Optimal Diagnosis and Management of Heart Failure

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ACP, February 2017

University of Colorado Hospital
Advanced Heart Failure Center
ANSCHUTZ MEDICAL CAMPUS

University of Colorado Hospital
UNIVERSITY OF COLORADO HEALTH

Presenter Disclosure Information

- I will not discuss off label use or investigational use in my presentation.
- I have financial relationships to disclose:
  - Employee of: University of Colorado
  - Consultant for: J&J/Janssen, Novartis, St. Jude, ZS Pharma
  - Stockholder in: None
  - Research support from: NIH / NHLBI, PCORI, AHA
  - Honoraria from: None

Reading/References

ACCF/AHA Practice Guideline

2013 ACCF/AHA Guideline for the Management of Heart Failure

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines

http://circ.ahajournals.org/content/128/16/e240.full.pdf+html

EUROPEAN SOCIETY OF CARDIOLOGY®

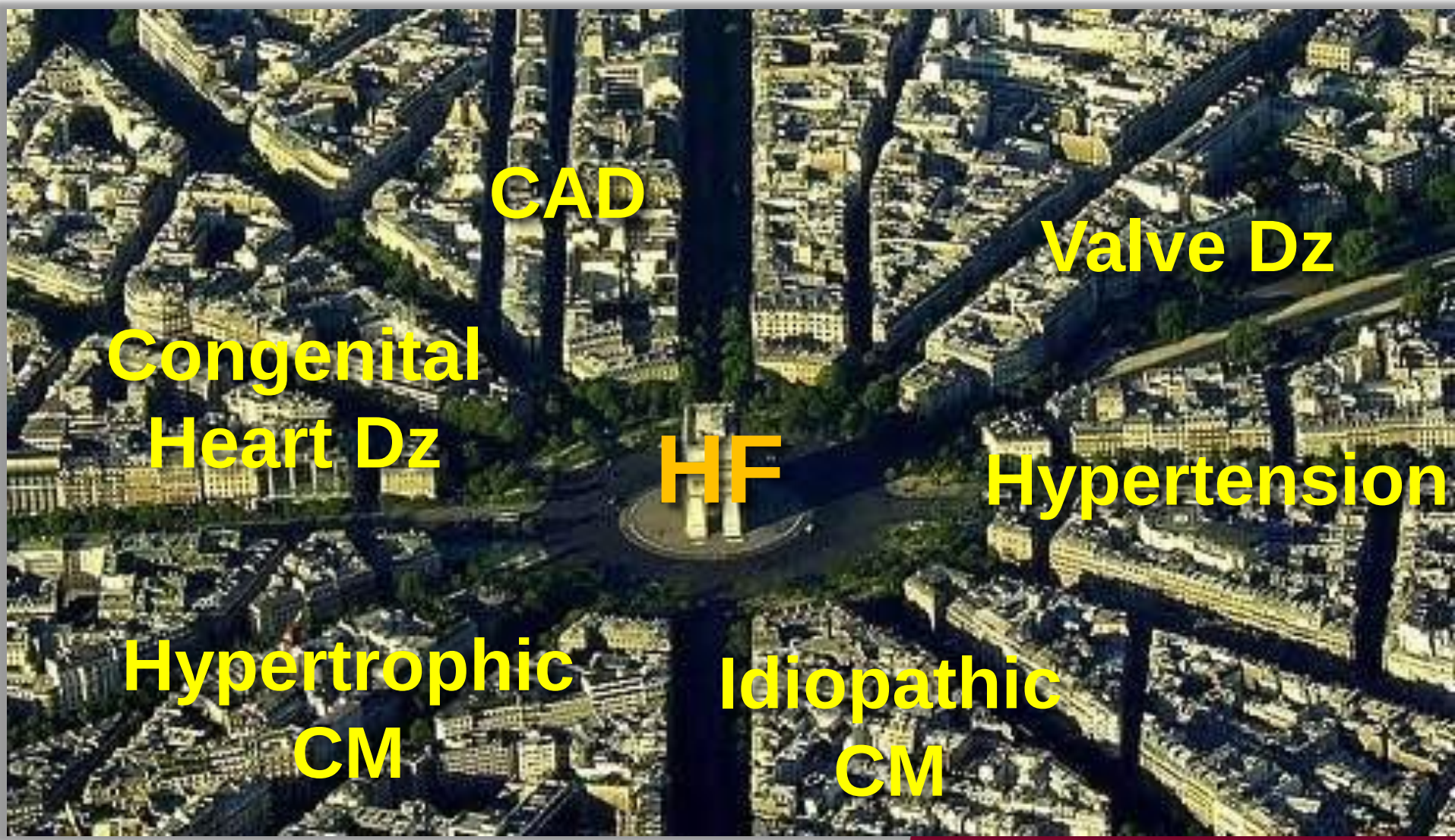
European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

http://www.escardio.org/guidelines-surveys/esc-guidelines/Pages/acute-chronic-heart-failure.aspx

All Roads Lead to HF



Epidemiology

- Common
  - ~6 million Americans have HF (prevalence)
  - ~550,000 Americans develop HF annually (incidence)
- Costly
  - 12,000,000 clinic visits
  - 1,200,000 hospitalizations in the US annually
    - Medicare: 7% of primary discharge diagnoses, #1 billing
  - Direct medical costs: ~$30 billion
- Deadly
  - Any mention HF: 281,000 / year
  - Primary HF: 57,000 / year

AHA. Heart Disease and Stroke Statistics. *Circulation* 2016

AHA Policy Statement

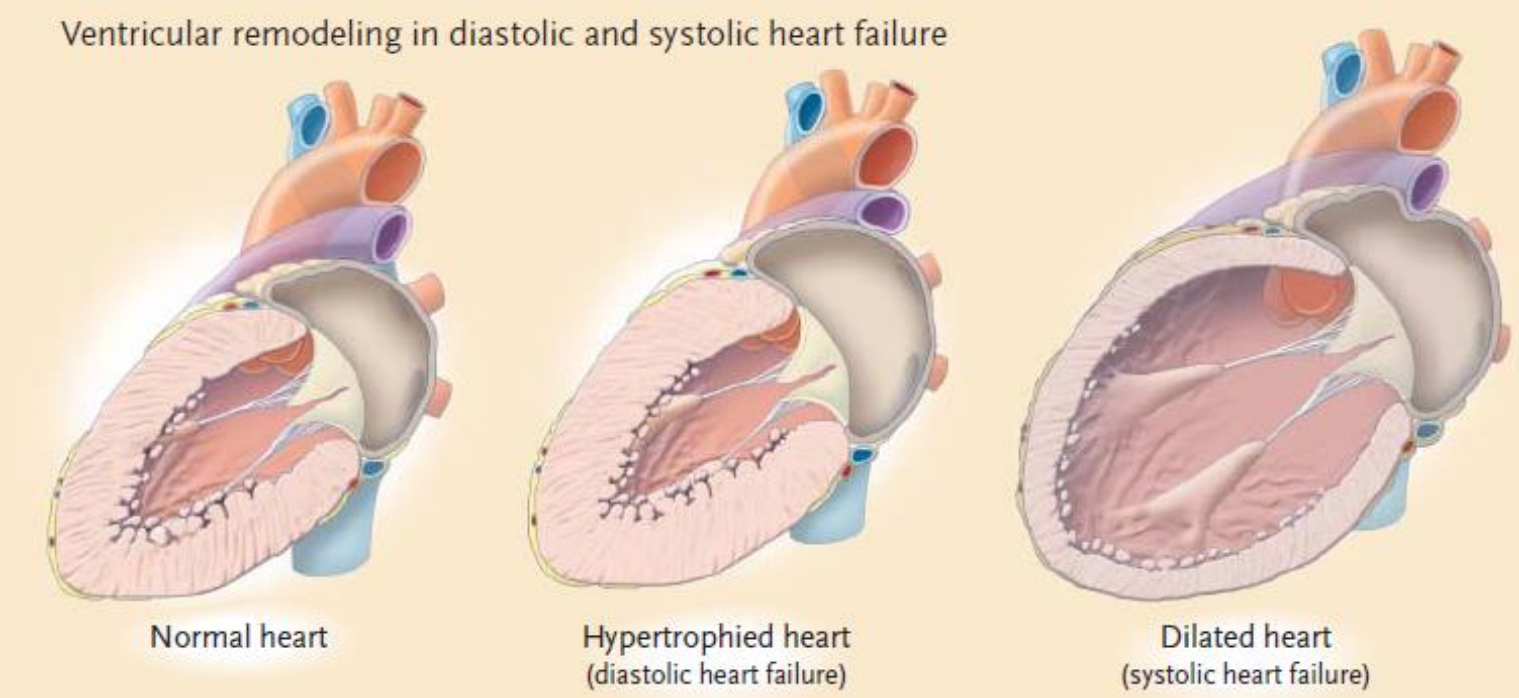
Forecasting the Impact of Heart Failure in the United States

A Policy Statement From the American Heart Association

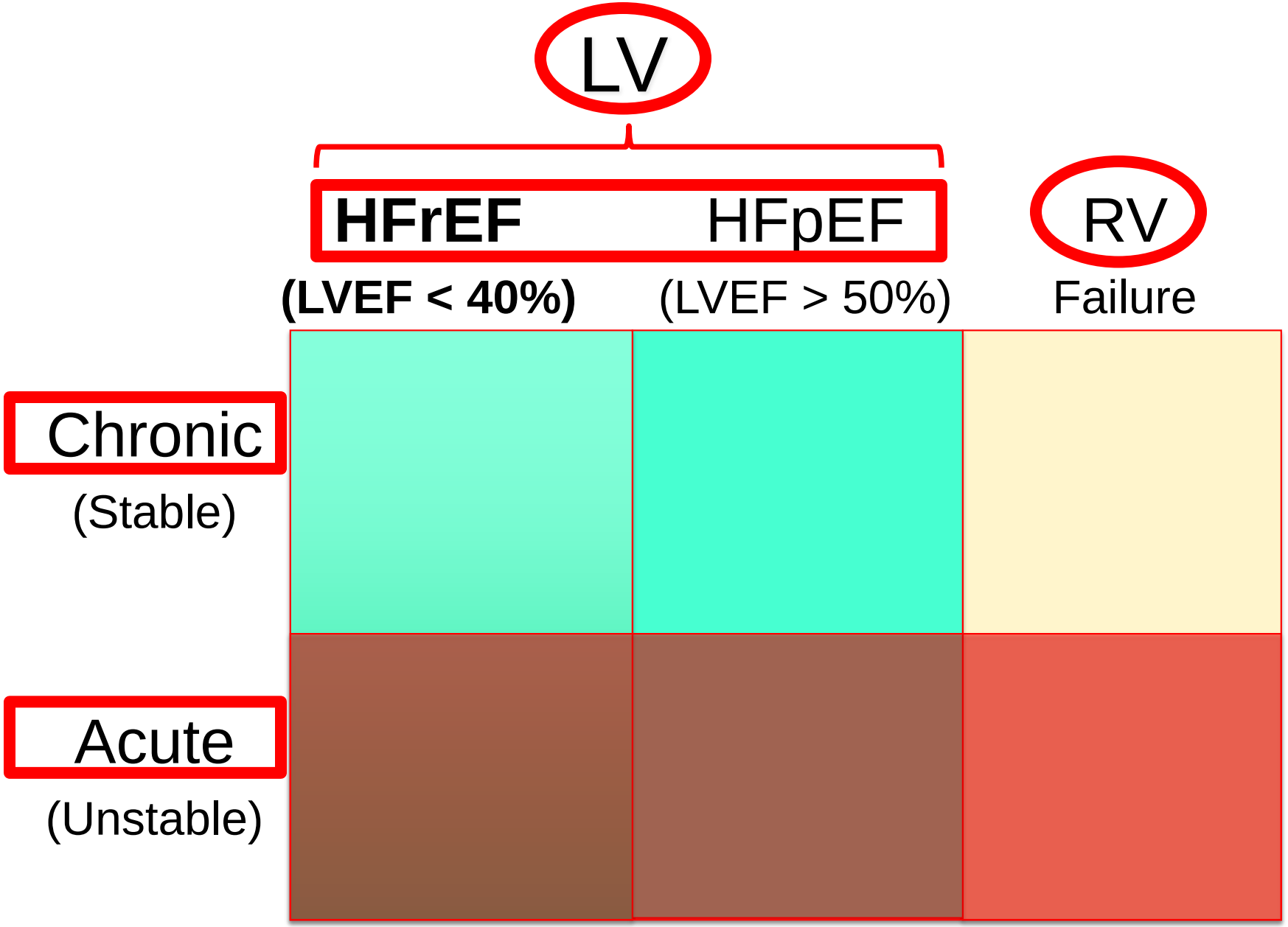
Paul A. Heidenreich, MD, MS, FAHA, Chair; Nancy M. Albert, PhD, RN, FAHA;

Year	All	18–44 y	45–64 y	65–79 y	≥80 y
2012	5 813 262	396 578	1 907 141	2 192 233	1 317 310
2015	6 190 606	402 926	1 949 669	2 483 853	1 354 158
2020	6 859 623	417 600	1 974 585	3 004 002	1 463 436
2025	7 644 674	434 635	1 969 852	3 526 347	1 713 840
2030	8 489 428	450 275	2 000 896	3 857 729	2 180 528

Diagnosis and Classification

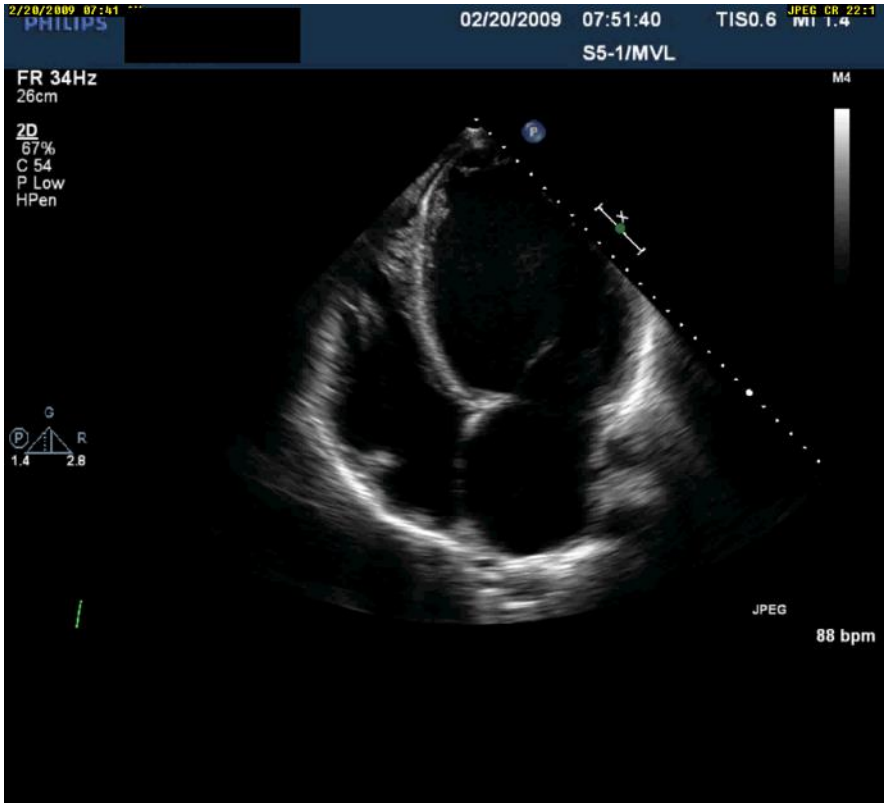


Jessup. NEJM 2003;348:2007-18.


LV
HFrEF
HFpEF
RV
(LVEF < 40%)
(LVEF > 50%)
Failure
Chronic
(Stable)
Acute
(Unstable)

HFrEF?


easy
STAPLES


PHILIPS
02/20/2009 07:51:40
TIS0.6
S5-1/MVL
FR 34Hz
26cm
2D
67%
C 54
P Low
HPen
M4
1.4
2.8
JPEG
88 bpm

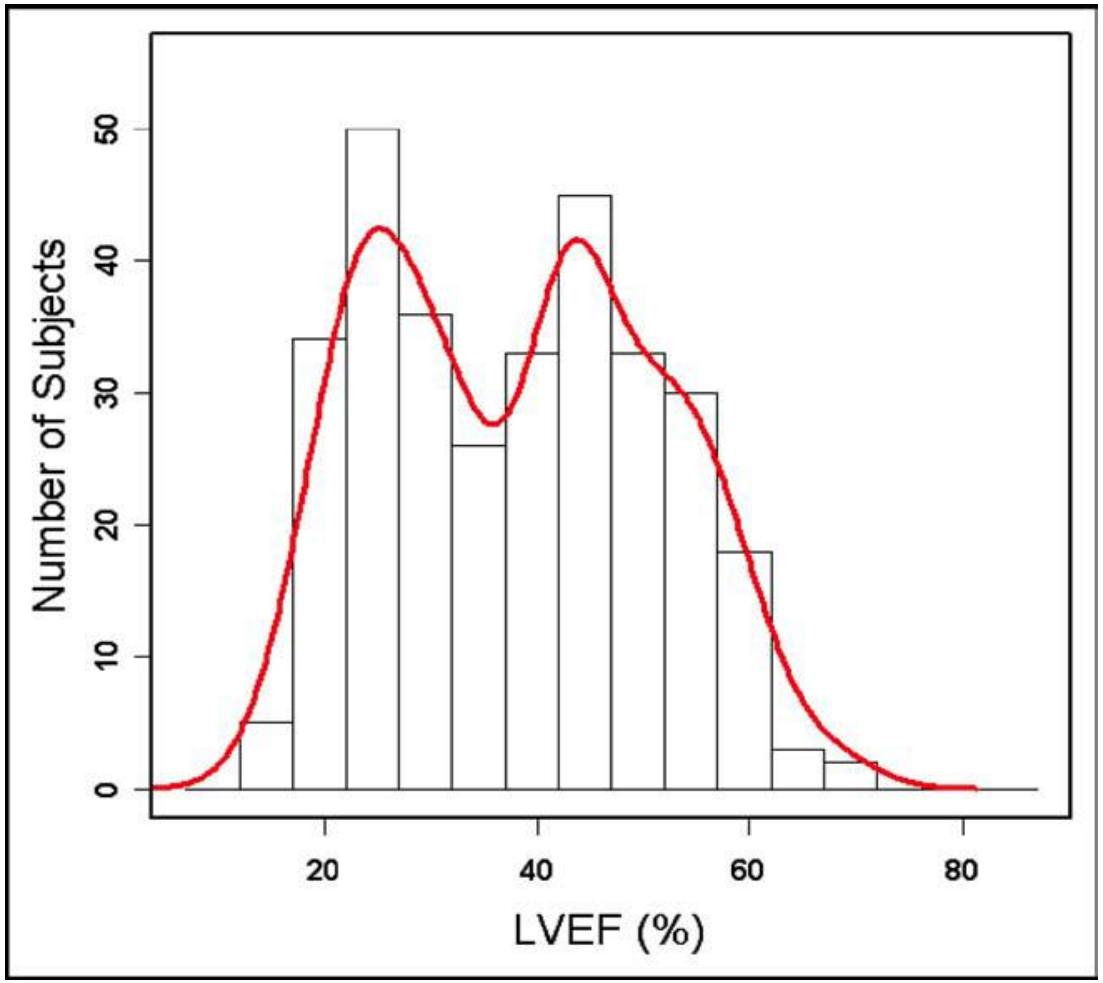
“The truth is rarely pure and never simple” – Oscar Wilde

