Heart Failure Therapeutics
PHAR 451

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Things to think about…

1. Cardiac output = _____ x _____.

2. CHF is primarily an imbalance between _____ and _____.

Objectives

After the session, and upon personal reflection and study, students will be able to

1. identify drug related-causes of heart failure.
2. describe the role, dosing, and monitoring parameters (efficacy and toxicity) of the following drugs in the treatment of HF:
   - diuretics
   - ACE inhibitors
   - ARBs
   - β-Blockers
   - spironolactone / eplerenone
   - digoxin
3. given a case of a patient with heart failure, determine an appropriate drug treatment regimen including monitoring parameters (efficacy and toxicity).
4. given a case of a HF patient on a given drug regimen, modify the regimen to resolve actual and potential drug-related problems, and list monitoring parameters (efficacy and toxicity).

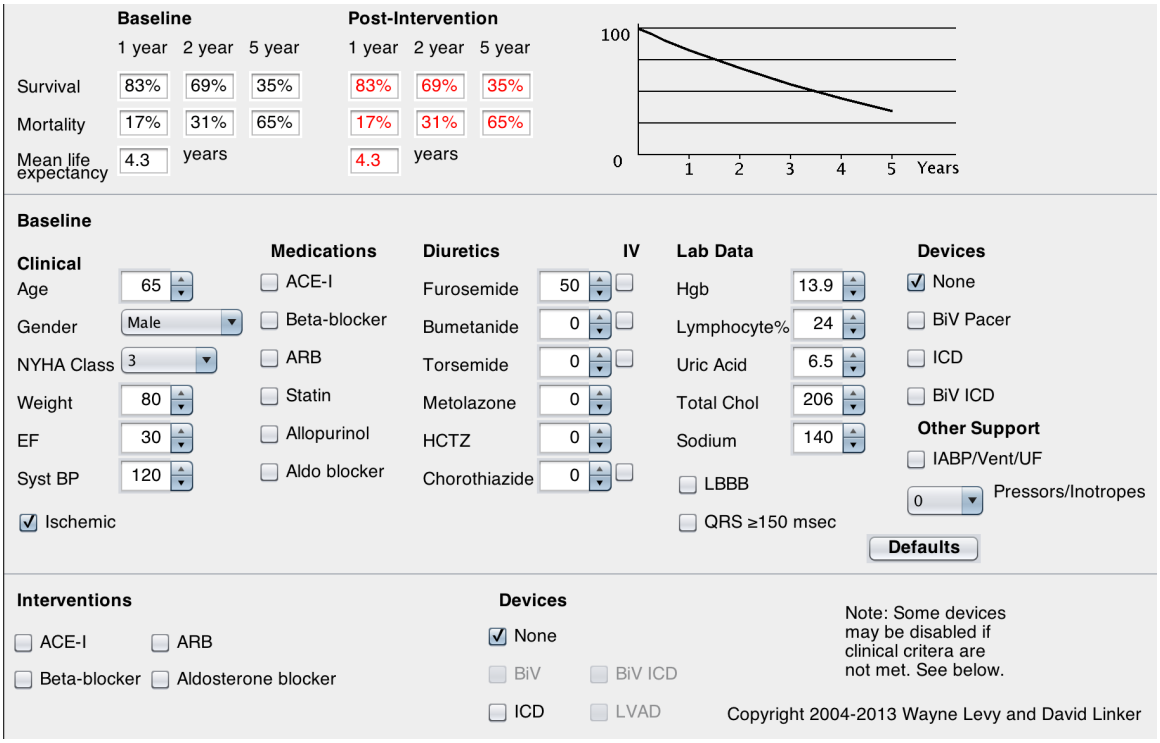
Case

- A 68y M patient with CHF presents you with a prescription for metoprolol 25mg PO bid
- PMH: CHF, AF
- On profile:
  - nitrospray ii PRN, nitropatch 0.4 mg/d, enalapril 10mg bid, ASA 325 mg/d, furosemide 40mg/d, warfarin 5mg daily, atorvastatin 40mg qHS
- What counselling would you provide this patient?

Functional Classification of HF:
The NYHA system

- **Class I:** Symptoms with more than ordinary activity
- **Class II:** Symptoms with ordinary activity
- **Class III:** Symptoms with minimal activity
  - Class IIIa: No Dyspnea at rest
  - Class IIIb: Recent Dyspnea at rest
- **Class IV:** Symptoms at rest

Risk Estimation



http://depts.washington.edu/shfm/
Circulation. 2006;113:1424-1433

MAGGIC

www.heartfailurerisk.org

European Heart Journal Advance Access published October 24, 2012

European Heart Journal
doi:10.1093/eurheartj/ehs337

CLINICAL RESEARCH

Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies

Stuart J. Pocock[1]*, Cono A. Ariti[1], John J.V. McMurray[2], Aldo Maggioni[3], Lars Køber[4], Iain B. Squire[5], Karl Swedberg[6], Joanna Dobson[1], Katrina K. Poppe[7], Gillian A. Whalley[7], and Rob N. Doughty[7], on behalf of the Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC)

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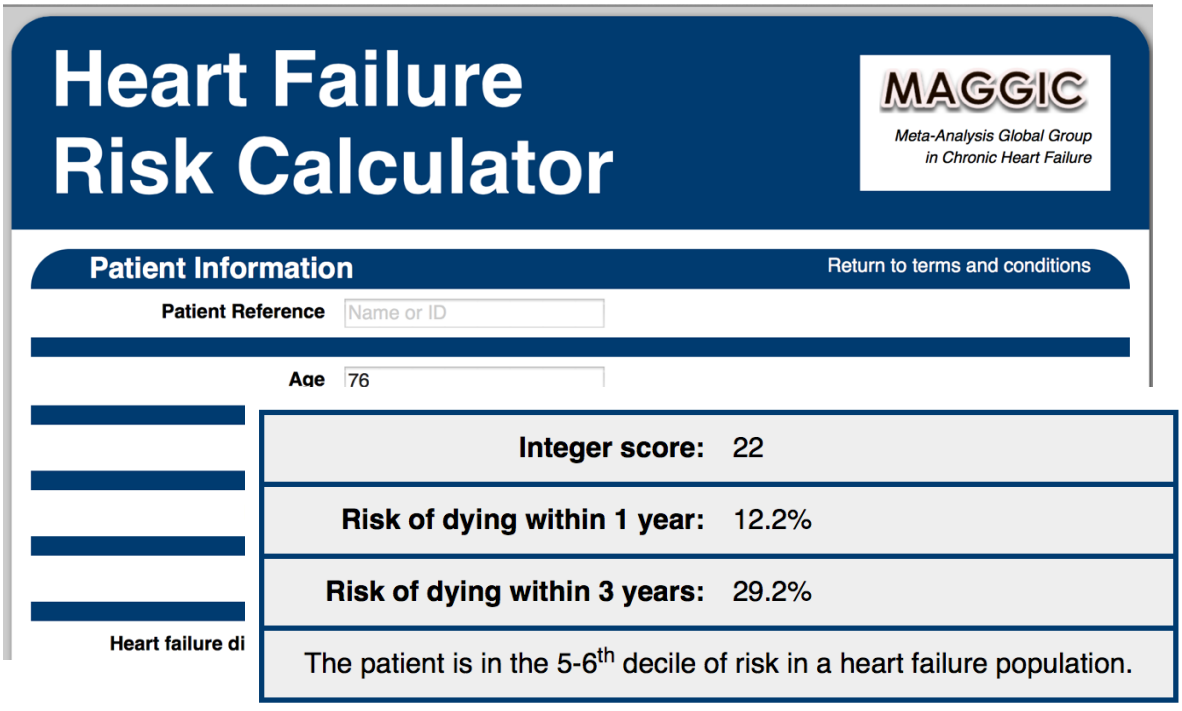


HF Precipitants

- Anemia
- Ischemia
- Arrhythmia (V or A)
- Infection
- Medication non-adherence
- **Drugs**: NSAIDs, glitazones, verapamil/ diltiazem, VW class I antiarrhythmics, B-Blockers, gliptins

NSAIDs and Heart Failure

- Elderly with CAD taking traditional NSAIDS: 26-fold ↑ risk of developing HF.
  Page et al. Arch Intern Med 2000;160:777-84.
- Patients with known HF: NSAIDS double risk of CHF-related hospitalization.
  Heerdink et al. Arch Intern Med 1998;158:1108-12.
- Celecoxib: ?safer than other NSAIDs?
  Mamdani et al. Lancet 2004;363:1751-6.
- Aspirin - WASH, WATCH

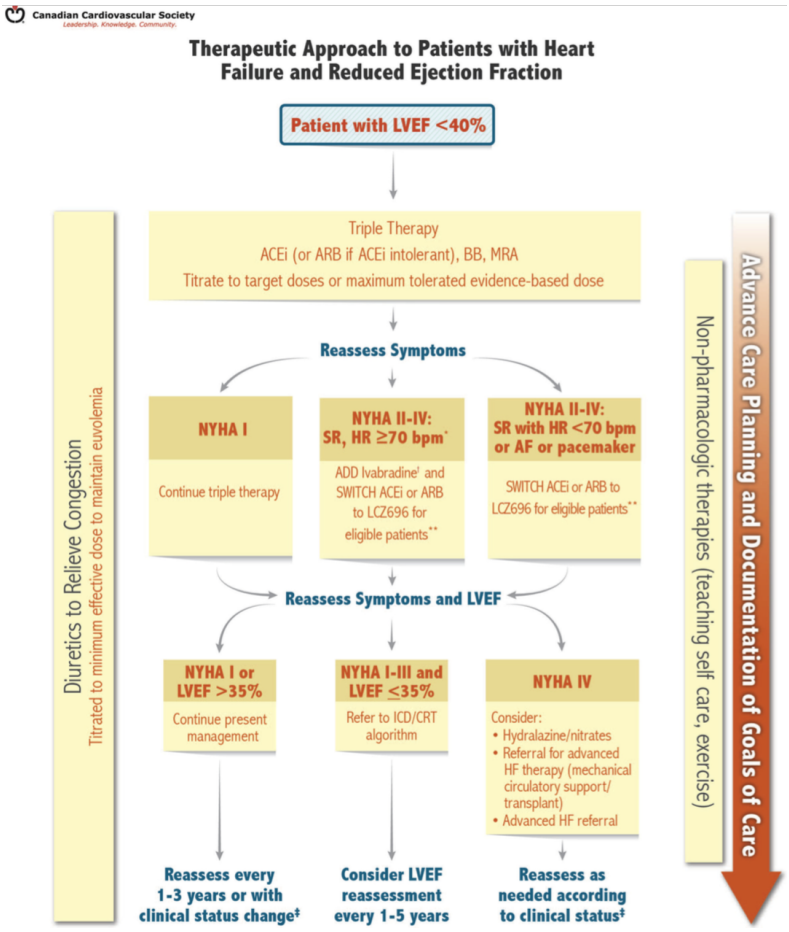
Diabetes Drugs & HF

- Rosiglitazone [Singh et al. JAMA 2007;298:1189-95]
  - heart failure OR 2.09 (1.52-2.88) vs. control
- Pioglitazone [Lincoff et al. JAMA 2007;298:1180-8]
  - serious heart failure HR 1.41 (1.14-1.76) vs. control
- Gliptins: saxagliptin, alogliptin: EXAMINE & SAVOR trials [2013: http://www.medscape.com/viewarticle/811705]

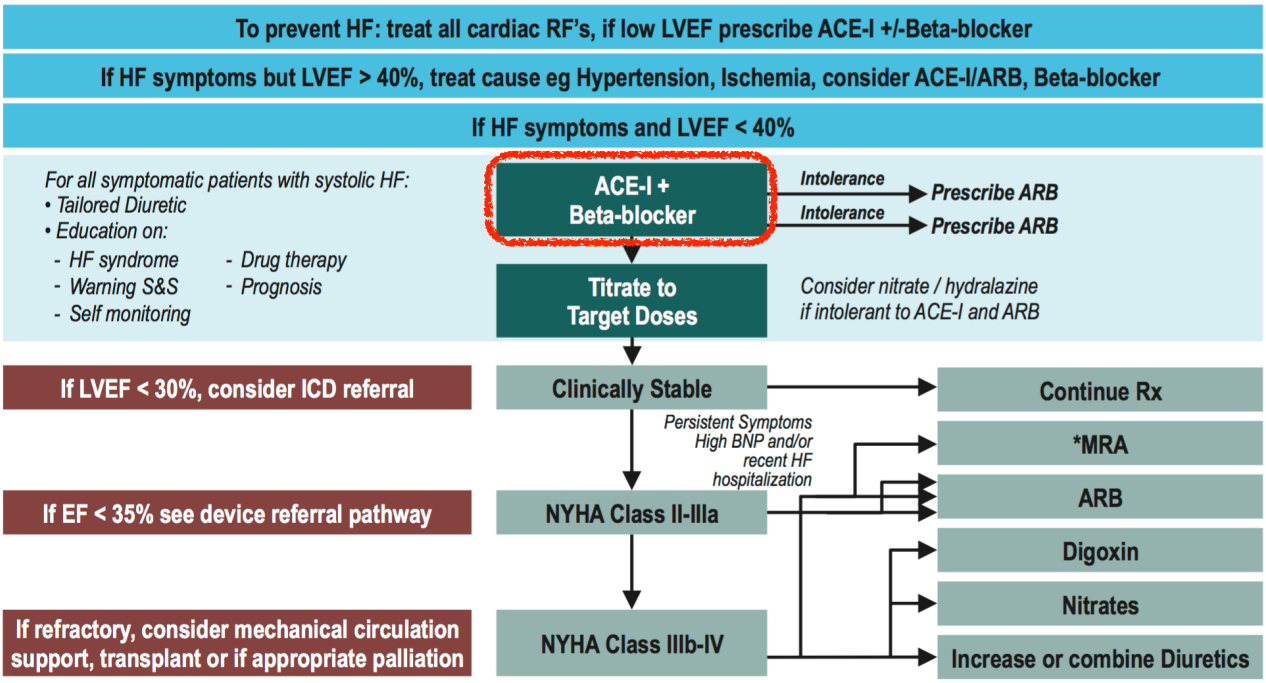
- Generally, avoid if known LV dysfunction
- If no known LV dysfunction, counsel re: edema

Goals of Therapy/Therapeutic Targets

- Prolong survival
- Reduce morbidity
  - Exercise tolerance
  - Hospitalization
  - Exacerbations
  - QOL



Howlett JG et al. The CCS Heart Failure Companion. Canadian Journal of Cardiology 2015;:1–15.



