Heart Failure Update 2011

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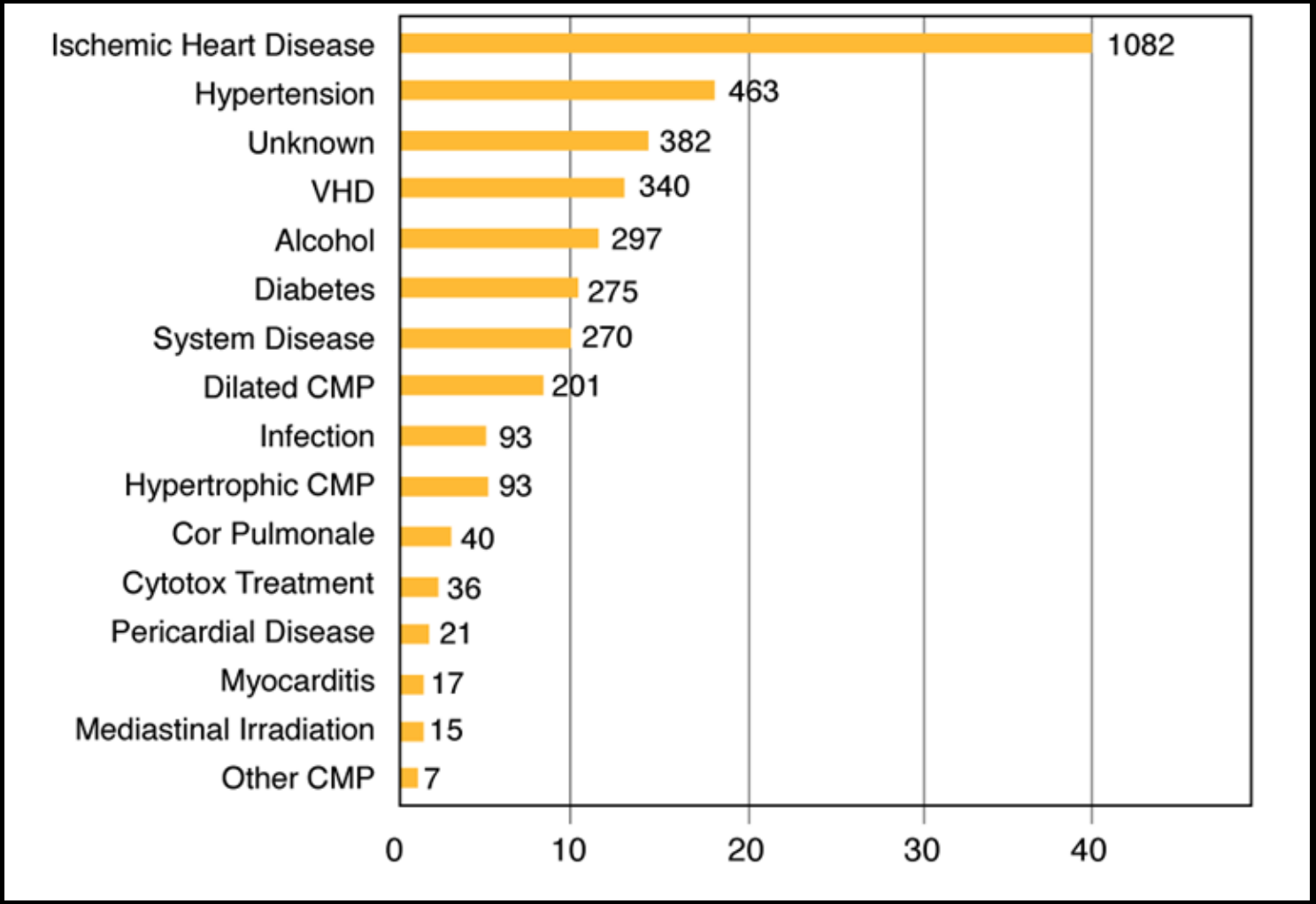
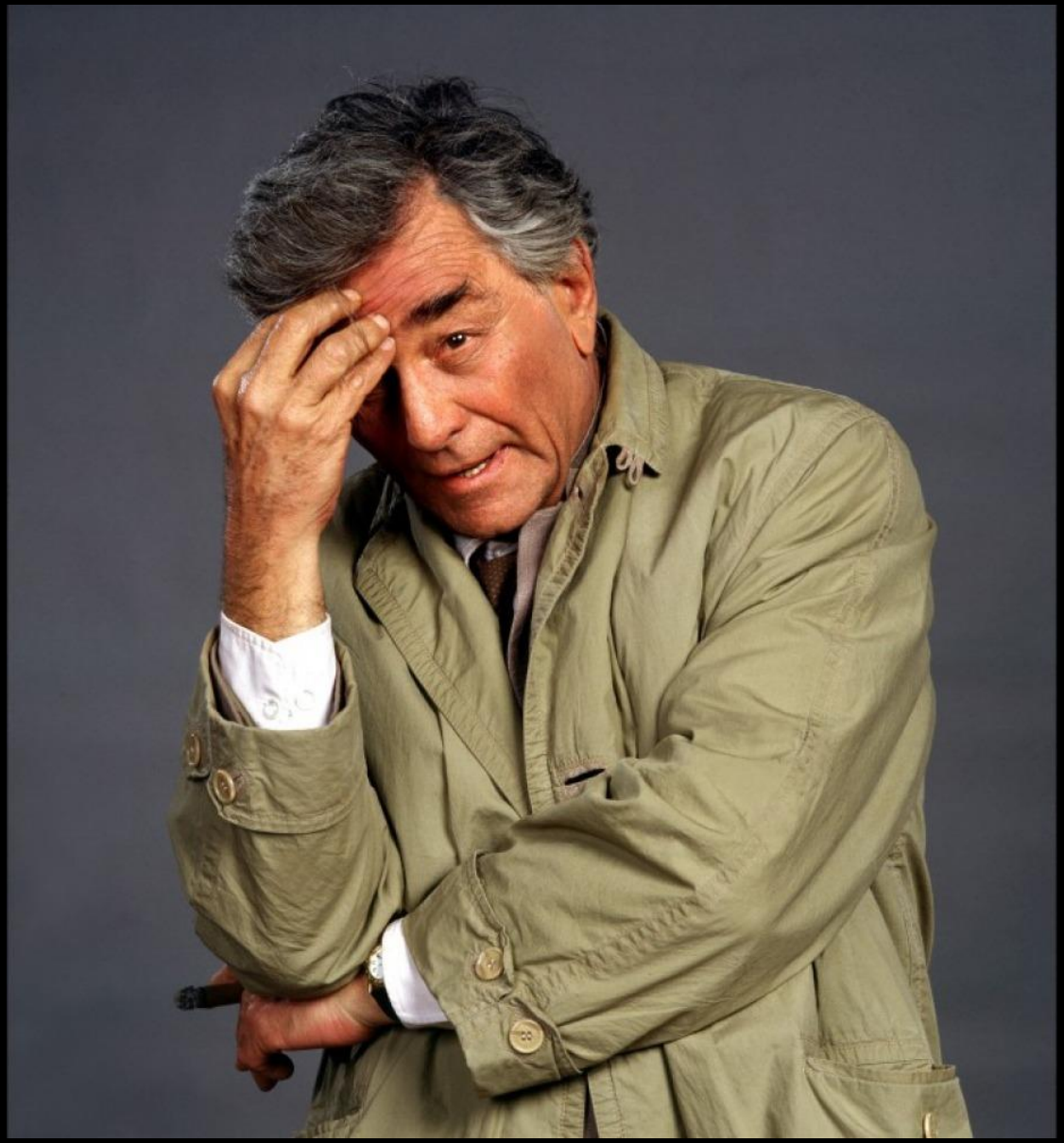
Causes of Heart Failure



