Optimization of medical therapy in HFrEF

Pearls and Pitfalls

Rungsrit Kanjanavanit MD.
Why HF is an important health problem?

- Common
- Disabling
- Deadly
- Costly

But... treatable
Evidences from large epidemiologic surveys suggested less than expected improvement in survival in patients with HF.

Why?

Survival curves for patients with heart failure
Olmsted County, Minnesota

Many faces of heart failure

Similar symptoms – Different pathology
### Classification of HF

<table>
<thead>
<tr>
<th>Classification</th>
<th>EF (%)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFrEF</td>
<td>≤40</td>
<td>Sys HF Efficacious therapy demonstrated</td>
</tr>
<tr>
<td>HFpEF</td>
<td>≥50</td>
<td>“diastolic” HF</td>
</tr>
<tr>
<td>HFpEF, borderline</td>
<td>40-49</td>
<td>Characteristics treatment, outcomes similar to HFpEF</td>
</tr>
<tr>
<td>HFpEF, improved</td>
<td>&gt;40</td>
<td>Previous HFrEF</td>
</tr>
</tbody>
</table>

ACC/AHA Guidelines 2013
Diastolic and systolic dysfunctions

Normal

Diastolic dysfunction
Sustained apex
S4

Systolic dysfunction
Diffused apex
S3
“Heart failure” should never be a final diagnosis.
Question to ask

- Is it HF?
- What is underlying cardiac pathology?
- Does the pathology responsible for HF signs and symptoms?
- What is the cause of the cardiac pathology?
- What is the precipitating cause of ADHF?
Time (yrs)

Symptom progression

Neurohormonal blockade

Cardiac performance

Secondary damage

Ejection fraction

asymptomatic

symptomatic

insults

Neurohormonal blockade
Injury to myocytes and extracellular matrix

Neurohumoral imbalance, increased cytokine expression, immune and inflammatory changes, altered fibrinolysis

Ventricular remodeling

Apoptosis, altered gene expression, energy starvation, oxidative stress

Electrical, ventilatory, vascular, muscle, renal, hematologic, and other effects

Heart-failure syndrome
Triple Therapy

GDHT : guideline-directed medical therapy

Angiotensin

Norepinephrine

ACEI / ARB

βB

Aldosterone Antagonist

Aldosterone
ABCDE of HF

A. ACEI, AA, ARB
B. Beta blocker
C. CRT
D. Digitalis, Diuretics
E. Education
Physicians adherence to GDMT

- **Beta-blocker**
  - Cardiologists: 70%
  - Internist/geriatricians: 40%
  - Primary care physicians: 30%

- **ACE inhibitor**
  - Cardiologists: 90%
  - Internist/geriatricians: 90%
  - Primary care physicians: 90%

Guideline adherence and cardiac events
(CVS death and rehospitalization)
Nakornping Hospital Chiang Mai, Thailand

Multivariate analysis
Suntheep Batra, Surarong Chinwong. APCHF 2012
Co-morbidities CMU HF clinic

- 44.4% had ≥ 3 comorbidities

- CAD: 15.6%
- DM: 33.3%
- HT: 62.2%
- Dyslipid: 60.0%
- CRF: 51.1%
- COPD: 11.1%
“optimized medical therapy”
Worsening renal function

- Some rise in BUN/Cr is to be expected and may actually be a marker of ACEi benefit
- An increase in Cr up to 50% above baseline or up to 3 mg% is acceptable
- K+ < 6 mmol/l is acceptable
- Stop NSAID’s, other nephrotoxic drugs
- Avoid excessive diuresis
- Try lower the dose before discontinue permanently
Cough while taking ACEI

- Exclude pulmonary edema or bronchial diseases
- Rarely requires discontinuation
- Intolerable, disturbs sleep and proven to be due to ACEi (withdrawal/rechallenge)
  - substitute with A II receptor blockers
When to use Angiotensin Receptor Blockers

- ARB is, at best, only as good as ACEI in treating HF
- Intolerant to ACE inhibitors *for reasons other than hyperkalemia or renal insufficiency*
- Do NOT use ARB instead of ACEI in patients who can tolerate ACEI
- Adding ARB to ACEI/ β-blocker can further reduce mortality and rehospitalization
- Angioedema has been reported with ARB
### HFSA 2010 Practice Guideline

**ARBs**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Initial Daily Dose</th>
<th>Target Dose</th>
<th>Mean Dose in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candesartan</td>
<td>Blopress</td>
<td>4-8 mg qd</td>
<td>32 mg qd</td>
<td>24 mg/day</td>
</tr>
<tr>
<td>Losartan</td>
<td>Cozaar</td>
<td>12.5-25 mg qd</td>
<td>150 mg qd</td>
<td>129 mg/day</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Diovan</td>
<td>40 mg bid</td>
<td>160 mg bid</td>
<td>254 mg/day</td>
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</tbody>
</table>
Implementation of β blocker therapy - When?

