Clinical Investigations

Favorable Effects of Vasodilators on Left Ventricular Remodeling in Asymptomatic Patients With Chronic Moderate-Severe Aortic Regurgitation and Normal Ejection Fraction: A Meta-Analysis of Clinical Trials

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ABSTRACT

Background: The role of vasodilator therapy in asymptomatic patients with chronic moderate to severe aortic regurgitation (AR) and normal left ventricular (LV) function is uncertain. We assessed the effects of vasodilator therapy (hydralazine, calcium channel blockers, and angiotensin-converting enzyme inhibitors) in this subgroup of patient population.

Hypothesis: Vasodilators have favorable effects on LV remodelling in asymptomatic patients with chronic moderate to severe aortic regurgitation and normal LV function.

Methods: We performed a systematic literature search for randomized clinical trials using long-term vasodilator therapy in asymptomatic patients with chronic severe AR and normal LV function. The magnitude of difference between the vasodilator and nonvasodilator groups was assessed by computing the mean difference (MD). Heterogeneity of the studies was analyzed by Cochran Q statistics. The MD for LV ejection fraction, LV end systolic volume index, and LV end diastolic volume index were computed by random effects model. The MD for LV end-systolic diameter and LV end-diastolic diameter were computed by fixed effects model. A 2-sided alpha error <0.05 was considered to be statistically significant.

Results: Seven studies with 460 patients were included. Meta-analysis of the studies revealed a significant increase in LVEF (MD: 5.32, 95% confidence interval [CI]: 0.37 to 10.26, $P = 0.035$), a significant decrease in LV end diastolic volume index (MD: -16.282, 95% CI: -23.684 to -8.881, $P < 0.001$), and a significant decrease in LV end diastolic diameter (MD: -2.343, 95% CI: -3.397 to -1.288, $P < 0.001$) in the vasodilator group compared with the nonvasodilator group. However, there was no significant decrease in LV end systolic volume index (MD: -6.105, 95% CI: -12.478 to 0.267, $P = 0.060$) or in LV end systolic diameter (MD: 0.00, 95% CI: -0.986 to 0.986, $P = 1.0$) in the vasodilator group compared with the nonvasodilator group.

Conclusions: In asymptomatic patients with chronic severe AR and normal LV function, vasodilators have favorable effects on LV remodeling.

Introduction

Chronic aortic regurgitation (AR) has been reported to occur in up to 10% of the middle-aged to older population who undergo echocardiography.[1] It is characterized by chronic volume and pressure overload of the left ventricle (LV), which leads to its insidious dilatation as well as hypertrophy. It has a long asymptomatic phase during which ventricular remodeling maintains normal cardiac function despite elevated afterload[2]; this phase may last for decades. It is usually followed by development of symptoms and signs of irreversible LV systolic dysfunction or LV dilation, which usually requires valve-replacement surgery.[3] Approximately 6% of patients with AR progress to symptoms of LV systolic dysfunction each year, and the mortality rate is about 10% per year in the presence of LV systolic dysfunction.[4]

Vasodilator therapy in asymptomatic patients with chronic AR and normal LV function has been shown to reduce the regurgitant volume, afterload, LV volumes, and wall stress in various studies.[5–9] This would in turn preserve LV function and prolong the compensated phase of asymptomatic patients who have volume-loaded left ventricles but normal systolic function, which might delay the need for aortic valve replacement (AVR).[9] However, other clinical trials have failed to show the beneficial effects of vasodilators

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Received: December 20, 2011
Accepted with revision: April 27, 2012

Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI:10.1002/clc.22019

on echocardiographic parameters of LV function.[5,10,11] As various clinical trials have demonstrated inconsistent results, we conducted this meta-analysis to evaluate the efficacy of vasodilator therapy (hydralazine, calcium channel blockers [CCB], and angiotensin-converting enzyme [ACE] inhibitors) in asymptomatic patients with chronic moderate to severe AR and normal LV function.

