

# Natural history and clinical significance of isolated complete left bundle branch block without associated structural heart disease

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## ABSTRACT

**Objective:** Left bundle branch block (LBBB), which is associated with underlying cardiac disease, is believed to play a role in the pathogenesis of cardiomyopathy through delays in interventricular conduction, leading to dyssynchrony. However, this has not been established in previous studies. It is unclear whether LBBB indicates clinically advanced cardiac disease or is an independent factor responsible for increased mortality and the development of heart failure. We investigated the natural history of isolated LBBB without any associated structural heart disease in order to determine its clinical significance.

**Methods:** We performed a retrospective chart review on consecutive patients who fulfilled the 12-lead electrocardiographic (ECG) criteria for complete LBBB and had a normal echocardiogram with no evidence of structural heart disease and left or right ventricular systolic dysfunction within three months of the initial ECG between January 1, 2000 and December 31, 2009. We excluded patients with documented coronary artery disease (CAD) at any time, any structural heart disease, or cardiac devices. We evaluated the primary endpoints of mortality and incidence of cardiomyopathy, as well as any heart failure hospitalizations over a 1- and 10-year period.

**Results:** We identified 2522 eligible patients. The mean follow-up duration was 8.4±3.2 years. The one-year mortality rate was 7.8%, with a 10-year mortality rate of 22.0%. The incidence of cardiomyopathy over one year was 3.2% and over 10 years was 9.1%. There was no significant difference in QRS duration between patients who were alive and those that were deceased at 10 years (141+/-18 vs. 141+/-17 ms; p=0.951) and patients with and without cardiomyopathy at 10 years (142±17 vs. 141±17 ms; p=0.532).

**Conclusion:** Isolated LBBB occurring without structural heart disease, ventricular dysfunction, or CAD is associated with a low mortality rate and incidence of cardiomyopathy.

**Keywords:** left bundle branch block, cardiomyopathy, heart failure, mortality

**Cite this article as:** Ashraf H, Agasthi P, Siegel RJ, Pujari SH, Allam M, Shen WK, et al. Natural history and clinical significance of isolated complete left bundle branch block without associated structural heart disease. *Anatol J Cardiol* 2021; 25: 170-6

## Introduction

Complete left bundle branch block (LBBB) is a characteristic pattern recognized on surface electrocardiogram (ECG) as a result of abnormal electrical conduction in the His-Purkinje system. The prevalence of LBBB was estimated to be 0.43% for men and 0.28% for women in a randomly-selected sample of the general population (1). The prevalence of LBBB is significantly higher among patients with pre-existing cardiovascular disease;

it occurs in one-third of congestive heart failure (CHF) patients (2, 3). The association of LBBB with underlying heart disease such as coronary artery disease (CAD) and CHF is supported by a large body of clinical evidence (4). LBBB has also been associated with increased mortality among patients with cardiovascular disease, especially those with myocardial infarction, and additionally portends progressive conduction abnormalities (5-9). Therefore, LBBB is more clinically significant than its benign counterpart, right bundle branch block (10).

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**Accepted Date:** 17.09.2020 **Available Online Date:** 14.01.2021

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DOI:10.14744/AnatolJCardiol.2020.10008



## HIGHLIGHTS

- Isolated LBBB occurring without structural heart disease is associated with a low mortality rate and low incidence of cardiomyopathy:
- One year mortality in patients with isolated LBBB was 7.8%, and 10-year mortality rate was 22.0%
- The incidence of cardiomyopathy in patients with isolated LBBB over one year was 3.2% and over 10 years was 9.1%

Whether LBBB is simply a marker for more severe and extensive CAD and heart failure, or is an independent risk factor for these conditions has not been well elucidated. Experimental animal studies suggest that LBBB itself is responsible for functional septal hypoperfusion and resultant adverse left ventricular remodeling and cardiomyopathy (11). LBBB seems to play a role in the development of cardiomyopathy through abnormal activation of the left ventricle and dyssynchrony which is underscored by the role of cardiac resynchronization therapy in patients with LBBB and systolic dysfunction. Previous studies have associated LBBB with increased mortality or more severe cardiovascular disease, but the general population of LBBB patients frequently has pre-existing cardiovascular disease, a potential confounder for the clinical implications of LBBB.

