Risk Factor Implications of Incidentally Discovered Uncomplicated Bundle Branch Block

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OBJECTIVE: **To evaluate the long-term outcome of a community-based patient population with incidentally discovered asymptomatic and uncomplicated bundle branch block (BBB).**

PATIENTS AND METHODS: **A retrospective observational cohort study was undertaken of patients in Olmsted County, Minnesota, who were evaluated between 1975 and 1999 and were incidentally diagnosed as having BBB. We performed Kaplan-Meier analyses of all-cause mortality and development of first cardiac morbidity after the diagnosis of BBB, along with matched control group comparisons.**

RESULTS: **A total of 723 patients with left BBB (LBBB) (58.1%) and right BBB (41.9%) met criteria. Mortality was higher in patients with BBB compared with controls (absolute difference of approximately 10% over 20 years; hazard ratio = 1.27; confidence interval, 1.02-1.58; *P*=.03) as was the development of first cardiac-related morbidity (hazard ratio = 1.32; confidence interval, 1.14-1.54; *P*<.001). Patients with BBB and without the risk factors of diabetes, hypertension, and/or hypercholesterolemia showed increased long-term mortality compared with matched controls (no BBB) also without risk factors (*P*=.02). However, comparable mortality was shown between patients with BBB who did not have these risk factors and matched control patients who had these risk factors. The risk of developing cardiac-related morbidity also was increased in the presence of BBB, particularly LBBB.**

CONCLUSIONS: **Uncomplicated asymptomatic BBB (notably LBBB) with normal left ventricular ejection fraction is not benign. Our findings indicate that the presence of isolated BBB denotes a high-risk patient subgroup that has a compromised long-term outcome comparable to patients with conventional cardiovascular risk factors.**

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BBB = bundle branch block; ECG = electrocardiography; LBBB = left BBB; LVEF = left ventricular ejection fraction; RBBB = right BBB

It is conventional wisdom that the electrocardiographic (ECG) presence of bundle branch block (BBB) in the absence of symptoms or underlying structural heart disease does not presage adverse short-term or long-term consequences. Bundle branch block often is discovered on routine ECG in individuals without clinical evidence of heart disease. However, recent evidence suggests that ventricular asynchrony, possibly including that related to BBB, is associated with an adverse prognosis over time.[1-8] Accordingly, the purpose of this study was to examine the long-term natural history of patients with incidentally discovered asymptomatic and uncomplicated BBB.

PATIENTS AND METHODS

A retrospective observational cohort study of patients in Olmsted County, Minnesota, seen at the Mayo Clinic and the Olmsted Medical Center in Rochester, Minn, was undertaken between 1975 and 1999. These 2 facilities provide most medical care for the residents of Olmsted County (population 124,700 in 2000 census). Both facilities use a medical records system in which patient data are collected by health care providers and saved into a single patient file. These data are retrievable through the extensive Mayo Clinic indices of diagnoses and procedures, which have been maintained for several decades. The files are linked through the centralized Rochester Epidemiology Project, which allows patient data acquisition.

The total number of Olmsted County and non–Olmsted County patients with BBB identified from computerized medical records of resting 12-lead ECG was 104,580. Of these patients, 723 were residents of Olmsted County who were seen for primary care treatment without physician referral and who met the following prospective criteria: left ventricular ejection fraction (LVEF) of 50% or greater; no known regional wall motion abnormalities (other than those associated with the presence of BBB); older than 18 years; and no symptoms (chest pain or pressure, inappropriate shortness of breath), findings, or diagnosis of ischemic, structural, or cardiomyopathic heart disease (ie, no coronary artery disease, myocardial infarction, cardiomyopathy, congestive heart failure, valvular heart disease, pacemaker implantation, or atrial fibrillation/flutter).

