HEART FAILURE WITH REDUCED EJECTION FRACTION STATE OF THE ART

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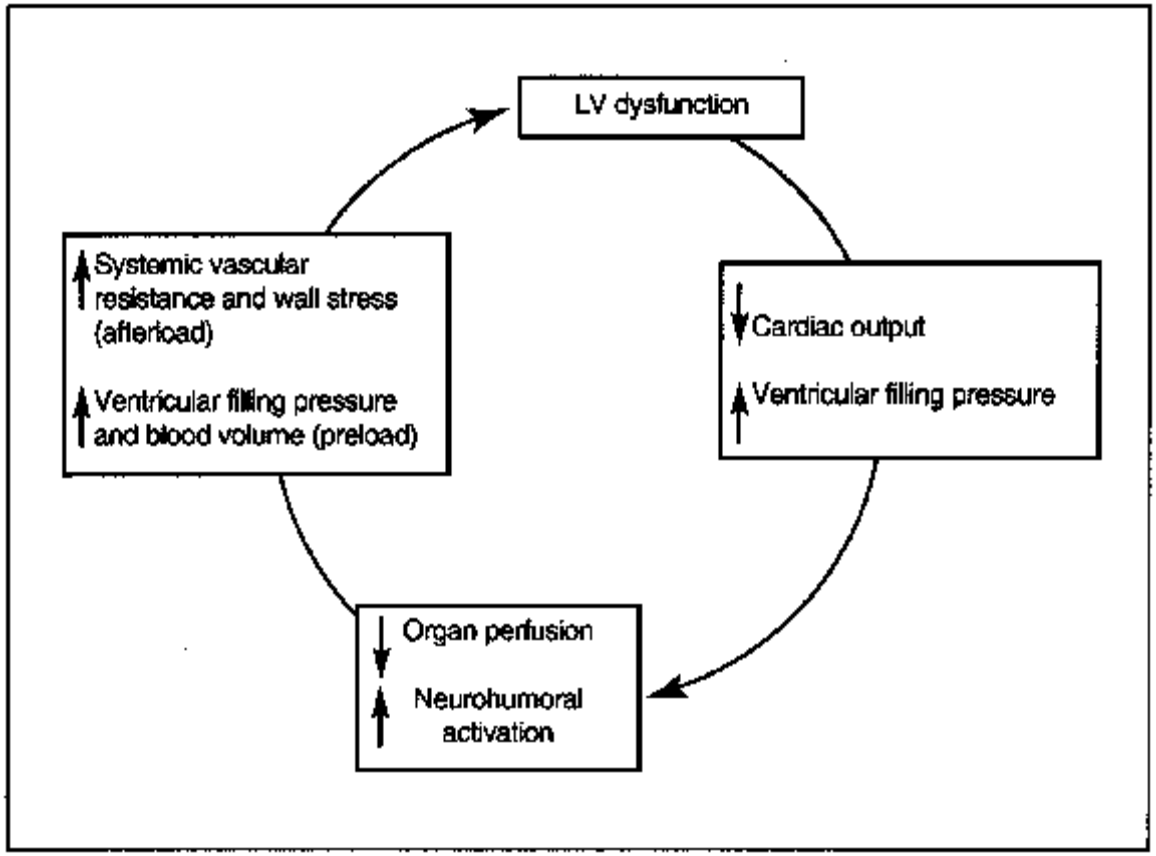
April 29, 2018

Heart Failure Management
If your only tool is a hammer…

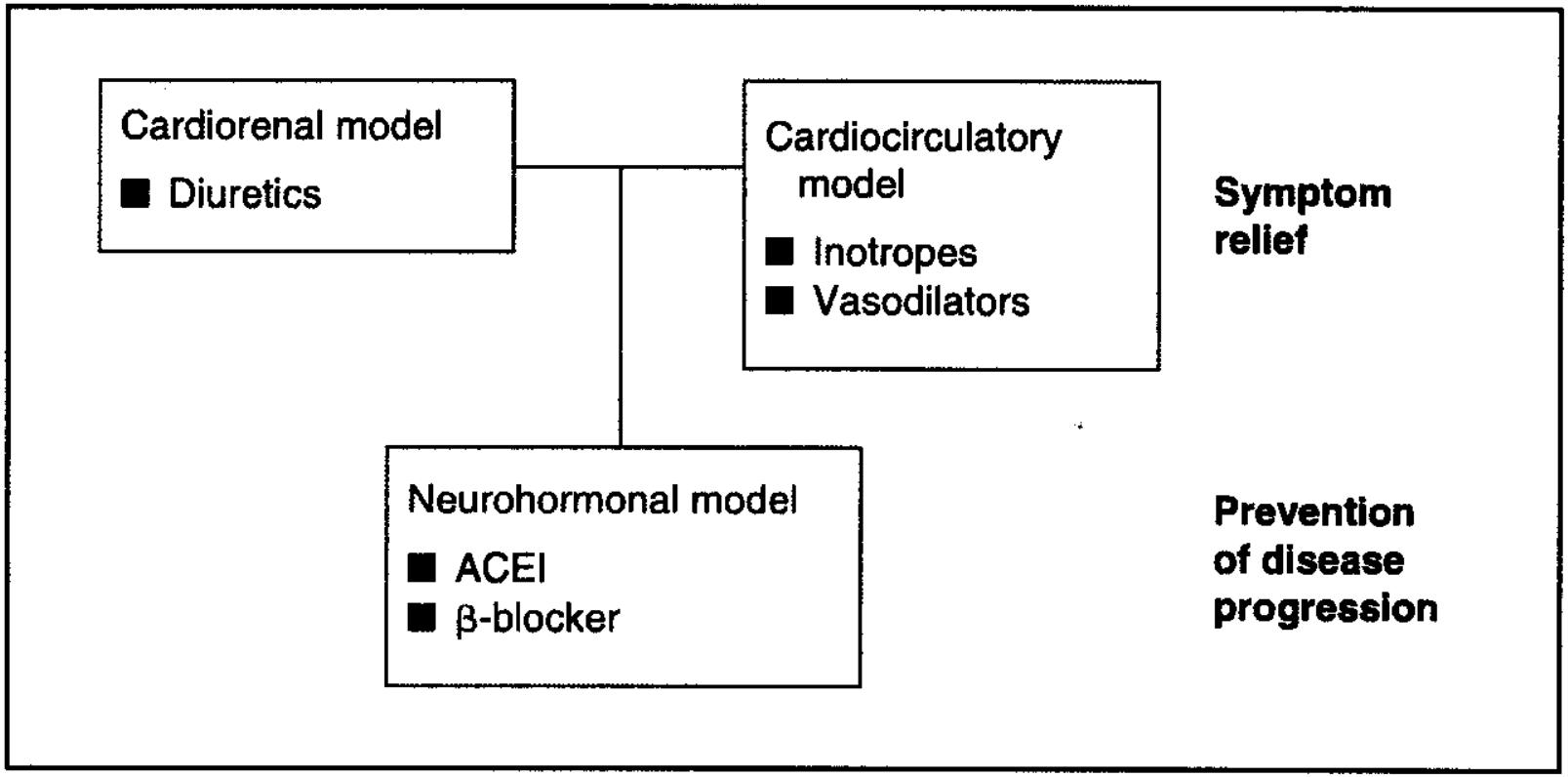
- Models of pharmacologic management
  - Volume overload

