Association of Prolonged QRS Duration With Death in a Clinical Trial of Pacemaker Therapy for Sinus Node Dysfunction

Michael O. Sweeney, MD; Anne S. Hellkamp, MS; Kerry L. Lee, PhD; Gervasio A. Lamas, MD; for the Mode Selection Trial (MOST) Investigators

**Background**—Prolonged QRS duration (QRSd) is an important prognostic indicator for death and heart failure hospitalization in patients with systolic heart failure. The relationship of baseline QRSd to death and heart failure hospitalization in patients with sinus node dysfunction who require pacemaker therapy is unknown.

**Methods and Results**—Baseline QRSd from 12-lead ECGs before pacemaker implantation were analyzed in the Mode Selection Trial (MOST), a 6-year, 2010-patient randomized trial of dual-chamber versus ventricular pacing in sinus node dysfunction. Baseline QRSd was ≥120 ms in 23.4% of patients and was associated with older age, lower ejection fraction, cardiomyopathy, and prior heart failure. Adjusted Cox models demonstrated baseline QRSd ≥120 ms was a strong independent predictor of death (hazard ratio [95% CI] 1.35 [1.07, 1.70], P=0.010) but not heart failure hospitalization. The risk of death increased with increased QRSd from 60 to 120 ms (P=0.002 and hazard ratio [95% CI] 1.14 [1.05, 1.23] for 10-ms increase in this range) after adjustment for other death predictors.

**Conclusions**—Baseline QRSd ≥120 ms was associated with increased risk of death during pacemaker therapy for sinus node dysfunction. (Circulation. 2005;111:2418-2423.)

**Key Words:** pacing ■ heart failure ■ mortality

Prolonged QRS duration (QRSd) is an important prognostic indicator in patients with systolic heart failure.1–4 Prolonged QRSd is due to delayed ventricular electrical activation, most commonly left bundle-branch block. This altered electrical activation sequence may result in mechanical dyssynchrony.5,6 The resulting alteration in mechanical activation may result in impaired hemodynamic performance,7–11 mitral regurgitation,12 and redistribution of cardiac mass.13 The common consequence of these adverse effects is reduced ventricular pumping function and increased risk of heart failure and death.

The effect of prolonged baseline QRSd on mortality in typical pacemaker patients with sinus node dysfunction (SND) is unknown. The purpose of this study was to examine the relationship of prolonged baseline QRSd to death and heart failure hospitalization (HFH) in a prospective, randomized trial of single- versus dual-chamber pacemaker therapy for SND.

**Methods**

The Mode Selection Trial (MOST) was a 6-year, prospective, randomized comparison of ventricular (VVIR) pacing versus dual-chamber (DDDR) pacing in 2010 patients with SND.14 Our study sample consisted of the 1877 (93.4%) MOST patients with baseline QRSd reported. Eligible patients received DDDR pacing systems for SND and were in sinus rhythm at the time of implantation. Ventricular pacing leads were placed at the right ventricular apex. After successful pacing system implantation, the programmed pacing mode was randomized (DDDR versus VVIR). For both groups, the lower rate was programmed to ≥60 bpm and the upper rate to ≥110 bpm. For the DDDR group, the programmed AV delay was recommended to be in the optimal physiological range (120 to 200 ms) for right ventricular pacing.15

Baseline demographic and clinical data were collected, and baseline QRSd was obtained from automated measurements made with 12-lead ECGs ≤4 weeks before pacemaker implant. Normal baseline QRSd was defined as <120 ms; prolonged QRSd was defined as ≥120 ms.16 Median follow-up was 33.1 months. The MOST secondary end points of death and HFH were used in the present study.14 In addition, end points of cardiac death, left ventricular dysfunction death, arrhythmic death, and a composite of HFH/left ventricular dysfunction death were used. A Clinical Events Committee blinded to assigned pacing mode adjudicated all deaths and first HFHs.

