ORIGINAL ARTICLE

WILEY

Myocardial recovery after cardiac resynchronization therapy in left bundle branch block-associated idiopathic nonischemic cardiomyopathy: A NEOLITH II substudy

Norman C. Wang | Aliza Hussain | Evan C. Adelstein | Andrew D. Althouse | Michael S. Sharbaugh | Sandeep K. Jain | Alaa A. Shalaby | Andrew H. Voigt | Samir Saba

Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

Correspondence

Norman C. Wang, UPMC Presbyterian, 200 Lothrop Street, South Tower, 3rd Floor, Room E352.9, Pittsburgh, PA 15213.
Email: wangnc@upmc.edu

Abstract

Background: Baseline predictors of myocardial recovery after cardiac resynchronization therapy (CRT) in left bundle branch block (LBBB)-associated idiopathic nonischemic cardiomyopathy (NICM) are unknown.

Methods: A retrospective study included subjects with idiopathic NICM, left ventricular ejection fraction (LVEF) $\leq 35\%$, and LBBB. Myocardial recovery was defined as post-CRT LVEF $\geq 50\%$. Logistic regression analyses described associations between baseline characteristics and myocardial recovery. Cox regression analyses estimated the hazard ratio (HR) between myocardial recovery status and adverse clinical events.

Results: In 105 subjects (mean age 61 years, 44% male, mean initial LVEF $22.6\% \pm 6.6\%$, 81% New York Heart Association class III, and 98% CRT-defibrillators), myocardial recovery after CRT was observed in 56 (54%) subjects. Hypertension, heart rate, and serum blood urea nitrogen (BUN) had negative associations with myocardial recovery in univariable analyses. These associations persisted in multivariable analysis: hypertension (odds ratio (OR), 0.40; 95% confidence interval (CI), 0.17–0.95; $p = 0.04$), heart rate (OR per 10 bpm, 0.69; 95% CI, 0.48–0.997; $p = 0.048$), and serum BUN (OR per 1 mg/dl, 0.94; 95% CI, 0.88–0.99; $p = 0.04$). Subjects with post-CRT LVEF $\geq 50\%$, when compared to $<50\%$, had lower risk for adverse clinical events (heart failure hospitalization, appropriate implantable cardioverter-defibrillator shock, appropriate anti-tachycardia pacing therapy, ventricular assist device implantation, heart transplantation, and death) over a median follow-up of 75.9 months (HR, 0.38; 95% CI, 0.16–0.88; $p = 0.02$).

Conclusion: In LBBB-associated idiopathic NICM, myocardial recovery after CRT was associated with absence of hypertension, lower heart rate, and lower serum BUN. Those with myocardial recovery had fewer adverse clinical events.

KEYWORDS

cardiac resynchronization therapy, left bundle branch block, left ventricular ejection fraction, myocardial recovery, nonischemic cardiomyopathy, outcomes

1 | INTRODUCTION

Heart failure (HF) with reduced left ventricular ejection fraction (LVEF) is a heterogeneous condition where myocardial recovery is infrequently observed (Mann, Barger, & Burkoff, 2012; Wilcox et al., 2015). A common metric for treatment success is LVEF improvement. Those with recovered LVEF are not well described, but appear to have more favorable outcomes compared to those with persistently reduced LVEF (Basuray et al., 2014; Yancy et al., 2013). These observations extend to cardiac resynchronization therapy (CRT) recipients, which are recommended for select individuals (Ruwald et al., 2014).

Reported predictors for CRT super-response include nonischemic cardiomyopathy (NICM) and left bundle branch block (LBBB; Hsu et al., 2012). The strictest definition of super-response is LVEF $\geq 50\%$, or myocardial recovery (Steffel & Ruschitzka, 2014). To date, no studies have reported predictors of myocardial recovery in those with LBBB-associated idiopathic NICM. Theoretically, identifying clinical predictors may offer insight into optimizing CRT response. In addition, myocardial recovery after CRT is one criterion in a proposed definition of LBBB-induced cardiomyopathy (Vaillant et al., 2013).

The NEw-Onset LBBB-Associated Idiopathic Nonischemic Cardiomyopathy (NEOLITH) II study was conducted in CRT recipients with LBBB at the time of initial diagnosis of idiopathic NICM (Wang, Li, et al., 2018). This substudy sought to address two hypotheses: (a) baseline characteristics would differ between those who did and did not exhibit myocardial recovery and (b) clinical outcomes would differ between those who did and did not exhibit myocardial recovery.

2 | METHODS

2.1 | Study population and design

The NEOLITH II study was a retrospective cohort study conducted at the University of Pittsburgh Medical Center (Wang, Li, et al., 2018). Subjects implanted with CRT devices between January 1998 and April 2016 were identified from a prospectively maintained database. The derivation of the original study cohort, definition of idiopathic NICM, and exclusion criteria have been previously reported (Wang, Li, et al., 2018). This substudy consisted of the 105 subjects with LVEF assessment after CRT.

All subjects had LBBB at the time of initial diagnosis of NICM. LBBB was determined by 12-lead electrocardiograms recorded at 25 mm/s with automated QRS duration confirmed by a board-certified cardiologist. The definition of LBBB used was that recommended by the American Heart Association, the American College of Cardiology Foundation, and the Heart Rhythm Society (Surawicz, Childers, Deal, & Gettes, 2009). The presence of "strict" LBBB was assessed, but not used in analyses (Strauss, Selvester, & Wagner, 2011).

CRT implants were performed using a transvenous approach by electrophysiologists at the University of Pittsburgh Medical Center. Lateral and posterior coronary sinus branches were primary targets. Epicardial left ventricular (LV) leads were surgically placed when transvenous approaches were unsuccessful. The final lead position was determined by chest radiography using a standardized technique (Wilton et al., 2008). Device programming was at the discretion of the treating physicians. The study was approved by the University of Pittsburgh Institutional Review Board. Informed consent was not required because of the retrospective nature of the study.

2.2 | Covariates and outcomes

Clinical information documented as part of routine clinical care was collected from electronic medical records. Baseline demographics, laboratory values, medical history, echocardiographic data, and medications were those measured on the morning of CRT implantation or closest outpatient visit prior to CRT implant. Race/ethnicity was self-described. Alcohol consumption was categorized based on a previously validated scale (Kloner & Rezkalla, 2007). Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB) use were merged into one variable. Percent target dose achieved for ACEIs/ARBs, beta-blockers, and aldosterone antagonists were calculated as previously described (Wang et al., 2016). The time from diagnosis to CRT was measured from the date of the first imaging modality to reveal an LVEF $\leq 35\%$ to the date of CRT implant. Δ QRS was the change in QRS duration during the CRT implant visit, defined as the difference between the CRT-paced and the LBBB QRS durations.

