Treatment Approach for the Patient with Heart Failure

Stage A
At high risk, no structural disease

Therapy
• Treat Hypertension
• Treat lipid disorders
• Encourage regular exercise
• Discourage alcohol intake
• ACE inhibition

Stage B
Structural heart disease, asymptomatic

Therapy
• All measures under stage A
• ACE inhibitors in appropriate patients
• Beta-blockers in appropriate patients

Stage C
Structural heart disease with prior/current symptoms of HF

Therapy
• All measures under stage A
Drugs:
• Diuretics
• ACE inhibitors
• Beta-blockers
• Digitals
• Dietary salt restriction

Stage D
Refactory HF requiring specialized interventions

Therapy
• All measures under stages A, B, and C
• Mechanical assist devices
• Heart transplantation
• Continuous (not intermittent) IV inotropic infusions for palliation
• Hospice care

Hunt, SA, et al. ACC/AHA Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult, 2001

Treatment of Heart Failure

Two distinct settings:

Treatment of Acute Decompensated Heart Failure

Goal:
Stabilise the patient, return the filling pressures to as close as possible to normal and restore organ perfusion.

Chronic Stable Heart Failure

Goal:
Enhance survival and minimise symptoms.
At All Times Treat Important

Precipitating Factors

Change a compensated condition to frank heart failure. (Can occur in up to 93% of patients)

Ghali et al. Arch Int Med 1986

- Inappropriate reduction in therapy
- Arrhythmias (including abnormal intra-ventricular conduction)
- Myocardial infarction/ischaemia
- Systemic infection
- Pulmonary embolism
- Drugs causing myocardial depression
- Oestrogens, corticosteroids, NSAIDS.
- Development of another form of heart disease

Pharmacologic Management

ACE Inhibitors

- Blocks the conversion of angiotensin I to angiotensin II; prevents functional deterioration.
- Recommended for all heart failure patients.
- Relieves symptoms and improves exercise tolerance.
- Reduces risk of death and decreases disease progression.
- Benefits may not be apparent for 1-2 months after initiation.
Pharmacologic Management

Angiotensin Receptor Blockers (ARBs)

- Block AT1 receptors, which bind circulating angiotensin II.
- Examples: valsartan, candesartan, losartan.
- Should not be considered equivalent or superior to ACE inhibitors.
- In clinical practice, ARBs should be used to treat patients who are ACE intolerant due to intractable cough or who develop angioedema.

Pharmacologic Management

Beta-Blockers

- Cardioprotective effects due to blockade of excessive SNS stimulation.
- In the short-term, beta blocker decreases myocardial contractility; increase in EF after 1-3 months of use.
- Long-term, placebo-controlled trials have shown symptomatic improvement in patients treated with certain beta-blockers. ¹
- When combined with conventional HF therapy, beta-blockers reduce the combined risk of morbidity and mortality, or disease progression. ¹

MOCHA: β blocker therapy reverses remodelling over 6 months

![Graph showing LVEF improvement with Carvedilol doses](image1)


CARMEN: β blocker + ACE inhibitor therapy reverses remodelling over 18 months

![Graph showing LVESVi improvement with different treatments](image2)

Remme et al Cardiovasc Drugs and Therapy 2004;18:57-66
Pharmacologic Management

Aldosterone Antagonists

- Generally well-tolerated.
- Shown to reduce heart failure-related morbidity and mortality.
- Generally reserved for patients with NYHA Class III-IV HF.
- Side effects include hyperkalemia and gynecomastia. Potassium and creatinine levels should be closely monitored.

Program

Lecture 1:
UPDATE ON CHRONIC HEART FAILURE

- Background Information
- ESC Guidelines on chronic heart failure 2012
- Adaptation to the ESC guidelines by South Africa Heart Association
Evidence-based Doses Of Disease-modifying Drugs Used In Key Randomized Trials In Heart Failure (Or After Myocardial Infarction) (ESC Guidelines 2012)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting dose (mg)</th>
<th>Target dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Captopril</td>
<td>62.5 mg/d</td>
<td>50 mg/d</td>
</tr>
<tr>
<td>Enalapril</td>
<td>2.5 mg/d</td>
<td>10–20 mg/d</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>2.5–5.0 mg/d</td>
<td>20–35 mg/d</td>
</tr>
<tr>
<td>Ramipril</td>
<td>2.5 mg/d</td>
<td>5 mg/d</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>0.5 mg/d</td>
<td>4 mg/d</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>1.25 mg/d</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>3.125 mg/d</td>
<td>25–50 mg/d</td>
</tr>
<tr>
<td>Metoprolol succinate (CR/V)</td>
<td>12.5 mg/d</td>
<td>200 mg/d</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>1.25 mg/d</td>
<td>10 mg/d</td>
</tr>
<tr>
<td>ARB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>4 or 8 mg/d</td>
<td>32 mg/d</td>
</tr>
<tr>
<td>Valsartan</td>
<td>40 mg/d</td>
<td>160 mg/d</td>
</tr>
<tr>
<td>Losartan</td>
<td>50 mg/d</td>
<td>150 mg/d</td>
</tr>
<tr>
<td>MRA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>25 mg/d</td>
<td>50 mg/d</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>25 mg/d</td>
<td>25–50 mg/d</td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; b.i.d. = bis in die (twice daily); MRA = mineralocorticoid receptor antagonist; q.d. = quae diie (once daily); t.i.d. = ter in die (three times daily).

