Optimizing Heart Failure

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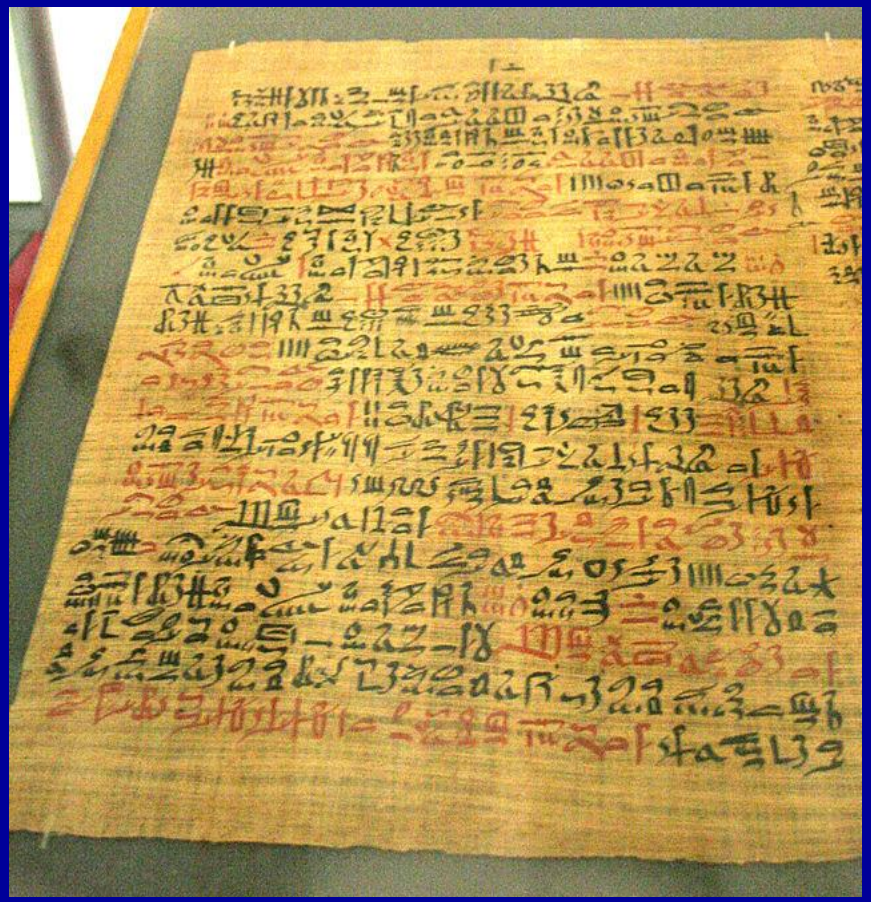
Outline

- Definitions and scope of problem
- Diagnosing and classifying heart failure
- Approach to management of CHF
  - Oral drug therapy (ACE-I, ARB, betablockers, aldosterone blockade, digoxin)
  - Device therapy
- Future directions and exciting developments

A Historical Perspective

- Ebers Papyrus
  - Dated circa 1550 BC
  - Early description of the heart and circulatory system
  - Passages describe heart failure

    "His heart is flooded. This is the liquid of the mouth. His body parts are all together weak"
  - Remedy is one which will *"cause an emptying"*



Congestive Heart Failure

- **Heart (or cardiac) failure** is the state in which the heart is unable to pump blood at a rate commensurate with the requirements of the tissues or can do so only from high pressures

Braunwald 8th Edition, 2001

Types of Heart Failure

- Systolic (or squeezing) heart failure
  - Decreased pumping function of the heart, which results in fluid back up in the lungs and heart failure
- Diastolic (or relaxation) heart failure
  - Involves a thickened and stiff heart muscle
  - As a result, the heart does not fill with blood properly
  - This results in fluid backup in the lungs and heart failure

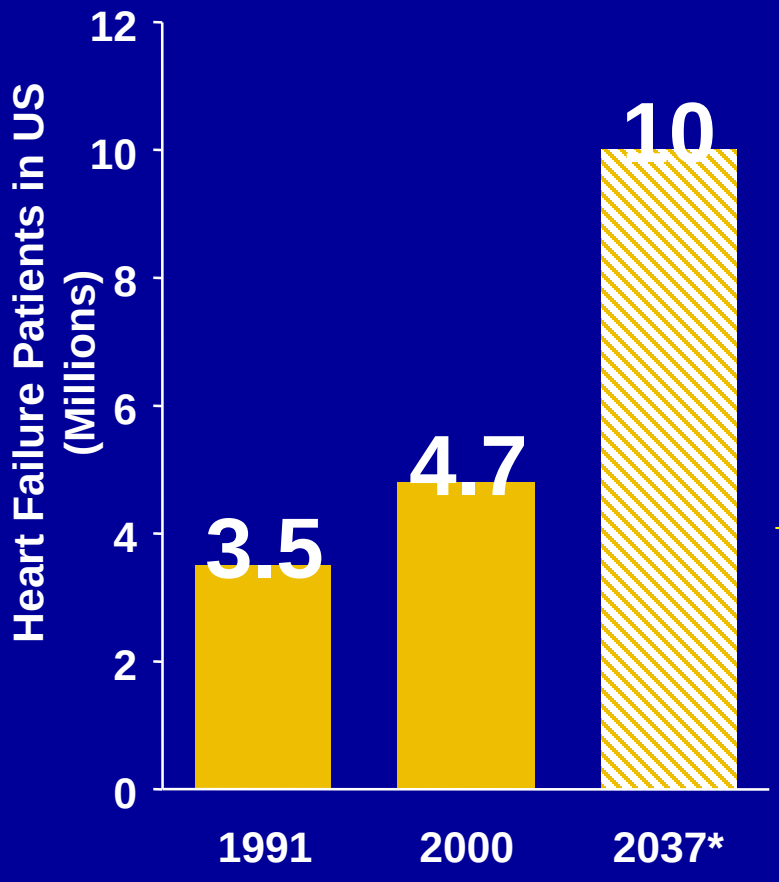
Risk Factors for Heart Failure

- Coronary artery disease
- Hypertension (LVH)
- Valvular heart disease
- Alcoholism
- Infection (viral)

- Diabetes
- Congenital heart defects
- Other:
  - Obesity
  - Age
  - Smoking
  - High or low hematocrit level
  - Obstructive Sleep Apnea

CAD=coronary artery disease; LVH=left ventricular hypertrophy.