All study group ECGs were reviewed to confirm a diagnosis of BBB and to exclude confounding variables of left ventricular hypertrophy and nonspecific intraventricular conduction delay. The LVEF measurement closest to the index date of the diagnosis of BBB on ECG was selected for all patients (86% at or after time of BBB diagnosis and

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all obtained within 6 months of BBB index ECG). Because of the extensive clinical record system of the Rochester Epidemiology Project, we were also able to select a control cohort of patients who had a normal index ECG (with no prior abnormal ECG) and without diagnoses of heart disease. Control patients were required to be free of symptoms/history/diagnosis and findings of cardiovascular disease before and at the time of their index ECG (similar to the criteria for patients with BBB), have normal LVEF, and be matched to patients with BBB according to sex, age within ±5 years, and date of medical evaluation. Based on all these criteria, matched controls were found for 540 of the 723 patients with BBB. The remainder could not be matched for either date of index ECG or date of medical evaluation including LVEF assessment. There were no differences in clinical characteristics between the matched and unmatched patients with BBB. In approximately 85% of patients, LVEF was determined on echocardiography, and in the remainder by radionuclide or contrast ventriculography. Follow-up data of the Olmsted County patients were analyzed from computerized access to the previously described comprehensive clinical records. Follow-up was determined in 96% of study patients (some patients moved away or were lost to follow-up). Mayo Foundation and Olmsted Medical Center institutional review board approval was obtained for the study, and consent for participation in the retrospective data analysis was confirmed as required by Minnesota statute 144.355/CFR 21 (Part 50).

Definitions

Left BBB (LBBB) was diagnosed if the following criteria were met: (1) QRS duration of 120 ms or longer in the presence of normal sinus rhythm or supraventricular rhythm (not atrial fibrillation); (2) QS or rS complex in lead V_1; (3) broad R waves in leads I, aVL, V_5-V_6 (or an rS pattern in V_5-V_6); and (4) absence of Q waves in leads V_5, V_6, or I.

Right BBB (RBBB) was diagnosed if the following criteria were met: (1) QRS duration of 120 ms or longer in the presence of normal sinus rhythm or supraventricular rhythm; (2) R or rSR′ complex in lead V_1; and (3) rS in leads V_5, V_6, I, or aVL with prolonged shallow S wave.

The clinical diagnoses of hypertension, elevated lipid profile, and/or diabetes were accepted from patients' computerized medical records as diagnosed by their primary care provider and/or by noting the use of therapy for the specific disorder such as insulin for diabetes.

Statistical Analyses

The primary end points were all-cause mortality and cardiac morbidity. Follow-up time for mortality was computed as the time after diagnosis of BBB (or index ECG) to date of death, or if alive, to the most recent clinical evaluation. Similarly, follow-up time for cardiac morbidity was the time from diagnosis of BBB (or index ECG) to date of the first post-BBB (post–index ECG) diagnosis of coronary artery disease, myocardial infarction, atrial fibrillation or flutter, pacemaker implantation, congestive heart failure, ischemic or dilated cardiomyopathy, or valvular heart disease as derived from the computerized medical records, or if no cardiac disease diagnosis, the time to the most recent clinical evaluation. The Kaplan-Meier product-limit estimator was used to estimate cumulative survival and cumulative survival free of cardiac disease after diagnosis of BBB. Kaplan-Meier curves were compared by using the log-rank test. Kaplan-Meier analysis comparing long-term survival of patients with BBB with general population survival also was undertaken. Expected survival for our population was constructed with use of age- and sex-specific mortality rates from the Minnesota white population. Expected survival was compared with observed by using a 1-sample log-rank test.

Multivariate Cox proportional hazards regression models were used to adjust for differing risk factor distributions between groups. The adjusting variables used were the presence or absence of hypertension, diabetes, and hypercholesterolemia. The proportional hazards assumption was assessed by including the product of the individual terms with time in the models. The proportional hazards assumption was not rejected for each of the potential risk factors. Comparisons of categorical variables between groups were made by using χ^2 tests. A 2-sample *t* test was used to compare continuous variables when appropriate; otherwise, a Wilcoxon rank sum test was used. All tests were 2-sided, and $P \leq .05$ was considered statistically significant. Because a complete comparison control group was unavailable, we undertook an additional analysis that divided patients with BBB and control patients into groups with and without risk factors of hypertension, hypercholesterolemia, and diabetes.