LVEF was determined from transthoracic echocardiography using biplane Simpson's method and Teichholz's formula and confirmed by board-certified cardiologists. When reported as a range, the midpoint was assigned (i.e., 32.5 for LVEF reported as 30%–35%). Additional parameters recorded included LV end-diastolic dimension, LV end-systolic dimension, and left atrial dimensions. These were indexed to body surface area, using the Mosteller formula (Lang et al., 2015; Mosteller, 1987).

The primary outcome was myocardial recovery after CRT. It was defined as a "post-CRT LVEF" measurement of $\geq 50\%$ on the most recent transthoracic echocardiogram. This threshold represents normalization of LVEF (Yancy et al., 2013). The LVEF measurement after optimal GDMT and immediately prior to CRT was designated the "post-GDMT LVEF". For descriptive purposes, we calculated the difference between post-CRT LVEF and post-GDMT LVEF, or Δ LVEF_{CRT}. A threshold of Δ LVEF_{CRT} $\geq 15\%$ approximates a previously reported metric for super-response (Hsu et al., 2012).

The primary clinical outcome was a composite of adverse clinical events that included HF hospitalization, appropriate implantable cardioverter-defibrillator (ICD) shock, appropriate anti-tachycardia pacing (ATP) therapy, ventricular assist device implantation, heart transplantation, and death. The secondary clinical outcome was all-cause mortality. Time to clinical outcome events was measured from the date of CRT implantation.

TABLE 1 Baseline characteristics by post-CRT LVEF

	Total (n = 105)	Post-CRT LVEF <50% (n = 49)	Post-CRT LVEF ≥50% (n = 56)	p Value ^a
Age at diagnosis (years)	60.9 ± 12.6	62.3 ± 13.6	59.6 ± 11.5	0.26
Sex				
Male	46 (43.8)	21 (42.9)	25 (44.6)	0.85
Female	59 (56.1)	28 (57.1)	31 (55.4)	
Race/ethnicity				
White	99 (94.3)	44 (89.8)	55 (98.2)	0.06
African American	6 (5.7)	5 (10.2)	1 (1.8)	
Body mass index (kg/m ²)	30.2 ± 6.6	29.5 ± 5.8	30.8 ± 7.1	0.30
NYHA class				
II	19 (18.1)	10 (20.4)	9 (16.1)	0.56
III	85 (81.0)	39 (79.6)	46 (82.1)	
IV	1 (1.0)	0 (0.0)	1 (1.8)	
Heart rate (bpm)	72.6 ± 11.9	75.6 ± 12.0	70.0 ± 11.3	0.02
QRS duration (ms)	164 ± 17	164 ± 18	164 ± 16	0.94
LVEF (%)	22.6 ± 6.6	22.5 ± 6.8	22.7 ± 6.6	0.91
LVEDD Index (cm/m ²)	3.2 ± 0.6	3.3 ± 0.5	3.2 ± 0.6	0.24
LVESD Index (cm/m ²)	2.7 ± 0.6	2.9 ± 0.5	2.6 ± 0.7	0.07
LA Index (cm/m ²)	2.2 ± 0.4	2.3 ± 0.4	2.2 ± 0.4	0.62
Systolic blood pressure (mmHg)	126 ± 18	125 ± 18	128 ± 18	0.43
Serum sodium level (mmol/L)	139 ± 3	139 ± 4	139 ± 3	0.80
Serum blood urea nitrogen level (mg/dl)	18.7 ± 8.3	21.1 ± 8.7	16.6 ± 7.4	0.005
Serum creatinine level (mg/dl)	1.05 ± 0.56	1.08 ± 0.48	1.02 ± 0.62	0.61
Coronary angiography				
Yes	101 (96.2)	46 (93.9)	55 (98.2)	0.25
No	4 (3.8)	3 (6.1)	1 (1.8)	
Hypertension	54 (51.4)	33 (67.3)	21 (37.5)	0.002
Hyperlipidemia	40 (38.1)	22 (44.9)	18 (32.1)	0.18
Diabetes	29 (27.6)	18 (36.7)	11 (19.6)	0.051
Atrial fibrillation	5 (4.8)	3 (6.1)	2 (3.6)	0.54
Atrial flutter	2 (1.9)	0 (0.0)	2 (3.6)	0.18
Stroke or transient ischemic attack	7 (6.7)	1 (2.0)	6 (10.7)	0.08
Peripheral vascular disease	0 (0.0)	0 (0.0)	0 (0.0)	NA
Chronic obstructive pulmonary disease	8 (7.6)	4 (8.2)	4 (7.1)	0.84
Obstructive sleep apnea	7 (6.7)	3 (6.1)	4 (7.1)	0.83
End-stage renal disease	1 (1.0)	0 (0.0)	1 (1.8)	0.35
Depression	11 (10.5)	6 (12.2)	5 (8.9)	0.58
Smoking				
Never	54 (51.4)	26 (53.1)	28 (50.0)	0.73
Current	13 (12.4)	7 (14.3)	6 (10.7)	
Former	38 (36.2)	16 (32.7)	22 (39.3)	

(Continues)

2.3 | Statistical methods

Descriptive data were presented by post-CRT LVEF group (<50% vs. ≥50%). Categorical variables were presented as frequencies

and percentages with comparisons using chi-square or Fisher's exact tests as appropriate. Continuous variables were presented as mean and standard deviation with comparisons using Student's t tests. Select variables were presented as median and interquartile

TABLE 1 (Continued)

	Total (n = 105)	Post-CRT LVEF <50% (n = 49)	Post-CRT LVEF ≥50% (n = 56)	p Value ^a
Alcohol use				
None	49 (46.7)	23 (46.9)	26 (46.4)	0.74
Light or moderate	47 (44.8)	21 (42.9)	26 (46.4)	
Heavy or binge	3 (2.9)	1 (2.0)	2 (3.6)	
Former heavy or binge	6 (5.7)	4 (8.2)	2 (3.6)	

Notes. CRT: cardiac resynchronization therapy; LA: left atrial; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; NA: not applicable; NYHA: New York Heart Association.

Values are mean ± SD or n (%).

^aPost-CRT LVEF <50% group vs. post-CRT LVEF ≥50% group.

range (IQR) with comparisons using Wilcoxon–Mann–Whitney tests.

Logistic regression was used to estimate the odds ratios (ORs) between subject characteristics and post-CRT LVEF ≥50% vs. <50%. Time-to-event outcomes were summarized using Kaplan–Meier survival curves. Cox regression was used to estimate the hazard ratios (HRs) between groups for adverse clinical events and all-cause mortality. Multivariate analyses were performed, adjusting sequentially for potential confounders. We did not assign a value for “significance” for *p* values, as suggested by the American Statistical Association, but recognize the traditional threshold of *p* < 0.05 (Wasserstein & Lazar, 2016). Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary NC).

