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QRS Duration Is a Predictor of Adverse Outcomes in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

OBJECTIVES This study examined the relationship between baseline QRS duration and clinical outcomes in subjects enrolled in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial.

BACKGROUND Heart failure with preserved ejection fraction (HFPEF) is a heterogeneous clinical syndrome. Whether QRS duration identifies HFPEF subjects at an increased risk of adverse outcomes has not been well studied.

METHODS QRS duration was analyzed as a dichotomous variable (≥120 ms or <120 ms) and as a continuous variable to determine its relation to the primary outcome (composite of cardiovascular death, aborted cardiac arrest, or HF hospitalization [HFH]) and to each component of the primary outcome. Multivariate analyses were conducted in the entire study cohort as well as in separate analyses for subjects enrolled only from North and South America, or from Russia and Georgia.

RESULTS The QRS duration of ≥120 ms was independently associated with an increased risk of the primary outcome ($p = 0.009$) and HFH ($p = 0.003$) in the entire study cohort and in the subset enrolled in the Americas. There was a linear relation of QRS duration with risk of the primary outcome and HFH. No interaction was observed between treatment with spironolactone and QRS duration. The risk of adverse outcomes was increased independently of the type of conduction abnormality underlying prolonged QRS duration.

CONCLUSIONS This post hoc analysis demonstrated that prolonged QRS duration identifies HFPEF subjects at a higher risk of adverse clinical outcomes and that spironolactone had a similar effect on outcomes independent of QRS duration. (Aldosterone Antagonist Therapy for Adults With Heart Failure and Preserved Systolic Function [TOPCAT]; NCT00094302) (J Am Coll Cardiol HF 2016;4:477–86) © 2016 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

COPD = chronic obstructive pulmonary disease

HFH = heart failure hospitalizations

HFPEF = heart failure with preserved ejection fraction

HFREF = heart failure with reduced ejection fraction

IVCD = intraventricular conduction defect

LBBB = left bundle branch block

LVEF = left ventricular ejection fraction

RBBB = right bundle branch block

VPR = ventricular paced rhythm

Heart failure with preserved ejection fraction (HFPEF) is a common clinical syndrome that, based on current guidelines, includes all patients with a clinical diagnosis of heart failure and a preserved left ventricular ejection fraction (LVEF) (1–3). It is increasingly recognized that the significant heterogeneity of this condition is a major barrier to elucidate its pathophysiology and to design appropriate clinical trials (4,5). Identifying single or composite clinical characteristics to classify HFPEF into subcategories is a promising approach to address the pathophysiologic and therapeutic uncertainty of this highly prevalent condition (6). QRS duration on 12-lead ECG is an easily available clinical measurement with the potential to identify high-risk HFPEF subjects. Increased QRS duration, indicating dyssynchronous contraction

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and relaxation of the left and right ventricles is a marker of poor prognosis in heart failure with reduced ejection fraction (HFREF) (7). However, the importance of prolonged QRS duration in HFPEF is not well understood. For example, the prevalence rate of prolonged QRS duration in HFPEF is reported to vary widely from 10% to 60% (8). Although a report from the Swedish Heart Failure Registry demonstrated a significant association of prolonged QRS duration with mortality independent of LVEF (9), another report from the Korean Acute Heart Failure Registry did not demonstrate prognostic significance for QRS duration in subjects with preserved LVEF (10). Hence we examined the prevalence and prognostic importance of QRS duration and of ventricular conduction blocks in a large cohort of HFPEF patients enrolled in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) study.

METHODS

STUDY POPULATION. Detailed methodology of the TOPCAT trial has been described previously (11,12). Investigator-reported QRS duration and data for specific conduction defects (i.e., right bundle branch block [RBBB], left bundle branch block [LBBB], intraventricular conduction defect [IVCD], and ventricular paced rhythm [VPR]) were available at baseline for 3,426 of 3,445 subjects (99.4%).

Baseline electrocardiography (ECG) was not available for most subjects because it was not a required source document in the trial. During review of study source documents, we were able to identify 75 subjects whose source documents contained baseline ECGs. A board-certified cardiologist, blinded to the reported data, manually analyzed these 75 baseline ECGs to obtain QRS duration. Data were compared to site-entered baseline QRS duration. Results of this quality control analysis demonstrated that investigator-measured QRS duration was highly correlated with site-entered QRS duration ($r = 0.82$) with no systematic bias ($p = 0.93$). The ratio of validated ECGs with QRS duration <120 ms to ≥120 ms was 2:1. Most ECGs obtained for validation were from subjects enrolled in North and South America (approximately two-thirds of ECGs obtained for validation analysis were from the Americas) with approximately 21% from subjects enrolled in Russia. In the majority of the subjects assessed, variation in QRS duration between investigator-measured and site-entered data was minimal (55% within 2 ms and 75% within 8 ms).

