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SYSTEMATIC REVIEW REPORT

Medical Therapy for Systemic Right Ventricles: A Systematic Review (Part 1) for the 2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines

Evidence Review Committee Members

Elisa Zaragoza-Macias, MD, MPH
Ali N. Zaidi, MD, FACC
Nandini Dendukuri, PhD
Ariane Marelli, MD, MPH, FACC, FAHA, *Chair*

ACC/AHA Task Force Members

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Susan J. Pressler, PhD, RN, FAHA*
Barbara Riegel, PhD, RN, FAHA*
Frank W. Sellke, MD, FACC, FAHA*
Win-Kuang Shen, MD, FACC, FAHA*
Duminda N. Wijeysundera, MD, PhD

*Former Task Force member; current member during the writing effort.

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ABSTRACT

Patients with systemic morphological right ventricles (RVs), including congenitally corrected transposition of the great arteries and dextro-transposition of the great arteries with a Mustard or Senning atrial baffle repair, have a high likelihood of developing systemic ventricular dysfunction. Unfortunately, there are a limited number of clinical studies on the efficacy of medical therapy for systemic RV dysfunction.

We performed a systematic review and meta-analysis to assess the effect of angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta blockers, and aldosterone antagonists in adults with systemic RVs. The inclusion criteria included age ≥18 years, systemic RVs, and at least 3 months of treatment with ACE inhibitor, ARB, beta blocker, or aldosterone antagonist. The outcomes included RV end-diastolic and end-systolic dimensions, RV ejection fraction, functional class, and exercise capacity. EMBASE, PubMed, and Cochrane databases were searched. The selected data were pooled and analyzed with the DerSimonian-Laird random-effects meta-analysis model. Between-study heterogeneity was assessed with Cochran's Q test. A Bayesian meta-analysis model was also used in the event that heterogeneity was low. Bias assessment was performed with the Newcastle-Ottawa Scale and Cochrane Risk of Bias Tool, and statistical risk of bias was assessed with Begg and Mazumdar's test and Egger's test.

Six studies met the inclusion criteria, contributing a total of 187 patients; treatment with beta blocker was the intervention that could not be analyzed because of the small number of patients and diversity of outcomes reported. After at least 3 months of treatment with ACE inhibitors, ARBs, or aldosterone antagonists, there was no statistically significant change in mean ejection fraction, ventricular dimensions, or peak ventilatory equivalent of oxygen. The methodological quality of the majority of included studies was low, mainly because of a lack of a randomized and controlled design, small sample size, and incomplete follow-up.

In conclusion, pooled results across the limited available studies did not provide conclusive evidence with regard to a beneficial effect of medical therapy in adults with systemic RV dysfunction. Randomized controlled trials or comparative-effectiveness studies that are sufficiently powered to demonstrate effect are needed to elucidate the efficacy of ACE inhibitors, ARBs, beta blockers, and aldosterone antagonists in patients with systemic RVs.

TABLE OF CONTENTS

INTRODUCTION

Adults with congenitally corrected transposition of the great arteries (CCTGA) or dextro-transposition of

the great arteries (d-TGA) with an atrial baffle repair (Mustard or Senning) support the systemic circulation with a morphological right ventricle (RV). These patients have a high likelihood of developing RV dysfunction and heart failure (HF) (1–3). Approximately 18% to 22% of adults ≥18 years of age with a d-TGA atrial-level switch develop systemic ventricular dysfunction, and up to 65% of adults ≥45 years of age with CCTGA will have symptomatic HF (3–5). Systemic ventricular dysfunction is a known predictor of death for both groups of patients (5,6). Despite the risk associated with systemic ventricular dysfunction, only a few small studies have evaluated the efficacy of "standard" HF medications, such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta blockers, and aldosterone antagonists, in patients with systemic RV dysfunction. Accordingly, there are currently no evidence-based recommendations on how to treat these patients.

On the basis of the "ACCF/AHA Clinical Practice Guideline Methodology Summit Report" (7), the American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Clinical Practice Guidelines recognized the need for an objective review of available randomized controlled trials (RCTs) and observational studies by an independent evidence review committee (ERC) to inform any recommendations in the "2018 AHA/ACC Guideline for the Management of Adults With Congenital Heart Disease" (8). We performed a systematic review and meta-analysis to determine if pooled data could be used to quantify the effectiveness of ACE inhibitors, ARBs, beta blockers, and aldosterone antagonists in patients with CCTGA and d-TGA with atrial-level switch.

Relationships With Industry and Other Entities

The ACC and AHA sponsor the guidelines without commercial support, and members volunteer their time. The ACC/AHA Task Force on Clinical Practice Guidelines avoids actual, potential, or perceived conflicts of interest that might arise through relationships with industry or other entities. All ERC members are required to disclose current industry relationships or personal interests, from 12 months before initiation of the writing effort. The ERC chair and all ERC members may not have any relevant relationships with industry or other entities (Appendix 1). For transparency, ERC members' comprehensive disclosure information is available online. Comprehensive disclosure information for the Task Force is available online.

