Clinical Implications of QRS Duration in Patients Hospitalized With Worsening Heart Failure and Reduced Left Ventricular Ejection Fraction

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Context Hospitalization for heart failure is associated with high postdischarge mortality and morbidity. The predictive value of the QRS duration during admission for heart failure has not been well studied.

Objective To investigate the predictive value of the QRS duration in patients hospitalized for heart failure with reduced left ventricular ejection fraction (LVEF).

Design, Setting, and Participants Retrospective, post hoc analysis from the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST), an event-driven, randomized, double-blind, placebo-controlled study in patients hospitalized for heart failure and having an LVEF of 40% or less. A total of 4133 patients were enrolled at 359 North American, South American, and European sites between October 7, 2003, and February 3, 2006. After excluding 1029 patients with a pacemaker, implantable cardioverter-defibrillator, or both at enrollment and 142 patients without a reported baseline QRS duration, 2962 patients were included in the analysis: 1641 had a normal QRS duration (<120 ms) and 1321 had a prolonged QRS duration (≥120 ms).

Main Outcome Measures Dual primary end points were all-cause mortality and the composite of cardiovascular death or hospitalization for heart failure.

Results During a median follow-up of 9.9 months, all-cause mortality was 18.7% for patients with a normal baseline QRS duration and 28.1% for patients with a prolonged baseline QRS duration (hazard ratio [HR], 1.61; 95% confidence interval [CI], 1.38-1.87). The composite of cardiovascular death or hospitalization for heart failure was 32.4% for patients with a baseline QRS duration less than 120 ms and 41.6% for patients with a baseline QRS duration of 120 ms or greater (HR, 1.40; 95% CI, 1.24-1.58). The increased risk associated with prolonged QRS duration was confirmed after adjusting for multiple variables for all-cause mortality (HR, 1.24; 95% CI, 1.02-1.50) and the composite of cardiovascular death or hospitalization for heart failure (HR, 1.28; 95% CI, 1.10-1.49). Only 105 patients (3.6%) who presented with a prolonged baseline QRS duration had a normal QRS duration on their last inpatient electrocardiogram.

Conclusion A prolonged QRS duration appears common in patients with reduced LVEF who are hospitalized for heart failure and is an independent predictor of high postdischarge morbidity and mortality.

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HOSPITALIZATION FOR HEART failure is a major public health problem in the developed world, with the United States and Europe each reporting more than 1 million admissions per year.[1,2] For patients who survive, the mortality rate is highest in the early postdischarge period, with the majority of deaths attributable to progressive heart failure and sudden cardiac death.[3] In addition, nearly one-third of patients are rehospitalized within 3 months postdischarge.[4]

Electrical dyssynchrony, defined as a QRS duration of 120 milliseconds (ms) or greater, is associated with increased mortality in outpatients with heart failure.[5-8] In select outpatients with stable heart failure symptoms and reduced left ventricular ejection fraction (LVEF), therapy targeted at cardiac dyssynchrony has been shown to improve clinical outcome.[9] The predic-

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tive value of a prolonged QRS duration during an admission for heart failure is limited and inconsistent.[10-16] Establishing the prognostic value of a prolonged QRS duration during hospitalization for heart failure may aid in tailoring therapy to improve postdischarge morbidity and mortality.

The Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) studied the effect of tolvaptan compared with placebo in a population of patients with chronically reduced LVEF who were hospitalized for worsening heart failure while receiving standard medical therapy. In this study, we investigated the relationship of the baseline QRS duration and the changes in QRS duration during the course of the hospitalization to the end points of all-cause mortality and the composite of cardiovascular death or hospitalization for heart failure.

METHODS

Study Overview

This was a retrospective, post hoc analysis from the EVEREST program. The design of the EVEREST program has been published previously.[17] Institutional review board or ethics committee approval was obtained at each site, and all participants provided written informed consent. EVEREST consisted of 3 trials designed to explore both the short-term and long-term impact of the vasopressin V_2 receptor antagonist tolvaptan in patients with reduced LVEF (≤40%) and hospitalized with worsening heart failure.

A total of 4133 patients were enrolled and randomized to receive oral tolvaptan (30 mg/d) or placebo in a double-blinded fashion between October 7, 2003, and February 3, 2006. All patients underwent randomization at 359 centers in 20 countries categorized into 4 distinct geographic regions: 1251 patients in North America (Canada and the United States), 699 in South America (Argentina and Brazil), 564 in Western Europe (Belgium, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland, and the United Kingdom), and 1619 in Eastern Europe (Bulgaria, Czech Republic, Lithuania, Poland, Romania, and Russia).

Ethnicity was classified by both the patient and the individual screening the patient. The options were defined by the investigators as white, black, Hispanic, Asian, or other. Race and ethnicity were collected for the purpose of evaluating subgroup differences.

Exclusion criteria in the EVEREST program included planned revascularization procedures, electrophysiologic device implantation, cardiac mechanical support implantation, cardiac transplantation, or other cardiac surgery within 30 days following study enrollment; a history of biventricular pacer placement within the last 60 days; a history of sustained ventricular tachycardia or ventricular fibrillation within 30 days, unless in the presence of an implantable cardioverter-defibrillator (ICD); a comorbid condition with an expected survival less than 6 months; acute myocardial infarction at the time of hospitalization; hemodynamically uncorrected primary cardiac valvular disease; and refractory end-stage heart failure. Background therapy was left to the discretion of the treating physician, but specific recommendations for optimal medical therapy based on published guidelines were included in the study protocol.[17]