- Borderline / middle range (HFmrEF): LVEF 41-49%
- Improved (HFiEF): LVEF was <40% now >50%

Table 3. Definitions of HF*r*EF and HF*p*EF

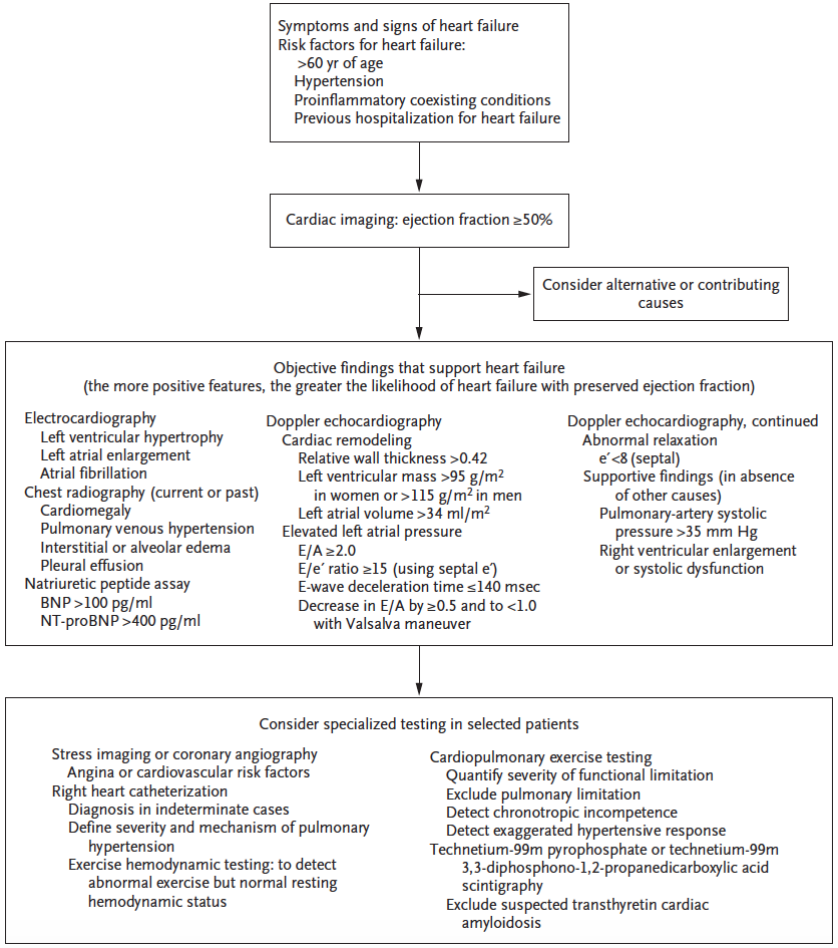
Classification	EF (%)	Description
I. Heart failure with reduced ejection fraction (HF*r*EF)	≤40	Also referred to as systolic HF. Randomized controlled trials have mainly enrolled patients with HF*r*EF, and it is only in these patients that efficacious therapies have been demonstrated to date.
II. Heart failure with preserved ejection fraction (HF*p*EF)	≥50	Also referred to as diastolic HF. Several different criteria have been used to further define HF*p*EF. The diagnosis of HF*p*EF is challenging because it is largely one of excluding other potential noncardiac causes of symptoms suggestive of HF. To date, efficacious therapies have not been identified.
a. HF*p*EF, borderline	41 to 49	These patients fall into a borderline or intermediate group. Their characteristics, treatment patterns, and outcomes appear similar to those of patients with HF*p*EF.
b. HF*p*EF, improved	>40	It has been recognized that a subset of patients with HF*p*EF previously had HF*r*EF. These patients with improvement or recovery in EF may be clinically distinct from those with persistently preserved or reduced EF. Further research is needed to better characterize these patients.

Distribution of LVEF



Gaasch WH et al. Am J Cardio 2009;104:1413
De Keulenaer GW, Brutsaert DL. Circ 2009;119:3044

HFpEF?



- Exclude other causes
- BNP?
- Echo findings?
- RHC?

Gestalt

Redfield. N Engl J Med 2016;375:1868-77.

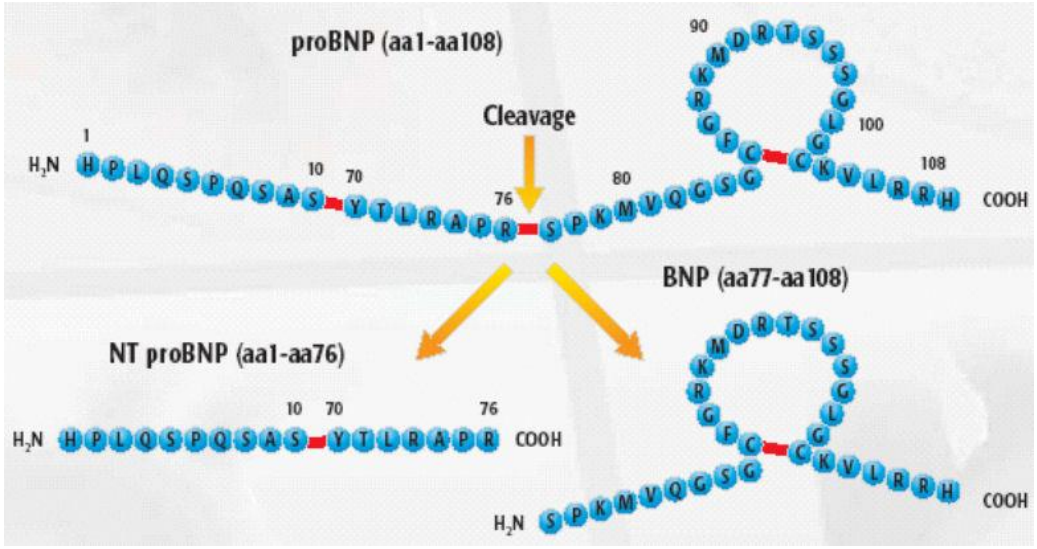
Testing: Echo + BNP/NTpro + ?

Recommendations	Class [a]	Level [b]
The following diagnostic tests are recommended/should be considered for initial assessment of a patient with newly diagnosed HF in order to evaluate the patient's suitability for particular therapies, to detect reversible/treatable causes of HF and co-morbidities interfering with HF:		
- haemoglobin and WBC - sodium, potassium, urea, creatinine (with estimated GFR) - liver function tests (bilirubin, AST, ALT, GGTP) - glucose, HbA1c - lipid profile - TSH - ferritin, TSAT = TIBC	I	C
- natriuretic peptides	IIa	C
Additional diagnostic tests aiming to identify other HF aetiologies and comorbidities should be considered in individual patients with HF when there is a clinical suspicion of a particular pathology (see Table 3.4 on HF aetiologies).	IIa	C
A 12-lead ECG is recommended in all patients with HF in order to determine heart rhythm, heart rate, QRS morphology, and QRS duration, and to detect other relevant abnormalities. This information is needed to plan and monitor treatment.	I	C
Exercise testing in patients with HF:		
- is recommended as a part of the evaluation for heart transplantation and/or mechanical circulatory support (cardiopulmonary exercise testing);	I	C
- should be considered to optimize prescription of exercise training (preferably cardiopulmonary exercise testing);	IIa	C
- should be considered to identify the cause of unexplained dyspnoea (cardiopulmonary exercise testing).	IIa	C
- may be considered to detect reversible myocardial ischaemia.	IIb	C
Chest radiography (X-ray) is recommended in patients with HF to detect/exclude alternative pulmonary or other diseases, which may contribute to dyspnoea. It may also identify pulmonary congestion/oedema and is more useful in patients with suspected HF in the acute setting.	I	C
Right heart catheterization with a pulmonary artery catheter:		
- is recommended in patients with severe HF being evaluated for heart transplantation or mechanical circulatory support;	I	C
- should be considered in patients with probable pulmonary hypertension assessed by echocardiography in order to confirm pulmonary hypertension and its reversibility before the correction of valve/structural heart disease;	IIa	C
- may be considered in order to adjust therapy in patients with HF who remain severely symptomatic despite initial standard therapies and whose haemodynamic status is unclear.	IIb	C
EMB should be considered in patients with rapidly progressive HF despite standard therapy when there is a probability of a specific diagnosis which can be confirmed only in myocardial samples and specific therapy is available and effective.	IIa	C
Thoracic ultrasound may be considered for the confirmation of pulmonary congestion and pleural effusion in patients with AHF.	IIb	C
Ultrasound measurement of inferior vena cava diameter may be considered for the assessment of volaemia status in patients with HF.	IIb	C

2016 ESC Guideline

- CBC, CMP
- TSH
- Ferritin
- CXR
- EKG
  - Holter?
- 24hr BP
- MRI v cath?

Natriuretic Peptides



- Two assays:
  - BNP
    - Normal? (<100)
    - *Clearance decreased by ARNI (sacubitril)*
  - NT-proBNP
    - N-terminus breakdown product of BNP
    - Inactive
    - Half life ~120 minutes (BNP 20 minutes)
      - *~6 times the BNP*

- Both increase with age

Specific HF Goals of Rx

1. Correction of the underlying cause of HF
   - e.g. revascularization for ischemia
   - not possible for many causes (e.g. infarcted tissue)
2. Elimination of precipitating factors
   - e.g. infection, anemia, etc
3. Reduction of congestion
4. Improve blood flow
   - Modulate neurohormal activation
   - Devices / transplantation

2004 to 2015

Since 2015…

- Cardiac rehabilitation for HFrEF

Since 2015…

- Cardiac rehabilitation for HFrEF
- CardioMEMS PA monitor

Since 2015…

- Cardiac rehabilitation for HFrEF
- CardioMEMS PA monitor
- Ivabradine
- Sacubitril/valsartan
- Patiromer

(sacubitril/valsartan) tablets
24/26mg · 49/51mg · 97/103mg

(ivabradine) 5 mg 7.5 mg tablets

(patiromer) for oral suspension

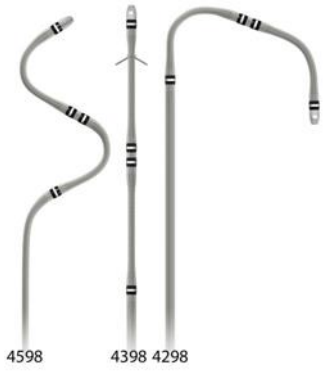
Since 2015…

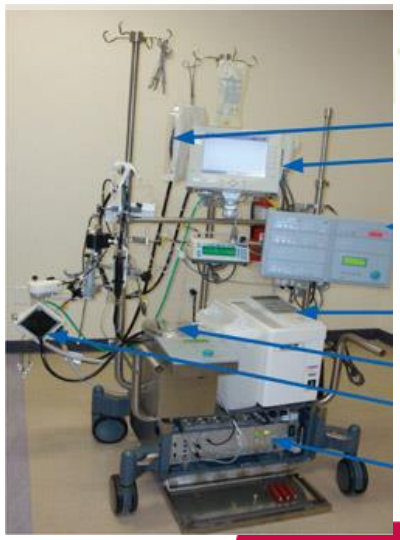
- Cardiac rehabilitation for HFrEF
- CardioMEMS PA monitor
- Ivabradine
- Sacubitril/valsartan
- Patiromer
- CRT refinements
- SQ-ICD
- MCS options

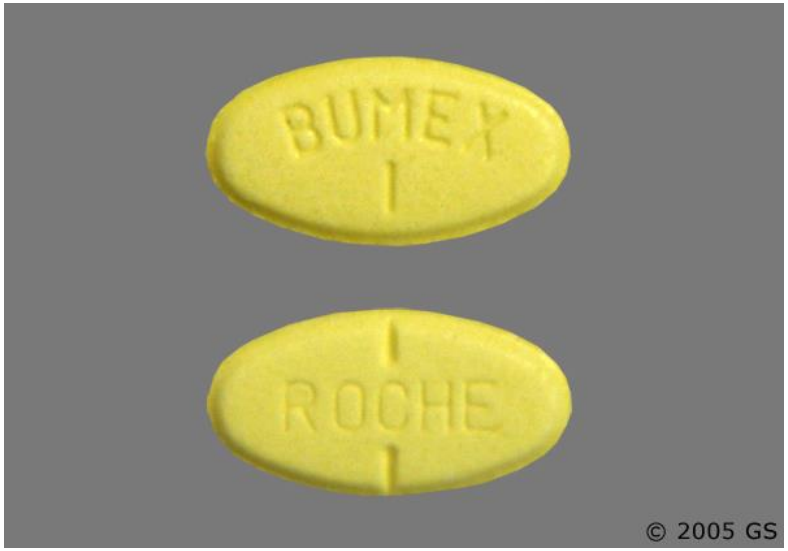
(sacubitril/valsartan) tablets
24/26mg · 49/51mg · 97/103mg

(ivabradine) 5 mg 7.5 mg tablets

tiromer) for oral suspension







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Regardless of HF Type, Diuresis PRN

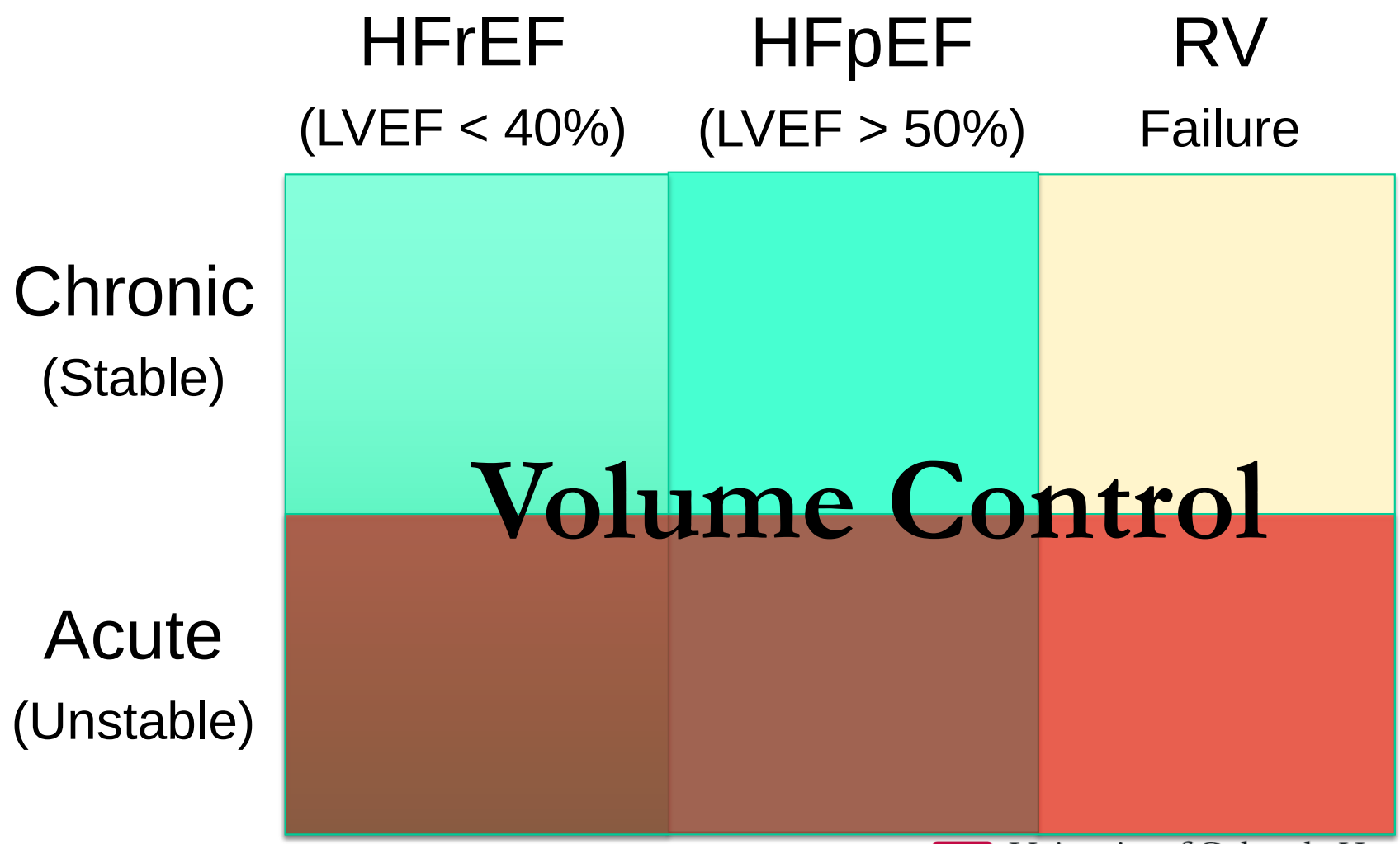


Table 2. Pharmacokinetics of the Loop Diuretics[12-18]

Property	Furosemide	Bumetanide	Torsemide
Bioavailability (%)	10–100 (average = 50)	80–100	80–100
Affected by food	yes	yes	no
Metabolism	50% renal conjugation	50% hepatic	80% hepatic
Half-life (h)			
normal	1.5–2	1	3–4
renal dysfunction	2.8	1.6	4–5
hepatic dysfunction	2.5	2.3	8
heart failure	2.7	1.3	6
Onset (min)			
oral	30–60	30–60	30–60
intravenous	5	2–3	unavailable
Potency	40	1	20
Usual 24hr dosing	20-480 mg	0.5-10 mg	10-240 mg
Cost	$4/mo	$4/mo	??

Ann Pharmacother 2009;43:1836-47.

