Accepted Manuscript

Meta-analysis of the Relation of Baseline Right Ventricular Function to Response to Cardiac Resynchronization Therapy

Abhishek Sharma, MD, Jerome J. Bax, MD, Ajay Vallakati, MD, Sunny Goel, MD, Carl J. Lavie, MD, John Kassotis, MD, Debabrata Mukherjee, MD, MS, Andrew Einstein, MD, Ph.D, Nikhil Warrier, MD, Jason M. Lazar, MD, MPH

PII: S0002-9149(16)30151-5

DOI: 10.1016/j.amjcard.2016.01.029

Reference: AJC 21675

To appear in: *The American Journal of Cardiology*

Received Date: 6 December 2015

Revised Date: 17 January 2016

Accepted Date: 19 January 2016

Please cite this article as: Sharma A, Bax JJ, Vallakati A, Goel S, Lavie CJ, Kassotis J, Mukherjee D, Einstein A, Warrier N, Lazar JM, Meta-analysis of the Relation of Baseline Right Ventricular Function to Response to Cardiac Resynchronization Therapy, *The American Journal of Cardiology* (2016), doi: 10.1016/j.amjcard.2016.01.029.

Meta-analysis of the Relation of Baseline Right Ventricular Function to Response to Cardiac Resynchronization Therapy

Abhishek Sharma[1], MD; **Jerome J Bax**[2]**, MD; Ajay Vallakati**[3], MD; **Sunny Goel**[4], MD; **Carl J Lavie**[5], MD; **John Kassotis**[1], MD; **Debabrata Mukherjee**[6], MD, MS; **Andrew Einstein**[7], MD, Ph.D; **Nikhil Warrier**[1]**,** MD**; Jason M Lazar**[1], MD, MPH.

1. Division of Cardiovascular Medicine, State University of New York Downstate Medical Center, NY
2. Department of Cardiology, Leiden University Medical Center, Leiden, the Netherlands
3. Division of Cardiology, Metrohealth Medical Center, Case Western Reserve University, Cleveland, OH
4. Department of Medicine, Maimonides Medical Center, NY
5. Department of Cardiovascular Diseases, John Ochsner Heart and Vascular Institute, Ochsner Clinical School-the University of Queensland School of Medicine, New Orleans, LA
6. Division of Cardiology, Texas Tech University, El Paso, TX
7. Division of Cardiology, Department of Medicine, and Department of Radiology, Columbia University Medical Center, New York, NY

Running title: ***CRT and RV function***

Corresponding Author: Abhishek Sharma, MD
Postal address: Division of Cardiovascular diseases
SUNY Downstate Medical Center
450 Clarkson Ave, Brooklyn, NY 11203
Phone# 201-892-6548
Fax: 718-270-2917
Email: abhisheksharma4mamc@gmail.com
Conflict of interest: All authors declare no conflict of interest

Abstract:

Right ventricular (RV) dysfunction has been associated with adverse clinical outcomes in patients with heart failure (HF). Cardiac resynchronization therapy (CRT) improves left ventricular (LV) size and function in patients with markedly abnormal ECG QRS duration. However, relationship of baseline RV function with response to CRT has not been well described. In this study we aim to investigate the relation of baseline RV function with response to CRT as assessed by change in LV ejection fraction (EF). A systematic search of studies published between 1966 to May 31, 2015 was conducted using Pub Med, CINAHL, Cochrane CENTRAL and the Web of Science databases. Studies were included if they have reported a) parameters of baseline RV function [tricuspid annular plane systolic excursion (TAPSE) or RV ejection fraction (RVEF) or RV basal strain or RV fractional area change (FAC)] and b) LVEF before and after CRT. Random-effects meta-regression was used to evaluate the effect of baseline RV function parameters and change in LVEF. Sixteen studies (N=1764) were selected for final analysis. Random-effects meta-regression analysis showed no significant association between the magnitude of the difference in EF pre and post CRT with baseline TAPSE (beta 0.005, p 0.989); baseline RVEF (beta 0.270, p 0.493); baseline RVFAC (beta -0.367, p 0.06); baseline basal strain (beta -0.342, p= 0.462) after a mean follow up period of 10.5 months. In conclusion, baseline RV function as assessed by TAPSE, FAC, basal strain or RVEF, does not determine response to CRT as assessed by change in LVEF.

Key words: Right ventricle function, Cardiac resynchronization therapy, Left ventricular ejection fraction

INTRODUCTION

Right ventricular (RV) function is an independent prognostic marker for heart failure (HF) patients and; also plays an important role in determining the response to medical therapy in patients with HF [1, 2]. Recently, it has been suggested that baseline echocardiographic parameters of RV function could be helpful in identifying patients who respond more favorably to Cardiac resynchronization therapy (CRT) [3, 4]. However, studies have reported conflicting results, and the relationship of baseline RV function with response to CRT remains unclear [3-19]. In this study, we performed a meta-analysis of published studies and investigated the relationship of various baseline echocardiographic parameters of RV function with response to CRT, as assessed by change in LV ejection fraction (EF).