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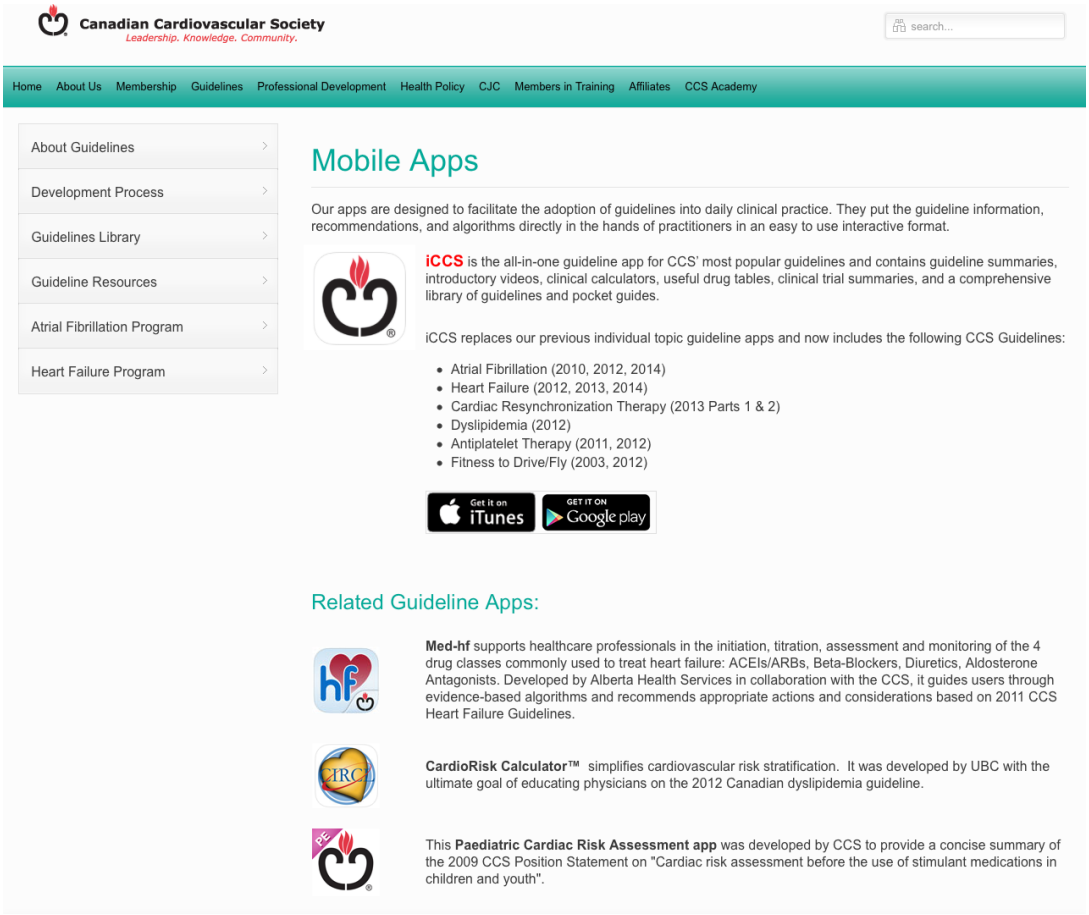


http://www.ccs.ca/index.php/en/resources/mobile-apps

Overall Effects of ACE-I

Per 3 years of treatment	RRR	NNT x 3y
Mortality	~20%	~18
HF admission	~25%	~28
Reinfarction (if prior MI)	~20%	~42

Flather MD, et al. Lancet 2000; 355:1575–81

ACE-I Flashcard

Benefits	Mortality, Class I-IV Morbidity (hospitalization)
Landmark Trials	CONSENSUS I & II, SAVE, SOLVD, TRACE, AIRE.
Dosing strategy	Start low, titrate to target doses over several weeks.
Risks/ monitoring	Hypotension, hyperkalemia, renal dysfunction, cough, angioedema.

Pre-ACE-I checklist

- ☑ Allergy/intolerance (ACE-I cough?)
- ☑ Hypovolemia
- ☑ Hypotension
- ☑ Renal dysfunction
- ☑ Hyperkalemia
- ☑ Bilateral renal artery stenosis or RAS in pt with solitary kidney
- ☑ Aortic stenosis

Evidence-based drugs and oral doses as shown in large clinical trials

Drug	Start dose	Target dose
ACE inhibitor		
Captopril	6.25 mg to 12.5 mg tid	25 mg to 50 mg tid
Enalapril	1.25 mg to 2.5 mg bid	10 mg bid
Ramipril	1.25 mg to 2.5 mg bid	5 mg bid*
Lisinopril	2.5 mg to 5 mg od	20 mg to 35 mg od
Trandolapril	1mg od	4mg od

CCS 2006 Guidelines. Can J Cardiol 2006;22:23-45
UPDATE: Canadian Journal of Cardiology 2013;29:168–81

ACE-I: Does dose matter?

Trials exploring ACE inhibitor dosing regimens in heart failure

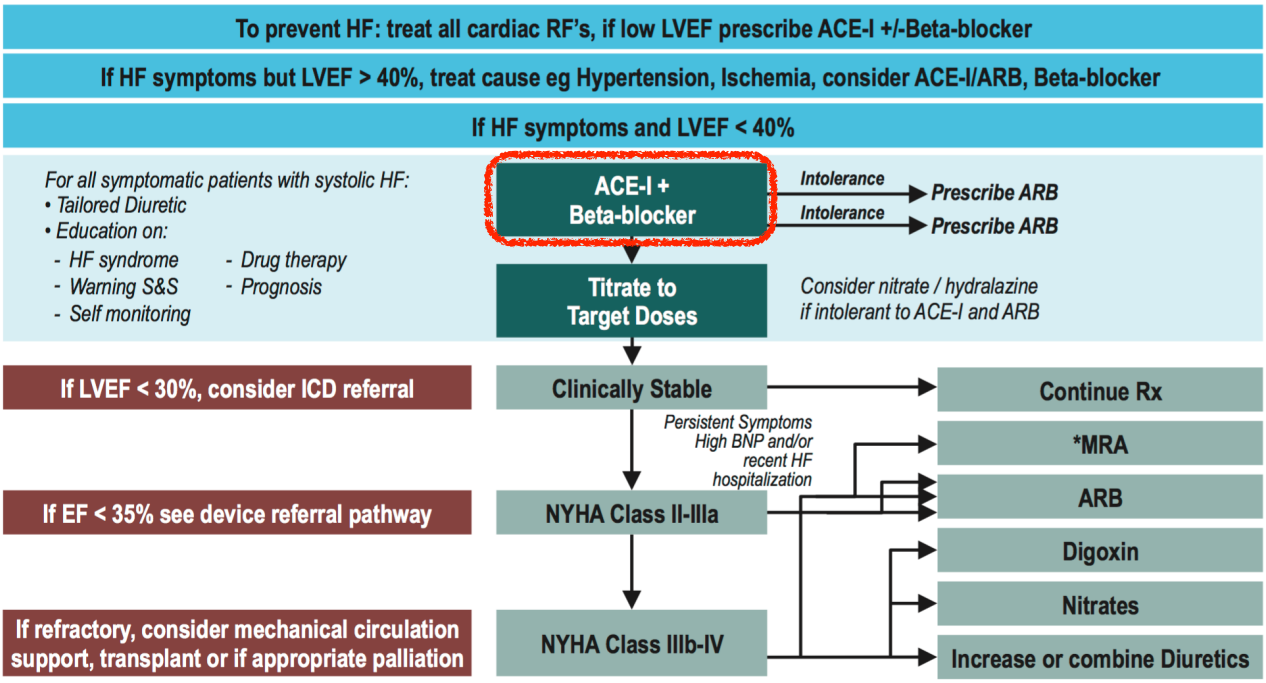
Trial	ACE-I regimens (daily doses)	
NETWORK (n=1532)	Enalapril 2.5 mg bid vs 5 mg bid vs 10 mg bid Follow-up: 5.5 months	hosp'n: NS death: NS
ATLAS (n=3164)	Lisinopril 2.5–5 mg od vs 32.5–35 mg od Follow-up:46 months	hosp'n: 24% RRR death: NS
CHIPS (n=298)	Captopril 25 mg bid vs 50 mg bid Follow-up: 2 years	hosp'n: NS death: NS
HEDS (n=248)	Enalapril 20 mg vs 60 mg Follow-up: 12 months	hosp'n: NS death: NS

Bottom line: PROBABLY for morbidity. Not for mortality.

Lon E. Curr Control Trials Cardiovasc Med 2001, 2:155–159 (adapted)

ACE-I and Renal Dysfunction

- Generally contraindicated when SCr>200 mcmol/L
- Can worsen renal function when:
  - Volume depleted / heavily diuresed
  - Low GFR to start with
  - Hyponatremia
  - Renal artery stenosis
  - What to do?
    - ↓ diuretic dose
    - ↑ Na intake slightly
    - ↓ ACE-I dose
- Can improve renal function when
  - CHF d/t ↑ SVR / ↑ BP



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Overall Effects of B-Blockers

Per 1 year of treatment	RRR	NNT x 1y
Mortality	~30%	~26
HF admission	~30%	~25

Brophy JM et al. Ann Intern Med. 2001;134:550-560

B-Blocker Flashcard

Benefits	Mortality, Class I-IV Morbidity (hospitalization)
Landmark Trials	MERIT-HF (metoprolol SR), CIBIS II (bisoprolol), MOCHA (carvedilol), US Carvedilol Study, COMET (metoprolol vs. carvedilol)
Dosing strategy	Start low, work toward target doses from trials over several weeks.
Risks/ monitoring	See checklist. Also: abrupt withdrawal, worsening HF symptoms during first 1-12 weeks.

Evidence-based drugs and oral doses as shown in large clinical trials

Drug	Start dose	Target dose
Beta-blocker		
Carvedilol	3.125 mg bid	25 mg bid
Bisoprolol	1.25 mg od	10 mg od
Metoprolol CR/XL†	12.5 mg to 25 mg od	200 mg od

CCS 2006 Guidelines. Can J Cardiol 2006;22:23-45

	STARTING DOSE	TITRATION	TARGET DOSE
Carvedilol (preferred)	3.125 mg PO BID	Increase by 50-100% q2-4 weeks	25 mg PO BID if <75 kg 50 mg PO BID if >75 kg
Bisoprolol	1.25 mg PO daily		10 mg PO daily
Metoprolol Tartrate or LCA	12.5 mg PO BID		100 mg PO BID*

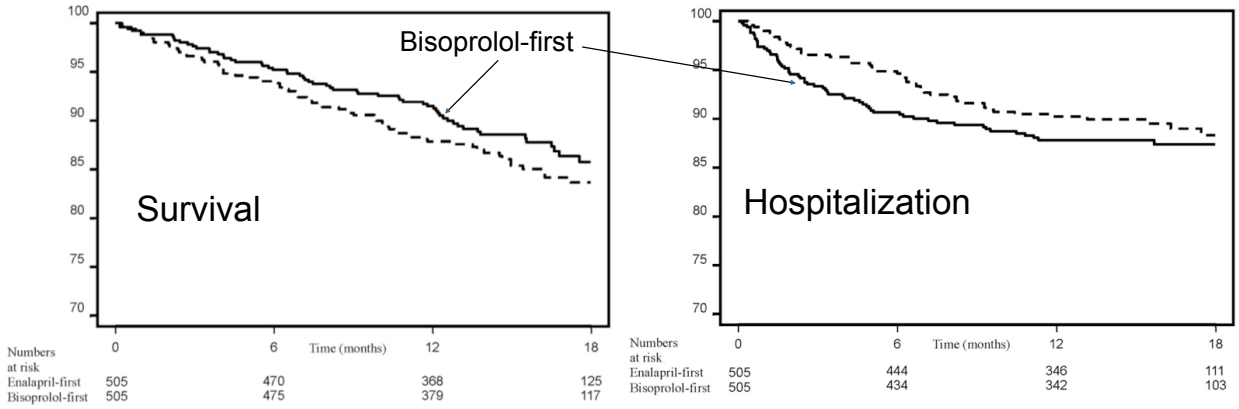
http://www.bcguidelines.ca

Pre-B-blocker checklist

- ☑ Allergy/intolerance
- ☑ Bradycardia
- ☑ Hypotension
- ☑ Heart block >1°
- ☑ Asthma / severe COPD
- ☑ Severe PVD
- ☑ Hypoglycemia risk

Start with B-Blocker or ACE-I?

- N=1010 ACEI and BBlkr naiive patients with EF<40%, Class II & III
- Randomized to bisoprolol 10 QD vs. enalapril 10 bid x 6 mos, then added the other x 6-24 mos.



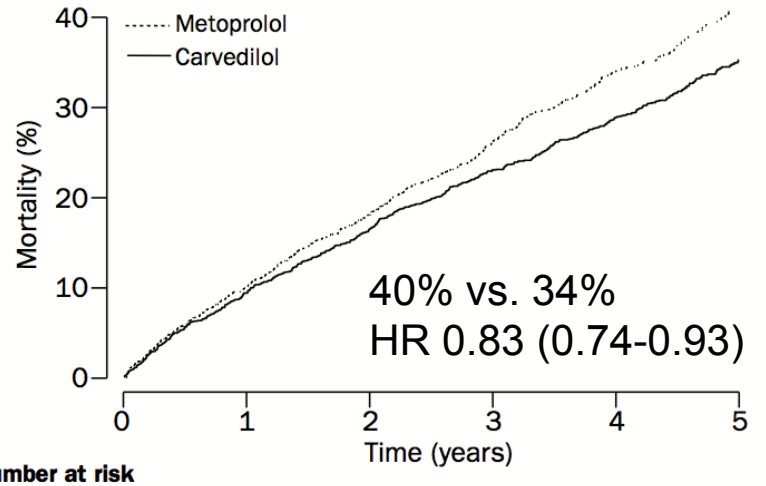
HR 0.88 (0.63-1.22)

HR 1.25 (0.87-1.81)

CIBIS III. Circulation 2005;112:2426-2435

Are all B-Blockers the same?

DB-RCT, N=1511
carvedilol 25 bid vs. metoprolol 50 bid



Number at risk

Carvedilol	1511	1366	1259	1155	1002	383
Metoprolol	1518	1359	1234	1105	933	352

Figure 2: **All-cause mortality**

COMET. Lancet 2003; 362: 7–13

"The benefits of β blockers in patients with heart failure with reduced ejection fraction seem to be mainly due to a class effect, as no statistical evidence from current trials supports the superiority of any single agent over the others."

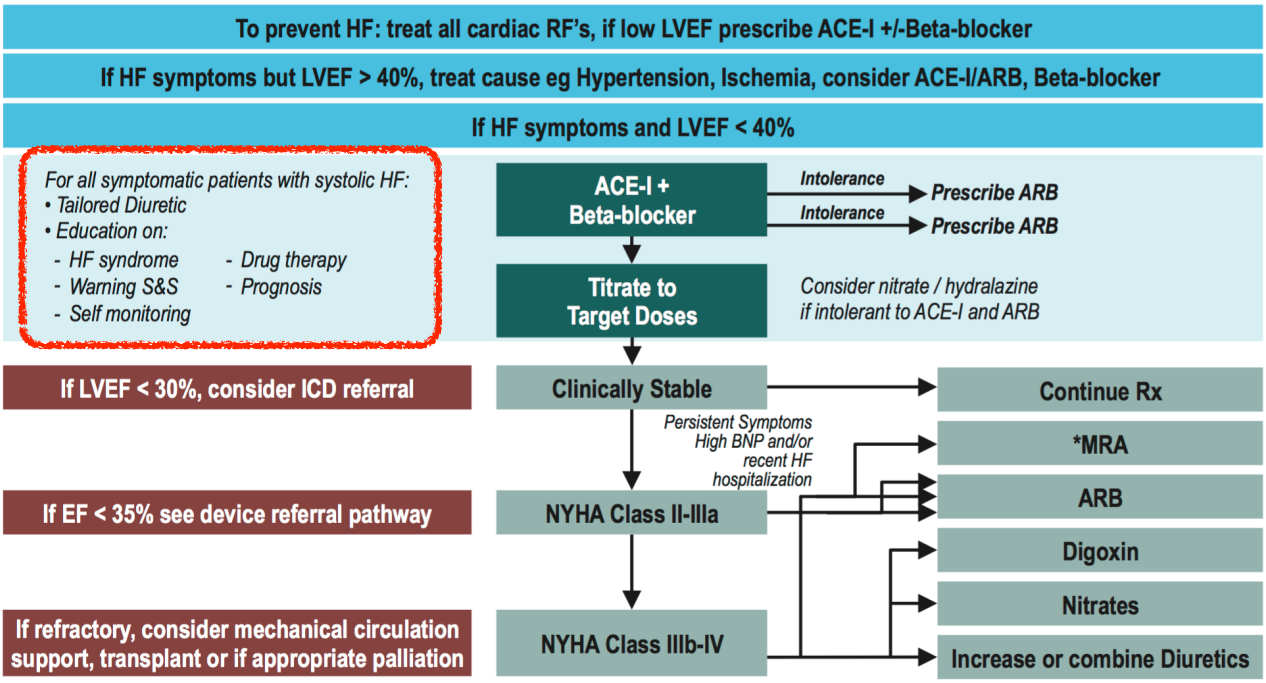
Chatterjee S, et al. Benefits of beta-blockers in patients with heart failure and reduced ejection fraction: network meta-analysis. BMJ. 2013 Jan 16;346(jan16 1):f55–5.

