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Clinical outcomes according to QRS duration and morphology in the Eplerenone in Mild Patients: Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF)

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Aims We examined the relationship between different degrees of QRS prolongation and different QRS morphologies and clinical outcomes in patients with heart failure, reduced ejection fraction (HF-REF), and mild symptoms in the Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure trial (EMPHASIS-HF). We also evaluated the effect of eplerenone in these patients according to QRS duration/morphology.

Methods and results Patients were categorized as: QRS duration (ms) (i) <120 (n = 1375); (ii) 120–149 (n = 517); and (iii) ≥150 (n = 383), and QRS morphology (i) normal (n = 1252); (ii) left bundle branch block (BBB) (n = 608); and (iii) right BBB/intraventricular conduction defect (IVCD) (n = 415). The outcomes examined were the composite of cardiovascular death or heart failure hospitalization and all-cause mortality. Both abnormal QRS duration and QRS morphology were associated with higher risk, e.g. the rates of the composite outcome were: 10.2, 17.6, and 15.5 per 100 patient-years in the <120, 120–149, and ≥150 ms groups, respectively. Eplerenone reduced the risk of the primary outcome and mortality, compared with placebo, consistently across the QRS duration/morphology subgroups.

Conclusion We found that even moderate prolongation of QRS duration and right BBB/IVCD were associated with a high risk of adverse outcomes in HF-REF. Eplerenone was similarly effective, irrespective of QRS duration/morphology.

Keywords Systolic heart failure • Clinical trial • Eplerenone

Introduction

The advent of CRT brought into focus the importance of QRS prolongation on the surface 12-lead ECG and bundle branch block (BBB) as markers of poor outcome in heart failure with reduced ejection fraction (HF-REF).[1–7] Following a series of seminal clinical trials, there is consensus that the benefits of CRT are substantial in patients with an LVEF ≤35%, a QRS duration of ≥150 ms, and LBBB QRS morphology.[1–10] The benefits in patients with a QRS duration between 120 and 150 ms are less certain, especially in patients with milder symptoms, and there is even the suggestion that CRT might cause harm in patients without a LBBB QRS pattern.[8–15] Clearly, therefore, it is important to demonstrate that pharmacological therapy is effective in these high-risk subgroups

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who might not benefit from CRT. We have, therefore, examined the effect of mineralocorticoid receptor antagonist (MRA) therapy according to QRS duration and morphology in the Eplerenone in Mild Patients Hospitalization and SurvIval Study in Heart Failure trial (EMPHASIS-HF).[16,17]

Methods

The design and results of EMPHASIS-HF have been published.[16,17] EMPHASIS-HF was a multinational, randomized, double-blind trial designed to evaluate the effect of eplerenone on mortality and morbidity in patients with chronic systolic HF and mild symptoms. Overall, 2737 patients (recruited from 278 centres in ~30 countries) with NYHA class II heart failure and an LVEF of no more than 35% were randomly assigned to receive eplerenone (up to 50 mg daily) or placebo, added to optimal background treatment including an ACE inhibitor or ARB and a beta-blocker, unless contraindicated. Patients were also required to be aged at least 55 years, have a LVEF of no more than 30% (30–35% if the ECG QRS duration was >130 ms) and have a cardiovascular hospitalization within the past 6 months or, if not hospitalized, an elevated BNP. Key exclusion criteria were acute myocardial infarction, NYHA class III or IV heart failure, a serum potassium level exceeding 5.0 mmol/L, an estimated glomerular filtration rate (GFR) of <30 mL/min/1.73 m^2, or a need for a potassium-sparing diuretic. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure.

QRS duration and morphology

Investigators were asked to provide a report of the patient's ECG at the trial screening visit using a structured case report form. This form asked the investigator to record the patient's QRS width (in ms) in a free text box and QRS morphology by check box. The categories of QRS morphology listed were right or left BBB. There was also space for free text if the ECG abnormality was not listed as an option on the case report form. We used this information to divide the patients into three QRS duration categories (<120, 120–149, and ≥150 ms) and three QRS morphology categories [no BBB, LBBB, RBBB or 'intraventricular conduction defect' (IVCD)]. The latter QRS morphology category was created by adding together patients with a check box completed for RBBB and patients with a QRS duration ≥120 ms but neither LBBB nor RBBB reported on the case report form. Patients with a pacemaker (conventional or a resynchronization device) were excluded in the present analysis, as were patients with implausible QRS widths (<60 and >220 ms).

Clinical outcomes

The clinical outcomes of interest in this analysis were the primary composite outcome in EMPHASIS-HF (cardiovascular death or heart failure hospitalization) and its components, as well as death from any cause.

Statistical analyses

Event rates for each of the outcomes of interest in each of the QRS duration and morphology categories were calculated per 100 person-years of follow-up and also illustrated using Kaplan–Meier curves.

The effect of randomized treatment in each subgroup was estimated using a multivariable Cox proportional hazards model adjusting for the EMPHASIS-HF risk score.[18] Interaction parameters between randomized treatment and baseline QRS width and morphology were included to explore whether these modified the effect of eplerenone. The statistical significance of the interaction parameters was tested using likelihood ratio tests.