STATISTICAL ANALYSIS. The relationship between QRS duration and outcomes was examined in 3 separate analyses. First, a dichotomous approach was used to separate the entire study population into those with QRS duration <120 ms and those with QRS duration ≥120 ms. Subsequently, we analyzed the specific conduction block responsible for a QRS width ≥120 ms (RBBB, LBBB, IVCD, or VPR), in comparison with those with QRS duration <120 ms. Last, we analyzed QRS duration as a continuous variable to assess the prognostic impact of QRS durations that were less than the widely used cutoff of 120 ms.

Descriptive analysis was performed to compare baseline demographics, comorbidities, medications, and lifestyle factors in subjects with compared to those without QRS prolongation. Survival analysis was performed using Cox proportional hazards model to examine the relationship between baseline QRS duration, by using the 3 classification schemes described above, with the primary outcome (composite of cardiovascular [CV] death, aborted cardiac arrest, or HF hospitalization) and the following secondary outcomes: all-cause mortality, CV death, sudden death or aborted cardiac arrest, and HF hospitalizations. For all non-fatal events, only the first event was included in the analyses. Analysis was also performed to determine any interaction between treatment effect and QRS duration. Incidence rates of each outcome per 100 person years as well as unadjusted and adjusted hazard ratios (see later text) were obtained.

Due to regional differences in outcomes observed in TOPCAT (13), we repeated the above analyses separately for subjects enrolled in the Americas and those enrolled in Russia and Georgia. In addition, multivariate analysis was conducted to adjust for

variables that were significant correlates of QRS duration ≥120 ms in the full population and in subjects enrolled in the Americas and in Russia and Georgia. All baseline variables listed in Table 1 and Online Table 1 from the TOPCAT primary publication (11) were considered candidates. We then fit a logistic regression model with elevated QRS as the outcome and used backward stepwise selection with a p value of 0.10 for removal and a p value of 0.05 for entry to produce a final set of potential confounders. This selection process was performed once using all data to produce a global model and then separately by geographic region. Although true confounders of the effect of QRS duration on outcomes are those associated with both QRS duration and outcomes, we included variables associated with QRS duration in the multivariate analyses in order to avoid producing separate models for each outcome. No adjustment was made for multiple testing. p values of <0.05 were considered statistically significant. All analyses were conducted using STATA version 14.1 software (Stata Corp., College Station, Texas).

RESULTS

BASELINE DEMOGRAPHIC DIFFERENCES BETWEEN SUBJECTS WITH NORMAL QRS DURATION AND THOSE WITH WIDE (≥120 MS) QRS DURATION. The prevalence of QRS duration ≥120 ms at baseline was 17.9%; more subjects enrolled in the Americas (25.3%) had wide QRS at baseline than subjects enrolled from Russia and Georgia (10.2%). Table 1 demonstrates the differences in baseline demographic parameters between those with and without prolonged QRS duration in the entire study. Multiple covariates were found to be more prevalent in the group with QRS duration ≥120 ms, including older age, males, lower LVEF, atrial fibrillation, diabetes, chronic kidney disease, hemoglobin concentration, chronic obstructive pulmonary disease (COPD), and increased use of diuretics. Table 2 lists multivariate predictors of QRS duration ≥120 ms in the whole sample and in subjects from Americas and Russia and Georgia. In the entire sample, region (Americas) was a significant predictor of prolonged QRS duration along with a few of the covariates found to be significant on demographic analysis described in Table 1; for example, warfarin use was more common in those with prolonged QRS duration. On comparing the predictors of QRS duration ≥120 ms in Americas with those in Russian and Georgian subjects, the major differences were the predictive effects of white race, hemoglobin concentration, and renal dysfunction in Americas and that COPD, diabetes, and warfarin use were

TABLE 1 Demographic Differences Between Subjects With QRS Duration <120 ms and QRS Duration ≥120 ms in the Entire Sample

