Kamol Sindhvanandha
Honorary Lecture
Updates to the Heart Failure Guidelines 2017

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Vice Chair of Medicine for Informatics
Chair, Member Section Steering Committee, ACC
Associate Professor of Medicine, University of Pennsylvania
Kamol Sindhvanandha, MD

• Studied in the United States
  – Barnes – St. Louis
  – Harvard Beth Israel – Boston (Dr. Louis Wolff)
  – University of Pennsylvania – Philadelphia

• Involved in Public Health with the World Health Organization
  – Rheumatic Heart Disease 1984

• Pioneer in Cardiology
WHO Rheumatic Heart Disease

WHO/CVD INTENSIFIED PROGRAMME

ACTION TO PREVENT RHEUMATIC FEVER/RHEUMATIC HEART DISEASE (RF/RHD)

Report on Planning Meeting
Geneva, 4-5 April 1984

Dr Lu urged the meeting to concentrate on strategies for establishing and maintaining the services required for the prevention of RF/RHD, within the context of primary health care and the existing national health care delivery system.

1.1.1 Election of officers

Dr Kamol Sindhvananda was elected Chairman and Dr Edward Kaplan was elected Rapporteur.
Risk Factors for Heart Failure Across Asia

Regional and ethnic differences among patients with heart failure in Asia: the Asian sudden cardiac death in heart failure registry
Heart Failure May Not Be the Same in Asia

May need specific trials in Asia to understand impact of therapies
CENTRAL ILLUSTRATION  HF Phenotype and Treatment in Asia Compared With Other Regions

- Younger Age
- Historically less ischemic etiology
- Fewer ICDs and CRT
- Higher prevalence of infectious diseases such as RHD
- Similar ACE/ARB use, more MRA use and less beta-blocker use
- More use of IV vasodilators and inotropes during AHF
- Historically less atrial fibrillation
- High prevalence of diabetes


ACE/ARB = angiotensin-converting enzyme/angiotensin receptor blocker; AHF = acute heart failure; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist; RHD = rheumatic heart disease.
ACC/AHA Heart Failure Guidelines

• Two recent updates
  – 2013
  – 2016

• Major update expected to be released later in 2017
What’s New in 2013 ACC/AHA Guideline Update

- Harmonization with other guidelines
- Emphasis on transitions and heart failure education as well as performance measures
- Team based care
- Risks and benefits of ICD’s including ability to deactivate
- Sodium restriction is “reasonable” in heart failure with volume overload
What’s New in 2013 Update
Drugs and Devices

• Aldosterone antagonists – broadened to include NYHA Class II

• BiV pacing expanded to include NYHA Class 2 patients with left bundle branch block and QRS $\geq 150$ ms (but not indicated in NYHA II, non LBBB and QRS $<150$ ms)
What’s New in 2013 Update
Advanced Therapies

• Expansion of mechanical circulatory support (VADs) now Class 2 as bridge to decision, bridge to recovery and destination therapy
What’s New 2016 Update: Use of Newer Drugs for Heart Failure

- 2016 ACC/AHA/HFSA focused update
- Released simultaneously with ESC HF guideline update and endorsed by HFSA – more unified worldwide guideline

<table>
<thead>
<tr>
<th>Sacubitril-Valsartan (ARNI)</th>
<th>Ivabradine</th>
</tr>
</thead>
<tbody>
<tr>
<td>• In patients with NYHA class II-III chronic symptomatic HFrEF who tolerate ACE inhibitor or ARB, replacement by ARNI is recommended to further reduce morbidity and mortality</td>
<td>Can reduce HF hospitalization in patients with NYHA class II-III stable chronic HFrEF (LVEF ≤35%) who are receiving GDMT, including maximally tolerated β-blocker, and who are in sinus rhythm with heart rate ≥70 bpm</td>
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## Classification of Heart Failure

<table>
<thead>
<tr>
<th>Stage</th>
<th>“Course of Disease”</th>
<th>Class</th>
<th>“Symptoms at that moment”</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At high risk for HF but without structural heart disease or symptoms of HF</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>Structural heart disease but without signs or symptoms of HF</td>
<td>I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause HF symptoms</td>
</tr>
<tr>
<td>C</td>
<td>Structural heart disease with prior or current symptoms of HF</td>
<td>I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause HF symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>II</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in HF symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>III</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes HF symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV</td>
<td>Unable to carry on any physical activity without HF symptoms, or symptoms at rest</td>
</tr>
<tr>
<td>D</td>
<td>Refractory HF requiring specialized interventions</td>
<td>IV</td>
<td>Unable to carry on any physical activity without HF symptoms, or symptoms at rest</td>
</tr>
</tbody>
</table>

