

# Electrocardiographic QRS Duration and the Risk of Congestive Heart Failure

## The Framingham Heart Study

Ravi Dhingra, Michael J. Pencina, Thomas J. Wang, Byung-Ho Nam, Emelia J. Benjamin, Daniel Levy, Martin G. Larson, William B. Kannel, Ralph B. D'Agostino, Sr, Ramachandran S. Vasan

**Abstract**—Prolonged electrocardiographic QRS duration is frequently observed in congestive heart failure (CHF) patients. We hypothesized that CHF risk increases with longer QRS interval in individuals free of CHF. We evaluated 1759 Framingham Study participants (mean age, 69 years; 63% women) without prior myocardial infarction or CHF who attended a routine examination. QRS duration was analyzed as a continuous (log-transformed) and a categorical variable [referent, <100 ms; incomplete bundle branch block (BBB), 100 to 119 ms; complete BBB,  $\geq 120$  ms]. During follow-up (mean, 12.7 years), 324 participants (205 women) developed CHF. CHF incidence increased across the 3 baseline QRS duration categories in both sexes. Each SD increment in log-QRS duration was associated with a multivariable-adjusted 23% increase in CHF risk [95% confidence interval [CI] 8% to 38%;  $P < 0.001$ ]. In time-dependent models with QRS category and risk factors updated every 2 years, incomplete BBB was associated with a 1.4-fold (95% CI, 1.05 to 1.96;  $P = 0.03$ ) and complete BBB with a 1.7-fold (95% CI, 1.28 to 2.35;  $P < 0.001$ ) risk of CHF. These associations were maintained on adjustment for baseline left ventricular mass. In our community-based sample, longer electrocardiographic QRS was associated with increased CHF risk, consistent with the hypothesis that depolarization delay may increase CHF risk. (*Hypertension*. 2006;47:861-867.)

**Key Words:** electrocardiography ■ epidemiology ■ heart failure

Approximately one fourth of congestive heart failure (CHF) patients have a prolonged QRS interval ( $\geq 120$  ms) on the surface ECG.<sup>1</sup> On a parallel note, men with a complete bundle branch block (BBB) experience a higher incidence of CHF prospectively.<sup>2</sup> In addition, prolonged electrocardiographic QRS interval is associated with increased echocardiographic left ventricular (LV) mass cross-sectionally in individuals without prior history of CHF or myocardial infarction (MI).<sup>3</sup> These observations raise the possibility that prolongation of the QRS duration may be a marker of adverse ventricular remodeling. Indeed, QRS prolongation has been the focus of intense research, because cardiac resynchronization therapy has emerged as a therapeutic option in CHF patients who have a QRS duration  $\geq 130$  ms.<sup>4</sup> Cardiac resynchronization therapy has been reported to reduce morbidity<sup>4</sup> and mortality<sup>5</sup> and to reverse LV remodeling in CHF patients.<sup>6</sup>

It is unclear, however, whether the association of complete BBB with elevated CHF risk<sup>2,7</sup> is because of a greater burden

of risk factors,<sup>2,8</sup> the consequence of associated higher LV mass<sup>3,9,10</sup> or systolic dysfunction,<sup>11</sup> or if it is attributable to dyssynchronous contraction.<sup>2,11,12</sup> It is also uncertain whether lesser degrees of QRS prolongation (<120 ms) portend future risk of CHF.

We hypothesized that a gradient of increasing CHF risk exists with increasing electrocardiographic QRS interval and that the association of QRS interval with CHF risk may be mediated by increased LV mass and/or asymptomatic LV systolic dysfunction.<sup>3,9-11</sup> Accordingly, we examined the relations of QRS duration on a routine ECG to CHF incidence on follow-up in a large, community-based sample.