METHODS

A systematic review of the literature was performed according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement [20]. We systematically searched PubMed, CINAHL, Cochran CENTRAL, Embase, Scopus and Web of Science databases for all studies that reported parameters of RV function at baseline and LVEF before and after CRT implantation. All relevant combinations of the following keywords related to CRT were included in the search: RV function, tricuspid annular plane systolic excursion (TAPSE), RV diameters, RV short axis diameter, RV long axis diameter, RV fractional area change (FAC), LVEF. The search was conducted from the inception of each database to May 31, 2015. No language or age restrictions were applied. Pertinent trials were also searched in clinicaltrials.gov and in the proceedings of major international cardiology meetings (American College of

Cardiology, American Heart Association, European Society of Cardiology, Heart Rhythm Society). Studies were included if they met each of the following three criteria: 1) human studies with participants of any age requiring CRT for any indication, 2) reported at least one parameter of baseline RV function [TAPSE, and/or RVEF, and/or RV long axis diameter, and/or RV basal strain and/or RVFAC] and 3) reported LVEF before and after CRT. Two independent reviewers (AS, SG) screened the titles and abstracts for relevance. Discrepancies between reviewers were discussed until consensus was reached. The manuscripts of selected titles/abstracts were reviewed for inclusion and authors were contacted if additional data were needed. Using the above mentioned selection criteria, these two reviewers independently determined the articles to be included and excluded, and data from the relevant articles were extracted using pre-defined extraction forms. Any disagreements in data extraction were discussed until consensus was reached.

In this analysis, Review Manager Version 5.1 (The Nordic Cochrane Center, The Cochrane Collaboration, 2008, Copenhagen) was used. A random-effects model with inverse variance weighting was used to calculate pooled mean difference in LVEF and corresponding confidence interval. Heterogeneity between studies was assessed using Cochrane's Q test and I^2 statistic, which denotes the percentage of total variation across studies that is a result of heterogeneity rather than chance. Heterogeneity was considered significant if the p value was less than 0.05. Publication bias was assessed by Begg's test and Egger's regression test. The influence of individual studies was examined by removing each study at a time to assess the degree to which meta-analysis estimate depends on a particular study (exclusion sensitivity analysis). Open Meta-Analyst

software was utilized to perform random-effects meta-regression to evaluate the effect of baseline RV function parameters on change in LVEF [21].

RESULTS

We identified seventeen studies, which reported parameters of baseline RV function and LVEF (Figure 1) [3-19]. One study was not included in the final analysis, as it did not provide data in terms of absolute number (and standard deviation) for baseline RV function parameters and LVEF before and after CRT [19]. Sixteen studies were selected for final analysis [3-18]. Details of the studies and baseline characteristics are summarized in Table 1 and 2.

Pooled analysis of sixteen studies reporting LVEF and RV function revealed that CRT led to an absolute increase of 5.82 % (95% CI 4.23 – 7.41) in mean LVEF (Figure 2). There was significant heterogeneity across the studies ($p < 0.001$, $I^2 = 91\%$). Sensitivity analysis did not demonstrate any significant change in effect size with exclusion of any particular study.

Pooled analysis of the ten studies that reported the effect of baseline TAPSE on Δ LVEF (N=1368) showed that CRT improved LVEF by 5.96 % (95% CI 4.64 – 7.29) (supplementary figure 1). Random-effects meta-regression analysis showed no significant association between the magnitude of the difference in LVEF pre and post CRT with baseline TAPSE (beta 0.005, p = 0.989) (Figure 3). Similar improvement in LV function was noted after pooling the studies presenting baseline RVEF [5.91% (95% CI 0.06-11.76), (N=168), (supplementary figure 2)], RV FAC [6.26% (95% CI 4.50 – 8.03), (N=1245), (supplementary figure 3)], RV basal strain [6.08 %, (95% CI 2.37 – 9.79), (N=191), (supplementary figure 4)] and RV long axis diameter [5.18%, (95% CI 2.96-

7.41), (N=216), (supplementary figure 5)]. Meta-regression revealed that baseline RVEF (beta 0.270, p = 0.493) (Figure 4) and baseline RV FAC (beta - 0.367, p = 0.06) (Figure 5) did not significantly impact Δ LVEF. Similarly, there was no significant association between baseline RV basal strain (beta -0.342, p= 0.462) (Figure 6) and RV long axis diameter (beta -.0.222, p=0.423) (Figure 7) with Δ LVEF.

DISCUSSION

Our results show that there is no significant association between baseline RV function and response to CRT as assessed by change in LVEF. There was no statistically significant relationship of the magnitude of the difference in pre- and post-CRT LVEF with any baseline echocardiographic parameters of RV function. Thus, assessment of RV function might not be useful in selecting patients for improvement in LVEF after CRT.