Epidemiology of Heart Failure in the US



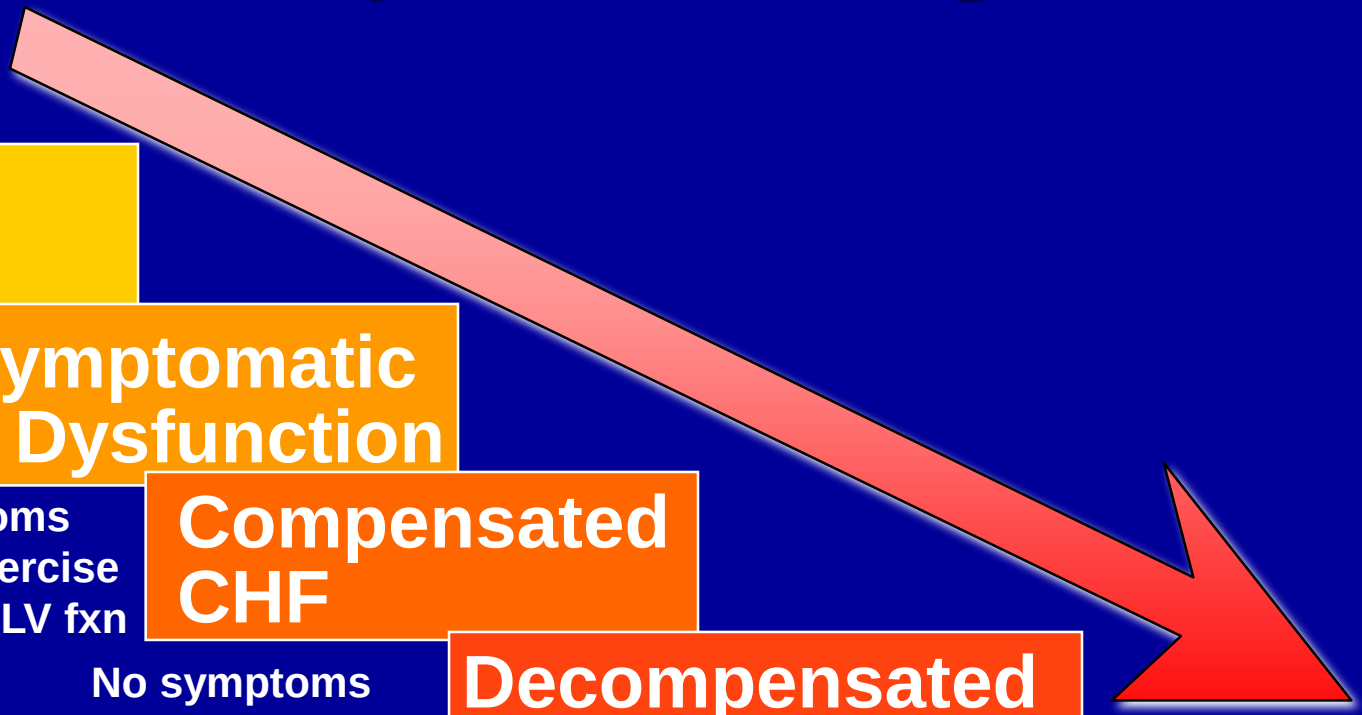
- More deaths from heart failure than from all forms of cancer combined
- 550,000 new cases/year
- 4.7 million symptomatic patients; estimated 10 million in 2037

*Rich M. *J Am Geriatric Soc*. 1997;45:968–974.
American Heart Association. 2001 *Heart and Stroke Statistical Update*. 2000.

Congestive Heart Failure

- Symptoms:
  - Shortness of breath
  - Leg swelling (edema)
  - Breathing worsens with lying flat (orthopnea)
  - Fatigue
  - Decrease Exercise Tolerance

Chronic Congestive Heart Failure
Evolution of Clinical Stages



NORMAL

No symptoms
Normal exercise
Normal LV fxn

Asymptomatic LV Dysfunction

No symptoms
Normal exercise
Abnormal LV fxn

Compensated CHF

No symptoms
Exercise
Abnormal LV fxn

Decompensated CHF

Symptoms
Exercise
Abnormal LV fxn

Refractory CHF

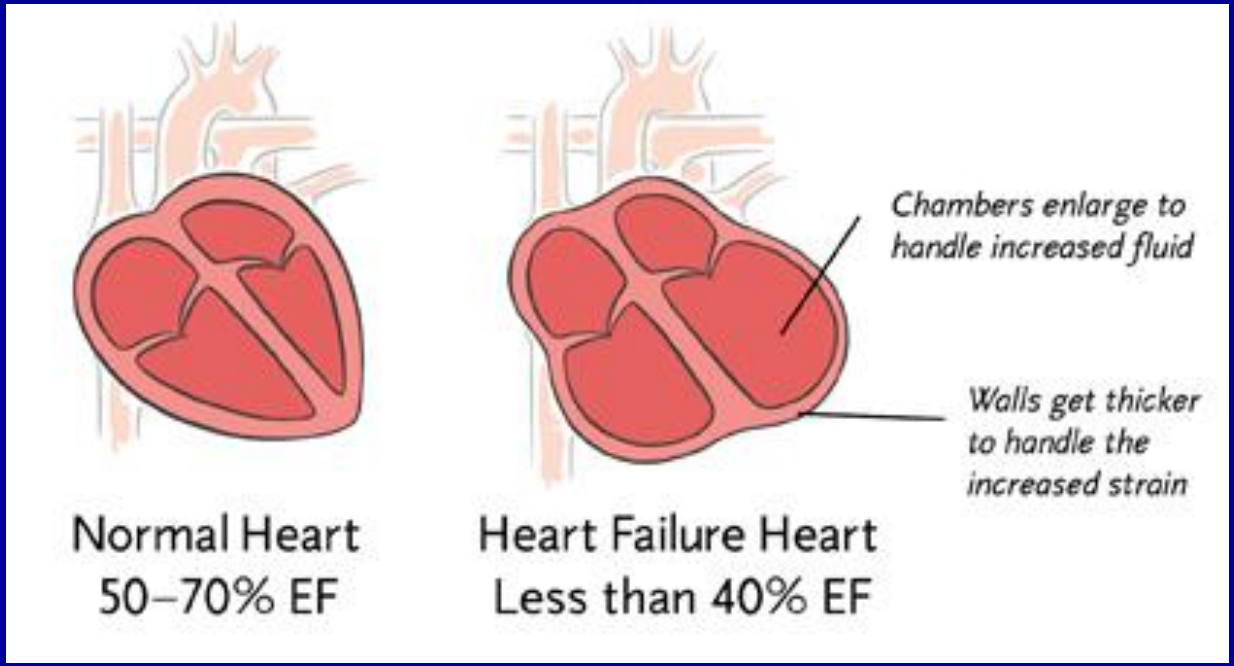
Symptoms not controlled with treatment

Classifying Heart Failure: Terminology and Staging

A Key Indicator for Diagnosing Heart Failure

Ejection Fraction (EF)

- Ejection Fraction (EF) is the percentage of blood that is pumped out of your heart during each beat



Echocardiographic Evaluation of CHF

- LV function (EF),chamber size,wall motion
- Segmental dysfunction-coronary disease
- MS-severity, valve area
- AS- valve gradient, valve area
- AR/MR severity
- TR- RV systolic pressure = PA pressure
- RV function
- R/O IHSS, HCM
- R/O Pericardial Disease
- R/O rare causes e.g. myxoma, infiltrative disorders- restrictive cardiomyopathy
- Diastolic function
- Hyperdynamic states

Classification of HF: Comparison Between ACC/AHA HF Stage and NYHA Functional Class

ACC/AHA HF Stage[1]	NYHA Functional Class[2]
A At high risk for heart failure but without structural heart disease or symptoms of heart failure (eg, patients with hypertension or coronary artery disease)	None
B Structural heart disease but without symptoms of heart failure	I Asymptomatic
C Structural heart disease with prior or current symptoms of heart failure	II Symptomatic with moderate exertion
	III Symptomatic with minimal exertion
D Refractory heart failure requiring specialized interventions	IV Symptomatic at rest

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

[2]New York Heart Association/Little Brown and Company, 1964. Adapted from: Farrell MH et al. *JAMA.* 2002;287:890–897.