### Methods

The design and selection criteria of Framingham Heart Study have been described previously.<sup>13</sup> Individuals from the original cohort who attended the 16th (1979-1981) or the 17th (1982-1984) biennial examination cycles and had computerized ECG recordings available at these examinations were eligible ( $n = 2081$ ). ECG recordings were obtained on attendees over 2 consecutive cycles (from

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From the Framingham Heart Study (R.D., M.J.P., T.J.W., B.N., E.J.B., D.L., M.G.L., W.B.K., R.B.D., R.S.V.), National Heart, Lung, and Blood Institute, Framingham, Mass; Massachusetts Veterans Epidemiology Research and Information Center (R.D.), VA Boston Healthcare System and the Division of Aging, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass; Division of Cardiology (T.J.W.), Massachusetts General Hospital, Harvard Medical School, Boston, Mass; National Heart, Lung, and Blood Institute (D.L.), Bethesda, Md; Department of Mathematics and Statistics (M.J.P., B.N., M.G.L., R.B.D.), Boston University, Boston, Mass; Cardiology Section (R.S.V., E.J.B.) and Department of Preventive Medicine and Epidemiology (E.J.B., D.L., M.G.L., W.B.K., R.S.V.), Boston University School of Medicine, Boston, Mass.

Correspondence to Ramachandran S. Vasan, Framingham Heart Study, 73 Mount Wayte Ave, Suite 2, Framingham, MA 01702-5803. E-mail vasan@bu.edu

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the middle of examination 16 to the initial part of examination 17). At each examination, participants underwent medical history, physical examination including measurement of blood pressure, anthropometry, and laboratory assessment of risk factors. Attendees also underwent transthoracic 2D guided M-mode echocardiography at examination cycle 16.

We excluded individuals at the baseline examinations for the following reasons: prevalent CHF (by the Framingham criteria, see below; Reference 14) or MI [presence of 2 of 3 criteria (suggestive clinical symptoms, diagnostic ECG changes, and diagnostic serum enzymes);  $n=135$ ] or use of antiarrhythmic medications or prior permanent pacemaker implantation ( $n=187$ ). After exclusions, 1759 participants (1113 women) remained eligible. Informed consent was obtained from all of the participants, and the study was approved by the Institutional Review Board at the Boston Medical Center.

### Ascertainment of CHF

All of the Framingham Study participants are under continuous surveillance for the development of cardiovascular disease events, including CHF. A panel of 3 experienced investigators reviews all of the medical records for adjudication of suspected cardiovascular disease events. The diagnosis of a first episode of CHF is based on the Framingham Heart Study criteria,<sup>14</sup> which have a high specificity for the detection of CHF.<sup>15</sup> The presence of 2 major or of 1 major and 2 minor criteria was used to define an episode of CHF. Criteria were attributed to CHF only in the absence of an alternative explanation for the symptoms and signs by other medical conditions (eg, cirrhosis, renal failure, or chronic pulmonary disease).

### Electrocardiographic Measurements

At the baseline examinations, computerized ECGs were obtained on a 3-channel simultaneous system (Marquette Electronics). Standard 12-lead configuration and XYZ orthogonal leads were recorded in analog form and digitized and read by the IBM Bonner (V2) program.<sup>16</sup> The program analyzed all 12 of the leads and measured the maximum QRS duration to the nearest 2 ms.

At each subsequent biennial examination, a standard 12-lead computerized resting ECG was obtained. ECGs at these visits were interpreted by a Heart Study physician, and the maximum QRS duration was recorded to the nearest 10 ms, based on assessment of all 12 of the leads.

The following criteria advocated by a World Health Organization working group<sup>17</sup> were used to categorize BBB: left BBB (LBBB) was defined as a QRS  $\geq 120$  ms, absence of Q waves, and presence of wide-notched R waves in  $V_5$  and  $V_6$ ; presence of monophasic QS in  $V_1$  and  $V_2$ ; and absence of secondary R waves in  $V_1$ .<sup>17</sup> Criteria used for right BBB (RBBB) were QRS duration  $\geq 120$  ms; broad, notched R waves (rsr', rsR', or rSR' patterns) in  $V_1$  and  $V_2$ ; and wide, deep, and notched S waves in  $V_5$  and  $V_6$ .<sup>17</sup> All of the ECGs with QRS  $\geq 120$  ms that did not meet the criteria for LBBB or RBBB were categorized as "indeterminate."<sup>17</sup>

### Echocardiographic Measurements

All of the attendees underwent routine transthoracic 2D guided M-mode echocardiography at the 16th examination cycle. For participants with computerized electrocardiographic measurements at examination 17, we used echocardiographic data from examination 16 ( $\approx 2$  years prior). All of the echocardiographic measurements were obtained by using a "leading edge" technique.<sup>18</sup> LV mass was calculated by using the standardized formula.<sup>19</sup> LV fractional shortening (FS) was used as an indicator of LV systolic function, with a value of  $<0.29$  indicating systolic dysfunction.<sup>20</sup>

### Statistical Analyses

The primary outcome of interest was the incidence of a first episode of CHF on follow-up through December 2003.

