THE KENNETH L. BAUGHMAN MEMORIAL LECTURE

HEART FAILURE THERAPY: PAST, PRESENT, AND FUTURE

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• I have no disclosures or potential conflicts of interest related to this presentation
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- Director, Advanced Heart Disease Program, BWH
- Master Clinician
- World authority on myocarditis and the cardiomyopathies
- Friend, mentor, and role model to generations of cardiology fellows and faculty
TOPICS TO BE ADDRESSED

• Heart Failure: Past Successes and Failures
  – Hemodynamic vs. neurohormonal hypotheses
• Current Treatment: Pharmacology and Devices
  – Biomarker-guided therapy
  – New therapeutic targets:
    • Cardiorenal syndrome
    • Anemia and iron deficiency
  – Device-based treatment
  – Heart failure with preserved ejection fraction
• Future Management of Heart Failure
  – Cardiac regeneration
    • Cellular and gene therapies
  – Mechanical circulatory support
HEART FAILURE THERAPY

GOALS

- Improve Survival
- Eliminate or ↓ symptoms
- ↑ Exercise Tolerance
- ↓ Hospitalizations
- Ameliorate Progression of LV Dysfunction
HEART FAILURE THERAPY
HISTORICAL PERSPECTIVE (1980-1995)

• Hemodynamic hypothesis: Heart failure signs and symptoms are manifestations of a “weak pump” and therapies that increased myocardial contractility would improve symptoms, exercise capacity, and survival

• Agents:
  – β-agonists (dobutamine)
  – Phosphodiesterase III inhibitors (milrinone, amrinone)
  – Digoxin
MULTICENTER DOBUTAMINE TRIAL FOR REFRACTORY HEART FAILURE

- 60 Patients with NYHA class IV symptoms were randomized to receive 48 hrs of high dose dobutamine (mean: 8 mcg/kg/min) or placebo as outpatient therapy. Frequent cross-over of patients occurred during the trial.

<table>
<thead>
<tr>
<th>Exercise Duration</th>
<th>Mortality</th>
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<tbody>
<tr>
<td>Placebo</td>
<td>13%</td>
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<tr>
<td>Dobutamine</td>
<td>91%</td>
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<td>P-value</td>
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MILRINONE IN ACUTE HEART FAILURE
OPTIME-CHF TRIAL RESULTS

NEUROHORMONAL ANTAGONIST ERA (1985-2000)

SUMMARY OF MAJOR CLINICAL TRIALS

Vasodilator Hypothesis

- BHAT, 1982
- VHeFT-I, 1986
- CONSENSUS-I, 1987
- CAST, 1989
- PROMISE, 1991
- VEST, 1993
- FIRST, 1997
- MOXCON, 1999
- RECOVER, 2001
- OPTIME, 2002

Neurohumoral Hypothesis

- SOLVD-T, 1991
- SAVE, 1992
- AIRE, 1993
- TRACE, 1995
- US Carvedilol, 1996
- DIG, 1997
- RALES, 1999
- CIBIS-II, 1999
- MERIT-HF, 2000
- COPERNICUS, 2001
- VaHeFT, 2002
- CAPRICORN, 2003
- CHARM, 2003
- EPESUS, 2003

The Future
- Pharmacogenomics
- Prevention

N=20

Positive Clinical Trials

- N=20

Negative Clinical Trials

- N=7

Equivocal Clinical Trials

- N=7

Italics = Post-MI trials.
AHA/ACC CLASS I RECOMMENDATIONS FOR TREATMENT OF PATIENTS WITH SYMPTOMATIC LEFT VENTRICULAR SYSTOLIC DYSFUNCTION (STAGE C DISEASE)

- Beta-blockers (specifically bisoprolol, carvedilol, or sustained release metoprolol succinate) are recommended for all patients with current or prior heart failure symptoms, unless contraindicated (Level of evidence: A)

