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CME

Effects of Treatment on Exercise Tolerance, Cardiac Function, and Mortality in Heart Failure With Preserved Ejection Fraction

A Meta-Analysis

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Effects of Treatment on Exercise Tolerance, Cardiac Function, and Mortality in Heart Failure With Preserved Ejection Fraction

A Meta-Analysis

Objectives We sought to determine whether pharmacologic interventions changed exercise capacity, diastolic function, and mortality in a meta-analysis of trials in heart failure with preserved ejection fraction.

Background Treatment strategies for heart failure with preserved ejection fraction remain unproven despite several large-scale trials.

Methods Trials were included in the systematic review where clear comparisons between trial drug and diuretic or placebo were available. Exercise tolerance was assessed by treadmill time, and changes in diastolic function were quantified by transmitral flow (E/A ratio). The primary outcome was all-cause mortality. Weighted mean differences (MDs) and relative risks (RRs), along with their corresponding 95% confidence intervals (CIs), were computed using random-effects models for continuous and dichotomous variables, respectively. The impact of potential covariates was assessed by meta-regression.

Results Data from 53,878 patients enrolled in 30 published reports were collated, including 18 randomized controlled trials (n = 11,253) and 12 observational studies (n = 42,625). In the randomized controlled trials, exercise tolerance was improved by combined therapy (n = 183; weighted MD = 51.5; 95% CI: 27.3 to 75.7; $p < 0.001$), whereas E/A ratio was not (n = 472; weighted MD = −0.01, 95% CI: −0.02 to 0.02; p = 0.54) even after accounting for baseline E/A (p = 0.87). Over a mean follow-up of 18.6 months, all-cause mortality was not improved by therapy in randomized controlled trials (RR: 0.99, 95% CI: 0.92 to 1.06; p = 0.70), despite accounting for baseline ejection fraction (p = 0.72). In observational reports, there was a reduction in all-cause mortality with therapy in the unadjusted analyses (RR: 0.80, 95% CI: 0.66 to 0.97; p = 0.27), but not after adjustment for clinical and demographic data (RR: 0.93, 95% CI: 0.84 to 1.02; p = 0.10).

Conclusions Pharmacotherapy of heart failure with preserved ejection fraction demonstrates a quantifiable improvement in exercise tolerance but not mortality. (J Am Coll Cardiol 2011;57:1676–86)

Estimated costs associated with the heart failure (HF) epidemic have been steadily increasing over previous decades and now stand at $39.2 billion per year in the United States (1), with similar trends reported in other developed countries (2,3). Hospitalizations for HF have tripled over the past 3 decades (4), with important contributions from the aging population and improved treatments of underlying conditions (5). Importantly, up to one-half of all HF cases demonstrate normal left ventricular (LV) systolic function (6) and are subsequently labeled as having heart failure with preserved ejection fraction

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(HFpEF). In contrast to patients with systolic heart failure (SHF), those with HFpEF are generally older, more often female, and have a higher prevalence of hypertension, LV hypertrophy, diabetes mellitus, and atrial fibrillation (6–9), yet are at similar risk of adverse events as patients with SHF (6–8). Although there has been increasing success of pharmacological therapy to improve outcomes of SHF, prognosis for HFpEF remains unchanged (7), with no individual large-scale randomized controlled trial (RCT) demonstrating significant treatment benefits.

Despite the failure to provide effective pharmacotherapy for improving primary endpoints of mortality, there are a number of trials in HFpEF demonstrating a range of secondary benefits in response to various agents. As patients with HFpEF are often older than their SHF counterparts, these findings may provide support for therapies that improve symptoms, rather than mortality. However, to date, there are no data combining experiences from published HFpEF trials. In this meta-analysis of pharmacological trials in HFpEF, we hypothesized that since previous studies have been neutral, combining them might bring a different result for treatment effects not only on mortality but also on exercise tolerance and diastolic function. The detection of a response beyond those witnessed in individual studies might inform clinical practice and future studies.

Methods

Search strategy. A search of PubMed, the Cochrane Controlled Trials Registry, and the U.S. Clinical Trials databases was performed using these key terms: *heart failure, diastolic heart failure, heart failure normal ejection fraction, heart failure preserved ejection fraction*. From these lists, published clinical trials investigating the effects of various interventions on HFpEF were identified, for both interventional and observational studies. To ensure the identification of all relevant trials, the reference lists of these articles were then scrutinized to further identify studies pertinent to the topic. In some cases,

Abbreviations and Acronyms

ACEI = angiotensin-converting enzyme inhibitor
ARB = angiotensin-receptor blocker
CI = confidence interval
E/A = ratio of early to late transmitral flow
EF = ejection fraction
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
HR = hazard ratio
LV = left ventricular
MD = mean difference
RCT = randomized controlled trial
RR = relative risk
SHF = systolic heart failure

subgroup analyses in HFpEF were performed within trials primarily investigating SHF. These trials were also identified through the various search strategies. The search strategy, study selection and analysis adhered to QUOROM guidelines for meta-analyses (10).