### QRS Duration as a Categorical Variable

We defined 3 QRS interval categories<sup>17</sup>:  $<100$  ms (referent), 100 to 119 ms (incomplete BBB), and  $\geq 120$  ms (complete BBB). CHF

event rates were calculated per 1000 person-years for each QRS category and also by type of BBB. Kaplan-Meier curves were estimated to illustrate the relations of baseline QRS categories to survival free of CHF. We verified that the assumption of proportionality of hazards was met.

Multivariable Cox proportional hazard regression<sup>21</sup> was used to compare CHF incidence in participants with an incomplete BBB and complete BBB with that in individuals with a normal QRS duration (referent group). We also tested for a trend for increasing CHF across the 3 QRS categories. Two sets of regression models were evaluated, adjusting for: (1) age and sex; and (2) age, sex, body mass index (BMI), smoking status, diabetes mellitus, systolic blood pressure, use of antihypertensive treatment, valve disease ( $\geq$  grade 3/6 systolic murmur or any diastolic murmur on physical examination), and MI on follow-up. All of the covariates, including the QRS duration category, were modeled as time-dependent variables; values were updated every 2 years based on observations obtained at routine Heart Study examinations.

We examined whether the potential associations of QRS interval with CHF incidence was mediated by increased LV mass<sup>3,9,10</sup> or by LV systolic dysfunction<sup>11,22</sup> by performing additional analyses. Initially, we repeated all of the analyses after excluding individuals with a FS  $<0.29$  (Table 3, model 2). Next, we repeated analyses in the subgroup noted previously adjusting for baseline LV mass (as a continuous variable) in addition to all of the other covariates (all covariates modeled as time-dependent variables other than LV mass; Table 3, model 3). Lastly, we repeated the analyses noted above but with additional adjustment for baseline FS as a continuous variable (Table 3, model 4).

### Baseline QRS Duration as a Continuous Variable

We evaluated Cox models with baseline QRS duration modeled as a continuous variable (logarithmically transformed to normalize the distribution). Two sets of models were evaluated adjusting for the following: (1) age and sex; and (2) all of the other covariates at baseline (as listed above). In contrast to QRS categories, we did not update continuous QRS duration values every 2 years, because the follow-up examinations did not use the same IBM program for QRS measurements; as noted previously, measurements at subsequent examinations were made to the nearest 10 ms, whereas measurements at the baseline examinations were made to the nearest 2 ms.

To gain insights into potential nonlinearity of associations between QRS duration and CHF risk, we examined generalized additive Cox models using penalized splines.<sup>23</sup> The spline analysis permits the dose-response relation between QRS duration and CHF risk to be examined more accurately than by standard analyses using QRS categories, which may not adequately describe the trends in the data and do not make efficient use of within-category information.<sup>24</sup>

### Additional Analyses

#### Effect Modification

We evaluated for effect modification by age ( $<$  versus  $\geq 70$  years), sex, BMI ( $<$  versus  $\geq 30$  kg/m<sup>2</sup>), and hypertension by incorporating appropriate interaction terms in multivariable models testing for increasing trend across the QRS duration categories.

#### QRS Duration Within the Normal Range and CHF Incidence

Whereas primary analyses focused on the entire range of QRS values, we performed supplementary analyses to investigate whether a gradient of increasing CHF risk was present for QRS duration within the normal range ( $<100$  ms). For this purpose, we used time-dependent analyses in which individuals with QRS  $<100$  ms were categorized at each biennial examination into 2 groups: QRS  $\leq 80$  ms (referent) and QRS  $>80$  ms.

#### Type of BBB at Baseline and CHF Incidence

We also investigated whether CHF incidence varied according to the type of baseline BBB in Cox models (adjusting for baseline clinical covariates and MI on follow-up) that compared individuals with left,

right, and indeterminate BBB (as defined above) with the referent group (QRS interval <100 ms).

