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QRS duration predicts sudden cardiac death in hypertensive patients undergoing intensive medical therapy: the LIFE study

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Aims To determine whether QRS duration predicts sudden cardiac death (SCD) in patients with left ventricular hypertrophy and treated hypertension.

Methods and results Over 4.8 ± 0.9 years follow-up of 9193 hypertensive patients with electrocardiographic evidence of LVH who were treated with atenolol- or losartan-based regimens, 178 patients (1.9%) suffered SCD. In multivariable analysis including randomized treatment, changing blood pressure over time, and baseline differences between patients with and without SCD, QRS duration was independently predictive of SCD (HR per 10 ms increase = 1.22, $P < 0.001$). Baseline QRS duration remained a significant predictor of SCD even after controlling for the presence or absence of left bundle branch block (HR = 1.17, $P = 0.001$) and for changes in ECG LVH severity over the course of the study (HR = 1.16, $P = 0.017$).

Conclusion In the setting of aggressive antihypertensive therapy, prolonged QRS duration identifies hypertensive patients at higher risk for SCD, even after controlling for left bundle branch block, other known risk factors for SCD, and changes in blood pressure and severity of left ventricular hypertrophy.

Keywords Hypertension • Left ventricular hypertrophy • QRS duration • Sudden cardiac death

Introduction

Sudden cardiac death (SCD) accounts for more than half of all deaths due to cardiovascular disease in the United States, with an annual incidence estimated at 184 000–400 000.[1] While a history of myocardial infarction and depressed left ventricular ejection fraction, especially in the presence of certain Holter-based parameters, are the most well-established risk factors for SCD, patients with left ventricular hypertrophy (LVH) are also at particularly high risk.[2–5]

The relations of QRS duration (QRSd) and specific QRS morphologies (i.e. bundle branch block) to the risk for SCD are less clear. In patients with congestive heart failure, prolonged QRSd has been associated with a higher incidence of SCD and decreased overall survival.[6,7] Some previous studies have shown that patients with left bundle branch block (LBBB), but not right bundle branch block, suffer higher overall mortality[6,8] and have a greater risk for SCD.[9] However, in a population of patients with implanted cardioverter-defibrillators, QRSd did not predict ventricular arrhythmia, regardless of the presence or absence of bundle-branch block.[10]

In a previous analysis of the LIFE study population, QRSd predicted all-cause and cardiovascular mortality in hypertensive patients with electrocardiographic LVH in the setting of aggressive hypertensive therapy.[11] However, it remains unclear whether QRSd predicts the subset of mortality caused by SCD among

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hypertensive patients with LVH, and the concomitant effect of LBBB on the predictive value of QRSd has not been examined. Therefore, the current study, performed *post hoc*, used data collected during the LIFE study to examine whether QRSd predicts SCD, and to determine whether the presence or absence of LBBB affects this relationship.

Methods

Study design and results

The LIFE study was a prospective, randomized, double blinded, parallel group study ($n = 9193$) with double dummy technique that evaluated the long-term effects of losartan- compared with atenolol-based antihypertensive therapy in patients with hypertension and electrocardiographic LVH. The main outcome as well as the complete study protocol with study design, organization, clinical measures, exclusion criteria, basis for choice of comparative agents, statistical considerations, and baseline characteristics have been extensively published.[12–14] Briefly, patients aged 55–80, having previously treated or untreated hypertension and electrocardiographic LVH, were randomized to initial therapy with losartan or atenolol and treated to a target blood pressure of <140/90 mmHg.[13,15] If needed, upward dose titration of the randomized treatment, and/or the addition of hydrochlorothiazide (and ultimately other agents), was used to achieve this blood pressure goal.[12] Measurements of systolic and diastolic blood pressure, the magnitude of ECG LVH, and QRSd were performed at baseline, 6 months, and yearly thereafter. The study was conducted in compliance with the Declaration of Helsinki, and was approved by the respective institutions' institutional review committees. All subjects gave informed consent.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Electrocardiography

