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

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

Methods and Results—We evaluated the 12-lead ECGs of 10,899 Finnish middle-aged subjects from the general population (52% of whom were men; mean age 44.0 ± 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 QRS duration was defined as QRS >110 ms and intraventricular conduction delay as QRS >110 ms, without the criteria of complete or incomplete bundle-branch block. QRS duration >110 ms was present in 1.3% (n = 147) and intraventricular conduction delay in 0.6% (n = 67) of the subjects. Prolonged QRS duration 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 intraventricular conduction delay had increased all-cause mortality (RR 2.01; CI 1.52–2.66; P < 0.001), increased 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). Left bundle-branch block also weakly predicted arrhythmic death (P = 0.04), but right bundle-branch block was not associated with increased mortality.

Conclusions—Prolonged QRS duration in a standard 12-lead ECG is associated with increased mortality in a general population, with intraventricular conduction delay 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 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 have suggested that subjects with left bundle-branch block (LBBB) have a higher risk of cardiac death.7,8

Clinical Perspective on p 710

There is a 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 conducted in 35 populations from different geographic areas of Finland representative of the middle-aged Finnish population. The study cohort comprises a total of 10,957 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 10,899 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 provided previously.9

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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.

ECG Measurement

A standard 12-lead ECG was recorded with the subject at rest using a paper speed of 50 mm/s (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 according to the Sokolow-Lyon criteria was assessed, and QT interval (corrected for heart rate according to Bazett’s formula) was measured by 9 trained readers at the time of baseline examinations. All baseline ECGs were later independently reevaluated by a group of 5 physicians for the presence of BBB and IVCD, and the duration of QRS complex and JTc interval (corrected QT interval – QRSd) was measured where the widest complex and longest QT interval were seen. Standard ECG criteria were used to diagnose complete and incomplete LBBB and RBBB.10 QRSd ≥110 ms without criteria for complete or incomplete LBBB or RBBB and without preexcitation was classified as IVCD. Although the measurement of QRSd was performed manually, the paper speed of 50 mm/s enabled a reliable determination of the QRSd. To further minimize errors in the evaluation process, we assessed 270 ECGs for interobserver and intraobserver variation (κ-value for QRSd 0.66 and 0.68, respectively). All ECGs with QRSd of ≥110 ms were double-checked, and the presence of BBB and IVCD was established by consensus.

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 due to arrhythmia, cardiac death, and death of any cause. The mortality data were obtained from the Causes of Death Register maintained by Statistics Finland. Fewer 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.11 Death due to cardiac causes was determined from the relevant International Classification of Diseases (ICD) codes. To identify cases of sudden death due to arrhythmia, all deaths due to cardiac causes were reviewed by experienced cardiologists (O.A., H.V.H.) on the basis of the definitions presented in the Cardiac Arrhythmia Pilot Study,12 as described by our group previously.13 After reviewing data available from death certificates and hospital records, the cardiac deaths were classified as probable arrhythmic deaths or deaths that were probably not associated with arrhythmia. Death due to arrhythmia was defined as the spontaneous cessation of respiration and blood circulation with loss of consciousness in 1 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 (eg, 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 receiver operating characteristic curve for QRSd was calculated with all-cause mortality, cardiac death, and sudden arrhythmic death as end points to verify that the cutoff of 110 ms for QRSd, which included IVCD together with partial and complete BBBS, also best predicted the outcomes in this population. This cutoff was then used as a dichotomized variable in the assessment of the hazard ratios and 95% confidence intervals (CIs) for end points in a Cox proportional hazards model. Separate analyses were performed according to the morphology of prolonged QRSd, ie, LBBB, RBBB, or IVCD. The primary adjustments to these models were for age and sex, with further adjustments for covariates that differed between the groups or that 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 ECG 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 are 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<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. A total of 1.9% of the subjects had QRSd ≤70 ms, 43.6% had QRSd 80 to 89 ms, 40.0% had QRSd 90 to 99 ms, and 13.1% had QRSd 100 to 109 ms. QRSd ≥110 ms was present in 147 (1.3%) of 10 899 subjects. Of these subjects, 84 (0.8%) had QRSd ≥120 ms and 39 (0.4%) had QRSd ≥140 ms. 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 ≥110 ms. The remaining 3 subjects with prolonged QRSd had a preexcitation pattern in their ECGs and were excluded. Subjects with prolonged QRSd were older and more often were male, had higher systolic blood pressure, and had a shorter JTc interval. There was no difference in the history of prior myocardial infarction between the 2 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 had a shorter JTc interval. There was no difference in the history of angina pectoris or previously diagnosed myocardial infarction.

