Systematic Review and Meta-Analysis

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Etiologic impact on difference on clinical outcomes of patients with heart failure after cardiac resynchronization therapy

A systematic review and meta-analysis

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Abstract

Objective: To compare long-term clinical outcomes between patients with heart failure due to non-ischemic cardiomyopathy (NICM) and those due to ischemic cardiomyopathy (ICM) after cardiac resynchronization therapy (CRT).

Methods and Results: EMbase, PubMed, and Cochrane Library were searched for published studies up to December 2017. Twenty-one observational studies with 12,331 patients were enrolled in the present meta-analysis. The results demonstrated that the all-cause mortality in NICM patients was significantly lower than that in ICM patients (RR 1.37, 95% CI 1.16–1.61). In terms of echocardiographic parameters, NICM patients exhibited statistically significant improvement in left ventricular ejection fraction (LVEF) (MD 2.70, 95%CI -4.13 to -1.28), and a significant decrement in left ventricular end-systolic volume (LVESV) (MD 10.41,95% CI 2.10–18.73) and left ventricular end diastolic diameter (LVEDD) (MD 7.63, 95% CI 2.59–12.68) as compared with ICM patients. No significant difference was observed in the improvement of New York Heart Association Functional Classification (MD 0.05, 95% CI -0.05 to 0.15), pulmonary arterial systolic pressure (PASP) (MD -0.61, 95% CI -4.36 to 3.14), and severity of mitral regurgitation (MD 0.00, 95% CI -0.08 to 0.07) between the 2 groups.

Conclusions: Our meta-analysis illustrated that patients with HF due to NICM tended to have better clinical outcomes and LV reverse remodeling as compared with those due to ICM. This finding may help clinicians select patients who respond favorably to CRT, though further research is required to clarify the potential confounding factors and underlying mechanisms for this phenomenon.

Abbreviations: ACEI = angiotensin converting enzyme inhibitor, CRT = cardiac resynchronization therapy, CRT-D = cardiac resynchronization therapy-defibrillator, HF = heart failure, ICM = ischemic cardiomyopathy, LVEF = left ventricular ejection fraction, LVESV = left ventricular end-systolic volume, MR = mitral regurgitation, NICM = non-ischemic cardiomyopathy, NYHA = New York Heart Association, PASP = pulmonary arterial systolic pressure.

Keywords: cardiac resynchronization therapy, etiology, heart failure, meta-analysis, outcomes

1. Introduction

Heart failure (HF) is the final stage of the most common cardiovascular syndrome around the world.[1,2] It is enumerated that about 25% HF patients experienced varying degrees of asynchronous cardiac contraction.[3–6] Cardiac resynchronization therapy (CRT) that aims to correct impaired ventricular electromechanical coupling, reverse structural remolding and create a more uniform distribution of myocardial blood has been established as a cornerstone for drug-refractory HF.[7–9]

The American College Cardiology and European Society Cardiology (ACC/ESC) HF guidelines recommend prophylactic implantation and CRT for symptomatic patients with HF in sinus rhythm and a pronged QRS interval despite optimal medical therapy.[1,2,10] However, there are still about 30% HF patients who failed to respond to CRT.[11] Some previous studies suggested that different etiologies of HF might affect the responsiveness to CRT.

There are two relevant meta-analyses reported by Chen et al and Makki et al.[12,13] Chen et al searched Medline, Embase, and Cochrane Library from inception to 2012 and included 14 observational studies with 3463 patients. Makki et al searched several databases up to 2013 and included 6 studies. However, the definition of primary endpoints in these 2 studies is ambiguous. In addition, the statistical results in some previous studies[2,14,15] are not sufficiently reliable and even controversial due to the lack of rigorous research types, incomplete database indexes, and small sample sizes. The aim of the present meta-analysis is intended to make a more comprehensive assessment on the effectiveness of CRT on HF due to ischemic cardiomyopathy (NICM) and ischemic cardiomyopathy (ICM) by summarizing

Editor: Ovidiu Constantin Baltatu.

X-WN contributed equality to this work.

Supplemental Digital Content is available for this article.

The authors have no conflicts of interest to disclose.

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Medicine (2018) 97:52(e13725)

Received: 19 June 2018 / Accepted: 26 November 2018

http://dx.doi.org/10.1097/MD.0000000000013725

studies published in related databases, hoping to draw a more reliable conclusion.

2. Methods

2.1. Data source and search strategy

We searched PubMed, Cochrane Library, and EMBASE databases up to December 2017 for evaluating the effect of CRT on clinical outcomes and long-term prognosis between patients with HF due to ICM and those due to NICM. The following medical subject heading terms were used:

1) HF;
2) cardiomyopathy; and
3) CRT.

This search was then supplemented with careful examination of reference lists of identified reports for any relevant studies missed initially. There were no language restrictions. The detailed search strategies are displayed in Figure 1.

2.2. Inclusion and exclusion criteria

Studies were considered for inclusion if they met the following qualified criteria:

1) performed a contemporaneous comparison between ICM and NICM groups in response to CRT (including CRT alone or CRT-defibrillator [CRT-D], but not including implantable cardioverter defibrillator [ICD]alone);

1. originally reported the primary and/or secondary outcomes;
2. had more than 30 participants;
3. had a minimum follow-up period of 6 months; and
4. reported relative risk (RR) with 95% confidence interval (CI), or provided base-line data that could be calculated.

Studies were excluded if they were

1) animal experiments, non-original literature, reviews, editorials or case reports; and
2) data that could not be extracted, calculated, or were not associated with CRT intervention.

2.3. Outcome definition

The all-cause mortality rate was considered to be the main clinical outcome during the follow-up period. In addition, the New York Heart Association (NYHA) functional classification was also used as an indicator of clinical outcomes. We assessed the left ventricular (LV) function and size measured by echocardiography, including LV ejection fraction (LVEF), LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), mitral regurgitation (MR) severity, and pulmonary arterial systolic pressure (PASP).