BNP Diagnostic Cut Points for CHF JACC 2001;37(2):379-85.

BNP > 400 pg/L – acute CHF present

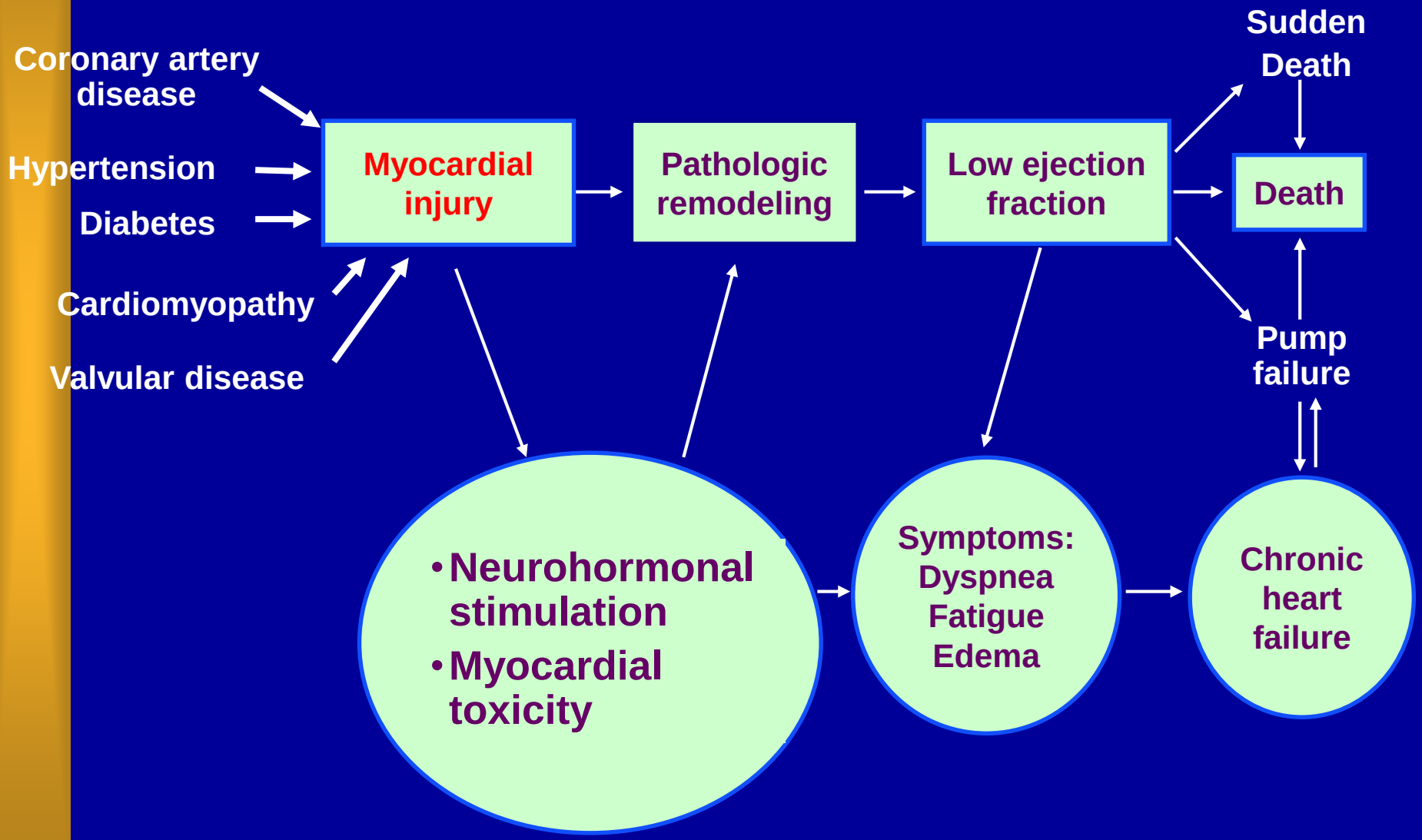
BNP 100 pg/L – 400 pg/L

- Diagnostic of CHF with
  - Sensitivity 90%
  - Specificity 76%
  - Predictive accuracy 83%
  - R/O pulmonary embolism, LV dysfunction without acute CHF or cor pulmonale

