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Left bundle branch block—Innocent bystander, silent menace, or both

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ABSTRACT

Left bundle branch block (LBBB) causes immediate electrical and mechanical dyssynchrony of the left ventricle (LV) and gradual structural damages in the Purkinje cells and myocardium. Mechanical dyssynchrony reduces the LV ejection fraction (EF) instantly, but only to ≈55% in an otherwise normal heart. Because of the heart's in-built functional redundancy, a patient with LBBB does not always notice the heart's reduced efficiency straightaway. After a variable period of time (which could be from days to decades), the patient may become symptomatic with heart failure (HF), which classifies as HF with preserved EF ≥50% (HFpEF). The LVEF drops further because of continuous adverse remodeling and inefficient cardiac contraction. The patient transits to HF with moderately reduced EF 35%–50% (HFmrEF) and then reduced EF ≤35% (HFrEF) over 5–21 years. Cardiac resynchronization therapy (CRT) is currently only indicated in guidelines for HFrEF and LBBB. LBBB shortens the median survival of patients with HFmrEF by 5.5 years. Randomized controlled trials have shown that CRT improves echocardiographic indices for HFmrEF with LBBB. CRT in HFpEF with LBBB is a promising but underexplored/underused therapy. There have been anecdotal reports that CRT produced symptom relief in patients debilitated by HFpEF with LBBB, who constitute ≈6% of all patients with HF and an adequate pool of potential randomized controlled trial participants. Conduction system pacing in the form of left bundle branch area pacing is an emerging pacing strategy that might reverse and forestall the deleterious effects of LBBB.

KEYWORDS Left bundle branch block; Cardiomyopathy; Heart failure with preserved ejection fraction; Cardiac resynchronization therapy; Conduction system pacing; Reverse modeling; Causality; Epidemiology; Natural history

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Introduction

Left bundle branch block (LBBB) was historically considered a benign incidental finding with limited recognition of its association with cardiomyopathy (CM); however, contemporary evidence increasingly highlights its potential role in structural and functional cardiac abnormalities, although some clinicians may still perceive it as incidental in certain contexts.[1] LBBB is probably never totally innocuous and could directly cause rather than just correlate with functional and structural damages to the heart. Coincidence and correlation do not equate to causation. The insidious onset of LBBB-induced CM might explain why it has escaped more intense clinical scrutiny so far. Cardiac resynchronization therapy (CRT), a form of cardiac physiological pacing that also includes conduction system pacing (CSP), mitigates electrical and mechanical dyssynchrony associated with or caused by LBBB.[2] Response to a remedy such as CRT could be used to infer causality between correlated factors such as LBBB and heart failure (HF). Left ventricular (LV) ejection fraction (EF) is the "final arbiter" in CRT indications for HF with LBBB in guidelines by virtue of its role as a binary cutoff eligibility criterion in previous randomized controlled trials (RCTs) despite its lack of sensitivity for mechanical dyssynchrony.[3–5] CRT is "indicated" only when LVEF is ≤35% (HF with reduced EF [HFrEF], reduced EF), but not 35%–50% (HF with moderately reduced EF [HFmrEF], mildly or moderately reduced EF) or ≥50% (HF with preserved EF [HFpEF], preserved EF). LBBB with LVEF ≥ 50% but no symptoms is probably subclinical LBBB-induced CM and preclinical HFpEF. Rare medical conditions with insidious onset do not lend themselves to RCTs, and the limited data from physiological and mechanistic studies and expert opinions might be the only evidence available to guide their management.[2] HFmrEF with LBBB has been shown to benefit from CRT, albeit only in terms of surrogate measures (physiological parameters) rather than

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clinical events.[6,7] CRT, though not listed as indicated for HFpEF in guidelines, might be considered in selected patients with demonstrated mechanical dyssynchrony for immediate symptom relief and potential prognosis uplift. RCTs would help clarify the role of cardiac physiological pacing (be it CRT or CSP) in the clinical management of HFpEF with LBBB.[8–10]

Coincidence, correlation, and causation

Factors/events **A** and **B** appearing within spatial or temporal proximity may be related. If **A** and **B** appear together only once, it is a coincidence and impossible to prove causality (Figure 1A). If **A** and **B** appear together repeatedly, it is a correlation whose strength could be measured statistically. The *P* value of statistical analyses gives the upper limit of the probability **A** and **B** appearing together if they were independent random events. However, correlation does not imply causation (Figure 1A), but a strong correlation is generally accepted as "proof" that the treatment given to **A** causes the clinical response observed **B** in RCTs (Figure 1B). $P < .05$ could still occur by chance from too many comparisons. Correlation could occur because of a common cause (Figure 1C) or an intermediary step (Figure 1D) **C** between 2 factors/events **A** and **B**. In many situations, the causal links between factors/events are complex and might be multidimensional and bidirectional (Figure 1E). Judiciousness needs to be exercised in inferring causality between factors/events. False inference of causality or inference of false causality could have disastrous consequences.

The opposite of imputing unwarranted causality is overlooking probable ones, especially when the cause is common and the consequence manifests only after long latency or rarely (Figure 1F). Even though long-term exposure to low-dose ionizing radiation may theoretically increase the lifetime cancer risk of health care professionals who use fluoroscopy for work, definite causality has not been statistically established.[11] However, anecdotal reports[12] and mechanistic plausibility[13] are concerning. Alternatively, if low-dose ionizing radiation is truly "innocuous," the as low as reasonably achievable principle would not be needed,[14] and the effort and resources expended on developing and performing fluoroless electrophysiological procedures would have been in vain.[15]

LBBB has long been known to be associated with increased risks of cardiac disease, HF, and mortality,[16–23] but confounding factors (aging and comorbidities) (Figure 1E) and insidious onset (Figure 1F) make it difficult to prove causality. Active experimentation, a cornerstone of the scientific method, is more effective in proving causality than passive observation. However, the Declaration of Helsinki explicitly forbids intentionally inflicting harm on human subjects in scientific experiments.[24] The direct harm from LBBB on an otherwise healthy heart could only be experimentally studied in animal models.[25,26]

Inferring causality from remedy

The logical statement "**A**→**B**" (if **A**, then **B**) could be interpreted as **A** "causes" **B**, but not necessarily mechanistically (Figure 1D). For illustration, consider the relationships between an occluded coronary artery (OCA) **A** and a chest pain episode **B** (Table 1(a)). The OCA could be the culprit and causes chest pain (cell C1R1, C for column, R for row) or a bystander that continues to exist without chest pain (cell C1R2). Chest pain could be caused by the OCA (cell C2R1) but could also be due to an unrelated cause (eg, microvascular angina and esophageal spasm) (cell C2R3). Obstructive angina is defined by logical equivalence to the OCA (C3): obstructive angina is chest pain that exists only in the presence of an OCA (cells C1R1, C2R1, and C3R1) and disappears as soon as the OCA is opened (cells C1R4, C2R4, and C3R4). Nonobstructive angina chest pain is defined by exclusion ("negation" in logical terms) of obstructive angina (C4).

