Intraventricular Conduction Delay in a Standard 12-Lead Electrocardiogram as a Predictor of Mortality in General Population

Running title: Aro et al.; IVCD and Mortality in General Population

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Abstract:

**Background** - Prolonged duration of QRS complex (QRSd) in a 12-lead electrocardiogram (ECG) is associated with adverse prognosis in patients with cardiac disease, but its significance is not well established in general population. In particular, there is paucity of data on the prognostic significance of nonspecific intraventricular conduction delay (IVCD) in apparently healthy subjects.

**Methods and Results** - We evaluated the 12-lead ECGs of 10899 Finnish middle-aged subjects from the general population (52% males, mean age 44±8.5 years) between 1966 and 1972 and followed them for 30±11 years. Primary end points were all-cause mortality, cardiac mortality, and arrhythmic death. Prolonged QRSd was defined as QRS $\geq$ 110 ms and IVCD as QRS $\geq$ 110 ms without the criteria of complete or incomplete bundle branch block. QRSd $\geq$ 110 ms was present in 1.3% (N=147) and IVCD in 0.6% (N=67) of the subjects. Prolonged QRSd predicted all-cause mortality (multivariate adjusted relative risk [RR] 1.48; 95% confidence interval [CI] 1.22-1.81; P<0.001), cardiac mortality (RR 1.94; CI 1.44-2.63; P<0.001), and sudden arrhythmic death (RR 2.14; CI 1.38-3.33; P=0.002). Subjects with IVCD had increased all-cause mortality (RR 2.01; CI 1.52-2.66; P<0.001), cardiac mortality (RR 2.53; CI 1.64-3.90; P<0.001), and an elevated risk of arrhythmic death (RR 3.11; CI 1.74-5.54; P=0.001). LBBB also weakly predicted arrhythmic death (P=0.04), but RBBB was not associated with increased mortality.

**Conclusions** - Prolonged QRSd in a standard 12-lead ECG is associated with increased mortality in general population, IVCD being most strongly associated with an increased risk of arrhythmic death.

**Key words:** mortality, electrocardiography, population, QRS duration, intraventricular conduction delay
Prolonged duration of the QRS complex (QRSd) in a 12-lead electrocardiogram (ECG) is associated with adverse prognosis in patients with cardiac disease \(^1\)\(^4\), but in the general population the significance of QRSd is not as well established. Right bundle branch block (RBBB) is considered to be a benign finding in the absence of cardiac disease \(^5\)\(^6\), but some previous studies suggest that subjects with left bundle branch block (LBBB) suffer a higher risk of cardiac death \(^7\)\(^8\).

There is paucity of studies that have investigated the long-term prognostic significance of prolonged QRSd and nonspecific intraventricular conduction delay (IVCD) in a general population. Therefore, we conducted a community-based study in a large middle-aged population with a mean follow-up of 30 years to assess the significance of prolonged QRSd and IVCD on all-cause mortality, cardiac mortality and arrhythmic death.

**Methods**

**Study Population**

The study population consists of subjects in the Finnish Social Insurance Institution’s Coronary Heart Disease Study (CHD Study) who had undergone clinical baseline examinations between 1966 and 1972. The CHD Study was part of a large, prospective Mobile Clinic Health Survey, which was carried out in 35 populations from different geographic areas of Finland representative of the middle-aged Finnish population. The study cohort comprises a total of 10957 subjects between the ages of 30 and 59 years, but we excluded 58 ECGs that had missing data or were otherwise unreadable. Thus, our final study group included 10899 subjects (52% of whom were men; mean age 44.0 ± 8.5 years) from the original cohort.
A detailed account of the study rationale and procedures performed at the baseline examination has been described previously. Briefly, in addition to having a standard 12-lead ECG taken, blood pressure, body-mass index and serum cholesterol were measured. The subjects also completed a questionnaire regarding their health habits, medication and known diseases or illnesses. A specially trained nurse then checked the questionnaire to make sure all the questions were answered appropriately. All symptoms of cardiovascular disease were documented during the examination.

