

Management of End-Stage Heart Failure

Mark R. Vesely, M.D.

Department of Medicine

University of Maryland School of Medicine

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Heart Failure: The Problem

Heart Failure is a progressive syndrome with a 1 in 5 lifetime risk¹ and 8-18% one-year mortality² despite optimized medical therapy.

¹ Lloyd Jones, 2002

² Hunt, 2001

Heart Failure: Outline of Talk

- I. HF definition and epidemiology
- II. HF is a progressive clinical syndrome
- III. Therapy in end-stage HF
 - A. Pharmacological therapy
 - B. Cardiac transplant
 - C. Mechanical circulatory support
 - D. Therapy in development

Heart Failure: Definition

“**Heart failure** represents a complex clinical syndrome characterized by abnormalities of *left ventricular function* and *neurohormonal regulation*, which are accompanied by effort intolerance, fluid retention and reduced longevity.”

Heart Failure: Epidemiology

- High incidence & prevalence in US
 - Incidence: 550,000 new cases each year¹
 - Steadily increasing over last 2 decades²
 - Prevalence: estimated 5 million current cases¹
 - 300,000 – 800,000 with advanced HF (NYHA class III/IV)^{3,4}
 - Prevalence increases with age^{5,6}
 - 1-2% in age 50-59 yrs
 - ~10% if > 75 yrs
- Annual direct & indirect costs: \$24.3 billion¹

1 AHA, 2002

2 He, 2001

3 Adams, 1998

4 Warner Stevenson, 2003

5 Massie, 1997

6 Ho, 1993

Heart Failure: Epidemiology (2)

■ US Heart Failure Morbidity

- the most common Medicare diagnosis-related group¹
- the cause of >20% of hospital admissions in pts >65 yrs²

■ Annual US Mortality: ~300,000³

■ From index-hospitalization in 66,547 Scottish pts⁴

- one-year mortality from 1986 - 1995 was 44.5%
- with median survival in 1995 of 1.64 years

1 Massie, 1997

2 AHA, 2000

3 Hunt, 2001

4 MacIntyre, 2000

Heart Failure: Risk Factors

■ NHANES study: Independent Risk Factors

- Coronary heart disease (AR 61.6%)
- Diabetes (AR 3.1%)
- Cigarette smoking (AR 17.1%)
- Valvular heart disease (AR 2.2%)
- Hypertension (AR 10.1%)
- Overweight (AR 8.0%)
- Male sex (AR 8.9%)
- Low physical activity (AR 9.2%)
- Less than high school education (AR 8.9%)

■ Additional underlying etiologies include thyroid disease, alcohol and other cardiac toxins

(AR = Attributable Risk)

Heart Failure: Cardinal Manifestations

- *Symptoms* include dyspnea and fatigue
 - Leading to reduced exercise tolerance
- *Physical Signs* derive from fluid retention
 - Pulmonary congestion
 - Peripheral edema
- Diagnostic Criteria:
 - Framingham major and minor criteria (see text)

Heart Failure: Functional Classification

■ NYHA Classification system describes functional status¹

- **Class I:** asymptomatic with ordinary physical activity
- **Class II:** symptomatic with moderate physical activity
- **Class III:** symptomatic with minimal physical activity
- **Class IV:** symptomatic at rest