Anderson,B .Am Heart J 1993;126:632-40

It is now well-established that at least one-half of the patients presenting with symptoms and signs of heart failure will have a normal left ventricular ejection fraction.

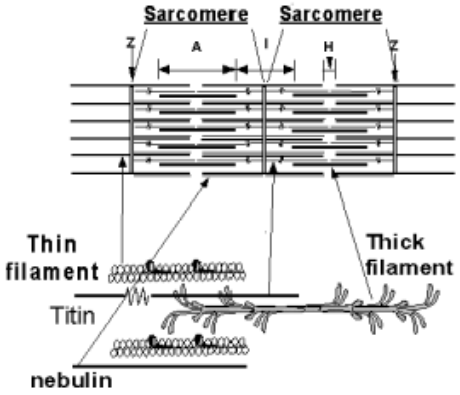
JACC 54:36–46, 2009



Heart Failure With Preserved Ejection Fraction (HFpEF = heff-peff).

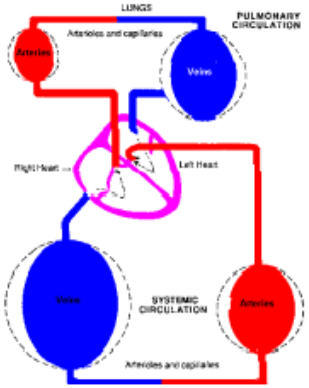
Risk Markers	Old age - Female gender - Hypertension - Obesity - Diabetes mellitus - Left ventricular hypertrophy

Dimension 1: Molecular Factors



1. Changes in the sarcomere appear to play a fundamental role in development of HFpEF.
2. Titin (like the race of elder gods), is a huge protein that acts as a molecular spring. It is compressed during sarcomeric contraction and is supposed to recoil during relaxation. Titin is a major determinant of LV stiffness. Different isoforms of Titin have different mechanical properties, and the population of Titin isoforms may play a key role in determining LV relaxation properties.
3. Collagen crosslinking characteristics may be key factors in determining LV relaxation properties. Crosslinks involving glucose ("glycation") are especially hard to digest.
4. Crosslinks may eventually emerge as a therapeutic target.
5. Therapy targeting reactive oxygen species by recoupling nitric oxide synthase has shown promise in animal studies.

Dimension 2: Hemodynamic Factors



1. Increased vascular stiffness in the elderly results in decreased ability of the heart to eject blood into the vessels without generating very high pressures.
2. The left ventricle in turn adapts, and develops increased systolic stiffness. (Molecular basis: See left hand panel.)
3. Increased LV systolic stiffness produces delayed diastolic relaxation with resultant elevated LV filling pressures.
4. Elevated LV filling pressures can produce increased left atrial size and diminished left atrial function. This may be the straw that breaks the camel's back,producing atrial fibrillation.
5. Virtually all pts. with flash pulmonary edema have high BP.
6. Flash pulmonary edema is probably the result of systemic venous constriction (85% of volume is ordinarily in the veins), with rapid redistribution into the compartment that functions as the lowest-pressure storage bin, the lungs.

Heart Failure with Preserved Ejection Fraction (HFpEF)

- Recent studies have identified abnormalities in torsional mechanics, demonstrating that diastolic heart failure is accompanied by abnormalities in systolic function.