Methods

We performed this review in accordance with the Quality of Reporting of Meta-analysis (QUOROM) statement and the Consolidated Standards of Reporting Trials (CONSORT) Group recommendations.[12]

Literature Search

We performed a computerized search to identify all human randomized controlled trials (RCTs) using long-term vasodilator therapy in asymptomatic chronic moderate to severe AR with normal LV function, published in English from 1980 through October 2011 in the Excerpta Medical Database (EMBASE), Cumulative Index to Nursing and Allied Health Literature (CINAHL), PubMed, and Cochrane databases. The following search terms were used: "angiotensin-converting enzyme inhibitor," "calcium channel blockers," the individual names of all drugs in these classes, "hydralazine," and "chronic aortic regurgitation."

Study Selection: All titles and abstracts from the results of our computerized search were reviewed by the authors for potential inclusion in our study. Studies were selected for this review if both reviewers felt that they met the following criteria: (1) RCTs with parallel design; (2) that involved the use of vasodilators including ACE inhibitors, CCBs, or hydralazine and $\geq$1 comparison group; (3) that included asymptomatic patients with chronic moderate to severe AR and normal LV function; and (4) that provided data on LV ejection fraction (LVEF), LV end-systolic volume index (LVESVI), LV end-diastolic volume index (LVEDVI), LV end-systolic diameter (LVESD), and LV end-diastolic diameter (LVEDD) after a follow-up period of $\geq$4 weeks. In addition to our computerized search, we manually reviewed the reference list of all retrieved articles to complete our search.

Data Abstraction and Validity Assessment

After identifying all relevant articles, we extracted characteristics of the study (author, year, duration, sample size, vasodilator regimen used) and participants (age). Two reviewers independently extracted data and assessed outcomes. Both investigators used the criteria developed by the US Preventive Services Task Force to determine internal validity of the individual studies included in the meta-analysis.[13] Studies were rated in 3 categories ("good," "fair," and "poor") on the basis of these criteria. We resolved disagreements by mutual discussion and, if required, by consulting a third investigator.

Statistical Analysis

A systematic review of the literature revealed 7 eligible studies. The magnitude of difference between the vasodilator and nonvasodilator groups was assessed by computing the mean difference (MD). For the purpose of meta-analysis, heterogeneity of the studies was analyzed by the Cochran Q statistics, and I^2 was computed to quantify heterogeneity. If the studies were found heterogenic for an outcome, the meta-analysis was performed by using the random effects model; otherwise, the fixed effects model was used. A 2-sided α error <0.05 was considered to be statistically significant ($P < 0.05$).

Results

Literature Search

The computerized literature review yielded a total of 265 articles, of which 110 were deemed relevant to the topic of vasodilators and AR after title and abstract screening. Out of these 110 articles, we found only 70 relevant for vasodilators and chronic AR. So, these 70 articles were included for our review. Among these we identified a total of 41 clinical trials that were selected for a detailed review. Out of these, only those studies that studied the effect of vasodilators on echocardiographic parameters for a minimum of 12 weeks' duration were included in our analysis. So, from 41 trials, 22 trials were excluded from the analysis. From the remaining 19 studies, 12 studies did not meet the inclusion criteria, and eventually 7 studies were included for the meta-analysis.[5–11] The major reasons for exclusion included enrollment of symptomatic patients, patients with LV systolic dysfunction at baseline, or patients with mild AR and lack of data for echocardiographic parameters. Other reasons for exclusion were observational study design, lack of a comparison group, or direct comparison between 2 vasodilator groups.

