Management of Myocardial Infarction & Congestive Heart Failure

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Myocardial Infarction
Objectives of Medical Management

• Decrease morbidity

• Reduce further myocardial damage or injury

• Maintain or restore hemodynamic stability

• Minimize complications

• Relieve patient’s symptoms
Myocardial Infarction

• Initial treatment
  – Conservative (or)
  – Invasive
Nitrates

• Does not impact morbidity

• Can improve patient’s discomfort

• Works by
  – Dilate venous capacitance vessels and peripheral arterioles
  – Decrease preload and afterload
  – Lead to decrease in both myocardial wall stress and oxygen demand
  – Relieve coronary spasm in atherosclerotic vessels and increase oxygen delivery to the subendocardial region that is supplied by the severely narrowed coronary artery
Nitrates

• ISIS-4 and GISSI-3 studies

• Contraindicated:
  – Patients who have taken sildenafil, tadalafil, or vardenafil in the previous 24 hours
  – Systemic hypotension
  – Marked tachycardia
  – Severe aortic stenosis
  – Right ventricular infarct
B-Adrenergic Blockers

• Have been shown to decrease morbidity and mortality

• Overview of literature (1988) showed a 13% relative reduction in the risk of progression from UA to an MI

• Pooled analysis of 5 trials (2003) showed a 50% reduction in mortality at 30 days and 6 months
B-Blockers

- Recommended that ACS patients without contraindications should receive their initial dose of an oral B-blocker within the first 24 hours of medical therapy.

- Works by:
  - Decreasing sinus node rate and atrioventricular node conduction velocity, systolic blood pressure, and contractile responses at rest and during exercise.
  - Decrease myocardial oxygen demand and increase the length of diastole.
Calcium channel blockers

• Not routinely given to AMI patients due to lack of convincing evidence that they actually reduce death

• CCBs can be used as 3rd-line anti-ischemic agents (after nitrates and B-blockers) in patients who have elevated blood pressure or angina at rest

• Short acting nifedipine should be avoided due to increased adverse events
Calcium channel blockers

• Reduces myocardial contraction and relaxation of vascular smooth muscle, which increases coronary blood flow

• Decrease afterload and heart rate, while relaxing the left ventricle and increasing arterial compliance

• 2 major classes:
  – Dihydropyridine
    • Nifedipine, amlodipine
  – Nondihydropyridine
    • Verapamil, diltiazem
Antiplatelet therapy

- Acetylsalicylic acid (Aspirin)

- Thienopyridines
  - Ticlopidine
  - Clopidogrel
  - Prasugrel
Aspirin

- Works by
  - Preventing thromboxane A2 (TXA2) production and resultant platelet aggregation

- Reduces the risk of angina, death, or MI by approximately 30% in patients with CAD

- 1994 - the Antiplatelet Trialists’ Collaboration meta-analysis of 174 trials (70,000 pts)

- 2002 - meta-analysis of 287 studies (135,000 pts)
Thienopyridines

- Works by
  - Inhibiting platelet activation
  - Limit ADP-mediated conversion of GPIIb/IIIa to its active form
  - Mechanism of action is independent of and complementary to that of aspirin
Ticlopididine

• 1st-generation thienopyridine

• In combination with ASA, reduces rate of vascular death and MI by 46% in NSTEMI patients

• Used less frequently than the newer thienopyridines because of its potential for side effects:
  – Rash, nausea, neutropenia, thrombocytopenia
Clopidogrel

- 2nd-generation thienopyridine

- Most widely used and studied ADP-receptor-blocking agent
  - CAPRIE study (1996) : 19,185 pts
  - CURE trial (2001) : 12,562 pts
  - CHARISMA trial (2006)
  - PCI-CURE trial (2001)
Clopidogrel

- 9% relative risk reduction in adverse cardiovascular events (vascular death, MI, or ischemic stroke) when compared to aspirin - (CAPRIE)

- 20% reduction in the primary composite endpoint (cardiovascular death, MI, or stroke) up to 12 months of f/u - (CURE)

- 31% reduction in cardiovascular death or MI in patients undergoing PCI - (PCI-CURE)
Glycoprotein IIb/IIIa Inhibitors

• Platelets are activated through multiple pathways

• The “final common pathway” of platelet activation and aggregation involves a conformational change of the GPIIb/IIIa receptors from a resting state to an active state

• Examples
  – Abciximab, Tirofiban & Eptifibatide
Glycoprotein IIb/IIIa Inhibitors