The minimal required therapies to prevent progression and reduce morbidity and mortality

Therapies to reduce symptoms or trigger referral to advanced therapies or hospice

Stages, Phenotypes and Treatment of HF

At Risk for Heart Failure

STAGE A
At high risk for HF but without structural heart disease or symptoms of HF

- e.g., Patients with:
  - HTN
  - Atherosclerotic disease
  - DM
  - Obesity
  - Metabolic syndrome or
    Patients
    - Using cardiotoxins
    - With family history of cardiomyopathy

THERAPY
Goals
- Heart healthy lifestyle
- Prevent vascular, coronary disease
- Prevent LV structural abnormalities

Drugs
- ACEI or ARB as appropriate
  for patients with vascular disease or DM
- Statins as appropriate

STAGE B
Structural heart disease but without signs or symptoms of HF

- e.g., Patients with:
  - Previous MI
  - LV remodeling including LVH and low EF
  - Asymptomatic valvular disease

THERAPY
Goals
- Prevent HF symptoms
- Prevent further cardiac remodeling

Drugs
- ACEI or ARB as appropriate
- Beta blockers as appropriate

In selected patients
- ICD
- Revascularization or valvular surgery as appropriate

STAGE C
Structural heart disease with prior or current symptoms of HF

- e.g., Patients with:
  - Known structural heart disease and
    HF signs and symptoms

THERAPY
Goals
- Control symptoms
- Improve HRQOL
- Prevent hospitalization
- Prevent mortality

Drugs for routine use
- ACEI or ARB or ARNI
- Aldosterone antagonists

Options
- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation

Heart Failure

HFpEF

Goals
- Control symptoms
- Patient education
- Prevent hospitalization
- Prevent mortality

Drugs for use in selected patients
- Hydralazine/isosorbide dinitrate
- ACEI and ARB
- Digoxin

In selected patients
- CRT
- ICD
- Revascularization or valvular surgery as appropriate

HF/eF

Goals
- Control symptoms
- Improve HRQOL
- Reduce hospital readmissions
- Establish patient’s end-of-life goals

Options
- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation

STAGE D
Refractory HF

- e.g., Patients with:
  - Marked HF symptoms at rest
  - Recurrent hospitalizations despite GDMT

THERAPY
Goals
- Control symptoms
- Improve HRQOL
- Reduce hospital readmissions
- Establish patient’s end-of-life goals

Options
- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation
Review of Pharmacologic Management of Heart Failure

• Combining neurohormonal blockade with at least an angiotensin-renin (+/- neprilysin) and adrenergic (sympathetic) blocker is the cornerstone of therapy

• Additional pharmacologic and device therapies are added based on the stage and then symptoms
Current Pharmacologic Approach to Heart Failure

Recommended for routine use

ACE inhibitors

• Effect
  – Interferes with RAS; enhances actions of kinins, prostaglandin synthesis, delays remodeling
  – Alleviate symptoms, reduce death, hospitalizations

• Clinical use: systolic and diastolic heart failure
  – Given to all patients with systolic dysfunction

• Adverse effects
  – Hypotension, azotemia, hyperkalemia, cough, angioedema
ACEI dose effect

• **ATLAS**  *Eur Heart J* 1998; 19:481
  – 3164 patients: 2.5-5.0 or 32.5-35 mg lisinopril
  – No significant difference in mortality
  – Hospitalizations lower in high dose group

  Packer et al. *Circulation* 1999;100;2312

• **NETWORK**
  – 1532 patients: 5, 10, or 20 mg enalapril
  – CHF, hospitalizations, death: NS
Current Pharmacologic Approach to Heart Failure

*Recommended for routine use*

**Beta blockers**

- **Effect**
  - Inhibit the adverse effects of sympathetic system
  - Delays and reverses remodeling

- **Clinical use: systolic and diastolic heart failure**
  - Given to all patients with systolic HF in *absence of fluid overload*

- **Adverse effects**
  - Hypotension, bradycardia, worsening HF
# Effects of β-Blockade on Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (Class II–IV/III–IV)</th>
<th>Treatment</th>
<th>All-cause Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>US carvedilol program</strong></td>
<td>1094</td>
<td>Carvedilol</td>
<td>↓ 65% (P&lt;0.001)</td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>BEST</strong></td>
<td>2708</td>
<td>Bucindolol</td>
<td>↓ 10% (P=0.109, NS)</td>
</tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td><strong>CIBIS-II Trial HF</strong></td>
<td>2647</td>
<td>Bisoprolol</td>
<td>↓ 34% (P&lt;0.0001)</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td><strong>MERIT-HF</strong></td>
<td>3991</td>
<td>Metoprolol Succinate</td>
<td>↓ 34% (P=0.0062)</td>
</tr>
<tr>
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</tr>
<tr>
<td><strong>COPERNICUS</strong></td>
<td>2000</td>
<td>Carvedilol</td>
<td>↓ 35% (P=0.00014)</td>
</tr>
</tbody>
</table>

Should Physicians Increase the Dose of ACE Inhibitor or Add β-Blockade?

