ORIGINAL ARTICLE

Sex-specific clinical outcomes after cardiac resynchronization therapy in left bundle branch block-associated idiopathic nonischemic cardiomyopathy: A NEOLITH II substudy

Norman C. Wang¹ | Ure Mezu-Chukwu¹ | Evan C. Adelstein² | Andrew D. Althouse¹ | Michael S. Sharbaugh¹ | Sandeep K. Jain¹ | Alaa A. Shalaby¹ | Andrew H. Voigt¹ | Samir Saba¹

¹Heart and Vascular Institute, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania

²Albany Medical Center, Albany, New York

Correspondence

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

Abstract

Background: Sex differences in clinical outcomes for left bundle branch block (LBBB)-associated idiopathic nonischemic cardiomyopathy (NICM) after cardiac resynchronization therapy (CRT) are not well described.

Methods: A retrospective cohort study at an academic medical center included subjects with LBBB-associated idiopathic NICM who received CRT. Cox regression analyses estimated the hazard ratios (HRs) between sex and clinical outcomes.

Results: In 123 total subjects (mean age 62 years, mean initial left ventricular ejection fraction 22.8%, 76% New York Heart Association class III, and 98% CRT-defibrillators), 55 (45%) were men and 68 (55%) were women. The median follow-up time after CRT was 72.4 months. Similar 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) was observed between men and women (HR, 1.20; 95% confidence interval [CI] 0.57–2.51; $p = 0.63$). This persisted in multivariable analyses. Men and women had similar risk for all-cause mortality in univariable analysis, but men had higher risk in the final multivariable model that adjusted for age at diagnosis, QRS duration, and left ventricular end-diastolic dimension index (HR, 4.55; 95% CI, 1.26–16.39; $p = 0.02$). The estimated 5-year mortality was 9.5% for men and 6.9% for women.

Conclusions: In LBBB-associated idiopathic NICM, men have higher risk for all-cause mortality after CRT when compared to women.

KEYWORDS

cardiac resynchronization therapy, clinical outcomes, left bundle branch block, nonischemic cardiomyopathy, sex-specific

1 | INTRODUCTION

Cardiac resynchronization therapy (CRT) may confer greater benefit to women compared to men (Arshad et al., 2011; Zusterzeel et al., 2015). These associations may be at least in part due to differences in baseline characteristics, as women in both randomized controlled trials and registries have higher prevalence of nonischemic cardiomyopathy (NICM) and left bundle branch block (LBBB) when compared to men. These characteristics have been associated with "super-response" after CRT (Hsu et al., 2012).

Left bundle branch block-associated idiopathic NICM is of heightened interest given the evolving concept of LBBB-induced cardiomyopathy (Vaillant et al., 2013; Wang et al., 2016). CRT studies in populations consisting exclusively of subjects with NICM and LBBB are few. Sex-specific differences after CRT in LBBB-associated idiopathic NICM on left ventricular ejection fraction (LVEF) improvement have been described (Varma et al., 2017, 2014). However, surrogate end points in heart failure (HF) have limitations (Gheorghiade et al., 2003).

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). In this substudy, we sought to address the hypothesis that clinical outcomes after CRT implantation would differ between women and men.

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 of 123 subjects, definition of idiopathic NICM, and exclusion criteria have been previously reported.

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).

Cardiac resynchronization therapy 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 the 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 was 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 LBBB and the CRT-paced QRS durations.

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

2.3 | Statistical methods

Descriptive data were presented by sex. 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 range (IQR) with comparisons using Wilcoxon–Mann–Whitney tests.