Diuretic Dosing

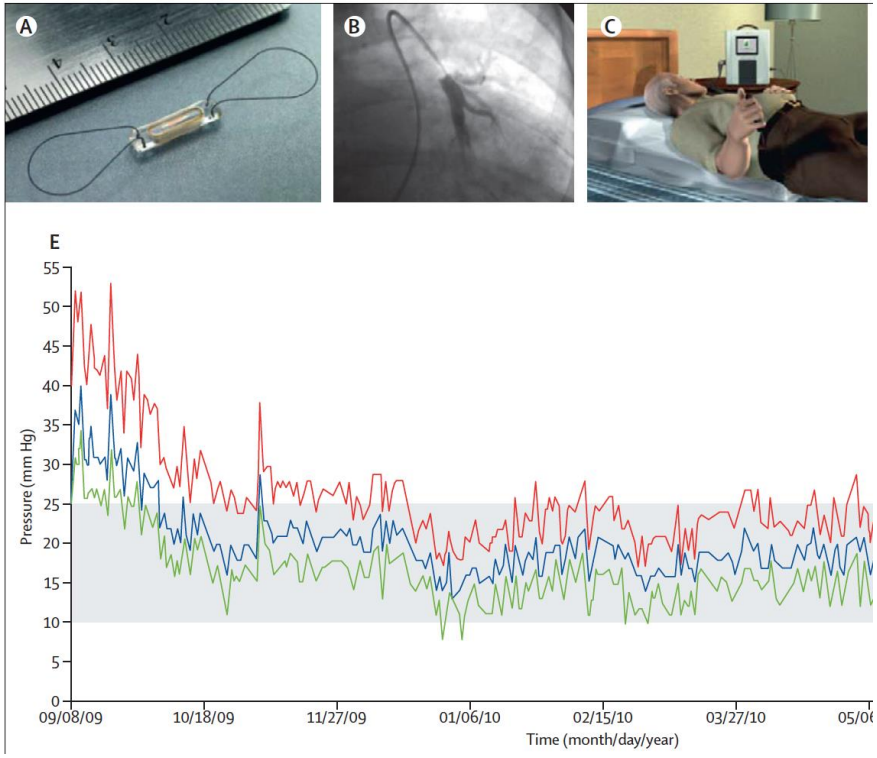
Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomised controlled trial

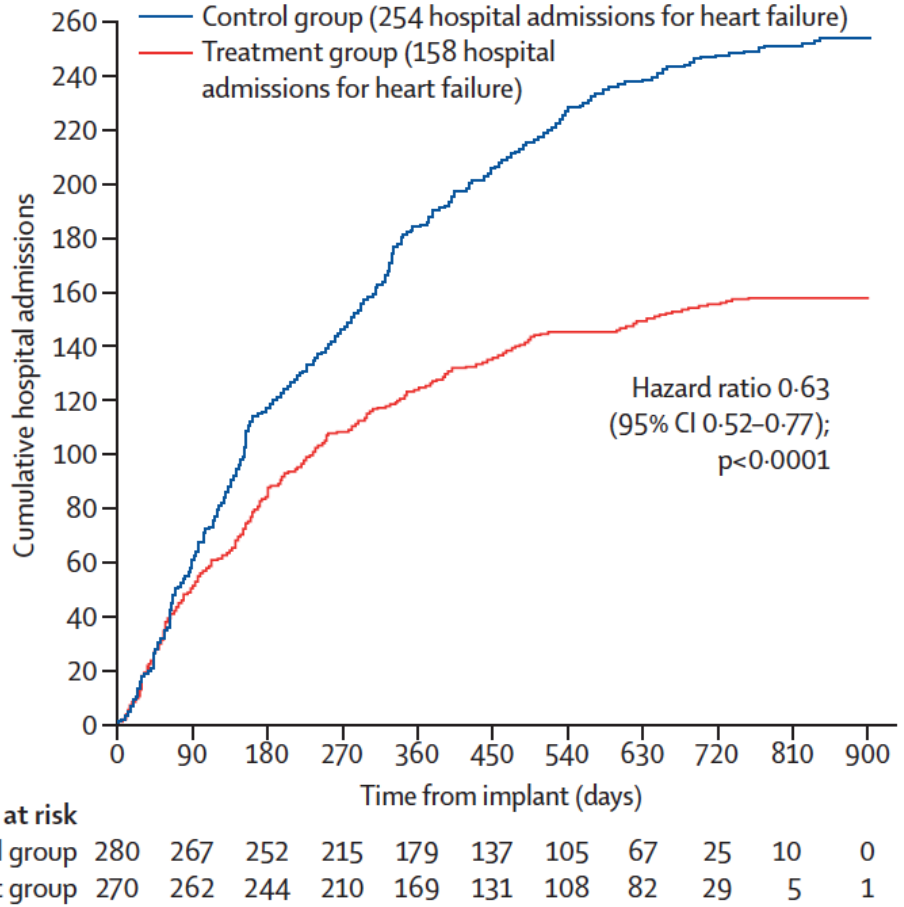
*William T Abraham, Philip B Adamson, Robert C Bourge, Mark F Aaron, Maria Rosa Costanzo, Lynne W Stevenson, Warren Strickland, Suresh Neelagaru, Nirav Raval, Steven Krueger, Stanislav Weiner, David Shavelle, Bradley Jeffries, Jay S Yadav, for the CHAMPION Trial Study Group**

Lancet 2011; 377: 658–66

Summary

Background Results of previous studies support the hypothesis that implantable haemodynamic monitoring





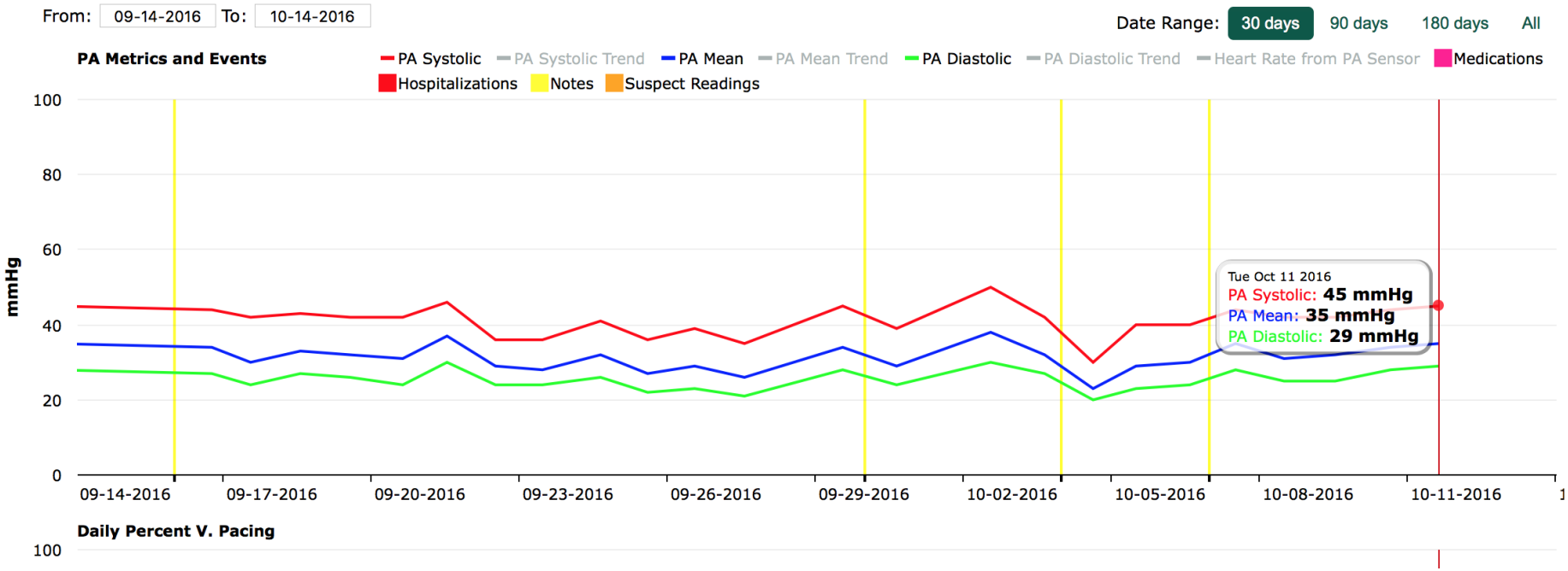
Number at risk

Control group	280	267	252	215	179	137	105	67	25	10	0
Treatment group	270	262	244	210	169	131	108	82	29	5	1

Table 1. Inclusion Criteria

Written informed consent and authorization to use and disclose health information.
18 years of age or older.
Diagnosis of HF for ≥3 months, with preserved or reduced LVEF.
Diagnosis of NYHA functional class III HF at screening visit.
If subject has a reduced LVEF, they must be receiving a beta-blocker for 3 months and an ACE-I or ARB for 1 month unless, in the investigator's opinion, the subject is intolerant to beta-blockers, ACE-I, or ARB. Beta-blocker and ACE-I (or ARB) doses should be stable for 1 month before study entry.
At least 1 HF-related hospitalization within 12 months of screening visit.
BMI ≤35 kg/m^2. Subjects with BMI >35 kg/m^2 require additional screening. If the BMI is >35 kg/m^2 and the chest circumference is >52 in and <65 in, the distance from the skin on the subject's back to the pulmonary artery must be <10 cm and confirmed by angiogram of the lateral view during the catheterization before placement of the pressure sensor. If the distance is >10 cm, the subject will not receive a sensor and will not be eligible for the study.
Pulmonary artery branch diameter between 7 and 15 mm.
Female subjects of childbearing age with a negative urine or serum pregnancy test at the screening visit and agreeing to use a reliable mechanical or hormonal form of contraception during the study.

Web-based interface



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(sacubitril/valsartan) tablets

24/26mg · 49/51mg · 97/103mg

	HFrEF (LVEF < 40%)	HFpEF (LVEF > 50%)	RV Failure
Chronic (Stable)			
Acute (Unstable)			

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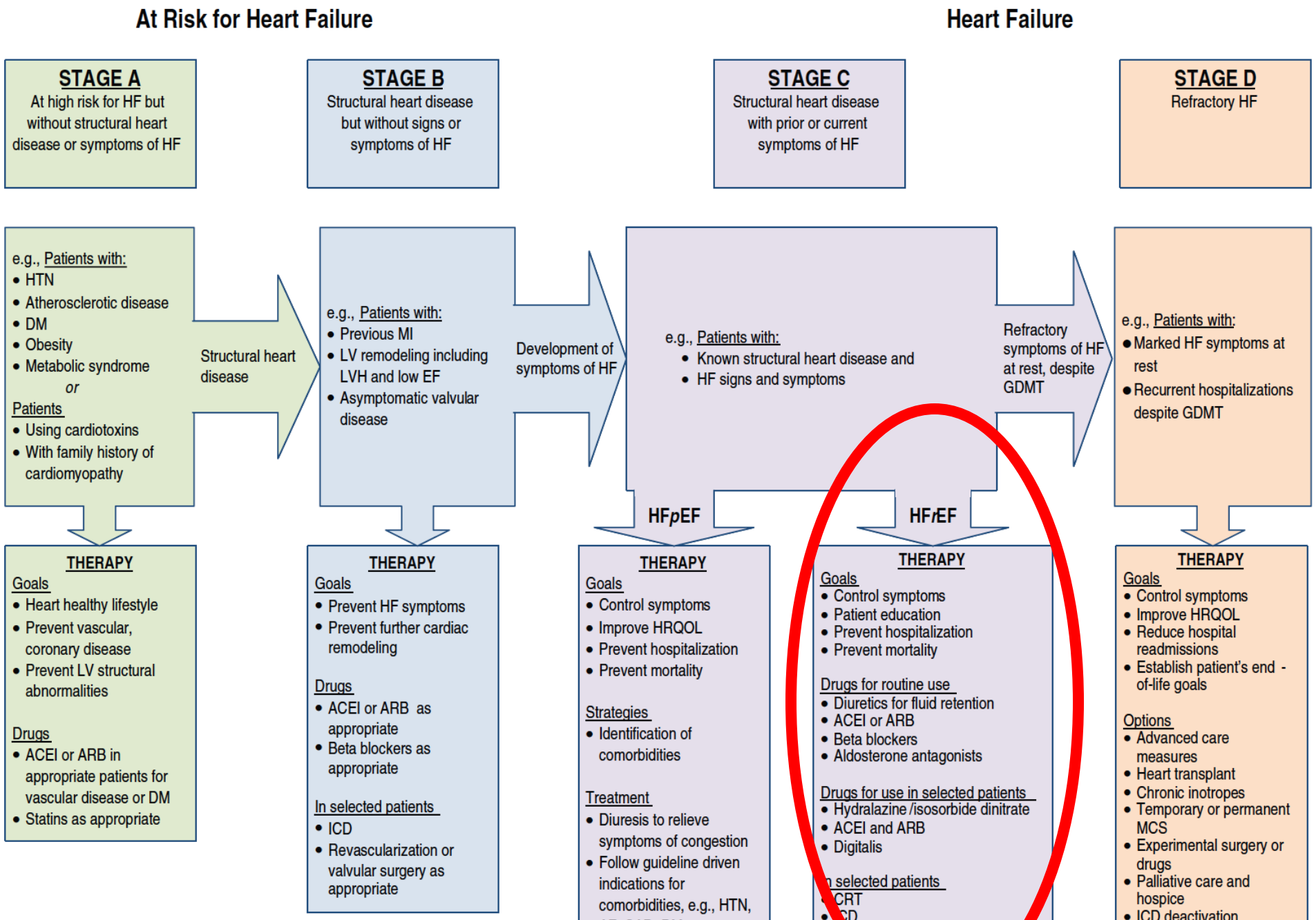
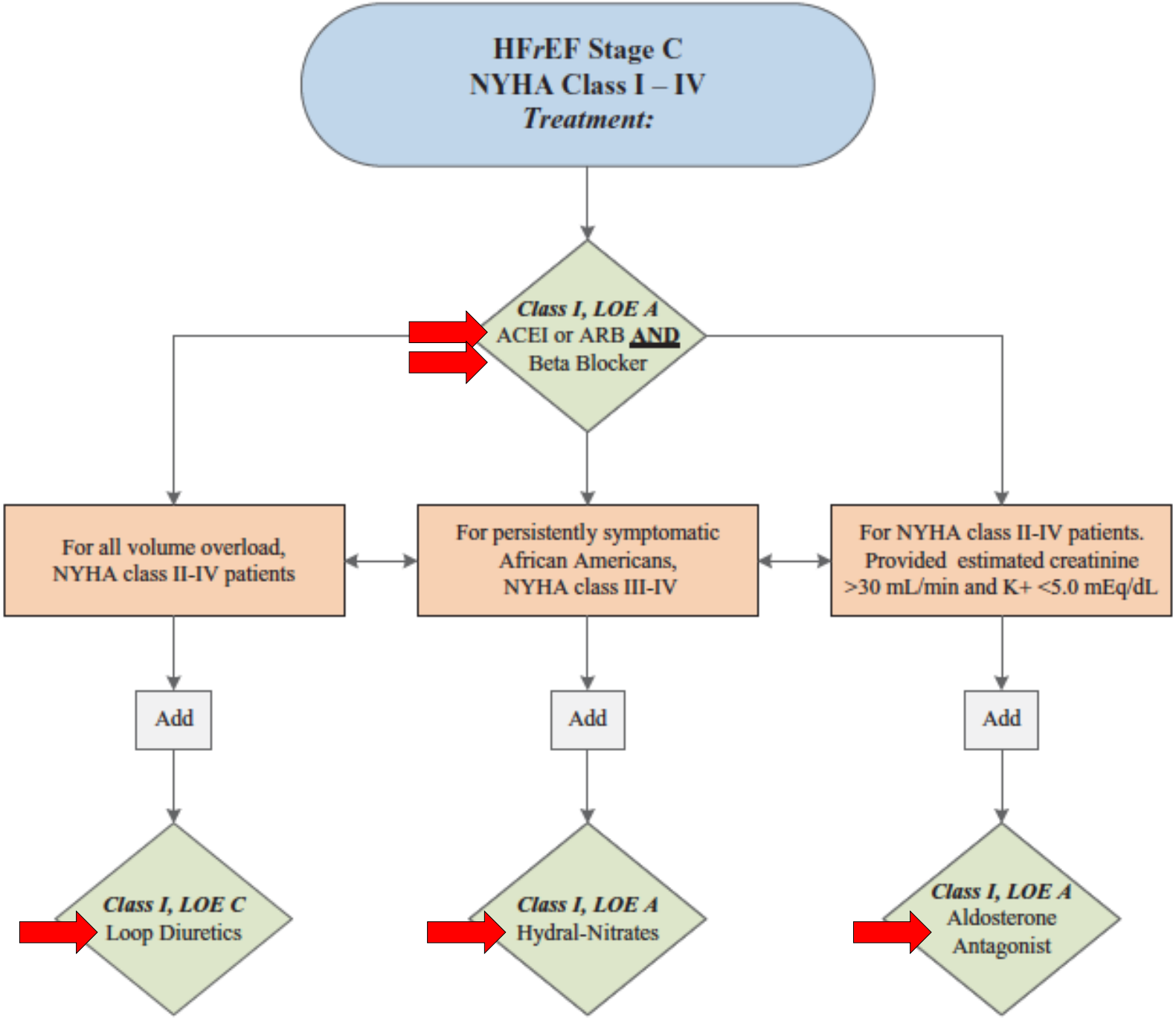
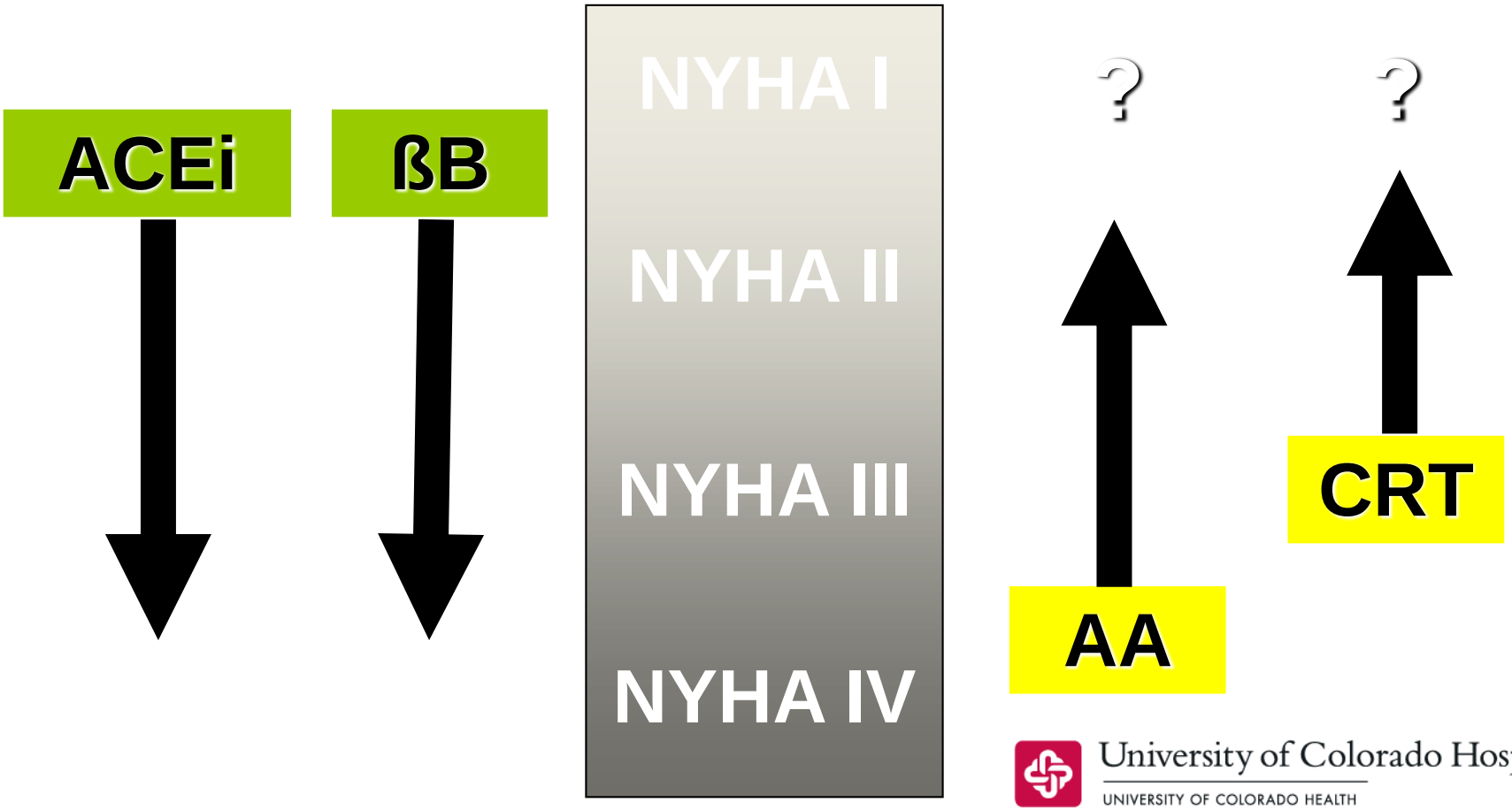