	QRS Duration <120 ms (n = 2,813)	QRS Duration ≥120 ms (n = 613)	p Value
Age, yrs	67.8 (60.3, 74.8)	72.9 (64.7, 79.5)	<0.0001
Age ≥75 yrs	692 (24.6%)	249 (40.6%)	<0.0001
Females (%)	1,539 (54.7%)	231 (37.7%)	<0.0001
Whites (%)	2,499 (88.8%)	547 (89.2%)	0.78
% LVEF	57.0 (51.0, 62.0)	55.0 (50.0, 60.0)	<0.0001
NYHA functional classes (%)			
I	83 (3.0%)	24 (3.9%)	
II	1,817 (64.7%)	368 (60.0%)	0.12
III	899 (32.0%)	217 (35.4%)	
IV	11 (0.4%)	4 (0.7%)	
Strata (%)	2,060 (73.2%)	397 (64.8%)	<0.0001
Hospitalized in previous year with management of heart failure as major component			
Number of co-morbidities (%)			
Coronary artery disease	1,662 (59.1%)	352 (57.4%)	0.45
Atrial fibrillation	930 (33.1%)	278 (45.4%)	<0.0001
Diabetes mellitus	884 (31.4%)	230 (37.5%)	0.0035
Insulin-treated	553 (19.7%)	138 (22.5%)	0.11
Chronic kidney disease (eGFR <60 ml/min/1.73 m^2)	1,036 (36.8%)	288 (47.0%)	<0.0001
Hypertension	2,584 (91.9%)	549 (89.6%)	0.07
Myocardial infarction	720 (25.6%)	170 (27.7%)	0.27
PCI or CABG	621 (22.1%)	186 (30.3%)	<0.0001
Dyslipidemia	1,654 (58.8%)	409 (66.7%)	0.0003
Chronic obstructive pulmonary disease	305 (10.8%)	95 (15.5%)	0.0011
Stroke	213 (7.6%)	52 (8.5%)	0.44
Current smokers (%)	308 (11.0%)	49 (8.0%)	0.03
Systolic blood pressure, mm Hg	130.0 (120.0, 140.0)	130.0 (120.0, 138.0)	0.24
Diastolic blood pressure, mm Hg	80.0 (70.0, 81.0)	75.0 (65.0, 80.0)	<0.0001
Heart rate, beats/min	67.0 (60.0, 75.0)	67.0 (60.0, 75.0)	0.62
Body mass index, kg/m^2	30.9 (27.2, 35.6)	31.0 (26.9, 35.9)	0.50
Serum potassium, mEq/l	4.3 (4.0, 4.6)	4.3 (4.0, 4.6)	0.07
Serum creatinine, mg/dl	1.0 (0.9, 1.2)	1.1 (0.9, 1.4)	<0.0001
eGFR, ml/min/1.73 m^2	66.2 (54.6, 79.5)	61.3 (50.3, 76.6)	<0.0001
Hemoglobin, g/dl	13.3 (12.2, 14.5)	13.0 (11.9, 14.1)	<0.0001
Number of medications (%)			
Diuretic	2,272 (80.8%)	531 (86.6%)	0.0007
ACE-I or ARB	2,386 (84.9%)	500 (81.6%)	0.04
Beta-blocker	2,184 (77.7%)	480 (78.3%)	0.73
Calcium channel blocker	1,076 (38.3%)	210 (34.3%)	0.06
Aspirin	1,859 (66.1%)	379 (61.8%)	0.04
Statin	1,425 (50.7%)	368 (60.0%)	<0.0001
Long-acting nitrate	413 (14.7%)	100 (16.3%)	0.3066
Warfarin	576 (20.5%)	209 (34.1%)	<0.0001
Regions of enrollment (Russia and Georgia)	1,506 (53.5%)	171 (27.9%)	<0.0001

Values are n (%).

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CABG = coronary artery bypass graft; eGFR = estimated glomerular filtration rate; LVEF = left ventricle ejection fraction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

TABLE 2 Independent Predictors of QRS Duration ≥120 ms

	Entire Sample		
	OR	95% CI	|z|
Region: Americas	2.44	1.94–3.06	7.68
Males	2.05	1.68–2.49	7.08
Age, per 5 yrs	1.18	1.12–1.25	6.25
LVEF, per 5%	0.83	0.78–0.89	5.54
Hemoglobin, per g/dl	0.92	0.87–0.97	2.81
Warfarin	1.32	1.07–1.62	2.57
Whites	1.42	1.04–1.94	2.22
Americas			
Male	2.06	1.62–2.62	5.92
LVEF, per 5%	0.81	0.75–0.88	5.23
Age, per 5 yrs	1.14	1.08–1.22	4.26
White	1.54	1.13–2.10	2.71
Hemoglobin, per g/dl	0.91	0.84–0.97	2.70
eGFR, <60	1.37	1.09–1.73	2.67
Russia and Georgia			
Age, per 5 yrs	1.28	1.16–1.41	4.98
Male	1.90	1.35–2.66	3.71
LVEF, per 5%	0.86	0.76–0.97	2.39
COPD	1.82	1.07–3.09	2.22
Diabetes	1.53	1.05–2.23	2.19
Warfarin	1.58	1.02–2.45	2.06

CI = confidence interval; COPD = chronic obstructive pulmonary disease; OR = odds ratio; other abbreviations as in Table 1.

independent predictors in Russia and Georgia. These factors (global and regional) were used in multivariate analysis of the relationship between the QRS duration and outcomes described below.

WIDE QRS DURATION AT BASELINE IS ASSOCIATED WITH WORSE OUTCOMES. Analyses of the association between QRS duration and reported outcomes are shown in Table 3 for the whole sample (Table 3), the Americas (Table 4), and Russia and Georgia (Table 5). The primary outcome was strongly associated with QRS duration ≥120 ms in the whole sample, even after adjusting for correlates of wide QRS. Whereas unadjusted analysis showed a highly significant association of the primary outcome with QRS duration ≥120 ms in the Americas and Russia and Georgia, these relationships were reduced to borderline statistical significance after adjusting for global and regional variables. Cardiovascular death was highly and significantly associated with QRS duration ≥120 ms in the entire sample and in Russia and Georgia on unadjusted analysis, and this association remained of borderline significance in subjects from Russia and Georgia after adjusting for global and regional variables. All-cause mortality was significantly associated with QRS duration ≥120 ms in the entire group and in the Americas on unadjusted analysis (borderline statistical significance in Russia and Georgia) but not after adjustment for correlates of wide QRS duration. Rates of aborted cardiac arrest, a component of the primary endpoint, were too low to derive any firm conclusions. Heart failure hospitalizations were highly and significantly associated with QRS duration ≥120 ms in the entire group and in the Americas on unadjusted and multivariate analyses; the rate of occurrence of this event was markedly lower in Russia and Georgia and was not significantly associated with QRS duration.