BNP < 100 pg/L – 98% negative predictive accuracy

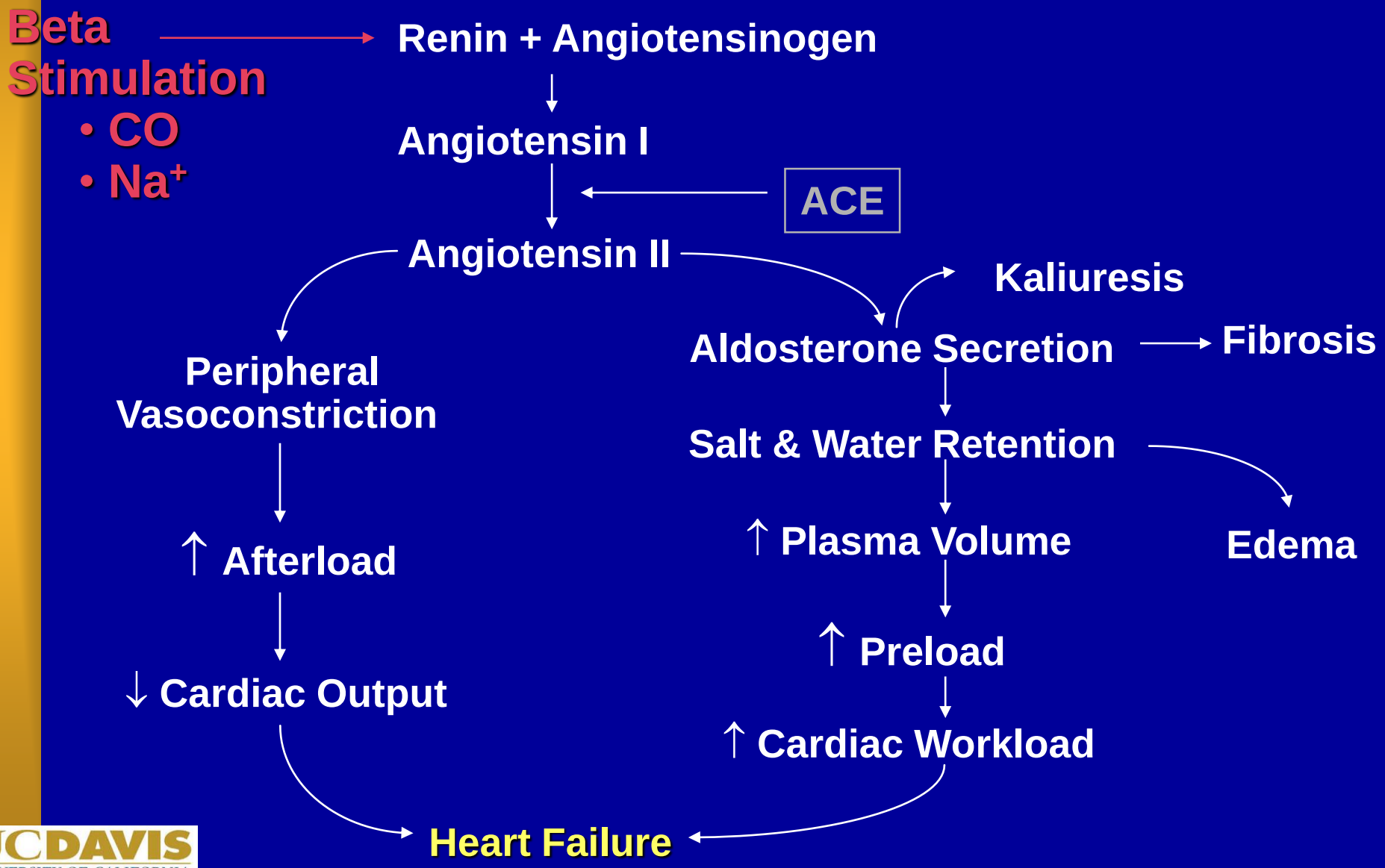
Pathophysiology

Pathologic Progression of CV Disease



Adapted from Cohn JN. *N Engl J Med*. 1996;335:490–498.

Compensatory Mechanisms:
Renin-Angiotensin-Aldosterone System



Drug Therapy

Rational for Medications

- Improve Symptoms
  - Diuretics (water pills)
  - digoxin

- Improve Survival
  - Betablockers
  - ACE-inhibitors
  - Aldosterone blockers
  - Angiotensin receptor blockers (ARB's)

DIET *Approach to the Patient With Heart Failure*

- ***D***iagnose
  - Etiology
  - Severity (LV dysfunction)
- ***I***nitiate
  - Diuretic/ACE inhibitor
  - β-blocker
  - Spirololactone
  - Digoxin
- ***E***ducate
  - Diet
  - Exercise
  - Lifestyle
  - CV Risk
- ***T***itrate
  - Optimize ACE inhibitor
  - Optimize β-blocker

General Rx Strategies in HF

Asymptomatic | Mild/Mod | Severe | Refractory

Inotropes, mitral repair, VAD, Tx

Correct Cause:
Arrhythmias
Ischemia
Pressure Load

Tailored Rx

Digoxin

Diuretics (Spironolactone)

Carvedilol/ β-Blockers

Angiotensin Converting Enzyme Inhibitors

No Added Salt → 2 gm Na

Activity as Tolerated → Customized Ex Training

Modified from Warner-Stevenson, ACC HF Summit

ACE Inhibitors in CHF

Study	No.	Males	Age	EF%	Class	Drug	F/U	Mortality Reduction %
V-HeFT	642	100%	58	30	II.III	HDZN/ ISDN	2.3 yrs.	11
CONCENSUS	253	70%	70	NA	IV	Enalapril	188 Days	27
V-HeFT II	804	100%	61	29	II,III	Enalapril	2.5 yrs.	14
SOLVD Treatment	2569	80%	61	25	II,III	Enalapril	41.4 mo.	16
SOLVD Prevention	4228	89%	59	28	I,II	Enalapril	37.4 mo.	8

Optimal Dosing of ACE Inhibitors

- General Guideline:
- Start low and titrate to the target dose used in the clinical trials or the **MAXIMUM TOLERATED DOSE** (ATLAS trial)

- Captopril 6.25-12.5 mg ⇒50 mg BID-TID (SAVE)
- Enalapril 2.5 mg BID ⇒20 mg BID (SOLVD/X)
- Ramipril 2.5 mg BID ⇒ 5 mg BID (AIRE/EX)
- Lisinopril 10 mg OD ⇒ 30-40 mg OD (GISSI 3)
- Trandolapril 1mg ⇒ 4 mg (TRACE)

Summary – ARBs in CHF

	ELITE II	Val-HeFT	VALIANT	CHARM
	ARB vs ACEI	**ARB vs placebo (± ACEI ±BB)**	**Captopril, Valsartan or Combination**	**ARB vs placebo (± ACEI)**
# pts.	**3,152**	**5,010**	**4909/4909/4885**	**7,601**
Popula-tion	**Heart failure**	**Heart failure**	**Post MI with clinical or radiologic HF**	Symptomatic HF Class II-III/ ↓ LV function/preserved LVF (added+alternative/preserved)
End-points	**1º All-cause mortality, sudden death or resuscitated cardiac arrest: NS**	**1º All-cause mortality: NS** **1º Combined M/M: ACEI+ARB = -13.2%** **ACE intolerant: -33% all cause mortality**	**1º All-cause mortality: NS** **2º CV Death, MI, or HF:NS** **Valsartan non-inferior to Captopril**	**1º All-cause mortality: NS** **2º CV death or HF hospitalization:** **•CHARM Added:** **–ACEI+ARB = -15%** **•CHARM Alternative:** **–ARB = -30%** **•CHARM Preserved: NS**

Evidence for Various ARBs

	Diovan (valsartan)	Avapro (irbesartan)	Cozaar (losartan)	Atacand (candesartan cilexetil)	Micardis (telmisartan)	Teveten (eprosartan)
Reduction in microalbumin-uria with starting dose	-45%	-6%	-35%	-30%	N/a	N/a
Heart failure hospitaliza-tions	-27.5% (ValHeFT)	N/a	-8.1% (ELITE II)	-17% (CHARM)	N/a	N/a
CV outcome in CHF-treated patients	-13.3% (ValHeFT)	N/a	+7% (ELITE II)	-15% (CHARM)	N/a	N/a
Positive CV outcomes in CHF	Yes	N/a	No	Yes	N/a	N/a
Equivalent Efficacy to ACEi post MI	Yes	N/a	No	N/a	N/a	N/a

HF Trials Modulating β receptors

Trial	HF Pts	N	Rx	RR
US Carvedilol	II-III	1,094	Carvedilol	0.35
Aus-NZ	II	415	Carvedilol	0.74
CIBIS II	EF<35%	2,647	Bisoprolol	0.66
MERIT	EF<40%	3,991	Metopr-CR	0.66
COPERNICUS	EF<25%	2,289	Carvedilol	0.65

Background Rx = ACEi + Diuretics +/- Digoxin

Number Need to Rx in HF

TRIAL	Therapy	Annual Mortality-Placebo	Annual Mortality-Treatment	Absolute Risk Reduc'n	NNRx/year to Save One Life
SOLVD	Enalapril vs. Plac	12.5%	11.2%	1.3%	77
MERIT	Metoprolol vs. Plac	11.0%	7.2%	3.8%	26
CIBIS-2	Bisoprolol vs. Plac	13.2%	8.8%	4.4%	23
COPERNICUS	Carvedilol vs. Plac	18.5%	11.4%	7.1%	14
RALES	Spiro vs. Placebo	22.5%	15.8%	6.7%	15

Lee, Liu, Packer

β-adrenergic Blocking Agents

- Titrate to target dose
  - Bisoprolol 1.25 -10 mg OD
  - Carvedilol 3.125 - 25 mg BID
  - Metoprolol 12.5 - 50 to75 mg /BID
- If unable to tolerate high dose β-blocker maintain highest tolerated dose
- Continue indefinitely