*Indicates an ACE inhibitor where the dosing target is derived from post-myocardial infarction trials.

*Indicates drugs where a higher dose has been shown to reduce mortality—mortality compared with a lower dose of the same drug, but there is no substantive placebo-controlled randomized controlled trial and the optimum dose is uncertain.

*Indicates a treatment not shown to reduce cardiovascular or all-cause mortality in patients with heart failure or after acute myocardial infarction (or shown to be non-inferior to a treatment that does).

Other Treatments With Less-certain Benefits In Patients With Symptomatic (NYHA Class II–IV) Systolic Heart Failure (ESC Guidelines 2012)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Class*</th>
<th>Level*</th>
<th>Ref*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARB Recommended to reduce the risk of HF hospitalization and the risk of premature death in patients with an EF ≤40% and unable to tolerate an ACE inhibitor because of cough (patients should also receive a beta-blocker and an MRA).</td>
<td>I</td>
<td>A</td>
<td>108, 109</td>
</tr>
<tr>
<td>ARB Recommended to reduce the risk of HF hospitalization in patients with an EF ≥40% and persisting symptoms (NYHA class II–IV) despite treatment with an ACE inhibitor and a beta-blocker who are unable to tolerate an MRA.</td>
<td>I</td>
<td>A</td>
<td>110, 111</td>
</tr>
<tr>
<td>Indacarvon</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Should be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF &lt;35%, a heart rate remaining ≥70 bpm, and persisting symptoms (NYHA class II–IV) despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE inhibitor (or ARB), and an MRA (or ARB)*.</td>
<td>IIa</td>
<td>B</td>
<td>112</td>
</tr>
<tr>
<td>May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF &lt;35% and a heart rate &gt;70 bpm who are unable to tolerate a beta-blocker. Patients also receive an ACE inhibitor (or ARB) and an MRA (or ARB)*.</td>
<td>IIb</td>
<td>C</td>
<td>–</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF &lt;45% who are unable to tolerate a beta-blocker. Indacarvon is an alternative in patients with a heart rate &gt;70 bpm. Patients also receive an ACE inhibitor (or ARB) and an MRA (or ARB).</td>
<td>IIb</td>
<td>B</td>
<td>113</td>
</tr>
<tr>
<td>May be considered to reduce the risk of HF hospitalization in patients in sinus rhythm with an EF &lt;45% and persisting symptoms (NYHA class II–IV) despite treatment with a beta-blocker, ACE inhibitor (or ARB), and an MRA (or ARB).</td>
<td>IIb</td>
<td>B</td>
<td>113</td>
</tr>
</tbody>
</table>

*ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CR = cardiorespiratory; DCF = digitalis; EF = ejection fraction; HF = heart failure; HGIN = heart- and glucose intolerance; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; PRA = plasma renin activity; I = initially; II = increase as tolerated; III = increase as tolerated to maximum tolerated dose; IV = increase as tolerated to maximum tolerated dose. 

*Class of recommendation.

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>108, 109</td>
</tr>
<tr>
<td>B</td>
<td>110, 111</td>
</tr>
<tr>
<td>C</td>
<td>–</td>
</tr>
</tbody>
</table>

Doses varied in the CHARM-Added trial, consistent with the reduced cardiovascular mortality. 

*European Medicines Agency has approved indacarvon for use in patients with a heart rate >70 bpm. 

Preparation studied in post-mortem the GISSI-HF trial had no EF limit.
Other Treatments With Less-certain Benefits In Patients With Symptomatic (NYHA Class II–IV) Systolic Heart Failure cont.

Diuretics

Fluid retention may increase cardiac output by a Frank-Starling mechanism.

Other consequences of fluid retention include:

- **Increase diastolic pressure**
  - thus
- **Increase in wall stress**
  - thus
- **Hypertrophy and remodelling**

There may be oedema, dyspnoea and pulmonary oedema.

