The Future of Cardiovascular Disease
Congestive Heart Failure

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Objectives

• Review epidemiology of heart failure
  – Elderly
• Briefly review therapeutic advances
• Discuss major shortcomings in diagnosis and management of heart failure
• Future research directions
“Types” of heart failure

- Ischemic and non-ischemic systolic dysfunction
- Heart failure with normal ejection fraction (HFNEF)
- Acutely decompensated heart failure

- Heart failure with specific pathophysiology
  - Congenital heart disease
  - Primary valvular disease
  - Infiltrative diseases
  - Post-transplant graft failure
  - HOCM
  - Etc.
Advances in treatment:
Ischemic and non-ischemic systolic dysfunction

• Renin-angiotensin system modulation
• Beta-blockers
• Aldosterone antagonists
• Hydralazine/Nitrates
• Defibrillators
• BiV pacers
• Etc.
Incidence and Prevalence of Heart Failure in Elderly Persons, 1994-2003

Lesley H. Curtis, PhD; David J. Whellan, MD, MHS; Bradley G. Hammill, MS; Adrian F. Hernandez, MD, MHS; Kevin J. Anstrom, PhD; Alisa M. Shea, MPH; Kevin A. Schulman, MD

Figure 1. Age-specific incidence of heart failure among Medicare beneficiaries from January 1, 1994, through December 31, 2003. From 1994 through 2003, the incidence of heart failure increased slightly among the youngest Medicare beneficiaries and declined among older beneficiaries.

Arch Intern Med. 2008;168(4):418-424
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Table 3. Prevalence of Heart Failure in the Medicare 5% Sample by Sex and Year*

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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>53,390</td>
<td>58,456</td>
<td>62,520</td>
<td>66,309</td>
<td>68,942</td>
<td>70,465</td>
<td>72,133</td>
<td>74,177</td>
<td>76,376</td>
<td>78,709</td>
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<tr>
<td>2000</td>
<td>Female</td>
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*Data are given as number (rate). Rates shown are per 1000 eligible Medicare beneficiaries. P < .01 for females, males, and the overall group for all years.

Arch Intern Med. 2008;168(4):418-424
Hospital discharges for heart failure by sex
United States: 1979-2005

Source: NHDS, NCHS and NHLBI.

Note: Hospital discharges include people discharged alive, dead and status unknown.
Heart Failure Epidemic

- Over 5 million subjects in US have HF

- > 550,000 patients are diagnosed each year.

- Heart failure is the primary reason for 15 million office visits and 6.5 million hospital days each year.

- Annual number of hospitalizations has increased to > 1 million for HF as a primary diagnosis and from > 3 million for HF as a primary or secondary diagnosis.

- Re-hospitalization rates approximately 50% within 6 month of discharge among Medicare beneficiaries.

- It has been estimated that in 2005, the total direct and indirect cost of HF in the United States was equal to $27.9 billion.

AHA/ACC 2005 heart failure guideline update
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Figure 2. Mortality after onset of heart failure by year of incidence and sex. Risk-adjusted mortality at 30 days, 1 year, and 5 years decreased slightly from January 1, 1994, through December 31, 2003.

Arch Intern Med. 2008;168(4):418-424
Aging of the United States Population and Heart Failure Risk

• 78 million baby boomers are aging
• Approximately 1 in 5 Americans are expected to be over the age of 65 years by 2050
• In 2000, about 35 million Americans were age ≥65 and older (12% of the population).
• This number will increase in the next forty years to 80 million.

» The Booming Dynamics of Aging: The White House Conference on Aging
Past 5 years…

• Primarily negative trials !!!!
  – Endothelin blockers
  – Vasopressin antagonists
  – NEP inhibitors
  – Combination therapy
  – Implanted devices for pressure assessment
  – Calcium sensitizers
  – Chronic infusion of vasodilators
  – Less than 30% of the trials have been positive
## Acute Heart Failure: Neglected?