Initiating B-blocker therapy

- start LOW, go SLOW
  - e.g., q1-2 weekly dose ↑
- COUNSEL, COUNSEL, COUNSEL…then counsel more.

Initial Case

- A 68y M patient with CHF presents you with a prescription for metoprolol 25mg PO bid
- PMH: CHF, AF
- On profile:
  - nitrospray ii PRN, nitropatch 0.4 mg/d, enalapril 10mg bid, ASA 325 mg/d, furosemide 40mg/d, warfarin 5mg daily, atorvastatin 40mg qHS
- What counselling would you provide this patient?



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Diuretics Flashcard

furosemide, HCTZ, metolazone

Benefits	Morbidity, if fluid overloaded, Class II-IV
Landmark Trials	None
Dosing strategy	Furosemide 10-160 mg daily HCTZ may be added for synergy; add metolazone if really resistant to furosemide,
Risks/ monitoring	hypovolemia, hypokalemia, hypomagnesemia, hyperglycemia, hyperuricemia (HCTZ), hypocalcemia (furosemide)

Furosemide (Water Pill) Self Management Diary

Name:_____

Goal Weight Range: _____
Usual Furosemide Dose: _____
Dr. name and phone number: _____
_____

- If your weight is in the goal weight range, take your usual dose of furosemide and weigh again tomorrow
- If your weight is _____, increase furosemide dose to _____ and record on chart below.
- If your weight remains over _____ for more than 2 days, call your family doctor, Dr. _____
- If your weight is greater than _____, phone your family doctor, Dr. _____

	Date	MORNING Weight	MORNING Dose of Furosemide	AFTERNOON Dose of Furosemide	Other Action
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					

Normally: add an extra dose at lunchtime on days when the AM weight is >2 lb (~1kg) over target. If +/-2lbs (~1kg) of target weight, normal F dose in the AM. If >2lb (~1kg) BELOW target, omit tomorrow AM's furosemide dose.

Self-management Counseling in Patients With Heart Failure

The Heart Failure Adherence and Retention Randomized Behavioral Trial

Lynda H. Powell, PhD
James E. Calvin Jr, MD
Dejuran Richardson, PhD
Imke Janssen, PhD
Carlos F. Mendes de Leon, PhD
Kristin J. Flynn, PhD
Kathleen L. Grady, PhD
Cheryl S. Rucker-Whitaker, MD
Claudia Eaton, MS
Elizabeth Avery, MS
for the HART Investigators

Context Motivating patients with heart failure to adhere to medical advice has not translated into clinical benefit, but past trials have had methodological limitations.

Objective To determine the value of self-management counseling plus heart failure education, compared with heart failure education alone, for the primary end point of death or heart failure hospitalization.

Design, Setting, and Patients The Heart Failure Adherence and Retention Trial (HART), a single-center, multiple-hospital, partially blinded behavioral efficacy randomized controlled trial involving 902 patients with mild to moderate heart failure and reduced or preserved systolic function, randomized from the Chicago metropolitan area between October 2001 and October 2004 and undergoing follow-up for 2 to 3 subsequent years.

Interventions All patients were offered 18 contacts and 18 heart failure educational tip sheets during the course of 1 year. Patients randomized to the education group received tip sheets in the mail and telephone calls to check comprehension. Patients randomized to the self-management group received tip sheets in groups and were taught self-management skills to implement the advice.

Main Outcome Measure Death or heart failure hospitalization during a median of 2.56 years of follow-up.

Results Patients were representative of typical clinical populations (mean age, 63.6 years; 47% women, 40% racial/ethnic minority, 52% with annual family income less than $30 000, and 23% with preserved systolic function). The rate of the primary end point in the self-management group was no different from that in the education group (163 [40.1%)] vs 171 [41.2%], respectively; odds ratio, 0.95 [95% confidence interval, 0.72-1.26]). There were no significant differences on any secondary end points, including death, heart failure hospitalization, all-cause hospitalization, or quality of life.

Conclusions Compared with an enhanced educational intervention alone, the addition of self-management counseling did not reduce death or heart failure hospitalization in patients with mild to moderate heart failure.

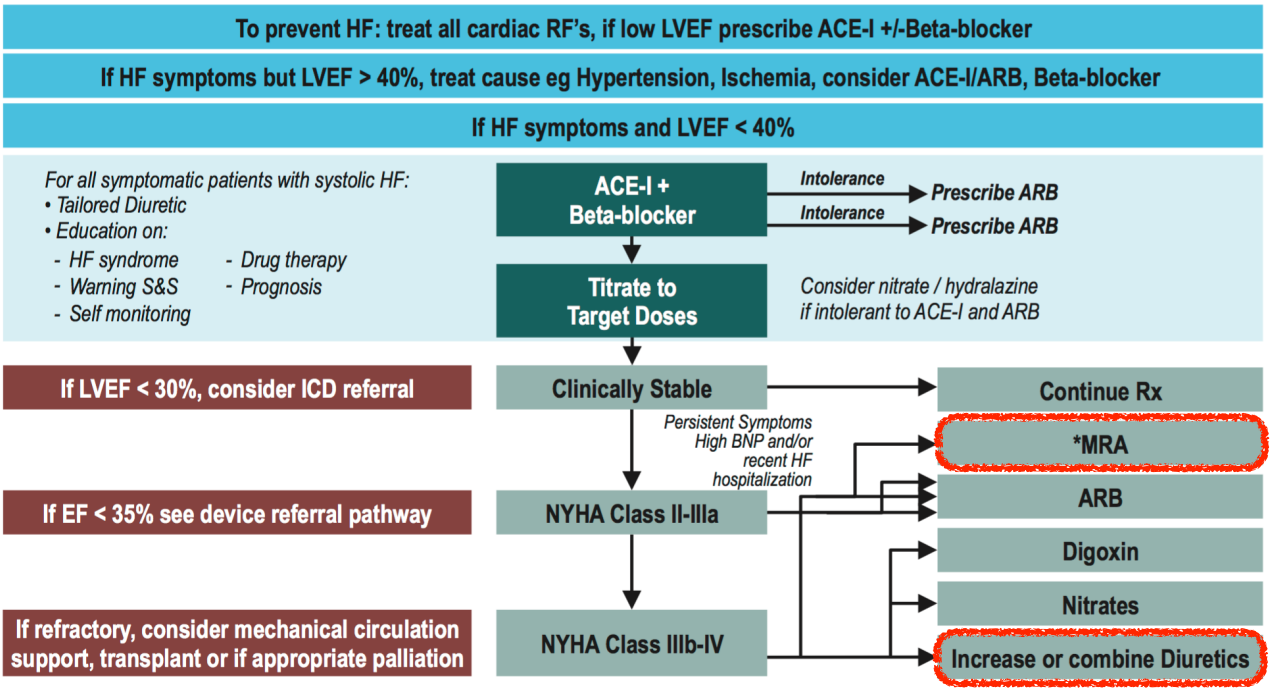
Trial Registration clinicaltrials.gov Identifier: NCT00018005

JAMA. 2010;304(12):1331-1338 www.jama.com

SUCCESS IN THE CONTROL OF THE heart failure epidemic has come from advances in understanding effective, evidence-based medical therapies.[1] Challenges remain, however, in the delivery of these therapies to patients. Patient nonadherence to heart failure drugs ranges from 30% to 60% and nonadherence to lifestyle recommendations from 50% to 80%, with higher rates occurring in more socioeconomically disadvantaged subgroups.[2]

To meet the challenge of delivering evidence-based therapies to patients with heart failure, research has turned to the evaluation of disease manage-

HART. JAMA 2010;304:1331-1338



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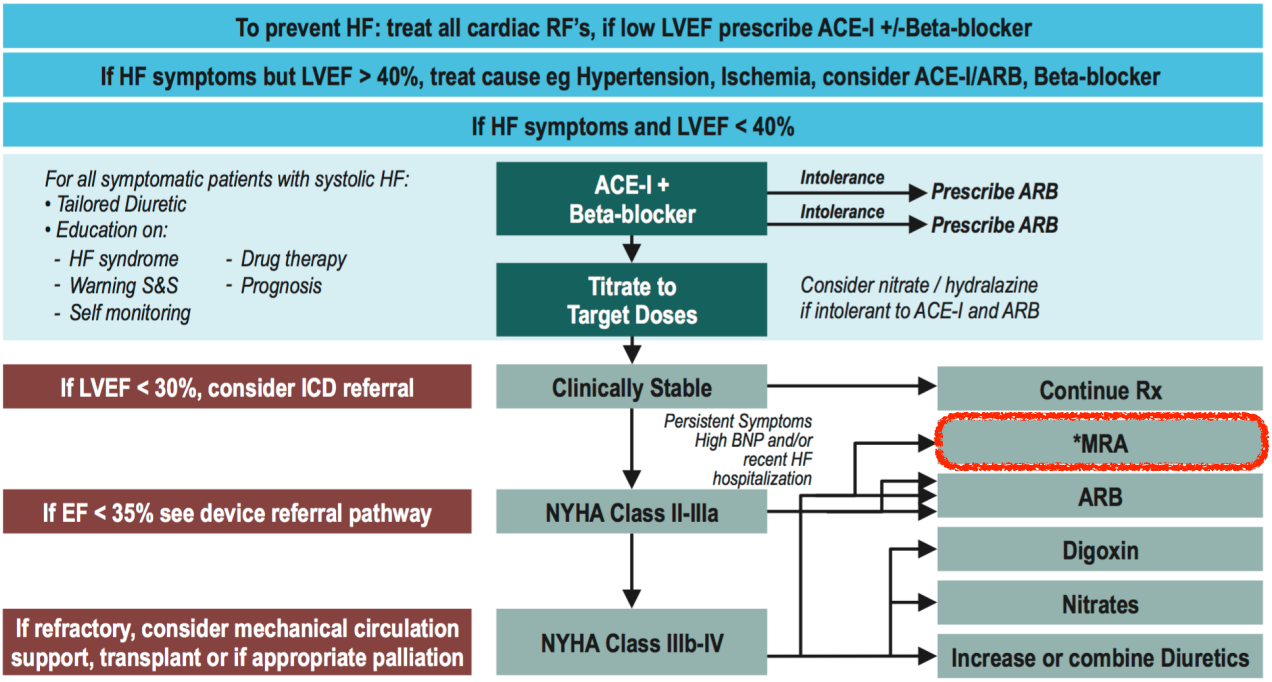

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MRA Flashcard

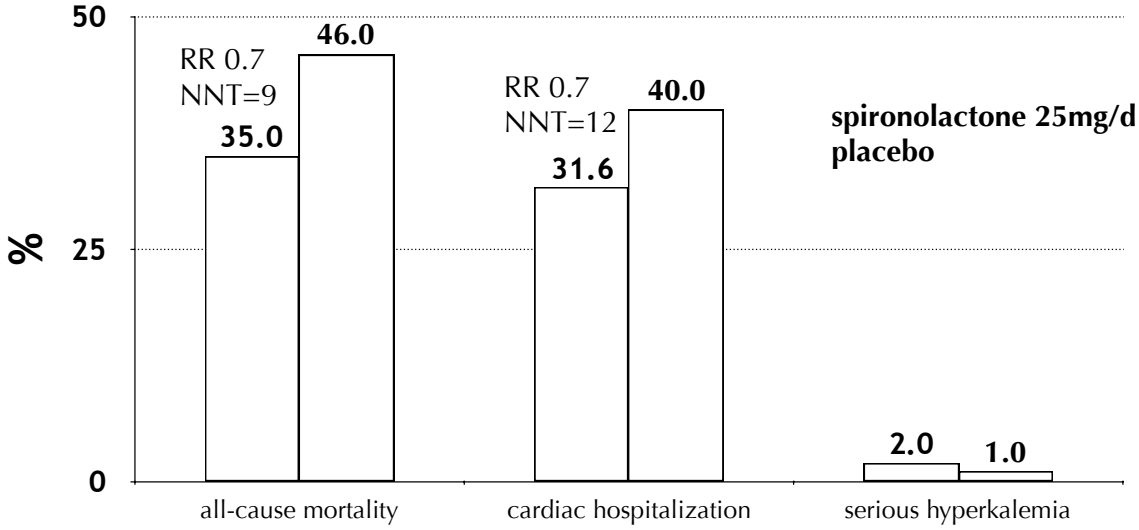
spironolactone, eplerinone

Benefits	Mortality, Class I-IV; Morbidity
Landmark Trials	RALES (spironolactone), EPHESUS, EMPHASIS-HF (eplerenone)
Dosing strategy	Add 25 mg once daily to stable Class III/IV patent already on ACEI + B-blocker.
Risks/ monitoring	**HYPERKALEMIA**, breast tenderness/ gynecomastia, hypotension

RALES

N=1663 with NYHA Class III/IV heart failure. 95% on ACE-I. 10% on B-blocker.

Median 24 months followup (stopped early).

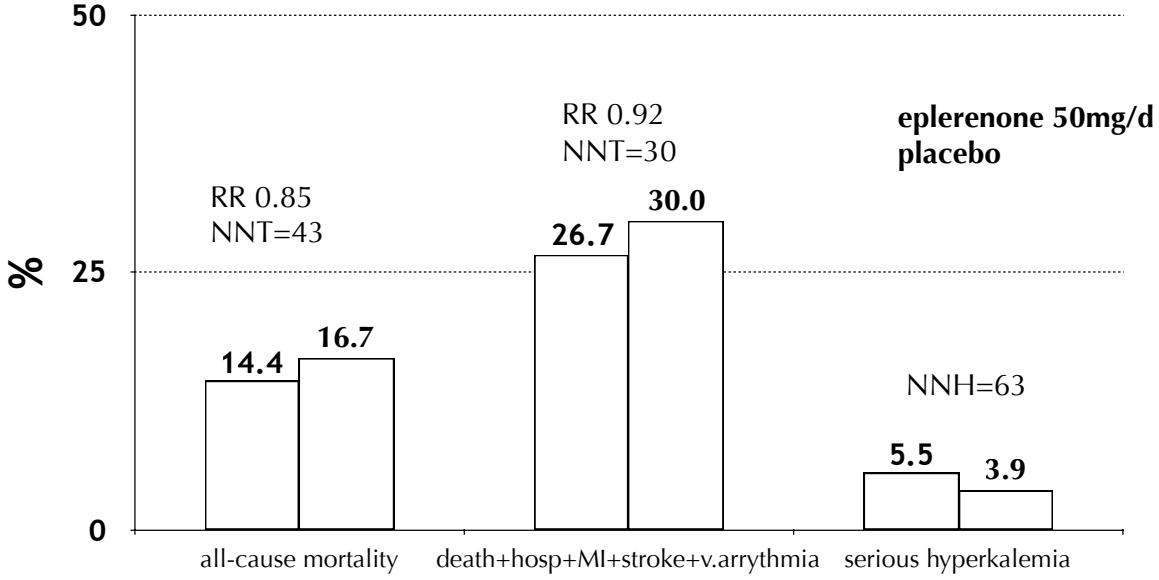


RALES. N Engl J Med 1999:341:709-17.