Previous studies have reported conflicting effects of baseline RV function on response to CRT. Almost a decade ago, in a small study (n=15), Boriani et al reported that RV dysfunction as assessed by radionuclide angiography did not determine relative benefits of CRT [7]. Later, Burri et al, reported that patients with baseline RV dysfunction (defined as RVEF≤35% by radionuclide angiography) were less likely to respond to CRT as assessed by improvement in NYHA classification, 6 minute walking distance and LVEF after a mean follow up of 9 months [8]. However, the presence of reduced baseline RVEF (assessed radionuclide angiography) alone cannot be used to exclude patients from CRT, as 47% of patients with reduced RVEF still showed improvement in NYHA classification [8]. In post hoc analysis of patients from Cardiac Resynchronization in Heart Failure (CARE-HF) trial, Damy et al reported that though presence of baseline RV

dysfunction correlated with overall poor prognosis, it does not predict response to response to CRT [19].

While understanding the relation of baseline RV function and response to CRT, it is important to distinguish between 'outcome' and 'response' to CRT. As shown by Damy and colleagues, the presence of baseline RV dysfunction among patients who received CRT is associated with poor clinical outcomes [19]. This could be partly due to the fact RV dysfunction itself is an independent prognostic marker and associated with worse clinical outcomes in patients with HF [1, 2]. However, patients with or without RV dysfunction appeared to respond to CRT to similar extent [19]. Thus, echocardiographic parameters of baseline RV function might not be helpful in selecting patients for CRT therapy, and therefore this therapy should not be denied to patients with baseline RV dysfunction.

This is the first meta-analysis to evaluate the relationship of baseline RV function with response to CRT. Echocardiography is the most common technique to assess RV function in clinical practice. Most of the studies included in our meta-analysis have used TAPSE as a measure of RV function; TAPSE is a relatively simple echocardiographic measure, which represents RV longitudinal function, which has been shown to have a good correlation with more precise measures of RV systolic function, such as radionuclide quantification of RVEF [22]. However, a major limitation of TAPSE is that it only measures the contribution of the RV free wall to predict RV global systolic function [23, 24]. A more global measure of RV systolic function is FAC, which has shown to correlate well with cardiac magnetic resonance imaging (MRI)-derived RVEF [25]. However, FAC is considered as more a measure of RV response to afterload than a

measure of contractility. However, due to asymmetric shape and complex geometry, use of a single echocardiographic parameter might not be sufficient to comprehensively assess RV function. Previous studies have used one or two echocardiographic parameters of RV function. To overcome this limitation, however, we have used various echocardiographic parameters of RV function to analyze the relationship of baseline RV function with response to CRT in 1764 patients from 16 studies with a mean follow up period of 10.5 months.

There are several limitations to our study. First, studies used in our analysis did not used advanced cardiac imaging modalities to evaluate RV function. The RV has a complex geometry and is volume dependent affected by preloading conditions, which pose a challenge in accurately determining the RV function [22]. Even so, with echocardiography being inexpensive and readily available, it remains by far the most widely used modality to measure RV function, which is why we focused on it for assessment of RV function in this meta-analysis. Since one echocardiographic measure might not accurately represent true RV function, we used multiple parameters of RV function. Importantly, our results were consistent across all parameters of RV function, including TAPSE and FAC, which have been reported to correlate well with measures of RV function obtained by cardiac MRI. Second, as mentioned above, we could not include a few studies in our analysis, as these studies did not report data in terms of absolute number for baseline RV function parameters and LVEF before and after CRT therapy, including the post hoc analysis of CARE-HF trial. However, results of sub-analysis of CARE-HF data are in agreement with our findings and its inclusion might if anything have made our findings stronger [19].

References:

1. Di Salvo TG, Mathier M, Semigran MJ, Dec GW. Preserved right ventricular ejection fraction predicts exercise capacity and survival in advanced heart failure. *J Am Coll Cardiol.* 1995;25:1143-1153.

2. Voelkel NF, Quaife RA, Leinwand LA, Barst RJ, McGoon MD, Meldrum DR, Dupuis J, Long CS, Rubin LJ, Smart FW, Suzuki YJ, Gladwin M, Denholm EM, Gail DB; National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure. *Circulation.* 2006; 114:1883-1891.

3. Leong DP, Höke U, Delgado V, Auger D, Witkowski T, Thijssen J, van Erven L, Bax JJ, Schalij MJ, Marsan NA. Right ventricular function and survival following cardiac resynchronisation therapy. *Heart.* 2013; 99:722-728.

4. Scuteri L, Rordorf R, Marsan NA, Landolina M, Magrini G, Klersy C, Frattini F, Petracci B, Vicentini A, Campana C, Tavazzi L, Ghio S. Relevance of echocardiographic evaluation of right ventricular function in patients undergoing cardiac resynchronization therapy. *Pacing Clin Electrophysiol* 2009; 32:1040 –1049.