<table>
<thead>
<tr>
<th>Dose of ACEI:</th>
<th>“Low” vs. “High”</th>
<th>“Average” + β-blockade†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Unchanged</td>
<td>Improved</td>
</tr>
<tr>
<td>Morbidity/mortality</td>
<td>↓ 12%</td>
<td>↓ 35%-40%</td>
</tr>
<tr>
<td>Mortality</td>
<td>↓ 8%</td>
<td>↓ 30%-35%</td>
</tr>
</tbody>
</table>

Current Pharmacologic Approach to Heart Failure

**ARB’s**

- **Effect**
  - Blocks effect of AG-II at receptor site; delays remodeling
  - Alleviate symptoms, reduce death, hospitalizations

- **Clinical use**
  - Given to patients if they cannot tolerate ACEI specifically angioedema, cough
  - Val-HeFT and CHARM: some improvement when used with ACEI

- **Adverse effects**
  - Hypotension, azotemia, hyperkalemia, rarely cough
Aldosterone Antagonists: Spironolactone/Eplerenone

• Improved mortality for class IIIB or class IV patients – RALES Trial
• Creatinine < 2.5 in men < 2.0 in women and Potassium < 5.0
• More recent studies with eplerenone showed benefits in NYHA Class II to IV (Expanded indication 2013)
• Contraindicated if on both ACE and ARB due to risk of hyperkalemia
• ? Role in HF with preserved ejection fraction
Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (EMPHASIS-HF)
Heart Failure Therapies Demonstrated to Increase Risk of Mortality and/or Hospitalization

Mortality and/or Hospitalizations

**NSAIDS**

**Calcium Channel Blockers (Dihydropyrididine)**

Inotropic Agents

RV pacing (induced dys-synchrony) (Block HF trial)
## New Therapies for the Treatment of HF With Novel Mechanisms of Action

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
</tr>
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<tbody>
<tr>
<td>Ivabradine</td>
<td>Selectively inhibits the sinus node $I_f$ channel, thereby decreasing heart rate</td>
</tr>
<tr>
<td>Angiotensin receptor-neprilysin inhibitor (ARNI)</td>
<td>Combines angiotensin receptor blockade with inhibition of neprilysin,* thereby inhibiting RAAS and augmenting natriuretic peptide activity</td>
</tr>
</tbody>
</table>

RAAS, renin-angiotensin-aldosterone system.
*The metallopeptidase neprilysin hydrolyzes natriuretic peptides.
Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

Karl Swedberg, Michel Komajda, Michael Böhm, Jeffrey S Borer, Ian Ford, Ariane Dubost-Brama, Guy Lerebours, Luigi Tavazzi, on behalf of the SHIFT Investigators*

Lancet 2010; 376: 875-85
Ivabradine Mechanism

• Inhibits the If “funny” (pacemaker) current in the sinoatrial node to decrease heart rate but does not impact contractility
Ivabradine Mechanism of Action

Sinus node: The pacemaker of the heart

Ivabradine selectively inhibits the f current in the sinus node

Ivabradine reduces the slow diastolic depolarization phase

Heart rate reduction

0 mv
-40 mv
-70 mv

ΔHR
Ivabradine for Moderate-to-Severe HF and LV Systolic Dysfunction: The SHIFT Study

• Study description
  – Phase 3 multicenter, randomized, double-blind, placebo-controlled, outcomes trial
  – Comparison of ivabradine to placebo added on to standard-of-care therapies including beta-blockers
  – >6500 patients with symptomatic chronic HF in sinus rhythm with reduced LV function and heart rate ≥70 bpm

SHIFT Primary Composite Endpoint
(CV death or hospital admission for worsening HF)

Cumulative frequency (%)

HR = 0.82 (0.75–0.90)
P < 0.0001

Placebo
18%

Ivabradine

Hospitalization for Heart Failure

Cumulative frequency (%)

HR = 0.74 (0.66–0.83)

P < 0.0001