EPHESUS

N=1663 with EF<40% 3-14 days **post-MI**. 86% on ACE-I, 75% on B-blocker, 60% on diuretics.

Mean 16 months followup.

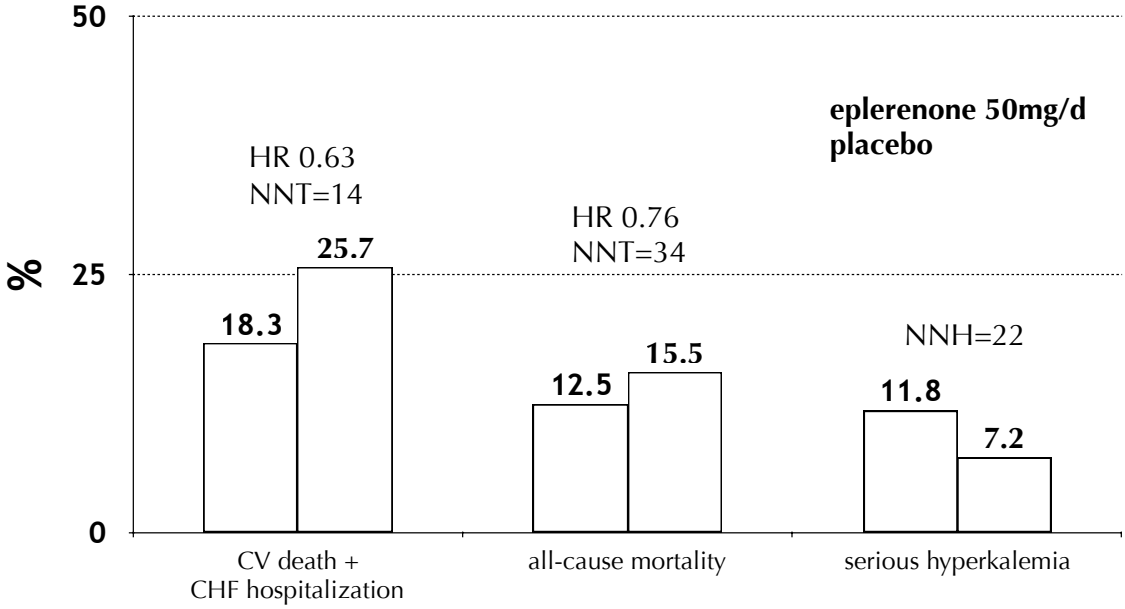


EPHESUS. N Engl J Med 2003;348:1309-21

EMPHASIS-HF

N=2737 with **NYHA class II** + EF<35%. 94% on ACE-I, 87% on B-blocker, 85% on diuretics.

Stopped early at median 21 mos.



EMPHASIS-HF. N Engl J Med 2010. 10.1056/NEJMoa1009492

Eplerenone Is Not Superior to Older and Less Expensive Aldosterone Antagonists

Saurav Chatterjee, MD,[a] Chaim Moeller, MD,[a] Nidhi Shah, MD,[a] Oluwaseyi Bolorunduro, MD, MPH,[a] Edgar Lichstein, MD,[a] Norbert Moskovits, MD,[a] Debabrata Mukherjee, MD, MS[b]

[a]Maimonides Medical Center, Brooklyn, NY; [b]Texas Tech University Health Sciences Center, El Paso

ABSTRACT

INTRODUCTION: Eplerenone is publicized to be extremely effective in reducing mortality from heart failure, with a reasonable side-effect profile. However, it is much more expensive compared with older aldosterone antagonists. We reviewed available evidence to assess whether increased expense was justified with outcomes data.

METHODS AND RESULTS: The authors searched the PubMed, CENTRAL, CINAHL, and EMBASE databases for randomized controlled trials from 1966 through July 2011. Interventions included aldosterone antagonists (Aldactone [Pfizer, NY, NY], canrenone, eplerenone) in systolic heart failure. The comparator included standard medical therapy or placebo, or both. Outcomes assessed were mortality in the intervention versus the comparator groups, and rates of adverse events at the end of at least 8 weeks of follow-up. Event rates were compared using a forest plot of relative risk (RR) (95% confidence interval [CI]) using a random-effects model (Mantel-Haenszel) between the aldosterone antagonists and controls. We included 13 studies for aldosterone antagonists other than eplerenone, and 3 studies for eplerenone. There was significant reduction of mortality with all aldosterone antagonists, but eplerenone (15% mortality relative reduction; RR 0.85; 95% CI, 0.77-0.93; $P = .0007$) was outperformed by other aldosterone antagonists, namely, spironolactone and canrenone (26% mortality relative reduction; RR 0.74; 95% CI, 0.66-0.83; $P < .0001$). Reduction in cardiovascular mortality with eplerenone was 17% (RR 0.83; 95% CI, 0.75-0.92; $P = .0005$), while that with other aldosterone antagonists was 25% (RR 0.75; 95% CI, 0.67-0.84, $P < .0001$), without contributing significantly to an improved side-effect profile.

CONCLUSION: Eplerenone does not appear to be more effective in reducing clinical events compared with older, less expensive aldosterone antagonists.

• *The American Journal of Medicine (2012) 125, 817-825*

KEYWORDS: Cost-benefit analysis; Heart failure; Meta-analysis

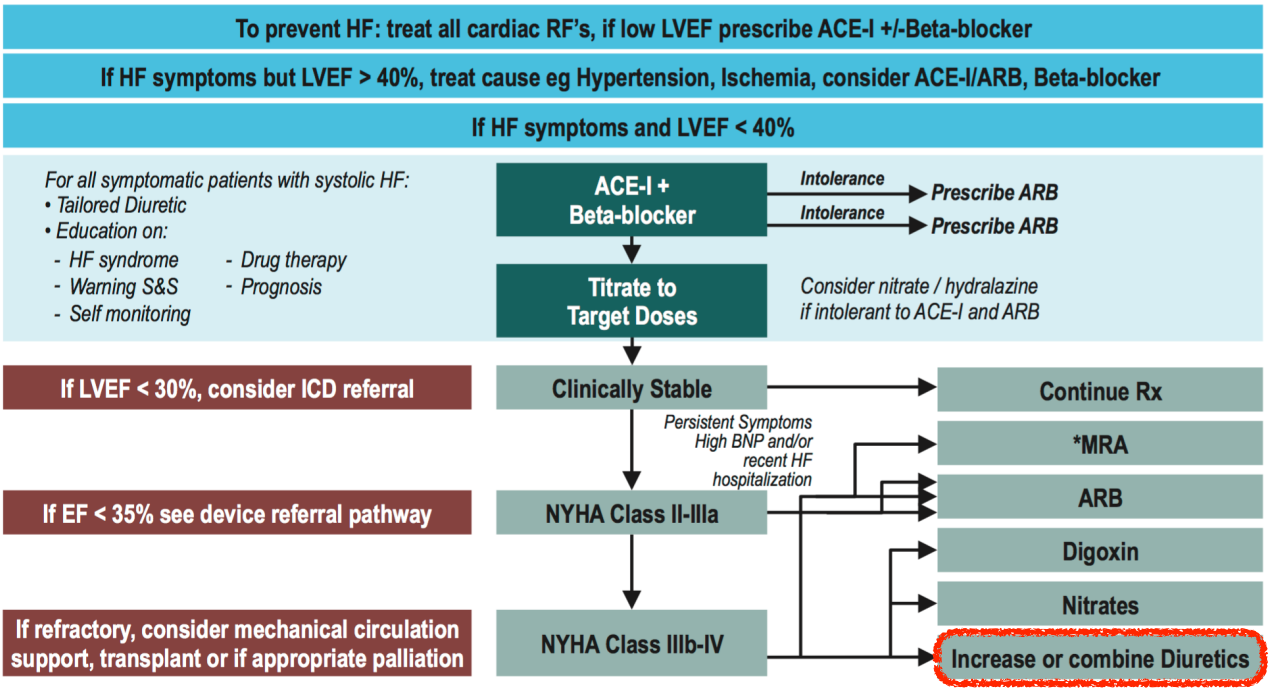
Chatterjee S, et al.. Am J Med 2012;125:817–25.

Pre-Spironolactone checklist

- ☑ Allergy/intolerance
- ☑ Hypotension
- ☑ NYHA Class III-IV heart failure
- ☑ Hyperkalemia

Eplerenone? CCS 2011 recommends in NYHA II.

Canadian Journal of Cardiology 27 (2011) 319 –338



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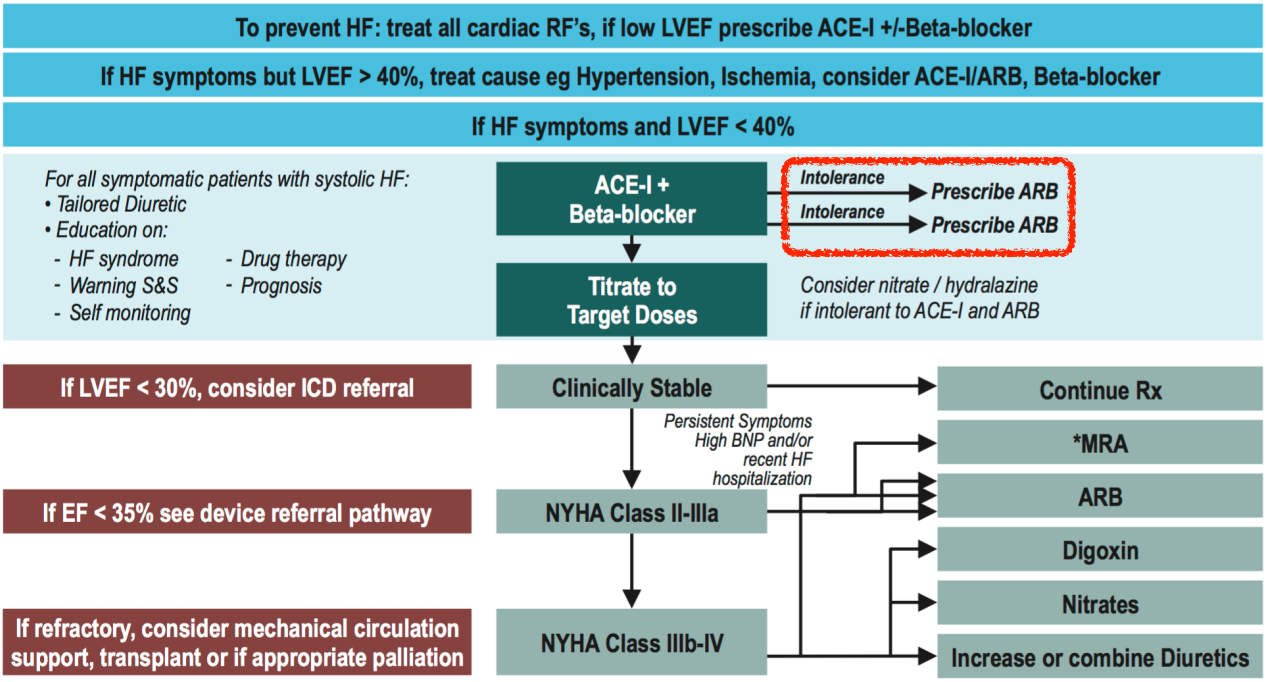

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ARB Flashcard

Benefits	Morbidity (vs. placebo, and when added to standard therapy), Class I-IV; Mortality (candesartan, whether or not on ACEI)
Landmark Trials	ValHEFT (valsartan), VALIANT (valsartan), CHARM trials (candesartan), ELITE II (losartan)
Dosing strategy	Start low go slow when adding to ACE-I therapy. When switching from ACE-I to ARB, may switch directly to a comparable dose.
Risks/ monitoring	Renal dysfunction. Hypotension. Hyperkalemia.

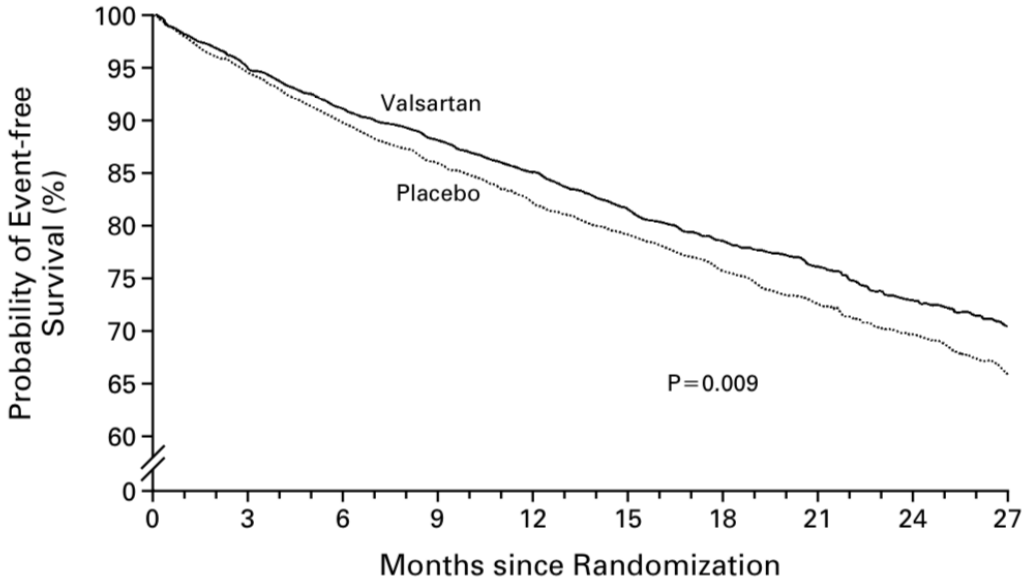
Evidence-based drugs and oral doses as shown in large clinical trials

Drug	Start dose	Target dose
ARB		
Candesartan	4 mg od	32 mg od
Valsartan	40 mg bid	160 mg bid

CCS 2006 Guidelines. Can J Cardiol 2006;22:23-45
UPDATE: Canadian Journal of Cardiology 2013;29:168–81

ValHeFT

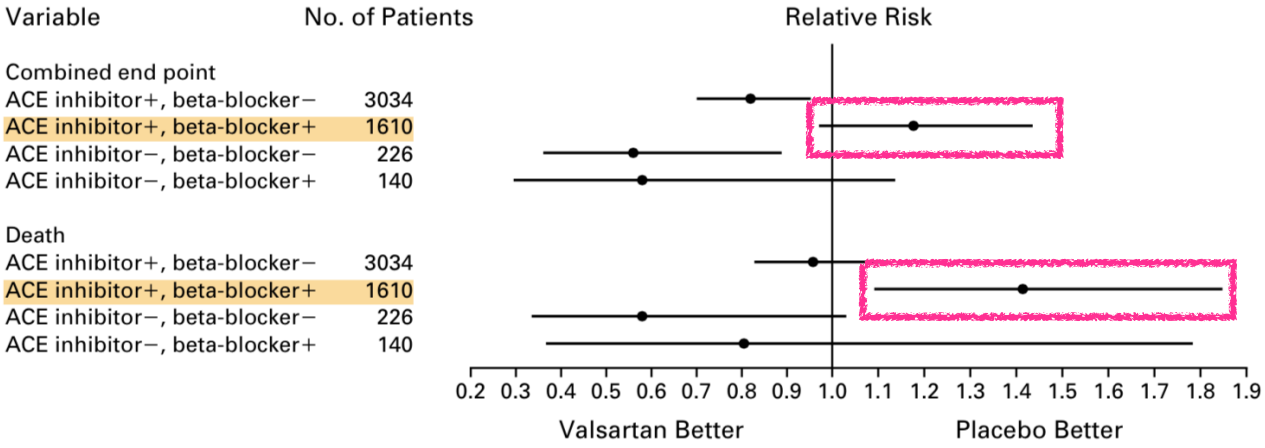
N=5010 with NYHA II,III,IV HF + LVEF<40% . ~24 months followup.
valsartan 160mg bid vs. placebo. 92% on ACE-I, 34% on b-blocker.