Overview of Study and Patient Characteristics

A total of 460 patients were included in the 7 RCTs that met the inclusion criteria. The inclusion criteria were (1) RCTs with parallel design; (2) that involved the use of vasodilators including ACE inhibitors, CCBs, or hydralazine and $\geq$1 comparison group; (3) that included asymptomatic patients with chronic moderate to severe AR and normal LV function; and (4) that provided data on LVEF, LVESVI, LVEDVI, LVESD, and LVEDD after a follow-up period of $\geq$4 weeks. The treatment duration ranged from 12 weeks to 7 years among various studies. The characteristics of the 7 RCTs included in the meta-analysis and results for study parameters are listed in tables 1 and 2. Six studies compared vasodilator with a placebo,[5–8,10,11] whereas 1 study compared vasodilator with digoxin.[9]

Imaging Modality

Three different imaging modalities were used in these studies. Three studies used echocardiography,[7,9,11] 3 used RVG,[5,6,8] and 1 study used MRI.[10]

Statistical Analysis

Studies were heterogeneous for LVEF, LVESVI, and LVEDVI and homogeneous for LVESD and LVEDD. Results of heterogeneity analysis are shown in Table 3. The MD for LVEF, LVESVI, and LVEDVI were computed by the random effects model. The MD for LVESD and LVEDD were computed by the fixed effects model.

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DOI:10.1002/clc.22019

Table 1. Various Studies and Their Characteristics Included in the Meta-Analysis

Study, Year, Journal	Study Quality	Sample Size		Mean Age, y	Mean Duration of Follow-Up	Imaging Modality	Medication Used	
		Total	Groups				Treatment	Control Group
Kleaveland et al, 1986, AJC	Good	14	Treatment 6 Control 8	68	6 mo	RVG	Hydralazine titrated, TID	Placebo
Greenberg et al, 1988, *Circulation*	Fair	37	Treatment 21 Control 16	66	24 mo	RVG	Hydralazine, 3 mg/kg in BID	Placebo
Scognamiglio et al, 1990, JACC	Good	70	Treatment 36 Control 34	65	12 mo	ECHO	Nifedipine, 20 mg BID	Placebo
Wilson et al, 1991, AJC	Fair	54	Treatment 28 Control 26	58	18 ± 6 mo	RVG	Hydralazine, 3 mg/kg in BID	Placebo
Scognamiglio et al, 1994, NEJM	Fair	143	Treatment 69 Control 74	63	6 y	ECHO	Nifedipine, 20 mg BID	Digoxin
Sondergaard et al, 2000, AHJ	Good	16	Treatment 8 Control 8	64	3 mo	MRI	Felodipine, 10 mg daily	Placebo
Evangelista et al, 2005, NEJM	Good	126	Nifedipine 32 Enalapril 32 Placebo 62	68	7 ± 2 y	ECHO	Nifedipine, 20 mg BID; enalapril, 20 mg daily	Placebo

Abbreviations: AHJ, American Heart Journal; AJC, *American Journal of Cardiology*; BID, twice a day; ECHO, echocardiogram; JACC, *Journal of American College of Cardiology*; MRI, magnetic resonance imaging; NEJM, *New England Journal of Medicine*; RVG, right ventriculogram; TID, 3 times a day.

Table 2. Various Structural Parameters Included in the Meta-Analysis

Study	Mean LVEF (%)		Mean LVEDVI (cc/m²)		Mean LVESVI (cc/m²)		Mean LVEDD (mm)		Mean LVESD (mm)	
	Baseline (D/P)	Follow-up (D/P)	Baseline (D/P)	Follow-up (D/P)	Baseline (D/P)	Follow-up (D/P)	Baseline (D/P)	Follow-up (D/P)	Baseline (D/P)	Follow-up (D/P)
Kleaveland et al, 1986, AJC	61/62	63/60	—	—	—	—	—	—	—	—
Greenberg et al, 1988, *Circulation*	66/64	68/62	169/161	145/156	58/57	46/49	66/68	67/68	43/43	43/43
Scognamiglio et al, 1990, JACC	60/58	72/48	136/134	110/138	—	—	—	—	—	—
Wilson et al, 1991, AJC	65/63	66.8/60.1	168/158	143/155	57/58	59/62	—	—	—	—
Scognamiglio et al, 1994, NEJM	64/62	62/58	126/128	112/140	52/49	51/56	—	—	—	—
Sondergaard et al, 2000, AHJ	55/50	56/50	129/156	128/154	58/78	56/77	—	—	—	—
Evangelista et al, 2005, NEJM	59/60	58/57	94/109	104/114	40/45	46/49	65/64	68/69	44/44	46/46
Evangelista et al, 2005, NEJM	58/60	57/57	114/109	124/114	49/45	53/49	68/64	70/69	46/44	48/46

