms additionally according to QRS morphology. Cox proportional hazard models were applied to calculate hazard ratios (HR) and cumulative event curves according to QRS morphology with patients with QRS duration <110 ms as reference. The adjusted Cox regression models included information on age, sex, race (Caucasian vs. all other), geographical region, study drug, NYHA class, LVEF, heart rate, systolic blood pressure, body mass index, eGFR, HF duration, ischaemic aetiology, history of recent HF hospitalization and history of myocardial infarction, history of diabetes, history of stroke and NT-proBNP. Log [−log(survival)] curves were used to evaluate the proportional hazards assumption. The assumption of linearity of continuous variables (age) was tested by including a variable of age squared. These were found to be valid unless otherwise specified. QRS duration at baseline as a continuous variable adjusted for other prognostic variables, is shown modelled as a restricted cubic spline (QRS duration 100 ms is the reference value). Predictors of new-onset QRS widening were analysed in a logistic regression model with similar adjustments as the Cox regression model. All *P*-values are two-sided, and a *P*-value of <0.05 was considered significant. Analyses were performed using Stata version 14 (Stata Corp., College Station, TX, USA).

Results

Of the overall 11 861 patients in the analysis, 6506 participants (55%) had a normal QRS duration (<110 ms) and 2588 (22%) had a mildly abnormal QRS (110–129 ms). The remaining 2767 patients (23%) had an abnormally wide QRS (≥130 ms). Among these individuals, 1789 (15% overall/65% of participants with QRS ≥130 ms) had LBBB, 524 (4%/19%) RBBB, and 454 (4%/16%) nsIVCD. The median (Q1, Q3) follow-up was 30 (20, 41) months (for all-cause death).

Baseline characteristics

Patients with wide QRS (≥130 ms) were, in general, older (65.2 vs. 63.0 and 62.2 years for QRS 110–129 ms and QRS <110 ms, respectively), had a slightly lower systolic blood pressure (122 vs. 123 and 124 mmHg), worse kidney function (median eGFR 69 vs. 71 and 72 mL/min/1.73 m^2), and longer duration of HF (>5 years in 32% vs. 29% and 21%) irrespective of morphology (*Table 1*).

Patients with LBBB were more likely to be women (30%) compared to RBBB (13%) or nsIVCD (20%) and older (65.5 vs. 65.4 vs. 63.9 years). Patients with LBBB were less likely to have an ischaemic aetiology (49% vs. 64% vs. 63%). NT-proBNP was highest, and LVEF lowest, in patients with the widest QRS or LBBB. Conversely, atrial fibrillation was less common in patients with the widest QRS or LBBB.

Outcomes according to baseline QRS duration and morphology

During a median follow-up of 2.7 years, the primary composite outcome of HF hospitalization or cardiovascular death occurred in 1543 patients (24%) with QRS <110 ms (reference), as compared to 826 patients (32%) with mildly abnormal QRS (110–129 ms), 937 patients (34%) with any QRS ≥130 ms, 168 patients (37%) with nsIVCD, 187 patients (35%) with RBBB, and 582 patients (33%) with LBBB (*Table 2*, *Figure 2*). In adjusted Cox regression analyses, this corresponded to significantly increased risk for those with QRS 110–129 ms [HR 1.35, 95% confidence interval (CI) 1.23–1.47], any QRS ≥130 ms (HR 1.44, 95% CI 1.32–1.57), nsIVCD (HR 1.65, 95% CI 1.40–1.94), RBBB (HR 1.54, 95% CI 1.31–1.79) and LBBB (HR 1.36, 95% CI 1.23–1.50).

All-cause mortality occurred in 19% of patients with QRS <110 ms as compared to 26% of those with QRS 110–129 ms, 27% of patients with any QRS ≥130 ms, 28% of patients with nsIVCD and 27% of patients with RBBB and 26% with LBBB. The risks in patients with a wider QRS remained significantly higher in adjusted analyses, using QRS <110 ms as the reference group (*Table 2*).

Table 1 Baseline characteristics according to QRS duration and morphology (in those with QRS ≥130 ms)

