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Bundle-branch block in middle-aged men: risk of complications and death over 28 years

The Primary Prevention Study in Göteborg, Sweden

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KEYWORDS
Bundle-branch block;
Ischaemic heart disease;
High-degree atrioventricular block;
Prognosis;
Sudden death

Aims To investigate the long-term fate of men with bundle-branch block (BBB) from a general population sample.

Methods and results Data were derived from 7392 men without a history of myocardial infarction or stroke, born between 1915 and 1925 and investigated between 1970 and 1973. All participants were followed from the date of their baseline examination until 1998. We identified 70 men with right-BBB and 46 men with left-BBB at baseline. In men with right-BBB, there was no increased risk of myocardial infarction, coronary death, heart failure, or all-cause mortality during follow-up. The multiple-adjusted hazard ratio for progression to high-degree atrioventricular block was 3.64 (99% confidence interval 0.79–16.72). In men with left-BBB, the hazard ratio for high-degree atrioventricular block was 12.89 (4.13–40.24). However, hazard ratio for all-cause mortality was 1.85 (1.15–2.97) when compared with men without BBB, mostly due to outside hospital coronary deaths, whose hazard ratio was 4.22 (1.90–9.34).

Conclusion The presence of BBB was strongly associated with future high-degree atrioventricular block that was more pronounced for left-BBB. Men with left-BBB have a substantially increased risk of coronary death, mainly due to sudden death outside the hospital setting.

Introduction

Interest in bundle-branch block (BBB) has focussed primarily on its role as a predictor of mortality and co-existing cardiovascular disease. The epidemiological data have mostly been derived from hospitalized patients,[1–8] with findings partly dependent on the characteristics of the patient cohort and the reason for carrying out an electrocardiogram (ECG). Studies performed in healthy populations have often had a wide age range with the majority of individuals with BBB found among the elderly.[9–12] In a previous study, we found no correlation with risk factors for coronary heart disease, indicating that although ischaemic heart disease and BBB often co-exist, their causes may not be the same.[13] Findings about future cardiovascular events have not been consistent,[14,15] but several studies have found an increased mortality among patients with BBB and concomitant cardiovascular disease.[1,3,8,16] In patients with acute myocardial infarction, the presence of BBB is a marker of worst outcome, which persists in the modern era of thrombolytic therapy.[17–19] However, whether it is the pathogenesis and morphology of the BBB itself or the combination with ischaemic heart disease that has an impact on mortality is unclear. Although the annual incidence of progression to high-degree atrioventricular block has been reported to be 1–4% in unselected populations, bradyarrhythmias and high-degree atrioventricular block do not seem to have a major impact on mortality, and pacemaker treatment has not been found to diminish the risk of death in patients with BBB.[3,20,21] Few studies have been able to investigate the long-term fate of individuals with BBB from a general population sample, with respect to ischaemic heart disease and other cardiovascular outcomes. In this study, we identified 70 men with right-BBB and 46 men with left-BBB in their 50s, followed them over a period of 28 years and compared them with 7276 men without BBB.***

Methods

Study population

The multifactor primary prevention trial started in Göteborg in 1970 and included all men in the city born between 1915 and 1925,

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except those born in 1923. A detailed account of the study rationale and design has been published.[22] The intervention group of 10 000 men comprised a random third of the men in the trial, with two control groups of 10 000 men each. This study deals only with the men in the intervention group ($n = 9998$), as only data from limited sub-samples were available for the control groups. In the intervention group, men who were found to be hypertensive, who had hypercholesterolaemia, or who smoked were referred to special intervention clinics. Ten years after entry, a 20% random sub-sample of the intervention group and one of the control groups were examined again. Serum cholesterol, smoking, and blood pressure had decreased in both groups, but there were no significant differences between the intervention and the control groups. In addition, there were no differences in outcome for cardiovascular, cancer, or all-cause mortality between the intervention and any of the control groups. The fact that the intervention was mainly targeted at subjects with very high risk and that changes in risk factors occurred among the general population as well contribute to explaining the lack of an overall effect of the intervention. So, we consider this study group to be reasonably representative of the background population in the city.

Table 1 ICD codes used to define end-points

	ICD version[a]	ICD number
Myocardial infarction	8–9	410
	10	I21
Coronary death	8–9	410–414
	10	I20–I25
High-degree atrioventricular block (AV conduction defect II or III)	8	427.20, 427.28
	9	426A
	10	I44.2
Atrial fibrillation	8	427.92
	9	427D
	10	I48
Heart failure	8	427.00, 427.10
	9	428A, 428B, 428X
	10	I50
Aortic stenosis	8	395, 424.10, 424.11, 424.19
	9	395, 424B
	10	I06, I35

[a]ICD 8 until 1986, ICD 9 until 1996, and ICD 10 from 1997.