Although LBBB is more commonly encountered in elderly patients with multiple comorbidities, it can also be an isolated finding in asymptomatic individuals with no abnormalities in cardiac structure (6). The natural history and incidence of LBBB without pre-existing CAD or structural abnormalities is unknown. Such knowledge would provide information about the prognosis of this particular cohort of patients, especially concerning the incidence and rate of mortality due to cardiomyopathy and heart failure. As such, we performed a retrospective chart review of patients with isolated LBBB to analyze their natural history, including all-cause mortality, incidence of cardiomyopathy, and incidence of heart failure hospitalizations.

## Methods

We conducted a retrospective chart review on all consecutive patients aged  $\geq 18$  years who fulfilled the 12-lead electrocardiographic criteria for complete LBBB at the three Mayo Clinic sites (AZ, FL, and MN) between January 1, 2000 and December 31, 2009. Electrocardiographic criteria for LBBB were based on standard guideline definitions at the time of diagnosis (12, 13). Patients had to have a structurally normal baseline echocardiogram within three months of the date of the initial ECG, which was designated as time 0, as well as follow-up echocardiograms at 1 year, 5 years, and 10 years.

Exclusion criteria were based on known associations with the development of cardiomyopathy, and the following patients

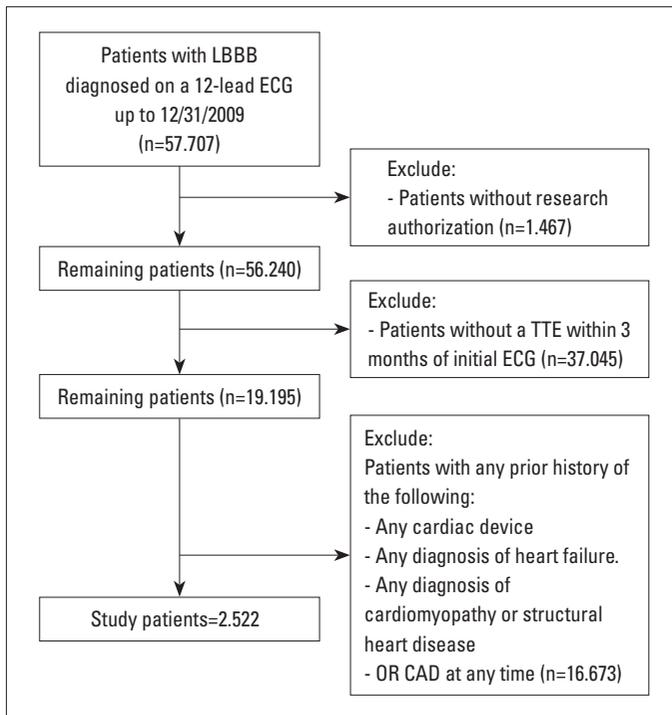
were excluded from this study: (1) patients with documentation of any CAD at any time, including both obstructive and non-obstructive CAD diagnosed using any modality including coronary angiography or the abnormal stress test; (2) patients with any evidence of structural heart disease based on echocardiographic criteria; these structural heart diseases included any valvular disease that was more than mild stenosis or regurgitation, wall thickening of any severity (including both concentric and eccentric thickening or remodeling based on volumetric or linear measurements), atrial dilatation or enlargement of any severity, ventricular dilatation of any severity (left ventricular end-diastolic dimension  $\geq 56$  mm), left ventricular ejection fraction (LVEF) less than 50%, or right ventricular systolic dysfunction. Patients with echocardiographic evidence of abnormal left ventricular longitudinal strain (less negative than -18%) were also excluded. Abnormal values for echocardiographic parameters were based on various American Society of Echocardiography guideline recommendations; (3) patients with history of valvular intervention; (4) patients who required temporary or permanent cardiac device placement at the time of the initial diagnosis of LBBB (time 0)  $\pm$  three months; (5) Patients with any diagnosis of heart failure, including both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) at time 0  $\pm$  three months; (6) patients with any diagnosis of cardiomyopathy including, but not limited to hypertrophic cardiomyopathy, amyloid cardiomyopathy, myocarditis, and others at time 0  $\pm$  3 months. Echocardiographic data were obtained from the Mayo Clinic Echocardiography Laboratory database, which archives echocardiographic interpretations by board-certified cardiologists and echocardiographers with level III training in echocardiography. The recruitment of patients into this study is demonstrated in Figure 1.

Patients with comorbidities such as dysrhythmias, chronic renal insufficiency, hypertension, dyslipidemia, and diabetes mellitus were included as long as they had neither any evidence of CAD nor any structural heart disease at the time 0 as defined above or at any point in time.