- ACE inhibitors (class effect) or ARBs (specifically candesartan, valsartan) are recommended for patients with current or prior symptoms of heart failure who are ACE intolerant or as first line therapy (Level of evidence: A)

- An aldosterone antagonist (spironolactone, eplerenone [post-MI]) is reasonable in selected patients with moderately severe to severe symptoms who can be carefully monitored for renal function and potassium concentration. (Level of evidence: B)

• Biomarker-directed care
• Novel targets:
  – Cardiorenal syndrome
  – Anemia & iron deficiency
• Device-based therapy
• Diastolic heart failure treatment

**Freedom from CHF Death or Hospitalization**

- CHF Deaths: 3 vs. 9
- CHF hospitalizations: 22 vs. 48 (p < 0.001)
- BNP < 100 pg/ml: 16%

220 NYHA class II or III patients receiving ACE and β-blockade were randomized to conventional or BNP-guided treatment at 3 month intervals.
MGH PROTECT TRIAL

PRIMARY ENDPOINT

*Logistic Odds \(_{NT-proBNP} = 0.44\)
(95% CI = .22-.84; \(P = .019\))

*Adjusted for age, LVEF, NYHA Class, and eGFR
MHG PROTECT TRIAL
OUTCOME WITH NT-PRO-BNP GUIDED THERAPY

NT-PRO-BNP GUIDED THERAPY AND CHANGE IN ECHOCARDIOGRAPHIC PARAMETERS

CARDIO-RENAL SYNDROME

Definition: >25% increase in serum creatinine or rise ≥ 0.3 mg/dL that occurs during attempted diuresis and persists after diuresis has been accomplished

- 2-fold increase in mortality in some but not all series

- Associated with: older age, elevated baseline creatinine, lower BP, longer duration of heart failure symptoms, hyponatremia

- Not associated with “low output” hemodynamics

- Occurs with both systolic and diastolic heart failure

- Potential therapies:
  - adenosine antagonists [rolofylline]
  - vasopressin antagonists [tolvaptan, conivaptan]
  - ultrafiltration

DOSING OF DIURETICS FOR INPATIENT HEART FAILURE

THE DOSE HF TRIAL

• 808 pts with ADHF randomized to continuous or IV bolus loop diuretic, high (2.5x) vs. low dose (1x) oral loop diuretic

Weight Loss

<table>
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<th>Weight Loss (lbs)</th>
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<tr>
<td>Bolus</td>
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<tr>
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<td>P=0.20</td>
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Change in Creatinine

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<tr>
<td>P=0.21</td>
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<table>
<thead>
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<th>Change in Creatinine (mg/dL)</th>
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<tbody>
<tr>
<td>High</td>
<td>0.08</td>
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</table>

200 Patients hospitalized for acute HF decompensation were randomized to ultrafiltration or intravenous diuretics

Mean age: 63 ±15 years; 69% men; mean LVEF< 40%: 70%

Medical therapy on admission:
- ACE/ARB: 66%
- β-blocker: 66%
- Loop diuretic: 75% (mean furosemide equiv:125 mg)
- Aldosterone antagonist: 22%

PRIMARY END POINT WEIGHT LOSS (48 HR)

FREEDOM FROM RE-HOSPITALIZATION FOR HEART FAILURE

POTENTIAL BENEFITS AND CONCERNS ABOUT ULTRAFLTRATION

• More rapid removal of fluid
• Isotonic fluid removal & higher clearance of sodium load
• Lack of further activation of the SNS, renin-angiotensin-aldosterone system
• Renal tubules “resensitized” to diuretic/Na\(^+\) handling

• Efficacy versus equally aggressive weight loss on diuretics alone remains unknown
• Single positive trial, no data on mortality
• No clear benefit on renal function
• Greater cost
• Specialized nursing expertise required
• Catheter-related complications (infection, thrombosis)

ACC/AHA 2009 class IIa indication for refractory HF*

Patients had already sustained rise in creatinine > 0.3 mg/dl before randomization.

