



MASSACHUSETTS
GENERAL HOSPITAL

HEART CENTER

CONTEMPORARY MANAGEMENT OF HEART FAILURE

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Disclosures: None



A Teaching Affiliate
of Harvard Medical School

TOPICS TO BE ADDRESSED

- Therapy of Systolic Dysfunction
 - Current pharmacological treatment
 - Cardiorenal syndrome
 - Role of biomarker-guided treatment
 - Cardiac resynchronization therapy
 - Ambulatory device-based treatment
- Therapy of Diastolic Dysfunction
 - Changing physiologic paradigm
 - Treatment goals
 - Current pharmacological treatment
 - Ongoing clinical trials



AHA/ACC CLASS I RECOMMENDATIONS FOR TREATMENT OF PATIENTS WITH SYMPTOMATIC LEFT VENTRICULAR SYSTOLIC DYSFUNCTION (STAGE C OR D DISEASE)

- ACE inhibitor therapy is recommended for all patients with current or prior heart failure symptoms, unless contraindicated (Level of evidence: A)
- ARBs (specifically: candesartan, valsartan) are recommended for patients with current or prior symptoms of heart failure who are ACE intolerant or as first line therapy (Level of evidence: A)
- Beta-blockers (specifically: bisoprolol, carvedilol, or sustained release metoprolol succinate) are recommended for all patients with current or prior heart failure symptoms, unless contraindicated (Level of evidence: A)
- (Level of evidence: A)
- An aldosterone antagonist is recommended for all patients with NYHA class II-IV symptoms, creatinine > 30 ml/min and $K^+ < 5.0$ mEq/L

Yancy CM, et al. *Circulation* 2013;128:e240-e327.



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CARDIO-RENAL SYNDROME

Definition: >25% increase in serum creatinine or rise ≥ 0.3 mg/dL that occurs during attempted diuresis and persists after diuresis has been accomplished

- 2-fold increase in mortality
- Associated with: older age, elevated baseline creatinine, lower BP, longer duration of heart failure symptoms, hyponatremia
- Not associated with “low output” hemodynamics
- Occurs with both systolic and diastolic heart failure
- Potential therapies:
 - adenosine antagonists [rolofylline]
 - vasopressin antagonists [tolvaptan, conivaptan]
 - ultrafiltration

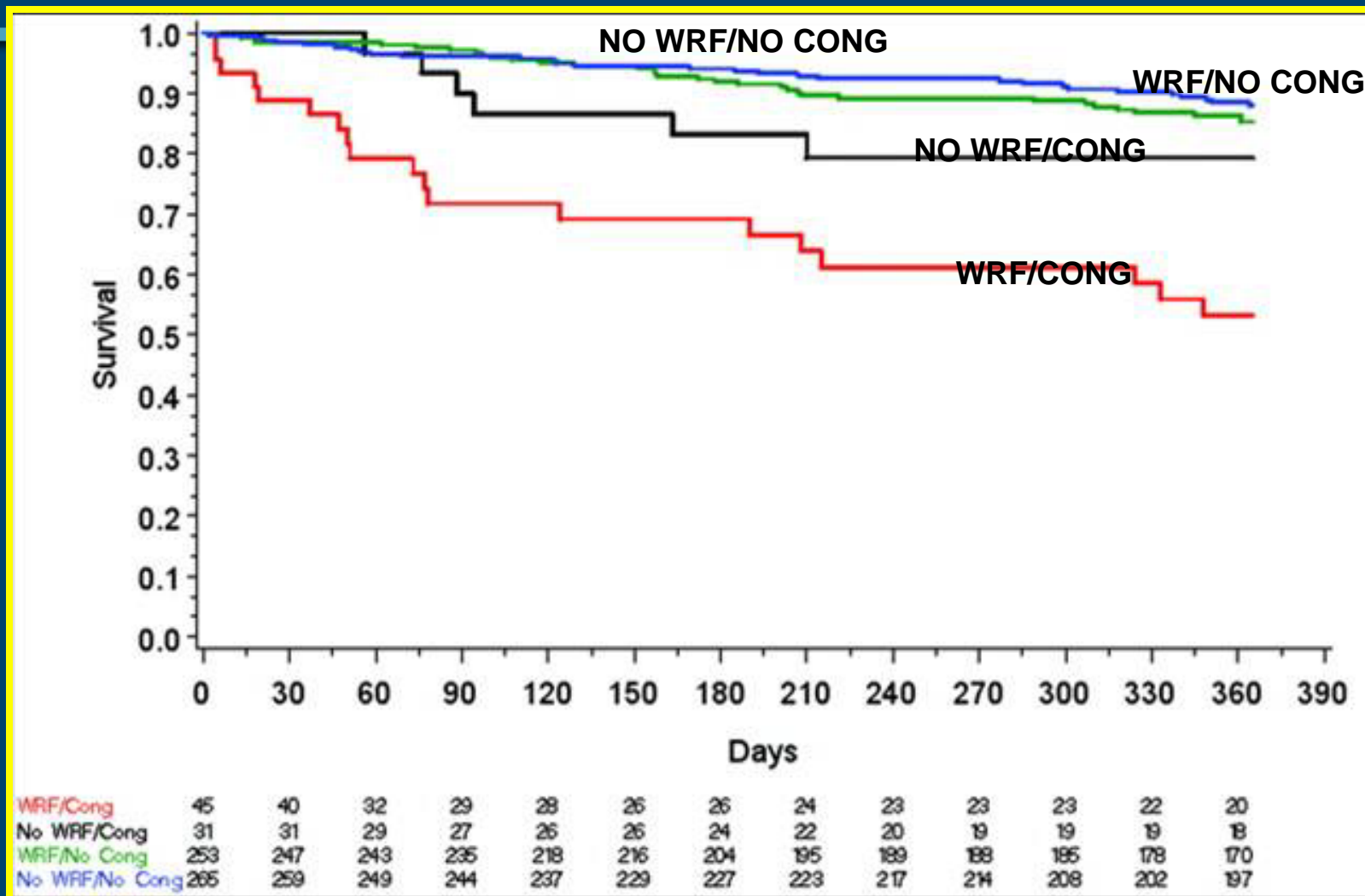
Shlipak MC, et al. *Circulation* 2004;110:1514-7.



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OUTCOME FOR DEATH OR TRANSPLANTATION BY RENAL FUNCTION AND VOLUME STATUS



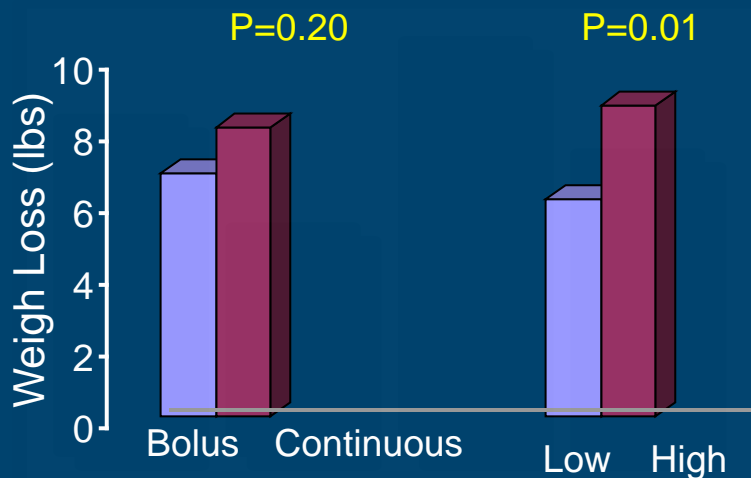
DOSING OF DIURETICS FOR INPATIENT HEART FAILURE MANAGEMENT

THE DOSE HF TRIAL

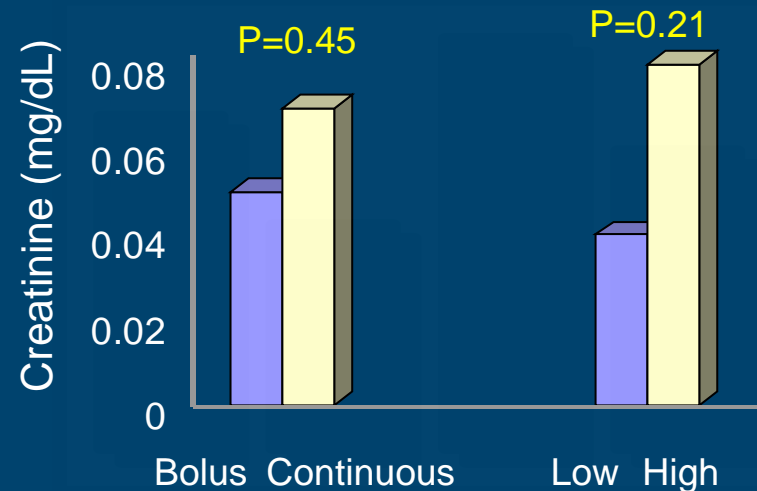
808 pts with ADHF randomized to receive:

- Continuous or IV bolus loop diuretic
- High dose IV (2.5 x oral) vs. low dose IV (1x oral) loop diuretic

Weight Loss



Change in Creatinine



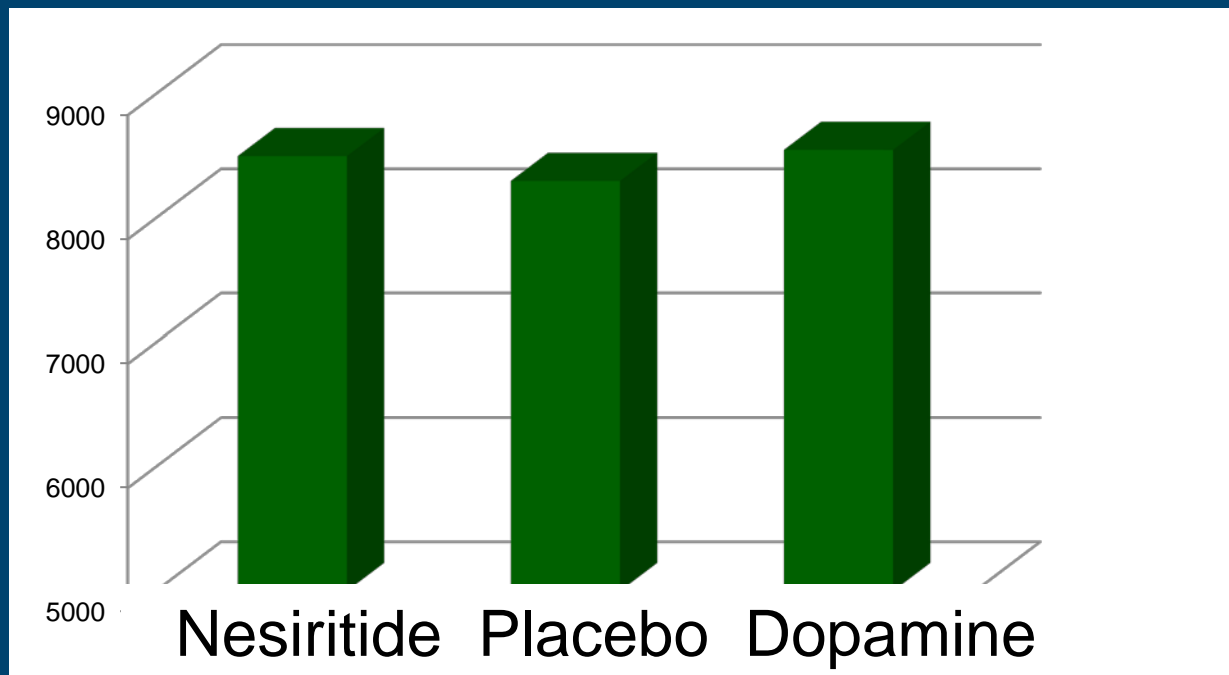
Felker GM, et al. *NEJM* 2011;364:797-805.



EFFECT OF NESIRITIDE OR DOPAMINE ON RENAL FUNCTION IN ACUTE DECOMPENSATED HEART FAILURE

ROSE-HF TRIAL

Urine Output (72 hours)



Δ Cystatin 0.11 in all 3 groups

- 360 patients admitted with ADHF and preexisting renal dysfunction were randomized to nesiritide (0.005 $\mu\text{g}/\text{kg}/\text{min}$) or dopamine (2 $\mu\text{g}/\text{kg}/\text{min}$)
- Baseline creatinine: 1.6 mg/dL

POTENTIAL BENEFITS AND CONCERNS ABOUT ULTRAFILTRATION

- More rapid removal of fluid
- Isotonic fluid removal & higher clearance of sodium load
- Lack of further activation of the SNS, renin-angiotensin-aldosterone system [???]
- Renal tubules “resensitized” to diuretic/Na⁺ handling

- Efficacy versus equally aggressive weight loss on diuretics alone remains unknown
- Single positive trial, no data on mortality
- No clear benefit on renal function
- Greater cost
- Specialized nursing expertise required
- Catheter-related complications (infection, thrombosis)

ACC/AHA 2009 class IIa indication for refractory HF*

Shin J, et al. *Circulation Heart Fail* 2009; 2:499-504.

