Prevention and Optimizing Heart Failure Management

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Overview

• Heart failure – an increasing problem
• Risk factors for development of Heart Failure
• Intervention to reduce risk
• Asymptomatic LV dysfunction
• Optimizing outpatient HF treatment
Heart Failure

• Estimated to affect up to 1-2% of adult population

• Increasing prevalence
  – better treatment of CAD, HPT
  – use of ACEI & BB, improved survival rates

• More common in elderly
Heart Failure – a major problem

• HF represents the final common pathway of many risk factors and cardiovascular diseases that cause acute or chronic cardiac injury

• Morbidity, mortality, health care costs (especially hospitalizations)
Common Causes of HF

- Ischaemic heart disease (present in > 50% of new cases)
- Hypertension (about two-thirds of cases)
- Idiopathic dilated cardiomyopathy (around 5%–10% of cases)
- Valve disease – rheumatic disease becoming less common
Heart Failure: Risk Groups

• At high risk of developing cardiac disease
• With cardiac disease but who still have normal myocardial function
• Who have impaired myocardial function but who do not as yet have signs or symptoms of HF
Individuals At High Risk of Cardiac Disease

• Those with risk factors for developing coronary artery disease (smoking, lipid, hypertension, family history etc)

• Those who already have evidence of atherosclerotic disease (e.g. cerebral, peripheral vascular disease)
Other risk factors for Heart Failure

- Diabetes
- Metabolic syndrome
- Family history of cardiomyopathy
- Thyroid disorders
- Chronic kidney disease
- Sleep disordered breathing
- Post chemotherapy (e.g. doxorubicin, cyclophosphamide, 5-fluorouracil, trastuzumab)
Heart Failure Development: Population-Attributable Risk

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence (%)</th>
<th>Attributable Risk (%)</th>
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</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>60</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>59</td>
</tr>
<tr>
<td>MI</td>
<td>10</td>
<td>34</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>13</td>
</tr>
<tr>
<td>Angina Pectoris</td>
<td>11</td>
<td>5</td>
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<tr>
<td></td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>LVH</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Valvular Disease</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

Levy et al 1996
Hypertension and HF

• 50 years ago, heart failure accounted for 40% of deaths from hypertension
• Now HF is less common in young, but delayed several decades – affecting mainly the elderly (>80% above 65 yrs of age), commonly associated with CAD
Progression from Hypertension to Heart Failure

- Obesity
- Diabetes
- Smoking
- Dyslipidaemia
- Diabetes

LVH (Left Ventricular Hypertrophy)

LV Remodelling

Normal LV Structure & Function

Systolic Dysfunction

Diastolic Dysfunction

Subclinical LV Dysfunction

HF (Heart Failure)

Overt Heart Failure

Time: decades

Time: months

Death
Benefit of treating Hypertension: Early Randomised Trials of Antihypertensive Drug Therapy

<table>
<thead>
<tr>
<th>Risk reduction (%)</th>
<th>Fatal/Nonfatal Stroke</th>
<th>Fatal/Nonfatal CHD</th>
<th>Vascular Deaths</th>
<th>Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-38%</td>
<td>-16%</td>
<td>-21%</td>
<td>-52%</td>
</tr>
</tbody>
</table>

Collins and Macmahon 1994  Moser & Herbert 1996
Hypertension Control

- Diuretics, ACE inhibitors, ARBs, and β-blockers have been shown to be effective in HF prevention
- 5 mmHg reduction in systolic BP reduce HF risk by 24%
Influence of LVH on Incident Heart Failure

Cardiovascular Health Study: a prospective, longitudinal, population-based study in 2506 subjects with 6-7 years follow-up

Incident heart failure free survival by LV mass gender-specific quartiles

<table>
<thead>
<tr>
<th>LV mass (g) Quartiles</th>
<th>% free of incident HF</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
</tr>
</tbody>
</table>

Time to incident HF (days)

Gardin et al 2001
Regression of Left Ventricular Hypertrophy with Antihypertensive Therapy by Drug Class

Mean % change in LV Mass from baseline (with 95% CI’s) adjusted for change in diastolic BP & duration of treatment

