Management of Heart Failure in the Community

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Beacon Hospital
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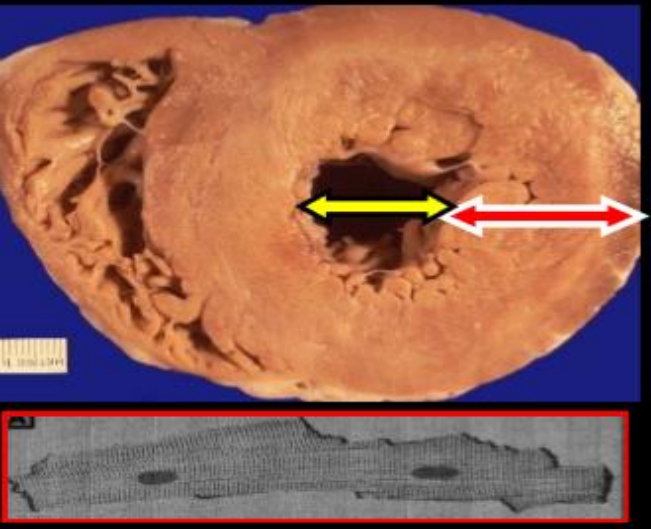
The Heart Failure Epidemic

	Prevalence	Incidence	Mortality	Hospital Discharges	Cost
Total population	5,700,000	670,000	277,193	990,000	$39.2 billion

Leading Cause of hospitalization in adults > 65 years

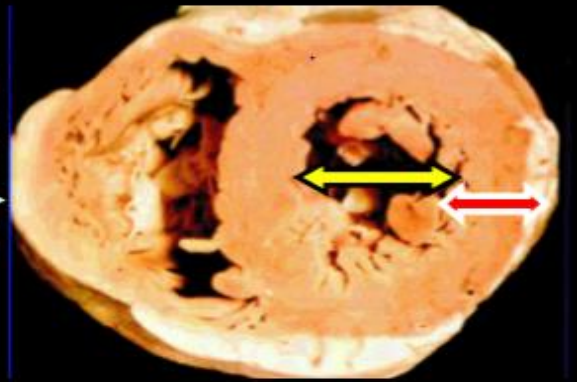
Pathology of Heart Failure



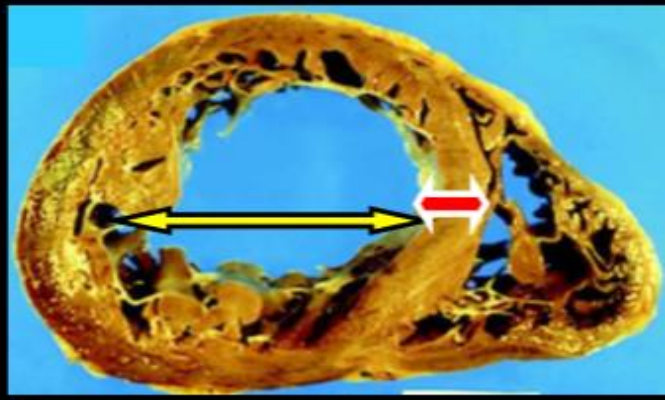
HF-PEF

Concentric Remodeling

↑ Thickness
↔ Volume
↓ Volume / Mass



normal

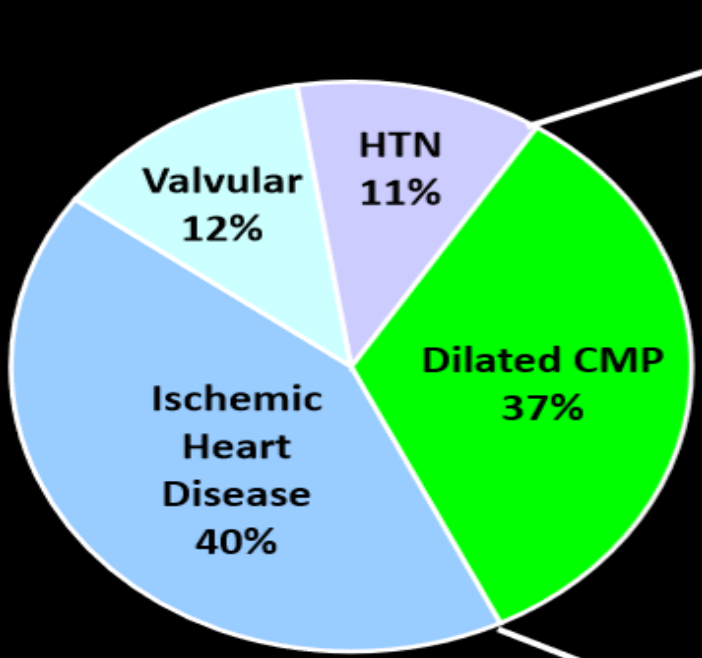


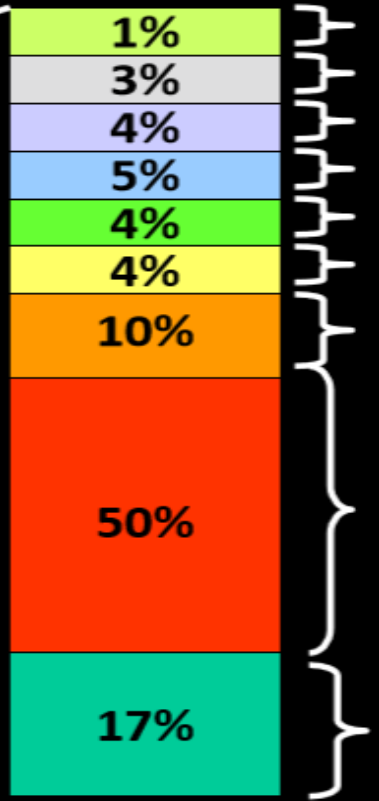
HF-Reduced EF

Eccentric Remodeling

↔ Thickness ↑
Volume ↑ Volume / Mass

Causes of Heart Failure





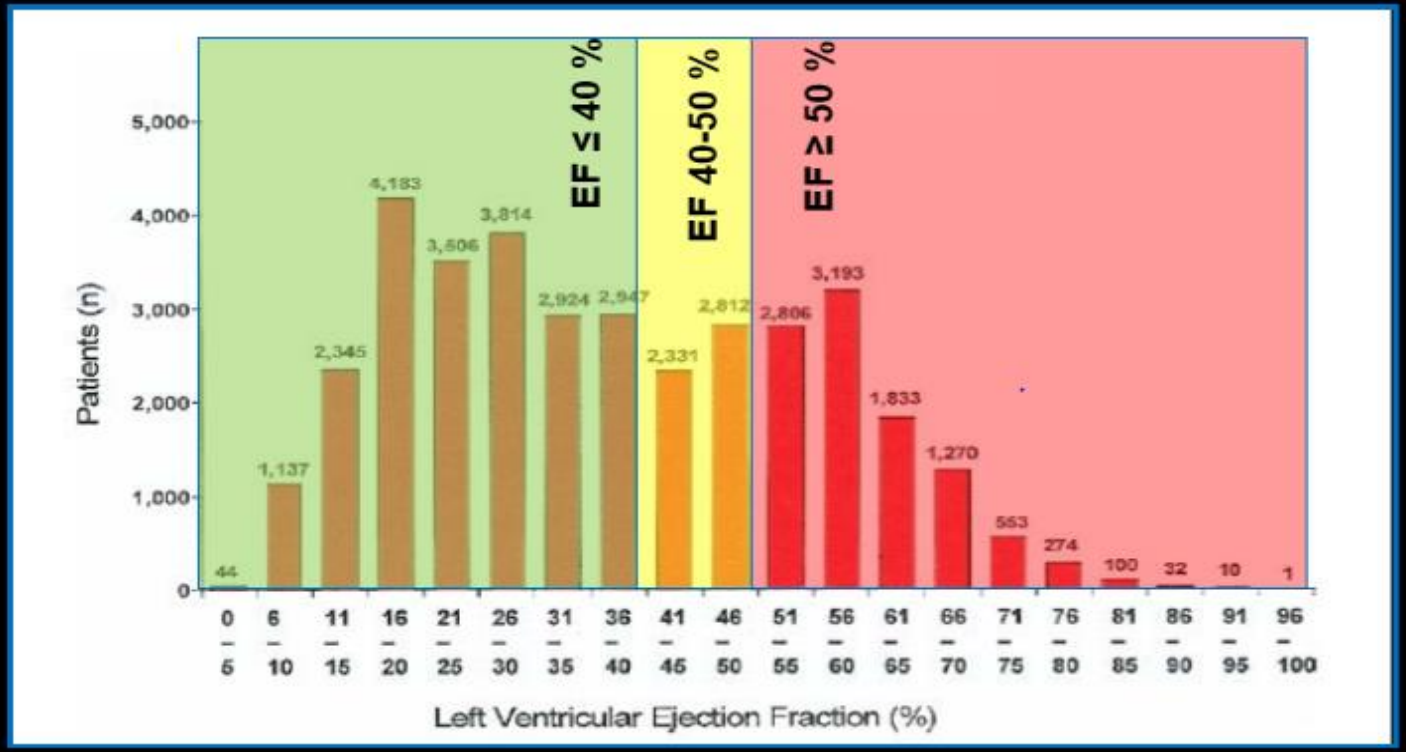
Chemotherapy (adriamycin)
Connective Tissue Disorder
HIV
Infiltrative
Peripartum
Toxins (ETOH, Cocaine)
Myocarditis
'Idiopathic'

