Ten Major Q & A's about ACS Controversies

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Introduction

- AMI incidence
  >3 million cases/year worldwide
- NSTTEMI incidence
  >4 million cases/year worldwide (+)
- Improvements in morbidity and mortality need a comprehensive approach (Fig 1)

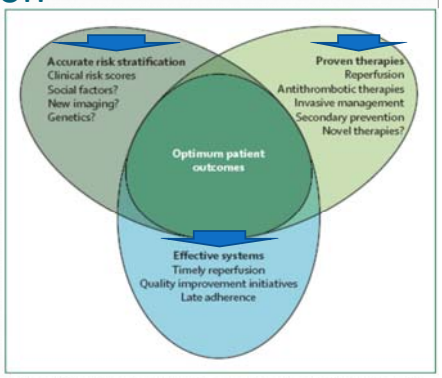


Figure 1: Framework for optimising patient outcomes in acute myocardial infarction

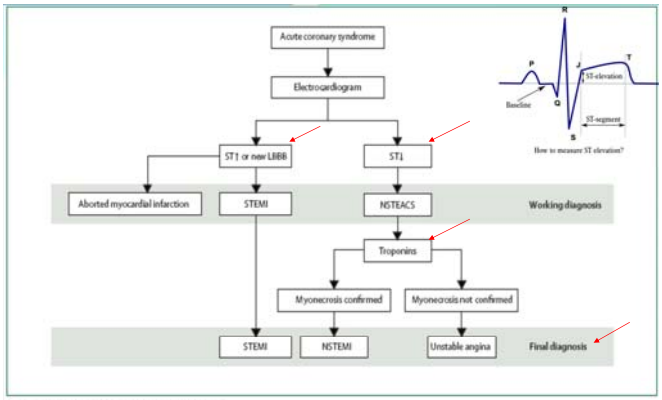


Figure 2: Classification of acute coronary syndromes
STEMI=ST-elevation myocardial infarction. NSTEACS=non-ST-elevation acute coronary syndromes. NSTEMI=non-ST-elevation myocardial infarction. LBBB=left bundle branch block.

Diagnosis of Myocardial Infarction

- Symptom and Sign
  - Typical Chest Pain
  - Atypical Chest Pain: DM, Elderly, Women
    - Angina Equivalent
- ECG findings
  - Evolutional Changes (Dynamic ST Changes)
  - New-onset LBBB pattern
- Cardiac Enzymes

Question 1

- What are the possible causes of elevated troponins besides AMI?

Panel 2: Causes of elevated troponin values in clinical settings other than acute myocardial infarction

Cardiac
- Tachyarrhythmia, bradyarrhythmia, heart block
- Hypertension, hypotension
- Congestive heart failure
- Aortic dissection
- Aortic stenosis or regurgitation
- Hypertrophic cardiomyopathy
- Rhabdomyolysis with cardiac myocyte necrosis
- Apical ballooning syndrome (Takotsubo cardiomyopathy)
- Transplant vasculopathy
- Myopericarditis
- Rheumatic fever
- Rheumatoid arthritis
- Systemic vasculitis
- Post-viral

Infiltrative diseases of the myocardium
- Amyloidosis
- Sarcoidosis
- Haemochromatosis
- Scleroderma

Traumatic
- Atrioventricular ablation
- Defibrillation
- Chest wall trauma
- Cardiac surgery

Miscellaneous
- Renal failure
- Transient ischaemic attack, stroke, or subarachnoid haemorrhage
- Drug toxicity (eg, adriamycin, 5-fluorouracil, daunorubicin, herceptin, etc)
- Hypothyroidism
- Pulmonary embolism
- Severe asthma
- Pulmonary hypertension
- Sepsis (including sepsis occurring with shock)
- Critically ill patients
- Phaeochromocytoma
- Severe burns
- Kawasaki disease
- Extreme exertion
- Snake venom

Question 2

- What are the possible causes of ST elevations besides AMI?

