Advances in Management of Heart Failure & Acute Pulmonary Oedema (APO)
Cardiac Emergency Symposium
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Consultant Cardiologist
IJN
Heart Failure (HF): An Epidemic Of The 21st Century

26 MILLION
ADULTS WORLDWIDE ARE LIVING WITH HEART FAILURE AND THIS NUMBER IS EXPECTED TO RISE\textsuperscript{1,2}

- AGING POPULATION\textsuperscript{2}
- INCREASING PREVALENCE OF RISK FACTORS\textsuperscript{2}
- IMPROVED POST-MI SURVIVAL\textsuperscript{2}

More than 1 million hospitalisations due to heart failure are reported annually in Europe.\textsuperscript{1,4}

Mi = myocardial infarction

Emerging Trends In Cardiovascular Diseases

Several drugs for HF have succeeded in preclinical and early-phase clinical trials, but most of them failed to show the real benefit in key clinical trials.
There has been substantial progress in the management of chronic HF with the availability of drugs such as:
- angiotensin-converting enzyme (ACE) inhibitors
- angiotensin receptor blockers (ARBs)
- beta-blockers (BB)
- mineralocorticoid receptor antagonist (MRA)

In 2015, the US Food and Drug Administration (FDA) approved two new drugs to treat HF:
- Ivabradine and sacubitril/valsartan (LCZ696)

Limited progress in the treatment of acute HF
Definition of Heart Failure

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

Braunwald 8th Edition 2001
Disabling Symptoms Of Heart Failure

Initially :
- Feel easily tired, weak or dizzy
- Short of breath on exertion
- Palpitations

Later :
- Short of breath at rest
- Swelling feet, abdomen due to water retention
- Weight gain despite poor appetite
- Short of breath, cough, wheezing on lying down (PND)
- Unable to sleep at night. Need to use several pillows (Orthopnoea)
Types of Heart Failure

- **Systolic heart failure = HF reduced EF = HFrEF**
  - Decreased systolic function of the heart
  - Causing fluid overloaded in the lungs and heart failure

- **Diastolic heart failure = HF preserved EF = HFpEF**
  - Involves a thickened and stiff heart muscle (hyperthrophy)
  - The heart does not fill with blood properly (reduce filling)
  - This results in fluid overloaded in the lungs and heart failure
Definition of HFrEF and HFpEF

HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction

Steinberg et al. Circulation 2012;126:65–75
HFpEF and HFrEF are associated with similarly high levels of mortality

- Survival rate among patients with a discharge diagnosis of HF in the USA was slightly higher among patients with HFpEF than those with HFrEF between 1987–2001\(^1\)
  - respective mortality rates were 29% and 32% at 1 year and 65% and 68% at 5 years

- HFpEF is associated with significant morbidity and mortality, despite having a slightly higher survival rate compared with HFrEF\(^2,3\)

HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction; USA: United States of America

<table>
<thead>
<tr>
<th>NYHA Functional Class (FC)</th>
<th>PROGNOSIS OF HF PATIENTS</th>
<th>1 Year Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FC I</strong></td>
<td><strong>Asymptomatic.</strong> Ordinary physical activity does not cause undue fatigue, breathlessness or palpitation.</td>
<td>&lt; 5 %</td>
</tr>
<tr>
<td><strong>FC II</strong></td>
<td><strong>Mild.</strong> Such patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, breathlessness or discomfort.</td>
<td>5 – 10 %</td>
</tr>
<tr>
<td><strong>FC III</strong></td>
<td><strong>Moderate.</strong> Although patients are comfortable at rest, less than ordinary activity will lead to symptoms.</td>
<td>20 – 40 %</td>
</tr>
<tr>
<td><strong>FC IV</strong></td>
<td><strong>Severe.</strong> Symptoms of congestive failure are present at rest. With any physical activity, increased discomfort is experienced.</td>
<td>50 – 80 %</td>
</tr>
</tbody>
</table>

** HF causes 2 to 3 times as many deaths as advanced cancers like bowel & breast cancer!
Classification of Heart Failure

• Acute heart failure
  – left ventricular failure
  – acute pulmonary oedema
  – cardiogenic shock

• Chronic heart failure
Risk Factors for Heart Failure

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

- Congenital heart defects
- Other:
  - Obesity
  - Age
  - Smoking
  - High or low hematocrit level
  - Obstructive Sleep Apnea
# Asian Sudden Cardiac Death in Heart Failure (ASIAN-HF) registry