	According to QRS duration				According to morphology in patients with QRS ≥130 ms			
	<110 ms	110–129 ms	≥130 ms	*P*-value	nsIVCD	RBBB	LBBB	*P*-value
No. of patients	6506 (54.9)	2588 (21.8)	2767 (23.3)		454 (3.8)	524 (4.4)	1789 (15.1)	
Age (years)	62.2 (12.0)	63.0 (11.5)	65.2 (11.3)	<0.001	63.9 (12.4)	65.4 (11.3)	65.5 (11.0)	0.026
Female sex	1649 (25%)	446 (17%)	697 (25%)	<0.001	89 (20%)	69 (13%)	539 (30%)	<0.001
QRS duration (ms)	91 (11)	118 (5)	157 (19)	<0.001	147 (18)	153 (17)	160 (19)	<0.001
Region				<0.001				<0.001
North America	161 (3%)	61 (2%)	87 (3%)		16 (4%)	18 (3%)	53 (3%)	
Latin America	1104 (17%)	484 (19%)	595 (22%)		73 (16%)	112 (21%)	410 (23%)	
Western Europe	1060 (16%)	527 (20%)	670 (24%)		104 (23%)	116 (22%)	450 (25%)	
Central Europe	2325 (36%)	879 (34%)	831 (30%)		134 (30%)	148 (28%)	549 (31%)	
Asia-Pacific	1856 (28%)	637 (25%)	584 (21%)		127 (28%)	130 (25%)	327 (18%)	
Systolic BP (mmHg)	124 (17)	123 (17)	122 (17)	0.028	122 (16)	122 (17)	123 (17)	0.45
Heart rate (bpm)	74 (13)	72 (12)	71 (12)	<0.001	71 (12)	71 (12)	71 (11)	0.66
BMI (kg/m^2)	28 (6)	28 (5)	27 (5)	0.065	27 (5)	28 (5)	27 (5)	0.66
eGFR (mL/min/1.73 m^2)	72 (59, 86)	71 (59, 84)	69 (56, 82)	<0.001	70 (57, 84)	67 (56, 81)	69 (56, 82)	0.23
Chronic kidney disease[a]	1700 (26%)	690 (27%)	856 (31%)	<0.001	130 (29%)	165 (32%)	561 (31%)	0.51
Ischaemic HF aetiology	3750 (58%)	1487 (58%)	1503 (54%)	0.0097	286 (63%)	335 (64%)	882 (49%)	<0.001
Time since diagnosis of HF				<0.001				0.65
<1 year	2664 (41%)	856 (33%)	834 (30%)		145 (32%)	162 (31%)	527 (30%)	
1–5 years	2476 (38%)	974 (38%)	1055 (38%)		161 (36%)	204 (39%)	690 (39%)	
>5 years	1363 (21%)	757 (29%)	878 (32%)		148 (33%)	158 (30%)	572 (32%)	
LV ejection fraction (%)	30 (6)	29 (6)	28 (6)	<0.001	29 (6)	30 (6)	28 (6)	<0.001
NT-proBNP (pg/mL)	1310 (720, 2509)	1455 (787, 2919)	1571 (821, 3099)	<0.001	1361 (710, 2847)	1560 (813, 3077)	1641 (849, 3199)	0.014
KCCQ CSS (Q1, Q3)	79 (61, 92)	79 (63, 92)	81 (64, 92)	0.033	82 (66, 92)	81 (64, 93)	80 (64, 92)	0.72
NYHA class				0.0012				0.73
I	282 (4%)	108 (4%)	86 (3%)		17 (4%)	20 (4%)	49 (3%)	
II	4458 (69%)	1755 (68%)	1974 (71%)		320 (71%)	377 (72%)	1277 (71%)	
III	1723 (27%)	689 (27%)	678 (25%)		110 (24%)	121 (23%)	447 (25%)	
IV	42 (1%)	32 (1%)	27 (1%)		6 (1%)	5 (1%)	16 (1%)	
Hypertension	4470 (69%)	1783 (69%)	1762 (64%)	<0.001	283 (62%)	327 (62%)	1152 (64%)	0.57
Diabetes	2050 (32%)	787 (30%)	827 (30%)	0.25	135 (30%)	184 (35%)	508 (28%)	0.012
Atrial fibrillation (history)	2425 (37%)	826 (32%)	814 (29%)	<0.001	148 (33%)	190 (36%)	476 (26%)	<0.001
Atrial fibrillation (ECG)	2004 (31%)	609 (24%)	524 (19%)	<0.001	95 (21%)	135 (26%	294 (16%)	<0.001
Prior HF hospitalization	3174 (49%)	1268 (49%)	1270 (46%)	0.025	201 (44%)	248 (47%)	821 (46%)	0.63
Prior myocardial infarction	2500 (38%)	1085 (42%)	1081 (39%)	0.0082	225 (50%)	257 (49%)	599 (34%)	<0.001
Prior stroke	477 (7%)	216 (8%)	199 (7%)	0.19	31 (7%)	47 (9%)	121 (7%)	0.22
Beta-blockers	6013 (92%)	2381 (92%)	2498 (90%)	0.0024	407 (90%)	471 (90%)	1620 (91%)	0.80
MRAs	2968 (46%)	1217 (47%)	1284 (46%)	0.45	210 (46%)	235 (45%)	839 (47%)	0.71
Diuretics	5068 (78%)	2092 (81%)	2244 (81%)	0.002	369 (81%)	435 (83%)	1440 (81%)	0.43
Digoxin	2116 (33%)	772 (30%)	866 (31%)	0.040	137 (30%)	163 (31%)	566 (32%)	0.83
Amiodarone	363 (6%)	235 (9%)	236 (9%)	<0.001	42 (9%)	42 (8%)	152 (9%)	0.79

BMI, body mass index; BP, blood pressure; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HF, heart failure; KCCQ CSS, Kansas City Cardiomyopathy Questionnaire clinical summary score; LBBB, left bundle branch block; LV, left ventricular; MRA, mineralocorticoid receptor antagonist; nsIVCD, non-specific intra-ventricular conduction delay; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; RBBB, right bundle branch block.
[a]Chronic kidney disease = eGFR<60 mL/min/1.73m^2.