**Electrocardiographic measurement**

A standard 12-lead ECG was recorded with the subject at rest using paper speed of 50 mm per second (standard paper speed in Finland) and a calibration of 1 mV per 10 mm. The presence or absence of bundle branch block (BBB) and left ventricular hypertrophy (LVH) according to the Sokolow-Lyon criteria was assessed and QT-interval (corrected for heart rate according to Bazett’s formula) was measured by nine trained readers at the time of baseline examinations. All baseline ECGs were later independently re-evaluated by a group of five physicians for the presence of BBB and IVCD, and the duration of QRS complex and JTc-interval (QTc – QRSd) was measured where widest complex and longest QT interval were seen. Standard ECG criteria were used for diagnosing complete and incomplete LBBB and RBBB. QRSd ≥ 110 ms without criteria for complete or incomplete LBBB or RBBB and without pre-exitation was classified as IVCD. Although the measurement of QRSd was done manually, paper speed of 50 mm per second enabled a reliable determination of the QRSd. To further minimize errors in the evaluation process, we assessed 270 ECGs for interobserver and intraobserver variation (kappa value for QRSd 0.66 and 0.68, respectively). All ECGs with QRSd of 110 ms or more were double-checked, and the presence of BBB and IVCD was established by consensus. In addition to the baseline examination, most of the subjects had a
control visit between 1973 and 1976, during which the ECGs were recorded in a similar manner to that described above.

**Follow-up**

From the baseline examination between 1966 and 1972, the subjects were followed up for a mean of 30 ± 11 years until the end of 2007. The primary end points were death from arrhythmia, cardiac death and death from any cause. The mortality data was obtained from the Causes of Death Register maintained by Statistics Finland. Less than 2 % of the subjects were lost to follow-up as a result of moving abroad, but even in this group, the survival status could still be determined for a majority of subjects. Because of extensive administrative registers in Finland every death in the country is recorded, and the quality and reliability of these registers have been well validated previously. Death from cardiac causes was determined from the relevant International Classification of Diseases (ICD) codes. To identify cases of sudden death from arrhythmia, all deaths from cardiac causes were reviewed by experienced cardiologists (OA, HVH) based on the definitions presented in the Cardiac Arrhythmia Pilot Study, as described by our group previously. After reviewing data available from death certificates and hospital records, the cardiac deaths were classified as probable arrhythmic deaths and deaths that were probably not associated with arrhythmia. Death from arrhythmia was defined as the spontaneous cessation of respiration and blood circulation with loss of consciousness in one of the following situations: witnessed and instantaneous without new or accelerating symptoms; witnessed and preceded or accompanied by symptoms attributable to myocardial ischemia in the absence of heart failure; witnessed and preceded by symptoms attributable to cardiac arrhythmia (e.g. syncope); and unwitnessed but with no other identifiable cause of death. In the presence of severe congestive heart failure, arrhythmia was considered as the immediate cause of death.
only if it was judged that the patient would probably have survived at least 4 months had the arrhythmia not occurred.

**Statistical analysis**

The ROC curve for QRSd was calculated using all-cause mortality, cardiac death, and sudden arrhythmic death as end points to verify that the cut-off 110 ms for QRSd, which included IVCD together with partial and complete BBBs, also predicted best the outcomes in this population. This cut-off was then used as a dichotomized variable in the assessment of the hazard ratios and 95% confidence intervals for end points, using Cox proportional hazards model. Separate analyses were done according to the morphology of prolonged QRSd, i.e. LBBB, RBBB, and IVCD. The primary adjustments to these models were for age and sex, with further adjustments for covariates that differed between the groups or are known to predict cardiovascular mortality. Age, serum cholesterol and JTC were added as continuous variables and sex, smoking, chronotropic medication, history of angina or myocardial infarction, and presence or absence of electrocardiographic signs of left ventricular hypertrophy, coronary artery disease or infarction were added as categorical variables. The general linear model was used to compare the age- and sex-adjusted mean values for continuous variables and the prevalence of categorical variables between the groups. All continuous data is presented as mean ± SD. Age and sex adjusted Kaplan-Meier survival curves were plotted for IVCD and prolonged QRSd and were compared by means of the log-rank test. The statistical analyses were performed with SAS software, version 9.1.3 (SAS Institute) and with the Statistical Package for Social Studies, version 14.0 (SPSS). P value of less than 0.05 was considered to indicate statistical significance.
Results