Carolyn S.P. Lam¹, Inder Anand², Shu Zhang³, Wataru Shimizu⁴, Calambur Narasimhan⁵, Sang Weon Park⁶, Cheuk-Man Yu⁷, Tachapong Ngarmukos⁸, Razali Omar⁹, Eugene B. Reyes¹⁰, Bambang Siswanto¹¹, Lieng H. Ling¹, and A. Mark Richards¹

## Etiology of Heart Failure

<table>
<thead>
<tr>
<th>Country</th>
<th>Hypertension</th>
<th>IHD</th>
<th>Valvular</th>
</tr>
</thead>
<tbody>
<tr>
<td>South Korea</td>
<td>20 %</td>
<td>42 %</td>
<td>28 %</td>
</tr>
<tr>
<td>Japan</td>
<td>14 %</td>
<td>25.4%</td>
<td>26.4%</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>37 %</td>
<td>31 %</td>
<td>15 %</td>
</tr>
<tr>
<td>China</td>
<td>12.4%</td>
<td>45 %</td>
<td>--</td>
</tr>
<tr>
<td>Thailand</td>
<td>12 %</td>
<td>47 %</td>
<td>19 %</td>
</tr>
<tr>
<td>Philippines</td>
<td>5.7 %</td>
<td>52 %</td>
<td>20 %</td>
</tr>
<tr>
<td>Indonesia</td>
<td>54.4%</td>
<td>50 %</td>
<td>--</td>
</tr>
<tr>
<td><strong>Malaysia</strong></td>
<td><strong>18.6%</strong></td>
<td><strong>49.5%</strong></td>
<td><strong>4.1%</strong></td>
</tr>
<tr>
<td>Singapore</td>
<td>20.2%</td>
<td>66.5%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Australia</td>
<td></td>
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</tr>
</tbody>
</table>
How Heart Failure Is Diagnosed

- Medical history is taken to reveal symptoms
- Physical exam
- Investigations
  - Chest X-ray
  - Blood tests
  - ECG
  - Echocardiogram
  - Coronary CT Angiogram/Cardiac MRI/ Nuclear scan
  - Coronary angiogram
Three Basic Treatment Strategies

- **Lifestyle Management**
- **Pharmacological Management**
- **Devices & Surgical Management**
## Lifestyle Management That Reduce Mortality & Improve Symptoms In Heart Failure

<table>
<thead>
<tr>
<th>Exercise Training</th>
<th>Consideration be given to patients with stable HF in FC II &amp; III for moderate intensity supervised aerobic exercise program to improve QOL &amp; exercise tolerance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education</td>
<td>Counsel patient &amp; family on prognosis, importance of medications &amp; warning signs of decompensation</td>
</tr>
<tr>
<td>Diet &amp; Nutrition</td>
<td>Advice on salt, fluid restriction &amp; weight reduction if obese</td>
</tr>
<tr>
<td>Lifestyle</td>
<td>Advice on smoking cessation, abstinence from alcohol &amp; avoidance of pregnancy if in FC III-IV</td>
</tr>
<tr>
<td>Immunization</td>
<td>Pneumococcal &amp; annual flu vaccination if no contraindication</td>
</tr>
</tbody>
</table>
Drugs That Reduce Mortality & Improve Symptoms In Heart Failure

<table>
<thead>
<tr>
<th>Drug Categories</th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-Inhibitors*</td>
<td>↓ 16 - 23%</td>
</tr>
<tr>
<td>B-Blockers*</td>
<td>↓ 34 - 35%</td>
</tr>
<tr>
<td>Mineralcorticoid receptor Antagonist (MRA)</td>
<td>↓ 24 - 30%</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Improve symptoms</td>
</tr>
</tbody>
</table>

* 1st line drug therapy
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC.