2.4. Data extraction and quality assessment

Two review authors (Chen JS and Wang J) independently extracted information from included trials using the proforma process piloted on a random sample of papers. Disagreements between the reviewers concerning the decision were resolved by consultation with the third reviewer (Niu XW). We reported details of study design, participants, interventions, mean follow-up time, QRS duration, NYHA functional classification and

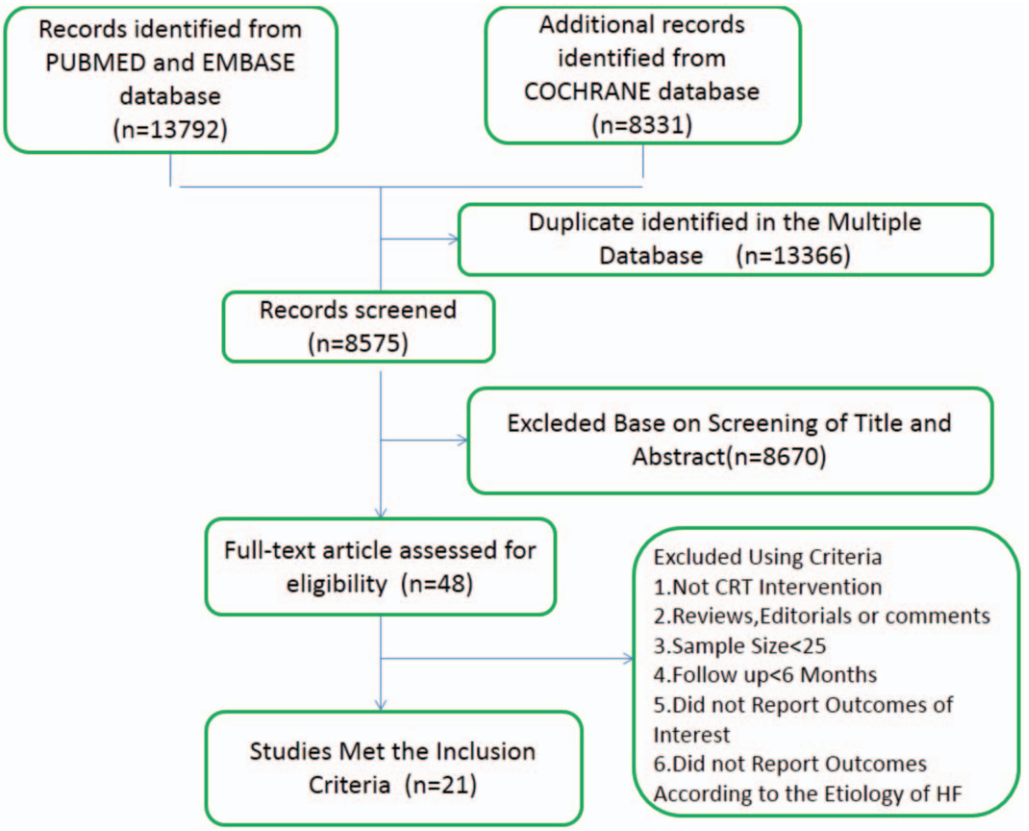

Figure 1. Flow diagram showing the study selection process.

efficacy outcomes. We also recorded details of relevant therapies provided to the patients. When a trial was presented in an abstract form, we further searched for information on the Internet and checked for the best available resources or publication. Full-text articles were included if they met the study criteria and provided pertinent information on outcomes. Quality assessment was performed by using the Newcastle-Ottawa Scale (NOS). Publication bias was quantified by the Egger's regression for which data from ten or more studies were available.

2.5. Statistical analysis

Continuous variables were analyzed using the mean difference (MD) with 95% CI. RR was used for dichotomous outcomes as the confirmatory effect size estimate. A random-effects meta-analysis of the study outcomes was performed with the pooled effect size. The between-study heterogeneity was assessed by the I^2 measure. With I^2 values of 50% or less, heterogeneity was acceptable referring to Cochrane handbook and in the case of a high level of heterogeneity with an I^2 value of 50% or larger. We performed a sensitivity analysis by comparing the results of meta-analysis of included studies with the results of the remaining studies after elimination of low-quality studies. All analyses were made using the R software. A P value $<.05$ was pre-specified to indicate statistical significance.

3. Results

3.1. Baseline characteristics of the included studies

Twenty-one studies [16–36] involving 12,331 patients (5736 ICM and 6595 NCM) met the inclusion criteria for meta-analysis. Most of these studies were prospective trials in nature, and 6 were retrospective trials. The length of follow-up ranged from 6 to 48 months (median 17.7 months). Age distributions of both groups were the same. Male patients in ICM group accounted for 83% and 66% NICM group. Most patients recruited to the identified studies were in NYHA class III and IV with LVEF<35%. The average QRS interval of the two sets was greater than 150 ms. The application rate of diuretics fluctuated from 74% to 100%. The use rate of angiotensin converting enzyme inhibitor (ACEI) was 70% to 96%. The median of the clinical application rate of β-adrenergic blockade and aldosterone receptor antagonists was 76.6% and 80% respectively. The characteristics of the included studies and the associated patient characteristics are summarized in Tables 1 and 2. Details of study quality assessment are shown in Table 3. The median of NOS scores was 8. The detailed scoring processes are reported in Supplementary 4., http://links.lww.com/MD/C704.

3.2. Impact of etiologic differences on the clinical outcome

3.2.1. All-cause mortality. After exclusion of 1426 patients whose primary endpoints were not available, 10905 patients were analyzed for the endpoint of all-cause mortality. During a 12-month follow-up period, the pooled analysis of observational studies showed that patients in ICM group had a greater risk for all-cause mortality than patients in NICM group (pooled RR=1.37, 95% CI=1.16–1.61) (Fig. 2). Test of heterogeneity (I2=38%, P=.01) with random-effect model was acceptable.

3.2.2. NYHA classification. We extracted data from 6 trials, totaling 1234 patients with ICM and 1248 patients with NICM. Comprehensive results of 6 observational studies showed no significant difference between the 2 groups when the NYHA classification was used (MD 0.05, 95%CI -0.05 to 0.15)(Fig. 3).

3.3. Impact of etiologic differences on echocardiographic outcomes

3.3.1. LVEF. Thirteen studies comprising 3925 patients performed echocardiography 6 months after CRT to ascertain whether the efficacy and effectiveness of CRT was affected by the

Table 1

Characteristics of the studies included in this Meta-analysis.