Our primary endpoints were mortality and the development of any cardiomyopathy based on ICD9/10 codes (Supplemental Data) or a drop in the ejection fraction (EF) to  $< 50\%$ , on follow-up echocardiograms. Also, we specifically evaluated the incidence of HFpEF (EF  $> 50\%$ ), HFrEF (EF  $< 50\%$ ), heart failure hospitalizations, atrial fibrillation, and stroke. The study was approved by the Institution Review Board at Mayo Clinic.

## Statistical analysis

Statistical analysis was performed on the LBBB cohort using the analysis of variance with the Shapiro Wilk F-test for continuous variables which are presented as a mean  $\pm$  SD, while the Chi square test and Fisher exact test were used for categorical variables, which are presented as frequencies and percentages. Survival curves with time-to-event analyses were performed with Kaplan–Meier estimates.



**Figure 1.** Patient inclusion and exclusion categorization  
LBBB - stands for left bundle branch block; ECG - electrocardiogram;  
TTE - transthoracic echocardiogram; and CAD - coronary artery disease

Multiple logistic regression analysis was performed to detect independent predictors of all-cause mortality. Demographic information (age, gender, etc.), comorbidities (COPD, DM, HTN, HLD, history of stroke, and malignancies), laboratory studies (glomerular filtration rate, troponin, BNP, and HDL), and echocardiographic variables (LVEF, left atrial volume index, and right ventricular systolic pressure) were included in the univariate analysis. Univariate clinical variables with p-values <0.05 were then entered into a multivariate model, the results of which are presented as odds ratio with 95% confidence interval. A Hosmer-Lemeshow goodness-of-fit test was used to assess the fit of the model, and the C-statistic was used to verify the accuracy of the multiple logistic regression model. Statistical analysis was performed using SAS version 9.4 (SAS Institute Inc).

## Results

We identified a total of 2522 patients who met the study criteria. The proportion of subjects with isolated LBBB and who met study criteria in the general population of study subjects was 0.84% (2522 of 299.650). The baseline characteristics of the population of LBBB patients are presented in Table 1, along with their baseline echocardiographic and laboratory characteristics. The mean follow-up duration was 8.4±3.2 years.

The average age of our patient population was 67.5 years, with the majority (62.8%) of the patients being women. By design, of our patients had a prior myocardial infarction, or heart

**Table 1. Baseline demographic and clinical data**

Age	67.5±14.4
Male	37.2
BMI	28.5±11.7
BSA	1.9±0.3
Hypertension	50.6
Dyslipidemia	37.6
Atrial fibrillation	14.6
Diabetes	3.9
Myocardial infarction	NA
CHF	NA
History of Stroke/TIA	0.6
Peripheral arterial disease	1.8
COPD	7.1
OSA	11.3
CKD	8.3
Metastatic solid tumor malignancy	1.0
Other malignancy	4.7
<b>Baseline echocardiographic characteristics</b>	
Left ventricular ejection fraction %	61.4±6.4
Left ventricular stroke volume index	36.8±10.8
Aortic regurgitation	NA
Aortic stenosis	NA
Mitral regurgitation	NA
LVEDD	46.4±5.3
LVESD	30.2±4.6
RVSP	32.7±9.7
E/A	1.3±0.7
E/e' (medial)	12.3±5.2
E/e' (lateral)	10.0±4.8
Left ventricular longitudinal strain %	-18.8±2.5
<b>Laboratory data</b>	
GFR, mL/min	69.3±28.1
ESR	4.2±18.4
CRP	21.5±55.3
LDL, mg/dL	99.9±94.9
HDL, mg/dL	42.4±26.5
Triglycerides, mg/dL	137.6±77.8

GFR - glomerular filtration rate, LVEDD - left ventricular end-diastolic dimension, LVESD - left ventricular end systolic dimension, RVSP - right ventricular systolic pressure, NA - patients with these characteristics were excluded from the study cohort

failure at the onset of the study. Only 1.8% of our patients had peripheral artery disease, and 0.6% had a history of stroke at baseline. Hypertension was the most commonly encountered comorbidity, occurring in 50.6% of patients, followed by dyslipidemia (37.6%), atrial fibrillation (14.6%), and diabetes (3.9%).