TABLE 3 Associations of QRS Duration With Outcomes in the Entire Sample

	QRS <120 ms (95% CL) (n = 2,813)	QRS ≥120 ms (95% CL) (n = 613)	HR (95% CL) p Value	Adjusted HR* (95% CL) p Value
Primary outcome	489 events, 5.4 per 100 py (5.0–5.9)	179 events, 10.8 per 100 py (9.4–12.6)	1.94 (1.64–2.31) <0.001	1.27 (1.06–1.52) 0.009
Cardiovascular death	251 events, 2.6 per 100 py (2.3–3.0)	84 events, 4.5 per 100 py (3.6–5.5)	1.72 (1.34–2.20) 0.001	1.13 (0.87–1.47) 0.35
Aborted cardiac arrest	7 events, 0.1 per 100 py (0.0–0.2)	1 event, 0.1 per 100 py (0.0–0.4)	–	–
All-cause mortality	382 events, 3.8 per 100 py (3.5–4.2)	140 events, 7.1 per 100 py (6.0–8.4)	1.87 (1.54–2.27) <0.001	1.14 (0.93–1.40) 0.22
Heart failure hospitalizations	316 events, 3.5 per 100 py (3.1–3.9)	133 events, 8.1 per 100 py (6.8–9.6)	2.20 (1.80–2.69) >0.001	1.38 (1.11–1.71) 0.003

*Globally adjusted for age, sex, region, ejection fraction, hemoglobin, warfarin, and white subjects.
CL = confidence limits; HR = hazard ratio; py = person years.

ASSOCIATIONS OF SPECIFIC CONDUCTION DISTURBANCES WITH OUTCOMES. We analyzed whether specific conduction disturbances causing prolongation of QRS duration were associated differently with outcomes in the entire sample. The highest prevalence was noted for RBBB (5%) and lowest for LBBB (3.9%), with IVCD and VPR prevalent at rates of 4.7% and 4.2%, respectively. Despite low number of subjects and events in each group, several significant associations were observed. Table 6 demonstrates the hazard ratios for the risk of each outcome when comparing subjects with RBBB, LBBB, IVCD, or VPR to study subjects with QRS duration <120 ms. On unadjusted analyses, the risks of the primary outcome and HF hospitalization were significantly increased in subjects with each conduction abnormality compared to those with a QRS duration of <120 ms (Table 6). The risk of all-cause mortality was increased in all groups except in subjects with LBBB, whereas risk of CV death was higher in all groups except subjects with IVCD ($p = 0.05$). After we adjusted for global correlates of a prolonged QRS duration, HF hospitalizations were found to be significantly associated with RBBB and LBBB, and the primary outcome was associated only with RBBB.

TABLE 4 Associations of QRS Duration With Outcomes in the Americas

	QRS <120 ms (n = 1,307)	QRS ≥120 ms (n = 442)	HR (95% CL) p Value	Adjusted HR* (95% CL) p Value	Adjusted HR† (95% CL) p Value
Primary outcome	365 events, 10.6 per 100 py (9.6-11.8)	154 events, 14.2 per 100 py (12.2-16.7)	1.33 (1.10-1.61) 0.003	1.23 (1.01-1.50) 0.036	1.20 (0.98-1.46) 0.072
Cardiovascular death	158 events, 4.1 per 100 py (3.5-4.7)	64 events, 4.9 per 100 py (3.9-6.3)	1.20 (0.90-1.61) 0.21	1.01 (0.75-1.37) 0.93	0.98 (0.73-1.33) 0.91
Aborted cardiac arrest	5 events, 0.13 per 100 py (0.05-0.31)	1 event, 0.08 per 100 py (0.01-0.55)	-	-	-
All-cause mortality	261 events, 6.5 per 100 py (5.7-7.2)	120 events, 8.9 per 100 py (7.4-10.6)	1.36 (1.10-1.69) 0.005	1.11 (0.88-1.39) 0.39	1.06 (0.85-1.33) 0.59
Heart failure hospitalizations	274 events, 7.9 per 100 py (7.1-8.9)	124 events, 11.5 per 100 py (9.6-13.7)	1.44 (1.16-1.78) 0.001	1.35 (1.08-1.69) 0.008	1.32 (1.05-1.65) 0.015

*Globally adjusted for age, sex, region, ejection fraction, hemoglobin, warfarin, and white subjects. †Region-specifically adjusted for age, sex, ejection fraction, hemoglobin, eGFR <60, and white subjects.

Abbreviations as in Table 3.

