Acute Myocardial Infarction

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Background:
- Incidence: 1.1 Million AMI’s per year
- Mortality:
  - approx. 25% die before hospitalization
  - of those hospitalized...
    - 1 year mortality is variable. Males 25% and 38% for Females*
    - Heart and Stroke Facts 2002 Stats Supplement AHA

Pathophysiology:
- AMI occurs due to profound imbalance of supply and demand of cardiac muscle
- coronary artery lumen narrowing due to atherosclerosis + vascular damage + artery spasm, clot formation --> distal insufficiency --> cell injury --> cell death
- AMI is at the end of a spectrum of acute coronary syndromes (ACS)

Clinical Presentation:
- Pain:
  - deep visceral pain, “heavy”, “squeezing”, “crushing” substernal with occasional radiation to arms, jaw, neck etc. (cf. angina)
- Signs and Symptoms:
  - Dyspnea, NV, diarrhea, palor, cold extremities, diaphoresis, apprehension, impending doom
- Vitals: HR, BP, RR, Temp
- CV Exam: (S4, S3)

Diagnosis:
1. History and clinical presentation:
2. ECG (evolving Q wave, ST elevation 1-2mm)
3. Cardiac Markers
   - Cardiac Troponin I (cTnI) or T increases above 1 mcg/L, usually increases about 3 hrs after onset of chest pain is suggestive of a poor prognosis post ischemic episode
   - CK-MB > 5 ng or units total or 5% of total CK (electrophoresis)
   - LDH : LDH1 > LDH2 = AMI
   - AST (less useful)
   *URL = upper reference limit

Major CHD Risk Factors Other Than LDL-C According to ATP-III

Positive risk factors:
- Age
- Male 45
- Woman 55
- Family history of premature CHD
- Cigarette smoking
- Hypertension: BP 140/90 mm Hg or on antihypertensive medication
- Low HDL-C: <40 mg/dL

Negative risk factor:
- High HDL-C: >60 mg/dL

*Negative one other risk factor
Acute Myocardial Infarction

**Drug Therapy**

**Analgesia:**
- Morphine 1-4 mg IV q4h
  - decreases venous tone
  - reduces arteriolar resistance
  - reduces anxiety due to pain
  - vagotonic effect (+/-)
- Meperidine 25-75 mg IV q4h
  - slight vagolytic effect

**Nitroglycerin:**
- Nitroglycerin 5-10 mcg min up to 200 mcg min incr. by 5-10 mcg min per BP and pain tolerance
- ISIS-4 (Lancet 1995;345:669) concluded there was no survival benefit associated with one month of oral mononitrate use (30-60mg QD). 5-week mortality = placebo arm, and subsequent analysis did not indicate any later survival advantage
- GISSI-3 (Lancet 1994;343:1115) indicated no mortality benefit following AMI with IV followed by chronic oral nitrates

**Oxygen:**
- 3-4 L/min for 24-48 hours
- to increase PaO2
- Indication:
  - shortness of breath of any etiology
- Precaution:
  - COPD patients

**Laxatives:**
- may be required to minimize constipating effects of narcotic analgesics, bedrest
- to avoid excessive vagal stimulation (Valsalva maneuver) while stooling
Acute Myocardial Infarction
Drug Therapy

**Anxiolytics:**
- Diazepam 2.5 to 5 mg bid or tid
- To minimize anxiety
- Will work with narcotic analgesics to sedate

**Anticoagulation:** (ACCP Chest 2002;119)
- All AMI pts should be given anticoagulant Tx (in absence of contraindication) for 48 hours (minimally 7,500 IU SC q12h of UH or LMWH until ambulation) (IA)
- Heparin or rPA or TNKase Heparin 60 U/kg IV bolus at time of initiating Heparin infusion TNKase (or 1st rPA bolus), initial maintenance 12U/kg/h (max 1,000 U/h) IV for up to 48 hours.
- OK or APSAC: IV heparin only if high risk (anterior MI, CHF previous embolus/afib) either if...
  - Initial maintenance 1,000 U/h “if IV at all” or 17,500 U SC q12h (2A)
  - SC LMWH (2A)
  - Convert to warfarin (INR 2-3) for <3 mo.
  - To keep APTT 1.5 to 2 times control
  - TNKase: intracoronary (TIMI-46), rPA = reteplase, CHF = congestive heart failure, Acute MI, STEMI

