

SUPPLEMENTAL MATERIAL

Expanded Methods & Results

Search Strategy

Databases: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R))

Date of search: April 28, 2015

1. exp Heart Failure/
2. Cardiomyopathy, Dilated/
3. (heart failure or cardiac failure or cardiac insufficiency or cardiomyopath\$.tw.
4. ((cardi\$ or myocard\$) adj2 (failure\$ or insufficien\$)).tw.
5. OR/1-4
6. (LCZ696 or LCZ 696 or LCZ-696).af
7. exp dipeptidyl carboxypeptidase inhibitor/ OR exp Angiotensin-Converting Enzyme Inhibitors/
8. (angiotensin converting enzyme inhibitor OR ACEI OR ACEI OR antagonist\$ OR inhibitor\$ benazepril OR captopril OR enalapril OR fosinopril OR imidapril OR lisinopril OR moexipril OR perindopril OR quinapril OR ramipril ORtrandolapril OR zofenopril OR alacepril OR cilazapril OR spirapril OR delapril).mp.
9. exp beta adrenergic receptor blocking agent/ OR exp Adrenergic beta-Antagonists/
10. (beta blocker\$ OR BB OR acebutolol OR atenolol OR betaxolol OR bisoprolol OR carvedilol OR labetalol OR metoprolol OR nadolol OR nebivolol OR penbutolol OR pindolol OR propranolol OR sotalol OR timolol).mp.
11. exp aldosterone antagonist/

12. (aldosterone antagonist\$ OR mineralocorticoid-receptor antagonist OR MRA OR eplerenone OR spironolactone).mp.
13. exp angiotensin receptor antagonist/
14. (angiotensin receptor blocker\$ OR angiotensin receptor antagonist\$ OR ARB OR azilsartan OR candesartan OR eprosartan OR irbesartan OR losartan OR olmesartan OR telmisartan OR valsartan).mp.
15. OR/6-14
16. "randomized controlled trial".pt.
17. (random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab.
18. (retraction of publication or retracted publication).pt.
19. OR/18-20
20. (animals not humans).sh.
21. ((comment or editorial or meta-analysis or practice-guideline or review or letter or journal correspondence) not "randomized controlled trial").pt.
22. (random sampl\$ or random digit\$ or random effect\$ or random survey or random regression).ti,ab. not "randomized controlled trial".pt.
23. 20 OR 21 OR 22
24. 19 NOT 23
25. (random\$ or placebo\$ or single blind\$ or double blind\$ or triple blind\$).ti,ab.
26. RETRACTED ARTICLE/
27. OR/25-26
28. (animal\$ not human\$).sh,hw.

29. (book or conference paper or editorial or letter or review).pt. not exp randomized controlled trial/
30. (random sampl\$ or random digit\$ or random effect\$ or random survey or random regression).ti,ab. not exp randomized controlled trial/
31. OR/28-30
32. 27 NOT 31
33. 24 OR 32
34. 5 AND 19 AND 33
35. limit 34 to "all adult (19 plus years)" [Limit not valid in Embase; records were retained]
36. limit 35 to (adult <18 to 64 years> or aged <65+ years>) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) In-Process; records were retained]
37. limit 36 to human
38. limit 37 to yr="1987 –July 2014"

Database: Cochrane Library of Clinical Trials

Date of search: April 28, 2015

- #1 MeSH descriptor: [Heart Failure] explode all trees
- #2 MeSH descriptor: [Cardiomyopathy, Dilated] explode all trees
- #3 (heart failure or cardiac failure or cardiac insufficiency or cardiomyopath\$):ti,ab,kw
(Word variations have been searched)
- #4 #1 or #2 or #3
- #5 (LCZ696 or LCZ 696 or LCZ-696) :ti,ab,kw
- #6 MeSH descriptor: [Angiotensin-Converting Enzyme Inhibitors] explode all trees

- #7 (angiotensin converting enzyme inhibitor or ACEI or ACEI or antagonist\$ or inhibitor\$
benazepril or captopril or enalapril or fosinopril or imidapril or lisinopril or moexipril or
perindopril or quinapril or ramipril ortrandolapril or zofenopril or alacepril or cilazapril
or spirapril or delapril):ti,ab,kw (Word variations have been searched)
- #8 MeSH descriptor: [Adrenergic beta-Antagonists] explode all trees
- #9 (beta blocker\$ or BB or acebutolol or atenolol or betaxolol or bisoprolol or carvedilol or
labetalol or metoprolol or nadolol or nebivolol or penbutolol or pindolol or propranolol or
sotalol or timolol):ti,ab,kw (Word variations have been searched)
- #10 MeSH descriptor: [Mineralocorticoid Receptor Antagonists] explode all trees
- #11 (aldosterone antagonist\$ or mineralocorticoid-receptor antagonist or MRA or eplerenone
or spironolactone):ti,ab,kw (Word variations have been searched)
- #12 MeSH descriptor: [Angiotensin Receptor Antagonists] explode all trees
- #13 (angiotensin receptor blocker\$ or angiotensin receptor antagonist\$ or ARB or azilsartan
or candesartan or eprosartan or irbesartan or losartan or olmesartan or telmisartan or
valsartan):ti,ab,kw (Word variations have been searched)
- #14 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
- #15 #4 and #14
- #16 human not animal
- #17 #15 and #16
- #18 #17 in trials
- #17 #18 (limit from 1987)

Supplementary Table 1: Drug classes of interest

Class	Generic name	Trade Name
ARNI	LCZ696 valsartan/ sacubitril	Entresto
ACEI	benazepril	Lotensin
	captopril	Capoten, Lopril
	enalapril	Vasotec, Renitec
	fosinopril	Monopril
	imidapril	Tanatril
	lisinopril	Prinivil, Zestril, Tensopril, Hipril, Lisodur, Novatec
	moexipril	Univasc, Perdix
	perindopril	Aceon, Coversyl
	quinapril	Accupril
	ramipril	Altace, Tritace, Ramace, Ramiwin, Prilace, Ramipro
	trandolapril	Mavik
	zofenopril	Bifril, Teoula, Zofepiril, Zopranol
	alacepril	Alacepul, Alaceril, Aprocorl, Asemipearl, Cenapride, Cetabavil, Cetapril, Cevozyl, Homerat, Iceden, Kananomin, Seplinok
	cilazapril	Cazaprol, Cilan, Cilazabace, Cilazil, Dynorm, Dynorm Plus, Inhibace Plus, Inhibace, Initiss, Inocar, Justor, Prilazid, Vaspace, Zobox, Cilazapril-Teva, CO Cilazapril, Gen-Cilazapril, Inhirook, Inibace Plus, Initiss Plus, Inocar Plus
	spirapril	Quadropril, Renormax, Renpress, Setrilan
	delapril	Beniod, Delaket, Delapride, Dinapres, Trinordiol, Adecut, Araplit, Cupressin, Defolder, Virace
BB	acebutolol	Sectral, Prent
	atenolol	Tenormin, Senormin
	betaxolol	Kerlone, Betoptic, Lokren
	bisoprolol	Zebeta
	carvedilol	Coreg, Carvil, Dilatrend, Eucardic, Carloc

Class	Generic name	Trade Name
	labetalol	Trandate, Normodyne
	metoprolol	Lopressor, Toprol, Selokeen, Minax, Metrol, Betaloc, Bloxan, Neobloc, Presolol, Corvitol, Metxl, Metolar, Starpress
	nadolol	Corgard, Anabet, Solgol, Corzide, Alti-Nadolol, Apo-Nadol, Novo-Nadolol
	nebivolol	Bystolic, Nebilet, Nebilong, Nebicard, Nubeta, Nodon, Lobivon
	penbutolol	Levatom, Levatomol, Lobeta, Paginol, Hostabloc, Betapressin
	pindolol	Visken, Betapindol, Blockin L, Calvisken, Cardilate, Decreten, Durapindol, Glauco-Visken, Pectobloc, Pinbetol, Prindolol, Pynastin
	propranolol	Inderal, InnoPran, Avlocardyl, Deralin, Dociton, Inderalici, Sumial, Anaprilinum, Bedranol
	sotalol	Betapace, Sotalex, Sotacor
	timolol	Blocadren, Timoptic
MRA	eplerenone	Inspira
	spironolactone	Aldactone, Novo-Spiroton, Aldactazide, Spiractin, Spirotone, Verospiron, Berlactone
ARB	azilsartan	Edarbi
	candesartan	Atacand, Blopress, Amias, Ratacand
	eprosartan	Teveten, Eprozar
	irbesartan	Avapro, Karvea, Aprovel
	losartan	Cozaar
	olmesartan	Benicar, Olmetec
	telmisartan	Micardis, Targit, Temax, Telmore
	valsartan	Diovan, Angiotan, Valtan, Valzaar, Tareg

Abbreviations: ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-II receptor antagonist; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta blocker; MRA = mineralocorticoid receptor antagonist; NR = not reported; PLBO = placebo

Supplementary Table 2: Study design and baseline patient characteristics of included RCTs

Trial/ Author year	Study design	# centers/ location	Study duration	N	Interventions	LVEF inclusion criteria	mean LVEF (%)	% male	mean age	NYHA class 1 (%)	NYHA class 2 (%)	NYHA class 3 (%)	NYHA class 4 (%)	duration of HF (months)	Ischaemic HF (%)	Prior MI (%)
CASSIS 1995 ¹	DB, MC, PC	18/ Czech and Slovak Rep	104 weeks	152 48 48	Spirapril Enalapril Placebo	≤40%	28%	83%	58	0%	25%	56%	19%	NR	70%	46%
CONSENSUS 1987 ²	DB, MC, PC	35/ Finland, Norway, Sweden	52 weeks	126 127	Enalapril Placebo	Reduced	NR	71%	70	0%	0%	0%	100%	NR	NR	48%
FEST 1995 ³	DB, MC, PC	42/ EU (8 countries)	12 weeks	155 153	Fosinopril Placebo	≤35%	26%	75%	63	0%	65%	36%	0%	NR	71%	NR
MHFT 1991 ⁴	DB, SC, PC	1/ Germany	2.7 years (median)	83 87	Captopril Placebo	≤35%	35%	78%	62	26%	50%	24%	0%	NR	58%	69%
SOLVD-prevent 1992 ⁵	DB, MC, PC	23/ US, Canada, Belgium	37.4 months (mean)	2111 2117	Enalapril Placebo	≤35%	28%	89%	59	0%	67%	33%	0%	NR	83%	80%
SOLVD-treat 1991 ⁶	DB, MC, PC	23/ US, Canada, Belgium	48 months	1285 1284	Enalapril Placebo	≤35%	25%	80%	61	11%	57%	30%	2%	NR	71%	66%
Beller 1995 ⁷	DB, MC, PC	12/ US	12 weeks	130 63	Lisinopril Placebo	<45%	28%	75%	60	0%	35%	56%	9%	36	NR	0%
Brown 1995 ⁸	DB, MC, PC	41/ US	24 weeks	116 125	Fosinopril Placebo	≤35%	25%	80%	62	0%	37%	54%	9%	NR	NR	NR
Chalmers 1987 ⁹	DB, MC, PC	13/ 10 countries	12 weeks	87 43	Lisinopril Placebo	<45%	NR	69%	58	0%	22%	65%	13%	45	NR	NR
Colfer 1992 ¹⁰	DB, MC, PC	22/ US	12 weeks	114 58	Benazepril Placebo	≤ 35%	25%	83%	62	0%	54%	45%	1%	48	56%	NR
Goldstein 1988 ¹¹	DB, SC, PC	NR/ NA	26 weeks	104 100	Captopril Placebo	≤ 40%	25%	82%	56	4%	85%	11%	1%	35	63%	NR

