Heart Failure

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Epidemiology of Symptomatic Heart Failure in the U.S.

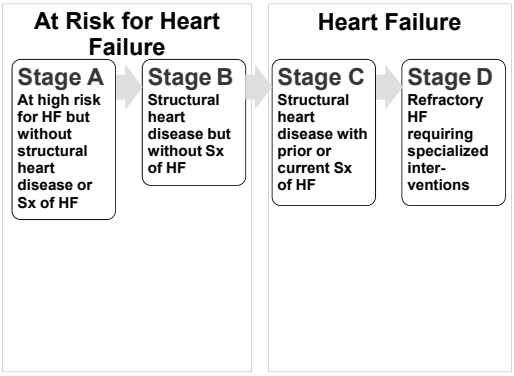
- **Major public health problem**
- **≈ 5.9 million Americans with heart failure**
- **≈ 500,000 new cases diagnosed each year**
- **Most frequent cause of hospitalization in patients older than 65 years**
- **Causes or contributes to 250,000 deaths/year**
- **1-Year mortality rate is about 10-15%**
- **5-Year mortality rate approaches 50%**

Definition of Heart Failure

HF is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood.

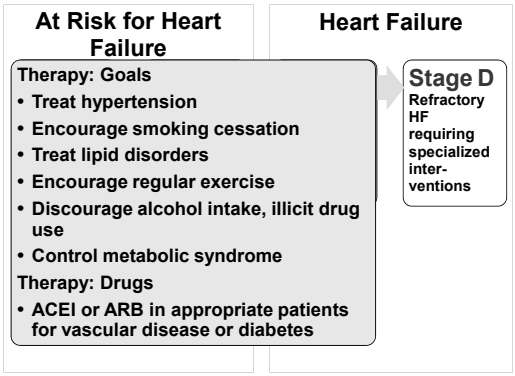
Yancy CW, Jessup M, Bozkurt B, et al. J Am Coll Cardiol 2013;62:e147–239.

ACC/AHA Guideline: HF Stages



Hunt SA, Abraham WT, Chin MH, et al, J Am Coll Cardiol. 2009;53:e1-e90.

ACC/AHA Guideline: HF Stages



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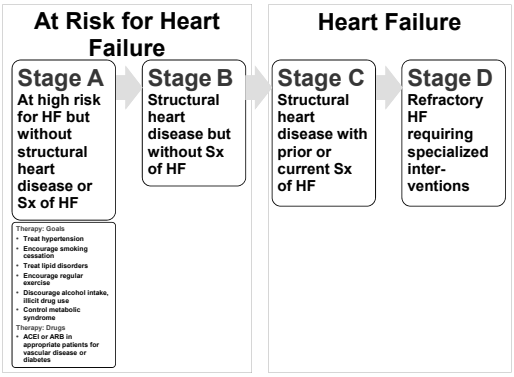

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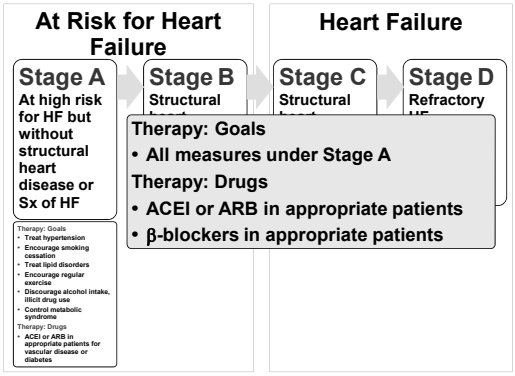

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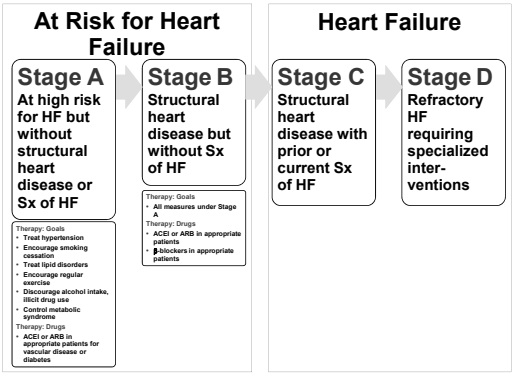