3 | RESULTS

In the NEOLITH II study, 105 of 123 (85%) subjects had post-CRT LVEF measurements and were included in the present study (Wang, Li, et al., 2018). The baseline characteristics of the final cohort and by post-CRT LVEF group are presented in Table 1. Characteristics of the 18

excluded subjects included mean age 71.6 ± 12.5 years, 9 (50%) male, 14 (78%) with history of hypertension, 14 (78%) with cardiac catheterization, and 13 (72%) with time from diagnosis to CRT >9 months. All subjects were in sinus rhythm at the time of CRT implant.

Myocardial recovery, or post-CRT LVEF ≥50%, was observed in 56 (53%) subjects. LBBB with QRS duration ≥150 ms prior to CRT was present in 45 (80%) in the post-CRT LVEF ≥50% group and 39 (80%) in the post-CRT LVEF <50% group (*p* = 0.92). “Strict” LBBB was present in 54 (96%) in the post-CRT LVEF ≥50% group and 45 (92%) in the post-CRT LVEF <50% group (*p* = 0.80). The median time from CRT to post-CRT LVEF measurement was 60.3 (IQR, 38.4–87.4) months for the post-CRT LVEF ≥50% and 41.2 (IQR, 17.9–89.8) months for the post-CRT LVEF <50% group.

Within the post-CRT LVEF <50% group, 24 (49%) had a post-CRT LVEF ≤35% and 25 (51%) had a post-CRT LVEF >35% and <50%. The absolute change in LVEF from before to after CRT ($\Delta\text{LVEF}_{\text{CRT}}$) of ≥15%, or 15 LVEF percentage points, was observed in 75 (71%) subjects (Figure 1).

Cardiovascular medications received at the time of CRT implant are listed in Table 2. ACEIs/ARBs included lisinopril (*n* = 56), enalapril (*n* = 7), quinapril (*n* = 5), ramipril (*n* = 1), captopril (*n* = 1), benazepril (*n* = 1), moexipril (*n* = 1), losartan (*n* = 12), valsartan (*n* = 8), irbesartan (*n* = 4), candesartan (*n* = 1), and olmesartan (*n* = 1). Beta-blockers included carvedilol (*n* = 84), carvedilol extended release (*n* = 3), metoprolol succinate (*n* = 6), metoprolol tartate (*n* = 6), atenolol (*n* = 1), and nadolol (*n* = 1). Reasons for not taking ACEI/ARB included low blood pressure (*n* = 3), renal dysfunction (*n* = 2), and unspecified (*n* = 2). Reasons for not taking beta-blockers included symptoms concerning for medications side effects (*n* = 3), low blood pressure (*n* = 1), and unspecified (*n* = 1). Aldosterone antagonists were all spironolactone (*n* = 21). No subjects were taking angiotensin receptor–neprilysin inhibitors or ivabradine.

CRT characteristics are listed in Table 2. Transvenous LV lead placement was achieved in 102 (97.1%) subjects; 3 (2.9%) received epicardial leads. The distribution of transvenous leads was similar between groups and consisted of 23 quadripolar, 64 bipolar, and 15 unipolar.

FIGURE 1 Distribution of subjects by $\Delta\text{LVEF}_{\text{CRT}}$ or change between post-GDMT LVEF and post-CRT LVEF. The number of subjects per $\Delta\text{LVEF}_{\text{CRT}}$ category are listed above each column. CRT: cardiac resynchronization therapy; GDMT: guideline-directed medical therapy; LVEF: left ventricular ejection fraction, $\Delta\text{LVEF}_{\text{CRT}}$: post-CRT LVEF – post-GDMT LVEF

3.1 | Associations of subject characteristics with myocardial recovery after CRT

Univariable logistic regression analyses are listed on Table 3. Negative associations were observed between post-CRT LVEF ≥50%

TABLE 2 Cardiovascular medications and CRT characteristics

	Total (n = 105)	Post-CRT LVEF <50% (n = 49)	Post-CRT LVEF ≥50% (n = 56)	p Value [*]
Medications				
ACEI/ARB	98 (93.3)	45 (91.8)	53 (94.6)	0.57
Beta-blocker	101 (96.2)	47 (95.9)	54 (96.4)	0.89
Aldosterone antagonist	21 (20.0)	12 (24.5)	9 (16.1)	0.28
Digoxin	23 (21.9)	11 (22.4)	12 (21.4)	0.90
Diuretic	76 (72.4)	35 (71.4)	41 (73.2)	0.84
Antiarrhythmic	0 (0.0)	0 (0.0)	0 (0.0)	NA
Aspirin	54 (51.4)	27 (55.1)	27 (48.2)	0.48
Anticoagulant	11 (10.5)	3 (6.1)	8 (14.3)	0.16
Statin	39 (37.1)	20 (40.8)	19 (33.9)	0.47
Medications, percent target dose achieved for subjects on treatment				
ACEI/ARB ^a	50 (25–100)	50 (16.7–60)	50 (25–100)	0.79
Beta-blocker ^a	43.8 (12.5–50.0)	25.0 (12.5–50.0)	50.0 (25.0–75.0)	0.33
Aldosterone antagonist ^a	100 (100–100)	100 (100–100)	100 (100–100)	0.74
Time from diagnosis to to CRT				
≤9 months	55 (52.4)	21 (42.9)	34 (60.7)	0.07
>9 months	50 (47.6)	28 (57.1)	22 (39.3)	
CRT type				
CRT-defibrillator	103 (98.1)	47 (95.9)	56 (100)	0.13
CRT-pacemaker	2 (1.9)	2 (4.1)	0 (0.0)	
CRT programmed parameters				
Mode				
DDD	96 (91.4)	45 (91.8)	51 (91.1)	0.84
DDDR	7 (6.7)	3 (6.1)	4 (7.1)	
Lower rate limit (bpm) ^b	50 (40,70)	50 (40,70)	50 (40,70)	0.43
Biventricular pacing (%) ^b	99.6 (64.0, 100)	99.4 (64.0, 100)	99.8 (77.0, 100)	0.07
Tachytherapy threshold (bpm) ^b	185 (150, 214)	185 (150, 200)	185 (171, 214)	0.39
ΔQRS duration (ms)	−18 ± 15	−18 ± 15	−19 ± 17	0.80
CRT lead positions				
Left ventricular lead, short axis				
Anterior	13 (12.4)	7 (14.3)	6 (10.7)	0.74
Lateral	64 (61.0)	28 (57.1)	36 (64.3)	
Posterior	28 (26.7)	14 (28.6)	14 (25.0)	
Left ventricular lead, long axis				
Basal	19 (18.1)	10 (20.4)	9 (16.1)	0.74
Mid	57 (54.3)	27 (55.1)	30 (53.6)	
Apical	29 (27.6)	12 (24.5)	17 (30.4)	
Right ventricular lead, long axis				
Apical	92 (87.6)	40 (81.6)	52 (92.9)	0.18
Septal	12 (11.4)	8 (16.3)	4 (7.1)	
Outflow tract	1 (1.0)	1 (2.0)	0 (0)	

Notes. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CRT: cardiac resynchronization therapy; LVEF: left ventricular ejection fraction; NA: not applicable; ΔQRS duration: change from LBBB to CRT-paced in QRS durations.

