

SOUTHWEST CARDIOVASCULAR SUMMIT 2008

Clyde W. Yancy, MD - The State of Heart Failure

“7th Annual Southwest Cardiovascular Summit”

“The State of Heart Failure”

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So you think I am an expert...

- Always listen to experts. They'll tell what can't be done and why. Then do it.
- It takes two things to be an expert - grey hair and hemorrhoids. The grey hair makes you look distinguished and the hemorrhoids make you look concerned.
- The creed for experts: In case of doubt, make it sound convincing.
- An expert is one who knows more and more about less and less, until he knows absolutely everything about nothing.
- To spot the expert, pick the one who predicts the job will take the longest and cost the most.
- After all is said and done, a hell of a lot more is said than done.
- If you consult enough experts, you can confirm any opinion.

Clyde W. Yancy, MD
Disclosure Information

- **Financial relationships to disclose:**
- **Employee of:** Baylor University Medical Center
- **Consultant for:** Astra Zenea, CHF Solutions, GlaxoSmithKline, Medtronic, Inc., Nitromed, Novartis, Scios
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- **Honoraria from:** Medtronic, Inc. Scios, GlaxoSmithKline

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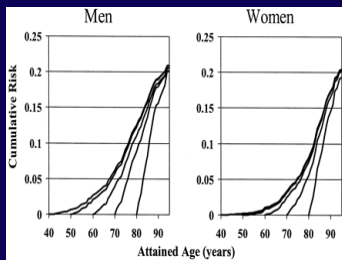
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Advances in the Treatment of Heart Failure

- Increased attention to prevention
- ACEI/ β -blocker combination established as the "cornerstone" of therapy
- Emergence of alternative approaches to blocking the RAS
- Recognition that "special populations" of HF patients may benefit from or require different approaches
- Integration of device therapy into the therapeutic regimen
- New strategies to improve utilization of existing therapies

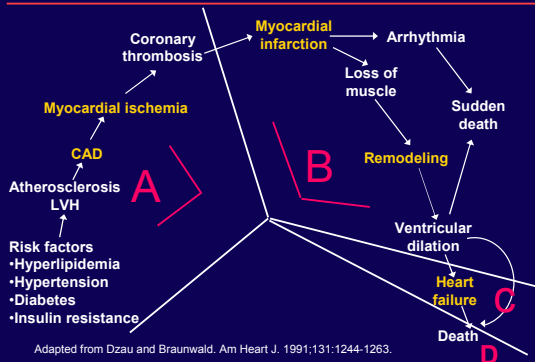
ACEI=angiotensin-converting enzyme inhibitor; RAS=renin-angiotensin system.

Comparison of short-term vs lifetime cumulative risks of CHF for men and women at selected index ages



ONE IN FIVE INDIVIDUALS WILL DEVELOP HF

From Risk Factors to Heart Failure: The Cardiovascular Continuum



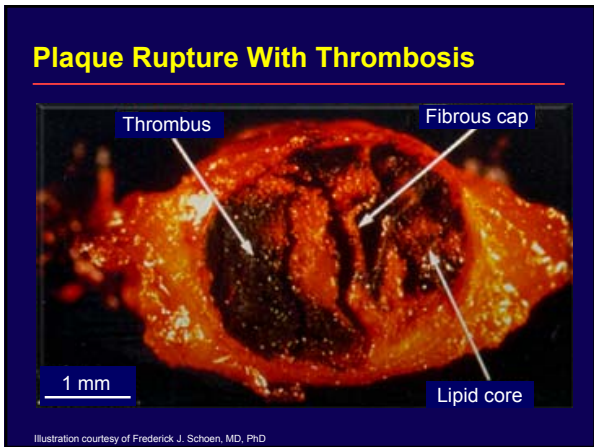
Adapted from Dzau and Braunwald. Am Heart J. 1991;131:1244-1263.

