Heart Failure Medications: Who Needs What Drug Now?

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Dalhousie

1

Disclosures

- Honoraria and educational grants from:
  - Actelion (medications for pulmonary hyptertension)
  - Bayer (rivaroxaban)
- I will discuss two medications that are unique classes, and therefore have no comparison medication

2

My (intended) Approach

- I hope to be as practical as possible, with an aim to provide guidance.
- I will aim to minimize “data overload” and summarize.
- I will intentionally focus on treatment strategies in **documented and investigated CHF**, and focus on **treatments that you can prescribe**

3

Outline for Presentation

1. Background:
   - Who are you?
   - Why are we talking about CHF?
   - Quiz your knowledge at outset
2. How and why we should use “old drugs” for CHF more effectively: “CHF is a team sport!”
3. FYI: “New medications” for CHF that you should know something about; a teaser to stimulate your reading

4

Audience Participation Practice

1. Please all raise both hands and keep them high
2. Left half of room lower left hand
3. Right half of room lower right hand
4. If you are left handed, lower both hands

5

Question 1

- In my practice, I follow this many patients with LV systolic heart failure: (All hands up now)

1. < 5	both hand stay up
2. 6-10	right hand up
3. 11-20	left hand up
4. > 20	both hands down

6

Question 2

- All patients with an EF of 30, and NYHA class two status should be treated with:

1. ACE + Beta blocker — both hand stay up
2. ACE + MRA — right hand up
3. ACE or ARB + BB — left hand up
4. ACE + MRA + BB — both hands down

7

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8

Question 3

- The optimal dose of CHF medications in chronic systolic heart failure is:

1. A futile endeavor	both hand stay up
2. The target dose in study	right hand up
3. The max tolerated dose	left hand up
4. The DC dose from hospital	both hands down

9

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10

Question 4

- The annual mortality/hospitalization in optimally treated FC 2-3 CHF patients recently discharged in clinical trials is about?

1.	< 1%	both hand stay up
2.	2-5%	right hand up
3.	6-10%	left hand up
4.	>10%	both hands down

11

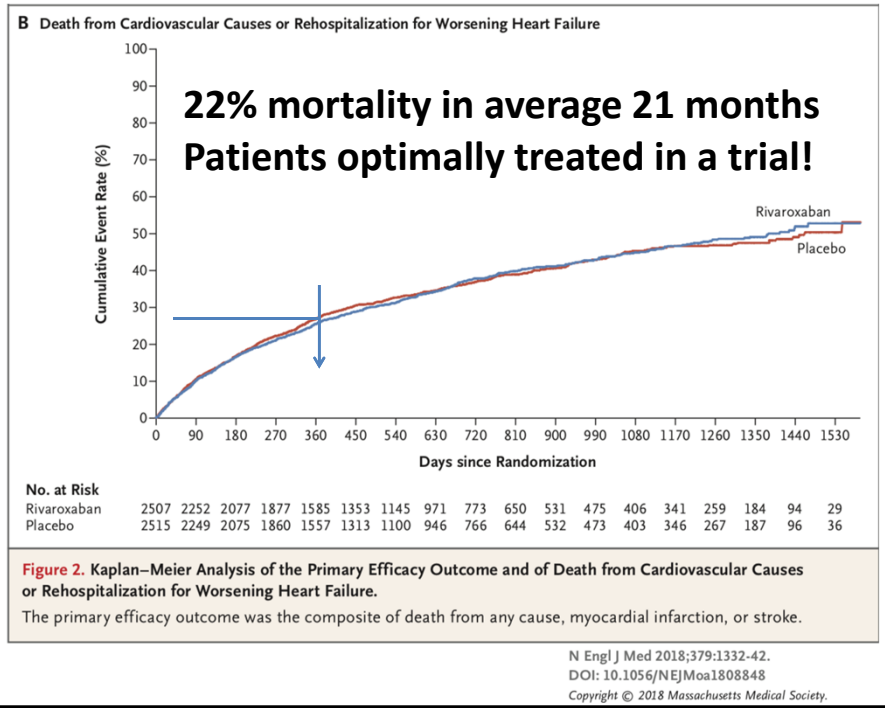

Figure 2. Kaplan–Meier Analysis of the Primary Efficacy Outcome and of Death from Cardiovascular Causes or Rehospitalization for Worsening Heart Failure.

The primary efficacy outcome was the composite of death from any cause, myocardial infarction, or stroke.

N Engl J Med 2018;379:1332-42.
DOI: 10.1056/NEJMoa1808848

12

Question 4

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2. 2-5% right hand up
3. 6-10% left hand up
4. **>10% both hands down**

13

Question 5

- Regarding sacubitril/valsartan (Entresto®) and ivabradine (Lancora®), I have:

1. Patients on both meds and a fair knowledge of medication
2. Patients on 1 of these meds and a some knowledge
3. Patients on 1 of these meds and little knowledge
4. I have no patients on either medication, and I have no knowledge
5. **I'm clearly in the wrong lecture (Its OK to leave!)**

14

What are we talking about?