Twelve-lead electrocardiograms (ECGs) were performed after 10 minutes of supine rest. Three valid baseline 12-lead ECGs were obtained at the initial screening day at least 5 minutes apart, and 1 ECG was obtained during subsequent prespecified, scheduled visits. The principal investigator or designee reviewed each ECG reading. Twelve-lead ECGs obtained at the study centers were forwarded to the centralized ECG vendor for final analysis and data reporting by a cardiologist. The QRS duration was reported as an integer. The final baseline QRS duration used for our analysis was the average obtained from the 3 baseline tracings. A normal QRS duration was defined as less than 120 ms and a prolonged QRS duration as 120 ms or greater. The presence of a right bundle-branch block or left bundle-branch block was defined by published standard criteria.[18]

Our analyses excluded patients who had a pacemaker, an ICD, or both at the time of enrollment. The study sample in our first analysis was limited to patients with reported baseline QRS duration. Substudy analyses were performed with regard to the presence or absence of coronary artery disease (CAD), sex, QRS morphology, treatment group, and geographic region. The study sample in our second analysis regarding QRS duration change during hospitalization was assessed by comparison of the QRS duration from the baseline ECG and the QRS duration from the last inpatient ECG obtained in the study protocol.

During hospitalization, patients had 1 scheduled ECG performed on the prespecified inpatient days 1, 3, 6, 8, and 10. An ECG was obtained at discharge only if the patient was discharged prior to hospital day 10. Therefore, the last inpatient ECG was either the one obtained on hospital day 10 or at discharge. The last inpatient ECG for those patients who died while hospitalized was either the last scheduled ECG if they died prior to hospital day 10 or the ECG on hospital day 10 if they died after hospital day 10. In the event of implantation of a pacemaker, ICD, or cardiac resynchronization therapy (CRT) device during hospitalization, the last scheduled ECG prior to device implantation was used as the last inpatient ECG.

Patients were categorized into 4 groups: baseline QRS duration less than 120 ms and last inpatient QRS duration less than 120 ms, baseline QRS duration less than 120 ms and last inpatient QRS duration 120 ms or greater, baseline QRS duration 120 ms or greater and last inpatient QRS duration less than 120 ms, and baseline QRS duration 120 ms or greater and last inpatient QRS duration 120 ms or greater. Patients who crossed over to another group between the baseline and last inpatient ECGs were compared with the

group who had a normal QRS duration on both their baseline and last inpatient ECGs.

Definition of Study End Points

The long-term outcome study had 2 primary end points: all-cause mortality and the composite of cardiovascular mortality or hospitalization for heart failure. Each of the 2 primary end points was primarily analyzed as time to first event. The primary end points for the present analyses were the same as those in the long-term EVEREST study and were analyzed at 3 months after enrollment and for the overall follow-up period. The date of the last follow-up was July 5, 2006.

The cause of death, cardiovascular hospitalization, and unscheduled visits for worsening heart failure events were adjudicated by a blinded clinical events committee. Sudden cardiac death was defined as an unexpected death in a previously stable patient, including those who were comatose and then died after attempted resuscitation. Patients should have had recent human contact before the event. Patients who died and who were out of human contact for 24 hours to 1 week prior to the event were classified as "presumed sudden cardiac death."

Data Analysis

Comparisons between groups were performed using the Wilcoxon rank sum test for continuous variables and the Pearson χ^2 test for categorical variables. Within each group, time-to-event outcomes were summarized using Kaplan-Meier survival curves, and differences between groups were summarized by the hazard ratio (HR) and a 95% confidence interval (CI) computed using the Cox proportional hazards model. The baseline characteristics were retained in the multivariable analysis for the baseline QRS duration analysis if they met $P < .05$ in the model for all-cause mortality. The same variables were maintained for the composite of cardiovascular mortality or hospitalization for heart failure and for both end points in the analysis of QRS duration change during hospitalization. Models to compare the QRS morphology of patients with a QRS duration of 120 ms or greater with patients having a QRS duration less than 120 ms were performed while adjusting for age, geographic region, LVEF, type of block, systolic blood pressure, β-blocker use, and serum urea nitrogen level.

All *P* values were based on 2-sided tests and were considered significant at $P < .05$. No formal adjustment for multiple comparisons was used because these analyses were not prespecified. All analyses were conducted using R version 2.6.1 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Of the 4133 participants in the EVEREST program, 142 were excluded because the QRS duration was not reported on the baseline ECG, and 1029 were excluded because of the presence of a pacemaker, ICD, or both at the time of enrollment. The final study sample in our first analysis consisted of 2962 patients (71.7%). During follow-up among these 2962 patients, pacemakers were implanted in 86 (2.9%), ICDs in 164 (5.5%), and a CRT device in 5 (0.17%). The median duration of follow-up was 9.9 months.

In the 1171 excluded patients, 938 (80.1%) were men, mean age was 68.6 (SD, 11.4) years, and mean LVEF was 25.5 (SD, 8.1%). Within this group, 402 (34.3%) had died and 620 (52.9%) had a cardiovascular death or hospitalization for heart failure at the end of the overall follow-up period.

Baseline Characteristics

Baseline QRS duration less than 120 ms was observed in 1641 patients (55.4%), and QRS duration of 120 ms or greater was observed in 1321 (44.6%). The mean QRS duration was 96.3 (SD, 10.6) ms (range, 71.1-119.7 ms) among all patients with QRS duration less than 120 ms and 144.6 (SD, 19.9) ms (range, 120.0-228.7 ms) among all patients with QRS duration of 120 ms or greater.

The baseline characteristics of the study patients by QRS duration are presented in TABLE 1. A QRS duration of 120 ms or greater was associated with older age, male sex, lower LVEF, lower systolic blood pressure, and higher levels of serum brain natriuretic peptide and serum urea nitrogen. There was no significant difference for New York Heart Association functional class.

Medical Regimen on Admission and Discharge

On admission, most patients were receiving standard medical therapy for heart failure with reduced LVEF (TABLE 2). Patients with a baseline QRS duration of 120 ms or greater were more likely to receive angiotensin receptor blockers (ARBs) (11.5% vs 9.4%, $P = .07$) and amiodarone (15.4% vs 9.7%, $P < .001$) and less likely to receive β-blocking agents (66.3% vs 71.3%, $P = .004$). In both groups, treatment with angiotensin-converting enzyme (ACE) inhibitors was 79%.