When the two principal modes of death were examined, wide QRS was associated with a higher risk of both pump failure death and sudden cardiac death. The increase in risk was numerically larger for pump failure death than for sudden death. The relation between QRS duration as a continuous variable and outcomes irrespective of morphology is illustrated in restricted cubic splines (online supplementary *Figure S1*).

Incidence and predictors of QRS widening and subsequent outcomes

Among 7888 patients without any type of intracardiac device, an ECG with QRS duration <130 ms at baseline, and at least one ECG performed during follow-up, 1234 (16%) developed QRS widening to ≥130 ms detected during follow-up visits (online supplementary

Table 2 Risk of adverse outcomes according to baseline electrocardiogram

	No. events/ patients	Crude rate per 100 py	Unadjusted HR (95% CI)	*P*-value	Adjusted[a] HR (95% CI)	*P*-value
Primary composite outcome						
Normal QRS duration (<110 ms)	1543/6506	9.6	1.00 (ref.)		1.00 (ref.)	
QRS 110–129 ms	826/2588	13.6	1.42 (1.30–1.54)	<0.001	1.35 (1.23–1.47)	<0.001
QRS ≥130 ms	937/2767	14.7	1.53 (1.41–1.66)	<0.001	1.44 (1.32–1.57)	<0.001
QRS ≥130 ms + nsIVCD	168/454	16.9	1.75 (1.49–2.05)	<0.001	1.65 (1.40–1.94)	<0.001
QRS ≥130 ms + RBBB	187/524	16.0	1.66 (1.42–1.93)	<0.001	1.54 (1.31–1.79)	<0.001
QRS ≥130 ms + LBBB	582/1789	13.9	1.44 (1.31–1.59)	<0.001	1.36 (1.23–1.50)	<0.001
HF hospitalization						
Normal QRS duration (<110 ms)	786/6506	4.9	1.00 (ref.)	<0.001	1.00 (ref.)	<0.001
QRS 110–129 ms	441/2588	7.3	1.48 (1.32–1.66)	<0.001	1.40 (1.24–1.58)	<0.001
QRS ≥130 ms	520/2767	8.2	1.66 (1.48–1.85)	<0.001	1.56 (1.39–1.75)	<0.001
QRS ≥130 ms + nsIVCD	91/454	9.1	1.84 (1.48–2.29)	<0.001	1.74 (1.39–2.17)	<0.001
QRS ≥130 ms + RBBB	111/524	9.5	1.92 (1.57–2.34)	<0.001	1.73 (1.41–2.13)	<0.001
QRS ≥130 ms + LBBB	318/1789	7.6	1.54 (1.35–1.76)	<0.001	1.46 (1.27–1.67)	<0.001
Cardiovascular death						
Normal QRS duration (<110 ms)	1028/6506	6.0	1.00 (ref.)		1.00 (ref.)	
QRS 110–129 ms	574/2588	8.7	1.45 (1.31–1.61)	<0.001	1.39 (1.25–1.54)	<0.001
QRS ≥130 ms	638/2767	9.0	1.51 (1.36–1.66)	<0.001	1.39 (1.26–1.55)	<0.001
QRS ≥130 ms + nsIVCD	106/454	9.4	1.56 (1.28–1.91)	<0.001	1.46 (1.19–1.79)	<0.001
QRS ≥130 ms + RBBB	126/524	9.7	1.62 (1.35–1.95)	<0.001	1.48 (1.23–1.79)	<0.001
QRS ≥130 ms + LBBB	406/1789	8.8	1.46 (1.30–1.64)	<0.001	1.35 (1.19–1.52)	<0.001
All-cause mortality						
Normal QRS duration (<110 ms)	1234/6506	7.2	1.00 (ref.)		1.00 (ref.)	
QRS 110–129 ms	667/2588	10.1	1.41 (1.28–1.55)	<0.001	1.35 (1.22–1.48)	<0.001
QRS ≥130 ms	740/2767	10.5	1.46 (1.33–1.59)	<0.001	1.33 (1.21–1.46)	<0.001
QRS ≥130 ms + nsIVCD	126/454	11.1	1.55 (1.29–1.86)	<0.001	1.45 (1.20–1.76)	<0.001
QRS ≥130 ms + RBBB	143/524	11.0	1.53 (1.29–1.82)	<0.001	1.37 (1.15–1.64)	<0.001
QRS ≥130 ms + LBBB	471/1789	10.2	1.41 (1.27–1.57)	<0.001	1.28 (1.15–1.44)	<0.001
Pump failure death						
Normal QRS duration (<110 ms)	192/6506	1.1	1.00 (ref.)		1.00 (ref.)	
QRS 110–129 ms	132/2588	2.0	1.79 (1.44–2.24)	<0.001	1.70 (1.36–2.14)	<0.001
QRS ≥130 ms	155/2767	2.2	1.96 (1.59–2.43)	<0.001	1.63 (1.30–2.03)	<0.001
QRS ≥130 ms + nsIVCD	25/454	2.2	1.98 (1.31–3.01)	0.001	1.73 (1.12–2.66)	0.013
QRS ≥130 ms + RBBB	38/524	2.9	2.63 (1.85–3.72)	<0.001	2.18 (1.53–3.13)	<0.001
QRS ≥130 ms + LBBB	92/1789	2.0	1.77 (1.38–2.27)	<0.001	1.44 (1.11–1.87)	0.006
Sudden cardiac death						
Normal QRS duration (<110 ms)	488/6506	2.8	1.00 (ref.)		1.00 (ref.)	
QRS 110–129 ms	260/2588	3.9	1.38 (1.19–1.61)	<0.001	1.33 (1.14–1.55)	<0.001
QRS ≥130 ms	281/2767	4.0	1.39 (1.20–1.62)	<0.001	1.37 (1.17–1.59)	<0.001
QRS ≥130 ms + nsIVCD	42/454	3.7	1.30 (0.95–1.78)	0.102	1.24 (0.90–1.71)	0.191
QRS ≥130 ms + RBBB	46/524	3.5	1.24 (0.91–1.67)	0.167	1.15 (0.84–1.57)	0.371
QRS ≥130 ms + LBBB	193/1789	4.2	1.46 (1.24–1.73)	<0.001	1.47 (1.23–1.76)	<0.001