**Hence the use of diuretics**
Classes of Diuretics

**Loop Diuretics**
Furosemide, torasemide, bumetamide

**Thiazide and Thiazide-like**

**Potassium Sparing Diuretics**
Amiloride, triamterine

**Mineralo Corticoid Inhibitory**
Spironolactone

**Carbonic Anhydrase Inhibitors**
Acetzolamide (diamox)

---

**Diuretics**

With the exception of spironolactone (an aldosterone antagonist) diuretics do not influence the natural history of chronic heart failure.


*However....*

Diuretics potentially improve congestive symptoms and may slow down ventricular remodelling.
Doses Of Diuretics Commonly Used To Treat Heart Failure (With And Without A Preserved Ejection Fraction, Chronic And Acute) (ESC Guidelines 2012)

<table>
<thead>
<tr>
<th>Diuretics</th>
<th>Initial dose (mg)</th>
<th>Usual daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loop diuretics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>20-40</td>
<td>40-240</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>0.5-1.0</td>
<td>1-5</td>
</tr>
<tr>
<td>Torsemide</td>
<td>5-10</td>
<td>10-20</td>
</tr>
<tr>
<td>Thiazides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beneflavone Beside</td>
<td>2.5</td>
<td>2.5-10</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>25</td>
<td>12.5-100</td>
</tr>
<tr>
<td>Metolazone</td>
<td>2.5</td>
<td>2.5-10</td>
</tr>
<tr>
<td>Indapamide</td>
<td>2.5</td>
<td>2.5-5</td>
</tr>
</tbody>
</table>

Potassium-sparing diuretics

<table>
<thead>
<tr>
<th>Drug</th>
<th>+ACEI/ ARB</th>
<th>-ACEI/ ARB</th>
<th>+ACEI/ ARB</th>
<th>-ACEI/ ARB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>12.5-25</td>
<td>50</td>
<td>50</td>
<td>100-200</td>
</tr>
<tr>
<td>Amiloride</td>
<td>2.5</td>
<td>5</td>
<td>5-10</td>
<td>10-20</td>
</tr>
<tr>
<td>Triamterene</td>
<td>25</td>
<td>50</td>
<td>100</td>
<td>200</td>
</tr>
</tbody>
</table>

Problems Encountered With Diuretics

1. **Metabolic Side Effects**
   - Hyperglycaemia, hyperuricaemia
2. **Electrolyte Imbalance**
3. **Volume Depletion**
   - Hypertension, interference with other medications (Ace I, ARB, beta blockade)
4. **Diuretic Resistance (Na=sodium)**
   - Net gain of Na with a high Na diet
   - Compensatory hypertrophy of tubular epithelial cells distal to their site of action
   - Other drugs NSAIDS
   - ↓ Renal perfusion
Cardiac Glycosides

- Have a definite inotropic effect (more Starling curve-calcium mediated).
- Does not decrease mortality.
- Beneficial effects in mild to moderate failure in sinus rhythm.
- Requires vigilance regarding toxic accumulation (NB: GFR, body mass).
- Measurement of serum levels advisable.
- Contra-indicated in predominantly diastolic dysfunction.

Medications Which Increase Serum Digoxin Levels Mainly By ↓ Renal Clearance

<table>
<thead>
<tr>
<th>Amiodarone</th>
<th>Amiloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verapamil</td>
<td>Triamterene</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Macrolide Antibiotics</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Quinidine</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Alprazolam</td>
</tr>
<tr>
<td>Captopril</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Cyclosporine Spironolactone</td>
</tr>
<tr>
<td>Saint John’s wort</td>
<td></td>
</tr>
</tbody>
</table>
**Vasodilators**

Decrease arteriolar tone $\uparrow$ CO  
Decrease venous preload $\downarrow$ congestion

**Acute Phase**  
Sodium nitroprusside  
Nitrates initially may also have a beneficial primary coronary effect, secondary $\uparrow$ CO.

**Chronic Stable Phase**  
**Oral Nitrates** – Note: Avoid nitrate resistance by having a drug free time.  
**Hydralazine** – Need for 3-4 times daily dose. (major increase in systemic and pulmonary after load).

---

**Treatments (Or Combinations Of Treatments) That May Cause Harm In Patients With Symptomatic (NYHA Class II–IV) Systolic Heart Failure**  
(ESC Guidelines 2012)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class Level</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinediones (glitazones) should not be used as they cause worsening HF and increase the risk of HF hospitalisation.</td>
<td>III A</td>
<td>131–133</td>
</tr>
<tr>
<td>Most CCBs (with the exception of amlopidine and felodipine) should not be used as they have a negative inotropic effect and can cause worsening HF.</td>
<td>III B</td>
<td>134</td>
</tr>
<tr>
<td>NSAIDs and COX-2 inhibitors should be avoided if possible as they may cause sodium and water retention, worsening renal function and worsening HF.</td>
<td>III B</td>
<td>135, 136</td>
</tr>
</tbody>
</table>