A simplified criteria

1. Edema free
2. Not requiring intravenous medication for HF
### Which and what dose

<table>
<thead>
<tr>
<th></th>
<th>Starting dose (mg)</th>
<th>Target dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisoprolol</td>
<td>1.25 od</td>
<td>10 od</td>
</tr>
<tr>
<td>Metoprolol CR/XL</td>
<td>12.5-25 od</td>
<td>200 od</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 bid</td>
<td>25-50 bid</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>1.25 od</td>
<td>10 od</td>
</tr>
</tbody>
</table>

**Titration period – weeks to months**
Mortality was significantly lower in patients receiving beta-blockers, irrespective of airway disease status.
Beta-blockers should be attempted in CHF with coexistent COPD

- Pulmonary function test
  - Non-reversible obstruction
    - $\beta_1$ selective $\beta$-blockers
    - Nonselective $\beta$-blockers
  - Reversible obstruction
    - $\beta_1$ selective $\beta$-blockers

Start with low dose, slowly titrate and closely monitor of symptoms, frequency of bronchodilator use, PFT
Patient came in with decompensated HF

What to do

- Wet and warm
  - IV diuretics
  - No need to decrease dose of β-blocker
  - Up-titrate dose of ACEi and β-blocker when stabilized

- Wet and cold
  - Positive inotropic support (PDE inhibitors)
  - Decrease the dose of β-blocker by 50%
  - Reintroduction or up-titrate β-blocker when stabilized
Fluid status

Dry

Warm

Wet and Warm

Dry and Cold

Wet and Cold

Perfusion

Evidence for congestion (elevated filling pressure)
Orthopnea
High jugular venous pressure
Increasing S₃
Loud P₂
Edema
Ascites
Rales (uncommon)
Abdominojugular reflux
Valsalva square wave

Evidence for low perfusion
Narrow pulse pressure
Pulsus alternans
Cool forearms and legs
May be sleepy, obtunded
ACE inhibitor-related symptomatic hypotension
Declining serum sodium level
Worsening renal function
Dealing with low heart rate

- If < 50 bpm, halve dose of β-blocker
- Review other medications

Drug interaction to look for:
- Digitalis
- Verapamil / diltiazem - should be discontinue
- Amiodarone
- Ivabradine?
Do not rely on pulse rate in BB dose adjustment

Pulse rate ≠ Heart rate

PR 75/min VS. HR 96/min
Problem solving: Hypotension

- Asymptomatic low BP does not require any change in therapy.
- HypoPERFUSION not hypoTENSION is the concern.
- Dizziness, light-headedness and confusion
  - D/C nitrates, CCB, other vasodilators
  - reducing dose of the diuretics if no signs/symptoms of congestion
Overdiuresis

- RAAS stimulation
- Worsening renal function
- Electrolytes imbalance
- Barrier to GDMT optimization
Detection of orthostatic hypotension

Always measure supine and upright BP in every HF patients at every visit
Diuretics to relieve symptoms/signs of congestion

ACE inhibitor (or ARB if not tolerated)

ADD a beta-blocker

Still NYHA class II–IV?

Yes

ADD a MR antagonist

Still NYHA class II–IV?

Yes

LVEF ≤35%?

Yes

Sinus rhythm and HR ≥70 beats/min?

Yes

ADD ivabradine

No

No

No
## Magnitude of benefit seen in RCTs

<table>
<thead>
<tr>
<th>GDMT</th>
<th>RRR in mortality (%)</th>
<th>NNT to save one life (36 mo)</th>
<th>RRR HF hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi /ARB</td>
<td>17</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>β-blocker</td>
<td>34</td>
<td>9</td>
<td>41</td>
</tr>
<tr>
<td>AA</td>
<td>30</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>Hydralazine/nitrate</td>
<td>43</td>
<td>7</td>
<td>33</td>
</tr>
</tbody>
</table>
Myocardial fibrosis

picrosirius red staining
Combined use of low doses of several drugs is preferred to a large dose of a single agent.
Do not kill the patients with hyperkalemia