ValHeFT. N Engl J Med, 2001;345;1667-75

ValHeFT

N=5010 with NYHA II,III,IV HF + LVEF<40% . ~24 months followup



ValHeFT. N Engl J Med, 2001;345;1667-75

VALIANT

N=10,000 with recent MI (<10 days prior) + LVEF<40%

Median 25 months followup

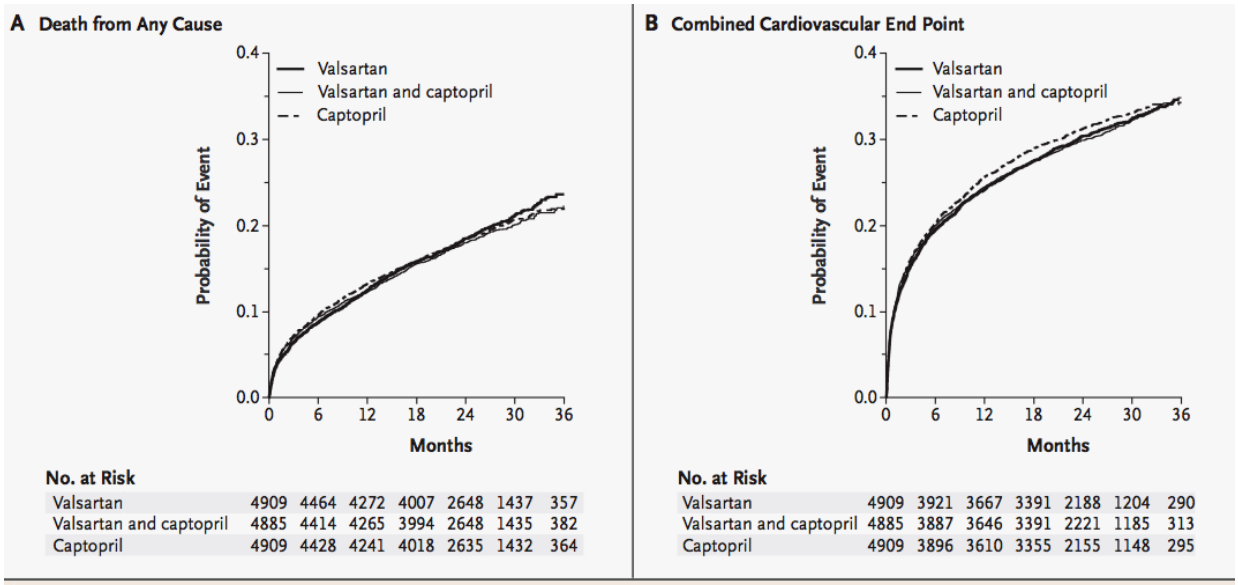
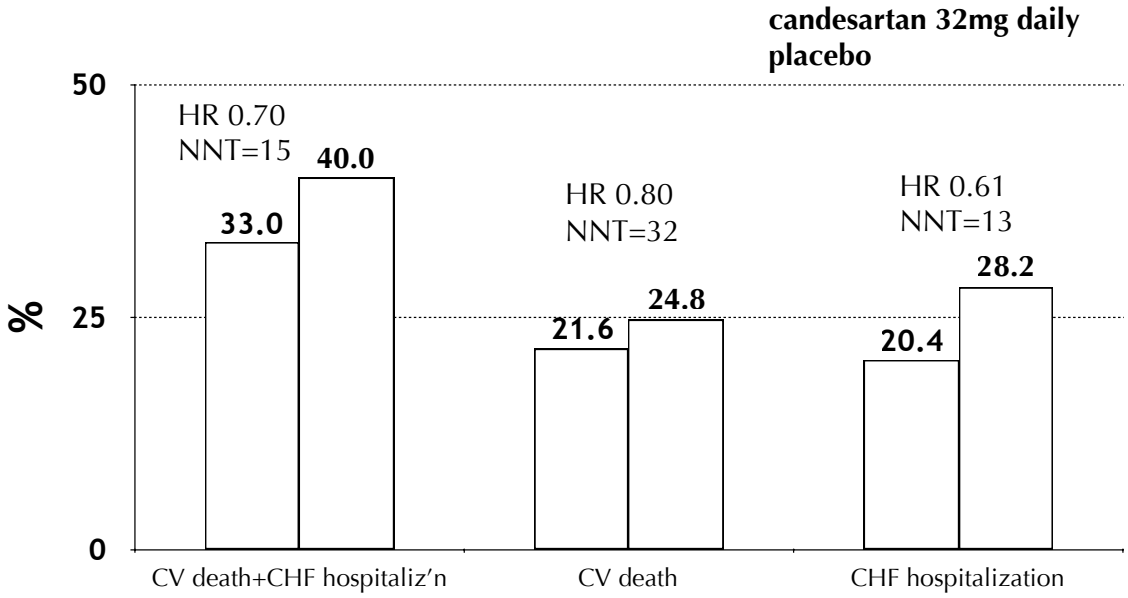


Figure 1. Kaplan–Meier Estimates of the Rate of Death from Any Cause (Panel A) and the Rate of Death from Cardiovascular Causes, Reinfarction, or Hospitalization for Heart Failure (Panel B), According to Treatment Group.

VALIANT. N Engl J Med 2003;349:1893-906.

CHARM-Alternative

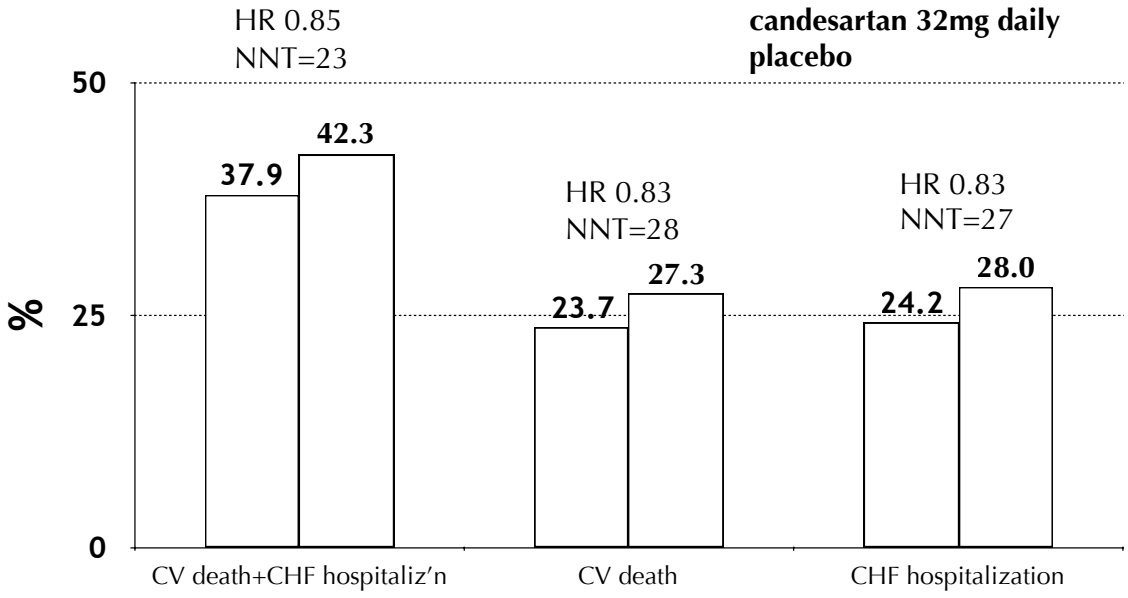
N=2028 with EF<40% intolerant to ACE-I. 55% on B-blocker.
Median 34 months followup.



CHARM-Alternative. Lancet 2003; 362:772–6

CHARM-Added

N=2548 with EF<40% on ACE-I. 56% on B-blocker.
Median 41 months followup.



CHARM-Added. Lancet 2003; 362:767–71

ARBs: Does dose matter?

Articles

The Lancet, Early Online Publication, 17 November 2009
doi:10.1016/S0140-6736(09)61913-9 Cite or Link Using DOI

Effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure (HEAAL study): a randomised, double-blind trial

Prof Marvin A Konstam MD [a], Prof James D Neaton PhD [b], Prof Kenneth Dickstein MD [c d], Prof Helmut Drexler MD [e *], Prof Michel Komajda MD [f], Prof Felipe A Martinez MD [g], Prof Gunter A J Riegger MD [h], William Malbecq PhD [i], Ronald D Smith PhD [j], Soneil Guptha MD [j], Prof Philip A Poole-Wilson MD [k †], for the HEAAL Investigators[‡]

Summary

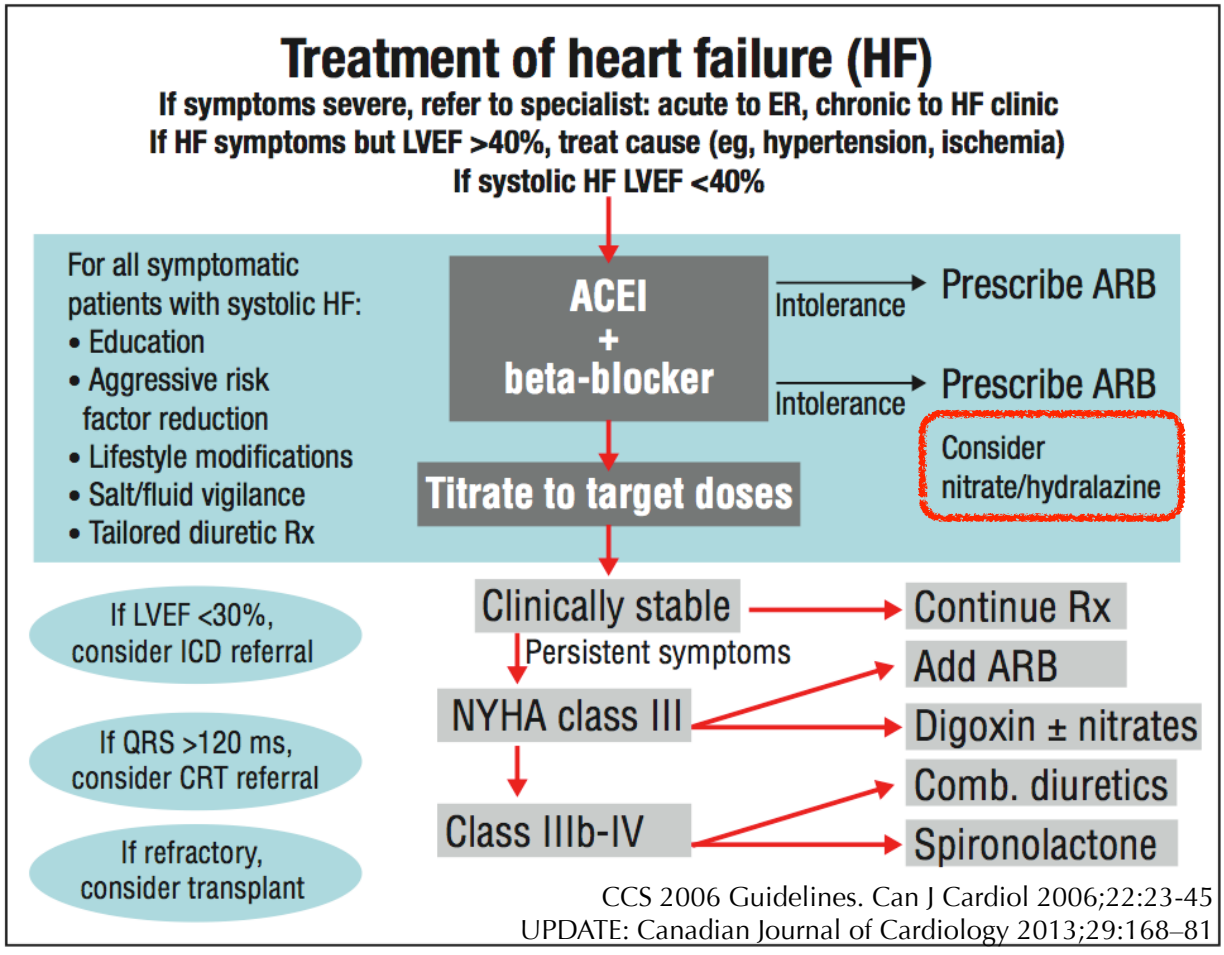
Background

Angiotensin-receptor blockers (ARBs) are effective treatments for patients with heart failure, but the relation between dose and clinical outcomes has not been explored. We compared the effects of high-dose versus low-dose losartan on clinical outcomes in patients with heart failure.

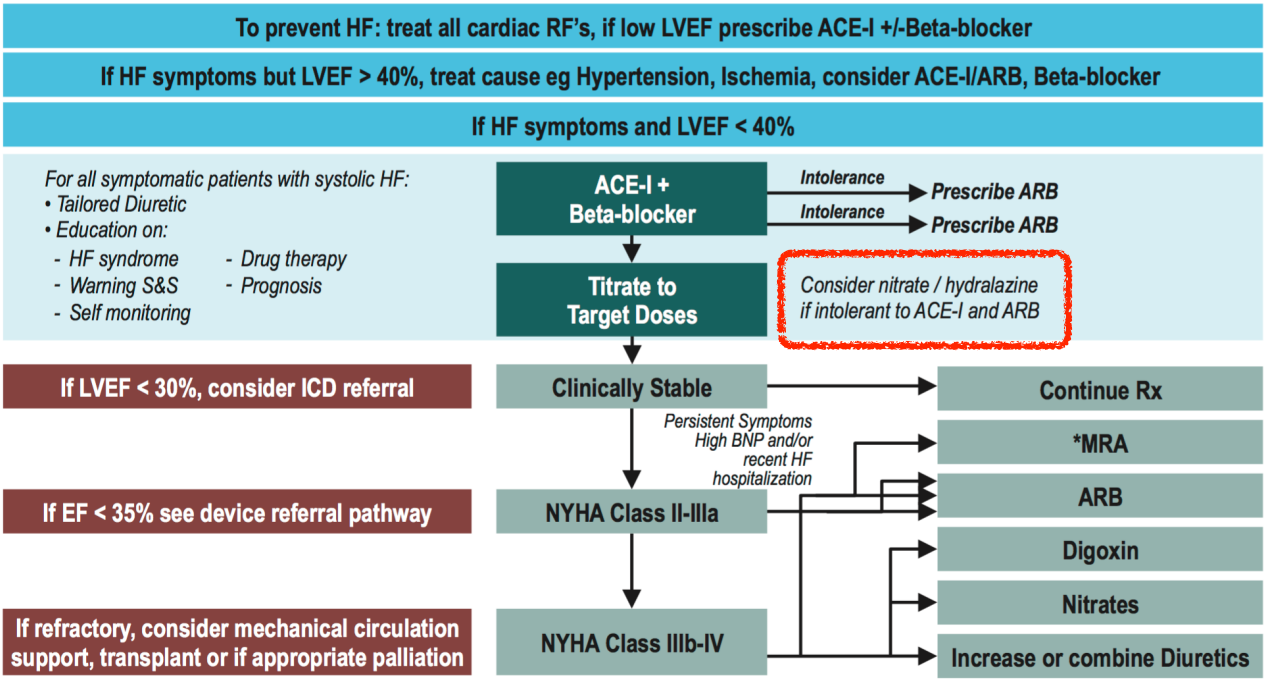
Methods

This double-blind trial was undertaken in 255 sites in 30 countries. 3846 patients with heart failure of New York Heart Association class II–IV, left-ventricular ejection fraction 40% or less, and intolerance to angiotensin-converting-enzyme (ACE) inhibitors were randomly assigned to losartan 150 mg (n=1927) or 50 mg daily (n=1919). Allocation was by block randomisation stratified by centre and presence or absence of B-blocker therapy, and all patients and investigators were masked to assignment. The primary endpoint was death or admission for heart failure. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00090259.