Lewis 1989 ¹²	DB, MC, PC	13/ AUS, EU, SA, NA, Africa (10 countries)	12 weeks	87 43	Lisinopril Placebo	NR	38%	NR	NR	0%	22%	64%	14%	48	NR	NR
Shettigar 1999 ¹³	DB, MC, PC	28/ US	12 weeks	102 104	Fosinopril Placebo	≤35%	24%	75%	62	0%	39%	52%	31%	NR	43%	34%
Veldhuisen 1999 ¹⁴	DB, MC, PC	25/ NtherInds, Germany, Belgium	12 weeks	182 62	Imidapril Placebo	<45%	34%	77%	61	0%	77%	23%	0%	35	63%	NR
SPICE 2000 ¹⁵	DB, MC, PC	270/ NA, EU	12 weeks	179 91	Candesartan Placebo	≤35%	27%	69%	66	0%	54%	41%	6%	NR	71%	62%
STRETCH 1999 ¹⁶	DB, MC, PC	86/ Germany, Czech Rep, Slovenia	12 weeks	633 211	Candesartan Placebo	30-45%	39%	69%	62	0%	81%	19%	0%	39	NR	NR
Mitrovic 2003 ¹⁷	DB, MC, PC	EU	12 weeks	174 44	Candesartan Placebo	≤40%	28%	85%	54	0%	61%	39%	0%	40	NR	NR
ELITE I 1997 ¹⁸	DB, MC	125/ US, SA, EU	48 weeks	352 370	Losartan Captopril	≤40%	30%	67%	73	0%	65%	34%	2%	NR	68%	50%
ELITE II 2000 ¹⁹	DB, MC	289/ NA, SA, EU	700 days	1578 1574	Losartan Captopril	≤40%	31%	70%	71	0%	52%	43%	5%	NR	79%	58%
REPLACE 2001 ²⁰	DB, MC	NR/ EU, Israel	12 weeks	301 77	Telmisartan Enalapril	<40%	26%	89%	64	0%	64%	36%	0%	NR	NR	69%
Dickstein 1995 ²¹	DB, MC	19/ Denmark, Finland, Norway, Sweden	8 weeks	108 58	Losartan Enalapril	≤35%	23%	78%	64	0%	0%	84%	16%	46	69%	63%
Lang 1997 ²²	DB, MC	16 / NA	12 weeks	78 38	Losartan Enalapril	≤45%	25%	78%	58	0%	47%	51%	2%	53	47%	NR
CIBIS III 2008 ²³	OL, MC	128/ EU and AUS and Tunisia	30 months	505 505	Bisoprolol Enalapril	≤35%	29%	68%	72	0%	49%	51%	0%	19	NR	49%

CARMEN 2004 ²⁴	DB, MC, PC	65/ EU	18 months	191 190 191	Carvedilol + Placebo Enalapril + Placebo Carvedilol + Enalapril	<40%	30%	81%	62	8%	65%	27%	0%	NR	67%	52%
CHARM-alternative 2003 ²⁵	DB, MC, PC	618/ NA, EU	3.5 years	1013 1015	Candesartan Placebo	≤40%	30%	68%	67	0%	48%	49%	4%	NR	68%	61%
HEAVEN 2002 ²⁶	DB, MC, PC	NR/ Sweden	12 weeks	70 71	Valsartan Enalapril	≤45%	NR	53%	67	0%	70%	30%	0%	47	43%	NR
RALES 1999 ²⁷	DB, MC, PC	195/ 15 countries	24 months (mean)	822 841	Spirololactone Placebo	≤35%	25%	73%	65	0%	0%	70%	29%	NR	54%	NR
Val-HeFT 2001 ²⁸	DB, MC, PC	302/ US, EU, Africa	23 months (mean)	2511 2499	Valsartan Placebo	<40%	27%	80%	63	0%	62%	36%	2%	NR	NR	NR
Hamroff 1999 ²⁹	DB, MC	4/ NR	6 months	16 17	Losartan Placebo	Reduced	26%	49%	61	NR	NR	NR	NR	NR	30%	NR
BEST 2008 ³⁰	DB, MC, PC	90/ US and Canada	3 years	1354 1354	Bucindolol Placebo	≤35%	23%	78%	60	0%	0%	92%	8%	37	42%	NR
CIBIS I 1994 ³¹	DB, MC, PC	NR/ EU	2 years	320 321	Bisoprolol Placebo	< 40%	17%	83%	60	0%	0%	95%	5%	38	54%	47%
CIBIS II 1999 ³²	DB, MC, PC	47/ Western and Eastern EU	1.3 years (mean)	1327 1320	Bisoprolol Placebo	≤35%	28%	81%	61	0%	0%	83%	17%	43	50%	NR
CELICARD 2000 ³³	DB, MC, PC	NR/ France, Poland	1 year	62 62	Celiprolol Placebo	<40%	26%	90%	57	0%	57%	43%	1%	NR	NR	40%
COPERNICUS 2001 ³⁴	DB, MC, PC	334/ NA, EU, AUS	28.7 months	1156 1133	Carvedilol Placebo	<25%	20%	79%	63	0%	NR	NR	NR	NR	67%	NR
ENECA 2005 ³⁵	DB, MC, PC	70/ NR	48 weeks	134 126	Nebivolol Placebo	≤35%	26%	73%	72	0%	49%	47%	5%	NR	NR	58%

MERIT-HF 1999 ³⁶	DB, MC, PC	14/ US, EU	18 months	1990 2001	Metroproprlol Placebo	≤40%	28%	78%	64	0%	41%	55%	4%	NR	66%	49%
MERIT-HF (pilot) 1999 ³⁷	DB, MC, PC	NR	6 months	42 19	Metroproprlol Placebo	≤40%	27%	75%	NR	0%	56%	41%	3%	NR	NR	NR
MIC 2000 ³⁸	DB, MC, PC	NR/ Germany, Sweden	6 months	26 26	Metroproprlol Placebo	<40%	28%	71%	54	0%	58%	42%	0%	NR	NR	NR
MOCHA 1996 ³⁹	DB, MC, PC	NR/ US	6 months	261 84	Carvedilol Placebo	≤ 35%	23%	76%	60	0%	53%	60%	2%	57	52%	NR
PRECISE 1996 ⁴⁰	DB, MC, PC	31/ US	6 months	133 145	Carvedilol Placebo	≤35%	22%	73%	60	0%	40%	56%	4%	NR	52%	NR
SYMPOXYDEX 2004 ⁴¹	DB, MC, PC	NR/ France	6 months	28 22	Carvedilol Placebo	≤40%	26%	84%	59	0%	78%	22%	0%	NR	40%	NR
Cohn 1997 ⁴²	DB, MC, PC	42 / US	6 months	70 35	Carvedilol Placebo	< 35%	22%	58%	60	0%	1%	86%	13%	49	45%	NR
Colucci 1996 ⁴³	DB, MC, PC	NR/ US	12 months	232 134	Carvedilol Placebo	≤ 35%	23%	85%	54	0%	85%	14%	0%	48	41%	NR
de Milliano 2002 ⁴⁴	DB, MC, PC	Netherlands	8 months	43 11	Metroproprlol Placebo	<35%	25%	67%	65	0%	54%	46%	0%	NR	56%	NR
Dubach 2002 ⁴⁵	DB, PC	NR	1 year	13 15	Bisoprolol Placebo	<40%	26%	NR	58	0%	NR	NR	0%	NR	57%	NR
Krum 1995 ⁴⁶	DB, PC	NR/ US	14 weeks	33 16	Carvedilol Placebo	≤ 35%	16%	78%	55	0%	27%	63%	10%	NR	10%	NR
Packer 1996 ⁴⁷	DB, MC, PC	NR/ US	6/12 months	696 398	Carvedilol Placebo	≤ 35%	23%	77%	58	0%	53%	44%	3%	NR	NR	NR
Palazzuoli 2005 ⁴⁸	DB, PC	Italy	12 months	33 25	Carvedilol Placebo	<40%	32%	66%	71	0%	0%	57%	43%	NR	69%	NR

Palazzuoli 2005 ⁴⁹	DB, PC	Italy	12 months	32 27	Carvedilol Placebo	<40%	32%	64%	71	0%	0%	58%	42%	NR	69%	NR
Sturm 2000 ⁵⁰	DB, SC, PC	1/ Austria	2 years	51 49	Atenolol + Enalapril Placebo + Enalapril (Candesartan, Enalapril, or Candesartan + Enalapril) + Metoprolol (Candesartan, Enalapril, or Candesartan + Enalapril) + Placebo	≤25%	17%	88%	52	0%	78%	20%	2%	NR	28%	NR
RESOLVD 2000 ^{51, 52}	DB, MC, PC	60/ NA, Italy	43 weeks	214 212	Atenolol + Enalapril Placebo + Enalapril (Candesartan, Enalapril, or Candesartan + Enalapril) + Metoprolol (Candesartan, Enalapril, or Candesartan + Enalapril) + Placebo	<40%	28%	82%	61	7%	69%	23%	1%	NR	69%	64%
CHARM-added 2003 ⁵³	DB, MC, PC	618/ NA, EU	3.5 years	1276 1272	Candesartan Placebo	≤40%	28%	79%	64	0%	24%	73%	0%	NR	62%	56%
AREA-IN CHF 2009 ⁵⁴	DB, MC, PC	46/ Italy	12 months	231 236	Canrenone Placebo	≤45%	40%	84%	63	0%	100%	0%	0%	NR	52%	NR
EMPHASIS-HF 2011 ⁵⁵	DB, MC, PC	278/ US, EU, AUS	3 years	1364 1373	Eplerenone Placebo	≤30%	26%	78%	69	0%	100%	0%	0%	58	69%	50%
Cicoira 2002 ⁵⁶	OL	Italy	12 months	54 52	Spirolactone Placebo	≤45%	33%	87%	62	NR	NR	NR	NR	NR	64%	NR
Vizzardi 2014 ⁵⁷	SB, SC, PC	1/Italy	44 months (mean)	65 65	Spirolactone Placebo	<40%	36%	NR	63	18%	82%	0%	0%	NR	NR	NR
PARADIGM-HF 2014 ⁵⁸	DB, MC	1043/ 46 countries	27 months (median)	4187 4212	Valsartan/ sacubitril Enalapril	≤40%	29%	78%	64	5%	70%	24%	1%	NR	60%	43%

Abbreviations: AUS = Australia; d = day(s); DB = double-blind; EU = Europe; heart failure = heart failure; MC = multicentre; mos = months; MI = myocardial infarction; NA = North America; NYHA = New York heart association; LVEF = left ventricular ejection fraction; mo = month(s); NR = not reported; OL = open label; PC = placebo controlled; SB = single blind; SC = single centre; US = United States; yrs= years; wk = week(s); yr = year(s)

Supplementary Table 3: Characteristics of included interventions and concomitant therapies reported at baseline