• EPIC trial (1994) - 35% reduction in primary composite endpoint (death, MI, recurrent ischemia) in pts given abciximab vs placebo

• CAPTURE trial (1997) - 30% relative reduction of death, MI, or recurrent ischemia in pts given abciximab

• PRISM study (1998) - 32% reduction in death, MI, or recurrent ischemia in pts given tirofiban

• PURSUIT trial (1998) - 10% reduction in the relative risk of death and MI in pts given eptifibatide
Anticoagulants

- Unfractionated heparin
- Low-molecular-weight heparin
  - Enoxaparin
  - Dalteparin
- Factor X inhibitors
  - fondaparinux
Heparin (UFH and LMWH)

- FRISC trial (1997) - 63% relative risk reduction in death or MI in pts given dalteparin vs placebo

- ESSENCE trial (1997) - the risk of death, MI, or recurrent angina was significantly lower in pts given enoxaparin vs UFH (16.6% vs 19.8%)

- TIMI 11B trial (1999) - 14.3% risk reduction of death, MI, or need of urgent revascularization in pts given enoxaparin vs UFH
Statins

- Work by
  - Stabilizes the endothelium
  - Decrease cholesterol

- Used in secondary prevention

- Part of the NICE guidelines
Early-Conservative and Early-Invasive Strategies

• In the early-invasive strategy, all patients without contraindications undergo coronary angiography with the intent to perform revascularization within 4 to 24 hours of hospital admission.

• The early-conservative strategy consists of aggressive medical therapy for patients
Early-Conservative and Early-Invasive Strategies

• Coronary angiography aids in defining the extent and location of CAD and in directing the definitive care strategy
  – PCI/stenting
  – CABG
  – Medical management

• Angiography is an invasive procedure and there is a small risk of serious complications (~1 in 1,000 cases)
TIMI-IIIIB trial

• Compared an early-invasive strategy to an early-conservative strategy in UA/NSTEMI pts (1994)

• Primary endpoint: composite of death, MI, or abnormalities on a exercise stress test at 6 weeks

• No significant difference in the occurrence of the composite endpoint between the groups.

• However, the average length of initial hospitalization, the incidence of rehospitalization within 6 weeks, and the number of days of rehospitalization all were significantly lower in the early-invasive group
VANQUISH trial

• Compared an early-conservative strategy to an early-invasive strategy (1998)

• Combined endpoint of death and non-fatal MI occurred in 3.3% of pts in the early-conservative group and 7.7% of pts in the early-invasive group

  – (No benefit of early-invasive strategy)
FRISC-II trial

• Compared an early-conservative strategy to an early-invasive strategy (1999)

• Incidence of the composite endpoint of death or MI was 9.4% in the early-invasive group and 12.1% in the early-conservative group

• Furthermore, angina symptoms and hospital readmissions were reduced by 50% with the use of the early-invasive strategy
Reperfusion therapy for patients with STEMI. The bold arrows and boxes are the preferred strategies.

Conclusions

• ACS is associated with high rates of adverse cardiovascular events, despite recent therapeutic advances

• Plaque composition and inflammation are more important in the pathogenesis of ACS than is the actual degree of stenosis
Conclusions

• The cornerstone of contemporary treatment remains early risk stratification and aggressive medical therapy, supplemented by coronary angiography in appropriately selected patients.
Conclusions

• An early-invasive treatment strategy is of most benefit to high-risk patients

• An early-conservative strategy is recommended for low-risk patients
Conclusions

• Adjunctive medical therapy with ASA, clopidogrel, GPIIb/IIIa inhibitors, and either LMWH or UFH, in the appropriate setting, further reduces the risk of ischemic events secondary to thrombosis

• Anticoagulation and short- and long-term inhibition of platelet aggregation should be achieved by appropriately evaluating the risk of bleeding complications in each patient
Congestive Heart Failure

Right-sided heart failure: Cyanosis, engorgement of jugular veins, enlargement of liver, ascites, dependent edema, elevated venous pressure

Elevated
Normal

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Goal of Management

• To minimize symptoms

• To alter the adverse response that results in dysfunction

• Treat the underlying disease process
Medical Management

- Aldosterone
- Angiotensin Converting Enzymes Inhibitors
- Angiotensin Receptor Blockers
- Beta Blockers
- Diuretics
- Digoxin
### Heart Failure Treatments: Medication Types