A Traditional Model for Chronic Heart Failure



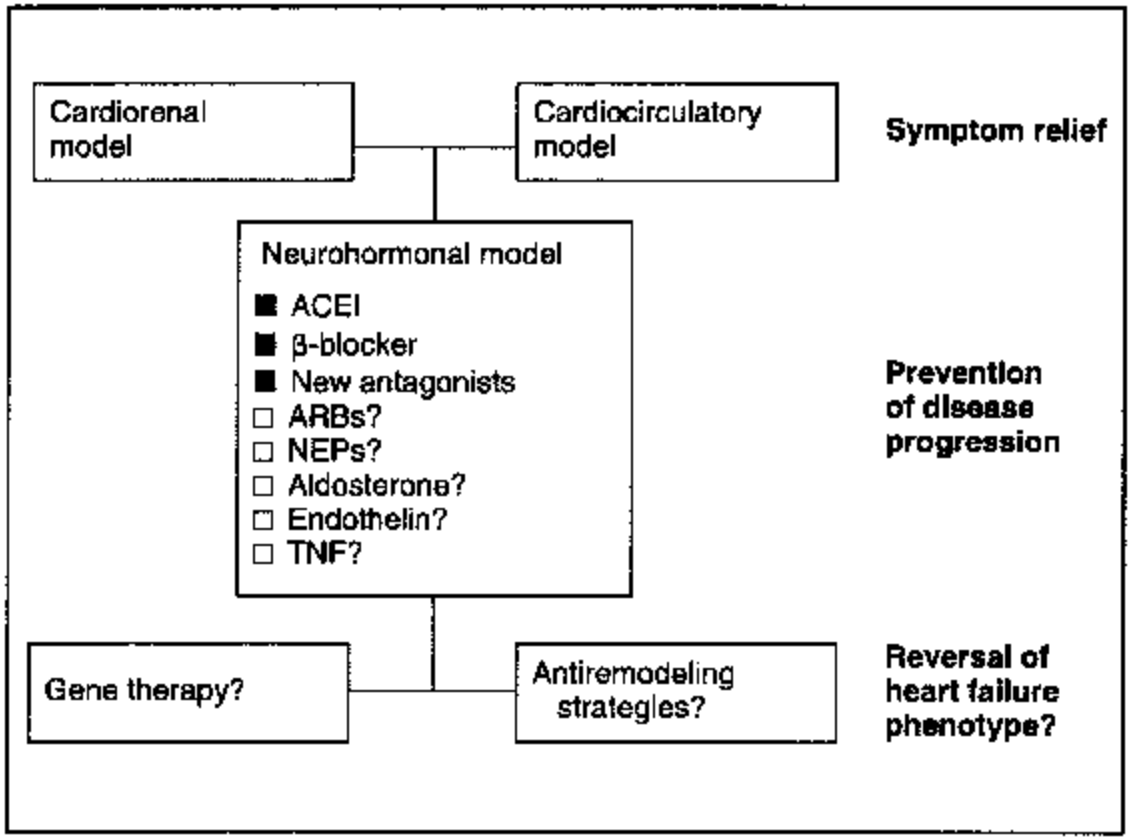
A Clinical Model

From Mann, DL *Circulation* 1999; 100: 999-1008



A Comprehensive Model

From Mann, DL *Circulation* 1999; 100: 999-1008



The New Paradigm, 2005

Electromechanical therapy

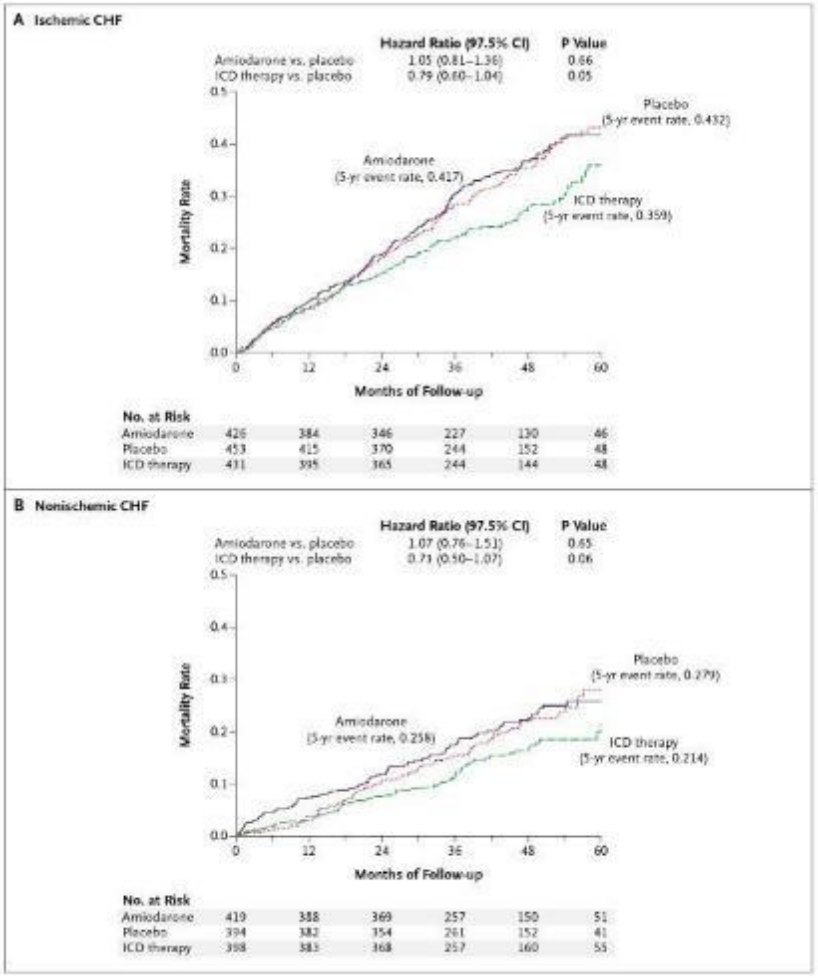
- AICD

Restoration of myocardial function

- Cardiac resynchronization therapy
- Restoration of myocardial twist
- Surgical approaches to remodeling