RELATIONSHIP BETWEEN QRS DURATION AS A CONTINUOUS VARIABLE AND RISK OF OUTCOMES. We examined the relationship between QRS duration as a continuous variable and clinical outcomes. As shown in **Figure 1A** and Online Table 1, adjusted analysis demonstrated a significant linear relationship between QRS duration and incidence of the primary outcome. After adjustment for global covariates, a threshold of 100 ms was obtained for a significant association with the primary outcome (**Figure 1A**, Online Table 1).

Figure 1B shows the adjusted analysis of the relation of QRS duration to HF hospitalizations. Similar to the primary outcome, the risk for HF hospitalizations also demonstrated a linear relation with an increased QRS duration above a threshold of approximately 100 ms. As shown in **Figure 1C**, there was no significant interaction of spironolactone treatment with QRS duration.

DISCUSSION

The heterogeneity of the clinical syndrome of HFPEF is a major hurdle in evaluating prognosis and treatments for this highly prevalent condition. There is a critical need to identify individuals at higher risk of

TABLE 5 Associations of QRS Duration With Outcomes in Russia and Georgia

	QRS <120 ms (95% CL) (n = 1,506)	QRS ≥120 ms (95% CL) (n = 171)	HR (95% CL) p Value	Adjusted HR* (95% CL) p Value	Adjusted HR† (95% CL) p Value
Primary outcome	124 events, 2.2 per 100 py (1.9-2.7)	25 events, 4.4 per 100 py (3.0-6.5)	1.96 (1.27-3.01) 0.002	1.50 (0.97-2.33) 0.071	1.44 (0.92-2.24) 0.10
Cardiovascular death	93 events, 1.6 per 100 py (1.3-2.0)	20 events, 3.4 per 100 py (2.2-5.3)	2.09 (1.29-3.39) 0.003	1.59 (0.97-2.61) 0.065	1.53 (0.93-2.51) 0.096
Aborted cardiac arrest	2 events, 0.04 per 100 py (0.00-0.14)	0 events, 0.00 per 100 py (0.00-0.00)	-	-	-
All-cause mortality	121 events, 2.0 per 100 py (1.7-2.4)	20 events, 3.2 per 100 py (2.1-5.0)	1.60 (1.00-2.59) 0.051	1.28 (0.79-2.07) 0.32	1.22 (0.75-1.98) 0.42
Heart failure hospitalizations	42 events, 0.8 per 100 py (0.6-1.0)	9 events, 1.6 per 100 py (0.8-3.0)	2.03 (0.99-4.18) 0.053	1.65 (0.79-3.45) 0.19	1.50 (0.70-3.18) 0.29

*Globally adjusted for age, sex, region, ejection fraction, hemoglobin, warfarin, and white subjects. †Region-specifically adjusted for age, sex, ejection fraction, COPD, diabetes and warfarin.

Abbreviations as in Tables 1 and 3.

TABLE 6 Associations of Specific Conduction Disturbances With Outcomes

	QRS <120 ms (95% CL) (N = 2,813)	RBBB (95% CL) (N = 174)	LBBB (95% CL) (N = 134)	IVCD (95% CL) (N = 160)	VPR (95% CL) (N = 145)
Primary outcome	489 events, 5.4 per 100 py (5.0-5.9)	55 events, 11.6 per 100 py (8.9-15.2)	36 events, 9.1 per 100 py (6.6-12.6)	44 events, 10.1 per 100 py (7.5-13.6)	44 events, 12.7 per 100 py (9.4-17.0)
Hazard ratio	-	2.10 (1.59-2.77) p < 0.001	1.66 (1.18-2.32) p = 0.003	1.81 (1.33-2.46) p < 0.001	2.22 (1.63-3.02) p < 0.001
Adjusted HR*	-	1.46 (1.09-1.94) p = 0.010	1.32 (0.94-1.86) p = 0.11	1.21 (0.89-1.66) p = 0.23	1.10 (0.80-1.51) p = 0.56
Interaction with region		0.60	0.35	0.13	0.98
Cardiovascular death	251 events, 2.6 per 100 py (2.3-3.0)	26 events, 4.8 per 100 py (3.3-7.1)	19 events, 4.3 per 100 py (2.8-6.8)	20 events, 4.1 per 100 py (2.6-6.3)	19 events, 4.6 per 100 py (2.9-7.1)
Hazard ratio	-	1.87 (1.25-2.79) p = 0.002	1.67 (1.05-2.66) p = 0.031	1.57 (1.00-2.48) p = 0.05	1.76 (1.10-2.80) p = 0.018
Adjusted HR*	-	1.32 (0.87-1.99) p = 0.19	1.27 (0.79-2.04) p = 0.32	1.08 (0.68-1.71) p = 0.74	0.89 (0.55-1.44) p = 0.64
Aborted cardiac arrest	7 events, 0.07 per 100 py (0.03-0.15)	0 events	0 events	1 event, 0.21 per 100 py (0.03-1.46)	0 events
All-cause mortality	382 events, 3.6 per 100 py (3.5-4.2)	41 events, 7.2 per 100 py (5.3-9.9)	24 events, 5.3 per 100 py (3.5-7.9)	38 events, 7.6 per 100 py (5.5-10.4)	37 events, 8.2 per 100 py (6.0-11.3)
Hazard ratio		1.91 (1.38-2.63) p < 0.001	1.39 (0.92-2.10) p = 0.12	2.01 (1.44-2.80) p < 0.001	2.17 (1.55-3.04) p < 0.001
Adjusted HR*		1.24 (0.89-1.72) p = 0.20	1.04 (0.69-1.57) p = 0.86	1.28 (0.91-1.79) p = 0.16	0.98 (0.69-1.40) p = 0.92
Heart failure hospitalizations	316 events, 3.5 per 100 py (3.1-3.9)	39 events, 8.2 per 100 py (6.0-11.3)	27 events, 6.8 per 100 py (4.8-9.8)	30 events, 6.9 per 100 py (4.8-9.9)	37 events, 10.6 per 100 py (7.7-14.7)
Hazard ratio	-	2.27 (1.63-3.17) p < 0.001	1.90 (1.29-2.82) p = 0.001	1.88 (1.29-2.73) p = 0.001	2.82 (2.00-3.96) p < 0.0001
Adjusted HR*	-	1.50 (1.07-2.12) p = 0.02	1.53 (1.03-2.27) p = 0.037	1.22 (0.84-1.79) p = 0.30	1.30 (0.91-1.86) p = 0.14