ONGOING CARDIORENAL CLINICAL TRIALS

- Ultrafiltration: AVOID-HF trial
  - 90 day rehospitalization rate
- Vasodilator: ROSE-HF trial
  - low dose dopamine versus low dose nesiritide
  - Renal function and rehospitalization rate
- Vasopressin Antagonist: TACTICS trial
  - Adjunctive tolvaptan to diuretic therapy
  - Renal function, rehospitalization rate
INCIDENCE OF ANEMIA BY HEART FAILURE SEVERITY

IRON DEFICIENCY AND IMPAIRED EXERCISE CAPACITY IN CHRONIC SYSTOLIC HEART FAILURE

DELETERIOUS EFFECTS OF IRON DEFICIENCY IN HEART FAILURE

- Decreased functional capacity (*maximal and submaximal*)
- Ultrastructural changes in myocytes
- Increased catecholamine production
- Stimulation of left ventricular hypertrophy
- Increased risk of mortality

EFFECT OF INTRAVENOUS IRON IN CHRONIC HEART FAILURE


- Randomized, double-blind placebo-controlled trial of 40 anemic patients
- 200 mg IV iron sucrose x 5 weeks
- Hemoglobin increased 1.4 g/dL at 6 months
- Outcomes in iron-treated cohort:
  - Decrease in NT-pro-BNP and CRP
  - Improvement in LVEF
  - Increase in 6-min walk distance
Study population:

• 18 anemic patients (hemoglobin < 12.5 g/dl) and 17 non-anemic patients (hemoglobin: 12.5-14.5 mg/dl) randomized to open-label observer blinded treatment with intravenous iron sucrose infusion or placebo infusion.

Protocol:

• 200 mg/week x 8 weeks; 200 mg/month x 3 months

Primary endpoint:

• peak VO₂ at 18 weeks

EFFECT OF INTRAVENOUS IRON ON EXERCISE CAPACITY IN HEART FAILURE
FERRIC-HF TRIAL RESULTS

• Peak VO₂ increased in anemic but not non-anemic patients
• Δ Peak VO₂ not related to Δ hemoglobin but to increase in transferrin saturation (TSAT)
• Improvement in NYHA functional class in both groups

ONGOING TREATMENT TRIAL OF IRON DEFICIENCY IN HEART FAILURE

• **IRONOUT-HF** (NHLBI Heart Failure Network Trial of oral iron replacement)
ACC/AHA/HRS GUIDELINES FOR CARDIAC RESYNCHRONIZATION THERAPY IN HEART FAILURE

Class I Indication (level of evidence: A)

- NYHA Class III or ambulatory class IV heart failure symptoms despite optimized diuretic, vasodilator and beta-blocker therapy
- Sinus rhythm
- QRS prolongation ($\geq 120$ msec)
- Severely impaired contractility (LVEF $\leq 35\%$)
- Mechanical dyssynchrony*:
  - Opposing wall (septal/posterior) motion delay by echocardiography
  - Tissue Doppler imaging (TDI)
  - Strain rate delay (radial)
  - Yu index (12 site time-to-peak velocity standard deviation)

BUNDLE BRANCH BLOCK MORPHOLOGY AND OUTCOME FOLLOWING CARDIAC RESYNCHRONIZATION THERAPY

MEDICARE REGISTRY

CARDIAC RESYNCHRONIZATION IN MILD TO MODERATE HEART FAILURE
THE MADIT-CRT TRIAL

- 1820 patients with NYHA class I (14%) or II symptoms (86%)
- Mean LVEF: 24% ± 6%
- LBBB: 70%
- ACE/ARB: 97%
- ß-blocker: 93%
- Diuretic: 75%

CARDIAC RESYNCHRONIZATION IN MILD TO MODERATE HEART FAILURE

THE MADIT-CRT TRIAL

REMOTE MONITORING FACILITATES FOCUSED CARE

- Provides early detection
- Cuts back on office visits, enables remote intervention
- Transmits device data + hemodynamic data
- Remote programming next step