### Type of Heart Failure Associated With Baseline QRS Duration Category

To obtain insights into the type of heart failure (systolic versus diastolic) associated with the QRS categories, we reviewed echocardiographic reports in a subgroup of participants who had evaluation of LV systolic function within 30 days of their first hospitalization for CHF in a contemporary time period (1989–1998). CHF was presumed to be because of systolic dysfunction if the estimated LV ejection fraction (LVEF) obtained from hospitalization records was <0.50, whereas an ejection fraction of  $\geq 0.50$  was considered consistent with diastolic CHF.<sup>25</sup>

All of the analyses were performed using SAS.<sup>26</sup> The display of the multivariable-adjusted hazards ratio on a logarithmic scale against the QRS duration was generated using S-Plus. A 2-sided *P* value <0.05 was considered statistically significant.

## Results

Baseline characteristics of our sample are displayed in Table 1. The prevalence of hypertension rose across the QRS duration categories.

### CHF Incidence on Follow-Up

During follow-up (mean, 12.7 years; range, 0.4 to 22.3 years), 324 participants (205 women) developed CHF, including 231 (17.3%) of 1339 individuals in the normal QRS group, 62 (20.2%) of 307 people with incomplete BBB, and 31 (27.4%) of 113 participants with complete BBB. The survival free of

CHF decreased with increasing baseline QRS duration category (Figure 1; log-rank *P*<0.0001). Incidence rates of CHF increased across the QRS duration categories in a graded manner in both sexes (Table 2). A history of antecedent MI within 1 week of CHF onset was present in 57 (24.7%) of 231 CHF events in the normal QRS group, in 10 (16.1%) of 62 CHF events in the incomplete BBB group, and in only 4 (12.9%) of 31 CHF events in the complete BBB group.

### Multivariable Models With QRS Duration Categories

In multivariable time-dependent Cox models (covariates and QRS duration categories updated every 2 years), incomplete BBB was associated with a 1.43-fold CHF risk (*P*=0.03), whereas individuals with complete BBB experienced a 1.74-fold risk of CHF (*P*<0.001) compared with the referent group (Table 3, model 1). The graded increase in CHF risk across QRS categories was confirmed in trend models.

At baseline, 1091 individuals (62%) had data on echocardiographic FS. We compared the group of individuals with adequate echocardiograms with those with inadequate echocardiograms and observed similar rates of CHF incidence overall and in the 3 QRS categories (data not shown). In the analyses of 1070 individuals with FS  $\geq 0.29$  (after excluding 21 individuals with diminished FS), the results of our primary analyses remained robust (Table 3, Model 2). On additional adjustment for baseline LV mass and FS sequentially (Table