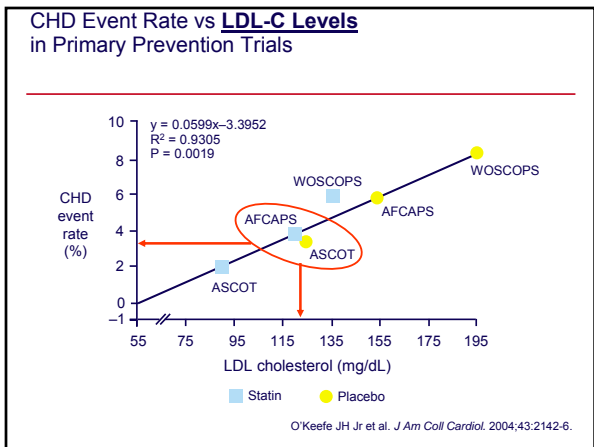
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Benefits of Lowering BP

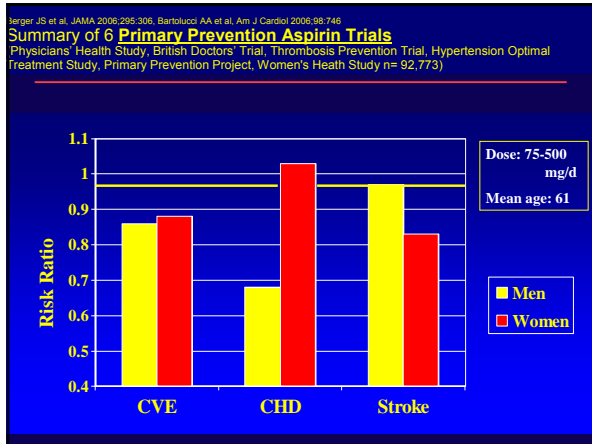
	Average Percent Reduction
Stroke incidence	35–40%
Myocardial infarction	20–25%
Heart failure	50%



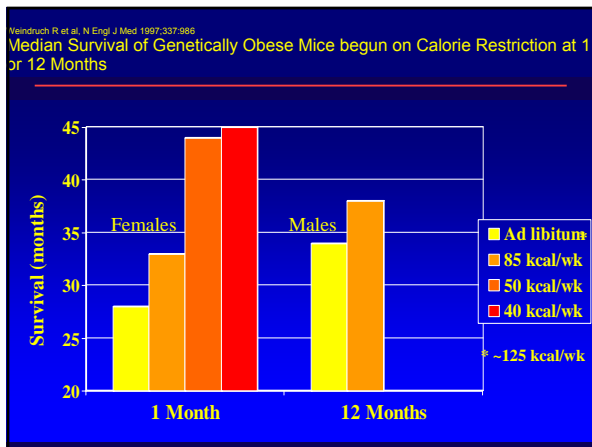


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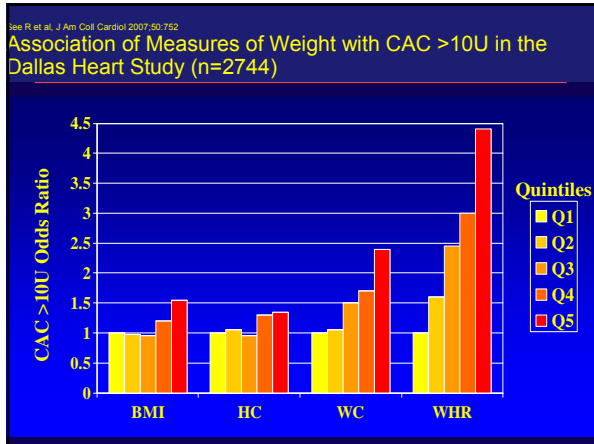