Diagnosis of Myocardial Infarction

- Symptom and Sign
  - Typical Chest Pain
  - Atypical Chest Pain: DM, Elderly, Women
    - Angina Equivalent
- ECG findings
  - Evolutional Changes (Dynamic ST Changes)
  - BBB pattern
    - LBBB/RBBB, Pacemaker Rhythm, WPW, LV Aneurysm
- Cardiac Enzymes

The most important cause of ST segment elevation is AMI

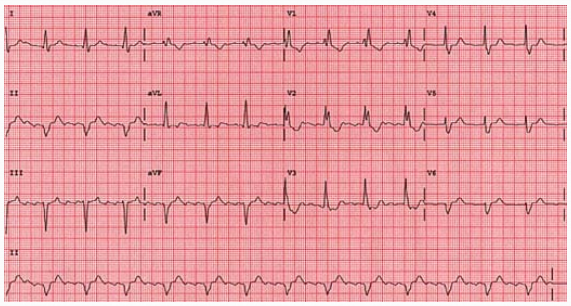
other causes are

- Early repolarization in normal variant
- Acute pericarditis: ST elevation in all leads except aVR
- Pulmonary embolism: ST elevation in V1 and aVR
- Hypothermia: ST elevation in V3-V6, II, III and aVF
- Hypertrophic cardiomyopathy: V3-V5 (sometimes V6)
- Hyperkalemia : V1-V2 (V3)
- During acute neurologic event: all leads, primarily V1-V6
- Acute sympathetic stress: all leads, especially V1-V6
- Brugada syndrome
- Cardiac aneurysm
- Cardiac contusion
- Left ventricular hypertrophy
- Idio-ventricular rhythm including paced rhythm

Question 3

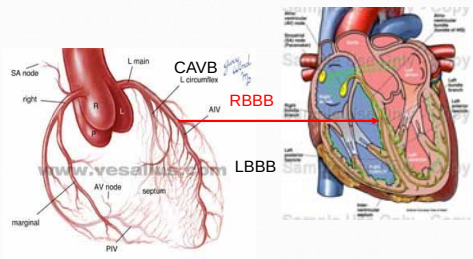
- What is the clinical significance of new-onset RBBB as the ECG manifestation of STEMI?

Pitfall~ RBBB Is NOT RV Problem!

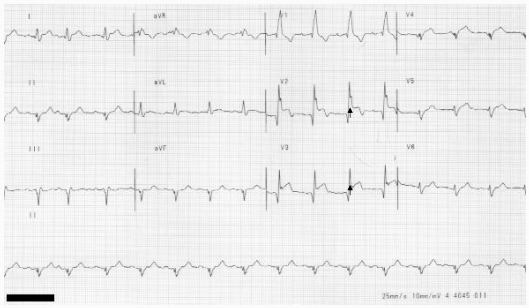


Pitfall~ RBBB Is NOT RV Problem!

- RBBB in AMI
  - Always means LAD proximal lesions instead of RCA



Pitfall~
RBBB Is NOT RV Problem!



Which is with better prognosis? Ant. MI with CAVB? Or Inf. MI with CAVB?

Question 4

- What are the definitions and clinical scopes of unstable angina?

Unstable Angina

- Common manifestations
  - New-onset angina pectoris
  - Crescendo angina pectoris
  - Rest angina pectoris
  - Post-infarct angina pectoris

What's More?

Unstable Angina

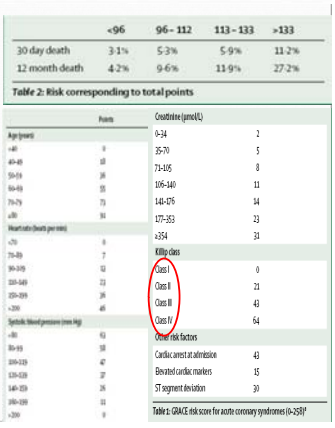
Severity		Clinical Circumstances		
		A	B	C
		Develops in presence of extracardiac condition that intensifies myocardial ischemia (secondary UA)	Develops in the absence of extracardiac condition (primary UA)	Develops within 2 weeks after acute myocardial infarction (postinfarction UA)
I	New onset of severe angina or accelerated angina; no rest pain	IA	IB	IC
II	Angina at rest within past month but not within preceding 48 hr (angina at rest, subacute)	IIA	IIB	IIC
III	Angina at rest within 48 hr (angina at rest, acute)	IIIA	IIIB Troponin negative IIIB Troponin positive	IIIC

Question 5

- What is the clinical significance of risk scores such as GRACE and TIMI?