Data were derived from 7392 (out of a total of 7495) participating men, born between 1915 and 1925, except those born in 1923, without a history of prior myocardial infarction or stroke, and investigated between 1970 and 1973. All participants gave their written informed consent to participation in the study. The study was approved by the Ethics Committee for Medical Research at Göteborg University. Information on smoking habits, physical activity during leisure time, diabetes, myocardial infarction and stroke, symptoms of chest pain and dyspnoea on exertion, and family history of cardiovascular disease was collected via a mailed questionnaire to all men in the intervention group, including a Rose questionnaire for the presence of possible anginal symptoms and dyspnoea on exertion. Men who returned the questionnaire were invited to the study centre. Screening examinations recording weight, height, and blood pressure were performed in the afternoon, and samples for serum cholesterol concentration were taken after fasting for at least 2 h. Smoking habits were coded into five categories: never smoked, former smoker of more than 1 month's duration, smoking 1–14 g of tobacco per day, smoking 15–24 g, and smoking 25 g or more per day. One cigarette was considered to contain 1 g of tobacco, a cigarillo 2 g, and a cigar 5 g of tobacco. Physical activity during leisure time was categorized into three levels: (1) sedentary, (2) moderate activity, such as walking or light gardening for at least 4 h per week, and (3) regular, strenuous activity, or very strenuous activity. Possible anginal pain was defined as discomfort or pain in the chest provoked by walking two flights of stairs or on the level, relieved within 10 min by stopping or slowing down.

Electrocardiogram

Standard 12-lead ECGs were recorded, with the patient at rest in the supine position. Paper speed was 50 mm/s and calibration was 1 mV:10 mm. All 12-lead ECGs were interpreted by one of the authors (P.E.), who was blinded to all data, and were classified

Table 2 Coronary risk factors by the absence or presence of right- or left-bundle-branch block at baseline in 1970–1972

	No bundle-branch block ($n = 7276$)	RBBB ($n = 70$)	LBBB ($n = 46$)	Any bundle-branch block ($n = 116$)	*P* for comparisons with men without bundle-branch block
Age, years, mean (SD)	51.6 (2.3)	52.4 (2.0)	52.1 (2.5)	52.3 (2.2)	
SBP (mmHg), mean (SD)	149 (22)	154 (23)	156 (25)	155 (24)	RBBB 0.039; LBBB 0.025; any BBB 0.003
DBP (mmHg), mean (SD)	95 (13)	97 (13)	100 (16)	98 (14)	LBBB 0.004; any BBB 0.006
Serum cholesterol (mmol/l), mean (SD)	6.46 (1.16)	6.39 (1.11)	6.57 (1.37)	6.46 (1.16)	
Body mass index (kg * m − 2), mean (SD)	25.5 (3.3)	25.8 (3.8)	25.9 (2.8)	25.9 (3.8)	
Smokers at baseline, % (*n*)	50 (3647)	50 (35)	49 (22)	50 (57)	
Sedentary physical activity, % (*n*)	26 (1865)	14 (10)	30 (14)	21 (24)	
Moderate activity, % (*n*)	59 (4270)	69 (48)	59 (27)	65 (75)	
Regular, strenuous activity or very strenuous activity, % (*n*)	16 (1141)	17 (12)	11 (5)	15 (17)	
Family history, % (*n*)	20 (1448)	17 (12)	20 (9)	18 (21)	
Diabetes, % (*n*)	2 (143)	1 (1)	2 (1)	2 (2)	
Treated hypertension, % (*n*)	5 (387)	6 (4)	11 (5)	8 (9)	
Presence of angina, % (*n*)	6 (465)	0	17 (8)	7 (8)	
Dyspnea walking 2 flights of stairs, % (*n*)	20 (1473)	14 (10)	20 (9)	16 (19)	

All comparisons are for the group without bundle-branch block.

according to the presence or absence of BBB. Left-BBB was defined as (1) QRS duration >120 ms, (2) PQ interval >120 ms, (3) predominantly upright complexes with slurred R waves in lead I, V5, and V6, and (4) QS or rS pattern in V1. Right-BBB was defined as (1) QRS duration >120 ms, (2) PQ interval >120 ms, (3) rSR′ in lead V1 or V2, and (4) S waves in lead I and in either V5 or V6. Two men with left-BBB had concomitant atrial fibrillation and in those men the criterion of PQ interval >120 was waived.