Other:
- Tachycardia
- Congenital HD
- Stress-related
- Chagas' Disease

Baldasseroni, Am Heart J 2002; 143: 398
Felker. New Engl J Med 2000: 342:1077

Up to 40% of those with an ‘idiopathic’ cardiomyopathy have inherited it

Hospitalized with HF



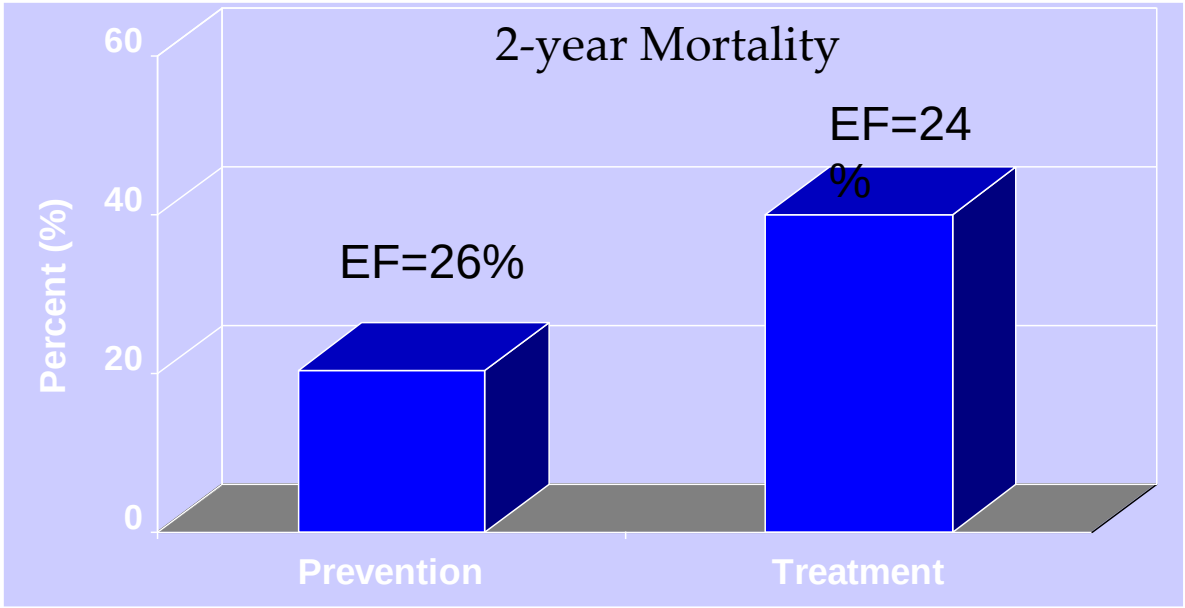
HF-PEF vs. HFrEF

- Older
- Female
- HTN
- CKD
- ↓ CAD

Fonarow G, et al. JACC 2007; 50:768-77

Prognosis of heart failure-EF

SOLVD Trials



Heart Failure is a Clinical Diagnosis

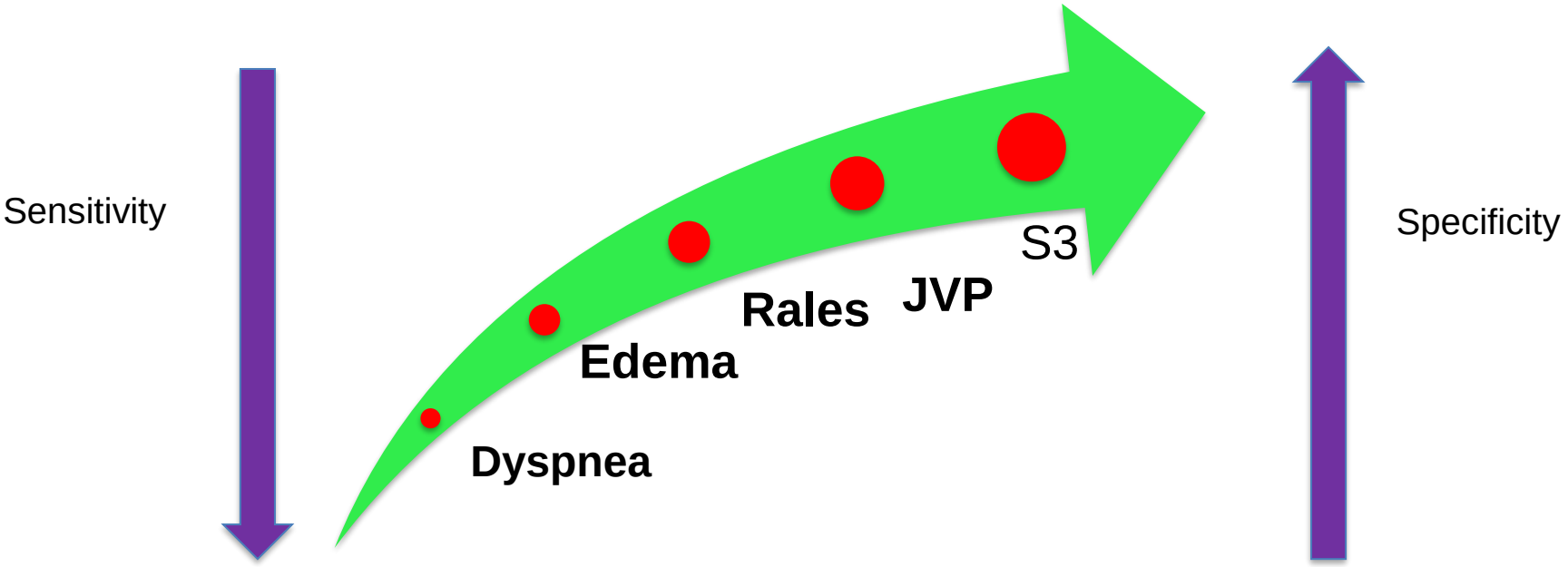
Major criteria

- Orthopnea / PND
- Venous distension
- Rales
- Cardiomegaly
- Acute pulm edema
- JVD > 16 cm
- HJR
- S3

Minor criteria

- Ankle edema
- Night cough
- Exertional dyspnea
- Hepatomegaly
- Pleural effusion
- Tachycardia (>120)
- Decreased VC
- Weight loss w/ CHF tx

Clinical Diagnosis of Heart Failure



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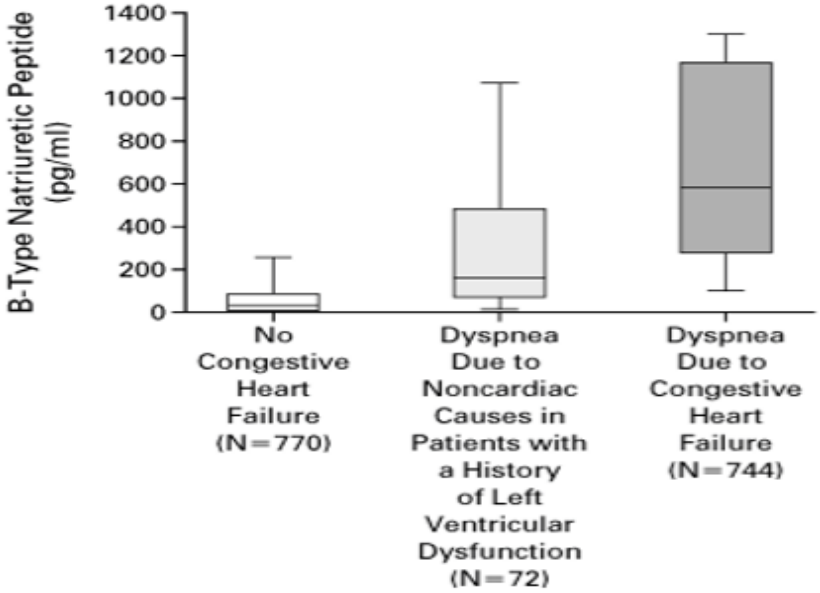
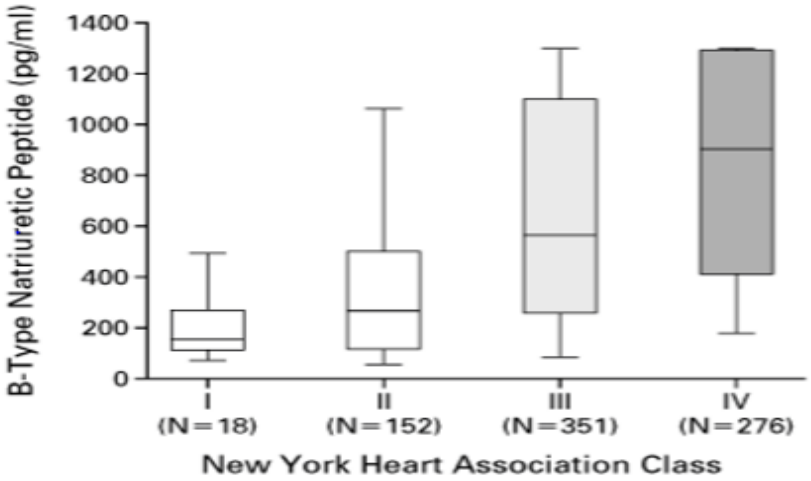
BNP for Diagnosis

1586 pts presenting to EW with dyspnea





Maisel AS, et al. NEJM 2002;347:161

BNP ≥ 100 pg/mL:
Positive Predictive Value 79%
Negative Predictive Value 89%

NT-pro BNP ≥ 900 pg/mL:
Positive Predictive Value 77%
Negative Predictive Value 92%

Limitations of BNP

- Biologic Variability
  - Levels may increase with age, female gender, pressure overload, renal failure
  - Levels decrease with obesity, treatment (e.g., carvedilol, spironolactone)
- Levels are lower in HF with preserved EF
- Insufficient specificity for use as a screening tool

The measurement of BNP is primarily useful when there is diagnostic uncertainty

Pre-Discharge BNP is a Strong Predictor of Post Discharge Events

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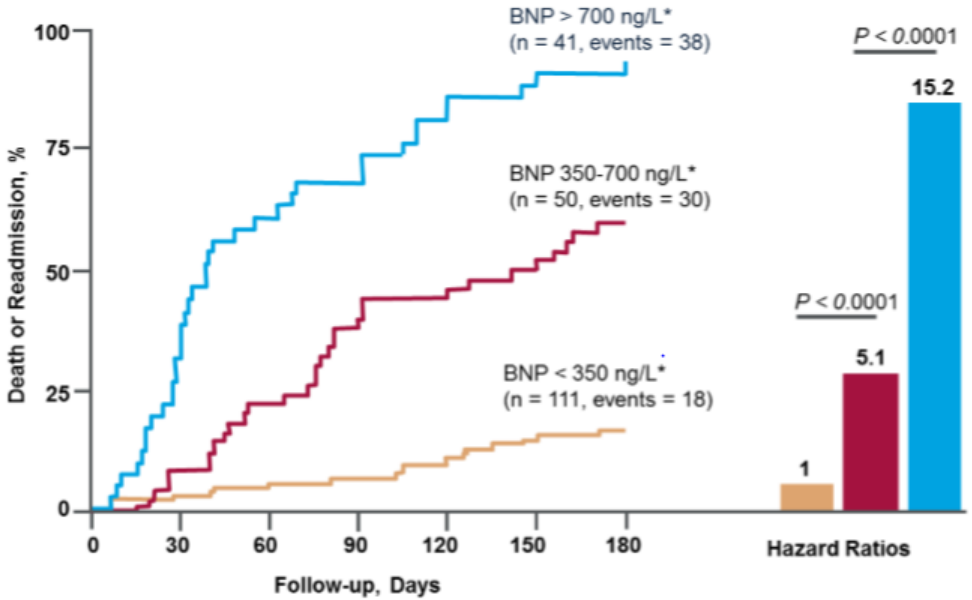

Logeart D, et al. *J Am Coll Cardiol.* 2004;43:635-41.

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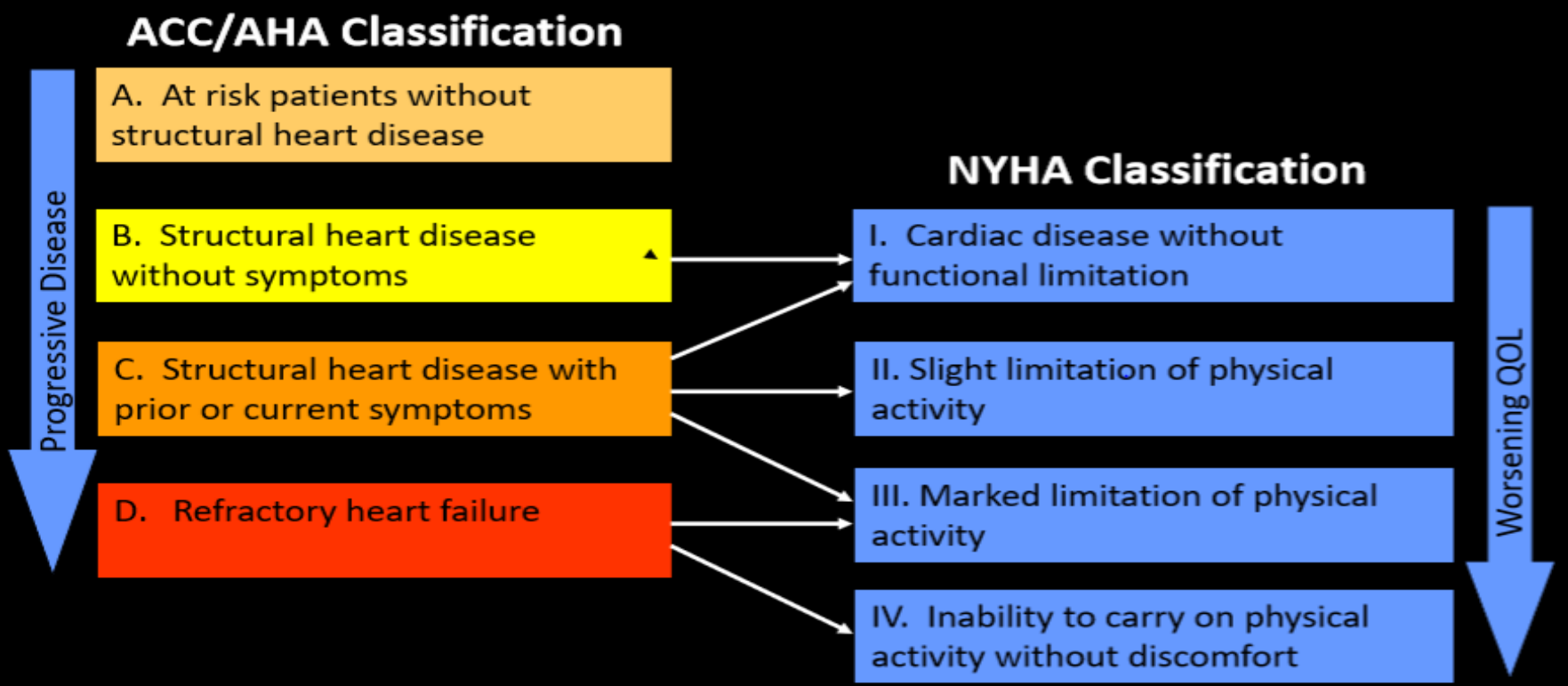
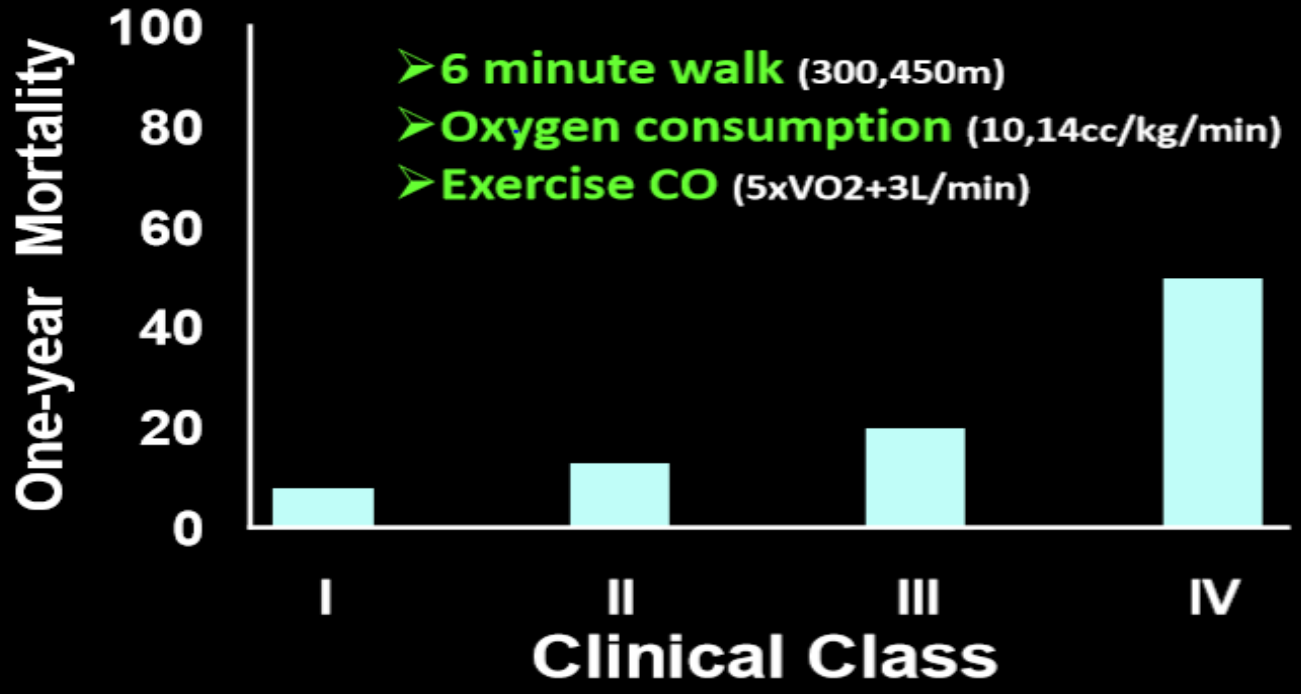
Staging Heart Failure: A New Paradigm



Hunt SA et al. *J Am Coll Cardiol.* 2001;38:2101–2113.