Abbreviations: AHJ, *American Heart Journal*; AJC, *American Journal of Cardiology*, D/P, mean of parameter in the study drug group and placebo group; JACC, *Journal of American College of Cardiology*; LVEDD, left ventricular end-diastolic diameter; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESVI, left ventricular end-systolic volume index; NEJM, *New England Journal of Medicine*.

Table 3. Results of Heterogeneity Among Various Studies Included in the Meta-Analysis

Parameter	Q Value	df (Q)	*P* Value	I^2	Result
LVEF	457.54	7	0.000	98.5	Heterogenic
LVEDVI	105.45	6	0.000	94.3	Heterogenic
LVESVI	76.02	5	0.000	93.4	Heterogenic
LVEDD	1.50	2	0.472	0.0	Homogenic
LVESD	0.00	2	1.000	0.0	Homogenic

Abbreviations: df, degrees of freedom; LVEDD, left ventricular end-diastolic diameter; LVEDVI, left ventricular end-diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESVI, left ventricular end-systolic volume index.

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DOI:10.1002/clc.22019

Outcome Results

In the pooled analysis, the common MD between the vasodilator therapy arm and placebo arm was estimated. Seven studies provided data for the result of LVEF, 6 for LVEDVI, 5 for LVESVI, and 2 for LVEDD and LVESD. Meta-analysis of all the studies revealed a significant increase in LVEF (MD: 5.32, 95% confidence interval [CI]: 0.37-10.26, $P = 0.035$) (Figure 1), a significant decrease in LVEDVI (MD: −16.282, 95% CI: −23.684 to −8.881, $P < 0.001$) (figure 2), and a significant decrease in LVEDD (MD: −2.343, 95% CI: −3.397 to −1.288, $P < 0.001$) (figure 3) in the vasodilator group compared with the nonvasodilator group. There was a trend toward decrease in LVESVI (MD: −6.105, 95% CI: −12.478 to 0.267, $P = 0.060$) (Figure 4), although statistically not significant. However, there was no significant decrease in LVESD (MD: 0.00, 95% CI: −0.986 to 0.986, $P = 1.0$) (Figure 5) in the vasodilator group compared with the nonvasodilator group. The results are summarized in Figure 6.

Discussion

This meta-analysis, based on 7 RCTs, indicates that vasodilator therapy has favorable effects on LV remodeling in asymptomatic patients with chronic severe AR. Our meta-analysis revealed a significant increase in LVEF, a significant decrease in LVEDVI, and a significant decrease in LVEDD in the vasodilator group compared with the nonvasodilator group. In addition, there was a small but statistically insignificant decrease in LVESVI indicating potential favorable effects of vasodilator therapy on this condition. All these favorable effects may prolong the compensated phase of asymptomatic patients who have volume-loaded left ventricles but normal systolic function.

A major consequence of AR is LV remodeling, characterized by progressive dilatation and hypertrophy of the LV.[2] Multiple echocardiographic parameters are used in various studies to assess LV remodeling in patients with AR. Among these, 5 studies regarding the natural history of asymptomatic patients with AR provide concordant information

