ORIGINAL ARTICLE

Predictors and implications of early left ventricular ejection fraction improvement in new-onset idiopathic nonischemic cardiomyopathy with narrow QRS complex: A NEOLITH substudy

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Background: Predictors and implications of early left ventricular ejection fraction (LVEF) improvement with guideline-directed medical therapy (GDMT) in new-onset idiopathic nonischemic cardiomyopathy (NICM) with narrow QRS complex are not well described. The objectives were to describe predictors of LVEF improvement after 3 months on GDMT and adverse cardiac events based on post-GDMT LVEF status ($\leq 35\%$ vs. $> 35\%$).

Methods: A retrospective cohort study was performed in subjects with new-onset NICM, LVEF $\leq 35\%$, and narrow QRS complex. Associations for baseline variables with post-GDMT LVEF improvement and absolute change in LVEF ($\Delta\text{LVEF}_{\text{GDMT}}$) were assessed. Cox proportional hazards models assessed associations for post-GDMT LVEF status with adverse cardiac events.

Results: In 70 subjects, 31 (44%) had post-GDMT LVEF $\leq 35\%$ after a median follow-up time of 97.5 days (interquartile range, 84–121 days). In final multivariable models, severely dilated left ventricular end-diastolic diameter (LVEDD), compared with normal LVEDD, strongly predicted post-GDMT LVEF $\leq 35\%$ (odds ratio, 7.77; 95% confidence interval [CI], 1.39–43.49; $p = .02$) and $\Delta\text{LVEF}_{\text{GDMT}}$ ($\beta = -15.709$; standard error = 4.622; $p = .001$). Subjects with post-GDMT LVEF $\leq 35\%$ were more likely to have adverse cardiac events over a median follow-up time of 970.5 days (unadjusted hazard ratio, 2.15; 95% CI, 0.93–4.96; $p = .07$). In the post-GDMT LVEF $\leq 35\%$ group, 9 of 26 subjects (35%) had long-term LVEF $> 35\%$.

Conclusion: In new-onset NICM with narrow QRS complex, nondilated LVEDD predicted early LVEF improvement. Those with post-GDMT LVEF $\leq 35\%$ had higher risk of adverse cardiac events, but a substantial proportion demonstrated continued long-term LVEF improvement.

KEYWORDS

medications, narrow QRS complex, nonischemic cardiomyopathy, outcomes, QRS duration

1 | INTRODUCTION

Left ventricular ejection fraction (LVEF) correlates with cardiovascular outcomes in heart failure (HF; Solomon et al., 2005). For those with new-onset idiopathic nonischemic cardiomyopathy (NICM) and LVEF $\leq 35\%$, LVEF reassessment at 3 months has important therapeutic considerations. The 2013 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guideline for the management of HF recommends implantable cardioverter defibrillator (ICD) consideration for primary prevention of sudden death after a minimum of 3 months on guideline-directed medical therapy (GDMT) if the LVEF remains $\leq 35\%$ (Yancy et al., 2013). The AHA Science Advisory has also issued a class IIb recommendation for a wearable cardioverter defibrillator (WCD) in the setting of newly diagnosed NICM during the waiting period, but cautions against “blanket use” (Piccini et al., 2016).

Prior studies suggest that approximately half of all subjects with new-onset idiopathic NICM and narrow QRS complex improve LVEF on GDMT such that they no longer meet criteria for ICD consideration (Teeter et al., 2012; Wang et al., 2016). Predictors and implications of LVEF improvement 3 months after initial diagnosis of NICM with narrow QRS complex are not well described. The pertinent current literature is limited by lack of a standardized time of diagnosis to study entry period, lack of standardized time to LVEF reassessment, and/or high GDMT use at study entry (Binkley et al., 2008; Cicoira et al., 2001; Kadish et al., 2006; Kawai, et al., 1999; McNamara et al., 2011; Schliamser et al., 2013; Teeter et al., 2012; Zecchin et al., 2012).

The NEw-Onset Left Bundle Branch Block-Associated Idiopathic Nonischemic CardiomyopaThy (NEOLITH) study assessed LVEF response to approximately 3 months of GDMT in newly diagnosed idiopathic NICM, LVEF $\leq 35\%$, and left bundle branch block or narrow QRS complex (Wang et al., 2016). This substudy, comprises the narrow QRS complex control subjects, sought to address three main hypotheses: (1) baseline characteristics predict early LVEF improvement, (2) early LVEF improvement predicts long-term clinical outcomes, and (3) some without early LVEF improvement will demonstrate LVEF improvement when followed for a longer time period.

2 | METHODS

2.1 | Study population and design

The NEOLITH study was a retrospective cohort study conducted at the University of Pittsburgh Medical Center (Wang et al., 2016). The 70 subjects in this study were those originally selected as narrow QRS complex controls. Subjects were prospectively identified based on a list used for clinical purposes to track those prescribed WCDs (ZOLL Medical Corporation, Pittsburgh, PA, USA) between January 2005 and April 2015. Subjects were prescribed WCDs for primary prevention during the GDMT waiting period. The derivation of the study cohort, the definition of new-onset idiopathic NICM, and exclusion criteria have been previously reported (Wang et al.,

2016). None were evaluated for myocarditis with viral serology or endomyocardial biopsy. The 12-lead electrocardiogram recorded at 25 mm/s at the time of the initial diagnosis of NICM was used to determine QRS duration. Automated measurements were confirmed by board-certified cardiologists. A QRS duration of <120 ms was classified as “narrow.”

The date of the first imaging modality to reveal a LVEF $\leq 35\%$ was designated the date of diagnosis. GDMT was administered at the discretion of treating cardiologists. For new-onset NICM, our electrophysiology group generally recommends a transthoracic echocardiogram to assess LVEF approximately 3 months after initiation of GDMT. Subjects with persistent LVEF $\leq 35\%$ are considered for ICDs in accordance with ACCF/AHA guideline recommendations (Yancy et al., 2013). ICD implants were performed using a transvenous approach by electrophysiologists at the University of Pittsburgh Medical Center. Device programming was at the discretion of the implanting physicians. This study was approved by the University of Pittsburgh Institutional Review Board. Informed consent was not required due to the retrospective design.