The addition of an ARB (or renin inhibitor) to the combination of an ACE inhibitor AND a mineralocorticoid antagonist is NOT recommended because of the risk of renal dysfunction and hyperkalemia.
Treatment Options For Patients With Chronic Symptomatic Systolic Heart Failure (NYHA Functional Class II–IV) (ESC Guidelines 2012)

Essential Topics That Should Be Covered During Patient Education, And The Skills And Self-care Behaviours That Should Be Taught In Relation To These Topics cont. (ESC Guidelines 2012)

<table>
<thead>
<tr>
<th>Educational topic</th>
<th>Patient skills and self-care behaviours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>• Modest intake of alcohol abstinence is recommended in patients with alcohol-induced cardiomyopathy. Otherwise, normal alcohol guidelines apply (2 units per day in men or 1 unit per day in women). 1 unit is 10 ml of pure alcohol (e.g. 1 glass of wine, 1/2 pint of beer, 1 measure of spirits)</td>
</tr>
<tr>
<td>Smoking and drugs</td>
<td>• Stop smoking and/or taking illicit drugs</td>
</tr>
</tbody>
</table>
| Exercise                | • Understand the benefits of exercise  
• Perform exercise training regularly  
• Be reassured and comfortable about physical activity                                                                                                                                         |
| Travel and leisure      | • Prepare travel and leisure activities according to physical capacity  
• When travelling, carry a written report of medical history and current medication regimen and carry extra medication. Monitor and adapt fluid intake particularly during flights and in hot climates. Beware adverse reactions to sun exposure with certain medications (e.g. amiodarone) |
| Sexual activity         | • Be reassured about engaging in sex and discuss problems with healthcare professionals. Stable patients can undertake normal sexual activity that does not provoke undue symptoms. For treatment of erectile dysfunction, see Section 11.10 |
| Immunization            | • Receive immunization against influenza and pneumococcal disease according to local guidelines and practice                                                                                         |
| Sleep and breathing disorders | • Recognize preventative behavior such as reducing weight in obese patients, smoking cessation, and abstinence from alcohol  
• Learn about treatment options if appropriate                                                                                                                                               |
| Psychosocial aspects    | • Understand that depressive symptoms and cognitive dysfunction are common in patients with heart failure and the importance of social support  
• Learn about treatment options if appropriate                                                                                                                                               |
Program

Lecture 1:
UPDATE ON CHRONIC HEART FAILURE

• Background Information to Therapeutic approach
• ESC Guidelines on chronic heart failure 2012
• Adaptation to the ESC guidelines by South Africa Heart Association
HEART FAILURE

- NATURETIC PEPTIDES SECRETED FROM HEART, KIDNEY, VASCULATURE, CNS
- REDUCE VASOCONSTRICTION AND Na RETENTION
- DEGRADED BY NEPROLYSIN
- INHIBITION OF NEPROLYSIN INCREASES PEPTIDES
- REDUCES VASOCONSTRICTION AND Na RETENTION
- NEPRILYSIN PLUS ACEI MORE EFFECTIVE MORE SIDE EFFECTS

HEART FAILURE

- NEPROLYSIN INHIBITOR SACUBITRIL PLUS ARB VALSARTAN
- MORE EFFECTIVE THAN ENALAPRIL ALONE
HEART FAILURE ARNI

- 8442 RANDOMISED CLASS II -IV
- EF 40% OR LESS
- LCZ 696 200MG B D
- ENALAPRIL 10MG B D
- PRIMARY OUTCOME
- DEATH FROM CARDIAC CAUSES
- HOSPITALISATION FROM HEART FAILURE
- TRIAL DESIGNED FOR DEATH FROM ANY CAUSE

HEART FAILURE

- TRIAL STOPPED AFTER 27 MONTHS BECAUSE PRESPECIFIED
- BOUNDARY FOR BENEFIT CROSSED
HEART FAILURE LCZ 696

- DEATH FROM CARDIAC CAUSE AND HF HOSPITALISATION
- PRIMARY OUTCOME
  - LCZ 696: 914 (21.8%)
  - ENALAPRIL: 1117 (26.5%)
- DEATH FROM ANY CAUSE
  - LCZ: 711 (711) 17%
  - ENALAPRIL: 835 (19.8%)
- DEATH FROM CV CAUSE
  - LCZ: 558 (13.3%)
  - ENALAPRIL: 693 (16.5%)
- REDUCTION OF HOSP RISK LCZ 696: 21%

HEART FAILURE ARNI

- HIGH PROPORTION OF HYPOTENSION AND NON SERIOUS ANGIO OEDEMA BUT LOWER PROPORTION WITH RENAL IMPAIRMENT, HYPERKALEMIA AND COUGH
- LCZ 696 SUPERIOR TO ENALAPRIL