METHODS

Two members of the ERC independently reviewed all abstracts and full articles to determine their eligibility for inclusion in the systematic review. Disagreements were resolved by consensus or through the involvement of a third reviewer (A. Marelli). Abstracted data were entered into the Indico Clinical Guideline Platform (Indico Solutions Ltd., Melbourne, Victoria, Australia), a Web-based software platform. For each included study, the ERC members abstracted data on study author and year of publication; sample size; inclusion and exclusion criteria; study design; setting (outpatient versus inpatient); participant characteristics (age, sex, and presence of structural heart disease); description of the tests/procedures and their results or acute outcomes; long-term outcomes, including sudden cardiac death or arrhythmic death, atrial fibrillation, regular supraventricular tachycardia, all-cause death, quality of life, hospitalization/readmission for cardiovascular events, and ablation-related complications; duration of follow-up; and loss to follow-up. Overall study quality was assessed on the basis of risk of bias, relevance to the study question, and fidelity of implementation (7). With regard to evaluation of risk of bias, the Cochrane Collaboration Risk of Bias Tool was used for RCTs (9), and the Newcastle-Ottawa Scale was used for cohort studies (10). An RCT was assigned an overall rating of low to intermediate risk of bias according to study quality.

In consultation with the guideline writing committee members, our clinical question was broadly defined as follows: *Are outcomes improved with ACE inhibitors, ARBs, beta blockers, or aldosterone antagonists, alone or in combination in patients with a systemic right ventricle?* Specific elements related to Population, Intervention, Comparison, Outcome, Timing, and Setting (PICOTS) comprised our PICOTS question inclusion criteria:

1) *Population*: Patients with systemic morphological RVs (CCTGA and d-TGA with atrial-level switch) ≥18 years of age.
2) *Intervention*: ACE inhibitors, ARBs, beta blockers, or aldosterone antagonists given for at least 3 months.
3) *Comparison*: Placebo or routine care.
4) *Outcome*: Improvement in systemic ventricular function, measured by a reduction in RV end-diastolic volume, RV end-systolic volume, or RV systolic function on cardiovascular magnetic resonance (CMR) imaging or echocardiogram. Secondary outcomes included functional capacity (measured by New York Heart Association functional class, 6-minute walk test,

or exercise testing), arrhythmia, hospitalization, and death.
5) *Timing*: Intervention and follow-up for at least 3 months.
6) *Setting*: Outpatient care.

Information Sources and Search Criteria

A systematic search strategy was developed, and 3 major databases were searched (PubMed, EMBASE, and Cochrane). The search criteria included the population of interest (patients with CCTGA and D-TGA) and the intervention of interest (ACE inhibitors, ARBs, beta blockers, and aldosterone antagonists). In brief, the search criteria included terms for populations with systemic RV, such as *CCTGA*, *D-TGA*, *Senning*, and *Mustard*, among others. Terms about treatment included *ACE inhibitors*, *ARB*, and *beta blockers*, as well as the individual medications in each group. Finally, the types of study included clinical trials, comparative studies, meta-analyses, and observational studies in adults ≥18 years of age. The full search strategy can be found in Online Data Supplement 1.

Study Selection

Figure 1 illustrates the screening process. Two independent experts in adult congenital heart disease screened all abstracts obtained by the systematic search. Only abstracts that met all PICOTS question criteria were included for full-text review. Afterward, the full-text articles were screened by 2 independent reviewers. The final selected articles met all PICOTS question criteria. Whenever there was conflict about the selection of one of the studies, a third reviewer (A. Marelli) helped determine inclusion or exclusion.

Data Collection and Risk-of-Bias Assessment

Data were extracted independently by 2 reviewers and checked for accuracy. Studies were graded for risk of bias with the Newcastle-Ottawa Scale for cohort studies and the Cochrane Risk of Bias Tool for RCTs.

Statistical Analysis

Outcomes

Four outcomes of interest were reported in >1 study:

1) RV ejection fraction (RVEF) measured with CMR imaging (%; ejection fraction measured by CMR),
2) RV end-diastolic volume (mL; RV end-diastolic volume),
3) RV end-systolic volume (mL; RV end-systolic volume), and
4) Peak oxygen consumption (peak $\dot{V}O_2$) (mL/kg/min).

For each outcome, we extracted summary statistics (mean and standard deviation) before and after the intervention. This was done separately for the treatment and control groups if the study was an RCT.

Treatment Effect

The treatment effect was measured by the difference in means before and after the intervention (and associated 95% confidence interval) for the 4 outcomes of interest. Where possible, we ensured that the same patients were present in the pre- and posttreatment groups. This was done separately for the treatment and control groups.

Descriptive Plots

Forest plots were used to visually examine the heterogeneity between studies. The null hypothesis of no heterogeneity between the studies was tested with Cochran's Q statistic. A small *P* value would suggest evidence of heterogeneity between studies. Funnel plots were used to examine the possibility of publication bias.

Meta-Analysis

The pooled treatment effect and associated 95% confidence interval across studies were estimated with the DerSimonian-Laird random-effects model (11). Separate meta-analysis models were fit for RCTs and for other study designs. For RCTs, we included results from the control arm. When there was evidence of between-study heterogeneity, a 95% prediction interval was also obtained. The confidence interval reflects the uncertainty in the average treatment effect, whereas the prediction interval reflects the uncertainty in the treatment effect in a future study. The impact of heterogeneity on the overall variance was measured by the I^2 statistic (12). When the Q statistic resulted in a nonsignificant *P* value, the estimated between-study standard deviation was small, and the overall treatment effect was significant, we planned to perform a Bayesian random-effects analysis (as the DerSimonian-Laird method is known) to estimate between-study heterogeneity (13). Publication bias was examined visually with funnel plots and/or Begg's test and the weighted regression test of Egger (14,15). The plots and meta-analyses were carried out with the metafor package in R (16).