Deaths were classified as cardiac, noncardiac, or unknown based on all available source documentation. Cardiac deaths were subclassified as arrhythmic (sudden death not preceded by heart failure or documented ischemic symptoms), ischemic (objective documentation of myocardial necrosis or increasing symptoms consistent with infarction), or left ventricular dysfunction (objective documentation of heart failure without evidence of active ischemia). Noncardiac deaths were subclassified as vascular (arterial [stroke or peripheral embolus] or venous [pulmonary embolism]) or nonvascular.

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From Brigham and Women’s Hospital and Harvard Medical School (M.O.S.), Boston, Mass; Duke Clinical Research Institute and Duke University Medical Center (A.S.H., K.L.L.), Durham, NC; and Mt. Sinai Medical Center (G.A.L.), Miami, Fla.
Correspondence to Michael O. Sweeney, MD, Cardiac Arrhythmia Service, Brigham and Women’s Hospital, 75 Francis St, Boston, MA 02115. E-mail mosweeney@partners.org

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2418
Statistical Analysis
Baseline characteristics were compared between QRSd classes with likelihood ratio χ² tests for categorical variables and Wilcoxon rank sum tests for continuous variables. Among patients with QRSd ≥120 ms, the relationship of baseline characteristics to QRSd subgroup was assessed with ordinal logistic regression.

Multivariable Cox proportional hazards models were used to assess the relationship of baseline QRSd to death and HFH. Each model included baseline QRSd class (<120 or ≥120 ms), randomized pacing mode, and variables that were unbalanced between the QRSd classes at P<0.002. Other predictors of each clinical event, identified during the development of multivariable models in all MOST patients, were also included (Table 2); because variables could be prognostic for some events but not others, models in the present analysis did not all contain the same set of adjustment variables. A pacing mode–by-QRSd class interaction term was tested in each model to determine whether the QRSd effect was different between the 2 pacing modes; where not significant, it was dropped from the final model. To further clarify the relationship between baseline QRSd and death, an alternative model was used in which QRSd was included as a continuous, rather than dichotomous, variable. Initial examination of the data showed that the relationship between baseline QRSd and death could be characterized with a 2-part linear spline function, ie, the relationship was allowed to have different slopes over different parts of the range of baseline QRSd. Relative risk is expressed as a hazard ratio (HR) and 95% CI. Kaplan-Meier plots are used to display the unadjusted relationship between baseline QRSd and death.

Results
Baseline QRSd and Clinical Characteristics
Baseline QRSd <120 ms was observed in 1438 (76.6%) of 1877 patients, and QRSd ≥120 ms was observed in 439 (23.4%). Among all patients with QRSd ≥120 ms, the mean±SD QRSd was 142.4±19.1 ms (range 120 to 204 ms). Of 948 DDDR patients, 732 (77.2%) had QRSd <120 ms, and 216 (22.8%) had QRSd ≥120 ms. Of 929 VVIR patients, 706 (76.0%) had QRSd <120 ms but was not specifically associated with risk of cardiac death of any mechanism or HFH (Table 2). The pacing mode–by-QRSd class interaction term was not significant in either the death or HFH model term was not significant in either the death or HFH model (both P>0.14), which indicates that the QRSd effect was not different between the 2 pacing modes for either end point. A Kaplan-Meier plot that related baseline QRSd class to risk of death showed a significant, early, and sustained increase in death rate among patients with baseline QRSd ≥120 ms (Figure 2).

Association of Baseline QRSd With Death and HFH
Baseline QRSd ≥120 ms was associated with a significantly increased risk of death (35% relative risk increase) compared with baseline QRSd <120 ms but was not specifically associated with risk of cardiac death of any mechanism or HFH (Table 2). The pacing mode–by-QRSd class interaction term was not significant in either the death or HFH model (both P>0.14), which indicates that the QRSd effect was not different between the 2 pacing modes for either end point. A Kaplan-Meier plot that related baseline QRSd class to risk of death showed a significant, early, and sustained increase in death rate among patients with baseline QRSd ≥120 ms (Figure 2).