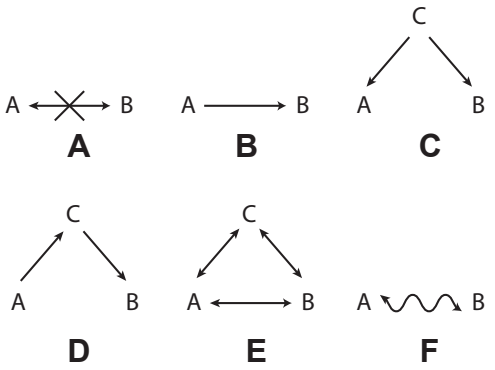

Figure 1
A: Pure coincidence or chance correlation but no causality between A and B. **B:** A directly causes B. **C:** A and B are correlated through a common cause C but no direct causality. **D:** A indirectly causes B through an intermediary step C. **E:** A, B and C could cause and be caused by one another - multi-dimensional network of positive feedback loops. **F:** A directly causes B, but only very slowly.

Suppose an OCA is found in a patient with chest pain (R1 and R2) (Table 1(b)). Opening up the occluded OCA would tell if chest pain is obstructive angina. If chest pain disappears, it is obstructive angina (R4) (Table 1(c)). If chest pain persists, it is nonobstructive angina chest pain (R3) (Table 1(d)). Thus, response to the remedy for obstructive angina could be used to infer causality between the OCA and the chest pain episode. **A**↔**B** trivially implies **A**→**B**. The definition of obstructive angina (C3) implies that the OCA "causes" the chest pain episode.

CRT-responsive HF with LBBB—Response measure and CRT institution

CRT was developed to mitigate the electrical and hence mechanical dyssynchrony associated with abnormal ventricular activation.[1,27–29] LBBB has consistently been one of the best predictors of response to CRT.[30] Thus, if response to CRT is used to define a subtype of HF, it would seem sensible to confine attention to HF with LBBB initially,[31] even though HF without LBBB (regardless of the EF) is also associated with LV mechanical dyssynchrony.[32–37] CRT might be used not only to treat but also to define LBBB-induced CM as CRT-responsive HF (regardless of EF) with LBBB.[38,39]

Response to CRT depends on (is confounded by) how it is measured and instituted.[40–42] Response to CRT has been measured in terms of (1) functional status and quality of life; (2) outcome events (eg, death and HF hospitalization); (3)

Table 1 Truth table for inferring causality from remedy

	Occluded coronary artery	Chest pain	Obstructive angina	Nonobstructive angina chest pain
(a) Symbol	A	B	A↔B	Not (A↔B)
Truth value	T	T	T	F
	T	F	F	T
	F	T	F	T
	F	F	T	F
(b) Symbol	A	B	A↔B	Not (A↔B)
Truth value	T	T	T	F
	T	F	F	T
	F	T	F	T
	F	F	T	F
(c) Symbol	A	B	A↔B	Not (A↔B)
Truth value	T	T	T	F
	T	F	F	T
	F	T	F	T
	F	F	T	F
(d) Symbol	A	B	A↔B	Not (A↔B)
Truth value	T	T	T	F
	T	F	F	T
	F	T	F	T
	F	F	T	F

F = false; T = true.

physiological parameters (eg, LVEF, LV dimensions, global longitudinal strain, and cardiac output); and (4) composites of the above. CRT response classifications and rates differ according to the measures used.[43] The clinical measures (1) and (2) matter more than the physiological measures (3) to patients, and the 2 categories only partially correlate.[44] Reverse remodeling (rise in LVEF and fall in LV dimensions) means little, if at all, to patients. For the "super-responders" with near renormalization of LV function and dimensions, their CRT-responsive HF with LBBB could be equated with LBBB-induced CM and their prior CM could be inferred to be largely, if not entirely, caused by LBBB.[45–47] Even substantial LV reverse remodeling might be functional rather than structural, though, as acute withdrawal of CRT caused immediate LV mechanical dyssynchrony and fall in LVEF.[48] LV lead placement over an infarcted area or near the apex could make CRT less effective.[49,50]

Subclinical LBBB-induced CM vs preclinical HFpEF

LBBB is associated with LV remodeling and mechanical dyssynchrony even in the absence of overt cardiovascular disease.[51,52] Compared to matched controls without LBBB, LVEF is lower (56%±7% vs 68%±6%; $P < .001$) and LV end-diastolic and end-systolic volumes are higher (145±34 mL vs 127±28 mL; $P < 0.01$ and 65±20 mL vs 42±14 mL; $P < .001$). In a study of "idiopathic" LBBB incidentally discovered in "young" adults aged <50 years (37±11 years), the LVEF was 59%±6% at baseline and LV mechanical dyssynchrony and late contrast enhancement on cardiac magnetic resonance imaging were present in 100% and 40% of subjects, respectively.[53] In 2 studies assessing deterioration in LVEF over time in patients with LBBB, the "normal" baseline LVEF was only ≈55% at an age of ≈67 years.[54,55]

It appears LBBB always induces CM and there is no safety limit in LVEF above which LBBB would not cause harm.[56] LBBB with LVEF ≥ 50% but no symptoms is subclinical LBBB-induced CM or preclinical HFpEF (Figure 2).[56] The disease has already manifested but in a way that escapes medical attention because of some arbitrary cutoff value of ≥50% for "normal" LVEF. A "low normal" LVEF of 50%–55% is in fact "abnormal" and pathological.