2.2 | Exposures and outcomes

Body mass index, heart rate, systolic blood pressure, serum sodium level, serum blood urea nitrogen level, and serum creatinine level were those measured on admission during the index hospitalization or closest to the index outpatient clinic appointment when WCDs were prescribed. Alcohol consumption was defined as none, light, moderate, heavy, binge, and prior heavy and/or binge drinking based on a previously recommended scale (Kloner & Rezkalla, 2007). For the analyses, light and moderate drinking were combined and heavy and binge drinking were combined. Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blocker (ARB) were collapsed into one variable. Percent target doses achieved for ACEIs/ARBs, β -blockers, and aldosterone antagonists were calculated as previously described (Wang et al., 2016). Antiarrhythmic medications were all Vaughan-Williams class III.

Left ventricular ejection fraction was determined by objective imaging techniques and confirmed by board-certified cardiologists. Transthoracic echocardiography was the most common modality and therefore used when available for consistency. LVEF was determined by visual estimation to confirm objective measurements, such as biplane Simpson's method and Teichholz's formula (Lang et al., 2015). When reported as a range, the midpoint was assigned (i.e., 32.5% for LVEF reported as 30%–35%). LVEF measurements were those originally reported and used to make clinical decisions.

Left ventricular end-diastolic diameter (LVEDD) was assessed on transthoracic echocardiography in the parasternal long-axis view. LVEDD was assessed as both categorical and continuous variables. LVEDD as a categorical variable was sex based as recommended by the American Society of Echocardiography and classified as normal (men, 4.2–5.8 cm; women, 3.8–5.2 cm), mildly dilated (men, 5.9–6.3 cm; women, 5.3–5.6 cm), moderately dilated (men, 6.4–6.8 cm; women,

5.7–6.1 cm), and severely dilated (men, ≥ 6.9 cm; women, ≥ 6.2 cm; Lang et al., 2015). We also analyzed LVEDD as a continuous variable without accounting for sex given similar supplementary analyses in other publications (McNamara et al., 2011).

The primary short-term outcome measure of LVEF approximately 3 months after starting GDMT was designated the “post-GDMT LVEF.” A categorical outcome was dichotomized as post-GDMT LVEF $\leq 35\%$ vs. $>35\%$. This threshold for LVEF improvement was selected based on guideline recommendations for primary prophylaxis ICDs (Yancy et al., 2013). A continuous outcome was defined as the absolute difference between post-GDMT LVEF and initial LVEF, or $\Delta\text{LVEF}_{\text{GDMT}}$.

The primary long-term outcome measure was a composite of adverse cardiac events including HF rehospitalization, appropriate WCD shock, resuscitated out-of-hospital cardiac arrest, appropriate anti-tachycardia pacing (ATP) therapy, appropriate ICD shock, ventricular assist device implantation, heart transplantation, and death. If appropriate ATP therapy and ICD shock occurred during the same event, only ICD shock was counted. The inception point of this time period was the date of initial NICM diagnosis. Long-term events were assessed by review of medical records on June 6, 2016. The “long-term LVEF” was the most recent available given the lack of a standardized time period for subsequent measurements.

2.3 | Statistical methods

Descriptive data were presented by post-GDMT LVEF $\leq 35\%$ and $>35\%$. Categorical variables were compared using chi-square or Fisher's exact tests as appropriate. Continuous variables were compared using Student's *t* test or Wilcoxon–Mann–Whitney test as appropriate.

Logistic regression models were used to assess associations between baseline characteristics and postdiagnosis medications with post-GDMT LVEF $\leq 35\%$ and $>35\%$. Linear regression models were used to assess associations between baseline characteristics and postdiagnosis medications with $\Delta\text{LVEF}_{\text{GDMT}}$. Time-to-event outcomes between post-GDMT LVEF groups were summarized using Kaplan–Meier survival curves, and differences between groups were summarized by the hazard ratio (HR) and 95% confidence interval (CI) computed using the Cox proportional hazards model. For multivariable analyses, variables that were found to be significantly associated with the outcomes at $p < .1$ were considered. Age, sex, and race/ethnicity were forced into the models. ACEIs/ARBs and β -blockers were also forced into the models given prior publications describing associations with LVEF improvement (Konstam et al., 1992; Packer et al., 2001). Sensitivity analysis was performed on subjects who received both ACEIs/ARBs and β -blockers. We did not assign a value for “significance” for reported *p*-values given the recent statement by the American Statistical Association, but recognize the traditional threshold of $p < .05$ (Wasserstein & Lazar, 2016). All analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

3 | RESULTS

The baseline characteristics of the total cohort and by post-GDMT LVEF status are presented in Table 1; 39 (56%) subjects demonstrated LVEF improvement to $>35\%$. The presenting rhythm was sinus in 69 subjects and atrial fibrillation in one subject. Tachycardia-induced cardiomyopathy was not felt to be of high consideration in the subject who presented with atrial fibrillation. Of the 70 subjects, 69 were diagnosed in an inpatient hospitalized setting and had a length of stay of 6.5 ± 5.4 days. The length of stay was similar in groups that did and did not have post-GDMT LVEF improvement (6.4 ± 4.7 days vs. 6.5 ± 6.3 days; $p = .73$). Imaging modalities used to assess initial LVEF included transthoracic echocardiography ($n = 64$), single photon emission computed tomography ($n = 2$), and ventriculography ($n = 4$).

Prediagnosis and postdiagnosis cardiovascular medications are listed in Table 2. Those with LVEF improvement received higher doses of β -blockers. ACEIs/ARBs used included lisinopril ($n = 45$), enalapril ($n = 6$), ramipril ($n = 4$), captopril ($n = 2$), quinapril ($n = 2$), valsartan ($n = 4$), and losartan ($n = 3$). β -blockers used included carvedilol ($n = 60$), metoprolol succinate ($n = 6$), metoprolol tartrate ($n = 1$), and atenolol ($n = 1$). Four were not on either ACEI or ARB due to renal dysfunction ($n = 2$), low blood pressure ($n = 1$), and a reason that was not specified ($n = 1$). Two subjects were not on β -blockers, one for non-compliance and the other for low blood pressure.

The median follow-up time to post-GDMT LVEF measurement was 97.5 days (interquartile range (IQR), 84–121 days) and similar between post-GDMT LVEF $\leq 35\%$ and $>35\%$ groups (91 days; IQR, 85–110 days vs. 103 days; IQR, 78–144 days; $p = .62$). Imaging modalities used to assess post-GDMT LVEF included transthoracic echocardiography ($n = 63$), multigated acquisition scan ($n = 4$), and cardiovascular magnetic resonance imaging (CMR) ($n = 3$). The mean post-GDMT LVEF was $23.3\% \pm 5.9\%$ in the $\leq 35\%$ group and $49.1\% \pm 8.4\%$ in the $>35\%$ group ($p < .0001$). Among those with LVEF improvement, 18 subjects had LVEF $\geq 50\%$. In the post-GDMT LVEF $>35\%$ group, 33 (84.6%) subjects had $\Delta\text{LVEF}_{\text{GDMT}} \geq 15\%$ compared with 3 (9.7%) subjects in the post-GDMT LVEF $\leq 35\%$ group ($p < .0001$). The mean $\Delta\text{LVEF}_{\text{GDMT}}$ was $16.1\% \pm 14.6\%$ for the entire cohort. The mean $\Delta\text{LVEF}_{\text{GDMT}}$ was $26.0\% \pm 10.8\%$ in the post-GDMT LVEF $>35\%$ group and $3.7\% \pm 7.3\%$ in the post-GDMT $\leq 35\%$ group ($p < .0001$).

