Supplementary Material

Supplemental material table 1: Search Strategy

Medline	EMBASE	Cochrane CENTRAL
1. Heart failure	1. Heart failure	In "Trials"
2. Normal ejection fraction	2. Normal ejection fraction	1. heart failure
3. Preserved cardiac function	3. Preserved cardiac function	2. preserved ejection fraction
4. Preserved ejection fraction	4. Preserved ejection fraction	3. preserved cardiac function
5. 1 and 2	5. 1 and 2	4. normal ejection fraction
6. 1 and 3	6. 1 and 3	5. 1 and 2
7. 1 and 4	7. 1 and 4	6. 1 and 3
8. Diastolic heart failure	8. Diastolic heart failure	7. 1 and 4
9. Diastolic dysfunction	9. Diastolic dysfunction	8. "diastolic heart failure"
10. HFPEF	10. HFPEF	9. "diastolic dysfunction"
11. HFNEF	11. HFNEF	10. "HFNEF"
12. Or/5-11	12. Or/5-11	11. "HFPEF"
13. Randomized Controlled Trials as Topic/	13. Clinical trial/	12. 5 or 6 or 7 or 8 or 9 or 10 or 11
14. Randomized controlled trial/	14. Randomized controlled trial/	
15. Random Allocation/	15. Randomization/	
16. Double Blind Method/	16. Single blind procedure/	
17. Single Blind Method/	17. Double blind procedure/	
18. Clinical trial/	18. Crossover procedure/	
19. Clinical trial, phase i.pt	19. Placebo/	
20. Clinical trial, phase ii.pt	20. Randomi?ed controlled trial$.tw.	
21. Clinical trial, phase iii.pt	21. Rct.tw.	
22. Clinical trial, phase iv.pt	22. Random allocation.tw.	
23. Controlled clinical trial.pt	23. Randomly allocated.tw.	
24. Randomized controlled trial.pt	24. Allocated randomly.tw.	
25. Multicenter study.pt	25. (allocated adj2 random).tw.	
26. Clinical trial.pt	26. Single blind$.tw.	
27. Exp Clinical Trials as topic/	27. Double blind$.tw.	
28. Or/13-27	28. ((treble or triple) adj (blind$).tw.	
29. (clinical adj trial$).tw	29. Placebo$.tw.	
30. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw	30. Prospective study/	
	31. Or/13-30	
	32. Case study/	
	33. Case report.tw.	

31. Placebos/
32. Placebo$.tw
33. Randomly allocated.tw
34. (allocated adj2 random$).tw
35. Or/29-34
36. 28 or 35
37. Case report.tw
38. Letter/
39. Historical article/
40. Or/37-39
41. 36 not 40
42. 12 and 41

34. Abstract report/ or letter/
35. Or/32-34
36. 31 not 35
37. 12 and 36

Supplemental material table 2: Summary of included studies

Author, Year	HFPEF definition	LVEF (%)	Sample size	Treatment and follow-up	Key outcomes
Aronow 1997 [1]	NYHA II-IV	40	Propranolol (n=79)	32 months	Significant decrease in total mortality plus non-fatal MI with propranolol (59% vs 82%, RRR 37%, p-=0.002)
	Clinical HF		No propranolol (n=79)		Significant increase in LVEF (p<0.0001) with propranolol vs. no propranolol
	Prior Q wave infarct				
Warner 1999 [2]	Diastolic dysfunction	50	Losartan (n=20)	2 weeks	Significant increase in exercise time with losartan (12.3 11.0, P<0.05)
	Peak SBP>200mmHg during exercise		Placebo (n=20)		Significant difference in QOL with losartan (MLHF score 18 vs. 22, p<0.05)
Nodari 2003 [3]	NYHA II-III	50	Atenolol (n=13)	6 months	NS change on clinical status, exercise capacity or echo parameters
	Diastolic dysfunction on echo		Nebivolol (n=13)		Significant change to some haemodynamic parameters with either
Yusuf 2003 [4]	NYHA II-IV	40	Candesartan (n=1514)	36.6 months	NS difference primary outcome (CV mortality, hospitalization) (HR 0.89, P=0.118)
			Placebo (n=1509)		Significant reduction HF hospitalization with candesartan (p=0·017), NS difference CV death
Mottram 2004[5]	Hypertension	50	Spironolactone (n=15)	6 months	NS change in exercise capacity
	NYHA II		Placebo (n=15)		
	Diastolic dysfunction				
Zi 2003 [6]	NYHA II-III	40	Quinapril (n=36)	6 months	NS difference in mean 6MWD (p=0.63), QOL scores (p=0.84) or NYHA class (p>0.05)
			Placebo (n=38)		NS decrease in likelihood of worsening HF (p=0.12) or hospitalisation (p=0.43)
Bergstrom 2004 [7]	Clinical HF	45	Carvedilol (n=47)	6 months	Significant improvement in E/A (p<0.05)
	Diastolic dysfunction		Placebo (n=50)		
Little 2004 [8]	NYHA II-IV	50	Candesartan (n=21)	2 weeks	Significant increase exercise time and QOL (p<0.05) with candesartan vs baseline
	Diastolic dysfunction		Verapamil (n=21)		NS improvement in exercise or QOL with verapamil
Takeda 2004 [9]	NYHA II-III	45	Carvedilol (n=19)	12 months	Significant improvement of all endpoints with carvedilol: BNP (175 to 106pg/ml, p<0.01), NYHA 2.37 to 1.56 (p<0.01), Specific Activity Scale (4.75 to
			No carvedilol (n=21)		5.68METs, p<0.02)
Kasama 2005 [10]	Non-ischemic HF	40	Candesartan (n=25)	6 months	Significant improvement NYHA with candesartan (p<0.05 vs placebo)
			Placebo (n=25)		Significant decrease in LVEDV and increase in LVEF (p<0.05)
Ahmed 2006 [11]	Clinical HF	45	Digoxin (n=492)	37 months	NS reduction primary outcome (HF hospitalization, HF mortality) (HR 0.82, p=0.136).
			Placebo (n=496)		NS reduction in HF hospitalisation (HR 0.79, p=0.094)
Cleland 2006 [12]	Clinical HF	40	Perindopril (n=424)	2.1 years	NS reduction in primary outcome (all-cause mortality, HF hospitalisation) after follow-up (HR 0.92, p=0.55)
	Diastolic dysfunction		Placebo (n=426)		NS reduction in primary outcome at 12 months (HR 0.69, p=0.055), but significant reduction hospitalization (HR 0.63, p=0.033), greater 6MWD
					(p=0.011), NS change BNP
Little 2006 [13]	Diastolic dysfunction	50	Losartan (n=19)	6 months	Significant improvement exercise time and QOL (p<0.05) with losartan
			Hydrochlorothiazide (n=21)		NS change exercise time (p=0.32) or QOL (p=0.43) with hydrochorothiazide