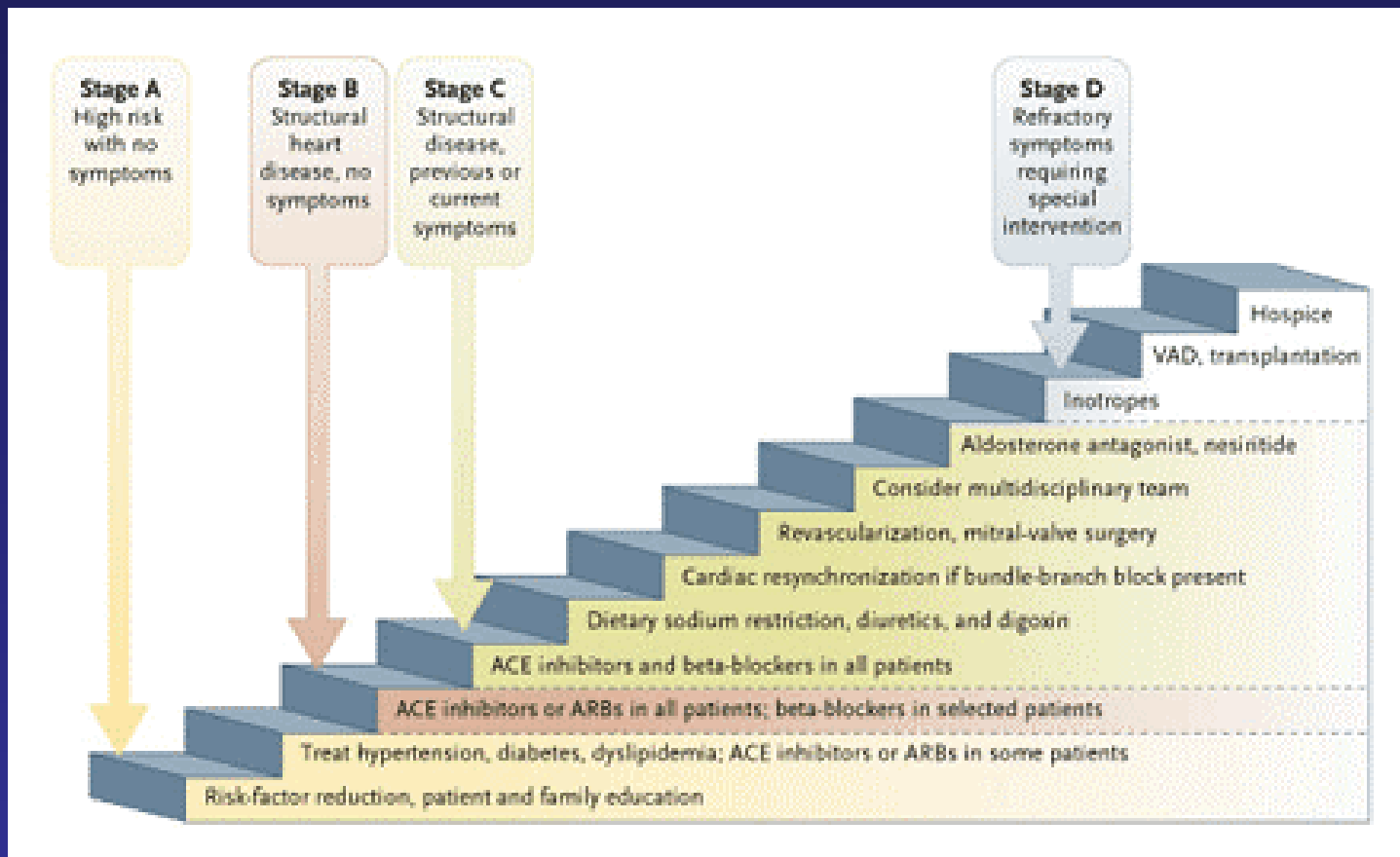
(Symptoms include fatigue, palpitation, dyspnea, or anginal pain)