Results

A total of 2737 patients were randomized in EMPHASIS-HF. Of these, 401 had a pacemaker and were therefore excluded from analysis. A further 61 patients had a missing QRS duration ($n = 19$) or a QRS duration that was implausibly low ($n = 28$) or high ($n = 14$), leaving 2275 patients for analysis. Overall, QRS duration was <120 ms in 1375 patients (60.4%), 120–149 ms in 517 (22.7%), and ≥150 ms in 383 patients (16.8%) (see the Supplementary material online, *Figure S1*). Investigators identified 608 patients as having LBBB and 157 patients with RBBB. Two-thirds of patients (1510) had no BBB. There were 258 patients with a QRS duration ≥120 ms but neither LBBB nor RBBB, i.e. patients designated as having IVCD. The median (interquartile range) QRS duration was 146 (120, 162), 140 (120, 156), and 100 (89, 120) ms in the LBBB, RBBB/IVCD, and the no BBB groups, respectively. Of the 383 patients with a QRS duration ≥150 ms, 280 (73%) had LBBB whereas only 234 (45%) and 94 (6.8%) of the 517 and 1375 patients with a QRS duration of 120–149 ms and <120 ms, respectively, had LBBB morphology.

Baseline characteristics

Table 1a shows the baseline characteristics of patients according to QRS duration category and *Table 1b* according to QRS morphology category. Patients with a longer QRS duration were older, had more co-morbidity and worse heart failure status, and were more likely to be white. A non-ischaemic aetiology was associated with a wider QRS. A broadly similar picture was seen when comparing patients with BBB/IVCD with those without.

Clinical outcomes according to QRS duration and morphology

Rates of the primary composite outcome and its components (cardiovascular death and heart failure hospitalization), along with death from any cause are shown in *Table 2*. As can be seen from *Table 2* (and *Figures 1* and *2*), both prolonged QRS duration and abnormal QRS morphology were associated with a considerably higher risk of the primary composite outcome. In patients with neither abnormality, the rate of the primary outcome was ~10 per 100 patient-years of follow-up, whereas in those with an abnormal QRS width or shape the rate was ~16 per 100 patient-years of follow-up. This higher risk was seen for both of the components of the primary composite, although the increment in risk seemed to be greater for heart failure hospitalization than for cardiovascular death (*Table 2*).

Table 1 Baseline characteristics

(a) According to QRS duration	QRS duration (ms)						*P*-value
	<120 (*n* = 1375)		120–149 (*n* = 517)		150+ (*n* = 383)		
Characteristic							
Age, years	67.6	(7.3)	69.1	(7.8)	69.0	(7.8)	<0.001
Male sex, *n* (%)	1057	(76.9)	413	(79.9)	275	(71.8)	0.02
Race, *n* (%)							0.02
White	1097	(79.8)	433	(83.8)	326	(85.1)	
Black	37	(2.7)	10	(1.9)	6	(1.6)	
Asian	198	(14.4)	60	(11.6)	33	(8.6)	
Other	43	(3.1)	14	(2.7)	18	(4.7)	
Heart rate, b.p.m.	74.5	(16.4)	73.3	(15.8)	71.7	(14.1)	0.008
Blood pressure, mmHg							
Systolic	125.6	(16.7)	123.8	(17.0)	122.5	(16.7)	0.002
Diastolic	76.1	(10.1)	73.7	(9.5)	73.3	(10.4)	<0.001
Left ventricular ejection fraction, %	26.4	(4.1)	26.2	(4.9)	25.2	(5.5)	<0.001
Body mass index	27.6	(4.9)	27.4	(4.6)	27.3	(4.8)	0.54
Principal cause of heart failure, *n* (%)							<0.001
Ischaemic	996	(72.4)	364	(70.4)	222	(58.0)	
Non-ischaemic	375	(27.3)	153	(29.6)	161	(42.0)	
Unknown	4	(0.3)	0	(0.0)	0	(0.0)	
Heart failure duration, years	3.8	(5.2)	5.2	(6.1)	5.3	(6.0)	<0.001
Medical history, *n* (%)							
Hospitalization for heart failure	661	(48.1)	292	(56.5)	218	(56.9)	<0.001
Hypertension	949	(69.0)	338	(65.4)	245	(64.0)	0.10
Angina	632	(46.0)	229	(44.3)	150	(39.2)	0.06
Previous MI	711	(51.7)	283	(54.7)	164	(42.8)	0.001
PCI	273	(19.9)	109	(21.1)	77	(20.1)	0.84
CABG	195	(14.2)	114	(22.1)	62	(16.2)	<0.001
Atrial fibrillation or flutter	412	(30.0)	150	(29.0)	93	(24.3)	0.09
Left bundle branch block	94	(6.8)	234	(45.3)	280	(73.1)	<0.001
Diabetes	451	(32.8)	166	(32.1)	105	(27.4)	0.13
Stroke	126	(9.2)	60	(11.6)	31	(8.1)	0.16
ICD	97	(7.1)	50	(9.7)	57	(14.9)	<0.001
Haemoglobin, g/dL	13.9	(1.5)	13.7	(1.5)	13.9	(1.6)	0.20
Serum creatinine, mg/dL	1.11	(0.29)	1.16	(0.32)	1.15	(0.30)	0.003
Estimated GFR, mL/min/1.73 m^2	74.1	(22.8)	69.0	(20.2)	68.6	(19.9)	<0.001
Estimated GFR <60 mL/min/1.73 m^2, *n* (%)	394	(28.7)	171	(33.2)	137	(36.0)	0.01
Serum potassium, mmol/L	4.3	(0.4)	4.3	(0.4)	4.3	(0.5)	0.32
Medication at randomization visit, *n* (%)							
Diuretic	1138	(82.8)	439	(84.9)	337	(88.0)	0.04
ACE inhibitor	1145	(83.3)	416	(80.5)	302	(78.9)	0.09
ARB	230	(16.7)	108	(20.9)	83	(21.7)	0.03
ACE inhibitor or ARB	1316	(95.7)	492	(95.2)	360	(94.0)	0.37
Beta-blockers	1200	(87.3)	452	(87.4)	318	(83.0)	0.08
Digoxin	247	(18.0)	98	(19.0)	85	(22.2)	0.17
Lipid-lowering drug	825	(60.0)	320	(61.9)	234	(61.1)	0.74
Aspirin	845	(61.5)	299	(57.8)	225	(58.7)	0.29
(b) According to BBB category	**BBB category**						***P*-value**
	Normal (*n* = 1252)		**RBBB/IVCD (*n* = 415)**		**LBBB (*n* = 608)**		
Characteristic							
Age, years	67.6	(7.3)	68.8	(7.7)	69.0	(7.8)	<0.001
Male sex, *n* (%)	959	(76.6)	346	(83.4)	440	(72.4)	<0.001
Race, *n* (%)							0.04
White	995	(79.5)	345	(83.1)	516	(84.9)	
Black	30	(2.4)	10	(2.4)	13	(2.1)	