Electrocardiograms (ECGs) were obtained at study baseline, at 6 months, and at yearly follow-up intervals until patient death or study termination, and were interpreted at the Core Laboratory and at Helsinki University Hospital, Helsinki, Finland as previously reported in detail.[13,14,16,17] For each patient, the maximum QRSd in any lead was measured to the nearest 4 ms. Cornell voltage–duration product (CVDP), QRSd · Cornell voltage (RaVL+SV3, with 6 mm added in women[18]) >2440 mm msec, and Sokolow–Lyon voltage (SV1+RV5/6) >38 mm[19] were used to identify electrographic LVH.[16,17] Left bundle branch block was classified according to Minnesota code criteria.[20]

Outcome measure

As previously described,[12] patients were followed for at least 4 years with regular visits. All screening, baseline, yearly, and endpoint ECGs were centrally assessed and Minnesota coded at one reading centre. An endpoint classification committee of two clinicians blinded to the results of ECGs at LIFE study clinic visits reviewed clinical records of all cardiovascular events reported by clinical centres to determine whether they met endpoint criteria (see in what follows). Disagreements about classification of endpoints were resolved by joint in-person reviews. Deaths were reported separately and directly to the independent safety monitoring board for validation.

Sudden death was defined as sudden, unexpected death within 24 h of symptom onset, including observed arrhythmic deaths and those not attributable to intractable heart failure or other identifiable cause. Patients with sudden loss of consciousness who were successfully resuscitated but ultimately died of other sequelae (e.g. pneumonia) were not included in the sudden death group.

Statistical methods

SPSS version 12.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. Results are expressed as mean ± standard deviation (SD), as median and interquartile range, or as *n* (%), where appropriate. Analyses of differences between groups were performed using Student's *t*-test for continuous variables and the χ^2 test for categorical variables. All endpoints were analysed using the intention-to-treat approach. All randomized patients were included in their randomized treatment group, and all available follow-up data were included from randomization until the study termination date.

Univariable Cox analysis was used to determine the hazard ratio for SCD associated with each 10 ms increase in baseline QRS duration as well as the hazard ratios for SCD associated with other potential predictor variables. To check the proportional hazards assumption for Cox regression analyses, partial residuals were plotted against survival times and visually examined. An adjusted hazard ratio was then determined using multivariable Cox analysis including as covariates the randomized treatment assignment (losartan vs. atenolol), time-varying systolic and diastolic blood pressure, time-varying Cornell voltage and Sokolow–Lyon voltage, and all other baseline variables that predicted SCD significantly ($P < 0.05$) in univariable Cox models. To determine the impact of LBBB on the association between QRSd and SCD, this analysis was repeated with the presence or absence of LBBB included in the model. To control for changes in blood pressure and electrocardiographic severity of LVH, systolic and diastolic blood pressure, Sokolow–Lyon voltage, and Cornell voltage were treated as time-varying covariates. Of note, CVDP was not included in multivariable models examining the utility of QRSd, as QRSd is a component of Cornell product. A final set of multivariable Cox models including in-treatment QRS duration as a time-varying covariate, with and without inclusion of baseline LBBB, was performed to assess the relationship of SCD to changing QRSd over time. In all analyses, patients for whom outcome information became unavailable during the study were censored at the time of last being known to be alive. In time-varying covariates analyses, data from the previous evaluation were carried forward if a participant missed a scheduled re-evaluation, and updated with new data obtained at the next clinic visit the patient attended. Each examined variable was included in each model (i.e. no stepwise process of variable inclusion or exclusion was employed).

Analysis for the cumulative incidence of death due to SCD after accounting for competing risk was done for quartiles of baseline QRS duration according to the method of Fine and Gray[21] and using the R package *cmprsk*. In all analyses, two-sided $P < 0.05$ was considered significant.

Results

After a median follow-up of 4.8 years (interquartile range, 4.6–5.4 years), SCD occurred in 178 patients (1.9%). Twelve other patients had sudden loss of consciousness and were successfully resuscitated, but ultimately died of other sequelae. These events were not counted as SCD. Baseline demographic and clinical characteristics of the study population are presented in *Table 1*.