Study selection. Studies included in this analysis were required to describe the method of HF diagnosis, report LV ejection fraction (EF), clearly define intervention and control groups, and provide information on primary endpoints such as mortality, hospitalization, or other outcomes such as exercise capacity, diastolic function, and quality of life. This review incorporates both interventional RCTs and observational studies. Prospective RCTs were required to stipulate pre-specified analyses and report baseline and follow-up data for both intervention and control groups. Observational studies were included where a specific diagnosis of HFpEF was made, and where EF was quantified. Trials were not included where EF could not be accurately substantiated or where data pertinent to the analysis (i.e., outcomes) were not available.

Data collation. Clinical, echocardiographic, and outcome data were extracted from individual studies by 2 experienced abstractors (D.J.H. and S.H.A.) and entered into an electronic database. Where available, these data included group numbers, primary and secondary endpoints, information on the diagnostic criteria for HFpEF, etiology, EF, clinical characteristics, age, sex, and length of follow-up. For multiple articles published from a single dataset, the largest study with primary findings or the more HFpEF-specific subgroup analysis was assessed. Despite inclusion in a common report, studies including >1 treatment arm were considered as individual trials, where comparison could be made between control and intervention groups. Data from the individual trial arms are cited throughout this analysis.

Outcome measures. Information on outcomes was extracted from individual studies containing a formal analysis

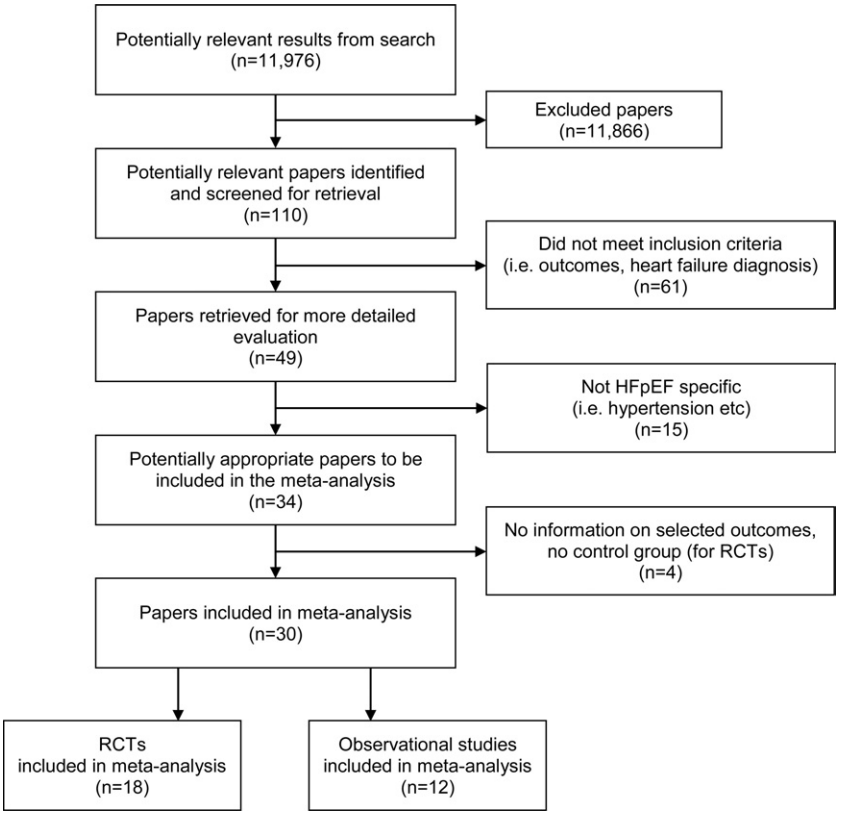

Figure 1 Flow Diagram for Inclusion of Studies in Meta-Analysis

Detailed evaluation was performed on 49 of 110 potentially relevant articles. After exclusions, 18 randomized controlled trials (RCTs) and 12 observational studies were entered into the meta-analysis. HFpEF = heart failure with preserved ejection fraction.

of prognosis. Endpoints were tallied to identify the outcomes common to most reports, with RCTs and observational studies analyzed separately. For this analysis, the primary outcome measure was all-cause mortality in individual analyses of RCTs and observational studies using hazard ratios (HRs) and 95% confidence intervals (CIs). Secondary endpoints included assessment of diastolic function quantified by the ratio of early to late diastolic transmitral flow (E/A ratio), and severity of symptoms determined by exercise tolerance (exercise capacity graded by treadmill time). Other outcome data were extracted, but in many cases, inconsistencies in reported outcomes prevented pooled analysis. Only studies reporting at least 1 of these endpoints were included in the analysis.