- HFrEF (systolic LV failure)
  - EF < 40% and symptoms of CHF
- Not HFpEF
  - EF > 50 and symptoms of CHF
- Not HFmrEF
  - EF 40-50 and symptoms of CHF

15

TABLE 1
Clinical presentations of heart failure

Common	Uncommon
Dyspnea	Cognitive impairment*
Orthopnea	Altered mentation or delirium*
Paroxysmal nocturnal dyspnea	Nausea
Fatigue	Abdominal discomfort
Weakness	Oliguria
Exercise intolerance	Anorexia
Dependent edema	Cyanosis
Cough	
Weight gain	
Abdominal distension	
Nocturia	
Cool extremities	

**May be a more common presentation in elderly patients*

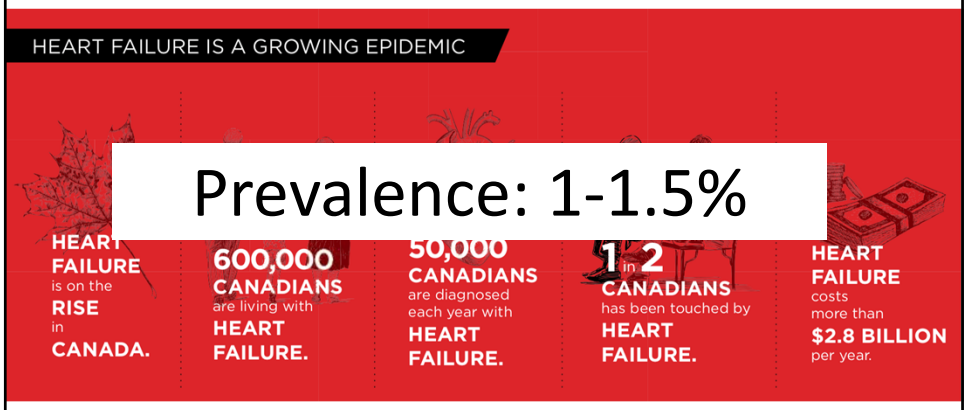
16

TABLE 2
New York Heart Association functional classification

Class	Definition
I	No symptoms
II	Symptoms with ordinary activity
III	Symptoms with less than ordinary activity
IV	Symptoms at rest or with any minimal activity

17

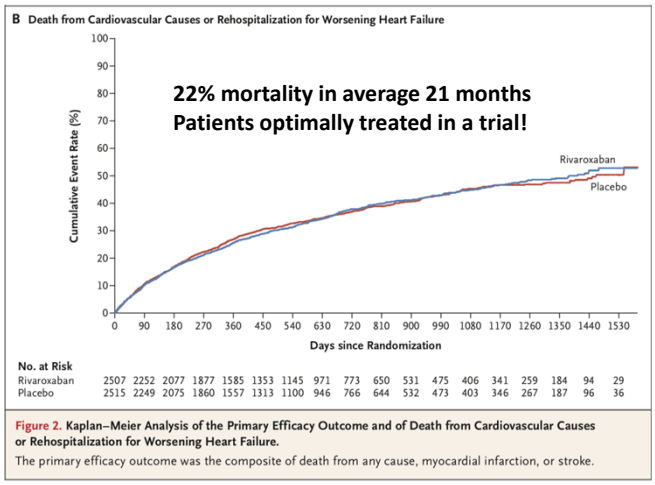
HSFC Report 2016



Prevalence: 1-1.5%

18

HFrEF is a lethal disease



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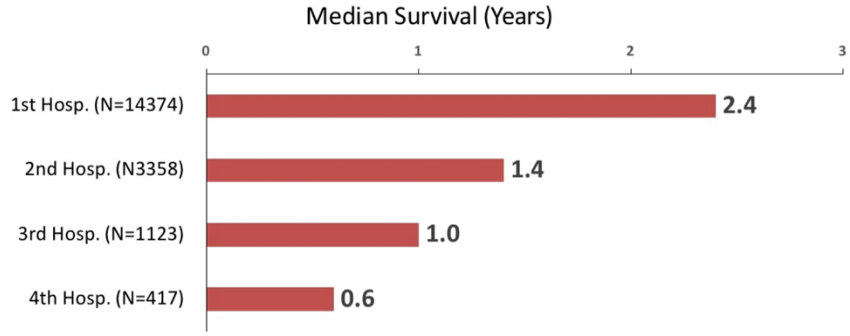
19

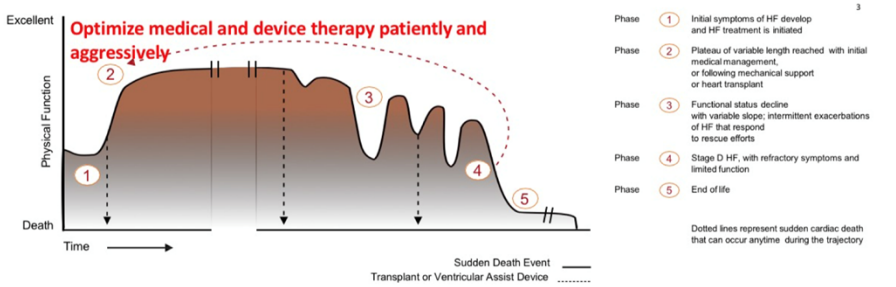
Prognosis Following HF Hospitalization in Canada



Setoguchi S et al., Am Heart J, 154(2), 203-205

20

HF is a Progressive Condition



1- Roger VL et al. JAMA 2004;292:344-350. 2- Gheorghiade & Pang. J Am Coll Cardiol2009;53:557–73.
3- Goodlin SJ. J Am Coll Cardiol. 2009 Jul 28;54(5):386-96.