Cleland J, et al. J Am Coll Cardiol; 2005; 45:1654-64
FREEDOM FROM HEART FAILURE EVENTS BASED UPON ESTIMATED PULMONARY ARTERY DIASTOLIC PRESSURE IN PREVIOUS WEEK

REMOTE MONITORING VIA ICD TELEMETRY

THE EVOLVO TRIAL

Implantable Hemodynamic Monitors

Bourge RC, et al. JACC 2008;51:1073-9

DAILY VARIATIONS IN LEFT ATRIAL PRESSURE

LAP = 3 mmHg

LAP = 26 mmHg

LAP = 14 mmHg

LAP = 50 mmHg
REMOTE HEMODYNAMIC MONITORING

HOMEOSTASIS TRIAL

• 40 patients with NYHA class III/IV symptoms

• Frequency of LAP > 25 mm Hg readings decreased by 67%

• NYHA class improved by 0.7 ± 0.8

• ACE/ARB/β-blocker doses up-titrated by 37% (p < 0.001)

• Diuretic doses decreased by 27% (p = 0.15)

LAPTOP-HF TRIAL
LEFT ATRIAL PRESSURE MONITORING TO OPTIMIZE
HEART FAILURE THERAPY

INSTRUCTIONS

PRESRIPTION

Review LAP Data

Download
CONVENTIONAL AND EMERGING THERAPIES FOR ADVANCED SYSTOLIC HEART FAILURE

Thinking “Outside of the Box”

- Diuretics
- Spironolactone
- Digoxin
- ACEIs
- Beta-blockers
- ARBs
- HYD/ISDN
- Lifestyle Δs

ICD

Bi-V pacing

Hemodynamic monitoring

Cell Tx

Gene Therapy

Surgical LV Remodeling

Surgery: CABG AVR MVR

Htx

VAD

Ultrafiltration

?? New Drugs: Vasopressin Ant

?? Anemia

?? Nesiritide

Adapted from Young JL
DIASTOLIC HEART FAILURE
NEW PATHOPHYSIOLOGIC PARADIGM

Heart
Restrictive filling pattern

Kidney
(impaired volume handling)

Vasculature
(↑vessel stiffness)

Neurohumoral Ventricular-vascular coupling
GOALS OF THERAPY IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

• Decrease diastolic filling pressures
  – Diuretics, nitrates
• Control blood pressure and heart rate
  – At rest and during exercise
• Prevent or regress left ventricular hypertrophy
  – RAS inhibitors, SNS antagonists, ? autonomic modulation
• Manage medical co-morbidities
  – Diabetes, obesity, ischemia, arrhythmias, sleep apnea
• Promote exercise and decrease deconditioning
TREATMENT EFFECT ON EXERCISE CAPACITY IN RANDOMIZED CONTROLLED TRIALS IN HEART FAILURE WITH PRESERVED EJECTION FRACTION


- ACE-I
- ARBs
- Verapamil
- Spironolactone
- β-blockers
216 patients randomized to sildenafil or placebo for 24 weeks

RELAX TRIAL: PDE5 INHIBITION IN HEART FAILURE WITH PRESERVED EJECTION FRACTION

Change in Peak VO\textsubscript{2}

\[ p = 0.90 \]

Data are median and IQR

NEW POTENTIAL THERAPEUTIC OPTIONS FOR DIASTOLIC HEART FAILURE

• Aldosterone Antagonists
  – TOPCAT Trial (spironolactone on composite endpoint of mortality and hospitalizations)

• Advanced Glycosylated End-product (AGE) Inhibitors
  – DIAMOND and PEDESTAL trials (open label trials of alagebrium on LV remodeling and mass)
  – BENEFICIAL trial (randomized placebo controlled trial of alagebrium on exercise tolerance diastolic function parameters)

• Neprilysin Inhibitors
  – PARAMOUNT Trial (randomized comparison of ARB to LCZ696C, combination of valsartan + endopeptidase inhibitor)