- Stroke volume and cardiac output are often reduced despite a normal ejection fraction.

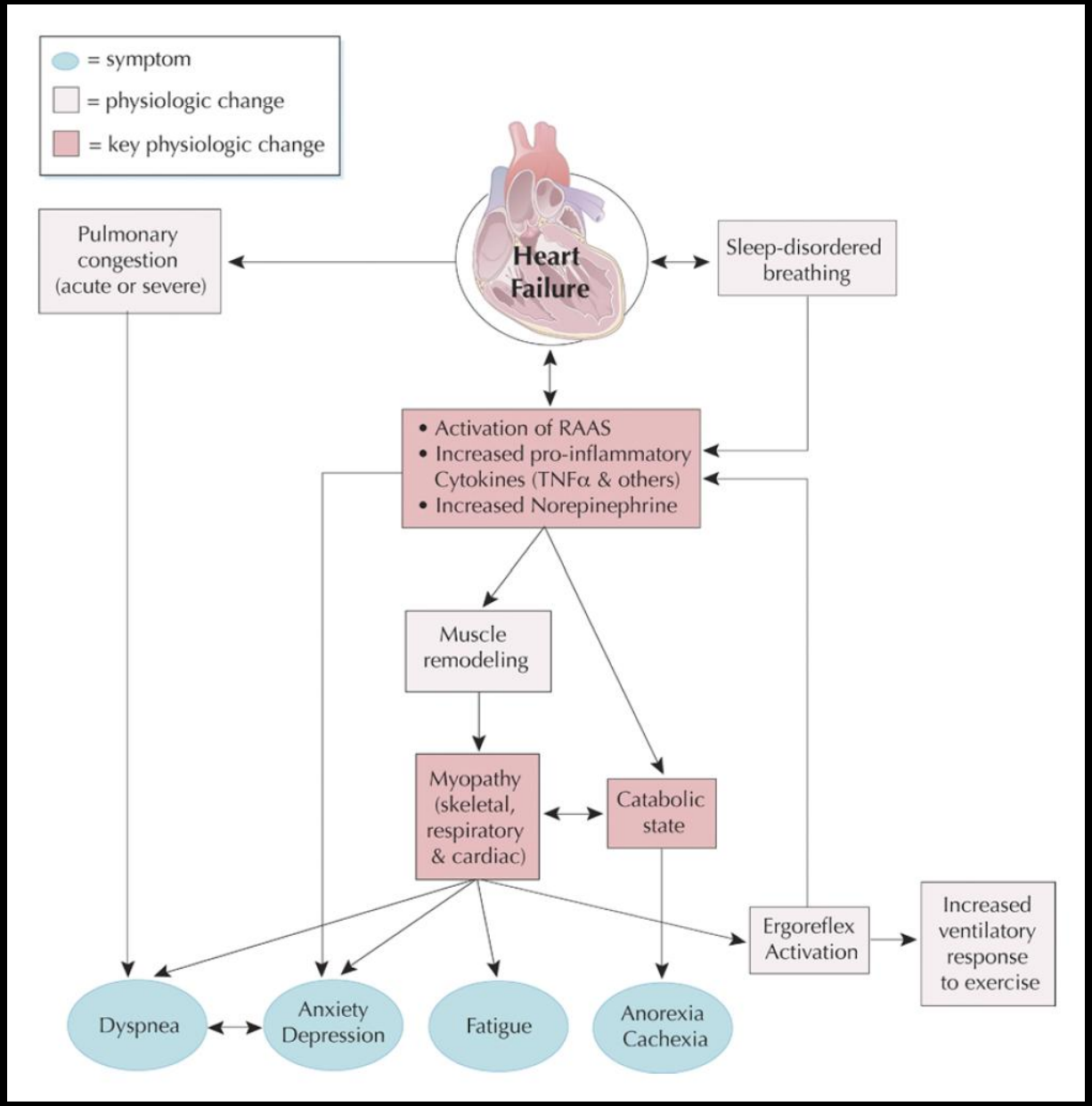
- Exercise is poorly tolerated. The heart with diastolic dysfunction cannot relax to accommodate the increased blood flow required to maintain a higher cardiac output, and perfusion is maintained via elevations in left atrial pressures, resulting in symptoms of dyspnea.

- Atrial fibrillation is particularly problematic, and the combined effects of the loss of atrial kick and the rapid heart rates further impair diastolic filling.

- Emerging data suggest that lowering blood pressure alleviates symptoms more effectively than therapy with specific agents

- 4 areas for treatment: blood pressure control, rate/rhythm control in underlying AF, control of pulmonary congestion with diuretic agents, and revascularization and correction of underlying ischemia when indicated.