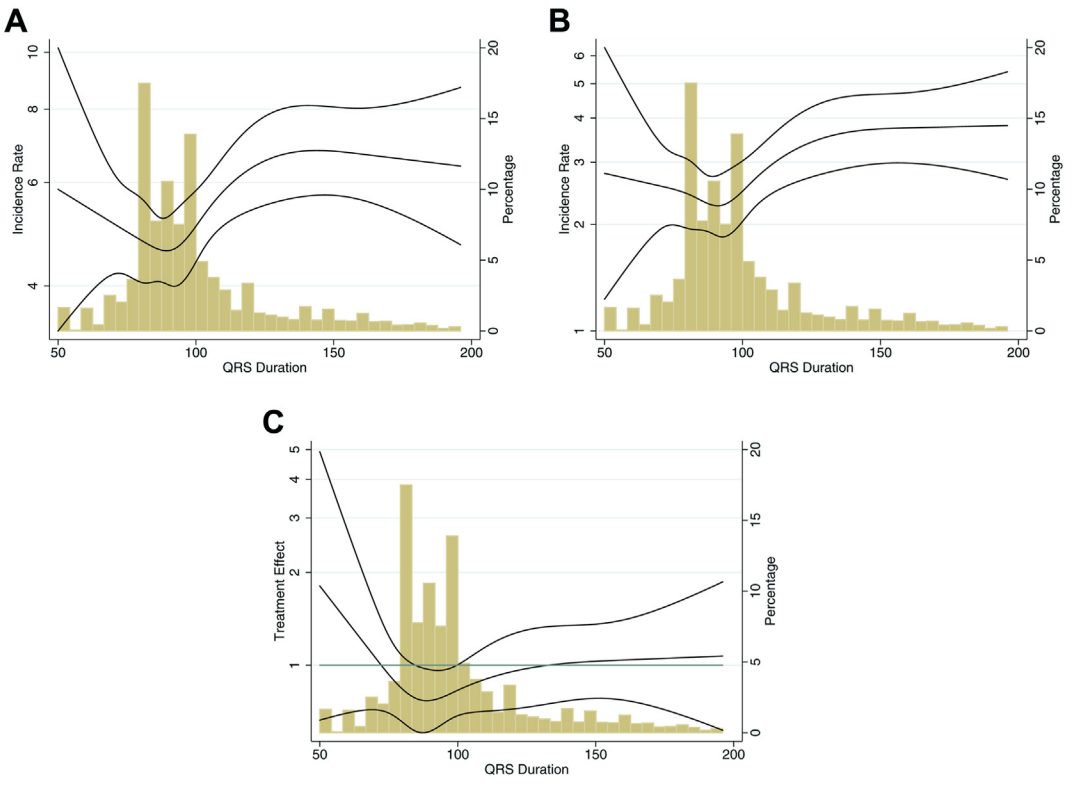
*Globally adjusted for age, sex, race, region, ejection fraction, hemoglobin, and warfarin therapy.

IVCD = intraventricular conduction delay; LBBB = left bundle branch block; RBBB = right bundle branch block; VPR = ventricular paced rhythm; other abbreviations as in Table 3.

adverse clinical outcomes in this population of patients (4). We examined the value of a simple and widely applicable criterion (i.e., QRS width measured on routine 12-lead ECG as a predictor of adverse outcomes in HFPEF) using data from the TOPCAT trial. Our study, the largest to date that examined the relationship between QRS duration and conduction blocks and outcomes in HFPEF, suggests that QRS duration, regardless of the type of underlying conduction block, could be an important clinical tool to identify HFPEF patients at higher risk of adverse outcomes.