5. Abu Sham'a R, Buber J, Grupper A, Nof E, Kuperstein R, Luria D, Feinberg MS, Eldar M, Glikson M. Effects of tricuspid valve regurgitation on clinical and echocardiographic outcome in patients with cardiac resynchronization therapy. *Europace.* 2013;15:266-272.

6. Bleeker GB, Schalij MJ, Nihoyannopoulos P, Steendijk P, Molhoek SG, van Erven L, Bootsma M, Holman ER, van der Wall EE, Bax JJ. Left ventricular dyssynchrony predicts right ventricular remodeling after cardiac resynchronization therapy. *J Am Coll Cardiol*. 2005;46:2264-2269.

7. Boriani G, Fallani F, Martignani C, Biffi M, Saporito D, Greco C, Ziacchi M, Levorato M, Pontone G, Valzania C, Diemberger I, Franchi R, Branzi A. Cardiac resynchronization therapy: effects on left and right ventricular ejection fraction during exercise. *Pacing Clin Electrophysiol*. 2005;28 Suppl 1:S11-14.

8. Burri H, Domenichini G, Sunthorn H, Fleury E, Stettler C, Foulkes I, Shah D. Right ventricular systolic function and cardiac resynchronization therapy. *Europace.* 2010;12:389-394.

9. D'Andrea A, Salerno G, Scarafile R, Riegler L, Gravino R, Castaldo F, Cocchia R, Limongelli G, Romano M, Calabrò P, Nigro G, Cuomo S, Bossone E, Caso P, Calabrò R. Right ventricular myocardial function in patients with either idiopathic or ischemic dilated cardiomyopathy without clinical sign of right heart failure: effects of cardiac resynchronization therapy. *Pacing Clin Electrophysiol.* 2009;32:1017-1029.

10. Donal E, Thibault H, Bergerot C, Leroux PY, Cannesson M, Thivolet S, Barthelet M, Rivard L, Chevalier P, Ovize M, Daubert JC, Leclerq C, Mabo P, Derumeaux G. Right ventricular pump function after cardiac resynchronization therapy: a strain imaging study. *Arch Cardiovasc Dis*. 2008;101:475-484.

11. Eder V, Fauchier L, Courtehoux M, Bonnet P, Babuty D. Segmental wall motion abnormality analyzed by equilibrium radionuclide angiography and improvement in ventricular function by cardiac resynchronization therapy. *Pacing Clin Electrophysiol.* 2007;30 Suppl 1:S58-61.

12. Esmaeilzadeh M, Poorzand H, Maleki M, Sadeghpour A, Parsaee M. Evaluation of Longitudinal Right Ventricular Mechanical Dyssynchrony before and Early after Cardiac Resynchronization Therapy: A Strain Imaging Study. *J Tehran Heart Cent.* 2011;6:24-30.

13. Knappe D, Pouleur AC, Shah AM, Bourgoun M, Brown MW, Foster E, Pfeffer MA, Moss AJ, Solomon SD; MADIT-CRT Investigators. Acute effects of withdrawal of cardiac resynchronization therapy on left and right ventricular function, dyssynchrony, and contractile function in patients with New York Heart Association functional class I/II heart failure: MADIT-CRT. *J Card Fail.* 2013;19:149-155.

14. Kusiak A, Wiliński J, Wojciechowska W, Jastrzębski M, Sondej T, Bacior B, Kloch-Badełek M, Czarnecka D. Effects of biventricular pacing on right ventricular function assessed by standard echocardiography. *Kardiol Pol*. 2012;70:883-888.

15. Praus R, Haman L, Tauchman M, Pudil R, Blaha V, Parizek P. Echocardiographic changes after cardiac resynchronisation therapy. *Kardiol Pol.* 2012;70:1250-1257.

16. Sade LE, Özin B, Atar I, Demir Ö, Demirtaş S, Müderrisoğlu H. Right ventricular function is a determinant of long-term survival after cardiac resynchronization therapy. *J Am Soc Echocardiogr*. 2013;26:706-713.

17. Szulik M, Streb W, Lenarczyk R, Stabryła-Deska J, Kowalski O, Kalarus Z, Kukulski T. The incremental value of right ventricular indices for predicting response to cardiac resynchronization therapy. *J Am Soc Echocardiogr*. 2011;24:170-179.

18. Vitarelli A, Franciosa P, Nguyen BL, Capotosto L, Ciccaglioni A, Conde Y, Iorio G, De Curtis G, Caranci F, Vitarelli M, Lucchetti P, Dettori O, De Cicco V. Additive value of right ventricular dyssynchrony indexes in predicting the success of cardiac resynchronization therapy: a speckle-tracking imaging study. *J Card Fail*. 2011;17:392-402.