Follow-up procedures

All participants in the multifactor Primary Prevention Study were followed from the date of their baseline examination until 31 December 1998, by running the data file of the men in the study against the Swedish national register on cause of death and the Swedish Hospital Discharge Register.[23] This process was approved by the review board of the Göteborg University Ethics Committee. The Hospital Discharge Register has been in operation since 1964 and has operated on a nation-wide basis since 1987. However, all discharges from Sahlgrenska Hospital, which was the single major hospital in the city until 1977, have been entered in the national register since 1970 for all years (except 1976, due to a legislative change for that single year), and all discharges from Östra Hospital, the other major hospital in the city that opened in 1978, were entered from the start. In addition, until March 1983, all fatal and non-fatal myocardial infarctions occurring in the study

Table 3 Cardiac end-points and hazard ratios by the absence or presence of right- or left-bundle-branch block at baseline in 1970–1972

	Number of cases	Cases per 10 000 person years	Age-adjusted hazard ratios (99% confidence interval)	Multiple-adjusted[a] hazard ratios (99% confidence interval)
Non-fatal myocardial infarction				
No bundle-branch block	1046	62	1.00	1.00
RBBB	11	64	1.00 (0.46–2.18)	1.11 (0.51–2.43)
LBBB	10	110	1.78 (0.79–4.04)	1.54 (0.68–3.49)
Acute myocardial infarction				
No bundle-branch block	1654	103	1.00	1.00
RBBB	15	95	0.85 (0.43–1.65)	0.94 (0.48–1.83)
LBBB	22	256	2.58 (1.49–4.49)	2.26 (1.29–3.94)
All coronary deaths				
No bundle-branch block	891	52	1.00	1.00
RBBB	6	35	0.59 (0.20–1.69)	0.65 (0.23–1.87)
LBBB	17	186	3.75 (2.00–7.05)	3.30 (1.75–6.24)
Out-of-hospital coronary deaths				
No bundle-branch block	450	26	1.00	1.00
RBBB	4	23	0.78 (0.21–2.83)	0.87 (0.24–3.18)
LBBB	11	121	4.76 (2.17–10.46)	4.22 (1.90–9.34)
High-degree atrioventricular block				
No bundle-branch block	82	5	1.00	1.00
RBBB	3	18	3.15 (0.69–14.34)	3.64 (0.79–16.72)
LBBB	7	80	17.77 (6.42–49.20)	12.89 (4.13–40.24)
Pacemaker				
No bundle-branch block	144	8	1.00	1.00
RBBB	6	36	3.91 (1.33–11.45)	4.45 (1.51–13.15)
LBBB	7	81	11.73 (4.32–31.85)	8.48 (2.85–25.30)
Atrial fibrillation				
No bundle-branch block	873	53	1.00	1.00
RBBB	12	72	1.27 (0.60–2.68)	1.33 (0.62–2.80)
LBBB	9	105	2.39 (1.01–5.68)	1.85 (0.74–4.63)
Heart failure				
No bundle-branch block	1032	62	1.00	1.00
RBBB	14	84	1.22 (0.61–2.43)	1.33 (0.66–2.66)
LBBB	15	177	3.54 (1.81–6.92)	3.26 (1.66–6.41)
Aortic stenosis				
No bundle-branch block	178	10	1.00	1.00
RBBB	2	12	1.00 (0.16–6.29)	1.10 (0.18–6.92)
LBBB	5	58	5.98 (1.86–19.26)	4.33 (1.16–16.13)
All-cause mortality				
No bundle-branch block	3219	190	1.00	1.00
RBBB	29	169	0.80 (0.50–1.30)	0.88 (0.54–1.42)
LBBB	30	329	1.92 (1.20–3.08)	1.85 (1.15–2.97)

[a]Adjustment for age, systolic blood pressure, serum cholesterol, body mass index, family history of myocardial infarction, treatment for hypertension, angina, diabetes, smoking, and leisure time physical activity.

population were recorded in the Göteborg AMI Register.[24] End-points were defined as hospitalization or death according to the international classification of diseases (ICD) codes as in *Table 1*. *Non-fatal myocardial infarction* was defined as being hospitalized with acute myocardial infarction and surviving for at least 28 days. *Out-of-hospital coronary death* was defined as dying outside the hospital from coronary disease, at least 28 days after last being discharged from hospital. *Pacemaker insertion* was defined as operation codes 3081, 3082, 3083, 3094, 3097, or 3098. It should be noted that ICD 8 did not have a separate code for AV conduction defect III.