Table 1 Baseline demographic and clinical characteristics of the study population ($n = 9193$)

Age, years	66.9 (7.0)
Sex, male, *n* (%)	4230 (46.0)
Race, non-black, *n* (%)	8660 (94.2)
Blood pressure (mmHg)	174/98 (14/9)
Heart rate (b.p.m.)	74 (11)
Body mass index, kg/m^2	28.0 (4.8)
Treatment allocation to atenolol, *n* (%)	4588 (49.9)
History of coronary artery disease, *n* (%)	1469 (16.0)
History of myocardial infarction, *n* (%)	569 (6.2)
History of congestive heart failure, *n* (%)	166 (1.8)
History of stroke or TIA, *n* (%)	728 (7.9)
History of peripheral vascular disease, *n* (%)	520 (5.7)
History of diabetes, *n* (%)	1195 (13.0)
History of atrial fibrillation, *n* (%)	324 (3.5)
History of smoking, *n* (%)	1499 (6.3)
Baseline total cholesterol (mmol/L)	6.0 (1.1)
Baseline HDL (mmol/L)	1.5 (0.4)
Baseline creatinine (μmol/L)	86.9 (20.2)
Baseline uric acid (μmol/L)	330.1 (78.2)
Baseline urine albumin/creatinine (mg/mmol)	7.6 (34.0)
Cornell voltage (mm)	27.8 (7.5)
Cornell voltage–duration product (mm ms 100)	28.2 (10.3)
Sokolow–Lyon voltage (mm)	30.0 (10.5)
Left bundle branch block, *n* (%)	566 (6.2)
Baseline QRS duration (ms)	101 (18)

Figures are expressed as *n* (SD) or *n* (%), as appropriate.
TIA, transient ischaemic attack.

Univariate analysis

As summarized in *Table 2*, older age, male gender, black race, histories of coronary artery disease, congestive heart failure, myocardial infarction, stroke or transient ischaemic attack, diabetes, or atrial fibrillation, and higher baseline heart rate, serum creatinine, serum uric acid, urine albumin/creatinine ratio, Sokolow–Lyon voltage, and CVDP, as well as lower HDL, were predictors of SCD in univariable Cox models ($P < 0.05$). Treatment allocation (atenolol vs. losartan), baseline systolic and diastolic BP, total cholesterol, body mass index, Cornell voltage, smoking, and peripheral vascular disease did not predict subsequent SCD ($P > 0.05$).

In univariable Cox analysis, each 10 ms increase in baseline QRS duration was associated with a 26% increased risk for SCD [HR 1.26 (95% CI 1.18–1.33), $P < 0.001$, *Table 2*]. As seen in *Figure 1*, after adjusting for competing risk of death from other causes, patients in higher quartiles of QRS duration had higher risk for SCD than those in lower quartiles, with an absolute SCD incidence approximately four times as high in the highest than in the lowest quartile of baseline QRSd after 5 years of follow-up. Compared with patients without LBBB, patients with LBBB had higher risk for sudden death [cumulative incidence 1.7 vs. 5.3%, HR 3.24 (95% CI 2.19–4.81), $P < 0.001$]. In part by definition, patients with left bundle branch block had a greater QRSd than those without (146 ± 15 vs. 98 ± 14 ms).

Multivariable analysis

The independent relationship of QRS duration to SCD was examined after adjusting for the possible effects of treatment allocation, in-treatment diastolic and systolic pressure, in-treatment Cornell and Sokolow–Lyon voltage, and all statistically significant univariable predictors of SCD (*Table 3*). After adjusting for these factors, each 10 ms increment in baseline QRS duration remained associated with a 22% higher risk for SCD [HR 1.22 (95% CI 1.14–1.31), $P < 0.001$].

Table 2 Univariate Cox regression analysis to assess the predictive value of various clinical indicators for the development of sudden cardiac death