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

TABLE 1 Baseline characteristics

	Total (n = 123)	Men (n = 55)	Women (n = 68)	p Value ^a
Age at diagnosis, years	62.4 ± 13.1	60.3 ± 12.8	64.1 ± 13.1	0.11
Race/ethnicity				
White	116 (94.3)	52 (94.5)	64 (94.1)	0.92
African-American	7 (5.7)	3 (5.5)	4 (5.9)	
Body mass index, kg/m ²	29.6 ± 6.5	29.9 ± 5.1	29.5 ± 7.5	0.73
NYHA class				
II	28 (22.8)	15 (27.3)	13 (19.1)	0.28
III	94 (76.4)	39 (70.9)	55 (80.9)	
IV	1 (0.8)	1 (1.8)	0 (0.0)	
Heart rate, bpm	71.5 ± 12.1	69.6 ± 12.1	73.1 ± 11.8	0.11
QRS duration, ms	163 ± 17	167 ± 15	160 ± 17	0.008
LVEF, %	22.8 ± 6.6	23.0 ± 7.1	22.7 ± 6.2	0.77
LVEDD Index, cm/m ²	3.2 ± 0.6	3.0 ± 0.5	3.3 ± 0.6	0.01
LVESD Index, cm/m ²	2.7 ± 0.6	2.6 ± 0.6	2.8 ± 0.7	0.06
LA Index, cm/m ²	2.2 ± 0.4	2.1 ± 0.4	2.3 ± 0.4	0.02
Systolic blood pressure, mmHg	128 ± 19	127 ± 18	128 ± 19	0.68
Serum sodium level, mM	139 ± 3	140 ± 3	139 ± 3	0.10
Serum blood urea nitrogen level, mg/dl	18.5 ± 8.1	18.6 ± 8.8	18.5 ± 7.7	0.94
Serum creatinine level, mg/dl	1.05 ± 0.52	1.16 ± 0.63	0.96 ± 0.40	0.03
Coronary angiography				
Yes	115 (93.5)	52 (94.5)	63 (92.6)	0.67
No	8 (6.5)	3 (5.5)	5 (7.4)	
Hypertension	68 (55.3)	35 (63.6)	33 (48.5)	0.09
Hyperlipidemia	48 (39.0)	21 (38.2)	27 (39.7)	0.86
Diabetes	33 (26.8)	16 (29.1)	17 (25.0)	0.61
Atrial fibrillation	5 (4.1)	1 (1.8)	4 (5.9)	0.26
Atrial flutter	4 (3.3)	2 (3.6)	2 (2.9)	0.83
Stroke or transient ischemic attack	9 (7.3)	6 (10.9)	3 (4.4)	0.17
Peripheral vascular disease	1 (0.8)	1 (1.8)	0 (0.0)	0.26
Chronic obstructive pulmonary disease	10 (8.1)	6 (10.9)	4 (5.9)	0.31
Obstructive sleep apnea	7 (5.7)	6 (10.9)	4 (5.9)	0.03
End-stage renal disease	1 (0.8)	1 (1.8)	0 (0.0)	0.26
Depression	11 (8.9)	5 (9.1)	6 (8.8)	0.96
Smoking				
Never	62 (50.4)	29 (52.7)	33 (48.5)	0.74
Current	14 (11.4)	7 (12.7)	7 (10.3)	
Former	47 (38.2)	19 (34.5)	28 (41.2)	
Alcohol use				
None	56 (45.5)	17 (30.9)	39 (57.4)	0.002
Light or moderate	57 (46.3)	29 (52.7)	28 (41.2)	
Heavy or binge	4 (3.3)	3 (5.5)	1 (1.5)	
Former heavy or binge	6 (4.9)	6 (10.9)	0 (0.0)	

Note. Values are mean ± SD or n (%).

LA: left atrial; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; NYHA: New York Heart Association.

^aMen versus women.

"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

The baseline characteristics by sex are presented in Table 1. All subjects were in sinus rhythm at the time of CRT implant. Women had shorter average QRS duration and larger indexed cardiac chamber sizes. QRS duration ≥ 150 ms prior to CRT was present in 50 (91%) men and 47 (69%) women ($p = 0.03$). "Strict" LBBB was present in 116 (94%) subjects. The median time from diagnosis to CRT was 9.7 (IQR, 4.9–36.7) months for the entire cohort and was similar between men and women ($p = 0.62$).

Cardiovascular medications received at the time of CRT implant and CRT characteristics are listed in Table 2. Additional information on medical therapy has been previously published (Wang, Li, et al., 2018). Transvenous LV lead placement was achieved in 120 (97.6%) subjects and 3 (2.4%) received epicardial leads. The distribution of transvenous leads was similar between groups and consisted of 30 quadripolar, 73 bipolar, and 17 unipolar.