The mortality and incidence of cardiovascular conditions over 1 and 10 years are presented in Table 2. One-year mortality was 7.8%, while 10-year mortality was 22.0%. The incidence of cardiomyopathy over 10 years was 9.1%, and only 2 of the

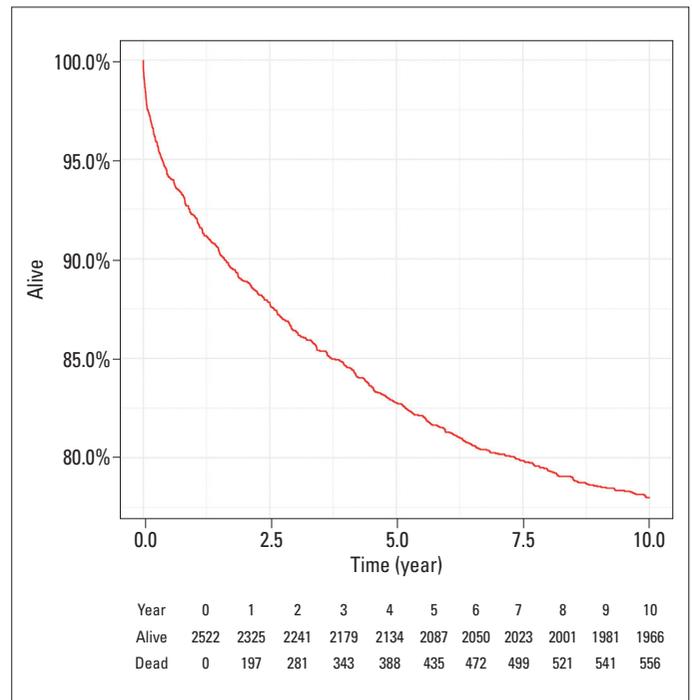
**Table 2. Mortality and incidence of cardiovascular conditions over 1 and 10 years**

	<b>1-year n=2522</b>	<b>10-year n=2522</b>
Mortality (%)	197 (7.8)	556 (22.0)
Any cardiomyopathy (%)	81 (3.2)	230 (9.1)
HFpEF (%)	74 (2.9)	212 (8.4)
HFrEF	7 (0.27)	18 (0.71)
Stroke (%)	153 (6.1)	257 (10.2)
Atrial fibrillation (%)	263 (10.5)	401 (15.9)

HFpEF - heart failure with preserved ejection fraction; HFrEF - heart failure with reduced ejection fraction

2522 patients were hospitalized due to heart failure during that time. The Kaplan–Meier Estimate Curves of both mortality and incidence of cardiomyopathy are presented in Figures 2 and 3. There was no difference in QRS duration between patients who were alive and deceased patients at 10 years ( $141\pm 18$  vs.  $141\pm 17$  ms;  $p=0.951$ ) and patients with and without cardiomyopathy at 10 years ( $142\pm 17$  vs.  $141\pm 17$  ms;  $p=0.532$ ).

Predictors of all-cause mortality identified through multivariate analysis are presented in Table 3, and of cardiomyopathy in Supplemental Table 1. Male gender, COPD, HTN, and RVSP were all identified as predictors of all-cause mortality. Though there was a proportion of 5.7% for all malignancies, including 1.0% of metastatic solid tumor malignancies, these were not predictive



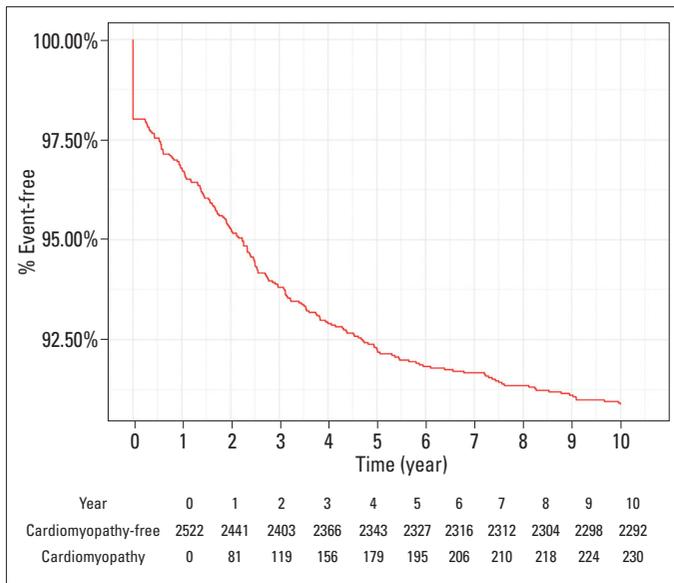
**Figure 2.** Kaplan–Meier curve demonstrating that the all-cause mortality in our isolated LBBB cohort was 7.8% over 1 year and a 10-year mortality of 22.0%. The drop in mortality was rapid in the first year, possibly due to non-cardiac causes of death, but then tapers off

of mortality. No echocardiographic parameters, except for an elevated RVSP, were found to be predictive of mortality in this population.