A prolonged QRS duration ≥120 ms is associated with worse clinical status and outcomes in HFREF (7,14). Restoring synchronous left and right ventricular activation by cardiac resynchronization therapy improves outcomes in HFREF, especially in patients with LBBB (3). The few studies that have examined the prevalence and prognostic relevance of QRS duration in HFPEF have yielded varying results. Varadarajan et al. (15), in a study of patients hospitalized for heart failure, estimated prevalence rates of 2% for LBBB and 9% for RBBB in HFPEF. In the CHARM (Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity) program, the prevalence of bundle branch block was 14.4% in HFPEF patients (16). A non-significant increase in risk of the composite primary endpoint was observed in

FIGURE 1 Association of QRS Duration With Primary Outcome



Association of QRS duration measured as a continuous variable with incidence of primary outcome **(A)** ($p = 0.008$ for linear trend and $p = 0.015$ for overall association), hospitalization for heart failure **(B)** ($p = 0.001$ for linear trend and $p = 0.006$ for overall association) in the entire study group after adjusting for global covariates (age, sex, race, region, left ventricular ejection fraction, hemoglobin, and warfarin). **(C)** The lack of significant association of QRS duration with spironolactone treatment effect ($p = 0.33$) is shown.

HFPEF subjects with bundle branch block (adjusted hazard ratio: 1.19; $p = 0.065$). In the ongoing KaRen (Karolinska Rennes) study and the Swedish Heart Failure Registry, QRS duration ≥120 ms was observed in 15% and 18% of HFPEF patients, respectively (9,17). In addition to electrical dyssynchrony, echocardiographically measured mechanical dysynchrony has also been observed in HFPEF. Small studies have demonstrated mechanical dyssynchrony during systole in HFPEF, albeit with a lower prevalence than in HFREF (18,19). A recent study from our group found that mechanical dyssynchrony was significantly worse in HFPEF subjects than in age- and sex-matched healthy controls and was related to an increase in QRS duration; mechanical dyssynchrony was observed even in subjects with "normal" QRS durations of <120 ms (20). Mechanical dyssynchrony was not evaluated in the current study.

The results of our analyses demonstrate the utility of QRS duration as a clinical marker to identify a group of HFPEF subjects at higher risk of adverse events. QRS duration ≥120 ms was significantly associated with an increased risk of all outcomes, except for aborted cardiac arrest in the entire sample and with the primary outcome and heart failure hospitalizations after adjustment for global covariates. These associations were less significant in the separate cohorts from Americas, Russia, and Georgia. HFH were significantly associated with QRS duration ≥120 ms in subjects enrolled from the Americas even after adjustment for global and regional covariates. A recent study from our group addressed differences in subject profile and outcomes between the Americas and Russian and Georgian subjects in the TOPCAT trial (13). Subjects from Russia and Georgia were younger, with less atrial fibrillation and diabetes and better renal function; however, they had higher

likelihood of prior myocardial infarction and lower LVEF than those enrolled from the Americas. Subjects enrolled in Russia and Georgia had a markedly lower incidence of all trial outcomes. Our observation that despite lower prevalence of prolonged QRS duration in Russia and Georgia, significant associations were observed between multiple trial outcomes and QRS duration, suggests that a prolonged QRS duration may help to identify HFPEF patients at higher risk of adverse events regardless of substantive regional variations in patient profiles.

A recent study by Lund et al. (9) demonstrated that the prevalence of prolonged QRS duration in subjects with LVEF ≥50% was 18% (similar to our study). In that study, even though LVEF did not significantly affect the predictive effect of QRS width on mortality, the association of prolonged QRS duration with mortality did not reach statistical significance in the subjects with LVEF of 40% to 49% or ≥50% when analyzed as a dichotomous variable (QRS duration ≥120 ms compared to <120 ms) but was significant when analyzed as a continuous variable. Another recent study by Park et al. (10) conducted in the Korean population demonstrated that prolonged QRS duration was associated with adverse outcomes in HFREF but not in HFPEF (10). Small studies such as that reported by Yerra et al. (21) have also demonstrated an association of increasing QRS duration below 120 ms with outcomes in patients with HFREF or HFPEF following myocardial infarction. Our findings of a significant association between QRS width measured as both a dichotomous and continuous variable and clinical outcomes in a large cohort of HFPEF patients are unambiguous and novel compared to previous studies. The increase in risk started at a threshold of 100 ms and did not appear to increase in a linear manner at QRS durations well above 120 ms unlike in HFREF (7,14). Because ventricular mechanical dyssynchrony is observed at QRS durations <120 ms in HFPEF (20), it is possible that this interesting result indicates an impact of mechanical dyssynchrony in HFPEF at lower QRS duration than in HFREF and that there is no further significant increase in mechanical dyssynchrony at very prolonged QRS durations in subjects with HFPEF.