The median WCD use time was 94.8 days (IQR, 40–111 days) and 20.6 hr/day (IQR, 15.9–23.2 hr/day). There were no appropriate WCD shocks.

The 31 subjects with post-GDMT LVEF $\leq 35\%$ underwent the following procedures: 20 had single-chamber ICDs, six had dual-chamber ICDs, one had a CRT-D, three were recommended ICDs but declined, and one met criteria for an ICD but sought treatment elsewhere. One subject with a QRS duration of 80 ms received a CRT-D device in the year 2006 on the basis of echocardiographic mechanical dyssynchrony.

In the 39 subjects with post-GDMT LVEF $>35\%$, two subjects received dual-chamber ICDs. No others received cardiovascular implantable electronic devices. One subject was implanted 9 days after initial diagnosis of NICM due to sinus pauses of >7 s in the absence of

TABLE 1 Baseline characteristics

Characteristic	Total (n = 70)	Post-GDMT LVEF ≤35% group (n = 31)	Post-GDMT LVEF >35% group (n = 39)	p ^a
Age at diagnosis, mean (SD), yr	54.4 (13.1)	51.1 (11.8)	57.0 (13.5)	.053
Sex, n (%)				
Male	39 (56)	20 (65)	19 (49)	.19
Female	31 (44)	11 (35)	20 (51)	
Race/ethnicity, n (%)				
Caucasian	58 (83)	23 (74)	35 (90)	.09
African American	12 (17)	8 (26)	4 (10)	
Body mass index, mean (SD), kg/m ²	30.5 (7.1)	30.6 (5.3)	30.5 (8.3)	.74
Presenting heart rate, mean (SD), bpm	95.9 (22.0)	100.1 (21.3)	92.5 (22.3)	.051
Presenting QRS duration, mean (SD), ms	96.3 (11.0)	98.5 (9.4)	94.6 (11.9)	.16
Initial LVEF, mean (SD), %	21.6 (6.7)	19.6 (5.7)	23.2 (7.1)	.02
Initial LVEDD (categorical), n (%)				
Normal	17 (27)	3 (11)	14 (41)	.008
Mildly dilated	13 (21)	8 (29)	5 (15)	
Moderately dilated	13 (21)	4 (14)	9 (26)	
Severely dilated	19 (31)	13 (46)	6 (18)	
Initial LVEDD (continuous), mean (SD), cm	6.1 (0.9)	6.5 (0.8)	5.8 (0.8)	.003
Systolic blood pressure, mean (SD), mmHg	138.9 (31.7)	134.6 (25.7)	142.4 (35.8)	.54
Serum sodium, mean (SD), mmol/L	138.0 (3.4)	138.2 (3.0)	137.8 (3.7)	.82
Serum blood urea nitrogen, mean (SD), mg/dl	19.4 (11.2)	18.7 (8.5)	20.0 (13.2)	.75
Serum creatinine, mean (SD), mg/dl	1.2 (0.8)	1.3 (1.0)	1.2 (0.6)	.88
Coronary angiography, n (%)				
Angiographically normal	52 (74)	24 (77)	28 (72)	.29
Mild coronary artery disease	15 (21)	7 (23)	8 (21)	
No coronary angiography	3 (4)	0 (0)	3 (8)	
Hypertension, n (%)	30 (43)	12 (39)	18 (46)	.53
Hyperlipidemia, n (%)	8 (11)	2 (6)	6 (15)	.29
Diabetes, n (%)	6 (9)	1 (3)	5 (13)	.22
Atrial fibrillation, n (%)	2 (3)	1 (3)	1 (3)	1.0
Stroke, n (%)	1 (1)	0 (0)	1 (3)	1.0
Peripheral vascular disease, n (%)	1 (1)	0 (0)	1 (3)	1.0
Chronic obstructive pulmonary disease, n (%)	7 (10)	3 (10)	4 (10)	1.0
Obstructive sleep apnea, n (%)	3 (4)	2 (6)	1 (3)	.58
End-stage renal disease, n (%)	1 (1)	1 (3)	0 (0)	.44
Depression, n (%)	8 (11)	4 (13)	4 (10)	1.0
Smoking, n (%)				
Never	33 (47)	14 (45)	19 (49)	.92
Current	23 (33)	11 (35)	12 (31)	
Former	14 (20)	6 (19)	8 (21)	
Alcohol use, n (%)				
None	33 (47)	15 (48)	18 (46)	.91
Light or moderate	23 (33)	11 (35)	12 (31)	
Heavy or binge	9 (13)	3 (10)	6 (15)	
Former heave or binge	5 (7)	2 (6)	3 (8)	

GDMT, guideline-directed medical therapy; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; SD, standard deviation; yr, year.

^aPost-GDMT LVEF ≤35% group versus post-GDMT LVEF >35% group.

discernible causes; her post-GDMT LVEF was 57.5%. Another was implanted for a post-GDMT LVEF of 37.5% and died of unknown causes 7 months after ICD placement.

3.1 | Associations of baseline characteristics and postdiagnosis medications with early LVEF improvement

In univariable logistic regression analyses, mildly and severely dilated initial LVEDD, when compared to normal initial LVEDD, were associated with lower odds of post-GDMT LVEF >35% (Table 3). This association was also present for the continuous initial LVEDD variable. These relationships were maintained in multivariable analyses (Table 4). Inverse adjusted odds ratios (ORs) modeled for the lack of LVEF improvement, or post-GDMT $\leq$ 35%, were 7.01 (95% CI, 1.17–42.0; $p = .03$) and 7.77 (95% CI, 1.39–43.49; $p = .02$) for mildly and severely dilated LVEDD, respectively, when referenced to normal initial LVEDD. No other variables, including initial LVEF, were significantly associated with LVEF improvement in the final multivariable models.