TABLE 1. Baseline Characteristics of Study Participants

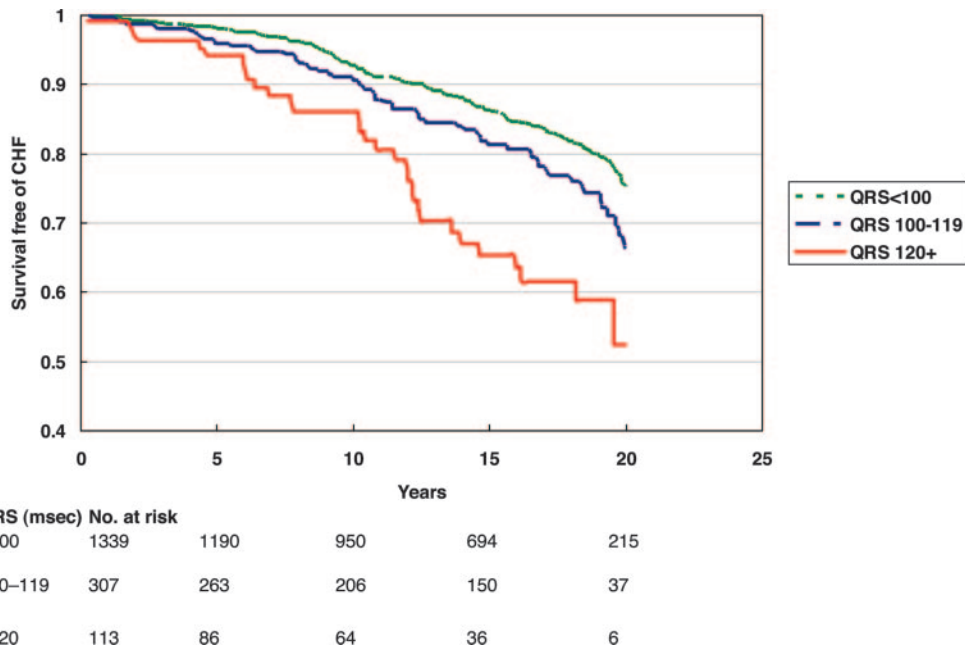
Characteristic	Total (N=1759)	By Baseline QRS Duration (ms)		
		<100 ms (n=1339)	100–119 ms (n=307)	$\geq 120$ ms* (n=113)
Clinical data				
Age, y	70 $\pm$ 7	70 $\pm$ 7	70 $\pm$ 7	72 $\pm$ 7
Women, %	63	70	40	42
BMI, kg/m <sup>2</sup>	26.5 $\pm$ 4.4	26.3 $\pm$ 4.2	27.4 $\pm$ 4.8‡	26.8 $\pm$ 4.2
Systolic blood pressure, mm Hg	142 $\pm$ 20	141 $\pm$ 20	143 $\pm$ 20	149 $\pm$ 19§
Diastolic blood pressure, mm Hg	78 $\pm$ 10	78 $\pm$ 10	79 $\pm$ 10	80 $\pm$ 9
Hypertension, %	67	64	73‡	76†
Antihypertensive treatment %	39	36	47§	46†
Diabetes, %	7	7	9	9
Cigarette smoking, %	19	20	17	10†
Interim MI, %	16	16	17	14
Total/HDL cholesterol	4.9 $\pm$ 1.6	4.8 $\pm$ 1.6	5.0 $\pm$ 1.5	5.1 $\pm$ 1.8
Valve disease, %	3.5	2.9	5.2	6.2
Mean QRS duration, ms	94 $\pm$ 16	87 $\pm$ 7	106 $\pm$ 5	140 $\pm$ 14
Log QRS duration	4.5 $\pm$ 0.2	4.5 $\pm$ 0.1	4.7 $\pm$ 0.1	4.9 $\pm$ 0.1
Echocardiographic data				
Fractional shortening	0.39 $\pm$ 0.05	0.39 $\pm$ 0.05	0.37 $\pm$ 0.05‡	0.37 $\pm$ 0.05†
LV mass, g	165 $\pm$ 52	155 $\pm$ 43	195 $\pm$ 62§	204 $\pm$ 71§
LV hypertrophy,   %	20.1	15.3	34.6	37.7

Values are mean $\pm$ SD or %. HDL indicates high-density lipoprotein.

\*Of 48 women with complete BBB (QRS  $\geq 120$  ms), 15 had LBBB, 25 had RBBB, and 8 had indeterminate BBB; of 65 men with complete BBB, 11 had LBBB, 34 had RBBB, and 20 had indeterminate BBB.

†*P*<0.05, ‡*P*<0.001, and §*P*<0.0001 for age- and sex-adjusted comparisons with referent category, QRS <100 ms.

||Defined as LV mass>sex-specific 80th percentile.



**Figure 1.** Kaplan-Meier curves for survival free of CHF according to the categories of QRS duration at baseline. The curve with small dashes represents individuals with a normal QRS duration, that with large dashes indicates people with incomplete BBB, and the intact line corresponds to participants with complete BBB. Numbers below the panel indicate number of individuals at risk at 5-year intervals.

3, models 3 and 4), the association of complete BBB with CHF risk was maintained, but the relations of incomplete BBB to CHF risk were rendered borderline statistically significant. In these models, the graded increase in CHF risk across QRS categories remained robust (trend across categories, Table 3, models 3 and 4).