RESULTS

Study Selection

A total of 439 articles met our search criteria. After a review of the abstracts, 44 studies were selected for full-text screening on the basis of our predefined PICOTS question inclusion criteria (Online Data Supplement 2). The main reason for excluding abstracts or full-text

articles was the lack of an intervention with ACE inhibitors, ARBs, beta blockers, or aldosterone antagonists. Another common reason was that the study population did not include patients ≥18 years of age or patients with a systemic morphological RV. From the studies that were initially included, 4 of the cohort studies in which the intervention was a beta blocker were excluded because of insufficient data attributable to the small number of patients and diversity of outcomes reported. The final 6 studies comprised 3 RCTs, 1 randomized controlled crossover trial, and 2 cohort studies. In all of the 6 final studies, the intervention consisted of an ACE inhibitor, ARB, or aldosterone antagonist (17-21). These studies included 131 patients in the RCTs and 71 in the cohort and crossover trials, totaling 202 patients. However, 1 patient from the RCT and 14 patients from the cohort and crossover trials were excluded from the final analysis, leaving a total of 187 patients. Because only 1 study reported death, arrhythmia, or hospitalization, these outcomes were not included in the final systematic review; however, we summarize the results relative to these outcomes in cases where the study met our PICOTS criteria in the results.

Study Characteristics

Table 1 is a summary of the final studies considered for the systematic review. As previously noted, only those in which the intervention was an ACE inhibitor, ARB, or aldosterone antagonist were included in the final systematic review. Across the included studies, the age ranged from 18.5 to 60.9 years, with a mean age of 28.7 years; median follow-up was 14.1 months; mean ejection fraction of the systemic ventricle ranged from 21% to 60%, with a mean of 45%; and mean peak $\dot{V}o_2$ was 26.7 mL/kg/min.

Synthesis of Results

Figure 2A shows the forest plots for the difference in means of systemic RV function measured by CMR ejection fraction before and after treatment as reported in 4 studies. This difference was not statistically significant (difference in means: 0.30; 95% confidence interval [CI]: −1.38 to 1.99). Three studies compared systemic RVEF of controls versus treated patients (**Figure 2B**); this was also not statistically different (difference in means: 1.06; 95% CI: −1.20 to 3.33).

Figure 3A shows the difference in means for the systemic RV end-diastolic dimensions by CMR (RV end-diastolic volume) before and after treatment as reported in 2 studies. This difference was not statistically significant (difference in means: 1.85; 95% CI: -5.50 to 9.20). Systemic RV end-diastolic dimension of controls versus treated patients was reported in 2 studies (**Figure 3B**) and was not statistically different (difference in means: -9.01; 95% CI: -34.26 to 16.24).

Figure 4A shows the difference in means for the systemic RV end-systolic dimensions by CMR before and after treatment as reported in 2 studies, which was not statistically different (difference in means: 1.37; 95% CI: −4.81 to 7.55). Two studies reported systemic RV end-systolic dimensions of controls versus treated patients (**Figure 4B**); the results showed no statistically significant difference (difference in means: −11.43; 95% CI: −27.01 to 4.15).

Finally, **Figure 5A** shows the difference in means for the peak $\dot{V}o_2$ before and after treatment as reported in 5 studies. The overall difference in peak $\dot{V}o_2$ was not statistically significant (difference in means: −1.13, 95% CI: −2.77 to 0.51). There was heterogeneity between studies, leading to a wide prediction interval. Two studies that reported a difference in peak $\dot{V}o_2$ for controls versus treated patients showed no statistical difference (**Figure 5B**; difference in means 0.06 [95% CI: −1.70 to 1.83]).

Heterogeneity

Of all of the outcomes assessed, only peak $\dot{V}o_2$ before and after treatment was found to have statistically significant heterogeneity across studies (P=0.011). Comparison of peak $\dot{V}o_2$ from RCTs did not show statistically significant heterogeneity. The rest of the outcomes were found to have no statistically significant heterogeneity either; however, it should be noted that because of the low number of studies and patients included, the power to detect between-study differences with the heterogeneity test was reduced (22). We did not carry out any Bayesian analyses because there were no instances in which the overall result was statistically significant, but evidence of heterogeneity was insufficient.

Risk of Publication Bias

Online Data Supplement 3 shows funnel plots for the outcomes of peak $\dot{V}o_2$ and RVEF, for which at least 4 studies were available. Because of the small number of studies, even for these outcomes, definitive conclusions cannot be drawn. For both peak $\dot{V}o_2$ and RVEF, funnel plot analysis showed no apparent publication bias.

The risk of methodological bias assessed through the Cochrane Collaboration Risk of Bias Tool and Newcastle-Ottawa Scale can be found in Online Data Supplements 4 and 5.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis to assess the effectiveness of ACE

inhibitors, ARBs, and aldosterone antagonists in patients with systemic RV dysfunction. The results show no significant treatment effect in terms of the following: improvement of ventricular function as shown by CMR imaging or echocardiography, reduction in ventricular dimensions as shown by CMR imaging or echocardiography, or improvement in exercise tolerance. Data were insufficient to pool analyses related to the death, arrhythmia, or hospitalization outcomes.