Statistical analysis. For the primary (dichotomous) outcome, relative risks (RRs) and 95% CI were computed using random-effects models (11). The weighted MD and corresponding 95% CI were computed using random-effects models for continuous variables. Between-studies heterogeneity was assessed using the Cochran Q test (based on the pooled RR by Mantel-Haenszel), as well as by measuring inconsistency (I^2 [the percentage of total variance across studies attributable to heterogeneity rather than chance]) of treatment effects across trials (12). We used Begg's funnel plot to assess for publication bias for the primary outcome of all-cause mortality (13). Quality assessment of the analyzed RCTs was performed by Jadad's method (14). Since the majority of included studies (13 of 14 treatment arms) had a quality score of 4/4 for mortality, suggesting high quality, a formal quality score and/or weighting of results was not calculated. For exercise capacity, only 1 study had nonblinded assessment of outcome. As a number of important baseline variables differed between studies (e.g., EF ranged from >35% to >50%), meta-regression was used to assess the influence of potential covariates (i.e., baseline variables) on the outcome measures. All therapy types were initially grouped to show an overall effect of treatment versus placebo (control). Some studies compared a treatment agent to standard therapy (for example, diuretic), and in these cases, standard care was accepted as the control group for comparison. Data were also analyzed by each drug class (e.g., angiotensin-converting enzyme inhibitors [ACEI] and angiotensin-receptor blockers [ARB], vasodilators, and β-blockers, as well as a combination of chronotropic agents, including digoxin, verapamil, and β-blockers) to show the effect of similar therapies. Forest plots were constructed to graphically describe the overall effects of intervention versus placebo. Statistical analysis was performed using standard software packages (STATA version 10.0, College Station, Texas; and SPSS version 17.0, SPSS Inc., Chicago, Illinois) with 2-tailed p values, and $p < 0.05$ considered significant.

Table 1 Study Characteristics for Randomized Controlled Trials

Trial or First Author (Ref #)	Arm	Year	Entry EF	Intervention Group(s) (n)	Control Group (n)	Total Group (n)	Intervention	Control	Follow-Up (Months)
ALLHAT* (31)	A	2008	≥50%	98	117	215	Lisinopril	Chlorthalidone	20.9
	B			110		110	Amlodipine		
	C			79	66	145	Doxazosin		18.6
CHARM-P* (18)		2003	40%	1,514	1,509	3,023	Candesartan	Placebo	36.6
DIG* (15)		2006	>45%	492	496	988	Digoxin	Placebo	37
Hong Kong DHF*† (16)	A	2008	>45%	56	50	106	Irbesartan + diuretic	Diuretic only	12
	B			45		45	Ramipril + diuretic		
I-PRESERVE* (17)		2009	≥45%	2,067	2,061	4,128	Irbesartan	Placebo	49.5
PEP-CHF* (19)		2006	WMI <1.4 (EF ≥40%)	424	426	850	Perindopril	Placebo	25.2
SENIORS* (20, 22)		2009	>35%	380	372	752	Nebivolol	Placebo	21
SENIORS Echo† (21)		2006	35%	27	34	61	Nebivolol	Placebo	12
SWEDIC† (23)		2004	WMI ≤1.2 (EF >45%)	47	50	97	Carvedilol	Placebo	6
V-HeFT I* (24)	A	1996	>35%	52	72	124	Prazosin	Placebo	27.6
	B			50		50	Hydralazine/isosorbide dinitrate		
V-HEFT II* (24)		1996	>35%	115	103	218	Enalapril	Hydralazine/ isosorbide dinitrate	30
Aronow et al.* (25)		1997	≥40%	79	79	158	Propanolol + diuretic + ACE	Diuretic + ACE only	12
Aronow et al.†‡ (26)		1993	>50%	10	11	21	Enalapril + diuretic	Diuretic only	3
Mottram et al.†‡ (27)		2004	>50%	15	15	30	Spironolactone	Placebo	6
Nodari et al.†‡ (28)		2003	≥50%	13	13	26	Nebivolol	Atenolol	6
Hung et al.†‡ (32)		2002	>50%	15	15	30§	Verapamil	Placebo	3
Setaro et al.†‡ (29)		1990	>45%	20	20	40§	Verapamil	Placebo	1.25
Kitzman et al.‡ (30)		2010	≥50%	35	36	71	Enalapril	Placebo	12

Endpoints: *mortality, †exercise capacity, ‡diastolic function. §Cross-over design where patients completed both arms of study.
ACE = angiotensin-converting enzyme; EF = ejection fraction; WMI = wall motion index.