Yancy et al. 2013 ACCF/AHA Heart Failure Guideline.
http://circ.ahajournals.org/content/128/16/e240.short?rss=1&ssource=mfr


HFrEF Stage C
NYHA Class I – IV
Treatment:
Class I, LOE A
ACEI or ARB AND
Beta Blocker
For all volume overload,
NYHA class II-IV patients
For persistently symptomatic
African Americans,
NYHA class III-IV
For NYHA class II-IV patients.
Provided estimated creatinine
>30 mL/min and K+ <5.0 mEq/dL
Add
Add
Add
Class I, LOE C
Loop Diuretics
Class I, LOE A
Hydral-Nitrates
Class I, LOE A
Aldosterone
Antagonist

ospital

Reverse remodeling Rx for HFrEF: Indicated for <u>nearly all Stage C</u>



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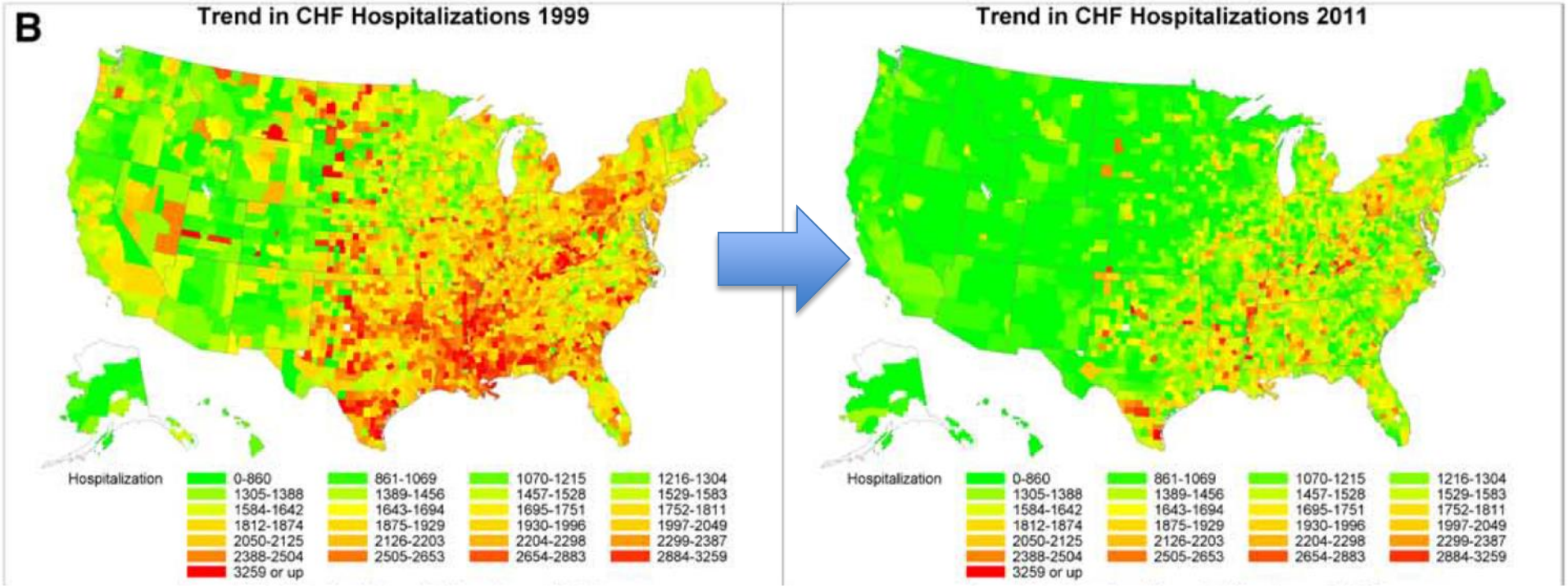
Progress?!



Conclusions—Hospitalizations for acute cardiovascular disease and stroke from 1999 through 2011 declined more rapidly than for other conditions. For these conditions, mortality and readmission outcomes improved. **(*Circulation*. 2014;130:966-975.)**

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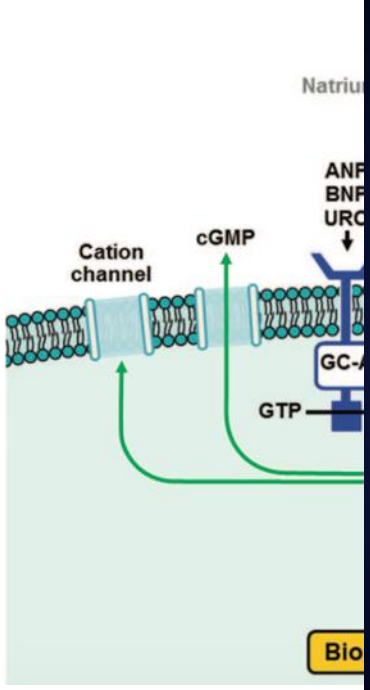
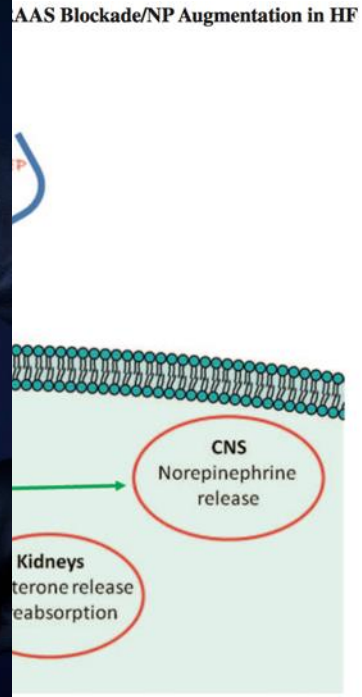
ARB+NEPi (ARNI)

(sacubitril/valsartan) tablets

24/26mg · 49/51mg · 97/103mg





Von Leuder CircHF 2013;594

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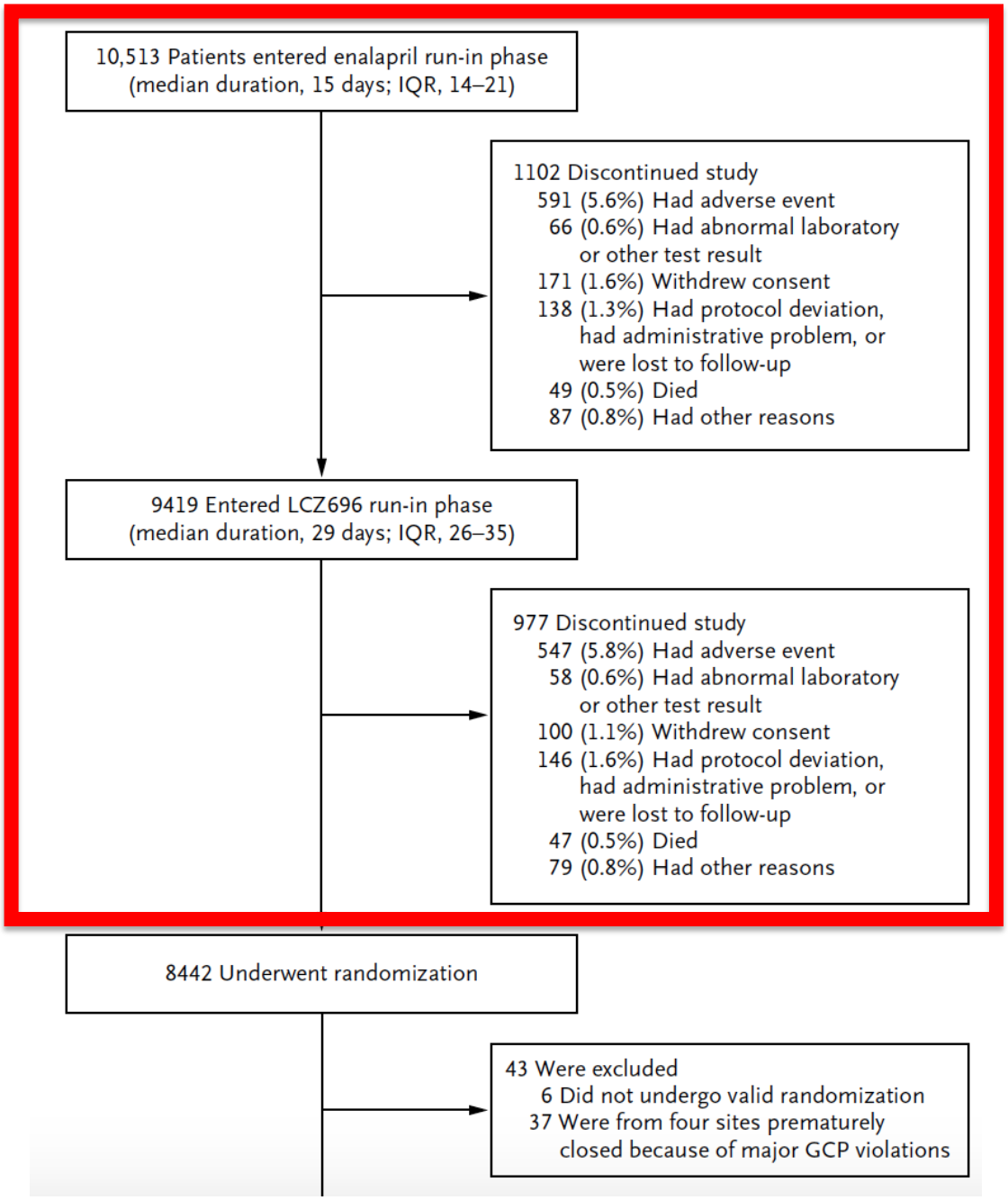
The NEW ENGLAND JOURNAL of MEDICINE

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*

- LCZ696 200 bid (valsartan + sacubutril) v. enalapril 10 bid
- 8441 pts: NYHA II-VI, LVEF <=40%
- Stopped early at 27 months


10,513 Patients entered enalapril run-in phase
(median duration, 15 days; IQR, 14–21)
1102 Discontinued study
591 (5.6%) Had adverse event
66 (0.6%) Had abnormal laboratory or other test result
171 (1.6%) Withdrew consent
138 (1.3%) Had protocol deviation, had administrative problem, or were lost to follow-up
49 (0.5%) Died
87 (0.8%) Had other reasons
9419 Entered LCZ696 run-in phase
(median duration, 29 days; IQR, 26–35)
977 Discontinued study
547 (5.8%) Had adverse event
58 (0.6%) Had abnormal laboratory or other test result
100 (1.1%) Withdrew consent
146 (1.6%) Had protocol deviation, had administrative problem, or were lost to follow-up
47 (0.5%) Died
79 (0.8%) Had other reasons
8442 Underwent randomization
43 Were excluded
6 Did not undergo valid randomization
37 Were from four sites prematurely closed because of major GCP violations

Outcomes

Outcome	LCZ696 (N=4187)	Enalapril (N=4212)
Primary composite outcome — no. (%)		
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)
Death from cardiovascular causes	558 (13.3)	693 (16.5)
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)
Secondary outcomes — no. (%)		
Death from any cause	711 (17.0)	835 (19.8)
Change in KCCQ clinical summary score at 8 mo†	–2.99±0.36	–4.63±0.36
New-onset atrial fibrillation‡	84 (3.1)	83 (3.1)
Decline in renal function§	94 (2.2)	108 (2.6)

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	

2016 ACC/AHA Guideline Update
ARNI

I	**ARNI: B-R**	**In patients with chronic symptomatic HF*r*EF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (19).**

III: Harm	**B-R**	**ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor (31, 32).**

Factors Associated With Noncompletion During the Run-In Period Before Randomization and Influence on the Estimated Benefit of LCZ696 in the PARADIGM-HF Trial

Akshay S. Desai, MD; Scott Solomon, MD; Brian Claggett, PhD; John J.V. McMurray, MD; Jean Rouleau, MD; Karl Swedberg, MD; Michael Zile, MD; Martin Lefkowitz, MD;

Background—The 8442 patients ran sin Receptor-Neprilysin Inhibitor With an Angiotensin-Converting I Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial, in eath and HF hospitalization more than enalapril, were a subset of 1(n periods (enalapril 10 mg twice daily for 2 weeks followed by LC re short-term tolerability of the 2 study medications. We identified th he implications of noncompletion for the overall study result.

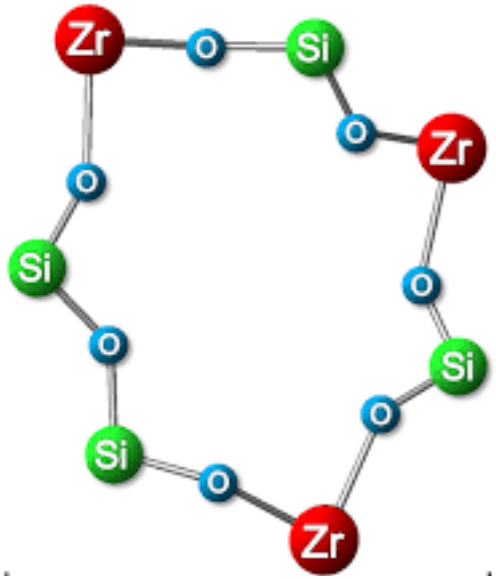
Methods and Results—Patient factors n multivariable logistic regression models. The effectiveness of LCZ69 ılation was estimated by weighting randomized patients according to th %) subjects discontinued the study during the run-in period, including 3%) during the LCZ696 phase. In multivariable models, lower systolic rate, higher N-terminal pro–B-type natriuretic peptide, and ischemic ca for run-in noncompletion. Repeat analysis of the effect of randomize nts resembling those who did not complete the run-in did not alter the hazard ratio favoring LCZ696 over enalapril for the primary end point of cardiovascular death or heart failure hospitalization, or the additional key end points of cardiovascular death and all-cause mortality.

Conclusions—Patients with lower blood pressure, lower glomerular filtration rate, and more severe heart failure were at higher risk for noncompletion during the run-in period of PARADIGM-HF. Weighted analysis of key study outcomes accounting for the effect of run-in noncompletion did not alter the benefit of LCZ696 over enalapril.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01035255.

(*Circ Heart Fail*. 2016;9:e002735. DOI: 10.1161/CIRCHEARTFAILURE.115.002735.)

(patiromer) for oral suspension



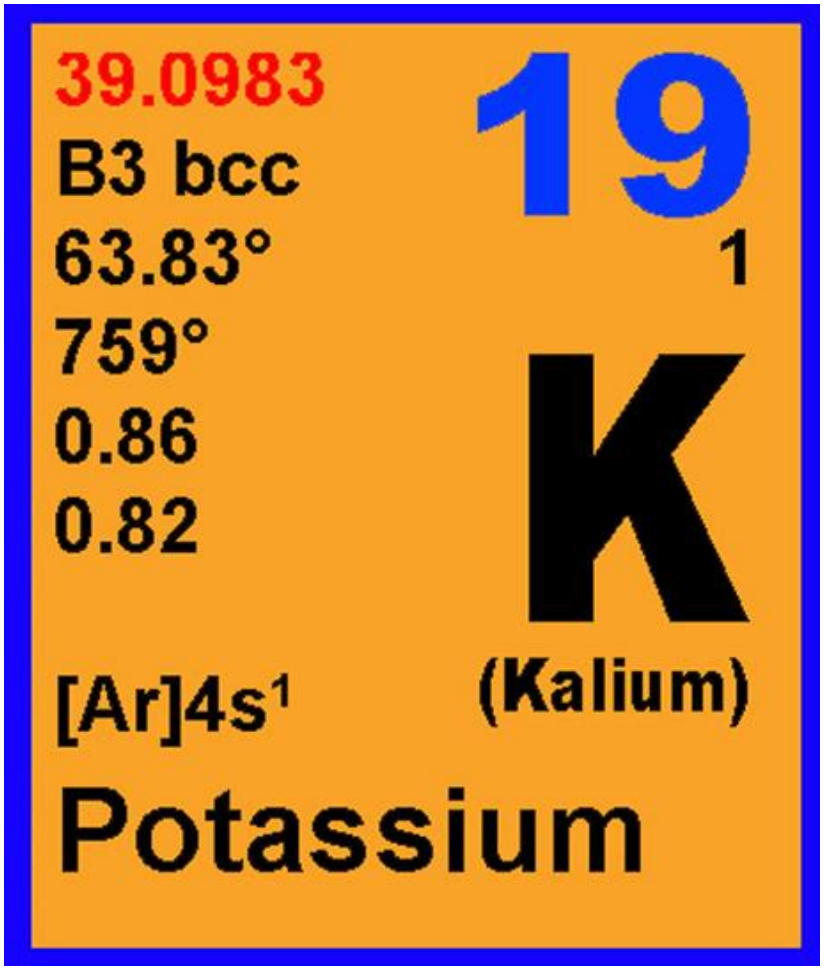
ACEI and ARNI HyperK

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

- Caveat: ~20% did not complete run-in phase, 1.2% due to abnormal lab value.

Hyperkalemia after MRA



RALES

39.0983
B3 bcc
63.83°
759°
0.86
0.82
19
1
K
[Ar]4s¹
(Kalium)
Potassium

Adverse Event	Placebo Group (N=841)	Spironolactone Group (N=822)
	no. of patients (%)	
One or more events	667 (79)	674 (82)*
Discontinuation because of adverse event	40 (5)	62 (8)
Serious hyperkalemia	10 (1)	14 (2)

EPHESUS

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B3 bcc
63.83°
759°
0.86
0.82
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1
K
[Ar]4s¹
(Kalium)
Potassium

Adverse Event	Eplerenone Group (N=3307)	Placebo Group (N=3301)
	no. of patients (%)	
≥1 Event	2608 (78.9)	2623 (79.5)
Cardiovascular disorder*	1606 (48.6)	1661 (50.3)
Respiratory disorder	729 (22.0)	803 (24.3)
Cough	167 (5.0)	207 (6.3)
Dyspnea	243 (7.3)	307 (9.3)
Pneumonia	92 (2.8)	123 (3.7)
Metabolic or nutritional disorder	568 (17.2)	635 (19.2)
Hyperkalemia†	113 (3.4)	66 (2.0)

EMPHASUS

Outcome	Eplerenone (N = 1364)	Placebo (N = 1373)	Adjusted Hazard Ratio (95% CI)
	no. of patients (%)		
Primary outcome: death from cardiovascular causes or hospitalization for heart failure	249 (18.3)	356 (25.9)	0.63 (0.54–0.74)
Prespecified adjudicated secondary outcomes			
Death from any cause or hospitalization for heart failure	270 (19.8)	376 (27.4)	0.65 (0.55–0.76)
Death from any cause	171 (12.5)	213 (15.5)	0.76 (0.62–0.93)
Death from cardiovascular causes	147 (10.8)	185 (13.5)	0.76 (0.61–0.94)
Hospitalization for any reason	408 (29.9)	491(35.8)	0.77 (0.67–0.88)
Hospitalization for heart failure	164 (12.0)	253 (18.4)	0.58 (0.47–0.70)
Hospitalization for cardiovascular causes	304 (22.3)	399 (29.1)	0.69 (0.60–0.81)
Fatal or nonfatal myocardial infarction	45 (3.3)	33 (2.4)	1.32 (0.84–2.06)
Death from any cause or hospitalization for any reason	462 (33.9)	569 (41.4)	0.75 (0.66–0.85)
Death from heart failure or hospitalization for heart failure	170 (12.5)	262 (19.1)	0.58 (0.48–0.70)
Fatal or nonfatal stroke	21 (1.5)	26 (1.9)	0.79 (0.44–1.41)
Implantation of a cardioverter–defibrillator	61 (4.5)	59 (4.3)	0.99 (0.69–1.42)
Implantation of a cardiac-resynchronization device	33 (2.4)	41 (3.0)	0.77 (0.49–1.22)
Hospitalization for worsening renal function†	9 (0.7)	8 (0.6)	0.97 (0.37–2.58)
Hospitalization for hyperkalemia†	4 (0.3)	3 (0.2)	1.15 (0.25–5.31)

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63.83°
759°
0.86
0.82
19
1
K
[Ar]4s¹
(Kalium)
Potassium

Real-world concerns?