Authors/Task Force Members: John V. McMurray (Chairperson) (UK)*, Stamatis Adamopoulos (Greece), Stefan D. Anker (Germany), Angelo Auricchio (Switzerland), Michael Böhm (Germany), Kenneth Dickstein (Norway), Volkanar Falk (Switzerland), Gerasimos Filippatos (Greece), Cândido Fonseca (Portugal), Miguel Angel Gomez Sanchez (Spain), Tiny Jaarsma (Sweden), Lars Kober (Denmark), Gregory Y. H. Lip (UK), Aldo Pietro Maggioni (Italy), Alexander Parkhomenko (Ukraine), Burkert M. Pieke (Austria), Bogdan A. Popenescu (Romania), Per K. Rannevik (Norway), Frans H. Rutten (The Netherlands), Juerg Schwitzer (Switzerland), Petar Seferovic (Serbia), Janina Stepinska (Poland), Pedro T. Trindade (Switzerland), Adriana A. Vroors (The Netherlands), Raiez Zannad (France), Andreas Zeiher (Germany).
ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

Treatment options for patients with chronic symptomatic systolic heart failure (NYHA functional class II–IV)

Diuretics
ACEI or ARB
Beta-blockers
MRA
Ivabradine
Device CRT/ICD
Digoxin or Nitrates
LVAD or transplant
Palliative
Initial assessment of patient with suspected acute heart failure

Suspected acute heart failure

- History/examination (including blood pressure and respiratory rate)
- Chest X-ray
- Echocardiogram or NP (or both)
- Blood chemistry

ECG
Oxygen saturation
Full blood count

Simultaneously assess for

- Ventilation/systemic oxygenation inadequate
- Life-threatening arrhythmia/bradycardia
- Blood pressure <85 mmHg or shock
- Acute coronary syndrome
- Acute mechanical cause/severe valvular disease

Urgent action if present

- Oxygen
- NIV
- ETT and invasive ventilation
- Electrical cardioversion
- Pacing
- Inotrope/vasopressor
- Mechanical circulatory support (e.g. IABP)
- Coronary reperfusion
- Antithrombotic therapy
- Echocardiography
- Surgical/percutaneous intervention

ECG = electrocardiogram; ETT = endotracheal tube; IABP = intra-aortic balloon pump; NIV = non-invasive ventilation; NP = natriuretic peptide.

*For example, respiratory distress, confusion SpO₂ <90%, or PaO₂ <60 mmHg (8.0 kPa).

*For example, ventricular tachycardia, third-degree atrioventricular block.

*Reduced peripheral and vital organ perfusion—patients often have cold skin and urine output ≤15 ml/h and/or disturbance of consciousness.

*Percutaneous coronary revascularization (or thrombolysis) indicated if ST-segment elevation or new left bundle branch block.

*Vasodilators should be used with great caution, and surgery should be considered for certain acute mechanical complications (e.g. inter-ventricular septal rupture, mitral valve papillary muscle rupture).
Algorithm for management of acute pulmonary oedema/congestion.

- **Acute pulmonary oedema/congestion**
  - **Intravenous bolus of loop diuretic**
    - Yes: Oxygen
    - No: Hypoxemia
  - **Hypoxemia**
    - Yes: Oxygen
    - No: Severe anxiety/distress
  - **Severe anxiety/distress**
    - Yes: Consider i.v. cpiate
    - No: Measure systolic blood pressure
  - **Systolic blood pressure**
    - SBP <85 mmHg or shock: Add non-vasodilating inotrope or vasopressor
    - SBP 85–110 mmHg: No additional therapy until response assessed
    - SBP >110 mmHg: Consider vasodilator (e.g., NTG)
  - **Adequate response to treatment?**
    - Yes: Continue present treatment
    - No: Re-evaluation of patient’s clinical status
  - **SpO₂ <90%**
    - Yes: Oxygen
    - No: Urine output <20 mL/h
  - **Urinary output <20 mL/h**
    - Yes: Bladder catheterization to confirm
    - No: Bladder catheterization to confirm

**Notes:**
1. In patients already taking diuretic, 2.5 times existing oral dose recommended. Repeat as needed.
2. Pulse oximeter oxygen saturation >90% or PaO₂ >60 mmHg (>9.3 kPa).
3. Usually starts with 40–60% oxygen, increasing to SpO₂ >90% cautiously in patients at risk of CO₂ retention.
4. For example, 4–8 mg of morphine plus 10 mg of metoclopramide, observe for respiratory depression. Repeat as needed.
5. Cold skin, low pulse volume, poor urine output, confusion, myocardiial ischaemia.
6. For example, start i.v. infusion of dopamine 2.5 μg/kg/min, doubling dose every 15 min according to response or tolerance (dose titration usually limited by excessive tachycardia, arrhythmia, or ischaemia). A dose >20 μg/kg/min is rarely needed. Even dopamine may have mild vasodilator activity as a result of beta-2 adrenoceptor stimulation.
7. Patient should be kept under regular observation (symptoms, heart rate, rhythm, SpO₂, urinary output) until stabilized and recovered.
8. For example, start i.v. infusion at 10 μg/kg/min and doubled every 10 min according to response and tolerability (usually dose up-titration is limited by hypotension).
9. Bladder catheterization to confirm: Increase dose of diuretic or use combination of diuretics.
11. Consider right-heart catheterization.
12. Consider ultrafiltration.
CHRONIC HEART FAILURE
Development of new drugs for HF