Mechanical dyssynchrony in HFpEF with and without LBBB

Mechanical dyssynchrony in LV contraction exists in HFpEF even when the QRS complex is narrow but is more pronounced when the QRS complex is wide.[34–37] The LV mechanical dyssynchrony in HFpEF with LBBB might be not just quantitatively more severe than, but also qualitatively different from, HFpEF without LBBB.[55,57] Patients with HFpEF with LBBB (≈12% of the total population with HFpEF)[58] should be regarded as distinct from those without[59] and might benefit from CRT (or CSP) just as much as HFrEF with LBBB.[60]

Experimental LBBB-induced CM

Artificially created LBBB not only injured the Purkinje fibers (fibrosis, fatty degeneration vacuolization, and impaired intercellular coupling from downregulation of the gap junction protein connexin 43) that form the heart's intraventricular electrical conduction system but also caused fibrosis of the myocardium, functional hypoperfusion of the LV septum, and ≈13%–23% LVEF reduction in otherwise healthy dogs over 16 weeks to 12 months.[25,26] The animal studies provide the most direct experimental proof of the deleterious effects

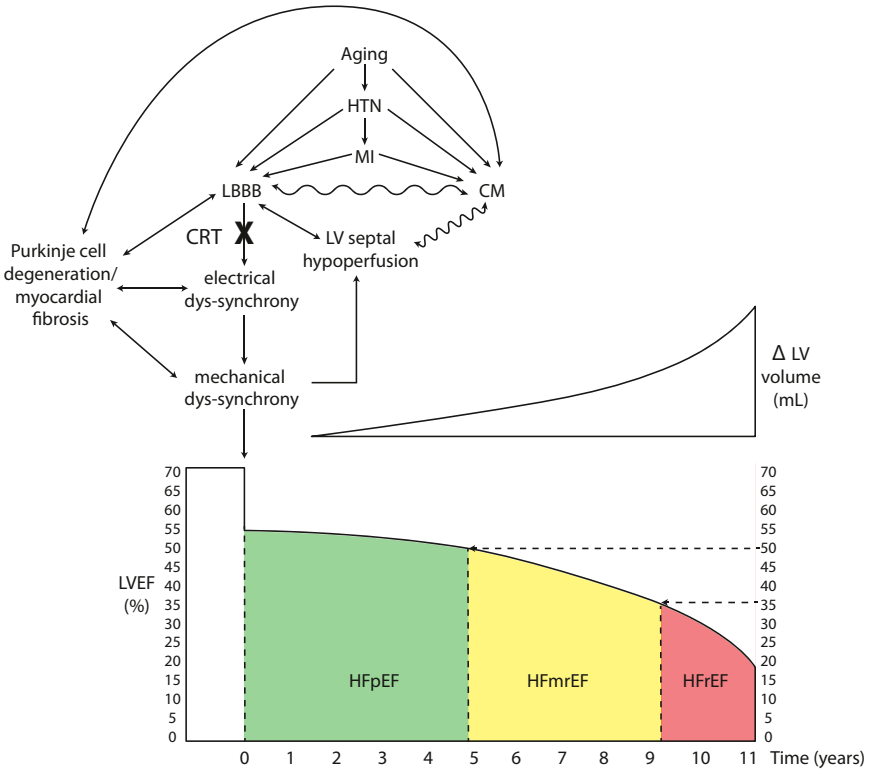

Figure 2
Schematic diagram of possible interconnections and interactions of factors involved in left bundle branch block (LBBB)–induced cardiomyopathy and heart failure. CM = cardiomyopathy; CRT = cardiac resynchronization therapy; HFmrEF = heart failure with mildly to moderately impaired ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; HTN = hypertension; LV = left ventricular; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

of LBBB, which extend beyond the conduction system into the myocardium and from functional impairment into structural abnormalities.

Epidemiology and natural history of LBBB

The prevalence of LBBB was 0.43% in men and 0.28% in women aged 33–71 years in a randomly selected Icelandic population from 1967 to 1977,[18] 0.69% in a Japanese population from 1958 to 2002,[17] and 0.4% at 50 years but 5.7% at 80 years in a Swedish study on men from 1967 to 1993 (Figure 3A).[22] LBBB was first detected at ≈65 years,[17,20] but the incidence rose rapidly with age (Figure 3B). Data on LBBB from US Air Force personnel[61,62] and retirees[63] are not representative of the general population and might explain the origin of the misconception that LBBB is a relatively benign condition.

Patients with LBBB but "normal" LVEF at baseline in fact had a "low normal" LVEF of ≈55% when LBBB was first detected.[51–55] Over time, their LVEF deteriorated and they

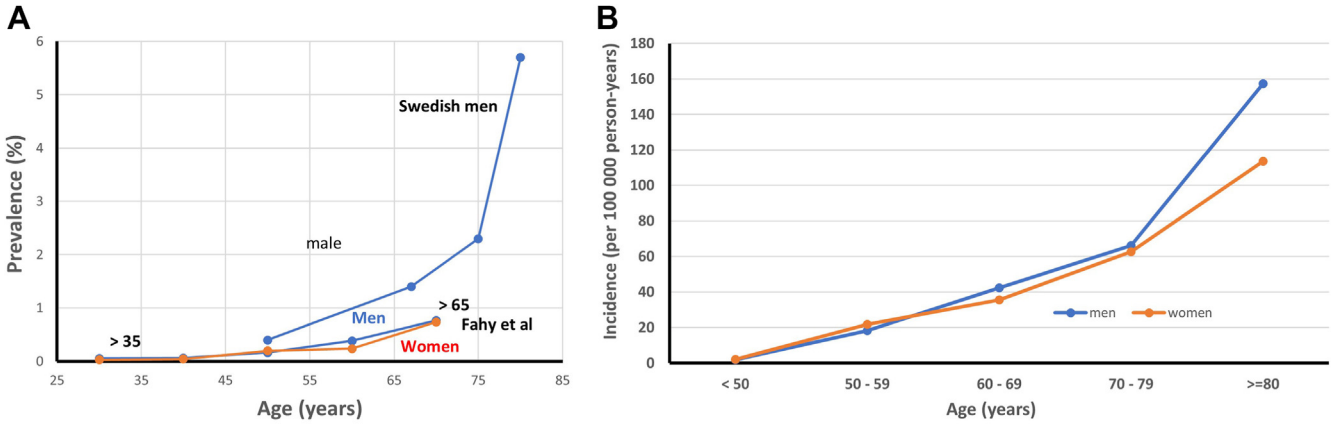

Figure 3
Age-dependent prevalence and incidence of left bundle branch block (LBBB). **A:** Age dependence of LBBB prevalence. Created from data in Fahy et al[16] and Eriksson et al.[22] **B:** Age dependence of LBBB incidence. Created from data in Imanishi et al.[17]