Repeated ECG Measurement

A second ECG measurement (an average of 5 years after the baseline examination) was available for 114 (78%) of the 147 subjects with baseline QRSd ≥110 ms. Of these 114 subjects, 107 (94%) also had QRSd ≥110 ms on the second ECG, and the average QRS duration was prolonged from 122±13 to 128±18 ms. Fifty-three 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 to 120±12 ms. Among the 27 subjects with LBBB who underwent the second ECG, LBBB was
present in 25 (93%), with QRSd increased from 133±11 to 144±14 ms. Of the 31 subjects with RBBB in the baseline ECG who had a second ECG available, 27 (87%) also had RBBB during the follow-up, with QRSd increased from 128±13 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 of cardiac causes, and 801 (40.5%) of these were due to cardiac causes, and death due to arrhythmia in subjects with prolonged QRSd are presented in Figure 1.

Subjects with IVCD had an increased risk of death due to any cause (RR 2.01, CI 1.52–2.66, **P**<0.001), an elevated risk.

Table 2 shows the relative risk of death due to any cause, cardiac causes, and arrhythmia associated with prolonged QRSd. Subjects with QRSd ≥110 ms had higher all-cause mortality (multivariate-adjusted relative risk [RR] 1.48, 95% 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 an increased risk of major end points. Age- and sex-adjusted Kaplan–Meier curves for all-cause mortality, death due to cardiac causes, and death due to arrhythmia in subjects with prolonged QRSd are presented in Figure 1.

Subjects with IVCD had an increased risk of death due to any cause (RR 2.01, CI 1.52–2.66, **P**<0.001), an elevated risk.

### Table 2. Clinical Outcomes Associated With Prolonged Duration of QRS Complex

<table>
<thead>
<tr>
<th>QRS Duration</th>
<th>No IVCD (n=10 832)</th>
<th>IVCD (n=67)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No IVCD</td>
<td>6045</td>
<td>110</td>
<td></td>
</tr>
<tr>
<td>Age- and sex-adjusted relative risk (95% CI)</td>
<td>1.30 (1.07–1.57)</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted relative risk (95% CI)*</td>
<td>1.48 (1.22–1.81)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac mortality</th>
<th>No of deaths</th>
<th>1934</th>
<th>46</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age- and sex-adjusted relative risk (95% CI)</td>
<td>1.57 (1.17–2.11)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted relative risk (95% CI)*</td>
<td>1.94 (1.44–2.63)</td>
<td><strong>&lt;0.001</strong></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sudden arrhythmic death</th>
<th>No of deaths</th>
<th>779</th>
<th>22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age- and sex-adjusted relative risk (95% CI)</td>
<td>1.82 (1.19–2.78)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Multivariate-adjusted relative risk (95% CI)*</td>
<td>2.14 (1.38–3.33)</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

*Adjusted for age and sex, smoking, serum cholesterol, cardiovascular disease, chronotropic medication, JTC (QTC–QRS duration), left ventricular hypertrophy, ECG signs of infarction, and history of angina pectoris or myocardial infarction.
of death due to cardiac causes (RR 2.53, CI 1.64–3.90, \(P < 0.001\)), and an even higher risk of death due to 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 (\(n = 10\,006\)) were analyzed separately, the results remained essentially the same. These subjects with QRSd \(\geq 110\) 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 due to cardiac causes (RR 1.87, CI 1.08–3.25, \(P = 0.04\)), and a high risk of death due to arrhythmia (RR 2.90, CI 1.49–5.63, \(P = 0.007\)).

**Discussion**

The main finding of the present 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 increased 3-fold even after multivariate adjustment. Moreover, prolonged QRS complex duration of \(\geq 110\) ms in general, including BBBS and IVCD, was a significant predictor of arrhythmic, cardiac, and all-cause mortality in this population.

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**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 of at least 110 ms on a standard 12-lead ECG had an elevated risk of death compared with those with QRS duration <110 ms, with a multivariate adjusted relative risk of 1.48 (95% confidence interval 1.22–1.81, \(P < 0.001\); A). The same subjects had relative risk of 1.94 (95% confidence interval 1.44–2.63, \(P < 0.001\)) for cardiac death (B) and 2.14 (95% confidence interval 1.38–3.33, \(P = 0.002\)) for arrhythmic death (C).