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0.86
0.82
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[Ar]4s¹
(Kalium)
Potassium

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study

David N. Juurlink, M.D., Ph.D., Muhammad M. Mamdani, Pharm.D., M.P.H., Douglas S. Lee, M.D., Alexander Kopp, B.A., Peter C. Austin, Ph.D., Andreas Laupacis, M.D., and Donald A. Redelmeier, M.D.

N Engl J Med 2004;351:543-51.

Real world concerns?

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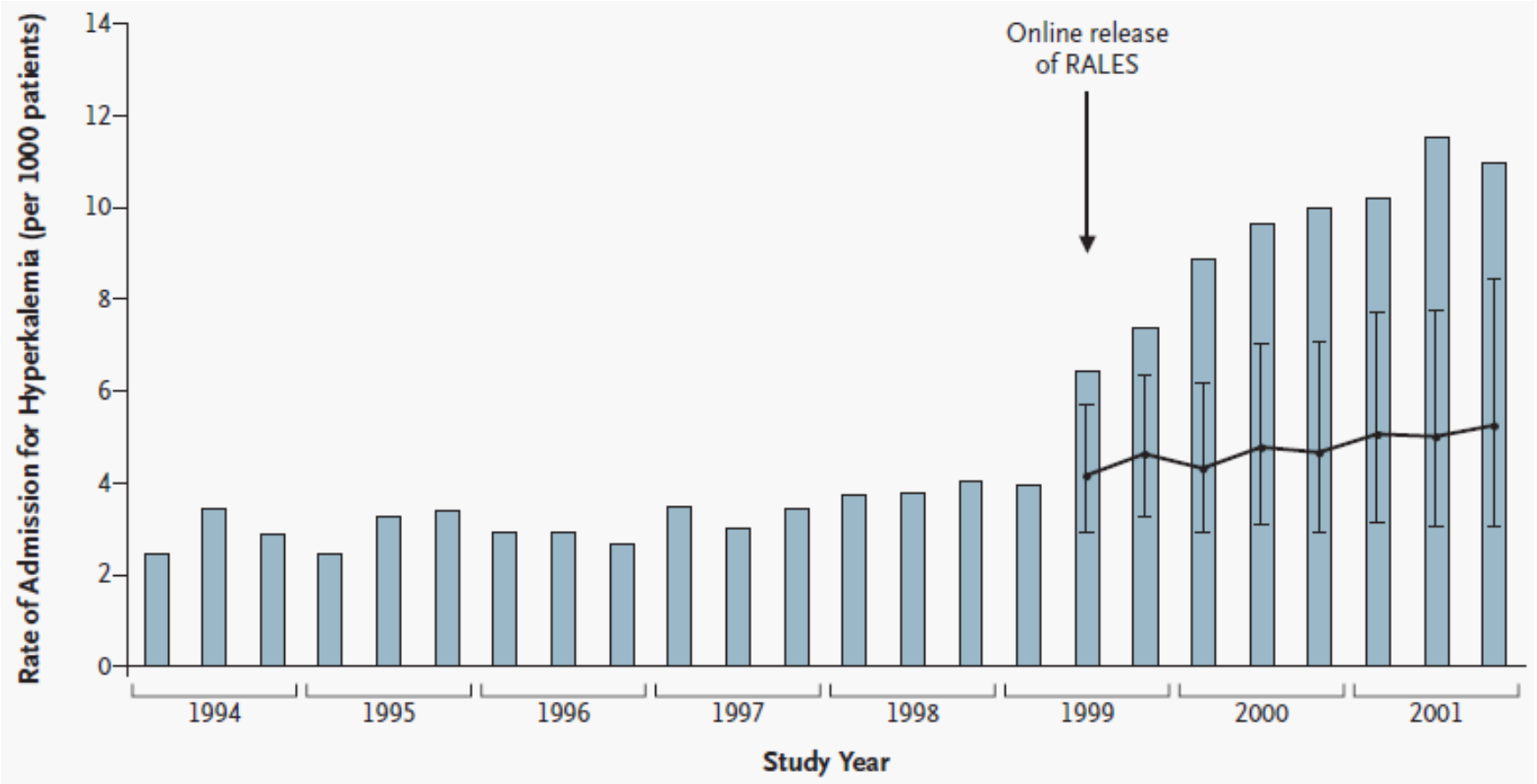
(Kalium)
Potassium



Juurlink. NEJM 2004;351:543.

AHA/ACC MRA Monitoring

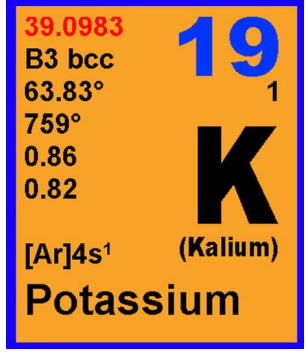


Table 7. Guidelines for Minimizing the Risk of Hyperkalemia in Patients Treated With Aldosterone Antagonists

1. Impaired renal function is a risk factor for hyperkalemia during treatment with aldosterone antagonists. The risk of hyperkalemia increases progressively when serum creatinine exceeds 1.6 mg/dL.* In elderly patients or others with low muscle mass in whom serum creatinine does not accurately reflect glomerular filtration rate, determination that glomerular filtration rate or creatinine clearance exceeds 30 ml per minute is recommended.
2. Aldosterone antagonists should not be administered to patients with

Close monitoring of serum potassium is required; potassium levels and renal function should be checked in 3 days and at 1 week after initiating therapy and at least monthly for the first 3 months.

doses of ACEIs (captopril greater than or equal to 75 mg daily, enalapril or lisinopril greater than or equal to 10 mg daily.

5. Non-steroidal anti-inflammatory drugs and cyclo-oxygenase-2 inhibitors should be avoided.
6. Potassium supplements should be discontinued or reduced.
7. Close monitoring of serum potassium is required; potassium levels and renal function should be checked in 3 days and at 1 week after initiating therapy and at least monthly for the first 3 months.
8. Diarrhea or other causes of dehydration should be addressed emergently.

People are worried enough to create mixed messaging

LARRY ALLEN
12605 E 16TH AVE
AURORA, CO 80045-2545
00000938 68 18985

April 2013

Dear Dr. ALLEN:

Medco works with Farmers Insurance Group to provide you with the **enclosed RationalMed® safety and health considerations for patients in your practice.***

These records:
- Highlight safety and health considerations
- Provide prescription and medical claim information
- Cite relevant references

The claims information may include treatment provided by other healthcare providers.

Please review the health information provided and **make any changes in therapy that you believe**

Confidential Patient Information
Safety and Health Considerations:

MICHAEL [redacted]

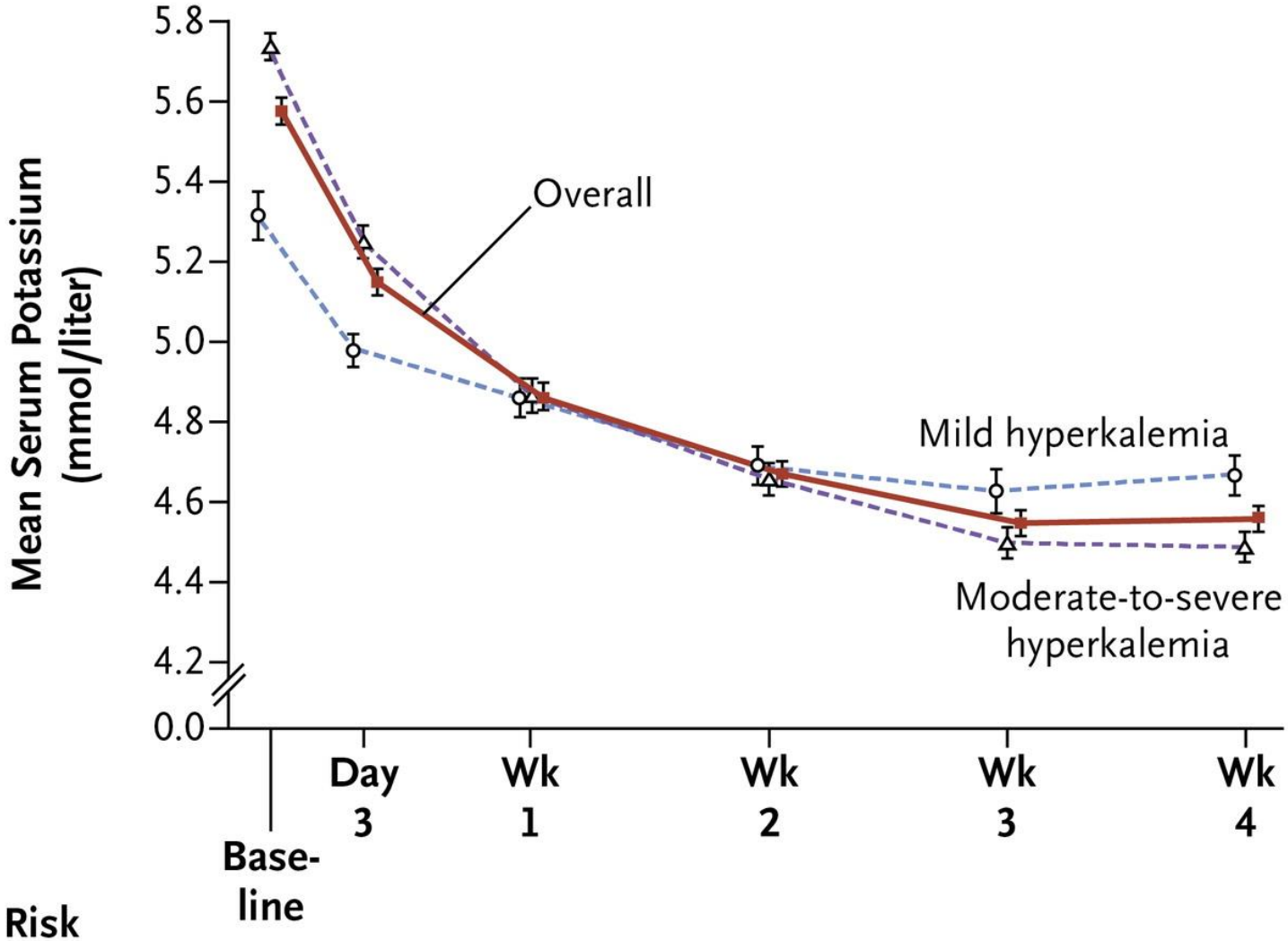
1. **Adverse Drug Interaction:** SPIRONOLACTONE and LISINOPRIL

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 15, 2015 VOL. 372 NO. 3

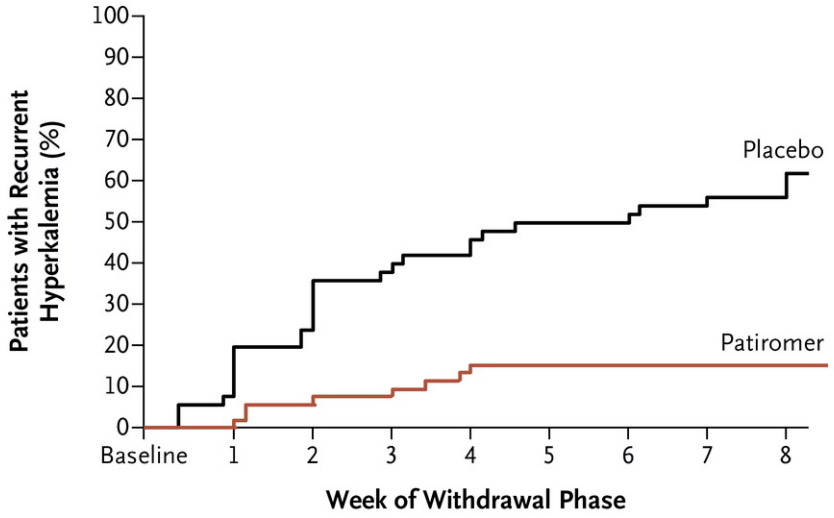
Patiromer in Patients with Kidney Disease and Hyperkalemia Receiving RAAS Inhibitors

Matthew R. Weir, M.D., George L. Bakris, M.D., David A. Bushinsky, M.D., Martha R. Mayo, Pharm.D., Dahlia Garza, M.D., Yuri Stasiv, Ph.D., Janet Wittes, Ph.D., Heidi Christ-Schmidt, M.S.E., Lance Berman, M.D., and Bertram Pitt, M.D., for the OPAL-HK Investigators*



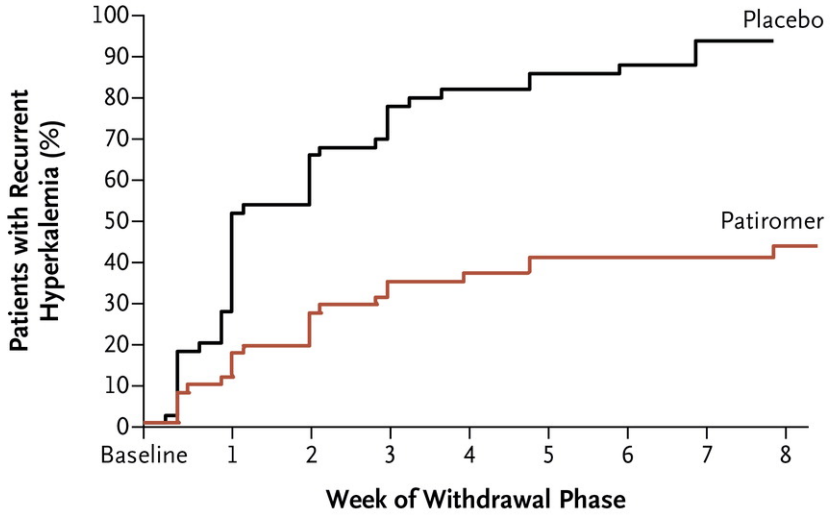
No. at Risk	Base-line	Day 3	Wk 1	Wk 2	Wk 3	Wk 4
Overall	243	217	237	228	221	219
Mild hyperkalemia	92	80	90	87	85	85
Moderate-to-severe hyperkalemia	151	137	147	141	136	134

A Time to First Serum Potassium Level ≥5.5 mmol/liter



No. at Risk									
Placebo	52	46	38	31	29	25	25	23	15
Patiromer	55	53	49	48	45	43	42	42	32

B Time to First Serum Potassium Level ≥5.1 mmol/liter



No. at Risk									
Placebo	52	37	24	16	10	8	8	7	1
Patiromer	55	47	42	36	34	30	29	29	23

Table 2. Adverse Events during the Initial Treatment Phase and through the Safety Follow-
Phase.*

Adverse Event
≥1 Adverse event†
Constipation
Diarrhea
Hypomagnesemia
Nausea
Anemia
Chronic renal failure
≥1 Serious adverse event‡

Table 3. Adverse Events during the Randomized
l through the Safety Follow-up
*

	Placebo (N=52)	Patiromer (N=55)
	no. of patients (%)	
	26 (50)†	26 (47)
	4 (8)	2 (4)
systoles	1 (2)	2 (4)
	0	2 (4)
	0	2 (4)
	0	2 (4)
ent	1 (2)‡	0