RESULTS

Study Group

Of 723 patients who met the criteria of uncomplicated asymptomatic BBB and normal LVEF, 420 (58.1%) had LBBB and 303 (41.9%) had RBBB ($P<.001$). Median follow-up from BBB diagnosis to death or most recent clinical evaluation was 7.7 years. Baseline characteristics of these patients are shown in Table 1. The prevalence of risk factors was high among patients with BBB but similar for LBBB and RBBB groups.

Kaplan-Meier curve analysis for overall long-term (20-year) survival was different for patients with BBB (observed) vs expected survival of the general population, which was matched according to age, sex, and geographic

TABLE 1. **Clinical Characteristics of Patients With Isolated BBB* and Normal LVEF**

Variable	Total BBB (N=723)	LBBB (n=420, 58.1%)	RBBB (n=303, 41.9%)	*P* value
LVEF (%)				
Mean ± SD	62.3±7.0	62.1±7.3	62.6±6.5	.23
Median	61.3	61.0	61.6	
Age (y)				
Mean ± SD	63.3±15.8	64.5±15.4	61.8±16.2	.03
Median	66.0	67.0	65.0	
Males, No. (%)	366 (50.6)	190 (45.2)	176 (58.1)	<.001
Hypertension, No. (%)	430 (59.5)	258 (61.4)	172 (56.8)	.21
Diabetes, No. (%)	166 (23.0)	94 (22.4)	72 (23.8)	.66
Hypercholesterolemia, No. (%)	109 (15.1)	55 (13.1)	54 (17.8)	.08

*No history or prior diagnosis of coronary artery disease, myocardial infarction, congestive heart failure, dilated cardiomyopathy, valvular heart disease, atrial fibrillation or flutter, or permanent pacemaker implantation. BBB = bundle branch block; LBBB = left BBB; LVEF = left ventricular ejection fraction; RBBB = right BBB.

region (*P*=.003; Figure 1). Long-term survival was not different between patients with isolated LBBB or RBBB (*P*=.17). Cardiovascular events (Figure 2, A) occurred earlier in patients with LBBB than in patients with RBBB (*P*=.03).

Comparisons With Control Group

The risk factor profile of the matched control group was more favorable than that of the patients with BBB (Table 2). Also, there was increased mortality (Figure 3, A) for patients with BBB compared with matched control patients (absolute difference of approximately 10% over 20 years; hazard ratio = 1.27; confidence interval, 1.02-1.58; *P*=.03).

Multivariate survival analysis was undertaken to adjust for the differences between patients with and without BBB (Table 3). Age, diabetes, and LBBB had increased hazard ratios; hypertension had an adjusted ratio of less than 1; and LBBB persisted as a significant risk factor for mortality (*P*=.01; Figure 3, B) and cardiovascular events (*P*<.001; Figure 2, B).

Figure 3, C shows the Kaplan-Meier survival analysis for patients with isolated BBB with (n=377) and without (n=163) the risk factors of diabetes, hypertension, and/or hypercholesterolemia and their corresponding matched control (no BBB) patients. Matched control patients with no risk factors (n=487) generally had the best prognosis. Patients with BBB and no risk factors and controls with risk factors (n=53) had comparable mortality risks. Patients with BBB and risk factors appeared to do the worst during the earlier years of follow-up compared with the other groups, but by 20 years, this patient subgroup and patients with BBB and no risk factors had similar survival rates. No statistical difference in mortality was shown by Kaplan-Meier analysis (*P*=.22) among patients with risk factor–free LBBB (n=66), RBBB (n=97), and controls (n=487), although the curve of patients with LBBB tended to diverge with higher mortality after about 13 years of follow-up.

The risk of long-term development of cardiovascular morbidity (Figure 2, C) also was worsened by the presence of uncomplicated BBB (hazard ratio = 1.32; confidence interval, 1.14-1.54; *P*<.001). This was again most notable in the group of patients with both BBB and risk factors (*P*<.001).