21

How do we change the natural history?

- Evaluate the cause
  - Disease specific treatments?
  - Don't miss
    - Alcohol
    - Thyroid disease
    - Iron overload
    - HIV
    - Treatable ischemia/valvular disease
    - "tachycardia induced cardiomyopathy"

22

How do we change (natural) history?

- Non-pharmacologically
  - NaCl reduction (< 2 gm/d)
  - Fluid restriction (< 2l/d)
  - Exercise
  - Compliance/adherence with treatments
- Avoid CHF precipitating medications
  - Anti inflammatory medications
  - Steroids

23

Medications can:

Reduce symptoms only	**Reduce hard endpoints**
Diuretics	ACEi
Digoxin	Betablocker
Nitrates alone	ARB in ACEi intolerant
	MRA's
	Hydralazine/Nitroglycerin
	Sacubitril/Valsartan
	Ivabradine

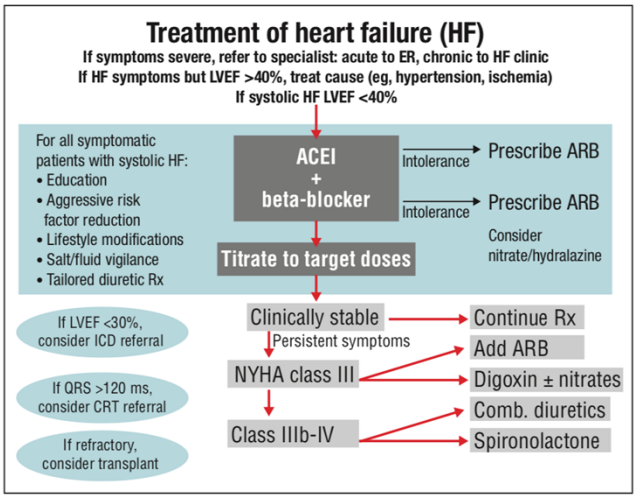
24

How do these drugs work?

- Low EF causes reduced CO (decrease stroke volume)
- In short term, body reacts to increase CO
  - Activate adrenergic system (flog a failing pump)
  - Vasoconstriction (move blood to critical organs)
  - Retain salt and water (increase circulating volume)
- Short term "reflexes" have adverse long term consequences