Clinical Class Remains the #1 Predictor Of Mortality in Heart Failure



- 6 minute walk (300,450m)
- Oxygen consumption (10,14cc/kg/min)
- Exercise CO (5xVO2+3L/min)

SAVE
SOLVD
VHeFT
CONSENSUS
Hy-C
GESICA
Pre-TRD 1000

Management

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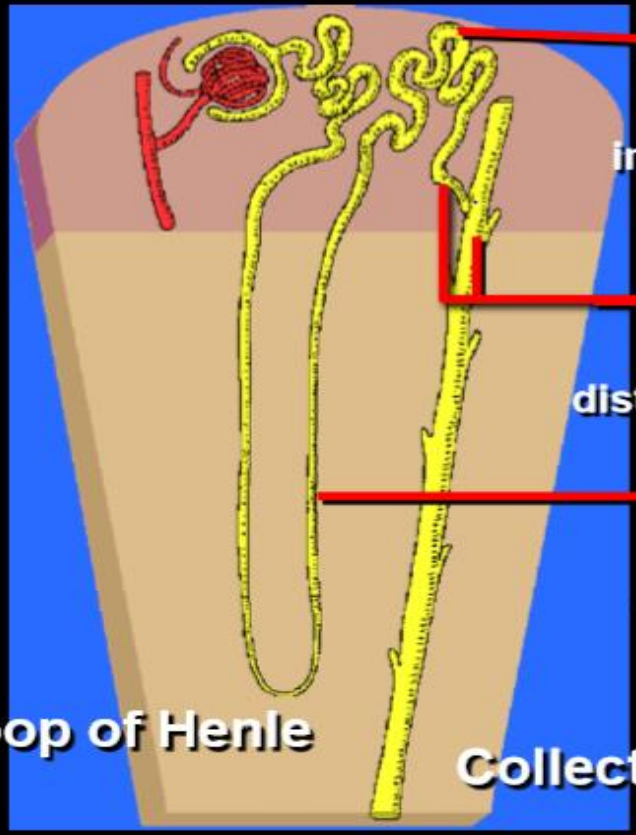
Heart Failure: Use of Diuretics

Cortex

Medulla



Thiazides

Inhibit active exchange of Cl-Na in the cortical diluting segment of the ascending loop of Henle

K-sparing

Inhibit reabsorption of Na in the distal convoluted and collecting tubule

Loop diuretics

Inhibit exchange of Cl-Na-K in the thick segment of the ascending loop of Henle

Diuretics for Heart Failure

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	Examples	Maximum Effect (% of filtered Na load)	Site of action in nephron
Carbonic Anhydrase Inhibitors	Acetazolamide	3-5%	Proximal Tubule
Loop Diuretics	Furosemide, Bumetanide, Torsemide	20-25%	Thick ascending limb of Loop of Henle
Thiazide Diuretics	HCTZ, metolazone	5-8%	Early distal tubule
Potassium-Sparing Diuretics	Spironolactone, amiloride	2-3%	Late Distal tubule and collecting duct

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Loop Diuretic Pharmacodynamics

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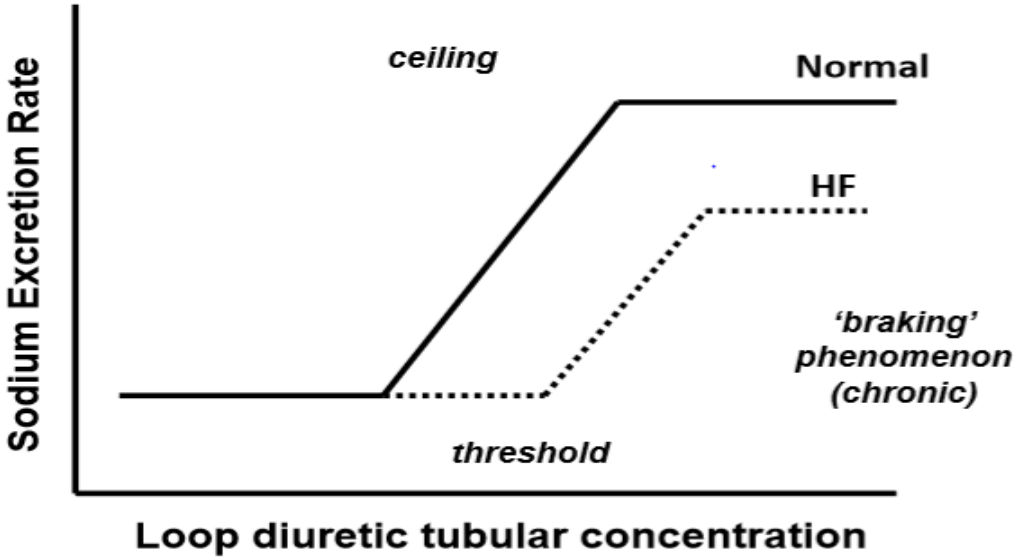

- Use an adequate initial dose
- Avoid overdosing
- More frequent administration of effective doses
- Combination diuretic therapy for diuretic resistance

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FOUR PILLARS OF HEART FAILURE MANAGEMENT

ACEi / ARB / ARNI

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ACE-Inhibitors in Heart Failure

- Improve symptoms, clinical status, and exercise capacity
- Improve cardiac function
- Reduce hospitalizations
- Attenuate remodeling
- Prolong survival
- Reduce vascular events (ie. HOPE)

Outcome Trials of ACE Inhibitors in Heart Failure

	Patients	NYHA Class	Placebo Mortality	Hazard ratio
V-HeFT II	804	I-III	25% *(Hyd/Iso)*	0.72
CONSENSUS I	253	IV	44%	0.66
SOLVD Tx	2569	II-III	40%	0.84
SOLVD Px	4228	I	16%	0.91
SAVE	2231	Post MI EF<40%	25%	0.81
ISIS-4	58,050	24h post MI	7.7%	0.93

ARBs in Heart Failure

- ACEI does not produce long-term suppression of Angiotensin II ("escape phenomenon")
- Angiotensin II can be generated by other pathways
- Circulating Ang II inhibition may not be equivalent to tissue Ang II inhibition
- 8-12 % of pts cannot tolerate ACEI

ARB Trials in Heart Failure

	ELITE I/II	ValHEFT	CHARM	OPTIMAAL	VALIANT
Patients (n)	NYHA II-IV 722/3152	NYHA II-IV 5010	NYHA II-IV 2548	Acute MI/CHF 5477	Acute MI/CHF 14,808
Study Design	Losartan or Captopril	Valsartan and ACEI	Candesartan and ACEI	Losartan or Captopril	Valsartan, Captopril, or both
β-blocker	16% / 23%	35 %	55 %	79 %	70 %
Mortality	No difference	No difference	No difference	Captopril better	No differences
HF Hosp	No difference	Both better	Both better	Capt better	Both better
Other	Losartan better tolerated	↑ Mort. w/ β-blker	↓ Mort. w/ β-blker	Losartan better tolerated	↓ BP w/ both

ARBs are excellent and proven alternatives to ACE inhibitors

Is More RAAS Inhibition Better?

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- **ARBs further reduce cardiovascular mortality (CHARM-Added) and heart failure hospitalization (CHARM-Added, Val-HeFT) when added to an ACE inhibitor.**
- **Aliskiren, a direct renin inhibitor, inhibits the rate limiting step in angiotensin II generation**
- **Does aliskiren add to the benefit of an ACE inhibitor or provide a better alternative to an ACE inhibitor?**

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Implications

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Combination therapy

- The addition of aliskiren to an evidence-based dose of enalapril led to more adverse events without an increase in benefit.
- This finding differs from the prior ARB "add-on" trials and may reflect a difference in study design (the previous trials did not require an evidence-based dose of background ACE inhibitor).
- There is probably a ceiling to RAS blockade in heart failure, above which there is no further benefit

Aliskiren monotherapy

- Non-inferiority was not demonstrated for aliskiren compared with enalapril.

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Neprilysin as a Therapeutic Target

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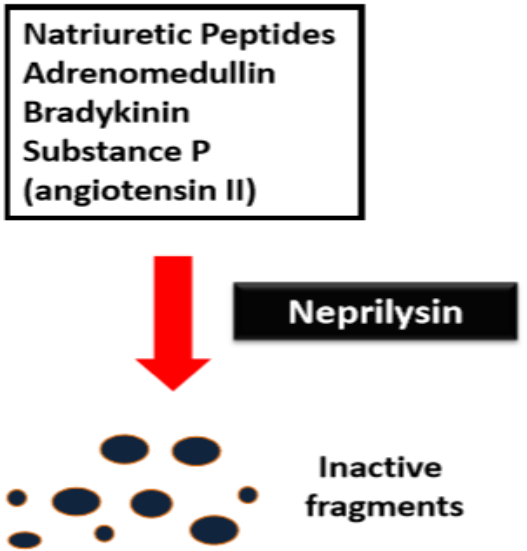
- **Neprilysin is responsible for the breakdown of a number of endogenous vasoactive peptides, including the natriuretic peptides**
- **Inhibition of neprilysin potentiates the action of those peptides**
- **Because angiotensin II is also a substrate for neprilysin, neprilysin inhibitors must be co-administered with a RAAS blocker**
- **The combination of a neprilysin inhibitor and an ACE-inhibitor is associated with unacceptably high rates of angioedema**



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Sacubitril/Valsartan (LCZ696):
A first-in-class angiotensin/neprilysin inhibitor (ARNi)