**Multivariable Models With Baseline QRS Duration as a Continuous Variable**

In multivariable models with baseline log-QRS duration modeled as a continuous variable, CHF incidence rose with longer QRS interval in age- and sex-adjusted models [hazard ratio (HR) per SD increment, 1.27; 95% CI, 1.14 to 1.41;  $P < 0.001$ ] and in multivariable models (HR per SD, 1.23; 95% CI, 1.08 to 1.38;  $P < 0.001$ ). A 1-SD (0.15) increase in log-QRS corresponds to a 1.2-fold increase in QRS duration in original units, or approximately a 20-ms increment; thus, it may represent an increase from 80 to 100 ms or from 100 to 120 ms. Examination of regression splines demonstrated an

increase in CHF hazard with increasing baseline QRS duration that became steeper for QRS values  $\geq 100$  ms (Figure 2).

**Additional Analyses**

*Effect Modification*

There was no effect modification by sex, BMI, or hypertension status. On stratification of our sample into 2 age groups ( $< 70$  versus  $\geq 70$  years), the association of QRS duration with CHF incidence remained statistically significant for individuals aged  $\geq 70$  years (HR per SD increment in log QRS, 1.26; 95% CI, 1.07 to 1.48;  $P = 0.005$ ) but was attenuated in those  $< 70$  years (HR per SD increment in log QRS, 1.13; 95% CI, 0.96 to 1.34;  $P = 0.13$ ).

*QRS Duration Within the Normal Range (<100 ms) and CHF Incidence*

In analyses restricted to individuals with a QRS  $< 100$  ms ( $n = 1339$ ), 66 (14.6%) of 453 individuals with a QRS  $\leq 80$  ms developed CHF compared with 165 (18.6%) of 886 persons with QRS  $> 80$  ms (but  $< 100$  ms). In time-dependent

**TABLE 2. Cumulative Incidence of CHF for Study Participants According to the Category of QRS Duration at Baseline**

Baseline QRS Duration (ms)	Women		Men	
	No. of Events/No. of Person-Year of Follow-Up	Event Rates per 1000 Person-Year of Follow-Up (95% CI)	No. of Events/No. of Person-Year of Follow-Up	Event Rates per 1000 Person-Year of Follow-Up (95% CI)
<100	166/13411	12.4 (10.6 to 14.4)	65/5153	12.6 (9.9 to 16.1)
100 to 119	26/1660	15.7 (10.7 to 23.0)	36/2378	15.1 (10.9 to 21.0)
$\geq 120$	13/546	23.8 (13.8 to 41.0)	18/702	25.6 (16.2 to 40.7)

**TABLE 3. Multivariable Cox Regression Examining the Relations of Time-Dependent QRS Duration Category to the Risk of CHF**

QRS Duration (ms)	Age- and Sex-Adjusted		Multivariable-Adjusted*	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Model 1: all individuals (n=1759)				
<100	Referent		Referent	
100 to 119	1.74 (1.29 to 2.35)	0.0003	1.43 (1.05 to 1.96)	0.03
≥120	1.95 (1.45 to 2.62)	<0.0001	1.74 (1.28 to 2.35)	0.0004
Trend across categories	1.43 (1.24 to 1.65)	<0.0001	1.33 (1.15 to 1.54)	<0.0001
Model 2: subgroup with available baseline echocardiogram and FS ≥0.29 (n=1070)†				
<100	Referent		Referent	
100 to 119	1.87 (1.25 to 2.78)	0.002	1.61 (1.06 to 2.43)	0.02
≥120	2.35 (1.61 to 3.43)	<0.0001	2.04 (1.37 to 3.03)	0.0004
Trend across categories	1.56 (1.31 to 1.87)	<0.0001	1.45 (1.20 to 1.75)	<0.0001
Model 3: Subgroup with FS ≥0.29: additional adjustment for LV mass (n=1070)†				
<100	Referent		Referent	
100 to 119	1.42 (0.93 to 2.17)	0.10	1.45 (0.96 to 2.21)	0.08
≥120	2.10 (1.43 to 3.07)	<0.0001	1.94 (1.30 to 2.88)	0.001
Trend across categories	1.45 (1.20 to 1.75)	<0.0001	1.40 (1.15 to 1.70)	0.0007
Model 4: subgroup with FS ≥0.29: additional adjustment for LV mass and FS (n=1070)†				
<100	Referent		Referent	
100 to 119	1.34 (0.88 to 2.04)	0.18	1.41 (0.93 to 2.15)	0.11
≥120	2.11 (1.44 to 3.10)	<0.0001	2.00 (1.35 to 2.98)	0.0006
Trend across categories	1.44 (1.19 to 1.74)	<0.0001	1.42 (1.17 to 1.72)	0.0005

\*All models are adjusted for age, sex, and other time dependent covariates (updated every 2 years), including BMI, systolic blood pressure, antihypertensive treatment, total/HDL cholesterol, diabetes mellitus, smoking, interim MI, and valve disease.