Table 1 Continued

(b) According to BBB category	BBB category						*P*-value
	Normal ($n = 1252$)		RBBB/IVCD ($n = 415$)		LBBB ($n = 608$)		
Asian	185	(14.8)	42	(10.1)	64	(10.5)	
Other	42	(3.4)	18	(4.3)	15	(2.5)	
Heart rate, b.p.m.	74.2	(16.3)	72.6	(15.0)	73.5	(15.7)	0.17
Blood pressure, mmHg							
Systolic	125.9	(16.5)	122.8	(16.2)	123.4	(17.6)	<0.001
Diastolic	76.2	(10.0)	73.4	(9.6)	73.8	(10.3)	<0.001
Left ventricular ejection fraction, %	26.4	(4.1)	26.5	(4.7)	25.4	(5.2)	<0.001
Body mass index	27.6	(5.0)	27.7	(4.5)	27.2	(4.8)	0.14
Principal cause of heart failure, *n* (%)							<0.001
Ischaemic	912	(72.8)	312	(75.2)	358	(58.9)	
Non-ischaemic	337	(26.9)	102	(24.6)	250	(41.1)	
Unknown	3	(0.2)	1	(0.2)	0	(0.0)	
Heart failure duration, years	3.8	(5.1)	5.4	(6.4)	5.0	(5.7)	<0.001
Medical history, *n* (%)							
Hospitalization for heart failure	587	(46.9)	227	(54.7)	357	(58.7)	<0.001
Hypertension	862	(68.8)	280	(67.5)	390	(64.1)	0.13
Angina	584	(46.6)	181	(43.6)	246	(40.5)	0.04
Previous MI	656	(52.4)	244	(58.8)	258	(42.4)	<0.001
PCI	252	(20.1)	98	(23.6)	109	(17.9)	0.08
CABG	180	(14.4)	104	(25.1)	87	(14.3)	<0.001
Atrial fibrillation or flutter	368	(29.4)	133	(32.0)	154	(25.3)	0.05
Diabetes	401	(32.0)	131	(31.6)	190	(31.3)	0.94
Stroke	113	(9.0)	51	(12.3)	53	(8.7)	0.11
ICD	87	(7.0)	53	(12.8)	64	(10.5)	<0.001
Haemoglobin, g/dL	13.9	(1.5)	13.8	(1.5)	13.8	(1.5)	0.36
Serum creatinine, mg/dL	1.11	(0.29)	1.17	(0.32)	1.14	(0.30)	<0.001
Estimated GFR, mL/min/1.73 m^2	74.3	(22.8)	70.1	(21.6)	68.6	(19.4)	<0.001
Estimated GFR <60 mL/min/1.73 m^2, *n* (%)	354	(28.4)	134	(32.4)	214	(35.4)	0.007
Serum potassium, mmol/L	4.3	(0.4)	4.3	(0.4)	4.3	(0.4)	0.34
Medication at randomization visit, *n* (%)							
Diuretic	1032	(82.4)	345	(83.1)	537	(88.3)	0.004
ACE inhibitor	1045	(83.5)	326	(78.6)	492	(80.9)	0.06
ARB	211	(16.9)	84	(20.2)	126	(20.7)	0.08
ACE inhibitor or ARB	1199	(95.8)	386	(93.0)	583	(95.9)	0.05
Beta-blockers	1095	(87.5)	354	(85.3)	521	(85.7)	0.40
Digoxin	225	(18.0)	82	(19.8)	123	(20.2)	0.45
Lipid-lowering drug	765	(61.1)	265	(63.9)	349	(57.4)	0.10
Aspirin	782	(62.5)	241	(58.1)	346	(56.9)	0.05

Baseline characteristics are summarised as means (standard deviations) for continuous variables and numbers (percentages) for categorical variables. A P-value of <0.05 was considered significant.