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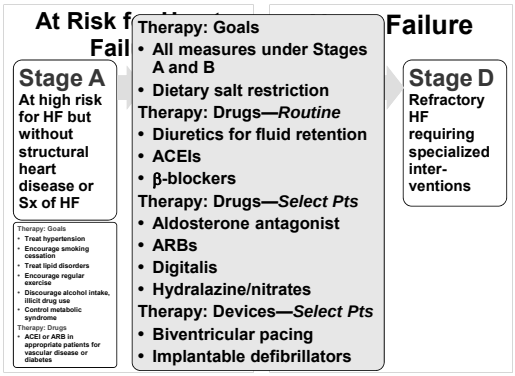

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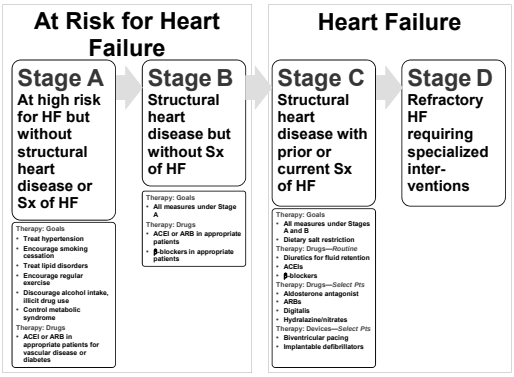

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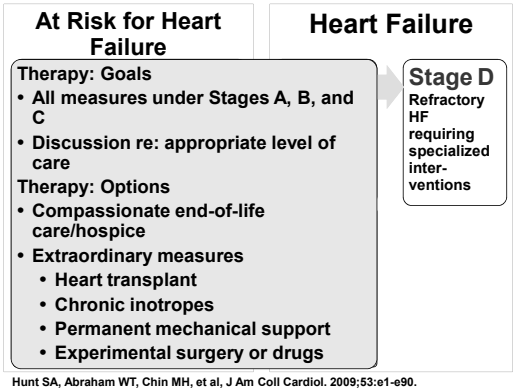
ACC/AHA Guideline: HF Stages



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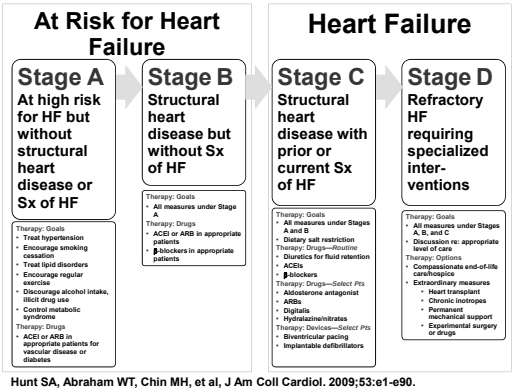

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Heart Failure Prevention

A careful and thorough clinical assessment, with appropriate investigation for known or potential risk factors, is recommended in an effort to prevent development of LV remodeling, cardiac dysfunction, and HF.

HF Risk Factor Treatment Goals

Risk Factor	Goal
Hypertension	Generally < 130/80
Diabetes	See ADA guidelines
Hyperlipidemia	See NCEP guidelines
Inactivity	20-30 min. aerobic 3-5 x wk.
Obesity	Weight reduction < 30 BMI
Alcohol	Men ≤ 2 drinks/day, women ≤ 1
Smoking	Cessation
Dietary Sodium	Maximum 2-3 g/day

Treating Hypertension to Prevent HF

- Aggressive blood pressure control:

Decreases risk of new HF by ~ 50% 56% in DM2

- Aggressive BP control in patients <u>with prior MI</u>:

Decreases risk of new HF by ~ 80%

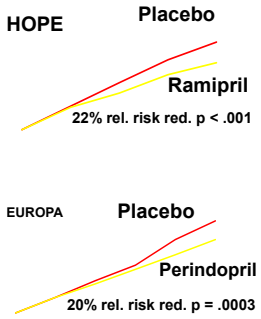
Lancet 1991;338:1281:1281-5 (STOP-Hypertension
JAMA 1997;278:212-6 (SHEP)
UKPDS Group. UKPDS 38. BMJ 1998;317:703-713