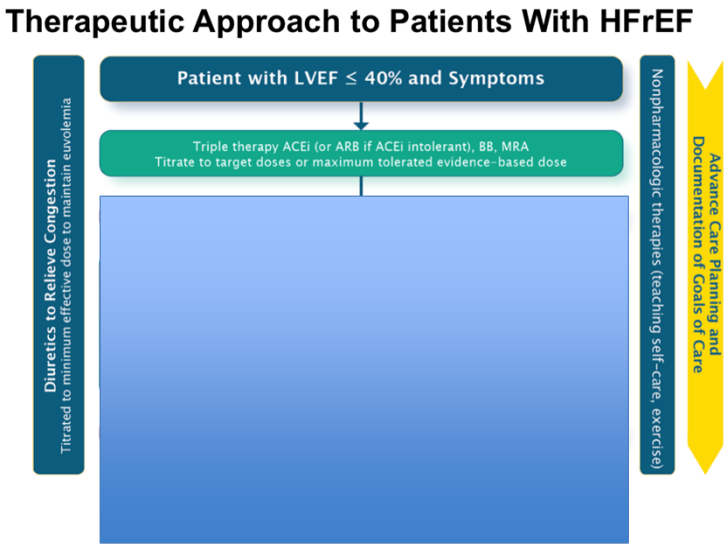
25

2006 CCS Guidelines



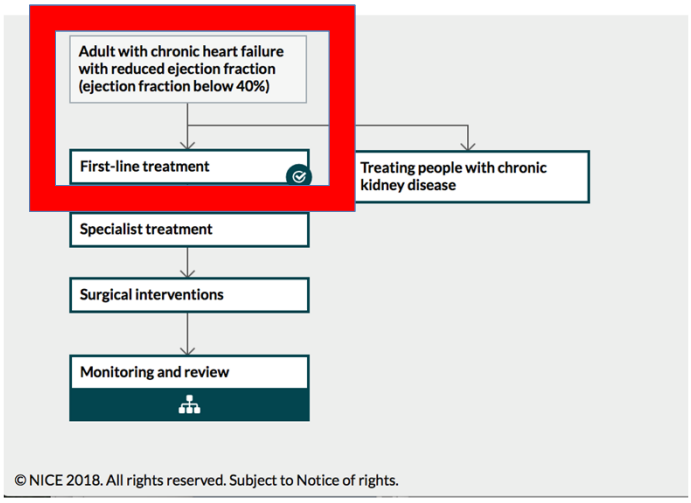
26

2017 CCS Guidelines



27

Treating chronic heart failure with reduced ejection fraction



28

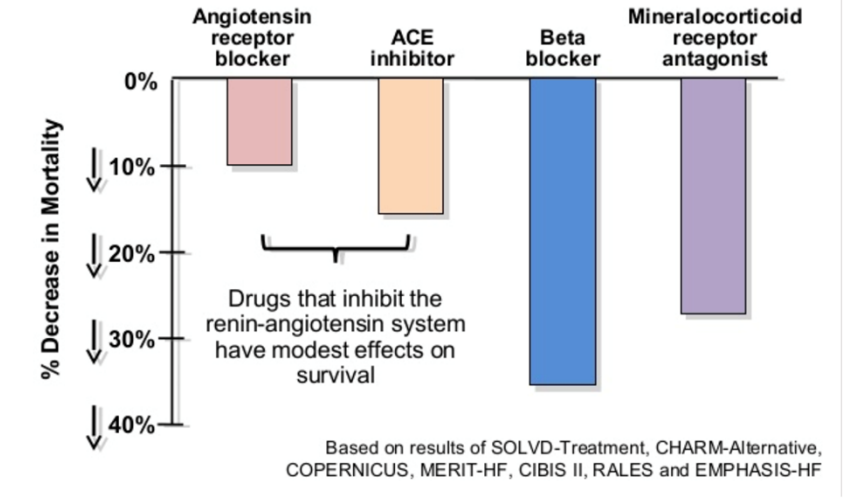
Triple Therapy for HFrEF

ACE INHIBITOR
+
B-BLOCKER
(max tolerated dose)

MRA
(max tolerated dose)

29

Drugs That Reduce Mortality in Heart Failure With Reduced Ejection Fraction



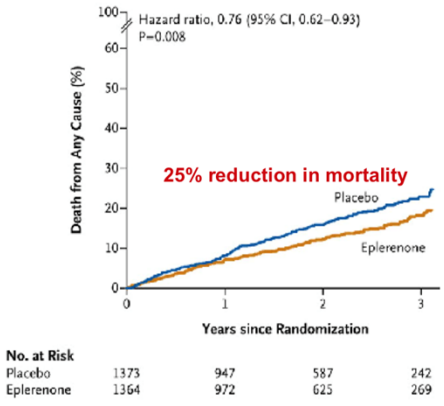
30

Aldo Antagonism (MRA) in HF

	Post-MI	Class II	Class III-IV HF
Trial	EPHESUS	EMPHASIS	RALES
Sample Size	6632	2737	1663
Baseline Mortality	12% / yr	9% / yr	23% / yr
Reduction in Mortality	↓ 15%	↓ 24%	↓ 30%
NNT/year to save 1 life	59	51	14

31

Triple Therapy
ACEi/ARB + beta blocker + MRA



EMPHASIS HF

2700+ patients, NYHA II

Eplerenone vs Placebo;

Median f/u 21mo

Mortality in placebo group = 15.5%

Baseline ACEi/ARB and beta blocker in 94% and 87%

Zannad et al NEJM 2011

32

TABLE 3
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
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
ARB		
Candesartan	4 mg od	32 mg od
Valsartan	40 mg bid	160 mg bid
Aldosterone antagonist		
Spironolactone	12.5 mg od	50 mg od
Eplerenone†	25 mg od	50 mg od
Vasodilator		
Isosorbide dinitrate	20 mg tid	40 mg tid
Hydralazine	37.5 mg tid	75 mg tid

33

Table. Demonstrated Benefits of Evidence-Based Therapies for Patients With Heart Failure and Reduced Ejection Fraction

Evidence-Based Therapy	Relative Risk Reduction in All-Cause Mortality in Pivotal Randomized Clinical Trial(s), %	NNT to Prevent All-Cause Mortality Over Time	NNT for All-Cause Mortality[a]
ACEI/ARB	17	22 over 42 mo	77
ARNI[b]	16	36 over 27 mo	80
β-Blocker	34	28 over 12 mo	28
Aldosterone antagonist	30	9 over 24 mo	18

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; CRT cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator, NNT, number needed to treat.

[a] Standardized to 12 months.

JAMA Cardiol. 2016;1(6):714-717. doi:10.1001/jamacardio.2016.1724
Published online June 22, 2016.

34

We need you.
This is a team sport

Your patients need you even more!