Massie 2008 [14]	NYHA II-IV	45	Irbesartan (n=2067)	49.5 months	NS effect on primary outcome (CV hospitalization, all-cause mortality) (HR 0.95, p=0.35). NS difference in other pre-specified outcomes (HF mortality
	Clinical HF		Placebo (n=2061)		or hospitalization, all-cause and CV mortality, and QOL)
Yip 2008 [15]	NYHA II-IV	45	Diuretic only (n=50)	12 months	Diuretics significantly improved symptoms and neither irbesartan nor ramipril had a significant additional effect.
	Clinical HF		Diuretic+Irbesartan (n=56)		Diuretics in combination with irbesartan or ramipril marginally improved LV systolic and diastolic longitudinal LV function, and lowered NT-proBNP.
			Diuretic+Ramipril (n=45)		
Mak 2009 [16]	Clinical features HF	45	Eplrenone 25-50mg (24)	12 months	Eplerenone prevents a progressive increase in pro-collagen type-III aminoterminal peptide
	Diastolic dysfunction		No eplenerone (n=20)		NS between group effect on diastolic function, QOL or BNP
Parthasarathy 2009 [17]	Clinical HF	40	Valsartan (n= 70)	14 weeks	Valsartan had no significant effect on exercise time, gas exchange, 6MWD , exertion-related symptoms, BNP levels, echo parameters, or QOL
	Diastolic dysfunction		Placebo (n= 82)		Valsartan significantly lowered peak exercise systolic BP vs. placebo ($P < 0.001$) and improved ratings of perceived exertion (Borg score) ($P = 0.008$).
Kitzman 2010 [18]	Clinical HF	50	Placebo (n=36)	12 months	Enalapril did not improve exercise capacity
			Enalapril (n=35)		NS improvement in QOL with enalapril (p=0.07)
Orozco-Gutierrez 2010 [19]	NYHA I-III	45	L-arginine (n=15)	2 months	Significant improvement in pulmonary artery pressure ($p<0.05$ in both) and treadmill duration ($p<0.05$ in both)
	Diastolic dysfunction		Citrulline (n=15)		
Deswal 2011 [20]	NYHA II-III	50	Eplenerone 50mg (n=21)	6 months	Significant improvement in 6MWD vs. baseline in both groups, but NS difference between groups (p=0.91)
	Diastolic dysfunction		Placebo (n=23)		NS between group difference in QOL, NYHA class or SBP
					Significant reduction in markers of collagen turnover and improvement in diastolic function
Conraads 2012 [21]	NYHA II–III	45	Nebivolol (n = 57)	6 months	Nebivolol did not improve exercise capacity in patients with HFPEF (actually decreased compared to placebo.)
	Diastolic dysfunction		Placebo (n = 59)		NS difference in QOL improvement vs placebo
Solomon 2012 [22]	NYHA II-III	45	LCZ696 (n=149)	12 weeks	Greater reduction NT-proBNP with LCZ696 at 12 weeks (P=0.005), NS at 36 weeks (p=0.20)
	Raised serum biomarkers		Valsartan (n=152)		NS difference in NYHA class at 12 weeks (p=0.11), but improvement in LCZ696 group at 36 weeks (p=0.05).
					NS difference in clinical composite assessment or QOL.
Cocco 2013 [23]	NYHA III	50	Ivabradine (n=21)	3 months	Significant improvement in NYHA, BNP and 6MWD for both treatments ($p<0.0001$)
	Diastolic dysfunction		Digoxin (n=21)		
Edelman 2013 [24]	NYHA II-III	50	Spironolactone (n=213)	12 months	Improved diastolic dysfunction
	Diastolic dysfunction		Placebo (n=209)		NS improvement symptoms, QOL, 6MWD or peak VO_2
					No effect hospitilisation or mortality
Kosmala 2013 [25]	ESC definition of HFPEF	50	Ivabradine (n=30)	7 days	Significant improvement in exercise capacity (+1.5mets, p=0.001) and peak VO_2 (+3ml/kg/min, p=0.004) with ivabradine, with significant difference in
	Clinical HF		Placebo (n=31)		change compared with placebo (+3 vs +0.4ml/kg/min, p=0.003)
	Diastolic dysfunction				
Maier[26]	Raised serum biomarkers	45	Ranolazine (n=12)	2 weeks	NS changes in echo parameters, cardiopulmonary exercise test parameters or NT-proBNP levels
	Diastolic dysfunction		Placebo (n=8)		
Redfield 2013 [27]	NYHA II-IV	50	Sildenafil (n=213)	24 weeks	NS difference in median changes in peak VO_2 (-0.2 vs -0.2ml/kg/min, p=0.9), mean clinical status rank score after treatment (94.2 vs 95.8, p=0.85) and
	Clinical heart failure		Placebo (n=213)		6MWD after treatment with sildenafil (5.0 vs. 15.0m, p=0.92)

