Program:

Module 1:
• Definition and Classification
• Epidemiology of Heart Failure
• Pathophysiology of Heart Failure
• Specific Diseases causing Heart Failure and practical case studies

Module 2:
• Diagnosis and Investigation of HF and Practical Case Studies
• Treatment of Heart Failure and Practical Case Studies
Treatment Approach for the Patient with Heart Failure

**Stage A**
At high risk, no structural disease

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

**Stage B**
Structural heart disease, asymptomatic

- 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

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

**Stage D**
Refractory HF requiring specialized interventions

- 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 \( AT_1 \) 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

LVEF Improvement

* p<0.005 vs placebo

* p<0.001

0 1 2 3 4 5 6 7 8

ΔLVEF

Placebo 12.5 mg 25 mg 50 mg

Carvedilol

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

Remme et al Cardiovasc Drugs and Therapy 2004;18;57-66
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.
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, turasemide, bumetamide

Thiazide and Thiazide-like

Potassium Sparing Diuretics
- Amiloride, triamterine

Mineralo Corticoid Inhibitory
- Spironolactone

Carbonic Anhydrase Inhibitors
- Acetezolamide (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.
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>
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<tbody>
<tr>
<td>Verapamil</td>
<td>Triamterene</td>
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<tr>
<td>Nifedipine</td>
<td>Macrolide Antibiotics</td>
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<td>Captopril</td>
<td>Itraconazole</td>
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<tr>
<td>Carvedilol</td>
<td>Cyclosporine</td>
</tr>
<tr>
<td>Saint John’s wort</td>
<td>Spironolactone</td>
</tr>
</tbody>
</table>
**Vasodilators**

Decrease arteriolar tone ↑ CO
Decrease venous preload ↓ congestion

**Acute Phase**
Sodium nitroprusside
Nitrates initially may also have a beneficial primary coronary effect, secondary ↑ 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 afterload).
Anticoagulants

The presence of heart failure markedly lowers the threshold for instituting anticoagulant therapy e.g. atrial fibrillation, bed rest.
Timing is Everything

“Either my watch has stopped or this guy is dead.”

Groucho Marx: A day at the races.
Prevalence of Inter- or Intraventricular Conduction Delay

General HF Population\textsuperscript{1,2}

- IVCD 15%

Moderate to Severe HF Population\textsuperscript{3,4,5}

- IVCD >30%

\textsuperscript{1} Havranek E, Masoudi F, Westfall K, et al. Am Heart J 2002;143:412-417
Determinants of Cardiac Synchrony
Interventricular Synchrony

Determinants: Bundle branches

\( x \) = Right bundle
\( xx \) = Left anterior fasicle
\( xxx \) = Left posterior inferior fasicle
Determinants of Cardiac Synchrony

Intraventricular Synchrony

Mainly affects LV (scar etc)
Bundle Branch Patterns of Activation

Source: J Cardiovasc Electrophysiol © 2005 Blackwell Publishing
Achiving Cardiac Resynchronization

Goal: Atrial synchronous biventricular pacing

Transvenous approach for left ventricular lead via coronary sinus

Back-up epicardial approach
Summary of Proposed Mechanisms Therapy

Cardiac Resynchronization

Intraventricular Synchrony
- \[ \uparrow dP/dt, \uparrow EF, \uparrow CO \] (\[ \uparrow \] Pulse Pressure)
- \[ \downarrow \text{MR} \]
- \[ \downarrow \text{LVESV} \]

Atrioventricular Synchrony
- \[ \downarrow \text{LA Pressure} \]
- \[ \uparrow \text{LV Diastolic Filling} \]

Interventricular Synchrony
- \[ \uparrow \text{RV Stroke Volume} \]

Reverse Remodeling

Ventricular Dysynchrony and Cardiac Resynchronization

Ventricular Dysynchrony¹

**Electrical:** Inter- or Intraventricular conduction delays typically manifested as left bundle branch block

**Structural:** Disruption of myocardial collagen matrix impairing electrical conduction and mechanical efficiency

**Mechanical:** Regional wall motion abnormalities with increased workload and stress—compromising ventricular mechanics

Cardiac Resynchronization

Therapeutic intent of atrial synchronized biventricular pacing

- Modification of interventricular, intraventricular, and atrial-ventricular activation sequences in patients with ventricular dysynchrony
- Complement to optimal medical therapy