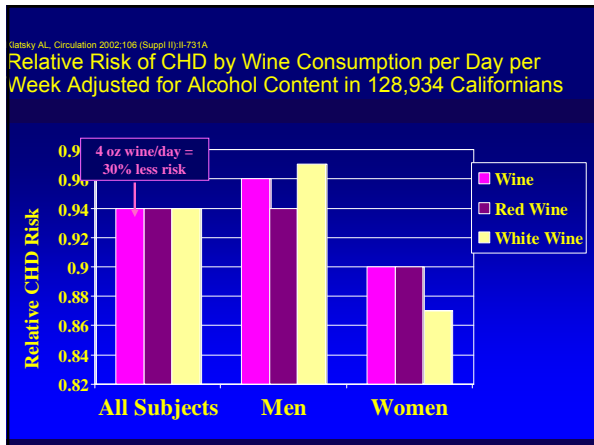


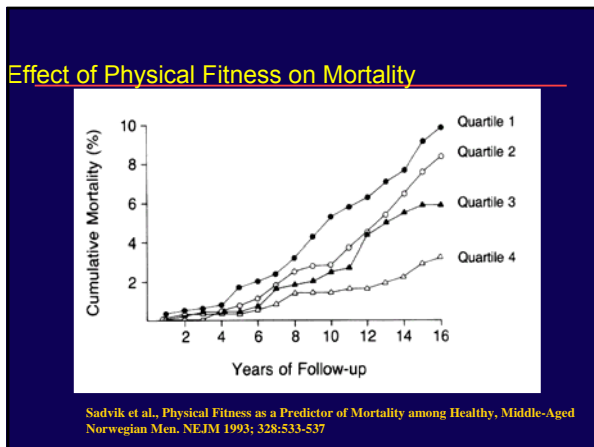


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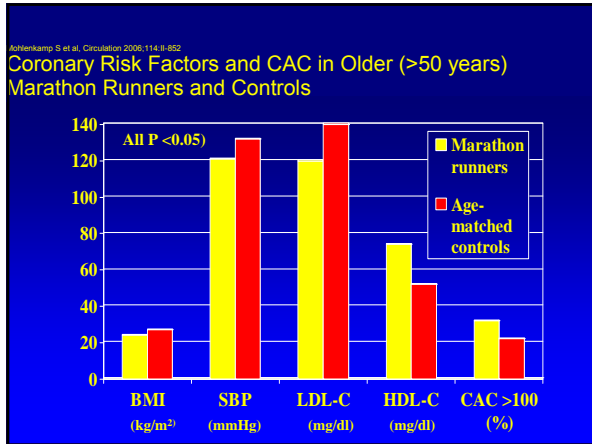






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The pyramid of heart failure and potential impact of a range of preventive and treatment strategies in lowering age-specific mortality

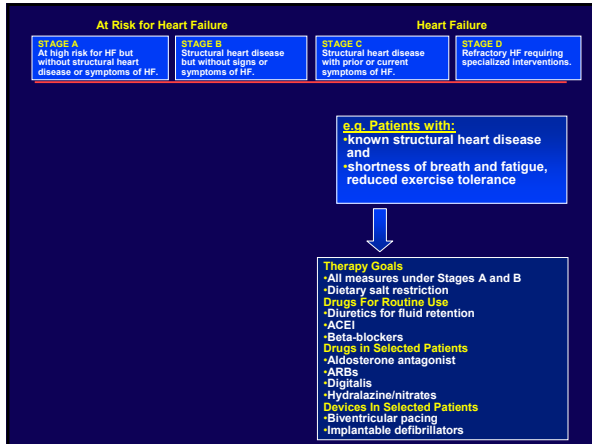
Percent (40+) affected	Type of Intervention	Impact
Class IV HF + low ejection fraction	Transplantation; left ventricular assist device, implantable cardiac defibrillator	Tiny
Any congestive HF	ACE inhibitors, B-blockers, spironolactone	Modest
High-risk individuals (eg, those with hypertension or who have had a myocardial infarction)	Antihypertensive therapy; drugs to lower cholesterol, ACE inhibitors, smoking cessation	Moderate
Obese or overweight individual (eg, body mass index >25), plus those in above category	Weight loss, plus above measures	Large

Yusuf et al. NEJM 2000;342:145-53

- ### Prevention of Heart Failure
- #### THERAPY
- Treat hypertension JNC 7 guidelines
 - Encourage smoking cessation
 - Prevents MI
 - Treat lipid disorders NCEP guidelines
 - Especially in metabolic syndrome, DM
 - Encourage regular exercise
 - Weight reduction, Prevents DM
 - Discourage alcohol intake
 - ?
 - illicit drug use
 - Amphetamines/cocaine
 - Control metabolic syndrome
 - Diet, Exercise
 - ? Metformin, TZD
 - Treat Diabetes (glycemic control) ADA guidelines
 - Drugs
 - ACEI or ARB in appropriate patients for vascular disease or diabetes or anthracycline chemotherapy

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ACE Inhibitor Recommendations

I IIa IIb III
A

- Recommended for all patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated
- Indicated in all patients with a recent or remote history of MI regardless of LVEF or presence of HF
- Should be used in patients with a reduced LVEF and no symptoms of HF, even if they have not experienced an MI

Underlining represents changes from 2001 guidelines.
 Hunt SA, et al. ACC/AHA 2005 Practice Guidelines. Available at: <http://www.acc.org>.