DISCUSSION

The results of this study suggest that in a community-based patient population with baseline normal LVEF and no diagnosed cardiac disease, the presence of uncomplicated isolated BBB is associated with an increased long-term risk of cardiovascular morbidity and all-cause mortality. Isolated LBBB is an independent predictor of mortality and seems to confer a risk similar to that of conventional cardiac risk factors. Patients with LBBB but no risk factors (ie, no diabetes, hypertension, or hypercholesterolemia) did better

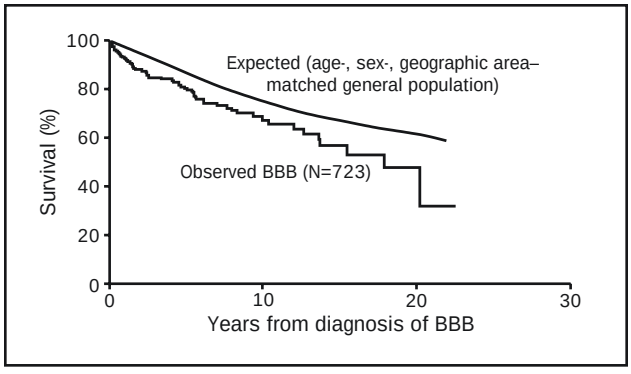

FIGURE 1. Kaplan-Meier survival curve of expected survival for age-, sex-, geographic area–matched general population compared with observed survival in bundle branch block (BBB) cohort.