Of the 2908 patients who survived hospitalization and were able to be discharged, 1621 (55.7%) had a baseline QRS duration less than 120 ms, and 1287 (44.3%) had a baseline QRS duration of 120 ms or greater. On discharge from the hospital, patients with a baseline QRS duration of 120 ms or greater were more likely to receive diuretics (94.3% vs 91.9%, $P = .01$), ARBs (11.9 vs 9.6%, $P = .048$), and amiodarone (16.3% vs 10.7%, $P < .001$). While the use of β-blocking agents increased in both groups, patients with a QRS duration of 120 ms or greater were less likely to receive them (72.2% vs 77.3%, $P = .002$). There was no difference in the use of ACE inhibitors (78.2% vs 79.8%, $P = .29$) or spironolactone (63.2% vs 60.4%, $P = .12$).

Association of Baseline QRS Duration With Adjudicated Causes of Death

There were 678 total deaths (307 of 1641 patients [18.7%] with a baseline QRS duration <120 ms and 371 of 1321 [28.1%] with a baseline QRS duration ≥120 ms). Irrespective of baseline QRS

duration, the most common cause of death was heart failure, followed by sudden cardiac death (TABLE 3). Among 307 patients with a QRS duration less than 120 ms who died, 110 (35.8%) died of heart failure and 93 (30.3%) died suddenly. Among 371 patients with a QRS duration of 120 ms or greater who died, 141 (38.0%) died of heart failure and 114 (30.7%) died suddenly. Acute myocardial infarction accounted for approximately 3% of total deaths in both groups. Therefore, the mode of death was similar, irrespective of whether the baseline QRS duration was normal or prolonged. A cause of death could not be determined in 69 cases (10.2%).

Association of Baseline QRS Duration With End Points

A baseline QRS duration of 120 ms or greater was associated with a significantly increased risk of death compared with a baseline QRS duration less than 120 ms 3 months after enrollment (11.6% vs 6.6%; HR, 1.77; 95% CI, 1.39-2.27) and at the end of the follow-up period (28.1% vs 18.7%; HR, 1.61; 95% CI, 1.38-1.87) (TABLE 4 and FIGURE). The composite of cardiovascular death or hospitalization for heart failure was also more frequent in patients with a baseline QRS duration of 120 ms or greater at 3 months after enrollment (21.1% vs 14.6%; HR, 1.52; 95% CI, 1.28-1.80) and at the end of the follow-up period (41.6% vs 32.4%; HR, 1.40; 95% CI, 1.24-1.58) (Table 4 and Figure).

Multivariable Analysis for the Baseline QRS Duration Analysis

Adjustment was performed for the baseline variables of age, race, geographic region, LVEF, systolic blood pressure, β-blocker use, and levels of brain natriuretic peptide and serum urea nitrogen (Table 4). Three months after enrollment, patients with a baseline QRS duration of 120 ms or greater were more likely to have a cardiovascular death or hospitalization for heart failure (HR, 1.40; 95% CI, 1.13-1.74) compared with those having a normal baseline QRS du-

Table 1. Baseline Patient Characteristics Categorized by Baseline QRS Duration

Characteristic	No. (%)[a] QRS Duration <120 ms (n = 1641)	No. (%)[a] QRS Duration ≥120 ms (n = 1321)	P Value
Age, mean (SD), y	63.6 (12.2)	66.0 (11.3)	<.001
Men	1156 (70.4)	981 (74.3)	.02
Race			
White	1380 (84.1)	1124 (85.1)	<.001
Black	159 (9.7)	65 (4.9)	
Other[b]	102 (6.2)	132 (10.0)	
Geographic region			
North America	365 (22.2)	267 (20.2)	<.001
South America	261 (15.9)	331 (25.1)	
Western Europe	185 (11.3)	187 (14.2)	
Eastern Europe	830 (50.6)	536 (40.6)	
Weight, mean (SD), kg	84.2 (19.2)	81.5 (17.9)	<.001
LVEF, mean (SD), %	29.6 (7.7)	26.7 (7.7)	<.001
QRS morphology			
Right bundle-branch block pattern	4 (0.2)	234 (17.7)	<.001
Left bundle-branch block pattern	21 (1.3)	909 (68.8)	<.001
NYHA class			
III	972 (60.4)	750 (58.2)	.23
IV	638 (39.6)	539 (41.8)	
Baseline cardiovascular assessment			
Dyspnea	1494 (92.1)	1178 (91.0)	.33
Fatigue	1361 (84.1)	1066 (82.9)	.38
Orthopnea	843 (52.0)	676 (52.4)	.83
Systolic blood pressure, mean (SD), mm Hg	125.4 (20.3)	119.8 (19.1)	<.001
Diastolic blood pressure, mean (SD), mm Hg	76.0 (12.7)	72.6 (11.8)	<.001
Heart rate, mean (SD), beats/min	82.7 (16.8)	79.7 (15.2)	<.001
Jugular venous distension ≥10 cm	420 (26.1)	372 (28.9)	.09
Murmur	857 (52.8)	783 (60.4)	<.001
Rales	1319 (81.3)	1060 (81.8)	.74
Pedal edema	1341 (82.7)	1036 (79.9)	.06
Medical history			
Coronary artery disease	1117 (68.1)	889 (67.4)	.68
Previous myocardial infarction	749 (45.7)	636 (48.2)	.18
PTCA	234 (14.3)	173 (13.1)	.36
CABG	224 (13.7)	233 (17.6)	.003
Hypertension	1198 (73.0)	917 (69.4)	.03
Valvular disease, mitral	434 (26.4)	368 (27.9)	.39
Heart failure hospitalization	1247 (76.3)	1036 (78.8)	.11
Atrial fibrillation or flutter	618 (37.7)	394 (29.8)	<.001
Peripheral vascular disease	349 (21.3)	236 (17.9)	.02
Diabetes mellitus	636 (38.8)	463 (35.0)	.04
Hypercholesterolemia	699 (42.9)	590 (44.9)	.28
Chronic renal insufficiency	297 (18.1)	288 (21.8)	.01
Chronic obstructive pulmonary disease	146 (8.9)	113 (8.6)	.74
Laboratory findings			
Serum sodium, mean (SD), mg/dL	139.9 (4.4)	139.9 (4.8)	.55
Serum urea nitrogen, mean (SD), mg/dL	27.0 (14.2)	29.3 (14.7)	<.001
Serum creatinine, mean (SD), mg/dL	1.27 (0.56)	1.35 (0.46)	<.001
Serum BNP, mean (SD), pg/mL	1050.3 (2414.2)	1217.6 (2671.5)	<.001