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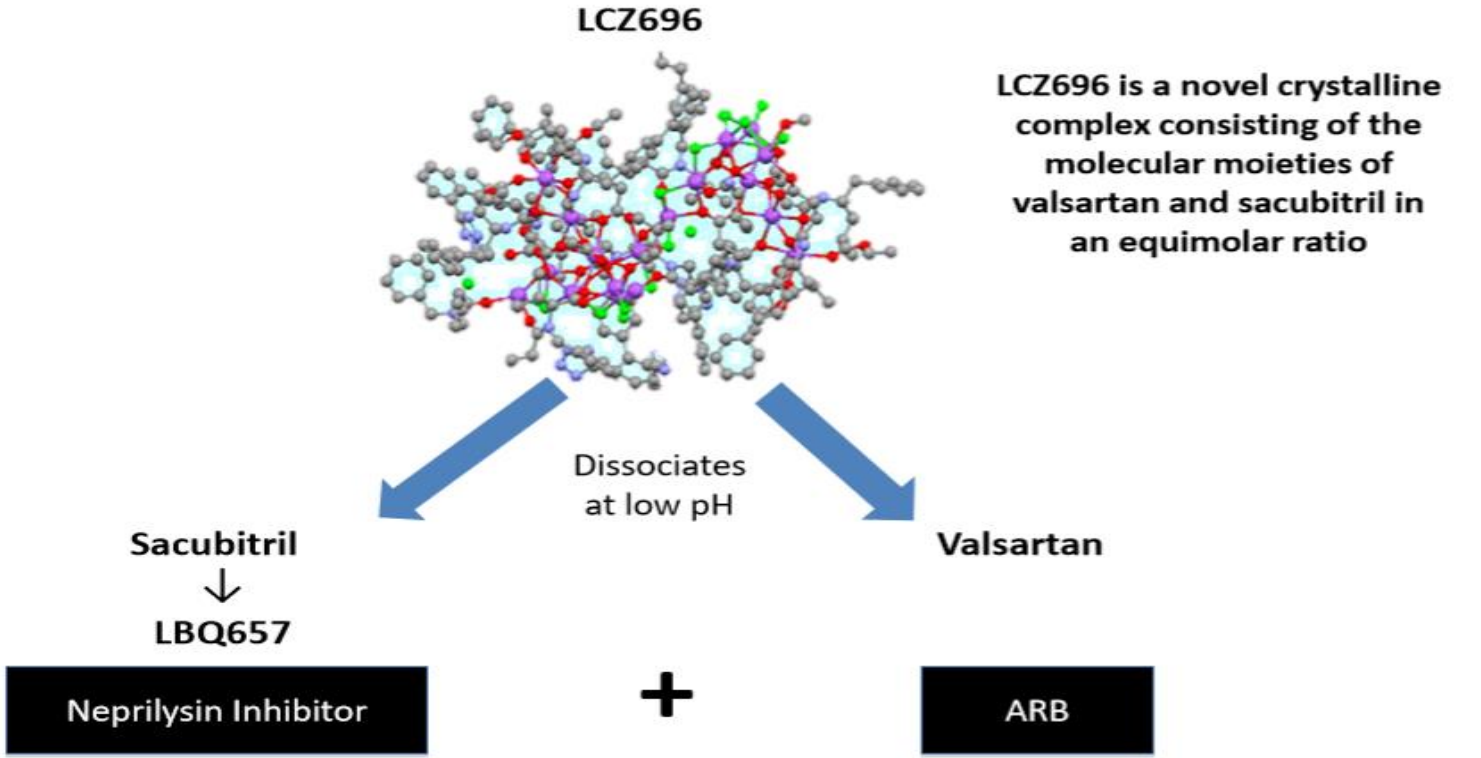

PARADIGM-HF: Who was eligible?

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Inclusion Criteria

- Chronic HF with LVEF ≤40%
- NYHA II-IV symptoms
- Elevated natriuretic peptides
- On guideline-directed medical therapy for > 4 weeks including:
  - ACEi or ARB (enalapril 10 mg daily or equivalent)
  - β-blocker (unless intolerant)
  - MRA if appropriate

Exclusion Criteria

- History of angioedema
- eGFR <30 mL/min/1.73 m^2
- Serum potassium >5.2 mmol/L
- SBP <100 mmHg or symptomatic hypotension
- Current Acute Decompensated HF

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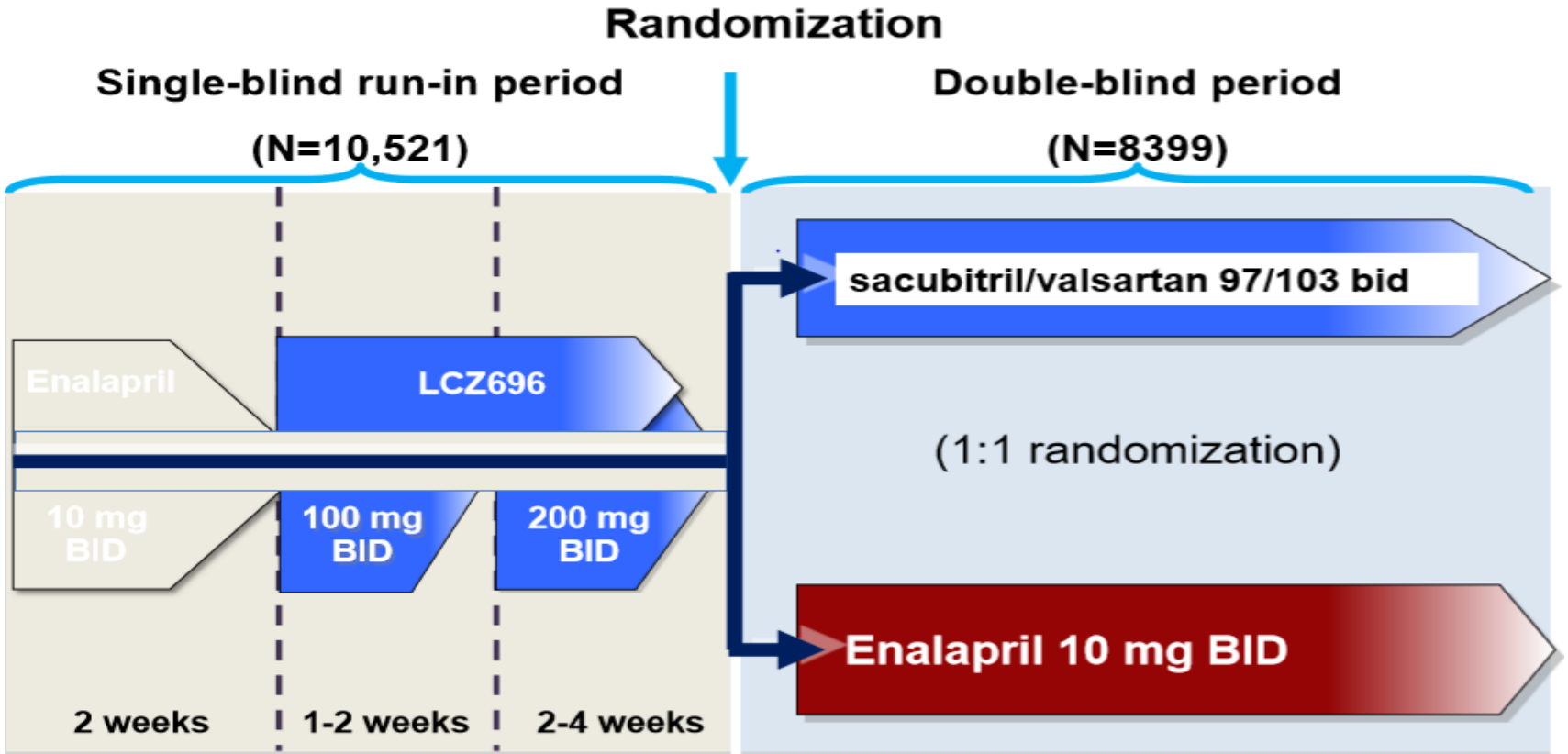
PARADIGM-HF Study Design



PARADIGM-HF: CV Death or HF Hospitalization (Primary Endpoint)

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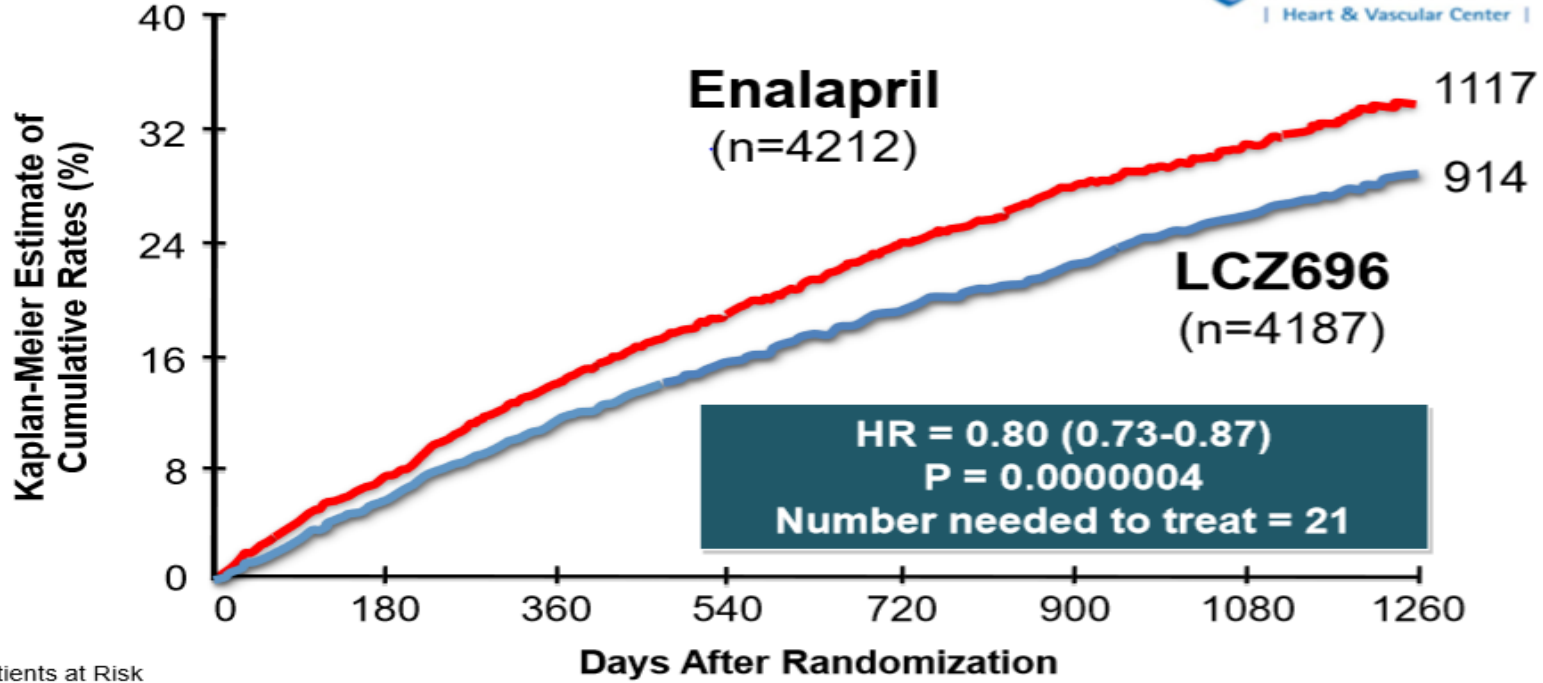

Patients at Risk								
LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

McMurray et al. NEJM 2014

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Other Key Endpoints

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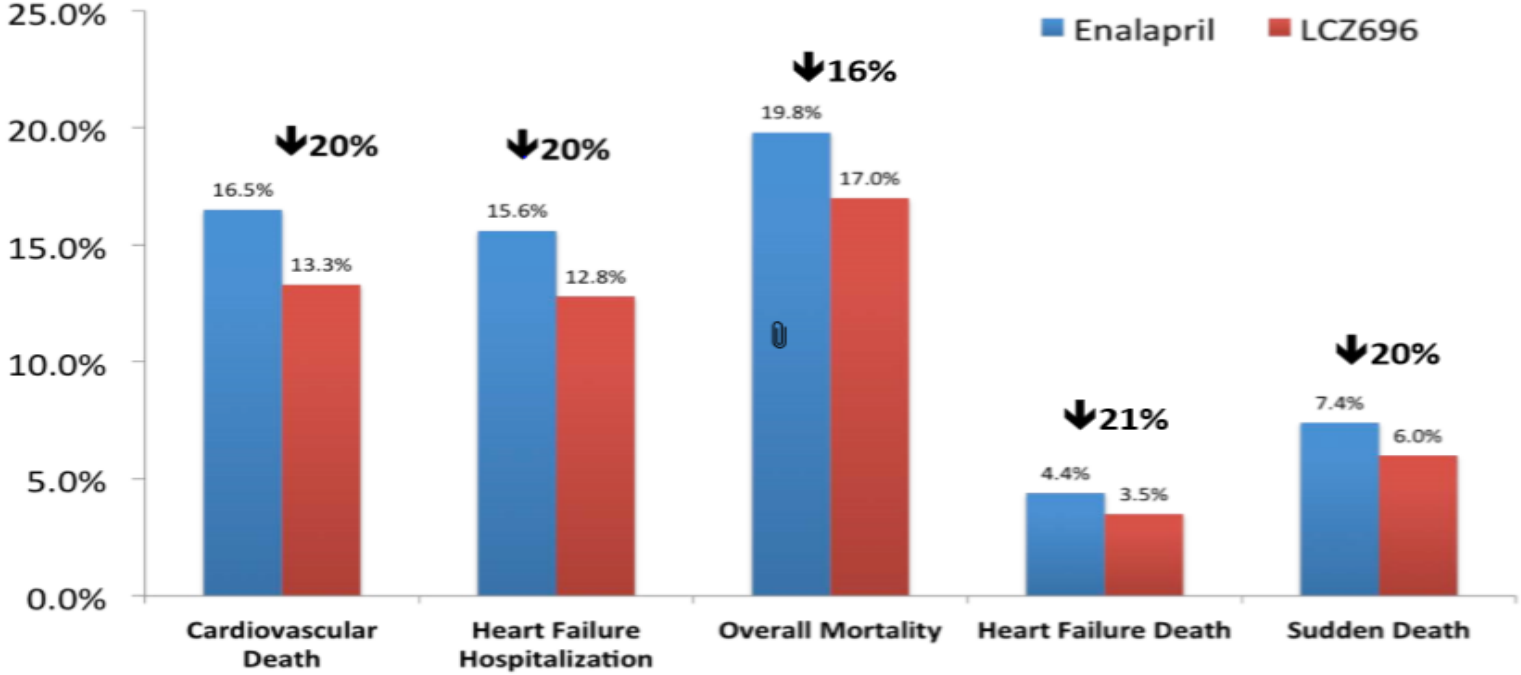