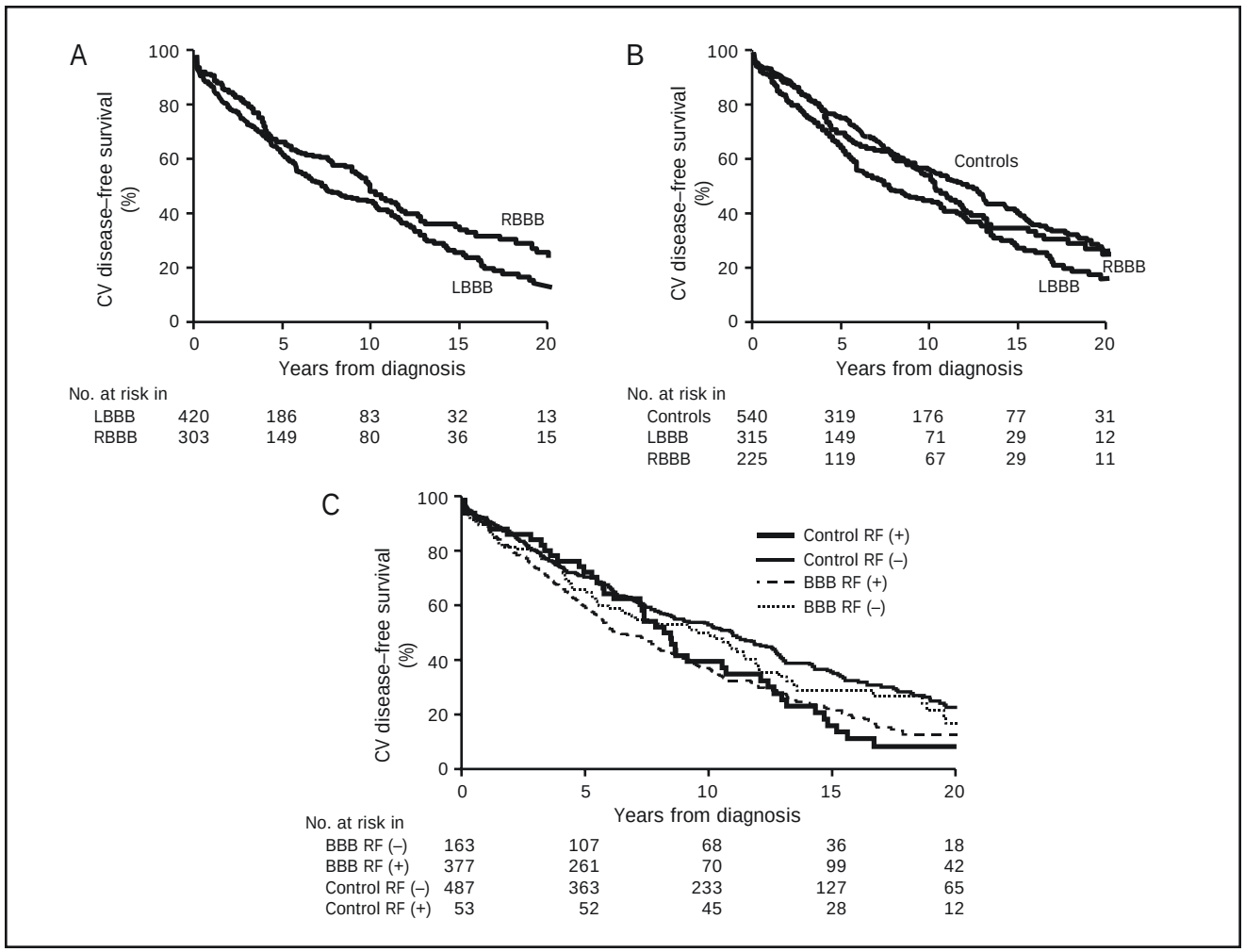

FIGURE 2. Kaplan-Meier morbidity curves. A, Time from diagnosis of isolated right bundle branch block (RBBB) and left BBB (LBBB) to first cardiovascular (CV) disease (*P*=.03 among all patient groups). B, Time to development of first disease for control (no BBB), patients with isolated LBBB, and patients with RBBB (*P*<.001 among all patient groups). C, Time to development of first CV disease for control (no BBB), and patients with BBB with and without diabetes, hypertension, and hypercholesterolemia (*P*<.001 among all patient groups). (+) indicates risk factors (RF) present; (–) indicates RF absent.

in early follow-up, but by 20 years showed mortality rates similar to those of patients with the risk factors but no BBB. Both LBBB and RBBB groups fared worse than their corresponding matched controls, despite correction for factors that may have affected the results.

Our findings contrast with some previous studies[9-12]; our study design also contrasts with other reports by requiring at study entry documented normal LVEF in all BBB and control patients, which we believe permitted a better-defined study cohort. The matched control patients were subject to the same selection factors; therefore, any bias was extended over both BBB and control patient groups.

The mechanism of the increased risk associated with isolated BBB is unknown and cannot be determined directly from our study. However, the pathogenesis could be related to the recent observations suggesting the deleterious consequences of ventricular asynchrony.[1-8] Our data fit with the concept that patients with BBB, particularly those with LBBB, are at increased risk of developing cardiac-related disease over time. Previous studies have suggested an increased likelihood of developing cardiac disease with acquired BBB[13] or sudden death as an early manifestation of heart disease in men with isolated LBBB,[14] whereas others have reported the prognosis of isolated LBBB to be relatively benign.[10,15-18]

In contrast to other studies,[9,19] our findings showed a slightly higher prevalence of LBBB than of RBBB. However, a predominance of patients with LBBB referred for evaluation was reported previously.[20] Long-term (20-year) mortality was not different between the RBBB and LBBB

TABLE 2. **Clinical Characteristics of Patients With Isolated BBB Compared With Age-, Sex-, and Medical Evaluation Date–Matched Patients With No Cardiovascular Disease or BBB Diagnoses***