*Hunt S, et al. *JACC* 2009;53:1343-82

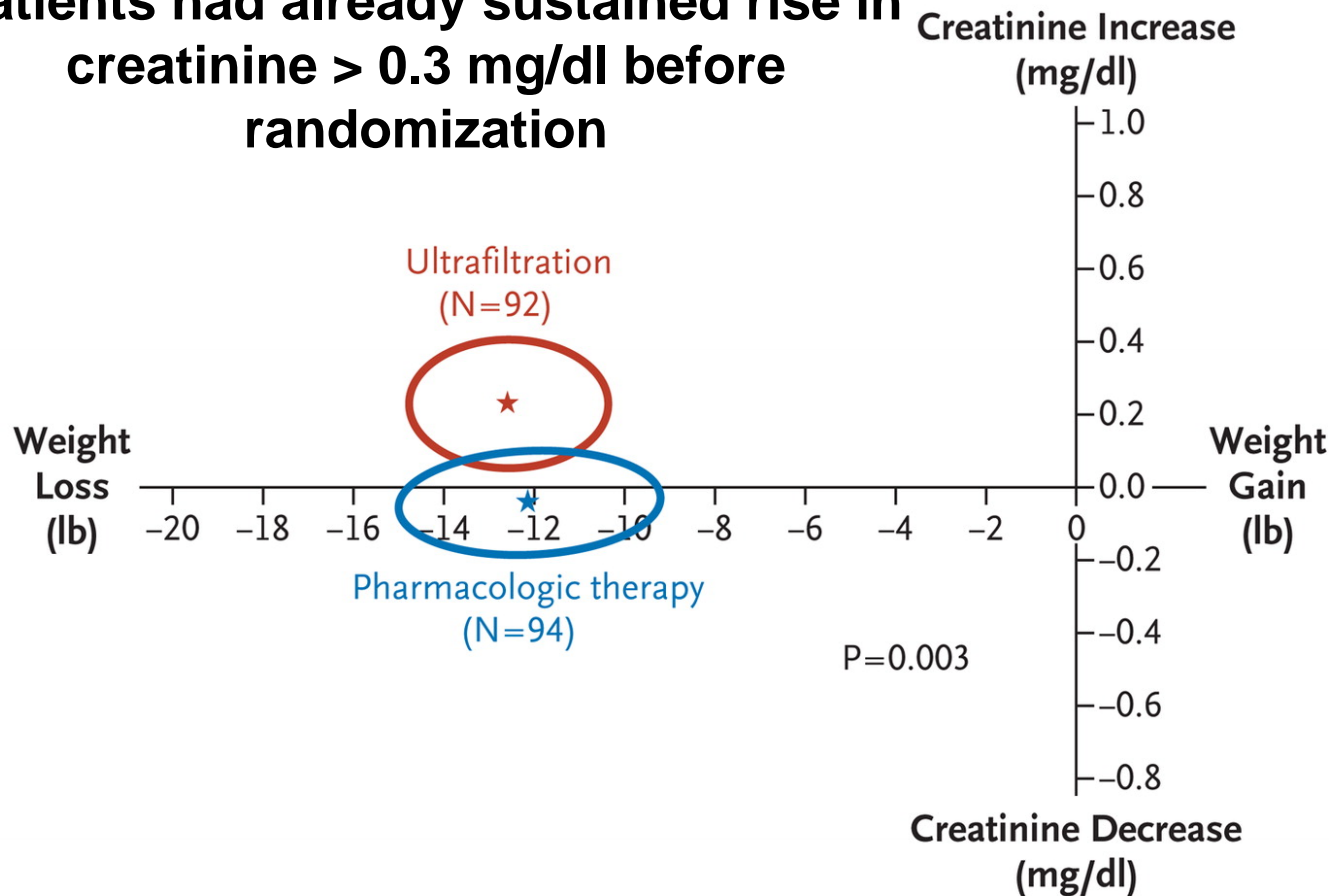


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ULTRAFILTRATION IN DECOMPENSATED HEART FAILURE WITH CARDIORENAL SYNDROME CARESS-HF TRIAL RESULTS

Patients had already sustained rise in creatinine > 0.3 mg/dl before randomization

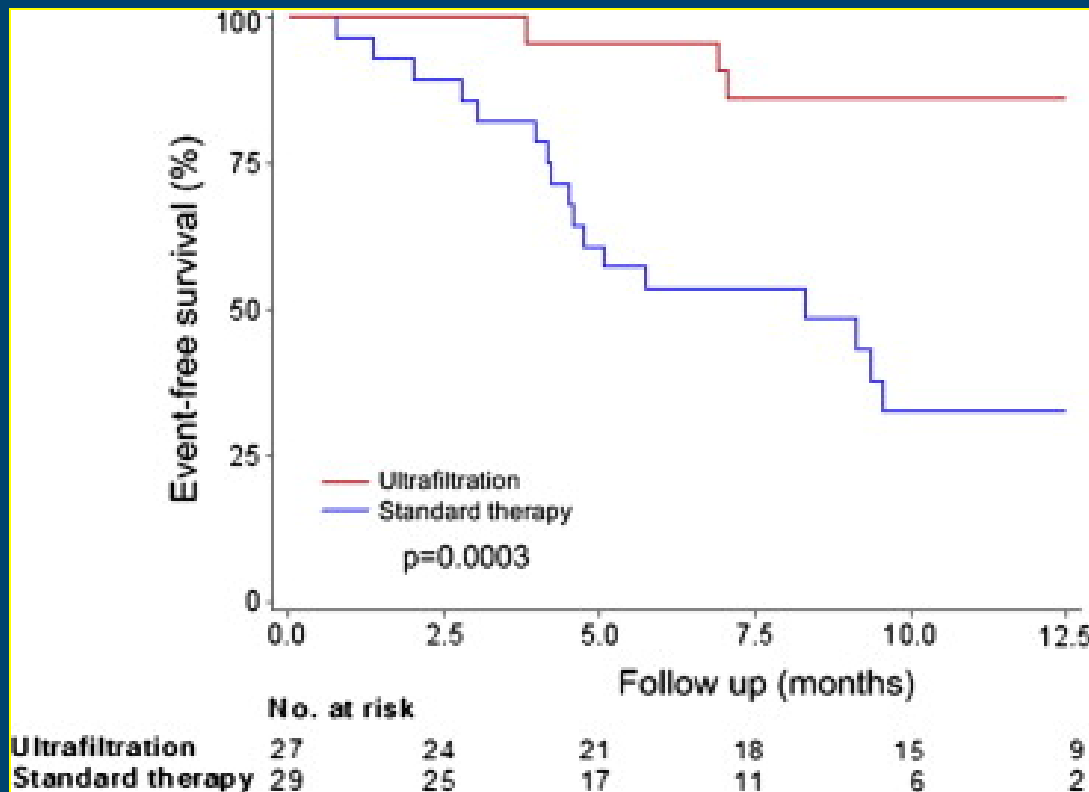


Bart BA, et al. *NEJM* 2012;367:2296-304.

ULTRAFILTRATION IN ACUTE HEART FAILURE

THE CUORE TRIAL

Freedom from HF Rehospitalization



- 56 pts with ADHF randomized to IV diuretics or UF x 1 day + IV diuretics
- Baseline BUN/creatinine: 102/1.8 mg%
- Weight loss: 7.5 kg UF vs. 7.9 kg for diuretic alone
- Mean dose of diuretics was equal between groups

Marenzi G, et al. *J Card Failure* 2014;20:9-17



ONGOING CARDIORENAL CLINICAL TRIALS

- Ultrafiltration: **AVOID-HF** trial
 - Ultrafiltration versus diuretics alone to achieve similar volume reductions during index hospitalization
 - Loop diuretic: 2.5 x oral dose; UF < 250 ml/hr
 - 90 day rehospitalization rate
- Vasopressin Antagonist: **TACTICS** trial
 - Adjunctive tolvaptan to diuretic therapy
 - Renal function and rehospitalization rate



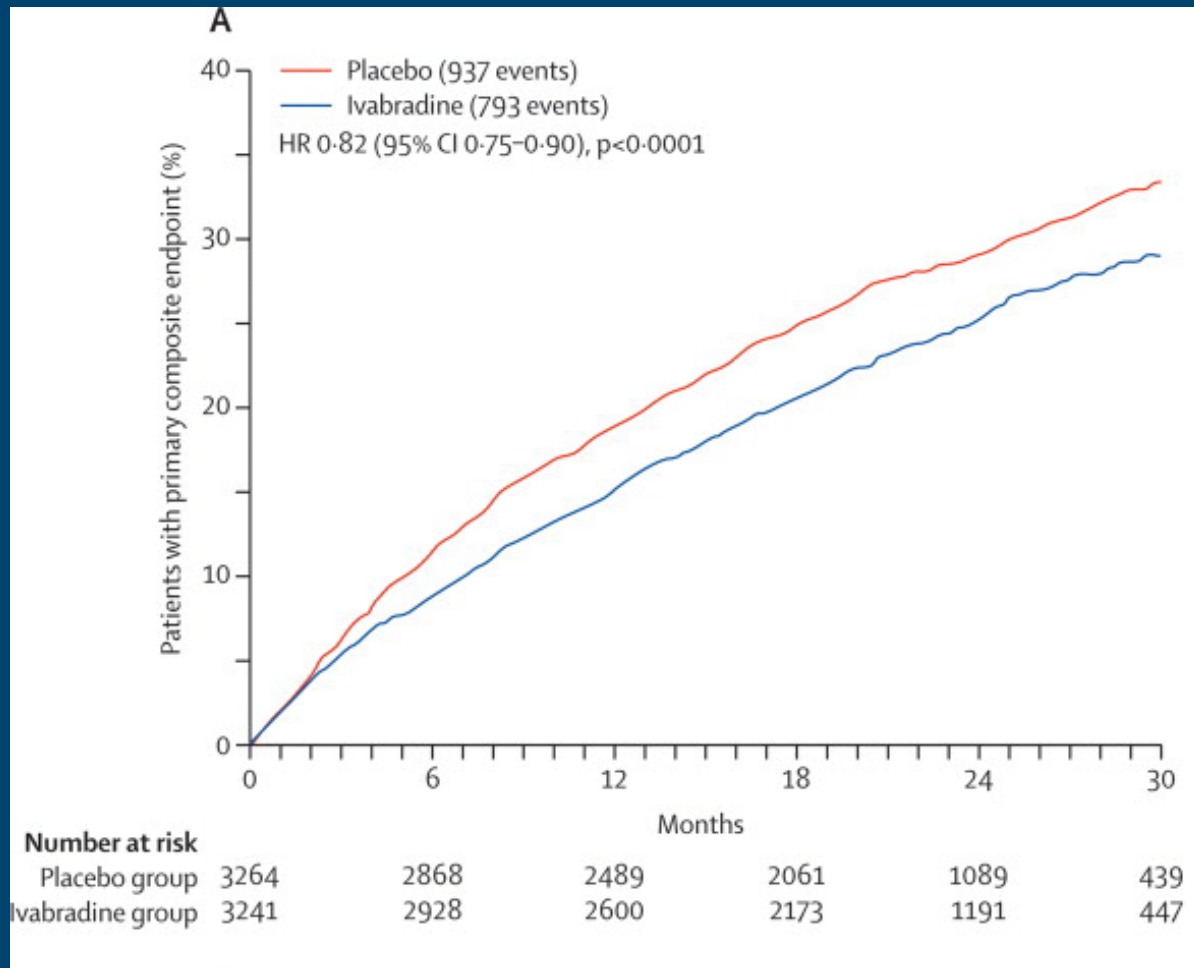
IVABRADINE IN SYSTOLIC HEART FAILURE *SHIFT TRIAL*

- Ivabradine inhibits I_f channel and selective slows sinus node [no effect on AV node or contractility]
- SHIFT RCT in 6558 patients with LVEF $\leq 35\%$, HR ≥ 70 BPM, stable NYHA class II-III HF, 90% were receiving a beta blocker
- Key Findings:
 - Ivabradine decreased HF hospitalizations (16% vs. 21%; $p < 0.001$)
 - Ivabradine lowered HF deaths (3% vs. 5%, $p=0.14$)
 - NYHA class improved on active treatment

Swedberg K, et al *Lancet* 2010;376:875-85.

SHIFT TRIAL

PRIMARY ENDPOINT: DEATH OR HF HOSPITALIZATION



Swedberg K, et al. *Lancet* 2010;376:875-85



ESC INDICATIONS FOR IVABRADINE

Scenario	LVEF	Class	LOE
NYHA class II-IV symptoms on GBMT (ACE/ARB, β -blocker, Aldo antagonist)*	$\leq 35\%$	IIA	B
NYHA class II-IV symptoms on GBMT and unable to tolerate β -blocker*	$\leq 35\%$	IIB	C
NYHA class II-IV HF + angina + intolerant to β -blocker		IIA	A
Symptomatic HF and active angina despite β -blocker		I	A

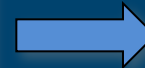
*HR ≥ 70 /min

McMurray J, et al. *Eur Heart J* 2012;33:1787-847.

Neprilysin Inhibition Potentiates Actions of Endogenous Vasoactive Peptides to Balance Maladaptive Mechanisms in Heart Failure

Endogenous vasoactive peptides

(natriuretic peptides, adrenomedullin, bradykinin, substance P, calcitonin gene-related peptide)



↓ Neurohormonal activation

↓ Vascular tone

↓ Cardiac fibrosis, hypertrophy

↓ Sodium retention



Neprilysin



Neprilysin inhibition

Inactive metabolites

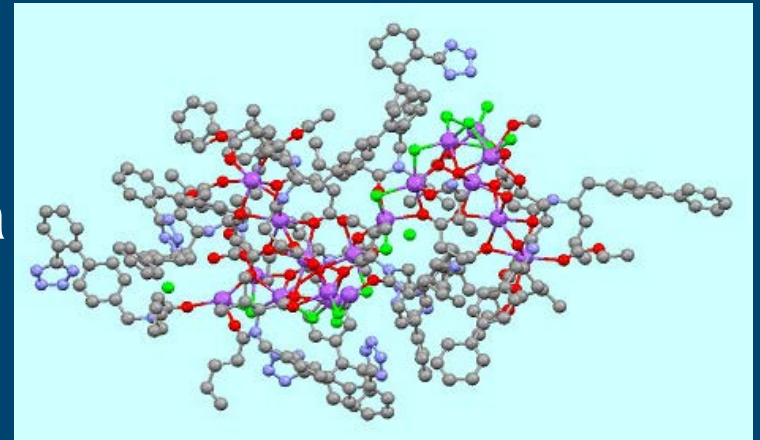


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SACUBITRIL/VALSARTAN (LCZ696): FIRST-IN-CLASS ANGIOTENSIN RECEPTOR NEPRILYSIN INHIBITOR

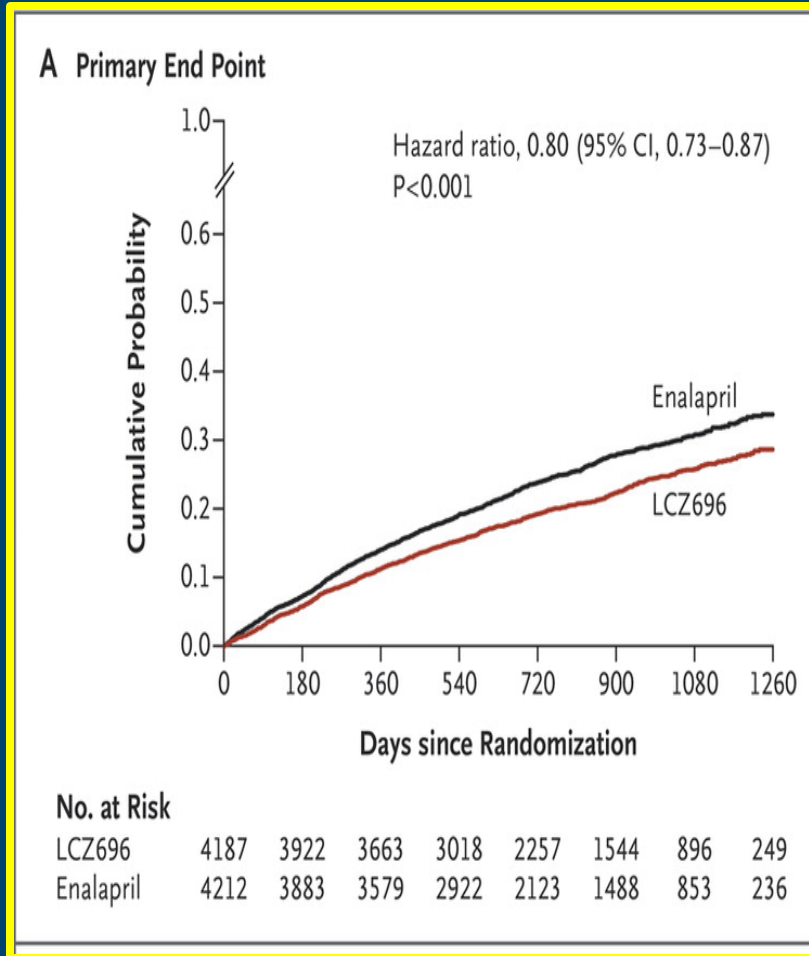
- Sacubitril/valsartan (Entresto) is a agent which delivers concomitant neprilysin (NEP) inhibition and angiotensin (AT₁) receptor blockade
- The drug results in increased levels of natriuretic peptides by inhibiting their breakdown and potent AT₁ receptor blockade