Risk stratification of AMI:
Grace score

- Time-critical resources—such as systems of transport, invasive management, and the coordinated use of pharmacotherapies—requires accurate risk assessment to optimise patient outcomes and mitigate adverse events and costs.
- The best risk score for prediction of death and MI seems to be the Global Registry for Acute Coronary Events (GRACE) score that incorporates renal dysfunction



	<96	96–112	113–133	>133
30 day death	3·1%	5·3%	5·9%	11·2%
12 month death	4·2%	9·6%	11·9%	27·2%

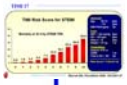
Table 2: Risk corresponding to total points

Points		Creatinine (μmol/L)	
Age (years)		0–34	2
<40	0	35–70	5
40–49	18	71–105	8
50–59	36	106–140	11
60–69	55	141–176	14
70–79	73	177–353	23
≥80	91	≥354	31
Heart rate (beats per min)		Killip class	
<70	0	Class I	0
70–89	7	Class II	21
90–109	13	Class III	43
110–149	23	Class IV	64
150–199	36	Other risk factors	
≥200	46	Cardiac arrest at admission	43
Systolic blood pressure (mm Hg)		Elevated cardiac markers	15
<80	63	ST segment deviation	30
80–99	58		
100–119	47		
120–139	37		
140–159	26		
160–199	11		
≥200	0		

Table 1: GRACE risk score for acute coronary syndromes (0–263)[1]

TIMI RISK SCORE for STEMI

HISTORICAL	POINTS
Age ≥ 75	3
65-74	2
DM or HTN or angina	1
EXAM	
SBP < 100 mmHg	3
HR >100 bpm	2
Killip II-IV	2
Weight < 67 kg (150 lb)	1
PRESENTATION	
Anterior STE or LBBB	1
Time to Rx > 4 hrs	1
RISK SCORE = Total points (0 -14)	



RISK SCORE	30-DAY MORTALITY IN InTIME II(%)*
0	0.8
1	1.6
2	2.2
3	4.4
4	7.3
5	12
6	16
7	23
8	27
>8	36

*Entry criteria: CP > 30 min, ST ↑, sx onset < 6hrs, fibrinolytic-eligible

For more info go to www.timi.org

Morrow et al. *Circulation* 2000; 102:2031-7

TIMI RISK SCORE for UA/NSTEMI

HISTORICAL	POINTS
Age ≥ 65	1
≥ 3 CAD risk factors (FHx, HTN, ↑ chol, DM, active smoker)	1
Known CAD (stenosis ≥ 50%)	1
ASA use in past 7 days	1
Double anti-platelet use in past 7 days?	
Recent (≤24H) severe angina	1
↑ cardiac markers	1
ST deviation ≥ 0.5 mm	1
RISK SCORE = Total Points (0 - 7)	

RISK SCORE	DEATH OR MI	DEATH, MI OR URGENT REVASC
0/1	3	5
2	3	8
3	5	13
4	7	20
5	12	26
6/7	19	41

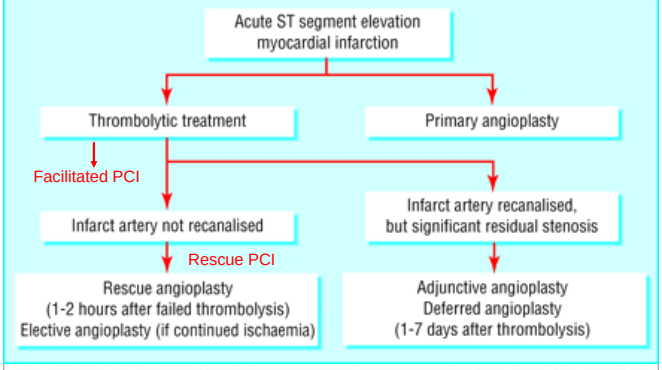
RISK OF CARDIAC EVENTS (%) BY 14 DAYS IN TIMI 11B*

*Entry criteria:UA or NSTEMII defined as ischemic pain at rest within past 24H, with evidence of CAD (ST segment deviation or +marker)

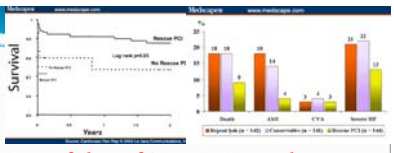
Antman et al *JAMA 2000*; 284: 835 - 842

Question 6

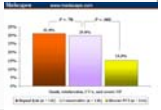
- What are the definitions and clinical roles of facilitated PCI and rescue PCI for STEMI?