McMurray, N Engl J Med 2014; Desai et al. European Heart Journal 2015

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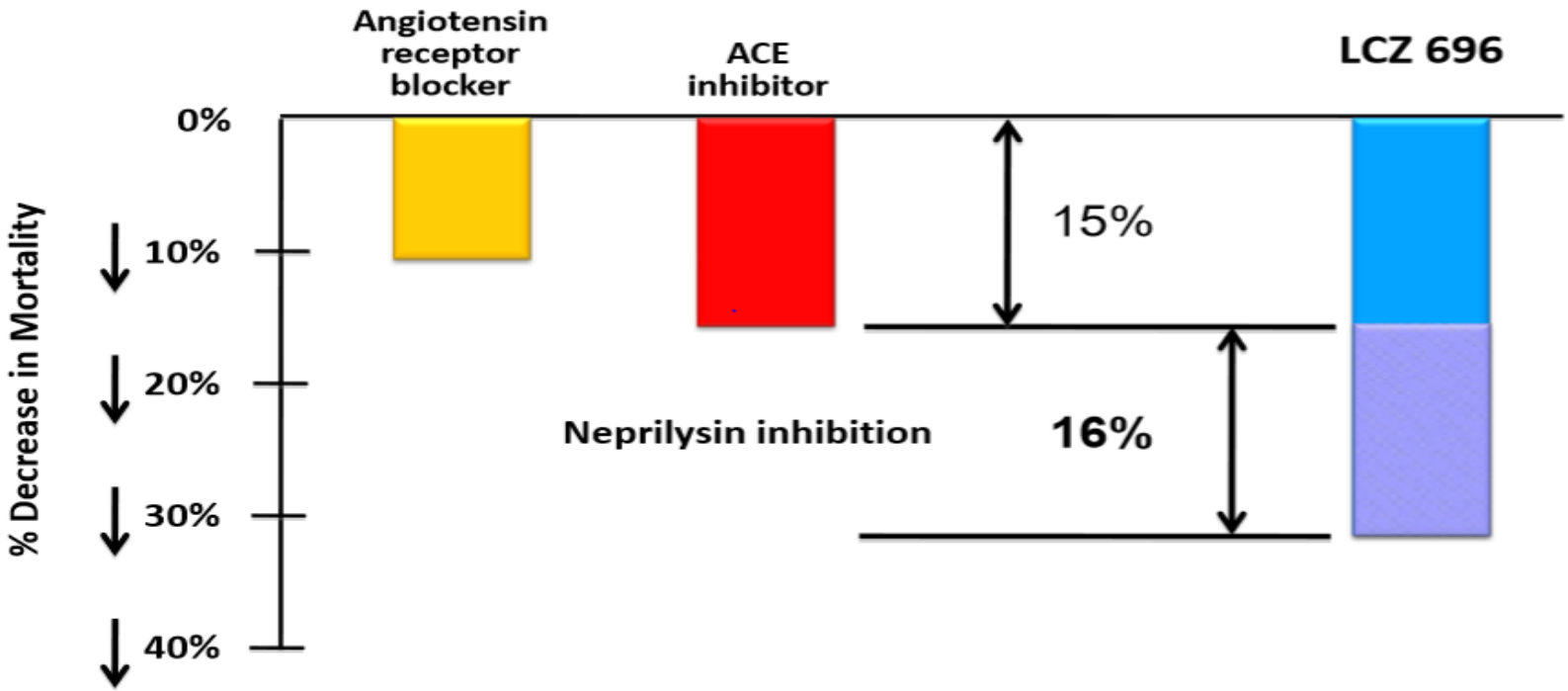
Doubling of Survival over ACE/ ARB



BETA BLOCKERS

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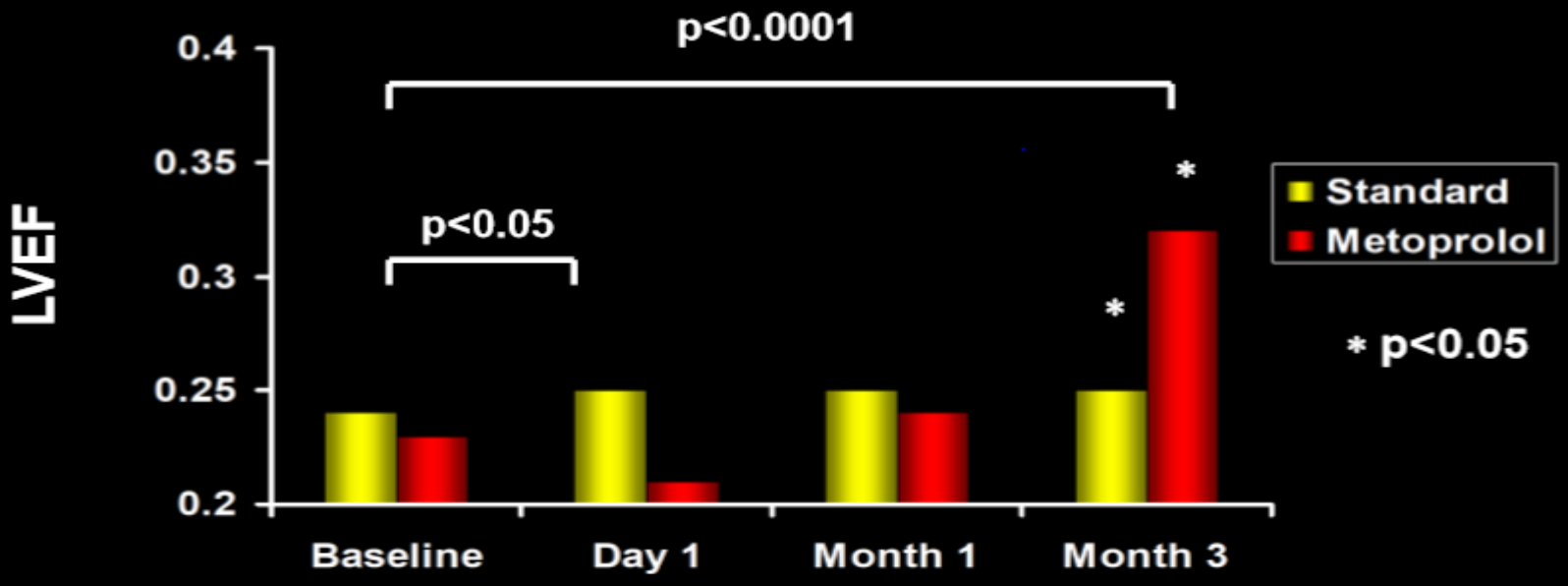
How Do Beta Blockers Improve Heart Failure?

- Upregulation of beta receptors
- Improved coupling of beta receptors to secondary intracellular signals
- Alterations in myocardial metabolism
- Improved calcium transport
- Increased protein synthesis and message expression
- Inhibition of renin-angiotensin system
- Inhibition of endothelin and cytokine release

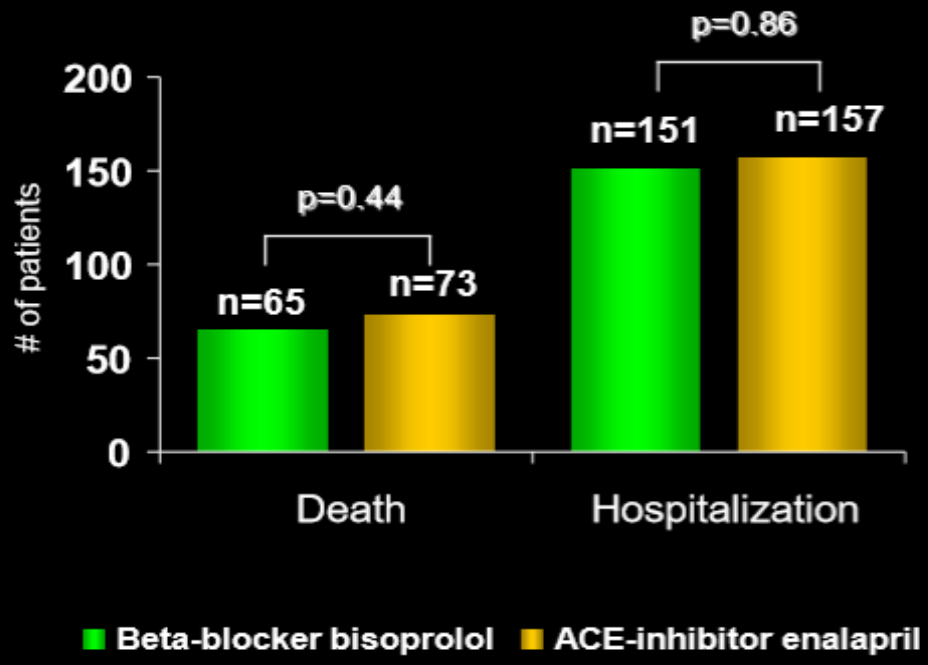
Effect of Beta Blockade on Ejection Fraction over Time



Hall, JACC 1995

Beta blockers are contraindicated in acutely decompensated heart failure

Which drug first?
ACE-I vs. Beta Blocker



CIBIS III

1010 pts, new dx HF

NYHA II-III, EF<=35%

Monotherapy for 6 mos, followed by combination rx

- In ITT population, bisoprolol-first strategy was noninferior to enalapril-first

Both drugs important, sequence of initiation likely not critical

ALDOSTERONE ANTAGONISTS

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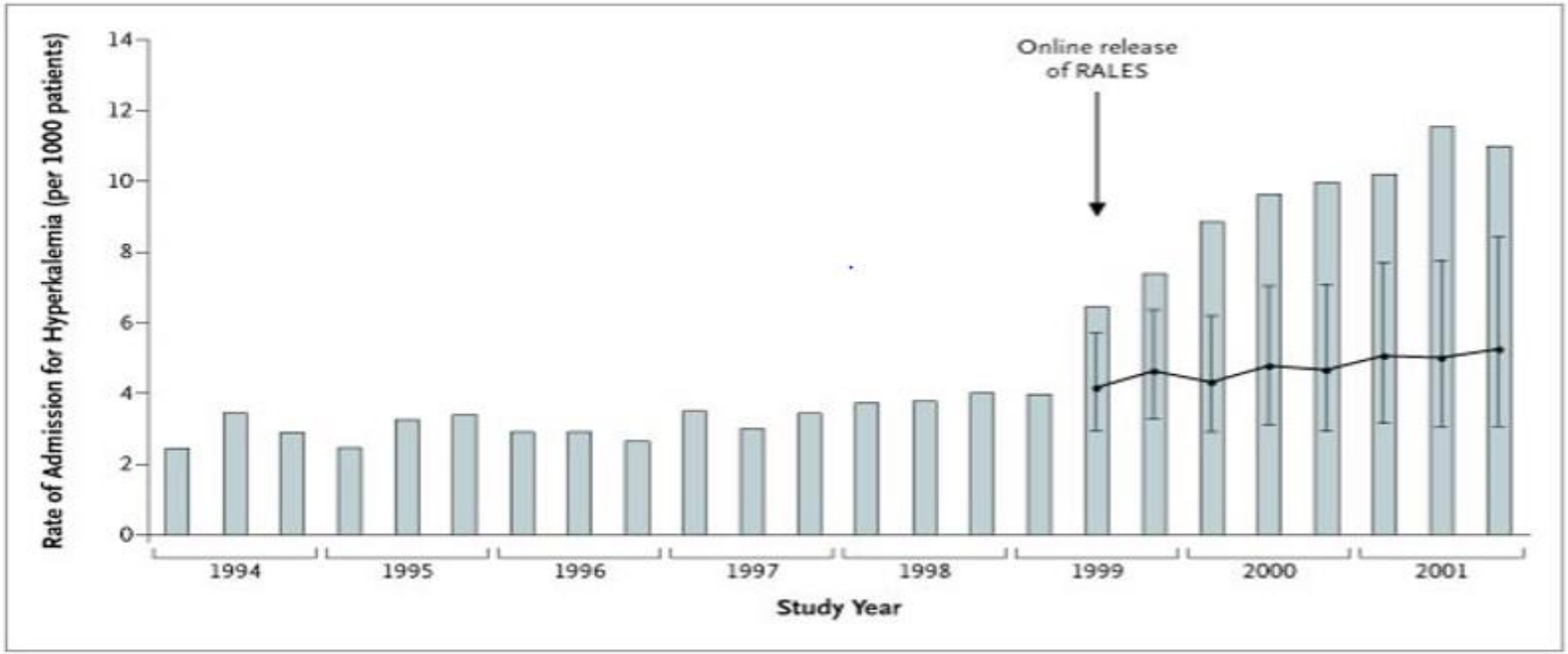
Aldosterone Antagonists in HF

Trial	N	LVEF	NYHA	End-pt	HR
RALES[1]	1663	≤ 35%	III-IV	All cause mortality	0.7, p<0.001
EPHESUS[2]	6632	Post-MI EF < 40%	II *or* I w/ DM	All cause mortality	0.85, P=0.008
EMPHASIS-HF[3]	2737	EF < 30% *or* EF 30-35% w/ QRS > 130	II	CV death or HF hosp.	0.63, p<0.0001

[1]Pitt, B et al. NEJM 1999;341:709-17;
[2]Pitt B et al. NEJM 2003;348:1309-21;

Aldosterone Antagonists: Safety

Rate of Hospital Admission for Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors (before/after RALES)



Juurlink et al. New Eng J Med 2004; 351: 543.