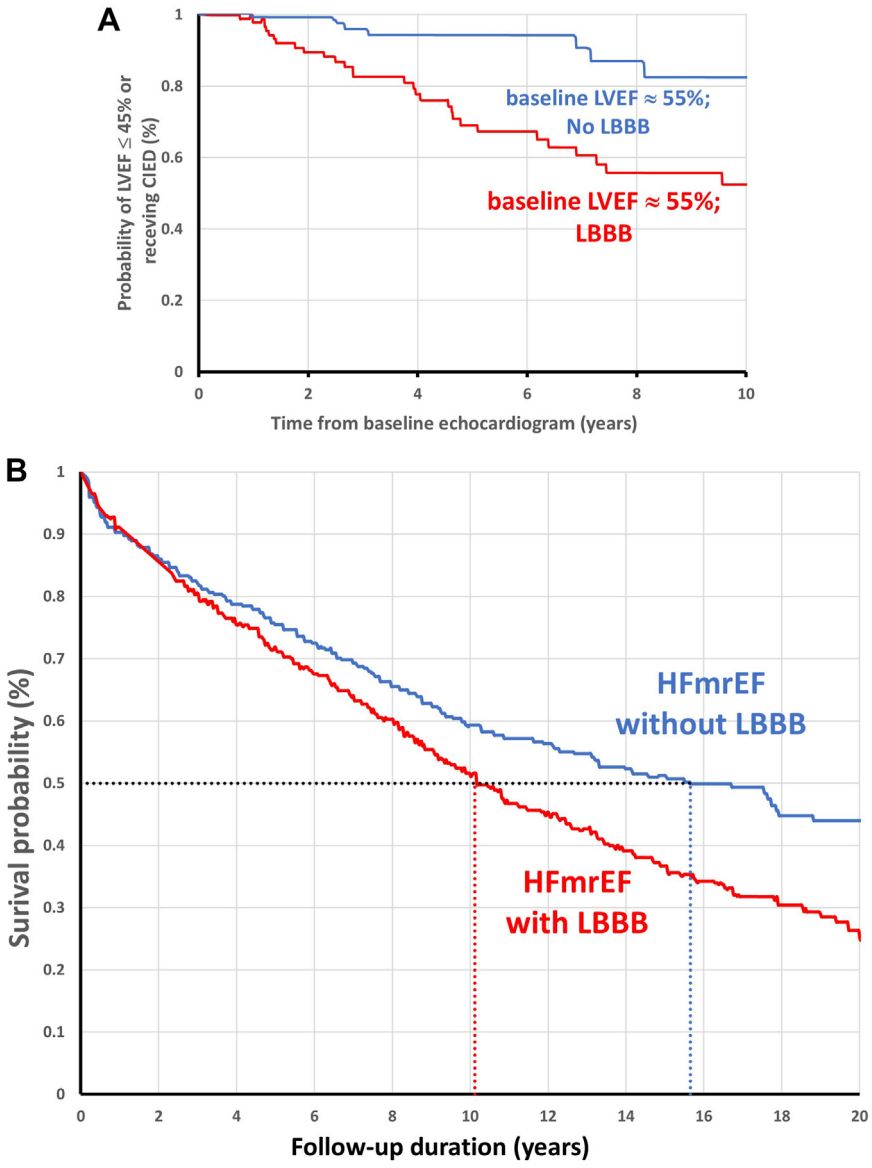

Figure 4

Prognosis of patients with preserved and mildly to moderately reduced left ventricular ejection fraction (LVEF) with and without left bundle branch block (LBBB). **A:** LBBB is associated with >20% higher probability of significant LVEF reduction and CIED implantation over 10 years. CIED = cardiac implantable electronic device. Modified from Sze et al.[55] **B:** LBBB shortened the median survival of patients with heart failure with mildly to moderately reduced left ventricular ejection fraction (HFmrEF) by 5.5 years. Modified from Witt et al.[57]

transited from HFpEF to HFmrEF and even HFrEF.[64,65] In one study, LVEF fell by ≈15%–≈37% over 4.3 years in approximately one-third of patients with a "normal" baseline LVEF of ≥50% (≈52%) and LBBB.[54] In another study, patients with "low normal" LVEF with LBBB had a 3.8 times higher risk (36% vs 10%) of progression to LVEF ≤ 45% or receiving a cardiac implantable electronic device than did those without over 10 years (Figure 4A).[55] After transitioning from HFpEF to HFmrEF, LBBB wreaks further havoc with patients' prognosis. Patients with HFmrEF with LBBB had a higher risk of HFrEF, cardiac implantable electronic device implantation, and death as well as a shorter median lifespan (by 5.5 years) (Figure 4B) than did those without.[57]

The late surge of LBBB onset in life (Figure 3) has 3 implications. First, many LBBB carriers would likely have significant comorbidities (eg, hypertension, LV hypertrophy, ischemic heart disease, and other forms of CM) by the time they develop LBBB, making it difficult to tease out whether LBBB is the cause or consequence of these comorbidities (Figure 1E).[16–23,66] Second, the direct adverse consequences of LBBB may not have the time to develop before the LBBB carriers die of unrelated (in the sense of competing risks) or unrecognized related causes (Figures 1F and 2).[16–18,20] The mean age of LBBB onset is ≈65 years, and LBBB-induced CM may take 5–21 years (mean 11.6 years) to cause symptomatic HF.[46] Thus, patients might only have symptoms from LBBB-induced CM if they live to 85 years and are likely to have comorbidities by then.[67] Third, LBBB incidentally found in young people (eg, younger than 40 years) should raise special concerns as that might be the early manifestation of an

incipient CM, whether LBBB is the cause, consequence, or both (ie, a positive feedback loop) (Figures 1E and 2). Low "normal" LVEF, LV mechanical dyssynchrony, and late contrast enhancement (in ≈40% of asymptomatic LBBB carriers[53]) are "abnormal" pathological findings, even if they might not be correlated with or cause immediate clinical harm. Long-term (decades) studies of systematic tracking of the evolution of LBBB-induced CM by magnetic resonance imaging would be difficult and costly to conduct and may have never been attempted.