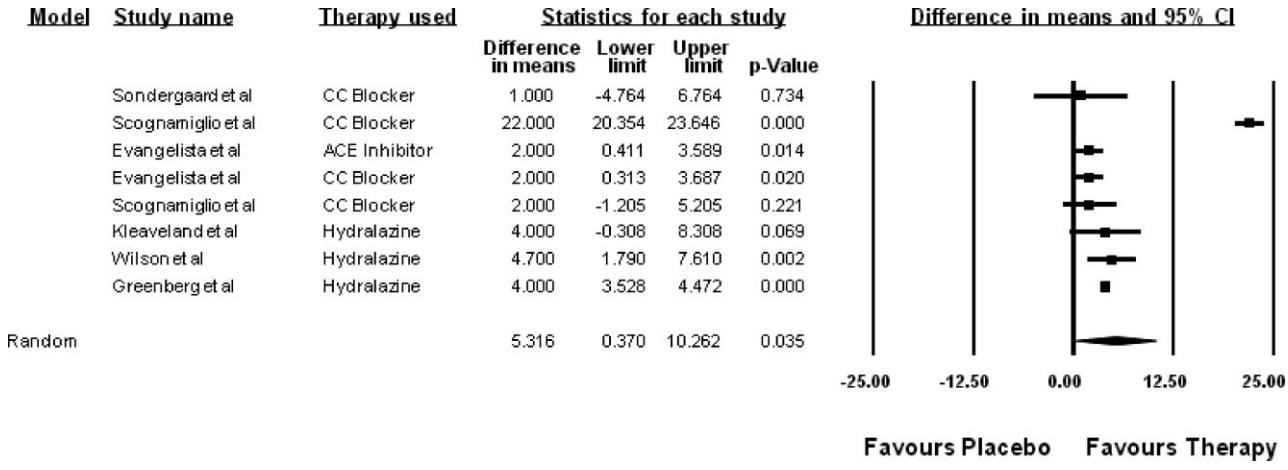

Figure 1. The Forest plot comparing the LVEF between vasodilator and placebo groups and showing statistically significant difference of 5.316 in favor of vasodilator group.(LVEF- Left ventricular ejection fraction). Abbreviations: ACE, angiotensin-converting enzyme; CC, calcium channel; CI, confidence interval.

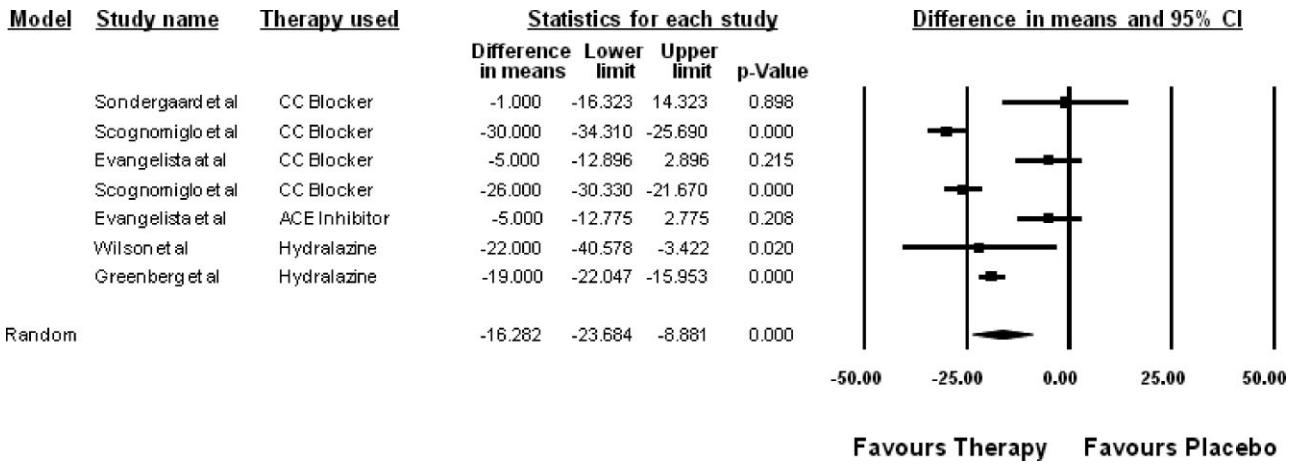

Figure 2. The Forest plot comparing the LVEDVI between vasodilator and placebo groups and showing statistically significant difference of 16.282 in favor of vasodilator group. (LVEDVI, left ventricular end-diastolic volume index.) Abbreviations: ACE, angiotensin-converting enzyme; CC, calcium channel; CI, confidence interval.