<table>
<thead>
<tr>
<th>Type</th>
<th>What it does</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE inhibitor</strong> (ACEi)</td>
<td>• Expands blood vessels which lowers blood pressure, neurohormonal blockade</td>
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<tr>
<td><strong>ARB</strong> (angiotensin receptor blockers)</td>
<td>• Similar to ACE inhibitor—lowers blood pressure</td>
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<tr>
<td><strong>Beta-blocker</strong></td>
<td>• Reduces the action of stress hormones and slows the heart rate</td>
</tr>
<tr>
<td><strong>Digoxin</strong></td>
<td>• Slows the heart rate and improves the heart’s pumping function (EF)</td>
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<tr>
<td><strong>Diuretic</strong></td>
<td>• Filters sodium and excess fluid from the blood to reduce the heart’s workload</td>
</tr>
<tr>
<td><strong>Aldosterone blockade</strong></td>
<td>• Blocks neurohormonal activation and controls volume</td>
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</tbody>
</table>
**Lifestyle Changes**

<table>
<thead>
<tr>
<th>What</th>
<th>Why</th>
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</thead>
<tbody>
<tr>
<td>Eat a low-sodium, low-fat diet</td>
<td>Sodium is bad for high blood pressure,</td>
</tr>
<tr>
<td></td>
<td>causes fluid retention</td>
</tr>
<tr>
<td>Lose weight</td>
<td>Extra weight can put a strain on the heart</td>
</tr>
<tr>
<td>Stay physically active</td>
<td>Exercise can help reduce stress and blood</td>
</tr>
<tr>
<td></td>
<td>pressure</td>
</tr>
<tr>
<td>Reduce or eliminate alcohol and caffeine</td>
<td>Alcohol and caffeine can weaken an already</td>
</tr>
<tr>
<td></td>
<td>damaged heart</td>
</tr>
<tr>
<td>Quit Smoking</td>
<td>Smoking can damage blood vessels and make the</td>
</tr>
<tr>
<td></td>
<td>heart beat faster</td>
</tr>
</tbody>
</table>
Pharmological Treatment of Heart Failure

• Two studies showed morbidity and mortality benefits of aldosterone antagonists.
  
• RALES
• EPHESUS
The RALE study was a double blind placebo controlled trial looking at 1663 patients with severe heart failure (NYHA III or IV). They were randomized to receive either spironolactone 25mg orally once daily or placebo and were followed for 24 months.

The study was premature discontinued because it demonstrated the efficacy in the treated group. Improvement in mortality in all groups were noted as well as a 30% reduction in sudden death and progression to heart failure and also a 35% reduction in frequency of hospitalization for worsening heart failure.

Side effects were severe hyperkalemia (esp. in persons with renal impairment) and 10% complained of breast pain and gynecomastia – endocrine side effects is due to non-selective binding to estrogen and progesterone receptors.
Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study

- The EPHESUS trial is a randomized, double blinded, placebo controlled trial using eplerenone 25 – 50mg daily. This selective aldosterone blocker was used in patients with acute myocardial infarction with left ventricular dysfunction (mean 35%) with heart failure. They were followed for 16 months. At 1 year, patients randomized to eplerenone had a significantly smaller rise in blood pressure compared with those on placebo and experienced no drop in blood pressure; most patients had a small but significant increase in both serum potassium and serum creatinine.

- Eplerenone showed a 15% reduction in total all-cause mortality and 13% fewer cardiovascular-related deaths and cardiovascular hospitalizations compared with the placebo group. Additionally there was also a significant 17% reduction in deaths attributed to cardiovascular causes.
ACE Inhibitors in Heart Failure

- In heart failure compensatory mechanisms become maladaptive and can cause worsening of heart failure symptoms. These include the sympathetic excess and the persistent activation of the Renin-Angiotensin-Aldosterone System. Angiotensin II working through AT1 receptors causes arteriole vasoconstriction thus increasing afterload, promote sodium and water resorption either directly or through the action of aldosterone thus increasing preload, stimulation of the CNS and AT1 receptor stimulation resulting in myocyte hypertrophy and maladaptive remodeling. Angiotensin II also promote endothelial dysfunction and severity of arterosclerosis. Blocking these effects will have beneficial effects.

- ACE inhibitors have demonstrated benefits in decreasing the severity of heart failure symptoms, asymptomatic LV dysfunction and after acute myocardial infarction. Meta-analysis also shows that ACE inhibitors decreases mortality, hospitalization and myocardial infarction but not stroke.
• **Co-operative North Scandinavian Enalapril Survival Study**
  The CONSENSUS study looked at the effects of enalapril on the prognosis of severe heart failure. It enrolled 253 patients to either receive enalapril or placebo. The study was halted early by the ethics committee as there was clear benefit in the enalapril group. There was decrease in all cause mortality and progression in heart failure. There was no difference between the two groups in sudden cardiac death.