Management of LBBB without structural heart disease

After initial assessment,[68] patients with LBBB but no gross structural heart abnormalities should ideally be reviewed periodically with serial imaging of the heart. There are no firm recommendations from guidelines on the monitoring of such patients with subclinical or preclinical disease. Extrapolating from guidelines on valvular heart disease,[69] a stratified approach seems reasonable. Patients could be reviewed less frequently (eg, once every 2–5 years) without symptoms and risk factors and more intensely (eg, once every 6 months) once HF symptoms and/or extracardiac conduction and/or structural heart abnormalities appear.

LBBB with HF symptoms but LVEF ≥ 50% could be regarded as HFpEF with LBBB. Sodium glucose cotransporter 2 inhibitors reduced HF hospitalization and cardiovascular death, improved exercise tolerance and quality of life,[70–72] but only produced no significant improvement in LV diastolic function or EF in RCTs on HFpEF/HFmrEF.[73–77] RCTs on HFpEF/HFmrEF did not stratify their results according to the presence or absence of LBBB. Guidelines on HFpEF[78] might thus apply differently, depending on whether LBBB is the cause (Figure 1B) or a co-consequence (Figure 1C) of HFpEF.

CRT in HFpEF with LBBB

CRT was trialed in 2 patients with HFpEF and LBBB and produced tremendous relief of their severe debilitating symptoms.[8,9] Both cases involved some form of physiological assessment of response to CRT, but only after the CRT devices had already been implanted. There has been a report of temporary CRT by pacing the LV endocardially with an electrophysiology catheter in 2 patients with HFpEF and LBBB.[79] Response was assessed by echocardiography.

Currently, there is no easy and reliable way to predict the clinical response of HFpEF with LBBB to CRT before and without actual device implantation. Improvements in physiological parameters (eg, pressure-volume loop, intracardiac pressures, and echocardiographic indices) are surrogate measures that might not translate into better clinical outcomes. Trialing CRT in HFpEF with LBBB is "empirical" (ie, no RCT data) to an extent but that would be based on sound physiological and mechanistic principles and the limited data available and hence clinically justifiable.[2] In contrast, ≈30% of patients meeting the current guideline indications do not respond to CRT.[40,41] Better patient selection for CRT is needed.[80–85]

CRT in HFmrEF with LBBB

CRT has been shown to confer benefits for patients with HFmrEF with LBBB (mean LVEF ≈ 43%) in terms of LV remodeling (rise in LVEF and fall in LV end-systolic volume) in the PROSPECT trial and another RCT published in 2024.[6,7] CRT has a Class IIb indication for HFmrEF with LBBB in the 2018 guidelines.[68]

CSP in HF with LBBB

CSP (mainly realized through left bundle branch area pacing) is an emerging treatment that holds huge promise and has rapidly gained traction in clinical practice.[2,86] However, the clinical evidence and experience of CSP is much less than that of CRT and it might be prudent to use CSP as an alternative in HF with LBBB only when conventional CRT by epicardial LV lead placement via a coronary sinus side branch fails (in the sense of a backup option).[87]

Conclusion—Cardiac physiological pacing in HFpEF with LBBB

The assertion that "*The prognosis of LBBB is relatively benign apart from its association with dilated cardiomyopathy*"[18(P1075)] is no longer tenable. The widespread attitude among physicians toward HFpEF and HFmrEF with LBBB might be an issue of "competency in medical knowledge."[57] The temporal trend in the interpretation and application of ethical and legal standards in medicine is that adverse outcomes or events are judged primarily by gravity and secondarily by frequency. If an adverse clinical event that is severe but rare (eg, 10 times the risk of sudden death over 5 years for LBBB,[88] 1.65 times the risk of sudden death over 4.1 years for HFpEF with LBBB than without,[89] and shortened median lifespan by 5.5 years over 20 years for HFmrEF with LBBB[57]) or not so severe but more common (eg, 2.9% of the 1-year rate of developing HFpEF with LBBB,[67] 13 times the risk of high-degree atrioventricular block,[19] and 36% deterioration in LVEF[54,55]) matters to the patients affected, it matters to all health care professionals involved in their care. Prevention is generally better than cure. Moreover, "*the law imposes a duty of care on a healthcare professional in situations where it is 'reasonably foreseeable' that they might cause harm to patients through their actions or omissions.*"[90] Not acting on ("omissions") HFpEF with LBBB falls into the latter category, as its harm to patients has been well characterized in multiple studies and is therefore "reasonably foreseeable."[91]

The evidence reviewed and the arguments made should provide adequate clinical justifications to perform CRT or CSP in patients with HFpEF/HFmrEF with LBBB and severe debilitating symptoms, not just for symptomatic relief but also for prognosis uplift. The "obsession" with LVEF ≤ 35% in deciding CRT eligibility is irrational and anachronistic. In the PROSPECT trial, the quarter (24%) of enrolled patients reassigned from LVEF ≤ 35% by the enrollment centers to LVEF

> 35% by the core echocardiographic laboratories also benefited similarly from CRT for response measured in terms of echocardiographic parameters and a composite clinical score comprising exercise tolerance, quality of life, HF class/hospitalization, and death.[6]

Assuming ≈55% of patients with HF have HFpEF[78,92] and ≈10%–12% of patients with HFpEF have LBBB,[58,89] ≈6% of all patients with HF have HFpEF with LBBB. This might be a large enough pool of potential treatment beneficiaries to motivate a large-scale RCT of CRT in HFpEF with LBBB.[39] Until then, the limited data from physiological and mechanistic studies and expert opinions are the only evidence available for guiding management of patients with pressing clinical needs.[2] Many breakthrough innovations in medicine, including CRT, originated from such dire dilemmas.[27,28] What matters for patients are their clinical outcomes and not whether their treatments are listed in guidelines.[8,9] CRT and CSP are invaluable treatment options for patients with HFpEF/HFmrEF with LBBB and severe debilitating symptoms, highlighting the value of prioritizing personalized care focused on patients' individual characteristics and clinical outcomes over rigid adherence to guidelines and traditional dogmas.