¹ Tavazzi L. Eur Heart J 2000;21:1211-1214
Benefits Sustained Through 2 Years

MIRACLE Study Program

Mean distance walked in 6 minutes (m)

<table>
<thead>
<tr>
<th>Months of Active CRT</th>
<th>Baseline</th>
<th>Follow-up</th>
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</thead>
<tbody>
<tr>
<td>6 (N=1124)</td>
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<tr>
<td>12 (N=693)</td>
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<tr>
<td>18 (N=320)</td>
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<tr>
<td>24 (N=68)</td>
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</tr>
</tbody>
</table>

P<0.001

Mean NYHA Functional Class

Paired Data Displayed

Mean QoL Score Improvement ↓

Source: Abraham, WT et al. AHA 2003
CRT Effect on LV Structure at 6 Months in Moderate to Severe Heart Failure

LVEDV Avg. Change (mL)

-40 -30 -20 -10 0 10

P<0.001 P=0.06 Not Reported

LVEDD Avg. Change (mm)

-6 -4 -2 0 2

P<0.05 P=0.81 P=0.001

MIRACLE MIRACLE ICD Contak CD

Data sources:
MIRACLE ICD: JAMA 2003;289:2685-2694
Contak CD: J Am Coll Cardiol 2003;2003;42:1454-1459
CARE-HF: CRT reduces death or unplanned hospitalisation for CV events in NYHA III/IV

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>CRT</th>
<th>Medical Therapy</th>
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<tbody>
<tr>
<td>CRT</td>
<td>409</td>
<td>404</td>
</tr>
<tr>
<td></td>
<td>323</td>
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</table>

% Patients Free of Death from Any Cause or Unplanned Hospitalisation for a Major CV Event

HR 0.63 (95% CI 0.51 - 0.77)
37% Relative Risk Reduction

P < 0.001

MICD II: CRT therapy may reverse remodelling over 6 months in mild HF

LV EF %

Baseline

6 months

p = 0.02

CRT n = 69

Medical therapy n = 85

LV ESV ml

Baseline

6 months

p = 0.01

CRT n = 69

Medical therapy n = 85

Abraham et al Circulation 2004;110:2864-68
Grade II NYHA

P = 0.03  Hazard Ratio = 0.47

53% reduction with CRT

Number at Risk

<table>
<thead>
<tr>
<th></th>
<th>CRT OFF</th>
<th>CRT ON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months Since Randomisation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>191</td>
<td>419</td>
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<tr>
<td>12</td>
<td>119</td>
<td>251</td>
</tr>
</tbody>
</table>

Grade II NYHA

P<0.0001

n=487

LVESVi (ml/mm$^2$)

0 75 80 85 90 95 100 105 110 115

Baseline 12 Months

CRT off
Δ = -1.3

CRT on
Δ = -18.4

Madit CRT

![Graph showing the probability of survival free of heart failure over years since randomization. The graph compares CRT-ICD and ICD only groups, with no significant difference indicated by the P<0.001. The table below shows the number at risk (probability of survival) for each group at various time points.]
Prediction of Sudden Death from History – Paris Study

Factors associated with sudden death during follow up (23 years):

- Resting heart rate.
- Systolic and diastolic blood pressure.
- Tobacco consumption.
- Body mass index.
- Diabetes.
- Serum cholesterol.
- Parental history of sudden death.
Most Cardiac Arrests (70%-80%) Occur At Home


Summary: Treatment

1. Acute Phase
   Treat fluid overload (oedema, pulmonary oedema).
   Remove/treat precipitating cause (ischaemia, infection, arrhythmia, thyrotoxicosis)

2. Chronic Phase
   Stop the vicious cycle
   a. ACE inhibitors, ARB
   b. Beta blockers
   c. Spironolactone
   d. Digoxin (?)
   e. Arrhythmias
   f. Incoordinate contractions

   REST
   REVERSE
   REPAIR