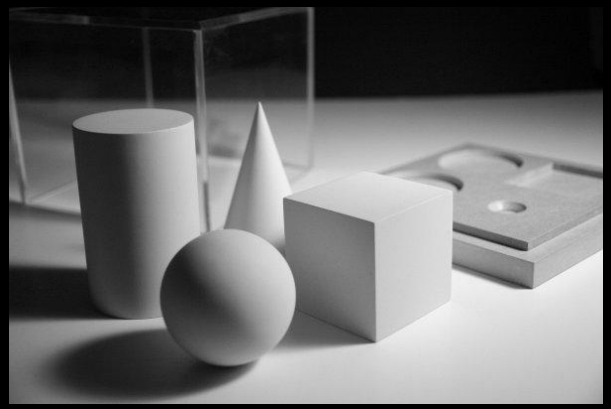
Systolic CHF: Physiology Begets Symptoms



JACC 54:386-396, 2009

CLINICAL PEARLS IN SUCCESSFUL HEART FAILURE THERAPY

Behavioral and Lifestyle Modifications Are Essential to Ensuring Success of Heart Failure Pharmacotherapy



Before initiation of pharmacotherapy patients must be counseled regarding

- The importance of dietary discretion
- Nutritional consultation should be provided
- Strict adherence should be emphasized
- The importance of daily weight measurements
- Patients should be provided with instructions regarding diuretic dosing adjustments for sudden changes in weight

Angiotensin-Converting Enzyme Inhibitors and β-Blockers Form the Cornerstone of CHF Pharmacotherapy

Summary Judgment

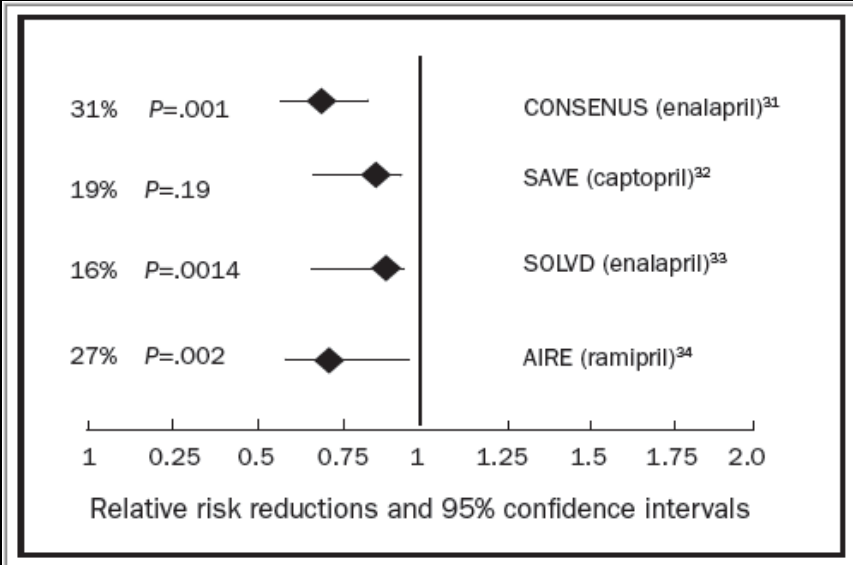


FIGURE 2. Angiotensin-converting enzyme inhibitor mortality trials: all-cause mortality results. AIRE = Acute Infarction Ramipril Efficacy; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; SAVE = Survival and Ventricular Enlargement; SOLVD = Studies of Left Ventricular Dysfunction.

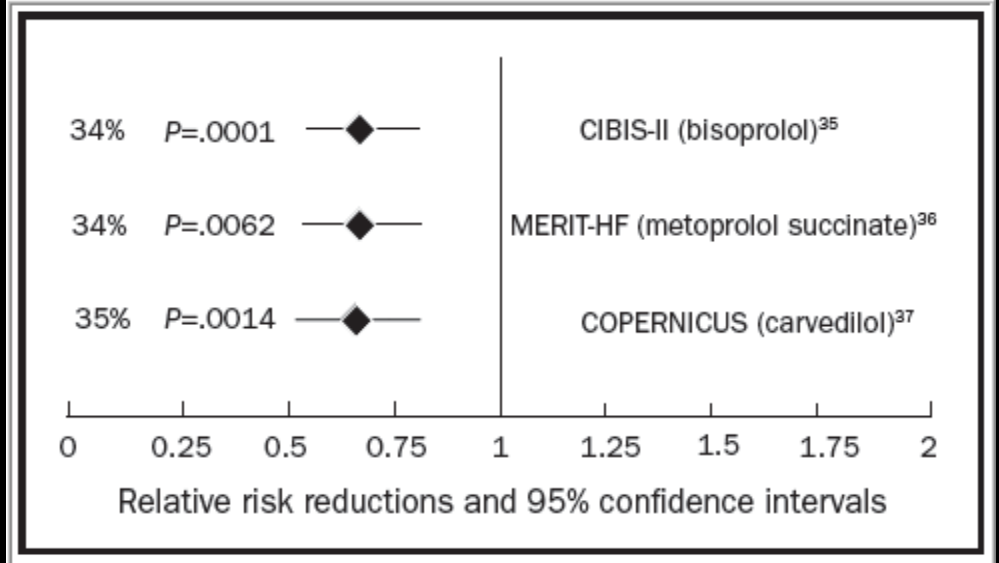
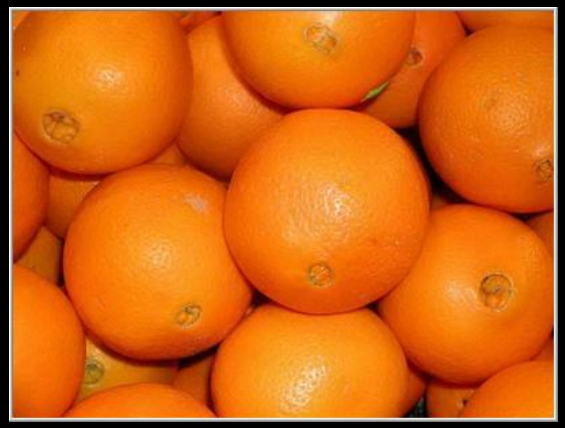


FIGURE 3. β-Blocker mortality trials: all-cause mortality results. CIBIS II = Cardiac Insufficiency Bisoprolol Study II; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; MERIT-HF = Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure.