Aldosterone Receptor Antagonists

- Consider in most patients with symptomatic heart failure and EF ≤ 40%, after optimization of ACEi/ARB and Beta-Blocker
- Monitor potassium and renal function frequently
- Avoid in patients with prior hyperkalemia or advanced CKD
- Caution in subgroups at high risk, such as diabetes, elderly
- Avoid combination of ACEi + ARB + spironolactone
- Spironolactone likely equivalent to eplerenone as long as dosing is adequate

SGLT2i

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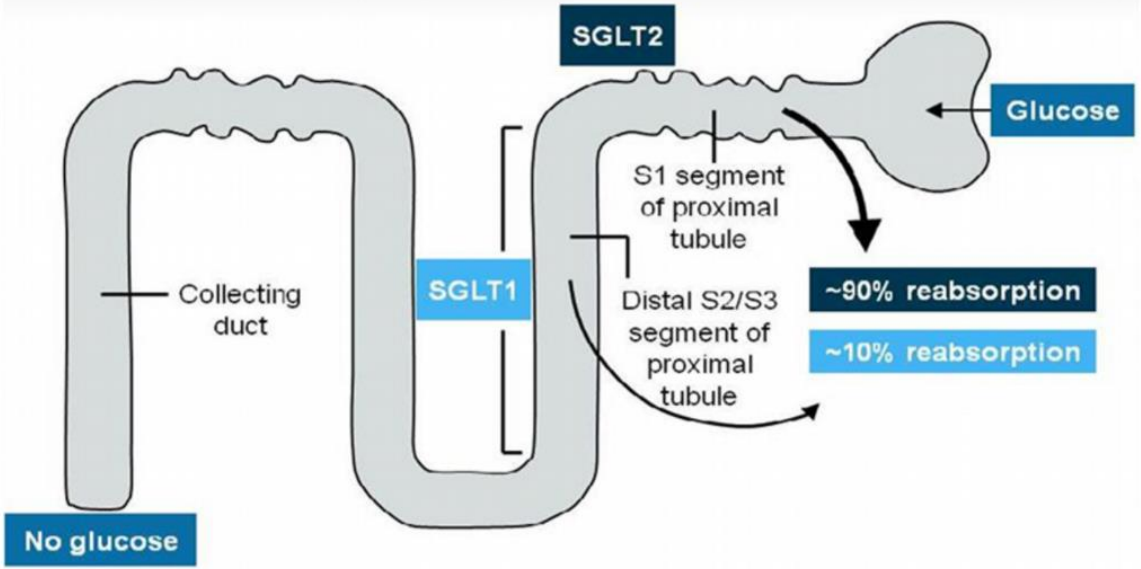
SGLT2 inhibitors



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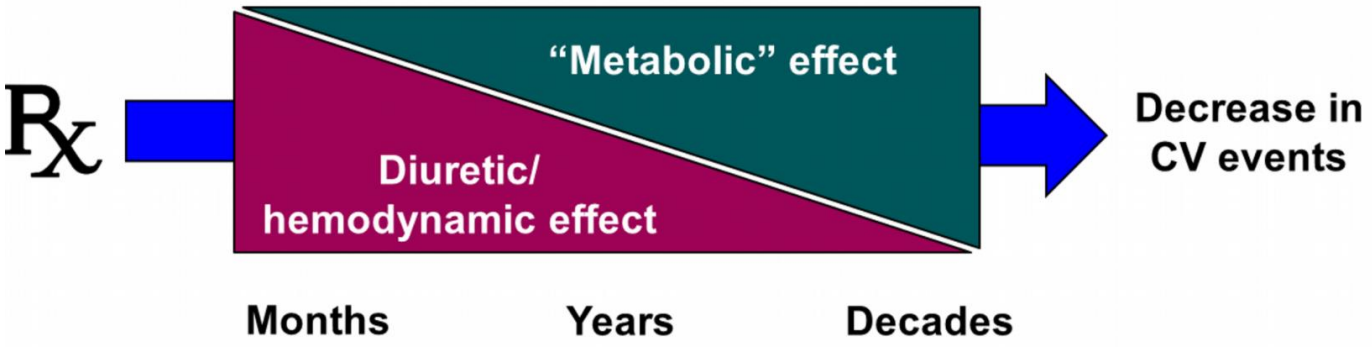
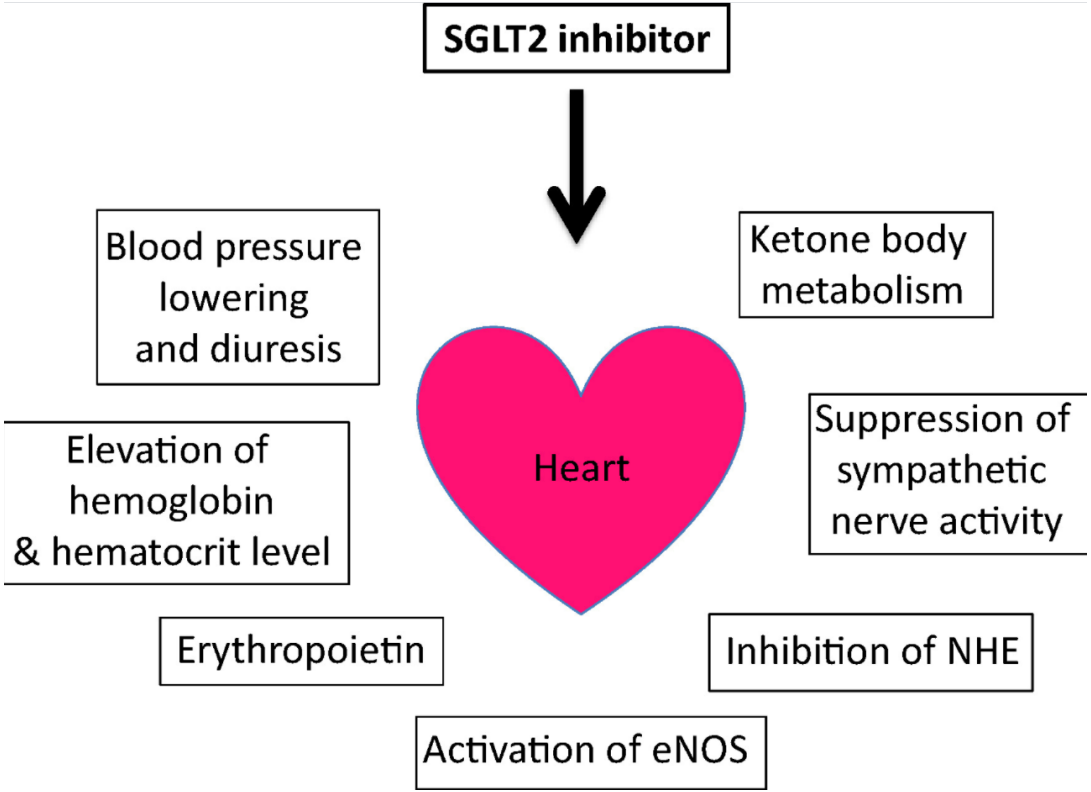
SGLT2 inhibitors



SGLT2 inhibitors



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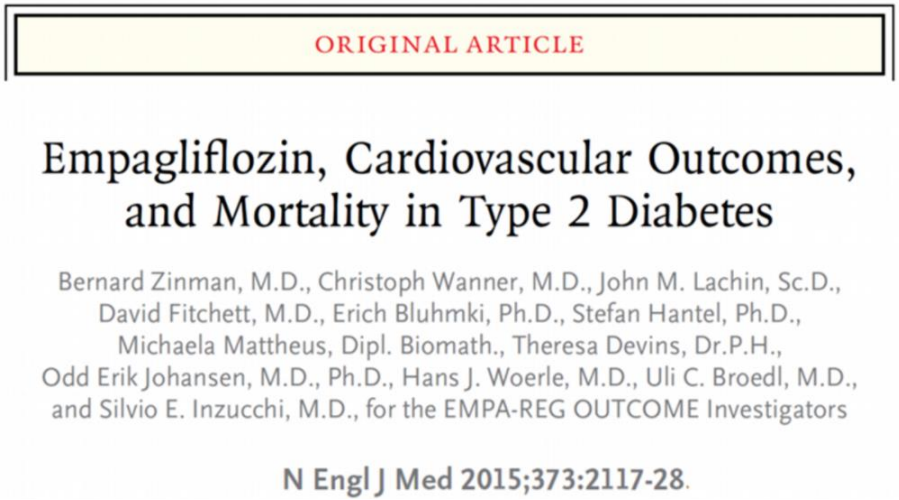
SGLT2 inhibitors

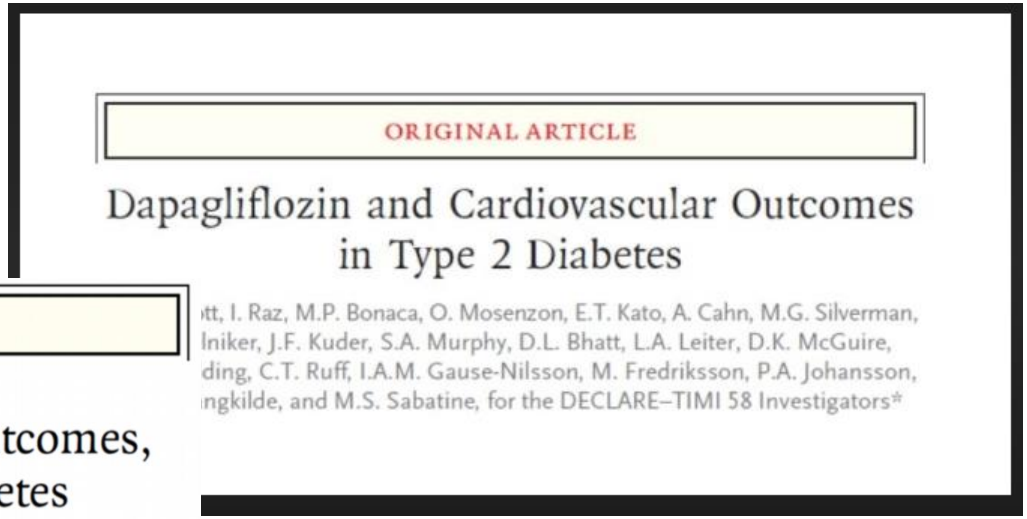


ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

N Engl J Med 2015;373:2117-28.