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Results

A total of 30 published reports investigating treatment options in 53,878 patients with HFpEF met the inclusion criteria (Fig. 1). There were 11,253 patients enrolled in 18 RCTs (15–32), with a mean follow-up of 18.6 months (range 6 weeks to 59.5 months). There were an additional 42,625 patients enrolled in 12 observational studies (33–44). When trials were separated into individual treatment arms, there were a total of 45 individual treatment groups (22 RCTs, 23 observational) compared with control (placebo/usual care). Formal analysis confirmed there was no publication bias (RCTs, $p = 0.13$; observational studies, $p = 0.32$). Subject characteristics of patients enrolled in RCTs and observational studies are presented in Tables 1 and 2, respectively.

Effect of therapy on mortality. The effect of therapy on outcomes in displayed in Table 3. Combined therapy from 14 treatment options in RCTs, did not improve outcome (RR: 0.99, 95% CI: 0.92 to 1.06; $p = 0.70$) (Fig. 2), even after accounting for baseline EF with meta-regression ($p = 0.72$). When analyzed by drug class, no individual therapy improved outcome compared with placebo (Table 3).

Observational studies reported both unadjusted and adjusted HRs. In 12 treatment arms with unadjusted analysis (Fig. 3A), combined therapy improved mortality (RR: 0.80, 95% CI: 0.66 to 0.97; $p = 0.027$). On individual analysis, both ACEI/ARBs and β-blockers improved outcome in unadjusted data (Table 3). After adjusting for a range of demographic and clinical features, combined therapy in 23 studies failed to demonstrate a significant mortality benefit (RR: 0.93, 95% CI: 0.84 to 1.02; $p = 0.103$) (Fig. 3B). Individual therapies (β-blockade or ACEI/ARB) also had no effect on adjusted mortality (Table 3).

Effect of therapy on exercise capacity. Overall, exercise capacity, reported in 183 patients enrolled in 6 RCTs, was significantly improved by combined treatment (weighted MD 51.5, 95% CI: 27.3 to 75.7; $p < 0.001$) (Fig. 4). By drug class, vasodilator therapy and chronotropic agents improved exercise capacity (Table 2). There were no differences in pre-intervention exercise time for combined and individual therapies ($p > 0.2$ for all).

Table 2 Study Characteristics for Observational Studies

Trial/First Author (Ref. #)	Arm	Year	Entry EF	Intervention Group (n)	Control Group (n)	Total Group (n)	Intervention	Study Type	Follow-Up (Months)
OPTIMIZE-HF, Hernandez et al. (41)		2009	≥40%	1,621	2,532	4,153	β-blockers	Retrospective study of registry-based dataset	12
OPTIMIZE-HF, Fonarow et al. (40)	A	2007	≥40%	48%	52%	21,149	ACE inhibitors	Retrospective study of registry-based dataset	2–3
	B			60%	40%		β-blockers		
Shamagian et al. (35)	A	2006	>50%	210	206	416	ACE inhibitors	Prospective follow-up study	144
	B			23.6%	76.4%		β-blockers		
	C			66.1%	33.9%		Diuretics		
	D			31.0%	69.0%		Calcium-channel antagonists		
Dauterman et al. (34)		2001	>40%	48%	52%	430	ACE inhibitors	Retrospective study of Medicare registry dataset	12
Dobre et al. (37)		2007	≥40%	227	216	443	β-blockers	Prospective follow-up study	25
Fukuta et al. (36)	A	2005	≥50%	68	69	137	Statins	Study of registry-based dataset	24
	B			75	62		ARB/ACE inhibitors		
	C			68	69		β-blockers		
	D			37	100		Calcium-channel antagonists		
Tribouilloy et al. (39)		2008	≥50%	165	193	358	ACE inhibitors	Population-based registry follow-up study	60
Shah et al. (38)	A	2008	>50%	2,313	11,220	13,533	Statins	Retrospective study of Medicare registry dataset	36
	B			6,413	7,120		ACE inhibitors		
	C			4,562	8,971		β-blockers		
Ouzounian et al. (42)		2009	>50%	—	—	706	Statins	Trial-based registry follow-up study	60
Philbin et al. (33)		2000	≥50%	137	165	312	ACE inhibitors	Study of registry-based dataset	6
Sueta et al. (44)	A	2003	≥50%	399	361	760	ARB/ACE inhibitors	Retrospective study of Medicare registry dataset	12
	B			172	588		β-blockers		
	C			235	525		Digoxin		
Ahmed et al. (43)		2002	≥40%	62	176	238	ACE inhibitors	Retrospective study of Medicare registry dataset	48

ARB = angiotensin-receptor blocker; other abbreviations as in Table 1.