Baseline Characteristics

The baseline characteristics of subjects with QRSd < 110 ms and those with QRSd ≥ 110 ms are shown in Table 1. 1.9% of the subjects had QRSd ≤ 70 ms, 43.6% had QRSd 80-89 ms, 40.0% had QRSd 90-99ms and 13.1% had QRSd 100-109 ms. QRSd ≥ 110 ms was present in 147 of 10899 subjects (1.3%). Of these subjects, 84 (0.8%) had QRSd ≥ 120ms and 39 (0.4%) had QRSd ≥ 140ms. Partial or complete LBBB was present in 33 (0.3%), partial or complete RBBB in 44 (0.4%) and IVCD in 67 (0.6%) of the 147 subjects with QRSd ≥ 110ms. The remaining 3 subjects with prolonged QRSd had a pre-exitation pattern in their ECGs and were excluded. Subjects with prolonged QRSd were older and more often males, had higher systolic blood pressure and a shorter JTc-interval. There was no difference in the history of prior myocardial infarction between the two groups, but a history of angina pectoris was less common in the group with prolonged QRSd.

IVCD was present in 67 (0.6% of the total population) of the 147 subjects with prolonged QRSd. The baseline characteristics of subjects with and without IVCD are shown in Table 1. Subjects with IVCD were older and predominantly males, had lower cholesterol values and a shorter JTc-interval. There was no difference in the history of angina pectoris or previously diagnosed myocardial infarction.

Repeated electrocardiographic measurement

A second electrocardiographic measurement (an average of 5 years after the baseline examination) was available for 114 (78%) of the 147 subjects with baseline QRSd ≥ 110 ms. 107 (94%) of these 114 subjects had QRSd ≥ 110ms also on the second ECG, and the average QRS duration was prolonged from 122 ± 13 ms to 128 ± 18 ms. 53 subjects with IVCD...
during the initial examination had a control ECG available, and IVCD was again observed in 47 (89%) of these subjects. The mean QRSd of the subjects with IVCD on the follow-up ECG increased from 114±9 ms to 120±12 ms. Among the 27 subjects with LBBB who underwent the second ECG, LBBB was present in 25 (93%) of the subjects, with QRSd increased from 133±11 ms to 144±14 ms. Of the 31 subjects with RBBB in the baseline ECG having the second ECG available, 27 (87%) had RBBB also during the follow-up, with QRSd increased from 128±13 ms to 133±14 ms.

Risk of Death

During the follow-up (mean follow-up 30±11 years) 6155 subjects (56.5%) died. Of these deaths 1980 (32.2% of all deaths) were from cardiac causes, and 801 (40.5%) of these were classified as sudden arrhythmic deaths. The area under the ROC curve (AUC) for QRSd using all-cause mortality as an end point was 0.516 (95% confidence interval [CI] 0.505-0.527; P=0.004), 0.510 (CI 0.495-0.524; P=0.175) for cardiac mortality, and 0.536 (CI 0.515-0.556; P=0.001) when arrhythmic death was used as an endpoint. QRSd ≥110 ms, which included IVCD and both partial and complete BBBS, gave the highest sum of sensitivity plus specificity for the primary end points.

Table 2 shows the relative risk of death from any cause, from cardiac causes, and from arrhythmia associated with prolonged QRSd. Subjects with QRSd ≥110 ms had higher all-cause mortality (multivariate-adjusted relative risk [RR] 1.48; 95% confidence interval [CI] 1.22-1.81; P<0.001), higher cardiac mortality (RR 1.94; CI 1.44-2.63; P<0.001), and a higher risk of sudden arrhythmic death (RR 2.14; CI 1.38-3.33; P=0.002). QRSd ≥110 ms with complete or incomplete LBBB pattern predicted sudden arrhythmic death (RR 2.71; CI 1.20-6.11; P=0.04) but not cardiac or all-cause mortality. Partial or complete RBBB was not
associated with increased risk of major endpoints. Age and sex adjusted Kaplan-Meier curves for all-cause mortality, death from cardiac causes and death from arrhythmia in subjects with prolonged QRSd are presented in Figure 1.