ORIGINAL ARTICLE

Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes

ıtt, I. Raz, M.P. Bonaca, O. Mosenzon, E.T. Kato, A. Cahn, M.G. Silverman, lniker, J.F. Kuder, S.A. Murphy, D.L. Bhatt, L.A. Leiter, D.K. McGuire, ding, C.T. Ruff, I.A.M. Gause-Nilsson, M. Fredriksson, P.A. Johansson, ıngkilde, and M.S. Sabatine, for the DECLARE–TIMI 58 Investigators*

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SGLT2 inhibitors

HFrEF

EMPEROR-Reduced[1]

- **Hypothesis:** Empagliflozin will be superior to placebo, added to SOC, in patients with symptomatic chronic HFrEF (patients with *and* without diabetes)
- **Population:** 2850 patients; symptomatic HF; EF ≤40%; EF 36-40%/NT-proBNP ≥2500 pg/ml; 31-35%/≥1000 pg/ml; ≤30% ≥600 pg/ml; eGFR ≥20 ml/min/1.73 m^2 ; SBP ≥100 mmHg
- **Primary endpoint:** CV death or HF hospitalization

Dapa-HF[2]

- **Hypothesis:** Dapagliflozin will be superior to placebo, added to SOC, in patients with symptomatic chronic HFrEF (patients with *and* without diabetes)
- **Population:** 4500 patients; symptomatic HF; EF ≤40%; NT-proBNP ≥600 pg/ml; eGFR ≥30 ml/min/1.73 m^2; SBP ≥95 mmHg
- **Primary endpoint:** CV death or worsening HF event

SGLT2 inhibitors

HFpEF

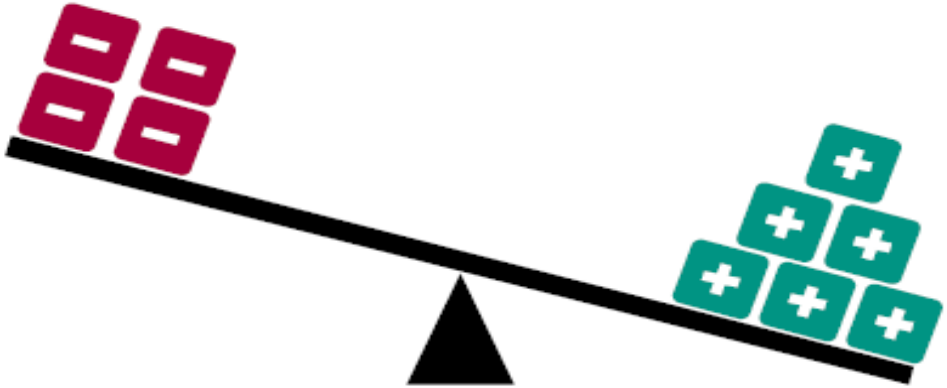
EMPEROR-Preserved[1]

- **Hypothesis:** Empagliflozin will be superior to placebo, added to background therapy, in patients with symptomatic chronic HFpEF (patients with *and* without diabetes)
- **Population:** 4126 patients; symptomatic HF; EF >40%; NT pro BNP >300 pg/ml (> 900 pg/ml for patients with AF); structural heart disease or HF hospitalisation in prior 12 months.
- **Primary endpoint:** CV death or HF hospitalization

DELIVER[2]

- **Hypothesis:** Dapagliflozin will be superior to placebo, added to background therapy, in patients with symptomatic chronic HFpEF (patients with and without diabetes)
- **Population:** 4500 patients; symptomatic HF: outpatient/ inpatient/recently discharged; EF >40%; structural heart disease; NT-proBNP ≥300 pg/ml; eGFR ≥30 ml/min/1.73 m^2; SBP ≥95 mmHg
- **Primary endpoint:** CV death or worsening HF event

SGLT2 inhibitors



Unfavourable effects

1. Genital infections
2. Diabetic ketoacidosis
3. Amputations
3. Fractures

Favourable effects

1. Prevention of heart failure
2. Preservation of renal function
3. Reduction in major adverse cardiovascular events
4. Reduction in blood pressure
5. Weight loss
6. Improvement in glycaemia

ADDITIONAL THERAPIES

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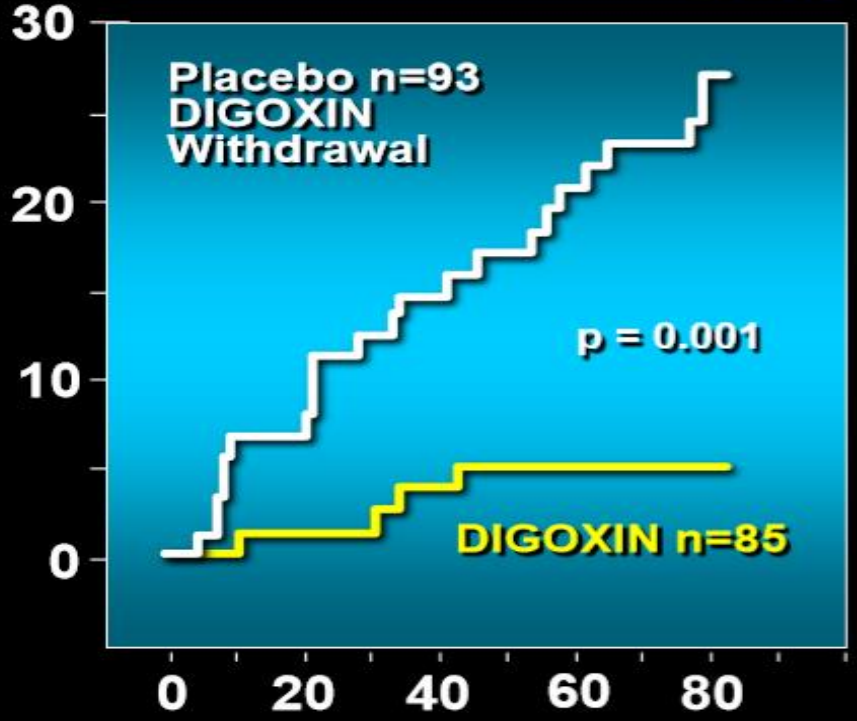
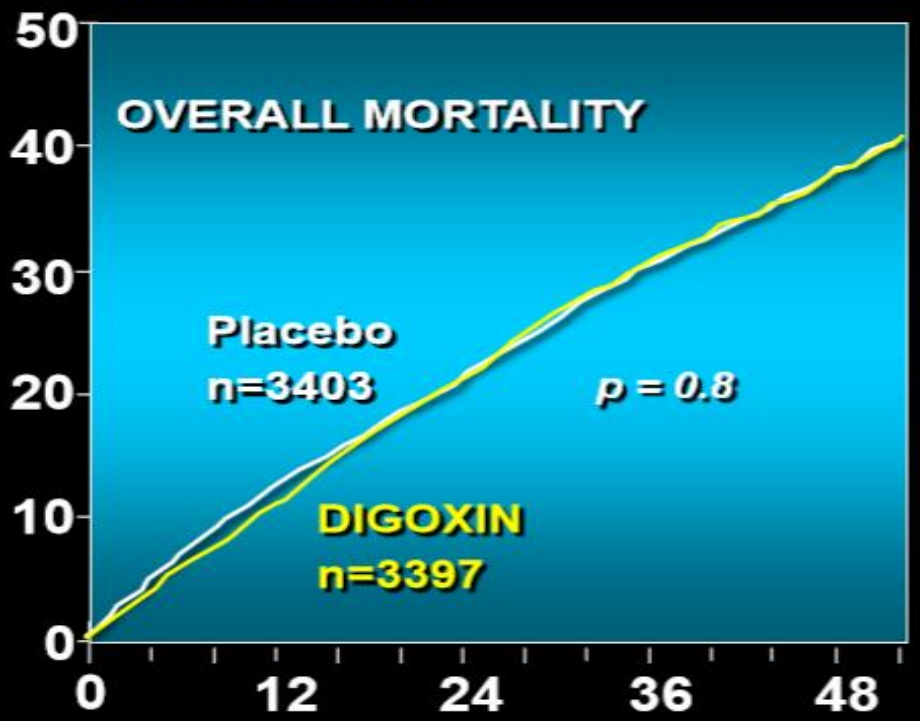
Digoxin: Improvement in Symptoms But Not Survival



RADIANCE
N Engl J Med 1993;329:1

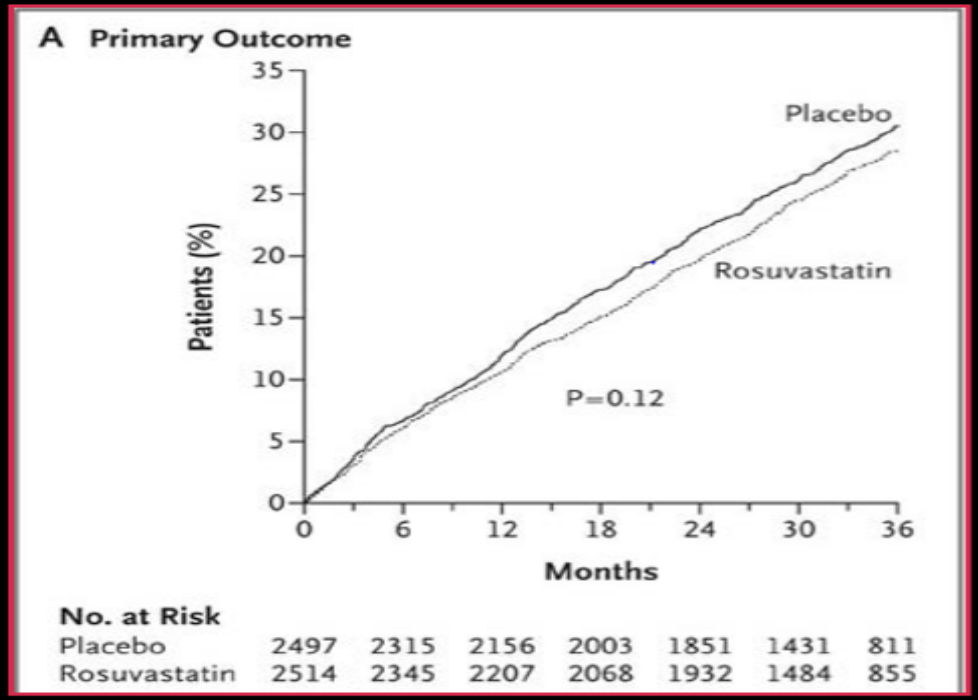


DIG Trial
N Engl J Med 1997;336:525

No incremental benefit (and potential harm) at Levels > 1.0 ng/mL

CORONA: Statins do not Reduce Mortality in HF Patients

5011 pts, Age>60 yrs, NYHA II-IV, ischemic CMP, LVEF≤40%
Cardiovascular mortality, nonfatal MI, nonfatal stroke

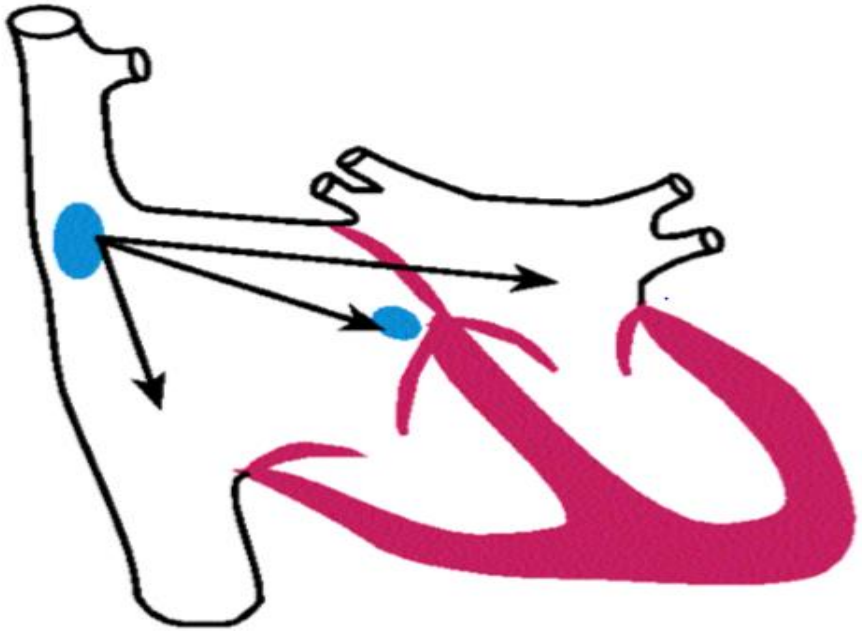


Fewer hospitalizations for HF management in rosuvastatin arm (p=0.01)

Kjekshus J et al. N Engl J Med 2007;10.1056/NEJMoa0706201

Sinus Node inhibition

BRIGHAM AND WOMEN'S HOSPITAL
| Heart & Vascular Center |



I_f current inhibition with ivabradine

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SHIFT

Sinus Node Inhibition in Chronic Heart Failure

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- **Hypothesis:** Heart rate reduction through sinus node inhibition will improve outcomes in chronic heart failure
- **Population:** 6558 patients with HF, NYHA II-IV symptoms, LVEF ≤35%, HF hospitalization in prior 12 months, and HR ≥70 beats/min. GDMT including a beta-blocker at target or maximally tolerated dose.
- **Primary endpoint:** CV death or HF hospitalization

Swedberg K, et al. Lancet 2010; 376: 875-885

Primary composite endpoint
(CV death or hospital admission for worsening HF)