Trial/Author year	Intervention class (>50%)	Main Intervention	ACEI %	ARB %	BB %	MRA %	Digoxin %	Diuretics %
CASSIS 1995	ACEI	Spirapril	5%	NR	NR	NR	91%	96%
CASSIS 1995	ACEI	Spirapril	5%	NR	NR	NR	91%	96%
CASSIS 1995	ACEI	Spirapril	5%	NR	NR	NR	91%	96%
CASSIS 1995	ACEI	Enalapril	5%	NR	NR	NR	91%	96%
CASSIS 1995	PLBO	Placebo	5%	NR	NR	NR	91%	96%
CONSENSUS 1987	ACEI	Enalapril	not allowed	NR	4%	NR	92%	100%
CONSENSUS 1987	PLBO	Placebo	not allowed	NR	2%	NR	94%	100%
FEST 1995	ACEI	Fosinopril	NR	NR	NR	NR	61%	100%
FEST 1995	PLBO	Placebo	NR	NR	NR	NR	62%	100%
MHFT 1991	ACEI	Captopril	NR	NR	23%	NR	59%	79%
MHFT 1991	PLBO	Placebo	NR	NR	23%	NR	59%	79%
SOLVD-prevent 1992	ACEI	Enalapril	not allowed	NR	NR	NR	12%	16%
SOLVD-prevent 1992	PLBO	Placebo	not allowed	NR	NR	NR	13%	17%
SOLVD-treat 1991	ACEI	Enalapril	not allowed	NR	8%	NR	66%	86%
SOLVD-treat 1991	PLBO	Placebo	not allowed	NR	7%	NR	68%	85%
Beller 1995	ACEI	Lisinopril	NR	NR	NR	NR	94%	99%
Beller 1995	PLBO	Placebo	NR	NR	NR	NR	86%	97%
Brown 1995	ACEI	Fosinopril	not allowed	NR	not allowed	NR	53%	100%
Brown 1995	PLBO	Placebo	not allowed	NR	not allowed	NR	54%	100%
Chalmers 1987	ACEI	Lisinopril	NR	NR	NR	10%	60%	55%
Chalmers 1987	PLBO	Placebo	NR	NR	NR	14%	72%	49%
Colfer 1992	ACEI	Benazepril	NR	NR	not allowed	NR	100%	100%
Colfer 1992	PLBO	Placebo	NR	NR	not allowed	NR	100%	100%
Goldstein 1988	ACEI	Captopril	NR	NR	NR	NR	60%	NR
Goldstein 1988	PLBO	Placebo	NR	NR	NR	NR	67%	NR
Lewis 1989	ACEI	Lisinopril	NR	NR	NR	NR	100%	100%
Lewis 1989	PLBO	Placebo	NR	NR	NR	NR	100%	100%

Shettigar 1999	ACEI	Fosinopril	not allowed	NR	not allowed	NR	42%	100%
Shettigar 1999	PLBO	Placebo	not allowed	NR	not allowed	NR	47% %	100%
Veldhuisen 1999	ACEI	Imidapril	NR	NR	not allowed	NR	23%	34%
Veldhuisen 1999	ACEI	Imidapril	NR	NR	not allowed	NR	26%	25%
Veldhuisen 1999	ACEI	Imidapril	NR	NR	not allowed	NR	24%	30%
Veldhuisen 1999	PLBO	Placebo	NR	NR	not allowed	NR	19%	25%
SPICE 2000	ARB	Candesartan	not allowed	not allowed	22%	NR	60%	NR
SPICE 2000	PLBO	Placebo	not allowed	not allowed	20%	NR	63%	NR
STRETCH 1999	ARB	Candesartan	not allowed	NR	1%	NR	40%	61%
STRETCH 1999	ARB	Candesartan	not allowed	NR	1%	NR	43%	63%
STRETCH 1999	ARB	Candesartan	not allowed	NR	0%	NR	42%	58%
STRETCH 1999	PLBO	Placebo	not allowed	NR	1%	NR	39%	58%
Mitrovic 2003	ARB	Candesartan	not allowed	not allowed	NR	NR	78%	NR
Mitrovic 2003	ARB	Candesartan	not allowed	not allowed	NR	NR	65%	NR
Mitrovic 2003	ARB	Candesartan	not allowed	not allowed	NR	NR	80%	NR
Mitrovic 2003	ARB	Candesartan	not allowed	not allowed	NR	NR	77%	NR
Mitrovic 2003	PLBO	Placebo	not allowed	not allowed	NR	NR	82%	NR
ELITE I 1997	ARB	Losartan	not allowed	not allowed	16%	NR	57%	74%
ELITE I 1997	ACEI	Captopril	not allowed	not allowed	17%	NR	56%	74%
ELITE II 2000	ARB	Losartan	not allowed	not allowed	23%	NR	50%	77%
ELITE II 2000	ACEI	Captopril	not allowed	not allowed	21%	NR	50%	79%
REPLACE 2001	ACEI	Enalapril	not allowed	not allowed	NR	NR	39%	NR
REPLACE 2001	ARB	Telmisartan	not allowed	not allowed	NR	NR	39%	NR
REPLACE 2001	ARB	Telmisartan	not allowed	not allowed	NR	NR	39%	NR
REPLACE 2001	ARB	Telmisartan	not allowed	not allowed	NR	NR	39%	NR
REPLACE 2001	ARB	Telmisartan	not allowed	not allowed	NR	NR	39%	NR
Dickstein 1995	ARB	Losartan	NR	NR	19%	NR	58%	NR
Dickstein 1995	ARB	Losartan	NR	NR	11%	NR	73%	NR
Dickstein 1995	ACEI	Enalapril	NR	NR	7%	NR	59%	NR
Lang 1997	ARB	Losartan	not allowed	NR	11%	NR	82%	100%
Lang 1997	ARB	Losartan	not allowed	NR	3%	NR	85%	100%
Lang 1997	ACEI	Enalapril	not allowed	NR	8%	NR	87%	97%

CIBIS III 2008	BB	Bisoprolol then Enalapril	not allowed	NR	not allowed	14%	33%	NR
CIBIS III 2008	ACEI	Enalapril then Bisoprolol	not allowed	NR	not allowed	12%	31%	NR
CARMEN 2004	BB	Carvedilol + placebo	not allowed	NR	not allowed	15%	44%	67%
CARMEN 2004	ACEI	Enalapril + placebo	not allowed	NR	not allowed	13%	44%	74%
CARMEN 2004	ACEI + BB	Carvedilol + enalapril	not allowed	NR	not allowed	12%	47%	73%
RALES 1999	ACEI + MRA	Spironolactone	95%	NR	11%	not allowed	75%	95%
RALES 1999	ACEI	Placebo	94%	NR	10%	not allowed	72%	94%
Val-HeFT 2001	ACEI + ARB	Valsartan	93%	not allowed	35%	NR	67%	NR
Val-HeFT 2001	ACEI	Placebo	93%	not allowed	35%	NR	68%	NR
Hamroff 1999	ACEI + ARB	Losartan	100%	NR	6%	NR	100%	100%
Hamroff 1999	ACEI	Placebo	100%	NR	6%	NR	94%	100%
BEST 2001	ACEI + BB	Bucindolol	91%	6%	not allowed	3%	93%	NR
BEST 2001	ACEI	Placebo	91%	7%	not allowed	4%	92%	NR
CELICARD 2000	ACEI + BB	Celiprolol	80%	NR	not allowed	NR	51%	NR
CELICARD 2000	ACEI	Placebo	90%	NR	not allowed	NR	66%	NR
CIBIS I 1994	ACEI + BB	Bisoprolol	89%	NR	NR	NR	57%	100%
CIBIS I 1994	ACEI	Placebo	91%	NR	NR	NR	56%	100%
CIBIS II 1999	ACEI + BB	Bisoprolol	96%	NR	NR	NR	53%	98%
CIBIS II 1999	ACEI	Placebo	96%	NR	NR	NR	51%	99%
COPERNICUS 2001	ACEI + BB	Carvedilol	97%*	97%*	not allowed	19%	67%	NR
COPERNICUS 2001	ACEI	Placebo	97%*	97%*	not allowed	20%	65%	NR
ENECA 2005	ACEI + BB	Nebivolol	91%	5%	not allowed	NR	60%	NR
ENECA 2005	ACEI	Placebo	92%	7%	not allowed	NR	53%	NR
MERIT-heart failure 1999	ACEI + BB	Metoprolol	89%	7%	not allowed	7%	63%	91%
MERIT-heart failure 1999	ACEI	Placebo	90%	6%	not allowed	8%	64%	90%
MERIT-heart failure (pilot) 1999	ACEI + BB	Metoprolol	95%	NR	NR	NR	91%	NR
MERIT-heart failure (pilot) 1999	ACEI	Placebo	89%	NR	NR	NR	90%	NR
MIC 2000	ACEI + BB	Metoprolol	92%	NR	not allowed	NR	51%	NR
MIC 2000	ACEI	Placebo	91%	NR	not allowed	NR	52%	NR
MOCHA 1996	ACEI + BB	Carvedilol (low-dose)	93%	NR	not allowed	NR	99%	98%
MOCHA 1996	ACEI + BB	Carvedilol (medium-dose)	99%	NR	not allowed	NR	88%	96%

MOCHA 1996	ACEI + BB	Carvedilol (high-dose)	89%	NR	not allowed	NR	90%	93%
MOCHA 1996	ACEI	Placebo	94%	NR	not allowed	NR	93%	93%
PRECISE 1996	ACEI + BB	Carvedilol	96%	NR	not allowed	NR	91%	98%
PRECISE 1996	ACEI	Placebo	97%	NR	not allowed	NR	88%	99%
SYMPOXYDEX 2004	ACEI + BB	Carvedilol	96%	NR	not allowed	NR	NR	100%
SYMPOXYDEX 2004	ACEI	Placebo	96%	NR	not allowed	NR	NR	100%
Cohn 1997	ACEI + BB	Carvedilol	94%	NR	NR	NR	90%	97%
Cohn 1997	ACEI	Placebo	91%	NR	NR	NR	89%	100%
Colucci 1996	ACEI + BB	Carvedilol	98%	NR	not allowed	NR	89%	NR
Colucci 1996	ACEI	Placebo	98%	NR	not allowed	NR	89%	NR
de Milliano 2002	ACEI + BB	Metoprolol	93%	NR	not allowed	NR	28%	NR
de Milliano 2002	ACEI	Placebo	91%	NR	not allowed	NR	36%	NR
Dubach 2002	ACEI + BB	Bisoprolol	100%	NR	not allowed	NR	5%	NR
Dubach 2002	ACEI	Placebo	100%	NR	not allowed	NR	9%	NR
Krum 1995	ACEI + BB	Carvedilol	90%	NR	NR	NR	NR	NR
Krum 1995	ACEI	Placebo	90%	NR	NR	NR	NR	NR
Packer 1996	ACEI + BB	Carvedilol	95%	NR	not allowed	NR	91%	95%
Packer 1996	ACEI	Placebo	95%	NR	not allowed	NR	90%	95%
Palazzuoli 2005	ACEI + BB	Carvedilol	100%	NR	not allowed	NR	NR	NR
Palazzuoli 2005	ACEI	Placebo	100%	NR	not allowed	NR	NR	NR
Palazzuoli 2005	ACEI + BB	Carvedilol	100%	NR	not allowed	NR	NR	NR
Palazzuoli 2005	ACEI	Placebo	100%	NR	not allowed	NR	NR	NR
Sturm 2000	ACEI + BB	Atenolol + enalapril	100%	NR	not allowed	NR	51%	NR
Sturm 2000	ACEI	Placebo + enalapril	100%	NR	not allowed	NR	49%	NR
HEAVEN 2002	ARB + BB	Valsartan	not allowed	not allowed	52%	NR	26%	NR
HEAVEN 2002	ACEI + BB	Enalapril	not allowed	not allowed	56%	NR	32%	NR
CHARM-alternative 2003	ARB + BB	Candesartan	not allowed	not allowed	55%	25%	60%	NR
CHARM-alternative 2003	BB	Placebo	not allowed	not allowed	55%	23%	63%	NR
RESOLVD 2000	ACEI + ARB + BB	(Candesartan, enalapril, or candesartan + enalapril) + metoprolol	ACEI alone: 14%	ARB alone: 45%	not allowed	NR	65%	NR
RESOLVD 2000	ACEI + ARB	(Candesartan, enalapril, or candesartan + enalapril) + placebo	ACEI + ARB: 41%	ARB alone: 40%	not allowed	NR	69%	NR