35

First Line Treatment

1. ACEi or ARB if ACEi intolerant
2. Beta-blockade
3. MRA if on two drugs and continue to have symptoms

- Drugs up-titrated about Q2 weeks.
- Each visit volume status, Vitals (postural if any concern), renal function if changing ACEi/ARB or MRA

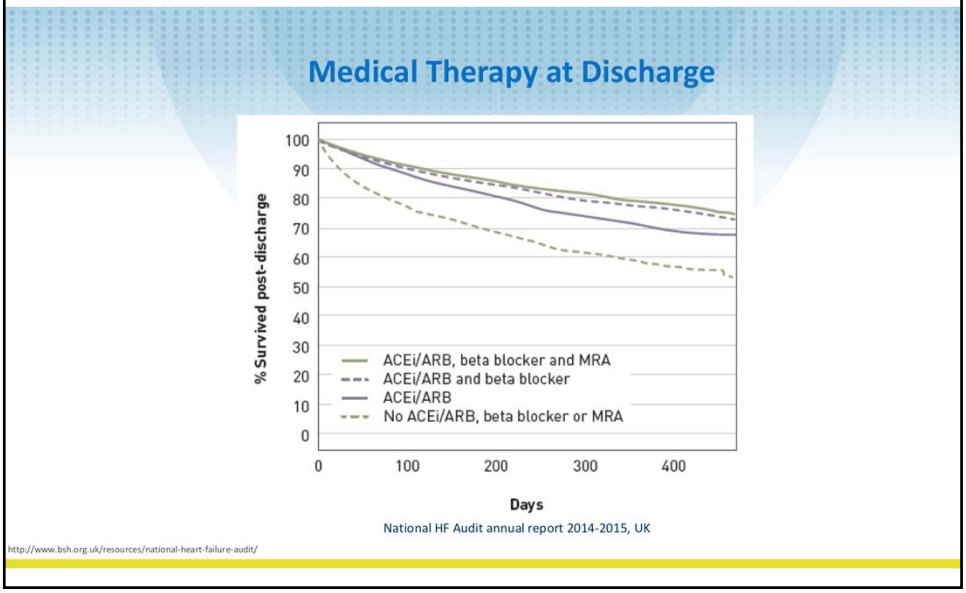
36

Problems with office based CHF optimization

1. I'm better, there is no need to increase medication
2. Monitoring required
   - BP, Cr, K, Postural hypotension
3. Training for a race…multiple visits
4. Diuretic dosing: minimum effective
5. Adverse effects as drug doses increase
6. "It's too complicated" "I don't have time"

37

UK Audit: Better treatment = better outcomes



38

How quickly can you get to target/max tolerated Rx?

- ACE trials:
  - SOLVD: 6 weeks to get to 10 mg BID
- BB trials: on ACE/ARB already
  - CIBIS II: 12 weeks to 10 mg daily
- MRA trials: on ACE/ARB and BB already
  - EMPHASIS: 4 weeks to 50 mg daily
- CCS HF guidelines consensus: 6 months long enough… so get to it!

SOLVD, AJC 1990; CIBIS, Lancet 1999; Zannad, NEJM 2011; Howlett CJC 2016

39

Managing chronic heart failure NICE Pathways

Clinical review

All people with chronic heart failure need monitoring. This monitoring should include:

- a clinical assessment of functional capacity, fluid status, cardiac rhythm (minimum of examining the pulse), cognitive status and nutritional status
- a review of medication, including need for changes and possible side effects
- an assessment of renal function. (This is a minimum. People with comorbidities or co-prescribed medications will need further monitoring. Monitoring serum potassium is particularly important if a person is taking digoxin or an MRA.)

40

Cost of therapies

- ACEi generic 16/month
- ARB generic
- B-Blocker generic 15/month
- MRA: 17/month
  - use aldactone unless gynecomastia in which case eplerenone (much more expensive)

41

Newer Therapies

Know about these medications

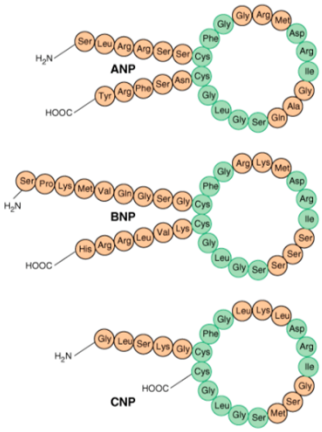
42

Neprilysin is an enzyme that breaks down “good hormones” that counteract CHF

More “good hormones” (naturetic peptides) helps the patient avoid further CHF

43

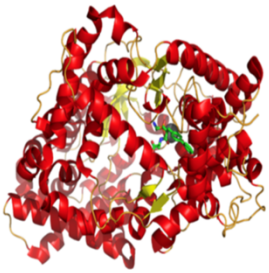
Natriuretic peptides: How the heart protects itself



- The heart is an endocrine organ
- It secretes A and B type natriuretic peptides into the circulation where they act on the blood vessels, kidneys, adrenal glands, brain etc
- These peptides protect the heart from volume and pressure overload

44

Neprilysin (neutral endopeptidase EC 3.4.24.11)



- A zinc-dependent membrane metalloprotease first identified in the renal brush-border
- Degrades ANP>CNP>BNP (and also urodilatin?)
- Also bradykinin, substance P, adrenomedullin, enkephalins, apelin, GLP-1
- Angiotensins, endothelins? Amyloid beta-peptides.
- Long history of attempts to develop neprilysin inhibitors alone (1989) and in combination with ACE inhibitors (1997)

45

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

CONCLUSIONS

LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure. (Funded by Novartis; PARADIGM-HF ClinicalTrials.gov number, NCT01035255.)