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**Table 3. Clinical Outcomes Associated With IVCD**

<table>
<thead>
<tr>
<th></th>
<th>No IVCD ((n = 10,832))</th>
<th>IVCD ((n = 67))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>6101</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Age- and sex-adjusted relative risk (95% CI)</td>
<td>1</td>
<td>1.65 (1.26–2.16)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Multivariate-adjusted relative risk (95% CI)*</td>
<td>1</td>
<td>2.01 (1.52–2.66)</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Cardiac mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>1958</td>
<td>22</td>
<td></td>
</tr>
<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>
</tr>
<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>Sudden arrhythmic death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of deaths</td>
<td>788</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Age- and sex-adjusted relative risk (95% CI)</td>
<td>1</td>
<td>2.48 (1.43–4.30)</td>
<td>(0.005)</td>
</tr>
<tr>
<td>Multivariate-adjusted relative risk (95% CI)*</td>
<td>1</td>
<td>3.11 (1.74–5.54)</td>
<td>(0.001)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval.

*Adjusted for age and sex, smoking, serum cholesterol, cardiovascular disease, chronotropic medication, JTc (QTc–QRS duration), left ventricular hypertrophy, ECG signs of infarction, and history of angina pectoris or myocardial infarction.
It has long been recognized that when associated with heart disease, prolonged QRSd in an ECG is an independent predictor of adverse outcome. In most patients with systolic left ventricular dysfunction, QRS prolongation presents as LBBB, and in these patients, increased QRSd is associated with a worse prognosis. For patients with coronary artery disease plus depressed ventricular function and nonsustained 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. In patients with suspected coronary artery disease referred for noninvasive evaluation of myocardial ischemia, QRSd was an independent predictor of cardiac death and nonfatal infarction, and in patients with suspected acute coronary syndrome, QRS prolongation predicted in-hospital and 1-year mortality. In a general medical inpatient and outpatient cohort of patients without BBB, an increase in QRSd from 110 to 130 ms was associated with a 1.8-fold increased risk of cardiovascular death. Furthermore, in hypertensive patients with left ventricular hypertrophy, prolonged QRSd predicted all-cause and cardiovascular mortality and identified patients at higher risk for sudden cardiac death. Prolonged QRS duration, especially BBB, is known to correlate with age. However, even after adjustment for potential confounding factors, the subjects in the present study with prolonged QRSd were twice as likely and those with IVCD were 3 times as likely to suffer arrhythmic death compared with the rest of the population. Traditionally, and especially when associated with heart disease, QRSd >120 ms has been considered abnormal. However, the cutoff 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 because of relatively small sample size and short follow-up time. In the present study, we primarily addressed the prognostic significance of QRSd ≥110 ms, and thus, partial and complete BBBs were analyzed together. In accordance with previous studies, 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 have higher cardiac mortality, although other studies have shown no difference in cardiovascular deaths related to LBBB. 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, and in a Framingham Study cohort, QRSd was not a precursor of coronary disease over 18 years of follow-up. 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 BBB, especially LBBB, the risk of sudden death due to bradyarrhythmia is low even with high-risk BBB, and pacemaker treatment has not been found to diminish the risk of death in these patients. 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, because several loci of the human genome have recently been associated with the duration of QRS interval. A potential pathophysiological mechanism for the adverse prognostic impact of increased QRSd and IVCD may be related to markedly abnormal electric and mechanical activation of the left ventricle. Although 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 the present 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 information on 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 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. In particular, IVCD in a 12-lead ECG carries a substantial risk of subsequent cardiac death and sudden arrhythmic death, and its presence should alert physicians to the need for a careful evaluation, including echocardiography, of subclinical heart disease even in asymptomatic subjects. Future studies are warranted to unravel the exact mechanisms that determine how ECG 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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DISCUSSIONS
None.
Prolonged QRS duration (QRSd) and nonspecific intraventricular conduction delay (IVCD) are associated with adverse outcomes in patients with cardiovascular disease. However, information on the prognostic significance of QRSd and IVCD in patients with suspected coronary artery disease referred for noninvasive evaluation of myocardial ischemia is limited. We evaluated ECGs of 10,899 Finnish middle-aged subjects from the general population, it is associated with a significant risk of sudden cardiac death. Therefore, its presence should alert physicians to perform a careful evaluation of subclinical heart disease, even in asymptomatic subjects.
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