		Inclusion Criteria			Sample Size (N)			
Study (year)	Study type	NYHA cclass	QRS (ms)	LVEF (%)	ICM (n)	NICM (n)	Mean follow-up (M)	Primary outcomes
QiWang (2017)[16]	prospective	III or IV	≧120	≦35	27	77	6	NA
Sérgio Barra (2017)[17]	prospective	III or IV	NA	≦35	2682	2625	41.4	death
AdamC Powell (2017)[18]	retrospective	III to IV	NA	NA	219	1084	12	hospitalization due to HF
Pieter Martens (2017)[19]	retrospective	II to IV	≧120	≦35	300	385	12	death /hospitalization due to HF
J.van't Sant (2016)[20]	prospective	I to IV	≧120	≦30	85	95	12	death
Akinori Sugano (2016)[21]	retrospective	II to IV	≧120	≦35	91	281	6	death /hospitalization due to HF
Christoffer TW (2015)[22]	prospective	II to IV	≧120	≦35	490	427	48	death
Zaca V (2011)[23]	retrospective	III or IV	>120	≦35	41	63	12	NA
Mcleod CJ (2011)[24]	retrospective	III or IV	>120	≦35	312	191	7.1	death
Kazemi SA (2009)[25]	retrospective	III or IV	>125	<35	48	35	6	NA
Zhang,Q (2009)[26]	prospective	III or IV	>120	<40	52	67	39	death/cardiovascular hospitalization
Boriani,G (2009)[27]	prospective	II to IV	>130	≦35	737	635	16	death any cause/urgent heart translantion
Marsan,N.A (2009)[28]	prospective	III or IV	>120	≦35	135	87	6	NA
Di Biase L (2008)[29]	prospective	III or IV	>120	≦35	219	179	52.8	combined for death and heart transplant
Vidal,B (2007)[30]	prospective	III or IV	>120	≦35	43	63	12	death/heart transplant
D'Andrea,A (2007)[31]	prospective	III or IV	>120	<35	43	47	6	NA
Soliman,O.I (2007)[32]	prospective	III or IV	>120	<35	36	38	24	cardiac-related death/hospitalization due to HF
Waggoner,AD (2006)[33]	prospective	III or IV	>150	<35	19	38	20	death/heart transplant/hospitalization due to HF
Leclercq C (2004)[34]	prospective	III or IV	>150	<35	48	55	12	death from any cause
Molhoek SG (2004)[35]	prospective	III or IV	>120	<35	34	40	ICM14.2 NICM13.8	death from any cause
Gasparini M (2003)[36]	prospective	II to IV	>110	<40	75	83	11.2	death

HF=heart failure, ICM=ischemic cardiomyopathy, LVEF=left ventricular ejection fraction, NICM=non-ischemic cardiomyopathy, NYHA=New York Heart Association.

Table 2

Characteristics of the patients enrolled in this Meta-analysis.

	QiWang (2017)		SergioBarra (2017)		Adamc. Powell (2017)		Pieter Martens (2017)		Soliman,O I (2007)	
	ICM	NICM	ICM	NICM	ICM	NICM	ICM	NICM	ICM	NICM
age	61.3±8.8	59.3±11.2	69.3±9.6	64.7±11.9	72.0±8.0	72.6±8.5	74.0±9.0	71.0±11.0	59.0±11.0	59.0±10.0
male	21	57	2339	1813	162	797	249	213	28	24
NYHA (III/IV)	27	77	2034	1855	NA	NA	187	230	36	38
Mean QRS	150.7±25.0	155.6±24.7	NA	NA	NA	NA	153.0±30.0	155.0±29.0	169.0±29.0	172.0±27.0
LVEF	27.4±5.4	28.4±4.7	26.2±8.0	25.6±8.0	NA	NA	30.0±9.0	30.0±9.0	19.0±4.0	17.0±4.0
History of AF	NA	NA	37%	34%	NA	NA	38%	37%	NA	NA
Stroke or TIA	NA	NA	8%	6%	NA	NA	29%	20%	NA	NA
DM	NA	NA	32%	20%	NA	NA	36%	18%	25%	5%
COPD	NA	NA	15%	13%	NA	NA	22%	13%	NA	NA
Diuretics%	100.0%	100.0%	NA	NA	NA	NA	NA	NA	NA	NA
ACEI/ARB%	74.1%	85.7%	80.9%	82.7%	NA	NA	83.0%	87.0%	NA	NA
B-RI%	70.4%	70.1%	77.0%	76.1%	NA	NA	84.0%	83.0%	NA	NA
Spironolactone%	92.6%	97.4%	38.5%	42.5%	NA	NA	62.0%	62.0%	NA	NA

	J. Van Sant (2016)		Akinorisugano (2016)		Christoffer Tobias (2015)		Zaca,V (2011)		Waggoner,A. D (2006)	
	ICM	NICM	ICM	NICM	ICM	NICM	ICM	NICM	ICM	NICM
age	NA	NA	68.8±10.6	64.6±12.4	70.1±8.6	64.2±11.8	67.2±7.5	65.4±8.7	63.0±11.0	60.0±12.0
male	NA	NA	77	175	430	303	30	42	18	25
NYHA (III/IV)	NA	NA	80	229	385	318	38	59	NA	NA
Mean QRS	NA	NA	158.1±28.7	160.6±31.2	166.2±28.0	166.6±25.4	175.5±27.1	179.5±28.3	180.0±20.0	180±30.0
LVEF	21.6±6.8		27.6±8.4	26.0±8.6	25.0±6.9	25.0±7.4	25.0±6.0	24.0±6.0	23.0±5.0	26.0±5.0
History of AF	NA	NA	NA	NA	17%	19%	NA	NA	NA	NA
Stroke or TIA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DM	NA	NA	NA	NA	12%	10%	NA	NA	NA	NA
COPD	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Diuretics%	90%		74.7%	84.4%	82.0%	82.0%	96.1%	97.8%	94.0%	80.0%
ACEI/ARB%	76.00%		73.6%	81.5%	89.0%	91.0%	95.9%	96.8%	88.0%	97.0%
B-RI%	157 (78)		75.8%	78.3%	76.0%	77.0%	NA	NA	NA	NA
Spironolactone%	NA	NA	NA	NA	52.0%	56.0%	59.7%	57.1%	65.0%	51.0%