19. Damy T, Ghio S, Rigby AS, Hittinger L, Jacobs S, Leyva F, Delgado JF, Daubert JC, Gras D, Tavazzi L, Cleland JG. Interplay between right ventricular function and cardiac

resynchronization therapy: an analysis of the CARE-HF trial (Cardiac Resynchronization-Heart Failure). *J Am Coll Cardiol*. 2013;61:2153-2160.

20. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.* 2009;151:W65-W94.

21. OpenMetaAnalyst: Wallace, Byron C., Issa J. Dahabreh, Thomas A. Trikalinos, Joseph Lau, Paul Trow, and Christopher H. Schmid. "Closing the Gap between Methodologists and End-Users: R as a Computational Back-End. *Journal of Statistical Software* 49 (2012): 5.

22. Kaul S, Tei C, Hopkins JM, Shah PM. Assessment of right ventricular function using two-dimensional echocardiography. *Am Heart J*. 1984;107:526-531.

23. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685-713.

24. Ghio S, Recusani F, Klersy C, Sebastiani R, Laudisa ML, CampanaC, Gavazzi A. Prognostic usefulness of the tricuspid annular plane systolic excursion in patients with congestive heart failure secondary to idiopathic or ischemic dilated cardiomyopathy. *Am J Cardiol* 2000; 85:837–842.

25. Lai WW, Gauvreau K, Rivera ES, Saleeb S, Powell AJ, Geva T. Accuracy of guideline recommendations for two-dimensional quantification of the right ventricle by echocardiography. *Int J Cardiovasc Imaging.* 2008; 24:691-698.

FIGURE LEGENDS:

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow sheet

Figure 2. Forest plot for change in LVEF with CRT for all studies.

Figure 3. Random-effects meta-regression analysis depicting the relationship between mean differences in left ventricular ejection fraction (Δ LVEF) (on Y axis) and baseline TAPSE on (X-axis). Each included study is represented by a circle, the size of which is proportional to its respective weight in the analysis. The line indicates the predicted effects (regression line). There was no significant association [β = 0.005, P = 0.989].

Figure 4. Random-effects meta-regression analysis depicting the relationship between mean differences in left ventricular ejection fraction (Δ LVEF) (on Y axis) and baseline right ventricular ejection fraction (on X-axis). Each included study is represented by a circle, the size of which is proportional to its respective weight in the analysis. The line indicates the predicted effects (regression line). There was no significant association [β = 0.270, P = 0.493].

Figure 5. Random-effects meta-regression analysis depicting the relationship between mean differences in left ventricular ejection fraction (Δ LVEF) (on Y axis) and baseline right ventricular fractional area change (RV FAC on X-axis). Each included study is

represented by a circle, the size of which is proportional to its respective weight in the analysis. The line indicates the predicted effects (regression line). There was no significant association [β = - 0.367, P = 0.06].

Figure 6. Random-effects meta-regression analysis depicting the relationship between mean differences in left ventricular ejection fraction (Δ LVEF) (on Y axis) and baseline right ventricular basal strain (on X-axis). Each included study is represented by a circle, the size of which is proportional to its respective weight in the analysis. The line indicates the predicted effects (regression line). There was no significant association [β = - 0.342, P = 0.462].

Figure 7. Random-effects meta-regression analysis depicting the relationship between mean differences in left ventricular ejection fraction (Δ LVEF) (on Y axis) and baseline right ventricular long axis diameter (on X-axis). Each included study is represented by a circle, the size of which is proportional to its respective weight in the analysis. The line indicates the predicted effects (regression line). There was no significant association [β = - 0.222, P = 0.423].

Supplementary figures:

Supplementary figure 1. Forest plot for change in LVEF with CRT for studies reporting baseline TAPSE.

Supplementary figure 2. Forest plot for change in LVEF with CRT for studies reporting baseline RVEF.

Supplementary figure 3. Forest plot for change in LVEF with CRT for studies reporting baseline FAC.

Supplementary figure 4. Forest plot for change in LVEF with CRT for studies reporting baseline basal strain.

Supplementary figure 5. Forest plot for change in LVEF with CRT for studies reporting baseline RV long axis diameter.