**Anticoagulation:** (ACCP Chest 2002;119)
- All patients who receive thrombolytics (rtPA or rPA or TNK-PA) and are at high risk for systemic embolism or VTE*
  - Maintain PTT 1.5-2 x control beyond 48 h, continue the IV heparin or offer either of...
    - SC UH 17,500 IU q12h (2A)
    - SC LMWH (2A)
    - Conversion to warfarin (INR 2-3) for <3 months (2A) indefinitely in pts. With AF (1A)

*Anterior Q-wave infarction, severe LV dysfunction, CHF, H/O systemic embolism or PE, 2D-echo evidence of mural thrombosis, AF

**Antiplatelet Agents:** (ACCPChest 2002;120)
- ASA (nonenteric coated) (75-162.5mg/d) used immediately O/A has decreased mortality (p<0.05) in AMI patients.
- Chew one non-enteric coated IR tablet O/A then one qd (indefinitely) Grade IA
- OK to give with Heparin (avoid if with warfarin?)
- Contraindications to ASA? - Aspirin (75mg/d) I.d.
- Warfarin (INR 3.3) is an alternative but more complex risk and cost (2A)
- Warfarin (INR 1.5-2.5) ASA (low dose 75-100mg) is recommended in pts. With recurrent ischemic episodes post AMI (2C)
- GPIIb/IIIa inhibitors: moderate to high risk patients (non STEMI) or refractory ischemia in absence of contraindications due to bleeding risk (more on this later)

**Arrhythmia Prophylaxis:**
- V-Fib most common cause of death post MI
- Benefits of prophylaxis in suspected MI has not been uniformly substantiated by literature
- Lidocaine administration not recommended.
- Prophylactic administration of class I agents clearly not warranted (CAST trial)
- A traditional post AMI, showed no benefit (EMIAT and CAMIAT) overall on cardiac mortality
- Drugs vs. ICDs: ICDs may be superior to conventional therapy for select patients (EF<35% and inducible V-tach) (MADIT).

**Beta-blockers:**
- Among the most extensively studied classes of agents for 2nd prevention post AMI
- Compounds most intensively investigated:
  - Propranolol (Roberts 1984, BHAT 1981)
  - Metoprolol (Halmarson 1981, Herlitz 1984)
  - Timolol (Peterson 1985)
  - Oxprenolol (Taylor 1982)
- Consistent demonstration of:
  1) Improved survival
  2) Reduced incidence of SCD (V. fibrillation) and reinfarction
### Acute Myocardial Infarction

**Drug Therapy**

#### ACE Inhibitors:
- Play a role in cardiac remodeling
- Proven mortality benefit in SAVE, ISIS-4 (captopril), GISSI-3 (lisinopril), SMILE (zofenopril) and AIRE (ramipril) vs. CONSENSUS II (aceonanaprilat IV then enalapril) with a negative outcome
- SAVE reduction in all cause mortality (EF < 0.4, 3-16 days out with no sx or symp of CHF)
- AIRE (oral, no EF cut off, between 2-16 days)
- ISIS-4 (oral, no EF cut off, within 24 hrs)

#### IV Magnesium
- Not recommended for routine use at this time (9/96)
- LIMIT II (Lancet 1992;339:1533)
- Reduction in mortality (7.8% Mg vs. 10.3% PL, P < 0.05)
- 2 grams MgSO4 (8 mmoleMg) over 15 to 30 min then 16 grams (65 mmoles) over 24 hours
- Risk of bradycardia (and possibly hypotension)
- ISIS 4 (Lancet 1995;345:669) no improvement in mortality post AMI

#### Conclusions for Beta-Blockers:
- A clear benefit has been repeatedly demonstrated for both "acute" (starting immediately) and "chronic" (starting days to weeks and continuing up to 2 years) use of beta-blockers
- Optimizing their use for some period of time post AMI may lead to reduced health care costs
- Beta-blockers for post AMI may be underutilized.