CI, confidence interval; HF, heart failure; HR, hazard ratio; LBBB, left bundle branch block; nsIVCD, non-specific intra-ventricular conduction delay; py, patient-years; RBBB, right bundle branch block.

[a]Adjusted Cox regression models included information on age, sex, race (Caucasian vs. all other), geographical region, study drug, New York Heart Association class, left ventricular ejection fraction, heart rate, systolic blood pressure, body mass index, estimated glomerular filtration rate, HF duration, ischaemic aetiology, history of recent HF hospitalization, history of myocardial infarction, history of diabetes, history of stroke and N-terminal pro B-type natriuretic peptide.

Table S1), and 495 (6.3% overall, 40% of patients developing QRS widening to ≥130 ms) had LBBB morphology (*Table 3*, *Figure 3*). These numbers corresponded to event rates of 6.1 and 2.4 per 100 patient-years, respectively. In a multivariable analysis, the following were independently significant predictors of incident QRS widening to ≥130 ms: QRS 110–129 ms vs. <110 ms [odds ratio (OR) 4.55 (3.98–5.19)], age per 5-year increase [OR 1.06 (1.03–1.10)], HF duration 1–5 years vs. <1 year [OR 1.23 (1.05–1.44)], >5 years vs. <1 year [OR 1.29 (1.08–1.54)], LVEF per 1% decrease [OR 1.03 (1.02–1.05)], heart rate (per 5 bpm decrease) [OR 1.06 (1.02–1.09)], and prior stroke [OR 0.77 (0.59–1.00)] (*Table 4*).