	Mcleod CJ (2011)		Kazemi S.A (2009)		zhang,Q (2009)		Boriani,G (2009)		Leclercq C (2004)	
	ICM	NICM	ICM	NICM	ICM	NICM	ICM	NICM	ICM	NICM
age	71.1±9.4	64.5±12.6	59.4±10.4	55.7±10.7	65.0±12.0	64.0±13.0	69.0±8.0	66.0±10.0	70.0±8.0	65.0±12.0
male	273	124	41	21	39	49	662	460	44	37
NYHA (III/IV)	NA	NA	NA	NA	52	67	597	514	48	55
Mean QRS	164.9±34.2	169.9±33.5	164.7±28.2	159.5±24.4	131.0±31.0	137.0±37.0	163.0±32.0	165.0±30.0	180.0±29.0	176.0±27.0
LVEF	23.1±6.9	23.3±7.8	20.6±5.5	19.28±5.09	27.2±6.8	26.4±9.2	26.0±7.0	26.0±7.0	22.0±6.0	22.0±8.0
History of AF	28%	36%	NA	NA	NA	NA	12%	17%	NA	NA
Stroke or TIA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DM	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
COPD	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Diuretics%	NA	NA	NA	NA	NA	NA	86.0%	89.0%	NA	NA
ACEI/ARB%	84.0%	83.0%	NA	NA	NA	NA	70.0%	74.0%	NA	NA
B-RI%	87.0%	84.0%	NA	NA	NA	NA	47.0%	53.0%	NA	NA
Spironolactone%	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

	Marsan,N,A (2009)		Di Biase L (2008)		Vidal,B (2007)		D Andrea,A (2007)		Molhoek SG (2004)		Gasparini M (2003)	
	ICM	NICM	ICM	NICM	ICM	NICM	ICM	NICM	65.0±10.0	64.0±11.0	66.8±87.8	64.6±0.1
age	65.0±10.0	67.0±17.0	71.1±9.4	63.0±12.5	69.0±7.0	69.0±8.0	53.6±11.3	51.3±8.3	30	27	69	52
male	57	28	189	110	NA	NA	23	25	NA	NA	62	66
NYHA (III/IV)	65	35	189	157	28	52	43	47	175.0±29.0	178.0±29.0	175.0±29.0	178.0±29.0
Mean QRS	143.0±28.0	153.0±33.0	NA	NA	140.0±28.0	154.0±29.0	NA	NA	21.0±9.0	23.0±13.0	21.0±9.0	23.0±13.0
LVEF	25.0±8.0	25.0±8.0	21.5±8.0	21.8±8.4	28.0±8.0	25.0±6.0	31.1±3.2	30.1±4.1	NA	NA	NA	NA
History of AF	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Stroke or TIA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DM	NA	NA	33%	19%	NA	NA	45%	30%	NA	NA	NA	NA
COPD	NA	NA	21%	15%	NA	NA	NA	NA	NA	NA	NA	NA
Diuretics%	96%		85.4%	83.2%	NA	NA	94.0%	96.0%	NA	NA	NA	NA
ACEI/ARB%	87%		83.6%	86.6%	78.0%	83.0%	95.0%	93.0%	NA	NA	NA	NA
B-RI%	78%		77.6%	73.5%	68.0%	64.0%	86.0%	82.0%	NA	NA	NA	NA
Spironolactone%	NA	NA	36.6%	30.7%	NA	NA	53.0%	58.0%	NA	NA	NA	NA

β-RI = β-adrenergic blockade, ACEI = angiotensin converting enzyme inhibitor, AF = atrial fibrillation, COPD = chronic obstructive pulmonary disease, DM = diabetes mellitus, HF = heart failure, ICM = ischemic cardiomyopathy, LVEF = left ventricular ejection fraction, LVESV = left ventricular end systolic volume, M = month, ms = milliseconds, NA = unavailable, NICM = non-ischemic cardiomyopathy, NYHA = New York Heart Association, TIA = transient ischemic attack.

underlying HF etiology. The LVEF improvement in NICM group was better than that in ICM group (MD -2.70, 95% CI -4.13 to -1.28). There existed heterogeneity (I2 75%, $P < .01$) with random-effect model (Fig. 4).

3.3.2. LVESV. In 9 studies, CRT was administered for more than 6 months, totaling 2998 patients with echocardiographic changes in a reduction in LVESV. The risk of prolonged (> 6-month) administration of CRT was higher in ICM patients than that in NICM patients (MD 10.41, 95% CI 2.10–18.73). Heterogeneity across trials was acceptable (I2 36%, $P = .13$) (Supplementary Fig. 5).

3.3.3. LVEDV. Nine studies involved the research on LVEDV. They reported that ventricular function in NICM group was

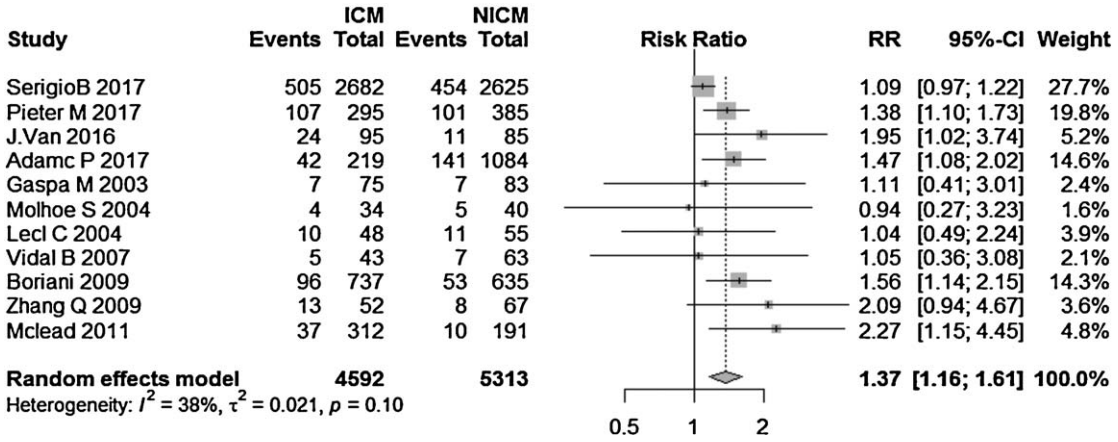

Figure 2. A forest plot for all-cause mortality.