Bloch B. *J Clin Hypertens* 2010;12:809–12;
Gu et al. *J Clin Pharmacol* 2010;50:401–14

PARADIGM HF TRIAL

CV Death or HF Hospitalization

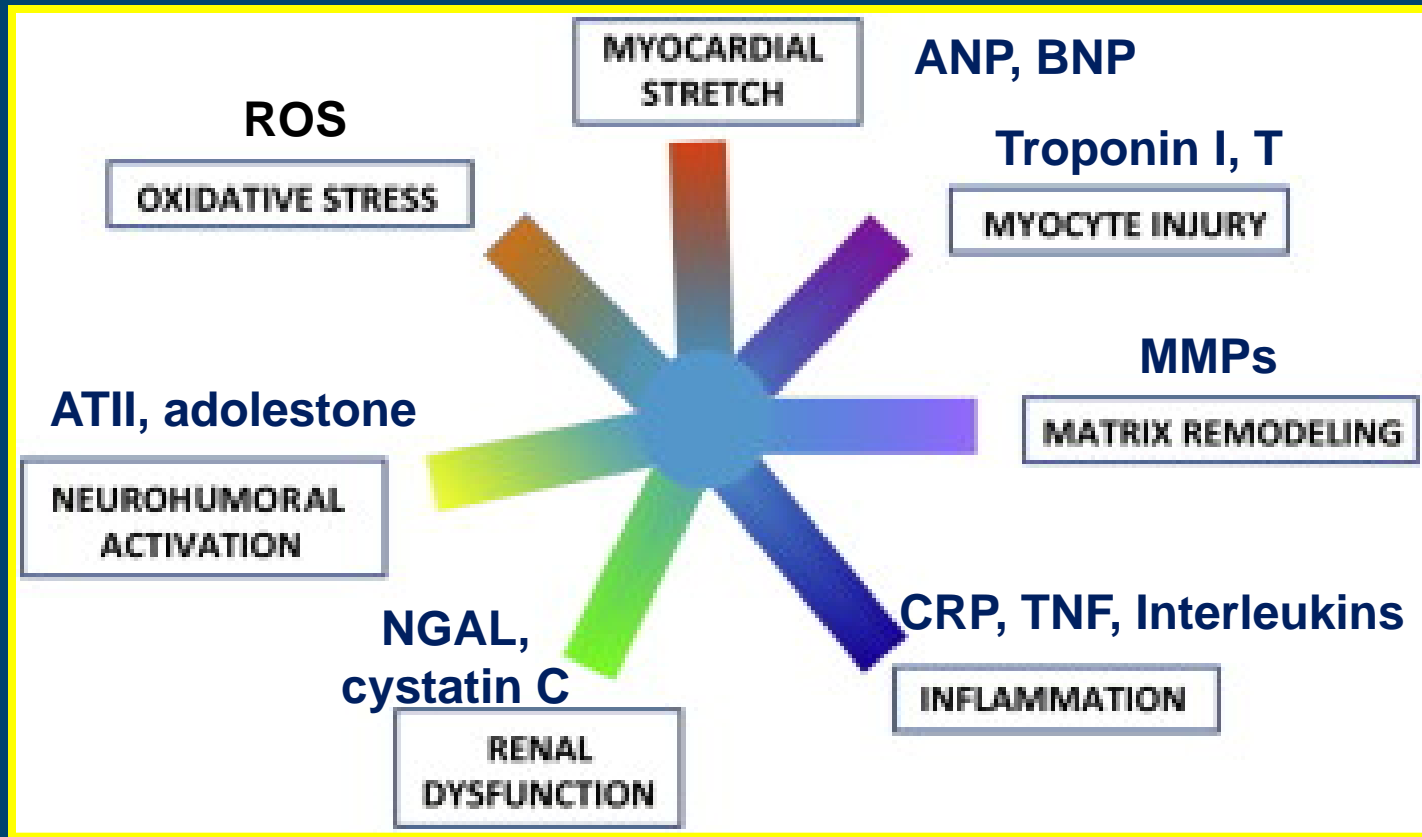


- 8442 patients randomized to enalapril 20 mg bid or sacubitil/valsartan 200 mg bid
- Mean LVEF: 29% ± 6%
- NYHA class I: 5%
- NYHA class II: 70%
- NYHA class III: 24%
- Mean creatinine: 1.2 mg%
- Median NT-proBNP: 1600 pg/ml

PARADIGM-HF: Adverse Events

	LCZ696 (n=4187)	Enalapril (n=4212)	P Value
Prospectively identified adverse events			
Symptomatic hypotension	588	388	< 0.001
Serum potassium > 6.0 mmol/l	181	236	0.007
Serum creatinine ≥ 2.5 mg/dl	139	188	0.007
Cough	474	601	< 0.001
Discontinuation for adverse event	449	516	0.02
Discontinuation for hypotension	36	29	NS
Discontinuation for hyperkalemia	11	15	NS
Discontinuation for renal impairment	29	59	0.001
Angioedema (adjudicated)			
Medications, no hospitalization	16	9	NS
Hospitalized; no airway compromise	3	1	NS
Airway compromise	0	0	----

BIOMARKER PROFILE IN HEART FAILURE



Braunwald E. *JACC Heart Fail* 2013;1:1-20.

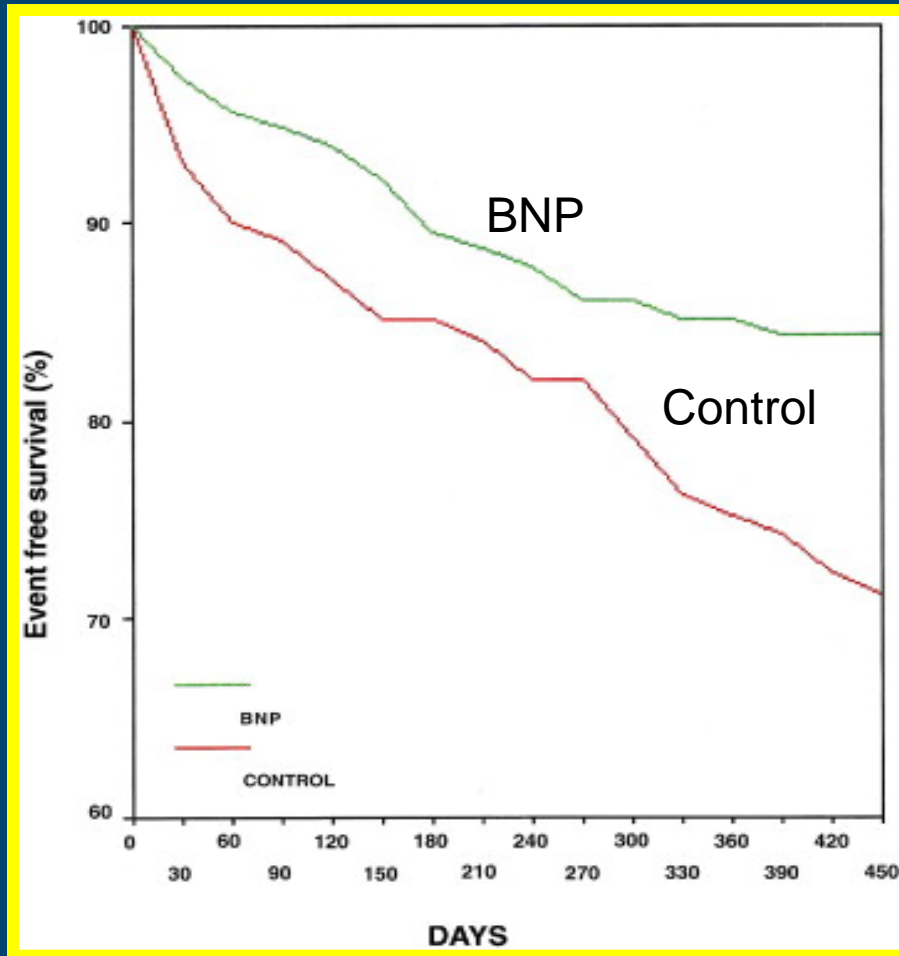


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BNP-GUIDED THERAPY IN HEART FAILURE

THE STARS-BNP STUDY

Freedom from CHF Death or Hospitalization

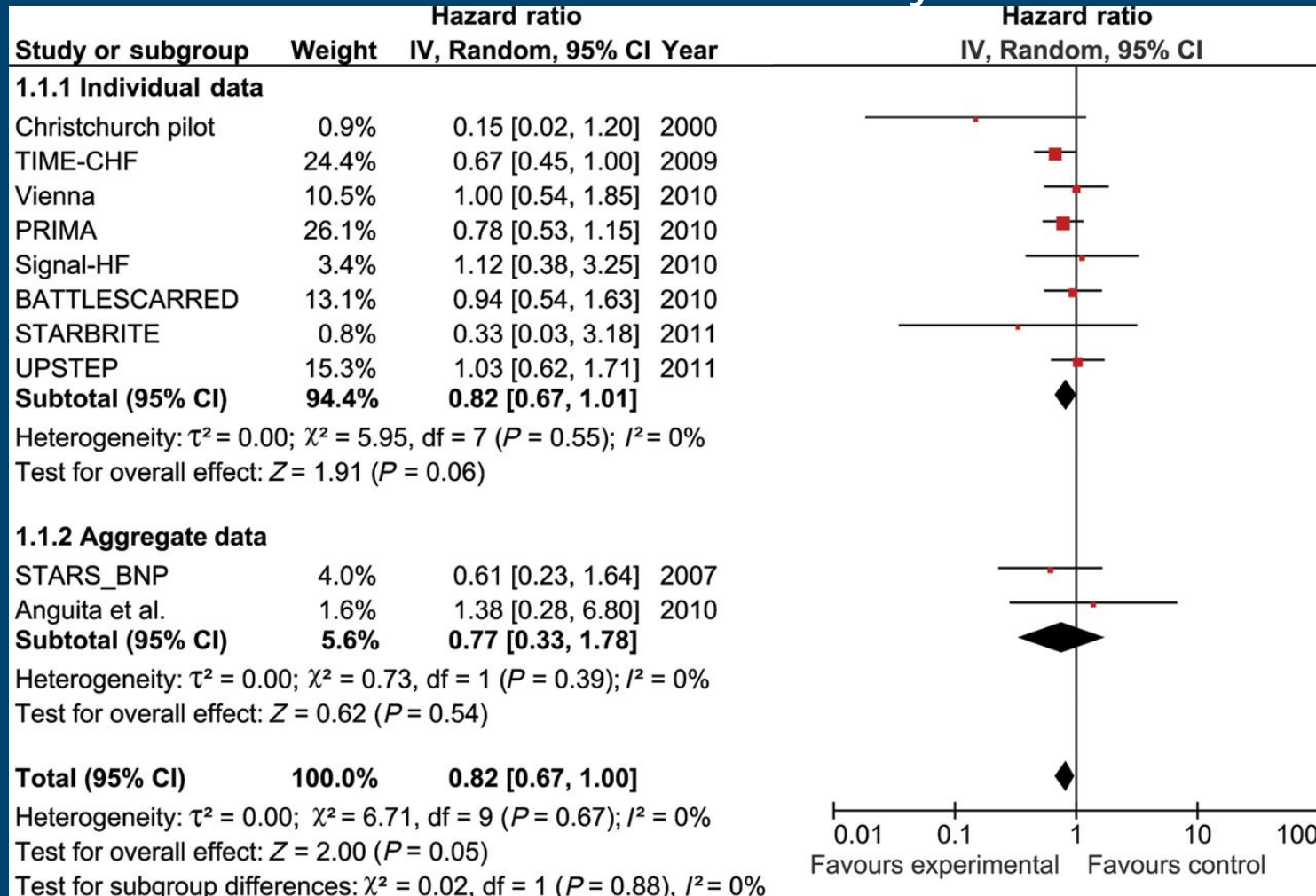


- 220 NYHA class II or III patients receiving ACE and β -blockade were randomized to conventional or BNP-guided treatment at 3 month intervals

- CHF Deaths: 3 vs. 9
- CHF hospitalizations: 22 vs. 48 ($p < 0.001$)
- BNP < 100 pg/ml: 16%

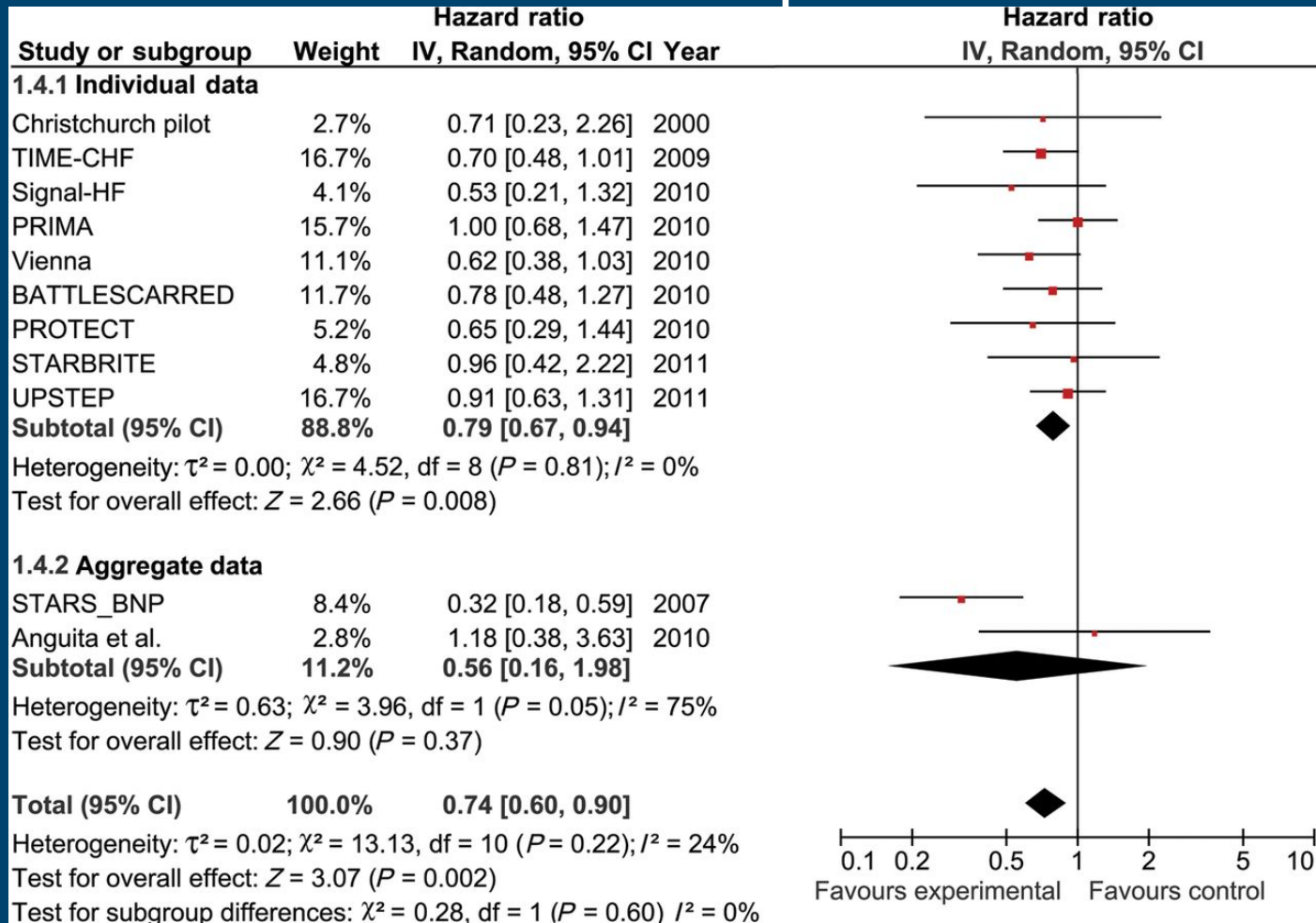
BNP-GUIDED HEART FAILURE THERAPY A META-ANALYSIS