Prevention: ACEI and Beta Blockers

- ACE inhibitors are recommended for prevention of HF in patients at high risk for this syndrome, including those with:
  - Coronary artery disease
  - Peripheral vascular disease
  - Stroke
  - Diabetes and another major risk factor
- ACE inhibitors and beta blockers are recommended for all patients with prior MI

Management of Patients with Known Atherosclerotic Disease But No HF

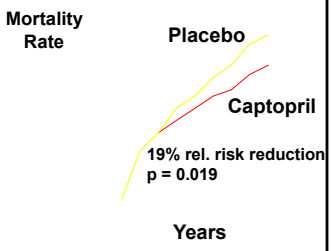
- Treatment with ACE inhibitors decreases the risk of CV death, MI, stroke, or cardiac arrest



NEJM 2000;342:145-53 (HOPE)
Lancet 2003;362:782-8 (EUROPA)

Treatment of Post-MI Patients with Asymptomatic LV Dysfunction (LVEF ≤ 40%)

- SAVE Study
  - All-cause mortality ↓19%
  - CV mortality ↓21%
  - HF development ↓37%
  - Recurrent MI ↓25%



Pfeffer et al. NEJM 1992;327:669-77

The Additional Value of Beta Blockers Post-MI: CAPRICORN

- Studied impact of beta blocker (carvedilol) on post-MI patients with LVEF ≤ 40% already receiving contemporary treatments, including revascularization, anticoagulants, ASA, and ACEI:
  - All-cause mortality reduced (HR = 0.077; p = 0.03)
  - Cardiovascular mortality reduced (HR = 0.75; p = .024)
  - Recurrent non-fatal MIs reduced (HR =.59; p = .014)

Dargie HJ. Lancet 2001;357:1385-90

Heart Failure Patient Evaluation

- Recommended evaluation for patients with a diagnosis of HF:
  - Assess clinical severity and functional limitation by history, physical examination, and determination of functional class*
  - Assess cardiac structure and function
  - Determine the etiology of HF
  - Evaluate for coronary disease and myocardial ischemia
  - Evaluate the risk of life threatening arrhythmia
  - Identify any exacerbating factors for HF
  - Identify co-morbidities which influence therapy
  - Identify barriers to adherence and compliance

**Metrics to consider include the 6-minute walk test and NYHA functional class*

Adams KF, Lindenfeld J, et al. J Card Fail 2006;12:e1-e122.

Evaluation: Follow Up Assessments

- Recommended Components of Follow-Up Visits
  - Signs and symptoms evaluated during initial visit
  - Functional capacity and activity level
  - Changes in body weight
  - Patient understanding of and compliance with dietary sodium restriction
  - Patient understanding of and compliance with medical regimen
  - History of arrhythmia, syncope, pre-syncope or palpitation
  - Compliance and response to therapeutic interventions
  - Exacerbating factors for HF, including worsening ischemic heart disease, hypertension, and new or worsening valvular disease

Adams KF, Lindenfeld J, et al. J Card Fail 2006;12:e1-e122.

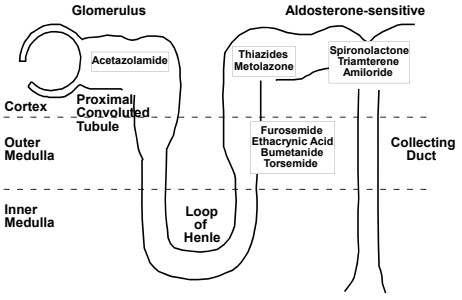
Guideline Directed Medical Treatment of Stage C Heart Failure

Yancy CW, Jessup M, Bozkurt B, et al. J Am Coll Cardiol 2013;62:e147–239.