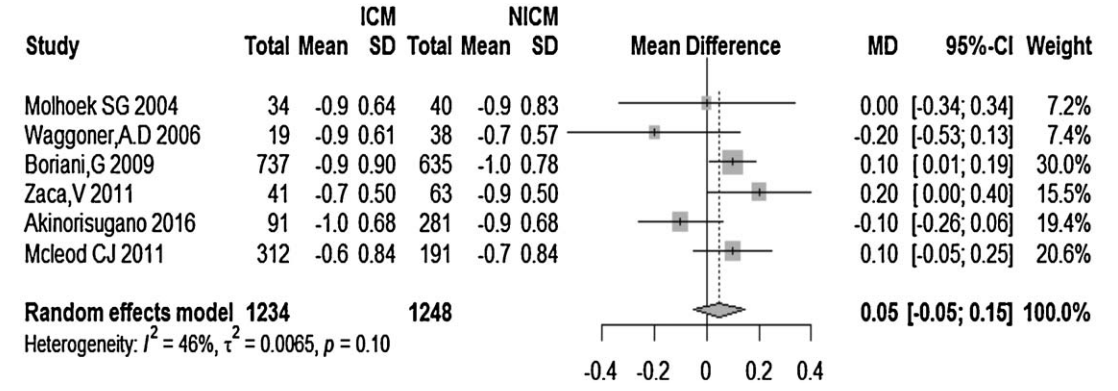

Figure 3. A forest plot for New York Heart Association. SD = standard deviation.

better than that in ICM group (MD 10.41, 95% CI 2.10to 18.73) (Supplementary Fig. 6).

3.3.4. MR severity and PASP. As shown in Figures 7 and 8, there was no significant difference in MR severity and PASP between the 2 groups (MD 0.00, 95%CI -0.08 to 0.07 vs MD -0.61, 95% CI-4.36 to 3.14).

3.4. Publication bias and sensitivity analysis

We did not observe significant bias based on the Egger regression (P = .69). We also conducted a sensitivity analysis of the results of significant heterogeneity (LVEF) to investigate their latent sources and evaluate the robustness of these outcomes. After eliminating each of the included studies 1 by 1 to each outcome,

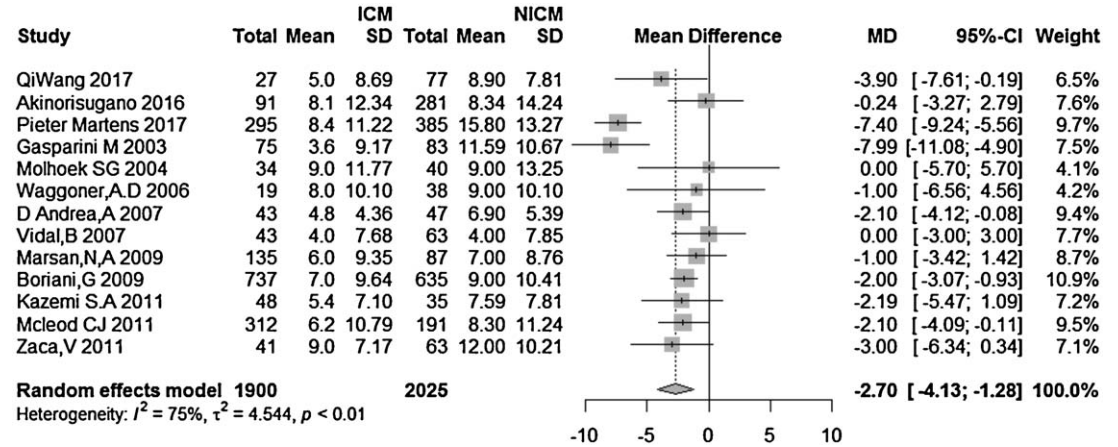

Figure 4. A forest plot for left ventricular ejection fraction. SD = standard deviation.

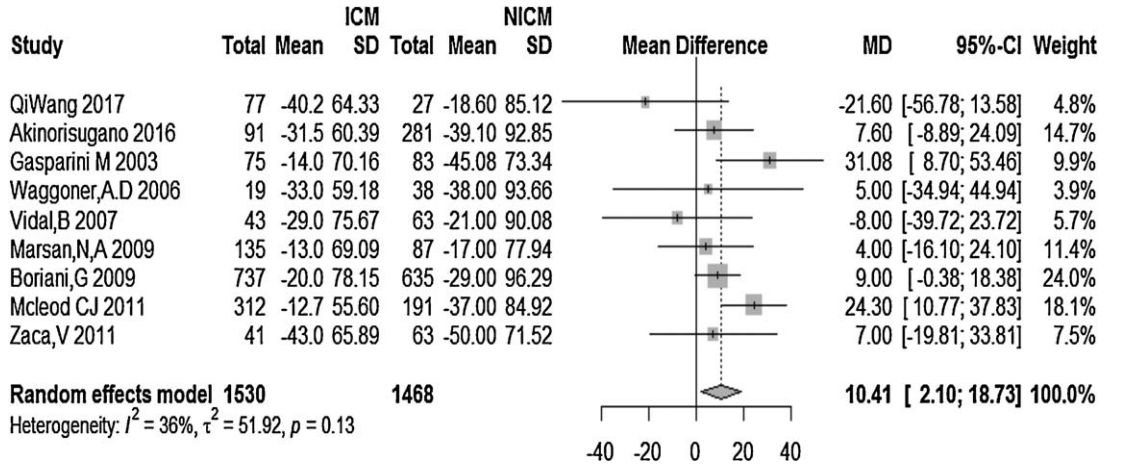

Figure 5. A forest plot for left ventricular end-systolic volume. SD = standard deviation.