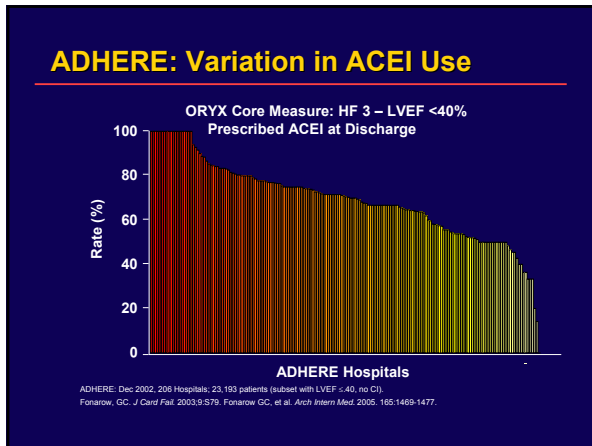
Effect of ACE Inhibitors on Mortality Reduction in Patients With Heart Failure

Trial	Mortality		RR (95% CI)
	ACEI	Controls	
Chronic CHF			
CONSENSUS I	39%	54%	0.56 (0.34–0.91)
SOLVD (Treatment)	35%	40%	0.82 (0.70–0.97)
SOLVD (Prevention)	15%	16%	0.92 (0.79–1.08)
Post-MI			
SAVE	20%	25%	0.81 (0.68–0.97)
AIRE	17%	23%	0.73 (0.60–0.89)
TRACE	35%	42%	0.78 (0.67–0.91)
Average	23%	27%	

Data shown from individual trials—not direct comparison data.
 Garg R et al. JAMA. 1995;273:1450–1456; Pfeffer MA et al. N Engl J Med. 1992;327:669–677. The AIRE Study Investigators. Lancet. 1993;342:821–828; Keber L et al. N Engl J Med. 1995;333:1670–1676. The SOLVD Investigators. N Engl J Med. 1992;327:695–691.

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ARB Recommendations

I IIa IIb III	• ARBs approved for the treatment of HF are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACEI-intolerant
B	
I IIa IIb III	• An ARB should be administered to post-MI patients without HF who are ACEI-intolerant and have a low LVEF
B	
I IIa IIb III	• Are reasonable to use as alternatives to ACEIs as first-line therapy for patients with mild to moderate HF and reduced LVEF, especially for patients already taking ARBs for other indications
A	
I IIa IIb III	• Can be beneficial in patients with low LVEF and no symptoms of HF who are ACEI-intolerant
C	
I IIa IIb III	• Addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy
B	

Underlining represents changes from 2001 guidelines.
Hunt SA, et al. ACC/AHA 2005 Practice Guidelines. Available at: <http://www.acc.org>.

Relative risk (RR) of adverse effects associated with combined ACE-inhibitor/ARB therapy, by clinical setting

End point	Chronic HF, RR (95% CI)	Post-MI with symptomatic LV dysfunction, RR (95% CI)
Discontinuing medications because of adverse effects	1.38 (1.22–1.55)	1.17 (1.03–1.34)
Symptomatic hypotension	1.50 (1.09–2.07)	1.48 (1.33–3.18)
Worsening renal function	2.17 (1.59–2.97)	1.61 (1.31–1.98)
Hyperkalemia	4.87 (2.39–9.94)	1.33 (0.90–1.98)

Phillips CO et al. Arch Intern Med 2007; 167:1930-1936.

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Aldosterone Antagonist Recommendations



- Reasonable in selected patients with moderately severe to severe symptoms of HF and reduced LVEF who can be carefully monitored for preserved renal function and normal potassium concentration.* Under circumstances where monitoring for hyperkalemia and renal dysfunction is not anticipated to be feasible, the risks may outweigh the benefits

*Creatinine ≤ 2.5 mg/dL in men or ≤ 2.0 mg/dL in women and $K^+ < 5.0$ mEq/L. Underlining represents changes from 2001 guidelines.

Hunt SA, et al. ACC/AHA 2005 Practice Guidelines. Available at: <http://www.acc.org>.

Case presentation

- 59 yr old man presents with dyspnea and decreased energy; known to have HF and is on ACE-I and BB therapy; an ICD is in place. He has had several admissions to the hospital for ADHF. PAST HX: HTN X 20 years, stage II; normal coronary arteries by cath 3 yrs prior; morbid obesity; LVEF known to be 0.27; SOC HX- African American; What approach is next most appropriate?
- 1. repeat cath
- 2. Add ARB
- 3. Add Aldo antagonist
- 4. Add Isosorbide dinitrate/Hydralazine

HF in African Americans: Overview

- Affects 3% of the AA population¹
- Atypical natural history²
- Unique epidemiology³⁻⁵
 - Lower incidence of associated epicardial coronary artery disease
 - More likely to be associated with a history of HTN
- Worrisome prognosis^{3,6}
 - Higher rate of hospitalization
 - ? Increased mortality rate: 1.8x for AA men; 2.4x for AA women
- Question of altered responses to medical therapy²