Serial Assessment and Management of Volume Status in Chronic Heart Failure

- Level I recommendation in 2005 ACC/AHA guidelines
- Assessment of all patients in all stages
  - *"Assessment should be made at each visit of volume status…"*
- Therapy for patients with symptomatic HF
  - *"Diuretics and salt restriction are indicated in patients…who have evidence of volume retention"*
- Advanced disease
  - *"Meticulous identification and control of fluid retention is recommended"*

Tubular Sites of Action of Commonly-Used Diuretics



Abraham and Schrier, 1994

Rationale for Evidence-Based Drug Selection in Heart Failure

- Within drug classes, agents may differ pharmacologically
- These pharmacological differences may translate into differences in clinical outcomes
- When multiple agents within a class produce discordant results on clinical outcomes, class effect cannot be presumed (e.g., β-blockers)

Hunt SA, Abraham WT, Chin MH, et al, J Am Coll Cardiol. 2009;53:e1-e90.

Effect of β-Blockade on Outcome in Patients With HF and Post-MI LVD

Study	Drug	HF Severity	Target Dosage (mg)	Outcome
US Carvedilol[1]	carvedilol	mild/ moderate	6.25-25 BID	↓48% disease progression† (*P*=.007)
CIBIS-II[2]	bisoprolol	moderate/ severe	10 QD	↓34% mortality (*P*<.0001)
MERIT-HF[3]	metoprolol succinate	mild/ moderate	200 QD	↓34% mortality (*P*=.0062)
COPERNICUS[4]	carvedilol	severe	25 BID	↓35% mortality (*P*=.0014)
CAPRICORN[5]	carvedilol	Post-MI LVD	25 BID	↓23% mortality (*P*=.031)

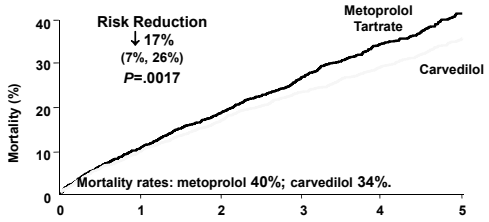
[1]Colucci WS, et al. *Circulation*. 1996;94:2800-2806. [2]CIBIS II Investigators and Committees. *Lancet*. 1999;353:9-13. [3]MERIT-HF Study Group. *Lancet*. 1999;353:2001-2007. [4]Packer M, et al. *N Engl J Med*. 2001;344:1651-1658. [5]The CAPRICORN Investigators. *Lancet*. 2001;357:1385-1390.

β-Blockers Differ in Their Long-Term Effects on Mortality in HF

Bisoprolol[1]	Beneficial
Bucindolol[2]	No effect
Carvedilol[3-5]	Beneficial
Metoprolol tartrate[6]	No effect
Metoprolol succinate[7]	Beneficial
Nebivolol[8]	No effect
Xamoterol[9]	Harmful

[1]CIBIS II Investigators and Committees. *Lancet*. 1999;353:9-13. [2]The BEST Investigators. *N Engl J Med* 2001; 344:1659-1667. [3]Colucci WS, et al. *Circulation* 1996;94:2800-2806. [4]Packer M, et al. *N Engl J Med* 2001;344:1651-1658. [5]The CAPRICORN Investigators. *Lancet*. 2001;357:1385-1390. [6]Waagstein F, et al. *Lancet*. 1993;342:1441-1446. [7]MERIT-HF Study Group. *Lancet*. 1999;353:2001-2007. [8]SENIORS Study Group. *Eur Heart J*. 2005; 26:215-225. [9]The Xamoterol in Severe heart Failure Study Group. *Lancet*. 1990;336:1-6.

COMET: Primary Endpoint of Mortality



Number at Risk:						
Metoprolol Tartrate	1,518	1,359	1,234	1,105	933	352
Carvedilol	1,511	1,366	1,259	1,155	1,002	383

Metoprolol mean dose: 85 mg QD; *Coreg* mean dose: 42 mg QD.

Poole-Wilson PA, et al. *Lancet*. 2003;362:7-13.