Patient Selection for Successful β - Blocker Initiation

- Stable symptoms
- Stable background heart failure medications
- No recent CV hospitalization
- Stable CV status (no hypotension or bradycardia)
- Euvolemic status
- Start low and titrate slowly

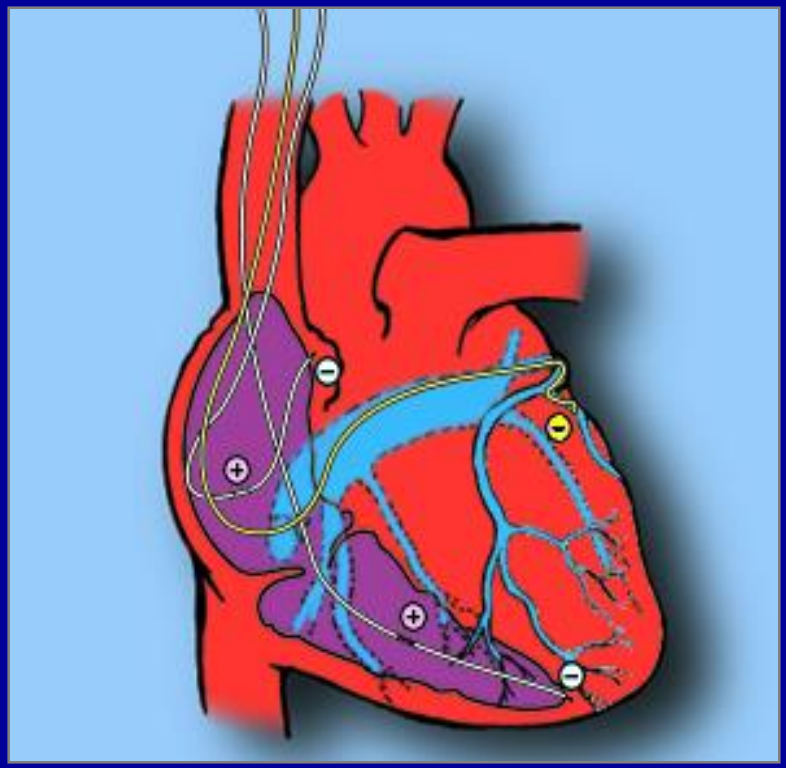
Patients With Heart Failure Who Should Not Be Started on β-blockers

- General Contraindications
  - Bronchospastic pulmonary disease
  - Severe bradycardia, high degree AV block, sick sinus syndrome
- Heart Failure Considerations
  - Congestive symptoms at rest (NYHA Class IV)
  - Patients who require intravenous therapy for HF
  - Unstable symptoms or recent changes in background medications
  - Hospitalized patients (especially for worsening HF)

Device Therapy: Biventricular Pacing

Cardiac Resynchronization Therapy (CRT)

- Atrial-biventricular stimulation
- Electrical synchronization → narrower QRS
- Mechanical synchronization → reverse remodeling



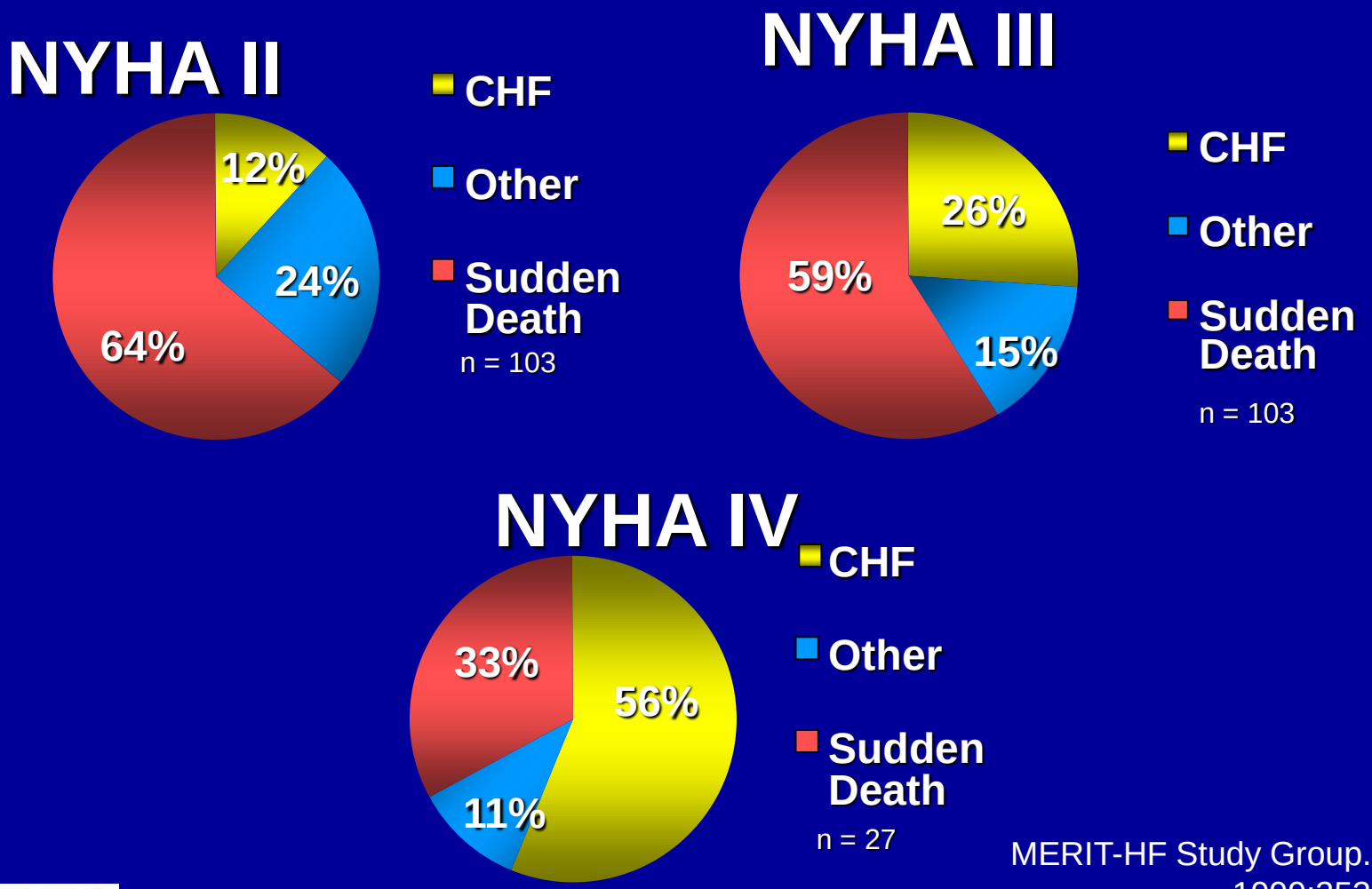
Cardiac Resynchronization Therapy Key Points

- **Indications**
  - Moderate to severe CHF who have failed optimal medical therapy
  - EF<30%
  - Evidence of electrical conduction delay

- Timing of Referral Important
  - Patients often not on optimal Medical Rx
  - Patients referred too late- Not a Bail Out