	HR	95% CI	*P*-value
Age, per 10 years increase	2.23	1.77–2.80	<0.001
Male sex	1.87	1.39–2.53	<0.001
Black race	1.97	1.19–3.25	0.008
Systolic blood pressure, per 10 mmHg increase	1.08	0.97–1.19	0.161
Diastolic blood pressure, per 10 mmHg increase	0.91	0.77–1.07	0.232
Heart rate, per 10 b.p.m. increase	1.33	1.18–1.50	<0.001
Body mass index, per 1 kg/m^2 increase	1.01	0.98–1.04	0.747
Treatment allocation randomized to atenolol	1.21	0.90–1.62	0.214
History of coronary artery disease	2.68	1.96–3.66	<0.001
History of myocardial infarction	2.88	1.91–4.34	<0.001
History of congestive heart failure	6.40	3.83–10.70	<0.001
History of stroke or TIA	2.75	1.89–4.02	<0.001
History of peripheral vascular disease	1.36	0.77–2.39	0.284
History of diabetes	2.27	1.61–3.19	<0.001
Smoking at baseline	1.15	0.79–1.67	0.480
History of atrial fibrillation	5.10	3.37–7.73	<0.001
Baseline total cholesterol, per mmol/L increase	1.05	0.92–1.20	0.488
Baseline HDL, per 0.1 mmol/L decrease	1.08	1.04–1.13	<0.001
Baseline creatinine, per 10 μmol/L increase	1.16	1.12–1.20	<0.001
Baseline uric acid, per 10 μmol/L increase	1.04	1.02–1.06	<0.001
Baseline urine albumin/creatinine, per 10 mg/mmol increase	1.03	1.01–1.04	0.002
Cornell voltage, per mm increase	1.01	0.99–1.03	0.609
Cornell voltage–duration product, per mm ms 100 increase	1.02	1.01–1.03	<0.001
Sokolow–Lyon voltage, per mm increase	1.02	1.00–1.03	0.030
Left bundle branch block	3.24	2.19–4.81	<0.001
QRS duration, per 10 ms increase	1.26	1.18–1.34	<0.001

CI, confidence interval; HR, hazard ratio; TIA, transient ischaemic attack.

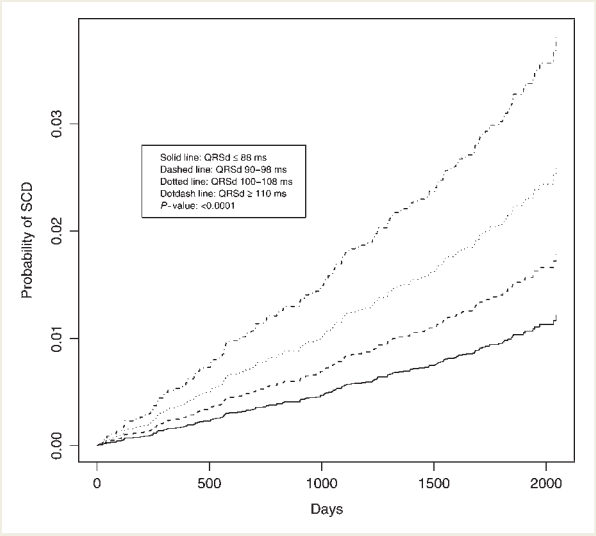

Figure 1 Cumulative incidence of sudden cardiac death, adjusting for competing risk of death from other causes, in relation to quartiles of baseline QRS duration. QRSd, QRS duration.

When the analysis was repeated with the presence or absence of left bundle branch block included in the model (*Table 4*), baseline QRS duration remained a significant predictor of SCD [HR per 10 ms increment: 1.17 (95% CI 1.06–1.29), $P = 0.001$]. In addition, baseline QRSd appeared to stratify risk of SCD similarly in patients with and without LBBB, as there was no significant interaction between LBBB and QRSd ($P = 0.606$) when evaluated within the adjusted model (HR 1.08, 95% CI 0.83–1.40 and HR 1.19, 95% CI 1.07–1.32, respectively). Of note, there also was no statistically significant difference in the predictive value of baseline QRSd for SCD between randomized treatment groups ($P = 0.50$ for interaction term) or between men and women ($P = 0.667$ for interaction) when evaluated within the adjusted model.

Because of the known association between regression of ECG LVH and reduction in the risk of SCD,[22] we then further examined the potential relationship between SCD and changing blood pressure and LVH severity over the course of the study. The increased risk associated with prolonged baseline QRS duration persisted after further adjustment for in-treatment Cornell voltage and Sokolow–Lyon voltage treated as time-varying covariates: each 10 ms increase in baseline QRSd remained associated with a 16% increased risk of SCD after further adjusting for these variables [HR 1.16 (95% CI 1.03–1.33), $P = 0.017$]. Of note, QRSd had poor to modest correlation with the other risk factors that entered the multivariable Cox model ($r = 0.024$–0.210).