**INOTROPICS**
- 1946 - DIGOXIN
- 1957 - HCTZ
- 1961 - SPIRONOLACTONE
- 1965 - FUROSEMIDE

**DIURETICS**
- 1974 - NITROGLYCERIN
- 1982 - NITROPRUSSIDE
- 1985 - DA, DOBUTAMINE
- 1987 - ACEIs
- 1988 - CALCIUM ANTAGONIST
- 1996 - β BLOCKERS
- 1999 - ARBs, ALDOSTERONE ANTAGONISTS
- 1999 - NESIRITIDE
- 2000s - A1R ANTAGONISTS
- LEVOSIMENDAN
- AVP ANTAGONISTS
- TNFα INHIBITORS, ET-1 INH.
- ULRATIDE, SILDENAFIL

**VASODILATATORS**

**NEUROHUMORAL INHIBITION**

**INFLAMMATION, APOPTOSIS, METABOLISM REMODELING.....**

- 2008 - ISTAROXIME, OMECAMTIV, IVABRADINE
- 2009 - RELAXIN, ALISKIREN, CINACIGUAT
- 2010 - CXL-1020, RANOLAZINE, 11β-HSD2 INH, GENE THERAPY...
Landmark trials in patients with HFrEF

- **SOLVD-TI** (1991)
  - 2,569 patients
  - Key benefits of enalapril (ACEI) vs placebo:
    - 16% ↓ all-cause mortality

- **CIBIS-II** (1999)
  - 2,647 patients
  - Key benefits of bisoprolol (BB) vs placebo:
    - 34% ↓ all-cause mortality

  - 2,028 patients
  - Key benefits of candesartan (ARB) vs placebo:
    - 23% ↓ CV mortality or HF hospitalization

- **SHIFT** (2010)
  - 6,558 patients
  - Key benefits of ivabradine (I, inhibitor) vs placebo:
    - 18% ↓ CV mortality or HF hospitalization

- **PARADIGM-HF** (2014)
  - 8,442 patients
  - Key benefits of LCZ696 (ARNI) vs enalapril:
    - 20% ↓ CV mortality or HF hospitalization

- **CHARM-Added** (2003)
  - 2,548 patients
  - Key benefits of candesartan (ARB) vs placebo:
    - 15% ↓ CV mortality or HF hospitalization

- **EMPHASIS-HF** (2014)
  - 2,737 patients
  - Key benefits of eplerenone (MRA) vs placebo:
    - 37% ↓ CV mortality or HF hospitalization

Percentages are relative risk reductions vs comparator.

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BB: beta blocker; CV: cardiovascular; HF: heart failure; HFrEF: heart failure with reduced ejection fraction; MRA: mineralocorticoid receptor antagonist. See notes for definitions of study names.

Heart Failure Mortality & Morbidity Remains Substantial Despite New Therapies

Euro Heart Survey II (2007)
Mortality according to number of prescribed drugs (BBs, ACEIs/ARBs, Aldosterone antagonists)

log-rank test $p < 0.001$

Patients at risk
n=2973 2528 2201 2061

Months after discharge

Close This Gap!!
What’s the update on Heart Failure

• Medical therapy
  – Chronic Heart Failure:
    – LCZ696 Sacubitril/Valsartan (Entresto)
    – Patiromer
  – Acute Heart Failure
    – Serelaxin
    – Urodilatin

• New study therapies
• Devices
• Heart transplant and Mechanical circulatory support
MEDICAL THERAPY FOR CHF
LCZ696 Sacubitril/Valsartan (Entresto)
The study was prematurely stopped in March 2014 after median follow up of 27 months for overwhelming benefit.