Abbreviations: BNP, brain-type natriuretic peptide; CABG, coronary artery bypass graft; LVEF, left ventricular ejection fraction; PTCA, percutaneous transluminal coronary angioplasty; NYHA, New York Heart Association.
SI conversion factors: To convert serum urea nitrogen values to mmol/L, multiply by 0.357; creatinine values to μmol/L, by 88.4.
[a] Data are presented as No. (%) unless otherwise specified.
[b] Includes individuals of Hispanic (n=69) and Asian (n=5) ethnicity.

ration. The adjusted rate of all-cause mortality 3 months after enrollment remained increased in patients with a prolonged QRS duration but was not statistically significant (HR, 1.30; 95% CI, 0.97-1.73). A baseline QRS duration of 120 ms or greater remained a significant predictor of increased mortality (HR, 1.24; 95% CI, 1.02-1.50) and the composite of cardiovascular death and hospitalization for heart failure (HR, 1.28; 95% CI, 1.10-1.49) for the overall follow-up period.

Subgroup Analyses

After adjusting for multiple variables, patients with prolonged QRS duration were at increased risk for all-cause mortality and the composite of cardiovascular death or hospitalization for heart failure at the end of the overall follow-up period when compared with patients with normal QRS duration, independent of CAD status or sex (TABLE 5). No statistically significant interactions were seen between either CAD status or sex and QRS duration group for any of these outcomes.

In the long-term EVEREST outcome trial, no statistically significant difference was seen in all-cause mortality or the composite of cardiovascular death or hospitalization for heart failure between those assigned to receive tolvaptan and placebo.[19] This was demonstrated both in patients with a normal QRS duration and those with a prolonged QRS duration for both primary end points.

Of the 1321 patients with a QRS duration of 120 ms or greater, 234 were classified as having a right bundle-branch block and 909 as having a left bundle-branch block. The remaining 178 were considered to have a nonspecific intraventricular conduction delay. No significant differences were seen in the increased rates of all-cause mortality and the composite of cardiovascular death and hospitalization for heart failure 3 months after enrollment and for the overall follow-up period based on QRS morphology (TABLE 6). All groups with a QRS duration of 120 ms or greater had higher event rates compared with the 1641 patients in the group with a QRS duration less than 120 ms.

In the EVEREST program, significant differences were seen in baseline patient characteristics, baseline medical regimens, and outcomes by geographic region. A baseline QRS duration of 120 ms or greater was consistently associated with increased event rates, although the magnitude varied across regions.

Table 2. Medications at Admission and Discharge Categorized by Baseline QRS Duration

Medication	No. (%) QRS Duration <120 ms	No. (%) QRS Duration ≥120 ms	*P* Value
Admission	n = 1641	n = 1321	
ACE inhibitor	1303 (79.4)	1048 (79.3)	.96
Angiotensin receptor blocker	155 (9.4)	152 (11.5)	.07
β-Blocking agent	1170 (71.3)	876 (66.3)	.004
Spironolactone	905 (55.1)	740 (56.0)	.64
Digoxin	788 (48.0)	651 (49.3)	.50
Diuretic	1587 (96.7)	1289 (97.6)	.16
Amiodarone	159 (9.7)	204 (15.4)	<.001
Serum lipid–reducing agent	523 (31.9)	422 (31.9)	.96
Peripheral vasodilator	45 (2.7)	26 (2.0)	.17
Calcium channel blocker	221 (13.5)	138 (10.4)	.01
Discharge	n = 1621	n = 1287	
ACE inhibitor	1287 (79.8)	1007 (78.2)	.29
Angiotensin receptor blocker	155 (9.6)	153 (11.9)	.048
β-Blocking agent	1246 (77.3)	929 (72.2)	.002
Spironolactone	974 (60.4)	814 (63.2)	.12
Digoxin	743 (46.1)	598 (46.5)	.84
Diuretic	1481 (91.9)	1213 (94.3)	.01
Amiodarone	172 (10.7)	210 (16.3)	<.001
Serum lipid–reducing agent	546 (33.9)	428 (33.3)	.73
Peripheral vasodilator	26 (1.6)	21 (1.6)	.97
Calcium channel blocker	183 (11.4)	92 (7.1)	<.001

Abbreviation: ACE, angiotensin-converting enzyme.

