Myocardial Infarction

Diagnosis, Treatment and Outcomes

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World Health Organization Diagnosis of Myocardial Infarction (MI) Requires ≥ 2 of the Following:

1) Prolonged ischemic-type chest discomfort
2) Serial electrocardiogram (ECG) changes
3) Rise and fall of serum cardiac markers

Ischemic-Type Chest Pain

- Typically prolonged (>30 min) and at rest
- Pattern and accompanying symptoms (including “a sense of doom”)
- 25% of patients admitted to “rule out MI” actually suffer an MI
- Can be mimicked by pericarditis, reflux, spontaneous pneumothorax, musculoskeletal disease (e.g., costochondritis)
- Clinical Pearl = 3 serious causes of severe chest pain – acute MI, aortic dissection, pulmonary embolus

ECG With ST-Segment Elevation

- ST-segment elevation (with compatible history) specificity=91%, sensitivity=46%
- The higher the elevation and the more the leads involved, the larger the infarct and the greater the mortality
- Watch out for other causes of of ST-segment elevation, such as pericarditis, old MI (aneurysm) and normal variant (early repolarization)

ECG Without ST-Segment Elevation

- Half of acute MI patients present without ST-segment elevation
- May see ST-segment depression, T-wave inversion, non-specific ST-T wave changes, or rarely, entirely normal ECG
- Left bundle branch block (LBBB) – largely precludes further analysis
- Interpretation of subtle ECG changes can be difficult

Serum Markers of MI: The Ideal Marker

- Presents early and late in the course of an evolving MI
- Highly specific – not elevated in other diseases
- Sensitive for small amounts of myocardial damage
- Measurements should be easy, accurate and inexpensive

Serum Markers of MI: Creatine Kinase (CK)

- Also known as CPK
- First detectable in 3-4 hours, peaks in 8-24 hours, lasts for 3-4 days
- Not very specific – abnormal in skeletal and smooth muscle injury as well as severe CNS injury
- Peak value commonly used as a index of MI size (e.g. “a 1,400 peak CK infarct”)

Serum Markers of MI: CKMB

- More specific for cardiac muscle than total CK (though not perfect)
- Rises and falls slightly earlier than total CK
- Should be considered the current standard for diagnosing MI

Serum Markers of MI: Troponins T and I

- Very sensitive and specific
- Similar early rise in serum levels as CK-MB (2-4 hours) but stays elevated longer (10-14 days)
- Good for patients presenting late after MI
- May be mildly elevated in unstable angina
- Worse prognosis

Serum Markers of MI: Lactate Dehydrogenase (LDH)

- Very nonspecific (in liver, red cells, etc.)
- High LDH_1 isoenzyme somewhat more specific
- Rises late and stays elevated 4-5 days
- Should be replaced by troponin T

Serum Markers of MI: Myoglobin

- First detectable in 1-4 hours, peaks in 6 hours, lasts for24 hours
- Non-specific – also present in skeletal muscle
- Not (yet) widely used, but may be useful for early detection of MI

Acute Coronary Syndromes

- Typically refers to unstable angina, non-Q wave MI, and Q-wave MI
- Actual diagnosis made only in retrospect
- Upon presentation, can only reliably categorize as ST-segment elevation MI versus all others

Acute Management of MI: General Measures

1) Oxygen by nasal prongs for 2-3 hours; modest hypoxemia common (V/Q mismatch)
2) Bedrest with bedside commode for 12 hours (longer if unstable); avoid constipation and Valsalva maneuver
3) ECG monitoring – 48-72 hours for acute MI, 12-36 hours to rule out MI; temporary pacer
4) Analgesics – commonly underdosed; ↓pain, ↓catecholamines, ↓myocardial O_2 consumed

Analgesic – Morphine Sulfate

- Good dose response, easily reversible; 2-5mg every 5-30 min (sometimes >30mg)
- Peripheral venous and arterial dilation; blocks sympathetic efferent discharge at CNS level; reduces preload and afterload – good with CHF
- Side effects - hypotension and bradycardia occur rarely; respiratory depression with severe COPD – rare in setting of severe chest pain or pulmonary edema