ACE, angiotensin convertingenzyme; ARB, angiotensin receptor blocker; BBB, bundle branch block; CABG, coronary artery bypass graft; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillator; IVCD, intraventricular conduction defect; LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention; RBBB, right bundle branch block.

Of note, the risk observed with a widened QRS was similar in patients with a QRS duration 120–149 ms and in those with a QRS duration ≥150 ms. Likewise, the risk associated with abnormal QRS morphology was similar in patients with LBBB and RBBB/IVCD.

Examination of the relationship between QRS width and shape and death from any cause revealed similar findings to those made for the primary composite outcome.

Clinical outcomes according to randomized treatment allocation

The effect of eplerenone compared with placebo on the outcomes of interest, according to QRS width and shape, are shown in *Table 2* and *Figures 3* and *4*. Compared with placebo, eplerenone reduced the risk of the primary endpoint and all-cause death, irrespective of QRS duration and morphology (*Table 2*, *Figure 3*). Inspection

Table 2 Endpoints according to QRS category.

	Overall ($n = 2275$)		Eplerenone ($n = 1142$)		Placebo ($n = 1133$)		Adjusted hazard ratio[a] (95% CI)		*P*-value[b]
Outcome									
(i) CV death or hospitalization for heart failure									
QRS category									
<120 ms	286	(10.2)	125	(8.5)	161	(12.0)	0.70	(0.56–0.89)	
120–149 ms	166	(17.6)	68	(13.8)	98	(21.7)	0.65	(0.47–0.88)	
≥150 ms	110	(15.5)	50	(14.0)	60	(17.1)	0.76	(0.52–1.12)	0.71
BBB category									
Normal	252	(9.8)	111	(8.2)	141	(11.4)	0.72	(0.56–0.92)	
RBBB/IVCD	117	(15.6)	48	(12.2)	69	(19.4)	0.58	(0.40–0.84)	
LBBB	193	(17.0)	84	(14.5)	109	(19.5)	0.75	(0.56–1.00)	0.46
(ii) Cardiovascular death									
QRS category									
<120 ms	175	(5.8)	81	(5.2)	94	(6.5)	0.82	(0.61–1.10)	
120–149 ms	96	(8.9)	48	(9.0)	48	(8.8)	1.00	(0.67–1.50)	
≥150 ms	61	(7.9)	24	(6.1)	37	(9.7)	0.54	(0.32–0.91)	0.25
BBB category									
Normal	150	(5.4)	71	(5.0)	79	(5.9)	0.86	(0.63–1.19)	
RBBB/IVCD	70	(8.5)	37	(8.9)	33	(8.1)	0.98	(0.61–1.57)	
LBBB	112	(8.7)	45	(7.0)	67	(10.5)	0.66	(0.45–0.96)	0.32
(iii) Hospitalization for heart failure									
QRS category									
<120 ms	181	(6.4)	70	(4.8)	111	(8.3)	0.56	(0.42–0.76)	
120–149 ms	113	(12.0)	42	(8.5)	71	(15.7)	0.55	(0.38–0.81)	
≥150 ms	76	(10.7)	40	(11.2)	36	(10.2)	1.03	(0.65–1.62)	0.06
BBB category									
Normal	159	(6.2)	62	(4.6)	97	(7.9)	0.58	(0.42–0.80)	
RBBB/IVCD	76	(10.1)	26	(6.6)	50	(14.0)	0.44	(0.27–0.71)	
LBBB	135	(11.9)	64	(11.1)	71	(12.7)	0.86	(0.62–1.21)	0.03
(iv) All-cause death									
QRS category									
<120 ms	204	(6.8)	97	(6.3)	107	(7.3)	0.86	(0.65–1.13)	
120–149 ms	108	(10.0)	51	(9.5)	57	(10.5)	0.90	(0.61–1.31)	
≥150 ms	70	(9.0)	27	(6.9)	43	(11.2)	0.52	(0.32–0.85)	0.26
BBB category									
Normal	150	(5.4)	71	(5.0)	79	(5.9)	0.90	(0.67–1.21)	
RBBB/IVCD	70	(8.5)	37	(8.9)	33	(8.1)	0.80	(0.51–1.25)	
LBBB	112	(8.7)	45	(7.0)	67	(10.5)	0.68	(0.47–0.97)	0.48

Results are presented as number of patients (rate per 100 person-years).
BBB, bundle branch block; CV, cardiovascular; IVCD, intraventricular conduction defect; LBBB, left bundle branch block; RBBB, right bundle branch block
[a]Adjusted for EMPHASIS-HF risk score, i.e. age, sex, systolic blood pressure, estimated glomerular filtration rate, diabetes, body mass index, haemoglobin, prior heart failure hospitalization, prior myocardial infarction/coronary artery bypass graft, and heart rate.
[b]*P*-value from interaction test.