- Prevention of sudden death

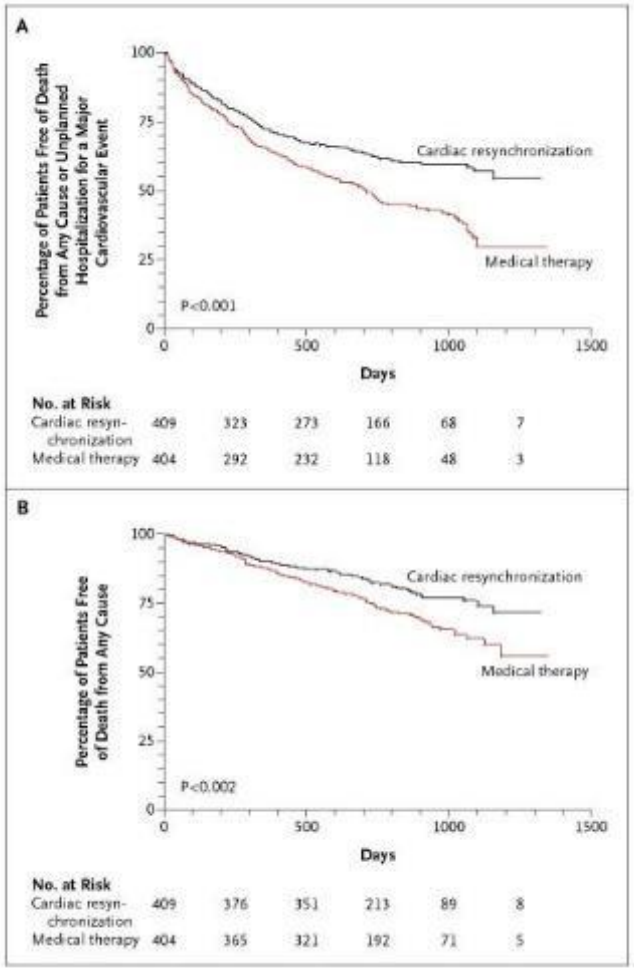
Amiodarone vs AICD in HFrEF



Bardy GH et al. N Engl J Med 2005;352:225-237.

CRT for HFrEF, CARE HF Study.

CARE – HF Trial of CRT vs medical therapy in HFrEF



Cleland JG et al. N Engl J Med 2005;352:1539-1549.

New models for management of HF

- Pharmacologic
- Electromechanical
- Mechanical
- Systemic

New models for management of HF

- Pharmacologic
  - Sacubritil/Valsartan
  - Beta blocker, MRA
  - Diuretic
- Electromechanical
  - AICD
  - CRT + AICD
- Mechanical
  - LVAD
  - Transplant
- Systemic
  - Sleep apnea
  - Exercise

New models for management of HF

- Pharmacologic
  - Sacubritil/Valsartan
  - Beta blocker, MRA
  - Diuretic
  - Anticoagulation
- Electromechanical
  - AICD
  - CRT + AICD
  - Pulmonary vein isolation for atrial fibrillation
- Mechanical
  - LVAD
- Systemic interventions:
  - Detection of CAD, Anemia, Sleep apnea

Not covered today

- Ivradabine
- Valvular interventions
  - TAVR
  - MAVR
  - TAVR
- Coronary artery revascularization
- Heart failure with mid-range ejection fraction (HFmrEF)

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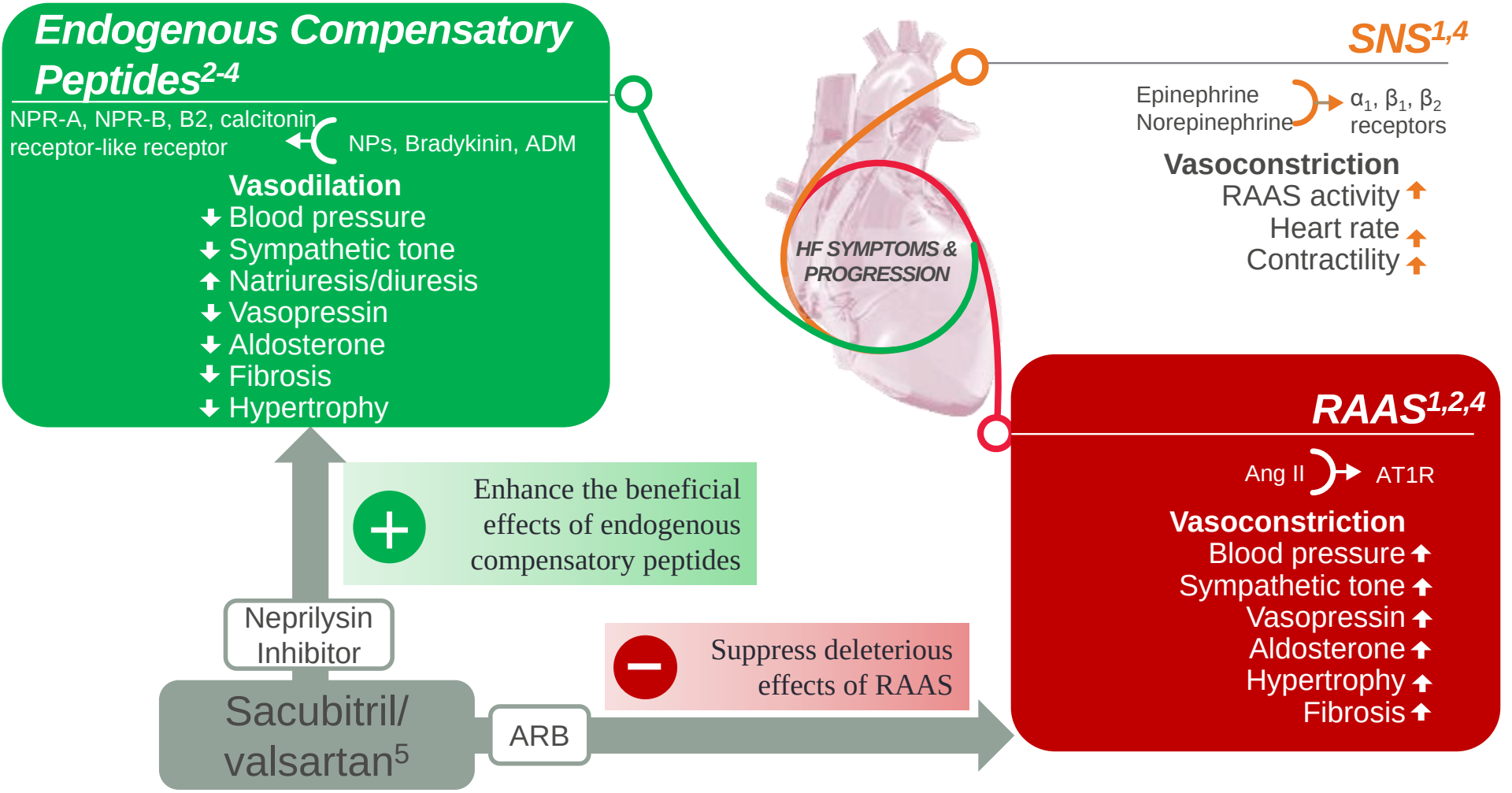
- Now, on to