3.1 | Associations of sex with clinical outcomes after CRT

The median follow-up time was 72.4 (IQR, 36.5–107.0) months for the entire cohort. Men, when compared to women, had similar risk for adverse clinical events (HR, 1.20; 95% confidence interval [CI], 0.57–2.51; $p = 0.63$) and all-cause mortality (HR, 1.62; 95% CI, 0.55–4.77; $p = 0.38$) (Table 3). No statistically significant interaction was demonstrated between QRS duration as a categorical variable (120–149 ms vs. ≥ 150 ms) for the associations between sex and either of the clinical end points, although the ability to test for this was limited by few men in the QRS duration 120–149 ms group. Kaplan–Meier curves for adverse clinical events and all-cause mortality, by sex, are presented in Figure 1 and Figure 2, respectively. The estimated 5-year adverse clinical event rates were 21.0% for the entire cohort, 22.1% for men, and 20.0% for women. The estimated 5-year mortality rates were 8.0% for the entire cohort, 9.5% for men, and 6.9% for women.

Multivariable Cox regression analyses demonstrated no modifications at $p < 0.1$ with any of the baseline characteristics on the relationship between sex and adverse clinical events or all-cause mortality, except for the effect of age at diagnosis on the association between sex and all-cause mortality. Other covariates assessed in multivariable analyses included body mass index, New York Heart Association class, heart rate, serum sodium level, serum blood urea nitrogen level, serum creatinine level, hypertension, hyperlipidemia, diabetes, atrial fibrillation, smoking, alcohol, and cardiovascular medications. For all-cause mortality, men had a higher risk compared

to women after adjustment for age at diagnosis (HR, 4.38; 95% CI, 1.35–14.18; $p = 0.01$) (Table 3). This persisted in final models that also included QRS duration and LVEF as well as QRS duration and LV end-diastolic dimension index. Adverse clinical events by sex are listed in Table 4.

4 | DISCUSSION

To the best of our knowledge, this analysis from the NEOLITH II study is the first to assess sex-specific clinical outcomes after CRT in a "pure" population of subjects with LBBB-associated idiopathic NICM. Women were slightly older and had shorter QRS durations than men. While both men and women had excellent long-term clinical outcomes, men were at higher risk for death after adjustment for baseline variables, primarily age.

Despite the lack of sex-specific guideline recommendations for CRT, it is of interest that women were slightly older than men by a mean age of nearly 4 years. It is conceivable that women have protection to the development of LBBB such that they develop it later in life. This is supported by population screening data of 110,000 subjects from the Irish Heart Foundation, where men had greater prevalence of LBBB, using the Minnesota code definition, in almost every age category (Fahy et al., 1996). This "frameshift" in age may need to be considered in the design of future CRT studies in LBBB-associated idiopathic NICM and further explored in epidemiological studies. The higher percentage of women with QRS < 150 ms in our population raises the possibility that women, once they manifest LBBB, are at more rapid risk for progression to HF.

Higher vulnerability at shorter QRS durations in women is supported by criteria proposed for "strict" LBBB where women have LBBB beginning at 130 ms and men at 140 ms (Strauss et al., 2011). However, it is notable that the difference in threshold was created to account for differences in heart sizes between men and women. Efforts to adjust for sex differences through LV mass or volume measurements have demonstrated promise in single-center studies (De Pooter et al., 2018; Varma et al., 2017). It is of interest that women in our study had greater indexed cardiac chamber sizes prior to CRT, yet better adjusted survival after CRT. Sex-specific differences in myocardial remodeling have been reported in a number of conditions (Piro, Della Bona, Abbate, Biasucci, & Crea, 2010). Greater cardiac vulnerability to LBBB with more dramatic remodeling after CRT in postmenopausal women, when compared to men, deserves further investigation.

American College of Cardiology Foundation and American Heart Association guideline recommendations for CRT use QRS duration as a criterion based on 120–149 and ≥ 150 ms without distinguishing by sex (Yancy et al., 2013). That the European Society of Cardiology does not even recommend CRT for QRS duration in the 120–129 ms range and, in fact, lists it as a class III recommendation, highlights the uncertainty in this area (Ponikowski et al., 2016). Ultimately, the best CRT criterion for electrical dyssynchrony may require an integrated approach using ECG and imaging modalities.