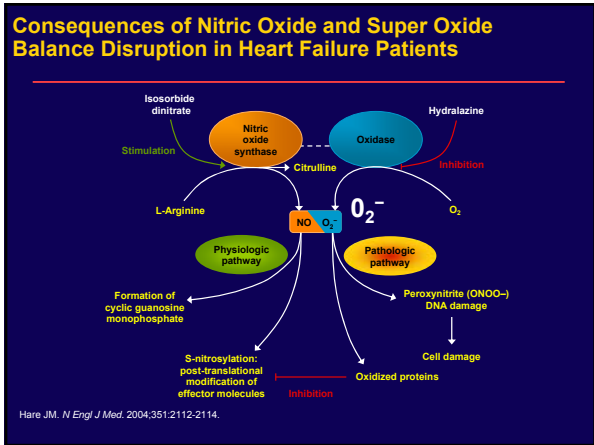
¹Statistical Fact Sheet—Populations. American Heart Association; 2004. ²Yancy CW. *J Card Fail*. 2000;6:183-188. ³Dries DL, et al. *N Engl J Med*. 1999;340:609-616. ⁴Atzal A, et al. *Clin Cardiol*. 1999;22:791-794. ⁵Mathew J, et al. *Am J Cardiol*. 1996;78:1447-1450. ⁶Gillum RF. *N Engl J Med*. 1996;335:1597-1599.

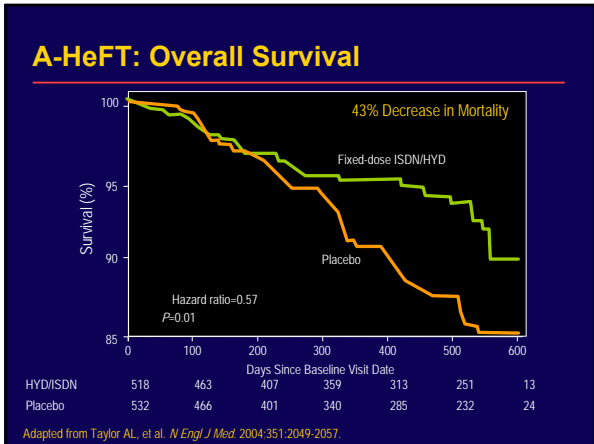
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Heart Failure in African Americans

What are the new pathophysiologic considerations associated with excessive CVD in African Americans?





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The NO Paradigm in HF

A System Out of Balance in AAs?

Vasodilating and growth inhibiting

- Natriuretic peptides
- Bradykinin
- NO

Vasoconstricting and growth promoting

- Norepinephrine
- Angiotensin II
- Endothelins
- Arginine vasopressin
- Aldosterone

Worsen hemodynamics, progressive remodeling

Improve hemodynamics, prevent remodeling

Yancy CW. Heart Failure in African Americans: The State of the Art. Presented at: 8th Annual Scientific Meeting of the Heart Failure Society of America. September 12, 2004; Toronto, Canada.

Combination Hydralazine-Nitrate Recommendations

I IIa IIb III

- Addition is reasonable in patients with reduced LVEF who are already taking an ACEI and β -blocker for symptomatic HF and who have persistent symptoms
- Addition to a standard medical regimen for HF, including ACEIs and β -blockers, is reasonable and can be effective in blacks with NYHA functional class III or IV HF. Others may benefit similarly, but this has not yet been tested

I IIa IIb III

- Might be reasonable in patients with current or prior symptoms of HF and reduced LVEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency

Underlining represents changes from 2001 guidelines.
Hunt SA, et al. ACC/AHA 2005 Practice Guidelines. Available at <http://www.acc.org>.