Change in LV Mass(%)
Diabetes and Heart Failure

- Diabetes have 2-5x higher risk of HF compared to non DM
- DM predispose to atherosclerosis, macro & microvascular CAD, obesity, LV hypertrophy, endothelial dysfunction, autonomic dysfunction, and metabolic abnormalities
Optimizing the control of diabetes

- With every 1% increase in HbA1c, there is an 8% to 16% increase in the risk of HF hospitalization and death
- Previously no data to show that controlling DM will prevent HF
- EMPA REG Outcome trial suggest benefit with empagliflozin
EMPA-REG Outcome Trial

**A Primary Outcome**

- **Hazard ratio**: 0.86 (95% CI, 0.74–0.99)  
  *P*=0.04 for superiority

**B Death from Cardiovascular Causes**

- **Hazard ratio**: 0.62 (95% CI, 0.49–0.77)  
  *P*<0.001

**C Death from Any Cause**

- **Hazard ratio**: 0.68 (95% CI, 0.57–0.82)  
  *P*<0.001

**D Hospitalization for Heart Failure**

- **Hazard ratio**: 0.65 (95% CI, 0.50–0.85)  
  *P*=0.002

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**Mortality**

- **Empagliflozin**: 4687, 4651, 4608, 4556, 4208, 3079, 2617, 1722, 414  
  **Placebo**: 2393, 2301, 2280, 2243, 2012, 1503, 1281, 825, 177

**Hospitalization**

- **Empagliflozin**: 4687, 4614, 4523, 4427, 3988, 2950, 2487, 1634, 395  
  **Placebo**: 2333, 2271, 2262, 2173, 1932, 1424, 1202, 775, 168

*NEJMed 2015; 373:2117-2128*
Management of Coronary Artery Disease

• Optimal medical therapy including:
  – Lifestyle measures (smoking cessation, exercise, weight reduction)
  – Risk factor control (lipid lowering, BP control)
  – Aspirin prophylaxis
  – ACE inhibitor

• Revascularization for severe CAD or ACS
Prevention of Heart Failure in patients with CAD

• Statins reduce risk of coronary events
  – Scandinavian Simvastatin Survival Study: Simvastatin versus placebo. Incidence of heart failure 8.3% versus 10.3% (P<0.015)

• ACE inhibitors reduce CV events and HF
  – HOPE (Ramipril), EUROPA (Perindopril) & PEACE (Trandolapril) showed significant (25-39% reduction) in risk of hospitalization for heart failure
Prevention of HF in patients with Acute Coronary Syndrome

- Early triage and treatment of the patient with myocardial infarction by early reperfusion (myocardial salvage)
- Early intervention in high risk acute ischemia
- In the Treating to New Targets trial, high dose atorvastatin had lower incidence of HF hospitalization cf low dose
Post Myocardial infarction

• Increase risk of HF 2-3X
  – Depletes functional myocyte reserve
  – Stimulates cardiac remodeling

• Studies suggest that the use of ACEi, betablockers, mineralocorticoid receptor antagonists and ARBs reduce hospitalization and mortality in post MI LV dysfunction
Patients with Asymptomatic LV dysfunction

• LVEF < 40%

• Treat the underlying cause wherever possible

• Detect and prevent progression to HF by modulating cardiac remodeling
  – ACE inhibitors
  – Betablockers
Prevention of Heart Failure in patients with asymptomatic LV dysfunction

- SOLVD Prevention:
  - Use of enalapril in pts with asymptomatic LV dysfunction reduce risk of death or HF hospitalization by 20%

- SAVE:
  - Use of captopril in pts with LVEF of <40% post MI reduce mortality by 20% and development of severe HF by 37%. Use of betablockers independently reduce CV death and HF by 30% and 21%
CAPRICORN: Carvedilol Post infarct Survival Controlled Evaluation

- Acute MI within 3-21 days (treated with aspirin, thrombolysis, PTCA), EF<40% on ACE inhibitor
- All cause mortality reduced by 23%
  - placebo (n=984): 15%
  - carvedilol (n=975): 12%; p=0.031
- Non Fatal MI reduced by 41%
Treatment for symptomatic HF patients

- Optimize use of ACEI, Betablockers
- Add mineralocorticoid receptor antagonists – spironolactone or eplerenone
- Loop diuretics - frusemide, bumetanide
- Digoxin – from class I to IIa
## Recommended doses of ACE-I used in CHF