  Pharmacologic therapy

Sacubitril/Valsartan

Effects of Sacubitril/valsartan in HFrEF



1. Kemp CD, Conte JV. *Cardiovasc Pathol.* 2012;21(5):365-371. 2. Mangiafico S et al. *Eur Heart J.* 2013;34:886-893. 3. Nathisuwan S, Talbert RL. *Pharmacotherapy.* 2002;22:27-42. 4. Hasenfuss G, Mann DL. Pathophysiology of heart failure. In: Mann DL et al, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia, PA: Elsevier; 2015. 5. Entresto (sacubitril/valsartan) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; August 2015.

ENTRESTO®

Effects on Neprilysin and RAAS

Increases effects of endogenous compensatory peptides
↑ Vasodilation
↑ Natriuretic and diuretic effects
↓ Proliferation
↓ Hypertrophy
↓ SNS outflow/sympathetic tone
↓ Aldosterone secretion
↓ Detrimental effects of vascular remodeling

Suppressing RAAS-mediated effects
↓ Vasoconstriction
↓ Sodium and water retention
↓ Ventricular hypertrophy/remodeling
↓ Aldosterone secretion
↓ Cardiac fibrosis
↓ Sympathetic tone
↓ Systemic vascular resistance

cGMP=cyclic guanosine monophosphate; RAAS=renin-angiotensin-aldosterone system; SNS=sympathetic nervous system

Levin et al. N Engl J Med 1998;339:321–8;
Nathisuwan & Talbert. Pharmacotherapy 2002;22:27–42;
Schrier & Abraham. N Engl J Med 2009;341:577–85;
Langenickel & Dole. Drug Discov Today: Ther Strateg 2012;9:e131–9

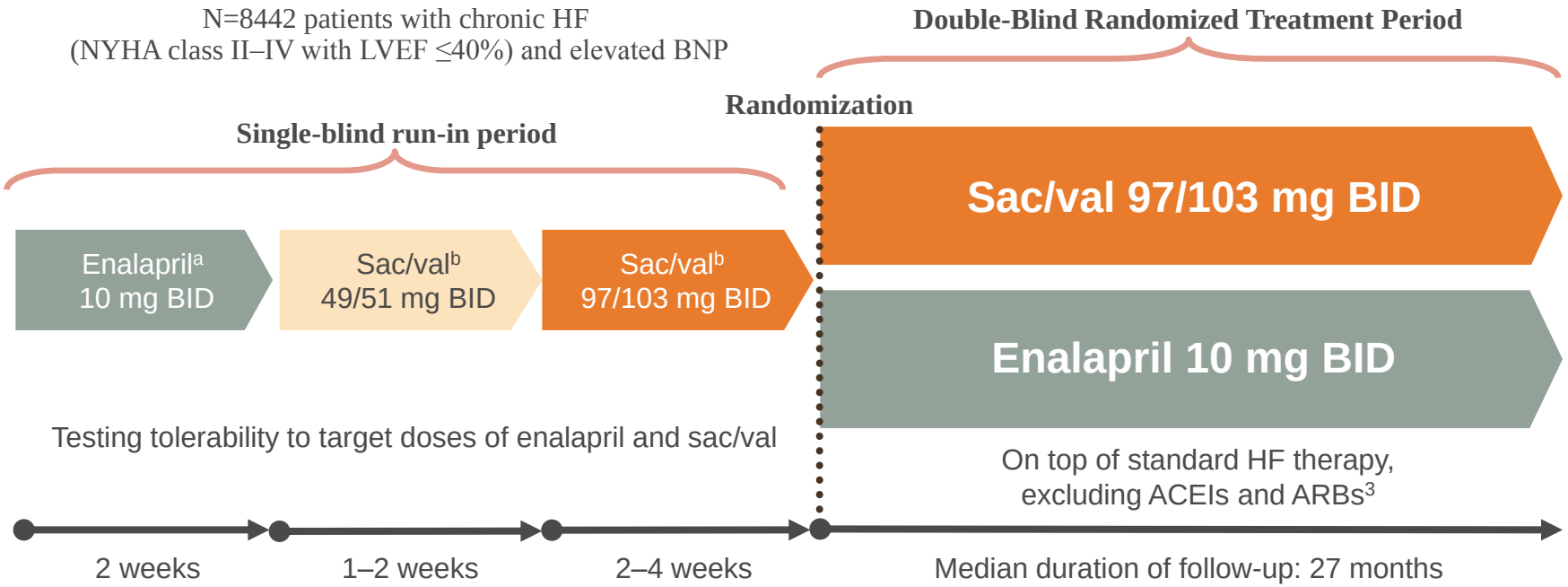
PARADIGM-HF TRIAL KEY FINDINGS

PARADIGM-HF

Study Design

Phase 3 Trial to Examine the Efficacy of Sacubitril/Valsartan vs Enalapril in Patients With HFrEF[1,2]

N=8442 patients with chronic HF
(NYHA class II–IV with LVEF ≤40%) and elevated BNP