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DOI:10.1002/clc.22019

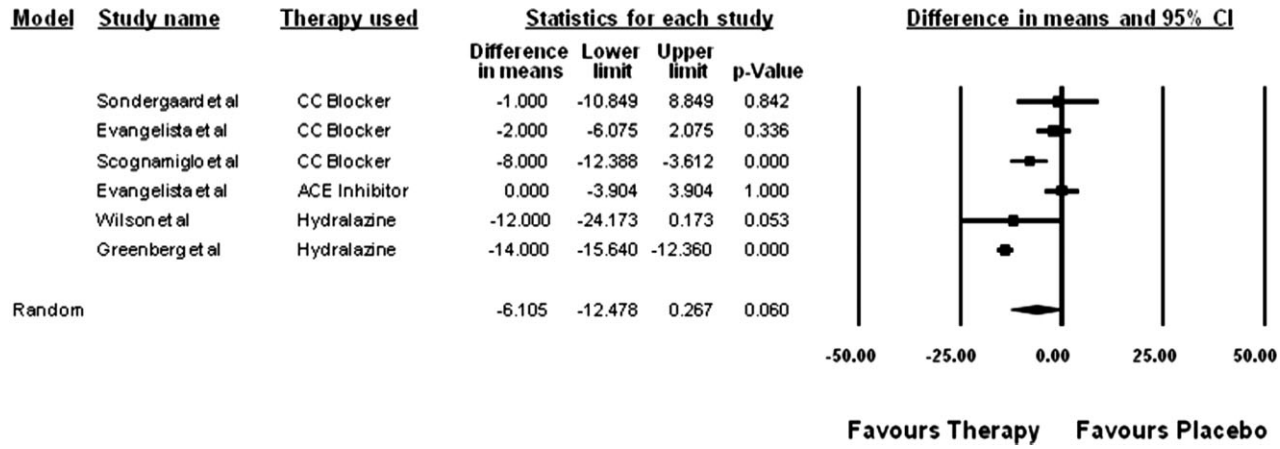

Figure 3. The Forest plot showing statistically non significant difference of LVESVI between vasodilator and placebo groups. (LVESVI, left ventricular end-systolic volume index). Abbreviations: ACE, angiotensin-converting enzyme; CC, calcium channel; CI, confidence interval.

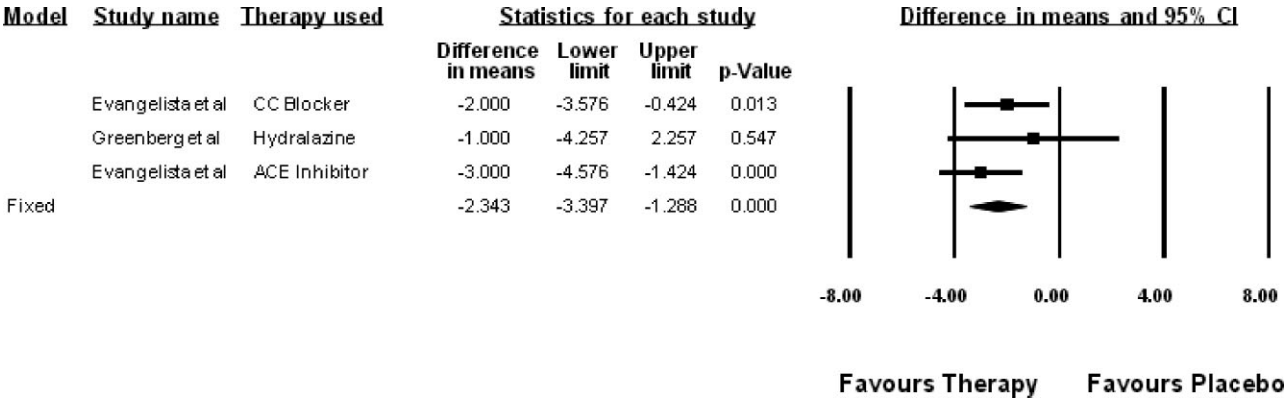

Figure 4. The Forest plot showing statistically significant difference of LVEDD between vasodilator and placebo groups with a p value of 0.000 in favor of vasodilator therapy.(LVEDD, left ventricular end-diastolic diameter). Abbreviations: ACE, angiotensin-converting enzyme; CC, calcium channel; CI, confidence interval.