In additional analyses which examined changing QRSd over the course of the study, in-treatment QRSd remained a significant predictor of SCD when examined as a time-varying variable in parallel multivariable Cox models. Without LBBB at baseline in the model, each 10 ms increase in in-treatment (time-varying) QRSd was associated with a 17% increased risk of SCD [HR 1.17 (95% CI 1.09–1.26), $P < 0.001$]. When baseline LBBB was included in the model, each 10 ms greater in-treatment QRSd remained associated with a 10% increased risk of SCD [HR 1.10 (95% CI 1.02–1.21), $P = 0.014$]. There was no significant difference in the predictive value of in-treatment QRSd among patients with and without LBBB when evaluated within the adjusted model (HR 1.08, 95% CI 0.88–1.34 and HR 1.11, 95% CI 1.01–1.21, respectively; $P = 0.855$ for interaction). Of note, in these models Sokolow–Lyon voltage, but not Cornell voltage, remained an independent predictor of sudden death.

Table 3 Cox regression analysis to assess the predictive value of QRS duration for the development of sudden cardiac death

	HR	95% CI	*P*-value
Statistically signifcant variables			
QRS duration, per 10 ms increase	1.22	1.14–1.31	<0.001
Heart rate, per 10 b.p.m. increase	1.34	1.19–1.50	<0.001
Age, per year increase	1.07	1.05–1.10	<0.001
Male sex	1.73	1.22–2.46	0.002
Baseline creatinine, per 10 μmol/L increase	1.09	1.03–1.16	0.001
History of coronary artery disease	1.51	1.08–2.11	0.016
History of congestive heart failure	2.52	1.45–4.36	0.001
History of diabetes mellitus	1.90	1.33–2.72	<0.001
History of atrial fibrillation	2.71	1.75–4.19	<0.001
Time-varying diastolic blood pressure, per 10 mmHg increase	1.38	1.15–1.64	<0.001
Time-varying Sokolow–Lyon voltage, per mm increase	1.34	1.17–1.53	<0.001
Statistically non-signifcant variables			
Treatment allocation randomized to atenolol	1.12	0.81–1.54	0.469
Black race	1.81	0.94–3.33	0.064
History of myocardial infarction	1.58	0.90–2.78	0.112
History of stroke or transient ischaemic attack	1.73	0.93–2.85	0.071
Baseline HDL cholesterol, per 1 mmol/L increase	0.74	0.48–1.15	0.177
Baseline uric acid, per 10 μmol/L increase	1.00	0.99–1.01	0.957
Baseline urine albumin/creatinine, per 10 mg/mmol increase	1.00	0.97–1.03	0.522
Time-varying systolic blood pressure, per 10 mmHg increase	1.00	0.95–1.05	0.946
Time-varying Cornell voltage, per mm increase	1.01	0.99–1.03	0.289

CI, confidence interval; HR, hazard ratio.

Discussion

Main findings

The main finding of this study is that in hypertensive patients with ECG evidence of LVH undergoing intensive antihypertensive therapy, prolonged QRSd is independently associated with

Table 4 Cox regression analysis to assess the predictive value of QRS duration for the development of sudden cardiac death, including in the model the presence or absence of left bundle branch block

	HR	95% CI	*P*-value
QRS duration, per 10 ms increase	1.17	1.06–1.25	0.001
Heart rate, per 10 b.p.m. increase	1.32	1.18–1.49	<0.001
Age, per year increase	1.07	1.05–1.10	<0.001
Male sex	1.79	1.26–2.54	0.001
Creatinine, per 10 μmol/L increase	1.09	1.03–1.16	0.001
Coronary artery disease	1.53	1.09–2.14	0.013
Congestive heart failure	2.53	1.46–4.37	0.001
Diabetes mellitus	1.93	1.35–2.75	<0.001
Atrial fibrillation	2.75	1.78–4.26	<0.001
Time-varying diastolic blood pressure, per 10 mmHg increase	1.38	1.15–1.64	<0.001
Time-varying Sokolow-Lyon voltage, per mm increase	1.32	1.15–1.52	<0.001
Left bundle branch block	1.47	0.80–2.67	0.212