RESOLVD 2003	ARB + BB	(Candesartan or enalapril) + metoprolol	ACEI + ARB: 41% 23%	77%	not allowed	NR	68%	82%
RESOLVD 2003	ACEI + ARB + BB	(Candesartan + enalapril) + metoprolol	not allowed	not allowed	not allowed	NR	62%	83%
RESOLVD 2003	ARB	(Candesartan or enalapril) + placebo	33%	67%	not allowed	NR	74%	85%
RESOLVD 2003	ACEI + ARB	(Candesartan + enalapril) + placebo	not allowed	not allowed	not allowed	NR	70%	83%
CHARM-added 2003	ACEI + ARB + BB	Candesartan	100%	not allowed	55%	17%	58%	NR
CHARM-added 2003	ACEI + BB	Placebo	100%	not allowed	56%	17%	59%	NR
AREA-IN CHF 2009	ACEI + BB + MRA	Canrenone	85%	12%	81%	not allowed	24%	NR
AREA-IN CHF 2009	ACEI + BB	Placebo	75%	24%	78%	not allowed	27%	NR
EMPHASIS-heart failure 2011	ACEI + BB + MRA	Eplerenone	78%	19%	87%	not allowed	27%	84%
EMPHASIS-heart failure 2011	ACEI + BB	Placebo	77%	19%	87%	not allowed	28%	86%
Cicoira 2002	ACEI + BB + MRA	Spirolactone	100%	NR	72%	not allowed	NR	NR
Cicoira 2002	ACEI + BB	Placebo	100%	NR	65%	not allowed	NR	NR
Vizzardi 2014	ACEI + BB + MRA	Spirolactone	100%*	100%*	97%	NR	NR	75%
Vizzardi 2014	ACEI + BB	Placebo	100%*	100%*	98%	NR	NR	86%
PARADIGM-heart failure 2014	ARNI + BB + MRA	Sacubitril/valsartan	not allowed	NR	93%	54%	29%	80%
PARADIGM-heart failure 2014	ACEI + BB + MRA	Enalapril	not allowed	NR	93%	57%	31%	80%

* data presented for ACEI/ARB

Abbreviations: ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-II receptor antagonist; ARNI = angiotensin receptor-neprilysin inhibitor; BB = beta blocker; MRA = mineralocorticoid receptor antagonist; NR = not reported; PLBO = placebo

Supplementary Table 4: Proportion of patients taking concomitant ACEI and ARB in RCTs that allow concomitant use of ACEI or ARB

Criteria for ACEI or ARB	n studies	% of studies
ACEI or ARB allowed	9	100%
$\geq 90\%$ patients taking ACEI	3/9	33%
$\geq 75\%$ patients taking ACEI	6/9	67%
Only present pooled % (ACEI or ARB)	2/9	22%
Treatment classification unclear*	1/9	11%

* RESOLVD trial ^{51,52}

Abbreviations: ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-II receptor antagonist

Supplementary Table 5: Treatment doses and schedules by molecule

Intervention class (>50%)	Trial/Author year	Main Intervention	Target dosage	Frequency	Target daily dosage	Treatment duration
ACEI	Colfer 1992	Benazepril	20mg	OD	20mg	12 weeks (titration first 8 weeks)
ACEI	MHFT 1991	Captopril	25mg	BID	40mg	Median: 2.7 years
ACEI	ELITE I 1997	Captopril	50mg	TID	150mg	48 weeks (uptitration every 7 days)
ACEI	ELITE II 2000	Captopril	50mg	TID	150mg	700 days
ACEI	Anonymous 1988	Captopril	50mg	TID	150mg	24 weeks (uptitrated from 25mg/day if tolerated)
ACEI	Dickstein 1995	Enalapril	10mg	BID	20mg	8 weeks
ACEI	REPLACE 2001	Enalapril	10mg	BID	20mg	12 weeks
ACEI	CARMEN 2004	Enalapril	10mg	BID	20mg	18 months (plus upward titration and downward titration, undefined lengths of time)
ACEI	CASSIS 1995	Enalapril	10mg	OD	10mg	12 weeks
ACEI	SOLVD-treat 1991	Enalapril	10mg	BID	20mg	48 months
ACEI	SOLVD-prevent 1992	Enalapril	10mg	BID	20mg	37.4 months (mean)
ACEI	CIBIS III 2008	Enalapril	10mg	BID	20mg/10mg	6 months
ACEI	CONSENSUS 1987	Enalapril	10mg-20mg	BID	20mg-40mg	52 weeks
ACEI	Lang 1997	Enalapril	20mg	BID	40mg	12 weeks
ACEI	Sturm 2000	Enalapril	40mg	OD	40mg	2 years (includes titration)
ACEI	Brown 1995	Fosinopril	20mg	OD	20mg	24 weeks
ACEI	FEST 1995	Fosinopril	40mg	OD	40mg	12 weeks
ACEI	Shettigar 1999	Fosinopril	40mg	OD	40mg	12 weeks (uptitration over first 4-weeks)
ACEI	Veldhuisen 1999*	Imidapril	2.5mg	OD	2.5mg	12 weeks
ACEI	Veldhuisen 1999*	Imidapril	5mg	OD	5mg	12 weeks
ACEI	Veldhuisen 1999	Imidapril	10mg	OD	10mg	12 weeks
ACEI	Beller 1995	Lisinopril	5mg-20mg	OD	5mg-20mg	12 weeks
ACEI	Chalmers 1987	Lisinopril	5mg-20mg	OD	5mg-20mg	12 weeks

ACEI	Lewis 1989	Lisinopril	5-20mg	OD	5-20mg	12 weeks
ACEI	CASSIS 1995*	Spirapril	1.5mg	OD	1.5mg	12 weeks
ACEI	CASSIS 1995*	Spirapril	3mg	OD	3mg	12 weeks
ACEI	CASSIS 1995	Spirapril	6mg	OD	6mg	12 weeks
ACEI	MERIT-heart failure 1999	Placebo	NA	NA	NA	18 months (including 6-8 week titration)
ACEI	MOCHA 1996	Placebo	NA	NA	NA	6 months (plus 2-4 week titration)
ACEI	SYMPOXYDEX 2004	Placebo	NA	NA	NA	6 months (including 6 weeks titration)
ACEI	Cohn 1997	Placebo	NA	NA	NA	6 months (plus 4 week titration)
ACEI	Val-HeFT 2001	Placebo	NA	NA	NA	38 months (including 4 weeks titration)
ACEI	de Milliano 2002	Placebo	NA	NA	NA	6 months (plus 10 wks titration)
ACEI	Dubach 2002	Placebo	NA	NA	NA	12 months (titration first month)
ACEI	ENECA 2005	Placebo	NA	NA	NA	48 weeks (includes 6 week titration period)
ACEI	BEST 2001	Placebo	NA	NA	NA	42 months (titration first 6 weeks)
ACEI	MIC 2000	Placebo	NA	NA	NA	6 months (including 6 week titration)
ACEI	MERIT-heart failure (pilot) 1999	Placebo	NA	NA	NA	26 weeks (titration first 8 weeks)
ACEI	Hamroff 1999	Placebo	NA	NA	NA	6 months
ACEI	CIBIS I 1994	Placebo	NA	NA	NA	2 years (mean duration 1.9)
ACEI	CIBIS II 1999	Placebo	NA	NA	NA	mean duration: 1.3 years (titration weeks 1-5)
ACEI	PRECISE 1996	Placebo	NA	NA	NA	6 months
ACEI	Packer 1996	Placebo	NA	NA	NA	6 months (plus 2-10 week titration (mild heart failure protocol; 12 months + titration)
ACEI	Colucci 1996	Placebo	NA	NA	NA	52 weeks (plus uptitration 2-6 weeks)
ACEI	Krum 1995	Placebo	NA	NA	NA	14 weeks (titration in first week)
ACEI	COPERNICUS 2001	Placebo	NA	NA	NA	28.7 months (includes approximately 8 week titration period)
ACEI	Palazzuoli 2005	Placebo	NA	NA	NA	12 months (titration first 7 weeks)
ACEI	Palazzuoli 2005	Placebo	NA	NA	NA	12 months (titration first 7 weeks)
ACEI	RALES 1999	Placebo	NA	NA	NA	24 months

ACEI	CELICARD 2000	Placebo	NA	NA	NA	1 year (including 1 month titration period)
BB	CIBIS III 2008	Bisoprolol	10mg	OD	10mg	26 weeks (including 10 week titration)
BB	CARMEN 2004	Carvedilol	25mg or 50mg if >85kg	BID	50mg or 100mg if >85kg	18 months (plus upward titration and downward titration, undefined lengths of time)
BB	CHARM-alternative 2003	Placebo	NA	NA	NA	33.7 months (median follow-up, plus 6 weeks titration period)
ARB	SPICE 2000	Candesartan	16mg	OD	16mg	12 weeks (including 4 weeks titration)
ARB	STRETCH1999*	Candesartan	4mg	OD	4mg	12 weeks
ARB	STRETCH1999*	Candesartan	8mg	OD	8mg	12 weeks
ARB	STRETCH1999	Candesartan	16mg	OD	16mg	12 weeks
ARB	Lang 1997	Losartan*	25mg	OD	25mg	12 weeks
ARB	Lang 1997	Losartan	50mg	OD	50mg	12 weeks
ARB	Mitrovic 2003*	Candesartan	2mg	OD	2mg	12 weeks (titration first 3 weeks)
ARB	Mitrovic 2003*	Candesartan	4mg	OD	4mg	12 weeks (titration first 3 weeks)
ARB	Mitrovic 2003*	Candesartan	8mg	OD	8mg	12 weeks (titration first 3 weeks)
ARB	Mitrovic 2003	Candesartan	16mg	OD	16mg	12 weeks (titration first 3 weeks)
ARB	Dickstein 1995*	Losartan	25mg	OD	25mg	8 weeks
ARB	Dickstein 1995	Losartan	50mg	OD	50mg	8 weeks
ARB	ELITE I 1997	Losartan	50mg	OD	50mg	48 weeks (uptitration every 7 days)
ARB	ELITE II 2000	Losartan	50mg	OD	50mg	700 days
ARB	REPLACE 2001*	Telmisartan	10mg	OD	10mg	12 weeks
ARB	REPLACE 2001*	Telmisartan	20mg	OD	20mg	12 weeks
ARB	REPLACE 2001*	Telmisartan	40mg	OD	40mg	12 weeks
ARB	REPLACE 2001	Telmisartan	80mg	OD	80mg	12 weeks
ACEI + ARB	RESOLVD 2003	(Candesartan + enalapril) + placebo	NA	NA	NA	19 weeks without placebo (including mean titration 93 days), placebo received for 24weeks (43 weeks total)
ACEI + ARB	Hamroff 1999	Losartan	50mg	OD	50mg	6 months
ACEI + ARB	Val-HeFT 2001	Valsartan	160mg	BID	320mg	38 months (including 4 weeks titration)

