Heart Failure Evidence Caveats

Just talking about medications for heart failure with reduced ejection fraction/systolic heart failure

Many of the trials are 20-30 years old

Inconsistent heart failure criteria used

Typically placebo controlled BUT always additive trials

Overall mortality and HF hospitalizations - key consistent outcomes measured

QOL rarely captured

Harms were poorly captured

TABLE 4 Evidence-based drugs: start and target doses as shown in large clinical trials

Drug	Starting dose	Titration	Target dose
ACEI			
Captopril	12.5 mg TID	Titrate every 2-4 weeks	25-50 mg TID
Enalapril	1.25-2.5 mg BID		10 mg BID
Lisinopril	2.5-5 mg daily		20-35 mg daily
Perindopril	2-4 mg daily		4-8 mg daily
Ramipril	1.25-2.5 mg BID		5 mg BID
Trandolapril	1-2 mg daily		4 mg daily
ARB			
Candesartan	4-8 mg daily	Titrate every 2-4 weeks	32 mg daily
Valsartan	40 mg BID		80 mg BID
Beta-blockers			
Carvedilol	3.125 mg BID	Titrate more slowly every 4 weeks	25 mg BID 50 mg BID if >85 kg
Bisoprolol	1.25 mg daily		10 mg daily
Metoprolol*	6.25-12.5 mg BID		100 mg BID
MRA			
Spironolactone	12.5 mg daily	Titrate every 2-4 weeks	50 mg daily
Eplerenone	12.5-25 mg daily		50 mg daily
ARNI			
Sacubitril/valsartan	50-100 mg BID	Titrate every 3-6 weeks	200 mg BID
I_f inhibitor			
Ivabradine	2.5-5 mg BID	Titrate every 2 weeks	Target to heart rate 50-60 bpm Maximum dose: 7.5 mg BID
Vasodilators			
Isosorbide dinitrate	20 mg TID	Titrate every 2-4 weeks	40 mg TID Equivalent dose: NTG patch ≈ 0.8-1.0 mg/h Isosorbide-5-mononitrate ≈ 60 mg daily
Hydralazine	37.5 mg TID		75-100 mg TID-QID
Loop diuretics			
Furosemide	20-40 mg daily-BID	Titrate to euvolemia	200 mg/day (caution with >120 mg)
Bumetanide	0.5-1 mg daily-BID		10 mg/day
Ethacrynic acid	25-50 mg daily- BID		400 mg/day (200 mg BID)
Thiazide diuretics			
Metolazone	2.5 mg daily	Titrate to euvolemia	20 mg/day

22 different medications

Mortality numbers with “no treatment”

Seattle Heart Failure Model

65 y/o	1 year	2 year	5 year
Class 1	~5%	~15%	~33%
Class 2-3	~15%	~25%	~50%
Class 4	~25%	~50%	~80%

Ball park numbers from clinical trials

2-3 years - CLASS 2/3

mortality ~15-25%

hospital admission for HF ~15-20%

Mortality/
Hospitalizations
for heart failure

−

Activity
Salt
Diuretics
Digoxin
Nitrates
ACEI
ARBS
Beta-blockers
MRAs (spironolactone/eplerenone)
ARNI (sacubitril/valsartan)
Ivadarabine
Gliflozins

−

Change in
Mortality/
Hospitalizations
for heart failure

Exercise-based rehabilitation for heart failure

33 trials - 4740 subjects

Evaluated aerobic and in some cases resistance training - ranged from 15 to 120 min, 1–7 sessions/week

compared with controls - all-cause mortality after 1-year 0.93 (0.69-1.27)

follow-up beyond 1 year - 0.88 (0.75-1.02)

heart failure-specific hospitalization 0.61 (0.46-0.80)

clinically important improvement? in the Minnesota Living with Heart Failure questionnaire (range 0-100) (mean difference seen was –5.8 points (–9.2 to –2.4)