Heart Failure: A Progressive Disorder

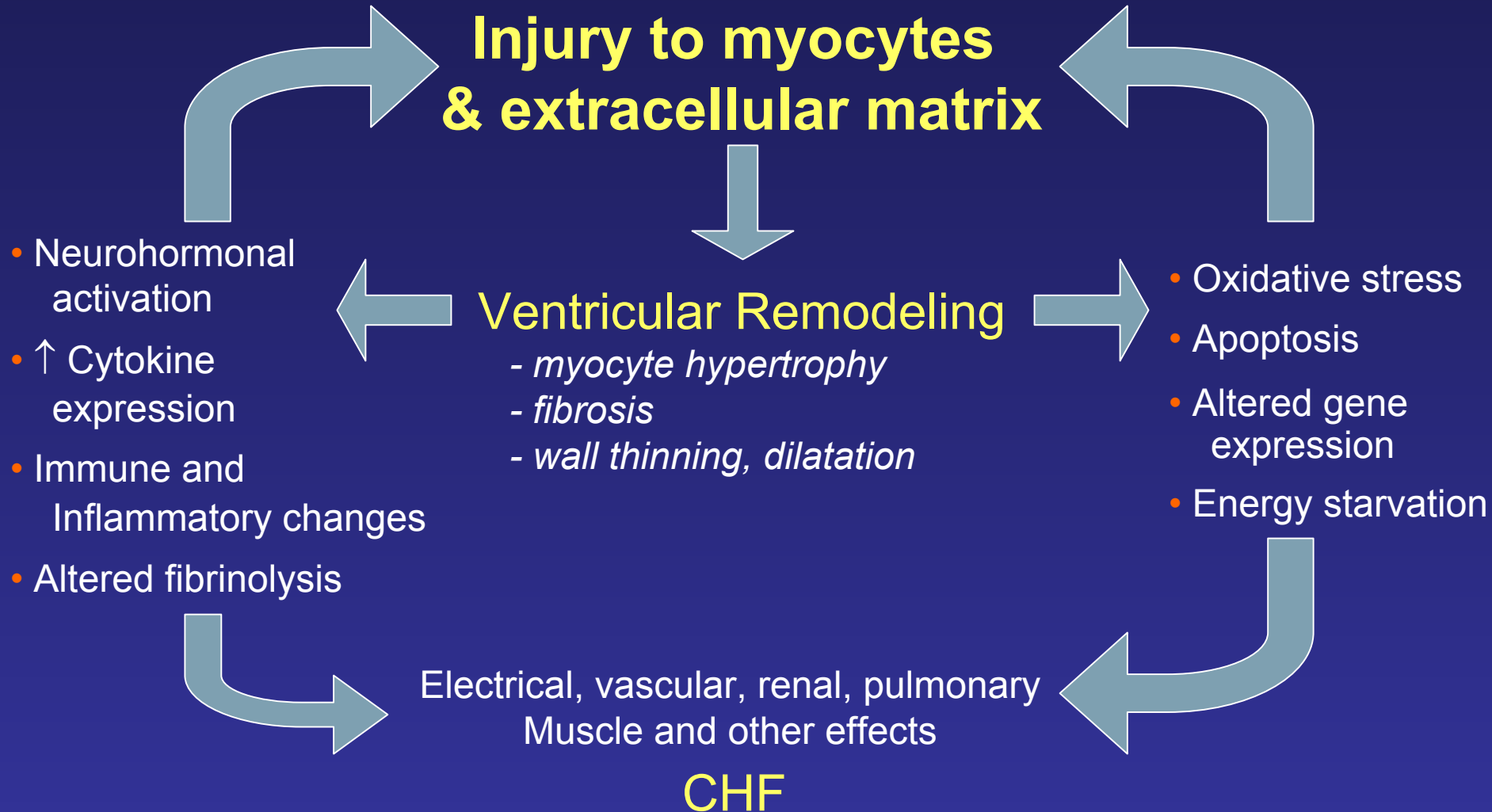
■ ACC/AHA Staging System¹

- **Stage A:** patient who is at risk for developing HF but has no structural disorder of the heart
- **Stage B:** patient with a structural disorder of the heart but who has never developed symptoms
- **Stage C:** patient with past or current symptoms of HF associated with underlying structural heart disease
- **Stage D:** patient with end-stage disease who requires specialized treatment strategies such as mechanical circulatory support, continuous inotropic infusions, cardiac transplantation, or hospice care

Heart Failure: Treatment by Stages



Heart Failure: A Vicious Cycle



Heart Failure:

Predicting Progression and Mortality

- No consistent prognostic factors on an individual level
 - ↓ LVEF loses utility if $<25\%$ ¹
 - Peak O₂ consumption
 - Integrates cardiac reserve & peripheral conditioning²
 - Predictive of mortality but can improve³
 - Neurohormonal (norepinephrine¹, endothelin⁴, BNP⁵) and cardiac biomarkers (troponin⁶) show promise in small population studies

1 Hunt, 2001
2 Mancini, 1991
3Stevenson, 1995

4 Berger, 2003
5 Bettencourt, 2004
6 Potluri, 2004

End-Stage HF Mortality:

Key Determinant

- Incidence and prevalence continue to rise, and despite numerous medical advances, progression to end-stage HF and mortality remain high.
- There are insufficient therapeutic options for end-stage HF patients
 - Until recently, cardiac transplant was the only therapeutic option with mortality benefit
 - Estimated 100,000 pts meet criteria for cardiac transplant but only 2200 donor hearts available yearly¹

End-stage HF: Stage D Therapy

- Pharmacological therapy
- Cardiac transplant
- Mechanical circulatory support (LVAD)
- Potential therapy
 - New pharmacological agents
 - Regeneration

End-stage HF:

Pharmacological Therapy

- IV inotropes/peripheral vasodilators
 - Dobutamine, dopamine, milrinone
 - Nitroglycerin and nitroprusside
- Aldosterone antagonists
- Continued from stages A/B/C
 - Neurohormonal inhibitors
 - (β -blockers, ACEI, ARB)
 - Diuretics
 - Digitalis