All-Cause Mortality



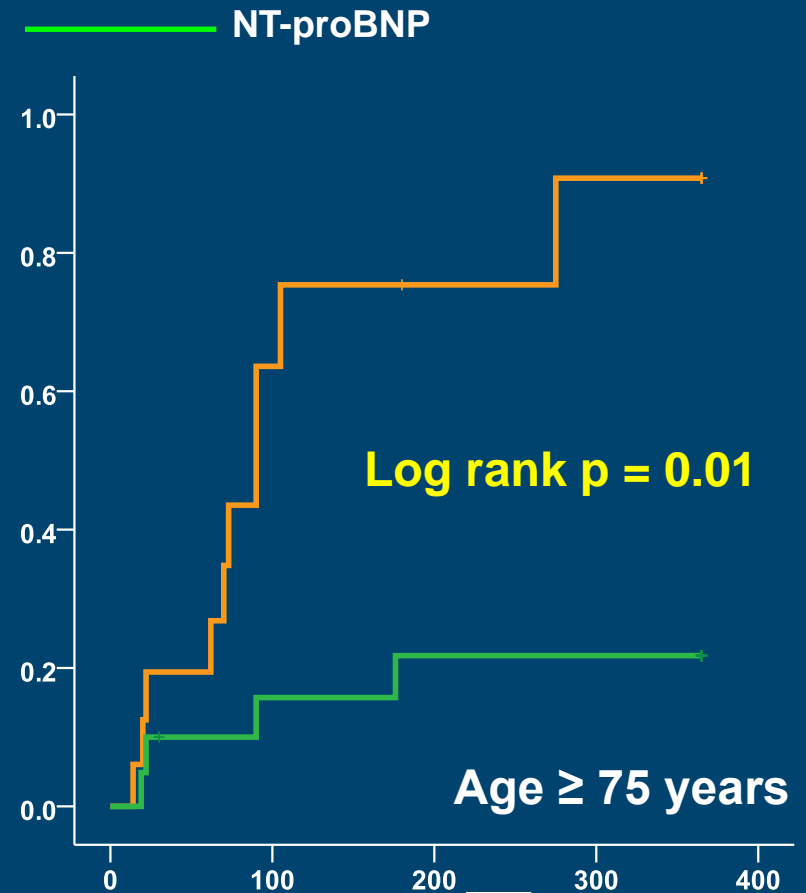
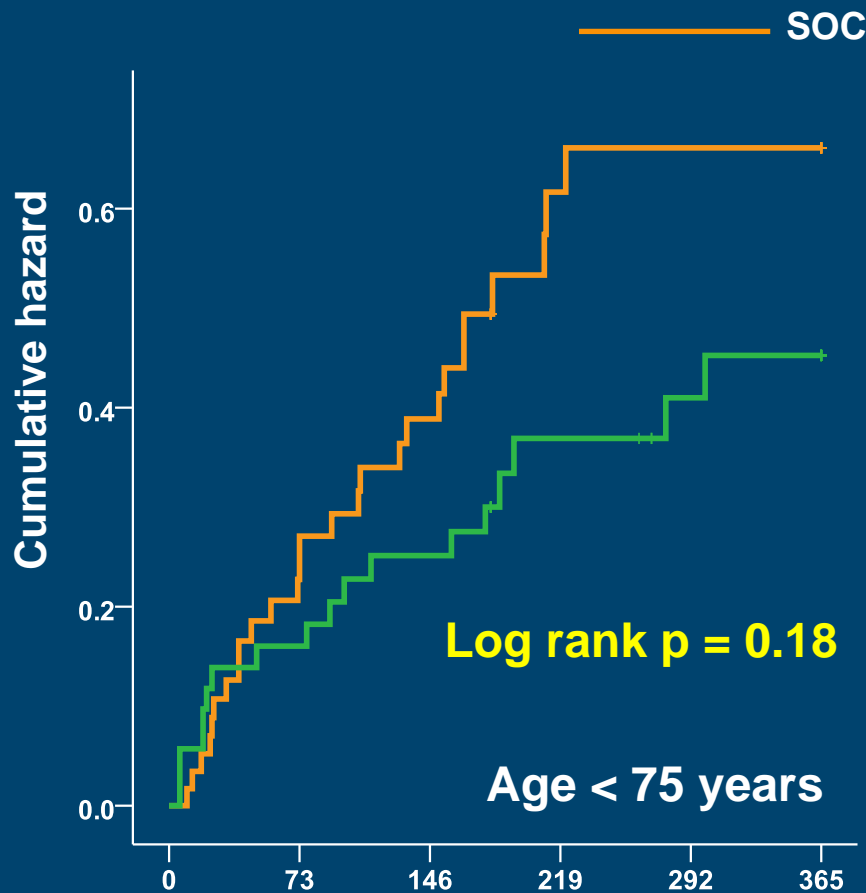
BNP-GUIDED HEART FAILURE THERAPY A META-ANALYSIS

Heart Failure Hospitalization

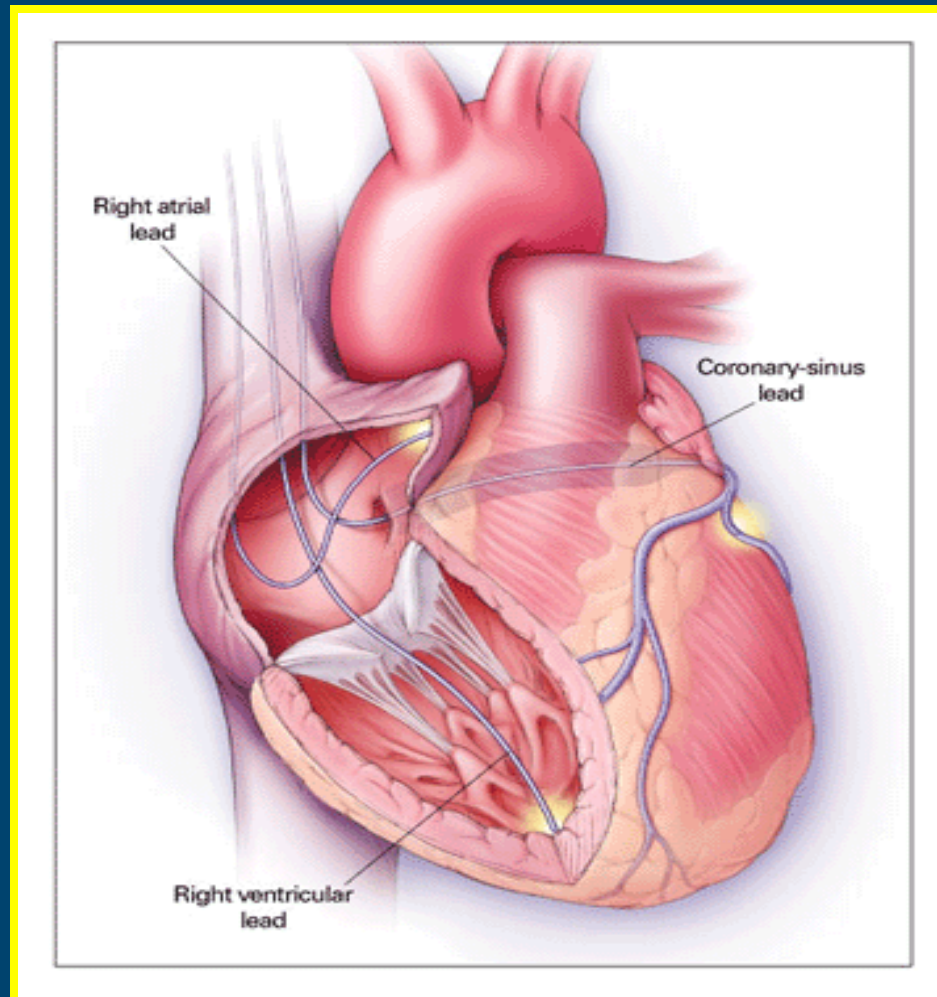


MGH PROTECT TRIAL

OUTCOME WITH NT-PRO-BNP GUIDED THERAPY



CARDIAC RESYNCHRONIZATION THERAPY



Hare JM. *NEJM* 2002;346:1903



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ACC/AHA/HRS 2012 GUIDELINES FOR CARDIAC RESYNCHRONIZATION THERAPY IN HEART FAILURE

Class I Indication (level of evidence: A)

- NYHA Class II, III or ambulatory class IV heart failure symptoms despite GDMT- diuretic, vasodilator and beta-blocker therapy
- Sinus rhythm
- LVEF ≤ 35
- QRS ≥ 150 msec
- LBBB

Class IIa Indication (level of evidence: B)

- NYHA Class II, III or ambulatory class IV heart failure symptoms despite GDMT- diuretic, vasodilator and beta-blocker therapy
- Sinus rhythm
- LVEF $\leq 35\%$
- QRS $\geq 120-149$ msec
- LBBB (NYHA II) or non-LBBB (NYHA class III/IV)

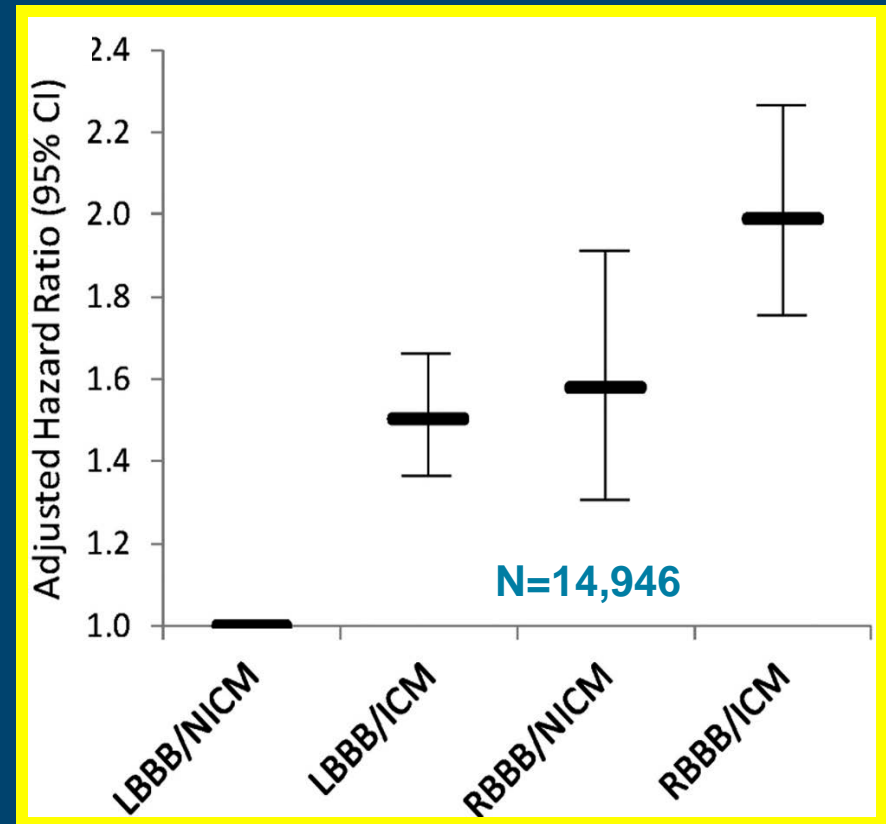
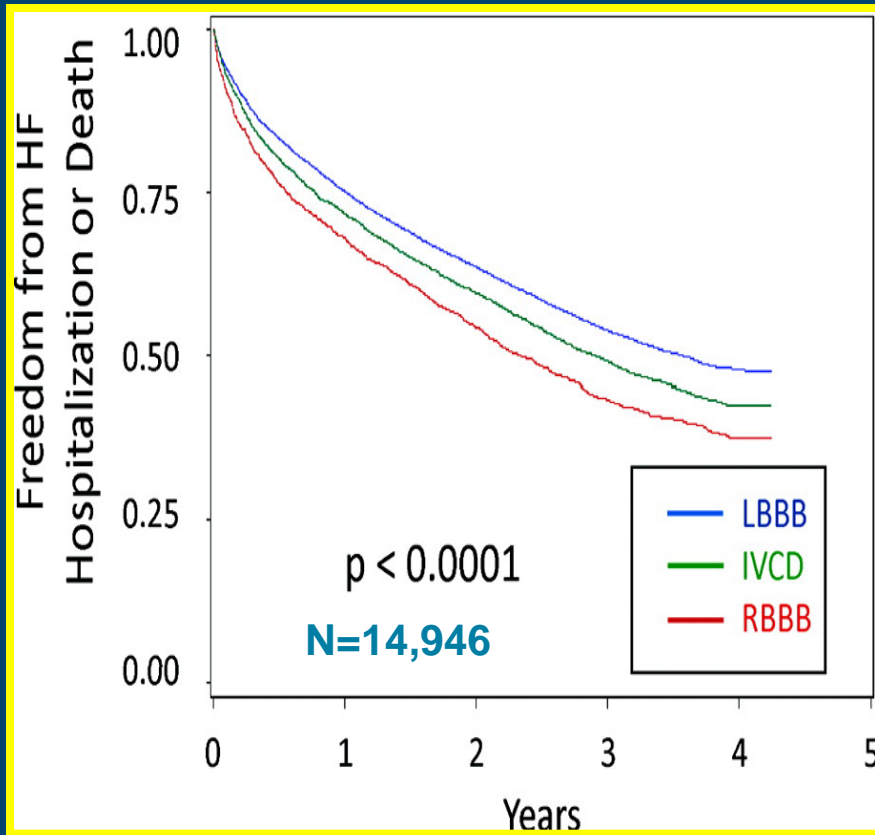
Tracey C, et al. *Circulation* 2012;126:1784-1800.