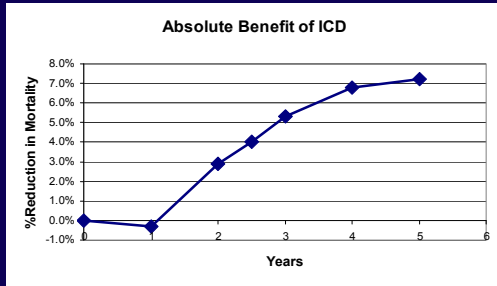
Device Therapy for Heart Failure

- Cardiac resynchronization therapy (CRT)
- Implantable cardioverter-defibrillators (ICD)

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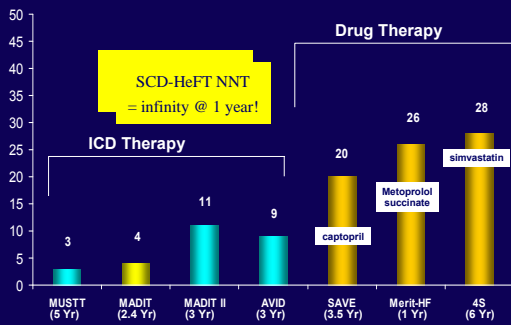
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Mortality Benefit of a Prophylactic ICD over Time in SCD-HeFT



Number Needed to Treat To Save A Life

$NNT_{x \text{ years}} = 100 / (\% \text{ Mortality in Control Group} - \% \text{ Mortality in Treatment Group})$



Calculating the benefit of ICD therapy

$NNT_{x \text{ years}} = 100 / (\% \text{ Mortality in Control Group} - \% \text{ Mortality in Treatment Group})$

If the mortality in the control group is 21% and the mortality in the treatment group is 17% at 5 years; the $NNT = 100/23-17 \sim 15$

If the mortality in the control group is 12% and the mortality in the treatment group is 12% at 1 year, the $NNT = 100/12-12 \sim 100/0 = \text{infinity}$

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CRT Recommendations

I IIa IIb III

A

Recommended in patients with LVEF less than or equal to 35%, sinus rhythm, NYHA functional class III or ambulatory class IV symptoms despite recommended, optimal medical therapy and who have cardiac dyssynchrony (QRS duration greater than 0.12 ms) unless contraindicated

Hunt SA, et al. ACC/AHA 2005 Practice Guidelines. Available at <http://www.acc.org>.

CARE-HF: CRT Long-Term Outcomes

Primary Endpoint
All-Cause Mortality or Hospitalization for Major Cardiovascular Event
P < .001

Secondary Endpoint
All-Cause Mortality
P < .002

Endpoint	CRT (%)	Control (%)
Primary Endpoint (All-Cause Mortality or Hospitalization for Major Cardiovascular Event)	39%	55%
Secondary Endpoint (All-Cause Mortality)	20%	30%

- Median LV ejection fraction was 25%
- Of the 409 patients randomized to the CRT device, 95% had a successful implantation
- The primary endpoint of all-cause mortality or hospitalization for a major CV event occurred less frequently in the CRT group than in the medical therapy alone group (HR 0.63, 95% CI 0.51-0.77)
- The major secondary endpoint of all-cause mortality was also lower in the CRT group (HR 0.64, 95% CI 0.48-0.85)

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

Pathophysiology of ADHF: A Hemodynamic Model?

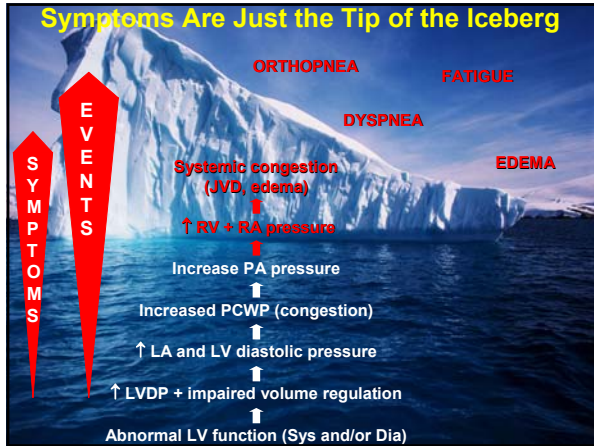
Most cases are associated with:

- ↑ SVR plus; ? ↑ PVR
- ↓ Systolic and diastolic functional reserve
- Increased wall stress
- Atrial hypertension

SVR, systemic vascular resistance. Adapted from: Mehra MR. *Am Heart J*. 2006.

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Most Heart Failure Hospitalizations are due to Worsening Chronic Heart Failure

- **~70%** Worsening chronic HF
 - Associated with reduced or preserved left ventricular systolic function (LVEF)
- **~25%** de novo HF
 - After a large MI; sudden increase in blood pressure superimposed on a noncompliant LV
- **~5%** Advanced HF
 - Refractory to therapy; with severe LV systolic dysfunction, associated with a worsening low-output state

Gheorghiade M. *Circulation*. 2005;112:3958-3968.