End-stage HF: Stage D Therapy

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- Cardiac transplant
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End-stage HF:

Cardiac Transplant –Indications*

- Severe functional impairment
 - Peak exercise O₂ consumption < 14 ml/kg/min
 - Continued dependence on IV inotropes
- Recurrent life-threatening ventricular arrhythmias
- Refractory angina

End-stage HF:

Cardiac Transplant – Mortality Benefit

- In pts with absolute indications, estimated 1-year survival without a transplant is <50% and 83% after transplantation
- 10 year survival post-transplant ~50%

End-stage HF:

Cardiac Transplant – Quality of Life

- Most studies focus from before to 5 years post transplant

Positive Effects

health status, domestic activities, leisure activities

depression, anxiety, symptom distress, well-being, life satisfaction, body image, perceived QOL, emotional functioning, mental functioning

family relationships, vocational functioning

Equivocal Effects

Level of stress

Coping use and effectiveness

Vocational functioning

Sexual functioning

Negative Effect

Financial situation

End-stage HF: Cardiac Transplant – not enough of a good thing

- < 50% of patients who qualify for heart transplant live for 1 year
- For O-blood-type patients receiving a cardiac transplant in 2000, the average wait time was 869 days (~29 mo)
- Estimated 100,000 pts meet criteria for cardiac transplant but only ~2200 donor hearts available yearly²

End-stage HF: Stage D Therapy

- Pharmacological therapy
- Cardiac transplant
- Mechanical circulatory support (LVAD)
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 - New pharmacological agents
 - Regeneration

End-stage HF:

Mechanical Circulatory Support (MCS)

- Short-term and Long-term support systems
- Three main types of MCS devices
 - Intra-Aortic Balloon Pump
 - Ventricular Assist Device (LVAD, BiVAD)
 - Total Artificial Heart

End-stage HF:

MCS – Indications and Usage

- Uses of long-term MCS
 - Bridge to transplant
 - Destination therapy
 - Bridge to recovery
- Indications for long-term MCS
 - Chronic HF c hemodynamic deterioration despite maximal drug therapy +/- IABP
 - PCWP >20 mm hg; CI \leq 2 l/min/m²; SBP \leq 80 mm hg
- 2001: ~20% of transplant recipients received MCS prior to transplant¹

¹ Frazier, 2003

End-stage HF:

MCS – Long-term Benefits

- Functionality often returns to NYHA class I
- 30% of 44 HeartMate pts discharged home returned to productive work or school⁴
- Improved mortality as bridge to transplant²
 - Survival to transplant: 71% c MCS vs. 30% s MCS
 - 1 yr survival p transplant: 90% c MCS vs. 67% s MCS
- Significantly improved QOL 1-2 weeks p surgery³
- 35-70,000 American pts could receive long-term MCS annually¹

1 Funk, 1991

2 Frazier, 1992

3 Grady, 2001

4 Morales, 2000

End-stage HF:

MCS - Complications

- Post-operative hemorrhage (60%)
- Sepsis (30-40%)
- Thromboembolism, renal failure, technical failure, neurologic sequelae
- Common cause of death is right-sided HF

End-stage HF:

MCS – Destination Therapy

- As of January, 2003: outpatient LVAD support¹
 - HeartMate: >1 yr: 217, >2 yr: 33, >3 yr: 3
 - Novacor: 1 pt > 4.5 yr
- Study for destination therapy: REMATCH²
 - 1 yr survival: 52% (LVAD) vs. 25% (med); 2 yr: 23% vs. 8%
 - Cause of death:
 - LVAD (41): LV dysfnctn(1), sepsis(17). LVAD failure(7),CVA (4)
 - Med (54): LV dysfunction(50), sepsis (1), AMI (1)
 - Predicts saving 270 annual deaths for every 1000 c LVAD
 - Compares to 70 per 1000 for β -blockers³, ACEI⁴

¹ Frazier, 2003

² Rose, 2001

³ Packer, 2001

⁴ Kjekshus, 1992

End-stage HF:

MCS – Bridge to Recovery

- Survivable LVAD explantation¹
 - 16 pts c poor prognosis c continued LVAD
 - 10 c favorable dobutamine stress, had LVAD explanted → 7 have survived “long-term”
- Reverse remodeling: improvements after LVAD¹
 - Myocyte morphology and function
 - Programmed cell death
 - Fibrosis
 - Altered gene expression