Open Heart 2015;2:e000163. doi:10.1136/openhrt-2014- 000163

Very similar findings in
Cochrane Database Syst Rev. 2019 Jan 29;1:CD003331

Reduced salt intake for heart failure

9 trials - 479 subjects (none >100)

Cardiovascular-associated mortality, all-cause mortality, stroke and myocardial infarction – insufficient data

2 studies - NYHA functional class was not improved by salt restriction

2 studies - significant improvements in NYHA functional class

JAMA Intern Med. doi:10.1001/jamainternmed.2018.4673

Diuretics for heart failure (some withdrawal trials)

2-12 months - all before beta-blockers used

	Mortality (%)	HF worsening (%)
Placebo	12	15
Diuretics (primarily loop)	3	0

Cochrane CD003838

BUT “the only certainty is that such therapies can relieve the patient’s symptoms and reduce vascular congestion”

“there is not enough strong evidence to recommend torasemide and bumetanide over furosemide”

“there is no clear evidence that any single thiazide-like diuretic is superior to another” for diuretic resistance

Eur Cardiol 2015;10:42-7

Digoxin

3800 patients NYHA 2/3 - 3 years

	Digoxin (%)	Placebo (%)
HF hospitalizations	26.8	34.7
Mortality	34.8	35.1

NEJM 1997;336:525-33

Nitrates/hydralazine

1050 black patients NYHA 3 - 10 months

	ISDN/ hydralazine (%)	Placebo (%)
HF hospitalizations	16.4	24.4
Mortality	6.2	10.2
Dizziness	29.3	12.2
Headache	47.5	19.2

NEJM 2004;351:2049-57

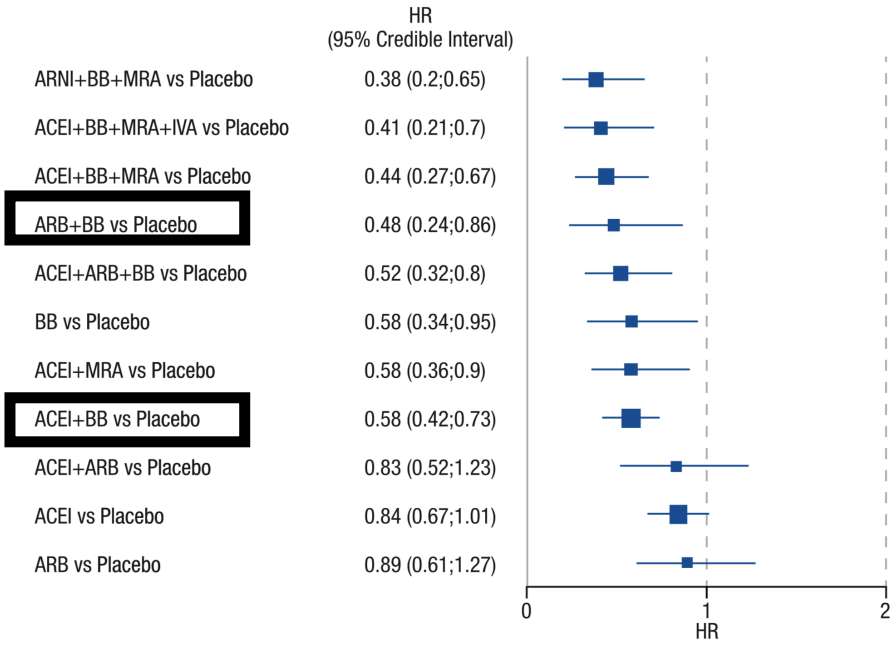
Meta-analyses of medications for heart failure - versus placebo