All subjects with initial LVEDD of 5.2 cm or less improved their post-GDMT LVEF to >35% (Figure 1). For the relationship of initial LVEDD to post-GDMT LVEF >35%, the area under the receiver operator curve was 0.73. Those who demonstrated LVEF improvement had a wide range of initial LVEDD values (range 4.5–7.8 cm).

Univariable linear regression analyses for $\Delta\text{LVEF}_{\text{GDMT}}$ are presented in Table 3. Mildly and severely (but not moderately) dilated initial LVEDD, when compared with normal initial LVEDD, were both negatively associated with $\Delta\text{LVEF}_{\text{GDMT}}$. The continuous initial LVEDD variable also demonstrated this relationship. These associations persisted in multivariable analyses (Table 4). Initial LVEF also remained associated with $\Delta\text{LVEF}_{\text{GDMT}}$ in the final linear regression models that used both categorical initial LVEDD (β , -0.696 ; standard error, 0.259; $p = .01$) and continuous initial LVEDD (β , -0.619 ; standard error, 0.263; $p = .02$).

Sensitivity analyses for logistic and linear regression for the 65 subjects who received both ACEIs/ARBs and β -blockers demonstrated similar results for the both categorical and continuous initial LVEDD variables (data not shown).

3.2 | Long-term adverse cardiac events

The median long-term follow-up period was 970.5 days (IQR, 321–1639 days). Adverse cardiac events were more common in the post-GDMT LVEF $\leq$ 35% group (Table 5 and Figure 2). The combination of appropriate ATP therapy and appropriate ICD shocks was higher in the post-GDMT LVEF $\leq$ 35% group compared with the post-GDMT LVEF >35% group (13% vs. 0%, $p = .03$). The univariable Cox proportional hazards model for the composite outcome measure of HF rehospitalization, resuscitated out-of-hospital cardiac arrest, appropriate WCD shock, appropriate ATP therapy, appropriate ICD shock, ventricular assist device implantation, heart transplantation, and death demonstrated higher risk in the post-GDMT LVEF $\leq$ 35% group when

compared with the post-GDMT LVEF >35% group (HR, 2.15; 95% CI, 0.93–4.96; $p = .07$). This relationship was attenuated in the multivariable analysis (HR, 1.70; 95% CI, 0.52–5.50; $p = .38$) after adjusting for age, sex, race/ethnicity, initial LVEDD category, initial LVEF, ACEI/ARB use, and β -blocker use. ACEI/ARB use was associated with lower risk of adverse cardiac events in the final model (HR, 0.10; 95% CI, 0.02–0.41; $p = .002$). When continuous initial LVEDD was used, the results for post-GDMT $\leq$ 35% (HR, 1.67; 95% CI, 0.53–5.30; $p = .38$) and ACEI/ARB use (HR, 0.11; 95% CI, 0.03–0.43; $p = .002$) were similar.

3.3 | Long-term LVEF in the post-GDMT LVEF $\leq$ 35% group

In 31 subjects with post-GDMT LVEF $\leq$ 35%, 26 had long-term LVEF assessments after a median follow-up time (measured from post-GDMT LVEF measurements) of 1051.5 days (IQR, 811–1,639; Table 6). There were nine (35%) subjects with long-term LVEF >35%, but two within this group had appropriate ICD therapies. One was a 37-year-old man with late gadolinium enhancement (LGE) on CMR suggestive of midwall myocardial fibrosis and nonsustained ventricular tachycardia (NSVT) up to 14 beats.

4 | DISCUSSION

This analysis of subjects with new-onset idiopathic NICM with narrow QRS complex from the NEOLITH study was unique due to complete absence of ACEI/ARB and β -blocker use for HF indications at the time of initial diagnosis and a standardized 3-month follow-up LVEF measurement after GDMT initiation. We noted several important observations. First, there were strong associations between mildly and severely dilated initial LVEDD and lack of early LVEF improvement, when compared with normal initial LVEDD. Second, lack of early LVEF improvement identified a population at potentially higher risk for long-term adverse cardiac events. Third, over one-third with LVEF $\leq$ 35% after 3 months of GDMT had continued improvement to LVEF >35% during long-term follow-up.

The Intervention in Myocarditis and Acute Cardiomyopathy-2 study enrolled subjects with NICM and symptoms for <6 months (McNamara et al., 2011). Subjects were already receiving GDMT at the time of enrollment as 91% were receiving ACEIs and/or ARBs and 82% were receiving β -blockers. ICDs were present in 7% at enrollment. LVEDD was the strongest predictor of LVEF improvement at 6 months. Despite study differences, our findings are complementary. The Genetic Risk Assessment of Defibrillator Events study evaluated subjects with LVEF $\leq$ 30% and ICDs (Aleong et al., 2015). Greater LVEDD, even after adjusting for LVEF, was associated with a higher risk for both appropriate ICD shocks and time to death, transplant, or ventricular assist device. Although the majority of subjects had ischemic etiology, the association persisted when adjusted for etiology of cardiomyopathy. This supports the concept that greater LVEDD represents a higher risk subgroup with potentially different pathophysiology underpinnings.

Characteristic	Total (n = 70)	Post-GDMT LVEF ≤35% group (n = 31)	Post-GDMT LVEF >35% group (n = 39)	p ^a
Prediagnosis medications, n (%)				
ACEI/ARB	11 (16)	3 (10)	8 (21)	.32
Beta-blocker	7 (10)	1 (3)	6 (15)	.12
Aldosterone antagonist	0 (0)	0 (0)	0 (0)	NA
Digoxin	0 (0)	0 (0)	0 (0)	NA
Diuretic	10 (14)	3 (10)	7 (18)	.49
Antiarrhythmic	0 (0)	0 (0)	0 (0)	NA
Aspirin	7 (10)	2 (6)	5 (13)	.45
Anticoagulant	1 (1)	1 (3)	0 (0)	.44
Statin	5 (7)	3 (10)	2 (5)	.65
Postdiagnosis medications, n (%)				
ACEI/ARB	66 (94)	29 (94)	37 (95)	1.0
Beta-blocker	68 (97)	30 (97)	38 (97)	1.0
Aldosterone antagonist	17 (24)	7 (23)	10 (26)	.77
Digoxin	12 (17)	6 (19)	6 (15)	.66
Diuretic	51 (73)	23 (74)	28 (72)	.82
Antiarrhythmic	5 (7)	3 (10)	2 (5)	.64
Aspirin	43 (61)	18 (58)	25 (64)	.61
Anticoagulant	11 (16)	5 (16)	6 (15)	1.0
Statin	18 (26)	7 (23)	11 (28)	.59
Percent target dose, median (IQR), %				
ACEI/ARB	50 (25–100)	50 (16.7–60)	50 (25–100)	.32
Beta-blocker	25 (25–50)	25 (12.5–25)	25 (25–50)	.02
Aldosterone antagonist	100 (100–100)	100 (100–100)	100 (100–100)	.82

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; GDMT, guideline-directed medical therapy; IQR, interquartile range; LVEF, left ventricular ejection fraction; NA, not applicable.