HEAAL. Lancet 2009; 17NOV09



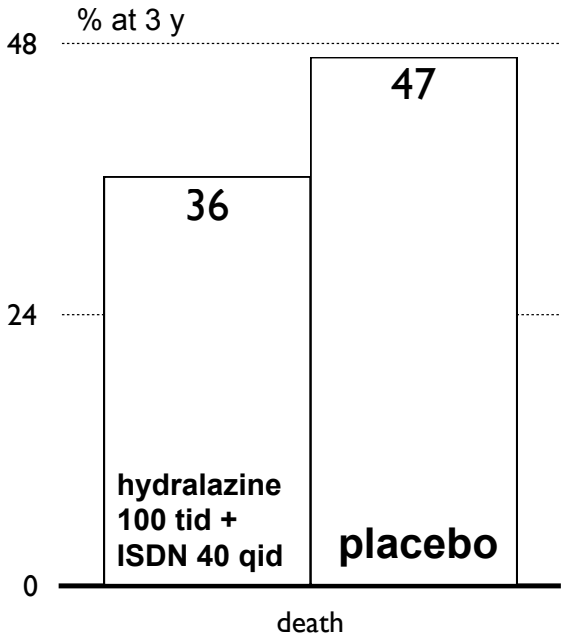
CCS 2006 Guidelines. Can J Cardiol 2006;22:23-45
UPDATE: Canadian Journal of Cardiology 2013;29:168–81



CCS 2006 Guidelines. Can J Cardiol 2006;22:23-45
UPDATE: Canadian Journal of Cardiology 2013;29:168–81
CCS Heart Failure Pocket Guide: January 2015: http://www.ccs.ca/images/Guidelines/PocketGuides_EN/HF_Gui_2014_PG_EN.PDF

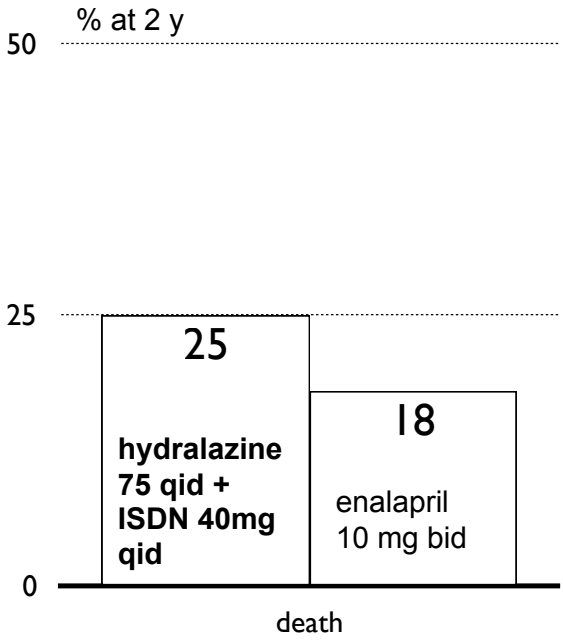
Hydralazine+Nitrate

N=642 men with CHF



V-HeFT. NEJM 1986;314:1547-52

N=804 men with CHF



V-HeFT II. NEJM 1991;325:303-10

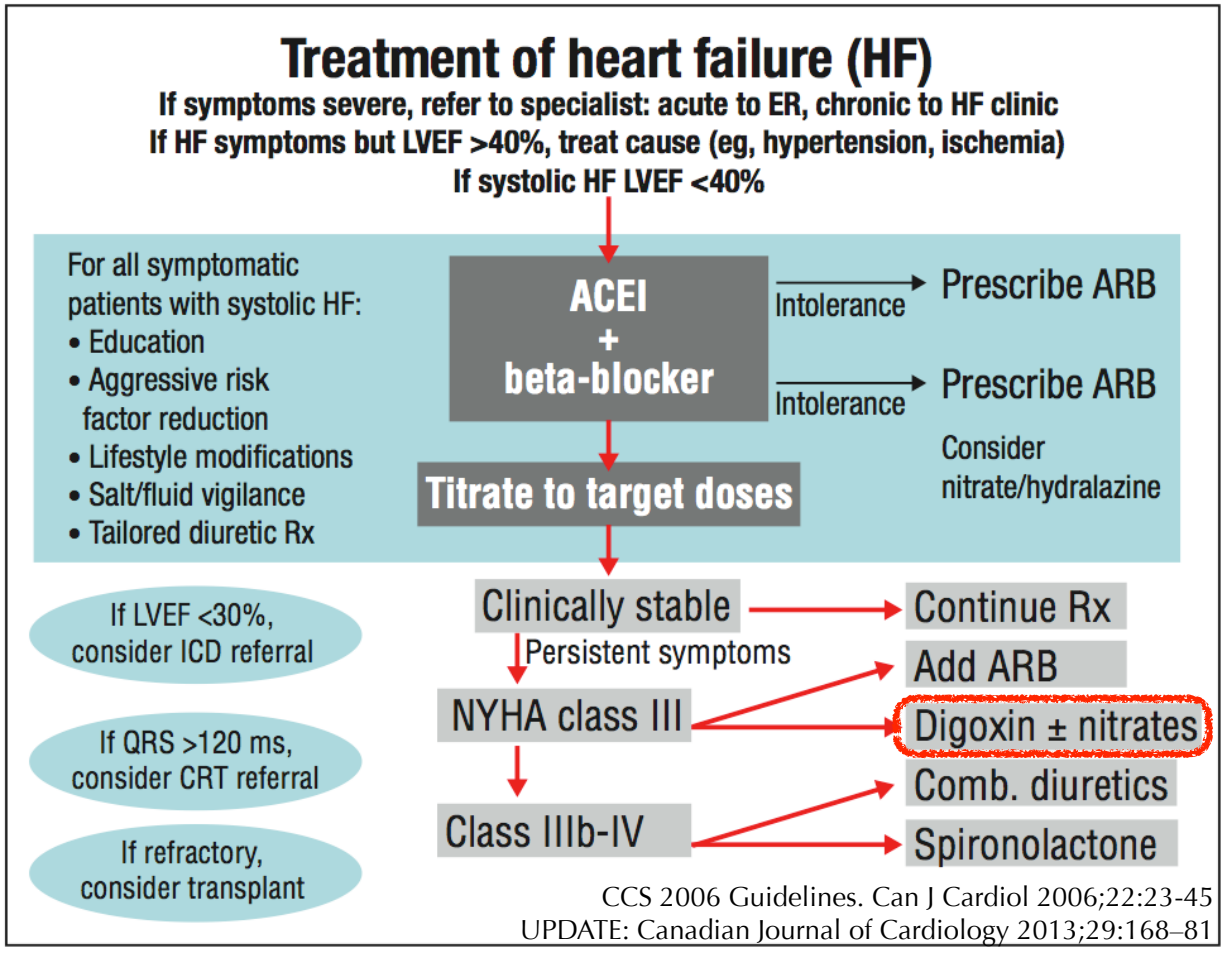
BC Heart Failure Guidelines

Goal/Dose

- Hydralazine and nitrates should be used concurrently

		STARTING DOSE	GOAL DOSE
	Hydralazine	37.5 mg TID	75 mg TID
or	Isosorbide Dinitrate	20 mg TID	40 mg TID
	Nitropatch	0.2-0.4 mg/h x 12h/day	0.6-0.8 mg/h x 12h/day

http://www.bcguidelines.ca



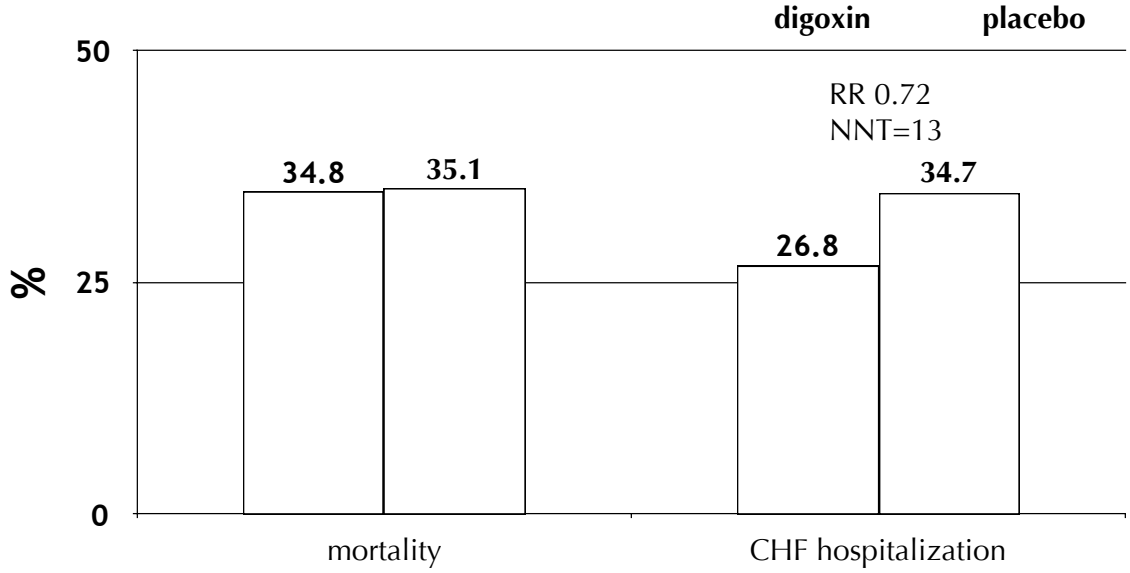
Digoxin Flashcard

Benefits	Morbidity, Class II-III
Landmark Trials	**DIG** RADIANCE, PROMISE
Dosing strategy	0.0625 - 0.375 mg QD depending on renal function, age, tolerability.
Risks/ monitoring	CNS ADRs (confusion, hallucinations), diarrhea, ↑ toxicity during hypokalemia, monitor RENAL FUNCTION.

DIG

N=6800 with EF<45%. 95% on ACE-I.

Mean 37 months followup.



DIG. N Engl J Med 1997;336:525-33

Safety and efficacy of digoxin: systematic review and meta-analysis of observational and controlled trial data

Oliver J Ziff,[1,2] Deirdre A Lane,[1,3] Monica Samra,[2] Michael Griffith,[4] Paulus Kirchhof,[1,3] Gregory Y H Lip,[1,3] Richard P Steeds,[4] Jonathan Townend,[1,4] Dipak Kotecha[1,3,4,5]

[1]University of Birmingham Centre for Cardiovascular Sciences, Birmingham, UK
[2]Royal Free London NHS Foundation Trust, London, UK
[3]Sandwell and West Birmingham NHS Trust, City Hospital, Birmingham, UK
[4]University Hospitals Birmingham NHS Trust, Birmingham, UK
[5]Monash Centre of Cardiovascular Research and Education in Therapeutics, Monash University, Melbourne, Australia
Correspondence to: D Kotecha, University of Birmingham Centre for Cardiovascular

ABSTRACT

OBJECTIVE

To clarify the impact of digoxin on death and clinical outcomes across all observational and randomised controlled trials, accounting for study designs and methods.

DATA SOURCES AND STUDY SELECTION

Comprehensive literature search of Medline, Embase, the Cochrane Library, reference lists, and ongoing studies according to a prospectively registered design (PROSPERO: CRD42014010783), including all studies published from 1960 to July 2014 that examined treatment with digoxin compared with control (placebo or no treatment).

DATA EXTRACTION AND SYNTHESIS

significant impact on mortality associated with digoxin, including markers of heart failure severity such as use of diuretics (P=0.004). Studies with better methods and lower risk of bias were more likely to report a neutral association of digoxin with mortality (P<0.001). Across all study types, digoxin led to a small but significant reduction in all cause hospital admission (risk ratio 0.92, 0.89 to 0.95; P<0.001; n=29 525).

CONCLUSIONS

Digoxin is associated with a neutral effect on mortality in randomised trials and a lower rate of admissions to hospital across all study types. Regardless of statistical analysis, prescription biases limit the value of observational data.

Ziff OJ et al. BMJ 2015;351:h4451.

Meta-analysis included 75 study analyses, with a combined total of 4 006 210 patient years of follow-up.

Mortality: Compared with control, the pooled risk ratio for death with digoxin was 0.99 in randomised controlled trials (0.93 to 1.05).