A 36 hour washout was required after single blind enalapril run-in and also at end of entresto single blind run-in prior to being randomized

- **Primary outcome:** To demonstrate superiority of sacubitril/valsartan over enalapril in reducing composite of death from CV causes or a first hospitalization for HF

BID, twice daily; BNP, brain natriuretic peptide; NYHA, New York Heart Association.
[a]Enalapril 5 mg BID for 1–2 weeks followed by enalapril 10 mg BID was an optional starting run-in dose for patients treated with ARBs or with a low dose of ACEI.
[b]Dosing in clinical trials was based on the total amount of both components of sac/val; 24/26 mg, 49/51 mg, and 97/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively. Sac/val was formerly known as LCZ696 in clinical trials.
1. Entresto (sacubitril/valsartan) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; August 2015. 2. McMurray JJ et al. *Eur J Heart Fail.* 2013;15(9):1062-1073. 3. McMurray JJ et al. *N Engl J Med.* 2014;371(11):993-1004.

PARADIGM-HF

Baseline Characteristics

Characteristic*	Sac/Val (N=4187)	Enalapril (N=4212)
Age, years	63.8 ± 11.5	63.8 ± 11.3
Female, n (%)	879 (21.0)	953 (22.6)
Ischemic cardiomyopathy, n (%)	2506 (59.9)	2530 (60.1)
LVEF (%)	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class, n (%) II III	 2998 (71.6) 969 (23.1)	 2921 (69.3) 1049 (24.9)
SBP, mm Hg	122 ± 15	121 ± 15
Heart rate, BPM	72 ± 12	73 ± 12
NT-proBNP, median, pg/mL (IQR)	1631 (885–3154)	1594 (886–3305)
BNP, median, pg/mL (IQR)	255 (155–474)	251 (153–465)
History of DM, n (%)	1451 (34.7)	1456 (34.6)
Treatments at randomization, n (%) Diuretics Digitalis Beta-blockers MRAs ICD CRT	 3363 (80.3) 1223 (29.2) 3899 (93.1) 2271 (54.2) 623 (14.9) 292 (7.0)	 3375 (80.1) 1316 (31.2) 3912 (92.9) 2400 (57.0) 620 (14.7) 282 (6.7)

BPM, beats per minute; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; SBP, systolic blood pressure.

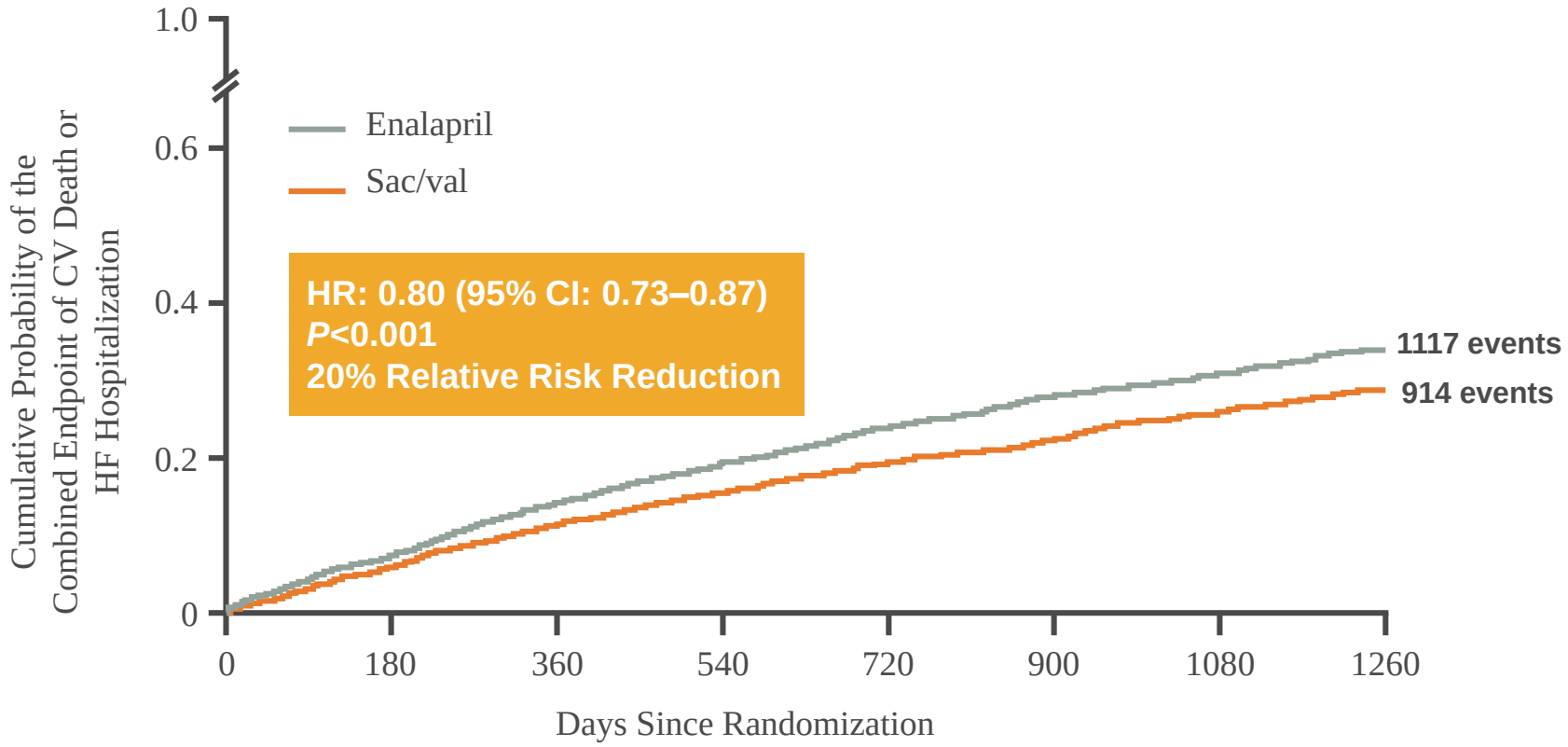
*Mean ± standard deviation, unless stated.

McMurray JJ et al. *N Engl J Med*. 2014;371:993-1004.

PARADIGM-HF

Primary Endpoint: Time to First Occurrence of CV Death or HF Hospitalization

The difference in favor of sacubitril/valsartan was seen early in the trial and at each interim analysis



No. at risk								
Sac/val	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

CI, confidence interval; HR, hazard ratio.