Table 3 Effect of Therapy on Mortality, Diastolic Function, and Exercise Capacity

	RR/MD	95% CI	p Value	p Value After Meta-Regression
Mortality in RCTs				
Combined therapy	0.99	0.92 to 1.06	0.699	0.722
ACEI/ARB	1.02	0.94 to 1.12	0.603	0.952
Vasodilators	1.02	0.93 to 1.11	0.694	—
Chronotropic agents	0.91	0.78 to 1.07	0.248	0.712
Mortality in observational studies (unadjusted data)				
Combined therapy	0.80	0.66 to 0.97	0.027	
ACEI/ARB	0.74	0.58 to 0.96	0.022	
β-blockers	0.86	0.77 to 0.96	0.006	
Mortality in observational studies (adjusted data*)				
Combined therapy	0.93	0.84 to 1.02	0.103	
ACEI/ARB	0.95	0.79 to 1.13	0.544	
β-blockers	0.93	0.83 to 1.04	0.196	
Diastolic function in RCTs (post-intervention E/A ratio)				
Combined therapy	−0.01	−0.03 to 0.02	0.541	0.868
ACEI/ARB	−0.01	−0.04 to 0.02	0.470	0.477
Vasodilators	−0.01	−0.04 to 0.02	0.351	0.979
Chronotropic agents	0.03	−0.03 to 0.09	0.387	0.335
Exercise capacity in RCTs (post-intervention treadmill time, s)				
Combined therapy	51.5	27.3 to 75.7	<0.001	
ACEI/ARB				
Vasodilators	48.3	20.5 to 76.2	0.001	
Chronotropic agents	61.0	12.3 to 109.7	0.014	

*Risk ratios generated from adjusted hazard ratios reported in trials after statistical consideration of demographic, clinical, or echocardiographic differences between groups.

ACEI = angiotensin-converting enzyme inhibitor; CI = confidence interval; MD = mean difference (weighted, continuous data); RCT = randomized controlled trial; RR = relative risk (dichotomous variables); other abbreviations as in Tables 1 and 2.

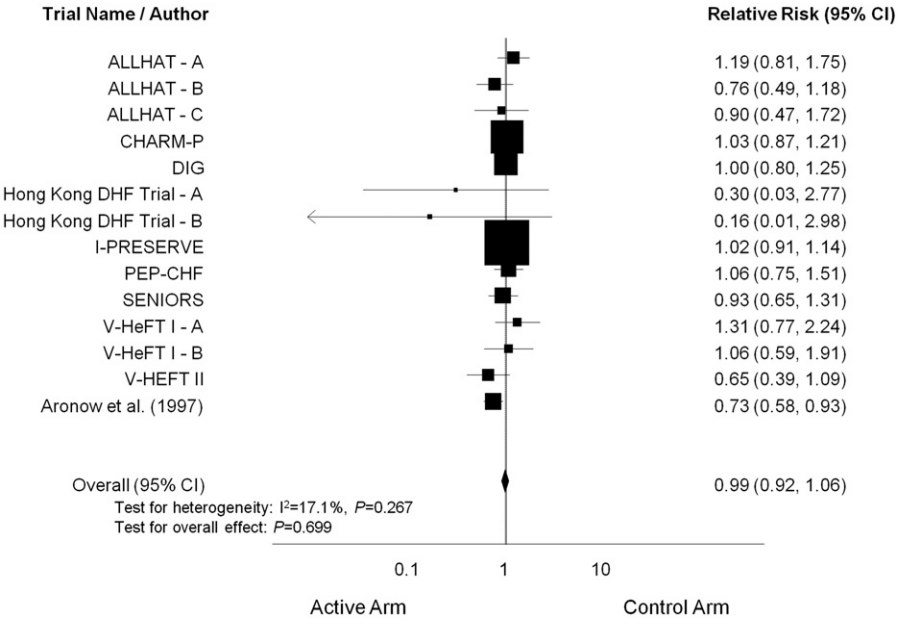

Figure 2 Forest Plot Showing Effect of Treatment on Mortality in RCTs

There is no significant effect on mortality (relative risk: 0.99; 95% confidence interval [CI]: 0.92 to 1.06) in randomized controlled trials (RCTs), and the results appear homogeneous.