ACEI + BB	Sturm 2000	Atenolol + enalapril	50mg-100mg/40mg	daily	50mg-100mg/40mg	2 years (includes titration)
ACEI + BB	Dubach 2002	Bisoprolol	10mg	daily	10mg	12 months (titration first month)
ACEI + BB	CIBIS I 1994	Bisoprolol	5mg	OD	5mg	2 years (mean duration 1.9)
ACEI + BB	CIBIS II 1999	Bisoprolol	2.5-10mg	OD	2.5-10mg	mean duration: 1.3 years (titration weeks 1-5)
ACEI + BB	BEST 2001	Bucindolol	50mg if <75kg; 100mg if >75kg	BID	100mg or 200mg	42 months (titration first 6 weeks)
ACEI + BB	SYMPOXYDEX 2004	Carvedilol	25mg	BID	50mg	6 months (including 6 weeks titration)
ACEI + BB	Cohn 1997	Carvedilol	25mg	BID	50mg	6 months (plus 4 week titration)
ACEI + BB	PRECISE 1996	Carvedilol	25mg	BID	50mg	6 months
ACEI + BB	Krum 1995	Carvedilol	25mg	BID	50mg	14 weeks (titration in first week)
ACEI + BB	Packer 1996	Carvedilol	25-50mg	BID	50mg-100mg	6 months (plus 2-10 week titration (mild heart failure protocol; 12 months + titration)
ACEI + BB	Colucci 1996	Carvedilol	25-50mg	BID	50-100mg	52 weeks (plus uptitration 2-6 weeks)
ACEI + BB	COPERNICUS 2001	Carvedilol	25mg	BID	50mg	28.7 months (includes approximately 8 week titration period)
ACEI + BB	Palazzuoli 2005	Carvedilol	50mg	daily	50mg	12 months (titration first 7 weeks)
ACEI + BB	Palazzuoli 2005	Carvedilol	50mg	daily	50mg	12 months (titration first 7 weeks)
ACEI + BB	MOCHA 1996*	Carvedilol (low-dose)	6.25mg	BID	12.5mg	6 months (plus 2-4 week titration)
ACEI + BB	MOCHA 1996*	Carvedilol (medium-dose)	12.5mg	BID	25mg	6 months (plus 2-4 week titration)
ACEI + BB	MOCHA 1996	Carvedilol (high-dose)	25mg	BID	50mg	6 months (plus 2-4 week titration)
ACEI + BB	CARMEN 2004	Carvedilol + enalapril	25mg or 50mg if >85kg/10mg	BID	50mg or 100mg if >85kg/20mg	18 months (plus upward titration and downward titration, undefined lengths of time)
ACEI + BB	CELICARD 2000	Celiprolol	100mg	OD	100mg	1 year (including 1 month titration period)

ACEI + BB	MERIT-heart failure 1999	Metoprolol	200mg	daily	200mg	18 months (including 6-8 week titration)
ACEI + BB	MERIT-heart failure (pilot) 1999	Metoprolol	150mg	o.d.	150 mg	26 weeks (titration first 8 weeks)
ACEI + BB	de Milliano 2002	Metoprolol	50, 100 or 150mg	daily	50, 100 or 150mg	6 months (plus 10 wks titration)
ACEI + BB	MIC 2000	Metoprolol	NR	NR	135mg (mean)	6 months (including 6 week titration)
ACEI + BB	ENECA 2005	Nebivolol	10mg	daily	10mg	48 weeks (includes 6 week titration period)
ACEI + BB	HEAVEN 2002	Enalapril	10mg	BID	20mg	12 weeks (including titration)
ACEI + BB	AREA-IN CHF 2009	Placebo	NA	NA	NA	12 months
ACEI + BB	Cicoira 2002	Placebo	NA	NA	NA	12 months (includes titration)
ACEI + BB	Vizzarda 2014	Placebo	25mg	OD	25mg	44 months (mean)
ACEI + BB	CHARM-added 2003	Placebo	NA	NA	NA	41 months (median follow-up, plus 6 weeks titration period)
ACEI + BB	EMPHASIS-heart failure 2011	Placebo	NA	NA	NA	3 years
ARB + BB	HEAVEN 2002	Valsartan	160mg	OD	160mg	12 weeks (including titration)
ARB + BB	CHARM-alternative 2003	Candesartan	32mg	OD	32mg	33.7 months (median follow-up, plus 6 weeks titration period)
ACEI + MRA	RALES 1999	Spironolactone	25-50mg	OD	25-50mg (mean 30mg)	24 months
ACEI + ARB + BB	RESOLVD 2003	(Candesartan + enalapril) + metoprolol	200mg	daily	200mg	19 weeks without metoprolol (including mean titration 93 days), metoprolol received for 24weeks (43 weeks total)
ACEI + ARB + BB	CHARM-added 2003	Candesartan	32mg	OD	32mg	41 months (median follow-up, plus 6 weeks titration period)
ACEI + BB + MRA	AREA-IN CHF 2009	Canrenone	50mg	OD	50mg	12 months
ACEI + BB + MRA	EMPHASIS-heart failure 2011	Eplerenone	50mg	OD	50mg	3 years
ACEI + BB + MRA	PARADIGM-heart failure 2014	Enalapril	10mg	BID	20mg	27 months (median)
ACEI + BB + MRA	Cicoira 2002	Spironolactone	50mg	OD	50mg	12 months (includes titration)

ACEI + BB + MRA	Vizzard 2014	Spirinolactone	25mg-100mg	OD-QID	25mg-400mg	44 months (mean)
ARNI + BB + MRA	PARADIGM-heart failure 2014	Sacubitril/valsartan	200mg	BID	400mg	27 months (median)
PLBO	Beller 1995	Placebo	5mg-20mg	OD	5mg-20mg	12 weeks
PLBO	Brown 1995	Placebo	NA	NA	NA	24 weeks
PLBO	Chalmers 1987	Placebo	5mg-20mg	OD	5mg-20mg	12 weeks
PLBO	STRETCH 1999	Placebo	NA	NA	NA	12 weeks
PLBO	Anonymous 1988	Placebo	NA	NA	NA	24 weeks (uptitrated from 25mg/day if tolerated)
PLBO	Colfer 1992	Placebo	NA	NA	NA	12 weeks (titration first 8 weeks)
PLBO	FEST 1995	Placebo	NA	NA	NA	12 weeks
PLBO	SPICE 2000	Placebo	NA	NA	NA	12 weeks (including 4 weeks titration)
PLBO	MHFT 1991	Placebo	NA	NA	NA	Median: 2.7 years
PLBO	Lewis 1989	Placebo	NA	NA	NA	12 weeks
PLBO	Mitrovic 2003	Placebo	NA	NA	NA	12 weeks (titration first 3 weeks)
PLBO	Shettigar 1999	Placebo	NA	NA	NA	12 weeks (uptitration over first 4-weeks)
PLBO	CONSENSUS 1987	Placebo	NA	NA	NA	52 weeks
PLBO	Veldhuisen 1999	Placebo	NA	NA	NA	12 weeks
PLBO	CASSIS 1995	Placebo	NA	NA	NA	12 weeks
PLBO	SOLVD-treat 1991	Placebo	NA	NA	NA	48 months
PLBO	SOLVD-prevent 1992	Placebo	NA	NA	NA	37.4 months (mean)

* Arm excluded from analysis (more common dose available)

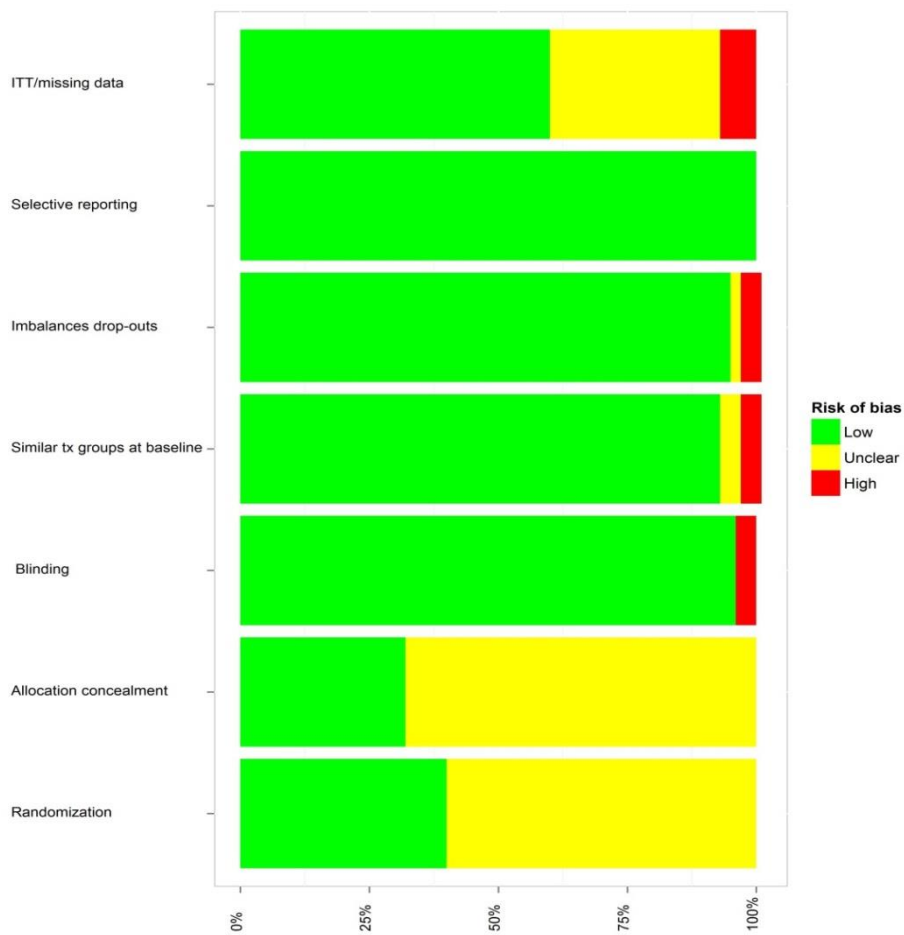
Abbreviations: ACEI = angiotensin-converting-enzyme inhibitor; ARB = angiotensin-II receptor antagonist; ARNI = angiotensin receptor-neprilysin inhibitor;

BB = beta blocker; BID = twice daily; mg = milligrams; MRA = mineralocorticoid receptor antagonist; NA = not applicable; NR = not reported; OD = once

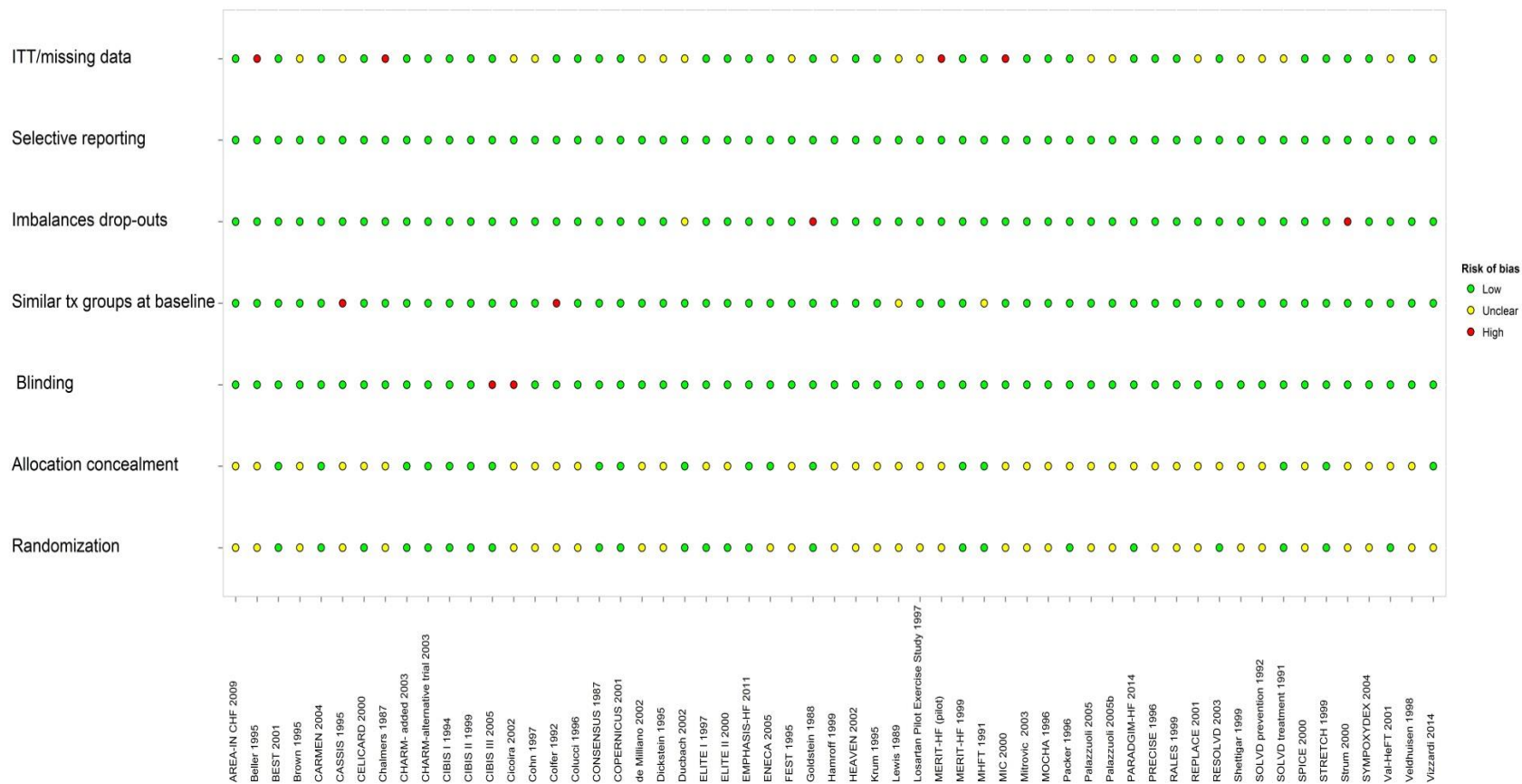
daily; PLBO = placebo; QID = four times daily; TID = three times daily