Table 1. Baseline characteristics of studies included in analysis

First Author (Year)	N	Follow up (months)	NYHA III/IV	Mean QRS duration (msec)	RV function parameters					LVEF	LVEF at end of follow up
					FAC	TAPSE	RVEF	RVLA	Basal Strain		
Abu Sham'a [2012][a]	35	26.5	59%/-	173 ± 33	+	-	-	-	-	22 ± 5%	24 ± 7%
Abu Sham'a [2012][b]	158	26.5	52%/-	161 ± 30	+	-	-	-	-	25 ± 7%	30 ± 9%
Bleeker [2005]	56	6	89%/11%	176 ± 30	-	-	-	+	-	19 ± 6%	26 ± 8%
Boriani [2005]	15	3	80%/13%	189 ± 26	-	-	+	-	-	21 ± 9%	29 ±13%
Burri [2010]	44	9	70%/30%	162 ± 25	-	-	+	-	-	24 ± 8%	29 ±12%
D'Andrea [2009][c]	29	6	82%/18%	149 ± 22	-	+	-	+	-	30 ± 5%	38 ±4%
D'Andrea [2009][d]	41	6	82%/19%	149 ± 22	-	+	-	+	-	31 ± 3%	38 ± 5%
D'Andrea [2009][e]	21	6	82%/18%	149 ± 22	-	+	-	+	-	31 ± 3%	33 ± 4%
D'Andrea [2009] [f]	19	6	82%/19%	149 ± 22	-	+	-	+	-	29 ± 5%	32 ± 4%
Donal [2008]	50	3	68%/32%	163 ± 28	-	+	-	+	+	22 ± 6%	27 ± 9%
Eder [2007] [g]	16	6	-	-	-	-	+	-	-	22 ± 2%	20 ± 1%
Eder [2007] [h]	12	6	-	-	-	-	+	-	-	20 ± 2%	30 ± 3%
Esmaeilzadeh[2011] [i]	16	0.25	-	143 ± 19	+	+	-	-	+	19 ± 5%	24 ±19%
Esmaeilzadeh[2011] [j]	20	0.25	-	144 ± 15	+	+	-	-	+	19 ± 6%	23 ±8%
Knappe [2013]	63	12	0	-	+	-	-	-	-	24 ± 5%	37 ± 5%

Kusiak [2012]	57	3	-	184 ± 28	-	+	-	-	-	22 ± 5%	26 ± 5%
Leong [2013]	738	6	68%/9%	155 ± 33	+	+	-	-	-	26 ± 8%	32 ±10%
Praus [2012] [k]	38	15	-	193 ± 28	-	+	-	-	-	22 ± 5%	33 ±12%
Praus [2012] [l]	19	15	-	195 ± 42	-	+	-	-	-	22 ± 7%	25 ±8%
Sade [2013] [m]	31	32	-	142 ± 21	-	+	-	-	+	21 ± 5%	25 ± 8%
Sade [2013] [n]	74	32	-	148 ± 22	-	+	-	-	-	24 ± 6%	35 ±11%
Scuteri [2009]	44	6	-	157 ± 25	+	+	-	-	-	23 ± 5%	31 ±9%
Szulik [2011]	90	18	64%/36%	176 ± 29	+	+	-	-	-	25 ± 8%	31 ±11%
Vitarelli [2011] [o]	50	6	-	189 ± 24	+	+	+	-	-	19 ± 11%	32 ±15%
Vitarelli [2011] [p]	31	6	-	171 ± 22	+	+	+	-	-	22 ± 8%	25 ±7%

a: Moderate to severe TR b: No or mild TR c: Responder ischemic DCM, d: Responder idiopathic DCM, e: Non responder Ischemic DCM, f: Non responder Idiopathic DCM, g: With increase in LVEF, h: Without increase in LVEF, i: Pt with RVMD, j: Pt without RVMD k: Responders, l: Non responders, m: Patient with events, n: Patient without events, o: Responders, p: non-responders

- =No information available

Table 2. Baseline patient characteristics in the studies included in the analysis

First Author (Year)	Mean age (yr.)	Male	IC/NIC Heart Failure	LBBB/ RBBB	DM	HTN	HLD	Smoker	Beta-blocker	ACE	Spironolac one/Loop Diuretic
Abu Sham'a [2012][a]	69 ± 12	83%	71%/29%	43%/ 14%	-	-	-	-	-	-	-
Abu Sham'a [2012][b]	69 ± 10	87%	70%/30%	52%/ 13%	-	-	-	-	-	-	-
Bleeker [2005]	64 ± 11	79%	52%/48%	-	-	-	-	-	50%	52%	- /82%
Boriani [2005]	62 ± 5	80%	47%/53%	-	-	-	-	-	-	-	-
Burri [2010]	72 ± 9	80%	57%/43%	73%/ 9%	12%	-	-	-	82%	95%	- /80%
D'Andrea [2009][c]	57 ± 11	52%	100%/0	-	46%	35%	58%	44%	86%	95%	53%/95%
D'Andrea [2009][d]	55+/-8	55%	0/100%	-	32%	33%	53%	35%	82%	94%	58%/96%
D'Andrea [2009][e]	57+/-11	52%	100%/0	-	46%	35%	58%	44%	86%	95%	53%/95%
D'Andrea [2009] [f]	55 ± 8	55%	0/100%	-	32%	33%	53%	35%	82%	94%	58%/96%
Donal [2008]	67 ± 10	75%	45%/55%	-	-	-	-	-	-	-	-
Eder [2007] [g]	-	67%	20%/80%	-	-	-	-	-	-	-	-
Eder [2007] [h]	-	77%	23%/77%	-	-	-	-	-	-	-	-
Esmaeilzadeh [2011] [i]	62 ± 10	58%	48%/56%	53%/ 6%	-	-	-	-	-	-	-
Esmaeilzadeh [2011] [j]	57 ± 13	58%	50%/50%	53%/ 7%	-	-	-	-	-	-	-
Knappe [2013]	64 ± 12	81%	51%/ -	78%/ -	-	-	-	-	84%	83%	43%/84%
Kusiak [2012]	66 ± 9	95%	72%/ -	-	40%	63%	77%	23%	96%	86%	- /88%
Leong [2013]	67	78%	60%/ -	68%/ -	21%	-	-	-	71%	89%	47%/83%