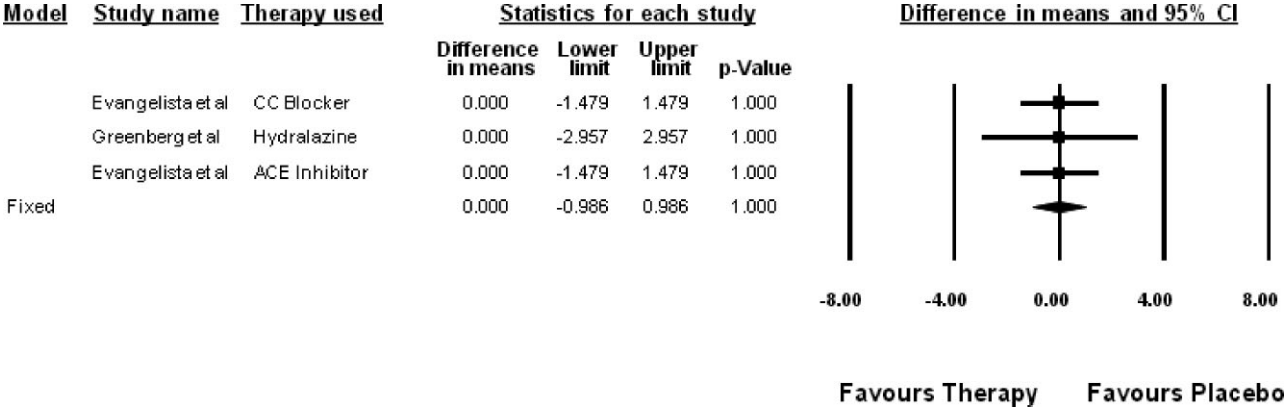

Figure 5. The Forest plot showing no significant difference of LVESD between vasodilator and placebo groups with a p value of 1.000. (LVESD, left ventricular end-systolic diameter). Abbreviations: ACE, angiotensin-converting enzyme; CC, calcium channel; CI, confidence interval.

on the echocardiographic variables that are associated with a higher risk of progression to symptoms, death, or LV dysfunction in these patients.[4,9,14–16] These variables are LVESD, LVEDD, and LVEF during exercise. In 2 multivariate analyses, only LVESD on initial study as well as the rate of increase in end-systolic dimension and decrease in resting ejection fraction during serial follow-up were found to be significantly associated with worse outcome.[4,16] Although American College of Cardiology/American Heart Association guidelines suggest linear LV dimensions as an

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DOI:10.1002/clc.22019

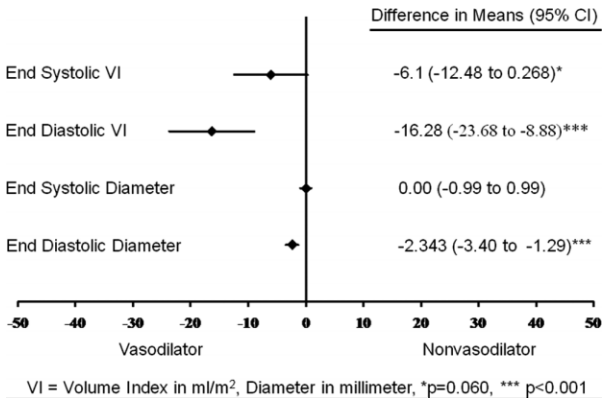

Figure 6. The forest plot summarizes the differences in LVESVI, LVEDI, LVESD, and LVEDD between the vasodilator and nonvasodilator groups. It shows statistically significant difference among diastolic parameters and nonsignificant difference among systolic parameters between the 2 groups. Abbreviations: CI, confidence interval; LVEDD, left ventricular end-diastolic diameter; LVEDVI, left ventricular end-diastolic volume index; LVESD, left ventricular end-systolic diameter; LVESVI, left ventricular end-systolic volume index; VI, volume index.