Whereas the Benefits of ACEI's Appear to Be Class Specific, β-Blocker Use Should Be Relegated to Clinical Trials



vs.

- ACEI's: There appears to be no significant difference in outcomes between agents
- Beneficial effects of β-blockers are thought to be limited to specific drugs
- β-Blockers with intrinsic sympathomimetic activity (xamoterol) and other agents, including bucindolol, have not demonstrated a survival benefit
- It is recommended that β-blocker use be restricted to carvedilol, bisoprolol, and metoprolol succinate, agents proven to improve survival in clinical trials
- Of these, carvedilol is usually treatment of first choice, due to its vasodilator properties, low cost and trial performance

In Patients With Newly Diagnosed CHF It Is Safe to Use Either a β-Blocker or an ACEI as First-Line Therapy

Which of these agents was used as initial therapy and which was added subsequently did not affect outcomes in CIBIS (Cardiac Insufficiency Bisoprolol Study) III.

Attempts Should Be Made to Attain Doses of Drugs Studied in Clinical Trials, and Rapid Outpatient Titration of Drugs Is Feasible

- Clinical trial data support a dose-dependent improvement in LV function and reductions in mortality and hospitalizations with β-blocker use.

- Although a variable dosing trial demonstrated no additional survival benefits with higher doses of ACEI, higher doses were associated with reduced hospitalizations.

- Clinical experience suggests that, in the absence of symptoms to suggest hypotension (eg, fatigue and dizziness), pharmacotherapy may be up-titrated every 2 to 3 weeks in otherwise hemodynamically stable and euvolemic outpatients.

- Factors associated with impaired carvedilol tolerance in CHF are age, low diastolic blood pressure, raised plasma urea concentration, and NYHA class . No single baseline variable is an independent marker of inability to tolerate carvedilol.

- Carvedilol tolerance was unrelated to the presence or absence of traditional precautions or relative contraindications to beta blockade, being 85% in chronic obstructive airways disease/asthma, 86% in diabetes, 84% in peripheral vascular disease, 83% in patients receiving concomitant amiodarone treatment, and 84% in those with heart rate <70 bpm.

European Heart Journal Supplements (2006) 8 (Supplement C), C19–C27

Aldosterone Antagonism Is Beneficial in Patients With Advanced (New York Heart Association III and IV) Heart Failure

TABLE 1. **Risk Factors for Hyperkalemia With Use of Inhibitors of the Renin-Angiotensin-Aldosterone System***

Chronic renal insufficiency
Increased risk with GFR <60 mL/min
Very increased risk with GFR <30 mL/min
Diabetes mellitus
Volume depletion (eg, diarrhea, overdiuresis)
Advanced age
Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors
Other potassium-sparing diuretics (triamterene, amiloride)
Trimethoprim
β-Adrenergic blockers
Increased potassium intake (salt substitutes, oral potassium supplements, high potassium diet)

*GFR = glomerular filtration rate.

Aldosterone Blockers: Complicated But Worth It

TABLE 3. **Suggested Algorithm for Initiation and Monitoring of Aldosterone Receptor Antagonists***

Step 1: Risk stratification (initial evaluation)
- Ensure patient is already following a standard heart failure regimen, including ACE inhibitors, angiotensin receptor blockers, and/or β-adrenergic blockers, with clinical history comparable to inclusion criteria for RALES or EPHESUS
- Pay extra attention to high-risk features for hyperkalemia
  - Diabetes mellitus
  - Advanced age
  - Drugs or potassium supplementation

Step 2: Correct hypovolemia and hyperkalemia
- Careful determination of volume status
  - If hypovolemic, reduce diuretic dose before initiating aldosterone receptor antagonist
- Check serum potassium level
  - If potassium level is >5.0 mEq/L and GFR is <60 mL/min per 1.73m^2 in diabetic patients or <50 mL/min per 1.73m^2 in nondiabetic patients, start low potassium diet (2-3 g/d)
  - Postpone drug initiation until potassium level is <5.0 mEq/L on weekly repeat check

Step 3: Initiation of therapy
- Initial dose if estimate GFR by the modified MDRD formula[69] is higher than 30 mL/min per 1.73m^2 (http://nephron.com/cgi-bin/MDRDSI.cgi)

$$\text{GFR (mL/min per 1.73 m}^2) = 186 \times (\text{plasma creatinine [mg/dL]})^{-1.154} \times (\text{age [years]})^{-0.203} \times (0.742\ [\text{if female}]) \times (1.210\ [\text{if African American}])$$

- Initial dose: spironolactone 25 mg/d or eplerenone 25 mg/d†

†25 mg of spironolactone is roughly equivalent to 50 mg of eplerenone; in patients with marginal creatinine clearance, considerations can be made to reduce the initial dose based on clinical judgment

Step 4: Clinical monitoring
- Check serum potassium and creatinine measurements at 1 week and 3-4 weeks, then every 3-6 months thereafter; recheck 1 week after any change in dose
- If hyperkalemia (potassium level, 5.5-5.9 mEq/L), worsening renal insufficiency, or hypotension occurs
  - Decrease dose by 50% (if 12.5 mg, can give every other day) or withhold temporarily
  - Identify precipitating cause (hypovolemia, drugs)
  - Repeat blood test in 3-4 days
  - If potassium level is ≥6.0 mEq/L, review electrocardiogram, withhold all RAAS drugs, standard management of hyperkalemia, and repeat blood test the next day; thiazide or loop diuretics may reduce potassium level

*ACE = angiotensin-converting enzyme; EPHESUS = Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; GFR = glomerular filtration rate; MDRD = Modification in Diet of Renal Disease; RAAS = renin-angiotensin-aldosterone system; RALES = Randomized Aldactone Evaluation Study.