Subjects with IVCD had an increased risk of death from any cause (RR 2.01; CI 1.52-2.66; P<0.001), an elevated risk of death from cardiac causes (RR 2.53; CI 1.64-3.90; P<0.001), and an even higher risk of death from arrhythmia (RR 3.11; CI 1.74-5.54; P=0.001) (Table 3). Figure 2 shows age and sex adjusted Kaplan-Meier curves for all-cause mortality, cardiac mortality and arrhythmic death in subjects with IVCD.

When subjects without any suspected heart disease (N=10006) were analyzed separately, the results remained essentially the same. These subjects with QRSd ≥ 110 ms had higher mortality (RR 1.34; CI 1.07-1.68; P=0.02), higher cardiac mortality (RR 1.72; CI 1.20-2.46; P=0.007) and a higher risk of sudden arrhythmic death (RR 2.03; CI 1.21-3.41; P=0.02).

Subjects with IVCD but no evidence of cardiac disease had an increased risk of death (RR 1.75; CI 1.27-2.40; P=0.002), an elevated risk of death from cardiac causes (RR 1.87; CI 1.08-3.25; P=0.04) and a high risk of death from arrhythmia (RR 2.90; CI 1.49-5.63; P=0.007).

Discussion

The main finding of this study is that nonspecific intraventricular conduction disturbance (IVCD) in an ECG is associated with increased mortality and a markedly elevated risk of sudden arrhythmic death in a general population. This relationship was independent of several factors that might be expected to predict cardiac death, and the risk of sudden arrhythmic death remained 3-fold even after multivariate adjustment. Moreover, prolonged
QRS complex duration of 110 ms or more in general including BBBs and IVCD was a significant predictor of arrhythmic, cardiac and all-cause mortality in this population.

It has long been recognized that when associated with heart disease, prolonged QRSd in an electrocardiogram is an independent predictor of adverse outcome. In most patients with systolic LV dysfunction, QRS prolongation presents as LBBB\textsuperscript{14} and in these patients increased QRSd is associated with a worse prognosis\textsuperscript{1,2}. For patients with coronary artery disease plus depressed ventricular function and non-sustained ventricular tachycardia, QRS prolongation resulting from LBBB or IVCD has been associated with a 50\% increase in the risk of both arrhythmic and total mortality\textsuperscript{3}. In patients with suspected coronary artery disease referred for non-invasive evaluation of myocardial ischemia, QRSd was an independent predictor of cardiac death and nonfatal infarction\textsuperscript{15} and in patients with suspected acute coronary syndrome QRS prolongation predicted in-hospital and 1-year mortality\textsuperscript{16}. In a general medical inpatient and outpatient cohort of patients without BBB, an increase in QRSd from \(\leq 110\) ms to over 130 ms was associated with a 1.8 fold increased risk of cardiovascular death\textsuperscript{17}. Furthermore, in hypertensive patients with left ventricular hypertrophy, prolonged QRSd predicted all-cause and cardiovascular mortality\textsuperscript{18} and identified patients at higher risk for sudden cardiac death\textsuperscript{19}. Prolonged QRS duration, especially BBB, is known to correlate with age\textsuperscript{20}. However, even after adjustment for potential confounding factors, the subjects in our study with prolonged QRSd were twice and those with IVCD three times more likely to suffer arrhythmic death compared to the rest of the population. Traditionally and especially when associated with heart disease, QRSd over 120 ms has been considered abnormal. However, the cut-off of 110 ms to define a prolonged QRSd as a risk factor was optimal in our general population sample, probably because it also included all the ECGs with IVCD and partial BBBs in the analyses.
Studies on the prognostic significance of BBB in healthy populations have given conflicting results, perhaps due to relatively small sample size and short follow-time \(^6,20\). In the present study, we primarily addressed the prognostic significance of QRSd \(\geq 110\) ms, and thus partial and complete BBBs were analyzed together. In accordance with previous studies \(^5\text{-}7\) RBBB was not associated with increased cardiovascular or overall mortality. However, some studies have suggested that subjects who are considered to be healthy but have LBBB suffer higher cardiac mortality \(^7,21\), although other studies have shown no difference in cardiovascular deaths related to LBBB \(^5,20,22\). In the present study, partial or complete LBBB predicted the occurrence of arrhythmic death, but no difference in cardiac or overall mortality was demonstrated.