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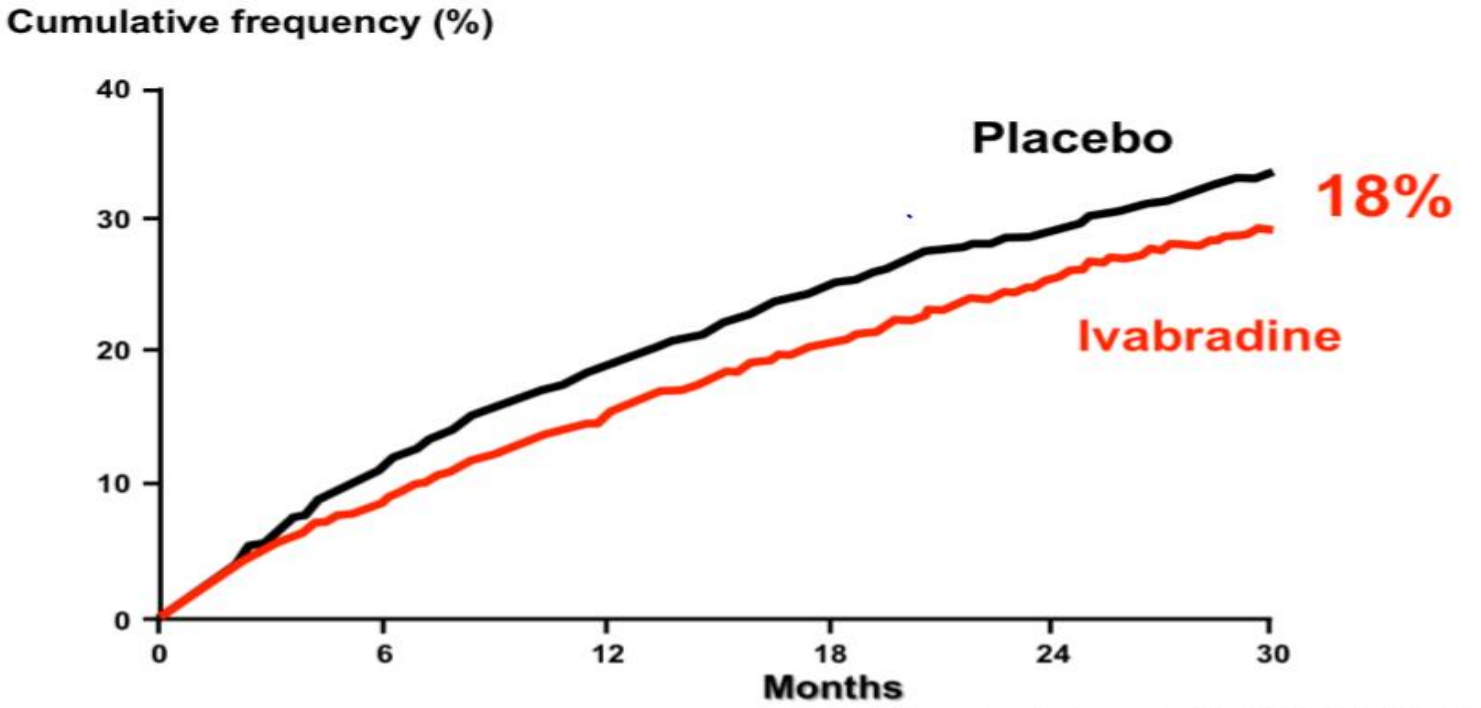

Swedberg K, et al. *Lancet*. 2010;376(9744):875-885

Guideline Update

BRIGHAM AND WOMEN'S HOSPITAL | Heart & Vascular Center |

COR	LOE	Recommendations
IIa	B-R	Ivabradine can be beneficial to reduce HF hospitalization for patients with symptomatic (NYHA class II-III), stable, chronic HFrEF (LVEF<=35%) who are receiving GDMT , including a beta-blocker at maximally tolerated dose, and who are in sinus rhythm with a HR>=70 bpm at rest

- **The incremental benefits of ivabradine are more pronounced in patients with higher resting heart rates**
- **The magnitude of HR reduction achieved with ivabradine+ß-blockade is the principal determinant of subsequent outcome**

Yancy, et al. Circulation 2016

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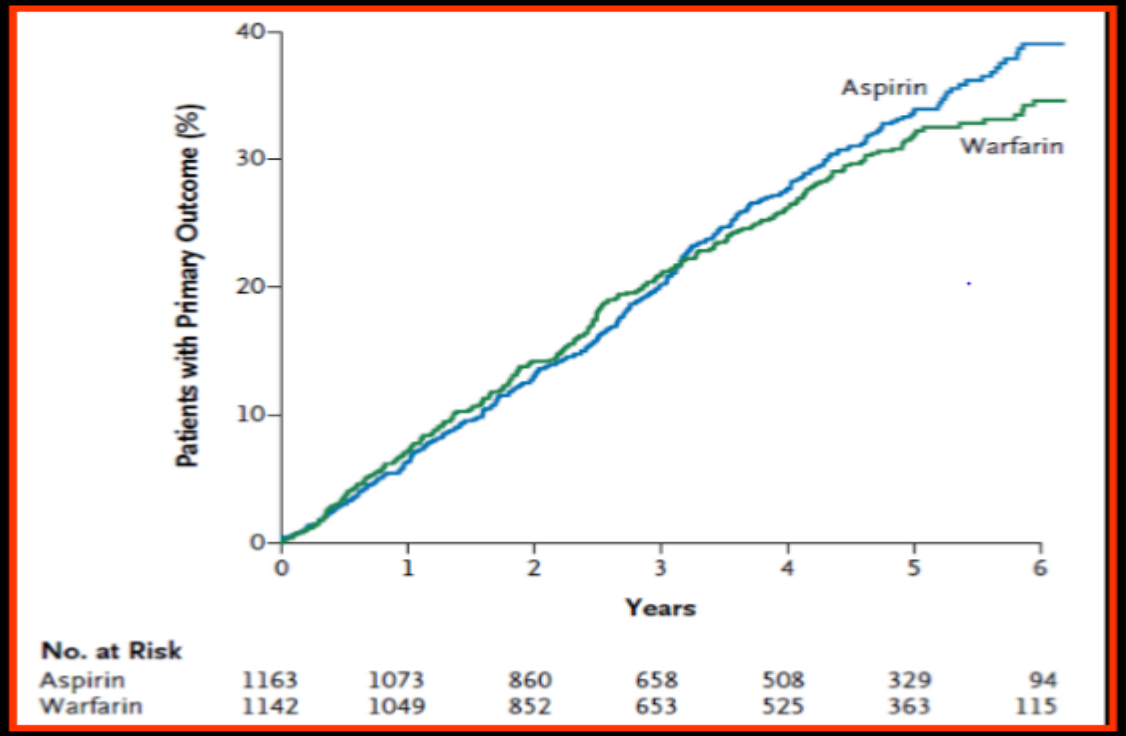
Anticoagulation in Patients with Heart Failure and Sinus Rhythm (WARCEF)



Reduced risk of ischemic stroke with warfarin offset by increase in major hemorrhage

Homma S, et al. N Engl J Med 2012;366: 1859-69.

OF COURSE...

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Heart Failure Management: More Than Just Drugs

- Dietary counseling
- Patient education
- Physical activity
- Medication compliance
- Aggressive follow-up
- Nonpharmacologic Therapies
  - CRT
  - Sleep Disordered Breathing
- Management of Related Risks
  - Sudden Death (ICD implantation)
  - Thromboembolism/Stroke

DEVICE BASED THERAPIES

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For patients on OMT, consider
CRT for
EF ≤ 35%
NYHA II-IV,
LBBB w/ QRS ≥ 150 msec

Indications for ICD Therapy in HF

- Cardiac Arrest
- Sustained VT
- EF<40%, CAD, NSVT, inducible VT
- EF<30%, > 40d post-MI or 3mths post-revascularization, NYHA I-III
- EF<35%, Non-ischemic CMP, NYHA II-III
- ***Contraindicated in NYHA IV, unless bridge to advanced therapies***

SUMMARY

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Congestive Heart Failure: Summary

- Heart failure is a clinical diagnosis
- BNP may be helpful when diagnosis of heart failure is uncertain but should not replace clinical assessment
- ACEi and Beta-blockers remain the cornerstone of HF therapy and should be titrated to goal carefully
- ARBs are useful in ACEi intolerant patients
- Substitution w/ ARNI should be considered in pts tolerant of ACEi or ARB to reduce HF mortality and hospitalization
- Beta blockers should not be started in acutely decompensated patients

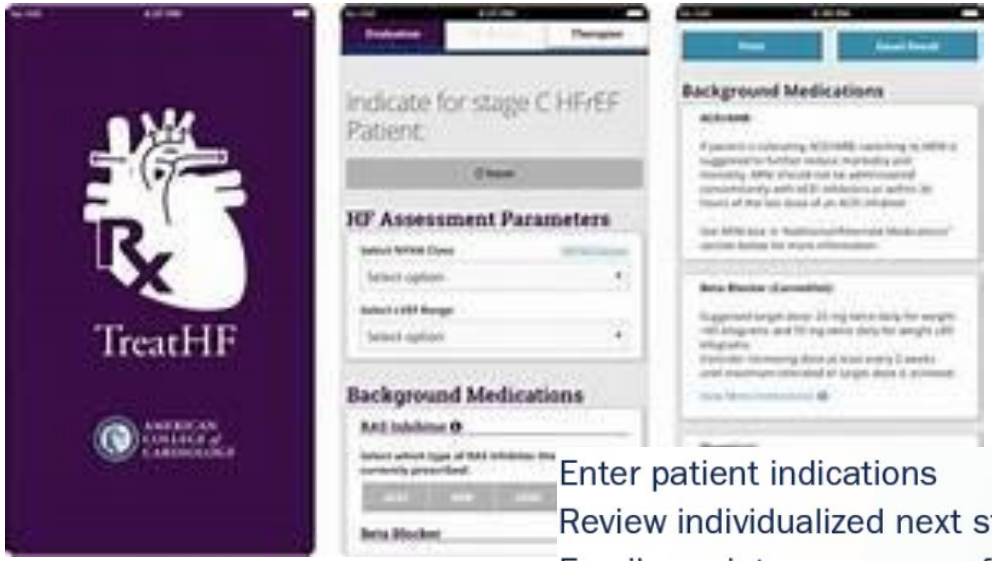
Congestive Heart Failure: Summary

- Aldosterone antagonists are increasingly the favored ‘second-line’ after ACEi/ARB and beta-blocker
- Hydralazine/Isordil is an alternative for the ACEi/ARB intolerant and may be added for those still symptomatic on ACEi/Beta-blocker/aldosterone antagonist
- Dig and ivabradine can be considered to reduce HF hospitalization
- Device Therapy (ICD +/- CRT) is appropriate for many HF patients with LVEF ≤ 35%
- Heart failure with preserved EF remains a poorly understood, heterogeneous disorder with limited therapeutic options

EVIDENCE BASED HFREF THERAPIES

Guideline Recommended Therapy	Relative Risk Reduction in Mortality	Number Needed to Treat for Mortality	NNT for Mortality (standardized to 36 months)	Relative Risk Reduction in HF Hospitalizations
ACEI/ARB	17%	22 over 42 months	26	31%
ARNI	16%	36 over 27 months	27	21%
Beta-blocker	34%	28 over 12 months	9	41%
Aldosterone Antagonist	30%	9 over 24 months	6	35%
Hydralazine/Nitrate	43%	25 over 10 months	7	33%
CRT	36%	12 over 24 months	8	52%
ICD	23%	14 over 60 months	23	NA
Ivabradine	NA	NA	NA	26%

HF APP



Enter patient indications

Review individualized next steps for medical therapy

Email or print a summary of the next steps

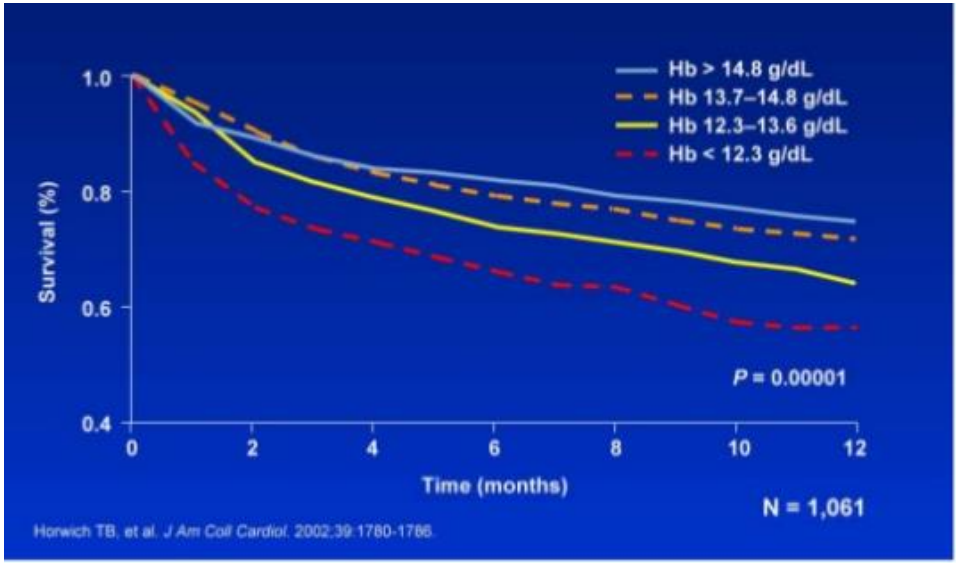
Reference detailed information on:

- Initiation, titration, and monitoring of each medication
- Guidance for optimizing your overall medication strategy

Mechanism of Anaemia in Heart Failure

- Concominant CKD (in 40-50% patients)—M.C.
- Inflammation and Cytokine activation (TNF-alpha, IL-6 and CRP)
- Aspirin usage (GI loss)
- ACE inhibitor and ARBs
- Decrease Fe absorption (Bowel edema, Inc Hepecidin)
- Hemodilution
- Nutritional

Mortality and Anaemia in Heart Failure



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THANK YOU

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