^aPost-GDMT LVEF ≤35% group versus post-GDMT LVEF >35% group.

Those with new-onset NICM have very low rates of sustained ventricular arrhythmias in the early postdiagnosis period (Kutyifa et al., 2015; Singh et al., 2015). No randomized controlled trials have demonstrated mortality reduction with WCD use in this population. WCDs for all subjects with new-onset NICM and LVEF ≤35% are not recommended by the AHA Science Advisory, but specific recommendations for identifying higher risk individuals who may potentially benefit were not issued (Piccini et al., 2016). It must also be recognized that the LVEF cutoffs are derived from randomized clinical trials for primary prevention ICDs with long-term follow-up times of several years. A 23% risk reduction in death was observed with ICDs in addition to GDMT in the Sudden Cardiac Death in Heart Failure Trial, but the median follow-up time was 3.8 years (Bardy et al., 2005).

Our results suggest a larger LVEDD deserves further investigation as a potential high-risk marker for which WCDs may be considered. Although we did not observe any appropriate WCD shocks, our

TABLE 2 Prediagnosis cardiovascular medications, postdiagnosis cardiovascular medications, and percent target dose achieved at post-GDMT LVEF measurement for subjects receiving treatment

sample size was relatively small. Unexpectedly, mild and severe dilated LVEDD were associated with less LVEF improvement compared with normal LVEDD, but moderately dilated LVEDD was not. This may be a statistical anomaly related to low sample size given the large strength of association observed in the other analyses. The cutoff, if any, at which point WCD may confer benefit should be investigated.

In our study, subjects without LVEF improvement 3 months after initial diagnosis, when compared with those with improvement, were at higher risk for long-term adverse cardiac events. ICDs may be considered at that time, but whether there is a difference in outcomes between ICD placement at 3 months compared with a later time period is unknown. Death from worsening HF is the primary cause of death in those hospitalized for decompensated HF and chronically reduced LVEF (Wang et al., 2008). The benefit of defibrillator therapy to decrease sudden death due to arrhythmias for many months postdischarge may, therefore, be nullified by the competing risk of HF death (Wang et al., 2010).

TABLE 3 Univariable logistic and linear regression analyses for LVEF response to GDMT

Characteristic	Post-GDMT LVEF >35%		Δ LVEF _{GDMT}	
	OR (95% CI)	p	β (SE)	p
Age at diagnosis	1.04 (0.998–1.08)	.06	0.336 (0.129)	.01
Sex	1.91 (0.73–5.04)	.19	5.157 (3.473)	.14
Race/ethnicity	0.33 (0.09–1.22)	.10	−9.518 (4.506)	.04
Body mass index	1.00 (0.93–1.07)	.98	−0.252 (0.248)	.31
Presenting heart rate	0.98 (0.96–1.01)	.16	0.039 (0.080)	.63
Initial LVEF	1.09 (1.01–1.18)	.03	−0.391 (0.259)	.14
Initial LVEDD (categorical)				
Normal	Reference		Reference	
Mildly dilated	0.13 (0.03–0.72)	.02	−10.847 (4.978)	.03
Moderately dilated	0.48 (0.09–2.68)	.40	−3.916 (4.978)	.43
Severely dilated	0.10 (0.02–0.48)	.004	−14.215 (4.511)	.003
Initial LVEDD (continuous)	0.33 (0.16–0.68)	.003	−6.690 (1.983)	.001
Systolic blood pressure	1.01 (0.99–1.02)	.31	0.082 (0.057)	.16
Serum sodium	0.96 (0.83–1.12)	.63	−0.259 (0.553)	.64
Serum blood urea nitrogen	1.01 (0.97–1.06)	.64	0.111 (0.164)	.50
Serum creatinine	0.92 (0.50–1.68)	.79	0.263 (2.295)	.91
Coronary angiography				
Angiographically normal	Reference		Reference	
Mild coronary artery disease	0.98 (0.31–3.10)	.97	−1.156 (4.292)	.79
Hypertension	1.36 (0.52–3.54)	.53	4.473 (3.501)	.21
Hyperlipidemia	2.64 (0.49–14.1)	.26	5.045 (5.476)	.36
Diabetes	4.41 (0.49–39.91)	.19	4.363 (6.240)	.49
Atrial fibrillation	0.79 (0.05–13.15)	.87	5.565 (10.501)	.60
Smoking				
Never	Reference		Reference	
Current	0.80 (0.28–2.35)	.69	−1.602 (3.998)	.69
Former	0.98 (0.28–3.48)	.98	−3.276 (4.695)	.49
Alcohol use				
None	Reference		Reference	
Light or moderate	0.91 (0.31–2.64)	.86	0.312 (4.012)	.94
Heavy or binge	1.67 (0.36–7.82)	.52	1.684 (5.555)	.77
Former heave or binge	1.25 (0.18–8.49)	.82	−6.327 (7.089)	.38
Postdiagnosis medications				
ACEI/ARB	1.28 (0.17–9.61)	.81	−0.828 (7.552)	.91
Beta-blocker	1.27 (0.08–21.10)	.87	1.126 (10.521)	.92
Aldosterone antagonist	1.18 (0.39–3.58)	.77	−0.459 (4.088)	.91
Digoxin	0.76 (0.22–2.63)	.66	−1.824 (4.646)	.70
Diuretic	0.89 (0.31–2.57)	.83	0.635 (3.941)	.87
Antiarrhythmic drug	0.51 (0.08–3.23)	.47	−3.548 (6.793)	.60
Aspirin	1.29 (0.49–3.40)	.61	0.907 (3.600)	.80
Anticoagulant	0.95 (0.26–3.45)	.93	1.722 (4.812)	.72
Statin	1.35 (0.45–4.02)	.59	−0.419 (4.011)	.92

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; GDMT, guideline-directed medical therapy; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; OR, odds ratio; SE, standard error; Δ LVEF_{GDMT}, post-GDMT LVEF – initial LVEF.