#### Beta-Blocker Use Post-MI in the US
- 45,308 had no contraindication to beta-blockers
- Only 50% (22,665) were given beta-blockers
- Use of beta-blockers was associated with:
  - One-year mortality was reduced from 12.6% to 7.7% (unadjusted)
  - A 4% decrease in 1-year mortality (adjusted) for baseline differences in demographic, clinical variables, and discharge medications
- Significant variation by state (30-77%) was observed


#### Beta-Blocks Post-MI: 2-year Mortality
- Nation-wide Medicare data from hospitals were merged with Social Security death records for 201,752 patients with MI during 8 months from 1994 to 1995
- Only 34% of the MI survivors received beta-blockers
- Use of beta-blockers was associated with a 40% reduction in 2-year mortality for "uncomplicated MIs".
- Essentially every subgroup showed a significant (typically 40%) reduction in mortality if they were given beta-blockers: non-Q-wave, CHF, blacks, hypertension, COPD, diabetes, asthma, and even low EF patients


### Acute Myocardial Infarction

**Drug Therapy**

#### Recommended Regimens of Beta-Blockers Post AMI:
- Metoprolol 5mg IV every 2-5 min times three, then 15 min after last IV dose give 50 mg bid for 2 days then 100 mg bid thereafter if tolerated
- Atenolol 5 mg IV over 5 min, wait 10 min then 5 mg then 10 mg after that, start 50 mg po bid for two doses and if tolerated 100 mg po qd
- Timolol 30 mg po bid
- Propranolol 180 to 240 mg / day po (given as IR 6d or qid)
Overview of CCBAs post AMI

None of the trials to date demonstrate an overall benefit for the CCB over placebo in terms of mortality.

Many trials of CCB’s post AMI have identified subgroups of pts at risk (e.g., pts with low EF) for non-significant excess or deaths (nifedipine-III, diltiazem IIb) and side effects.

Verapamil or diltiazem have been useful in select patients for control of VRR or for which ongoing ischemia exists with or without b-blockers (Class IIa).

*MDPRG NEJM 1988

Diltiazem in non-Q wave MIs may reduce early recurrent infarction (one tailed, p = 0.03, two tailed, p = 0.06) however demonstrates a non-significant excess of deaths and substantial excess of side effects (heart block).

Verapamil has produced mixed results, with one recent study showing favorable long-term effects only for pts without heart failure.

*AJC 1990; 66, 779, DA VI T II

Conclusions and Summary of CCBAs post AMI:

Given the proven benefit of beta-blockers to reduce mortality of post AMI patients, all patients devoid of significant contraindications should receive acute and chronic beta-blockers for at least 2 years.

A beneficial role for CCB’s in secondary prevention (post AMI) has not been demonstrated and their use for this endpoint cannot be supported (especially in pts with systolic dysfunction).

Management of Lipids

Aggressive therapy to manage all risk factors is encouraged.

Specific targets (see NCEP ATP III) to achieve goal LDL and secondary TG and HDL targets (new NCEP guidelines have eclipsed the AHA/ACC AMI guidelines).

THROMBOLYTICS

No Blood Flow

Bad

J Alexander 9-96 Seattle
**Blood Flow**

**Good**

J Alexander 9-96 Seattle

**Prompt Blood Flow**

**Very Good**

J Alexander 9-96 Seattle

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**Recommendations for Fibrinolytic Therapy**

(ACCP 6th Consensus 2001)

**Do NOT give IV fibrinolytic therapy (grade 1B)**

- Prior intracranial hemorrhage, stroke within the past year, or active bleeding

**Offer IV fibrinolytic therapy (grade 2B)**

- Symptoms characteristic of AMI for 12 to 24 h; ST-segment elevation or left bundle branch block on the ECG