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BUNDLE BRANCH BLOCK MORPHOLOGY AND OUTCOME FOLLOWING CARDIAC RESYNCHRONIZATION THERAPY MEDICARE REGISTRY



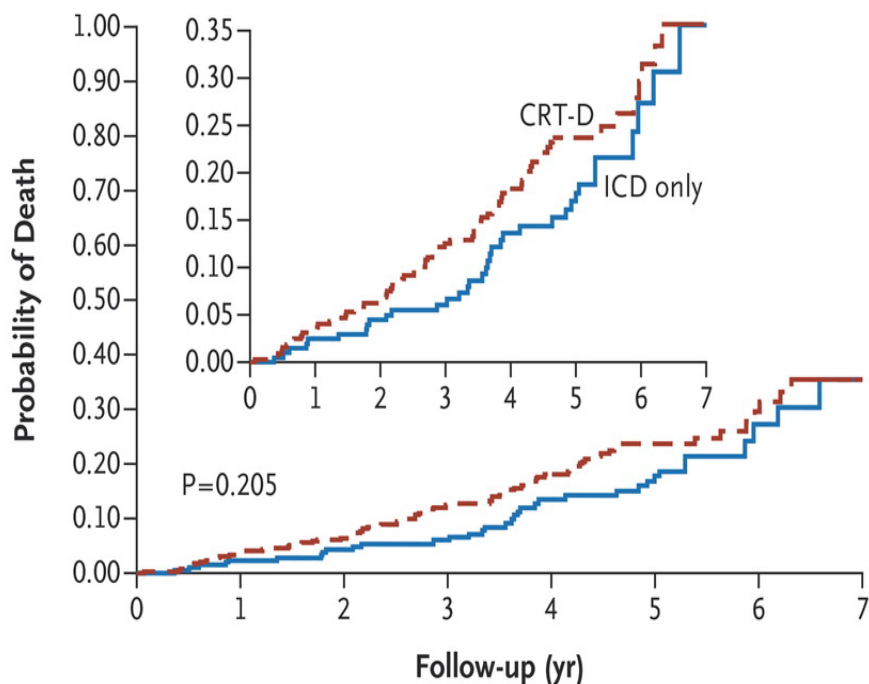
Bilchick KC, et al. *Circulation* 2010;122:2022-30.



MADIT-CRT TRIAL

SURVIVAL IN MILD HEART FAILURE

Non-LBBB



No. at Risk

ICD only	209	197	189	156	115	95	24	10
CRT-D	328	312	292	240	182	136	39	13

- 854 patients in post-trial registry from original 1818 patients
- NYHA class I (ischemic only): 15%
- NYHA class II: 85%
- LVEF < 25%: 63%
- LBBB: 74%
- ACE/ARB: 97%
- Beta-blocker: 95%



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MADIT-CRT LONG-TERM STUDY

TAKE HOME MESSAGE

- Early intervention with CRT-D was associated with a significant long-term survival [> 7 year] benefit in patients with NYHA class I/II symptoms, LBBB, and $QRS > 150$ msec
- No benefits were not observed among mild HF patients with RBBB or IVCD
- Beneficial response on survival or LV remodeling cannot be extrapolated to patients with LBBB and $QRS 120-149$ msec

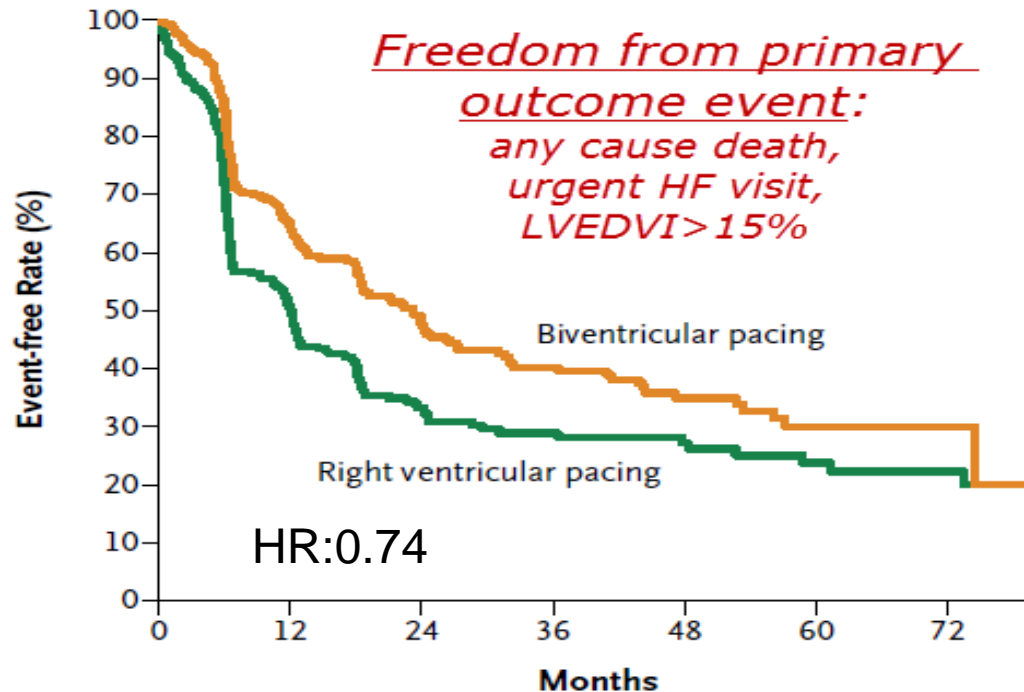


ACC/AHA/HRS GUIDELINES FOR CARDIAC RESYNCHRONIZATION THERAPY IN HEART FAILURE

Class IIb Indication

- Patients with LVEF \leq 35%, NYHA functional class I or II symptoms on optimal medical treatment, who are undergoing permanent pacemaker or ICD implantation with frequent anticipated ventricular pacing (level of evidence: C)

PACING STRATEGIES FOR HEART BLOCK WITH SYSTOLIC DYSFUNCTION



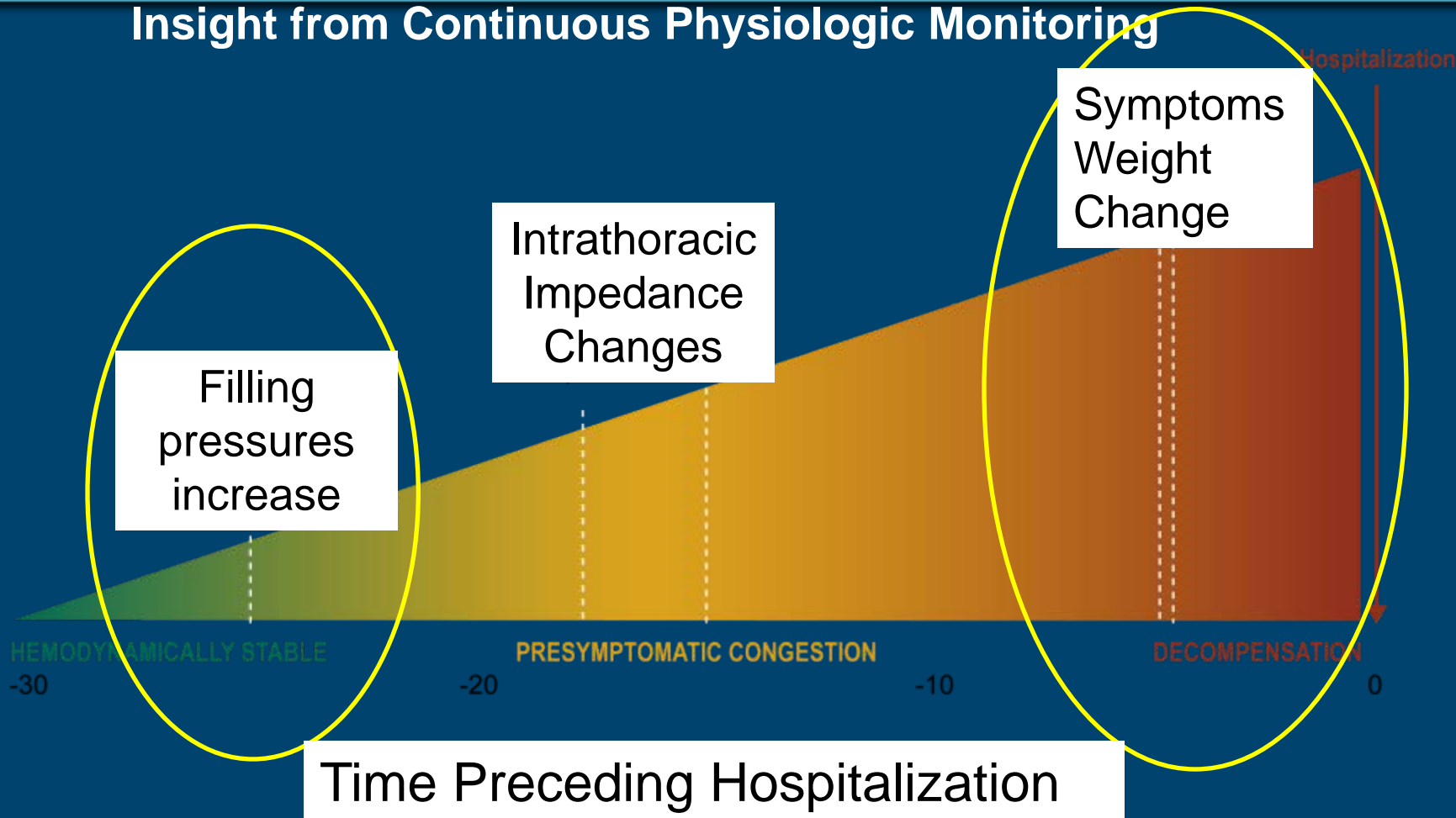
No. at Risk

Biventricular pacing	349	161	87	62	38	17	3
Right ventricular pacing	342	126	59	39	28	18	10

- 691 patients with 2nd or 3rd degree AV block
- LVEF for pacer only cohort: 42%
- LVEF for pacer + ICD cohort: 32%

DETECTION OF IMPENDING DECOMPENSATION

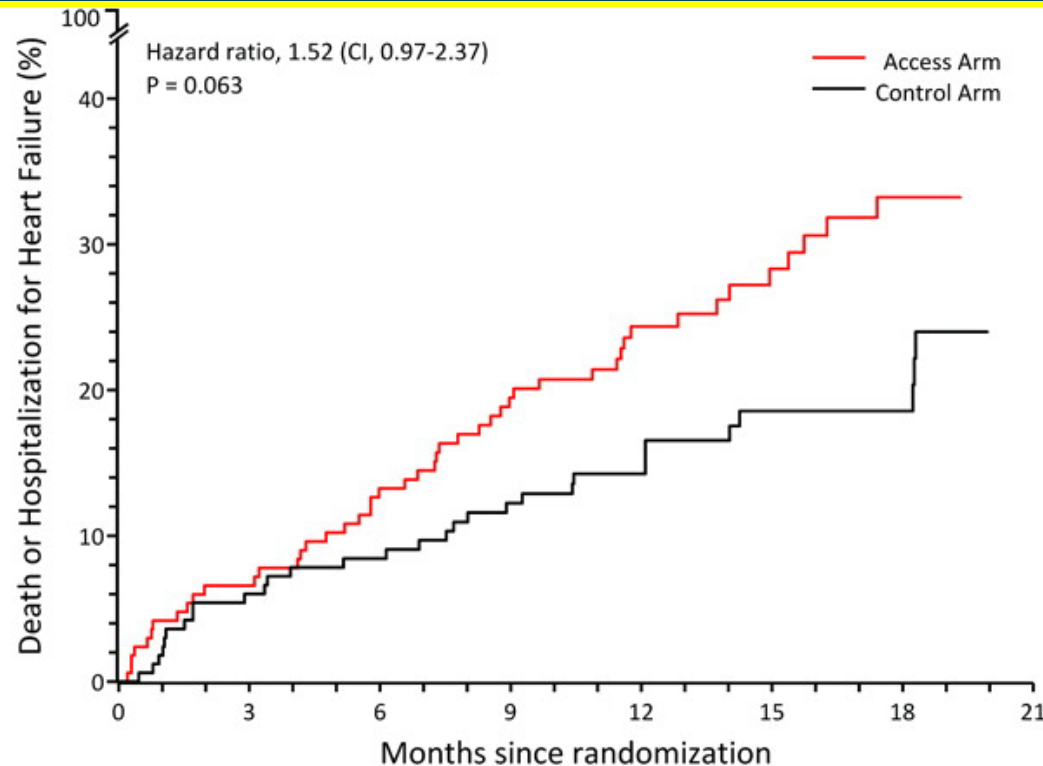
Insight from Continuous Physiologic Monitoring



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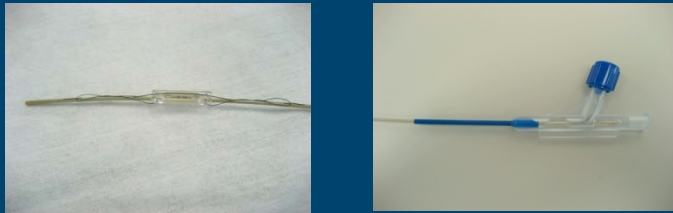
INTRATHORACIC IMPEDANCE MONITORING AND OUTCOME THE DOT-HF TRIAL



- 335 patients with ICD (20%) or CRT/ICD and OptiVol hemodynamic monitoring and alarms
- NYHA class: II (62%), III (35%)
- Mean LVEF: $25\% \pm 7\%$
- Primary Endpoint: death of HF hospitalization

CHAMPION TRIAL OF DIRECT PULMONARY ARTERY PRESSURE MONITORING

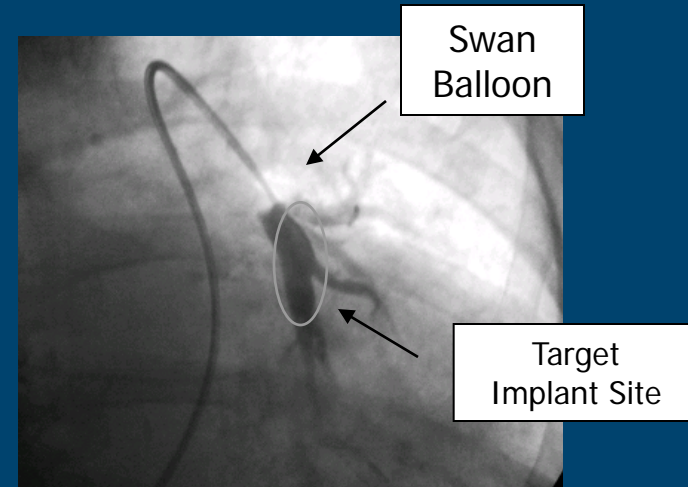
Catheter-based delivery system



Pressure sensor



Home electronics



Abraham WT, et al. *Lancet* 2011;377:658-66.