REMEMBER BASELINE - mortality ~15-25% and hospital admission for HF ~15-20%

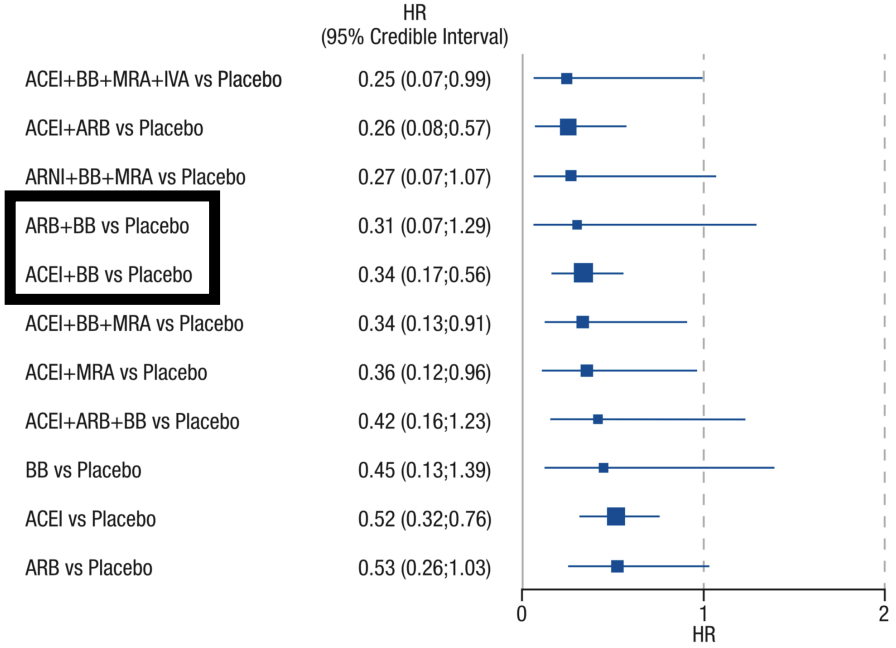
	Mortality	Hospitalization for HF	
Betablockers 1 year	0.65 (0.53-0.80) ~5% ARR	0.64 (0.53-0.79) ~6% ARR	**Ann Intern Med 2001;134:550-60**
ACEI 3 years	0·80 (0·74-0·87) ~3.5% ARR	0·67 (0·61–0·74) ~5% ARR	**Lancet 2000;355:1575-81**
ARB 2-3 years	0.83 (0.69-1.00) ~3% ARR	0.64 (0.53-0.78) ~9% ARR	**Ann Intern Med 2004;141:693-704**
MRA (spironolactone/eplerenone) 15 months	0.81 (0.75-0.87) ~3.5% ARR	0.76 (0.64-0.90) ~6% ARR	**BMC Cardiovasc Disord 2016;16:246**
Exercise 1 year	~0.9	~0.6	**Open Heart 2015;2:e000163. doi: 10.1136/openhrt-2014- 000163**

Incremental benefit of drug therapies for chronic heart failure with reduced ejection fraction: a network meta-analysis

All cause mortality



Hospitalization for heart failure



European Journal of Heart Failure 2018;20:1315–22

Combined ACEI and ARBs

Admissions for heart failure - RR 0.81 (0.72-0.91)

Overall hospitalizations - RR 0.92 (0.82-1.05)
Mortality - RR 0.97 (0.92-1.03)

Fatal MI - RR 0.97 (0.76-1.22)
Non fatal Mis - RR 0.91 (0.78-1.07)

Worsening renal function RR 1.91 (1.40-2.6)
Symptomatic hypotension RR 1.57 (1.44-1.71)

Hyperkalemia RR 1.95 (0.85-4.48)