When analyzed as a continuous variable, baseline QRSd was an incremental predictor of death (Figure 3). The risk of death increased with increasing QRSd from 60 to 120 ms (P=0.002, HR 1.14 [95% CI 1.05 to 1.23] for a 10-ms increase in this range) after adjustment for other death predictors and correlates of baseline QRSd.

There was no association between further increases in QRSd and risk above 120 ms (P=0.88 and HR 0.99 [95% CI 0.92 to 1.08] for a 10-ms increase in this range). A test of whether these 2 risk relationships were different was marginally significant (P=0.07). The equivalence of risk of death at QRSd >120 ms is reflected in the raw death rates by QRSd subgroup (Table 3).

Adjudicated Classification of Deaths
There were 386 deaths (250 [17.4%] of 1438 patients with baseline QRSd <120 ms versus 136 [31%] of 439 with baseline QRSd ≥120 ms; Table 3). A cause of death could not be determined in 66 (17.1%) of 386 cases because of inadequate source documentation. When these cases were excluded, 135 (42.2%) of 320 deaths were cardiac and 185 (57.8%) were noncardiac. Although the incidence of cardiac death among patients with baseline QRSd ≥120 ms was

<table>
<thead>
<tr>
<th>TABLE 1. Baseline Characteristics of the Study Population</th>
</tr>
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<tbody>
<tr>
<td>Baseline Characteristic</td>
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<tr>
<td>-------------------------</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Nonwhite race</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
</tr>
<tr>
<td>Current smoker</td>
</tr>
<tr>
<td>Prior myocard infarction</td>
</tr>
<tr>
<td>Prior heart failure</td>
</tr>
<tr>
<td>NYHA class I or II</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Prior stroke</td>
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<tr>
<td>Diabetes</td>
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<tr>
<td>Chronic pulmonary Disease</td>
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<td>Prior cardiac procedures</td>
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<tr>
<td>PCI</td>
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<td>CABG</td>
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<tr>
<td>Other cardiac surgery</td>
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<tr>
<td>Prior atrial arrhythmias</td>
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<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Other atrial tachycardia</td>
</tr>
<tr>
<td>AV conduction disturbance</td>
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<tr>
<td>PR interval, ms</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association heart failure class; PCI, percutaneous coronary intervention.
Values are percent (n), except for age and PR interval, which are shown as median (25th, 75th percentile).
*Ejection fraction <0.50 or clinical impression of any left ventricular dysfunction.
double that observed for QRSd <120 ms (11.6% versus 5.8%, respectively), this was not statistically significant. Nearly half of cardiac deaths in both baseline QRSd groups were sudden arrhythmic (45.2% with baseline QRSd <120 ms, 45.1% with baseline QRSd ≥120 ms). Left ventricular dysfunction accounted for more cardiac deaths among patients with baseline QRSd ≥120 ms (37.3%) than among those with QRSd <120 ms (25.0%), but this difference was not statistically significant. The remaining cardiac deaths were attributed to acute ischemic events and other causes and were similar between baseline QRSd groups.

**Discussion**

This is the first report of an increased risk of death in patients with prolonged baseline QRSd who participated in a clinical trial of pacemaker therapy for SND. Baseline QRSd ≥120 ms was associated with a 35% increased risk of death compared with QRSd <120 ms. Although patients with prolonged baseline QRSd were older and had more comorbidities and heart disease, the increased mortality risk persisted when models were adjusted for all known predictors of death in the study population and all baseline imbalances between QRSd classes. The effect of baseline QRSd on death was insensitive to randomized pacemaker mode.