Table 3. Adjudicated Causes of Death Categorized by Baseline QRS Duration

Cause of Death	Total Deaths, No. (%) QRS Duration <120 ms (n = 307)	Total Deaths, No. (%) QRS Duration ≥120 ms (n = 371)
Heart failure	110 (35.8)	141 (38.0)
Sudden cardiac death	93 (30.3)	114 (30.7)
Acute myocardial infarction	10 (3.3)	11 (3.0)
Stroke	10 (3.3)	8 (2.2)
Other cardiovascular mortality	12 (3.9)	19 (5.1)
Noncardiovascular mortality	36 (11.7)	45 (12.1)
Unknown	36 (11.7)	33 (8.9)

QRS Duration Change During Hospitalization

From the 4133 participants in the EVEREST program, a total of 1198 patients were excluded for the second analysis: 129 did not have a baseline or last inpatient QRS duration reported, 13 had a baseline QRS duration but not a last inpatient QRS duration reported, 27 had a last inpatient but not a baseline QRS duration reported, and 1029 had a pacemaker, ICD, or both at the time of enrollment. The final study

sample in our second analysis thus consisted of 2935 patients (71.0%).

The mean number of days between the baseline ECG and the last inpatient ECG was 6.47 (SD, 3.17). In 1463 patients (49.8%), the QRS duration was less than 120 ms on both the baseline ECG (mean, 95.1 [SD, 10.1] ms) and last inpatient ECG (mean, 94.2 [SD, 10.2] ms). In 1204 patients (41.0%), the QRS duration was 120 ms or greater on both the baseline ECG (mean, 146.1 [SD, 19.8] ms) and last inpatient ECG (mean, 146.1 [SD, 20.4] ms). One hundred sixty-three patients (5.6%) were admitted with a baseline QRS duration less than 120 ms (mean, 107.5 [SD, 8.5] ms) and had a last inpatient QRS duration of 120 ms or greater (mean, 125.9 [SD, 6.9] ms). Conversely, 105 patients (3.6%) were admitted with a baseline QRS duration of 120 ms or greater (mean, 126.8 [SD, 10.1] ms) and had a last inpatient QRS duration less than 120 ms (mean, 107.0 [SD, 9.1] ms).

Compared with patients who had a normal QRS duration on their baseline and last inpatient ECGs, those who presented with a normal QRS duration but who developed a prolonged QRS duration during hospitalization had significantly increased rates of all-cause mortality 3 months after enrollment (12.9% vs 6.3%; HR, 2.14; 95% CI, 1.33-3.43) and for the overall follow-up period (28.2% vs 17.6%; HR, 1.81; 95% CI, 1.32-2.47) (TABLE 7). The composite of cardiovascular death or hospitalization for heart failure was also significantly increased at the end of the overall follow-up period (42.9% vs 31.4%; HR, 1.51; 95% CI, 1.18-1.95) in the unadjusted model. After adjustment for multiple variables, the composite of cardiovascular death or hospitalization for heart failure at the end of the overall follow-up period remained significant (HR, 1.43; 95% CI, 1.04-1.96).

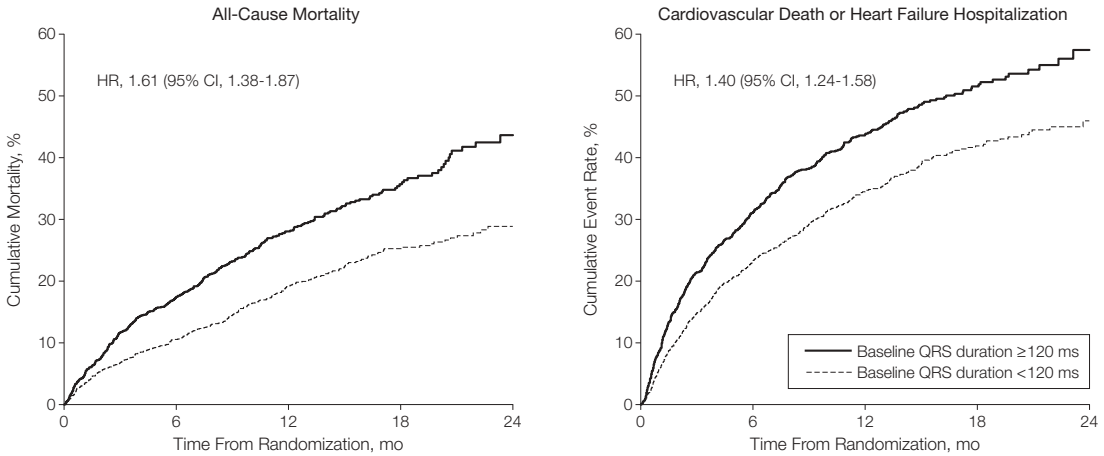
Patients who presented with a prolonged QRS duration on their baseline ECG but who had a normal QRS duration on their last inpatient ECG had

Table 4. All-Cause Mortality and the Composite of Cardiovascular Death or Hospitalization for Heart Failure Categorized by Baseline QRS Duration

Outcome	QRS Duration <120 ms (n = 1641), No. (%)	QRS Duration ≥120 ms (n = 1321), No. (%)	HR (95% CI)	
			Unadjusted	Adjusted[a]
3 mo				
All-cause mortality	109 (6.6)	153 (11.6)	1.77 (1.39-2.27)	1.30 (0.97-1.73)
Cardiovascular death/heart failure hospitalization	239 (14.6)	280 (21.1)	1.52 (1.28-1.80)	1.40 (1.13-1.74)
Overall				
All-cause mortality	307 (18.7)	371 (28.1)	1.61 (1.38-1.87)	1.24 (1.02-1.50)
Cardiovascular death/heart failure hospitalization	532 (32.4)	549 (41.6)	1.40 (1.24-1.58)	1.28 (1.10-1.49)

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Adjusted for age, race, geographic region, left ventricular ejection fraction, systolic blood pressure, β-blocker use, and levels of serum brain-type natriuretic peptide and serum urea nitrogen.