Acute Management of MI: Pharmacotherapy - Aspirin

1) Acute Aspirin – ASA 325mg chewed immediately on presentation
2) ISIS-2 results (Lancet 2:349, 1988) based on 17,187 patients; reduced one month mortality 19% (from 13.2% with placebo to 10.7% with ASA)
3) Additive effect to streptokinase – reduced one-month mortality 23% (from 10.4% to 8.0%)
4) Give immediately to anyone with suspected MI unless STRONG contraindication

Acute Management of MI: Pharmacotherapy – Nitroglycerin (NTG)

- Sublingual NTG given to all patients initially if systolic blood pressure >90
- Avoid long-acting nitrates initially
- Meta-analysis of 10 studies show 10-30% reduction in mortality (Lancet 1:1088, 1988)
- Data from trials show acute MI pain due to continued ischemia rather than completed myocardial necrosis so NTG may be rational choice for ongoing ischemic pain
- Helpful in pulmonary edema

Acute Management of MI: NTG (continued)

- Dosage – 5-10 μg/minute, increase 5-10 μg/minute every 5 to 10 minutes
- Nitrate tolerance after > 24 hours
- Recommend routinely for most MI's for 24 – 48 hours (particularly with CHF), hypertension or recurrent ischemia) and regularly for unstable angina

Acute Management of MI: NTG Side Effects

1) Headache – quite common; decreases with time
2) Hypotension – particular care needed with right ventricle infarction
3) Hypoxemia from V/Q mismatch – need to be alert for this phenomenon
4) Bradycardia with hypotension – under appreciated

Acute Management of MI: Pharmacotherapy - Atropine

- Sinus bradycardia with evidence of ↓ output
- Mobitz type I 2° AV block with evidence of ↓ output
- Asystole
- Rarely helpful for Type II 2° degree AV block
- Helpful for 3° block only at the AV nodal level (e.g. inferior MI, narrow QRS)
- Dose 0.5mg every 5 minutes x 3 if needed; peak effect in 3 minutes
- Too low a dose → paradoxical bradycardia

Acute Management of MI: Pharmacotherapy - Lidocaine

- Treatment of choice sustained ventricular tachycardia (VT) and fibrillation (VF) and shock if necessary
- More benign ventricular arrhythmias (including nonsustained VT) generally not treated
- Prophylactic use no longer advised – meta analysis of 14 randomized trials showed ↓ VF by 33% but slight ↑ mortality possibly due to asystole and electromechanical dissociation

Acute Management of MI: Lidocaine (continued)

- Dose – 1mg/kg (100 mg max) followed by 0.5mg/kg every 10 minutes to 4mg/kg max
- Maintenance 20-50μg/kg/minute IV
- $t_{1/2}$ 1-2 hours in normal individuals, 4-6 hours with MI, >20 hours with bad CHF secondary to ↓ liver metabolism

Acute Management of MI: Lidocaine Side Effects

1) Frequent
2) CNS – dizziness, confusion, drowsiness, nausea, slurred speech, perioral numbness, tremor, respiratory depression, double vision
3) Cardiovascular – bradycardia, hypotension, sinus arrest
4) Consider IV amiodarone and procainamide as alternatives

Acute Management of MI: Pharmacotherapy - Heparin

1) Potential Uses
   - To aid in recannalization or reduce reocclusion of coronary artery
   - To reduce systemic embolism and stroke from left ventricle mural thrombus
   - To reduce deep venous thrombosis and pulmonary embolus

Acute Management of MI: Heparin (continued)

2) Definite indication for IV heparin (for 48 hrs)
   - Unstable angina
   - As adjunctive therapy for thrombolysis with tissue plasminogen activator (tPA)
   - As adjunctive therapy for primary angioplasty
   - Large anterior MI or known mural thrombus (to reduce stroke)
3) Definite indication for subcutaneous heparin (7500 U b.i.d.) in patients not receiving thrombolytics (↓ DVT 12% to 4%)

Acute Management of MI: Heparin (continued)

- Controversial after streptokinase or other nonselective thrombolytic agent
- Ideal target dose – aPTT = 50-75 sec; higher doses lead to intracranial hemorrhage
- Be aware of hypercoagulable state with abrupt termination of heparin
- Give to large majority of patients with acute coronary syndromes

Heparin-Induced Thrombocytopenia

1) 3% incidence
2) Most often occurs after day 4
3) Check platelets daily
4) Associated with prothrombotic events, particularly deep venous thrombosis