of *Figure 4* shows that the relative risk reduction with eplerenone was similar in all ECG categories. Examination of the components of the primary composite raised the possibility that the effect of eplerenone on cardiovascular death might be different from the effect on heart failure hospitalization, depending on the baseline ECG findings. Inspection of *Table 2* suggests that in patients with the widest QRS duration and in those with LBBB, eplerenone had no effect on heart failure hospitalization (but possibly a greater effect on cardiovascular death) compared with the other ECG categories. The interaction *P*-values for heart failure hospitalization were statistically significant or borderline significant, i.e. 0.03 and 0.06 for BBB and QRS duration, respectively. This apparent interaction was, however, confined to QRS duration ≥150 ms and LBBB, and was not apparent for QRS duration 120–149 ms or RBBB/IVCD.

The effect of eplerenone on all-cause mortality according to ECG category was similar to that seen for cardiovascular mortality.

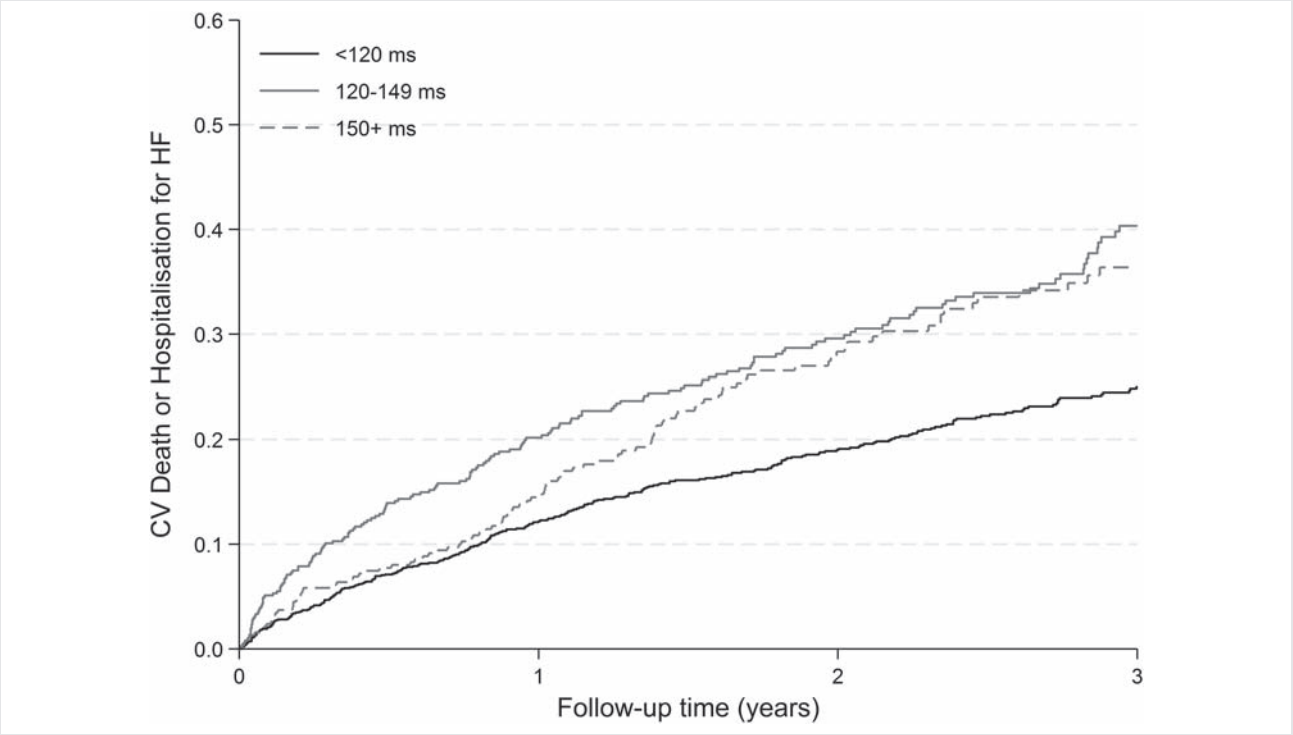

Figure 1 Cardiovascular (CV) death or hospitalization for heart failure (HF) according to QRS duration. Event rate shown as a fraction of 1 e.g. 0.5 = 50%. ms = milliseconds.