β-Blockers: Stage C Heart Failure

- **Class I Indication: β-blockers (using 1 of 3 proven to reduce mortality, ie, bisoprolol, carvedilol, and sustained-release metoprolol succinate) are recommended for all stable patients with current or prior symptoms of HF and reduced LVEF, unless contraindicated**

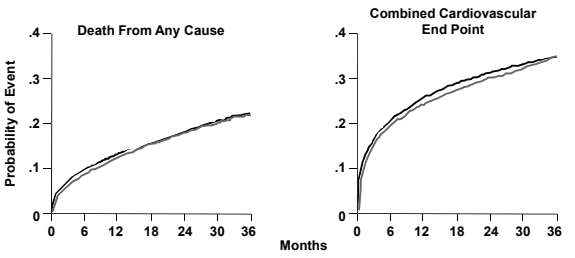
  Level of Evidence: A

CHARM and Val-HeFT Trials

- **Addition of candesartan[1] or valsartan[2] to ACEI and β-blocker in NYHA functional Class II-III**
- **0%-10% lower risk of death (P>.05)**
- **13%-15% lower risk of death or hospitalization for HF in both trials (both P<.01)**
- **Higher risk for hypotension, renal insufficiency, and hyperkalemia with ARB treatment**

[1]Pfeffer MA, et al. Lancet. 2003;362:759-766. [2]Cohn JN, et al. N Engl J Med. 2001;345:1667-1675.

VALIANT: ACE Inhibitor, Angiotensin Receptor Blocker, or Both in Post-MI LVD



Number at Risk:													
Valsartan	4,909	4,464	4,272	4,007	2,648	1,437	357	4,909	3,921	3,667	3,391	2,188	1,204	290
Valsartan + captopril	4,885	4,414	4,265	3,994	2,648	1,435	382	4,885	3,887	3,646	3,391	2,221	1,185	313
Captopril	4,909	4,428	4,241	4,018	2,635	1,432	364	4,909	3,896	3,610	3,355	2,155	1,148	295

[1]Pfeffer MA et al. *N Engl J Med.* 2003;349:1893-1906.

ARBs: Stage C Heart Failure

- **Class I Indication: ARBs are recommended in patients with current or prior symptoms of HF and reduced LVEF who are ACEI intolerant**

  Level of Evidence: A
- **Class IIa Indication: ARBs 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**

  Level of Evidence: A

ARBs: Stage C Heart Failure (cont'd)

- **Class IIb Indication: The addition of an ARB may be considered in persistently symptomatic patients with reduced LVEF who are already being treated with conventional therapy (ie, ACEI and β-blocker)**

  Level of Evidence: B

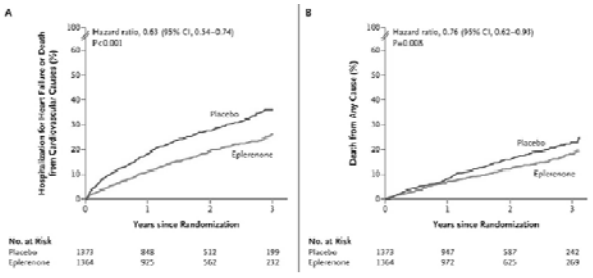
Trials With Aldosterone Antagonists

All-Cause Mortality

Trial	Placebo	Aldosterone Antagonist	Hazard Ratio	Log-rank *P* Value
EPHESUS (Class I)	554/3,319	478/3,313	.85 (.75, .96)	.008
EMPHASIS (Class II)	213/1,373	171/1,364	.76 (.62, .93)	.008
RALES (Class III-IV)	386/841	284/822	.70 (.60, .82)	<.001

Pitt B, et al. *N Engl J Med.* 2003;348:1309-1321. Pitt B, et al. *N Engl J Med.* 1999;341:709-717.
Zannad F, et al. *N Engl J Med* 2011; 364:11-21.