Statistical methods

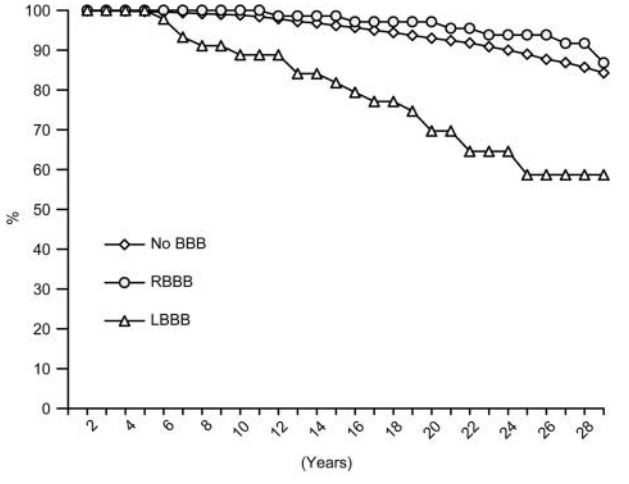
We used the SAS statistical package (version 8e). For the cross-sectional analyses, Pearson's correlation tests were used for continuous variables and Mantel–Haenszel tests for categorical variables. All tests were two-sided and a P value of <0.05 was considered significant. In the prospective part of the study, age-adjusted proportional hazard analyses were used to calculate relative risks. Time at risk was calculated until 31 December 1998, death or hospitalization for any of the end-points. We used two final regression models, one with and one without the inclusion of covariates that may be intermediate factors in the causal chain between BBB and ischaemic heart disease. Thus, one regression model included only age, and two variables created from the two different types of BBB. The second model added systolic blood pressure, body mass index, serum cholesterol (entered as continuous variables), family history of myocardial infarction, treatment for hypertension, angina, diabetes, smoking, and leisure time physical activity. These variables were selected because they were significantly associated with AMI and coronary death in univariate analysis. We checked the assumption of proportional hazards by entering time-dependent variables related to the factors we studied. The impact of these variables was not significant on the model fit, which indicates that the assumption is valid. The linearity assumption was assessed by visual means. No adjustments were made to the significance levels to account for multiple testing; however, because we considered several outcomes, hazard ratios are presented with 99% confidence intervals.

Results

We identified 116 men with BBB (70 with right-BBB and 46 with left-BBB) at baseline. Men with BBB had higher mean blood pressure. There were no significant differences between men with (separately or combined) and without BBB for serum cholesterol, body mass index, smoking habits, leisure time physical activity, diabetes, or family history of myocardial infarction (*Table 2*).

Among men with right-BBB at baseline there was no increased risk of myocardial infarction or coronary death, atrial fibrillation, heart failure, and aortic stenosis or all-cause mortality during the 28 years of follow-up. However, the risk of developing high-degree atrioventricular block and/or to have a pacemaker inserted was increased approximately four times, compared with men without BBB (*Table 3*).

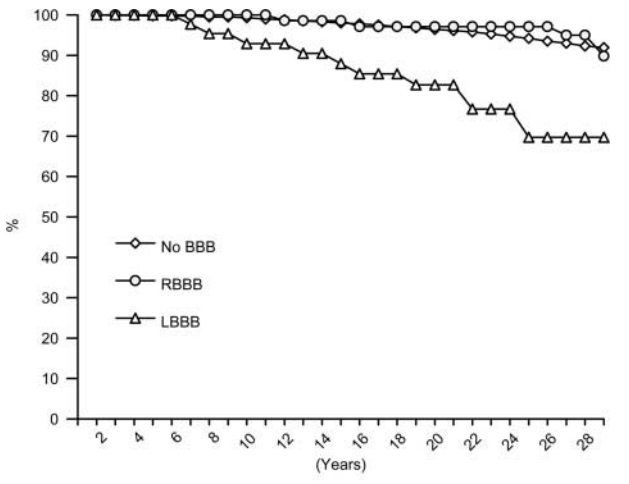
Men with left-BBB had an increased risk of myocardial infarction, mainly due to more fatal cases, particularly those occurring outside hospital, with a four-fold increase in risk that persisted after adjustment for systolic blood pressure and other risk factors. They had an 18-fold increased hazard of being diagnosed with high-degree atrioventricular block during follow-up and a 12-fold increased risk of requiring a pacemaker. Adjustment for blood pressure and other factors attenuated hazard ratios to some degree. Increased hazard of being hospitalized with heart failure or aortic stenosis was also observed (*Table 3*). The overall hazard of dying during follow-up was approximately twice