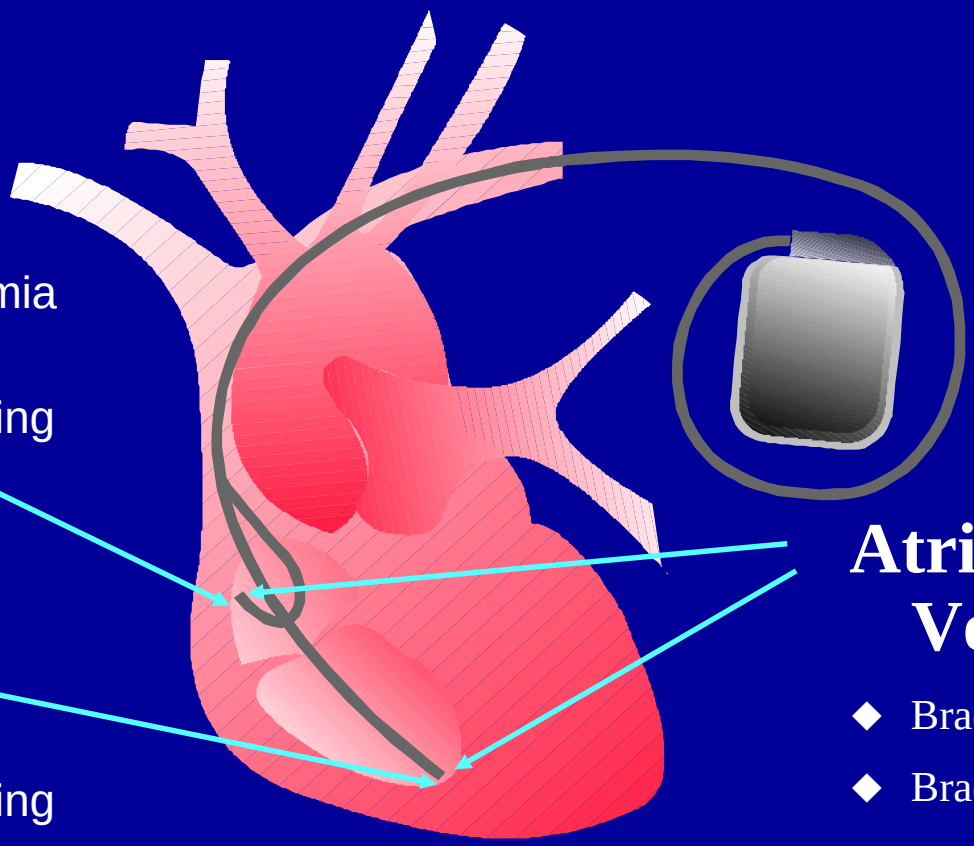
Defibrillators (ICD's)

Severity of Heart Failure
Modes of Death



MERIT-HF Study Group. LANCET 1999;353:2001-07.

Therapies Provided by Today's Dual-Chamber ICDs



Atrium

- AT/AF tachyarrhythmia detection
- Antitachycardia pacing
- Cardioversion

Ventricle

- VT/ VF detection
- Antitachycardia pacing
- Cardioversion
- Defibrillation

Atrium & Ventricle

- Bradycardia sensing
- Bradycardia pacing

SCD-HeFT: Primary Conclusions

1. In class II or III CHF patients with EF $\leq$ 35% on good background drug therapy, the mortality rate for placebo-controlled patients is 7.2% per year over 5 years
2. Simple, single lead, shock-only ICDs decrease mortality by 23%
3. Amiodarone, when used as a primary preventative agent, does not improve survival

Sudden Cardiac Death
SCD-HeFT
Heart Failure
Trial

UNIVERSITY OF CALIFORNIA

Bardy G et al.
NEJM 2005; 352:3

Implantable Cardiac Defribrillators

EBM Therapies	Relative Risk Reduction	Mortality 2 year
ACE-I	↓ 23%	27%
B-Blockers	↓ 35%	12%
Aldosterone Antagonists	↓ 30%	19%
ICD	↓ 31%	8.5%

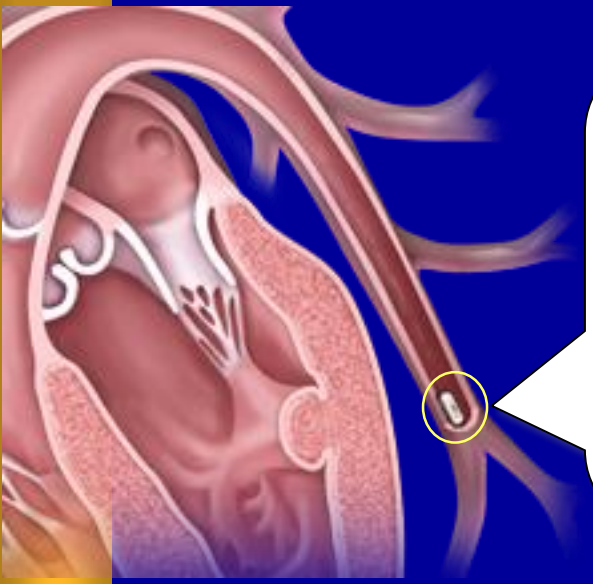
Who should Consider an ICD?

- Patients with weakend heart, New York Heart Association (NYHA) Class II and III heart failure, and measured left ventricular ejection fraction (LVEF) ≤ 35%

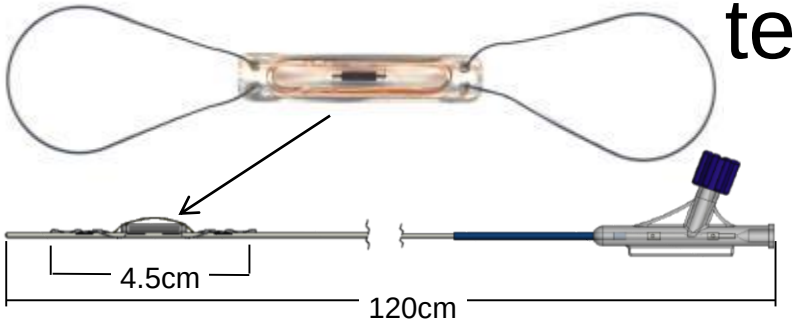
- Patients who meet all current requirements for a cardiac resynchronization therapy (CRT) device and have NYHA Class IV heart failure;