Variable	LBBB (n=315)	RBBB (n=225)	Total BBB (N=540)	Matched controls no BBB (N=540)	*P* value
LVEF (%)					
Mean ± SD	62.1±7.5	62.4±6.4	62.3±7.1	63.3±7.5	.04
Median	61.0	61.6	61.3	63.0	
Age (y)					
Mean ± SD	63.0±14.5	61.6±14.6	62.6±14.5	62.2±14.2	.53
Median	66.0	64.0	65.0	64.0	
Males, No. (%)	129 (41.0)	119 (52.9)	248 (45.9)	248 (45.9)	>.99
Hypertension, No. (%)	192 (61.0)	136 (60.4)	328 (60.7)	53 (9.8)	<.001
Diabetes, No. (%)	69 (21.9)	56 (24.9)	125 (23.1)	23 (4.3)	<.001
Hypercholesterolemia, No. (%)	47 (14.9)	46 (20.4)	93 (17.2)	14 (2.6)	<.001
Length of follow-up (y)					
Mean ± SD			9.8±7.0	11.0 ± 6.9	
Median			9.0	10.3	

*BBB = bundle branch block; LBBB = left BBB; LVEF = left ventricular ejection fraction; RBBB = right BBB.

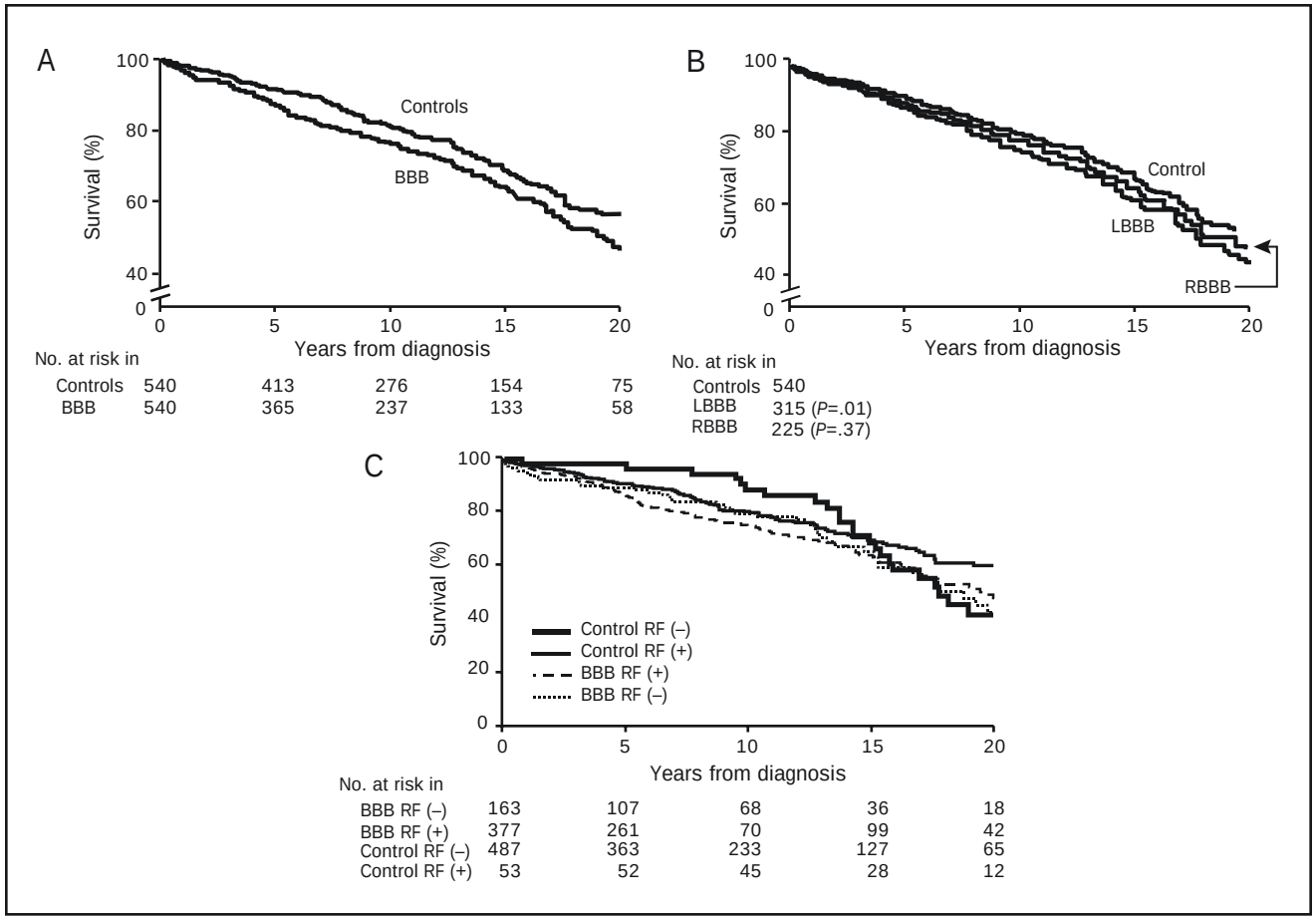

FIGURE 3. A, Kaplan-Meier survival curves for control patients (no bundle branch block [BBB]) and patients with isolated BBB (*P*=.03). B, Cox-adjusted Kaplan-Meier survival curves for control patients (no BBB), patients with isolated left BBB (LBBB), and patients with right BBB (RBBB). Adjusted for age, sex, presence of diabetes, hypertension, and hypercholesterolemia (multivariate Cox proportional hazard regression model). C, Kaplan-Meier survival curves for control patients (no BBB) and patients with isolated BBB with and without diabetes, hypertension, and hypercholesterolemia (*P*=.04 among all the patient groups). (+) indicates risk factors (RF) present; (–) indicates RF absent.

TABLE 3. **Multivariate Cox Proportional Hazard Model Comparing BBB With No BBB Matched Controls, Adjusting for Risk Factor Variables***

Variable	Hazard ratio (95% CI)	*P* value
Diabetes	1.76 (1.30-2.39)	<.001
LBBB	1.49 (1.09-2.03)	.01
RBBB	1.18 (0.85-1.65)	.32
Male	1.14 (0.90-1.45)	.27
Age	1.09 (1.08-1.10)	<.001
Hypercholesterolemia	0.97 (0.64-1.45)	.87
Hypertension	0.64 (0.48-0.86)	.003

*BBB = bundle branch block; CI = confidence interval; LBBB = left BBB; RBBB = right BBB.

groups in our study. Also, risk factor profiles were comparable for patients with RBBB and LBBB; therefore, one conduction pattern would not be suspected to occur over the other.