†There were 1091 individuals with available data on echocardiographic FS; 21 with FS <0.29 were excluded. There were 179 CHF events among 1070 participants with FS ≥0.29. Other significant predictors of heart failure from multivariable analyses were age, BMI, systolic blood pressure, diabetes, smoking, interim MI, and valve disease.

analyses, a QRS >80 ms was associated with a borderline significant 1.34-fold risk of CHF (95% CI, 0.95 to 1.91;  $P=0.09$ ) in age- and sex-adjusted models and a 1.41-fold risk (95% CI, 0.92 to 2.17;  $P=0.11$ ) in multivariable models compared with the group with QRS ≤80 ms.

#### Type of BBB at Baseline and CHF Incidence

Among individuals with complete BBB at baseline, those with LBBB experienced the highest CHF rates, those with RBBB had the lowest rates, and those with indeterminate BBB had intermediate CHF rates (Table I, available in an online supplement at <http://www.hypertensionaha.org>). In multivariable analyses, LBBB and indeterminate BBB were associated with a higher incidence of CHF (adjusted HR, 4.45; 95% CI, 2.33 to 8.51 for LBBB;  $P=0.0001$ ; adjusted HR, 2.18; 95% CI, 1.13 to 4.20 for indeterminate BBB;  $P=0.02$ ), whereas individuals with RBBB did not have a statistically significant increased risk of CHF (adjusted HR, 1.73; 95% CI, 0.93 to 3.21;  $P=0.08$ ) when compared with those with a QRS duration <100 ms.

#### Type of Heart Failure Associated With Baseline QRS Duration Category

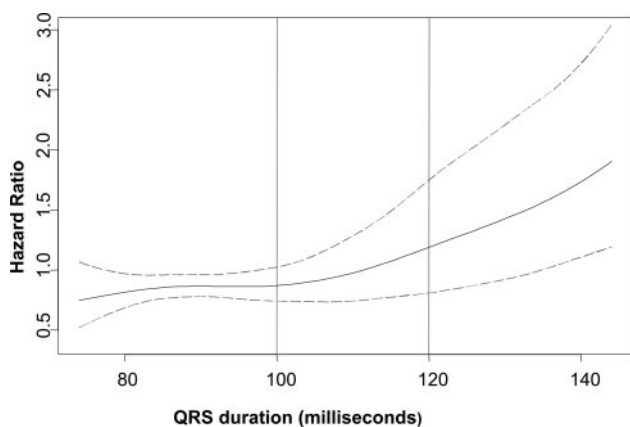
In exploratory analyses, we evaluated 82 participants (25% of CHF cases) who underwent echocardiographic evaluation within 30 days of their first hospitalization for CHF (using

estimates of LVEF from hospitalization records). Of these CHF cases, 64% (37 of 58) in the normal QRS duration group, 50% (7 of 14) in the incomplete BBB group, and 50% (5 of 10) in the complete BBB category had an LVEF <0.50.

## Discussion

### Principal Findings

Our principal findings are 3-fold. First, we observed a significant association of longer QRS duration with rising CHF risk. Incomplete and complete BBB were associated with a 1.5- and 2-fold risk of CHF, respectively. On adjustment for baseline LV mass and FS, the association of complete BBB with CHF risk remained robust. However, the association of incomplete BBB with CHF risk became borderline significant, suggesting that a greater LV mass and lower systolic function may mediate, in part, the greater CHF risk in this group. In secondary analyses restricted to individuals with a QRS <100 ms, we observed a trend for increasing CHF within this range that did not achieve statistical significance, consistent with the steeper hazard for CHF beyond this threshold in regression splines. Second, baseline incomplete and complete BBB accounted for a modest proportion (30%) of CHF events on follow-up. We had limited statistical power to analyze the variation in CHF risk according to the