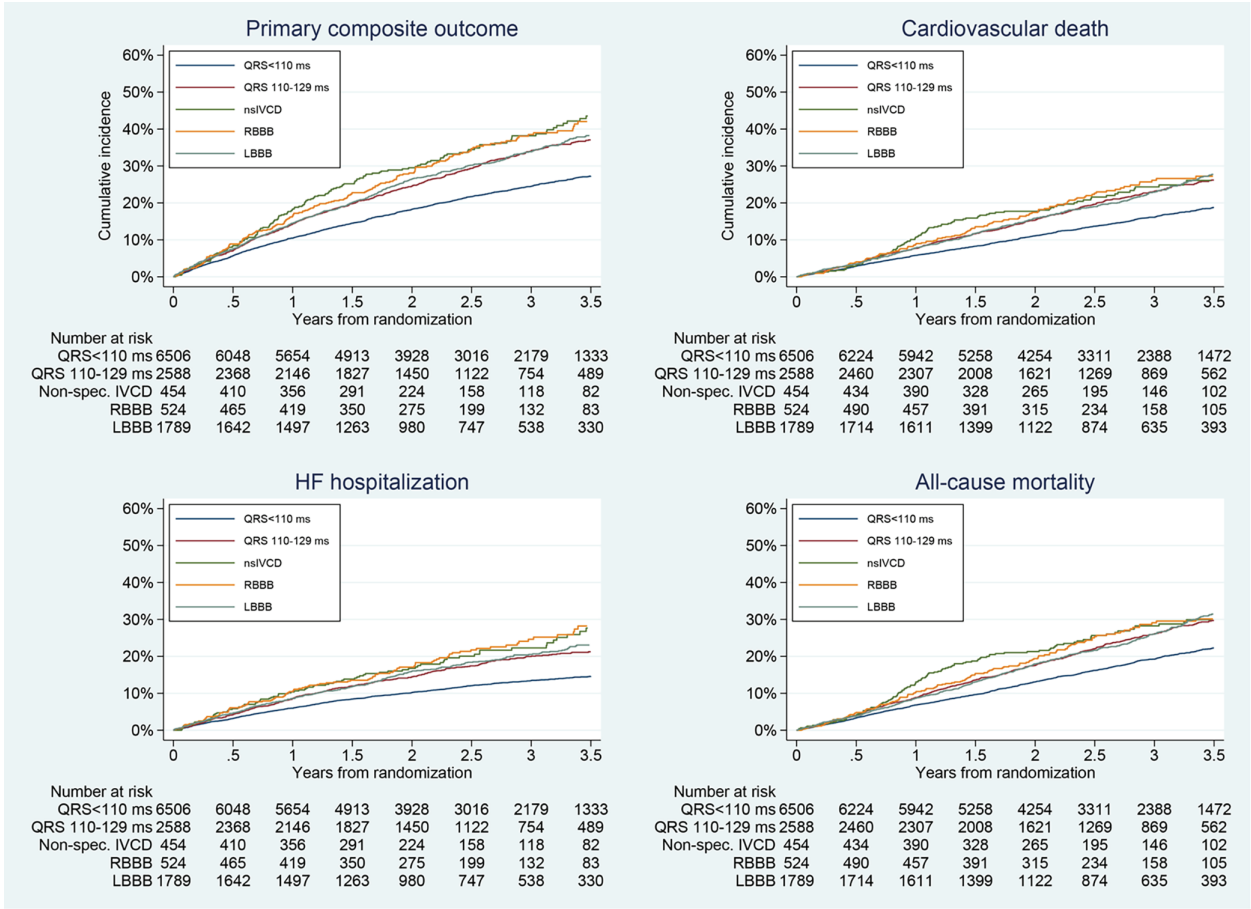

Figure 2 Cumulative incidence of study outcomes according to baseline QRS duration and morphology. HF, heart failure; IVCD, intra-ventricular conduction delay; LBBB, left bundle branch block; RBBB, right bundle branch block.

Patients with incident QRS ≥130 ms had subsequently higher event rates of the primary composite outcome (13.9 vs. 7.4 per 100 patient-years) and all-cause mortality (13.0 vs. 4.4 per 100 patient-years), respectively. In adjusted Cox regression analyses this yielded HRs of 1.49 (95% CI 1.25–1.76) for the primary outcome and 1.69 (95% CI 1.43–2.00) for all-cause mortality. A similar pattern was seen when restricting the comparison to new-onset LBBB vs. no LBBB (*Table 5*). Modes of death (i.e. pump failure or sudden cardiac death) were not examined because of the small numbers of events.

Discussion

There are three principal findings in this study. First is the clear demonstration that each of RBBB and nsIVCD, which together accounted for about a third of patients with QRS duration ≥130 ms, were predictive of a higher risk of both cardiovascular death or HF hospitalization and all-cause mortality, and remained so after adjustment for other predictors of worse outcomes, including natriuretic peptides. Second, in the present study, even patients with a 'mildly abnormal' QRS (110–129 ms) had a substantially elevated risk, an important finding given that there were almost as many individuals in this category (22% of overall participants) as there were individuals with QRS duration ≥130 ms (23% of participants). Third, and perhaps the most novel finding of the present study, our quantification of the incidence of new QRS widening, along with the predictors and consequences of developing new QRS widening. New QRS widening was associated with a much higher subsequent rate of fatal and non-fatal outcomes. The strongest predictor of new-onset QRS widening was a QRS duration of 110–129 ms and, in these patients, incident LBBB occurred at a rate of approximately 6% per year.

The finding of similarly high risk in patients with modest increases in QRS duration, and in patients with RBBB and nsIVCD as well as LBBB, stands in stark contrast to the evidence that CRT is most clearly beneficial in HFrEF patients with a QRS duration ≥130 ms and a LBBB configuration and may even be harmful in individuals with a QRS duration <130 ms.[16–25] However, a prior study in a large Danish cohort has also shown that even a QRS >100 ms may represent a threshold duration for a step change in risk in patients with HF.[26] Possibly relevant here is the more frequent finding of an ischaemic aetiology and prior myocardial infarction among

Table 3 Risk of developing intraventricular conduction disorder according to QRS duration at baseline