Non-significant variables: race, time-varying systolic blood pressure, body mass index, randomized treatment, myocardial infarction, stroke or transient ischaemic attack, peripheral vascular disease, total cholesterol, HDL cholesterol, uric acid, urine albumin/creatinine, time-varying Cornell voltage.
CI, confidence interval; HR, hazard ratio.

increased risk for SCD. This relationship is independent of several other clinical factors that may be expected to predict SCD. Of particular note is the finding that the association between QRSd and SCD persists even after correction for the presence or absence of LBBB, and that QRSd appears to provide similarly useful risk stratification in patients either with or without LBBB.

Prior analyses of the LIFE population showed that QRSd is associated with LVH severity and overall mortality.[11,23] The present study further investigated whether QRSd was a predictor of SCD in this population, which previously had not been studied. We observed that QRSd was indeed an independent predictor of SCD. This is a novel finding in patients with hypertension and LVH that may be an important factor in risk stratification for SCD.

Another recent analysis of the LIFE population revealed an association between lower SCD risk and regression of ECG LVH by either Cornell product or Sokolow–Lyon voltage.[22] In the present study, we show specifically that increased QRSd, one component of the Cornell product, implies higher SCD risk independent of Cornell voltage. In addition, Sokolow–Lyon voltage, but not Cornell voltage, remained a significant predictor after correction for QRSd. For the purpose of sudden death risk-stratification, therefore, CVDP should be disregarded in favour of its QRSd component, but Sokolow–Lyon voltage remains additionally predictive even after correction for QRSd.

Prior investigations

Previous studies in other populations examining the relationship between QRSd and risk for SCD have come to disparate conclusions. Some, such as the Valsartan in Acute Myocardial Infarction Trial, have shown in populations with heart failure and/or prior myocardial infarction that longer QRSd was a risk factor for SCD.[6,24] In contrast, other investigators found no relationship between QRSd and the incidence of appropriate defibrillator therapy.[10] However, these prior populations primarily consisted of patients with cardiomyopathy, while patients with known significant LV systolic dysfunction or active heart failure were expressly excluded from the LIFE population.[13] While QRSd has been shown to predict overall mortality in otherwise unselected patients late after myocardial infarction and revascularization, in that population QRSd was not associated with sudden death or serious arrhythmic events.[25] However, our population had a low prevalence of prior myocardial infarction (6.2%), and largely was without any indication for defibrillator implantation. Thus, our population differs significantly from those studied previously, and this is the first study to relate QRSd to SCD in a population with no known left ventricular dysfunction.

Possible pathophysiological mechanisms

Although the design of this study does not allow definitive conclusions to be drawn regarding the pathophysiology relating QRSd to SCD, some potential mechanisms may be postulated. For example, increased QRSd is known to be related to LV dysfunction, and the relationship between depressed LV ejection fraction and SCD has been well established.[26–28] Although the LIFE study excluded patients with known depressed LV ejection fraction, only ~10% of the population was included in the LIFE echocardiography substudy and underwent evaluation of LV function after inclusion in LIFE (showing a mean LV ejection fraction of 61%).[13,29] Thus, subclinical LV systolic dysfunction may have existed among the subpopulation of patients with prolonged QRSd, and the relationship of increasing QRSd to SCD may have resulted from a common relationship to LV systolic dysfunction. Alternatively, prolonged QRSd may be related to LV diastolic dysfunction, which has been linked to SCD.[30] As only a small minority of patients were included in the LIFE echocardiography substudy, additional investigations with more complete echocardiographic diastolic data (e.g. E/E' ratio and strain rate imaging) would be required to evaluate this relationship further.