Aldosterone Antagonism in Mild Heart Failure



Panel A: hospitalization for HF or CV death;
Panel B: death from any cause

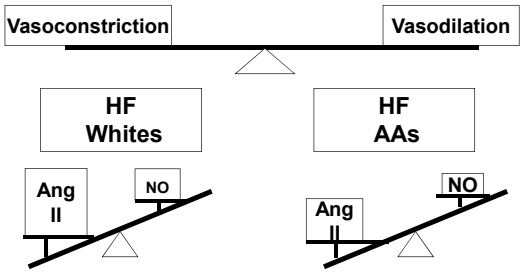
Zannad et al, NEJM 2011; 364:11-21

Aldosterone Antagonists: Stage C Heart Failure

- **Class I Indication: Aldosterone receptor antagonists (or mineralocorticoid receptor antagonists) are recommended in patients with NYHA class II–IV HF and who have LVEF of 35% or less, unless contraindicated, to reduce morbidity and mortality. Patients with NYHA class II HF should have a history of prior cardiovascular hospitalization or elevated plasma natriuretic peptide levels to be considered for aldosterone receptor antagonists. Creatinine should be 2.5 mg/dL or less in men or 2.0 mg/dL or less in women (or estimated glomerular filtration rate >30 mL/min/1.73 m2), and potassium should be less than 5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely followed thereafter to minimize risk of hyperkalemia and renal insufficiency.**

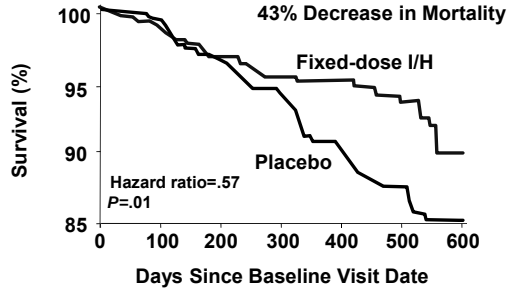
  Level of Evidence: B

Endothelial Dysfunction and HF in African Americans



Adapted from Cohn JN, et al. *J Card Fail.* 2003;9:S198.

A-HeFT: All-Cause Mortality



Fixed-dose I/H	518	463	407	359	313	251	13
Placebo	532	466	401	340	285	232	24

Taylor AL, et al. *N Engl J Med.* 2004;351:2049-2057.

Nitrates/Hydralazine: Stage C Heart Failure

- Class I Indication: The addition of isosorbide dinitrate and hydralazine 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

  Level of Evidence: A
- Class IIa Indication: A combination of hydralazine and a nitrate might be reasonable in patients with current or prior symptoms of HF and a reduced LVEF who cannot be given an ACEI or ARB because of drug intolerance, hypotension, or renal insufficiency

  Level of Evidence: C

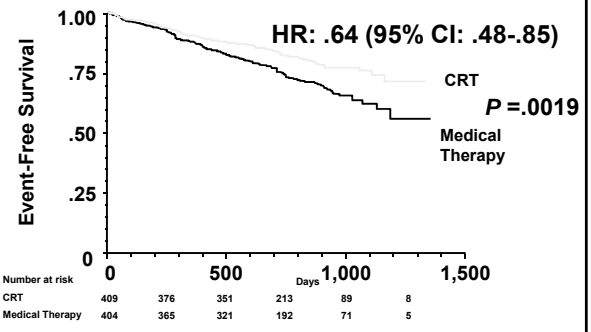
Cardiac Resynchronization in Heart Failure

- >8,500 patients evaluated in landmark randomized controlled trials
- Consistent improvement in quality of life, functional status, and exercise capacity*
- Strong evidence for reverse remodeling
  - ↓ LV volumes and dimensions
  - ↑ LVEF
  - ↓ Mitral regurgitation
- Reduction in heart failure and all-cause morbidity and mortality

*demonstrated in NYHA Class III-IV patients only

Abraham WT, 2010

CARE-HF: Effect of CRT Without an ICD on All-Cause Mortality



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

2012 Guideline Recommendations for CRT

CRT is indicated for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration greater than or equal to 150 ms, and NYHA class II, III, or ambulatory IV symptoms on guideline-directed medical therapy (GDMT).

CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, LBBB with a QRS duration 120 to 149 ms, and NYHA class II, III, or ambulatory IV symptoms on GDMT.

CRT can be useful for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class III/ambulatory class IV symptoms on GDMT.

Tracy C, et al., 2012 ACCF/AHA/HRS Focused Update of the 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. Circulation 2012; 126:1784-1800.

2012 Guideline Recommendations for CRT

CRT can be useful in patients with atrial fibrillation and LVEF less than or equal to 35% on GDMT if a) the patient requires ventricular pacing or otherwise meets CRT criteria and b) AV nodal ablation or pharmacologic rate control will allow near 100% ventricular pacing with CRT.