Sine wave - Hyperkalemia: $K^+ = 8.2 \text{ mEq/L}$
How to avoid fatal hyperkalemia
# HFSA 2010 Practice Guideline

## Aldosterone Antagonists

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<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Initial Dose</th>
<th>Daily</th>
<th>Target Dose</th>
<th>Mean Dose in Clinical Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>Aldactone</td>
<td>12.5-25 mgqd</td>
<td>25 mgqd</td>
<td>25 mgqd</td>
<td>26 mg/day</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>Inspra</td>
<td>25 mgqd</td>
<td>50 mgqd</td>
<td></td>
<td>42.6 mg/day</td>
</tr>
</tbody>
</table>

- Do not use high dose AA
- Never use Triple A's combination (ACEi/ARB/AA)
Do not use aldosterone receptor antagonists when

Cr > 2.5 mg/dL in men or > 2.0 mg/dL in women

(GFR<30 mL/min/1.73 m2)

K^+ > 5.0 mEq/L
K⁺ monitoring should reflect protocols followed in clinical trials

- K⁺ and Cr rechecked within 2 to 3 days and again at 7 days after initiation of AA
- Recheck at least monthly for the first 3 months and every 3 months thereafter
- The addition or an increase in dosage of ACE inhibitors or ARBs should trigger a new cycle of monitoring

ACC/AHA HF Guidelines 2013
Do not use salt supplement
How to use digitalis

- A third-line drug
- If digoxin needed, use low dose.
- SDC >1.0 ng/ml may do harm
- Suggested new therapeutic level 0.5-0.9 ng/ml

Do not use high dose digoxin
Do not use digoxin in small old frail ladies

### Current Guidelines for Digoxin

<table>
<thead>
<tr>
<th>Recommend</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>IIb</td>
<td>B</td>
</tr>
</tbody>
</table>

**ACC/AHA 2013**

**ESC 2012**
Ivabradine: Pure HR reduction

\[ K^+ \]

\[ I_{f \text{channel}} \]

\[ \text{Ivabradine} \]

\[ \text{SHIFT} \]

Systolic Heart failure treatment with the inhibitor ivabradine Trial
Ivabradine effect on outcomes

Primary composite endpoint

Cumulative frequency (%)

Placebo

Ivabradine

HR = 0.82
P < 0.0001
- 18%

Hospitalization for heart failure

Cumulative frequency (%)

Placebo

Ivabradine

HR = 0.74
P < 0.0001
- 26%

Cardiovascular death

Cumulative frequency (%)

Placebo

Ivabradine

HR = 0.91
P = 0.128

Role for Ivabradine

Sinus rhythm with an EF \(\leq 35\%\) and HR \(\geq 70\) /min

- Difficult to up-titrate \(\beta\)-blockers for other reasons other than bradycardia
- Hypotension
- Low output syndrome

DO NOT substitute ivabradine for \(\beta\) blockers in patients with CHF who had not optimally up-titrated

Class IIa B
Class IIb C

ESC Guidelines 2012
What to do with AF in HF

1. Rhythm control
2. Rate control
AF Rate control VS Rhythm control in HF

Do not attempt AF rhythm control with antiarrhythmic drug

How to slow AF rate in HFREF?

- β-blocker
- Digoxin
- Amiodarone
- AV nodal ablation with CRT-P

No role of ivabradine

Non dihydropyridine CCB: absolute contraindication
Hydralazine / Nitrates

43% Decrease in Mortality

Survival %

Fixed Dose ISDN/HDZN

Placebo

P = 0.01

Days Since Baseline Visit

LV dysfunction

Neurohormonal activation

Natriuretic peptides

Renin-Angiotensin-Aldosterone –System
Sympathetic nervous system
Endothelin

Compensatory mechanism for hemodynamic derangement

Diuresis
Vasodilation
Decrease salt appetite

Cardiac remodeling

Atria and ventricular stretches

Prolonged stimulation

Apoptosis
Myocyte hypertrophy
Interstitial fibrosis
neurohormonal modulation
ARB + Neprilysin inhibitor NI

= Angiotensin Receptor Neprilysin Inhibitor - ARNI
Primary endpoint:
Death from CV causes or first hospitalization for HF

Hazard ratio = 0.80 (95% CI: 0.73–0.87)
p<0.001
HFrEF: The building blocks of therapy

1. **Tx**
2. **VAD**
3. **CRT**
4. **ICD**

- CABG
- Digoxin
- Ivabradine
- HDZ-ISDN
- ARNi
- ACEi/ARB
- MRA
- β-blockers
- Should LCZ696 replace ACEi?
Cardiac / renal function

Acute cardiac event

ADHF

congestion hypoperfusion

death
Refractory HF?