	No. events/ patients	Event rate per 100 py	Unadjusted OR (95% CI)	*P*-value	Adjusted[a] OR (95% CI)	*P*-value
Any QRS ≥130 ms	**1234/7888**	**6.1**				
Baseline QRS <110 ms	511/5691	3.4	1.00 (ref.)		1.00 (ref.)	
Baseline QRS 110–129 ms	723/2197	14.1	4.97 (4.38–5.65)	<0.001	4.59 (4.01–5.24)	<0.001
QRS ≥130 ms nsIVCD	**549/7888**	**2.7**				
Baseline QRS <110 ms	264/5691	1.8	1.00 (ref.)		1.00 (ref.)	
Baseline QRS 110–129 ms	285/2197	5.5	3.06 (2.57–3.65)	<0.001	2.87 (2.39–3.45)	<0.001
QRS ≥130 ms RBBB	**190/7888**	**0.9**				
Baseline QRS <110 ms	75/5691	0.5	1.00 (ref.)		1.00 (ref.)	
Baseline QRS 110–129 ms	115/2197	2.1	4.14 (3.08–5.56)	<0.001	3.67 (2.68–5.01)	<0.001
QRS ≥130 ms LBBB	**495/7888**	**2.4**				
Baseline QRS <110 ms	172/5691	1.1	1.00 (ref.)		1.00 (ref.)	
Baseline QRS 110–129 ms	323/2197	5.9	5.53 (4.56–6.70)	<0.001	5.15 (4.21–6.29)	<0.001

CI, confidence interval; LBBB, left bundle branch block; nsIVCD, non-specific intra-ventricular conduction delay; OR, odds ratio; py, patient-years; RBBB, right bundle branch block.

[a]Adjusted logistic regression models included information on age, sex, race (Caucasian vs. all other), geographical region, study drug, New York Heart Association class, left ventricular ejection fraction, N-terminal pro B-type natriuretic peptide, heart rate, systolic blood pressure, body mass index, estimated glomerular filtration rate, heart failure duration, ischaemic aetiology, history of recent heart failure hospitalization, history of myocardial infarction, history of diabetes and history of stroke.

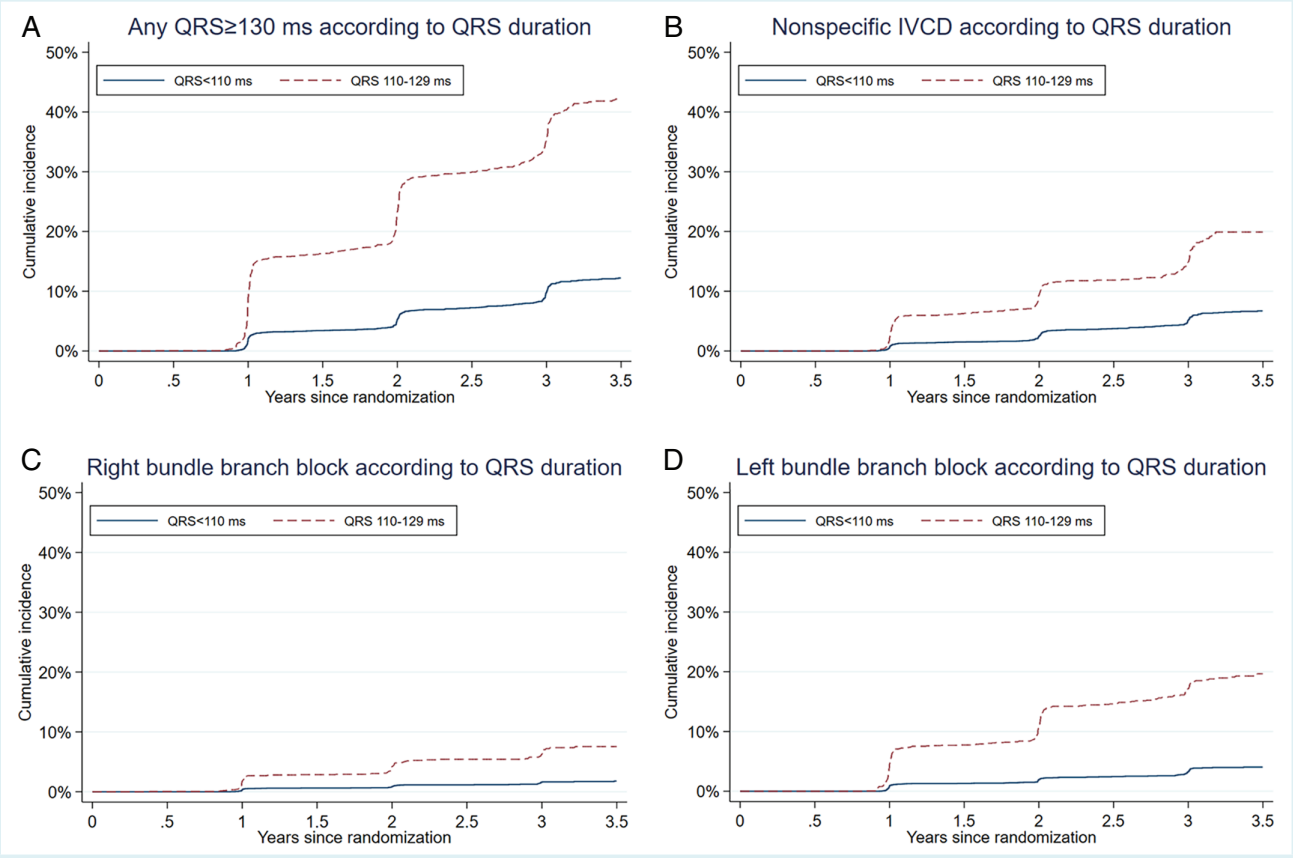

Figure 3 Cumulative incidence of any QRS ≥130 ms (*A*), incident non-specific intra-ventricular conduction delay (nsIVCD) (*B*), incident right bundle branch block (*C*), and incident left bundle branch block (*D*).