46

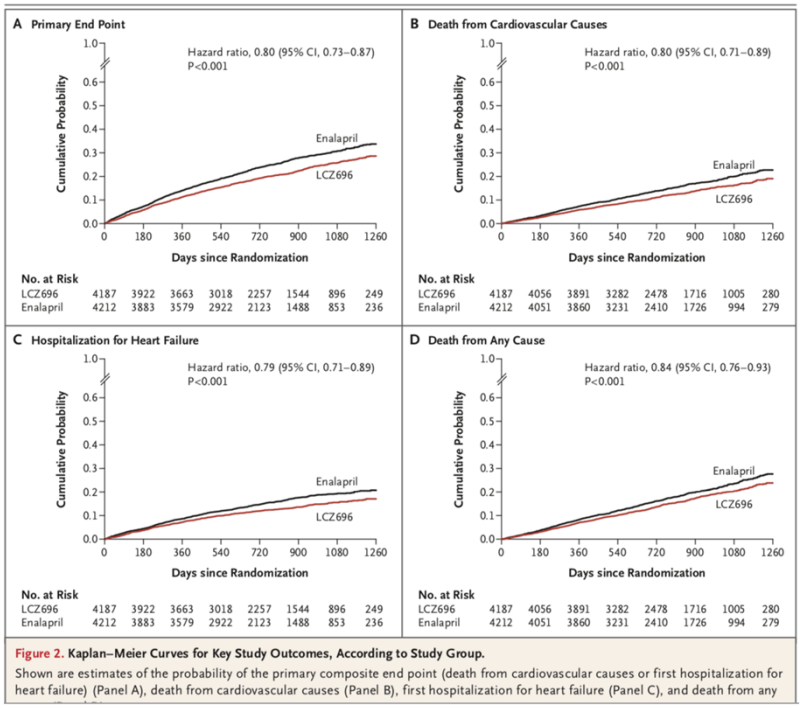


Figure 2. Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.
Shown are estimates of the probability of the primary composite end point (death from cardiovascular causes or first hospitalization for heart failure) (Panel A), death from cardiovascular causes (Panel B), first hospitalization for heart failure (Panel C), and death from any

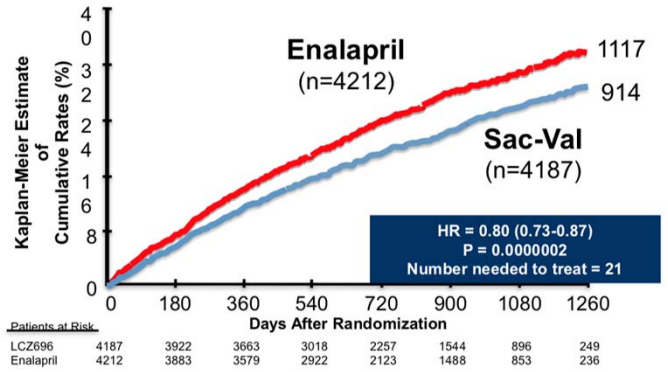
47

Table 3. Adverse Events during Randomized Treatment.*

Event	LCZ696 (N=4187)	Enalapril (N=4212)	P Value
	no. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dl	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dl	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/liter	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/liter	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema†			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Use of catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalization without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	—

48

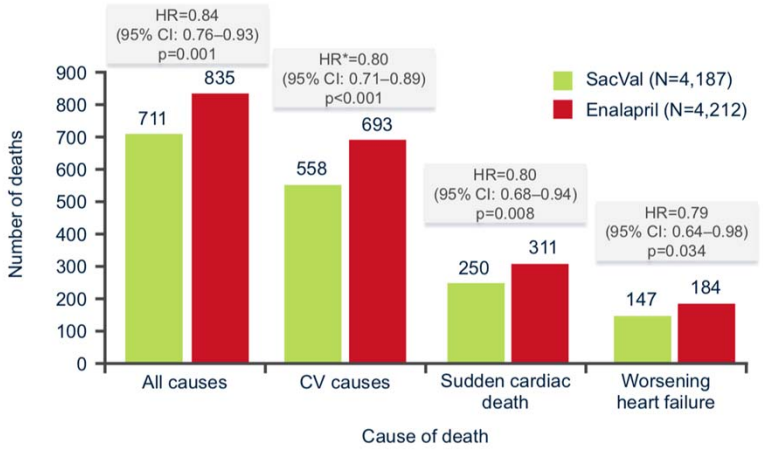
PARADIGM-HF: Primary endpoint (CV death or HF hospitalization)



McMurray et al. N Engl J Med 2014;371(11):993-1004

49

PARADIGM-HF
Mode of Death



The majority (>80%) of deaths in PARADIGM-HF had a CV cause
The mortality benefit of LCZ696 is related to the observed reduction in sudden cardiac death and death due to worsening heart failure

50

Issues

- How to use: transition from and ACEi requires drug holiday
- Hypotension and renal dysfunction
- Cost
  - 60 tabs any dose 268.84 (9$/day)
- Public reimbursement in all provinces but NS
- Remains for now… a specialist drug, suspect this may change
- It has better outcomes, based upon a large, single RCT.
- **PREDICTION: You will see more of this medication.**