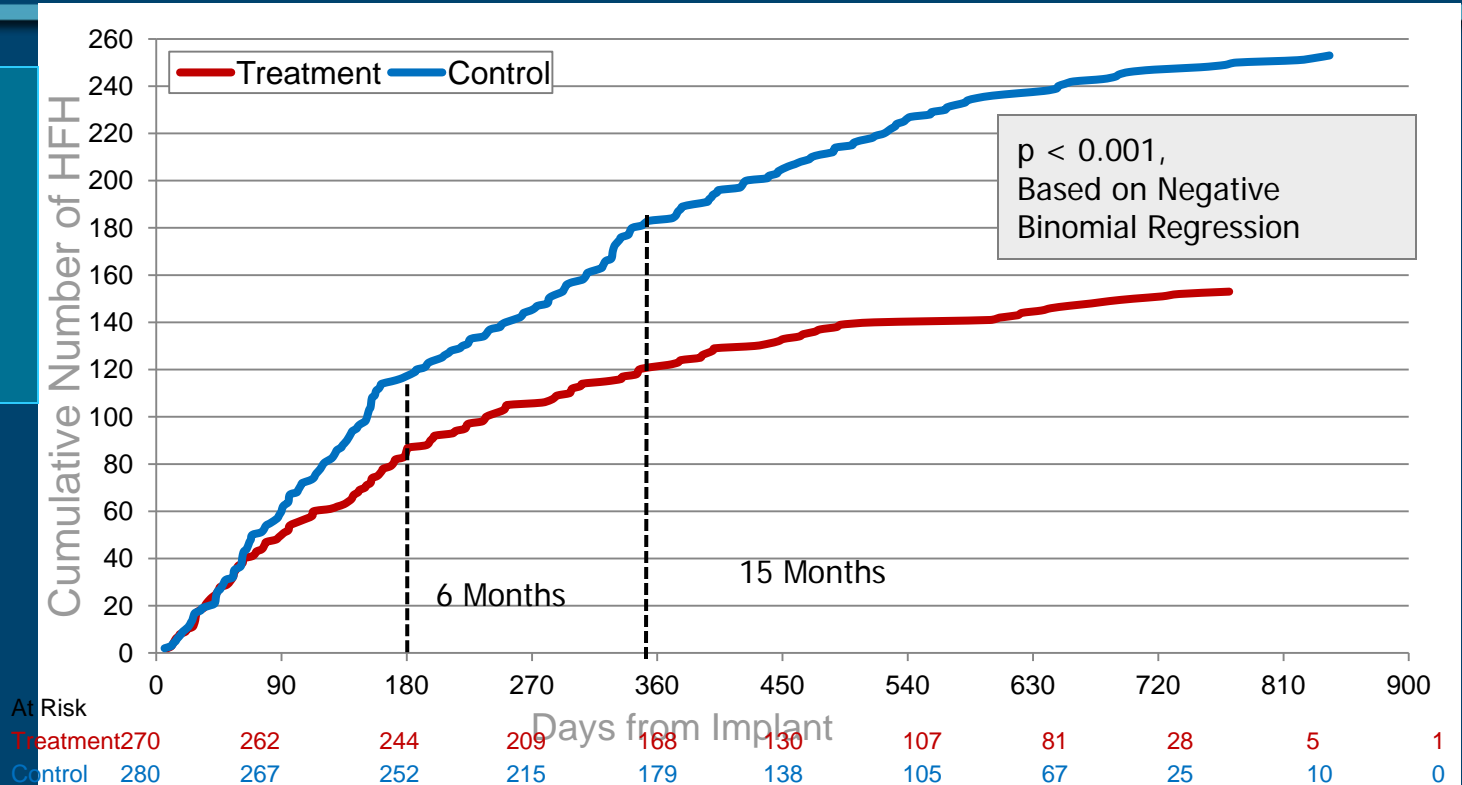
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CHAMPION TRIAL

Cumulative Heart Failure Hospitalizations

Target range (mmHg):

- PA systolic: 15-35
- PA diastolic: 8-20
- PA mean: 10-25



- 30%↓ in HF hospitalizations at 6 months
- 35%↓ in annualized heart failure hospitalization rate
- ↑Quality of life score with treatment group

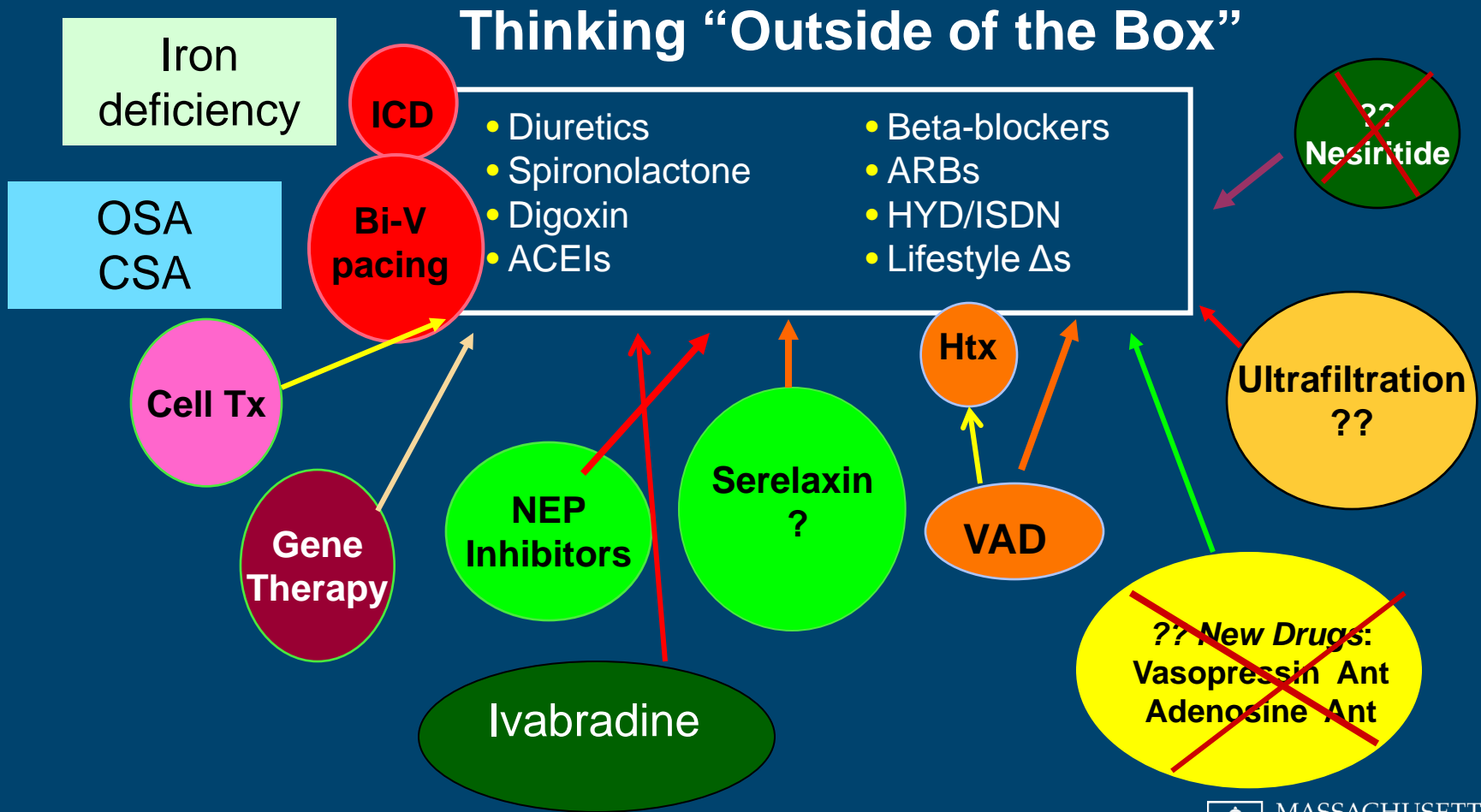
Abraham WT, et al. *Lancet* 2011;377:658-66.



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CONVENTIONAL AND EMERGING THERAPIES FOR ADVANCED SYSTOLIC HEART FAILURE

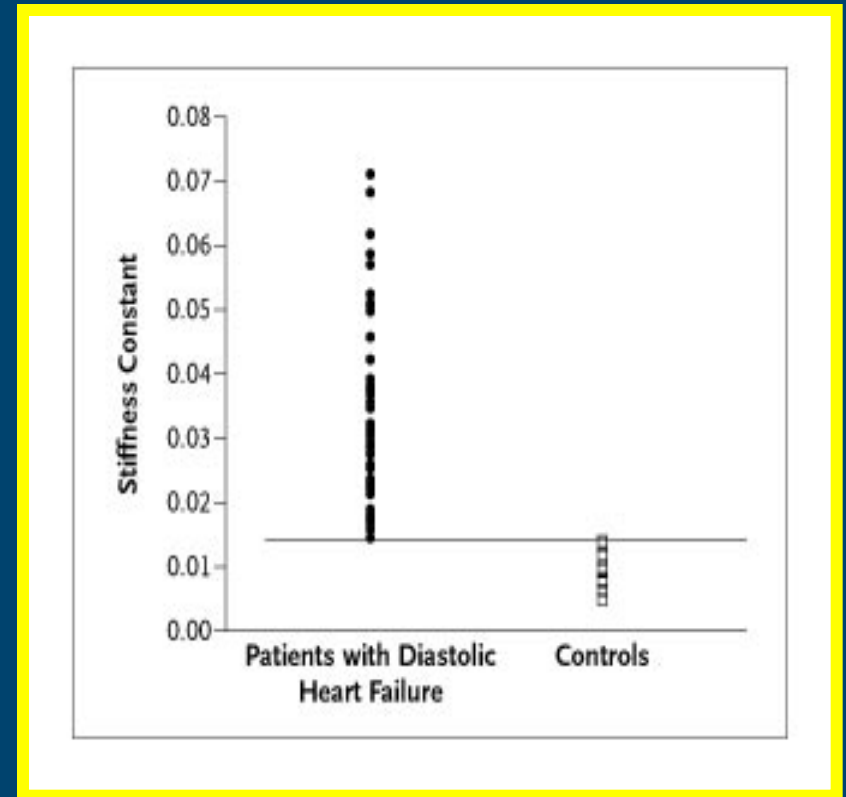
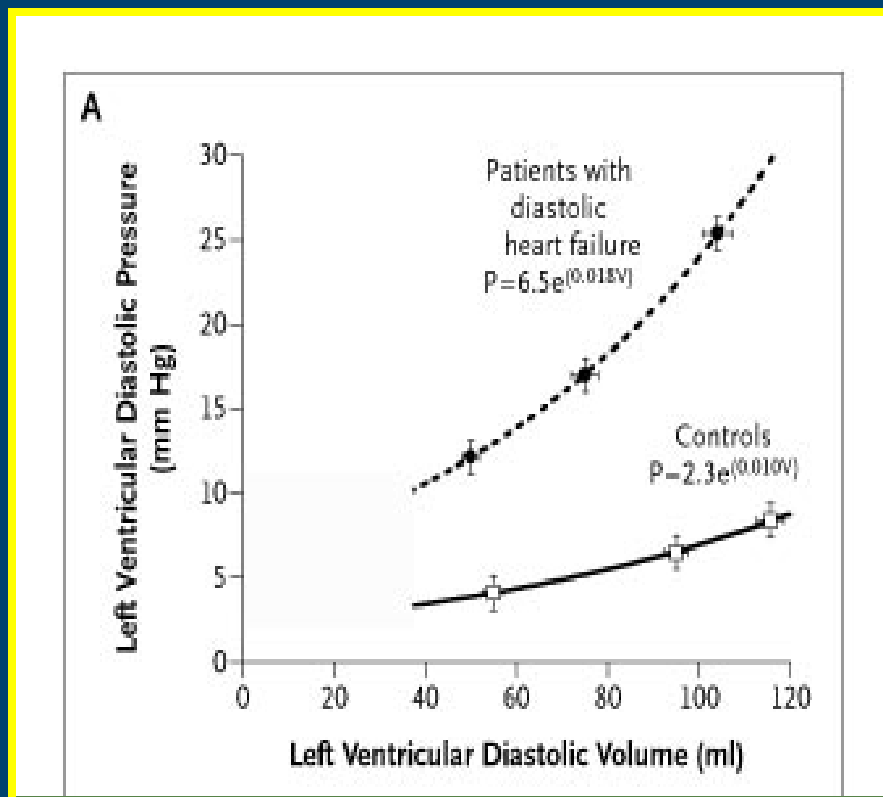


Adapted from Young JL

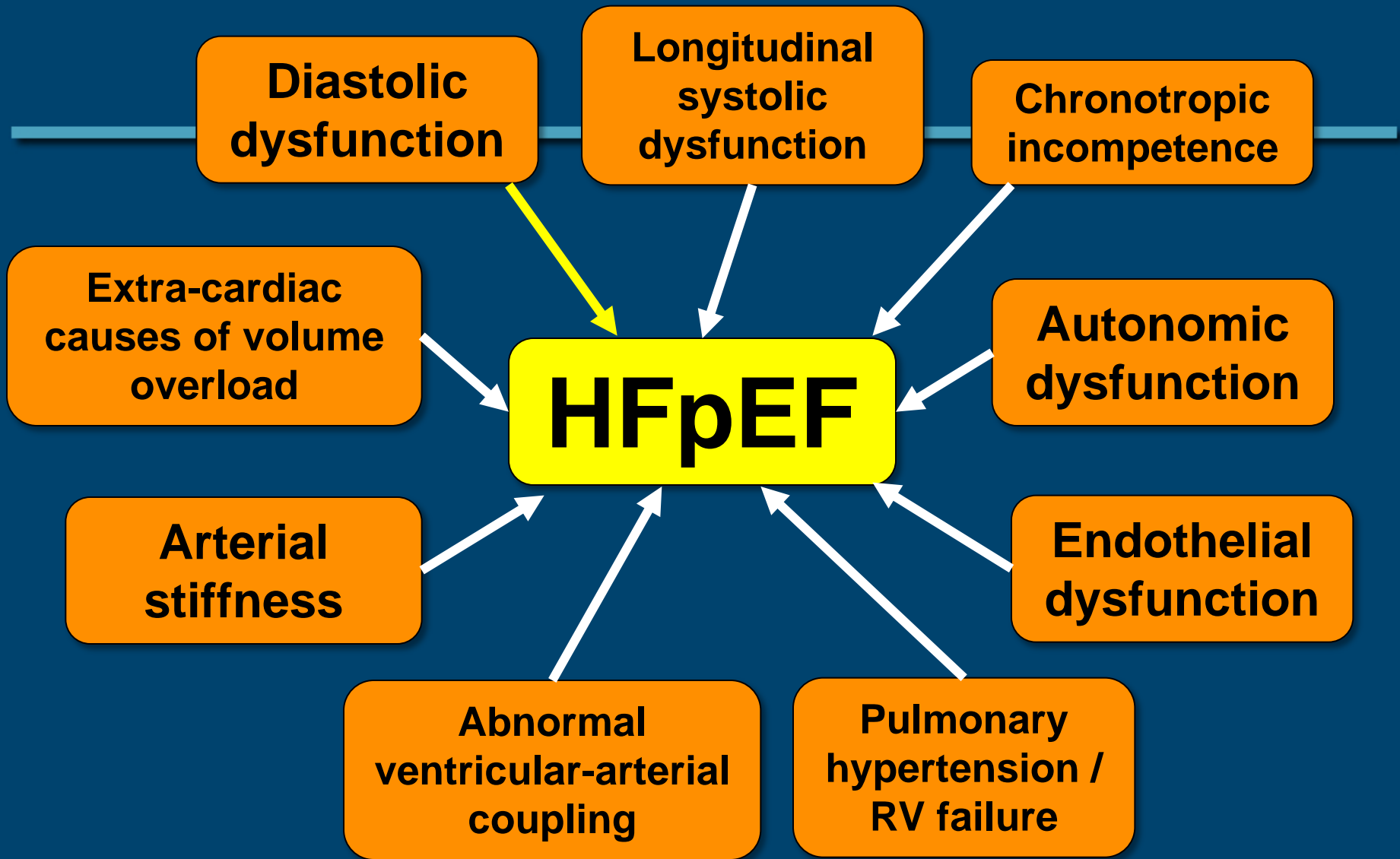
DIASTOLIC HEART FAILURE

OLD PARADIGM: *PRESSURE-VOLUME RELATION*

Approximately 40% of heart failure cases occur in patients with normal or near normal (LVEF >45%) ventricular systolic function



Zile MR, et al. *NEJM* 2004;350:1953-9.