Values are mean ± SD, n (%).

^aMedian (first quartile-third quartile). ^bMedian (range). ^{*}Post-CRT LVEF <50% group vs. post-CRT LVEF ≥50% group.

TABLE 3 Univariable logistic regression analyses for myocardial recovery after CRT

	Post-CRT LVEF $\geq 50\%$		
	OR	95% CI	p Value
Age at diagnosis	0.98	0.95, 1.01	0.26
Sex (male vs. female)	1.08	0.50, 2.33	0.85
Race/ethnicity (African American vs. white)	0.16	0.02, 1.42	0.10
Body mass index	1.03	0.97, 1.10	0.30
NYHA class (III/IV vs. II)	1.34	0.49, 3.62	0.57
Heart rate, per 10 bpm	0.66	0.46, 0.93	0.02
QRS duration	1.00	0.98, 1.02	0.94
LVEF	1.00	0.95, 1.06	0.91
LVEDD Index	0.65	0.31, 1.35	0.25
LA Index	0.76	0.26, 2.22	0.61
Systolic blood pressure	1.01	0.99, 1.03	0.43
Serum sodium level	1.02	0.90, 1.15	0.80
Serum blood urea nitrogen level	0.93	0.88, 0.98	0.008
Serum creatinine level	0.83	0.41, 1.69	0.61
Hypertension	0.29	0.13, 0.65	0.003
Hyperlipidemia	0.58	0.26, 1.29	0.18
Diabetes	0.42	0.17, 1.01	0.054
Stroke or transient ischemic attack	5.76	0.67, 49.59	0.11
Chronic obstructive pulmonary disease	0.87	0.20, 3.66	0.84
Obstructive sleep apnea	1.18	0.25, 5.55	0.84
Depression	0.70	0.20, 2.46	0.58
Smoking			
Never	Reference		
Current	0.80	0.24, 2.68	0.71
Former	1.28	0.55, 2.95	0.57
Alcohol use			
None	Reference		
Light or moderate	1.10	0.49, 2.45	0.82
Heavy or binge	1.77	0.15, 20.81	0.65
Former heavy or binge	0.44	0.07, 2.64	0.37
ACEI/ARB	1.57	0.33, 7.39	0.57
Beta-blocker	1.15	0.16, 8.48	0.89
Aldosterone antagonist	0.59	0.22, 1.55	0.29
Digoxin	0.94	0.37, 2.38	0.90
Diuretic	1.09	0.46, 2.58	0.84
Aspirin	0.76	0.35, 1.64	0.48
Anticoagulant	2.61	0.65, 10.46	0.18
Statin	0.74	0.34, 1.65	0.47
Δ QRS duration	1.00	0.97, 1.02	0.80
Time from diagnosis to CRT (>9 vs. ≤ 9 months)	0.48	0.22, 1.05	0.07

Note. ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CI: confidence interval; CRT: cardiac resynchronization therapy; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; NYHA = New York Heart Association; OR: odds ratio.

and hypertension (OR, 0.29; 95% confidence interval (CI), 0.13–0.65; $p = 0.003$), heart rate (OR per 10 bpm, 0.66; 95% CI, 0.46–0.93; $p = 0.02$), and serum BUN (OR per 1 mg/dl, 0.93; 95% CI, 0.88–0.98;

$p = 0.008$). Diabetes had a moderately negative association with post-CRT LVEF $\geq 50\%$ (OR, 0.42; 95% CI, 0.17–1.01; $p = 0.054$). Time from diagnosis to CRT, >9 months compared to ≤ 9 months, was

TABLE 4 Multivariable logistic regression analyses for myocardial recovery after CRT

	Post-CRT LVEF $\geq 50\%$		
	OR	95% CI	p Value
Model 1			
Hypertension	0.44	0.18, 1.06	0.07
Diabetes	0.69	0.26, 1.82	0.45
Heart rate, per 10 bpm	0.71	0.49, 1.03	0.07
Serum blood urea nitrogen	0.94	0.89, 0.99	0.04
Model 2			
Hypertension	0.40	0.17, 0.95	0.04
Heart rate, per 10 bpm	0.69	0.47, 0.997	0.048
Serum blood urea nitrogen	0.94	0.88, 0.99	0.04
Model 3			
Diabetes	0.55	0.21, 1.39	0.21
Heart rate, per 10 bpm	0.69	0.47, 0.99	0.045
Serum blood urea nitrogen	0.93	0.88, 0.98	0.01

Note. CI: confidence interval; CRT: cardiac resynchronization therapy; LVEF: left ventricular ejection fraction; OR: odds ratio.

nonsignificantly associated with post-CRT LVEF $\geq 50\%$ (OR, 0.48; 95% CI, 0.22–1.05; $p = 0.07$).

Multivariable logistic regression analyses are listed in Table 4. Multicollinearity was apparent when hypertension and diabetes were analyzed in the same model (model 1). Therefore, hypertension and diabetes were analyzed in separate models, models 2 and 3, respectively. Our final model included hypertension, heart rate, and serum BUN (model 2). Associations observed in univariable analyses persisted in the final multivariable model.

3.2 | Clinical outcomes

The median follow-up time was 75.9 (IQR, 40.8–109.0) months for the entire cohort. Subjects with post-CRT LVEF $\geq 50\%$ had lower risk for adverse clinical events when compared to those with post-CRT LVEF $< 50\%$ (HR, 0.38; 95% CI, 0.16–0.88; $p = 0.02$; Figure 2). This effect was driven primarily by greater risk of appropriate ICD shocks and appropriate ATP therapies in the post-CRT LVEF $< 50\%$ group. Adverse clinical events are listed in Table 5.

The post-CRT LVEF $\geq 50\%$ group had similar risk for all-cause mortality when compared to the post-CRT LVEF $< 50\%$ group (HR, 0.55; 95% CI, 0.16–1.82; $p = 0.33$) (Figure 3). The estimated 5-year mortality was 4.0% in the LVEF $\geq 50\%$ group and 7.4% in the LVEF $< 50\%$ group.

4 | DISCUSSION

This analysis from the NEOLITH II study is the first to assess predictors of myocardial recovery, or post-CRT LVEF $\geq 50\%$, after CRT in

subjects with LBBB confirmed at the time of initial diagnosis of idiopathic NICM. Over half in our study experienced normalization of LVEF. Hypertension, higher heart rate, and higher serum BUN were negatively associated with myocardial recovery. LVEF normalization after CRT was associated with fewer adverse clinical events. These findings may lend insight into pathophysiologic processes underlying LBBB-associated NICM, provide outcome data to assist in directing patient care, and identify areas of future investigation.