* The safety follow-up period was 1 to 2 weeks after dis-

(ivabradine) 5 mg 7.5 mg tablets

University of Colorado Hospital
UNIVERSITY OF COLORADO HEALTH

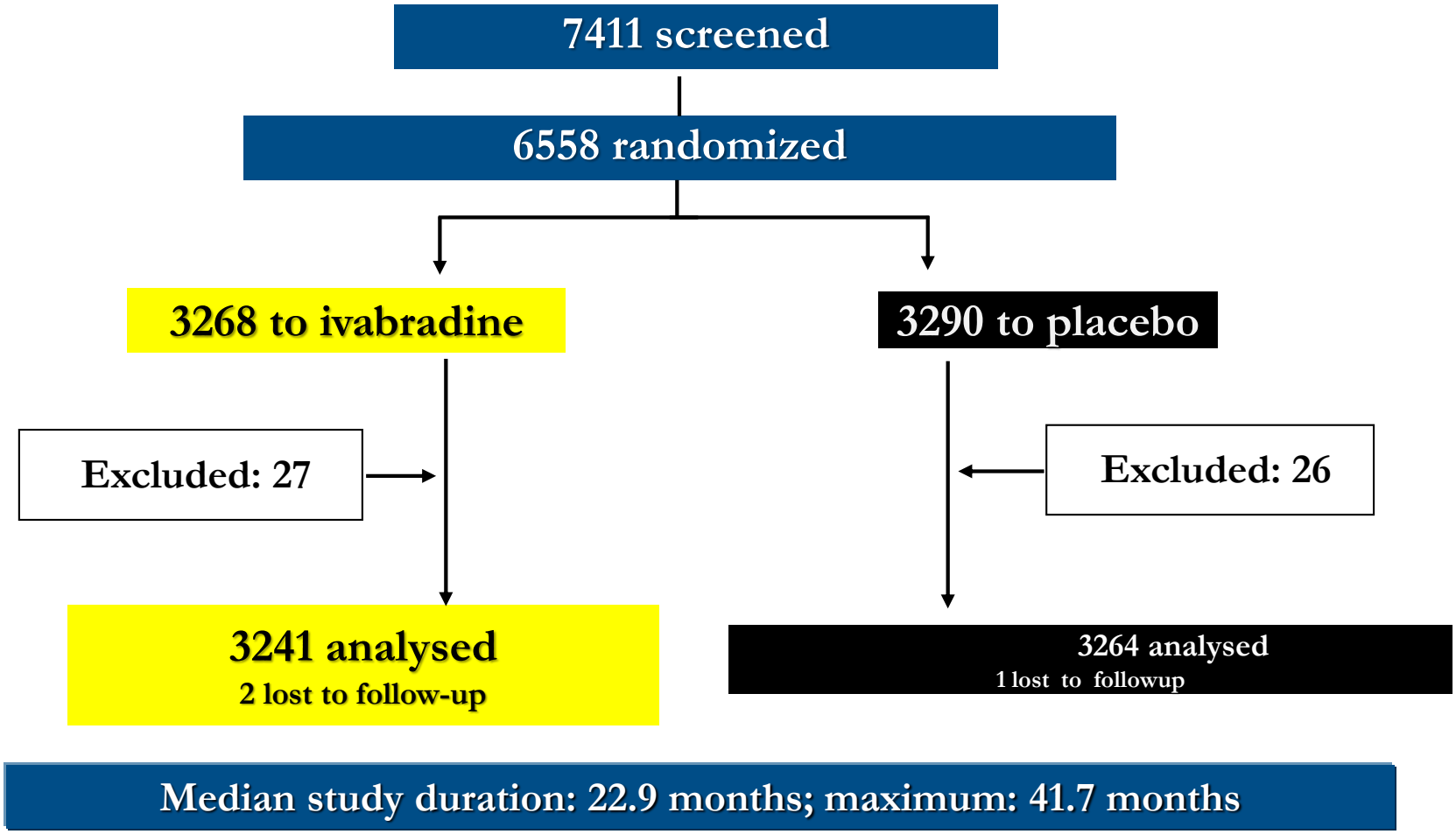
(ivabradine) 5 mg 7.5 mg tablets

Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial

Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

*Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators**

Lancet 2010; 376: 875–85



2010;376(9744):875-885

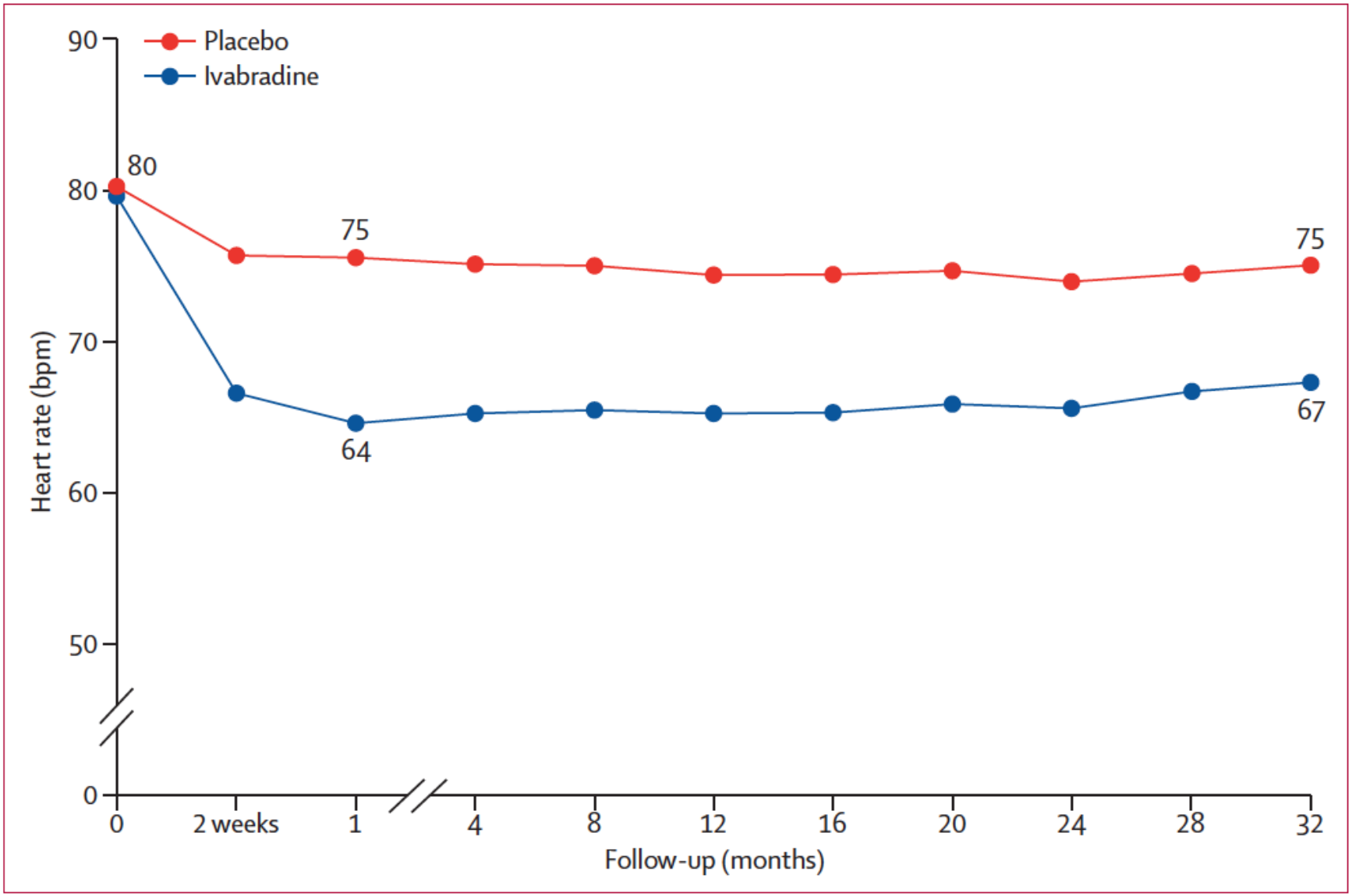


Figure 2: **Mean heart rate during the study in the total study population, by allocation groups**

	Ivabradine group (n=3241)	Placebo group (n=3264)	HR (95% CI)	p value
Primary endpoint				
Cardiovascular death or hospital admission for worsening heart failure	793 (24%)	937 (29%)	0·82 (0·75–0·90)	<0·0001
Mortality endpoints				
All-cause mortality	503 (16%)	552 (17%)	0·90 (0·80–1·02)	0·092
Cardiovascular mortality	449 (14%)	491 (15%)	0·91 (0·80–1·03)	0·128
Death from heart failure	113 (3%)	151 (5%)	0·74 (0·58–0·94)	0·014
Other endpoints				
All-cause hospital admission	1231 (38%)	1356 (42%)	0·89 (0·82–0·96)	0·003
Hospital admission for worsening heart failure	514 (16%)	672 (21%)	0·74 (0·66–0·83)	<0·0001
Any cardiovascular hospital admission	977 (30%)	1122 (34%)	0·85 (0·78–0·92)	0·0002
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction	825 (25%)	979 (30%)	0·82 (0·74–0·89)	<0·0001

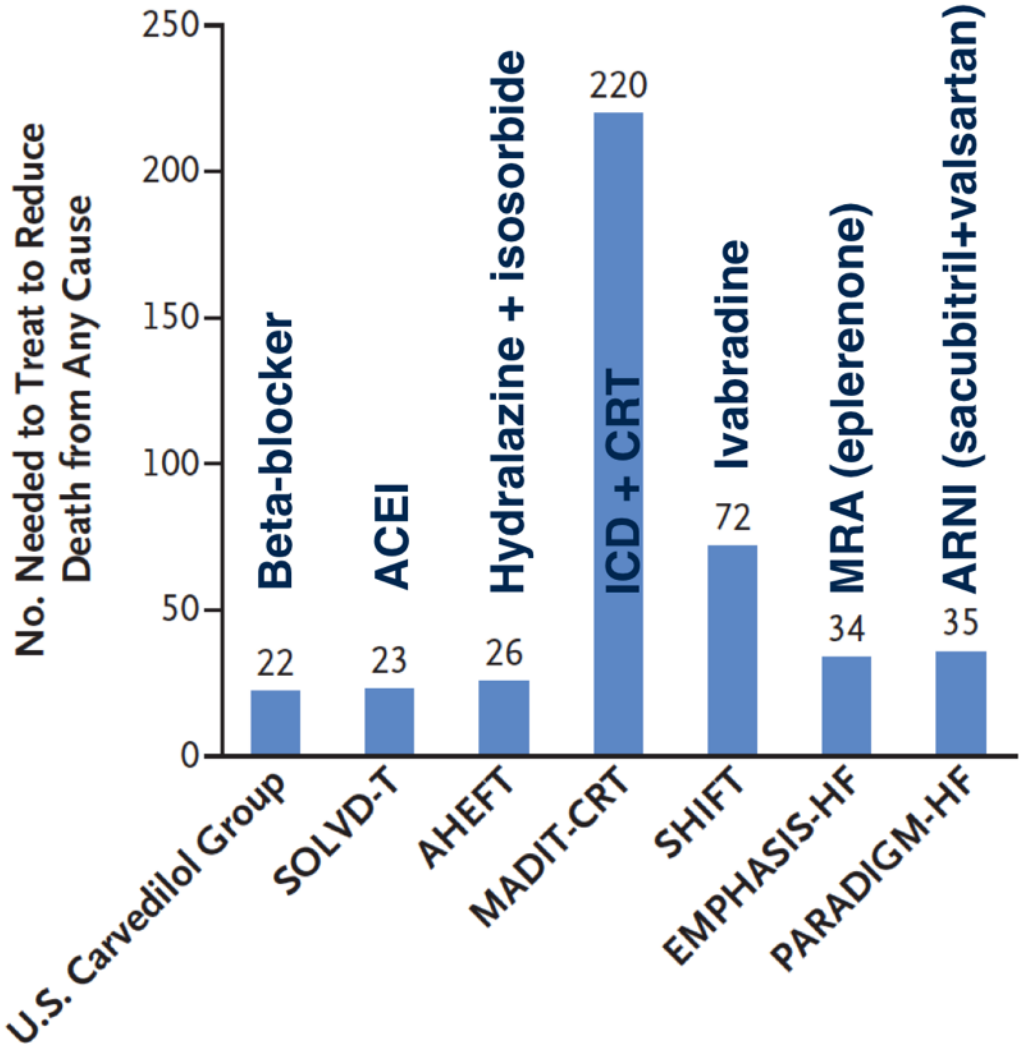
Data are number of first events (%), hazard ratio (HR; 95% CI), and p values.

Table 3: **Effects on primary and major secondary endpoints**

2016 ACC/AHA Guideline Update

IIa	**B-R**	**Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III) stable chronic HF*r*EF (LVEF ≤35%) who are receiving GDEM, including a beta blocker at maximum tolerated dose, and who are in sinus rhythm with a heart rate of 70 bpm or greater at rest (37-40).**

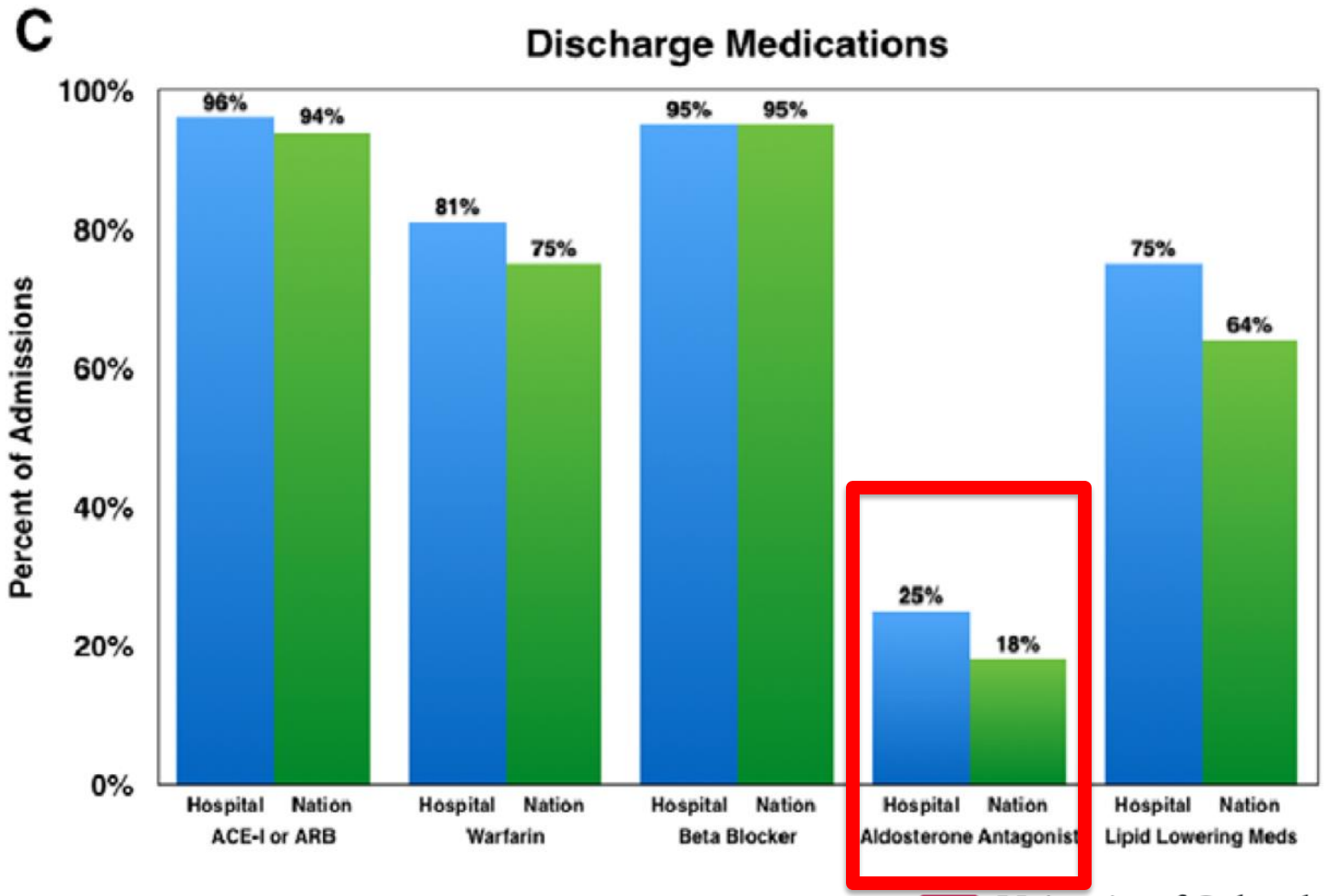
Relative NNT: Improved survival in HFrEF



Challenges

It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was **the season of Darkness, it was the spring of hope,** it was the winter of despair, we had everything before us, we had nothing before us, we were all going direct to Heaven, we were all going direct the other way– in short, the period was so far like the present period, that some of its noisiest authorities insisted on its being received, for good or for evil, in the superlative degree of comparison only.

Challenge #1: Failure to **Prescribe**

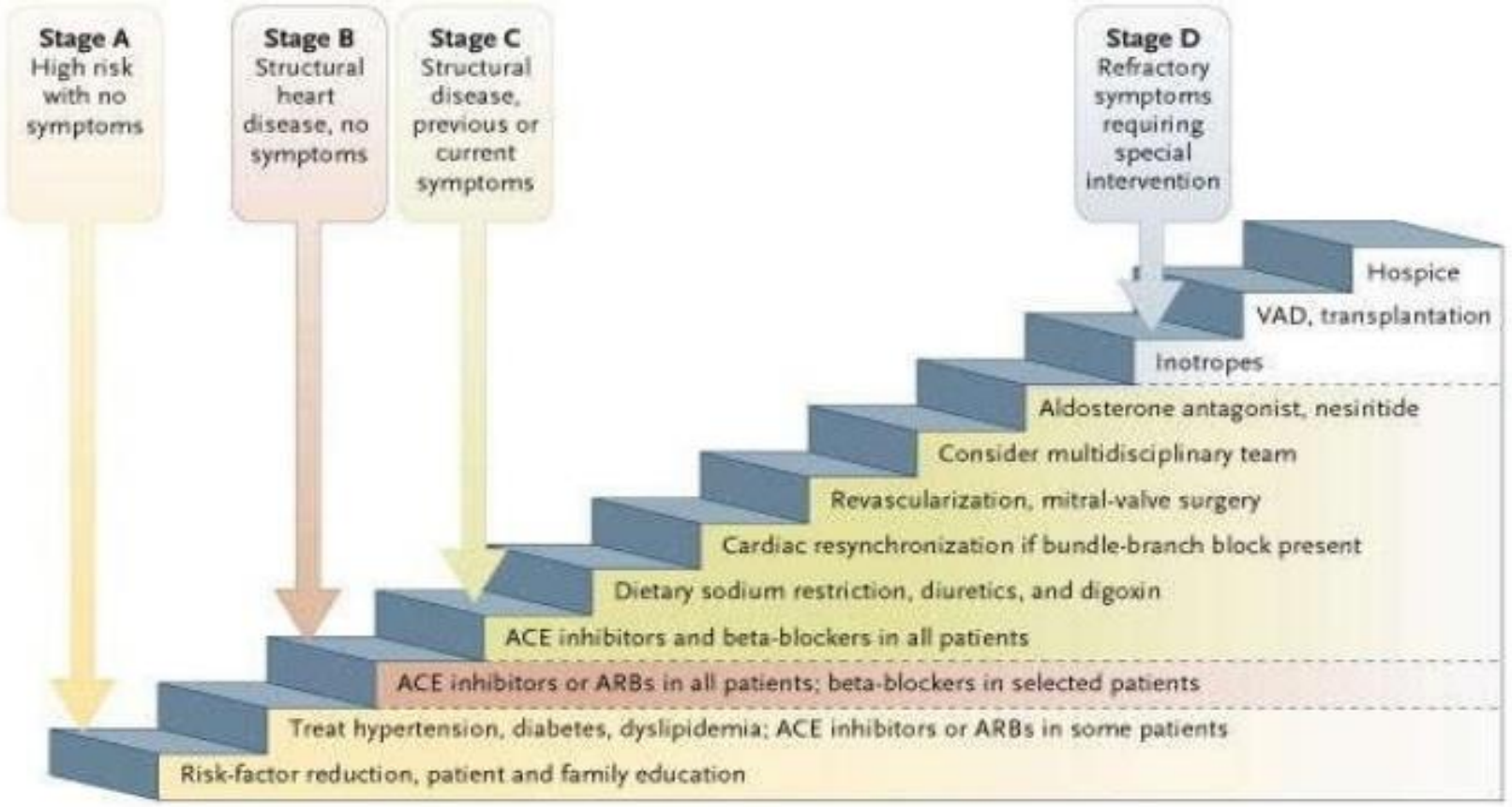


Circ Cardiovasc Qual Outcomes. 2015;8:421-427.