TABLE 2 Cardiovascular medications and CRT characteristics

	Total (n = 123)	Men (n = 55)	Women (n = 68)	p Value ^a
Medications				
ACEI/ARB	114 (92.7)	52 (94.5)	62 (91.2.6)	0.48
Beta-blocker	117 (95.1)	52 (94.5)	65 (95.6)	0.79
Aldosterone antagonist	22 (17.9)	10 (18.2)	12 (17.6)	0.94
Digoxin	28 (22.8)	12 (21.8)	16 (23.5)	0.82
Diuretic	85 (69.1)	36 (65.5)	49 (72.1)	0.43
Antiarrhythmic	2 (1.6)	2 (3.6)	0 (0.0)	0.11
Aspirin	66 (53.7)	36 (65.5)	30 (44.1)	0.02
Anticoagulant	14 (11.4)	10 (18.2)	4 (5.9)	0.04
Statin	46 (37.4)	21 (38.2)	25 (36.8)	0.87
Medications, percent target dose achieved for subjects on treatment, median (IQR)				
ACEI/ARB ^b	50 (25–100)	50 (25–100)	50 (25–100)	0.77
Beta blocker ^b	37.5 (12.5–50)	50 (25–100)	25 (12.5–50)	0.40
Aldosterone antagonist ^b	100 (100–100)	100 (100–100)	100 (100–100)	0.67
Time from diagnosis to CRT	9.7 (4.9, 36.7)	11.0 (5.3–42.0)	8.2 (4.6–33.9)	0.62
CRT type				
CRT-defibrillator	121 (98.4)	55 (100)	66 (97.1)	0.20
CRT-pacemaker	2 (1.6)	0 (0.0)	2 (2.9)	
CRT programed parameters				
Mode				
DDD	111 (90.2)	49 (89.1)	62 (91.2)	0.72
DDDR	10 (8.1)	5 (9.1)	5 (9.1)	
Lower rate limit, bpm ^c	50 (40,70)	50 (40,70)	50 (40,70)	0.47
Biventricular pacing, % ^c	99.5 (64.0, 100)	99.5 (64.9, 100)	99.5 (64.0, 100)	0.90
Tachytherapy threshold, bpm ^c	185 (150, 214)	185 (150, 200)	185 (167, 214)	0.97
ΔQRS duration, ms	−18 ± 15	−19 ± 16	−18 ± 15	0.72
CRT lead positions				
Left ventricular lead, short axis				
Anterior	14 (11.4)	7 (14.3)	6 (10.7)	0.06
Lateral	71 (57.7)	28 (57.1)	36 (64.3)	
Posterior	38 (30.9)	14 (28.6)	14 (25.0)	
Left ventricular lead, long axis				
Basal	23 (18.7)	6 (10.9)	17 (25.0)	0.07
Mid	63 (51.2)	28 (50.9)	35 (51.5)	
Apical	37 (30.1)	21 (38.2)	16 (23.5)	
Right ventricular lead, long axis				
Apical	108 (87.8)	49 (89.1)	59 (86.8)	0.42
Septal	14 (11.4)	5 (9.1)	9 (13.2)	
Outflow tract	1 (0.8)	1 (1.8)	0 (0)	

Note. ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin II receptor blocker; CRT: cardiac resynchronization therapy; ΔQRS duration: change from left bundle branch block to CRT-paced in QRS durations.

Values are mean ± SD, n (%).

^aMen versus women. ^bMedian (first quartile, third quartile). ^cMedian (range).

Data from population cohort studies suggest that LBBB prior to the manifestation of overt HF signs and symptoms should be considered stage A HF (Azadani et al., 2012; Dhingra et al., 2006; Yancy et

al., 2013; Zhang et al., 2013). Population screening for LBBB is currently not recommended (US Preventive Services Task Force, 2018). For those with incidentally discovered idiopathic LBBB, there is at

Variable(s)	Adverse clinical events		All-cause mortality	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Univariable model				
Sex (men vs. women)	1.20 (0.57–2.51)	0.63	1.62 (0.55–4.77)	0.38
Multivariable model 1: Age at diagnosis				
Sex (men vs. women)	1.83 (0.84–3.97)	0.13	4.38 (1.35–14.18)	0.01
Multivariable model 2: Age at diagnosis, QRS duration				
Sex (men vs. women)	1.56 (0.70–3.48)	0.28	3.68 (1.10–12.35)	0.04
Multivariable model 3: Age at diagnosis, QRS duration, LVEF				
Sex (men vs. women)	1.55 (0.70–3.47)	0.28	3.71 (1.09–12.54)	0.04
Multivariable model 4: Age at diagnosis, QRS duration, LVEDD index				
Sex (men vs. women)	2.11 (0.87–5.09)	0.10	4.55 (1.26–16.39)	0.02

Note. CI: confidence interval; HR: hazard ratio; LVEDD: left ventricular end-diastolic dimension; LVEF: left ventricular ejection fraction.

least the theoretical basis for surveillance monitoring for the development of LBBB-induced cardiomyopathy (Angheloiu et al., 2013; Vaillant et al., 2013). Once LBBB develops, women may need more vigilant evaluations at shorter QRS durations. These theories should be examined in longitudinal studies. Serial evaluation for LVEF decline and recommending CRT when appropriate are critical given poor outcomes otherwise (Wang et al., 2008).