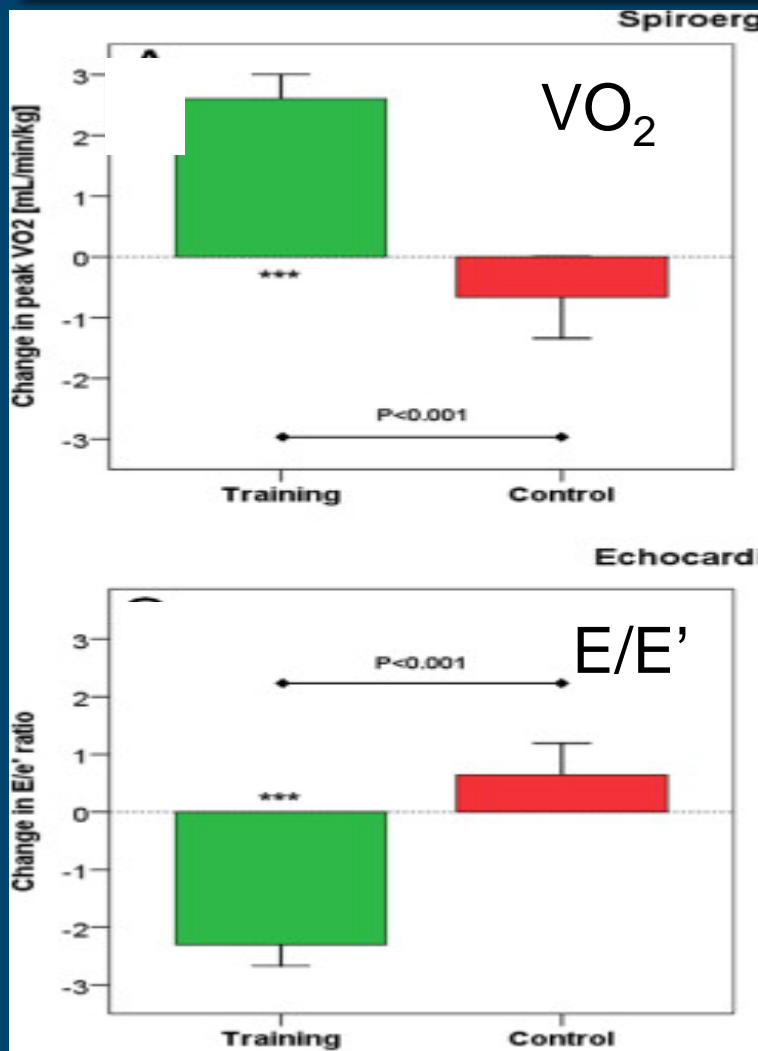
GOALS OF THERAPY IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

- Decrease diastolic filling pressures
 - Diuretics, nitrates
- Control blood pressure and heart rate
 - Rest and exercise
- Prevent or regress left ventricular hypertrophy
 - RAS inhibitors, SNS antagonists, ? autonomic modulation
- Manage medical co-morbidities
 - Diabetes, obesity, ischemia, arrhythmias, sleep apnea
- Promote exercise and decrease deconditioning



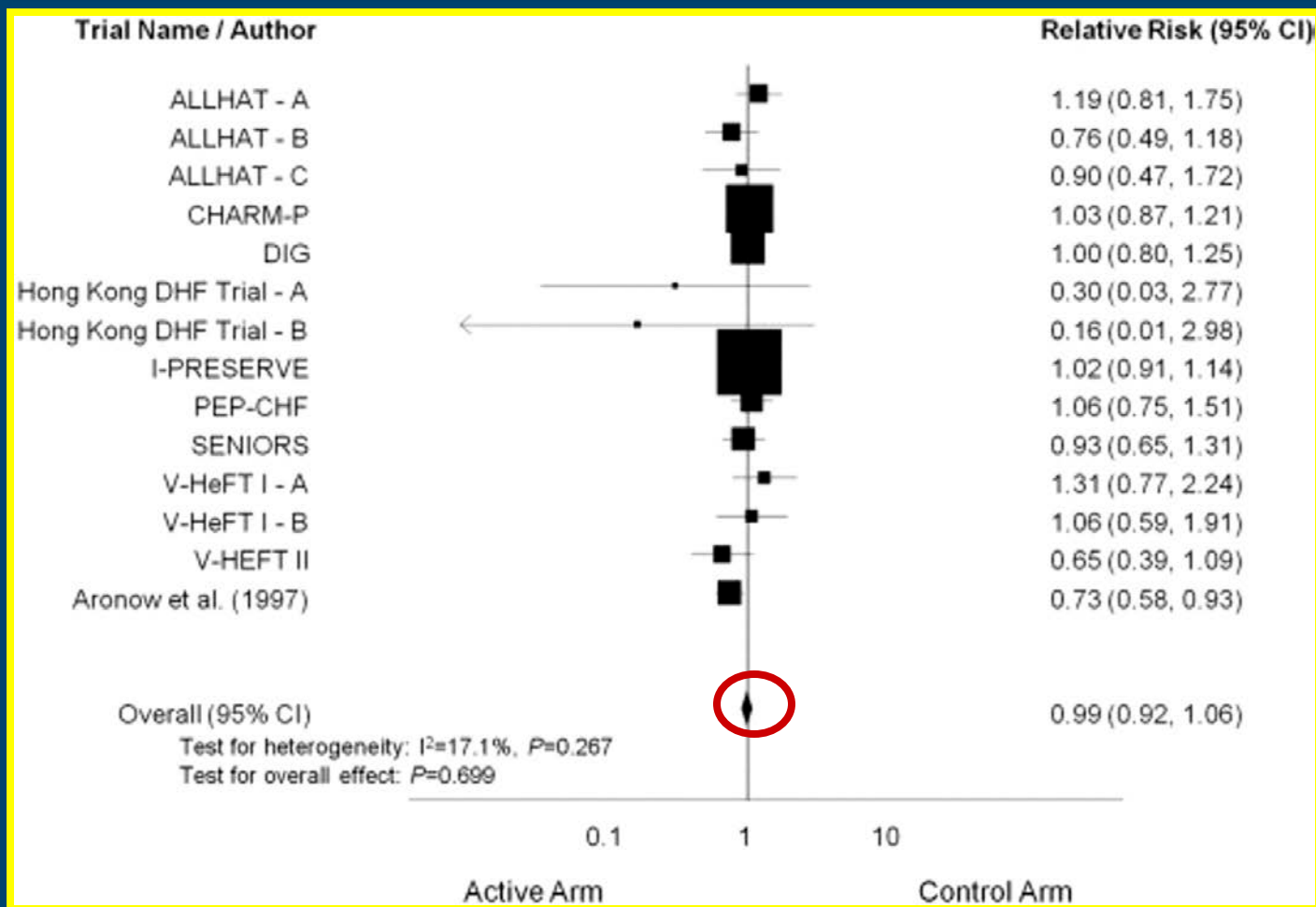
EXERCISE TRAINING IN HF-PEF

THE EX-DHF PILOT STUDY



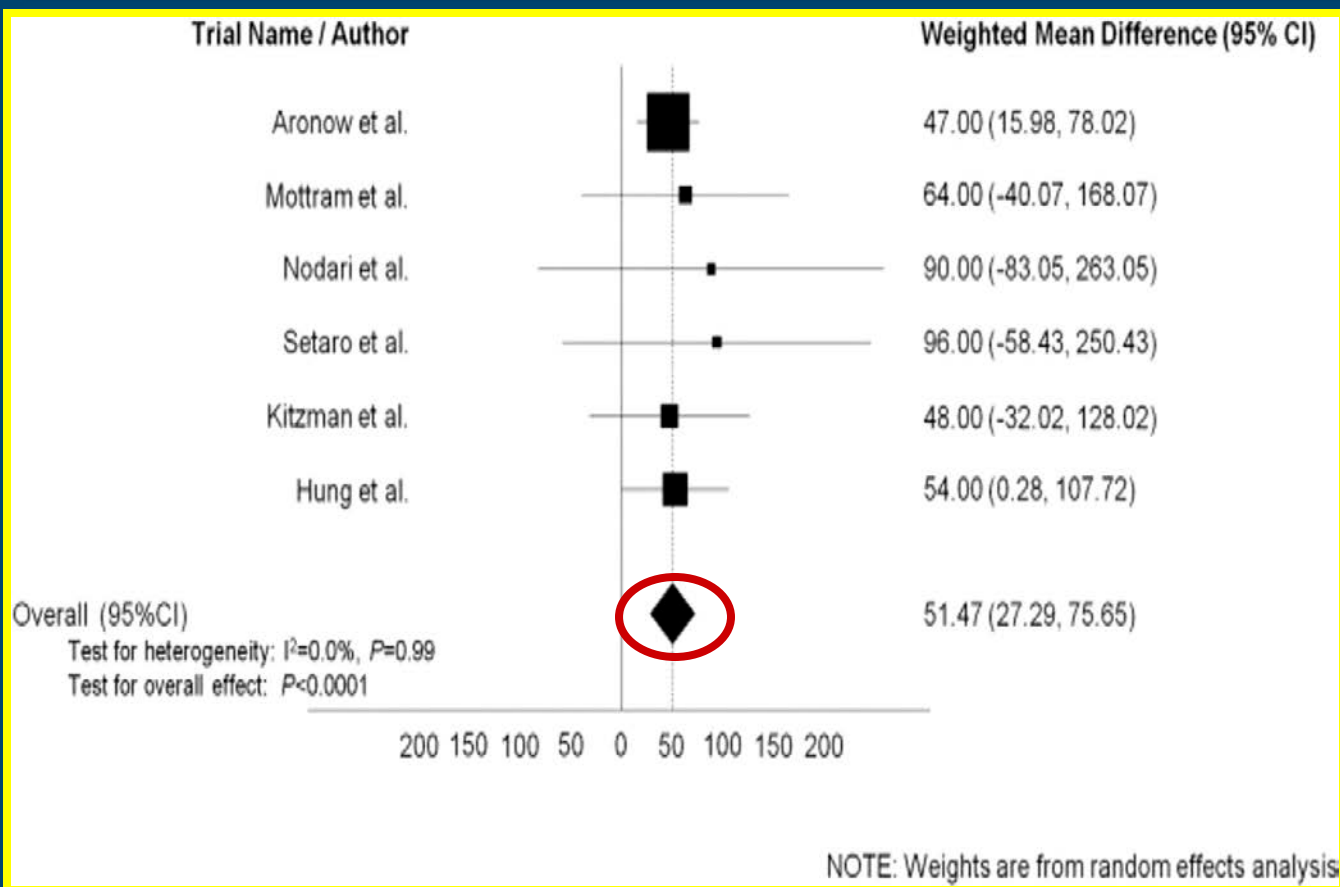
- 64 patients with HF-PEF were randomized to 3 months (32 sessions) of supervised endurance/resistance training versus usual care
- Sessions 2X per week for first month increasing to 3x per week
- Mean age: 65 years
- Mean LVEF:67%± 8%
- NYHA class II: 84%; III: 16%

TREATMENT EFFECT ON MORTALITY IN RANDOMIZED CONTROLLED TRIALS OF HEART FAILURE WITH PRESERVED EJECTION FRACTION



- ACE-I
- ARBs
- Vasodilators
 - hydralazine
 - nitrates
 - prazosin
- β -blockers

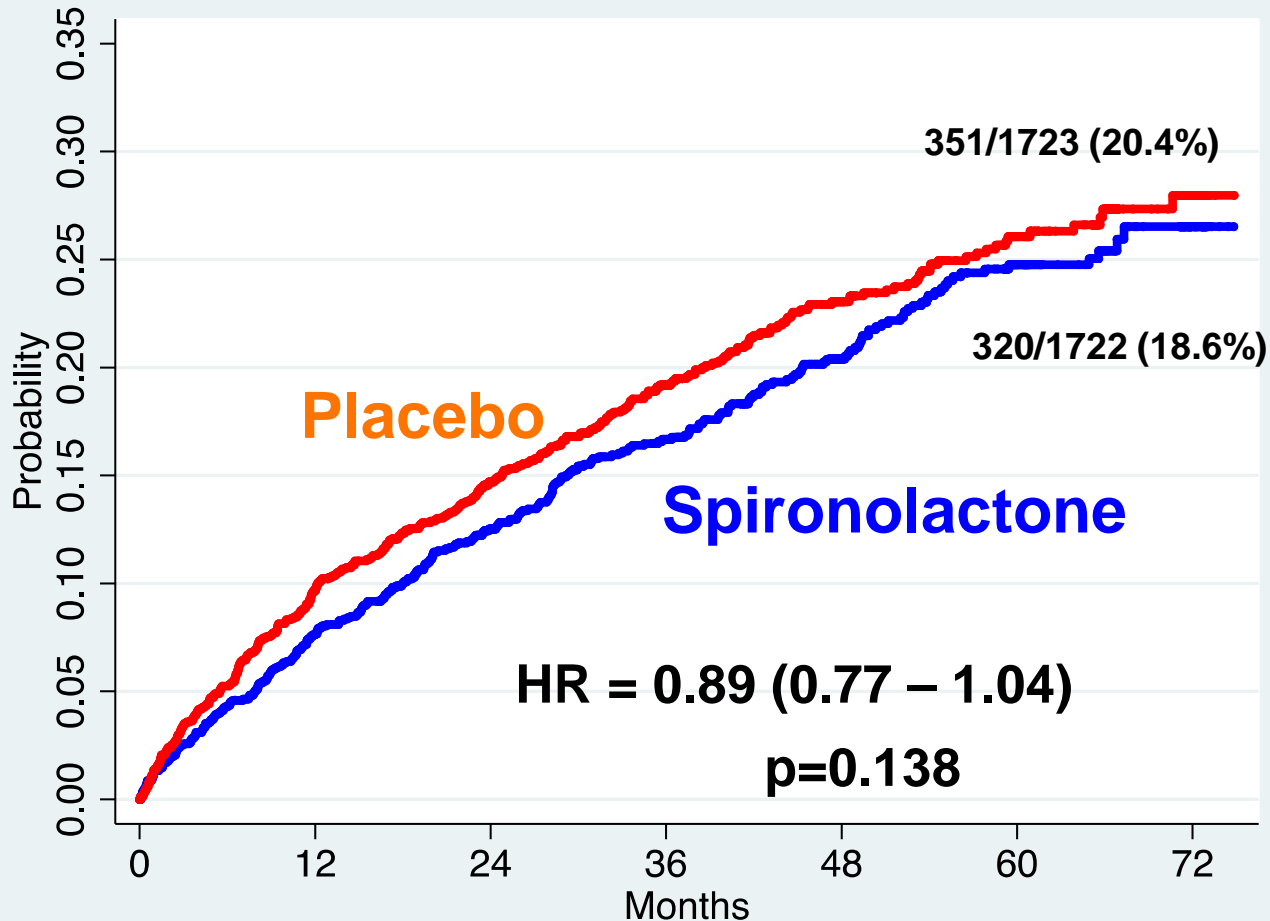
TREATMENT EFFECT ON EXERCISE CAPACITY IN RANDOMIZED CONTROLLED TRIALS IN HEART FAILURE WITH PRESERVED EJECTION FRACTION