There is increasing evidence that LBBB-induced cardiomyopathy is a distinct clinical entity. A proposed definition included normalization of LVEF after CRT as a criterion (Vaillant et al, 2013). Our results suggest that approximately half who met the inclusion and exclusion criteria of the NEOLITH II study have LBBB-induced cardiomyopathy. Subjects who achieved myocardial recovery had significantly fewer adverse clinical events than those who did not. This population has limited response to GDMT alone and has high postdischarge event rates after HF hospitalization (Sze et al., 2018; Wang et al., 2008, 2016). Not only does CRT appear to be critical in the optimal treatment of these patients, but earlier implant may also confer additional beneficial (Wang, Li, et al., 2018). Time from diagnosis to CRT was not significantly associated with myocardial recovery in the present analysis, but this may be related to our modest sample size.

The favorable results we observed provide additional evidence that switching from CRT-defibrillators to CRT pacemakers may be reasonable in those without prior appropriate ICD therapies. Thus, ICD leads with IS-1 connectors are preferred in current generation CRT-defibrillator systems (Sticherling & Burri, 2012). The high percentage of myocardial recovery and low associated rates of adverse clinical events may have contributed to the lack of survival benefit in the Danish Study to Assess the Efficacy of ICDs in Patients with Nonischemic Systolic Heart Failure on Mortality given the high rate of LBBB and CRT in the study population (Køber et al., 2016). In fact, blanket use of ICDs in NICM patients who receive CRT is questionable (Golwala, Bajaj, Arora, & Arora, 2017). Larger LV end-diastolic dimension prior to CRT implant and LV midwall fibrosis may be useful risk stratification tools to recommend CRT-defibrillators over CRT pacemakers (Adelstein et al., 2017; Leyva et al., 2012).

An analysis from the Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy utilized an increase in LVEF percentage points of 14.5% or greater as a metric for CRT super-response (Hsu et al., 2012). In this heterogeneous population, 25% achieved this level of improvement. Nearly three-fourths in our study had an increase in LVEF percentage points of 15 or greater. This wide variation of responses emphasizes the need to perform dedicated studies in specific phenotypes. It is also of note that 10% in our study had no improvement in LVEF. Further research is needed in these subjects who, despite having characteristics favoring good response to CRT, did not derive any benefit.

A higher rate of hypertension among CRT recipients who did not achieve myocardial recovery may indicate the coexistence of hypertensive cardiomyopathy. It has been theorized that hypertensive

FIGURE 2 Kaplan-Meier curve for probability of survival from adverse clinical events after CRT by myocardial recovery status, or post-CRT LVEF $\geq 50\%$. Subjects with myocardial recovery had lower risk for adverse clinical events compared to those without myocardial recovery. CRT: cardiac resynchronization therapy; LVEF: left ventricular ejection fraction

	Total (n = 105)	Post-CRT LVEF < 50% (n = 49)	Post-CRT LVEF $\geq 50\%$ (n = 56)	p Value*
Any event ^a , n (%)	24 (22.9)	15 (30.6)	9 (16.1)	0.08
All events				
HF hospitalization, n (%)	12 (11.4)	8 (16.3)	4 (7.1)	0.15
Appropriate ICD shock, n (%)	7 (6.7)	6 (12.2)	1 (1.8)	0.03
Appropriate ATP therapy, n (%)	5 (4.8)	4 (8.2)	1 (1.8)	0.13
Ventricular assist device implantation, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Heart transplantation, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	NA
Death, n (%)	11 (10.5)	6 (12.2)	5 (8.9)	0.58

Notes. ATP: anti-tachycardia pacing; CRT: cardiac resynchronization therapy; HF: heart failure; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; NA: not applicable. Values are n (%).

^aOnly the first event per subject was counted. *Post-CRT LVEF < 50% group vs. post-CRT LVEF $\geq 50\%$ group.

TABLE 5 Adverse clinical events by post-CRT LVEF

dilated cardiomyopathy may occur without interval concentric hypertrophy (Garg & Drazner, 2016). A study in hypertensive patients with normal coronary angiography demonstrated late gadolinium enhancement suggesting microvascular disease and fibrosis (Andersen et al., 2009). Midwall fibrosis in CRT recipients with NICM has been associated with poor remodeling and clinical outcomes (Leyva et al., 2012). Subjects in our study who did and did not achieve myocardial recovery had similar systolic blood pressure at the time of CRT implantation. Yet, we cannot exclude prior damage from a period of unchecked hypertension. Fibrosis quantity and patterns on cardiac magnetic resonance imaging may play a role in differentiating pure LBBB-induced cardiomyopathy from mixed LBBB-induced and hypertensive cardiomyopathy.

The relationship between elevated heart rate and worse prognosis in chronic HF with reduced LVEF has been described (Lechat et al., 2001). Reduction in heart rate is one benefit ascribed to beta-blockade (Vukadinović et al., 2017). Although maximal titration of beta-blockers is recommended, additional heart rate reduction through inhibition of the I_f current by ivabradine results in added risk reduction of HF events (Fiuzat et al., 2016; Swedberg et al., 2010; Yancy et al., 2013). CRT decreases heart rate within months of implant and may allow higher doses of beta-blockers to be administered due to increases in systolic blood pressure (Biton et al., 2015; Fantoni et al., 2005). The additional benefit of ivabradine in CRT recipients is unclear given lack of representation in the Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (Swedberg et al., 2010).

FIGURE 3 Kaplan–Meier curve for probability of survival from all-cause mortality after CRT by myocardial recovery status, or post-CRT LVEF $\geq 50\%$. Subjects with myocardial recovery had similar risk for all-cause mortality compared to those without myocardial recovery. CRT: cardiac resynchronization therapy; LVEF: left ventricular ejection fraction

Ivabradine has been associated with further increase in LVEF in subjects with coronary artery disease, reduced LVEF, and high use of beta-blockers (Ceconi et al., 2011). Thus, higher heart rate in those who did not have myocardial recovery in our study may represent a target for beta-blocker optimization and I_f current inhibition.

Elevated serum BUN concentration is a surrogate marker for renal neurohormonal activation in HF (Testani, Cappola, Brensinger, Shannon, & Kimmel, 2011). BUN increases are related to complex mechanisms involving increased renin–angiotensin–aldosterone system activity, increased sympathetic nervous system activity, and higher levels of arginine vasopressin (Kazory, 2010). In patients with reduced LVEF who are hospitalized with decompensated HF, elevated baseline serum BUN is associated with higher postdischarge mortality that may be related to use of high-dose loop diuretics (Filippatos et al., 2007; Testani et al., 2011). Different combinations of neurohormonal antagonism may have different effects on cardiac remodeling (McKelvie et al., 2003). Given the association between loop diuretics and adverse outcomes in those with elevated serum BUN, alternative agents such as vasopressin V2 receptor antagonists, may be more beneficial toward LVEF improvement in select HF patients (Jujo et al., 2016).