The observation that patients with isolated BBB have similar risks of cardiac-related morbidity and mortality as do patients with conventional cardiovascular risk factors suggests that a comprehensive approach to evaluation and follow-up should be undertaken in patients identified with isolated BBB, particularly LBBB. In the presence of cardiovascular risk factors, especially diabetes, LBBB has significant incremental risk; therefore, patients should be monitored closely to treat any early development of cardiac disease.

An association also is recognized between BBB and hypertension. However, in our multivariate analysis, hypertension was not found to be a high-risk variable for poor outcome but indeed was associated with better outcome. This may be explained in part by the pervasive medical treatment of hypertension and its beneficial effect in mitigating cardiovascular morbidity. Also, given the low rate of pacemaker placement (5% overall), it is unlikely that our results reflect the effects of progressive symptomatic conduction system disease.

This study is a retrospective analysis of computerized clinical medical records and is subject to the inherent limitations of such a study design. Also, we did not have serial risk factor profiles, which may have been elucidating. Finally, we were unable to enroll a totally matched control cohort with equal representation of risk factors such as hypertension. Nonetheless, our results suggest that the clinical implications of uncomplicated BBB are significant and support a need to pursue additional studies in this often-neglected area of clinical research.

CONCLUSIONS

Isolated BBB is not benign, even in patients with no known cardiac disease and normal LVEF. The presence of isolated BBB denotes a high-risk patient subgroup with a long-term outcome comparable to patients with conventional cardiovascular risk factors. Bundle branch block, particularly LBBB, should be considered a risk factor for increased cardiac morbidity and mortality when identified, even in the absence of conventional cardiac risk factors. However, the presence of risk factors, particularly diabetes associated with LBBB, further increases the risk of cardiac morbidity compared with either isolated BBB or risk factors alone and identifies a particularly high-risk subgroup of patients who should be monitored closely for risk factor management.

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