The rationale behind the use of ACE inhibitors, ARBs, beta blockers, and aldosterone antagonists in HF in patients with systemic RVs is 2-fold. First, these medications have been shown extensively in noncongenital systemic left ventricular (LV) failure to improve LV function, reduce ventricular size, attenuate LV remodeling, and reduce fibrosis (23–25). Second, in patients with LV HF after treatment, there is a significant and dose-related decrease in deaths and hospitalizations and an improvement in exercise tolerance (23,24,26,27).

In adults with a systemic RV, incidence of ventricular dysfunction is high. The mechanisms for ventricular dysfunction are multifactorial. Some studies have demonstrated that patients with dilated systemic RVs have increased levels of norepinephrine and epinephrine, as well as increased fibrosis of the systemic RV (21,28–31). The extent of increased fibrosis is correlated with the degree of ventricular dysfunction and with higher incidence of clinical events, such as arrhythmia or syncope. Thus, given the increase in neurohormones and fibrosis in patients with a systemic RV, it appears plausible that treatments used for LV HF may result in improved outcomes in patients with systemic RV dysfunction.

In the present meta-analysis, treatment with ACE inhibitors, ARBs, or aldosterone antagonists showed no evidence of a significant protective effect on the clinical outcomes related to ventricular function. Nevertheless, the search strategy produced a paucity of studies. Of the initial predefined outcomes analyzed, the outcomes of arrhythmia, death, or hospitalization were assessed in only 1 study (17). Thus, only the outcomes of RV size, RV function, and exercise capacity were found in at least 2 studies that were used for this meta-analysis.

The largest study included was an RCT by van der Bom et al. (17). In that study, only 88 of the originally calculated 102 patients were recruited. Albeit potentially underpowered, this study did not show a statistically significant difference after treatment with valsartan for up to 3 years in terms of change in RVEF, RV dimensions, or peak $\dot{V}O_2$, as compared with controls. This was the only study that included the outcomes of death, hospitalization, and arrhythmia. It did not show any difference in these outcomes as compared with the control group (17).

The randomized, double-blind, placebo-controlled crossover trial by Dore et al. was a small study consisting of 29 patients (18). Although the population was small, according to their assumptions, the study was powered to detect a difference between groups, and there was no loss of follow-up. In that study, there was no difference in peak $\dot{V}O_2$ or other parameters of exercise capacity obtained by cardiopulmonary exercise testing. The main 2 study design disadvantages were that (18). Follow-up was short at only 4 months, which would be a very short follow-up as compared with clinical trials that looked at similar therapies for LV dysfunction.

In the study by Therrien et al. (20), the main limitation was related to the lack of specification of population size/power calculation. Of the 70 patients originally screened, 38 were ineligible (20 were excluded because they were already taking ACE inhibitors, 11 because they had pacemakers precluding magnetic resonance imaging, 3 for claustrophobia, and 4 for intolerance to ACE inhibitors), and 5 declined to participate. Of the final 27 patients enrolled, only 17 finished the study, constituting a >50% dropout rate. The study showed no improvement in ventricular function and showed a reduction in exercise capacity for both treatment (enalapril) and placebo groups. However, given the significant dropout rate, there was a risk of type II error.

Potential for type II error was also high in the study by Dos et al. (19), which analyzed the effect of eplerenone in a randomized, double-blind, controlled trial. It had significant underrecruitment, with only 26 of the estimated 117 patients being recruited. There was no difference in RV mass, size, or function on CMR imaging. Importantly, the population of treated patients had a starting RVEF of 55%, and the majority were in New York Heart Association functional class I. It would be difficult to assess a significant improvement without a much larger population when the included patients had near-normal RV function.

The 2 cohort studies included were retrospective studies with limited population size. In the cohort study by Hechter et al. (31), only 14 patients who received an ACE inhibitor (enalapril) were included. No statistically significant differences were found in ventricular function or parameters of cardiopulmonary exercise testing. However, there was a slight trend toward an improvement in overall exercise time and peak $\dot{V}O_2$. In the study by Tutarel et al. (21), the levels of brain natriuretic peptide were decreased after an average of 13 months of treatment with an ACE inhibitor; however, no difference in peak $\dot{V}O_2$ was seen.

The 4 studies in which beta blocker was the intervention could not be analyzed in the present systematic review because of the small number of patients and

diversity of outcomes reported. In 3 of these studies, methodological quality was judged to be low, mainly because of the low sample size and the fact that the retrospectively selected patients were not truly representative (32-34). The fourth and largest study (35) compared 31 patients treated with beta blockers for systemic RV failure with 29 that were not. Patients and controls differed mainly in that the treated population had pacemakers. After a mean of 10 ± 7 months, the systemic RV dimension was statistically significantly smaller in patients treated with beta blockers; however, RV function was not statistically different between cases and controls. The study also found a statistically significant change in New York Heart Association functional class. Pooled analysis was not performed for the effect of beta blockers because of the lack of at least 2 studies that had comparable data and a sufficiently large sample size.

Risk of Bias and Limitations

Consistent with other meta-analyses, there is risk of publication bias. However, through the inclusion of various search engines, any possible studies that matched our search criteria were captured.

The present systematic review and meta-analysis has certain limitations. First, the total population included is very small, which may mean it is underpowered to detect a true difference. The 2 largest RCTs found through database searches did not meet recruitment goals, so both studies were underpowered (17,19). Only the study by Dore et al. (18) achieved full recruitment, and even that study did not show an effect of ACE inhibitors.