Technological evolution of CRT may lead to even greater recovery rates. The recent development of quadripolar transvenous LV leads has allowed for more pacing vectors. Compared to bipolar leads, quadripolar leads have been associated with decreased risk of death and HF hospitalization (Leyva et al., 2017; Turakhia et al., 2016). Potential reasons include fewer re-interventions for LV lead migration and premature battery drain from high capture threshold. Additional vectors may also allow optimization of the QLV interval, which has been associated with improved reverse remodeling (Gold et al., 2011). Only 22% of our study population had quadripolar leads.

Delivery of current transvenous LV leads is limited by venous anatomy. Nonresponders may benefit from wireless LV endocardial pacing electrodes that are in development (Reddy et al., 2017).

Permanent His-bundle pacing is a theoretically attractive option for “true” electrical resynchronization in LBBB-associated NICM (Ajiola, Upadhyay, Macias, Shivkumar, & Tung, 2017; Narula, 1977; Teng, Massoud, & Ajiola, 2016). It is currently limited by modest rates of successful implantation. A recent multicenter study also reported a 7% rate of late increase in capture threshold that resulted in loss of electrical resynchronization and/or increased battery drain (Sharma et al., 2018). Long-term data are needed to assess progression of conduction system disease distal to the His-bundle electrode. Conventional CRT with quadripolar LV leads should be the current preferred system with permanent His-bundle pacing reserved as a bailout strategy for failed or suboptimal transvenous LV lead delivery.

4.1 | Study strengths and limitations

The primary strength of the study was rigorous selection of subjects. A notable feature of the NEOLITH and NEOLITH II studies was the requirement of LBBB at the time of initial diagnosis of NICM (Wang et al., 2016; Wang, Li, et al., 2018). Subjects with other potential contributing causes to cardiomyopathy were excluded. This increased the likelihood that many had pure LBBB-induced cardiomyopathy (Wang, Adelstein, Singh, Voigt, & Saba, 2018).

Our study was retrospective and therefore hypothesis-generating. Multicenter prospective studies are needed to confirm our findings. Not all NEOLITH II study subjects had follow-up echocardiograms. Nevertheless, if all 18 subjects excluded for lacking follow-up LVEF measurements were considered nonresponders, myocardial recovery would still have been seen in 46%. Our population was almost entirely of white race/ethnicity. While we only had six African American subjects, they appeared less likely to achieve myocardial recovery. GDMT and CRT programming were not standardized. We did not have uniform time from CRT to follow-up LVEF measurement, yet the median time in both groups was well over

1 year. Therefore, we expect maximum CRT response to have been achieved in both groups. There was no core laboratory for LVEF measurements.

5 | CONCLUSIONS

In LBBB-associated idiopathic NICM, approximately half achieved myocardial recovery after CRT. These subjects had fewer adverse clinical events when compared to those without the same level of improvement. Myocardial recovery after CRT was associated with absence of hypertension, lower baseline heart rate, and lower serum BUN. These findings suggest a high proportion of those with LBBB-associated idiopathic NICM have pure LBBB-induced cardiomyopathy, provide data to optimize patient care, and identify areas for future research.

DISCLOSURES

Dr. Wang has received research support from Boston Scientific and fellowship support from Abbott and Medtronic. Dr. Adelstein has received research support from Abbott and Medtronic. Dr. Jain has received research support from Medtronic. Dr. Saba serves as an unpaid consultant for and has received research support from Abbott, Boston Scientific, and Medtronic. The remaining authors reported no conflicts of interest.

ORCID

Norman C. Wang <http://orcid.org/0000-0002-8388-2146>

REFERENCES

- Adelstein, E. C., Schwartzman, D., Jain, S., Bazaz, R., Wang, N. C., & Saba, S. (2017). Left ventricular dimensions predict risk of appropriate shocks but not mortality in cardiac resynchronization therapy-defibrillator recipients with left bundle-branch block and non-ischemic cardiomyopathy. *EP Europace*, 19(10), 1689–1694. <https://doi.org/10.1093/europace/euw323>
- Ajila, O. A., Upadhyay, G. A., Macias, C., Shivkumar, K., & Tung, R. (2017). Permanent His-bundle pacing for cardiac resynchronization therapy: Initial feasibility study in lieu of left ventricular lead. *Heart Rhythm: the Official Journal of the Heart Rhythm Society*, 14(9), 1353–1361. <https://doi.org/10.1016/j.hrthm.2017.04.003>
- Andersen, K., Hennersdorf, M., Cohnen, M., Blondin, D., Mödder, U., & Poll, L. W. (2009). Myocardial delayed contrast enhancement in patients with arterial hypertension: Initial results of cardiac MRI. *European Journal of Radiology*, 71(1), 75–81. <https://doi.org/10.1016/j.ejrad.2008.03.009>
- Basuray, A., French, B., Ky, B., Vorovich, E., Olt, C., Sweitzer, N. K., ... Fang, J. C. (2014). Heart failure with recovered ejection fraction: Clinical description, biomarkers, and outcomes. *Circulation*, 129(23), 2380–2387. <https://doi.org/10.1161/CIRCULATIONAHA.113.006855>
- Biton, Y., Moss, A. J., Kutiyifa, V., Mathias, A., Sherazi, S., Zareba, W., ... Goldenberg, I. (2015). Inverse relationship of blood pressure to long-term outcomes and benefit of cardiac resynchronization therapy in patients with mild heart failure: A Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy (MADIT-CRT) long-term follow-up substudy. *Circulation: Heart Failure*, 8(5), 921–926. <https://doi.org/10.1161/CIRCHEARTFAILURE.115.002208>
- Cecconi, C., Freedman, S. B., Tardif, J. C., Hildebrandt, P., McDonagh, T., Gueret, P., ... BEAUTIFUL Echo-BNP Investigators. (2011). Effect of heart rate reduction by ivabradine on left ventricular remodeling in the echocardiographic substudy of BEAUTIFUL. *International Journal of Cardiology*, 146(3), 408–414. <https://doi.org/10.1016/j.ijcard.2010.10.125>
- Fantoni, C., Raffa, S., Regoli, F., Giralaldi, F., La Rovere, M. T., Prentice, J., ... Auricchio, A. (2005). Cardiac resynchronization therapy improves heart rate profile and heart rate variability of patients with moderate to severe heart failure. *Journal of the American College of Cardiology*, 46(10), 1875–1882. <https://doi.org/10.1016/j.jacc.2005.06.081>
- Filippatos, G., Rossi, J., Lloyd-Jones, D. M., Stough, W. G., Ouyang, J., Shin, D. D., ... Gheorghiade, M. (2007). Prognostic value of blood urea nitrogen in patients hospitalized with worsening heart failure: Insights from the Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Chronic Heart Failure (ACTIV in CHF) study. *Journal of Cardiac Failure*, 13(5), 360–364. <https://doi.org/10.1016/j.cardfail.2007.02.005>
- Fiuza, M., Wojdyla, D., Pina, I., Adams, K., Whellan, D., & O'Connor, C. M. (2016). Heart rate of beta-blocker dose? Association with outcomes in ambulatory heart failure patients with systolic dysfunction: Results from the HF-ACTION trial. *Journal of the American College of Cardiology: Heart Failure*, 4(2), 109–115. <https://doi.org/10.1016/j.jchf.2015.09.002>
- Garg, S., & Drazner, M. H. (2016). Refining the classification of left ventricular hypertrophy to provide new insights into the progression from hypertension to heart failure. *Current Opinion in Cardiology*, 31(4), 387–393. <https://doi.org/10.1097/HCO.0000000000000299>
- Gold, M. R., Birgersdotter-Green, U., Singh, J. P., Ellenbogen, K. A., Yu, Y., Meyer, T. E., ... Tchou, P. J. (2011). The relationship between ventricular electrical delay and left ventricular remodeling with cardiac resynchronization therapy. *European Heart Journal*, 32(20), 2516–2524. <https://doi.org/10.1093/eurheartj/ehr329>
- Golwala, H., Bajaj, N. S., Arora, G., & Arora, P. (2017). Implantable cardioverter-defibrillator for nonischemic cardiomyopathy: An updated meta-analysis. *Circulation*, 135(2), 201–203. <https://doi.org/10.1161/CIRCULATIONAHA.116.026056>
- Hsu, J., Solomon, S. D., Bourgoun, M., McNitt, S., Goldenberg, I., Klein, H., ... MADIT-CRT Executive Committee (2012). Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) study. *Journal of the American College of Cardiology*, 59(25), 2366–2373. <https://doi.org/10.1016/j.jacc.2012.01.065>
- Jujo, K., Saito, K., Ishida, I., Furuki, Y., Kim, A., Suzuki, Y., ... Hagiwara, N. (2016). Randomized pilot trial comparing tolvaptan with furosemide on renal and neurohumoral effects in acute heart failure. *ESC Heart Failure*, 3(3), 177–188. <https://doi.org/10.1002/ehf2.12088>
- Kazory, A. (2010). Emergence of blood urea nitrogen as a biomarker of neurohormonal activation in heart failure. *American Journal of Cardiology*, 106(5), 694–700. <https://doi.org/10.1016/j.amjcard.2010.04.024>
- Kloner, R. A., & Rezkalla, S. H. (2007). To drink or not to drink? That is the Question. *Circulation*, 116(11), 1306–1317. <https://doi.org/10.1161/CIRCULATIONAHA.106.678375>
- Køber, L., Thune, J. J., Nielsen, J. C., Haarbo, J., Videbæk, L., Korup, E., ... for the DANISH Investigators (2016). Defibrillator implantation in patients with nonischemic systolic heart failure. *New England Journal of Medicine*, 375(3), 1221–1230. <https://doi.org/10.1056/NEJMoa1608029>