Supplementary Figure 1: Quality assessment results A) Summary by domain, B) Summary by RCT

A)

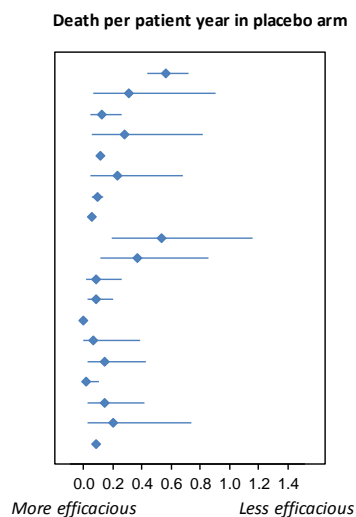


B)



Supplementary Figure 2: Rates per patient year sorted by publication year and presented by treatment arm for A) Placebo, B) ACEI, C) all other treatment arms

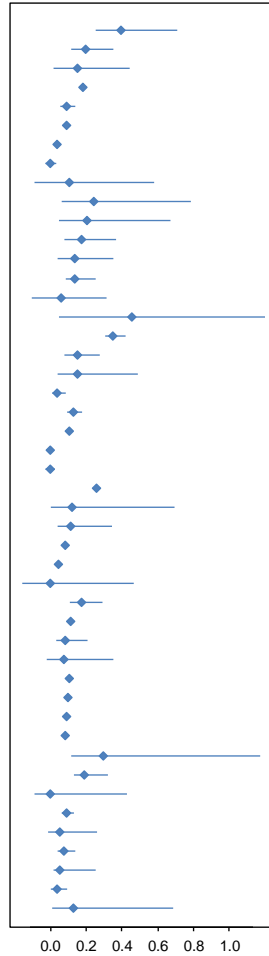
A)



Tx class	Trial	Follow-up # (months)	# randomized	# completers	Person years at risk	Deaths	Rate (per patient year)	95% CrI low	95% CrI high
PLBO	CONSENSUS 1987	12.0	126	108	117	66	0.56	0.72	0.44
PLBO	Chalmers 1987	3.0	43	35	10	3	0.31	0.90	0.06
PLBO	Goldstein 1988	6.0	100	100	50	6	0.12	0.26	0.04
PLBO	Lewis 1989	3.0	43	43	11	3	0.28	0.82	0.06
PLBO	SOLVD treat 1991	55.0	1284	752	4667	510	0.11	0.12	0.10
PLBO	Colfer 1992	3.0	58	45	13	3	0.23	0.68	0.05
PLBO	MHFT 1992	36.5	87	74	245	22	0.09	0.14	0.06
PLBO	SOLVD prevent 1992	48.0	2117	1164	6563	334	0.05	0.06	0.05
PLBO	CASSIS 1995	3.0	48	42	11	6	0.53	1.16	0.19
PLBO	Beller 1995	3.0	63	46	14	5	0.37	0.85	0.12
PLBO	FEST 1995	3.0	153	118	34	3	0.09	0.26	0.02
PLBO	Brown 1995	6.0	125	74	50	4	0.08	0.21	0.02
PLBO	RALES (dosing) 1996	3.0	40	40	10	0	0.00	0.00	0.00
PLBO	Veldhuisen 1998	3.0	62	54	15	1	0.07	0.38	0.00
PLBO	Shettigar 1999	3.0	104	60	21	3	0.15	0.43	0.03
PLBO	STRETCH 1999	3.0	211	211	53	1	0.02	0.11	0.00
PLBO	SPICE 2000	3.0	91	79	21	3	0.14	0.41	0.03
PLBO	Mitrovic 2003	3.0	44	34	10	2	0.21	0.74	0.02
PLBO	CHARM-halt 2003	42.0	1015	1015	3553	296	0.08	0.09	0.07

B)

Death per patient year in ACEI arm

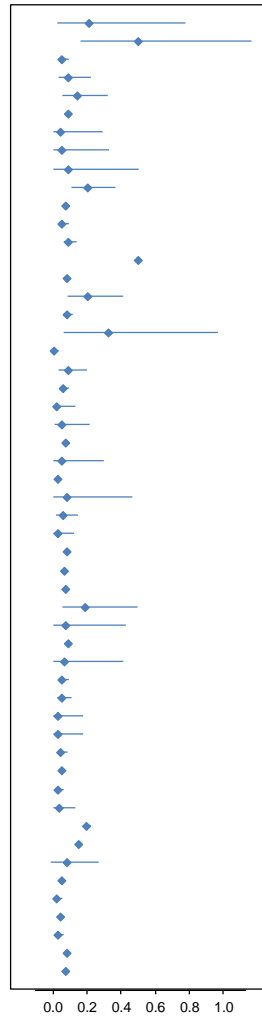


Tx class	Trial	Follow-up (months)	# randomized	# completers	Person years at risk	Deaths	Rate (per patient year)	95% CrI low	95% CrI high
ACEI	CONSENSUS 1987	12.0	127	105	116	46	0.40	0.53	0.29
ACEI	Chalmers 1987	3.0	87	72	20	4	0.20	0.52	0.05
ACEI	Goldstein 1988	6.0	104	104	52	8	0.15	0.30	0.07
ACEI	Lewis 1989	3.0	87	87	22	4	0.18	0.47	0.05
ACEI	SOLVD treat 1991	55.0	1285	867	4933	452	0.09	0.10	0.08
ACEI	MHFT 1992	40.4	83	59	239	22	0.09	0.14	0.06
ACEI	SOLVD prevent 1992	48.0	2111	1942	8106	313	0.04	0.04	0.03
ACEI	Colfer 1992	3.0	114	98	27	0	0.00	0.00	0.00
ACEI	CIBIS I 1994	26.0	321	239	607	67	0.11	0.14	0.09
ACEI	CASSIS 1995	3.0	51	47	12	3	0.24	0.72	0.05
ACEI	Dickstein 1995	2.0	58	58	10	2	0.21	0.75	0.02
ACEI	CASSIS 1995	3.0	48	42	11	2	0.18	0.64	0.02
ACEI	FEST 1995	3.0	155	127	35	5	0.14	0.33	0.05
ACEI	Beller 1995	3.0	130	105	29	4	0.14	0.35	0.04
ACEI	Brown 1995	6.0	116	81	49	3	0.06	0.18	0.01
ACEI	Krum 1995	3.5	16	14	4	2	0.46	1.65	0.05
ACEI	MOCHA 1996	6.0	84	63	37	13	0.35	0.60	0.19
ACEI	Packer 1996	6.0	398	398	199	31	0.16	0.22	0.11
ACEI	PRECISE 1996	6.0	145	145	73	11	0.15	0.27	0.08
ACEI	Colucci 1996	12.0	134	134	134	5	0.04	0.09	0.01
ACEI	Cohn 1997	6.0	35	27	16	2	0.13	0.47	0.01
ACEI	ELITE I 1997	11.0	370	259	288	32	0.11	0.16	0.08
ACEI	Lang 1997	3.0	38	38	10	0	0.00	0.00	0.00
ACEI	Veldhuisen 1998	3.0	60	56	15	0	0.00	0.00	0.00
ACEI	RALES 1999	24.0	841	630	1471	386	0.26	0.29	0.24
ACEI	Hamroff 1999	6.0	17	13	8	1	0.13	0.70	0.00
ACEI	MERIT-HF 1999	12.0	2001	1691	1846	217	0.12	0.13	0.10
ACEI	Shettigar 1999	3.0	102	85	23	2	0.09	0.31	0.01
ACEI	CIBIS II 1999	46.0	1320	1320	5063	228	0.05	0.05	0.04
ACEI	Goldstein 1999	6.0	19	16	9	0	0.00	0.00	0.00
ACEI	MIC 2000	6.0	26	19	11	2	0.18	0.64	0.02
ACEI	Sturm 2000	24.0	49	20	69	8	0.12	0.23	0.05
ACEI	ELITE II 2000	24.0	1574	1353	2927	250	0.09	0.10	0.08
ACEI	CELICARD 2000	12.0	66	39	53	4	0.08	0.20	0.02
ACEI	REPLACE 2001	3.0	75	75	19	2	0.11	0.39	0.01
ACEI	COPERNICUS 2001	21.0	1133	953	1825	190	0.10	0.12	0.09
ACEI	BEST 2001	42.0	1354	1351	4734	449	0.09	0.10	0.09
ACEI	Val-HeFT 2001	27.0	2499	2499	5623	484	0.09	0.09	0.08
ACEI	HEAVEN 2002	3.0	71	62	17	5	0.30	0.70	0.10
ACEI	de Milliano 2002	6.0	11	10	5	1	0.19	1.06	0.00
ACEI	Dubach 2002	12.0	15	15	15	0	0.00	0.00	0.00
ACEI	SYMFOXYDEX 2004	6.0	22	21	11	1	0.09	0.52	0.00
ACEI	CARMEN 2004	18.0	190	133	242	14	0.06	0.10	0.03
ACEI	Palazzuoli 2005b	12.0	27	24	26	2	0.08	0.28	0.01
ACEI	ENECA 2005	11.0	126	112	119	7	0.06	0.12	0.02
ACEI	Palazzuoli 2005	12.0	25	22	24	1	0.04	0.24	0.00
ACEI	CIBIS III 2008	6.0	505	456	240	32	0.13	0.19	0.09

More efficacious Less efficacious

C)