McMurray JJ et al. *N Engl J Med.* 2014;371:993-1004.

PARADIGM-HF

Summary of Key Findings

Endpoint	Sac/Val N=4187 n (%)	Enalapril N=4212 n (%)	HR (95% CI)	*P* Value
Primary composite endpoint of CV death or HF hospitalization	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.0001
CV death as first event	377 (9.0)	459 (10.9)		
HF hospitalization as first event	537 (12.8)	658 (15.6)		
Number of patients with events[a]				
CV death[b]	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	
HF hospitalizations	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	
All-cause mortality	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	0.0009

[a]Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity.
[b]Includes subjects who had HF hospitalization prior to death.
Entresto (sacubitril/valsartan) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; August 2015.

2016 ACC/AHA/HFSA Focused Update

Pharmacological Treatment for Stage C HFrEF: Recommendations

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI (cont'd)

COR	LOE	Recommendations
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.**

"In patients with mild-to-moderate HF (characterized by either [1] mildly elevated natriuretic peptide levels, BNP [B-type natriuretic peptide] >150 pg/mL or NT-proBNP [N-terminal pro-B-type natriuretic peptide] ≥600 pg/mL; or [2] BNP ≥100 pg/mL or NT-proBNP ≥400 pg/mL with a prior hospitalization in the preceding 12 months) who were able to tolerate both a target dose of enalapril (10 mg twice daily) and then subsequently an ARNI (valsartan/sacubitril, 200* mg twice daily, with the ARB component equivalent to valsartan 160 mg), hospitalizations and mortality were significantly decreased with the valsartan/sacubitril compound compared with enalapril."

*Dosing in clinical trials was based on the total amount of both components of sacubitril/valsartan, i.e., 24/26 mg, 49/51 mg, and 97/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively.
ARNI, angiotensin receptor-neprilysin inhibitor
Yancy CW, et.al. , 2016 ACC/AHA/HFSA Focused Update on New Pharmacological Therapy for Heart Failure: An Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure, *Journal of the American College of Cardiology* (2016), doi: 10.1016/ j.jacc.2016.05.011.

Comprehensive Receptor Blockade

- Maximum dose (determined by BNP and/or guidelines) of

- Sacubitril/valsartan
- + Beta blocker (metoprolol succinate, carvedilol, bisoprolol)
- + Mineralocorticoid antagonist (spironolactone)

- Optimal diuretic therapy

BNP in outpatient management

- Ouwerkerk, et al. *JACC* 2018; 71: 386-98, Jan 30, 2018
- 2,516 patients with worsening heart failure from the BIOSTAT-CHF study compared with 3 theoretical treatment scenarios
  - A. All patients up-titrated to >50% of recommended doses
  - B. Patients up-titrated according to biomarker selection model
  - C. No patient is up-titrated to >50% of recommended doses
- Outcome measures: death or heart failure hospitalization
- Assessment: 161 biomarkers

BNP in outpatient management

- Results

- Guideline-based up titration
  - ACEi/ARB Prevent 9.8 events per 100 pt at 24 months
  - B Blocker Prevent 1.3 events
  - MRA Prevent 12.3 events
- Biomarker based up titration
  - ACEi/ARB Prevent 9.9 events
  - B Blocker Prevent 4.7 events
  - MRA Prevent 13.1 events

Guideline based targets (AHA, ESC)

- ACEi
  - Enalapril 10-20 mg BID
  - Lisinopril 20-40 mg daily (ESC 20-35)
- ARB
  - Losartan 150 mg
- Beta blocker
  - Metoprolol succ. 200 mg
- MRA
  - Spironolactone 50 mg

- Results
  - A biomarker-based treatment up titration choice in patients with heart failure was favorable over up titration to >50% recommended ACEi/ARB and beta blocker and over ≥50% MRA
- However, differences were small between the 2 up titration groups.

- RECOMMENDATION. Up titration should always be attempted in heart failure patients

Use of sacubitril/valsartan

- Sangaralingham LR, et al. *Circ H Fail* 2018;11: e004302

- ARNI was approved by the FDA July 2015
- Its adoption and prescription costs were assessed in the next 18 months
- Large US insurance database + Medicare Advantage
  - 2244 patients initiated ARNI (3%)
  - Cost

Health plan	$328.37	
Out of pocket	$71.10, median	$40.27
Adherence at 180 days		59.1%

ARNI and SCD

ARNI and Sudden Cardiac Death

From Carlos de Diego, et al., *Heart Rhythm* 2018; 15: 395-402.

Prospectively included 120 patients with ICD and EF < 40%

For 9 months, 100% ACEi or ARB + Beta blockers + MRA

After 9 months, ACEi or ARB was changed to sac/valsartan, followed for 9 months.

Analysis:

Appropriate shocks, NS-VT. PVC burden, BiV pacing percentage.

ARNI and Sudden Cardiac Death

- Results
  - Age 69 ± 8 years
  - LV EF 30.4%, 82% ischemic
  - Use of B-blockers (98%), MRA (97%) and AAD similar before & after sacubitril/valsartan

Outcomes	ACEi/ARB	Sac/val
NS-VT	15 ± 1.7	5.4 ± 0.5
Appropriate ICD	6.7%	0.8%
PVCs per hour	78 ± !5%	33 ± 12
BiV pacing	95 ± 6%	98.8 ± 1.3%