Natural history studies of idiopathic dilated NICM previously estimated the 5-year mortality at 50% (Dec & Fuster, 1994). In our study, the 5-year mortality was <10% for both men and women. The response to current guideline-directed medical therapy and CRT is therefore quite remarkable. While men had higher risk of death than women in our final multivariable models, the excellent outcomes indicate that both men and women should be strongly considered for CRT. In a NEOLITH II substudy of those with follow-up LVEF measurements, similar proportions of men and women exhibited myocardial recovery (Wang, Hussain, et al., 2019).

There is no existing multicenter, randomized controlled trial with a mortality end point for CRT in LBBB-associated idiopathic NICM (Golwala, Bajaj, Arora, & Arora, 2017). Uncertainties that such trials could answer include the optimal timing of CRT, the role of cardiac MRI in the selection of CRT-defibrillators versus CRT-pacemakers, and the potential for downgrade from CRT-defibrillators to CRT-pacemakers at the time of battery depletion in those with myocardial recovery. Permanent His bundle pacing for “true” electrical resynchronization of LBBB is a developing attractive therapy. Randomized controlled trials against CRT are of significant interest for the future (Huang et al., 2018). Our findings indicate the need for such studies to be stratified a priori by sex and provide data for projected rates of adverse clinical events. Finally, as the evolution of pacing therapy progresses, the potential for interventions with less cost and less hardware may lead to treatment of patients with LBBB and lesser degrees of reduced LVEF that currently do not meet criteria for CRT (Witt et al., 2016).

TABLE 3 Univariable and multivariable Cox regression analyses for associations between sex and clinical outcomes

FIGURE 1 Kaplan–Meier curve for probability of survival from adverse clinical events after CRT by sex. Men and women had similar risk for adverse clinical events. CRT: cardiac resynchronization therapy

FIGURE 2 Kaplan–Meier curve for probability of survival from all-cause mortality after CRT by sex. Men and women had similar risk for all-cause mortality. CRT: cardiac resynchronization therapy

TABLE 4 Adverse clinical events

	Total (n = 123)	Men (n = 55)	Women (n = 68)
Any event ^a , n (%)	29 (23.6)	14 (25.5)	15 (22.1)
All events			
HF hospitalization, n (%)	13 (10.6)	6 (10.9)	7 (10.3)
Appropriate ICD shock, n (%)	8 (6.5)	4 (7.3)	4 (10.3)
Appropriate ATP therapy, n (%)	5 (4.1)	4 (7.3)	1 (1.5)
Ventricular assist device implantation, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Heart transplantation, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Death, n (%)	14 (11.4)	8 (14.5)	6 (8.8)

Note. ATP: antitachycardia pacing; HF: heart failure; ICD: implantable cardioverter-defibrillator. Values are n (%).

^aOnly the first event per subject was counted. Men versus women.

4.1 | Study strengths and limitations

The primary strength of the study was rigorous selection of subjects. LBBB was required at the time of initial diagnosis of NICM. 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. Our population was almost entirely of white race/ethnicity. GDMT and CRT programming were not standardized. There was no core laboratory for LVEF measurements. Underlying differences may have existed between men and women despite stringent selection criteria for LBBB-associated idiopathic cardiomyopathy in the NEOLITH II study (Wang, Li, et al., 2018). These may be related to genetic and/or other pathophysiologic processes (Eisenberg, Di Palo, & Piña, 2018; Japp, Gulati, Cook, Cowie, & Prasad, 2016). Cardiac magnetic resonance imaging may have provided additional insight (Leyva et al., 2012), but were not available. Residual confounding

related to lifestyle choices may have also contributed to differences as, for example, men had higher rates of alcohol use.