Characteristic	Post-GDMT LVEF >35%		Δ LVEF _{GDMT}	
	OR (95% CI)	p	β (SE)	p
Model 1: age, sex, race/ethnicity				
Initial LVEDD (categorical)				
Normal	Reference		Reference	
Mildly dilated	0.12 (0.02–0.71)	.02	–10.359 (4.922)	.04
Moderately dilated	0.58 (0.09–3.91)	.58	–2.684 (5.207)	.61
Severely dilated	0.10 (0.02–0.53)	.007	–12.789 (4.607)	.008
Model 2: age, sex, race/ethnicity, initial LVEF				
Initial LVEDD (categorical)				
Normal	Reference		Reference	
Mildly dilated	0.15 (0.03–0.88)	.04	–12.764 (4.742)	.009
Moderately dilated	0.70 (0.10–4.93)	.72	–4.516 (4.974)	.37
Severely dilated	0.13 (0.02–0.70)	.02	–16.185 (4.535)	.0008
Model 3: age, sex, race/ethnicity, initial LVEF, ACEI/ARB, beta blocker				
Initial LVEDD (categorical)				
Normal	Reference		Reference	
Mildly dilated	0.14 (0.02–0.86)	.03	–12.939 (4.782)	.009
Moderately dilated	0.70 (0.10–4.90)	.72	–4.403 (5.058)	.39
Severely dilated	0.13 (0.02–0.72)	.02	–15.709 (4.622)	.001
Model 1: age, sex, race/ethnicity				
Initial LVEDD (continuous)	0.35 (0.16–0.77)	.009	–5.484 (2.205)	.02
Model 2: age, sex, race/ethnicity, initial LVEF				
Initial LVEDD (continuous)	0.38 (0.17–0.86)	.02	–6.683 (2.182)	.003
Model 3: age, sex, race/ethnicity, initial LVEF, ACEI/ARB, beta blocker				
Initial LVEDD (continuous)	0.39 (0.17–0.88)	.02	–6.460 (2.209)	.005

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; GDMT, guideline-directed medical therapy; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; OR, odds ratio; SE, standard error; Δ LVEF_{GDMT}, post-GDMT LVEF – initial LVEF.

Some HF centers reserve ICD consideration based on LVEF assessment 6 months after reaching maximally tolerated doses of β -blockers (Teeter et al., 2012). A trade-off exists between implanting too early in those who may further improve LVEF and implanting too late in those who may have ventricular arrhythmias while waiting. A small study comprised mostly NICM subjects demonstrated continuous improvement in remodeling over 18 months (Hall et al., 1995). They observed LVEF measurements of $24\% \pm 8\%$ at baseline, $33\% \pm 10\%$ at 3 months, and $44\% \pm 13\%$ at 18 months. It is theoretically possible for some with large LVEDD to have similar rates of LVEF recovery as those with normal LVEDD if given more time on GDMT. High rates of GDMT adherence may be one reason for lack of ICD benefit in the Danish Study to Assess the Efficacy of ICDs in Patients with Nonischemic Systolic Heart Failure on Mortality (Køber et al., 2016).

Over one-third of our subjects with LVEF $\leq 35\%$ at 3 months demonstrated continued LVEF improvement with longer duration of treatment, suggesting that a longer time period than 3 months may be prudent prior to ICD consideration. Appropriate ICD therapies for ventricular arrhythmias, however, still occurred in this group over long-term follow-up. One subject had both NSVT and late gadolinium enhancement on CMR. In the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation trial, subjects with NICM of ≤ 3 months duration demonstrated a lower rate of death when ICDs were used in addition to GDMT, whereas the death rate was not lower in the ICD group when the NICM duration was >3 months (Kadish et al., 2006). This may reflect referral bias of subjects with perceived higher sudden death risk being referred earlier for study enrollment. Ventricular ectopy, defined as NSVT 3–15 beats at >120 bpm or >10

TABLE 4 Multivariable logistic and linear regression analyses for associations between initial LVEDD and LVEF response to GDMT

FIGURE 1 Box plot of post-GDMT LVEF improvement and initial LVEDD measurements. Lines and diamonds within the boxes represent medians and means, respectively. Lines at the bottom and top of the boxes represent first and third quartiles, respectively. Whiskers outside the boxes indicate variability outside upper and lower quartiles. GDMT, guideline-directed medical therapy; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction

FIGURE 2 Kaplan-Meier curve for probability of survival from adverse cardiac events based on post-GDMT LVEF status. In the post-GDMT LVEF ≤35% group, compared with the >35% group, the unadjusted hazard ratio for adverse cardiac events was 2.15 (95% confidence interval, 0.93–4.96; $p = .07$). GDMT, guideline-directed medical therapy; LVEF, left ventricular ejection fraction

TABLE 5 Long-term adverse cardiac events based on post-GDMT LVEF status

Adverse cardiac event	Total (n = 70)	Post-GDMT LVEF ≤35% group (n = 31)	Post-GDMT LVEF >35% group (n = 39)	p ^a
Any event ^b	23 (33)	14 (45)	9 (23)	.07
All events				
HF rehospitalization	15 (21)	11 (35)	4 (10)	.02
Appropriate WCD shock	0 (0)	0 (0)	0 (0)	NA
Resuscitated out-of-hospital cardiac arrest	0 (0)	0 (0)	0 (0)	NA
Appropriate ATP therapy	2 (3)	2 (6)	0 (0)	.19
Appropriate ICD shock	2 (3)	2 (6)	0 (0)	.19
Ventricular assist device	3 (4)	3 (10)	0 (0)	.08
Heart transplantation	0 (0)	0 (0)	0 (0)	NA
Death	8 (11)	3 (10)	5 (13)	1.00

ATP, antitachycardia pacing; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NA, not applicable; WCD, wearable cardioverter defibrillator.

^aPost-GDMT LVEF ≤35% group versus post-GDMT LVEF >35% group.

^bFor any event, only the first event per subject was counted.

premature ventricular complexes per hour, was an inclusion criteria in this trial (Kadish et al., 2004). This risk marker may be useful when considering WCD and/or earlier ICD recommendation.