University of Colorado Hospital
UNIVERSITY OF COLORADO HEALTH

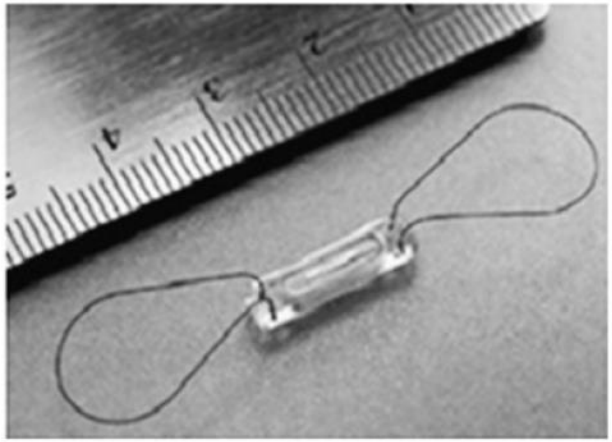
Challenge #2: Add-on Therapy

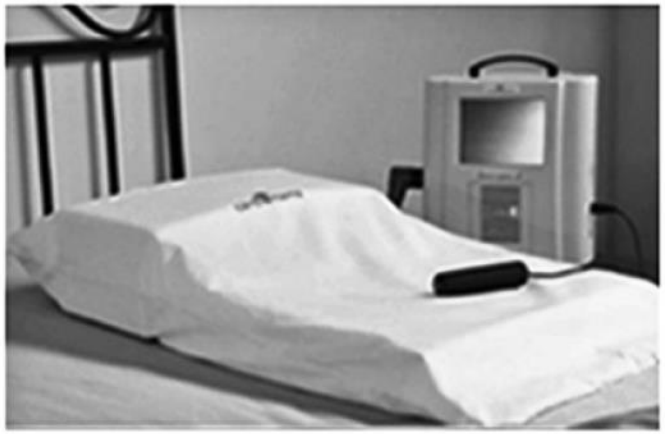
The cumulative burden of success

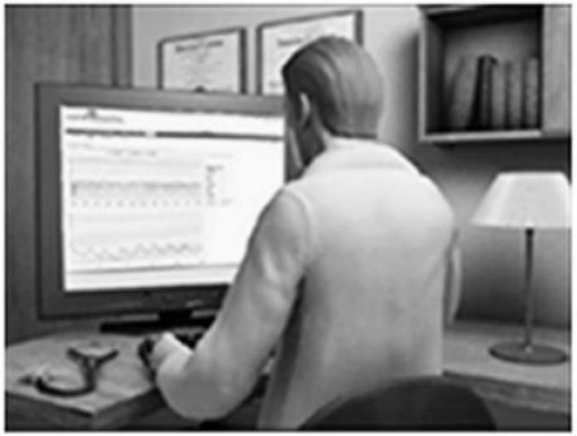


Jessup M, Brozena S. N Engl J Med 2003;348:2007-2018.

Challenge #3: Big Data v. Data Overload

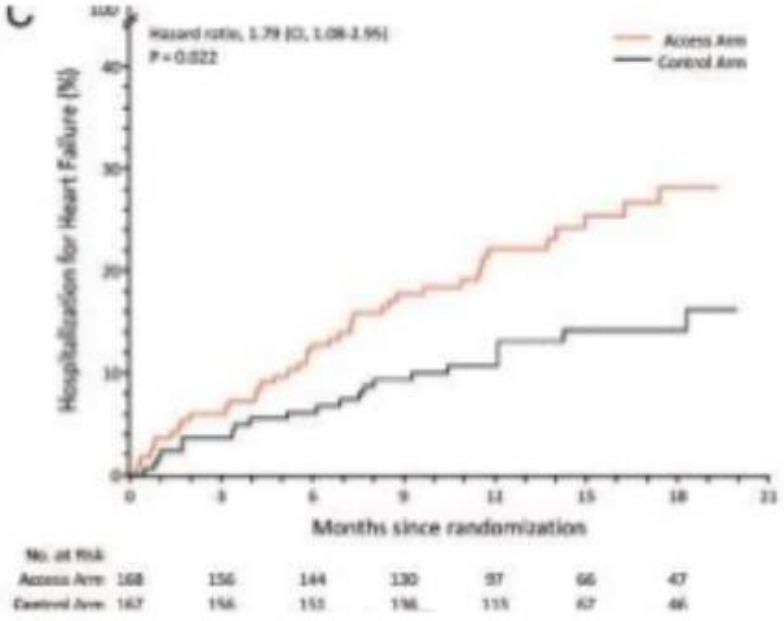






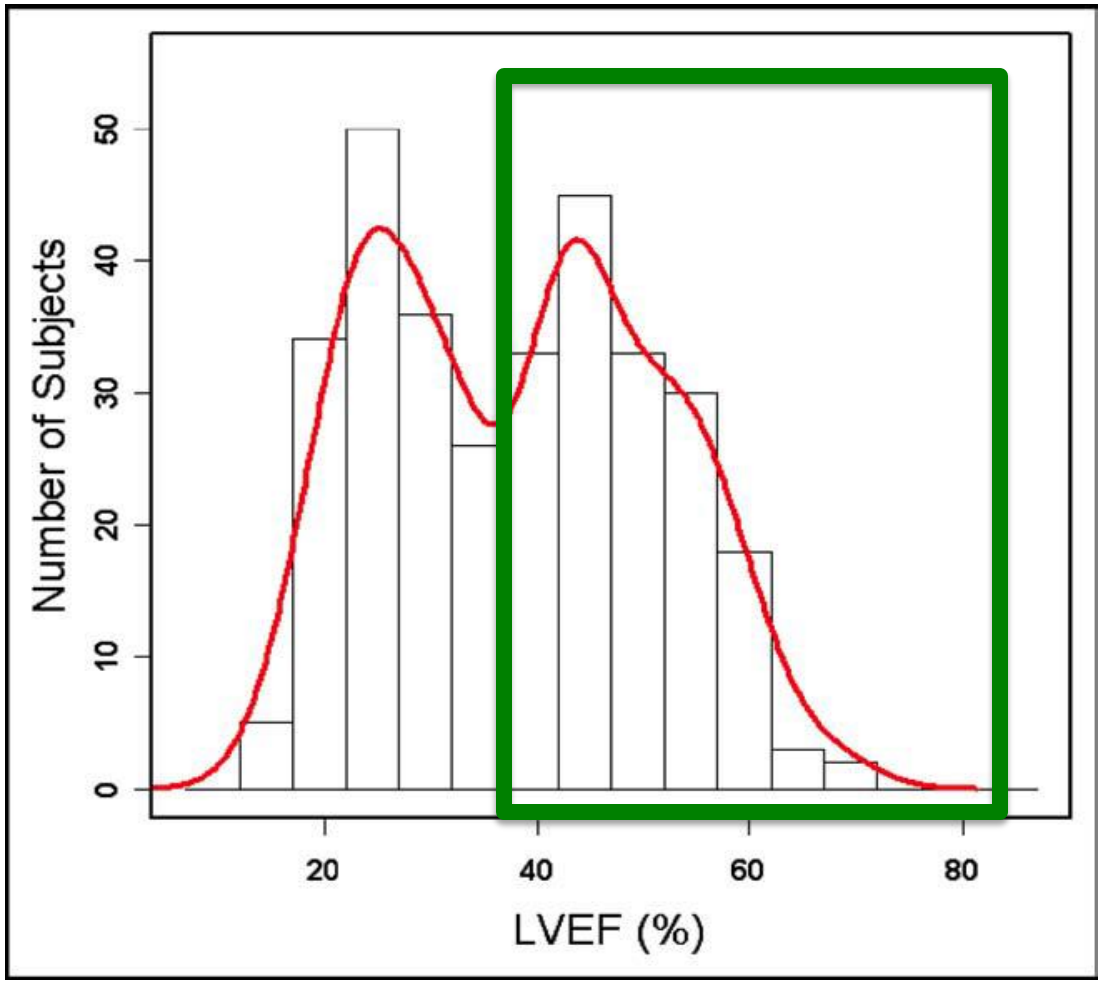
Diagnostic Outcome Trial in Heart Failure (DOT-HF Trial)

- 335 patients; average follow-up of 15 months
- Intrathoracic impedance monitoring associated with a significant increase in outpatient clinic visits (240 vs 84)
- Intrathoracic impedance monitoring associated with a significant increase in HF hospitalizations (HR = 1.79, 95% CI 1.08-2.95, p=0.022)



van Veldhuisen DJ, et al. Circulation 2011

Challenge #4: HFpEF?



Gaasch WH et al. Am J Cardio 2009;104:1413
De Keulenaer GW, Brutsaert DL. Circ 2009;119:3044

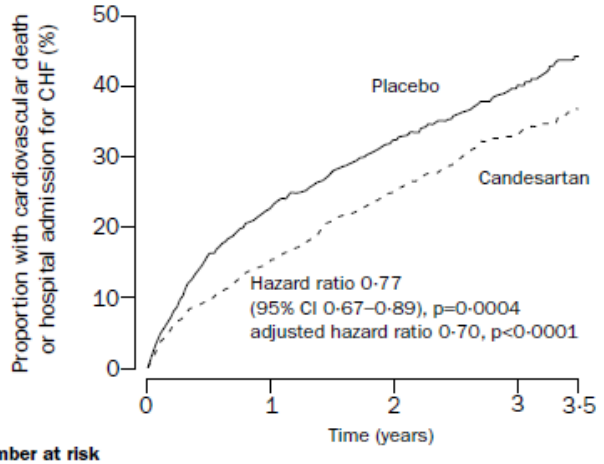
Guidelines HFpEF: radio silence

Table 21. Recommendations for Treatment of HF*p*EF

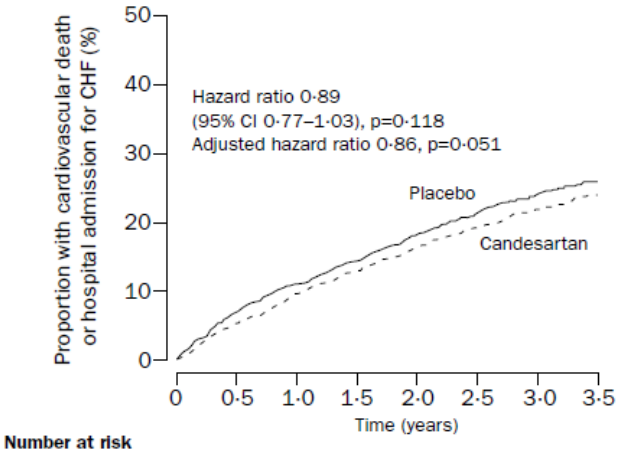
Recommendations	COR	LOE
Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines	I	B[27,28]
Diuretics should be used for relief of symptoms due to volume overload.	I	C
Coronary revascularization for patients with CAD in whom angina or demonstrable myocardial ischemia is present despite GDMT	IIa	C
Management of AF according to published clinical practice guidelines for HF*p*EF to improve symptomatic HF	IIa	C
Use of beta-blocking agents, ACE inhibitors, and ARBs for hypertension in HF*p*EF	IIa	C
ARBs might be considered to decrease hospitalizations in HF*p*EF	IIb	B[29]
Nutritional supplementation is not recommended in HF*p*EF	III: No Benefit	C

ARB: HFrEF v. HFpEF

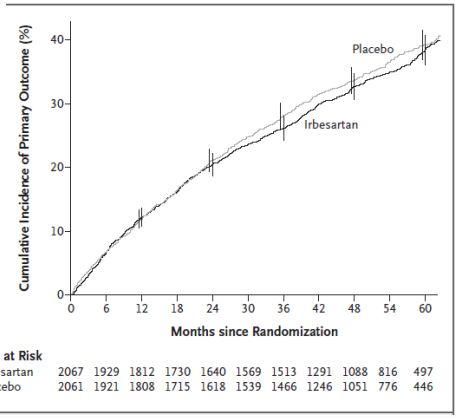
CHARM Alternative



CHARM Preserved



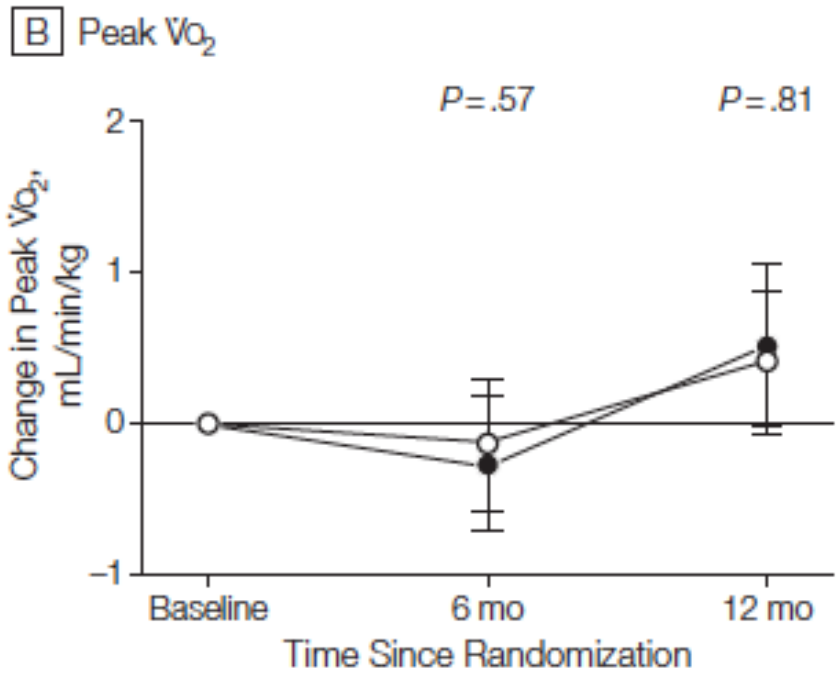
I-PRESERVE



HFrEF

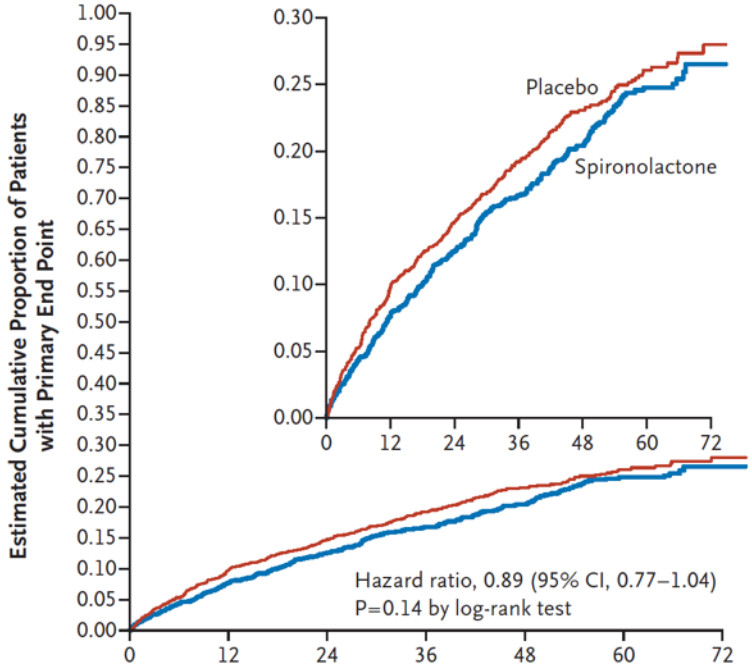
HFpEF

MRA for HFpEF: Nope



Aldo-DHF

JAMA. 2013;309(8):781-791

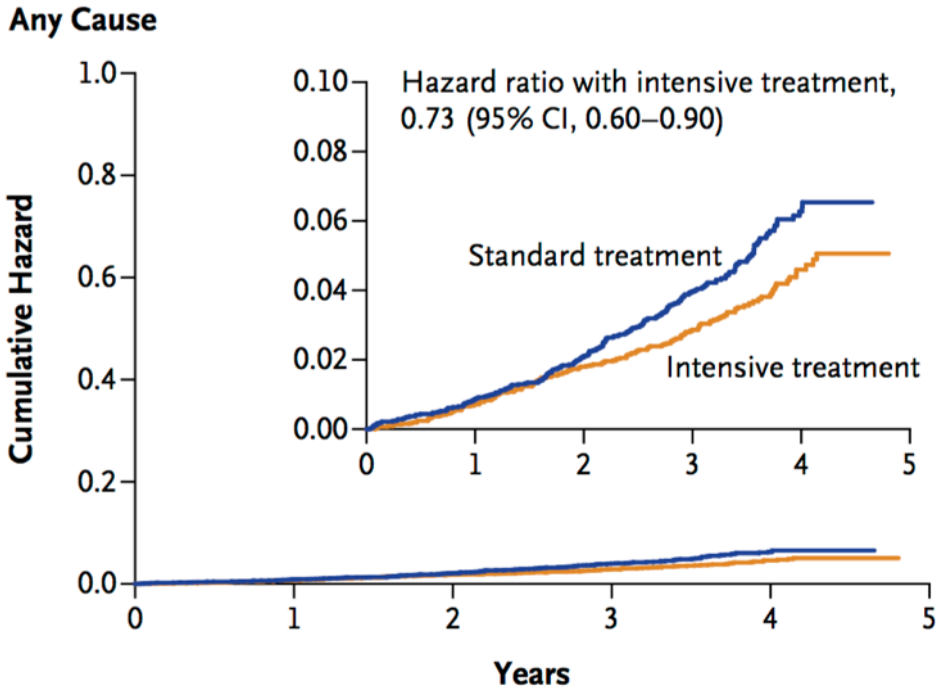


TOPCAT

N Engl J Med 2014;370:1383-92.