**IV fibrinolytic therapy (unless contraindications exist) (grade 1A)**

- Ischemic symptoms characteristic of AMI for < 12 h; ST-segment elevation or left bundle branch block on the ECG

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**Choice of Fibrinolytic Agent**

**Adjunctive Therapy with Heparin**

(ACCP 6th Consensus 2001)

- **Reteplase** is equivalent to streptokinase (grade 1A)

- **Tenecteplase** is equivalent to alteplase (grade 1A)

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**Adjunctive Therapy with Heparin**

(ACCP 6th Consensus 2001)

- **ST-segment elevation or left bundle branch block on the ECG**

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**Implications**

Methodologic Strength of Supporting Evidence

- Clear
- Strong recommendation; apply to most patients without reservation
- Strong recommendation; likely to apply to most patients
- Randomized controlled trials (RCTs) without important limitations
- Intermediate-strength recommendation; best action may differ, depending on circumstances
- Observational studies
- Unclear
- No RCTs, but RCT results can be extrapolated; or overwhelming evidence from observational studies
- Weak recommendation; alternative approaches likely better
- Intermediate-strength recommendation; other alternatives may be equally reasonable
- Very weak recommendation; other alternatives may be equally reasonable

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**Quality of Evidence**

Methodologic Strength of Supporting Evidence

- Quality
- Clarity of risk/benefit
- Grade

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**Choice of Fibrinolytic Agent**

**Adjunctive Therapy with Heparin**

(ACCP 6th Consensus 2001)

**FACTOR**

**RECOMMENDATION**

- ** Duration of symptoms ≤ 12 hrs**
  - Streptokinase, anistreplase, or alteplase (grade 1A, compared with placebo)

- ** Duration of symptoms > 6 hrs**
  - Alteplase is recommended over streptokinase (grade 1A)

- ** Known allergy or sensitivity to streptokinase**
  - Alteplase, tenecteplase, or reteplase (grade 1A+)

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**Reteplase** is equivalent to streptokinase.

**Tenecteplase** is equivalent to alteplase.
Acute Myocardial Infarction
Drug Therapy

Thrombolytics:
- "strongly recommended that every patient with evolving acute MI should be considered for some form of acute revascularization"
- IV thrombolytic therapy reduces mortality

Issues:
- (A) Certainty of Diagnosis
- (B) Time Post-MI Onset
- (C) Patient Subgroups:
- (D) Contraindications:

Thrombolytic Issues:
- (A) Certainty of Diagnosis
  - at least 0.5 hrs of ischemic cardiac pain
  - ECG changes (at least 1mm ST segment elevation in 2 adjacent limb leads or 1.2mm in at least 2 adjacent precordial leads or complete BBB (if no ST segment elevation, lytics should not be given)

Time Post-MI Onset:
- give if patients present within 6 hrs of onset of CP
- Many patients should be given lytics if presenting within 12 hrs as well (recognizing absolute benefit decreases with increasing time from onset) this is especially true if CP and ST segment elevation persists
- Patients presenting from 13-24 hours after symptom onset should not receive lytics routinely
- Start lytic ASAP (target within 1 hr of presentation)

Patient Subgroups:
- absolute benefit/risk should be considered: in general, lytics are appropriate for inferior and anterior, first and subsequent MI and regardless of pt. age (< or >75 yrs).
- The likelihood of death is lower with inferior, first and in younger patients, in spite of the relative benefit being proved in these cases. The absolute benefit (lives saved per 1000 treated) is therefore less in groups with a lower likelihood of death. Since the risk of side effects may be equally high in these subgroups, the risk to benefit ratio is most favorable in subgroups with a high likelihood of death.