• Matrix metalloproteinase inhibitors
RENAL SYMPATHETIC DENERVATION FOR REFRACTORY HYPERTENSION

Bertog SC, et al. JACC Interventions 2012;5:229-58
REGRESSION OF LEFT VENTRICULAR HYPERTROPHY BY RENAL SYMPATHETIC DENERVATION

SIMPLICITY HTN-2 TRIAL RESULTS

THE FUTURE OF HEART FAILURE THERAPY 2015-25

- Gene Therapy
- Cell-based Therapy
- Destination Mechanical Circulatory Support
GENE THERAPY FOR CHRONIC HEART FAILURE

Braunwald E. JACC Heart Failure 2013;1:1-10
POTENTIAL TARGETS FOR GENE THERAPY

Calcium Handling
- SERCA2a [CUPID trial]
- Phospholamban
- Kv4.3
- Na/Ca Exchanger
- S100A
- Myofibrillar proteins
- Adenyl cyclase-6

Apoptosis Pathways
- Bcl-2

Adrenergic Signaling
- β2-AR
- βARK

Adapted from Dr. Roger Hajjar
CELL SHORTENING AND CALCIUM TRANSIENT CURRENT

Failing Myocyte + Ad.GFP

Non-Failing Myocyte + Ad.GFP

Failing Myocyte + Ad.SERCA2a

POTENTIAL CELL TYPES FOR CARDIAC REPAIR

18-MONTH OUTCOME OF THE BOOST TRIAL

C-kit+ cells obtained from right atrium during CABG and infused in infarct related artery at 4 months

- 20 treated patients and 13 controls
- LVEF assessed by serial MRI studies
- No data shown for control group

Chugh AR, et al. Circulation 2012;126[Suppl 1]:S54-S64
CARDIAC STEM CELL THERAPY

THE CADUCES TRIAL


- CardioSphere autologous stem cells derived from endomyocardial biopsy after MI
- Patients received intracoronary CDCs or placebo in 2:1 randomization via infract related artery
- Primary endpoint: safety
- Secondary endpoints: change in LV function, scar tissue characterization
CARDIAC STEM CELL THERAPY

THE CADUCES TRIAL

12 Month Findings

Δ LVEF  Δ LVEDV  Δ LVESV

Simpler design, less costly to manufacture, small, low energy requirement, few moving parts to wear and fail. No evidence that absence of pulsatile blood flow is associated with physiologic abnormalities during long-term support.
EVOLUTION OF MECHANICAL CIRCULATORY SUPPORT DEVICES IN ADVANCED HEART FAILURE

Fang J. *NEJM* 2009;361
LVAD THERAPY AS A BRIDGE TO RECOVERY

- 15 pts with non-ischemic cardiomyopathy (LVEF 12% ± 6%)
- LVAD support (320 ± 186 days)
- Rx: ACE, β-blocker, ARB, & aldosterone blocker
- Clenbuterol (β₂-agonist) added when LVEDD had stabilized
- 11/15 devices weaned
- Final LVEF 64% ± 12%

Birks EJ, et al. NEJM 2006;355:1873-84
LEFT VENTRICULAR ASSIST DEVICES
THIRD GENERATION DESIGN

HeartWare Device
Mini mechanical blood bearing centrifugal pump

MagLev Device
Bearingless, centrifugal magnetically levitated impellar Passive system of support in three axis
CONCLUSION

• Heart failure incidence and prevalence will continue to increase as the population ages
• Effective treatment options for heart failure with preserved ejection fraction are urgently needed and will shape the focus of clinical trials the next decade
• New therapeutic targets are being studied: iron deficiency, cardiorenal syndrome
• Hemodynamic monitoring may soon compliment more traditional disease management strategies
• Devices, not drugs, are likely to shape the future of chronic heart failure care
• Therapies that promote myocardial recovery or regeneration remain on the horizon