Biggest HF Trials in 2015…

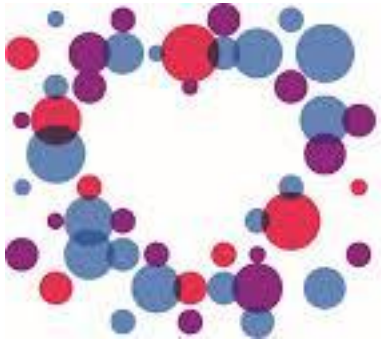
Biggest HF Trials in 2015…

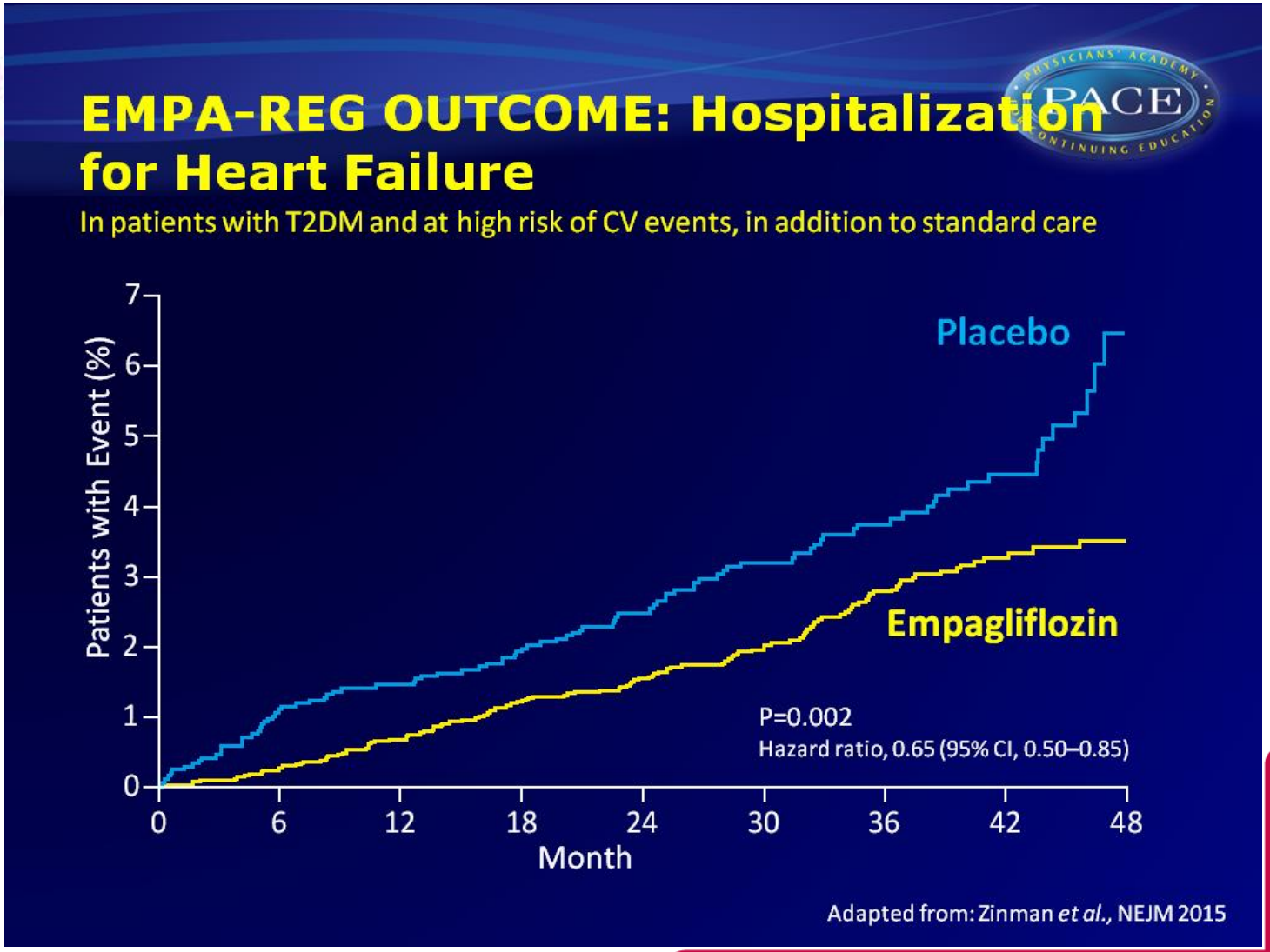


Secondary outcomes						
Myocardial infarction	97 (2.1)	0.65	116 (2.5)	0.78	0.83 (0.64–1.09)	0.19
Acute coronary syndrome	40 (0.9)	0.27	40 (0.9)	0.27	1.00 (0.64–1.55)	0.99
Stroke	62 (1.3)	0.41	70 (1.5)	0.47	0.89 (0.63–1.25)	0.50
Heart failure	62 (1.3)	0.41	100 (2.1)	0.67	0.62 (0.45–0.84)	0.002

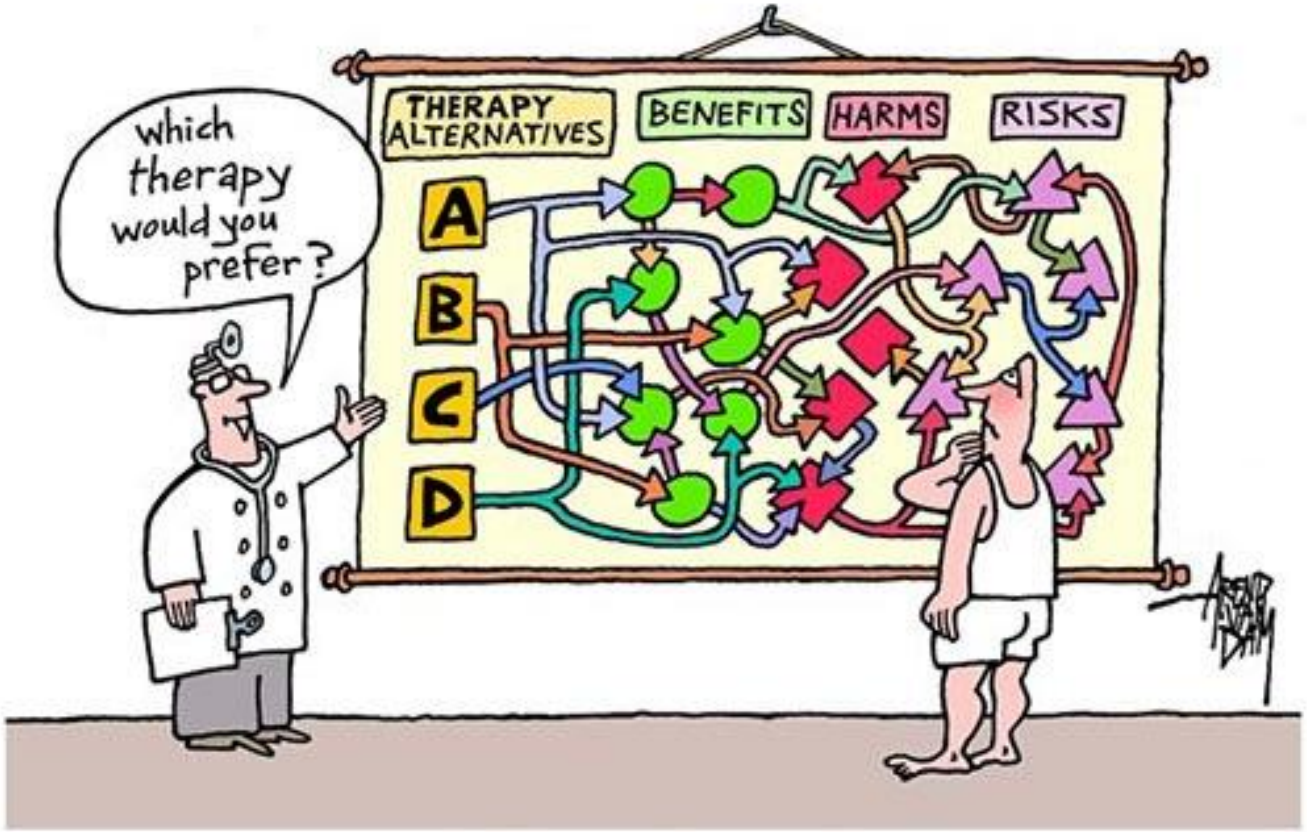
N Engl J Med 2015;373:2103-16.

Biggest HF Trials in 2015…





Challenge #5: Complex patients in complex systems

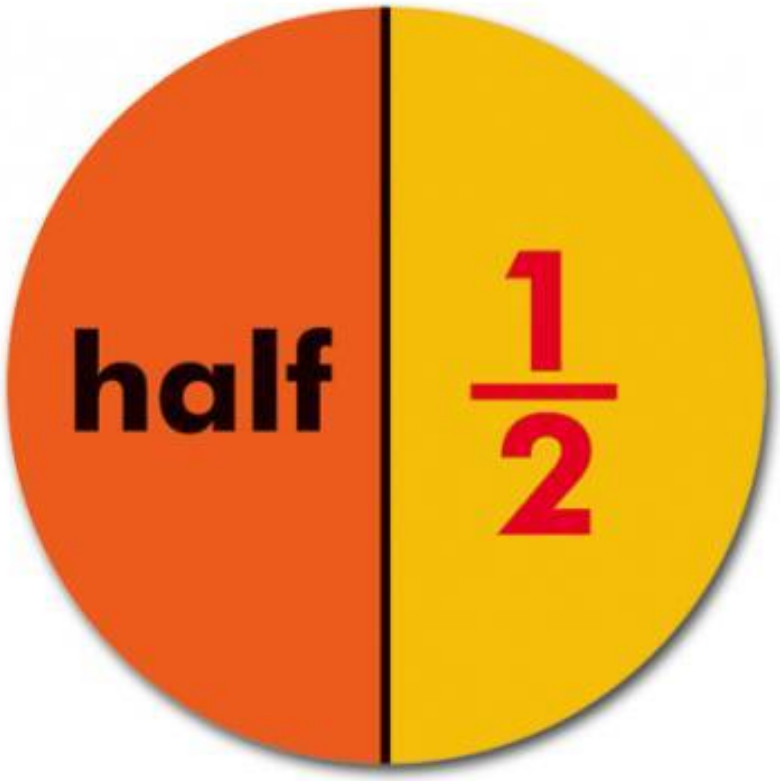


Older Americans and Multimorbidity

3 or more

Managing Multiple Health Problems in Older Adults

#3orMore



University of Colorado Hospital

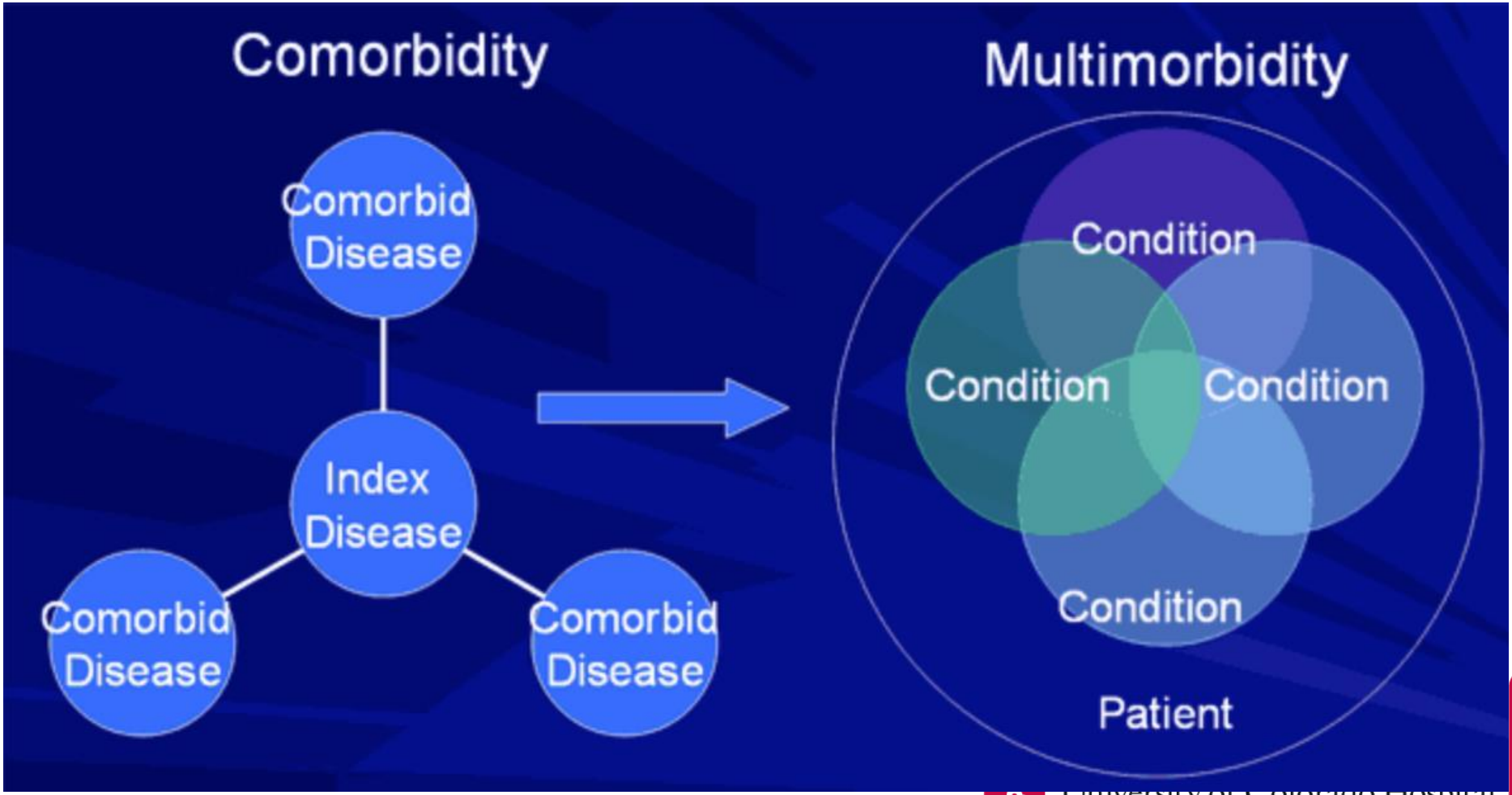
UNIVERSITY OF COLORADO HEALTH

Patterns of Comorbidity in Older Adults with Heart Failure: The Cardiovascular Research Network PRESERVE Study

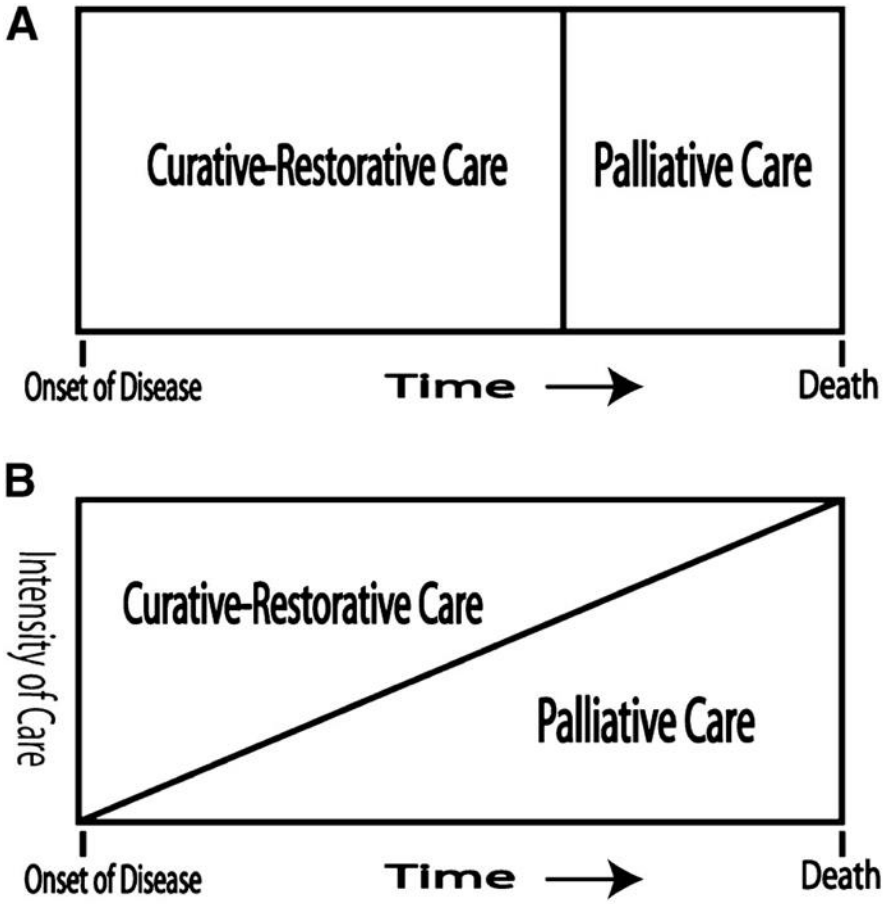
Jane S. Saczynski, PhD,[a,b,c] Alan S. Go, MD,[d,e,f] David J. Magid, MD,[g,h,i] David H. Smith, PhD,[j] David D. McManus, MD,[a,c,k] Larry Allen, MD,[l] Jessica Ogarek, MS,[a] Robert J. Goldberg, PhD,[a,c] and Jerry H. Gurwitz, MD[a,b]

- 23,435 individuals identified with HF
- Multimorbidity common – addition to HF:
  - 2%: no comorbdity
  - 76%: 3+ co-occurring conditions
  - **52%: 5+ co-occurring conditions**
- HFpEF compared to HFrEF :
  - 53% v. 47%
  - mean 4.5 vs 4.4 comorbidities

Re-Conceptualization



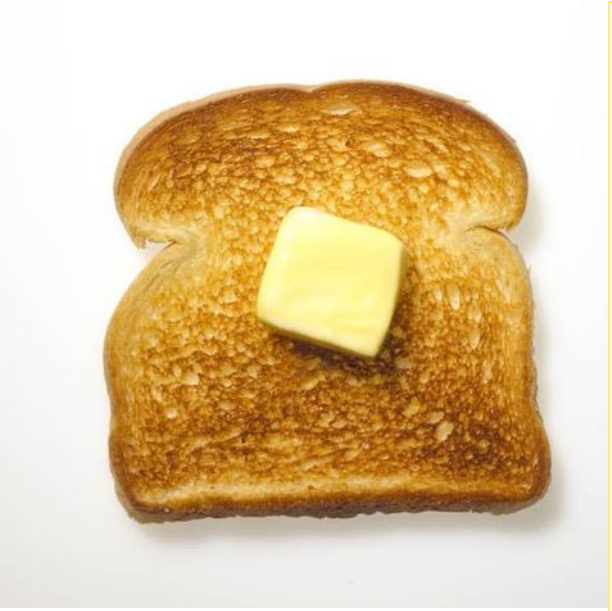
HOSPICE
Peace, Comfort & Dignity



Lanken PN et al. Am J Respir Crit Care Med 2008.

Summary: Going Forward

1. Rx for HFrEF is where the data is:
   - do it right!



ESC 2016

Stage C HFrEF

Class I
Class IIa

Patient with symptomatic[a] HFrEF[b]

Therapy with ACE-I[c] and beta-blocker
(Up-titrate to maximum tolerated evidence-based doses)

Still symptomatic and LVEF ≤35%? No

Yes

Add MR antagonist[d,e]
(up-titrate to maximum tolerated evidence-based dose)

Yes

Still symptomatic and LVEF ≤35%? No

Yes

- Able to tolerate ACEI (or ARB)[f,g] → ARNI to replace ACE-I
- Sinus rhythm, QRS duration ≥130 msec → Evaluate need for CRT[i,j]
- Sinus rhythm,[h] HR ≥70 bpm → Ivabradine

These above treatments may be combined if indicated

Resistant symptoms?

Yes → Consider digoxin or H-ISDN or LVAD, or heart transplantation

No → No further action required
Consider reducing diuretic dose

Diuretics to relieve symptoms and signs of congestion

If LVEF ≤35% despite OMT or a history of symptomatic VT/VF, implant ICD

Summary: Going Forward

1. Rx for HFrEF is where the data is:
   - do it right!
2. Future systems of care will need to be:
   - patient-centered
   - longitudinal
   - team-based
   - with clinician and patient decision support

Summary: Going Forward

1. Rx for HFrEF is where the data is:
   - do it right!
2. Future systems of care will need to be:
   - patient-centered
   - longitudinal
   - team-based
   - with clinician and patient decision support
3. Expand from Stage C HFrEF to:
   - HFpEF
   - Stage A prevention
   - Stage D end-of life

- **7 board-certified Advanced Heart Failure & Transplant Cardiologists**
  - Gene Wolfel, MD
  - Andreas Brieke, MD (Director MCS)
  - Larry Allen, MD, MHS (Director HF)
  - Amrut Ambardekar, MD (Director Txplt)
  - Natasha Altman, MD
  - Prateeti Khazanie, MD
  - William Cornwell, MD

- **5 Dedicated Advanced HF NPs**
- **4 MCS Coordinators**
- **4 Advanced Heart Failure RNs**
- **4 Transplant Coordinators**
- **1 HF Clinical Nurse Specialist**
- **4 CT Surgery**
- 18 Fellows, including advanced HF

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Objectives

1. Understand the major goals of heart failure management, including identification of underlying etiology, correction of any reversible causes, reduction of congestion, and optimization of cardiac function.
2. Understand that most specific heart failure therapies are indicated for patients with reduced ejection fraction (HFrEF); for the approximately 50% of patients with heart failure and relatively preserved ejection fraction (HFpEF), treatment consists largely of diuretic titration and management of comorbidities.
3. Know the major classes of medications for heart failure, including newly approved sacubitril/valsartan and ivabradine.
4. Be familiar with other non-pharmacologic therapies for heart failure, including electrical therapies (defibrillatiors and resynchronization), invasive pressure monitoring (CardioMEMS), and advanced therapies (transplantation, mechanical support devices, and hospice).
5. Recognize the importance of prevention and list specific prevention goals.