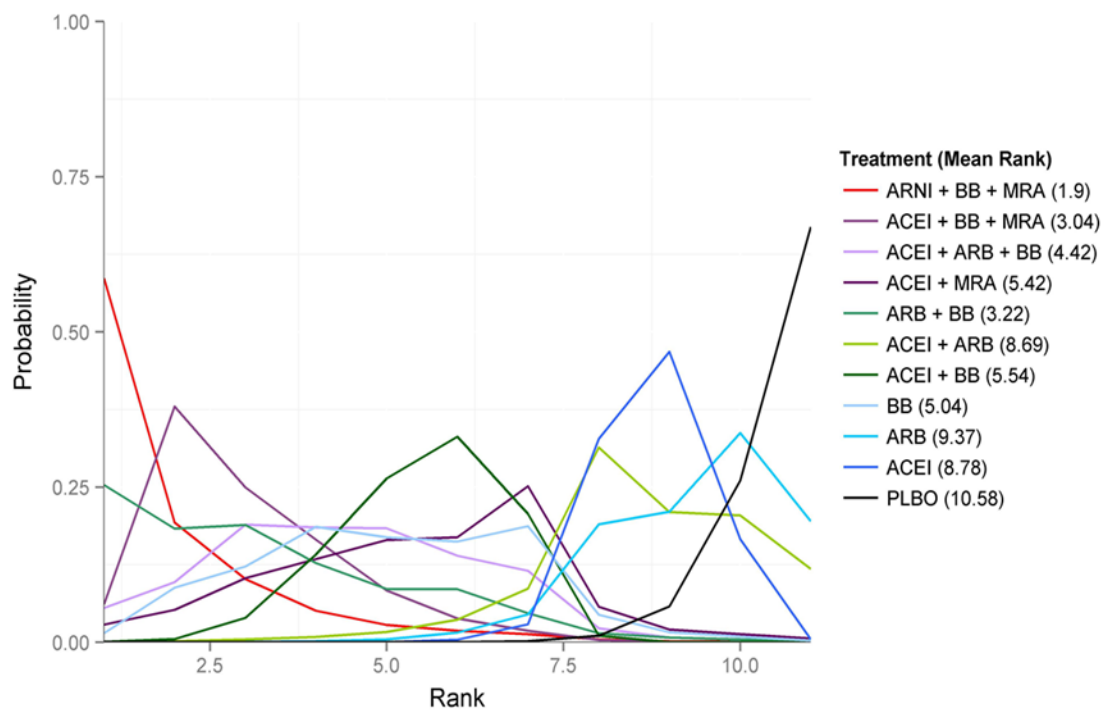
Death per patient year in other arms



More efficacious Less efficacious

Tx class	Trial	Follow-up (months)	# randomized	# completers	Person years at risk	Deaths	Rate (per patient year)	95% CrI low	95% CrI high
ARB	Dickstein 1995	2.0	56	56	9	2	0.21	0.77	0.02
ARB	Lang 1997	3.0	40	40	10	5	0.50	1.17	0.16
ARB	ELITE I 1997	11.0	352	287	293	17	0.06	0.09	0.03
ARB	STRETCH 1999	3.0	213	213	53	5	0.09	0.22	0.03
ARB	SPICE 2000	3.0	179	148	41	6	0.15	0.32	0.05
ARB	ELITE II 2000	24.0	1578	1453	3031	280	0.09	0.10	0.08
ARB	REPLACE 2001	3.0	77	77	19	1	0.05	0.29	0.00
ARB	HEAVEN 2002	3.0	70	65	17	1	0.06	0.33	0.00
ARB	Mitrovic 2003	3.0	44	44	11	1	0.09	0.51	0.00
ARB	RESOLVD 2003	6.0	126	122	57	12	0.21	0.37	0.11
ARB	CHARM-alt 2003	42.0	1013	1013	3546	265	0.07	0.08	0.07
BB	CARMEN 2004	18.0	191	134	244	14	0.06	0.10	0.03
BB	CIBIS III 2008	6.0	505	470	244	23	0.09	0.14	0.06
ACEI + ARB	Hamroff 1999	6.0	16	13	7	5	0.50	0.00	0.00
ACEI + ARB	Val-HeFT 2001	27.0	2511	2511	5650	495	0.09	0.10	0.08
ACEI + ARB	RESOLVD 2003	6.0	86	82	39	8	0.21	0.41	0.09
ACEI + BB	CIBIS I 1994	26.0	320	245	612	53	0.09	0.11	0.06
ACEI + BB	Krum 1995	3.5	33	29	9	3	0.33	0.97	0.07
ACEI + BB	Colucci 1996	12.0	232	232	232	2	0.01	0.03	0.00
ACEI + BB	PRECISE 1996	6.0	133	133	67	6	0.09	0.20	0.03
ACEI + BB	Packer 1996	6.0	696	696	348	22	0.06	0.10	0.04
ACEI + BB	MOCHA 1996	6.0	89	82	43	1	0.02	0.13	0.00
ACEI + BB	Cohn 1997	6.0	70	66	34	2	0.06	0.21	0.01
ACEI + BB	MERIT-HF 1999	12.0	1990	1711	1851	145	0.08	0.09	0.07
ACEI + BB	Goldstein 1999	6.0	42	33	19	1	0.05	0.30	0.00
ACEI + BB	CIBIS II 1999	46.0	1327	1327	5090	156	0.03	0.04	0.03
ACEI + BB	MIC 2000	6.0	26	22	12	1	0.08	0.46	0.00
ACEI + BB	Sturm 2000	24.0	51	28	79	5	0.06	0.15	0.02
ACEI + BB	CELICARD 2000	12.0	66	48	57	2	0.04	0.13	0.00
ACEI + BB	BEST 2001	42.0	1354	1349	4730	411	0.09	0.10	0.08
ACEI + BB	COPERNICUS 2001	21.0	1156	1010	1896	130	0.07	0.08	0.06
ACEI + BB	Cicoira 2002	12.0	52	46	49	4	0.08	0.21	0.02
ACEI + BB	de Millano 2002	6.0	43	39	21	4	0.20	0.50	0.05
ACEI + BB	Dubach 2002	12.0	13	13	13	1	0.08	0.43	0.00
ACEI + BB	CHARM-added 2003	42.0	1272	1272	4452	412	0.09	0.10	0.08
ACEI + BB	SYMPOXYDEX 2004	6.0	28	26	14	1	0.07	0.41	0.00
ACEI + BB	CARMEN 2004	18.0	191	132	242	14	0.06	0.10	0.03
ACEI + BB	ENECA 2005	12.0	134	124	129	7	0.05	0.11	0.02
ACEI + BB	Palazzuoli 2005b	12.0	32	30	31	1	0.03	0.18	0.00
ACEI + BB	Palazzuoli 2005	12.0	33	31	32	1	0.03	0.17	0.00
ACEI + BB	AREA-IN CHF 2009	12.0	236	236	236	12	0.05	0.09	0.03
ACEI + BB	EMPHASIS-HF 2011	36.0	1373	1145	3777	213	0.06	0.06	0.05
ACEI + BB	Vlzzardi 2014	44.0	65	65	238	8	0.03	0.07	0.01
ARB + BB	RESOLVD 2003	6.0	125	108	53	2	0.04	0.13	0.00
ACEI + MRA	RALES 1999	24.0	822	600	1422	284	0.20	0.22	0.18
ACEI + ARB + BB	RESOLVD 2003	6.0	89	77	38	6	0.16	0.34	0.06
ACEI + ARB + BB	CHARM-added 2003	42.0	1276	1276	4466	377	0.08	0.09	0.08
ACEI + BB + MRA	Cicoira 2002	12.0	54	47	51	3	0.06	0.17	0.01
ACEI + BB + MRA	AREA-IN CHF 2009	12.0	231	231	231	6	0.03	0.06	0.01
ACEI + BB + MRA	EMPHASIS-HF 2011	36.0	1364	1142	3759	171	0.05	0.05	0.04
ACEI + BB + MRA	Vlzzardi 2014	44.0	65	65	238	8	0.03	0.07	0.01
ACEI + BB + MRA	PARADIGM-HF 2014	27.0	4212	4203	9467	835	0.09	0.09	0.08
ARNI + BB + MRA	PARADIGM-HF 2014	27.0	4187	4176	9408	711	0.08	0.08	0.07

Supplementary Figure 3: Results of random effect network meta-analysis probability rank for all-cause mortality



Supplemental References

(List of Studies Included in the Systematic Literature Review and Network Meta-Analysis)

1. Widimsky J, Kremer HJ, Jerie P and Uhlir O. Czech and Slovak spirapril intervention study (CASSIS). A randomized, placebo and active-controlled, double-blind multicentre trial in patients with congestive heart failure. *Eur. J. Clin. Pharmacol.* 1995;49:95-102.
2. Swedberg K. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N. Engl. J. Med.* 1987;316:1429-35.
3. Erhardt L, MacLean A, Ilgenfritz J, Gelperin K and Blumenthal M. Fosinopril attenuates clinical deterioration and improves exercise tolerance in patients with heart failure. Fosinopril Efficacy/Safety Trial (FEST) Study Group. *Eur. Heart J.* 1995;16:1892-9.
4. Kleber FX and Niemoller L. Long-term survival in the Munich Mild Heart Failure Trial (MHFT). *Am. J. Cardiol.* 1993;71:1237-9.
5. Yusuf S. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. The SOLVD Investigators. *N. Engl. J. Med.* 1992;327:685-91.
6. S. Y. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. The SOLVD Investigators. *N. Engl. J. Med.* 1991;325:293-302.
7. Beller B, Bulle T, Bourge RC, Colfer H, Fowles RE, Giles TD, Grover J, Whipple JP, Fisher MB, Jessup M and et al. Lisinopril versus placebo in the treatment of heart failure: the Lisinopril Heart Failure Study Group. *J. Clin. Pharmacol.* 1995;35:673-80.
8. Brown EJ, Jr., Chew PH, MacLean A, Gelperin K, Ilgenfritz JP and Blumenthal M. Effects of fosinopril on exercise tolerance and clinical deterioration in patients with chronic congestive heart failure not taking digitalis. Fosinopril Heart Failure Study Group. *Am. J. Cardiol.* 1995;75:596-600.
9. Chalmers JP, West MJ, Cyran J, De La Torre D, Englert M, Kramar M, Lewis GR, Maranhao MF, Myburgh DP, Schuster P and et al. Placebo-controlled study of lisinopril in congestive heart failure: a multicentre study. *J. Cardiovasc. Pharmacol.* 1987;9 Suppl 3:S89-97.

10. Colfer HT, Ribner HS, Gradman A, Hughes CV, Kapoor A and Laidlaw JC. Effects of once-daily benazepril therapy on exercise tolerance and manifestations of chronic congestive heart failure. The Benazepril Heart Failure Study Group. *Am. J. Cardiol.* 1992;70:354-8.
11. Anonymous. Comparative effects of therapy with captopril and digoxin in patients with mild to moderate heart failure. The Captopril-Digoxin Multicenter Research Group. *JAMA.* 1988;259:539-44.
12. Lewis GR. Comparison of lisinopril versus placebo for congestive heart failure. *Am. J. Cardiol.* 1989;63:12D-16D.
13. Shettigar U, Hare T, Gelperin K, Ilgenfritz JP, Deitchman D and Blumenthal M. Effects of fosinopril on exercise tolerance, symptoms, and clinical outcomes in patients with decompensated heart failure. *Congest Heart Fail.* 1999;5:27-34.
14. van Veldhuisen DJ, Genth-Zotz S, Brouwer J, Boomsma F, Netzer T, Man In TVAJ, Pinto YM, Lie KI and Crijns HJ. High- versus low-dose ACE inhibition in chronic heart failure: a double-blind, placebo-controlled study of imidapril. *J. Am. Coll. Cardiol.* 1998;32:1811-8.
15. Granger CB, Ertl G, Kuch J, Maggioni AP, McMurray J, Rouleau JL, Stevenson LW, Swedberg K, Young J, Yusuf S, Califf RM, Bart BA, Held P, Michelson EL, Sellers MA, Ohlin G, Sparapani R and Pfeffer MA. Randomized trial of candesartan cilexetil in the treatment of patients with congestive heart failure and a history of intolerance to angiotensin-converting enzyme inhibitors. *Am. Heart J.* 2000;139:609-17.
16. Riegger GA, Bouzo H, Petr P, Munz J, Spacek R, Pethig H, von Behren V, George M and Arens H. Improvement in exercise tolerance and symptoms of congestive heart failure during treatment with candesartan cilexetil. Symptom, Tolerability, Response to Exercise Trial of Candesartan Cilexetil in Heart Failure (STRETCH) Investigators. *Circulation.* 1999;100:2224-30.
17. Mitrovic V, Willenbrock R, Miric M, Seferovic P, Spinar J, Dabrowski M, Kiowski W, Marks DS, Alegria E, Dukat A, Lenz K and Arens HA. Acute and 3-month treatment effects of candesartan cilexetil on hemodynamics, neurohormones, and clinical symptoms in patients with congestive heart failure. *Am. Heart J.* 2003;145:E14.
18. Pitt B, Segal R, Martinez FA, Meurers G, Cowley AJ, Thomas I, Deedwania PC, Ney DE, Snavely DB and Chang PI. Randomised trial of losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the Elderly Study, ELITE). *Lancet.* 1997;349:747-52.
19. Pitt B, Poole-Wilson PA, Segal R, Martinez FA, Dickstein K, Camm AJ, Konstam MA, Riegger G, Klingler GH, Neaton J, Sharma D and Thiyagarajan B. Effect of losartan compared with captopril on

mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. *Lancet*. 2000;355:1582-7.