Despite several differences in demographic and clinical variables between subjects with prolonged QRS duration and those without, only a few were independent predictors of prolonged QRS duration. Coronary artery disease was not an independent predictor of prolonged QRS duration suggesting that prolonged conduction was not the result of focal ischemic damage. Although White race was associated with higher prevalence of prolonged QRS duration in our study, a recent report from the Jackson Heart Study demonstrated that prolonged QRS duration was highly prevalent in African Americans (30% at baseline) and that it was associated with an increased incidence of HFH (22). Multiple studies have associations of comorbidities with outcomes in HFPEF (23,24). In subjects with atrial fibrillation and heart failure (not separated into HFPEF and HFREF) prolonged QRS duration has been shown to predict death and hospitalization (25). Because QRS duration remained associated with increased risk of primary outcome and HFH in the TOPCAT cohort, even after adjusting for multiple risk factors and comorbidities, this suggests an independent association of cardiac electrical dyssynchrony with adverse outcomes in HFPEF. Whether electrical dyssynchrony has a biologic influence on progression of HFPEF and whether cardiac resynchronization therapy is warranted in this setting is the subject of the ongoing KaRen study (17).

A few studies have analyzed the impact of various conduction blocks on outcomes in HFREF and healthy subjects. While LBBB and IVCD have been shown to predict arrhythmic and total mortality in HFREF, RBBB has not been shown to be associated with outcomes in HFREF (26,27). Associations of LBBB and RBBB with adverse cardiovascular outcomes in subjects without heart failure have been reported by the Framingham Study (28,29). Our analysis of differential impact of RBBB, LBBB, IVCD, and VPR on risk of adverse outcomes was limited by the small number of subjects and events in each subgroup. However, the risk of the primary outcomes and HF hospitalizations was significantly increased in all 3 groups of abnormal ventricular conduction and in subjects with paced rhythm. All-cause mortality and CV death were associated significantly with 3 of the 4 types of prolonged QRS duration. Our data suggest that the association of worse outcomes with a prolonged QRS duration is not dependent on the type of conduction disturbance and is also seen in those with ventricular pacing. The observation of a strong prognostic significance of RBBB on outcomes may be due to the impact of prevalent or incipient pulmonary hypertension and right ventricular dysfunction on outcomes. Pulmonary hypertension has been suggested to occur due to pulmonary arterial changes over and above those resulting from an elevation of pulmonary venous pressure (30). Right ventricular dysfunction is common in HFPEF in the community and is associated with worse outcomes (31,32). Similarly, in a prospective analysis of pathophysiologic markers in HFPEF, right ventricular

remodeling assessed by echocardiography was one of the strongest predictors of adverse outcomes (33). Because the incidence of COPD in LBBB (14.8%) was similar to that in RBBB (14.7%) in our study, concomitant lung disease is unlikely to have influenced the results.

The pathobiology of prolonged QRS duration in HFPEF is unclear. An autopsy study of adult hearts that examined the relationship between QRS duration and multiple biological parameters demonstrated that myocardial fibrosis was the only independent factor associated with prolonged QRS duration (34). Our finding that the effect of spironolactone was not greater in subjects with prolonged QRS duration is intriguing since spironolactone has beneficial effects on myocardial matrix metabolism (35); this could indicate that prolonged QRS duration in HFPEF may be secondary to focal rather than diffuse fibrosis, or that spironolactone did not reduce myocardial fibrosis in this cohort of HFPEF patients. Recent studies have shown that extra-cardiac comorbidities may cause progression of adverse myocardial remodeling in HFPEF (36); hence it is possible that QRS duration integrates both myocardial and extra-myocardial factors that promote progression of HFPEF and worse outcomes.

STUDY LIMITATIONS. The primary limitation is the dependence on site-based ECG readings to evaluate QRS duration and presence of specific conduction blocks. However, the strong concordance between site-based QRS durations and those determined by a study-designated reader enhance confidence in the validity of the site ECG data. The sample sizes of subjects with specific conduction blocks were small and may have been underpowered to demonstrate significant differences in outcomes. As no correction was made for multiple testing, there is a chance that some results from these analyses may be false positives. Finally, we were not able to assess serial changes in QRS duration in this study, which could have yielded important prognostic data.

CONCLUSIONS

HFPEF is a clinical syndrome with significant heterogeneity that necessitates the use of clinical or demographic data to identify subgroups that may be at greater risk of adverse outcomes or may respond to specific therapies. The regional heterogeneity reported in the TOPCAT trial highlights the need for simple clinical tools to identify HFPEF subjects at high-risk of adverse events (13). Our results suggest that QRS duration is an independent marker of adverse outcomes in heart failure regardless of the underlying conduction block. Further studies are needed to understand the biologic mechanisms underlying this association.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Heart failure with preserved ejection fraction is a heterogeneous clinical syndrome.

TRANSLATIONAL OUTLOOK 1: QRS duration identifies a higher risk subgroup of HFPEF independent of regional variations and common risk factors. Prolonged QRS duration could be used to identify high risk patients for multidisciplinary treatment programs and clinical trials.

TRANSLATIONAL OUTLOOK 2: The current study did not address the physiological or biologic correlates of a prolonged QRS duration in subjects with HFPEF. Future studies should examine whether biomarkers of cardiac remodeling or fibrosis is associated with prolonged QRS duration in HFPEF.

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KEY WORDS dyssynchrony, electrocardiogram, heart failure with preserved ejection fraction, outcomes

APPENDIX For a supplemental table, please see the online version of this article.