- Lang, R. M., Badano, L. P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L., ... Voigt, J. U. (2015). Recommendations for cardiac chamber quantification by echocardiography in adults: An update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Journal of the American Society of Echocardiography*, 28(1), 1–39.e14. <https://doi.org/10.1016/j.echo.2014.10.003>
- Lechat, P., Hulot, J. S., Escolano, S., Mallet, A., Leizorovicz, A., Werhlen-Grandjean, M., ... Dargie, H. (2001). Heart rate and cardiac rhythm relationships with bisoprolol benefit in chronic heart failure in the CIBIS II trial. *Circulation*, 103(10), 1428–1433. <https://doi.org/10.1161/01.CIR.103.10.1428>
- Leyva, F., Taylor, R. J., Foley, P. W. X., Umar, F., Mulligan, L. J., Patel, K., ... Prasad, S. K. (2012). Left ventricular midwall fibrosis as a predictor of mortality and morbidity after cardiac resynchronization therapy in patients with nonischemic cardiomyopathy. *Journal of the American College of Cardiology*, 60(17), 1659–1667. <https://doi.org/10.1016/j.jacc.2012.05.054>
- Leyva, F., Zegard, A., Qiu, T., Acquaye, E., Ferrante, G., Walton, J., & Marshall, H. (2017). Cardiac resynchronization therapy using quadripolar versus non-quadripolar left ventricular leads programmed to biventricular pacing with single-site left ventricular pacing: Impact on survival and heart failure hospitalization. *Journal of the American Heart Association*, 6(10), e007026. <https://doi.org/10.1161/JAHA.117.007026>
- Mann, D. L., Barger, P. M., & Burkoff, D. (2012). Myocardial recovery and the failing heart: Myth, magic, or molecular target? *Journal of the American College of Cardiology*, 60(24), 2465–2472. <https://doi.org/10.1016/j.jacc.2012.06.062>
- McKelvie, R. S., Rouleau, J. L., White, M., Afzal, R., Young, J. B., Maggioni, A. P., ... Yusuf, S. (2003). Comparative impact of enalapril, candesartan or metoprolol alone or in combination on ventricular remodeling in patients with congestive heart failure. *European Heart Journal*, 24(19), 1727–1734. [https://doi.org/10.1016/S0195-668X\(03\)00477-9](https://doi.org/10.1016/S0195-668X(03)00477-9)
- Mosteller, R. D. (1987). Simplified calculation of body-surface area. *New England Journal of Medicine*, 317, 1098. <https://doi.org/10.1056/NEJM198710223171717>
- Narula, O. S. (1977). Longitudinal dissociation in the His bundle: Bundle branch block due to asynchronous conduction within the His bundle in man. *Circulation*, 56(6), 996–1006. <https://doi.org/10.1161/01.CIR.56.6.996>
- Reddy, V. Y., Miller, M. A., Neuzil, P., Søgaard, P., Butter, C., Seifert, M., ... Riahi, S. (2017). Cardiac resynchronization therapy with wireless left ventricular endocardial pacing: The SELECT-LV study. *Journal of the American College of Cardiology*, 69(17), 2119–2129. <https://doi.org/10.1016/j.jacc.2017.02.059>
- Ruwald, M. H., Solomon, S. D., Foster, E., Kutyla, V., Ruwald, A. C., Sherazi, S., ... Zareba, W. (2014). 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*, 130(25), 2278–2286. <https://doi.org/10.1161/CIRCULATIONAHA.114.011283>
- Sharma, P. S., Dandamudi, G., Herweg, B., Wilson, D., Singh, R., Napierkowski, A., ... Vijayaraman, P. (2018). Permanent His-bundle pacing as an alternative to biventricular pacing for cardiac resynchronization therapy: A multicenter experience. *Heart Rhythm: the Official Journal of the Heart Rhythm Society*, 15(3), 413–420. <https://doi.org/10.1016/j.hrthm.2017.10.014>
- Steffel, J., & Ruschitzka, F. (2014). Superresponse to cardiac resynchronization therapy. *Circulation*, 130(1), 87–90. <https://doi.org/10.1161/CIRCULATIONAHA.113.006124>
- Sticherling, C., & Burri, H. (2012). Introduction of new industry standards for cardiac implantable electronic devices: Balancing benefits and unexpected risks. *Europace*, 14(8), 1081–1086. <https://doi.org/10.1093/europace/eus034>
- Strauss, D. G., Selvester, R. H., & Wagner, G. S. (2011). Defining left bundle branch block in the era of cardiac resynchronization therapy. *American Journal of Cardiology*, 107(6), 927–934. <https://doi.org/10.1016/j.amjcard.2010.11.010>
- Surawicz, B., Childers, R., Deal, B. J., & Gettes, L. S. (2009). AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: Part III: Intraventricular conduction disturbances: A scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. *Journal of the American College of Cardiology*, 53(11), 976–981. <https://doi.org/10.1016/j.jacc.2008.12.013>
- Swedberg, K., Komajda, M., Böhm, M., Borer, J. S., Ford, I., Dubost-Brama, A., ... on behalf of the SHIFT Investigators (2010). Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. *Lancet*, 376(9744), 875–885. [https://doi.org/10.1016/S0140-6736\(10\)61198-1](https://doi.org/10.1016/S0140-6736(10)61198-1)
- Sze, E., Samad, Z., Dunning, A., Campbell, K. B., Loring, Z., Atwater, B. D., ... Daubert, J. P. (2018). Impaired recovery of left ventricular function in patients with cardiomyopathy and left bundle branch block. *Journal of the American College of Cardiology*, 71(3), 306–317. <https://doi.org/10.1016/j.jacc.2017.11.020>
- Teng, A. E., Massoud, L., & Ajjola, O. A. (2016). Physiological mechanisms of QRS narrowing in bundle branch block patients undergoing permanent His bundle pacing. *Journal of Electrocardiology*, 49(5), 644–648. <https://doi.org/10.1016/j.jelectrocard.2016.07.013>
- Testani, J. M., Cappola, T. P., Brensinger, C. M., Shannon, R. P., & Kimmel, S. E. (2011). Interaction between loop diuretic-associated mortality and blood urea nitrogen concentration in chronic heart failure. *Journal of the American College of Cardiology*, 58(4), 375–382. <https://doi.org/10.1016/j.jacc.2011.01.052>
- Turakhia, M. P., Cao, M., Fischer, A., Nabutovsky, Y., Sloman, L. S., Dalal, N., & Gold, M. R. (2016). Reduced mortality associated with quadripolar compared to bipolar left ventricular leads in cardiac resynchronization therapy. *JACC: Clinical Electrophysiology*, 2(4), 426–433. <https://doi.org/10.1016/j.jacep.2016.02.007>
- Vaillant, C., Martins, R. P., Donal, E., Leclercq, C., Thébault, C., Behar, N., ... Daubert, J. C. (2013). Resolution of left bundle branch block-induced cardiomyopathy by cardiac resynchronization therapy. *Journal of the American College of Cardiology*, 61(10), 1089–1095. <https://doi.org/10.1016/j.jacc.2012.10.053>
- Vukadinović, A. N., Vukadinović, D., Borer, J., Cowie, M., Komajda, M., Lainscak, M., ... Böhm, M. (2017). Heart rate and its reduction in chronic heart failure and beyond. *European Journal of Heart Failure*, 19(10), 1230–1241. <https://doi.org/10.1002/ehf.902>
- Wang, N. C., Adelstein, E. C., Singh, M., Voigt, A. H., & Saba, S. (2018). Left bundle branch block-associated cardiomyopathies and early cardiac resynchronization therapy: Conceptualizing a tailored approach. *Journal of the American College of Cardiology*, 71(17), 1943–1944. <https://doi.org/10.1016/j.jacc.2018.02.060>
- Wang, N. C., Li, J. Z., Adelstein, E. C., Althouse, A. D., Sharbaugh, M. S., Jain, S. K., ... Saba, S. (2018). New-onset left bundle branch block-associated nonischemic cardiomyopathy and time from diagnosis to cardiac resynchronization therapy: The NEOLITH II study. *Pacing and Clinical Electrophysiology*, 41(2), 143–154. <https://doi.org/10.1111/pace.13264>
- Wang, N. C., Maggioni, A. P., Konstam, M. A., Zannad, F., Krasa, H. B., Burnett, J. C. J., ... for the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators (2008). Clinical implications of QRS duration in patients hospitalized with worsening heart failure and reduced left ventricular ejection fraction. *JAMA*, 299(22), 2656–2666. <https://doi.org/10.1001/jama.299.22.2656>