Malaysia participated in the trial!
Aim Of The PARADIGM-HF Trial

Prospective comparison of ARNI with ACEI to determine impact on global mortality and morbidity in heart failure trial (PARADIGM-HF)

LCZ696 400 mg daily ↔ Enalapril 20 mg daily

Specifically designed to replace current use of ACEI and ARB as the cornerstone of the treatment of heart failure
**LCZ696 is a novel drug which delivers simultaneous neprilysin inhibition and AT$_1$ receptor blockade**\(^1\)\(^–\)\(^3\)

- LCZ696 is a salt complex that comprises the two active components in a 1:1 molar ratio:\(^2\)\(^,\)\(^3\)
  - sacubitril (AHU377) – a pro-drug; further metabolized to the neprilysin inhibitor LBQ657, and
  - valsartan – an AT$_1$ receptor blocker in a 1:1 molar ratio

\(\text{ARNI}:\) angiotensin receptor neprilysin inhibitor; \(\text{AT}_1:\) angiotensin II type 1

PARADIGM-HF: study design

Randomization n=8,442

Double-blind Treatment period

LCZ696 200 mg BID

Enalapril 10 mg BID

Enalapril 10 mg BID for 1–2 weeks followed by enalapril 10 mg BID (20 mg TDD) as an optional starting run-in dose for those patients who are treated with ARBs or with a low dose of ACEI; †200 mg TDD; ‡400 mg TDD; §20 mg TDD

ACEI: angiotensin-converting-enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BID: twice daily; HFrEF: heart failure with reduced ejection fraction; PARADIGM-HF: Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure; TDD: total daily dose

PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

Kaplan-Meier Estimate of Cumulative Rates (%)

Enalapril
(n=4212)

LCZ696
(n=4187)

HR = 0.80 (0.73-0.87)
P = 0.0000002
Number needed to treat = 21

Patients at Risk

<table>
<thead>
<tr>
<th></th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>4187</td>
<td>4212</td>
</tr>
<tr>
<td>180</td>
<td>3922</td>
<td>3883</td>
</tr>
<tr>
<td>360</td>
<td>3663</td>
<td>3579</td>
</tr>
<tr>
<td>540</td>
<td>3018</td>
<td>2922</td>
</tr>
<tr>
<td>720</td>
<td>2257</td>
<td>2123</td>
</tr>
<tr>
<td>900</td>
<td>1544</td>
<td>1488</td>
</tr>
<tr>
<td>1080</td>
<td>896</td>
<td>853</td>
</tr>
<tr>
<td>1260</td>
<td>249</td>
<td>236</td>
</tr>
</tbody>
</table>
Use of LCZ696 compared to enalapril was also shown to significantly reduce:

• Cardiovascular deaths by 20%
• Heart failure hospitalizations by 21%
• All cause mortality by 16%
Adverse Events

• More symptomatic hypotension
  – 14% vs 9.2%, p < 0.001

• Less elevation of serum creatinine > 2.5 mg/dl
  – 3.3% vs 4.5%

• Less cough
  – 11.3% vs 14.3%

• No significant increased incidence of angioedema
LAUNCH OF ENTRESTO IN MALAYSIA
Who to Prescribe

• Patients who are still symptomatic (FC II or more) with systolic HF and on ACE I or ARB

• If patients have adverse effect with ACE I
  – Angioedema
  – cough

• Probably not all systolic HF patients
  – FC I
  – ACE I or ARB naïve)
Other concerns

• Should not be used with ACEi:
  – Can cause angioedema and hypotension
  – Recommended a 36 hour washout

• Cost
  – Between RM 400-700/month (USD 380/month)
  – Enalapril RM 60/month
  – Valsartan RM 180/month
Hyperkalemia: New potassium absorbent

- Hyperkalemia is common especially in patients with CKD
- Currently, non-invasive treatment of hyperkalemia is limited by a lack of safety, efficacy, and tolerability
- Now, there are two novel potassium absorbent designed to increase potassium loss via the gastrointestinal tract
  - patiromer calcium
  - zirconium silicate (ZS-9)
- Although they have not yet been approved by the FDA, both have demonstrated efficacy and safety in recent trials.
The OPAL-HK trial

- Assess the efficacy and safety of patiromer in 243 patients with CKD on RAAS inhibitors with high levels of serum potassium

Result

- Mean reduction in plasma potassium levels was 1.0 mEq/l after the initial 4 weeks of active treatment

- When patiromer treatment was stopped at the end of the active treatment period, hyperkalemia rapidly recurred over 8 weeks
DEVICE THERAPY FOR CHF
# Devices That Reduce Mortality & Improve Symptoms in Heart Failure