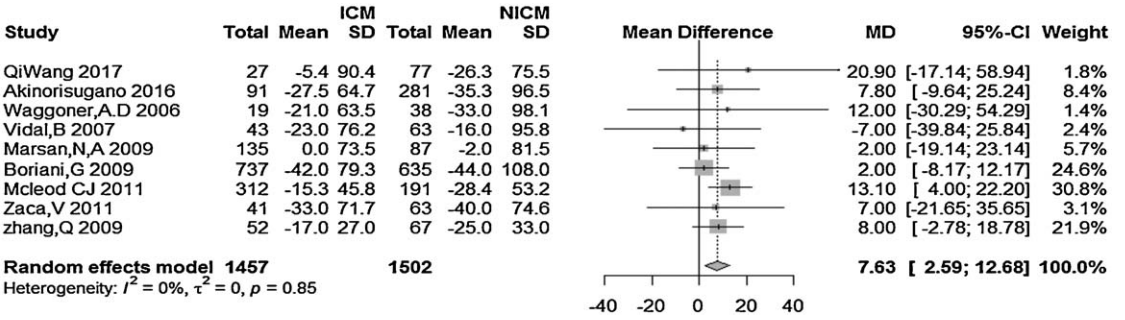

Figure 6. A forest plot for left ventricular end-diastolic volume. SD = standard deviation.

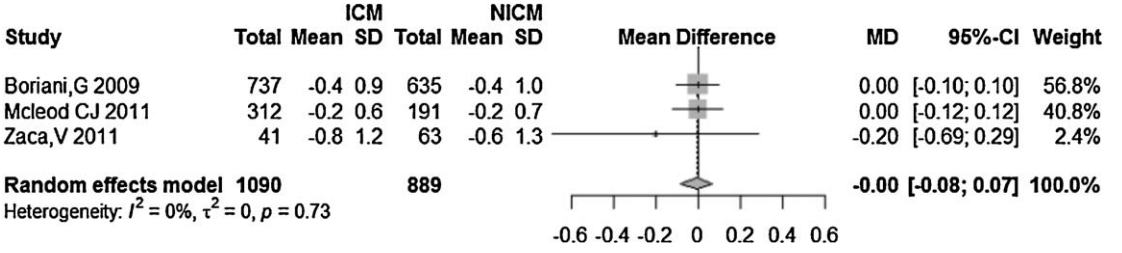

Figure 7. A forest plot for MR severity. SD = standard deviation.

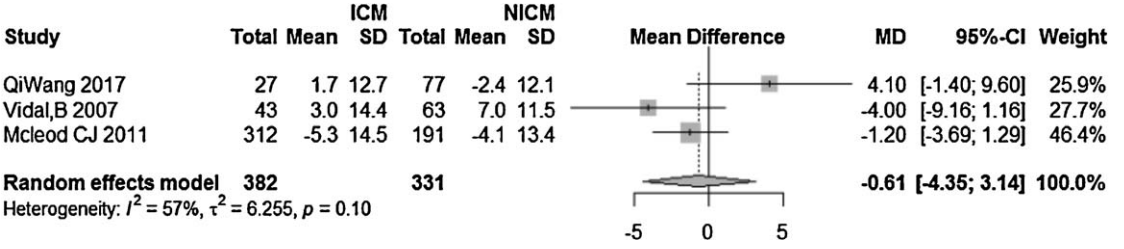

Figure 8. A forest plot for PASP. SD = standard deviation.

we found that Gasparini et al might be the sources of heterogeneity for LVEF, and heterogeneity of the pooled data analysis decreased significantly after excluding that study ($I^2 = 45$, $P = .05$). In addition, study exclusion may also affect the pooled analysis (pooled MD -2.18, 95%CI -3.23 to -1.13).

4. Discussion

The results of the present meta-analysis suggest that NICM patients are associated with a greater reduction in the primary clinical endpoint of all-cause mortality but are comparable to the secondary clinical endpoints including NYHA symptomatic class as compared with ICM patients. With respect to echocardiographic outcomes, NICM patients tended to obtain significant reverse LV remodeling compared with ICM patients treated with CRT.

CRT has been shown to improve prognosis (all-cause mortality) and cardiac function in HF patients. However, there is a significant discrepancy in the utilization of CRT between ICM and NICM case, indicating that the impact of CRT on symptoms, quality of life, morbidity, and mortality is similar between patients with and without ICM such as MIRACLE, Zweerink, and CARE-HF.[14,37] This disparity can also be found in our study (47% vs 53%). It was found in our study that NICM patients obtained a significant reduction in all-cause mortality compared with ICM patients. Pooled analysis by Chen et al who assessed etiologic differences in response to CRT showed that NICM acquired a statistically significant greater reduction in the risk of mortality or HF hospitalization.[12]The MADIT-CRT study involving symptomatic ICM and NICM patients showed a significant difference in response to CRT-D, suggesting that risk of assessment for CRT-D should be etiology-specific.[14]

The reasons behind these differentials remain unclear, though potential explanations have been presented. First, the present study showed that the presence of myocardial scar tissues is a predictor of poor responsiveness,[38,39] which might affect the results of our meta-analysis. However, no study reported data regarding the location and the size of the infracted myocardium (total scar burden) which is important for response to CRT, so we were unable to perform subgroup analysis. Second, the incidence of metabolic syndrome, cerebrovascular disease and renal insufficiency in ICM patients is high. These factors may indirectly affect the long-term prognosis of patients after CRT. It cannot improve the hemodynamic state of patients with HF patients.[20,40] Data from our study also support this interpretation. Our study also showed a significant difference in the occurrence of diabetes mellitus between ICM and NICM patients (31% vs 17%).

This study also demonstrated that NICM obtained greater benefits from CRT in the secondary endpoint in LVESV and LVESV, most probably due to inexorable progression of ischemic disease. However, no significant difference was observed between NICM and ICM patients in the other echocardiographic outcomes such as MR severity and PASP. On the one hand, we only discussed the improvement of PASP 6 months after CRT in HF patients due to ICM and NICM. The REVERSE study showed that LV remolding and symptom benefits from CRT sustained 12 months in HF patients.[41] There are insufficient data to explore the improvement in PSBP after longer follow-up periods. On the other hand, studies have shown that the effect of CRT in improving the degree of MR is limited.[42] Severe LV dilatation, irreversible MR and extremely severe regurgitation may be the reasons why CRT was unresponsive in these studies. Hence, longer follow-up observations to obtain more accurate ultrasonic parameters are required to see whether NICM patients could also benefit more from CRT in terms of the MR severity and PASP in the long run.