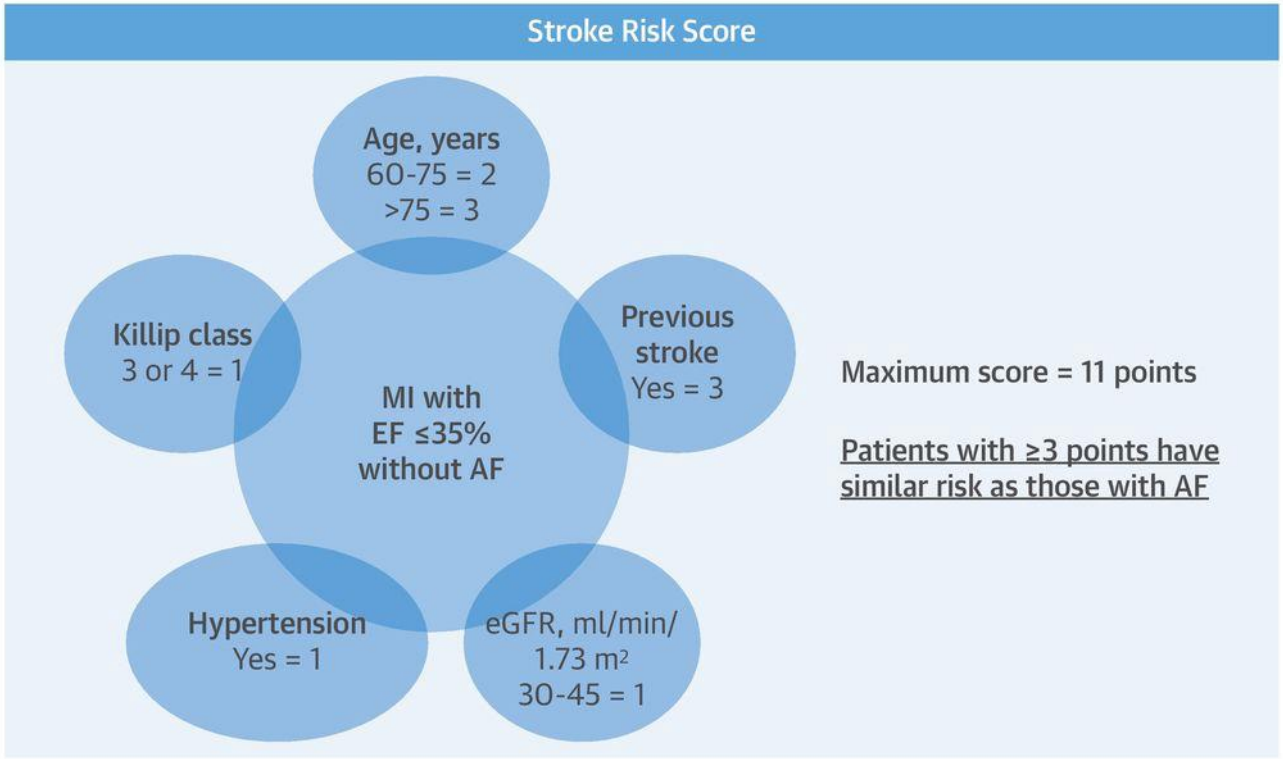
ARNI and Sudden Cardiac Death

- Why would ARNI reduce ventricular arrhythmias?
  - ARNI suppresses cardiac fibrosis and remodeling compared to ACEi alone
  - Natriuretic peptide levels translate the degree of myocardial stress, are associated with changes in electrophysiologic properties
  - Natriuretic peptide decreases sympathetic tone

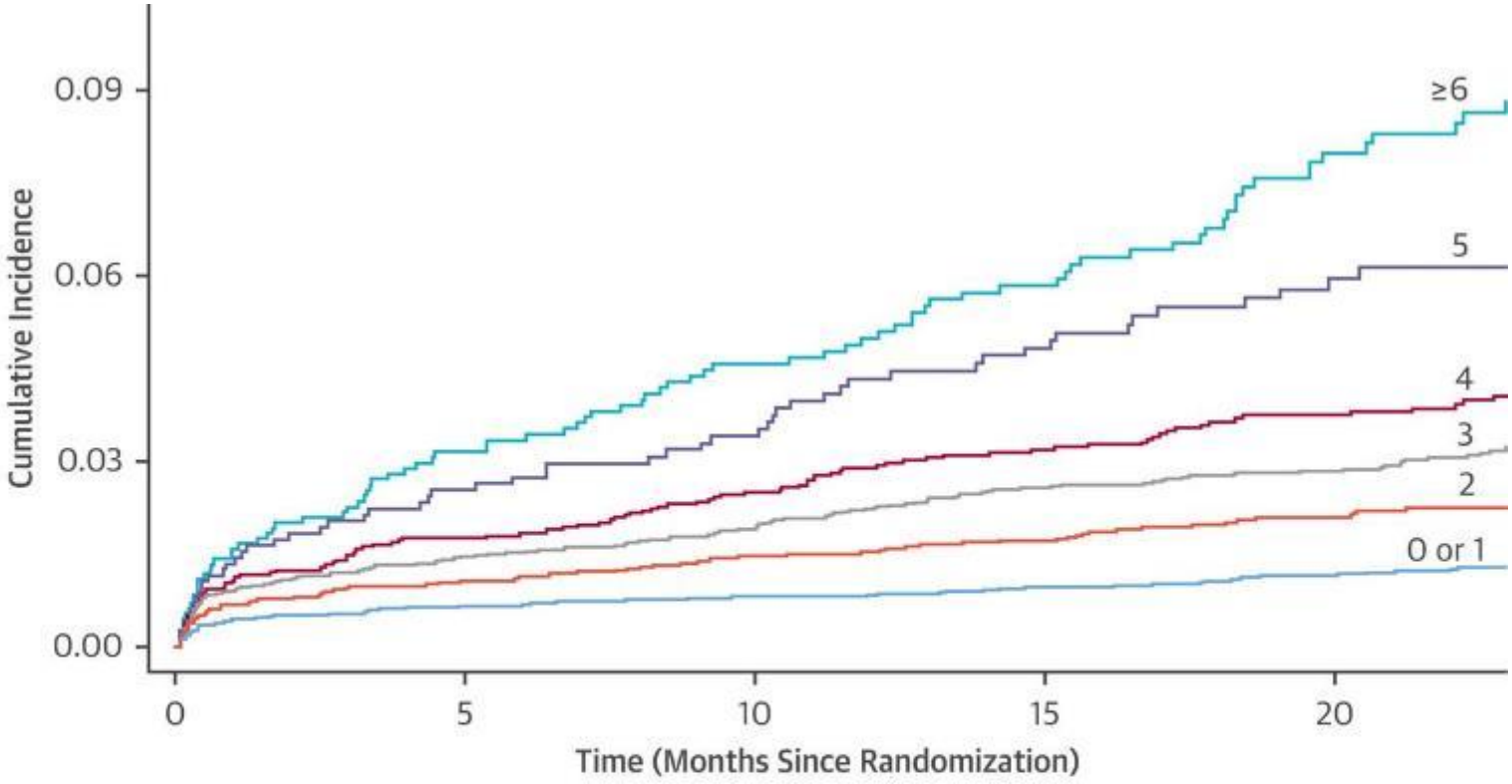
Stroke risk in patients with HFrEF

- Meta-analysis of 4 trials. 22,904 patients with myocardial infarction without A Fib
- Follow up of 1.9 years. 660 patients had a stroke. (2.9%)
- Final stroke risk model
  - Older age
  - Killip Class 3 or 4 MI
  - eGFR $\leq$ 45 ml/min/1.73 m^2
  - Hypertension history
  - History of previous stroke

CENTRAL ILLUSTRATION: Stroke Risk Score for Patients With MI Complicated With Systolic Dysfunction and/or HF



Ferreira, J.P. et al. J Am Coll Cardiol. 2018;71(7):727-35.