indicator for AVR in patients with asymptomatic severe AR, recent studies by Uretsky et al and Dujardin et al and have demonstrated that, in comparison with linear dimensions, LV volume parameters are better indicators for assessing LV remodeling in patients with AR.[17,18]

Because of progressive dilatation and hypertrophy, the ventricle is able to maintain normal stroke volume despite elevated afterload in the early phase of AR.[19,20] With progression of disease, there is marked increased in end-systolic dimensions and ventricular wall stress, which leads to gradual decline in LV function and development of symptoms. Severe deterioration of LV function usually occurs insidiously and improves after correction of the regurgitation.[21] Decline in LVEF is associated with excess mortality and poor outcomes even after valve-replacement surgery.[22–24] These observations provide a rationale for attempting to interrupt the cycle of increased afterload, increased wall stress, and increased end-systolic dimension early in the course of AR, which all lead to further increase in end-systolic wall stress. For the same reason, vasodilators played a central role in management of asymptomatic patients with chronic AR for many years.[25] However, there is limited clinical evidence supporting their use in patients with chronic AR and normal LV function. Two small clinical trials have examined the effects of vasodilators on clinical outcomes in asymptomatic patients with chronic AR. Evangelista et al studied the clinical outcomes in 95 asymptomatic patients with chronic severe AR, comparing enalapril (20 mg), nifedipine (20 mg), or no treatment in an open-label study. There was no significant difference in any group for the time to AVR, AR volume, or LV function after a mean follow-up period of 7 years.[11] This finding is in contrast to the study obtained by Scognamiglio et al, who randomized 143 asymptomatic patients with chronic severe AR to either nifedipine or digoxin. Patients treated with nifedipine had a significantly lower rate of progression to AVR than those treated with digoxin at the end of 6 years of follow-up. Postoperative LVEF after AVR were found to be significantly higher in patients treated with nifedipine than with digoxin.[9] Because of the scarcity as well inconsistency of these clinical outcomes, the 2006 American College of Cardiology/American Heart Association guidelines recommended a class IIb indication for the use of vasodilators in asymptomatic patients with chronic severe AR and normal LV function.[3] A recently published large retrospective cohort study by Elder et al also investigated clinical outcomes in 2266 patients with chronic AR, comparing ACE inhibitor/angiotensin II receptor blocker therapy with no treatment. This study showed a significant reduction in all-cause mortality and fewer cardiovascular and AR events in patients treated with an ACE inhibitor/angiotensin II receptor blocker compared with the placebo group.[26] Our meta-analysis also demonstrates the beneficial effects of vasodilator therapy in the light of emerging clinical evidence.

However, as with any meta-analysis, our study has some limitations. First, we included only published data, and therefore there is a potential of publication bias. However, we also included only RCTs, which should reduce this bias. Second, there was inconsistency among trials in the duration of follow-up. Third, there was a difference in use of vasodilator regimen among studies. Fourth, the methodology used for measurement of outcome variables was different in different studies, which may lead to detection bias; this could not be corrected in our meta-analysis. However, because serial measurements were taken for all these variables and the MD was taken for analyzing the effect of vasodilator therapy in individual studies, the effect of this bias seems to be small.

Conclusion

In this meta-analysis of RCTs, vasodilators have favorable effects on LV remodeling in asymptomatic patients with chronic severe AR and normal LV function. Large-scale randomized trials investigating the possibility that vasodilators prolong the compensated phase of asymptomatic patients who have volume-loaded LVs but normal systolic function are necessary to complete the totality of evidence. Additional prospective research is also required to clarify the impact of one vasodilator agent vs another.

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DOI:10.1002/clc.22019