Second, in most cohort studies, the analyses were at risk of misclassification bias because of the considerable number of patients lost to follow-up. Because most studies did not report a pairwise preintervention and postintervention difference with an associated standard deviation, we treated the pre- and postintervention outcome measures as independent, thereby obtaining wider confidence intervals for the treatment effect.

Third, although there was no statistically significant heterogeneity for most outcomes, these studies included a significantly heterogeneous population. Recruitment characteristics varied, as did grades of systolic dysfunction and symptoms. Although we would expect treatment to be effective in all patient groups, the effect might be more pronounced and thus better assessed in those who have well-defined or advanced symptomatic HF. Furthermore, there was significant patient heterogeneity in terms of age at initial repair, residual anatomic lesions, number of operations, residual valvular abnormalities, arrhythmias, and pacemaker use, among other clinically relevant characteristics.

Fourth, because of the limited population available in this meta-analysis, patients with CCTGA and patients with d-TGA were analyzed together. Although in both patient groups, the morphological RV supports the systemic circulation, these are 2 diverse populations in terms of exposure to operations, age at development of HF, and percentage of rhythm disturbances, among other characteristics. A targeted trial to include a more specific and homogeneous population would prove useful.

Fifth, the included population varied in terms of the degree of RV dysfunction. Many of the studies included patients with near-normal systemic RV function who were not symptomatic at baseline. This is important because some of the studies that have looked at the use of ACE inhibitors, ARBs, or aldosterone antagonists in patients with HF and LV ejection fraction >40% to >45% failed to show a difference in outcomes, and most studies that showed differences included a population with ejection fraction <40% (36-40).

Finally, the treatment included ACE inhibitors, ARBs, and aldosterone antagonists. It is possible that some of these agents are effective in larger studies, whereas others may prove to be ineffective.

CONCLUSION

Only a limited number of studies have explored the effectiveness of ACE inhibitors, ARBs, beta blockers, and aldosterone antagonists in adults with systemic RV dysfunction. Our results show that pooled results across the limited available studies did not provide conclusive evidence with regard to a beneficial effect of medical therapy in adults with systemic RV dysfunction. Larger prospectively randomized trials to confirm the effect of ACE inhibitors, ARBs, beta blockers, and aldosterone antagonists are needed. Multicenter collaboration would be important for recruiting sufficient numbers of patients to allow for the use of strict inclusion criteria and sufficiently long follow-up.