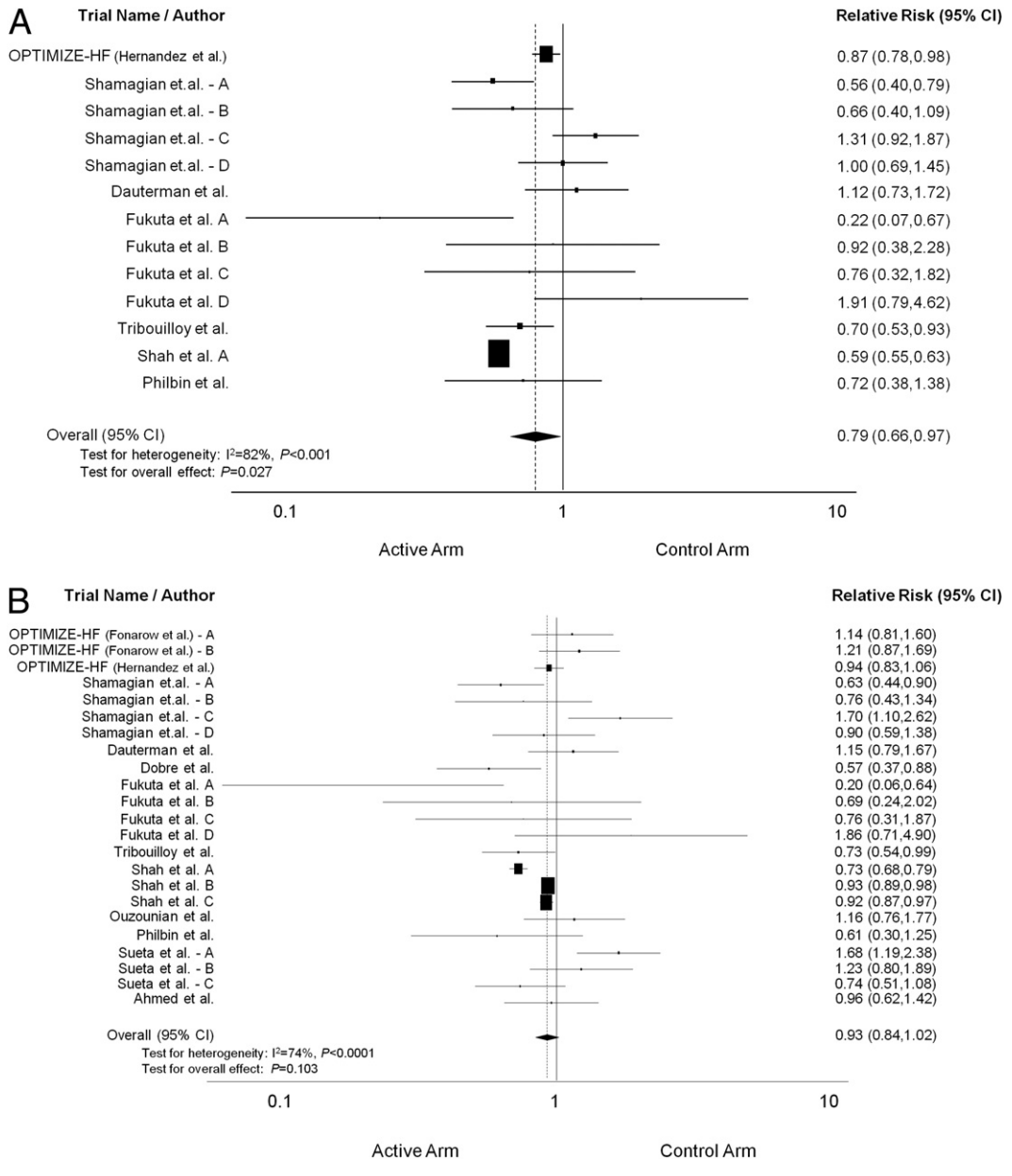

Figure 3 **Forest Plots of Unadjusted Data of Treatment Effect on Mortality in Observational Studies and Adjusted Data of Treatment Effect on Mortality in RCTs**

(A) Forest plot of unadjusted data showing effect of treatment on mortality in observational studies. There appears to be a favorable effect on mortality (relative risk: 0.79, 95% CI: 0.66 to 0.97), but with greater heterogeneity than among the RCTs. **(B)** Forest plot of adjusted data showing effect of treatment on mortality in RCTs. There is no significant effect on mortality (relative risk: 0.93; 95% CI: 0.84 to 1.02), and there is greater heterogeneity than in the RCTs. Abbreviations as in Figure 2.

Effect of therapy on diastolic function. The E/A ratio was the most common diastolic function variable, reported in 472 patients enrolled in 9 RCTs. There were no baseline differences in pre-intervention E/A ratio ($p > 0.1$ for all). Overall, there was no effect of treatment on the E/A ratio (weighted MD −0.01, 95% CI: −0.03 to 0.02; $p = 0.54$) (Fig. 5), even after accounting for baseline E/A ratio by meta-regression ($p = 0.87$). Separation of trials into respective drug classes—ACEI/ARB, β-blockers, vasodilators, or combined chronotropic agents—did not demonstrate any improvement in the E/A ratio compared with control, even after meta-regression to correct for baseline diastolic function ($p > 0.3$ for all).