Figure. Kaplan-Meier Analyses of All-Cause Mortality and the Composite of Cardiovascular Death or Hospitalization for Heart Failure in Patients With a Baseline QRS Duration ≥120 ms Compared With Patients With a Baseline QRS Duration <120 ms



For all-cause mortality, 307 events occurred in patients with QRS duration <120 ms and 371 in those with QRS duration ≥120 ms; for the composite of cardiovascular death or hospitalization for heart failure, 532 events occurred in patients with QRS duration <120 ms and 549 in those with QRS duration ≥120 ms. CI indicates confidence interval; HR, hazard ratio.

significantly increased rates in the unadjusted model for the end points of all-cause mortality for the overall follow-up period (26.7% vs 17.6%; HR, 1.67; 95% CI, 1.13-2.47) and the composite of cardiovascular death and hospitalization for heart failure, both 3 months after enrollment (23.8% vs 14.6%; HR, 1.75; 95% CI, 1.15-2.64) and for the overall follow-up period (42.9% vs 31.4%; HR, 1.59; 95% CI, 1.17-2.17) (Table 7). In the multivariable analysis, the composite of cardiovascular death and hospitalization for heart failure remained significant 3 months after enrollment (HR, 1.93; 95% CI, 1.21-3.10) and for the overall follow-up period (HR, 1.65; 95% CI, 1.15-2.37).

Patients who presented with a prolonged QRS duration on their baseline and last inpatient ECGs had significantly increased rates of all-cause mortality and the composite of cardiovascular death and hospitalization for heart failure 3 months after enrollment and for the overall follow-up period. These were significant in both the unadjusted and adjusted models (Table 7).

COMMENT

To the best of our knowledge, our study is the first report using data from a large-scale, prospective, multicenter trial to address the predictive value of a prolonged QRS duration in patients with reduced LVEF who were hospitalized for worsening heart failure. The long-term EVEREST outcome trial demonstrated that despite standard medical therapy including β-blocking agents and ACE inhibitors, ARBs, or both, more than one-fourth of the entire study population was deceased at a median follow-up of 9.9 months.[19] The present analyses demonstrated that a prolonged baseline QRS duration was common, present in nearly half the patients, and identified a particular subgroup with a 24% increased mortality risk when compared with a normal baseline QRS duration. The majority of patients died of progressive heart failure or sudden cardiac death, with worsening heart failure the major mode of death. In addition, we demonstrated that a prolonged QRS duration at admission or late in the hospitalization, despite a normal QRS duration at other times during the hospitalization, was associated with increased event rates.

The adverse contribution of a prolonged QRS duration for the majority

Table 5. All-Cause Mortality and the Composite of Cardiovascular Death or Hospitalization for Heart Failure Categorized by Baseline QRS Duration and by Presence or Absence of Coronary Artery Disease and Sex

Outcome	QRS Duration <120 ms, No. (%)[a]	QRS Duration ≥120 ms, No. (%)	HR (95% CI)	
			Unadjusted	Adjusted[b]
CAD present	1117 (55.7)	889 (44.3)		
3 mo				
All-cause mortality	73 (6.5)	96 (10.8)	1.68 (1.24-2.28)	1.13 (0.79-1.61)
Cardiovascular death/heart failure hospitalization	158 (14.1)	180 (20.2)	1.49 (1.20-1.84)	1.27 (0.97-1.65)
Overall				
All-cause mortality	211 (18.9)	253 (28.5)	1.64 (1.37-1.97)	1.13 (0.89-1.42)
Cardiovascular death/heart failure hospitalization	369 (33.0)	375 (42.2)	1.41 (1.22-1.63)	1.21 (1.01-1.46)
CAD absent	523 (54.9)	430 (45.1)		
3 mo				
All-cause mortality	36 (6.9)	56 (13.0)	1.92 (1.26-2.92)	1.70 (1.00-2.90)
Cardiovascular death/heart failure hospitalization	81 (15.5)	99 (23.0)	1.57 (1.17-2.11)	1.70 (1.17-2.47)
Overall				
All-cause mortality	96 (18.4)	116 (27.0)	1.51 (1.16-1.99)	1.52 (1.05-2.21)
Cardiovascular death/heart failure hospitalization	163 (13.2)	174 (40.5)	1.38 (1.12-1.71)	1.48 (1.11-1.97)
Men	1156 (54.1)	981 (45.9)		
3 mo				
All-cause mortality	76 (6.6)	108 (11.0)	1.70 (1.26-2.27)	1.30 (0.91-1.84)
Cardiovascular death/heart failure hospitalization	158 (13.7)	205 (20.9)	1.60 (1.30-1.97)	1.47 (1.14-1.90)
Overall				
All-cause mortality	216 (18.7)	281 (28.6)	1.66 (1.39-1.99)	1.27 (1.01-1.60)
Cardiovascular death/heart failure hospitalization	365 (31.6)	418 (42.6)	1.51 (1.31-1.74)	1.39 (1.16-1.67)
Women	485 (58.8)	340 (41.2)		
3 mo				
All-cause mortality	33 (6.8)	45 (13.2)	2.00 (1.28-3.13)	1.27 (0.74-2.20)
Cardiovascular death/heart failure hospitalization	81 (16.7)	74 (21.8)	1.36 (0.99-1.87)	1.15 (0.77-1.72)
Overall				
All-cause mortality	91 (18.8)	90 (26.5)	1.48 (1.10-1.98)	1.13 (0.78-1.65)
Cardiovascular death/heart failure hospitalization	167 (34.4)	131 (38.5)	1.15 (0.92-1.45)	0.99 (0.73-1.33)

Abbreviations: CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio.
[a] For CAD analyses, CAD information was missing for 1 patient in the QRS duration <120 ms group and 2 in the QRS duration ≥120 ms group.
[b] Table 4 footnote lists variables used.

of patients with reduced LVEF is thought to be related to the presence of underlying left ventricular dyssynchrony. In 60% to 70% of patients with a QRS duration of 120 ms or greater and ejection fraction less than 35%, left ventricular dyssynchrony by tissue Doppler imaging is present.[20] Biventricular pacing has been tested as a means to improve hemodynamic indices, with improvements seen almost immediately.[21] Both isovolumetric systolic dysfunction and functional mitral regurgitation have been shown to significantly improve.[22,23] In addition, myocardial oxygen consumption is diminished,[24] while myocardial efficiency is increased.[25] The benefits of reverse left ventricular remodeling have been demonstrated in long-term follow-up.[9,26]