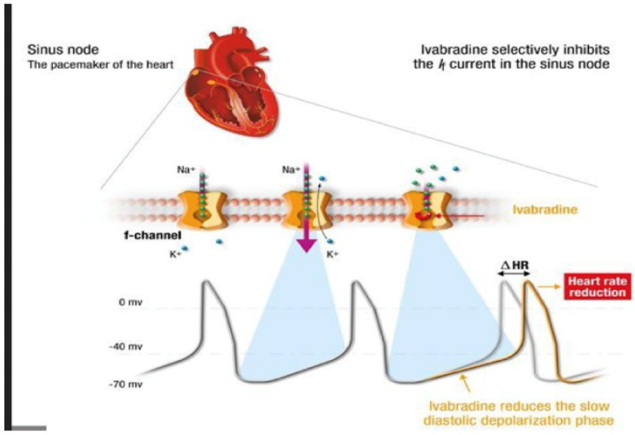
51

Ivabridine

An I(f) current blocker that slows sinus rate, but does not apparently impact the heart otherwise.

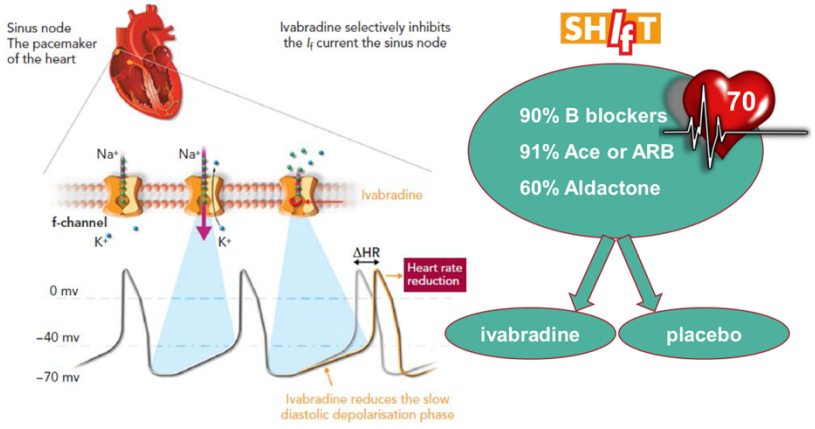
52

Newer therapies: Ivabradine



53

Newer Therapies for HFrEF: Ivabradine

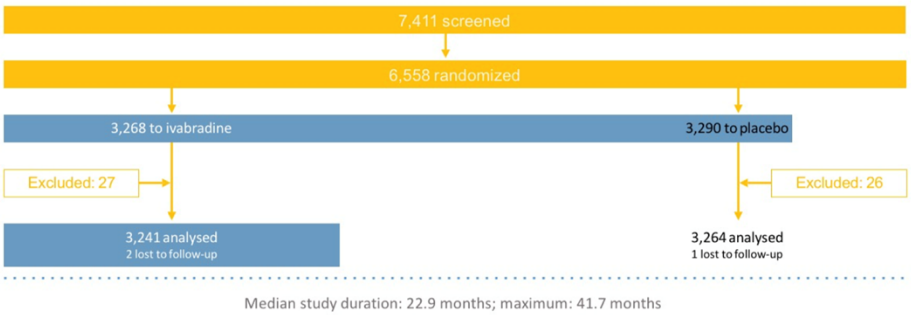


Cardiac Fail Review Vol 3(1) Apr 27, 2017

Swedberg K, et al. Eur j Heart Fail 2010;12:75-81

54

Newer therapies: Ivabradine



Swedberg K, et al. SHIFT Investigators. Lancet. 2010;376(9744):875-85

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Primary objective

To evaluate whether the I_f inhibitor ivabradine improves cardiovascular outcomes in patients with

1. Moderate to severe chronic heart failure
2. Left ventricular ejection fraction ≤35%
3. Heart rate ≥70 bpm in sinus rhythm
4. Best recommended therapy

Swedberg K, et al. *Eur J Heart Fail.* 2010;12:75-81

www.shift-study.com

56

Ivabradine Significantly Reduced Mortality

The higher the HR at baseline, the greater the benefits

- Patients with baseline HR ≥ 70 and ≥ 77 bpm

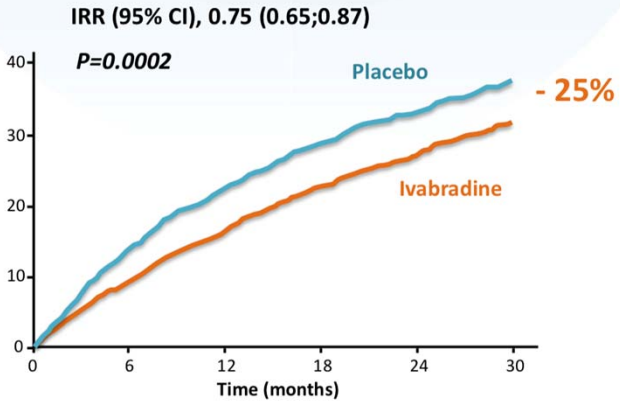
	Significant reduction	
	≥ 70 bpm	≥ 77 bpm
Primary endpoints		
CV death or hospital admission for worsening HF	18% (p<0.0001)	25% (p<0.0001)
Mortality endpoints		
All-cause mortality	10% (*p* = 0.092)	19% (p=0.0074)
Cardiovascular mortality	9% (*p* = 0.128)	19% (p=0.0137)
Death from HF	26% (p=0.014)	39% (p=0.0017)
Other endpoints		
All-cause hospital admission	11% (p=0.003)	18% (p=0.0002)
Any CV hospital admission	15% (p=0.0002)	21% (p<0.0001)
Hospital admission for worsening of HF	26% (p<0.0001)	31% (p<0.0001)

Swedberg et al. *Lancet* 2010; 376: 875-85;
Krum & Sindone. *Heart Lung Circ* 2013; 22: s87-8.