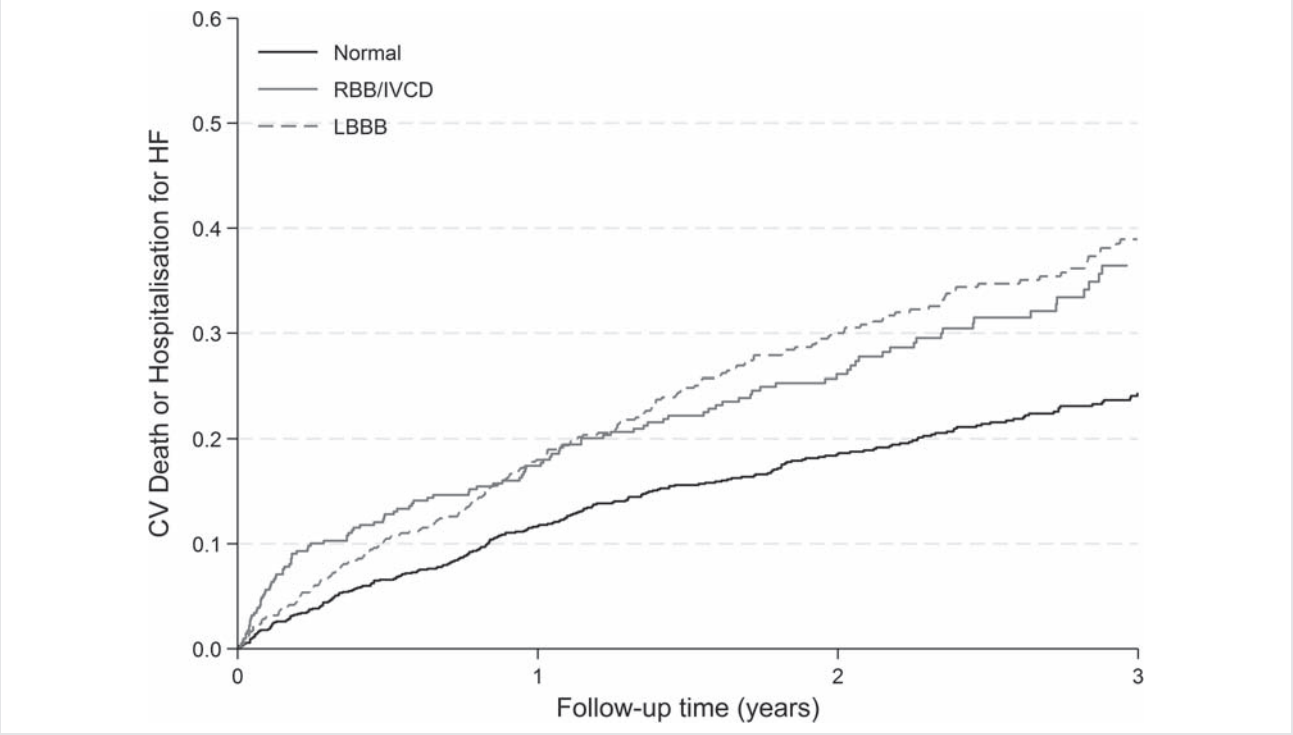

Figure 2 Cardiovascular (CV) death or hospitalization for heart failure (HF) according to QRS morphology. IVCD, intraventricular conduction defect; LBBB, left bundle branch block; RBBB, right bundle branch block.