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References

1. Huizar JF, Kaszala K, Tan A, et al. Abnormal Conduction-Induced Cardiomyopathy: JACC Review Topic of the Week. J Am Coll Cardiol 2023;81:1192–1200.
2. Chung MK, Patton KK, Lau C-P, et al. 2023 HRS/APHRS/LAHRS guideline on cardiac physiologic pacing for the avoidance and mitigation of heart failure. Heart Rhythm 2023;20:e17–e91.
3. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. Europace 2022;24:71–164.
4. Halliday BP, Senior R, Pennell DJ. Assessing left ventricular systolic function: from ejection fraction to strain analysis. Eur Heart J 2021;42:789–797.
5. Potter E, Marwick TH. Assessment of left ventricular function by echocardiography: the case for routinely adding global longitudinal strain to ejection fraction. JACC Cardiovasc Imaging 2018;11:260–274.
6. Chung ES, Katra RP, Ghio S, et al. Cardiac resynchronization therapy may benefit patients with left ventricular ejection fraction >35%: a PROSPECT trial substudy. Eur J Heart Fail 2010;12:581–587.
7. Cha YM, Lee HC, Mulpuru SK, et al. Cardiac resynchronization therapy for patients with mild to moderately reduced ejection fraction and left bundle branch block. Heart Rhythm 2024;21:2250–2259.
8. Penicka M, Kocka V, Herman D, Trakalova H, Herold M. Cardiac resynchronization therapy for the causal treatment of heart failure with preserved ejection fraction: insight from a pressure-volume loop analysis. Eur J Heart Fail 2010;12:634–636.
9. Anand V, Bradley D, Frye RL, Borlaug BA. Things are not always as they seem: multimodality exercise assessment in the evaluation of dyspnea. Circulation 2021;143:2502–2507.
10. Maass AH, van Veldhuisen DJ. Device therapy in patients with heart failure and preserved ejection fraction (HFPEF): a new frontier? Eur J Heart Fail 2010;12:527–529.
11. Chartier H, Fassier P, Leuraud K, et al. Occupational low-dose irradiation and cancer risk among medical radiation workers. Occup Med (Lond) 2020;70:476–484.
12. Roguin A, Goldstein J, Bar O, Goldstein JA. Brain and neck tumors among physicians performing interventional procedures. Am J Cardiol 2013;111:1368–1372.
13. Reeves RR, Ang L, Bahadorani J, et al. Invasive cardiologists are exposed to greater left sided cranial radiation: the BRAIN Study (Brain Radiation Exposure and Attenuation During Invasive Cardiology Procedures). JACC Cardiovasc Interv 2015;8:1197–1206.
14. Andresz S, Allisy-Roberts P, Economides S, et al. Synthesis of the European ALARA network 20th workshop 'ALARA for interventional radiology and nuclear medicine'. J Radiol Prot 2024;44.
15. Preda A, Bonvicini E, Coradello E, et al. The fluoroless future in electrophysiology: a state-of-the-art review. Diagnostics (Basel) 2024;14:182.
16. Fahy GJ, Pinski SL, Miller DP, et al. Natural history of isolated bundle branch block. Am J Cardiol 1996;77:1185–1190.
17. Imanishi R, Seto S, Ichimaru S, Nakashima E, Yano K, Akahoshi M. Prognostic significance of incident complete left bundle branch block observed over a 40-year period. Am J Cardiol 2006;98:644–648.
18. Hardarson T, Arnason A, Elíasson GJ, Pálsson K, Eyjólfsson K, Sigfússon N. Left bundle branch block: prevalence, incidence, follow-up and outcome. Eur Heart J 1987;8:1075–1079.
19. Miller WL, Hodge DO, Hammill SC. Association of uncomplicated electrocardiographic conduction blocks with subsequent cardiac morbidity in a community-based population (Olmsted County, Minnesota). Am J Cardiol 2008;101:102–106.
20. Schneider JF, Thomas HE Jr, Kreger BE, McNamara PM, Kannel WB. Newly acquired left bundle-branch block: the Framingham study. Ann Intern Med 1979;90:303–310.
21. Schneider JF, Thomas HE Jr, Sorlie P, Kreger BE, McNamara PM, Kannel WB. Comparative features of newly acquired left and right bundle branch block in the general population: the Framingham study. Am J Cardiol 1981;47:931–940.
22. Eriksson P, Hansson PO, Eriksson H, Dellborg M. Bundle-branch block in a general male population: the study of men born 1913. Circulation 1998;98:2494–2500.
23. Eriksson P, Wilhelmsen L, Rosengren A. Bundle-branch block in middle-aged men: risk of complications and death over 28 years. The Primary Prevention Study in Göteborg, Sweden. Eur Heart J 2005;26:2300–2306.
24. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191–2194.
25. Wang X, Ge B, Miao C, et al. Beyond conduction impairment: unveiling the profound myocardial injury in left bundle branch block. Heart Rhythm 2024;21:1370–1379.
26. Vernooy K, Verbeek XA, Peschar M, et al. Left bundle branch block induces ventricular remodelling and functional septal hypoperfusion. Eur Heart J 2005;26:91–98.
27. Cazeau S, Ritter P, Lazarus A, et al. Multisite pacing for end-stage heart failure: early experience. Pacing Clin Electrophysiol 1996;19:1748–1757.
28. Cazeau S, Leclercq C, Lavergne T, et al. Effects of multisite biventricular pacing in patients with heart failure and intraventricular conduction delay. N Engl J Med 2001;344:873–880.
29. Yu CM, Chau E, Sanderson JE, et al. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. Circulation 2002;105:438–445.
30. Rickard J, Michtalik H, Sharma R, et al. Predictors of response to cardiac resynchronization therapy: a systematic review. Int J Cardiol 2016;225:345–352.
31. Sanna GD, Merlo M, Moccia E, et al. Left bundle branch block-induced cardiomyopathy: a diagnostic proposal for a poorly explored pathological entity. Int J Cardiol 2020;299:199–205.
32. Yu CM, Yang H, Lau CP, et al. Regional left ventricle mechanical asynchrony in patients with heart disease and normal QRS duration: implication for biventricular pacing therapy. Pacing Clin Electrophysiol 2003;26:562–570.
33. Yu CM, Lin H, Zhang Q, Sanderson JE. High prevalence of left ventricular systolic and diastolic asynchrony in patients with congestive heart failure and normal QRS duration. Heart 2003;89:54–60.
34. Santos AB, Kraigher-Krainer E, Bello N, et al. Left ventricular dyssynchrony in patients with heart failure and preserved ejection fraction. Eur Heart J 2014;35:42–47.
35. Morris DA, Vaz Pérez A, Blaschke F, Eichstädt H, Ozcelik C, Haverkamp W. Myocardial systolic and diastolic consequences of left ventricular mechanical dyssynchrony in heart failure with normal left ventricular ejection fraction. Eur Heart J Cardiovasc Imaging 2012;13:556–567.
36. Lee AP, Song JK, Yip GW, et al. Importance of dynamic dyssynchrony in the occurrence of hypertensive heart failure with normal ejection fraction. Eur Heart J 2010;31:2642–2649.
37. Phan TT, Abozguia K, Shivu GN, et al. Myocardial contractile inefficiency and dyssynchrony in heart failure with preserved ejection fraction and narrow QRS complex. J Am Soc Echocardiogr 2010;23:201–206.
38. Marques CA, Cabrita A, Pinho AI, et al. Left bundle branch block cardiomyopathy (LBBB-CMP): from the not-so-benign finding of idiopathic LBBB to LBBB-CMP diagnosis and treatment. Heart Vessels 2025;40:62–71.
39. Kloosterman M, Loh KP, van Veen TAB. Left bundle branch block-induced cardiomyopathy: a distinctive form of cardiomyopathy that might require a dedicated form of treatment. Heart Rhythm 2024;21:1380–1381.