Despite the limitations of the QRS duration in predicting the presence of underlying mechanical dyssynchrony, it has nevertheless been the major criterion for dyssynchrony in published randomized trials evaluating the impact of biventricular pacing (ie, CRT). The Cardiac Resynchronization Therapy in Patients With Heart Failure and Narrow QRS (RethinQ) study evaluated the impact of CRT on patients with an ejection fraction of 35% or less, New York Heart Association class III heart failure, a QRS duration less than 130 ms, and evidence of mechanical dyssynchrony on echocardiography.[27] At a follow-up time of 6 months there was no difference in peak oxygen consumption. Therefore, electrical dyssynchrony, as evidenced by a prolonged QRS duration, remains the currently accepted clinical indicator for dyssynchrony and the criterion used in guidelines to evaluate potential candidates for CRT.

The Cardiac Resynchronization in Heart Failure (CARE-HF) study demonstrated that CRT improved symptoms and reduced the risk of death in patients with reduced ejection fraction and prolonged QRS duration in the outpatient setting.[9] Patients were required to have stable, chronic heart failure prior to enrollment.[28] At present,

Table 6. All-Cause Mortality and the Composite of Cardiovascular Death or Hospitalization for Heart Failure Categorized by QRS Morphology[a]

Outcome	HR (95% CI) LBBB vs QRS <120 ms (n = 909)	HR (95% CI) RBBB vs QRS <120 ms (n = 234)	HR (95% CI) IVCD vs QRS <120 ms (n = 178)	*P* Value[b]
3 mo				
All-cause mortality	1.44 (1.08-1.93)	1.88 (1.27-2.79)	1.20 (0.71-2.01)	.27
Cardiovascular death/heart failure hospitalization	1.40 (1.14-1.71)	1.53 (1.12-2.07)	1.37 (0.97-1.95)	.90
Overall				
All-cause mortality	1.38 (1.16-1.65)	1.56 (1.20-2.02)	1.44 (1.07-1.95)	.60
Cardiovascular death/heart failure hospitalization	1.27 (1.11-1.46)	1.27 (1.02-1.59)	1.40 (1.11-1.78)	.80

Abbreviations: CI, confidence interval; HR, hazard ratio; IVCD, intraventricular conduction delay; LBBB, left bundle-branch block; RBBB, right bundle-branch block.
[a] Results obtained adjusting for age, geographic region, left ventricular ejection fraction, type of block, systolic blood pressure, β-blocker use, and serum urea nitrogen level.
[b] *P* values are for difference in outcome among RBBB, LBBB, and IVCD in patients with QRS duration ≥120 ms.

Table 7. All-Cause Mortality and the Composite of Cardiovascular Death or Hospitalization for Heart Failure Categorized by Baseline and Last Inpatient QRS Duration

End Point	No. (%)	HR (95% CI)[a] Unadjusted	HR (95% CI)[a] Adjusted[b]
Baseline QRS Duration <120 ms			
Last inpatient QRS duration <120 ms	1463 (49.8)		
3 mo			
All-cause mortality	92 (6.3)		
Cardiovascular death/heart failure hospitalization	213 (14.6)		
Overall			
All-cause mortality	257 (17.6)		
Cardiovascular death/heart failure hospitalization	459 (31.4)		
Last inpatient QRS duration ≥120 ms	163 (5.6)		
3 mo			
All-cause mortality	21 (12.9)	2.14 (1.33-3.43)	1.65 (0.93-2.91)
Cardiovascular death/heart failure hospitalization	27 (16.6)	1.18 (0.79-1.75)	1.02 (0.63-1.66)
Overall			
All-cause mortality	46 (28.2)	1.81 (1.32-2.47)	1.42 (0.95-2.14)
Cardiovascular death/heart failure hospitalization	70 (42.9)	1.51 (1.18-1.95)	1.43 (1.04-1.96)
Baseline QRS Duration ≥120 ms			
Last inpatient QRS duration <120 ms	105 (3.6)		
3 mo			
All-cause mortality	10 (9.5)	1.52 (0.79-2.92)	0.96 (0.43-2.11)
Cardiovascular death/heart failure hospitalization	25 (23.8)	1.75 (1.15-2.64)	1.93 (1.21-3.10)
Overall			
All-cause mortality	28 (26.7)	1.67 (1.13-2.47)	1.26 (0.77-2.07)
Cardiovascular death/heart failure hospitalization	45 (42.9)	1.59 (1.17-2.17)	1.65 (1.15-2.37)
Last inpatient QRS duration ≥120 ms	1204 (41.0)		
3 mo			
All-cause mortality	145 (12.0)	1.96 (1.51-2.54)	1.47 (1.08-2.00)
Cardiovascular death/heart failure hospitalization	255 (21.2)	1.52 (1.27-1.83)	1.38 (1.10-1.73)
Overall			
All-cause mortality	336 (27.9)	1.71 (1.46-2.01)	1.32 (1.07-1.63)
Cardiovascular death/heart failure hospitalization	501 (41.6)	1.45 (1.28-1.64)	1.31 (1.12-1.55)

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] HRs are calculated with baseline QRS duration <120 ms, last inpatient QRS duration <120 ms as the reference group.
[b] See Table 4 footnote for variables used.

the optimal timing of CRT device implantation around the time of a hospitalization for heart failure is unknown. Data from the Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients With Heart Failure (OPTIMIZE-HF) registry and performance improvement program suggest that inpatient CRT device implantation is associated with a significantly lower risk of death or rehospitalization in the first 60 to 90 days postdischarge.[29]