This is the first report of an increased risk of cardiac and arrhythmic death associated with IVCD in a general population. Although there were no differences in the history of myocardial infarction or angina pectoris between the groups, it is possible that LBBB and IVCD are merely markers of an underlying subclinical coronary artery disease that progresses to adverse outcomes. However, several studies have failed to identify a relationship between the location of coronary stenosis and the presence of BBB \(^23,24\), and in a Framingham Study cohort, QRSd was not a precursor of coronary disease over 18 years of follow-up \(^25\).

Bradyarrhythmias may not be the most probable explanation for the increased mortality associated with prolonged QRSd either. Even though future high-degree atrioventricular block is strongly associated with the presence of bundle branch block, especially LBBB \(^7\), the risk of sudden death due to bradyarrhythmia is low even with high risk bundle branch block and pacemaker treatment has not been found to diminish the risk of death in these patients \(^26\text{-}28\). However, undiagnosed structural heart disease other than coronary artery disease, such as
dilated or hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy, may well explain the association between IVCD and the risk of sudden arrhythmic death. All forms of cardiomyopathy previously mentioned may long remain clinically silent but are often associated with intraventricular conduction abnormalities. Another explanation for differences in QRSd could be related to genetic predisposition, as several loci of the human genome have recently been associated with the duration of QRS interval. A potential pathophysiologic mechanism for the adverse prognostic impact of increased QRSd and IVCD may be related to markedly abnormal electrical and mechanical activation of the left ventricle. While a BBB is a sign of disturbance in the conduction system, the prolonged QRSd in IVCD reflects the abnormal depolarization of the myocardium itself. These changes in depolarization may play a direct role in the genesis of arrhythmias via facilitation of reentrant tachyarrhythmias. In addition, abnormalities in depolarization can lead to changes of the vulnerable repolarization phase, which in turn might expose the individual to an increased risk of sudden ventricular tachyarrhythmias.

The strengths of our study include the large number of subjects and the long and complete follow-up of these subjects, but the study also has some limitations. Echocardiography was not generally available at the time of the baseline examination, and so the information on the left ventricular ejection fraction is not available. Coronary artery disease was rare in the study population, but the diagnosis was based only on past medical history and clinical examination. Some of the subjects may therefore have had an underlying structural cardiac disease that was not evident during the clinical examination, but yet caused prolongation of QRSd in their 12-lead ECGs.
In conclusion, our community-based study shows that in a general middle-aged population, prolonged QRS duration of 110 ms or more is, independent of several baseline prognostic variables, associated with increased cardiac and all-cause mortality. Especially IVCD in a 12-lead ECG carries a substantial risk of subsequent cardiac death and sudden arrhythmic death, and therefore its presence should alert physicians to the need for a careful evaluation of the subclinical heart disease, including echocardiography, even in asymptomatic subjects. Future studies are warranted to unravel the exact mechanisms how electrocardiographic prolongation of depolarization exposes the individual to the risk of arrhythmia, and ultimately to develop strategies to prevent premature death in these individuals.

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**Conflict of Interest Disclosures:** None

**References:**


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<th>Table 1. Characteristics of the subjects at baseline*</th>
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<tr>
<td>Males, % †</td>
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<tr>
<td>Age, years ‡</td>
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<tr>
<td>Current smoker, % §</td>
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<tr>
<td>Total cholesterol, mmol/l §</td>
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<tr>
<td>Heart rate, beats/min §</td>
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<tr>
<td>Diastolic</td>
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<td>QTc duration, ms §</td>
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<tr>
<td>QRS duration, ms §</td>
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<tr>
<td>JTc duration, ms §</td>
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<tr>
<td>LVH, % §</td>
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<tr>
<td>Prior myocardial infarction,</td>
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<tr>
<td>History of angina pectoris,</td>
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</table>

LVH indicates electrocardiographic left ventricular hypertrophy according to the Sokolow-Lyon criteria

*Plus-minus values are means ± SD. QTc denotes QT corrected for heart rate. JTc is defined as QTc – QRS duration. To convert the values of cholesterol to milligrams per decilitre, divide by 0.02586.