Acute Management of MI: Pharmacotherapy – Beta-Blockers

1) Beta-blockers experimentally, significantly ↓ MI size by enzymes, ST segments, etc.
2) Evidence in humans is less clear
   - MILIS study (NEJM, 311:218, 1984) propranolol at mean 8 hours no ↓ MI size
   - MIAMI trial (Eur H J, 6:199, 1985) 5600 patients, MI smaller with metoprolol if treated within 7 hours, 15-day mortality reduced (4.9%-4.3%)
   - TIMI II (NEJM 320:618, 1989) + thrombolytics ↓ ischemia and reinfarction but not mortality

Acute Management of MI: Beta-blockers (continued)

3) ↓ mortality evident by day 1 and sustained
4) Quickly reversed by isoproterenol
5) Surprisingly safe
6) Good candidate patients – early presentation, ↑HR, ↑BP, anterior MI
7) Contraindications – HR<60, BP<100, moderate/severe CHF, AV block, bad COPD
8) Typical dose metoprolol 5mg IV every 5 minutes x 3, atenolol 5-10mg IV

Acute Management of MI: Pharmacotherapy – Ace Inhibitor

1) Definite indication – within 24 hours of moderate or large anterior MI's or MI's associated with CHF or EF < 40%
2) Controversial indication – all MI's within first 24 hours, stopped in 4-6 weeks if no CHF or significant left ventricular dysfunction (EF<40%) evident

All Early ACE Inhibitor Trials Have Shown Mortality Benefit

1) SAVE study – 2231 patients 3-13 days post-MI, half received 50mg captopril TID ↓ 4 year mortality 19% (20% vs 25%), ↓severe CHF 35%, ↓recurrent MI 25% (NEJM 327:669, 1992)
2) GISSI-3 – lisinopril in >19,000 patients ↓ mortality at 6 weeks 12% (Lancet 343:1115, 1994)

All ACE Inhibitor Trials Show Mortality Benefit (continued)

3) ISIS-4 – 58,000 patients showed 7% ↓ 5 week mortality with captopril (7.19% vs 7.69%; Lancet 345:8951, 1995)
4) Meta-analysis – 4.6 fewer deaths per 1000 patients treated
5) Contraindication – SBP<100, significant renal failure
6) Give ACE inhibitors in the first few hours to all MI's or at least large MI's or MI's associated with CHF or ↓ ejection fraction

Acute Management of MI: Pharmacotherapy – Acute Calcium Antagonists

Generally best avoided unless patient experiences continued ischemia unresponsive to nitrates or beta-blocker

Acute Management of MI: Pharmacotherapy – Magnesium

1) Meta-analysis – showed 50% ↓ mortality (BMJ 303:1499, 1991)
2) LIMIT-2 trial – 24% ↓ mortality with 8 mmol $MgSO_4$ for 5 min then 3 mmol/hour (Lancet 339:8809, 1992)
3) ISIS-4 – no difference in mortality with Mg^{++} but given late (Lancet 345:8951, 1995)
4) MAGIC trial - ?
5) Mg^{++} best used in high risk (elderly) and non-thrombolytic candidates

Acute Management of MI: Invasive Intra-Arterial Pressure Monitoring

1) Indications
   - Severe hypotension (<90mmHg) or cardiogenic shock
   - Vasopressor agents (e.g., moderate or high dose dopamine)
   - Potent vasodilators (e.g., niroprusside)
2) Don’t leave in for more than 72 hours (thrombosis, infection)

Acute Management of MI: Balloon flotation right heart catheter monitoring (Swan-Ganz Catheter)

Indications

1) Severe or progressive CHF/pulmonary edema
2) Progressive hypotension or cardiogenic shock
3) Suspected mechanical complication of MI (VSD, papillary muscle rupture, pericardial tamponade)
4) Hypotension without pulmonary congestion unresponsive to fluid challenge (Uncertain fluid status)

Acute Management of MI: Intra-aortic balloon Counterpulsation ("Balloon Pump")

Improves coronary flow and ↓ myocardial O_2 demand. Indications:

1) Unresponsive cardiogenic shock (as a "bridge" to angiography and revascularization)
2) Refractory post-MI angina (as a "bridge" to angiography and revascularization)
3) Acute mitral regurgitation or VSD
4) Almost always used to stabilize the patient until more definitive treatment (such as PTCA or CABG) is performed

Acute Management of MI: Reperfusion by Thrombolysis

1) Rationale:
   - ST-segment MI nearly always due to acute coronary thrombosis
   - All thrombolytic agents work by converting plasminogen to plasmin
2) Clearly saves lives:
   - Meta-analysis – 35 day mortality ↓ by 18% (9.6% vs 11.5%); mortality ↓ 21% if you include only ST-segment elevation
   - 18 lives saved per 10000 treated

Acute Management of MI: Reperfusion by Thrombolysis (continued)

3) GISSI – 11,700 patients using streptokinase ↓ mortality 18% (10.7% vs 13%) with difference persisting at one year (Lancet 2:871, 1987)
4) ISIS-2 – 17,200 patients using streptokinase (± ASA) ↓ one year mortality 23% (9.1% vs 11.8%) with significant improvement noted even when treatment started 12-24 hours after the onset of symptoms

Acute Management of MI: Reperfusion by Thrombolysis (continued)

5) Underused – Use in good candidates 50-70%; in patients >65 years = 20%
6) Indications
   - ST elevation
   - Left bundle branch block (obscuring ST-segment analysis)
   - MI <12 hours since onset

Acute Management of MI: Reperfusion by Thrombolysis (continued)

7) Controversial potential contraindications:
   - Patients >75 years old
   - Late presentations (12-24 hours)
   - Hypertension (>180/100 mmHg)
8) Clear contraindications:
   - CVA/TIA within one year (avoidance of stroke)
   - Hemorrhagic CVA at any time
   - Intracranial neoplasm
   - Active internal bleeding (not include menses)
   - Suspected aortic dissection

Acute Management of MI: Reperfusion by Thrombolysis (continued)

9) Time to delivery is critical:
   - <1 hour – 35 lives saved per 1000; 7-12 hours – 16 lives saved per 1000
   - Community education programs
   - Educate your own patients with coronary artery disease
   - Hospital goal – “door to needle” time of <30 minutes
   - Thrombolytic “code” team

Acute Management of MI: Choice of Thrombolytic Agent

1) tPA:
   - Less allergic reactions
   - Less fibrinogen depletion (“clot selective”)
   - Faster thrombolysis
   - Slightly lower overall mortality
2) Streptokinase (SK):
   - Less expensive ($300 vs $2500)
   - Lower stroke rate (0.3% vs 0.8%)
   - Can’t use again secondary to antibody formation

Acute Management of MI: Choice of Thrombolytic Agent (continued)

3) 90 minute patency better with rt-PA than SK (70% vs 55% in Euro Coop Study and 70% vs 43% in TIMI-1)
4) Patency at 24 hours roughly equal between tPA and SK
5) ISIS-3 – mortality identical in head to head comparison of tPA and SK

Acute Management of MI: Choice of Thrombolytic Agent (continued)

6) GUSTO trial – 41,021 patients (1993)

	mortality	CVA
SK+SQ heparin	7.2%	0.49%
SK+IV heparin	7.4%	0.54%
tPA +IV heparin	6.3%	0.72%
SK+tPA+IV heparin	7.0%	0.94%

Acute Management of MI: Choice of Thrombolytic Agent (continued)

7) GUSTO III trial – 15,059 patients comparing rPA (mutant of tPA) and altepase (tPA) showed identical rates of mortality and CVA
8) IV heparin clearly indicated with tPA; heparin with SK less clear but should probably be given (after completing infusion)

Thrombolytics: Bottom Line

Generally choose tPA for large MI's presenting early or in patients who have previously received streptokinase, otherwise choose streptokinase because of cost

Acute Management of MI: Reperfusion by Primary PTCA

1) Theoretic advantages – higher early vessel patency (90% vs 50-75%) and less strokes
2) Only 10% US hospitals capable of emergent PTCA
3) “Door-to-balloon-inflation” time should be <90 minutes
4) If can’t $\rightarrow$ PTCA, manage conservatively; consider 2B3A inhibitors