Acute Decompensated Heart Failure: Patient Characteristics

Characteristic	ADHERE ¹ (N = 105,388)	OPTIMIZE-HF ² (N = 48,612)
Mean age (yrs)	72.4	73
> 75 years (%)	50	ND
Male (%)	48	48
Caucasian (%)	72	ND
Prior HF history (%)	75	87

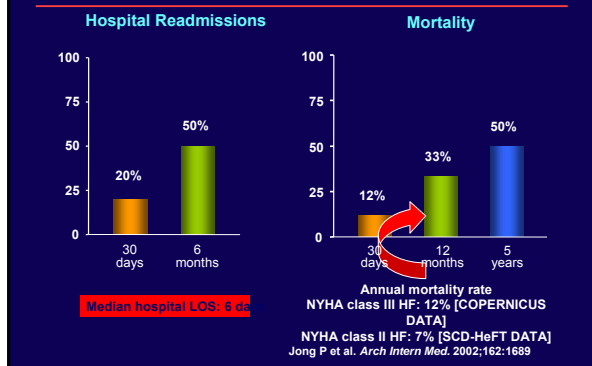
ADHERE=Acute Decompensated HEart failure national REgistry
OPTIMIZE-HF=Organized Program To Initiate life-saving treatment In HospitalIZed patients with Heart Failure

1. Adams KF, et al. *Am Heart J*. 2005;149:209-216; 2. Gheorghiade M. *Circulation*. 2005;112:3958-3968.

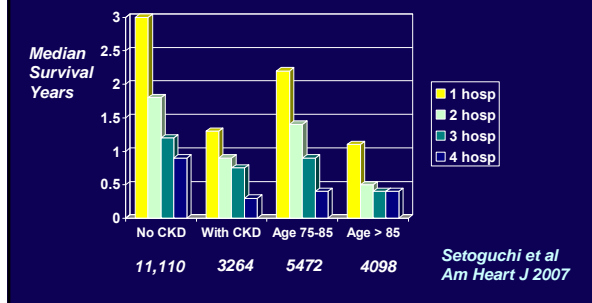
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Outcomes in Patients Hospitalized with HF



Survival After HF Hospitalizations

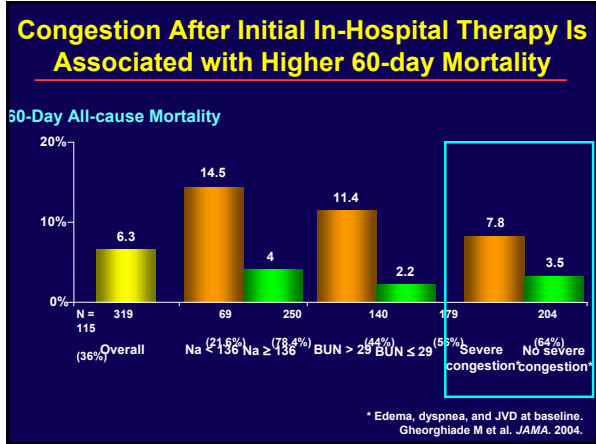


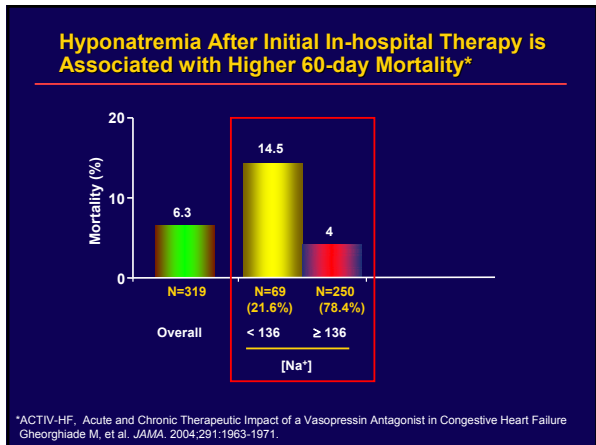
Major Predictors of Increased Mortality in Patients with ADHF