Praus [2012] [k]	67 ± 9	-	47%/47%	-	-	-	-	-	-	-	-
Praus [2012] [l]	67 ± 9	-	74%/21%	-	-	-	-	-	-	-	-
Sade [2013] [m]	60 ± 11	82%	71%/ -	68%/ 13%	-	-	-	-	83%	63%	83%/87%
Sade [2013] [n]	63 ± 11	81%	53%/ -	72%/ 5%	-	-	-	-	92%	92%	71%/84%
Scuteri [2009]	59 ± 10	81%	31%/ -	-	-	-	-	-	83%	95%	70%/100%
Szulik [2011]	57 ± 9	62%	41%/59%	88%/ -	22%	-	52%	-	100%	88%	84%/89%
Vitarelli [2011] [o]	65 ± 13	64%	58%/42%	-	-	-	-	-	70%	93%	-
Vitarelli [2011] [p]	63 ± 16	68%	68%/32%	-	-	-	-	-	84%	86%	-

a: Moderate to severe TR b: No or mild TR c: Responder ischemic DCM, d: Responder idiopathic DCM, e: Non responder Ischemic DCM, f: Non responder Idiopathic DCM, g: With increase in LVEF, h: Without increase in LVEF, i: Pt with RVMD, j: Pt without RVMD k: Responders, l: Non responders, m: Patient with events, n: Patient without events, o: Responders, p: non-responders

IC: Ischemic Cardiomyopathy; NIC: Non-ischemic cardiomyopathy; LBBB: Left bundle branch block; RBBB: Right bundle branch block; DM: Diabetes mellitus; HTN: Hypertension; HLD: Hyperlipidemia; ACE: Angiotensin converting enzyme inhibitors