**Table 3. Predictors of all-cause mortality: univariate and multivariate analysis**

	<b>Univariate analysis</b>		<b>Multivariate analysis</b>	
	<b>Hazard ratio (95% confidence interval)</b>	<b>P value</b>	<b>Hazard ratio (95% confidence interval)</b>	<b>P value</b>
Age	1.0 (0.99-1.01)	0.805		
Gender, male	1.38 (1.16-1.64)	<0.001	1.50 (1.17-1.92)	0.001
COPD	2.33 (1.31-4.15)	0.011	2.58 (1.21-5.47)	0.014
Diabetes mellitus	1.38 (1.11-1.71)	0.003	0.76 (0.56-1.04)	0.087
Hypertension	1.54 (1.30-1.82)	<0.001	0.69 (0.52-0.91)	0.009
Hyperlipidemia	1.46 (1.21-1.74)	<0.001	0.89 (0.67-1.18)	0.413
Stroke	1.49 (1.17-1.90)	<0.001	0.85 (0.61-1.19)	0.341
Metastatic solid tumor malignancy	1.99 (1.24-3.20)	0.010	1.85 (0.96-3.56)	0.066
Other malignancy	1.52 (1.15-2.03)	0.006	1.09 (0.68-1.74)	0.713
LVEF	1.01 (0.99-1.02)	0.391		
RVSP	1.35 (1.03-1.77)	0.033	1.41 (1.07-1.86)	0.013
LAVI	1.01 (0.98-1.03)	0.682		
GFR	1.01 (1.00-1.01)	0.020	1.00 (0.99-1.01)	0.175
Troponin	1.01 (1.00-1.01)	0.002	1.00 (0.99-1.01)	0.458
BNP	1.10 (1.05-1.17)	<0.001	0.97 (0.84-1.12)	0.708
HDL	0.99 (0.98-1.00)	0.026	0.99 (0.98-1.01)	0.613

COPD - chronic obstructive pulmonary disease, LVEF - left ventricular ejection fraction, RVSP - right ventricular systolic pressure, LAVI - left atrial volume index



**Figure 3.** Kaplan–Meier curve demonstrating the incidence of cardiomyopathy in our isolated LBBB cohort over 10 years

## Discussion

We identified 2522 patients with LBBB without any associated structural heart disease and CAD. The proportion of patients with isolated LBBB was similar to that mentioned in older epidemiological studies that reported a prevalence ranging from 0.2%-1.1% (5, 14, 15). However, if adjusted for age (our average age was 67.5 years), our proportion would be less than that

commonly cited (0.4% at age 50, and 2.3% at age 75) (16). This is unsurprising, given the scarcity of CAD and structural heart disease in our cohort.

This study is the first to trace the natural clinical course of a large population of healthy patients with isolated LBBB over a period of 10 years. We chose a 10-year period to allow sufficient time for the development of cardiovascular disease. The mortality rate in this cohort of patients was 7.8% over the first year after the initial diagnosis of LBBB, and 22.0% over a 10-year period. Although the survival dropped more rapidly in the first year, it leveled out after that. This is probably due to non-cardiac deaths that would be expected to be seen at a tertiary care center (Table 3). At the average age of 67.5 of this cohort, a 22% mortality over 10 years does not differ significantly from what would be expected for a similar-aged cohort of American patients (17).

In our patient population, there was a small incidence of cardiomyopathy with LVEF reduced to <50%. The one-year incidence was only 0.27%, with a 10-year incidence of 0.71%. This incidence is, like mortality, similar to the incidence of heart failure in the general population (incidence rate of 34.1 per 10,000 person-years at an average age of 67.5) (18). This suggests that isolated LBBB is not necessarily a risk factor for worsening left ventricular systolic function and the development of cardiomyopathy in the absence of associated cardiovascular disease; or that at worst, it is not a very strong risk factor. Among those who do develop cardiomyopathy, which in our population was strictly non-ischemic, the incidence rate was gradual, without an early decline in LV systolic function, as has been reported in other studies (19).