<table>
<thead>
<tr>
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<th>Acute Decompensated Heart Failure</th>
<th>Acute MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalizations/year</td>
<td>1,000,000</td>
<td>1,000,000</td>
</tr>
<tr>
<td>Inpatient Mortality</td>
<td>3-4%</td>
<td>3-4%</td>
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<tr>
<td>30-day Readmission</td>
<td>10-20%</td>
<td>6-8%</td>
</tr>
<tr>
<td>Guidelines for Risk Stratification</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Guidelines for Therapy</td>
<td>Yes (ESC), No (AHA/ACC)</td>
<td>Yes</td>
</tr>
<tr>
<td>Largest Randomized Trial</td>
<td>N=1412</td>
<td>N=41,021</td>
</tr>
<tr>
<td>Medline Citations (1965-2006)</td>
<td>472</td>
<td>33,908</td>
</tr>
</tbody>
</table>
Reasons for trends

- What is the taxonomy and different pathophysiologic sub-groups of ADHF?
- Low vs. normal vs. high BP?
- Low cardiac output vs. high SVR or combination?
- Treat volume and or hemodynamics without having any idea of either
  - Use pressure as a surrogate
  - Could BNP change this?
Worsening hospitalization and readmission rates: Reasons for trends

- No idea how to treat!
  - Diuretics
  - Worsening renal function, complications, mortality!
  - Risk marker vs. risk factor?
- No idea when to discharge!
- Goals of treatment?
- Importance of co-morbidity
- Risk stratification
Heart Failure with Preserved EF

Distribution of Ejection Fraction
5297 Pts Hospitalized with HF

Data from Trials

DHF
Women

Men

LV Ejection Fraction

Data from EHJ 2003; 24: 442
Kaplan-Meier Survival Curves for Patients with Heart Failure and Preserved or Reduced Ejection Fraction

Comparable effect on
Symptoms
QoL
Complications
Hospitalization rate

Heart Failure with Preserved EF

• Trials
  – DIG trial
  – CHARM Preserved Arm
  – PEP-CHF
Number at risk:
Candesartan  1514  1458  1377  833  182
Placebo     1509  1441  1359  824  195

CV death or HF hospitalization (%)

HR 0.89 (95% CI 0.77-1.03), \( P=0.118 \)
Adjusted HR 0.86, \( P=0.051 \)

11% risk reduction

CHARM-Preserved
*Primary Endpoint*

HF, heart failure; HR, hazard ratio; CI, confidence interval.
Perindopril in HFNEF in elderly

Large cross-over from placebo to treatment arm

Eur Heart J 2006
Do these patients really have HF?

• Clinical symptoms of heart failure with normal ejection fraction
  – Heart failure symptoms (SOB, fatigue) and physical examination (edema, JVD) are non-specific
Patterns of Left Ventricular Diastolic Filling as Shown by Standard Doppler Echocardiography

Burden of Systolic and Diastolic Ventricular Dysfunction in the Community
Appreciating the Scope of the Heart Failure Epidemic

Figure 4. Kaplan-Meier Mortality Curves for Participants With Normal Diastolic Function vs Subjects With Mild or Moderate or Severe Diastolic Dysfunction

<table>
<thead>
<tr>
<th>Diastolic Function</th>
<th>Normal</th>
<th>Moderate or Severe Dysfunction</th>
<th>Mid Dysfunction</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk</td>
<td>1277</td>
<td>1277</td>
<td>1275</td>
<td>985</td>
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<tr>
<td>Months</td>
<td>366</td>
<td>361</td>
<td>246</td>
<td>122</td>
</tr>
<tr>
<td>Year</td>
<td>131</td>
<td>126</td>
<td>94</td>
<td>59</td>
</tr>
</tbody>
</table>

Logrank $P < .001$
CHARM Preserved: Diastolic Function Echo / Doppler

Free of HF Hosp or Death

Normal
Mild
Moderate
Severe

{ 44% }
Brain natriuretic peptide predicts mortality in the elderly

![Survival Curve Graph]

Heart 1997;77:264-267
• Patients who have HF do not have HF and those who do not have HF, have HF?
How to diagnose HFNEF

Symptoms or signs of heart failure

Normal or mildly reduced left ventricular systolic function
LVEF > 50%
and
LVEDVI < 97 mL/m²