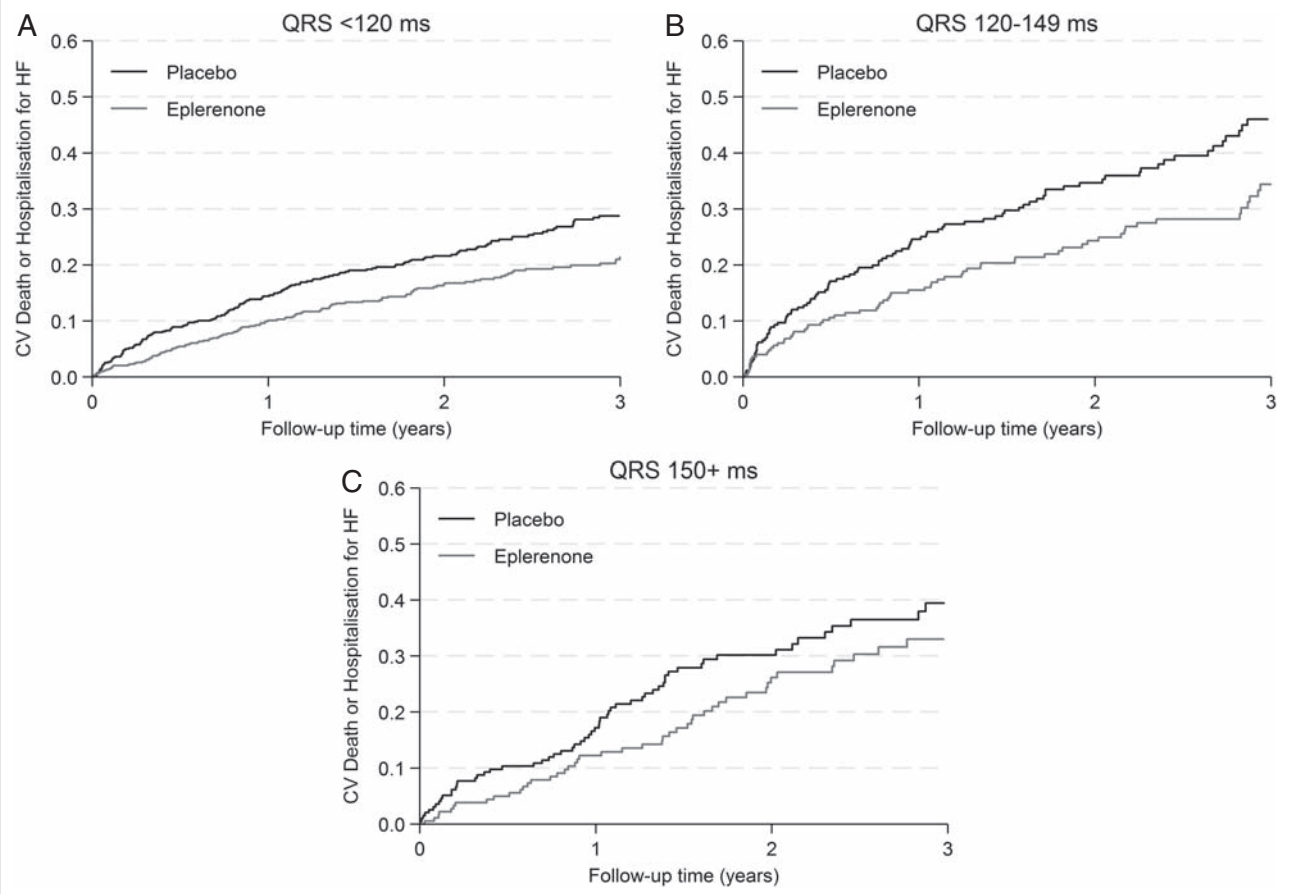

Figure 3 Effect of eplerenone compared with placebo on cardiovascular (CV) death or hospitalization for heart failure (HF) according to QRS duration. (*A*) QRS <120 ms; (*B*) QRS 120–149 ms; (*C*) QRS ≥150 ms.

Discussion

The main findings in this study were that among the HF-REF patients with mild symptoms, those with a prolonged QRS duration or BBB experienced a considerably higher risk of the primary composite outcome of cardiovascular death or heart failure hospitalization, compared with patients without these ECG abnormalities, and the MRA eplerenone reduced the risk of this composite irrespective of patients' QRS duration or morphology.

Additional findings of note were that QRS abnormalities were more common in patients with a non-ischaemic aetiology and, in this trial, QRS duration 120–149 ms vs. ≥150 ms and LBBB vs. RBBB/IVCD carried similar risk relative to <120 ms and no BBB/normal QRS duration, respectively. It was also of note that QRS prolongation/BBB seemed to be associated with an even greater elevated risk of heart failure hospitalization than of cardiovascular mortality, although we cannot be sure that this difference is real because of the low power for this analysis.

Prior reports from the Swedish Heart Failure Registry and the EFFECT study also found that QRS prolongation was more common in non-ischaemic heart failure and that non-LBBB QRS prolongation was associated with at least as high unadjusted risk of death as LBBB, although this has not been found in all studies.[19–21] However, we do not know of any previous report of the relationship between the degree of QRS prolongation and outcome. So, while there may be concern about the value of CRT in patients with lesser degrees of QRS prolongation and non-LBBB morphology, it seems clear that these patients are at high risk and merit intervention to reduce this risk. Our findings show that MRA therapy is one such intervention.

The finding of a possible stronger association between QRS abnormalities and heart failure hospitalization, compared with death, is one of the most interesting findings in the present study. This has been hinted at before. The Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) investigators divided their patients into those with and without LBBB, i.e. the latter group included patients with RBBB, IVCD, and normal QRS duration (although QRS duration was not described).[22] Those with LBBB were significantly more likely to experience the primary composite outcome of cardiovascular death or heart failure hospitalization, compared with the remainder of patients. The increment in risk appeared to be greater for heart failure hospitalization than for cardiovascular mortality.[22] Additional support comes from the Enhanced Feedback For Effective Cardiac