Discussion

In contrast to evidence-based therapy for SHF, treatment options for patients with HFpEF remain unproven. Current recommendations support the treatment of un-

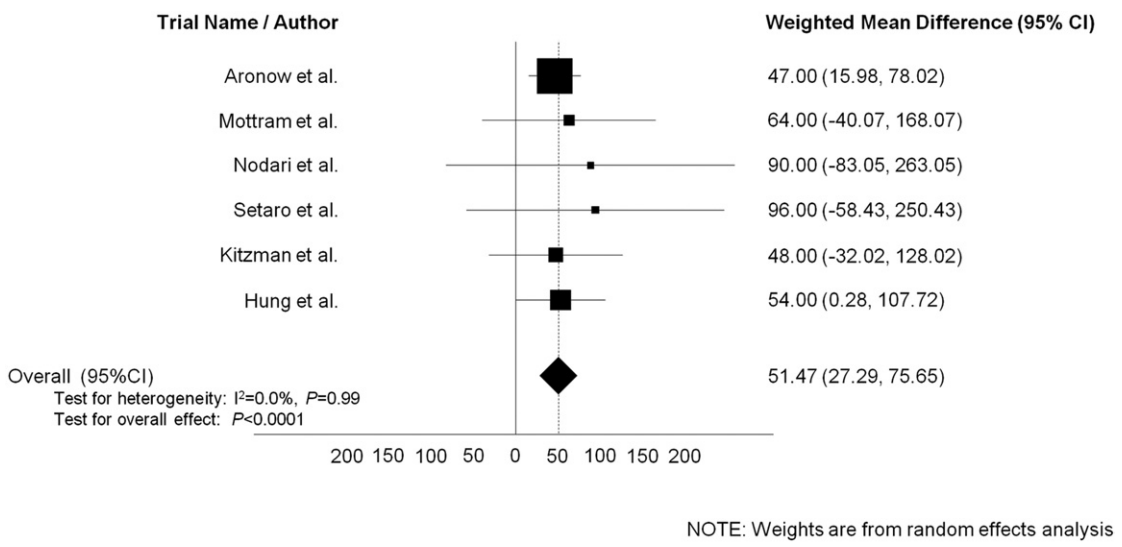

Figure 4 **Forest Plot Showing Treatment Effect on Exercise Capacity in RCTs**

There appears to be a significant effect on exercise capacity (weighted difference 51.47; 95% CI: 27.29 to 75.65) in RCTs, and the results appear homogeneous. Abbreviations as in Figure 2.

derlying etiologies (5), although the associated benefits of these therapies on hard endpoints are anticipated rather than proven in this group. This analysis adds to existing literature by providing the first report pooling data from major trials and demonstrates a number of important issues. The major finding of this study was the improvement of exercise capacity in the absence of improvements in diastolic function or benefits on the primary outcome of mortality. As patients with HFpEF are usually older than patients with SHF, improvement of symptoms, rather than mortality rates, may present an important consideration for therapeutic strategies in this patient cohort. With only 6 trials (183 patients) reporting the effect of drug therapy on exercise capacity, this endpoint requires further investigation as it is a major determinant of quality of life in patients with HF.

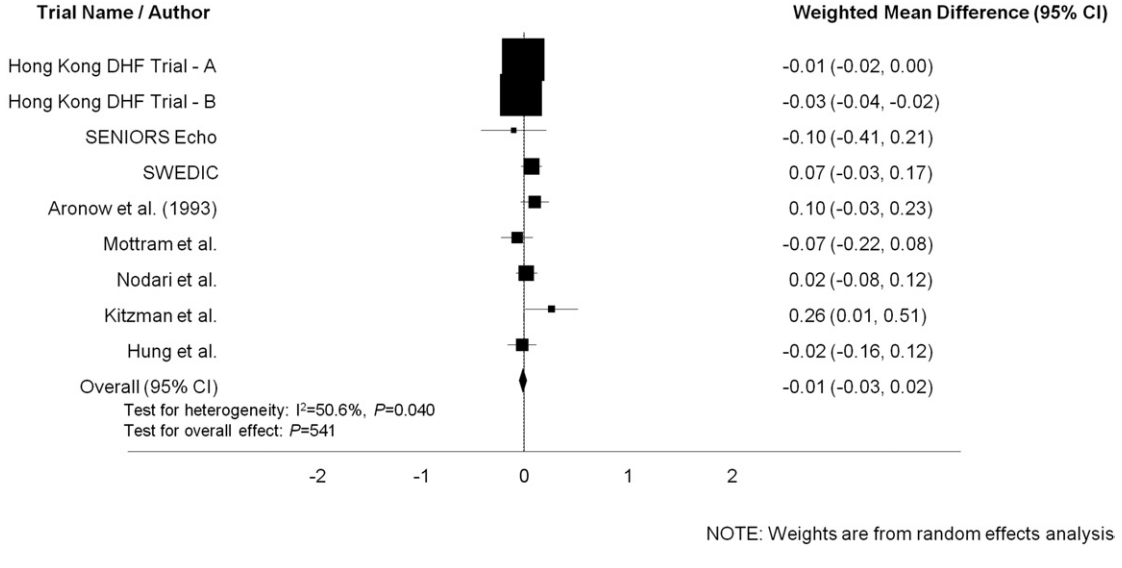

Figure 5 **Forest Plot Showing Treatment Effect on Diastolic Function in RCTs**

There is no significant effect on diastolic function (E/A ratio [weighted difference −0.01; 95% CI: −0.03 to 0.02]) in RCTs, and there is some heterogeneity of the results. Abbreviations as in Figure 2.