Other clinical studies have tried to elucidate the mechanisms underlying the advantages of NICM patients in response to CRT during the follow-up period.[43,44] Some researchers found that NICM patients seemed more likely to experience death from pump failure, while ICM patients were more likely to experience sudden cardiac death.[45] This provides a potential explanation that NICM patients might derive more benefits from CRT, and male patients might probably obtain more survival benefits from the use of CRT-D. In addition, a recommended dose of ACEI and β-adrenergic blockade after CRT is the decisive factor in improving the mortality and hospitalization rate of HF patients.[46] In our study, the application rate of ACEI was different (NICM 87% vs ICM 83%), which may also be a potential factor affecting the prognosis of patients.

This meta-analysis provides new clues to support the hypothesis that NICM patients could obtain better clinical benefits from CRT than ICM patients, suggesting that different etiologies of HF may affect the response to CRT. To improve the symptoms and reduce the morbidity of cardiomyopathies including HF, it is reasonable to recommend that CRT should be considered as a priority in NICM patients with sinus rhythms, an extended QRS duration, LBBB QRS morphology, and left bundle branch block with LVEF$\leq$35% despite optimal medical therapy. In addition, appropriate amendments in the currently available guidelines about the use of CRT seem necessary by considering the impact of etiologic differences on CRT performance in selected patients.

5. Highlights and limitations

This meta-analysis is a summary of evidence from cohort studies published until 2017 with regard to response to CRT between ICM and NICM patients by setting up explicit inclusion and exclusion criteria during the integration of the literature to improve the stability of the results of the study. Meanwhile, data were extracted by two investigators independently and closely, and any disagreement was resolved by discussion with a third opinion so as to reduce the occurrence of migration. The number of participants included in the study was three times that of the previous ones. Meanwhile, there are a few methodological shortcomings. First, some observational studies included in this meta-analysis treated the patients in a non-random way, which may confound the comparison between primary and secondary outcomes. In addition, different loss to follow-up is also a concern in the meta-analyzed cohorts, knowing that dropouts are more likely to occur in patients at higher risk of ICM, which may induce a selection bias in comparison of changes in LVEF and LVESV because of information censoring.

6. Conclusion

Overall, NICM patients may obtain more beneficial effects from CRT than ICM patients with respect to the clinical and echocardiographic outcomes. Larger randomized controlled trials and long-term follow-up observations are necessary to clarify the potential association between the etiology of HF and reactivity after CRT.

Author contributions

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References

[1] Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American college of cardiology/American heart association task force on clinical practice guidelines and the heart failure society of America. J Card Fail 2017;23:628–51.

[2] Ponikowski P, Voors AA, Anker SD, et al. 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). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2016;18:891–975.

[3] Prinzen FW, Vernooy K, Deboeck BW, et al. Mechano-energetics of the asynchronous and resynchronized heart. Heart Fail Rew 2011;16:215–24.

[4] Mor M, Mulla W, Elyagon S, et al. Speckle-tracking echocardiography elucidates the effect of pacing site on left ventricular synchronization in the normal and infarcted rat myocardium. Heart Rhythm 2013;10:1744–5.

[5] Fournet M, Bernard A, Marechaux S, et al. Pilot study using 3D-longitudinal strain computation in a multi-parametric approach for best selecting responders to cardiac resynchronization therapy. Cardiovasc Ultrasound 2017;15:1–0.

[6] Kuijpers NH, Hermeling E, Bovendeerd PH, et al. Modeling cardiac electromechanics and mechanoelectrical coupling in dyssynchronous and failing hearts: insight from adaptive computer models. J Cardiovasc Transl Res 2012;5:159–69.

[7] Zweerink A, Allaart CP, Kuijer JPA, et al. Strain analysis in CRT candidates using the novel segment length in cine (SLICE) post-processing technique on standard CMR cine images. Eur Radiol 2017;27:5158–68.

[8] Russell K, Eriksen M, Aaberge L, et al. Assessment of wasted myocardial work: a novel method to quantify energy loss due to uncoordinated left ventricular contractions. Am J Physiol Heart Circ Physiol 2013;305: H996–1003.

[9] Lindenfeld J, Albert NM, Boehmer JP, et al. HFSA 2010 comprehensive heart failure practice guideline. J Cardiac Fail 2010;16:e1–94.

[10] McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012:the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;33:1787–847.

[11] Bax JJ, Bleeker GB, Marwick TH, et al. Left ventricualr dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. J Am Coll Cardio 2004;44:1834–40.

[12] Chen Y, Duan C, Liu F, et al. Impact of etiology on the outcomes in heart failure patients treated with cardiac resynchronization therapy: a meta-analysis. PloS One 2014;9:e94614.

[13] Makki N, Swaminathan PD, Olshansky B, et al. Does cardiac resynchronization therapy benefit patients with ischemic and non-ischemic cardiomyopathy similarly. Int J Cardiol 2013;168:4378–80.

[14] Barsheshet A, Goldenberg I, Moss AJ, et al. Response to preventive cardiac resynchronization therapy in patients with ischaemic and nonischaemic cardiomyopathy in MADIT-CRT. Eur Heart J 2011;32:1622–30.

[15] Wikstron G, Blomstrom-Lundqvist C, Bertil A, et al. The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE-HF trial. Eur HeartJ 2009;30:782–8.

[16] Wang Q, Chen KY, Yu F, et al. Abnormal diastolic function underlies the different beneficial effects of cardiac resynchronization therapy on ischemic and non-ischemic cardiomyopathy. Clinics (Sao Paulo) 2017;72:432–7.

[17] Barra S, Boveda S, Providencia R, et al. Adding defibrillation therapy to cardiac resynchronization on the basis of the myocardial substrate. J Am Coll Cardiol 2017;69:1669–78.

[18] Powell AC, Rogstad TL, Deshmukh UU, et al. An exploration of the association between ischemic etiology and the likelihood of heart failure hospitalization following cardiac resynchronization therapy. Clin Cardiol 2017;40:1090–4.

[19] Martens P, Nijst P, Verbrugge FH, et al. Profound differences in prognostic impact of left ventricular reverse remodeling after cardiac resynchronization therapy relate to heart failure etiology. Heart Rhythm 2018;15:130–6.

[20] Van ' T, Sant J, Mast TP, et al. Echo response and clinical outcome in CRT patients. Neth Heart J 2016;24:47–55.