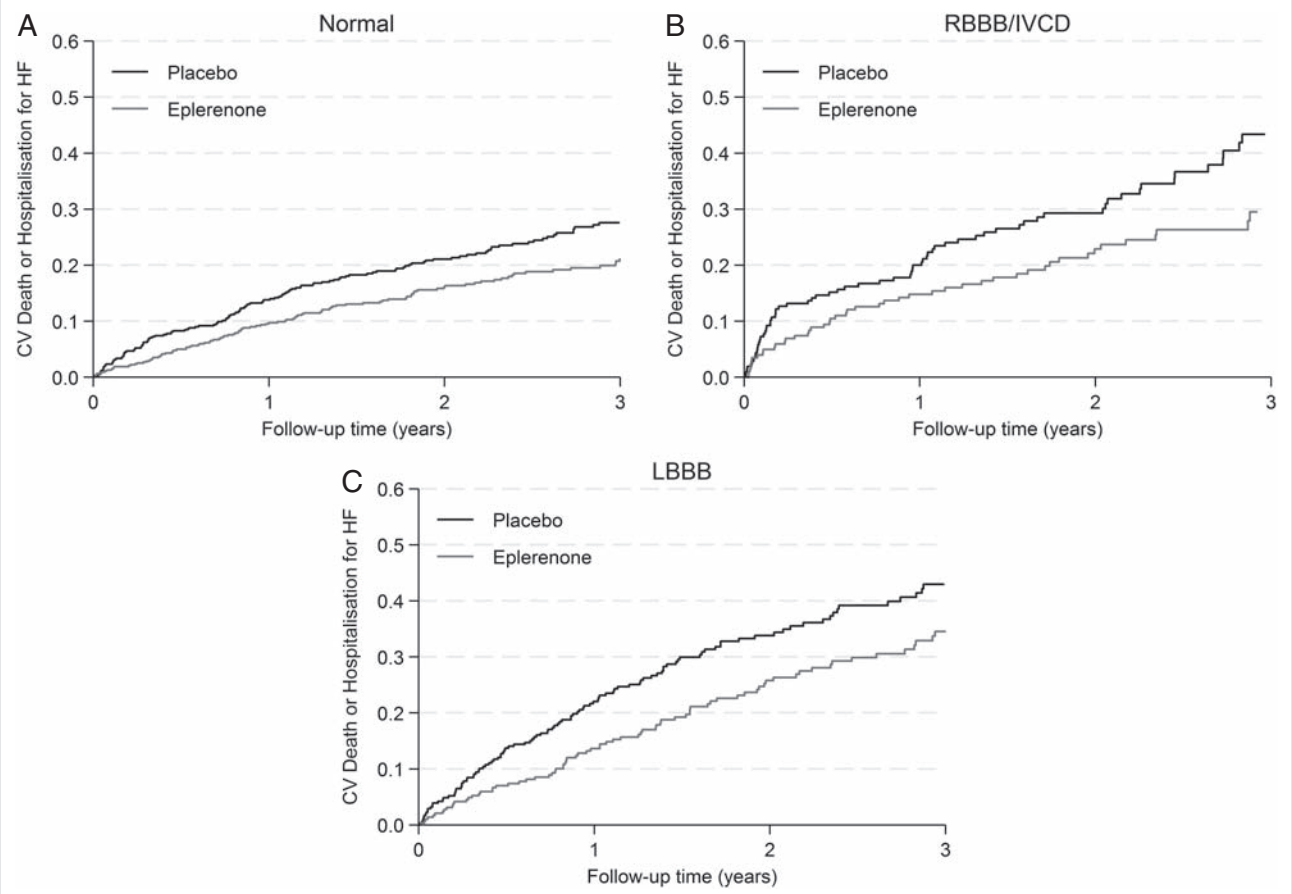

Figure 4 Effect of eplerenone compared with placebo on cardiovascular (CV) death or hospitalization for heart failure (HF) according to QRS morphology. (*A*) Normal morphology; (*B*) non-LBBB morphology [right bundle branch block (RBBB)/intraventricular conduction defect (IVCD)]; (*C*) LBBB morphology.

Treatment study (EFFECT), a study in 9487 patients admitted to participating hospitals in Ontario with heart failure between 1999 and 2001.[20] In that study, the adjusted hazard ratio for risk of death in patients with LBBB ($n = 1480$) vs. no BBB ($n = 6951$) was 1.10 [95% confidence interval (CI) 1.02–1.18] whereas it was 1.32 (95% CI 1.20–1.46) for heart failure hospitalization. However, the findings in that study for RBBB were not as consistent. In those patients ($n = 651$), the comparable hazard ratios were 1.10 (95% CI 0.99–1.21) and 1.10 (95% CI 0.95, 1.27), respectively. The Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity Program (CHARM) also gave inconsistent findings. Comparison of outcomes in HF-REF patients with BBB (it was not possible to differentiate between right and left in CHARM) and those without BBB gave an adjusted hazard ratio for cardiovascular death of 1.32 (95% CI 1.17–1.50), whereas the hazard ratio for heart failure hospitalization was 1.34 (95% CI 1.18–1.51).[23]

Another finding in the present study that should be commented on for the sake of completeness was the possibly differential effect of eplerenone on cardiovascular death, compared with heart failure hospitalization, in patients with LBBB/the widest QRS duration. The most likely explanation must be play of chance given the retrospective nature of this analysis, the multiple comparisons conducted, and the fact that this difference was seen for only one of the two abnormal QRS duration and morphology categories. Interpretation of the effect of treatment on heart failure hospitalization alone has to take account of the competing risk of death (which appeared to be reduced by the greatest amount in the groups with the least reduction in heart failure hospitalization). In addition, we cannot think of any other plausible mechanistic explanation for this finding.

The most important finding in this study was that eplerenone reduced the risk of death and hospitalization, irrespective of patients' QRS duration, or morphology—including abnormalities that were associated with a high risk of adverse outcomes but without a clear indication for CRT. These high-risk individuals had large absolute benefits from MRA therapy, even when added to an ACE inhibitor/ARB and beta-blocker, and although patients had only mild symptoms.

As with any analysis of this type, there are limitations. It was not prospectively planned, i.e. was retrospective. This plus the examination of six subgroups and four endpoints increases the risk of chance findings. Original ECGs were not available, and this

analysis was based on information provided by investigators on study case report forms.

In summary, we found that HF-REF patients with mild symptoms but a prolonged QRS duration or BBB experienced a considerably higher risk of the primary composite outcome of cardiovascular death or heart failure hospitalization (and especially the latter), compared with patients without these ECG abnormalities. Of note, QRS duration 120–149 ms vs. ≥150 ms (and LBBB vs. RBBB/IVCD) carried a similar risk relative to <120 ms (and no BBB/normal QRS duration). The MRA eplerenone reduced the risk of death and hospitalization irrespective of patients' QRS duration or morphology.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Distribution curve of patients by QRS duration and BBB morphology.

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