<table>
<thead>
<tr>
<th>ACEI</th>
<th>Initiating Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>6.25 mg tid</td>
<td>50 mg tid</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg bid</td>
<td>10-20 mg bid</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5 mg daily</td>
<td>20-40 mg daily</td>
</tr>
<tr>
<td>Quinapril</td>
<td>2.5-5 mg daily</td>
<td>20 mg bid</td>
</tr>
<tr>
<td>Perindopril</td>
<td>2 mg daily</td>
<td>8 mg daily</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1.25-2.5 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>10 mg daily</td>
<td>20 mg daily</td>
</tr>
</tbody>
</table>
# Recommended doses of Beta Blockers used in CHF

<table>
<thead>
<tr>
<th>β-Blockers</th>
<th>Initiating Dose</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol</td>
<td>3.125 mg daily</td>
<td>25 mg bid</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg daily</td>
<td>10 mg daily</td>
</tr>
<tr>
<td>Metoprolol succinate CR</td>
<td>12.5 – 25 mg daily</td>
<td>200 mg daily</td>
</tr>
<tr>
<td>Nevibolol</td>
<td>1.25 mg</td>
<td>10 mg daily</td>
</tr>
</tbody>
</table>
Eplerenone in Mild Patients Hospitalization And Survival Study in Heart Failure (EMPHASIS-HF)

**Figure A**
Hazard ratio, 0.63 (95% CI, 0.54–0.74)
P < 0.001

**Figure B**
Hazard ratio, 0.76 (95% CI, 0.62–0.93)
P = 0.008

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Years since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1373 848 512 199</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>1364 925 362 232</td>
</tr>
</tbody>
</table>

NEJM 2011; 364: 11-21
Other Drugs

• Angiotensin receptor blockers
• Angiotensin receptor nephrilysin inhibitor (ARNI) – valsartan-sacubitril (or Entresto)
• Ivabradine
Angiotensin Receptor Nephrilysin Inhibitor – LCZ 696 or Entresto
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**

**Days After Randomization**

<table>
<thead>
<tr>
<th>Days</th>
<th>LCZ696</th>
<th>Enalapril</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</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>
PARADIGM HF Results

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%
Use of Entresto in CHF

- Symptomatic HF (EF < 35%) despite on optimal ACEI/ARB
- Stop ACEI 36 hrs before starting Entresto
- Check if CHF patient on Entresto before giving ACEI/ARB
- Watch out for hypotension
Use of Ivabradine

- Symptomatic HF with reduced EF
- On top of optimal medical therapy i.e. ACEi, Beta blockers
- HR > 70 and in sinus rhythm
- Shown to be beneficial as add on therapy
SHIFT: Ivabradine in HF
Primary composite endpoint
(CV death or hospital admission for worsening HF)

Cumulative frequency (%)

HR = 0.82 (0.75–0.90)
$P < 0.0001$

# Evolution of Heart Failure

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Cellular Pathophysiology</th>
<th>Ventricular Remodeling</th>
<th>Ventricular Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>Hypertrophy</td>
<td>LVH</td>
<td>Systolic Dysfunction</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Infarction</td>
<td>Dilatation</td>
<td>Diastolic Dysfunction</td>
</tr>
<tr>
<td>Smoking</td>
<td>Accelerated</td>
<td>Both</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Apoptosis</td>
<td>Both</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genes</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

- **Stage A**: Structural Heart Disease Without Symptoms
- **Stage B**: Symptomatic Heart Failure
- **Stages C and D**: AHA / ACC Stages of Heart Failure
# Current Therapy for Heart Failure

<table>
<thead>
<tr>
<th>Asymptomatic</th>
<th>Symptomatic</th>
<th>Severe</th>
<th>Refractory</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Betablockers/Ivabradine (or +)</strong></td>
<td><strong>ACE Inhibitors/ARB (or Entresto)</strong></td>
<td>Tailored combinations</td>
<td>Transplant/devices</td>
</tr>
<tr>
<td><strong>Diuretics</strong></td>
<td><strong>Mineralocorticoid Receptor Antagonists</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Digoxin</strong></td>
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</tr>
</tbody>
</table>

- **Na restriction**: 4g (Asymptomatic), 2g (Symptomatic, Severe, Refractory)
- **Fluid restriction**: 1-2 litres (Symptomatic, Severe, Refractory)