Numbers at risk:

Year	0	5	10	15	20	25
No BBB	7276	7118	6804	6281	5588	4406
RBBB	70	70	69	64	58	46
LBBB	46	44	38	34	28	19

Figure 1 Survival curves for coronary deaths in men with left-BBB, right-BBB, and without BBB at baseline.



Numbers at risk:

Year	0	5	10	15	20	25
No BBB	7276	7118	6804	6281	5588	4406
RBBB	70	70	69	64	58	46
LBBB	46	44	38	34	28	19

Figure 2 Survival curves for sudden deaths in men with left-BBB, right-BBB, and without BBB at baseline.

that of the other men in the study. Survival curves for coronary deaths and sudden death are shown in *Figures 1 and 2*, respectively. An analysis restricted to men without possible angina pain or dyspnoea (5628 men without BBB, 60 with right-BBB, and 31 with left-BBB) did not decrease the hazard ratios associated with left-BBB (*Table 4*). However, the findings with respect to LBBB and aortic stenosis were no longer significant, largely because only three cases were diagnosed among men with LBBB [HR 3.77 (99% confidence interval 0.59–24.00)], and there was no significant association with all-cause mortality.

Discussion

Over almost 30 years of follow-up in this study we found that men with left, but not right, BBB had a markedly increased risk of dying from coronary disease and that two-thirds of these deaths occurred outside hospital, indicating probable fatal arrhythmia. One in six of the men with left-BBB progressed to high-degree atrioventricular block or to requiring a pacemaker. Men with right-BBB also progressed to high-degree atrioventricular block and/or to requiring a pacemaker to a greater extent than men without BBB, but

Table 4 Cardiac end-points and hazard ratios by the absence or presence of right- or left-bundle-branch block in 5719 men without angina or dyspnoea at baseline in 1970–1972

	Number of cases	Age-adjusted hazard ratios (99% confidence interval)	Multiple-adjusted[a] hazard ratios (99% confidence interval)
Non-fatal myocardial infarction			
No bundle-branch block	761	1.00	1.00
RBBB	9	1.02 (0.43–2.43)	1.08 (0.45–2.57)
LBBB	6	1.68 (0.58–4.84)	1.59 (0.551–4.58)
Acute myocardial infarction			
No bundle-branch block	1199	1.00	1.00
RBBB	11	0.78 (0.36–1.70)	0.81 (0.37–1.77)
LBBB	14	2.58 (1.29–5.15)	2.50 (1.245–5.02)
All coronary deaths			
No bundle-branch block	614	1.00	1.00
RBBB	3	0.38 (0.09–1.69)	0.39 (0.09–1.72)
LBBB	11	3.96 (1.81–8.67)	3.95 (1.80–8.70)
Out-of-hospital coronary deaths			
No bundle-branch block	315	1.00	1.00
RBBB	2	0.49 (0.08–3.07)	0.50 (0.08–3.14)
LBBB	8	5.62 (2.23–14.14)	5.21 (2.06–13.21)
High-degree atrioventricular block			
No bundle-branch block	56	1.00	1.00
RBBB	2	2.74 (0.43–17.51)	2.99 (0.46–19.34)
LBBB	5	21.83 (6.54–72.90)	15.92 (3.93–64.50)
Pacemaker			
No bundle-branch block	96	1.00	1.00
RBBB	5	4.40 (1.35–14.38)	4.57 (1.39–15.04)
LBBB	5	14.74 (4.51-48.15)	10.98 (2.87-41.91)
Atrial fibrillation			
No bundle-branch block	645	1.00	1.00
RBBB	10	1.27 (0.56–2.90)	1.31 (0.58–2.99)
LBBB	5	1.96 (0.62–6.22)	1.31 (0.36–4.77)
Heart failure			
No bundle-branch block	730	1.00	1.00
RBBB	9	0.98 (0.41–2.32)	1.00 (0.42–2.39)
LBBB	10	3.77 (1.66–8.56)	3.73 (1.63–8.51)
Aortic stenosis			
No bundle-branch block	127	1.00	1.00
RBBB	1	0.61 (0.05–8.17)	0.62 (0.05–8.28)
LBBB	3	5.82 (1.29–26.21)	3.77 (0.59–24.00)
All-cause mortality			
No bundle-branch block	2279	1.00	1.00
RBBB	22	0.76 (0.44–1.33)	0.80 (0.46–1.39)
LBBB	17	1.70 (0.91–3.19)	1.74 (0.93–3.27)