**Table 2. Clinical Events by Baseline QRSd**

<table>
<thead>
<tr>
<th>End Point</th>
<th>QRSd &lt;120 ms (n=1438)</th>
<th>QRSd ≥120 ms (n=439)</th>
<th>HR (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>17.4 (250)</td>
<td>31.0 (136)</td>
<td>1.35 (1.07–1.70)</td>
<td>0.010</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>5.8 (84)</td>
<td>11.6 (51)</td>
<td>1.25 (0.85–1.84)</td>
<td>0.25</td>
</tr>
<tr>
<td>Arrhythmic death</td>
<td>2.6 (38)</td>
<td>2.5 (23)</td>
<td>1.40 (0.79–2.50)</td>
<td>0.25</td>
</tr>
<tr>
<td>LVD</td>
<td>1.5 (21)</td>
<td>4.3 (19)</td>
<td>1.41 (0.70–2.84)</td>
<td>0.33</td>
</tr>
<tr>
<td>HFH/LVD death</td>
<td>11.1 (159)</td>
<td>18.0 (79)</td>
<td>1.09 (0.80–1.47)</td>
<td>0.60</td>
</tr>
<tr>
<td>HF hospitalization</td>
<td>10.4 (149)</td>
<td>16.4 (72)</td>
<td>1.09 (0.79–1.49)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

LVD indicates left ventricular dysfunction; HF, heart failure.

Data are shown as percent (n).

*HR for QRSd ≥120 ms vs QRSd <120 ms.

Death, cardiac death, arrhythmic death, and LVD death models included significant predictors of death: Charlson Index, age, Karnofsky score, gender, cardiomyopathy, New York Heart Association class, Mini-Mental State Exam score, weight, and prior myocardial infarction. HFH model included significant predictors of HFH: low ejection fraction, antiarrhythmic therapy at admission, Charlson Index, Karnofsky score, prior HF, pulse, age, weight, prior AV block, New York Heart Association class, murmur of mitral regurgitation, and peripheral vascular disease. HFH/LVD death model included predictors from both HFH and death models above. Variables significantly (P<0.002) unbalanced between QRS groups were included where not already present in above lists: gender, prior myocardial infarction, prior HF, cardiomyopathy, prior coronary artery bypass surgery, other cardiac surgery, prior atrial fibrillation or flutter, prior ventricular tachycardia or fibrillation, prior AV block, diabetes, and prior implantable cardioverter-defibrillator implantation.
This is particularly notable because unlike prior studies that demonstrated increased mortality risk associated with prolonged QRSd among patients with systolic heart failure,\textsuperscript{1–4} the majority of patients in the present study had normal or near-normal left ventricular systolic function and no or minimal symptoms of heart failure. When interpreting the results of this retrospective analysis, one must keep in mind that the modest differences in survival might simply be due to the effect of uncontrollable confounders. Nonetheless, the emerging evidence on the clinical importance of left ventricular synchrony for optimal hemodynamics strongly suggests that the excess mortality observed in patients with prolonged QRSd may well be caused by the long-term consequences of delayed electrical activation, dysynchronous ventricular contraction, and impaired hemodynamic performance at increased metabolic cost.\textsuperscript{7–9} Reductions of myocardial blood flow\textsuperscript{9,21,22} and wall thickness in regions of early activation\textsuperscript{13} result in a remodeling effect that could theoretically contribute to progression of left ventricular dysfunction.

In the present study, cardiac and noncardiac death rates trended higher among patients with prolonged versus normal baseline QRSd. Similarly, there was a trend toward relatively more heart failure deaths in the prolonged QRSd group, consistent with the proposed pathophysiology as stated above. The incidence of sudden arrhythmic death was expectedly low overall because the vast majority of patients in the present study had normal ventricular function and no prior history of sustained ventricular arrhythmia. Nonetheless, sudden arrhythmic deaths accounted for \(\approx 50\%\) of all cardiac deaths in both groups. However, the specific causes of increased mortality associated with prolonged baseline QRSd in this and other studies remain uncertain. It is reasonable to speculate that acute ischemic events contributed to the increased risk of death, because patients with prolonged baseline QRSd were more likely to have prior myocardial infarction and bypass surgery.