Contraindications:
- Absolute:
  - Aortic dissection
  - Acute pericarditis
  - Active bleeding
  - Previous cerebral hemorrhage, cerebral neoplasm or intracranial vascular disease
- Relative:
  - (a) Potential hemorrhagic focus
    - GI, GU, stroke (within 6 months)
    - major surgery organ biopsy, prolonged chest compressions, major trauma or minor head trauma (within 24 weeks)
    - diabetic proliferative retinopathy
    - severe uncontrolled hypertension (SBP >200 and/or DBP >120)
    - (b)H/O of bleeding diathesis, hepatic dysfn, CA
    - (c) pregnancy
Thrombolytics (GUSTO NEJM 1990;329:673)

- **Purpose**: Evaluate relative efficacy of SK and t-PA and roles of IV vs. sq Heparin for AMI
- **Methods**: 41021 patients with AMI were randomized to one of four groups
- **Endpoint**: Primarily 30 day mortality

**Dosing:**
- **SK and sq Heparin**: 1.5 Million Units over 1 hour with sq heparin
  - 12,500 U bid beginning 4 hours after lytic therapy
- **SK and IV Heparin**: 1.5 Million Units over 1 hour with IV heparin
  - 5000 U bolus, then 1000 U/hr (1200 U/hr if >80 Kg) to APTT between 60-85 seconds
- **t-PA and IV Heparin**: 15 mg bolus dose, 0.75 mg/kg over 30 min (not > 50 mg) then 0.5 mg/kg over 60 min (not > 35 mg) with IV heparin 5000 U bolus, then 1000 U/hr (1200 U/hr if > 80 Kg) to APTT between 60-85 seconds
- **t-PA + SK and IV Heparin**: 1mg/kg over 60 min (not > 90 mg) with 10% given as a bolus dose and SK 1.0 Million U over 60 min, plus IV heparin as above

**Results**

<table>
<thead>
<tr>
<th>Tx</th>
<th>SK+SQH</th>
<th>SK+IVH</th>
<th>tPA</th>
<th>tPA +SK</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9796</td>
<td>10377</td>
<td>10344</td>
<td>10328</td>
</tr>
<tr>
<td>Mortality*</td>
<td>7.2</td>
<td>7.4</td>
<td>6.3</td>
<td>7.0</td>
</tr>
</tbody>
</table>

*30 Day Mortality %

**Strokes**: approx. excess of 2 hemorrhagic strokes per 1000 patients for t-PA vs. both SK regimens (p = 0.03)

*SK may be an appropriate thrombolytic agent for patients over age 75, with small inferior infarctions, and those presenting more than 6 hours after onset of symptoms*

*TPA may be preferred over SK for those under 75 yo, presenting with anterior or large infarcts within 6 hours of onset of symptoms and for those who have had previous exposure to SK or APSAC*

**Issues**

- Small net benefit, or none, for t-PA over SK among patients
  - over 75 yo (in whom hemorrhagic stroke with t-PA was increased)
  - inferior myocardial infarctions vs other
  - presenting more than 6 hours after onset of symptoms
  - However: this study lacked statistical power to exclude a therapeutic benefit in these subgroup
t-PA Dosing

**tPA Front-End Loaded**

**90 Minute Dosing**

- 15 mg bolus over 2 minutes
- 0.75 mg/kg over 30 minutes (not > 50 mg)
- 0.50 mg/kg over 60 minutes (not > 35 mg)
- Total dose 100 mg or less

Streptokinase Dosing

**Streptokinase**

1.5 million units over 1 hour

APSAC* Dosing

30 Units over 5 minutes

*Anisoylated plasminogen streptokinase activated complex

Comparative FDA-Approved Intravenous Dosage of Thrombolytics Used in the Therapy of AMI

<table>
<thead>
<tr>
<th>Thrombolytic</th>
<th>Recommended Dosage</th>
<th>Accelerated Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reteplase</td>
<td>rtPA is a non-glycosylated deletion mutation of tPA, indicated for AMI therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dose: 10U+10U double bolus injection, each bolus given IV over 2 min. The second bolus given 30&quot; after the first.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cost: same/similar as per tPA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Efficacy/Toxicity: generally similar (mortality, bleeding, ICH) when compared to tPA although with less experience. (GUSTO III, NEJM 1997;337:1118)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adjusted dose heparin is used with rPA</td>
<td></td>
</tr>
</tbody>
</table>