† Adjusted for age, ‡ Adjusted for sex, § Adjusted for age and sex
Table 2. Clinical outcomes associated with prolonged duration of QRS complex

<table>
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<tr>
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<th>QRS &lt; 110ms (N = 10752)</th>
<th>QRS ≥ 110ms (N = 147)</th>
<th>P Value</th>
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<td><strong>All-cause mortality</strong></td>
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<tr>
<td>No. of Deaths</td>
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<td>110</td>
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<td>Multivariate adjusted relative risk (95% CI)*</td>
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<td>1.48 (1.22-1.81)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Cardiac Mortality</strong></td>
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<tr>
<td>No. of Deaths</td>
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<td>Age- and sex-adjusted relative risk (95% CI)</td>
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<td>1.57 (1.17-2.11)</td>
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<td>Multivariate adjusted relative risk (95% CI)*</td>
<td>1</td>
<td>1.94 (1.44-2.63)</td>
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<td><strong>Sudden Arrhythmic Death</strong></td>
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<tr>
<td>No. of Deaths</td>
<td>779</td>
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<td>Age- and sex-adjusted relative risk (95% CI)</td>
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<td>1.82 (1.19-2.78)</td>
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<td>2.14 (1.38-3.33)</td>
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* Adjusted for age and sex, smoking, serum cholesterol, cardiovascular disease, chronotropic medication, JTc, LVH, ECG signs of infarction, and history of angina pectoris or myocardial infarction

Table 3. Clinical outcomes associated with IVCD

<table>
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<th>No IVCD (N = 10832)</th>
<th>IVCD (N = 67)</th>
<th>P Value</th>
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<tr>
<td>No. of Deaths</td>
<td>6101</td>
<td>54</td>
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<td>Age- and sex-adjusted relative risk (95% CI)</td>
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<td>1.65 (1.26-2.16)</td>
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<td>Multivariate adjusted relative risk (95% CI)*</td>
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<td>2.01 (1.52-2.66)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Cardiac Mortality</strong></td>
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<tr>
<td>No. of Deaths</td>
<td>1958</td>
<td>22</td>
<td></td>
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<tr>
<td>Age- and sex-adjusted relative risk (95% CI)</td>
<td>1</td>
<td>1.89 (1.24-2.28)</td>
<td>0.007</td>
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<tr>
<td>Multivariate adjusted relative risk (95% CI)*</td>
<td>1</td>
<td>2.53 (1.64-3.90)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Sudden Arrhythmic Death</strong></td>
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<tr>
<td>No. of Deaths</td>
<td>788</td>
<td>13</td>
<td></td>
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<tr>
<td>Age- and sex-adjusted relative risk (95% CI)</td>
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<td>2.48 (1.43-4.30)</td>
<td>0.005</td>
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<tr>
<td>Multivariate adjusted relative risk (95% CI)*</td>
<td>1</td>
<td>3.11 (1.74-5.54)</td>
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* Adjusted for age and sex, smoking, serum cholesterol, cardiovascular disease, chronotropic medication, JTc, LVH, ECG signs of infarction, and history of angina pectoris or myocardial infarction
Figure Legends:

Figure 1. Age and sex adjusted Kaplan-Meier survival plots for all-cause mortality, cardiac death and sudden arrhythmic death in subjects with prolonged QRS. Subjects with duration of QRS complex at least 110 ms on a standard 12-lead ECG had an elevated risk of death as compared with those with QRS duration less than 110 ms, with a multivariate adjusted relative risk (RR) of 1.48 (95% CI 1.22-1.81; P<0.001) (Panel A). The same subjects had RR of 1.94 (95% CI 1.44-2.63; P<0.001) for cardiac death (Panel B) and RR of 2.14 for arrhythmic death (95% CI 1.38-3.33; P=0.002) (Panel C).

Figure 2. Age and sex adjusted Kaplan-Meier survival plots for all-cause mortality, cardiac death and sudden arrhythmic death in subjects with IVCD. Subjects with IVCD on a standard 12-lead ECG had an elevated risk of death as compared with those without IVCD, with RR of 2.01 (95% CI 1.52-2.66; P<0.001) (Panel A). The same subjects had RR of 2.53 (95% CI 1.64-3.90; P<0.001) for cardiac death (Panel B) and RR of 3.11 for arrhythmic death (95% CI 1.74-5.54; P=0.001) (Panel C).
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