40. Carità P, Corrado E, Pontone G, et al. Non-responders to cardiac resynchronization therapy: insights from multimodality imaging and electrocardiography. A brief review. Int J Cardiol 2016;225:402–407.
41. Naqvi SY, Jawaid A, Goldenberg I, Kutyifa V. Non-response to cardiac resynchronization therapy. Curr Heart Fail Rep 2018;15:315–321.
42. Nguyên UC, Prinzen FW, Vernooy K. Left ventricular lead placement in cardiac resynchronization therapy: current data and potential explanations for the lack of benefit. Heart Rhythm 2024;21:197–205.
43. Daubert C, Behar N, Martins RP, Mabo P, Leclercq C. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. Eur Heart J 2017; 38:1463–1472.
44. Menet A, Guyomar Y, Ennezat PV, et al. Prognostic value of left ventricular reverse remodeling and performance improvement after cardiac resynchronization therapy: a prospective study. Int J Cardiol 2016;204:6–11.
45. Manne M, Rickard J, Varma N, Chung MK, Tchou P. Normalization of left ventricular ejection fraction after cardiac resynchronization therapy also normalizes survival. Pacing Clin Electrophysiol 2013;36:970–977.
46. Vaillant C, Martins RP, Donal E, et al. Resolution of left bundle branch block-induced cardiomyopathy by cardiac resynchronization therapy. J Am Coll Cardiol 2013;61:1089–1095.
47. Ruwald MH, Solomon SD, Foster E, et al. Left ventricular ejection fraction normalization in cardiac resynchronization therapy and risk of ventricular arrhythmias and clinical outcomes: results from the Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) trial. Circulation 2014;130:2278–2286.
48. Knappe D, Pouleur AC, Shah AM, et al. Acute effects of withdrawal of cardiac resynchronization therapy on left and right ventricular function, dyssynchrony, and contractile function in patients with New York Heart Association functional class I/II heart failure: MADIT-CRT. J Card Fail 2013;19:149–155.
49. Leyva F, Foley PW, Chalil S, et al. Cardiac resynchronization therapy guided by late gadolinium-enhancement cardiovascular magnetic resonance. J Cardiovasc Magn Reson 2011;13:29.
50. Merchant FM, Heist EK, McCarty D, et al. Impact of segmental left ventricle lead position on cardiac resynchronization therapy outcomes. Heart Rhythm 2010; 7:639–644.
51. Akhtari S, Chuang ML, Salton CJ, et al. Effect of isolated left bundle-branch block on biventricular volumes and ejection fraction: a cardiovascular magnetic resonance assessment. J Cardiovasc Magn Reson 2018;20:66.
52. Yılmaz S, Kılıc H, Ağac MT, et al. Left ventricular twist was decreased in isolated left bundle branch block with preserved ejection fraction. Anatol J Cardiol 2017;17:475–480.
53. Delise P, Rivetti L, Poletti G, et al. Clinical and prognostic significance of idiopathic left bundle-branch block in young adults. Cardiol Res Pract 2021; 2021:6677806.
54. Atwater BD, Emerek K, Samad Z, et al. Predicting the development of reduced left ventricular ejection fraction in patients with left bundle branch block. Am J Cardiol 2020;137:39–44.
55. Sze E, Dunning A, Loring Z, et al. Comparison of incidence of left ventricular systolic dysfunction among patients with left bundle branch block versus those with normal QRS duration. Am J Cardiol 2017;120:1990–1997.
56. Sze E, Daubert JP. Left bundle branch block: Is it "unsafe at any speed". JACC Heart Fail 2016;4:904–906.
57. Witt CM, Wu G, Yang D, Hodge DO, Roger VL, Cha YM. Outcomes with left bundle branch block and mildly to moderately reduced left ventricular function. JACC Heart Fail 2016;4:897–903.
58. Danciu SC, Gonzalez J, Gandhi N, Sadhu S, Herrera CJ, Kehoe R. Comparison of six-month outcomes and hospitalization rates in heart failure patients with and without preserved left ventricular ejection fraction and with and without intraventricular conduction defect. Am J Cardiol 2006;97:256–259.
59. Borlaug BA. The pathophysiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 2014;11:507–515.
60. Friedman DJ, Emerek K, Kisslo J, Søgaard P, Atwater BD. Left bundle-branch block is associated with asimilar dyssynchronous phenotype in heart failure patients with normal and reduced ejection fractions. Am Heart J 2021;231:45–55.
61. Hiss RG, Lamb LE. Electrocardiographic findings in 122,043 individuals. Circulation 1962;25:947–961.
62. Rotman M, Triebwasser JH. A clinical and follow-up study of right and left bundle branch block. Circulation 1975;51:477–484.
63. Edmands RE. An epidemiological assessment of bundle-branch block. Circulation 1966;34:1081–1087.
64. Sharma S, Barot HV, Schwartzman AD, et al. Risk and predictors of dyssynchrony cardiomyopathy in left bundle branch block with preserved left ventricular ejection fraction. Clin Cardiol 2020;43:1494–1500.
65. Angheloiu GO, Saul M, Edelman K, Shah H, Mezu UL, Saba S. Predictors of left ventricular function deterioration in patients with left bundle branch block and ejection fraction >50%. Congest Heart Fail 2013;19:E1–E4.
66. Baldasseroni S, Opasich C, Gorini M, et al. Left bundle-branch block is associated with increased 1-year sudden and total mortality rate in 5517 outpatients with congestive heart failure: a report from the Italian network on congestive heart failure. Am Heart J 2002;143:398–405.