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Criteria for HFpEF. This analysis highlights important issues regarding patient selection and characterization of HFpEF. Our analysis was limited by the widespread disparity in patient selection criteria in many of the trials investigating HFpEF. Many of the RCTs collated in this analysis were planned and conducted before objective criteria were developed (45–48). Though not proven, it is possible that more uniform criteria may improve the ability of trials to reach pre-specified endpoints. Historically considered a diagnosis of exclusion, recent guidelines suggest employing objective clinical and imaging criteria for HFpEF that include protocols for excluding HFpEF (48). The poor correlation between published HFpEF criteria and the selection process employed in large clinical trials was highlighted in a recent analysis of HFpEF trials (49). In this review, <40% of major clinical trials required a normal EF (>50%), and only 7 of the 21 major trials required evidence of diastolic dysfunction. Many trials reporting interventions in HFpEF required an EF >35%—a threshold generally not considered "preserved." These observations support the need for adherence to strict diagnostic criteria so that a more homogenous group can be identified to avoid recruiting patients with unsubstantiated HFpEF (50).

In addition, many of the observational trials included in this meta-analysis analyzed HFpEF as a subgroup within SHF trials. That much of the evidence used for treatment of HFpEF has been drawn directly from experience with SHF may partly explain the lack of available HFpEF-specific treatment options. In general, the results of this analysis suggest that the current evidence base not only demonstrates a lack of effective treatment strategies in HFpEF, but also that the use of standard diagnostic criteria and pre-specified analyses may facilitate the investigation of treatment options for these patients.

Current therapy and future directions in HFpEF therapy. Current recommendations for the treatment of HFpEF primarily include control of underlying comorbidities such as hypertension, ventricular rate in atrial fibrillation, pulmonary congestion, and peripheral edema (5,51). Subsequent considerations are the identification (5) and treatment of coronary artery disease (6,7) and the restoration of normal sinus rhythm in atrial fibrillation.

The selection of specific pharmacotherapy would be desirable, but remains elusive. Identification of a homogenous patient group may present better opportunities for intervention. Patients with HFpEF are typically characterized by multiple comorbidities for which the effective treatment of underlying conditions remains the primary objective of therapeutic intervention. Specifically, impaired ventricular-vascular coupling, myocardial fibrosis, and uncontrolled hypertension are emerging areas with the TOPCAT (Treatment of Preserved Cardiac function heart failure with an Aldosterone anTagonist) and ALDO-DHF (ALDOsterone receptor blockade in Diastolic Heart Failure) trials currently investigating the role of spironolactone in HFpEF. There are also data from a small trial of advanced glycation end product breakers, demonstrating promising improvements in diastolic function and quality of life (52). However, further investigations are needed and are under way.

Finally, large RCTs have focused on mortality endpoints in HFpEF. In SHF, mortality endpoints do not correlate well with change in exercise tolerance or quality of life—evident in examples of improved survival with limited or no symptom change (53,54), and symptomatic improvement without survival benefit (55,56). The results of this analysis suggest that a similar dissociation between endpoints may be present in HFpEF, and that changes in exercise capacity and diastolic function are not necessarily covariates. As these patients are often older and require treatment for concomitant conditions, endpoints such as quality of life and functional capacity may be more clinically relevant. With only 6 trials in this analysis investigating the effect of treatment on exercise capacity, there is great scope for future trials to further explore this issue.

Study limitations. While every attempt was made to extract and collate data from individual studies, there are inherent gaps in the data stemming from inconsistently recorded variables and discrepancies in HFpEF diagnostic criteria. That was particularly the case in relation to diastolic function data, the modern markers of which (such as E/e′) are rarely reported. In addition, primary and secondary outcome measures varied considerably across studies, and some only assessed smaller endpoints such as quality of life. In some cases, we were limited, therefore, in our ability to combine datasets for specific outcomes and can only report results from individual studies. Compared with mortality endpoints, trials investigating exercise capacity may also be more vulnerable to publication bias, with neutral or negative results evading publication. Finally, an important issue pertains to the differences in patient demographics between RCTs and observational trials. Patients in observational studies were older, more often women, and had a greater number of comorbidities, likely a result of retrospective diagnoses based on exclusion of other conditions.

Conclusions

Meta-analysis of drug trials in HFpEF reveals significant improvement in symptomatic status measured by exercise capacity in the absence of changes in diastolic function or mortality benefits. As patients with HFpEF are often older than their SHF counterparts, improvement of symptoms, rather than reduction of mortality, may present more important and pragmatic outcomes. Furthermore, adherence of trial recruitment to endorsed HFpEF criteria and the utilization of more effective screening tools may provide a more homogenous study group for future trials.

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