Hospitalization: Across all study types, digoxin led to a small but significant reduction in all cause hospital admission (risk ratio 0.92, 0.89 to 0.95; P<0.001; n=29 525)

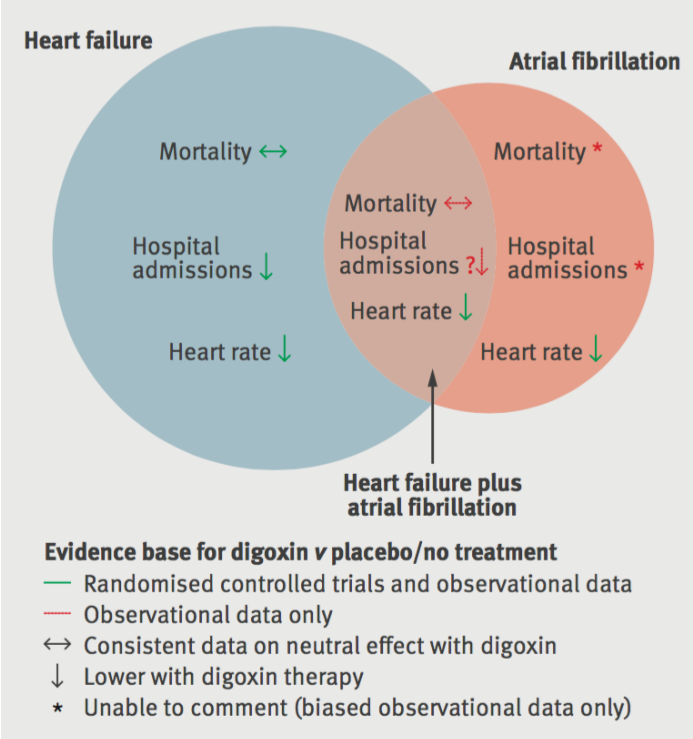
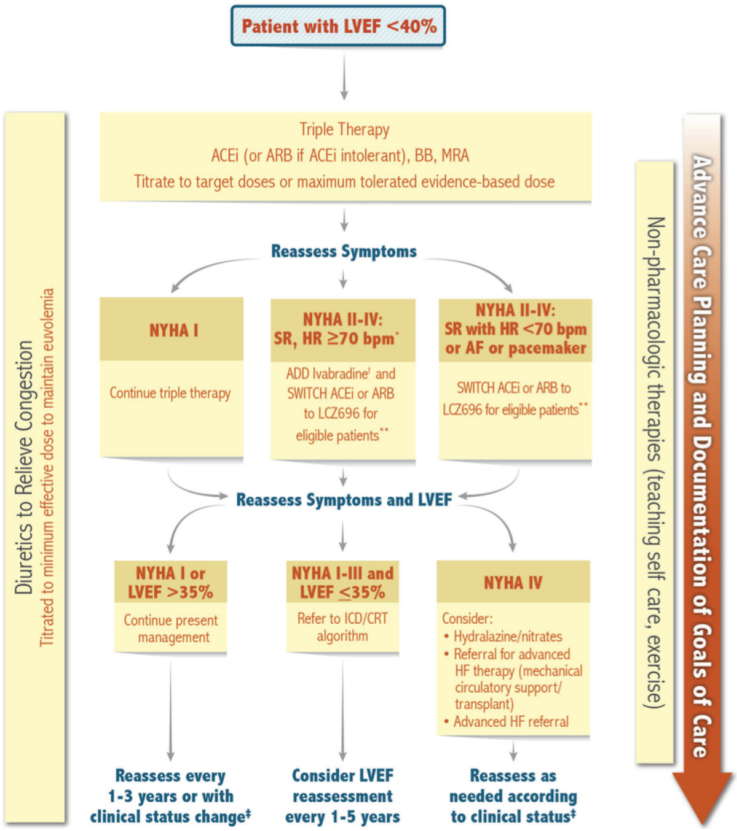


Fig 5 | Overview of evidence base for digoxin versus placebo/no treatment

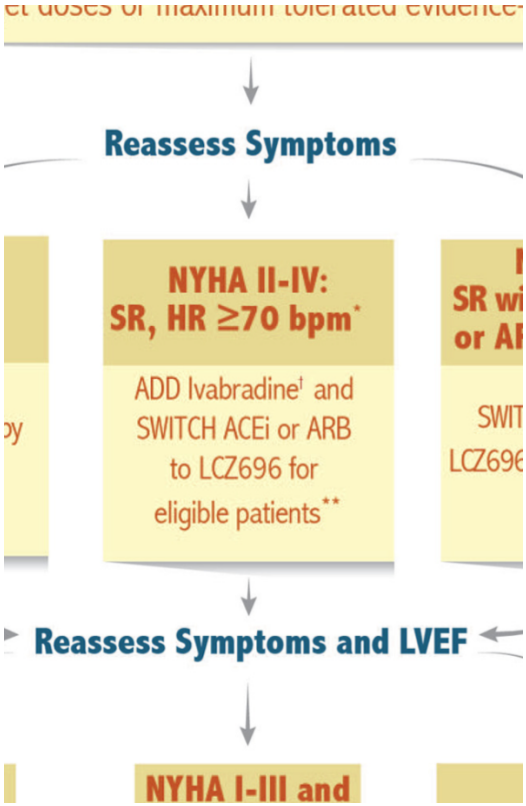
Ziff OJ et al. BMJ 2015;351:h4451.

Canadian Cardiovascular Society
Leadership. Knowledge. Community.

Therapeutic Approach to Patients with Heart Failure and Reduced Ejection Fraction



Howlett JG et al. The CCS Heart Failure Companion. Canadian Journal of Cardiology 2015;:1–15.



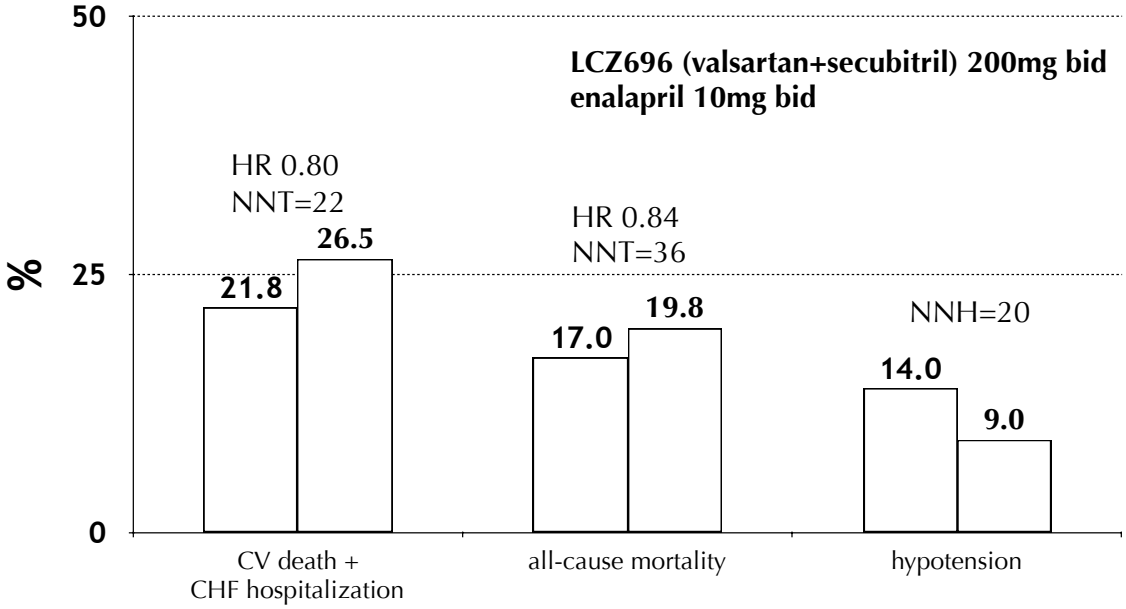
*Pending Health Canada approval
†Ivabradine may be added when available in Canada
**LCZ696, when available in Canada, will replace ACEi or ARB in patients with elevated NP or recent hospitalization (BNP >150pg/ml or NT-pro-BNP >600 pg/ml)
‡Refer to Table 4

Howlett JG et al. The CCS Heart Failure Companion. Canadian Journal of Cardiology 2015;:1–15.

secubitril+valsartan (LCZ696): PARADIGM-HF

N=8442 with **NYHA class II, III, IV** + EF<40%.

Stopped early after median 27 mos.

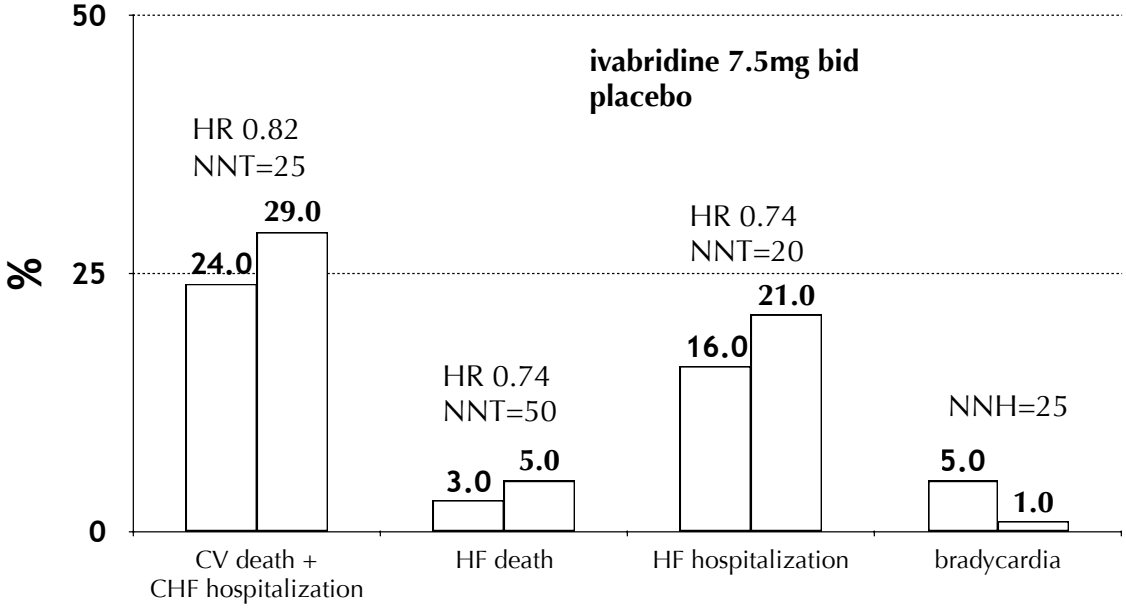


PARADIGM-HF. New Eng J Med 2014;371:993–1004

ivabridine: SHIFT

N=6558 with HF symptoms + EF<35% + NSR + HR≥70

Median 23 mos. followup.



SHIFT. The Lancet 2010;376:875–85.

Some Debatable Therapies

Sodium & Water Restriction

Fluid / Na+ Restriction

- **Na+ reduction/restriction**
  - <2-3 g/d “no added salt diet”
  - 1-2 g/d “low salt diet”
- Exercise
- Fluid restriction if edematous or diuretic-resistant
  - 1.5-2 L/d

CCS 2006 Guidelines. Can J Cardiol 2006;22:23-45
UPDATE: Canadian Journal of Cardiology 2013;29:168–81

Low sodium versus normal sodium diets in systolic heart failure: systematic review and meta-analysis

James J DiNicolantonio,[1] Pietro Di Pasquale,[2] Rod S Taylor,[3] Daniel G Hackam[4]

► Additional materials are published online only. To view these files please visit the journal online (http://dx.doi.org/10.1136/heartjnl-2012-302337).

[1]Wegmans Pharmacy, Ithaca, New York, USA
[2]Chief Division of Cardiology, “Paolo Borsellino”, G.F. Ingrassia Hospital, Palermo, Italy
[3]Peninsula Medical School, University of Exeter, Exeter, UK
[4]Division of Clinical Pharmacology, Department of Medicine, and Departments of Clinical Neurological Sciences and Epidemiology & Biostatistics, University of Western Ontario; Stroke Prevention and Atherosclerosis Research Centre (SPARC), Robarts Research Institute, and the Premature Atherosclerosis

ABSTRACT

Context A low sodium diet has been proposed to reduce the risk of heart failure (HF) hospitalisations and is currently advocated in consensus guidelines, yet some evidence suggests adverse neurohumoral activation for sodium restriction in the HF setting.

Objectives To evaluate the effects of a restricted sodium diet in patients with systolic HF.

Data sources A systematic review and meta-analysis of randomised trials OVID MEDLINE, PubMed, Excerpta Medica (Embase), the Cochrane Controlled Trials Register, Scopus, Web of Science and Google Scholar were searched up to April 2012.

Study selection Two independent reviewers selected studies for inclusion on the basis of a randomised controlled trial design that included adults with systolic HF receiving a restricted salt diet or control diet and reporting mortality (all-cause, sudden death or HF-related) and HF-related hospitalisations.

Data extraction and analysis Descriptive and

North American and European guidelines for the management of HF consistently advise dietary sodium restriction for patients with both systolic HF and HF with preserved ejection fraction.[6] US guidelines recommend an intake of 2–3 g/day with further restriction (below 2 g/day) to be considered in moderate to severe HF. These recommendations are based on level C evidence, that is, expert consensus opinion and results from observational studies. Therefore, a comprehensive systematic review of randomised trials was undertaken comparing sodium-restricted diets with non-restricted diets in patients with systolic HF.

METHODS

A systematic review of the available literature according to the PRISMA guidelines for the conduct of systematic reviews of intervention studies was performed.[7]

SALT | WATER

Dinicolantonio JJ, et al. Heart. 2013 Mar 12.

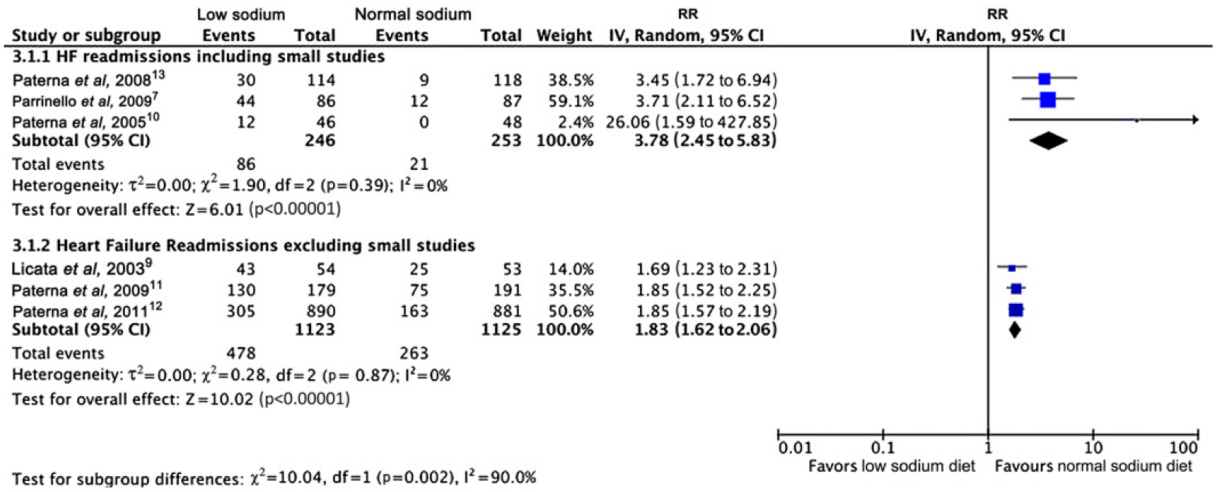


Figure 4 Forest plot of relative risks for heart failure readmissions excluding small studies.

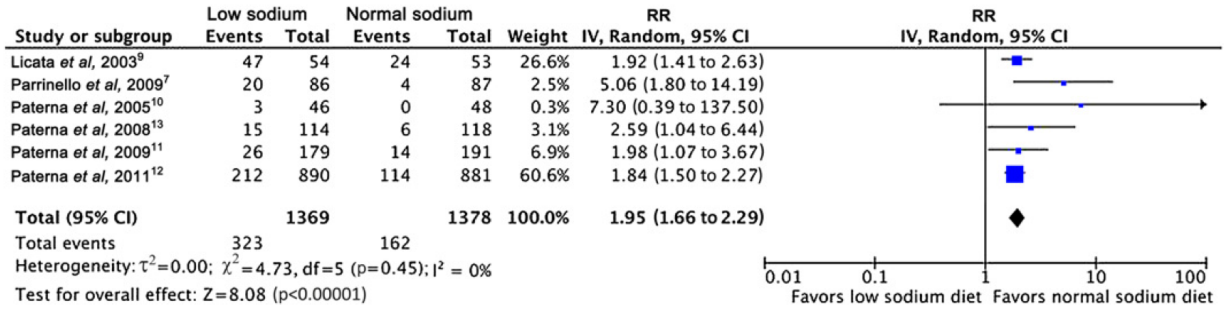


Figure 6 Forest plot of relative risks for mortality.