Reperfusion by Primary PTCA: Comparative Data

1) Meta-analysis of 7 trials – 6-week mortality and reinfarction reduced
2) PTCA + thrombolytics vs thrombolytics alone much less favorable
3) PAMI trial – 395 patients randomized to tPA vs primary angioplasty (12 hours)
   - 97% success rate of PTCA
   - In-hospital mortality PTCA 2.6% and tPA 6.5% (p=0.06)
   - Stroke PTCA 0% and tPA 2%
   - Results persisted 6 months

Reperfusion by Primary PTCA: Comparative Data (continued)

4) GUSTO IIb Study – 1138 patients showed mortality 5.7% with PTCA and 7% for tPA (p=0.055)
5) MITI Trial – over 3,000 patients in retrospective and community based study showed in-hospital mortality identical for PTCA and thrombolytics

Reperfusion by Primary PTCA: Indications

1) Reperfusion candidates (ST-segment elevation <12 hours, etc.) with contraindications to thrombolysis (such as recent CVA)
2) Reperfusion candidates as an alternative to thrombolysis in an experienced high volume center
3) Suitable candidates in cardiogenic shock

Reperfusion by Primary PTCA - Conclusion

If quickly available in a good quality center, PTCA is a reasonable alternative to thrombolysis, especially in high-risk patients presenting early, or in patients likely to bleed with thrombolytics

Long-Term Management After MI

1) Aspirin
   - 13% ↓ mortality, 31% ↓ nonfatal MI
   - Ticlid unproven alternative
   - Give to nearly everyone lifelong
2) Beta-blocker
   - metoprolol, timolol, propranolol all shown to reduce mortality 1 to 6 years in more than 35,000 patients
   - ↓ mortality 30%
   - Give to nearly everyone indefinitely

Long-Term Management After MI

3) ACE Inhibitor
   - Best if started early (25% ↓ mortality)
   - Probably should be stopped in 4-6 weeks for patients with preserved left ventricular (LV) function and no CHF symptoms
   - Continue indefinitely if LV dysfunction/CHF is present

Long-Term Management After MI

4) Lipid Lowering Agents
   - Prognosis improved even in post-MI with "normal" cholesterol level
   - CARE trial – mean cholesterol 209, LDL 139 at entry showed 24% ↓ mortality/nonfatal MI at 5 years with pravastatin
   - Aggressive approach to lipid control (goal LDL<100) mandatory for all patients with CAD

Long-Term Management After MI

5) Estrogen – in post-menopausal women improves lipid profile and lowers fibrinogen; ↑ risk of MI early with established CAD (HERS trial)
6) Vitamin E and other antioxidants – the HATS trial suggests antioxidants may inhibit HDL

Long-Term Management After MI

7) Warfarin (Coumadin)
   - 13% ↓mortality (most patients not on ASA)
   - CARS trial – ASA 180mg worked as well as ASA 80mg+1-3mg Warfarin
   - Definitely indicated for – post-MI patients with large anterior MI's with/without thrombus or patient's with atrial fibrillation (to prevent systemic embolism from LV thrombus)
   - Use for 3 months for LV thrombus or large anterior MI
   - Use indefinitely for atrial fibrillation

Long-Term Management After MI

8) Homocysteine
   - Significant risk factor for CAD at ↑ serum levels
   - Homocysteine levels can be ↓ with folate and B_6 unless genetic mutations preclude this
   - No randomized data to date on whether vitamin supplementation to reduce homocysteine ↓ risk, but worth considering in CAD patients with ↑ serum levels
9) Lifestyle modification
   - Smoking
   - Diet
   - Exercise

Long-Term Management After MI

10) Exercise testing and stress testing

a) Three goals post-MI:

- assess functional capacity
- evaluate efficacy of patient's current medical regimen
- risk stratification

a) Use submaximal exercise test (at 3-5 days) or maximal exercise test (at>5 days)

b) For post-MI patients lacking spontaneous angina who are potential revascularization candidates, an exercise/stress test can be used to select appropriate candidates for coronary angiography

Long-Term Management After MI

11) Coronary angiography
   - Use post-MI varies widely in different regions and in different countries
   - Post-MI patients who are potential revascularization candidates and who experience spontaneous or inducible ischemia (post-infarct angina or abnormal stress test) should undergo cardiac catheterization with coronary angiography
   - Other patients at high risk (such as CHF, EF<45%, etc.) could be considered as well