[21] Sugano A, Seo Y, Yamamoto M, et al. Optimal cut-off value of reverse remodeling to predict long-term outcome after cardiac resynchronization therapy in patients with ischemic cardiomyopathy. J Cardiol 2014;20: S187–187.

[22] Witt CT, Kronborg MB, Nohr EA, et al. Adding the implantable cardioverter-defibrillator to cardiac resynchronization therapy is associated with improved long-term survival in ischaemic, but not in non-ischaemic cardiomyopathy. Europace 2016;18:413–9.

[23] Zaca V, Baiocchi C, Gaddi R, et al. Influence of aetiology on long-term effects of resynchronization on cardiac structure and function in patients treated with beta-blockers. J Cardiovasc Med (Hagerstown) 2011 2011;12:227–33.

[24] McLeod CJ, Shen WK, Rea RF, et al. Differential outcome of cardiac resynchronization therapy in ischemic cardiomyopathy and idiopathic dilated cardiomyopathy. Heart Rhythm 2011 2011;8:377–82.

[25] Kazemi Saeid A, Bozorgi A, Davoodi G, et al. Comparison of benefits from cardiac resynchronization therapy between patients with ischemic cardiomyopathy and patients with idiopathic dilated cardiomyopathy. J Tehran Univ Heart Center 2011;4:119–20.

[26] Zhang Q, Fung JW, Chan JY, et al. Difference in longterm clinical outcome after cardiac resynchronisation therapy between ischaemic and non-ischaemic aetiologies of heart failure. Heart 2009 2009;95:113–8.

[27] Boriani G, Gasparini M, Landolina M, et al. Effectiveness of cardiac resynchronization therapy in heart failure patients with valvular heart disease: comparison with patients affected by ischaemic heart disease or dilated cardiomyopathy. Eur Heart J 2009 2009;30:2275–83.

[28] Marsan NA, Bleeker GB, van Bommel RJ, et al. Comparison of time course of response to cardiac resynchronization therapy in patients with ischemic versus nonischemic cardiomyopathy. Am J Cardiol 2009;103:690–4.

[29] Di Biase L, Auricchio A, Sorgente A, et al. The magnitude of reverse remodelling irrespective of aetiology predicts outcome of heart failure patients treated with cardiac resynchronization therapy. Eur Heart J 2008;29:2497–505.

[30] Vidal B, Sitges M, Delgado V, et al. Influenceof cardiopathy etiology on responses to cardiac resynchronization therapy. RevEsp Cardiol 2007;60:1264–71.

[31] D'Andrea A, Caso P, Romano S, et al. Different effects of cardiac resynchronization therapy on left atrial function in patients with either idiopathic or ischaemic dilated cardiomyopathy: a two-dimensional speckle strain study. Eur Heart J 2007;28:2738–48.

[32] Soliman OI, Theuns DA, Ten CF, et al. Baseline predictors of cardiac events after cardiac resynchronization therapy in patients with heart failure secondary to ischemic or nonischemic etiology. Am J Cardiol 2007;100:464–9.

[33] Waggoner AD, Rovner A, de Las FL, et al. Clinical outcomes after cardiac resynchronization therapy: importance of left ventricular diastolic function and origin of heart failure. J Am Soc Echocardiogr 2006;19:307–13.

[34] Leclercq C, Gras D, Tang A, et al. Comparative effects of ventricular resynchronization therapy in heart failure patients with or without coronary artery disease. Ann Cardiol Angeiol (Paris) 2004;53:171–6.

[35] Molhoek SG, Bax JJ, van Erven L, et al. Comparison of benefits from cardiac resynchronization therapy in patients with ischemic cardiomyopathy versus idiopathic dilated cardiomyopathy. Am J Cardiol 2004;93:860–3.

[36] Gasparini M, Mantica M, Galimberti P, et al. Is the outcome of cardiac resynchronization therapy related to the underlying etiology? Pacing Clin Electrophysiol 2003;26:175–80.

[37] Wikstron G, Blomstrom-Lundqvist C, et al. The effects of aetiology on outcome in patients treated with cardiac resynchronization therapy in the CARE-HF trial. Eur Heart J 2009;30:782–8.

[38] Chinitz JS, d'Avila A, Goldman M, et al. Cardiac resynchronization therapy: who benefits. Ann Glob Health 2014;80:61–8.

[39] Khan FZ, Virdes MS, Palmer CR, et al. Targeted left ventricular lead palcement to guide cardiac resynchronization therapy: the TARGET

study:a randomized controlled trial. J Am Coll Cardiol 2012;59: 1509–18.
[40] Stahlberg M, Sander M, Mortensen L, et al. Increase in paced heart rate reduces muscle sympathetic nerve activity in heart failure patients treated with cardiac resynchronization therapy. Europace 2015;17: 439–46.
[41] Linde C, Abraham WT, Gold MR, et al. Cardiac resynchronization therapy in asymptomatic or mildly symptomatic heart failure patients in relation to etiology: results from the REVERESE (Resynchronization reverses Remodeling in Systolic Left Ventricular Dysfunction) study. J Am Coll Cardiol 2010;56:1826–31.
[42] Atta S, Bashandy M, et al. Baseline QRS width and mitral regurgitation behavior after cardiac resynchronization therapy among patients with dilated cardiomyopathy. Egypt Heart J 2014;66:335–42.
[43] Zweerink A, Allaart CP, Kuijer JPA, et al. Strain analysis in CRT candidates using the novel segment length in cine (SLICE) post-processing technique on standard CMR cine images. Eur Radiol 2017;7:5158–68.
[44] Wong JA, Yee R, Stirrat J, et al. Influence of pacing site characteristics on response to cardiac resynchronization therapy. Cir Cardiovasc Imaging 2013;6:542–50.
[45] Rho RW, Patton KK, Poole JE, et al. Important differences in mode of death between men and women with heart failure who would qualify for a primary prevention implantable cardioverter-defibrillator. Circulation 2012;126:2402–7.
[46] Adlbrecht C, Hulsmann M, Gwechenberger M, et al. Outcome after device implantation in chronic heart failure is dependent on concomitant medical treatment. Eur J Clin Invest 2009;39:1073–81.