Other Therapies

CardioMEMS™ HF System

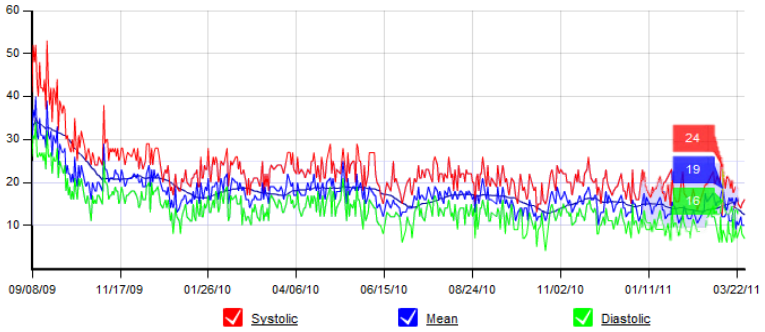


PA Pressure Sensor on Ca tem

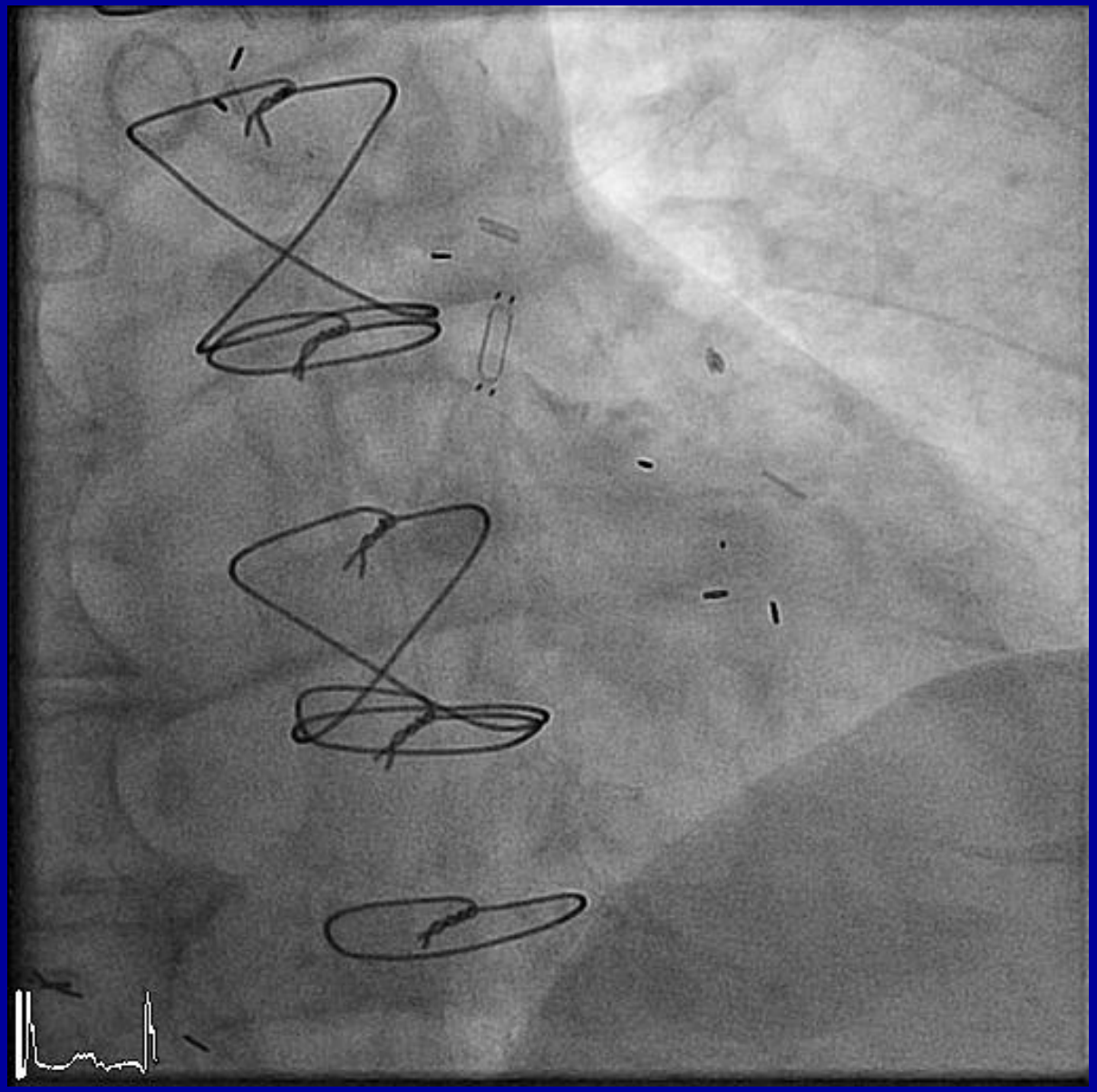


Patient Home Electronics Unit

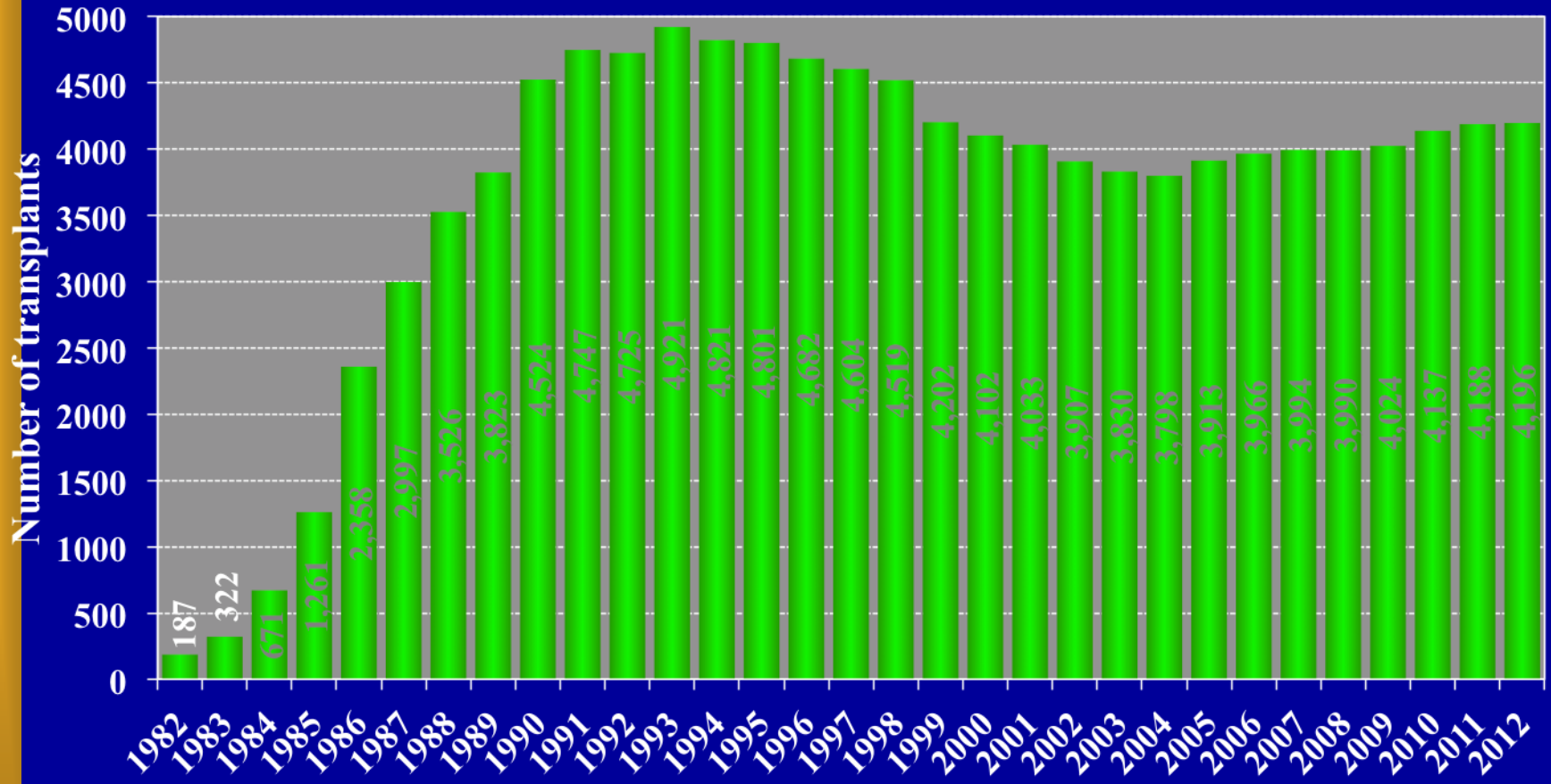
PA Pressure



Physician Access Via Secure Website



Adult and Pediatric Heart Transplants
Number of Transplants by Year

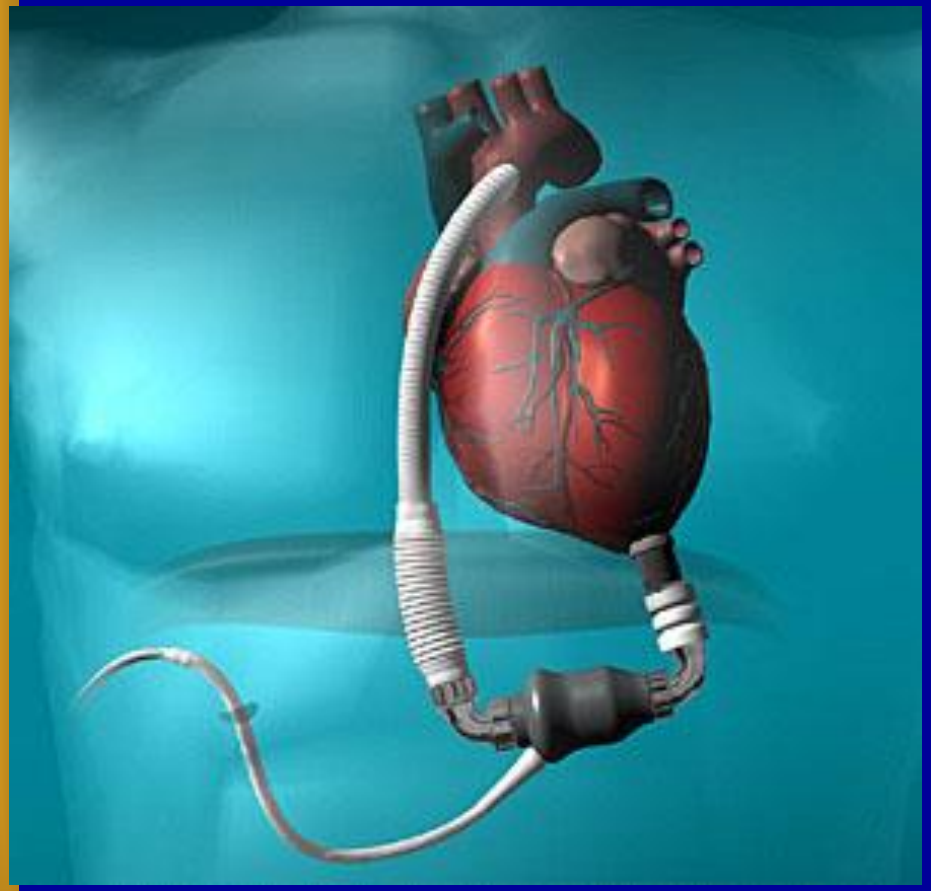


JHLT. 2014 Oct; 33(10): 996-1008

Ventricular Assist Devices (VAD)

- The first VADs were developed in the 1960s.
- Successful use did not occur until 1980s, but their use has been limited to heart transplant centers
  - Durability measured in days to weeks
  - Large in size
  - Many moving parts
  - Exclusively bridge to transplant
- Widespread use in the HF population has not been seen until recently

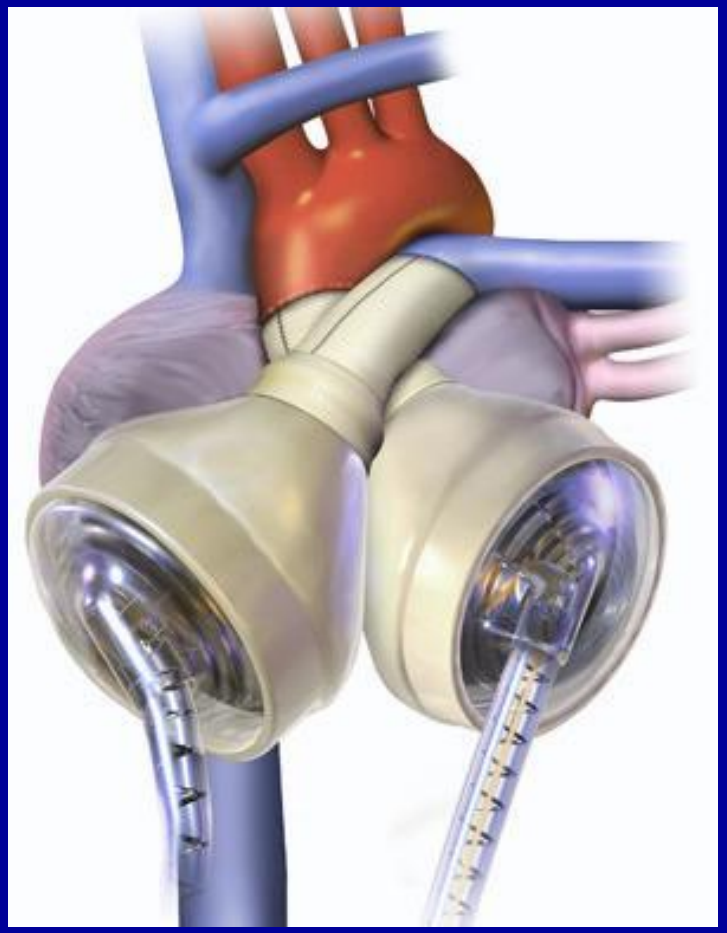
HeartMate II



- FDA approved as a bridge to transplant 2008.
- FDA approved as destination therapy in 2010
- Appropriate for end-stage systolic heart failure patients

Total Artificial Heart

- Bridge to transplant
  - Biventricular failure
  - Refractory arrhythmias
  - Restrictive cardiomyopathy
- Longest “run” 46 months
- Pneumatic
- Patients can be outpatient



Final Frontier

Heart Recovery/Cure?

- VADs + aggressive neurohormonal blockade
  - Myocardial recovery and VAD explant
- Gene Therapy?
- Stem Cells?

What have we learned?

Goals & Outcomes

- Improve symptoms
- Improve quality of life
- Prevent progression of LV dysfunction
- Reduce hospitalization and morbidity
- Reduce mortality
  - Progression of HF
  - Sudden death

In Summary….

- Heart failure is common and has high mortality
- Drug therapy improves survival
  - Betablockers, ACE-I, aldosterone antagonists
- Newer device therapies are showing promise for symptom relief and improved survival
  - Biventricular pacing, ICD's, LVADs

Summary

- Chronic disease management models of multidisciplinary teams and home monitoring will be a mainstay of therapy
- The standard of care ranges from medical therapy to surgical therapy
- Other therapies continue to be developed

THANK YOU