ACE vs ARB based on cough and cost

ONTARGET trial showed similar results

http://www.plosone.org/article/info:doi/10.1371/journal.pone.0009946

Other relevant trials

	Duration/ Subjects	Mortality	Hospitalization for heart failure	Adverse effects
Carvedilol vs metoprolol **COMET** Lancet 2003;362:7-13	58 months 1511 CLASS 2/3	0.83 (0.74-0.93) 40%(Met)→34%(Car)	Not reported	
Ivabradine SHIFT Lancet 2010;376:875–85	23 months 6558 CLASS 2/3	0.90 (0.80-1.02) 17%(PLACEBO)→16%	0.74 (0.66-0.83) 21%(PLACEBO)→16%	Symptomatic bradycardia 4% ARI
Sacubitril/valsartan (ARNI) vs ramipril (ACE) **PARADIGM-HF** NEJM 2014;371:993–1004	24 months 8442 CLASS 2/3	0.84 (0.76-0.93) 19.8%(ACE)→17%(ARNI)	0.79 (0.71-0.89) 15.6%(ACE)→12.8%(ARNI)	Symptomatic hypotension 5% ARI (ARNI)
Dapagliflozin DAPA-HF NEJM 2019;Sept 19	18 months 4744 40%diabetics CLASS 2/3	0.83 (0.71 to 0.97) 13.9%(PLACEBO)→11.6%	0.70 (0.59-0.83) 13.4%(PLACEBO)→9.7%	

Heart failure - if you can get to higher doses

(Absolute differences)

Mortality no difference

OUTCOME	ACEI ~ 2 years	ARB ~ 4 years	BB ~ 1.5 years
Hospitalization for heart failure	No difference	3% less	No difference
Heart failure worsening	5% less	3% less	No difference
Hypotension	3% more	2.5% more	No difference
Dizziness	5% more	Not reported	14% more
Hyperkalemia	2.5% more	3% more	Not reported
Increase SCr	2.5% more	6% more	Not reported
Cough	2.5% less	Not reported	Not reported

PLOS ONE Meta-analysis Feb 28th, 2019

Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial

51 patients - pilot trial - previous dilated cardiomyopathy ~70% idiopathic - now asymptomatic and EF had improved to >50% ~61% EF, 100% ACE/ARB, 88% BB, 15% loop, 47% MRA

randomly assigned to withdrawal or continue therapy

attempted to stop/taper HF medications

primary endpoint - relapse within 6 months = a reduction in LVEF of more than 10% and to less than 50%, an increase in LVEDV by more than 10% and to higher than the normal range, a two-fold rise in NT-pro-BNP concentration and to more than 400 ng/L, or clinical evidence of heart failure

44% relapse in withdrawal arm, 0% continue therapy - BUT ONLY 1 WAS SYMPTOMATIC

Lancet 2019; 393: 61–73

Effectiveness of serial B-type natriuretic peptide blood testing to guide up-titration of medication compared with symptom-guided up-titration

14 RCTs

hospital admission for HF - HR 0.81 (0.68-0.98)

mortality - HR 0.87 (0.75-1.01)

Quality of evidence ranged from low to very low

Systematic Reviews 2018;7:112

CLASS 2-3 heart failure

Mortality	MOST MEDICATIONS	Mortality
~25% over 2-3 years	**~20% ⬇**	**~20% over 2-3 years**
Hospitalizations for heart failure	MOST MEDICATIONS	Hospitalizations for heart failure
~15% over 2-3 years	**~30% ⬇**	**~10% over 2-3 years**

Final EBP medication thoughts

Most classes of medications ⬇ mortality **~15-20%** and HF hospitalizations **~25-35%**

Benefits are likely somewhat additive - but once you are on 2 agents (plus PRN diuretics) there is somewhat limited additional benefit from more medications - except maybe CLASS 4

Only spironolactone has been studied in CLASS 3/4

Over 3 years, ~90% of people get no benefit from any 1 medication - I believe any adverse effects are unacceptable

Start with “low” doses - start just one at a time? TITRATE BASED ON TOLERABILITY

More benefit from adding medications rather than increasing doses

QOL data is typically not available - poor quality? It’s all tricky, heart failure definitely ⬇QOL but unsure if medications improve QOL - but they do ⬇ hospitalizations and these medications all have the potential for causing adverse effects

Diuretics/spironolactone ~$5/month, ACEI/ARB/BB cost ~$10-15/month, ivabradine/eplerenone ~$75/month, sacubitril/valsartan ~$250 a month