**Figure 2.** Multivariable-adjusted relations of baseline QRS duration and incidence of CHF on follow-up. Solid line shows estimated relation of HRs (y axis) and QRS duration (x axis) when time to new-onset heart failure is modeled as a function of penalized regression splines of QRS duration controlling for all other covariates. Dotted lines are 95% confidence limits of the resulting HRs. Vertical lines represent upper and lower limits of QRS duration for incomplete BBB (100 to 119 ms).

type of BBB. A majority of CHF events occurred in individuals with a normal baseline QRS duration. Third, in secondary analyses of a subgroup of individuals who underwent echocardiographic evaluation within 30 days after their first hospitalization for CHF, incomplete and complete BBB were associated with both systolic and diastolic CHF.

### Possible Mechanisms for the Association of Longer QRS Duration With CHF Risk

There are several mechanisms that may explain the observed association of longer QRS duration with CHF risk. First, it is possible that the association of electrocardiographic QRS with CHF is confounded by the greater burden of risk factors, such as hypertension,<sup>8</sup> diabetes<sup>2</sup> or ischemic heart disease,<sup>27</sup> in individuals with BBB. To reduce potential confounding, we excluded participants with prevalent CHF and MI at baseline and adjusted for hypertension and other risk factors (including MI).

Second, it is conceivable that longer QRS duration may be associated with alterations in LV structure and function.<sup>3,9–11,22,28</sup> We performed additional analyses excluding participants with a reduced FS and adjusted for LV mass and FS. In these analyses, the association of complete BBB with greater CHF risk remained robust, but the relations of incomplete BBB to CHF risk were attenuated. These results suggest that association of longer QRS duration with structural and functional LV changes<sup>3,9–11,22</sup> may partly explain the increased CHF risk observed with incomplete BBB.

A third mechanism may be the greater prevalence of ventricular dyssynchrony in individuals with longer QRS, which may promote CHF risk. Because the baseline examination antedated use of 2D and Doppler echocardiography, we could not explore this possibility. Overall, it is conceivable that all 3 of the pathophysiological mechanisms contribute to the increased risk of CHF in individuals with longer QRS duration.

### Limitations

It is difficult to conclude on the basis of our epidemiological study that the association of longer QRS duration with greater CHF risk is a causal one. Even if QRS duration were simply a marker (and not a cause) of CHF risk, the ease of measurement and routine availability would render it a potentially useful indicator of risk. It is noteworthy, though, that QRS duration satisfies several of Hill's criteria<sup>29</sup> for causality of associations, including prolongation of QRS duration antedated CHF (temporal relations), observed dose-response relation, consistent findings in multiple models, and a biologically plausible causal association is (as detailed in the section above). The measurement of QRS duration is known to be operator dependent, and measurement reproducibility is reduced by the presence of conduction abnormalities.<sup>30</sup> For some of our analyses that used QRS categories, we combined assessment of QRS categories at baseline (that were computerized) with that at follow-up examinations (that were manually determined by physicians); we submit that ascertainment of QRS category status will not be biased in a major way by this strategy. However, we used only baseline QRS measurements when QRS duration was modeled as a continuous variable. Our sample of individuals with available echocardiograms was modest in size; hence, results of our subgroup analyses warrant confirmation by large studies. The use of FS by M-mode echocardiography as an indicator of LV systolic function is an additional limitation, because such assessment reflects systolic function of the basal LV segments. In addition, although we adjusted for LV mass, we did not account for LV diastolic function, because such measures were not available at the baseline examinations. It is important to emphasize the limited generalizability of our results to other ethnicities given the overwhelmingly white Framingham sample.

### Conclusions

In our large, community-based sample of middle-aged and elderly individuals free of prior CHF and MI, longer electrocardiographic QRS duration was associated with elevated risk of CHF. The association was most striking in individuals with complete BBB, who experienced a 2-fold risk of CHF compared with people with a normal QRS duration (<100 ms). Additional prospective studies of larger multiethnic samples size are warranted to confirm our findings and to elucidate the mechanisms underlying the observed association.

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