The perturbed depolarization associated with QRS prolongation may also play a direct role in SCD via facilitation of reentrant tachyarrhythmias. Abnormal myocardial depolarization is associated with abnormal repolarization, which can lead to spatial and temporal repolarization dispersion, thereby facilitating electrical reentry.[31,32] This mechanism may underlie the previous observation that patients with prolonged QRSd have an increased prevalence of inducible ventricular tachyarrhythmias at the time of electrophysiology study.[33] Thus, the association of prolonged QRSd to inducible tachyarrhythmia during programmed ventricular stimulation may in part explain the higher incidence of SCD in patients with prolonged QRSd. However, the mechanism of dominant ventricular tachyarrhythmias may differ significantly between patients at risk for SCD by virtue of prior MI and those at risk primarily due to LVH (i.e. monomorphic VT due to reentry around a discrete area of infarction vs. polymorphic VT using multiple loops of reentry within diffusely fibrotic tissue). Nonetheless, prolonged QRSd in patients with hypertension and LVH may be a manifestation

of factors that would predispose to such reentry, such as changes in tissue architecture including increased extracellular fibrosis and reduced intercellular coupling efficacy at gap junctions.[34,35]

Relationship of QRS duration, left bundle branch block, and sudden death

It is particularly interesting that in our study the increased SCD risk associated with prolonged QRSd was independent of the presence or absence of LBBB. Previous trials have concluded that patients with LBBB or non-specific intraventricular conduction delay, but not right bundle branch block, suffer greater risk for arrhythmia and total mortality than those with normal QRS.[8,36–38] The increased SCD risk associated with LBBB observed in this and other trials could be predicted by any one or several of the possible mechanisms described earlier. In our study, the fact that SCD risk was associated with increasing QRSd independent of the presence or absence of LBBB is consistent with risk attributable to similar mechanisms in patients with or without LBBB. However, superimposed additional risk specific to complete block in the left bundle branch cannot be excluded. The lack of a statistical interaction between QRSd and LBBB suggests that QRSd per se is similarly effective for prediction of SCD in patients either with or without LBBB.

Clinical implications and suggestions for further study

While several multicentre, randomized, controlled studies have clearly demonstrated that implantable cardioverter-defibrillators improve mortality in patients with cardiomyopathy (ischaemic or non-ischemic) with a reduced left ventricular ejection fraction (LVEF),[39–42] most instances of SCD occur among the population with preserved ejection fraction.[43] Thus, a screening strategy using *only* severely depressed LVEF to identify high-risk patients would miss the majority of patients who would ultimately suffer SCD. If we wish to identify as many high-risk patients as possible, the development of additional screening strategies in those with preserved LVEF remains imperative. Our study offers more evidence that QRSd may be a valuable addition to these strategies, and suggests that further study is warranted. In addition, the correlation of increased QRSd with SCD raises the question of whether signal-averaged ECG may be of some utility for risk-stratification in these patients.

Although our investigation examined specifically the value of QRSd for risk prediction, other variables also were found to be independently predictive. Thus, one could hypothesize that a risk calculation tool employing other independent predictors, such as heart rate, age, atrial fibrillation, coronary artery disease, diabetes, and heart failure, may be even more useful than QRSd alone.

Limitations

The LIFE study was not primarily designed to assess the effect of QRSd on risk for SCD. Therefore, the present investigation has the same limitations as all *post hoc* analyses. While we were able to correct for many known risk factors for SCD, some such risk factors may not have been available. Data on use of antiarrhythmic agents and drugs with strongly proarrhythmic potential were not systematically assembled. In addition, because the LIFE study included only hypertensive patients with ECG evidence of LVH, the generalizability of our study's conclusion is limited to these patients. However, it has been estimated that 7.8 million adults could meet LIFE entry criteria in 15 member states of the European Union, and nearly as many in the United States and in East Europe.[44] The ability of QRSd to predict SCD should also be studied in an unselected population of hypertensive patients and in other populations of interest (e.g. patients with a history of myocardial infarction, symptomatic coronary heart disease, or heart failure).

Whether QRSd is only a marker of risk or represents a potential target for therapy requires further study. Lastly, it must be recognized that sudden death is not necessarily the same as *arrhythmic* sudden death. Further evaluation of the specific mode of sudden death (i.e. arrhythmic or non-arrhythmic) would require data not acquired in this study, including systematic monitoring of heart rhythm.

Conclusion

In the setting of aggressive blood pressure lowering, prolonged QRSd identifies hypertensive patients at increased risk for SCD. The direct relationship between QRSd and SCD risk persists even after controlling for the presence or absence of LBBB, the effects of hypertensive treatment, and other known risk factors for SCD.

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