Table 4 Predictors of incident QRS widening >130 ms during follow-up (irrespective of morphology)

	Univariate model OR (95% CI)	*P*-value	Multivariable model OR (95% CI)	*P*-value
QRS 110–129 ms vs. <110 ms	4.97 (4.38–5.65)	<0.001	4.55 (3.98–5.19)	<0.001
Age per 5-year increase	1.05 (1.02–1.08)	<0.001	1.06 (1.03–1.10)	0.001
Men vs. women	1.32 (1.13–1.53)	<0.001	1.13 (0.95–1.34	0.155
HF duration				
1–5 years vs. <1 year	1.61 (1.37–1.88)	<0.001	1.23 (1.05–1.44)	0.009
>5 years vs. < 1 year	1.28 (1.11–1.48)	0.001	1.29 (1.08–1.54)	0.004
NYHA class III/IV vs. I/II	1.14 (0.99–1.31)	0.067	1.14 (0.98–1.34)	0.091
LVEF per 1% decrease	1.03 (1.02–1.05)	<0.001	1.03 (1.02–1.05)	<0.001
Pulse per 5 bpm decrease	1.09 (1.06–1.12)	<0.001	1.06 (1.02–1.09)	<0.001
SBP per 5 mmHg decrease	0.99 (0.98–1.01)	0.524	0.99 (0.97–1.01)	0.277
BMI per 1-unit increase	1.00 (0.99–1.01)	0.84	1.01 (0.99–1.02)	0.236
NT-proBNP per 100 pg/mL increase	1.00 (1.00–1.00)	0.388	1.00 (1.00–1.00)	0.586
eGFR per 5-unit increase	0.99 (0.98–1.01)	0.314	1.01 (1.00–1.03)	0.109
Atrial fibrillation	0.79 (0.69–0.90)	<0.001	0.88 (0.75–1.02)	0.093
Prior myocardial infarction	1.28 (1.13–1.44)	<0.001	1.14 (0.99–1.31)	0.077
Prior stroke	0.83 (0.65–1.06)	0.129	0.77 (0.59–1.00)	0.048
Prior HF hospitalization	0.90 (0.80–1.02)	0.101	0.93 (0.82–1.07)	0.318
Diabetes	1.06 (0.93–1.21)	0.396	1.07 (0.92–1.23)	0.377

BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; OR, odds ratio; SBP, systolic blood pressure.

patients with RBBB and nsIVCD, compared to patients with LBBB. Therefore, patients with RBBB and nsIVCD may have greater scar burden and, accordingly, less response to CRT.[27]

Whatever the doubts about the value of CRT in patients with non-LBBB morphology, it is clear these patients are at high risk and merit intervention to reduce this risk. Whether RBBB (and nsIVCD) is merely a marker of severity of heart muscle disease or whether some other, targeted, intervention, in addition to optimal pharmacological treatment, might be beneficial in these patients is unknown. His bundle pacing might be such an approach, although this needs to be tested in appropriately designed prospective clinical trials. In patients with RBBB, right ventricular septal pacing can shorten QRS duration and this pacing modality achieved electrical resynchronization and improved LVEF and HF symptoms in a study of patients with HFrEF and isolated RBBB.[28,29]

We found that 16% of patients developed new-onset QRS widening to ≥130 ms over a median follow-up of 2.5 years (6.1 per 100 patient-years). Incident LBBB occurred in 6.3% of patients (2.4 per 100 patient-years). New-onset QRS widening, irrespective of QRS morphology, was associated with a much higher subsequent rate of fatal and non-fatal outcomes. There were several independent predictors of new-onset QRS widening to ≥130 ms of which the strongest was a QRS duration of 110–129 ms, with new QRS widening occurring at more than twice the overall rate (14.1 per 100 patient-years), which was also the case for incident LBBB (5.9 per 100 patient-years) in individuals with a baseline QRS duration of 110–129 ms.