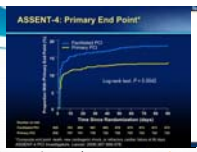
Rescue PCI



- Defined as ongoing chest-pain, failure of ST-segment resolution by more than 50% at 90 min after fibrinolysis, or both.
- Meta-analysis of 1117 patients, rescue PCI → lower rates of death, heart failure, and reinfarction by 6 months (29·2% vs 41·0%, p<0·001) than conservative strategy
- A non-significant reduction in mortality (odds ratio [OR] 0·69,p=0·09) & associated with a 3% (p=0·02) absolute increase in the risk of stroke.
- Rescue PCI is also better than repeated fibrinolysis



Facilitated PCI



- Routine emergent PCI after fibrinolysis (ie, very early PCI < 6 hours without ongoing evidence of failed reperfusion) has not been associated with benefit.
- Whether a facilitated PCI strategy has a role in clinical settings where primary PCI is associated with substantial delays (6–12 h) needs more study.
- Routine PCI within post-tPA12-24 hrs is better than ischemia-guided PCI <24hrs
- TIMI flow improved in facilitated PCI but not translated into primary endpoint – FINESSE trial

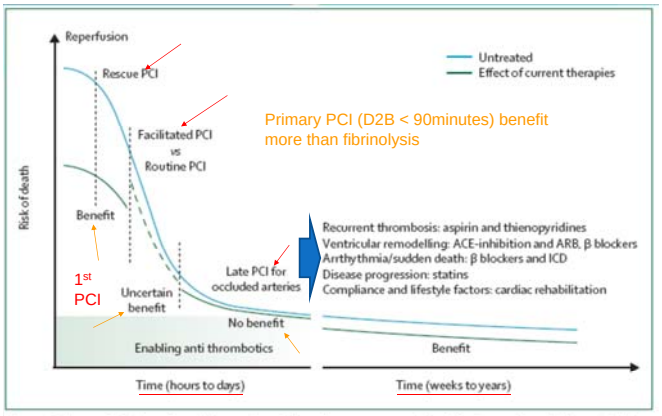


***Figure 3*: Schematic integration of therapies and invasive management to effect an early and late mortality reduction in patients with myocardial infarction**
ICD=implantable cardioverter-defibrillator. ARB=angiotensin receptor blockers. ACE=angiotensin converting enzyme. PCI=percutaneous coronary intervention.

Indications for Transfer for Angiography After Fibrinc

	COR	LOE
Immediate transfer for cardiogenic shock or severe acute HF irrespective of time delay from MI onset	I	B
Urgent transfer for failed reperfusion or reocclusion	IIa	B
As part of an invasive strategy in stable* patients with PCI between 3 and 24 h after successful fibrinolysis	IIa	B

*Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

Indications for Coronary Angiography
Who Were Managed With Fibrinolytic Therapy or Who Did Not Receive Reperfusion Therapy

	COR	LOE
Cardiogenic shock or acute severe HF that develops after initial presentation	I	B
Intermediate- or high-risk findings on predischarge noninvasive ischemia testing	I	B
Spontaneous or easily provoked myocardial ischemia	I	C
Failed reperfusion or reocclusion after fibrinolytic therapy	IIa	B
Stable* patients after successful fibrinolysis, before discharge and ideally between 3 and 24 h	IIa	B

*Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

Indications for PCI of an Infarct Artery in Patients Who Were Managed With Fibrinolytic Therapy or Who Did Not Receive Reperfusion Therapy

	COR	LOE
Cardiogenic shock or acute severe HF	I	B
Intermediate- or high-risk findings on predischarge noninvasive ischemia testing	I	C
Spontaneous or easily provoked myocardial ischemia	I	C
Patients with evidence of failed reperfusion or reocclusion after fibrinolytic therapy (as soon as possible)	IIa	B
Stable* patients after successful fibrinolysis, ideally between 3 and 24 h	IIa	B
Stable* patients >24 h after successful fibrinolysis	IIb	B
Delayed PCI of a totally occluded infarct artery >24 h after STEMI in stable patients	III: No Benefit	B

*Although individual circumstances will vary, clinical stability is defined by the absence of low output, hypotension, persistent tachycardia, apparent shock, high-grade ventricular or symptomatic supraventricular tachyarrhythmias, and spontaneous recurrent ischemia.

Question 7

- What are reperfusion signs after any treatment of STEMI ?