Yamamoto 2013 [28]	Modified Framingham criteria	40	Carvedilol (n=120)	3.2 years	NS difference in primary outcomes (composite CV death, HF hospitalization) - carvedilol (29), control (34) (HR 0.902, 95% CI 0.50-1.17, p=0.69)
			No carvedilol (n=125)		Carvedilol dose >7.5mg showed significantly less primary outcome than control (HR 0.54, 95% CI 0.30-0.96, P=0.04)
Kurrelmeyer 2014 [29]	NYHA II-III	50	Spironolactone (n=24)	6 months	Stable clinical status - significant worsening of clinical composite score with placebo only (p=0.02)
	Diastolic dysfunction		Placebo (n=24)		Improvement in diastolic function – Increased lateral e' (p=0.003) and decreased E/e' (p=0.0001)
	Raised serum biomarkers				NS change in BNP or 6MWD
Pitt 2014 [30]	Clinical HF or HF hospitalisation	45	Spironolactone (n=1722)	3.3 years	NS difference in primary outcome (composite CV death, aborted cardiac arrest, HF hospitalization) with spironolactone (18.6% vs 20.4%, HR 0.89 95%
	Raised serum biomarkers		Placebo (n=1723)		CI 0.77-1.04, P=0.14)
					Significantly lower incidence hospitilisation in spironolactone group (12.0% vs 14.2%, HR 0.83, CI 0.69-0.99), no effect on mortality
Van Tassel 2014 [31]	NYHA II-III	50	Anakinra (n=12)	2 weeks	Significant increase in peak VO2 (+1.2ml/kg/min p=0.009)
	Diastolic dysfunction		Placebo (n=12)		NS difference in BNP or Duke Activity Status Index
Zile 2014 [32]	NYHA II-III	50	Sitaxsentan (n=128)	24 weeks	Significant increase in median treadmill time (90s vs 37s, p=0.03) with sitaxsentan
	Diastolic dysfunction		Placebo (n=64)		NS difference in QOL, NYHA class, death or hospitalisation
Redfield 2015 [33]	Clinical HF	50	ISMN (n=110)	12 weeks	NS trend towards lower daily activity with ISMN vs placebo, significant decrease in hours active/day (-0.3h, p=0.02)
	Diastolic dysfunction		Placebo (n=110)		NS difference between groups for 6MWD, QOL scores, NT-proBNP levels
	Raised serum biomarkers				

Footnote: HFPEF - heart failure with preserved ejection fraction, LVEF - left ventricular ejection fraction, NYHA - New York Heart Association functional classfication, HF - heart failure, MI - myocardial infarction, SBP - systolic blood pressure, QOL - quality of life, MLHF - Minnesota Living with Heart Failure questionnaire, NS - no significant, CV - cardiovascular, 6MWD - 6-minute walking distance, BNP - Brain natriuretic peptide, NT-proBNP - N-terminus proBNP, LVEDV - left ventricular end diastolic volume, HR - hazard ratio, CI - confidence interval, ESC - European Society of Cardiology, ISMN - isosorbide mononitrate

Supplemental Material References

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