Some studies have shown that prolonged baseline QRSd is associated with sudden death,\textsuperscript{1–3,23,24} and this risk appears to correlate with the degree of ventricular dyssynchrony in patients with systolic heart failure,\textsuperscript{6} but the mechanisms of sudden death are probably diverse. Although prolonged QRSd correlates with total mortality risk in patients at high risk for sudden death who receive implantable cardioverter defibrillators,\textsuperscript{25,26} it does not appear to predict the likelihood of appropriate therapies for spontaneous ventricular tachycardia or fibrillation.\textsuperscript{26,27} Interventricular and intraventricular conduction disturbances are the most common ECG pattern preceding the development of complete heart block, particularly in the presence of structural heart disease.\textsuperscript{23,24,28} It is possible that cardiac pacing prevented some sudden deaths due to ventricular asystole among patients with prolonged QRSd in the present study; however, the majority of sudden deaths among patients with prolonged QRSd due to interventricular and intraventricular conduction disturbances and reduced left ventricular function are more likely due to ventricular tachycardia or ventricular fibrillation,\textsuperscript{29,30} and permanent pacemakers have never been shown to reduce sudden death or prolong survival in this setting.\textsuperscript{24,31}

We observed that the risk of death increased linearly with baseline QRSd up to \(\approx 120\) ms and was level at higher values. In contradistinction, studies in patients with systolic heart failure have shown increasing mortality risk across all ranges of prolonged QRSd.\textsuperscript{1–3} A possible interpretation is that there is a “threshold” effect for QRSd in the present study population with relatively normal ventricular function, in whom greater prolongation does not confer additional risk. Alternatively, the low number of events and patients with QRSd

\begin{table}[h]
\centering
\caption{Death or HFH by Baseline QRSd Subgroups \(\geq 120\) ms}
\begin{tabular}{|l|c|c|c|c|}
\hline
\textbf{Event} & \textbf{QRSd 120–126 ms (n=108)} & \textbf{QRSd 127–140 ms (n=85)} & \textbf{QRSd 141–156 ms (n=132)} & \textbf{QRSd 157–204 ms (n=114)} \\
\hline
Death & 26.9\% (29) & 32.9\% (28) & 32.6\% (43) & 31.6\% (36) \\
HFF & 13.0\% (14) & 10.6\% (9) & 23.5\% (31) & 15.8\% (18) \\
\hline
\end{tabular}
\end{table}
120 ms in the present study may have been insufficient to disclose a similarly increasing relationship as seen among patients with systolic heart failure. In contrast to other studies, we observed a pattern of increasing risk even within QRS durations that were in the normal range.

We did not observe any association between baseline QRSd and HFH. In contrast, a recent analysis of the MOST population demonstrated that paced QRSd was positively correlated with increased risk of HFH, and this risk increased linearly from lowest to highest values of paced QRSd. This increased risk persisted despite adjustment for other predictors of HFH and was insensitive to pacemaker mode and baseline QRSd. The positive correlation between the magnitude of paced QRSd and risk of HFH is similar to the baseline QRSd. The positive correlation between the magnitude of paced QRSd and risk of HFH is similar to the relationship between spontaneously occurring QRSd prolongation and mortality and acute hemodynamic response to cardiac resynchronization therapy in systolic heart failure.

The lack of a correlation between baseline QRSd but not paced QRSd and HFH may be explained by the observation that ventricular pacing resulted in further prolongation of QRSd even among patients with prolonged baseline QRSd.

**Study Limitations**

The use of retrospective subgroup analysis introduces the possibility that the play of chance influenced the results. Baseline characteristics of the 2 baseline QRSd subgroups studied were different in many important respects. Although multivariable analyses controlled for those characteristics that were recorded according to the study protocol, there remains a chance that the present findings may be due to uncontrollable differences between groups. Thus, our findings must be interpreted as hypothesis generating rather than conclusive.

**Conclusions**

Baseline QRSd ≥120 ms was associated with increased risk of death during pacemaker therapy for SND. The increased risk of death associated with prolonged QRSd suggests possible roles for cardiac resynchronization and implantable cardioverter defibrillator therapy when pacing is required for SND, particularly among patients with systolic heart failure.

**Acknowledgments**

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**Disclosure**

Dr Sweeney is a paid consultant to Medtronic, Inc.

**References**


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