5 | CONCLUSIONS

In LBBB-associated idiopathic NICM, both men and women have favorable clinical outcomes following CRT. Men have higher risk of death, when compared to women, primarily after accounting for age at diagnosis. Further exploration regarding QRS duration differences between men and women, particularly in relation to LV mass and volume, is needed to refine guideline recommendations for CRT. Future randomized clinical trials for CRT should account for sex differences in their designs.

DISCLOSURES

Dr. Wang serves as a research investigator for Boston Scientific and receives fellowship support from Abbott and Medtronic. Dr. Jain serves as a consultant for Medtronic; receives research

support from Medtronic; and serves as a research investigator for Abbott, Boston Scientific, and Medtronic. Dr. Saba serves as a consultant for and receives research support from Abbott, Boston Scientific, and Medtronic. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ORCID

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

REFERENCES

- Angheloiu, G. O., Saul, M., Edelman, K., Shah, H., Mezu, U. L., & Saba, S. (2013). Predictors of left ventricular function deterioration in patients with left bundle branch block and ejection fraction >50%. *Congestive Heart Failure*, 19(4), E1–E4. <https://doi.org/10.1111/chf.12028>
- Arshad, A., Moss, A. J., Foster, E., Padeletti, L., Barsheshet, A., Goldenberg, I., ... on behalf of the MADIT-CRT Executive Committee. (2011). Cardiac resynchronization therapy is more effective in women than in men: The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial With Cardiac Resynchronization Therapy) Trial. *Journal of the American College of Cardiology*, 57(7), 813–820. <https://doi.org/10.1016/j.jacc.2010.06.061>
- Azadani, P. N., Soleimanirahbar, A., Marcus, G. M., Haight, T. J., Hollenberg, M., Olgin, J. E., & Lee, B. E. (2012). Asymptomatic left bundle branch block predicts new-onset congestive heart failure and death from cardiovascular disease. *Cardiology Research*, 3(6), 258–263. <https://doi.org/10.4021/cr214w>
- De Pooter, J., Kamaoen, V., El Haddad, M., Stroobandt, R., De Buyzere, M., Jordaens, L., & Timmermans, F. (2018). Gender differences in electro-mechanical characteristics of left bundle branch block: Potential implications for selection and response of cardiac resynchronization therapy. *International Journal of Cardiology*, 257, 84–91. <https://doi.org/10.1016/j.ijcard.2017.10.055>
- Dec, G. W., & Fuster, V. (1994). Idiopathic dilated cardiomyopathy. *New England Journal of Medicine*, 331(23), 1564–1575. <https://doi.org/10.1056/NEJM199412083312307>
- Dhingra, R., Pencina, M. J., Wang, T. J., Nam, B.-H., Benjamin, E. J., Levy, D., ... Vasan, R. S. (2006). Electrocardiographic QRS duration and the risk of congestive heart failure: The Framingham Heart Study. *Hypertension*, 47(5), 861–867. <https://doi.org/10.1161/01.HYP.0000217141.20163.23>
- Eisenberg, E., Di Palo, K. E., & Piña, I. L. (2018). Sex differences in heart failure. *Clinical Cardiology*, 41(2), 211–216. <https://doi.org/10.1002/clc.22917>
- Fahy, G. J., Pinski, S. L., Miller, D., McCabe, N., Pye, C., Walsh, M. J., & Robinson, K. (1996). Natural history of isolated bundle branch block. *The American Journal of Cardiology*, 77(14), 1185–1190. [https://doi.org/10.1016/S0002-9149\(96\)00160-9](https://doi.org/10.1016/S0002-9149(96)00160-9)
- Gheorghiade, M., Adams, K. F. Jr, Gattis, W. A., Teerlink, J. R., Orlandi, C., & O'Connor, C. M. (2003). Surrogate end points in heart failure trials. *American Heart Journal*, 145(2 Suppl), S67–S70. <https://doi.org/10.1067/mhj.2003.159>
- 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>
- Huang, W., Su, L., Wu, S., Xu, L., Xiao, F., Zhou, X., ... Ellenbogen, K. A. (2018). Long-term outcomes of His bundle pacing in patients with heart failure with left bundle branch block. *Heart*, 105(2), 137–143. <https://doi.org/10.1136/heartjnl-2018-313415>
- Japp, A. G., Gulati, A., Cook, S. A., Cowie, M. R., & Prasad, S. K. (2016). The diagnosis and evaluation of dilated cardiomyopathy. *Journal of the American College of Cardiology*, 67(25), 2996–3010. <https://doi.org/10.1016/j.jacc.2016.03.590>
- 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>
- 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>
- 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>
- Mosteller, R. D. (1987). Simplified calculation of body-surface area. *The New England Journal of Medicine*, 317(17), 1098. <https://doi.org/10.1056/NEJM198710223171717>
- Piro, M., Della Bona, R., Abbate, A., Biasucci, L. M., & Crea, F. (2010). Sex-related differences in myocardial remodeling. *Journal of the American College of Cardiology*, 55(11), 1057–1065. <https://doi.org/10.1016/j.jacc.2009.09.065>
- Ponikowski, P., Voors, A. A., Anker, S. D., Bueno, H., Cleland, J. G. F., Coats, A. J. S., ... van der Meer, P. (2016). 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). *European Journal of Heart Failure*, 18(8), 891–975. <https://doi.org/10.1002/ehf.592>
- Strauss, D. G., Selvester, R. H., & Wagner, G. S. (2011). Defining left bundle branch block in the era of cardiac resynchronization therapy. *The 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>
- US Preventive Services Task Force (2018). Screening for cardiovascular disease risk with electrocardiography: US Preventive Services Task Force Recommendation Statement. *JAMA*, 319(22), 2308–2314. <https://doi.org/10.1001/jama.2018.6848>
- 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>
- Varma, N., Lappe, J., He, J., Niebauer, M., Manne, M., & Tchou, P. (2017). Sex-specific response to cardiac resynchronization therapy: Effect