Score						
0 or 1	Number at risk	17072	6722	6423	5713	4617
2		23830	3521	3391	3080	2590
3		35354	4839	4574	4066	3337
4		43178	2726	2538	2230	1747
5		51154	935	854	743	563
≥6		61304	1065	966	832	643

João Pedro Ferreira et al. JACC 2018;71:727-735

Pulmonary vein isolation for HF + AF

- Atrial fibrillation and heart failure commonly occur together, with atrial fibrillation increasing the risk for stoke, hospitalization for heart failure and death.

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Pulmonary vein isolation for HF + AF

- Atrial fibrillation and heart failure commonly occur together, with atrial fibrillation increasing the risk for stoke, hospitalization for heart failure and death.
- Rhythm control with antiarrhythmic drugs is not superior to rate control in patients with atrial fibrillation.
- Catheter ablation is well-established as a treatment for atrial fibrillation in patients with normal LV function, and there is some evidence of benefit in patients with heart failure.

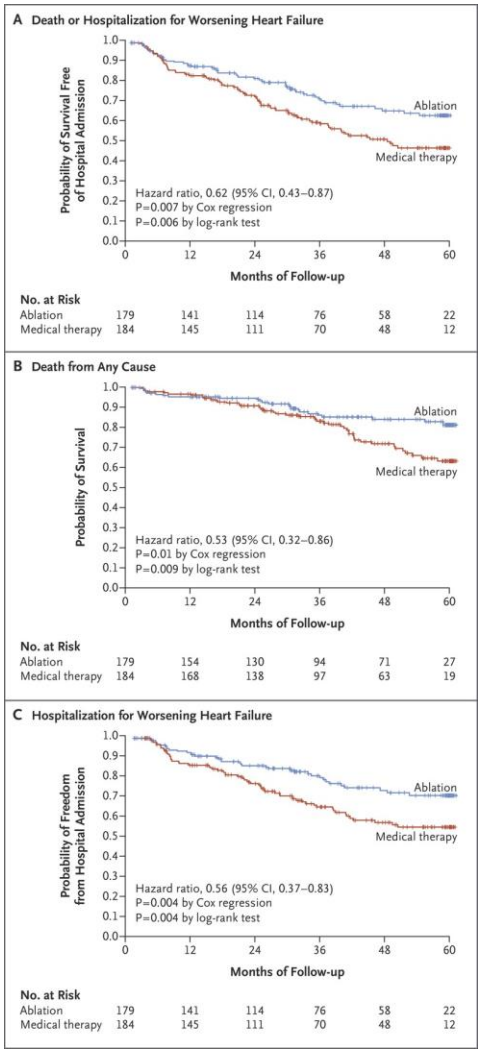
CASTLE-AF. Catheter ablation vs standard conventional therapy in patients with LV dysfunction and atrial fibrillation.

- Patients with paroxysmal or chronic atrial fibrillation and
  - LV EF < 35%
  - AICD
  - Standard therapy for HF

Randomized to:

- Pulmonary vein isolation - 179 patients
- Medical therapy (rate/rhythm control) - 184 patients

Outcomes of CASTLE-AF. NEJM Feb 1, 2018



The NEW ENGLAND JOURNAL of MEDICINE

Table 2. Primary and Secondary Clinical End Points.*

End Point	Ablation (N=179)	Medical Therapy (N=184)	Hazard Ratio (95% CI)	P Value	
				Cox Regression	Log-Rank Test
	number (percent)				
Primary†	51 (28.5)	82 (44.6)	0.62 (0.43–0.87)	0.007	0.006
Secondary					
Death from any cause	24 (13.4)	46 (25.0)	0.53 (0.32–0.86)	0.01	0.009
Heart-failure hospitalization	37 (20.7)	66 (35.9)	0.56 (0.37–0.83)	0.004	0.004
Cardiovascular death	20 (11.2)	41 (22.3)	0.49 (0.29–0.84)	0.009	0.008
Cardiovascular hospitalization	64 (35.8)	89 (48.4)	0.72 (0.52–0.99)	0.04	0.04
Hospitalization for any cause	114 (63.7)	122 (66.3)	0.99 (0.77–1.28)	0.96	0.96
Cerebrovascular accident	5 (2.8)	11 (6.0)	0.46 (0.16–1.33)	0.15	0.14

* All numbers and percentages represent the total numbers of events and raw event rates after a median follow-up of 37.8 months. Deaths and cerebrovascular accidents were evaluated at baseline and 12 weeks after baseline for hospitalizations in the two groups (the "blanking period"). For Kaplan–Meier estimates at 12, 36, and 60 months, see Table S6 in the Supplementary Appendix.

† The primary end point is a composite of death from any cause or hospitalization for worsening heart failure.

Underutilization of CAD Testing among patients hospitalized with new onset HF

- Retrospective cohort study of 67,161 patients with new onset HF
  - Only 17.5% had testing for ischemic CAD during index hospitalization, increasing to 27.4% at 90 days
  - Only 2.1% underwent revascularization during index hospitalization, increasing to 4.3% at 90 days
- ACC/AHA 2013 guidelines designate Class IIa indication to noninvasive and invasive assessment of ischemic CAD in HF patients.

CENTRAL ILLUSTRATION: Ischemic Work-Up in HF

Doshi, D. et al. J Am Coll Cardiol. 2016;68(5):450-8.

My epiphany about management of HFrEF

- We already have multiple effective treatments for heart failure with reduced EF.
- Before we clamor for new treatment modalities, we should optimize the therapies we now have available

Take home points

- Entresto (sacubitril/valsartan)
  - Comprehensive receptor blockade
  - Achieve goal-directed treatment for all patients
    - Sacubitril/valsartan (or ACE-i/ARB)
    - Beta-blocker
    - Spironolactone
- Consider stroke risk for patient in NSR post-MI with LV EF < 35%
- Catheter ablation for atrial fibrillation and LVEF < 35%
- Test for coronary artery disease in new onset heart failure