Evidence of abnormal LV relaxation, filling, diastolic distensibility, and diastolic stiffness

Invasive Haemodynamic measurements
mPCW > 12 mmHg
or
LVEDP > 16 mmHg
or
τ > 48 ms
or
b > 0.27

TD

E/E' > 15

15 > E/E' > 8

Biomarkers
NT-proBNP > 220 pg/ml
or
BNP > 200 pg/mL

Biomarkers
NT-proBNP > 220 pg/mL
or
BNP > 200 pg/mL

Echo – bloodflow Doppler
E/Aₜ₅₀ yr < 0.5 and DTₜ₅₀ yr > 280 ms
or
Ard–Ad > 30 ms
or
LAVI > 40 mL/m²
or
LVMI > 122 g/m² (♀); >149 g/m² (♂)
or
Atrial fibrillation

TD

E/E' > 8

HFNEF
Nearly 40% of patients with CHF had 5 non-cardiac comorbidities, this group accounted for 81% of the total inpatient hospital days experienced by all CHF patients.

After controlling for demographics and other diagnoses, comorbidities were associated with higher risks for CHF-preventable and all-cause preventable hospitalizations, and mortality.

Braunstein, JACC 2003;42:1226
Glass is looking pretty empty
Prevention of Heart Failure

• The best way to treat heart failure is to PREVENT heart failure
New Approach to the Classification of Heart Failure

A
High risk for developing heart failure (HF)
- Hypertension
- CAD
- Diabetes mellitus
- Family history of cardiomyopathy

B
Asymptomatic HF
- Previous MI
- LV systolic dysfunction
- Asymptomatic valvular disease

C
Symptomatic HF
- Known structural heart disease
- Shortness of breath and fatigue
- Reduced exercise tolerance

D
Refractory end-stage HF
- Marked symptoms at rest despite maximal medical therapy (eg, those who are recurrently hospitalized or cannot be safely discharged from the hospital without specialized interventions)
Prevention of Heart Failure

• Almost no specific data except treat individual risk factors!

• Multi-risk marker strategy?

• Elderly – risk factor importance differences?
  – CHS, 66% incident HF cases developed in subjects without baseline history of CAD; >50% never had a preceding coronary event

• Risk factor epidemiology and risk factor treatments are changing
  – PAR effects?
Next steps

• How to diagnose HF?
  – Medication use and HFNEF
  – Clinical diagnosis and HFNEF
  – Biomarker?
  – European guidelines
    • Feasibility?
    • Sensitivity/specificity
Prevention of Heart Failure

- How to identify elderly as risk
- Inter-play of multiple risk factors
- Details of treatment strategies
  - Not everything that lowers the BP lowers the risk the same!
- Life style modification?
Next step

• Systolic dysfunction
  – Continuing major effort in VADs, drugs, devices, regenerative medicine etc. on-going

• HFNEF and ADHF
  – Understand pathophysiology and mechanisms
    • Central and peripheral structure, function, determinants of both and outcomes
  – Define taxonomy
Genomic Era Analytic Tools

Genome

SNPs Analysis

Transcriptomics

Proteomics

Metabolomics

Ginsberg, JACC 2005
However . . . .

• Disease and outcomes determinants go beyond the “high-tech”
  – Social issues
  – Psychological issues
  – Behavioral
  – Perceptions
  – Etc.
Next steps

• Disease management vs. Patient management

• Cohort studies
**Normal Controls** (to compare distribution of risk factors)

- Not currently included
- Leverage other cohorts

**At risk population** (to understand HF development)

- Clinical Heart Failure

**New Onset**
- Not on optimal therapy
- Help understand progression/remodeling
- Help understand effect of therapy

**Established**
- Help understand outcomes

**Systolic dysfunction**
- HF with preserved EF
Science of Death

• Cancer vs. Heart Failure
• Futile end of life effort
• Family and patient acceptance of death
• Education – individuals and society
• Timely end of life discussions and plans
Limits of Discovery

... for there is only one universe to discover, and Newton discovered it

Pi
Director/Writer, Darren Aronofsky