**Supplemental Table 1. Predictors of cardiomyopathy: univariate and multivariate analysis**

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% confidence interval)	P value	Hazard ratio (95% confidence interval)	P value
Age	1.01 (1.00-1.02)	0.016	1.02 (0.98-1.05)	0.308
Gender, male	1.42 (1.10-1.85)	0.009	0.51 (0.22-1.14)	0.102
COPD	1.65 (0.73-3.72)	0.267		
Diabetes mellitus	3.92 (1.68-5.43)	0.002	1.71 (0.40-7.42)	0.472
Hypertension	1.95 (0.81-1.37)	0.699		
Hyperlipidemia	0.84 (0.64-1.10)	0.204		
CKD Stage III-V	2.82 (1.44-5.50)	0.009	1.05 (0.24-4.57)	0.948
Metastatic solid tumor malignancy	5.06 (1.59-16.07)	0.028	1.80 (0.42-7.73)	0.429
Other malignancy	3.01 (1.56-5.77)	0.004	5.92 (1.21-29.02)	0.028
LVEF	1.01 (0.98-1.03)	0.594		
E/e' (medial)	1.02 (0.99-1.05)	0.113		
RVSP	1.77 (1.08-2.93)	0.027	0.34 (0.07-1.77)	0.203
LAVI	1.08 (1.02-1.14)	0.008	1.15 (0.96-1.37)	0.131
Troponin	1.02 (1.01-1.03)	<0.001	1.04 (1.00-1.07)	0.689
BNP	1.14 (1.05-1.24)	0.004	1.28 (0.78-2.11)	0.333

COPD - chronic obstructive pulmonary disease, CKD - chronic kidney disease, LVEF - left ventricular ejection fraction, RVSP - right ventricular systolic pressure, LAVI - left atrial volume index

Although data demonstrating an association between LBBB and HFpEF are not as robust as those demonstrating the association between LBBB and HFrEF, there are studies that demonstrate an association between the two. Prior suggestions that LBBB in the HFpEF population leads to increased hospitalizations from acutely decompensated heart failure were not confirmed in our study (20). As noted earlier, there were only two hospitalizations in our cohort of 2522 patients, and fewer hospitalizations occurred with HFpEF. Nevertheless, further data might be needed to validate these findings.

The findings of our study are at odds with those of other studies that demonstrate a decline in LV systolic function and an increase in heart failure hospitalizations from LBBB. This was demonstrated in a small study of subjects with isolated LBBB who had significant deterioration in LV systolic function when compared to a matched-control cohort of patients without LBBB (19). These findings could be explained by our strict exclusion criteria, as we endeavored to ensure that all other causes of cardiomyopathy that were not similarly adopted in other studies were eliminated.

Given that there is limited pre-existing data on the clinical outcomes of patients with isolated LBBB, right ventricular (RV)-pacing-induced cardiomyopathy, for which there is compelling clinical data, could be cited to establish that LBBB might also be a risk factor for cardiomyopathy. RV pacing might be seen as a surrogate to LBBB, as there are similarities in the sequences of electrical activation of the myocardium between the two. The incidence of RV-pacing-induced cardiomyopathy is estimated to be around 8%–20% over a decade in patients with frequent (typically >40%) pacing (21–23). The difference in the incidence of cardiomyopathy between our isolated LBBB cohort and these patients can be attributed to the existence of different definitions of cardiomyopathy. More importantly, however, we very strictly excluded alternative potential confounding etiologies of cardiomyopathy such as myocardial ischemia and valvular heart disease, which was not attempted in these prior studies. Furthermore, although there are similarities in electrical activation, there are differences, such as RV apical pacing resulting in more dyssynchrony with more delayed basolateral left ventricular activation than in LBBB (24). Additionally, differences in patient demographics could also influence the outcomes. The predominance of the female gender in our cohort was equally remarkable. For instance the male gender has been proven to be a predictive factor in pacing-induced cardiomyopathy, as well as in hypertrophic, dilated, and stress-induced cardiomyopathies (21, 25, 26). As such, RV pacing cannot be entirely considered as a clinical substitute for LBBB.