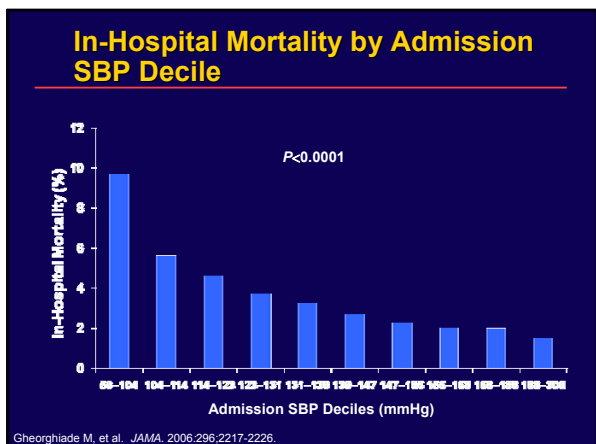
- Congestion
- Hyponatremia
- Blood pressure
- Renal insufficiency

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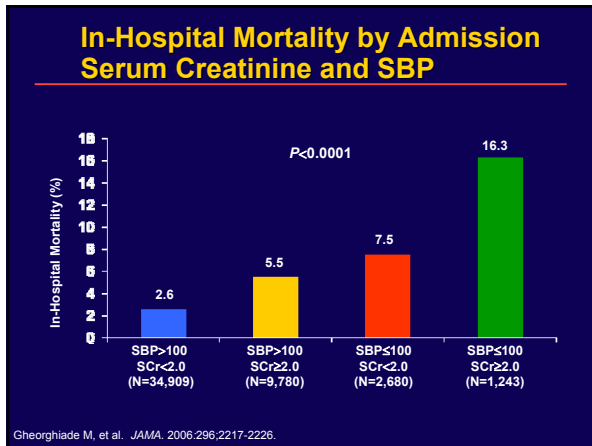


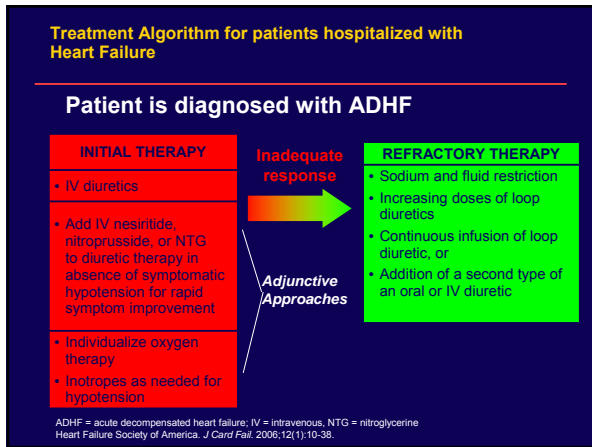




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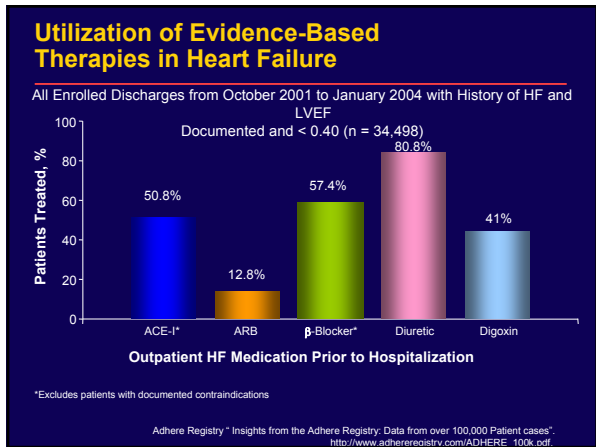


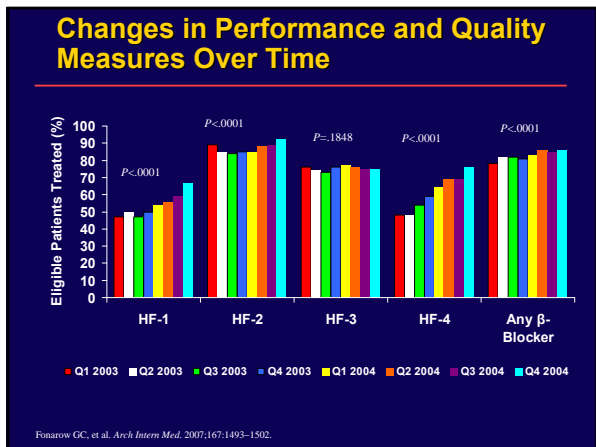
- ### The Conundrum of ADHF?
- Is congestion or injury the culprit?
 - Do we need another drug or a device?
 - Is a device strategy preferable?
 - Should we focus on the kidney?
 - Is mortality a suitable target?
 - What can be done now?
 - IMPROVE THE QUALITY OF CARE FOR HF

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Addressing Quality of Care; A new target in HF therapy





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