The contribution of a prolonged QRS duration to sudden cardiac death is not well established. Left bundle-branch block and intraventricular conduction delay have been shown to predict arrhythmic death in patients with CAD and reduced ejection fraction.[30] This may be due to arrhythmias induced by focal ventricular stretching occurring in the setting of differential ventricular loading.[31] Nevertheless, a prolonged QRS duration has not been shown to be predictive of ventricular tachyarrhythmias in patients with established CAD and an ICD.[32] Supporting the additional benefit of therapy targeting sudden death, the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial demonstrated that CRT combined with an ICD decreased mortality in patients with New York Heart Association class III or IV symptoms, ischemic or nonischemic cardiomyopathy, an LVEF of 35% or less, and a QRS duration of 120 ms or greater.[33] While patients with a hospitalization for heart failure in the previous 12 months were included, a significant exacerbation of heart failure in the month prior to enrollment was an exclusion criterion. Thus, these patients differed from those in our present analyses. The benefit of CRT with an ICD may be due both to treatment and to decreasing the episodes of lethal ventricular tachyarrhythmias.[34]

Several studies have shown that multidisciplinary interventions instituted after discharge from a hospitalization for an episode of heart failure have been shown to improve clinical outcomes.[35-37] In light of the high postdischarge event rates observed in our study, the importance of patient education and regular evaluation in the postdischarge period should be stressed. Regardless of QRS duration, the event rate was high despite standard medical therapy and the exclusion of major comorbid conditions.

In theory, a prolonged QRS duration distinguishes an important subgroup of patients with reduced LVEF, which has a potentially different pathophysiological state; the prognosis for these patients is severely affected by the changes that occur around the time of an exacerbation of heart failure. The presence of a prolonged QRS duration associated with reduced LVEF is not only a marker for significantly increased mortality but becomes a potential therapeutic target. Forty-five percent of the patients in our analysis had a baseline QRS duration of 120 ms or greater. While CRT device implantation 60 days prior to and 30 days following enrollment were exclusion criteria, only 69 patients (1.6%) screened for the EVEREST program were excluded.[19] Only 9 (0.2%) of the total patients in the EVEREST program received CRT during follow-up.

The increased rates of all-cause mortality and cardiovascular death or hospitalization for heart failure were present irrespective of whether left ventricular dysfunction existed in the presence or absence of CAD.

Sex differences have been demonstrated to exist in the QRS duration in individuals with no structural heart disease.[38] In our study no statistical interaction was seen between sex and QRS duration group for any postdischarge outcomes.

Increased event rates for both primary end points were present in all groups with a QRS duration of 120 ms or greater, irrespective of the QRS morphology. This challenges prior assertions that the effect of a prolonged QRS duration may depend on the morphology of the QRS complex in the setting of acute heart failure.[12,15,16]

Several studies have linked serial increases in QRS duration to an increase in adverse cardiac events.[39-41] Our study supported these findings, as patients who progressed from having a normal QRS duration on their baseline ECG to a prolonged QRS duration during hospitalization had increased postdischarge events when compared with patients having a normal QRS duration throughout their hospitalization. Aranda et al[42] demonstrated that the QRS duration in patients with heart failure has greater variability than the duration in patients without heart failure, leading them to conclude that repeat measurements of QRS duration should be performed in the outpatient setting to evaluate whether patients with a prolonged QRS duration during hospitalization remain candidates for CRT. Until now, outcomes in patients who progress from having a prolonged QRS duration to a normal QRS duration during the course of a hospitalization for heart failure have never been systematically studied. Patients who presented with a prolonged QRS duration at enrollment but who had a normal QRS duration later during their hospitalization still demonstrated an increased rate of events. The pathophysiological basis for this phenomenon is unclear. This phenomenon applied to a minority of patients, as the percentage of patients who changed QRS duration categories during hospitalization was approximately 10%.

Our study has several limitations. Our analysis was post hoc and therefore has inherent limitations; nevertheless, the ECG information was collected prospectively. The QRS duration prior to enrollment was not available for our analysis, so it is uncertain whether the prolonged QRS duration was new or preexisting at admission. Our findings may not be applicable to an unselected population, given the specific inclusion and exclusion criteria for the study. Also, the majority of patients were white, so our findings may not be applicable to those of other races. In addition, there was no systematic evaluation for echocardiographic (ie, mechanical) dyssynchrony in our study. In regard to patients with CAD, the

presence of underlying ischemia as a contributor to heart failure exacerbation was not systematically evaluated. Finally, this trial did not include patients with preserved LVEF, who constitute approximately 40% of admissions for heart failure.

CONCLUSIONS

In this analysis, a prolonged QRS duration was present in 45% of patients admitted with heart failure and reduced LVEF, did not appear to significantly change during hospitalization, and was independently associated with high postdischarge mortality and readmission rate. This high morbidity and mortality was observed even though patients were well-treated with standard medical therapy that included β-blockers and ACE inhibitors or ARBs.

Measurement of the QRS duration on an ECG has significant advantages as a tool in the clinical setting. It is relatively inexpensive, simple to perform, and yields an instant result. The measurement is objective and does not require specialized training to interpret. In addition, the QRS duration is stable in the majority of patients during the course of their hospitalization. Perhaps most important, a prolonged QRS duration becomes a potential target for intervention, which may improve postdischarge mortality and morbidity.

While CRT with or without an ICD has been shown to improve outcomes in patients with stable heart failure, reduced LVEF, and prolonged QRS duration, it is uncertain whether a similar benefit may be seen in patients hospitalized or immediately discharged from a recent hospitalization for heart failure. Because progressive heart failure and sudden cardiac death are the major causes of death in the postdischarge period in this patient population, further studies are needed to assess whether implantation of a CRT device with or without an ICD before or soon after discharge from a hospitalization for heart failure can reduce morbidity and mortality.

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