20. Dunselman PH and Replacement of Angiotensin Converting Enzyme Inhibition I. Effects of the replacement of the angiotensin converting enzyme inhibitor enalapril by the angiotensin II receptor blocker telmisartan in patients with congestive heart failure. The replacement of angiotensin converting enzyme inhibition (REPLACE) investigators. *Int. J. Cardiol*. 2001;77:131-8; discussion 139-40.

21. Dickstein K, Chang P, Willenheimer R, Haunso S, Remes J, Hall C and Kjekshus J. Comparison of the effects of losartan and enalapril on clinical status and exercise performance in patients with moderate or severe chronic heart failure. *J. Am. Coll. Cardiol*. 1995;26:438-45.

22. Lang RM, Elkayam U, Yellen LG, Krauss D, McKelvie RS, Vaughan DE, Ney DE, Makris L and Chang PI. Comparative effects of losartan and enalapril on exercise capacity and clinical status in patients with heart failure. The Losartan Pilot Exercise Study Investigators. *J. Am. Coll. Cardiol*. 1997;30:983-91.

23. Dobre D, van Veldhuisen DJ, Goulder MA, Krum H and Willenheimer R. Clinical effects of initial 6 months monotherapy with bisoprolol versus enalapril in the treatment of patients with mild to moderate chronic heart failure. Data from the CIBIS III Trial. *Cardiovasc. Drug Ther*. 2008;22:399-405.

24. Komajda M, Lutiger B, Madeira H, Thygesen K, Bobbio M, Hildebrandt P, Jaarsma W, Riegger G, Ryden L, Scherhag A, Soler-Soler J, Remme WJ, investigators C and co o. Tolerability of carvedilol and ACE-Inhibition in mild heart failure. Results of CARMEN (Carvedilol ACE-Inhibitor Remodelling Mild CHF EvaluationN). *Eur. J. Heart Fail*. 2004;6:467-75.

25. Granger CB, McMurray JJ, Yusuf S, Held P, Michelson EL, Olofsson B, Ostergren J, Pfeffer MA, Swedberg K, Investigators C and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors: the CHARM-Alternative trial. *Lancet*. 2003;362:772-6.

26. Willenheimer R, Helmers C, Pantev E, Rydberg E, Lofdahl P, Gordon A and Heart Failure Valsartan Exercise Capacity Evaluation Study G. Safety and efficacy of valsartan versus enalapril in heart failure patients. *Int. J. Cardiol*. 2002;85:261-70.

27. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J and Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N. Engl. J. Med*. 1999;341:709-17.

28. Cohn JN, Tognoni G and Valsartan Heart Failure Trial I. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N. Engl. J. Med*. 2001;345:1667-75.

29. Hamroff G, Katz SD, Mancini D, Blaufarb I, Bijou R, Patel R, Jondeau G, Olivari MT, Thomas S and Le Jemtel TH. Addition of angiotensin II receptor blockade to maximal angiotensin-converting enzyme inhibition improves exercise capacity in patients with severe congestive heart failure. *Circulation*. 1999;99:990-2.
30. Eichhorn EJ. A trial of the beta-blocker bucindolol in patients with advanced chronic heart failure. *N. Engl. J. Med.* 2001;344:1659-67.
31. Lachat P. A randomized trial of beta-blockade in heart failure. The Cardiac Insufficiency Bisoprolol Study (CIBIS). CIBIS Investigators and Committees. *Circulation*. 1994;90:1765-73.
32. Lechat P. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. *Lancet*. 1999;353:9-13.
33. Witchitz S, Cohen-Solal A, Dartois N, Weisslinger N, Juste K and Darmon JY. Treatment of heart failure with celiprolol, a cardioselective beta blocker with beta-2 agonist vasodilatory properties. The CELICARD Group. *Am. J. Cardiol.* 2000;85:1467-71.
34. Krum H, Roecker EB, Mohacsi P, Rouleau JL, Tendera M, Coats AJ, Katus HA, Fowler MB, Packer M and Carvedilol Prospective Randomized Cumulative Survival Study G. Effects of initiating carvedilol in patients with severe chronic heart failure: results from the COPERNICUS Study. *JAMA*. 2003;289:712-8.
35. Edes I, Gasior Z and Wita K. Effects of nebivolol on left ventricular function in elderly patients with chronic heart failure: results of the ENECA study. *Eur. J. Heart Fail.* 2005;7:631-9.
36. Hjalmarson A. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). *Lancet*. 1999;353:2001-7.
37. Goldstein S, Kennedy HL, Hall C, Anderson JL, Gheorghide M, Gottlieb S, Jessup M, Karlsberg RP, Friday G and Haskell L. Metoprolol CR/XL in patients with heart failure: A pilot study examining the tolerability, safety, and effect on left ventricular ejection fraction. *Am. Heart J.* 1999;138:1158-65.
38. Genth-Zotz S, Zotz RJ, Sigmund M, Hanrath P, Hartmann D, Bohm M, Waagstein F, Treese N, Meyer J and Darius H. MIC trial: metoprolol in patients with mild to moderate heart failure: effects on ventricular function and cardiopulmonary exercise testing. *Eur. J. Heart Fail.* 2000;2:175-81.
39. Bristow MR, Gilbert EM, Abraham WT, Adams KF, Fowler MB, Hershberger RE, Kubo SH, Narahara KA, Ingersoll H, Krueger S, Young S and Shusterman N. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. MOCHA Investigators. *Circulation*. 1996;94:2807-16.

40. Packer M, Colucci WS, Sackner-Bernstein JD, Liang CS, Goldscher DA, Freeman I, Kukin ML, Kinhal V, Udelson JE, Klapholz M, Gottlieb SS, Pearle D, Cody RJ, Gregory JJ, Kantrowitz NE, LeJemtel TH, Young ST, Lukas MA and Shusterman NH. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. *Circulation*. 1996;94:2793-9.
41. Cohen Solal A, Jondeau G, Beauvais F and Berdeaux A. Beneficial effects of carvedilol on angiotensin-converting enzyme activity and renin plasma levels in patients with chronic heart failure. *Eur. J. Heart Fail*. 2004;6:463-6.
42. Cohn JN, Fowler MB, Bristow MR, Colucci WS, Gilbert EM, Kinhal V, Krueger SK, Lejemtel T, Narahara KA, Packer M, Young ST, Holcslaw TL and Lukas MA. Safety and efficacy of carvedilol in severe heart failure. The U.S. Carvedilol Heart Failure Study Group. *J. Card. Fail*. 1997;3:173-9.
43. Colucci WS, Packer M, Bristow MR, Gilbert EM, Cohn JN, Fowler MB, Krueger SK, Hershberger R, Uretsky BF, Bowers JA, Sackner-Bernstein JD, Young ST, Holcslaw TL and Lukas MA. Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. US Carvedilol Heart Failure Study Group. *Circulation*. 1996;94:2800-6.
44. de Milliano PA, de Groot AC, Tijssen JG, van Eck-Smit BL, Van Zwieten PA and Lie KI. Beneficial effects of metoprolol on myocardial sympathetic function: Evidence from a randomized, placebo-controlled study in patients with congestive heart failure. *Am. Heart J*. 2002;144:E3.
45. Dubach P, Myers J, Bonetti P, Schertler T, Froelicher V, Wagner D, Scheidegger M, Stuber M, Luchinger R, Schwitter J and Hess O. Effects of bisoprolol fumarate on left ventricular size, function, and exercise capacity in patients with heart failure: analysis with magnetic resonance myocardial tagging. *Am. Heart J*. 2002;143:676-83.
46. Krum H, Sackner-Bernstein JD, Goldsmith RL, Kukin ML, Schwartz B, Penn J, Medina N, Yushak M, Horn E, Katz SD and et al. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. *Circulation*. 1995;92:1499-506.
47. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM and Shusterman NH. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. *N. Engl. J. Med*. 1996;334:1349-55.
48. Palazzuoli A, Quatrini I, Vecchiato L, Calabria P, Gennari L, Martini G and Nuti R. Left ventricular diastolic function improvement by carvedilol therapy in advanced heart failure. *J. Cardiovasc. Pharmacol*. 2005;45:563-8.

49. Palazzuoli A, Quatrini I, Vecchiato L, Scali C, De Paola V, Iovine F, Martini G and Nuti R. Effects of carvedilol on left ventricular diastolic function and chamber volumes in advanced heart failure. *Minerva Cardioangiol.* 2005;53:321-8.
50. Sturm B, Pacher R, Strametz-Juranek J, Berger R, Frey B and Stanek B. Effect of beta 1 blockade with atenolol on progression of heart failure in patients pretreated with high-dose enalapril. *Eur. J. Heart Fail.* 2000;2:407-12.
51. McKelvie RS, Rouleau JL, White M, Afzal R, Young JB, Maggioni AP, Held P and Yusuf S. Comparative impact of enalapril, candesartan or metoprolol alone or in combination on ventricular remodelling in patients with congestive heart failure. *Eur. Heart J.* 2003;24:1727-34.
52. White M. Effects of metoprolol CR in patients with ischemic and dilated cardiomyopathy : the randomized evaluation of strategies for left ventricular dysfunction pilot study. *Circulation.* 2000;101:378-84.
53. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA, Investigators C and Committees. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet.* 2003;362:767-71.
54. Boccanelli A, Mureddu GF, Cacciatore G, Clemenza F, Di Lenarda A, Gavazzi A, Porcu M, Latini R, Lucci D, Maggioni AP, Masson S, Vanasia M, de Simone G and Investigators AI-C. Anti-remodelling effect of canrenone in patients with mild chronic heart failure (AREA IN-CHF study): final results. *Eur. J. Heart Fail.* 2009;11:68-76.
55. Zannad F, McMurray JJ, Krum H, van Veldhuisen DJ, Swedberg K, Shi H, Vincent J, Pocock SJ, Pitt B and Group E-HS. Eplerenone in patients with systolic heart failure and mild symptoms. *N. Engl. J. Med.* 2011;364:11-21.
56. Ciccoira M, Zanolla L, Rossi A, Golia G, Franceschini L, Brighetti G, Marino P and Zardini P. Long-term, dose-dependent effects of spironolactone on left ventricular function and exercise tolerance in patients with chronic heart failure. *J. Am. Coll. Cardiol.* 2002;40:304-10.
57. Vizzardi E, Nodari S, Caretta G, D'Aloia A, Pezzali N, Faden G, Lombardi C, Raddino R, Metra M and Dei Cas L. Effects of spironolactone on long-term mortality and morbidity in patients with heart failure and mild or no symptoms. *Am. J. Med. Sci.* 2014;347:271-6.

58. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR, Investigators P-H and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N. Engl. J. Med.* 2014;371:993-1004.