Cardiovascular magnetic resonance imaging may play a future role in guiding optimal timing for ICD recommendation. LGE detected on CMR has been shown to predict LVEF improvement on β -blocker

treatment (Bello et al., 2003). CMR has also been demonstrated to increase prediction for mortality and sudden death in subjects with NICM (Gulati et al., 2013). Echocardiographic LVEDD measurement may be valuable to determine which subjects with new-onset NICM should be referred for CMR for further risk stratification. Theoretically, those without LGE may be allowed a longer time on GDMT given

TABLE 6 Characteristics of 31 subjects with post-GDMT LVEF $\leq 35\%$, listed by long-term LVEF

Age (yr)/Sex	Initial LVEF, %	Initial LVEDD, cm	Post-GDMT LVEF, %	CIED	Long-term LVEF, %	Follow-up time (yr) ^a	Adverse cardiac events
Long-term LVEF >35%							
71/F	27.5	5.5	27.5	D-ICD	57.5	3.1	HF rehospitalization
53/F	12.5	5.5	25	D-ICD	52.5	4.6	
37/M	19	7.3	24	S-ICD	52.5	2.2	ICD shock
43/F	22.5	6.6	27.5	S-ICD	52.5	3.8	
70/F	22.5	6.1	32.5	S-ICD	52.5	2.3	
54/M	32.5	5.4	27	S-ICD	47.5	3.5	
51/M	17.5	7.0	17.5	S-ICD	42.5	2.4	HF rehospitalization
51/M	15	6.3	27.5	S-ICD	40	1.1	ATP therapy, ICD shock
70/F	15	5.6	32.5	Declined	37.5	0.4	
Long-term LVEF $\leq 35\%$							
60/M	15	5.6	25	D-ICD	35	7.9	HF rehospitalization
64/M	25	7.1	25	S-ICD	35	2.3	
43/M	12.5	5.9	17.5	D-ICD	32	5.9	
59/M	17.5	6.6	27.5	S-ICD	27.5	0.4	
63/M	18	7.3	15	D-ICD	27.5	2.7	
51/M	22.5	6.2	22.5	Declined	27.5	2.3	
54/M	17.5	5.6	17.5	S-ICD	22.5	2.1	ATP therapy
53/M	17.5	7.8	27.5	S-ICD	22.5	2.7	
49/F	17.5	6.9	12.5	S-ICD	22.5	3.7	
52/F	27.5	6.2	22.5	S-ICD	22.5	5.5	
33/M	17	6.2	32.5	D-ICD	17.5	6.8	HF rehospitalization, death
43/F	34		22.5	S-ICD	17.5	4.5	HF rehospitalization
36/M	17.5	7.3	32.5	S-ICD	12.5	1.2	HF rehospitalization, death
33/M	12		17.5	S-ICD	10	3.2	HF rehospitalization
47/M	17.5	7.2	12.5	S-ICD	VAD ^b	4.5	HF rehospitalization, VAD
41/F	17.5	5.8	22.5	CRT-D	VAD ^b	9.3	HF rehospitalization, VAD
32/F	12.5	8.0	12.5	S-ICD	VAD ^b	1.9	HF rehospitalization, VAD
Long-term LVEF measurement not performed							
75/M	25	5.9	27.5	Declined			HF rehospitalization, death
42/M	22.5	7.6	22.5	No follow-up			
41/M	20		22.5	S-ICD			
59/M	12.5	6.6	22.5	S-ICD			
53/F	25	6.5	20	S-ICD			

ATP, antitachycardia pacing; CIED, cardiovascular implantable electronic device; CRT-D, cardiac resynchronization therapy defibrillator; D-ICD, dual-chamber implantable cardioverter defibrillator; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; S-ICD, single-chamber implantable cardioverter defibrillator; VAD, ventricular assist device; yr, year.

^aFollow-up time was measured from post-GDMT to long-term LVEF measurements.

^bSubjects with VADs were noted to have severely depressed LVEF, but were not quantified.

higher chance of LVEF improvement and lower risk for arrhythmic death. Conversely, those with significant areas of LGE may be strongly considered for ICD placement at 3 months, or even sooner, if the LVEF remains $\leq 35\%$.

4.1 | Study limitations

Our findings should be considered hypothesis generating and not conclusive given the retrospective design of our study. Our subjects were

nevertheless identified in a prospective fashion. Prescription of WCDs for the cohort may have resulted in selection bias. However, WCD use allowed for monitoring for significant arrhythmias in the postdischarge period. Titration of GDMT was not standardized. An estimation of the percentage of eligible subjects with new-onset NICM and narrow QRS complex was not available. The relatively small cohort limited our ability to detect differences in long-term clinical events. Including appropriate ATP therapy and ICD shocks may have tilted the measure of adverse cardiac events against the post-GDMT group (Ellenbogen et al., 2006). We did not have a core echocardiography laboratory to standardize measurements. There was no systematic screening for ventricular ectopy. The overall use of CMR was low.

5 | CONCLUSION

In our study of subjects with new-onset idiopathic NICM with narrow QRS complex, severely dilated LVEDD strongly predicted lack of LVEF improvement after approximately 3 months on GDMT. Subjects without LVEF improvement at 3 months are at higher risk for adverse cardiac events, but a substantial number have further LVEF improvement over time. Further studies should assess the potential utility of initial LVEDD measurement by echocardiography to refine recommendations for postdischarge WCD prescription, duration of GDMT prior to LVEF assessment for ICD consideration, and CMR risk stratification to improve ICD timing.