57

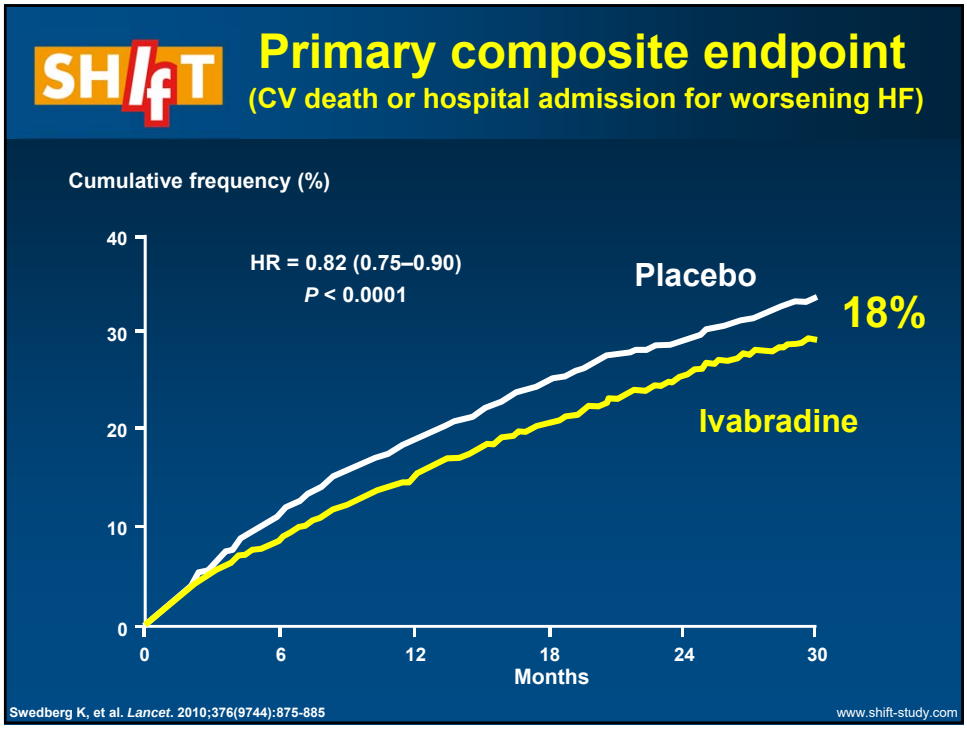
Effect of Ivabradine on Total HF Hospitalizations

Cumulative incidence of HF hospitalizations (first and repeated)



Borer J, et al. Eur Heart J 2012. Online 27 August 2012

58



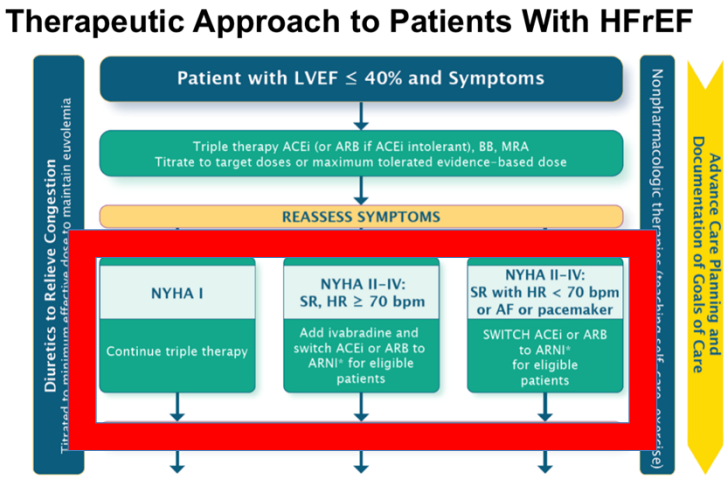
59

Ivabradine Issues

- Slow to market, approved 2017, but now on provincial formulary for 4 provinces
- When to use?
  - On optimal CHF treatment, in NSR, HR > 77, FC 2-3
- Small increase in AF (1% absolute)
- Cost:
  - 56 tab 5 bid 68.19
  - 56 tab 7.5 bid 114.23
- It works, in selected patients with reductions in major endpoints.

60

2017 CCS Guidelines



61

Conclusions

- HFrEF remains a lethal, common disease
- Optimal treatment require help from family physicians maximize benefit of “triple therapy”
- New medications appear to provide incremental benefits in hospitalization and CHF mortality, and total mortality.
- New agents increase complexity of care, cost, and need for follow up.

62