- anemia
- concomitant valvular dysfunction
- ischemia / hibernation
- poorly controlled arrhythmias - AF
- thyroid dysfunction
- diuretic resistant
- large LV aneurysm
- ventricular dyssynchrony
- obstructive sleep apnea
- malnutrition
- physical deconditioning
- depression
- dietary and medication non adherence
Iron deficiency - beyond anaemia - is associated with increased all-cause mortality in systolic HF.
CONFIRM HF

304 ambulatory symptomatic HFrEF patients
- elevated BNP
- Fe deficiency
  - ferritin<100 ng/mL or
  - 100–300 ng/mL if transferrin saturation < 20%

i.v. ferric carboxymaltose VS placebo

Primary end-point: change 6MWT distance at Week 24.
Secondary end-points NYHA QoL, HF rehospitalization

P. Ponikowski et al. EHJ 2014
High readmission rate

78% had at least two admission per year
40% within 3 months of discharge

Half of these readmissions may have been preventable!
Precipitating causes of heart failure

- Non compliance with medications
- Non compliance with dietary recommendations
- Inadequate diuretics programme
  - Increased cardiac demand
  - Concurrent illness
  - New cardiac event
- Use of new medications - NSAID’s
If the benefit seen in these clinical trials are to be replicated, patients must be prescribed treatment according to guidelines and patients must follow the prescribed treatment.
Drugs don’t work in patients who don’t take them.

C. Everett Koop, M.D.
“filling the GAP in the care of chronic diseases”

Pyramid of HF care

- Heart transplant
- Revascularization
- Resynchronization Therapy
- Pharmacologic Therapy
- Self management
- Patient education
- Disease management program

Low tech – high touch therapy
Comprehensive Heart Failure Program

Keeping heart failure patients away from hospitals
Low Tech, High Touch, High Efficiency
Multidisciplinary team
Case manager model
• General topics
  – Nature of heart failure
  – Be able to recognize early signs of worsening HF
The most important tool in HF management

Self daily weight monitoring:

- Weigh every morning
- After going to toilet
- Before getting dressed
- Before breakfast

Flexible diuretics regimen

If weight increases > 1 kg within 1 or 2 days

→ double the dose of diuretics, until returns to ideal BW
• ASA 100 mg od
• Ramipril 5 mg od
• ISDN 20 mg tid
• Carvedilol 12.5 mg bid
• Marforan 5 mg ½ tab od
• Atrova statin 20 mg hs
• Lasix 40 mg od
• Seretide 1 puff bid
• Theodur 200 mg od
• Singulair
• Allopurinol 300 mg ½ tab od
• Colchicine 0.6 mg od
• Pletaal
• Prosac 20 mg od
• Ativan 1 mg hs
• Caltrate
• Glakay
• Foscanet
• Cerebrex
• Mydocalm
• Glucosamine
• Neotica balm
• Pletaal
• Prosac 20 mg od
• Ativan 1 mg hs

• Allopurinol 300 mg ½ tab od
• Colchicine 0.6 mg od
• Sitagliptin 100 od

• Enalapril 5 mg bid
• Orfarin 3 mg od
• Metformin 500 mg tid
• Digoxin 0.25 mg od
• Moduretic 1 tab od
• Senekot 2 tab o hs
• Bactrim forte 1 tab bid

POLYPHARMACY
Keys to HF clinic success

1. An enthusiastic and visionary physician champion
2. Interdisciplinary collaboration
   - An independent and professionally competent full-time staff
3. A holistic approach
4. Evidence based approach
5. Easy access to the specialist nurse
6. Facilitation of self management
7. Vigilant follow up
10 Practical Tips - Summary

1. HF should never be a final diagnosis - Identify treatable cause of HF
2. Give evidence based medication
3. Optimized HF medication
4. Know how to use diuretics effectively
   1. Flexible regimen
   2. Dealing with diuretic resistance
5. Hypotension VS hypoperfusion
6. How to avoid fatal hyperkalemia
7. How to deal with acute decompensation
8. Intractable HF – always ask why? remind yourself of the frequently overlooked problems
9. Good drugs do not work on patients who do not take them
10. Nurses are doctor’s best friend