

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 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 LDH₁ 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 for 24 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 O₂ 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 $\mu\text{g}/\text{minute}$, increase 5-10 $\mu\text{g}/\text{minute}$ 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 20-50 μ g/kg/minute IV
- $t_{1/2}$ 1-2 hours in normal individuals, 4-6 hours with MI, >20 hours with bad CHF secondary to \downarrow 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 MgSO₄ 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., nitroprusside)

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 O₂ 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 (\pm 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)

| | <u>mortality</u> | <u>CVA</u> |
|-------------------|------------------|------------|
| 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 → 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 \uparrow serum levels
- Homocysteine levels can be \downarrow with folate and B₆ unless genetic mutations preclude this
- No randomized data to date on whether vitamin supplementation to reduce homocysteine \downarrow risk, but worth considering in CAD patients with \uparrow 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