¹ Delgado, 2003

² Warner Stevenson, 2003

End-stage HF: Stage D Therapy

- Pharmacological therapy
- Cardiac transplant
- Mechanical circulatory support (LVAD)
- Potential therapy
 - Investigational pharmacological agents
 - Regeneration

End-stage HF: Potential therapy – Investigational pharmacological agents

■ Endothelin antagonists¹

- In HF, ET-1 regulates peripheral hemodynamics, LV function and remodeling
- Initially adds inotropic support but overexpression may eventually produce focal vasospasm, myocyte necrosis, and increased fibrosis
- In HF pts, serum ET-1 levels correlate to LV function and prognosis
- **Bosentan** and **Enrasentan**: disappointing trial results
- **Tezosentan**: benefits in CI, PCWP, and vasc resistance in acute HF

¹ Mann, 2002

End-stage HF: Potential therapy – Investigational pharmacological agents

■ Vasopeptidase inhibitors¹

- In HF, diminished endogenous vasodilator system couples enhanced vasoconstrictor system (RAS)
- Small scale studies of **Omapatrilat** vs. ACEI
 - Improved cardiac function
 - Reduced risk of mortality and worsening HF
 - ? Utility 2° Increased risk of angioedema

¹ Hunt, 2001

End-stage HF: Potential therapy – Investigational pharmacological agents

■ Vasopressin Antagonists

- **Tolvaptan** added to lasix and other standard treatment for 4 weeks¹
 - Reduced body weight and edema
 - Normalized hyponatremia
 - No significant change in QOL
- No neurohormonal activation in animal studies²

¹ Gheorghiade, 2003

² Hirano, 2000

End-stage HF: Potential therapy – Investigational pharmacological agents

■ Cytokine antagonists

- High TNF levels lead to progressive LV dysfunction, pulmonary edema, LV remodeling, and fetal gene expression¹
- DCM pts treated c Pentoxifylline (blocks transcriptional activation) for 6 months showed improved functional class and LVEF compared to placebo²
- Large scale Enbrel (etanercept-TNF antagonist) studies showed lack of efficacy¹

¹ Mann, 2002

² Sliwa, 1998

End-stage HF: Potential therapy – Investigational pharmacological agents

■ Apoptosis inhibitors

- Cardiomyocyte apoptosis rate elevated in HF^{1,2,3}
 - Late-stage dilated CM: 80-250 per 10⁵ nuclei
 - Healthy human hearts: 1-10 per 10⁵ nuclei
- Multiple animal studies show a direct causal role of apoptosis and cardiomyopathy
- Caspase inhibitor (**IDN 1965**) improved cardiac function and delayed/prevented HF in a transgenic mouse model⁴
- Roadblocks to overcome⁵
 - Potential tumor induction
 - Targeted delivery system

¹ Olivetti, 1997

² Saraste, 1999

³ Guerra, 1999

⁴ Hayakawa, 2003

⁵ Webster, 2003

End-stage HF: Stage D Therapy

- Pharmacological therapy
- Cardiac transplant
- Mechanical circulatory support (LVAD)
- Potential therapy
 - New pharmacological agents
 - Regeneration

End-stage HF:

Potential therapy – Regeneration

■ Human studies

- Male human recipients of cardiac transplant from female donors have Y-chromosome (+) myocytes and coronary vessels^{1,2}
- Percutaneous skeletal myoblast transplantation yielded ↑ wall thickening and ↑ LVEF over 6 mos³
 - Likely arrhythmogenic

¹ Quaini, 2002

² Muller, 2002

³ Smits, 2003

End-stage HF:

Potential therapy – Regeneration

■ Murine studies

- Cultured murine bone-marrow mesenchymal stem cells differentiate to cardiomyocyte phenotype¹
- Induced-infarct mouse model²
 - Cytokine regime mobilized pluripotent stem cells
 - Formation of $\sim 15 \times 10^6$ new myocytes and new vascular supply
 - Resulted in cardiac regeneration 4 weeks later with decreased mortality, infarct size, cavitory dilatation, increased LVEF

1 Makino, 1999

2 Orlic, 2001

Summary

- HF is a progressive disease
- LVAD support is a powerful supplement to heart transplant as a therapeutic option for end-stage HF
- There is future hope in additional end-stage HF therapies currently under development