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REFERENCES

- Aleong, R. G., Mulvahill, M. J., Halder, I., Carlson, N. E., Singh, M., Bloom, H. L., ... London, B. (2015). Left ventricular dilatation increases the risk of ventricular arrhythmias in patients with reduced systolic function. *Journal of the American Heart Association*, 4, e001566. <https://doi.org/10.1161/JAHA.114.001566>
- Bardy, G. H., Lee, K. L., Mark, D. B., Poole, J. E., Packer, D. L., Boineau, R., ... for the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators. (2005). Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *New England Journal of Medicine*, 352, 225–237.
- Bello, D., Shah, D. J., Farah, G. M., Di Luzio, S., Parker, M., Johnson, M. R., ... Kim, R. J. (2003). Gadolinium cardiovascular magnetic resonance predicts reversible myocardial dysfunction and remodeling in patients with heart failure undergoing β -blocker therapy. *Circulation*, 108, 1945–1953.
- Binkley, P. F., Lesinski, A., Ferguson, J. P., Hatton, P. S., Yamokoski, L., Hardikar, S., ... Leier, C. V. (2008). Recovery of normal ventricular function in patients with dilated cardiomyopathy: Predictors of an increasingly prevalent clinical event. *American Heart Journal*, 155, 69–74.
- Cicoira, M., Zanolli, L., Latina, L., Rossi, A., Golia, G., Brighetti, G., & Zardini, P. (2001). Frequency, prognosis, and predictors of improvement of systolic left ventricular function in patients with 'classical' clinical diagnosis of idiopathic dilated cardiomyopathy. *European Journal of Heart Failure*, 3, 323–330.
- Ellenbogen, K. A., Levine, J. H., Berger, R. D., Daubert, J. P., Winters, S. L., Greenstein, E., ... for the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators (2006). Are implantable cardioverter-defibrillator shocks a surrogate for sudden cardiac death in patients with nonischemic cardiomyopathy? *Circulation*, 113, 776–782.
- Gulati, A., Jabbour, A., Ismail, T. F., Guha, K., Khwaja, J., Raza, S., ... Prasad, S. K. (2013). Association of fibrosis with mortality and sudden cardiac death in patient with nonischemic dilated cardiomyopathy. *JAMA*, 309, 896–908.
- Hall, S. A., Cigarroa, C. G., Marcoux, L., Risser, R. C., Grayburn, P. A., & Eichhorn, E. J. (1995). Time course of improvement in left ventricular function, mass and geometry in patients with congestive heart failure treated with beta-adrenergic blockade. *Journal of the American College of Cardiology*, 25, 1154–1161.
- Kadish, A., Dyer, A., Daubert, J. P., Quigg, R., Estes, N. A. M., Anderson, K. P., ... for the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) Investigators. (2004). Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. *New England Journal of Medicine*, 350, 2151–2158.
- Kadish, A., Schaechter, A., Subacius, H., Thattassery, E., Sanders, W., Anderson, K. P., ... Levine, J. (2006). Patients with recently diagnosed nonischemic cardiomyopathy benefit from implantable cardioverter-defibrillators. *Journal of the American College of Cardiology*, 47, 2477–2482.
- Kawai, K., Takaoka, H., Hata, K., Yokota, Y., & Yokoyama, M. (1999). Prevalence, predictors, and prognosis of reversal of maladaptive remodeling with intensive medical therapy in idiopathic dilated cardiomyopathy. *American Journal of Cardiology*, 84, 671–676.
- Kloner, R. A., & Rezkalla, S. H. (2007). To drink or not to drink? That is the question *Circulation*, 116, 1306–1317.
- Køber, L., Thune, J. J., Nielsen, J. C., Haarbø, 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, 1221–1230.
- Konstam, M. A., Rousseau, M. F., Kronenberg, M. W., Udelson, J. E., Melin, J., Stewart, D., ... for the SOLVD Investigators. (1992). Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. *Circulation*, 86, 431–438.
- Kutyifa, V., Moss, A. J., Klein, H., Biton, Y., McNitt, S., MacKecknie, B., ... Goldenberg, I. (2015). Use of the wearable cardioverter defibrillator in high-risk cardiac patients: Data from the Prospective Registry of Patients Using the Wearable Defibrillator (WEARIT-II Registry). *Circulation*, 132, 1613–1619.
- Lang, R. M., Badano, L. P., Mor-Avi, V., Afilalo, J., Armstrong, A., Ernande, L., ... Voigt, J.-E. (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, 1–39.
- McNamara, D. M., Starling, R. C., Cooper, L. T., Boehmer, J. P., Mather, P. J., Manosko, K. M., ... for the IMAC Investigators (2011). Clinical and demographic predictors of outcomes in recent onset dilated cardiomyopathy. *Journal of the American College of Cardiology*, 58, 1112–1118.

- Packer, M., Antonopoulos, G. V., Berlin, J. A., Chittams, J., Konstam, M. A., & Udelson, J. E. (2001). Comparative effects of carvedilol and metoprolol on left ventricular ejection fraction in heart failure: Results of a meta-analysis. *American Heart Journal*, 141, 899–907.
- Piccini Sr, J. P., Allen, L. A., Kudenchuk, P. J., Page, R. L., Patel, M. R., Turakhia, M. P., on behalf of the American Heart Association Electrocardiography and Arrhythmia Committee of the Council on Clinical Cardiology and Council on Cardiovascular and Stroke Nursing (2016). Wearable cardioverter-defibrillator therapy for the prevention of sudden cardiac death: A science advisory from the American Heart Association. *Circulation*, 133, 1715–1727.
- Schliamser, J. E., Kadish, A. H., Subacius, H., Shalaby, A., Schaechter, A., Levine, J., ... for the DEFINITE Investigators (2013). Significance of follow-up left ventricular ejection fraction measurements in the Defibrillators in Non-Ischemic Cardiomyopathy Treatment Evaluation trial (DEFINITE). *Heart Rhythm: The Official Journal of the Heart Rhythm Society*, 10, 838–846.
- Singh, M., Wang, N. C., Jain, S., Voigt, A., Saba, S., & Adelstein, E. C. (2015). Utility of the wearable cardioverter-defibrillator in patients with newly diagnosed cardiomyopathy: A decade-long single-center experience. *Journal of the American College of Cardiology*, 66, 2607–2613.
- Solomon, S. D., Anavekar, N., Skali, H., McMurray, J. J. V., Swedberg, K., Yusuf, S., ... for the Candesartan in Heart Failure Reduction in Mortality (CHARM) Investigators (2005). Influence of ejection fraction on cardiovascular outcomes in a broad spectrum of heart failure patients. *Circulation*, 112, 3738–3744.
- Teeter, W. A., Thibodeau, J. T., Rao, K., Brickner, M. E., Toto, K. H., Nelson, L. L., ... Drazner, M. H. (2012). The natural history of new-onset heart failure with a severely depressed left ventricular ejection fraction: Implications for timing of implantable cardioverter-defibrillator implantation. *American Heart Journal*, 164, 358–364.
- 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, 2656–2666.
- Wang, N. C., Piccini, J. P., Konstam, M. A., Maggioni, A. P., Traver, B., Swedberg, K., ... for the EVEREST Investigators. (2010). Implantable cardioverter-defibrillators in patients hospitalized for heart failure with chronically reduced left ventricular ejection fraction. *American Journal of Therapeutics*, 17, e78–e87.
- Wang, N. C., Singh, M. O., 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, 933–942.
- Wasserstein, R. L., & Lazar, N. A. (2016). The ASA's statement on p-values: Context, process, and purpose. *The American Statistician*, 70, 129–133. <https://doi.org/10.1080/00031305.2016.1154108>
- Yancy, C. W., Jessup, M., Bozkurt, B., Butler, J., Casey, D. E. Jr., 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. *Journal of the American College of Cardiology*, 62, e147–e239.
- Zecchin, M., Merlo, M., Pivetta, A., Barbati, G., Lutman, C., Gregori, D., ... Sinagra, G. (2012). How can optimization of medical treatment avoid unnecessary implantable cardioverter-defibrillator implantations in patient with idiopathic dilated cardiomyopathy presenting with “SCD-HeFT Criteria?”. *American Journal of Cardiology*, 109, 729–735.

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