67. Ashraf H, Agasthi P, Siegel RJ, et al. Natural history and clinical significance of isolated complete left bundle branch block without associated structural heart disease. Anatol J Cardiol 2021;25:170–176.
68. Kusumoto FM, Schoenfeld MH, Barrett C, et al. 2018 ACC/AHA/HRS Guideline on the evaluation and management of patients with bradycardia and cardiac conduction delay: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation 2019;140:e382–e482.
69. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA Guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2021;143:e72–e227.
70. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385:1451–1461.
71. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. N Engl J Med 2022; 387:1089–1098.
72. Nassif ME, Windsor SL, Borlaug BA, et al. The SGLT2 inhibitor dapagliflozin in heart failure with preserved ejection fraction: a multicenter randomized trial. Nat Med 2021;27:1954–1960.
73. Akasaka H, Sugimoto K, Shintani A, et al. Effects of ipragliflozin on left ventricular diastolic function in patients with type 2 diabetes and heart failure with preserved ejection fraction: the EXCEED randomized controlled multicenter study. Geriatr Gerontol Int 2022;22:298–304.
74. Ejiri K, Miyoshi T, Kihara H, et al. Effect of luseogliflozin on heart failure with preserved ejection fraction in patients with diabetes mellitus. J Am Heart Assoc 2020; 9:e015103.
75. Tanaka H, Soga F, Tatsumi K, et al. Positive effect of dapagliflozin on left ventricular longitudinal function for type 2 diabetic mellitus patients with chronic heart failure. Cardiovasc Diabetol 2020;19:6.
76. Hundertmark MJ, Adler A, Antoniades C, et al. Assessment of cardiac energy metabolism, function, and physiology in patients with heart failure taking empagliflozin: the randomized, controlled EMPA-VISION trial. Circulation 2023; 147:1654–1669.
77. Singh JSS, Mordi IR, Vickneson K, et al. Dapagliflozin versus placebo on left ventricular remodeling in patients with diabetes and heart failure: the REFORM trial. Diabetes Care 2020;43:1356–1359.
78. Borlaug BA, Sharma K, Shah SJ, Ho JE. Heart Failure With Preserved Ejection Fraction: JACC Scientific Statement. J Am Coll Cardiol 2023;81:1810–1834.
79. Friedman DJ, Emerek K, Søgaard P, Vejdani-Jahromi M, Kisslo J, Atwater BD. The mechanical and hemodynamic effects of left ventricular pacing in heart failure with preserved ejection fraction and left bundle branch block. J Electrocardiol 2018;51:859–862.
80. Friedman DJ, Olivas-Martinez A, Dalgaard F, et al. Relationship between sex, body size, and cardiac resynchronization therapy benefit: a patient-level meta-analysis of randomized controlled trials. Heart Rhythm 2024; 21:845–854.
81. Yamamoto N, Noda T, Nakano M, et al. Clinical utility of QRS duration normalized to left ventricular volume for predicting cardiac resynchronization therapy efficacy in patients with "mid-range" QRS duration. Heart Rhythm 2024; 21:855–862.
82. Higuchi K, Manne M, Tchou P, et al. Left ventricular mass as a modulator of ventricular arrhythmia risk and sex differences after CRT for nonischemic cardiomyopathy and LBBB. Heart Rhythm 2025;22:339–348.
83. Kodama N, Nakagawa M, Ishii Y, et al. R-R' interval in the left bundle branch block predicts long-term outcomes after cardiac resynchronization therapy by estimating greater mechanical dyssynchrony and viable myocardium. Heart Rhythm 2024;21:436–444.
84. Chen Z, Chu J, Wang J, et al. Horizontal QRS axis predicts response to cardiac resynchronization therapy in heart failure patients with left bundle branch block [published online ahead of print November 12, 2024]. Heart Rhythm. doi: 10.1016/j.hrthm.2024.11.011.
85. Saplaouras A, Vlachos K, Mililis P, et al. Cardiac resynchronization therapy in heart failure based on Strauss criteria for left bundle branch block. ESC Heart Fail 2025; 12:174–184.
86. Burri H, Jastrzebski M, Cano Ó, et al. EHRA clinical consensus statement on conduction system pacing implantation: endorsed by the Asia Pacific Heart Rhythm Society (APHRS), Canadian Heart Rhythm Society (CHRS), and Latin American Heart Rhythm Society (LAHRS). Europace 2023;25:1208–1236.
87. Ponnusamy SS, Vijayaraman P, Ellenbogen KA. Left bundle branch block-associated cardiomyopathy: a new approach. Arrhythm Electrophysiol Rev 2024;13:e15.
88. Rabkin SW, Mathewson FA, Tate RB. Natural history of left bundle-branch block. Br Heart J 1980;43:164–169.
89. Adabag S, Rector TS, Anand IS, et al. A prediction model for sudden cardiac death in patients with heart failure and preserved ejection fraction. Eur J Heart Fail 2014;16:1175–1182.
90. Ethics Toolkit: the doctor-patient relationship. British Medical Association (BMA) Web site, https://www.bma.org.uk/media/nalcxoal/the-doctor-patient-relationship2024.pdf. Accessed November 10, 2024.
91. Gatti P, Lind S, Kristjánsdóttir I, et al. Prognosis of CRT-treated and CRT-untreated unselected population with LBBB in Stockholm County. Europace 2023; 25:euad192.
92. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med 2006;355:251–259.