<table>
<thead>
<tr>
<th>Devices</th>
<th>Relative Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implantable Cardiac Defibrillators (ICD)</td>
<td>↓ 23 - 31%</td>
</tr>
<tr>
<td>Cardiac Resynchronization Therapy (CRT)</td>
<td>↓ 34 - 35%</td>
</tr>
</tbody>
</table>
Cardiac Resynchronization Therapy
Biventricular Pacing
For Ventricular Dysynchrony

• Abnormal ventricular conduction resulting in a mechanical delay and dysynchronous contraction
Cardiac Resynchronization Therapy
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)
Heart Failure and Sudden Cardiac Death

Sudden Cardiac Death (SCD)

– SCD is one of the leading causes of death in the U.S. – approximately 450,000 deaths a year

– Patients with heart failure are 6-9 times as likely to develop sudden cardiac death as the general population
Who should Consider an ICD?

The AHA/ACC and ESC recommend ICD placement for:

1. LVEF ≤35% from previous MI who are at least 40 days post-MI

2. Non ischemic cardiomyopathy; with an LVEF of 35% or less in NYHA class II or III; receiving optimal medical therapy; and expected to survive longer than 1 year with good functional status

3. Ischemic cardiomyopathy, at least 40 days post-MI; have an LVEF of 30% or less; in NYHA functional class I; are on chronic optimal medical therapy; and are expected to survive longer than 1 year with good functional status

4. Patient who have had ventricular fibrillation (VF)

5. Patients with documented hemodynamically unstable ventricular tachycardia (VT) and/or VT with syncope with an LVEF less than 40%; on optimal medical therapy; and expected to survive longer than 1 year with good functional status
Other Therapies?

- Heart Transplant
- Left ventricular assist device (LVAD)
- Total artificial heart
Devices And Surgical Therapies That Reduce Mortality & Improve Symptoms In Heart Failure

Ventricular Assist Device (VAD)

Heart Transplant Surgery
Heart Transplantation

• A good solution to the failing heart—get a new heart

• Unfortunately we are limited by supply, not demand

• Approximately 2200 transplants are performed yearly in the US, and this number has been stable for the past 20 years
Worldwide Heart Transplants
LVAD

Left Ventricular Assist Device

Mechanical Circulatory Support
LVAD

- Paracorporeal
- Pneumatic
- Pulsatile
- Uni-or biventricular
- Implantable
- Electric
- Pulsatile
- Large
- Multiple moving parts
- Implantable
- Electric
- Continuous flow
- Axial design
- Smaller
- Single moving part
- Implantable
- Electric
- Continuous flow
- Centrifugal design
- Smaller
- Bearingless
- Implantable
- Electric
- Continuous flow
- Axial design
- Smaller
- Partial support
ACUTE HEART FAILURE
Relaxin (human hormone)
Serelaxin (Recombinant form of Relaxin)

Pregnancy & the Heart

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>PREGNANCY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Output (L/min)</td>
<td>20% Increase</td>
</tr>
<tr>
<td>Systemic Vascular Resistance (dyn.s.cm²)</td>
<td>30% Decrease</td>
</tr>
<tr>
<td>Global Arterial Compliance (mL/mm Hg)</td>
<td>30% Increase</td>
</tr>
<tr>
<td>Renal Blood Flow (mL/min/1.73m²)</td>
<td>50-85% Increase</td>
</tr>
<tr>
<td></td>
<td>40-65% Increase</td>
</tr>
</tbody>
</table>

- Relaxin has been shown to mediate these changes, as well as to have anti-ischemic, anti-inflammatory, anti-fibrotic effects.
- Relaxin is elevated through 9 months of pregnancy and mediates physiologic hemodynamic adjustments to growing baby.
- Pharmacologic use of serelaxin may produce these beneficial effects in acute heart failure.