5628 men had no BBB, 60 men had RBBB, and 31 men had LBBB at baseline

[a]Adjustment for age, systolic blood pressure, serum cholesterol, body mass index, family history of myocardial infarction, treatment for hypertension, angina, diabetes, smoking, and leisure time physical activity.

otherwise did not have an increased risk of cardiovascular disease or death.

Classifying wide QRS complex as either right-BBB or left-BBB could be difficult, especially in the presence of ischaemia/acute myocardial infarction, when there is a risk of misinterpreting a peri-infarction block as BBB or a left-BBB as a sign of acute myocardial infarction. In our study, the ECG was taken routinely in a presumed healthy individual, in particular, excluding men with a history of acute myocardial infarction. Accordingly, we classified all participants with a QRS duration $>$120 ms as either right-BBB or left-BBB.

Several studies have tried to identify a relationship between the extent or location of coronary disease and the presence of BBB but have failed.[16,25,26] Among patients with known coronary disease, no association was found between any particular location of coronary stenosis or left ventricular wall motion abnormalities, indicating that the BBB was not the result of an infarction in the area around the proximal conduction system. Except for elevated blood pressure, we found no association between any of the major risk factors and BBB, in accordance with an earlier study that found that coronary risk factors did not predict subsequent development of BBB.[13] In this study, BBB was not significantly associated with future risk of non-fatal myocardial infarction, further supporting the hypothesis that coronary heart disease does probably not play a major role in the pathogenesis of BBB in a general male population.

The marked increase in mortality among patients with BBB observed in many studies is mainly seen in combination with concomitant cardiovascular disease, in particular, myocardial infarction.[16,17,19,27–30] In BBB, the depolarization phase is by definition prolonged, usually more pronounced in left than in right-BBB. The prolongation of the vulnerable re-polarization phase, in combination with an increased number of premature ventricular beats secondary to ischaemic heart disease, might expose the individual to an increased risk of sudden ventricular tachyarrhythmias. An unexpectedly high prevalence of BBB was found in patients who survive ventricular fibrillation.[31–33] This study supports the theory that individuals with left-BBB have a substantially increased risk of sudden death due to coronary causes, probably due to malignant tachyarrhythmias. The presence of BBB was strongly associated with future high-degree atrioventricular block that was more pronounced for left-BBB. This is in line with other studies that have shown a progression to high-degree atrioventricular block with an annual incidence of 1–4%.[20,33,34] Bradyarrhythmias and high-degree atrioventricular block do not seem to have a major impact on mortality, and pacemaker treatment has not been found to diminish the risk of sudden death among individuals with BBB.[14,20,21,35–37] For right-BBB, there was no increased risk of atrial fibrillation, heart failure, or aortic stenosis. In left-BBB, there was an increased risk of developing heart failure and aortic stenosis. We excluded men with known prior myocardial infarction or stroke, and men with BBB did not have more dyspnoea on exertion, but men with left-BBB had more possible anginal symptoms. Even so, an analysis that excluded men with these cardiovascular symptoms did not result in any change with respect to odds ratios, supporting the hypothesis that left-BBB is a marker for an adverse prognosis even in symptom-free men. Thus, BBB may be a marker of a slowly progressing disease that not only affects the conduction system.[13]

One of the limitations of this study was the fact that we had no information on subsequent development of BBB or of risk factors, i.e. diabetes or hypertension during the extended follow-up. In older individuals with more concomitant atherosclerosis, both the risk factor pattern and the outcome may be different. Also, we do not know to what extent a more detailed examination at baseline would have revealed other signs of heart disease. Owing to the small number of patients showing deviation of the frontal electrical axis, the contribution of this electrocardiographic pattern to the prognosis could not be determined. Another limitation is that we had no data on women. Meanwhile, the findings of this study indicate that a man in his 50s with right-BBB may be expected to have an increased risk of developing high-degree atrioventricular block but otherwise have normal longevity. Men with left-BBB have an even higher risk of developing high-degree atrioventricular block and more importantly have a substantially increased risk of coronary death, mainly due to sudden death outside the hospital setting.

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Conflict of interest: none declared

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