- of left ventricular size and QRS duration in left bundle branch block. *JACC: Clinical Electrophysiology*, 3(8), 844–853. <https://doi.org/10.1016/j.jacep.2017.02.021>
- Varma, N., Manne, M., Nguyen, D., He, J., Niebauer, M., & Tchou, P. (2014). Probability and magnitude of response to cardiac resynchronization therapy according to QRS duration and gender in nonischemic cardiomyopathy and LBBB. *Heart Rhythm*, 11(7), 1139–1147. <https://doi.org/10.1016/j.hrthm.2014.04.001>
- 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., Hussain, A., Adelstein, E. C., Althouse, A. D., Sharbaugh, M. S., Jain, S. K., ... Saba, S. (2019). Myocardial recovery after cardiac resynchronization therapy in left bundle branch block-associated idiopathic nonischemic cardiomyopathy: A NEOLITH II substudy. *Annals of Noninvasive Electrocardiology*, 24(2), e12603. <https://doi.org/10.1111/anec.12603>
- 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. Jr, ... 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*, 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. *The American Statistician*, 70(2), 129–133. <https://doi.org/10.1080/00031305.2016.1154108>
- 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>
- Witt, C. M., Wu, G., Yang, D., Hodge, D. O., Roger, V. L., & Cha, Y.-M. (2016). Outcomes with left bundle branch block and mildly to moderately reduced left ventricular ejection function. *Journal of the American College of Cardiology: Heart Failure*, 4(11), 897–903.
- Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E., Drazner, M. H., ... 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>
- Zhang, Z., Pautaharju, P. M., Soliman, E. Z., Manson, J. E., Martin, L. W., Perez, M., ... Prineas, R. J. (2013). Different patterns of bundle branch-blocks and the risk of incident heart failure in the Women's Health Initiative (WHI) study. *Circulation: Heart Failure*, 6(4), 655–661. <https://doi.org/10.1161/CIRCHEARTFAILURE.113.000217>
- Zusterzeel, R., Spatz, E. S., Curtis, J. P., Sanders, W. E., Selzman, K. A., Piña, I. L., ... Strauss, D. G. (2015). Cardiac resynchronization therapy in women versus men: Observational comparative effectiveness study from the National Cardiovascular Data Registry. *Circulation: Cardiovascular Quality and Outcomes*, 8(2_suppl_1), S4–S11. <https://doi.org/10.1161/CIRCOUTCOMES.114.001548>

How to cite this article: Wang NC, Mezu-Chukwu U, Adelstein EC, et al. Sex-specific clinical outcomes after cardiac resynchronization therapy in left bundle branch block-associated idiopathic nonischemic cardiomyopathy: A NEOLITH II substudy. *Ann Noninvasive Electrocardiol*. 2019;24:e12641. <https://doi.org/10.1111/anec.12641>