Low sodium versus normal sodium diets in systolic heart failure: systematic review and meta-analysis

James J DiNicolantonio, Pietro Di Pasquale, Rod S Taylor, Daniel G Hackam

NOTICE OF RETRACTION

This paper was published on-line in *Heart* on 21 August 2012. It reports a meta-analysis of six earlier papers.[1–6] It has come to our attention that two of these papers contain duplicate data in tables reporting baseline data and treatment effects.[3 4]

The matter was considered by *BMJ* Publishing Ethics Committee. The Committee considered that without sight of the raw data on which the two papers containing the duplicate data were based, their reliability could not be substantiated. Following inquiries, it turns out that the raw data are no longer available having been lost as a result of computer failure.

Under the circumstances, it was the Committee's recommendation that the *Heart* meta-analysis should be retracted on the ground that the reliability of the data on which it is based cannot be substantiated.

1 Licata G, Di Pasquale P, Parrinello G, *et al*. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. *Am Heart J* 2003;145:459–66.
2 Paterna S, Di Pasquale P, Parrinello G, *et al*. Changes in brain natriuretic peptide levels and bioelectrical impedance measurements after treatment with high-dose furosemide and hypertonic saline solution versus high-dose furosemide Alone in refractory congestive heart failure. *J Am Coll Cardiol* 2005;45:1997–2003.
3 Paterna S, Gaspare P, Fasullo S, *et al*. Normal-sodium diet compared with low-sodium diet in compensated congestive heart failure: is sodium an old enemy or a new friend? *Clin Sci* 2008;114:221–30.
4 Parrinello G, Di Pasquale P, Licata G, *et al*. Long-term effects of dietary sodium intake on cytokines and neurohormonal activation in patients with recently compensated congestive heart failure. *J Card Fail* 2009;15:864–73.
5 Paterna S, Parrinello G, Cannizzaro S, *et al*. Medium term effects of different dosage of diuretic, sodium, and fluid administration on neurohormonal and clinical outcome in patients with recently compensated heart failure *Am J Cardiol* 2009;103:93–102.
6 Paterna S, Fasullo S, Parrinello G, *et al*. Short-term effects of hypertonic saline solution in acute heart failure and long-term effects of a moderate sodium restriction in patients with compensated heart failure with New York heart Association Class III (Class C) (SMAC-HF study). *Am J Med Sci* 2011; 342:27–37.

SALT I WATER

Dinicolantonio JJ, et al. Heart. 2013 Mar 12.

ORIGINAL INVESTIGATION

ONLINE FIRST

Aggressive Fluid and Sodium Restriction in Acute Decompensated Heart Failure

A Randomized Clinical Trial

Graziella Badin Aliti, RN, ScD; Eneida R. Rabelo, RN, ScD; Nadine Clausell, MD, PhD; Luís E. Rohde, MD, ScD; Andreia Biolo, MD, ScD; Luis Beck-da-Silva, MD, ScD

"Aggressive fluid and sodium restriction has no effect on weight loss or clinical stability at 3 days and is associated with a significant increase in perceived thirst. We conclude that sodium and water restriction in patients admitted for acutely decompensated HF are unnecessary."

Aliti GB, et al. JAMA Internal Medicine 2013;173:1058–64

7.3.1.3. SODIUM RESTRICTION: RECOMMENDATION

CLASS IIa

1. **Sodium restriction is reasonable for patients with symptomatic HF to reduce congestive symptoms. *(Level of Evidence: C)***

"the AHA recommendation for restriction of sodium to 1500 mg/d appears to be appropriate for most patients with stage A and B HF"

"for patients with stage C and D HF, currently there are insufficient data to endorse any specific level of sodium intake"

SALT | WATER

2013 ACCF/AHA Guideline for the Management of Heart Failure. Journal of the American College of Cardiology. 2013 Oct 15;62(16):e147–239.

7.3.1.3. SODIUM RESTRICTION: RECOMMENDATION

CLASS IIa

1. **Sodium restriction is reasonable for patients with symptomatic HF to reduce congestive symptoms. *(Level of Evidence: C)***

"Effects of sodium restriction in nonwhite HF patients and those with preserved ejection fraction are virtually unknown."

SALT | WATER

2013 ACCF/AHA Guideline for the Management of Heart Failure. Journal of the American College of Cardiology. 2013 Oct 15;62(16):e147–239.

Treating Anemia in HF

treat nutritional anemias (iron, folate, B12 deficiencies)

DON'T use ESAs

Treatment of Anemia with Darbepoetin Alfa in Systolic Heart Failure

Karl Swedberg, M.D., Ph.D., James B. Young, M.D., Inder S. Anand, M.D., Sunfa Cheng, M.D., Akshay S. Desai, M.D., Rafael Diaz, M.D., Aldo P. Maggioni, M.D., John J.V. McMurray, M.D., Christopher O'Connor, M.D., Marc A. Pfeffer, M.D., Ph.D., Scott D. Solomon, M.D., Yan Sun, M.S., Michal Tendera, M.D., and Dirk J. van Veldhuisen, M.D., Ph.D., for the RED-HF Committees and Investigators*

CONCLUSIONS

Treatment with darbepoetin alfa did not improve clinical outcomes in patients with systolic heart failure and mild-to-moderate anemia. Our findings do not support the use of darbepoetin alfa in these patients. (Funded by Amgen; RED-HF ClinicalTrials .gov number, NCT00358215.)

RED-HF. NEJM 2013;368:1210–9

Antithrombotics in CHF? **WARCEF**

P: DB-RCT, N=2,305 with EF<35%, in NSR.

I/C: warfarin INR 2-3.5 vs. aspirin x up to 6 years

O: time to the first ischemic stroke, intracerebral hemorrhage, or death from any cause

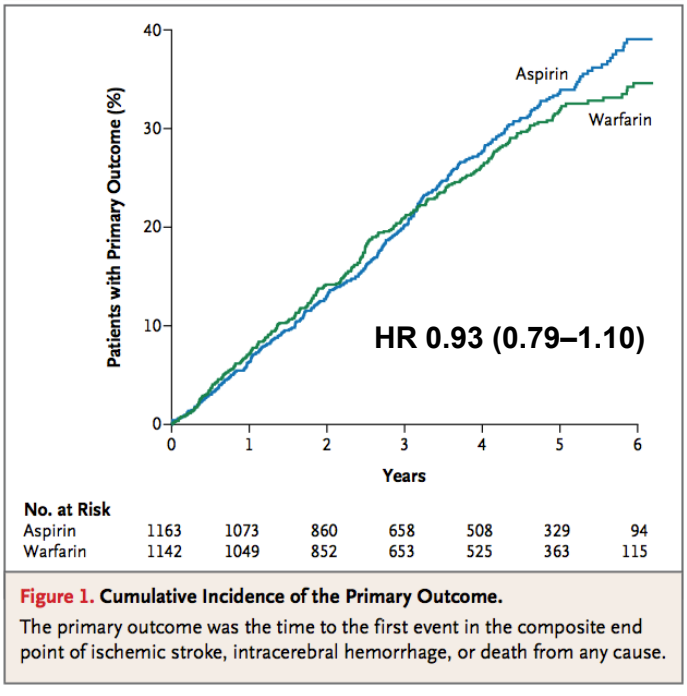


Figure 1. Cumulative Incidence of the Primary Outcome.
The primary outcome was the time to the first event in the composite end point of ischemic stroke, intracerebral hemorrhage, or death from any cause.

Ischemic stroke:
HR 0.52 (0.33-0.82)
NNT x 1 year: 46

Major bleeding:
OR 2.05 (1.36-3.12)
NNH over 1 year: 109

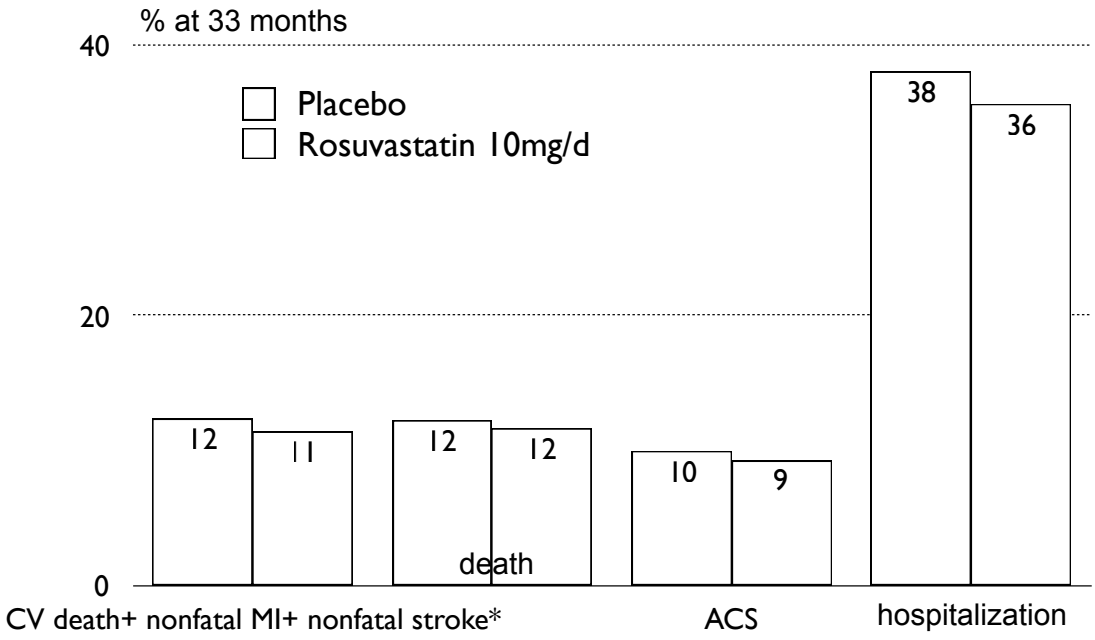
WARCEF. N Engl J Med 2012.

Antithrombotics in CHF?

- WASH [Am Heart J 2004;148:157-64] N=279
  - ASA vs. warfarin vs. no therapy
  - No difference in MI, death, stroke
  - More hospitalization in ASA group
- WATCH [unpublished, reported 10MAR04 heart.org] N=1,587
  - ASA vs. warfarin vs. clopidogrel
  - No difference in MI, death, stroke
  - More HF hospitalization in ASA group (22.2% vs. ~17% in other groups)

Statins and CHF - CORONA

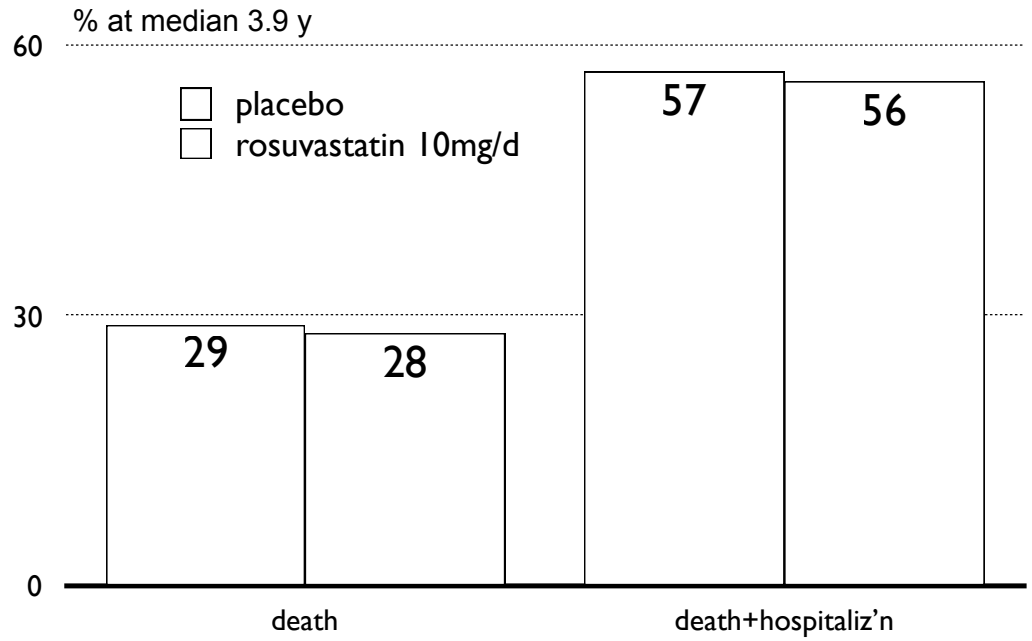
N=5011 >60y/o with EF<40%



CORONA.NEJM 2007;357:Nov6

Statins and CHF - GISSI-HF

N=4,574 with class II-IV CHF; 90% had EF<40%.



GISSI-HF.Lancet 2008;372;1231-9

Management of Acute HF Exacerbations

- furosemide [DOSE. N Engl J Med 2011;364:797-805]
- O_2
- morphine
- NTG
- Withhold B-blocker? No. [B-CONVINCED. Eur Heart J 2009;30;2186–2192]
- Aggressive H2O and Na depletion? No. [Aliti GB et al. JAMA Internal Medicine 2013;:1–7]
- Investigate for causes
  - Ischemia, Na+ intake, Medication non-adherence

Other Types of Heart Failure

Systolic dysfunction (= EF <40%)
Diastolic Dysfunction - HF-PEF
Valvular disease
High-Output failure (severe anemia, shock, thyrotoxicosis)

Systolic vs. Diastolic Dysfunction

	Systolic	**Diastolic**
Symptoms	identical	
EF	<35-40%	≥40%
Pathophys	Inability to eject blood from LV (contraction problem)	Inability to fill LV (relaxation problem)
Population	Mostly male, CAD	Mostly female, HTN
CXR	Enlarged heart (cardiothoracic ratio >0.55)	Normal heart size
Mortality rate	similar	
Drug efficacy (mortality)	ACE-I, B-blkr, spironolactone, hydralazine+ISDN, ARB?	?
Drug efficacy (morbidity)	digoxin, diuretics, others above	digoxin, candesartan, verapamil?, diltiazem?, B-blockers?, diuretics/ NOT: ACE-I, MRA

Case 1

- ID: A 74y M with CHF
- Profile: furosemide 40mg/d, ramipril 7.5mg/d, bisoprolol 10mg/d
- Issue: SCr previously stable at 130 mcmol/L. Slow rise to 165 mcmol/L over past 4 weeks.

- Possible interventions?

Case 2

- ID: A 70y F with CHF
- Profile: furosemide 20mg/d, bisoprolol 10mg/d, K-Dur 40 mEq/d.
- Issue: New Rx for spironolactone 25mg/d and candesartan 8mg/d

- What would you want to know before filling this Rx?

Case 3

- ID: A 79y M with CHF
- Profile: furosemide 80mg/d, bisoprolol 10mg/d, K-Dur 40 mEq/d, ramipril 10mg/d, spironolactone 25mg/d.
- Issue: Slow deterioration in exercise tolerance attributed to CHF progression.

  Can his CHF pharmacotherapy be augmented to improve his symptoms?

Case 4

- ID: A 82y M with CHF
- Profile: furosemide 80mg/d, ramipril 10mg/d. carvedilol 6.25mg bid added 1 week ago.
- Issue: Peripheral edema & exercise tolerance worsened in past 5 days.

- Possible interventions?

Case 5

- ID: A 82y M with CHF
- Profile: furosemide 80mg/d, ramipril 10mg, metoprolol 100 bid.
- Issue: developed a cough over the past 2 weeks.

- Analysis?

Case 6

- **ID**: 67 y/o M who had an NSTEMI 48h ago with pulmonary edema within 24h of the event. EF 25% today.
- **PMH**: hyperlipidemia, HTN, depression.
- **MPTA**: imagine it's a clean slate.
- **Profile**: imagine it's a clean slate.

- You're in charge of designing his drug therapy regimen today. What will it look like?