- =No information available

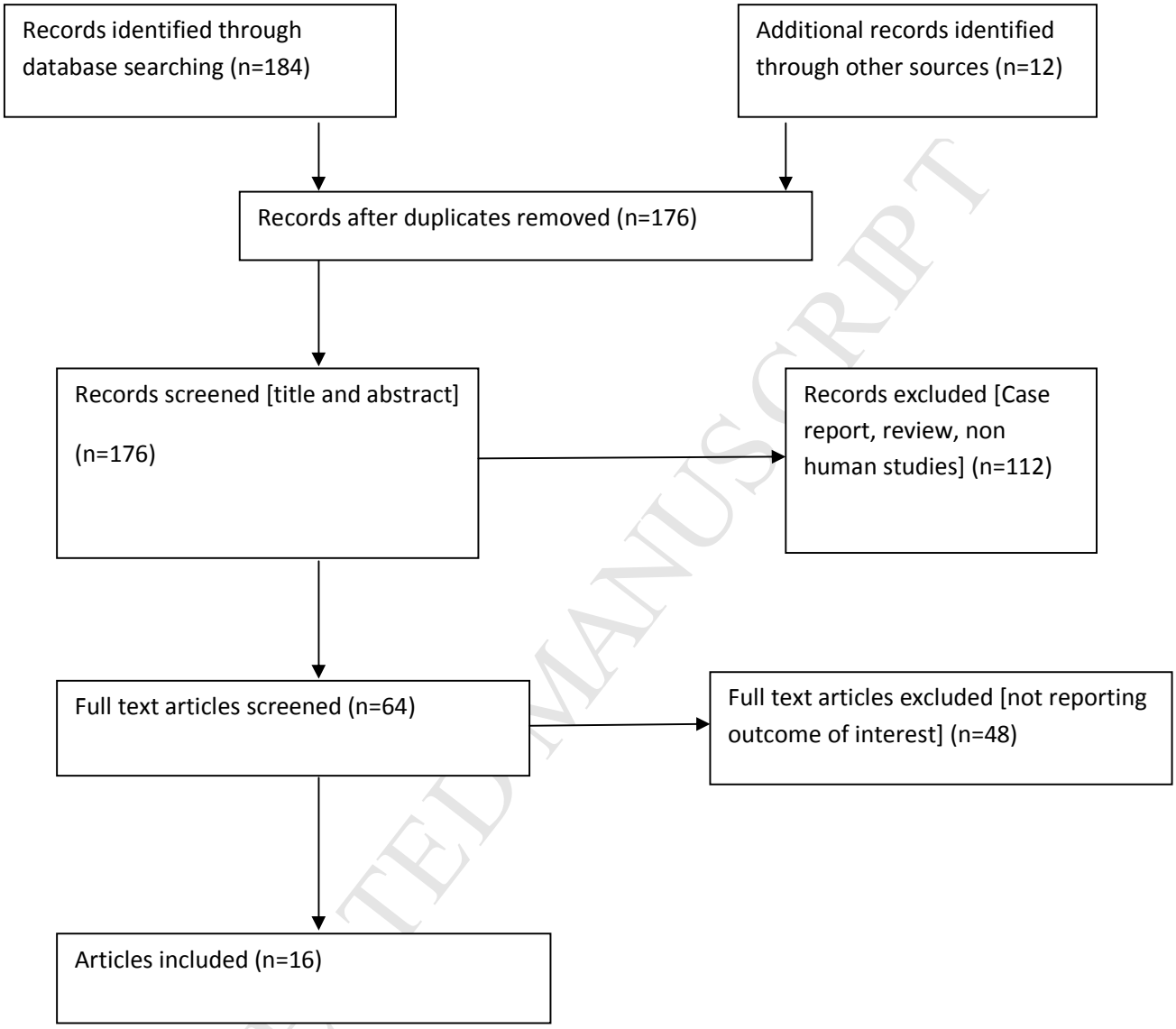

Figure 1. PRISMA Flowsheet

Study or Subgroup	Post CRT Mean	Post CRT SD	Post CRT Total	Pre CRT Mean	Pre CRT SD	Pre CRT Total	Weight	Mean Difference IV, Random, 95% CI
Abu Sham'a (+TR) 2012	24	7	35	22	5	35	4.2%	2.00 [-0.85, 4.85]
Abu Sham'a(No TR) 2012	30	9	158	25	7	158	4.6%	5.00 [3.22, 6.78]
Bleeker 2005	26	8	56	19	6	56	4.3%	7.00 [4.38, 9.62]
Boriani 2005	28.8	13.3	15	21.4	8.6	15	2.2%	7.40 [-0.62, 15.42]
Burri 2010	29.1	12.5	44	24	7.7	44	3.6%	5.10 [0.76, 9.44]
D'Andrea (NR-DCM) 2009	31.7	4.1	19	29.5	5.1	19	4.2%	2.20 [-0.74, 5.14]
D'Andrea (NR-ICM) 2009	32.7	4.1	21	31.1	3.2	21	4.5%	1.60 [-0.62, 3.82]
D'Andrea (R-DCM) 2009	38.4	5.1	41	31.1	3.1	41	4.6%	7.30 [5.47, 9.13]
D'Andrea (R-ICM) 2009	37.9	4.1	29	30.2	5.2	29	4.4%	7.70 [5.29, 10.11]
Donal 2008	27	9	50	22	6	50	4.2%	5.00 [2.00, 8.00]
Eder (GH) 2007	30	3	12	20	2.5	12	4.5%	10.00 [7.79, 12.21]
Eder (SWMA) 2007	20	1.6	16	22	2	16	4.7%	-2.00 [-3.25, -0.75]
Esmaeilzadeh (RVMD) 2011	24.2	19	16	18.8	5.5	16	1.7%	5.40 [-4.29, 15.09]
Esmaeilzadeh(No RVD) 2011	22.7	8	20	19	5.6	20	3.6%	3.70 [-0.58, 7.98]
Knappe 2013	37	5	63	27	4	63	4.7%	10.00 [8.42, 11.58]
Kusiak 2012	26.1	4.86	57	21.7	4.81	57	4.6%	4.40 [2.62, 6.18]
Leong 2013	32	10	738	26	8	738	4.8%	6.00 [5.08, 6.92]
Praus (NR) 2012	24.8	8.4	19	22.1	6.9	19	3.3%	2.70 [-2.19, 7.59]
Praus(R) 2012	32.8	12.5	38	22	5.4	38	3.6%	10.80 [6.47, 15.13]
Sade (Eve) 2013	24.6	7.7	31	20.9	5.2	31	4.0%	3.70 [0.43, 6.97]
Sade (No Eve) 2013	35.3	10.8	74	23.6	5.8	74	4.2%	11.70 [8.91, 14.49]
Scuteri 2009	31	9	44	23	5	44	4.1%	8.00 [4.96, 11.04]
Szulik 2011	31.4	11.5	90	24.6	7.6	90	4.2%	6.80 [3.95, 9.65]
Vitarelli (NR) 2011	25	7	31	22	8	31	3.8%	3.00 [-0.74, 6.74]
Vitarelli(R) 2011	32	15	50	19	11	50	3.2%	13.00 [7.84, 18.16]
Total (95% CI)			**1767**			**1767**	**100.0%**	**5.82 [4.23, 7.41]**

Heterogeneity: $Tau^2 = 13.50$; $Chi^2 = 257.97$, df = 24 ($P < 0.00001$); $I^2 = 91\%$

Test for overall effect: $Z = 7.17$ ($P < 0.00001$)