• The study clearly showed the benefit of ACE inhibitors in the treatment of heart failure.

• **Studies of Left Ventricular Dysfunction**
  The SOLVD study is a retrospective study looking at the effects of enalapril, an ACE inhibitor, on the incidence of diabetes in a group of 235 patients with congestive heart failure. The dose of 20mg daily was used and showed significant reduction in all cause mortality.

• This study followed patient up to 12 years and benefit narrowed over time and was no longer significant after 12 years.
Vasodilators

• **Vasodilator – Heart Failure Trial**
  • V-Heft was a multi-centered, randomized, double blind trial that compare the efficacy of enalapril to hydralazine plus isosorbide dinitrate. 804 patients were randomized and followed for a mean of 2.5 years. The primary end point was all cause mortality.

  • The study demonstrated that there was greater reduction in mortality in the enalapril arm primarily due to lower incidence of sudden cardiac death. There was also improvement in left ventricular ejection fraction in both groups. Of note, benefits seen only in white patients with hypertension.

• **Survival and Ventricular Enlargement Trial**
  • The SAVE trial was a placebo controlled trial that enrolled 2231 patients post myocardial infarction to either receiving placebo or captoril. The study demonstrated that when administered 3 to 16 days after acute myocardial infarction in selected patients, captoril, the angiotensin-converting enzyme inhibitor, reduces ventricular dilatation, prevents the development of congestive heart failure, and reduces morbidity and mortality.

  • Captopril decreased mortality by 19%, progression to heart failure by 37%, reduction in hospitalization by 22% and reduction in recurrent myocardial infarction by 25%
• Assessment of Treatment with Lisinopril and Survival Trial
  • ATLAS trial was a multi-centered, randomized double blind trial that enrolled 3164 patients with Class 2-3 heart failure. The patients randomized to receive either low dose (2.5mg) or high dose (35mg) of lisinopril. High dose was found to be superior and well tolerated.

• The results of the ATLAS trial strongly support the use of the high-doses of ACEIs employed in the randomized CHF trials as opposed to the current low-doses used in general clinical practice. High-dose lisinopril resulted in a statistically significant 12% reduction in death, a 14% reduction in death or CHF hospitalization ($P=0.002$), and a 24% reduction in CHF hospitalization ($P=0.002$) without significant increases in the rate of adverse events.
Beta Blockers in Heart Failure

• There is sympathetic activation in heart failure with increase circulation of catecholamine that cause increase in heart rate as well it can be directly toxic to the cardiac myocytes.

• Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure
  • The MERIT-HF was a randomized, double blind, placebo controlled trial that enrolled 3991 patients with NYHA Call II-IV and LVEF ≤ 40%. Patients were randomized to receive either placebo or metoprolol 12.5 or 25mg.

• Primary endpoint was all cause mortality. The study was stopped early because of the evidence of fewer cardiovascular deaths, sudden death and worsening heart failure in the study population.
Beta Blockers

• **Metoprolol in Dilated Cardiomyopathy**
  The MDC trial looked at 383 patients with idiopathy cardiomyopathy with LVEF of less than 40%. Patient was given metoprolol with a target dose of 100-150 per day. Primary end points were improvement of clinical symptoms, improvement in LV function. The results revealed that patients improved in terms of clinical symptoms and delayed the need for transplantation. The mortality did not improve.

• **Carvidilol Trial**
  This trial enrolled 1094 patients with NYHA class II-IV to receive carvidilol or placebo. Target dose for the study was 25mg to 50mg twice daily. The study was stopped early because of the obvious benefit. There was a 48% reduction in disease progression.
Valsartan Heart Failure Trial
The Val-HeFT was a randomized study that enrolled approximately 5000 patients with NYHA Class II-IV to receive either placebo or valsartan. The Primary outcomes were all cause deaths, mortality and morbidity such as cardiac arrest with resuscitation, hospitalization for heart failure or use of inotropic or vasodilatory therapy.

There was no changes in overall mortality however the combine endpoint were lower in the valsartan group. Hospitalization for heart failure, improved NYHA class and improved ejection fraction was noted in the valsartan group. Improved signs and symptoms of heart failure and improved quality of life was also noted.

Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity
The CHARM study enrolled 7599 patients with NYHA class II-IV to receive either placebo or candesartan. The results showed that there was reduced cardiovascular deaths and hospital admission for heart failure.
Questions?