Reteplase vs. Alteplase for AMI (GUSTO III, NEJM 1997;337:1118-23)

- Purpose: to compare rtPA to tPA
- Methods: 15,059 patients presenting within 6hrs randomized to receive r-PA (double bolus) vs tPA (accelerated infusion) and compared for 30 day mortality
- Results at 30 days: Mortality rate 7.47 (rtPA) vs 7.24 (tPA), Stroke 1.64 (r-PA) vs 1.79 (tPA), combined endpoint (death, non-fatal MI, disabling stroke) 7.89 (rtPA) vs 7.91 (tPA) all NS

30-Day Outcomes ASSENT-2 Study

<table>
<thead>
<tr>
<th>30-Day Events</th>
<th>Tenecteplase (n=8461)</th>
<th>Alteplase (n=8488)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>6.2%</td>
<td>6.2%</td>
<td>1.00 (0.89, 1.12)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>0.9%</td>
<td>0.9%</td>
<td>0.99 (0.73, 1.35)</td>
</tr>
<tr>
<td>Any stroke</td>
<td>1.8%</td>
<td>1.7%</td>
<td>1.07 (0.86, 1.35)</td>
</tr>
<tr>
<td>Death or nonfatal stroke</td>
<td>7.1%</td>
<td>7.0%</td>
<td>1.01 (0.91, 1.13)</td>
</tr>
</tbody>
</table>
**Recommended Tenecteplase Doses**

<table>
<thead>
<tr>
<th>Patient Weight (kg)</th>
<th>Tenecteplase (mg)</th>
<th>Volume of Tenecteplase to be Administered (mL)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60</td>
<td>30</td>
<td>6</td>
</tr>
<tr>
<td>60 to &lt; 70</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>70 to &lt; 80</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>80 to &lt; 90</td>
<td>45</td>
<td>9</td>
</tr>
<tr>
<td>90</td>
<td>50</td>
<td>10</td>
</tr>
</tbody>
</table>

*From one vial of tenecteplase reconstituted with 10 mL Sterile Water for Injection, USP

**Heparin Nomogram for Patients with Coronary Artery Disease**

<table>
<thead>
<tr>
<th>PTT</th>
<th>Bolus</th>
<th>Hold/ Min.</th>
<th>Rate(u/hr)</th>
<th>Repeat PTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>5000U</td>
<td>0</td>
<td>150/hr</td>
<td>6 hrs.</td>
</tr>
<tr>
<td>50-59</td>
<td>0</td>
<td>0</td>
<td>50/hr</td>
<td>6 hrs.</td>
</tr>
<tr>
<td>60-85</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>ned AM</td>
</tr>
<tr>
<td>86-95</td>
<td>0</td>
<td>0</td>
<td>50/hr</td>
<td>ned AM</td>
</tr>
<tr>
<td>96-120</td>
<td>0</td>
<td>30 min</td>
<td>100/hr</td>
<td>6 hrs.</td>
</tr>
<tr>
<td>&gt; 120</td>
<td>0</td>
<td>60 min</td>
<td>150/hr</td>
<td>6 hrs.</td>
</tr>
</tbody>
</table>

**Risk Assessment For Lytic Therapy**

- Pregnancy
- Septic thrombophlebitis
- Advanced age, (>75 yo??)
- Concurrent oral anticoagulant therapy
- Any condition in which bleeding would constitute a sign, risk or management problem
- SK or APSA/C administration within 5 days to 2 years of developing high titers to antibodies

**TIMI Classification of Bleeding**

- Major bleeding
  - ICH
  - Decrease in Hb ≥ 5g/ dL or HCT ≥ 15% points
- Minor bleeding
  - GI or GU bleeding
  - Observed bleeding with dec in Hb ≥ 3g/ dL or HCT ≥ 10%
  - No bleeding with Hb decr. ≥ 4 g/ dL or HCT ≥ 12%

**GUSTO Classification**

- Mild
  - No transfusion or hemodynamic compromise
- Moderate
  - Transfusion required
  - Severe Life Threatening
  - ICH
  - Hemodynamic compromise