We know of only one other moderately large study reporting the incidence of LBBB in patients HFrEF. Investigators in Hull, UK, described a cohort of 1418 newly referred outpatients with HFrEF.[30] Among the 473 patients without a pacemaker or baseline LBBB who had a 12-lead ECG at 1 year, 49 were found to have new LBBB (approximately 10%). This is clearly a considerably higher rate than in our study (2.4% per year). However, there are several explanations for this. Most importantly, in the prior report from Hull, bundle branch block was defined as a QRS duration of ≥120 ms, as was conventional at the time and, secondly, the Hull patients were considerably older (mean 70.5 years vs. 62.4 years) and more were in NYHA functional class III or IV (all predictors of bundle branch block). There is also the possibility that the estimate of incidence of LBBB in the Hull study is less precise, given that it was based on 49 cases (compared with 495 in the present study). In another small Israeli single-centre study, 178 patients with HFrEF were followed up for a median of 30 months, and incident LBBB was identified in 14 patients (7.9%).[31] This is closer to our estimate of an incidence of 6.3% over a median of 30 months. Consequently, we believe that it is reasonable assumption that our report gives the most robust estimate of clinically relevant incident LBBB in ambulatory HFrEF patients with generally mild symptoms. The clinical relevance is that QRS widening to ≥130 ms with a LBBB pattern is a potential indication for CRT implantation. Clearly, the question begged by our findings is whether an annual 12-lead ECG recording should be made in patients with HFrEF who have a mildly abnormal QRS width.

These findings have several important limitations. The analyses reported were not planned prospectively. ECGs were not analysed in a core laboratory, and QRS duration and morphology were investigator-reported by means of check boxes on the case report form. Sites did not receive specific instructions on how to measure QRS duration or define RBBB/LBBB. It is likely that some patients might have been misclassified. We defined wide QRS (LBBB/RBBB/nsIVCD) as ≥130 ms. The trial inclusion and

Table 5 Outcomes after incident QRS widening (≥130 ms)

	No. events/patients	Crude rate per 100 py	Adjusted HR (95% CI)	*P*-value
Any incident QRS ≥130 ms				
Primary composite				
No incident QRS ≥130 ms	1453/7888	7.4	1.00 (ref.)	
Any incident QRS ≥130 ms	157/880	13.9	1.49 (1.25–1.76)	<0.001
All-cause mortality				
No incident QRS ≥130 ms	905/7888	4.4	1.00 (ref.)	
Any incident QRS ≥130 ms	170/988	13.0	1.69 (1.43–2.00)	<0.001
Incident nsIVCD				
Primary composite				
No incident nsIVCD	1548/7888	7.7	1.00 (ref.)	
Incident ns IVCD	62/373	13.4	1.50 (1.16–1.95)	0.002
All-cause mortality				
No incident nsIVCD	1004/7888	4.7	1.00 (ref.)	
Incident nsIVCD	71/415	13.7	1.88 (1.47–2.40)	<0.001
Incident RBBB				
Primary composite				
No incident RBBB	1585/7888	7.7	1.00 (ref)	
Incident RBBB	25/149	13.3	1.34 (0.90–1.99)	0.15
All-cause mortality				
No incident RBBB	1047/7888	4.8	1.00 (ref.)	
Incident RBBB	28/168	12.7	1.51 (1.04–2.21)	0.032
Incident LBBB				
Primary composite				
No incident LBBB	1540/7888	7.6	1.00 (ref.)	
Incident LBBB	70/358	14.7	1.42 (1.12–1.82)	0.005
All-cause mortality				
No incident LBBB	1004/7888	4.7	1.00 (ref.)	
Incident LBBB	71/405	12.4	1.42 (1.11–1.81)	0.005

CI, confidence interval; HR, hazard ratio; LBBB, left bundle branch block; nsIVCD, non-specific intra-ventricular conduction delay; py, patient-years; RBBB, right bundle branch block.

exclusion criteria limit the generalizability of our findings and the duration of follow-up was limited. ECGs were only recorded at yearly intervals and, given the association of QRS widening with a greater risk of death, it is possible that more frequent ECG recording and longer follow-up might have identified a higher incidence of LBBB and evidence of QRS widening.

In conclusion, even a 'mildly abnormal' QRS duration (110–129 ms) identifies HFrEF patients at high risk. A significant proportion will progress to QRS duration ≥130 ms with a LBBB configuration and an indication for CRT. Advanced HF therapies may be considered in patients of this type with other QRS morphologies.

Supplementary Information

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

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Conflict of interest: P.J. reports consulting and speaker's fees from Novartis and research funding from Boehringer Ingelheim. L.K., K.D. and W.T.A. have received honoraria as steering committee members of ATMOSPHERE from Novartis. M.R.Z. reports consultant fees from Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Capricor, Corvia, Eli Lilly, Giliad, Ironwood, Medtronic, Merck, Novartis, St. Jude Medical and research support from NHLBI, VA, DOD, Medtronic and Novartis. A.D., J.L.R., K.S., and S.D.S. received honoraria as steering committee members of the PARADIGM-HF trial. J.J.V.M.'s employer, University of Glasgow, has received fees for his consulting or trial committee work with Abbvie, Amgen, AstraZeneca/Medimmune, Bayer, Bristol-Myers Squibb, DalCor, GlaxoSmithKline, Merck, Novartis, Resverlogix, Sanofi-Aventis and Stealth Therapeutics. All other authors have nothing to disclose.

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