TABLE AND FIGURES

FIGURE 1 Flow Diagram of Studies Included in Literature Search

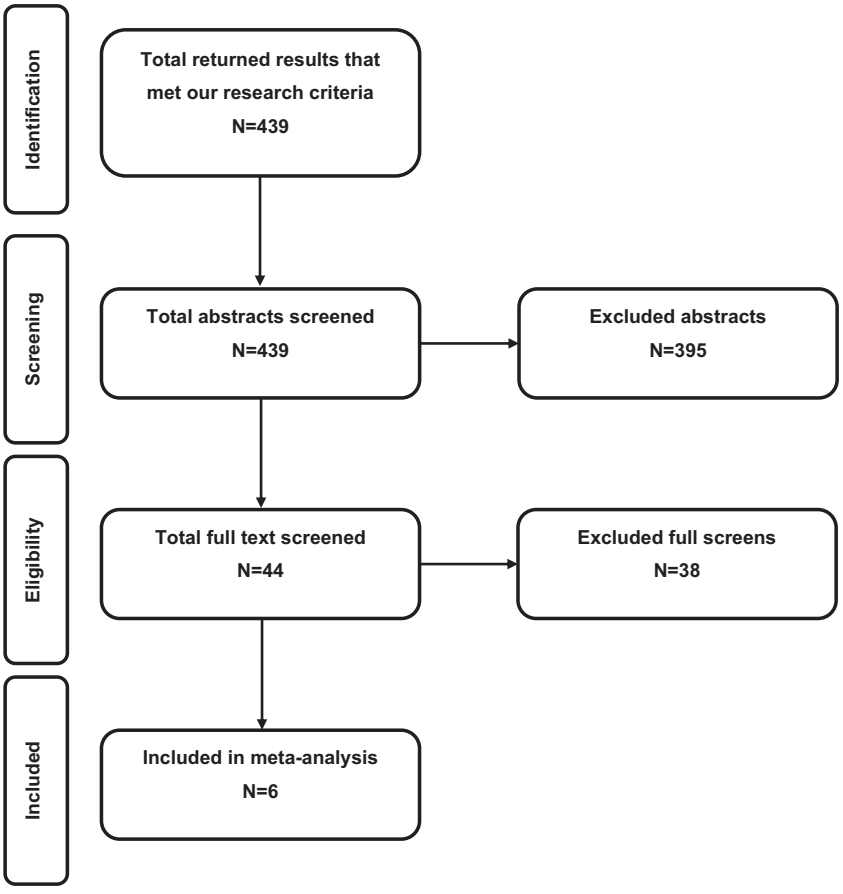


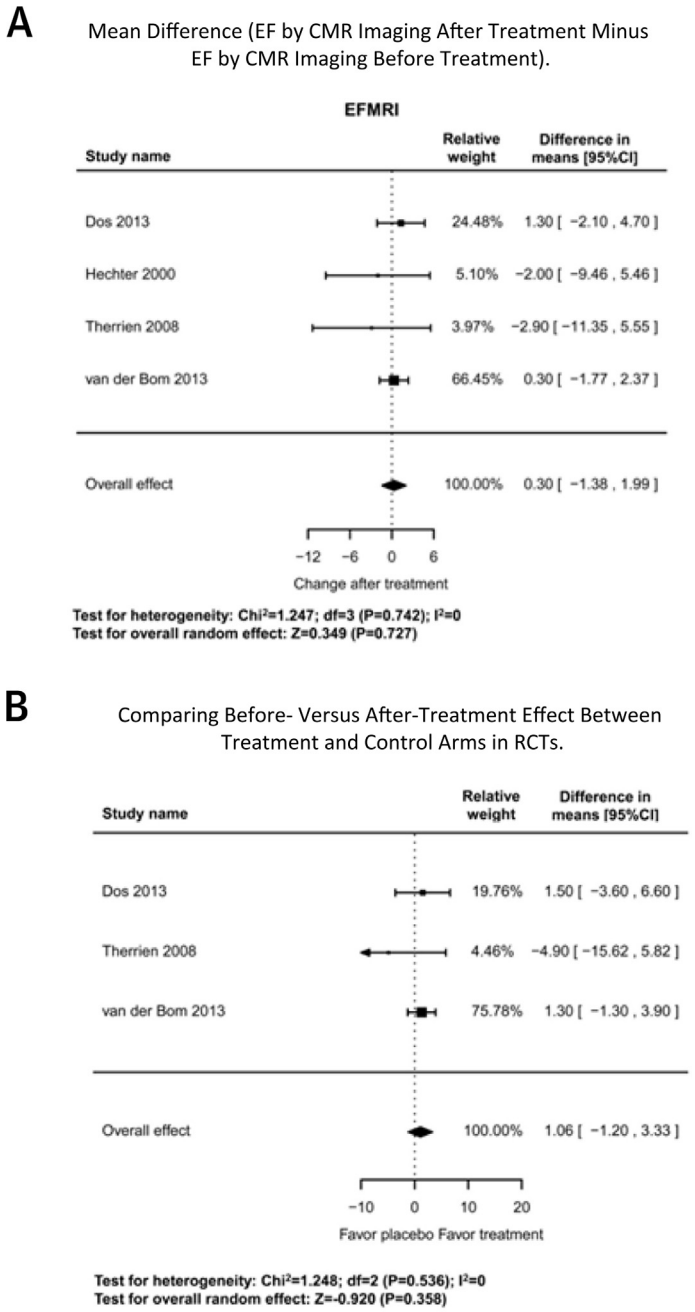
TABLE 1 Study Characteristics

First Author	Sample (N) Exp/Obs	Male (N)	Age Mean or Median (y) (SD or Range) Exp/Obs	Intervention	Diagnosis	Mean Follow-Up Time (mo)
RCT						
Dos et al. (19) 23972966	14*/12	8 (T) 8 (C)	24.9 ± 4.3 (T) 28.3 ± 6.1 (C)	Eplerenone	Abff	12
Therrien et al. (20) 18672299	8/9	3 (T) 8 (C)	27 ± 5.7 (T) 26 ± 5.2 (C)	ACE	Abff	12
Van der Bom et al. (17) 23247302	44/44	29 (T) 28 (C)	33 ± 10 (T) 33 ± 10 (C)	ARB	CCTGA/Abff	38
Other						
Dore et al. (18)† 16216961	29	24	30.3 ± 10.9	ARB	CCTGA/Abff	4
Hechter et al. (31) 11230861	14	12	31 (26, 42)	ACE	Abff	24
Tutarel et al. (21) 20843567	14/14	11 (T) 10 (C)	25.2 ± 3.5 (T) 24.6 ± 2.3 (C)	ARB	Abff	13
Giardini et al. (33)‡ 21882492	8	5	26 (18, 31)	BB	CCTGA/Abff	12
Doughan et al. (35)‡ 17317376	31/29	20 (T) 18 (C)	29 ± 6 (T) 27 ± 6 (C)	BB	Abff	10
Bouallal et al. (32)‡ 20519056	14	7	35 (24, 57)	BB	SV	13
Josephson et al. (34)‡ 16835671	8	5	29 (22, 37)	BB	Abff	36

*Of the 14 exposed patients, 1 was excluded in final analysis.
†Other, randomized clinical trial with crossover design or cohort study.
‡Excluded from analysis because of insufficient data.