### Study limitations

This study had several limitations. First, it was performed primarily in a patient population that is seen at three tertiary care centers, and this population might not have been representative of the wider general population. Additionally, this

was a single-arm study that was designed to describe the natural history of isolated LBBB. A study design comparing the existing cohort with a comparative arm of matched controls without LBBB could further elucidate the clinical effect of isolated LBBB in subjects without structural heart disease. Thirdly, although all-cause mortality was evaluated, a determination of mortality due to cardiovascular causes would have been beneficial. Given the retrospective nature of this study, accurately identifying cardiovascular death was not possible. Last, the retrospective study design comes with its inherent limitations, including incomplete records, confounding factors and variables, and an inability to differentiate association with causation.

## Conclusion

Patients with isolated LBBB and no associated structural heart disease, ventricular dysfunction, or CAD have 10-year mortality that is comparable to that of similar-aged individuals. In addition, these patients have a low rate of cardiomyopathy and heart failure hospitalizations. For patients with true isolated LBBB, prognosis is favorable and reassurance is reasonable.

**Acknowledgements:** This work was supported by the Mayo Clinic Department of Cardiovascular Diseases which provided internal funding.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

**Authorship contributions:** Concept – H.A., P.A., R.A.; Design – H.A., P.A., R.A.; Supervision – R.J.S., S.H.P., M.A., W.K.S., K.S., D.S., H.E.M., W.K.F., F.M., S.M., R.A.; Fundings – W.K.S., R.A.; Materials – H.A., P.A.; Data collection and/or processing – H.A., P.A.; Analysis and/or interpretation – H.A., P.A., R.A.; Literature search – R.J.S., S.H.P., M.A., W.K.S., K.S., D.S., H.E.M., W.K.F., F.M., S.M., R.A.; Writing – H.A., P.A.; Critical review – R.J.S., S.H.P., M.A., W.K.S., K.S., D.S., H.E.M., W.K.F., F.M., S.M., R.A.

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## Supplemental Data: ICD codes used during study.

### I. Exclusion criteria

- A. At any time:
  - 1. CAD (obstructive and non-obstructive; ICD 9 410x, 411x, 412x, 414x; ICD10 I21x, I22x, I23x, I24x, I25.x)
  - 2. Presence of cardiac devices (ICD 9 V45.0x; ICD 10 Z95.x)
- B. At time 0 plus/minus 3 months: patients with the following comorbidities
  - 1. Any diagnosis of Heart Failure
    - a. ICD 9: 428.x
    - b. ICD 10: I50.x
  - 2. Any diagnosis of cardiomyopathy
    - a. ICD 9: 425.x
    - b. ICD 10: I42.x

### II. Endpoints:

- A. The following conditions at any time after time 0 (should not be included if present at time 0): HFrEF (ICD 9 428.2x, 428.4x, ICD 10 I50.1x, I50.2x, I50.4x, I50.82), HFpEF(ICD9 428.3x, ICD10 I50.3x),

### III. Demographic information

#### 1. A fib:

- a. ICD 9 427.3x
- b. ICD 10 I48, I48.0x, I48.9x, I48.1x, I48.2x,

#### 2. HTN:

- a. ICD9 401x, 402x, 403x, 404x, 405x
- b. ICD 10 I10x, I11x, I12x, I13x, I14x, I15x, I16x, I60-I69x, H35.0x

#### 3. HLD:

- a. ICD 9 272.1, 272.3, 272.4
- b. ICD 10 E78.1x, E78.5x, E78.3x, E78.4x,

#### 4. Diabetes:

- a. ICD 9 250.0x, 250.01x, 250.2x, 250.3x, 250.4x, 250.5x, 250.6x, 250.7x, 250.8x, 250.9x, 250.x0, 250.x1, 250.x2, 250.x3
- b. ICD 10 codes: E08.x, E10.x, E11.x, E13.x

#### 5. Stroke/TIA:

- a. ICD 9 codes 362.3, 433.x1, 433.10, 433.x1, 434.x, 434.x1, 436.x, 430.x, 431.x, 435.x
- b. ICD 10 codes H34.1, I63.x, I64.x, I61.x, I60.x, G45.x

#### 6. COPD:

- a. ICD9 492x, 506.4x, 494x, 496x, 506x, 493.2x, 491x
- b. ICD 10 J40x, J41x, J42x, J43x, J44x

#### 7. OSA

- a. ICD9 327.23
- b. ICD10 G47.33, E66.2x

#### 8. CKD

- a. ICD9 585x
- b. N18.x, E08.22, E09.22, E10.22, E11.22, E13.22, I12.x, I13.x