Mayo Clin Proc 2005;80(12):1623-1630

Angiotensin II Receptor Blockers Should Be Used in Patients Intolerant of ACEI's, But Triple Neurohormonal Blockade (ACEI's, β-Blockers, and Angiotensin II Receptor Blockers) Should Be Avoided

A ceiling effect appears to exist beyond which additional neurohormonal blockade may no longer be beneficial and may even trend toward harm. Thus, the clinical dictum should be:

Use a 2-drug combination first (ACEI and β-blocker).

If β-blocker intolerant: ACEI and ARB.

If ACEI intolerant: ARB and β-blocker.

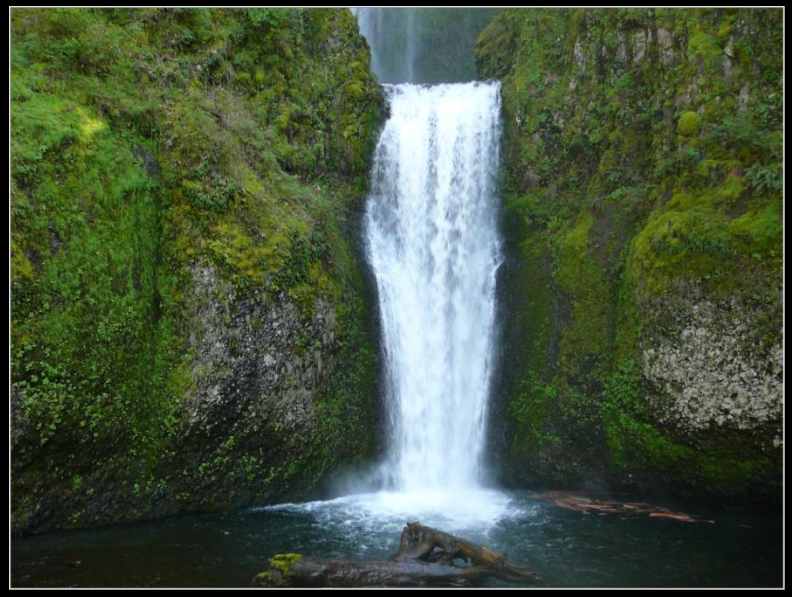
The Combination of Hydralazine and Nitrates Should Be Limited to Special Populations: Those Patients Who Remain Hypertensive With Neurohormonal Blockade and Those With Renal Insufficiency Prohibiting Use of ACEIs or ARBs

In Patients With Residual Symptoms Despite Optimization of Volume Status and Pharmacotherapy, Addition of Digoxin Should Be Considered

- Digitalis glycosides exert a mild inotropic effect, but more importantly, attenuate carotid sinus baroreceptors and have sympathoinhibitory effects that result in a decrease in serum norepinephrine levels, plasma renin levels, and possibly aldosterone levels

- Low doses of digoxin are sufficient to achieve potentially beneficial outcomes, and higher doses tend to breach the therapeutic safety index. Trough digoxin levels are checked to minimize the risk of toxicity, and although dose reductions are indicated for higher levels, no adjustment is made for low levels.

Adequate Dosing of Diuretic Agents Is Critical in Managing Symptoms and Functional Status



- Neurohormonal activation results in avid salt and water retention.
- Loop diuretic agents are often required because of their increased potency, and frequent dose adjustments may be necessary because of variable oral absorption and fluctuations in renal function.
- Importantly, clinical trial data confirming efficacy are limited, and no data suggest that these agents improve survival.
- Diuretic agents should ideally be used in tailored dosing schedules to avoid excessive exposure.

Routine Anticoagulation Has No role in the Patient With Heart Failure

The Second-Generation Calcium Channel–Blocking Agents Amlodipine and Felodipine Are Safe and Effective in Reducing Blood Pressure But Have No Effects on Morbidity, Mortality, or Quality of Life

TABLE 2. **Targets of Medical Therapy in Patients With Heart Failure**

Target of therapy	Therapeutic agent	Safety	Survival
Sympathetic nervous system	β-Blockers	Y	Y
RAAS	ACEIs	Y	Y
RAAS	ARBs	Y	Y
RAAS/cellular turnover	Aldosterone antagonists	Y	Y
Baroreceptor dysfunction	Digoxin	Y	N
Vasopressin antagonisn	Tolvaptan	Y	N
Altered systemic vascular resistance	Hydralazine and nitrates	Y	Y
Altered systemic vascular resistance	Dihydropyridine calcium channel blockers	Y	N
Altered systemic vascular resistance	Nondihydropyridine calcium channel blockers	N	N
Congestion and altered cardiorenal dynamics	Diuretic agents	Y	N
Coagulopathy	Warfarin	Y	N
Inflammation	Statins	Y	N

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; RAAS = renin-angiotensin-aldosterone system.

Sleep-Disordered Breathing

Sleep that knits up the ravell'd sleeve of care,
The death of each day's life, sore labour's bath,
Balm of hurt minds, great nature's second course,
Chief nourisher in life's feast…

Macbeth

- Sleep-disordered breathing encompasses obstructive sleep apnea and Cheyne-Stokes breathing in its extreme form.