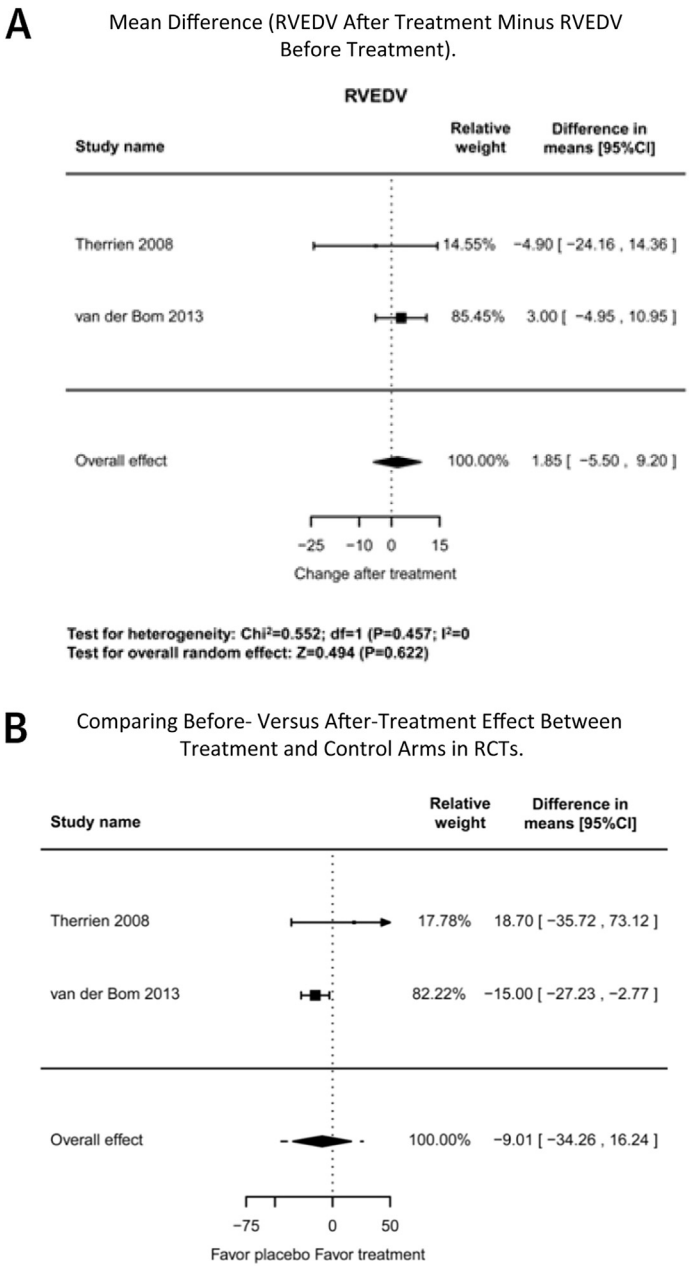
Abff indicates atrial baffle (Mustard or Senning operation) for complete transposition of the great arteries; ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blockers; BB, beta blockers; C, control; CCTGA, congenitally corrected transposition of the great arteries; Exp, experimental group; Obs, observation or control group; RCT, randomized clinical trial; SD, standard deviation; SV, single ventricle; and T, treated.

FIGURE 2 Mean Difference in Systemic RV Function Measured by CMR Imaging



CI indicates confidence interval; df, degrees of freedom; EF, ejection fraction; CMR, cardiovascular magnetic resonance; MRI, magnetic resonance imaging; RCT, randomized controlled trial; and RV, right ventricular.

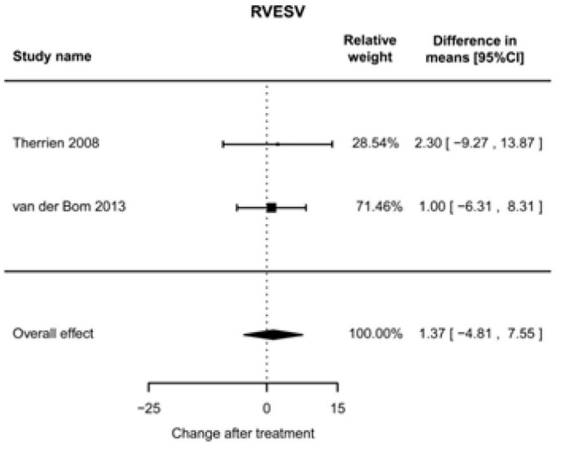
FIGURE 3 Mean Difference in Systemic RVEDV



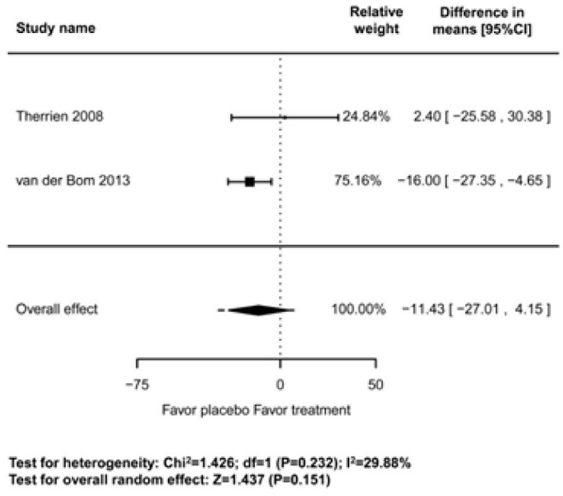
CI indicates confidence interval; df, degrees of freedom; RCT, randomized controlled trial; and RVEDV, right ventricular end-diastolic volume.

FIGURE 4 Mean Difference in Systemic RVESV

A Mean Difference (RVESV After Treatment Minus RVESV Before Treatment).



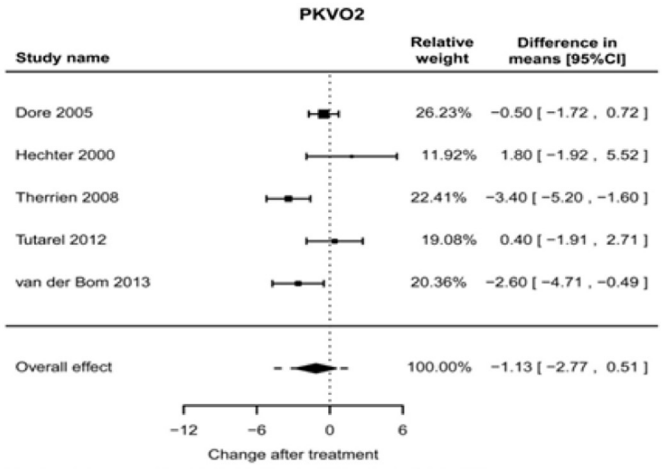
B Comparing Before- Versus After-Treatment Effect Between Treatment and Control Arms in RCTs.