- Wang, N. C., Singh, M., Adelstein, E. C., Jain, S. K., Mendenhall, G. S., Shalaby, A. A., ... Saba, S. (2016). New-onset left bundle branch block-associated idiopathic nonischemic cardiomyopathy and left ventricular ejection fraction response to guideline-directed therapies: The NEOLITH study. *Heart Rhythm: the Official Journal of the Heart Rhythm Society*, 13(4), 933–942. <https://doi.org/10.1016/j.hrthm.2015.12.020>
- Wasserstein, R. L., & Lazar, N. A. (2016). The ASA's statement on p-values: Context, process, and purpose. *American Statistician*, 70(2), 129–133. <https://doi.org/10.1080/00031305.2016.1154108>
- Wilcox, J. E., Fonarow, G. C., Ardehali, H., Bonow, R. O., Sauer, A. J., Epstein, S. E., ... Gheorghiade, M. (2015). "Targeting the heart" in heart failure: Myocardial recovery in heart failure with reduced ejection fraction. *Journal of the American College of Cardiology: Heart Failure*, 3(9), 661–669. <https://doi.org/10.1016/j.jchf.2015.04.011>
- Wilton, S. B., Shibata, M. A., Sondergaard, R., Cowan, K., Semeniuk, L., & Exner, D. V. (2008). Relationship between left ventricular lead position using a simple radiographic classification scheme and long-term outcome with resynchronization therapy. *Journal of Interventional Cardiac Electrophysiology*, 23(3), 219–227. <https://doi.org/10.1007/s10840-008-9287-1>
- Yancy, C. W., Jessup, M., Bozkurt, B., Casey, D. E., Jr., Drazner, M. H., Fonarow, G. C., ... Wilkoff, B. L. (2013). 2013 ACCF/AHA guideline for the management of heart failure: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*, 128(16), e240–e327. <https://doi.org/10.1161/CIR.0b013e31829e8776>

How to cite this article: Wang NC, Hussain A, Adelstein EC, et al. Myocardial recovery after cardiac resynchronization therapy in left bundle branch block-associated idiopathic nonischemic cardiomyopathy: A NEOLITH II substudy. *Ann Noninvasive Electrocardiol*. 2019;24:e12603. <https://doi.org/10.1111/anec.12603>