CRT can be useful for patients on GDMT who have LVEF less than or equal to 35% and are undergoing new or replacement device placement with anticipated requirement for significant (>40%) ventricular pacing.

CRT may be considered for patients who have LVEF less than or equal to 30%, ischemic etiology of heart failure, sinus rhythm, LBBB with a QRS duration of greater than or equal to 150 ms, and NYHA class I symptoms on GDMT.

Tracy C, et al., 2012 ACCF/AHA/HRS Focused Update of the 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. Circulation 2012; 126:1784-1800.

2012 Guideline Recommendations for CRT

CRT may be considered for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with QRS duration 120 to 149 ms, and NYHA class III/ambulatory class IV on GDMT.

CRT may be considered for patients who have LVEF less than or equal to 35%, sinus rhythm, a non-LBBB pattern with a QRS duration greater than or equal to 150 ms, and NYHA class II symptoms on GDMT.

CRT is not recommended for patients with NYHA class I or II symptoms and non-LBBB pattern with QRS duration less than 150 ms.

Tracy C, et al., 2012 ACCF/AHA/HRS Focused Update of the 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities. Circulation 2012; 126:1784-1800.

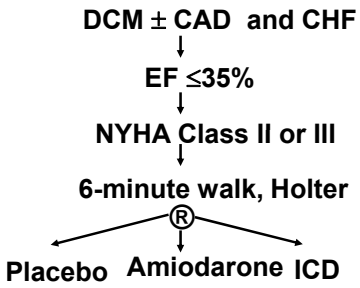
Rationale for Primary Prevention ICDs in Heart Failure

- Patients with left ventricular dysfunction (LVD) usually die as a consequence of either:
  - Progressive heart failure (pump dysfunction), or
  - Sudden cardiac death (cardiac arrhythmia)
- In order to optimally improve outcomes in LVD or heart failure, we must reduce morbidity and mortality related to both of these causes of death

ICDs Save Lives In Heart Failure

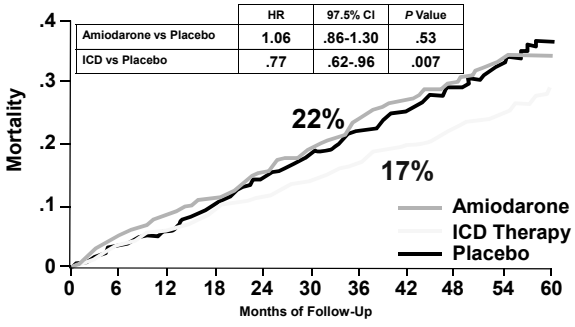
- Second Multicenter Automatic Defibrillator Implantation Trial (MADIT II) – 31% ↓
- Prophylactic Defibrillator Implantation in Patients with Nonischemic Dilated Cardiomyopathy (DEFINITE) trial – 30% ↓
- Sudden Cardiac Death-Heart Failure Trial (SCD-HeFT) – 23% ↓

SCD-HeFT: Enrollment Scheme



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

SCD-HeFT Trial: Mortality by Intention-to-Treat



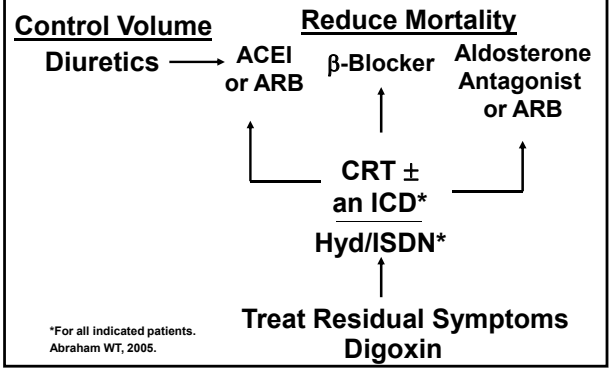
Bardy GH, et al. *N Engl J Med.* 2005;352:225-237.

ACC/AHA Heart Failure Guideline: ICDs in Heart Failure

- **Class I Indication:** ICD therapy is recommended for primary prevention of sudden cardiac death to reduce total mortality in patients with non-ischemic dilated cardiomyopathy or ischemic heart disease at least 40 days post-MI, a LVEF less than or equal to 35%, and NYHA functional class II or III symptoms while receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year

  Level of Evidence: A

Evidence-Based Treatment Across the Continuum of LVD and HF



*For all indicated patients.
Abraham WT, 2005.