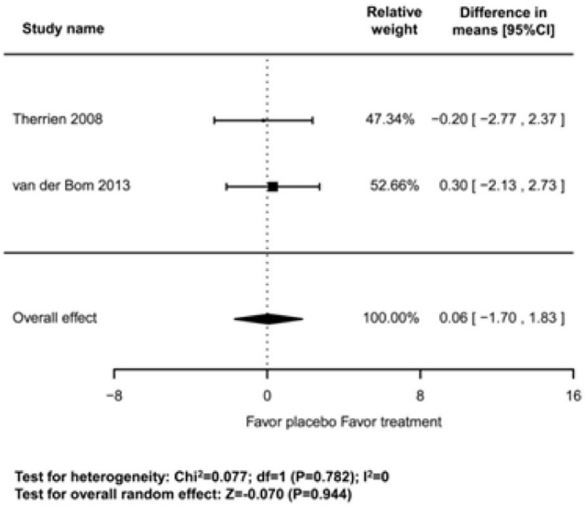
CI indicates confidence interval; df, degrees of freedom; RCT, randomized controlled trial; and RVESV, right ventricular end-systolic volume.

FIGURE 5 Mean Difference in Peak $\dot{V}o_2$ Measured by Cardiopulmonary Exercise Testing

A Mean Difference (Peak $\dot{V}o_2$ After Treatment Minus Peak $\dot{V}o_2$ Before Treatment).



B Comparing Before- Versus After-Treatment Effect Between Treatment and Control Arms in RCTs.



CI indicates confidence interval; df, degrees of freedom; PKVO2, peak ventilatory equivalent of oxygen; and RCT, randomized controlled trial.

PRESIDENTS AND STAFF

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KEY WORDS ACC/AHA Clinical Practice Guidelines, adults, congenital heart disease, beta blockers, angiotensin-converting enzyme, congenitally corrected transposition of the great arteries, dextro-transposition of the great arteries, Evidence Review Committee, heart failure, meta-analysis, systemic right ventricle

APPENDIX 1. EVIDENCE REVIEW COMMITTEE RELATIONSHIPS WITH INDUSTRY AND OTHER ENTITIES*† (RELEVANT)—MEDICAL THERAPY FOR SYSTEMIC RIGHT VENTRICLES: A SYSTEMATIC REVIEW (PART 1) FOR THE 2018 AHA/ACC GUIDELINE FOR THE MANAGEMENT OF ADULTS WITH CONGENITAL HEART DISEASE

Committee Member	Employment	Consultant	Speakers Bureau	Ownership/ Partnership/ Principal	Personal Research	Institutional, Organizational, or Other Financial Benefit	Expert Witness
Ariane Marelli (*Chair*)	McGill University Health Center—Director, MAUDE Unit	None	None	None	None	None	None
Nandini Dendukuri	McGill University—Director, Health Center; Associate Professor, Medicine and Epidemiology, Biostatistics and Occupational Health	None	None	None	None	None	None
Ali N. Zaidi	Montefiore Einstein Center for Heart and Vascular Care—Director, Adult Congenital Heart Disease Program; The Children's Hospital at Montefiore—Assistant Professor, Internal Medicine and Pediatrics	None	None	None	None	None	None
Elisa Zaragoza-Macias	University of Washington School of Medicine—ACHD Adjunct Faculty	None	None	None	None	None	None

This table represents the relationships of ERC members with industry and other entities that were determined to be relevant to this initiative. These relationships were reviewed and updated in conjunction with all conference calls of the ERC during the evidence review process. The table does not necessarily reflect relationships with industry at the time of publication. A person is deemed to have a significant interest in a business if the interest represents ownership of ≥5% of the voting stock or share of the business entity, or ownership of ≥$5,000 of the fair market value of the business entity; or if funds received by the person from the business entity exceed 5% of the person's gross income for the previous year. Relationships that exist with no financial benefit are also included for the purpose of transparency. Relationships in this table are modest unless otherwise noted.

According to the ACC/AHA, a person has a *relevant* relationship IF: a) the *relationship or interest* relates to the same or similar subject matter, intellectual property or asset, topic, or issue addressed in the *document*; or b) the *company/entity* (with whom the relationship exists) makes a drug, drug class, or device addressed in the document, or makes a competing drug or device addressed in the *document*; or c) the *person or a member of the person's household* has a reasonable potential for financial, professional, or other personal gain or loss as a result of the issues/content addressed in the document.

*For transparency, the ERC members' comprehensive disclosure information is available as an online supplement.

†The ACHD guideline began in March 2014. Over the initial years of the CMS Open Payment System, understandably, there have been issues related to accurate reporting of food and beverage payments. For this reason, the ACC and AHA have not considered these minor charges relevant relationships with industry.

ACC indicates American College of Cardiology; ACHD, adult congenital heart disease; AHA, American Heart Association; CMS, Centers for Medicare & Medicaid Services; ERC, Evidence Review Committee; and MAUDE, McGill Adult Unit for Congenital Heart Disease.