- Sleep-disordered breathing is common (61% of CHF patients - J Clin Sleep Med. 4: 38–42, 2008) and may coexist in patients with CHF despite optimal pharmacological treatment.

- The frequent periods of hypoxia and repeated nighttime arousals trigger adrenergic surges, which can worsen hypertension and impair systolic and diastolic function.

- Obstructive sleep apnea is an independent predictor of worsening outcomes in heart failure.

- Treatment with nocturnal positive airway pressure improves oxygenation, ejection fraction, and 6-minute walk distance. However, no firm data support improved survival with treatment

Atrial Fibrillation

- Atrial fibrillation (AF) is common in patients with heart failure, and the rapid ventricular rates are often poorly tolerated.
- Despite the burden of AF in heart failure, convincing data are lacking that AF incrementally increases mortality.
- Primary reasons to treat AF are to stabilize LV function and to manage symptoms.
- Multiple studies have shown no superiority of rhythm vs. rate control in this patient population.
- Rate control is typically achieved with beta-blockers and digoxin.
- Diltiazem and verapamil should be avoided.
- Given the high risk of thromboembolism, warfarin should be administered to all patients when possible, with strict monitoring of the INR.

Cardiac Electrical Devices

TABLE 4. **Indications for Cardiac Resynchronization Therapy**[a]

Cardiac resynchronization therapy indicated[b]
LVEF ≤35%
QRS duration >120 ms
NYHA II-IV symptoms with optimal medical therapy
Consider cardiac resynchronization therapy[b]
LVEF ≤35%
NYHA II-IV symptoms with frequent right ventricular pacing

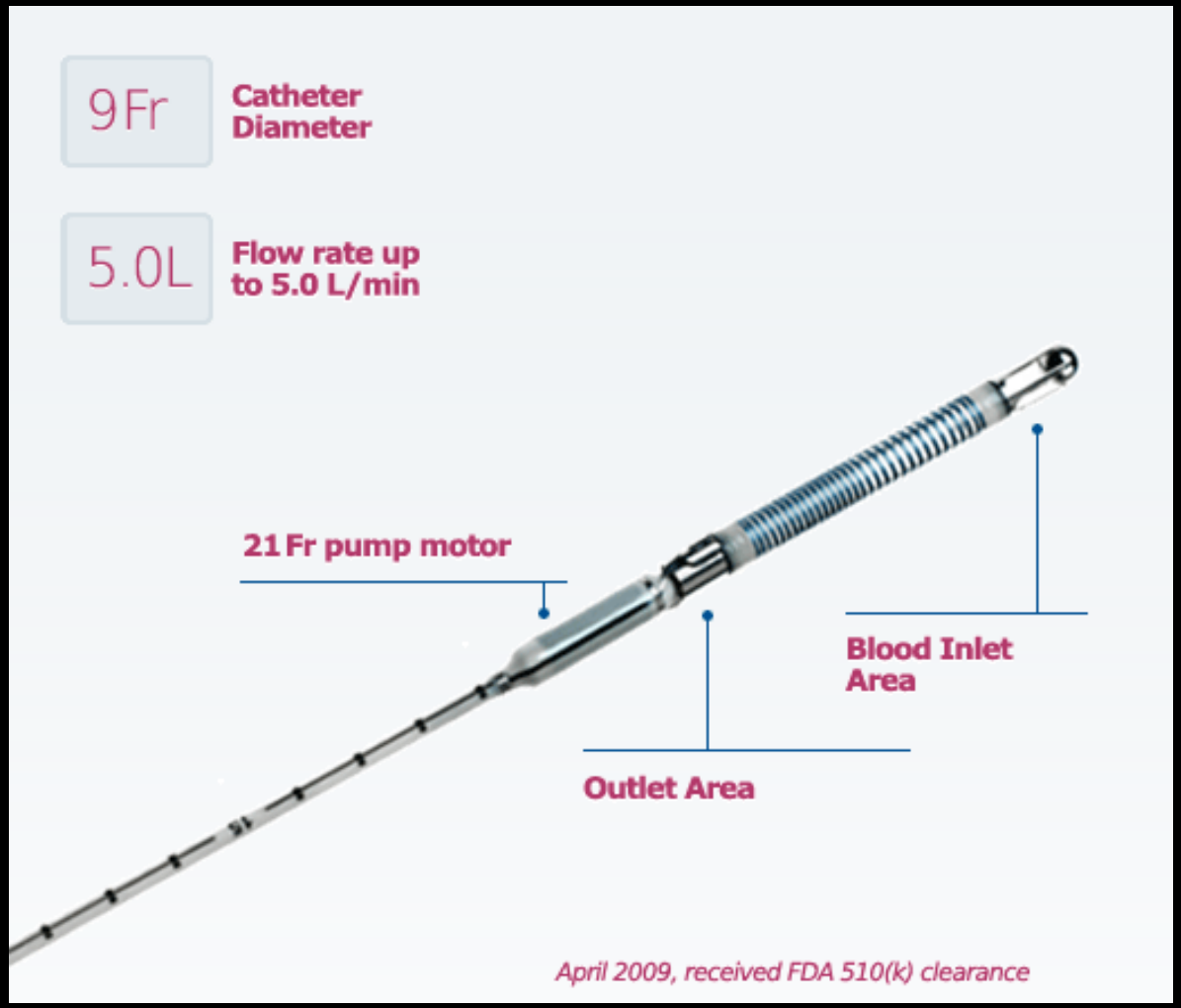
[a] LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.
[b] Only if all listed criteria are satisfied.