- ACE-I
- ARBs
- Verapamil
- Spironolactone
- β -blockers

TOPCAT TRIAL

CV Death, HF Hosp, or Resuscitated Cardiac Arrest



Number at risk

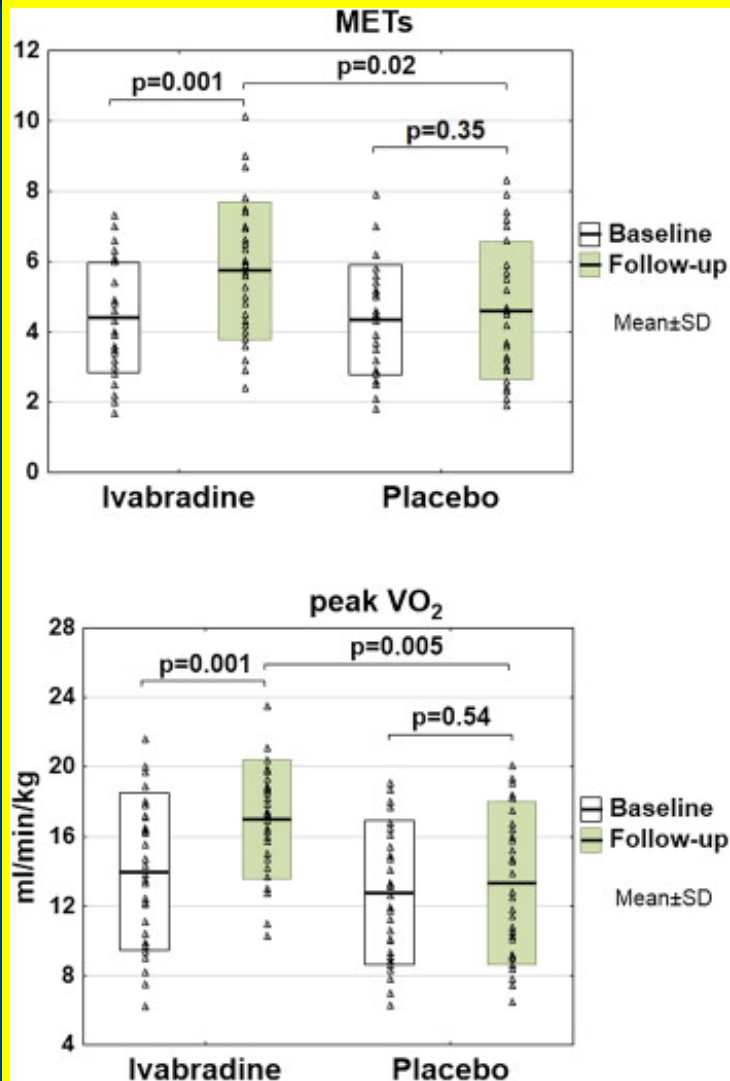
Spiro	1722	1502	1168	870	614	330	53
Placebo	1723	1462	1145	834	581	331	53

ACC/AHA Treatment Recommendations for Heart Failure with Preserved Ejection Fraction

Recommendations	COR	LOE
Systolic and diastolic blood pressure should be controlled according to published clinical practice guidelines	I	B
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 HFpEF to improve symptomatic HF	IIa	C
Use of beta-blocking agents, ACE inhibitors and ARBs for hypertension in HFpEF	IIa	C
ARBs might be considered to decrease hospitalizations in HFpEF	IIb	B
Nutritional supplementation is not recommended in HFpEF	III: No Benefit	C

AL

EFFECT OF IVABRADINE ON EXERCISE PERFORMANCE IN HEF-PEF



- 61 patients with HeF-PEF were randomized to placebo or ivabradine 5 mg twice daily

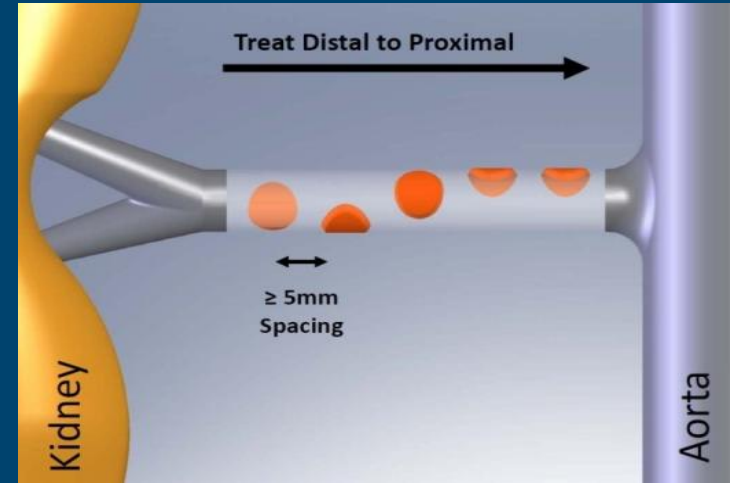
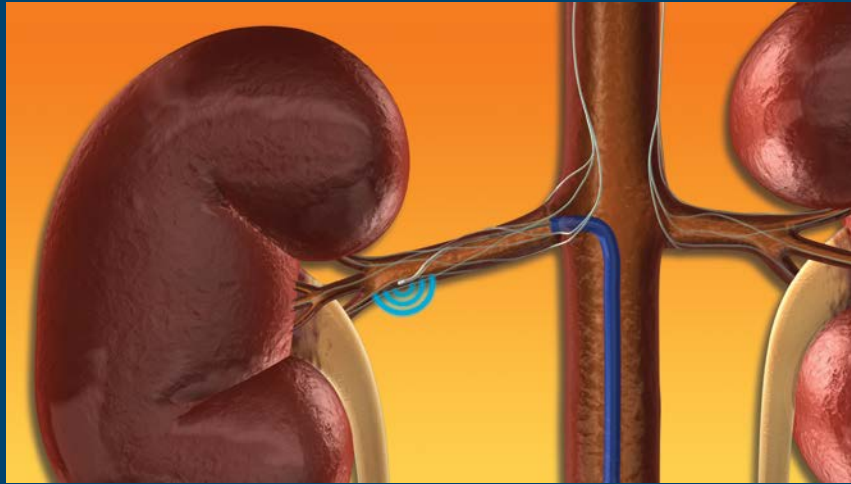
- Background therapy:
ACE: 97%; beta blocker: 54%;
calcium blocker: 38%; diuretic: 79%

- Heart rate reduction in treatment group: 72 to 62/min

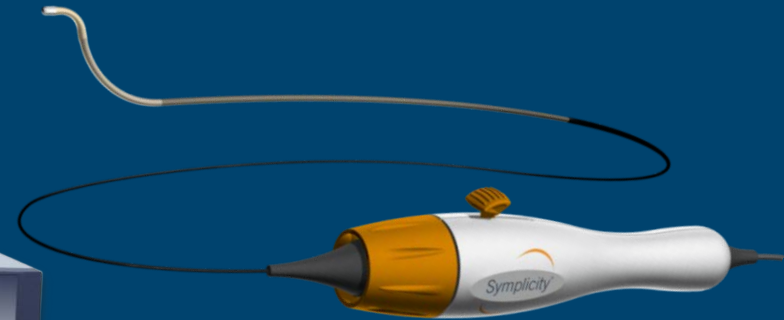
- MET increase 4.1 to 6.0

- VO₂ : 12.8 to 16.1

RENAL NERVE ANATOMY PERMITS A CATHETER-BASED APPROACH



- Standard interventional technique
- 4-6 two-minute treatments per artery

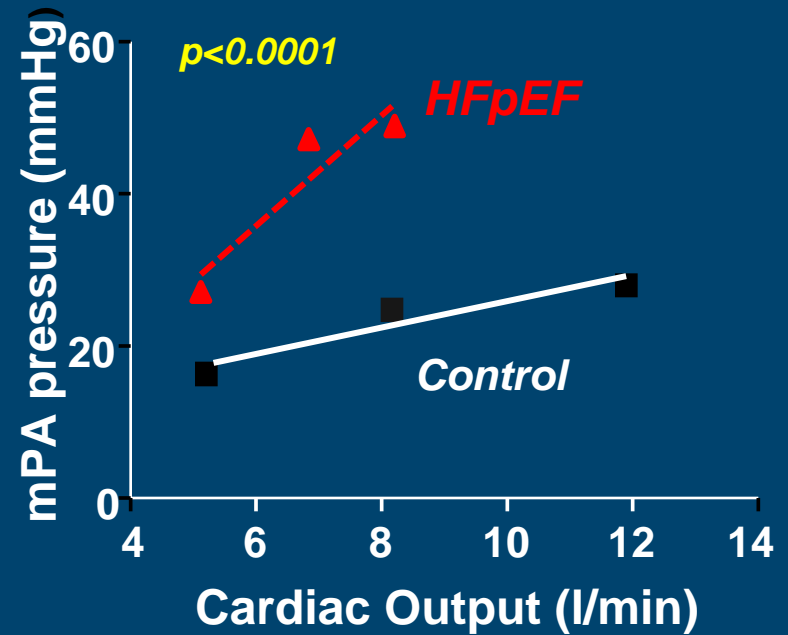
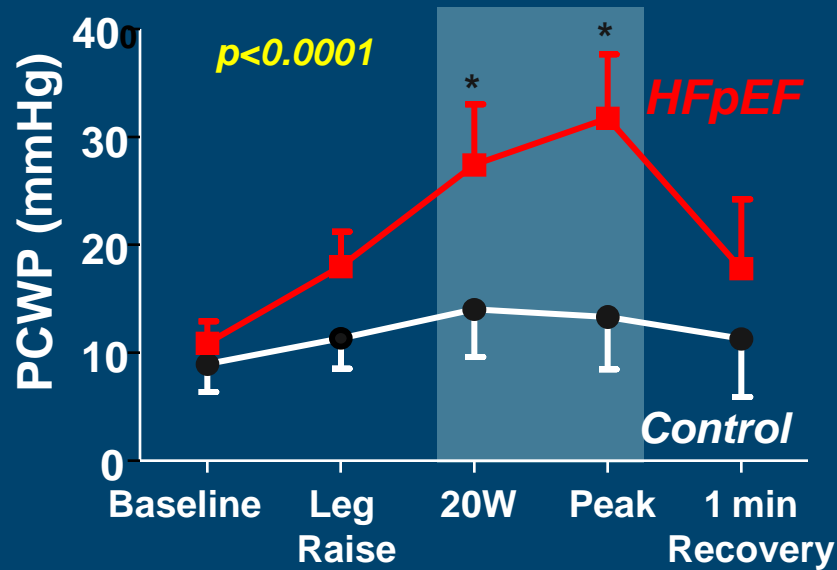


Courtesy of: Ardian

ONGOING CLINICAL TRIALS OF RENAL DENERVATION FOR HE-PEF

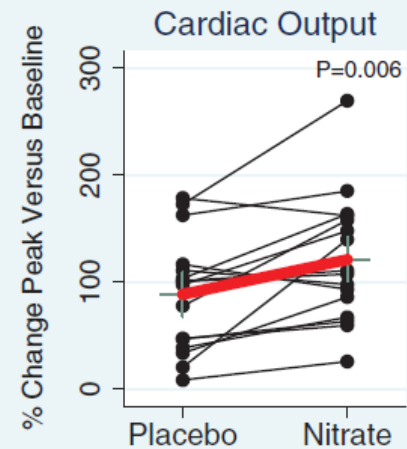
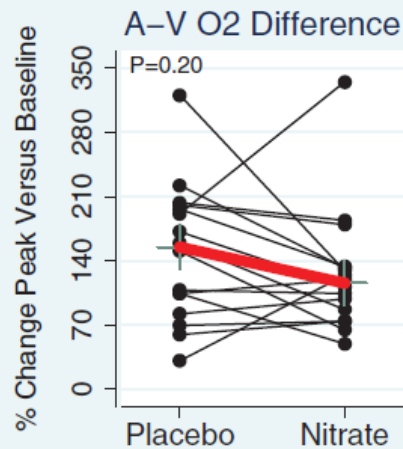
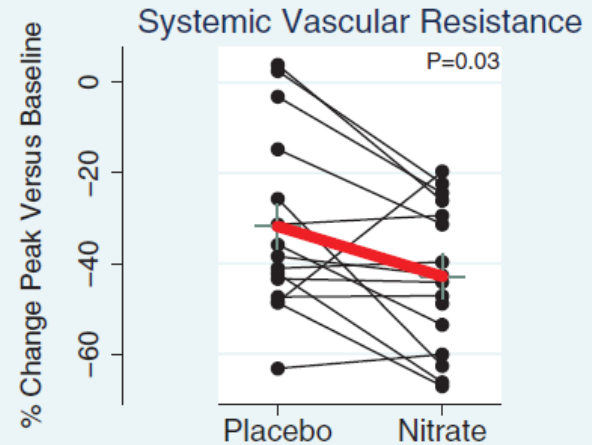
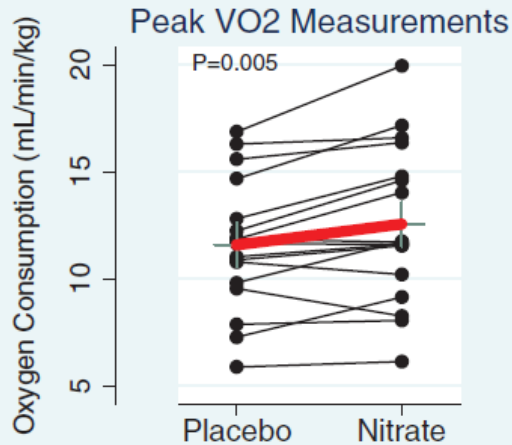
- **DIASTOLE** Change in E/E' at 12 months
- **RESPECT-HF** Change in LAVi and /or LVMI by cMRI at 6 months
- **RDT-PEF** Change in symptoms, exercise tolerance, biomarkers, LV filling and remodeling at 12 month

THE EPHEMERAL NATURE OF \uparrow PCWP IN HF-PEF



Borlaug et al. *Circ Heart Fail* 2010 & unpublished

BEETROOT JUICE (NO DONOR) IN HF-PEF



+ Sign and Red Line connect mean/median values

Zamani et al. *Circulation* 2015

HEART FAILURE WITH PRESERVED EJECTION FRACTION

“TAKE HOME MESSAGES”

- Current therapy should be aimed at improving symptoms and increasing functional capacity
 - Preload reduction (diuretics and nitrates)
 - Tight control of hypertension
- No agent has been shown to improve mortality which is actually similar to heart failure with systolic dysfunction
- Adequate rate control and ? rhythm control in atrial fibrillation can improve symptoms
- Regression of LVH (when present) is a therapeutic goal
- New agents are urgently needed