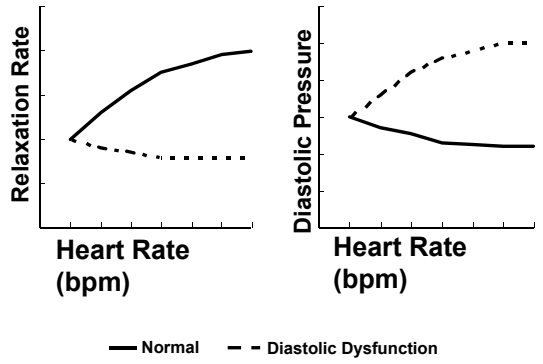
Diastolic Heart Failure: Definition

- Signs and symptoms of heart failure associated with preserved left ventricular systolic function (LVEF > 40-45%)
  - Also known as heart failure with preserved ejection fraction (HFPEF) and heart failure with normal ejection fraction (HFNEF)
- Measurement of diastolic function is confirmatory of diagnosis but not mandatory

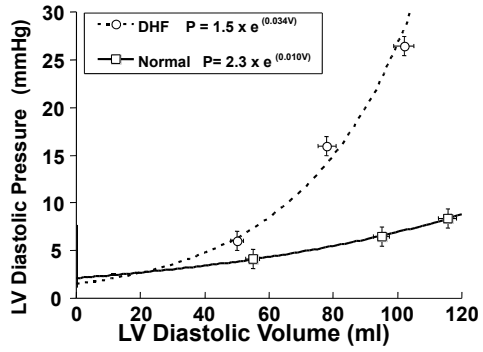
Risk Factors for Diastolic Heart Failure

- Aging
- Hypertension
- Diabetes
- Coronary Artery Disease
- Obesity
- Obstructive Sleep Apnea
- Others

Understanding Diastolic Heart Failure: Heart Rate Versus Pressure

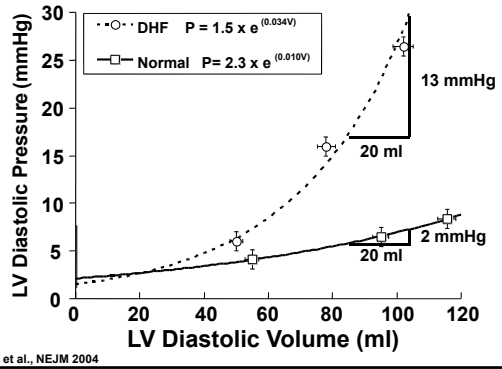


Understanding Diastolic Heart Failure: LV Response to Volume Loading



Zile M et al., NEJM 2004

Understanding Diastolic Heart Failure: LV Response to Volume Loading



Zile M et al., NEJM 2004

Evidence-Based Management of Diastolic Heart Failure

Guideline Recommendations* for the Management of Diastolic Heart Failure

Recommended Therapies for Routine Use:

- Treating known risk factors (e.g., hypertension) with therapy consistent with contemporary guidelines
- Ventricular rate control for all patients with AF
- Drugs for all patients
  - Diuretics
- Drugs for appropriate patients
  - ACEI
  - ARBs
  - Beta-Blockers
  - Digitalis
- Coronary revascularization in selected patients
- Restoration/maintenance of sinus rhythm in appropriate patients

Heart Failure Disease Management

- **Patients recently hospitalized for HF and other patients at high risk should be considered for referral to a comprehensive HF disease management program that delivers individualized care**

End-of-Life Care in Heart Failure

- End-of-life care should be considered in patients who have advanced, persistent HF with symptoms at rest despite repeated attempts to optimize pharmacologic and non-pharmacologic therapy, as evidenced by one or more of the following:
  - Frequent hospitalizations (3 or more per year)
  - Chronic poor quality of life with inability to accomplish activities of daily living
  - Need for intermittent or continuous intravenous support
  - Consideration of assist devices as destination therapy