TABLE 5. **Primary Prevention ICD Placement Guidelines**

Indicated
Prior MI, LVEF ≤35%, inducible VT on EP study, EP study performed 4 wk after MI
Prior MI and LVEF ≤30%
LVEF ≤35% with NYHA II or III CHF (CMS will not reimburse for ICD placement in newly diagnosed NICM until duration of 3-9 mo)
Excluded
MI within past 40 d
CABG/PCI within past 3 mo
Noncardiac disease associated with survival <1 y

CABG = coronary artery bypass grafting; CHF = chronic heart failure; CMS = Centers for Medicare & Medicaid Services; EP = electrophysiology; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NICM = nonischemic cardiomyopathy; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; VT = ventricular tachycardia.

Impella LV Support Device



Exercise Training

HF-ACTION: Trial Results

- A Controlled Trial Investigating Outcomes of Exercise Training investigated the short- (3-month) and long-term (12-month) effects of a supervised exercise program in patients with moderate heart failure.

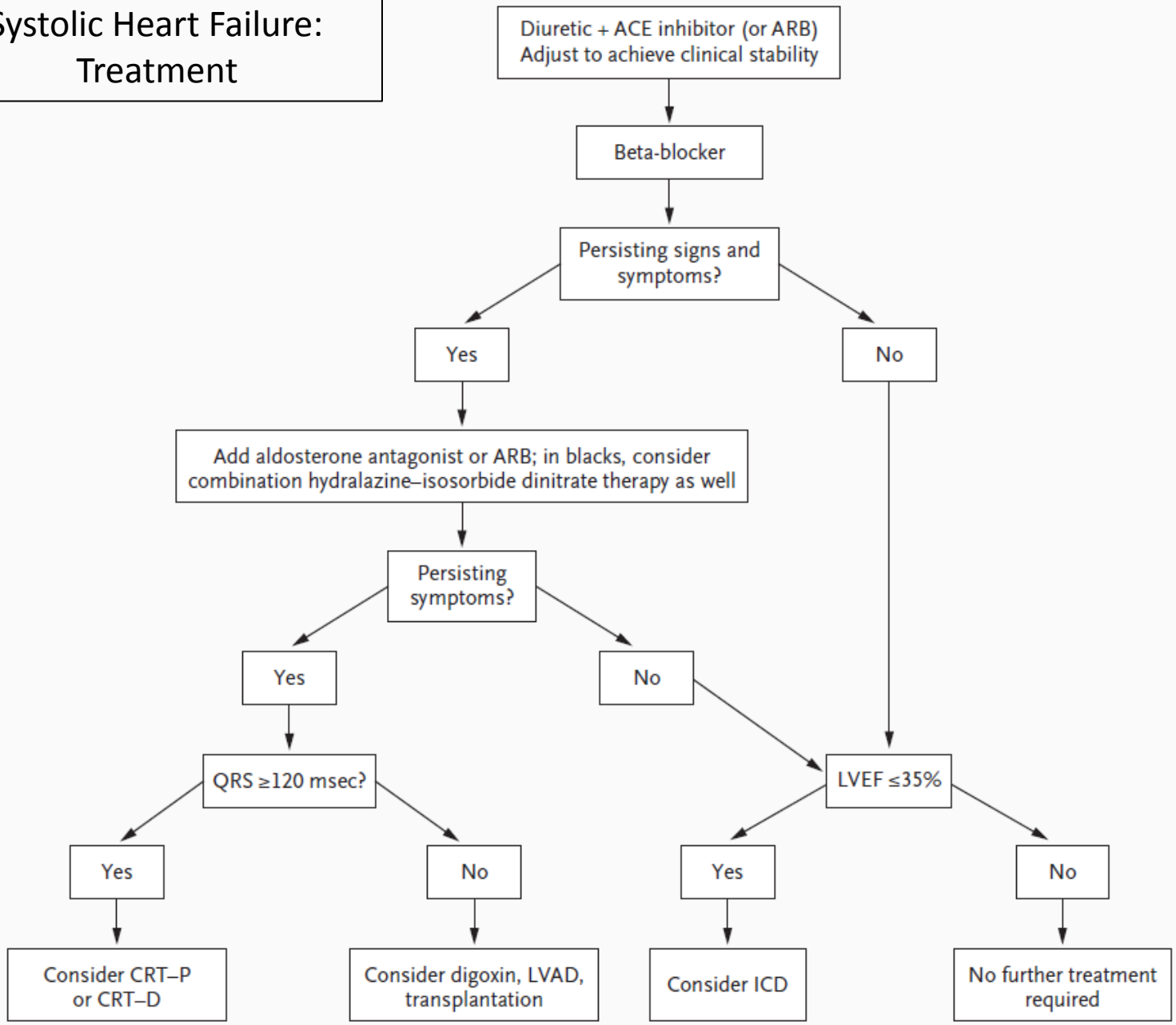
- Exercise was safe, improved patients' sense of well-being, and correlated with a trend toward mortality reduction.

- Maximal changes in 6-minute walk distance were evident at 3 months, but the effects were durable, with significant improvements in cardiopulmonary exercise time and peak oxygen consumption persisting at 12 months.

- It is critical that primary care physicians emphasize the importance of exercise to most patients with heart failure and ensure adherence to this recommendation during follow-up. Increase in thigh strength seems to be especially helpful.

In Summary…

Systolic Heart Failure: Treatment



NEJM 362;3,2010

DROPSY COURTING CONSUMPTION.


THANK YOU