The RELAX-AHF

- RCT 1,161 ADHF patients who have a systolic BP > 125 mmHg and renal dysfunction
- Randomly assigned to receive serelaxin 30 μg/kg per day or placebo
- Serelaxin given as a continuous 48-hour infusion within 16 hours from presentation
Result

• Serelaxin significantly improved
  – dyspnea, shortened the length of hospital stay, and decreased the incidence of worsening HF as compared with placebo

• There was also an improvement
  – in the 6-month mortality outcomes and no evidence of adverse effects of this agent on kidney function

• Larger trial RELAX-AHF2 (n = 2,685) and RELAX-Asia to validate long-term mortality benefit.
Ultrafiltration

Method of fluid removal particularly useful in patients with renal dysfunction and expected diuretic resistance
Diuretics resistance

- Heart failure and CKD are both associated with relative diuretic resistance
- “Braking Phenomenon”
  - A decrease in response to a diuretic after the first dose has been administered
- Long-term Tolerance
  - Tubular hypertrophy to compensate for salt loss
The Ultrafiltration vs iv diuretics for pts hospitalized for acute decompensated CHF (UNLOAD CHF) study

Costanzo MR et al. JACC 2007; 49(6):675-683 showed more effective fluid removal compared to standard care and suggested a trend to less rehospitalizations at 3 months.

- At 48 hours into treatment, the ultrafiltration group demonstrated over standard care a:
  - 38% greater weight loss ($p=0.001$)
  - 28% greater net fluid loss ($p=0.001$)
  - Equal improvement in dyspnea score ($p=0.35$)

- At 90 days following hospital discharge, the ultrafiltration group demonstrated over standard care a:
  - 43% reduction in patients requiring re-hospitalizations for heart failure ($p=0.037$)
  - 50% reduction in the total number of re-hospitalizations for heart failure ($p=0.022$)
  - 52% reduction in emergency department or clinic visits ($p=0.009$)
  - 63% reduction in total days re-hospitalized for heart failure ($p=0.022$)
Ultrafiltration

• UNLOAD trial demonstrated that ultrafiltration was superior to the use of IV diuretics in controlling net fluid loss and re hospitalization in hypervolaemic patients with heart failure

• Indication: patients with volume overloaded and Acute HF not responded well to moderate to large doses of diuretics treatment
NEW THERAPIES UNDER STUDY FOR HF
Effect of implanted device-based impedance monitoring with telemedicine alerts on mortality and morbidity in heart failure: results from the OptiLink HF study

OptiLink HF study

ICD capable of monitoring fluid status and sending alerts to physicians via telemonitoring

Does Intrathoracic Impedance Monitoring with an Automatic Wireless Telemedicine Notification Compared to Standard Clinical Assessment Reduces All-cause Death or Cardiovascular Hospitalizations?
Trial design: Patients with heart failure who underwent implantation of an ICD were randomized to telemonitoring (n = 505) vs. usual care (n = 497).

Results

- All-cause mortality or CV hospitalization: 45.0% of the telemonitoring group vs. 48.1% of the control group (p = 0.13)
- All-cause death: 6.2% with telemonitoring vs. 8.5% with control (p = 0.52)

Conclusions

- Among patients with heart failure and implantation of an ICD capable of monitoring fluid status and sending alerts to physicians, telemonitoring did not improve outcomes compared with usual care

Presented by Dr. Michael Boehm at ESC 2015
Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure

Martin R. Cowie, M.D., Holger Woehrle, M.D., Karl Wegscheider, Ph.D., Christiane Angermann, M.D., Marie-Pia d’Ortho, M.D., Ph.D., Erland Erdmann, M.D., Patrick Levy, M.D., Ph.D., Anita K. Simonds, M.D., Virend K. Somers, M.D., Ph.D., Faiez Zannad, M.D., Ph.D., and Helmut Teschler, M.D.

NEJM 2015; e-pub 1 September
SERVE-HF: Objective

To investigate the effects of adding ASV to guideline-based medical management on survival and cardiovascular outcomes in patients with heart failure with reduced ejection fraction (HFrEF) and predominant CSA\textsuperscript{1,2}

Symptoms and Quality of Life

- No significant differences in QoL between ASV and control groups
  - Minnesota Living with Heart Failure Questionnaire
  - EuroQol-5D
- No significant difference in NYHA functional status between ASV and control groups throughout trial
- Decreased exercise capacity in ASV recipients
  - 6MWD declined in both groups, but to a greater extent in the ASV group (p=0.04)
Summary

• Heart failure is common and has high mortality
• Drug therapy improves survival
  – Betablockers, ACE-I, aldosterone antagonists
  – Newer drugs ARNIs
• Device therapies are showing promise for symptom relief and improved survival
  – Biventricular pacing, ICD’s
• Heart transplant and MCS
• Ultrafiltration
• New devices
• New therapies-stem cells, nerve stimulation
One of the Best Devices for Monitoring Heart Failure

THANK YOU