Reperfusion signs

- Resolution of clinical manifestations such as chest pain
- Decline of ST elevation over 50% in ECG
- Early peaking of cardiac enzymes
- Reperfusion arrhythmia
  - AIVR
- TIMI grade 3 flow

Question 8

- What are clinical roles and timing of the following pharmaceutical agents for STEMI?
  - Aspirin
  - Thienopyridines
  - UFH or LMWH
  - Beta-blockers
  - ACEI's or ARB's

Reperfusion at a PCI-Capable Hospital

Antiplatelet Therapy to Support Primary PCI for STEMI

Antiplatelet Therapy to Support Primary PCI for STEMI

Aspirin 162 to 325 mg should be given before primary PCI.

After PCI, aspirin should be continued indefinitely.

Antiplatelet Therapy to Support Primary PCI for STEMI

A loading dose of a $P2Y_{12}$ receptor inhibitor should be given as early as possible or at time of primary PCI to patients with STEMI. Options include:

- Clopidogrel 600 mg; or
- Prasugrel 60 mg; or
- Ticagrelor 180 mg

Antiplatelet Therapy to Support Primary PCI for STEMI

$P2Y_{12}$ inhibitor therapy should be given for 1 year to patients with STEMI who receive a stent (BMS or DES) during primary PCI using the following maintenance doses:

- Clopidogrel 75 mg daily; or
- Prasugrel 10 mg daily; or
- Ticagrelor 90 mg twice a day*

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

Antiplatelet Therapy to Support Primary PCI for STEMI

It is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses after primary PCI.

Antiplatelet Therapy to Support Primary PCI for STEMI

It is reasonable to start treatment with an intravenous GP IIb/IIIa receptor antagonist at the time of primary PCI (with or without stenting or clopidogrel pretreatment) in selected patients with STEMI who are receiving UFH.

- Abciximab: 0.25 mg/kg IV bolus, then 0.125 mcg/kg/min (maximum 10 mcg/min); or

- High-bolus-dose tirofiban: 25 mcg/kg IV bolus, then 0.15 mcg/kg/min; or

- Double-bolus eptifibatide: 180 mcg/kg IV bolus, then 2 mcg/kg/min; a 2nd 180-mcg/kg bolus is administered 10 min after the 1st bolus.

Antiplatelet Therapy to Support Primary PCI for STEMI

It may be reasonable to administer intravenous GP IIb/IIIa receptor antagonist in the precatheterization laboratory setting (e.g., ambulance, ED) to patients with STEMI for whom primary PCI is intended.

It may be reasonable to administer intracoronary abciximab to patients with STEMI undergoing primary PCI.

Continuation of a $P2Y_{12}$ inhibitor beyond 1 year may be considered in patients undergoing DES placement.

Antiplatelet Therapy to Support Primary PCI for STEMI

Harm

Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack.

Reperfusion at a PCI-Capable Hospital

Anticoagulant Therapy to Support Primary PCI

Adjunctive Antithrombotic Therapy to Support Reperfusion With Primary PCI

	COR	LOE
Antiplatelet therapy		
Aspirin		
• 162- to 325-mg load before procedure	I	B
• 81- to 325-mg daily maintenance dose (indefinite)*	I	A
• 81 mg daily is the preferred maintenance dose*	IIa	B
$P2Y_{12}$ inhibitors		
Loading doses		
• Clopidogrel: 600 mg as early as possible or at time of PCI	I	B
• Prasugrel: 60 mg as early as possible or at time of PCI	I	B
• Ticagrelor: 180 mg as early as possible or at time of PCI	I	B

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.

Adjunctive Antithrombotic Therapy to Support Reperfusion With Primary PCI (cont.)

	COR	LOE
$P2Y_{12}$ inhibitors		
Maintenance doses and duration of therapy		
DES placed: Continue therapy for 1 y with:		
• Clopidogrel: 75 mg daily	I	B
• Prasugrel: 10 mg daily	I	B
• Ticagrelor: 90 mg twice a day*	I	B
BMS† placed: Continue therapy for 1 y with:		
• Clopidogrel: 75 mg daily	I	B
• Prasugrel: 10 mg daily	I	B
• Ticagrelor: 90 mg twice a day*	I	B
DES placed:		
• Clopidogrel, prasugrel, or ticagrelor* continued beyond 1 y	IIb	C
• Patients with STEMI with prior stroke or TIA: prasugrel	III: Harm	B

*The recommended maintenance dose of aspirin to be used with ticagrelor is 81 mg daily.
†Balloon angioplasty without stent placement may be used in selected patients. It might be reasonable to provide $P2Y_{12}$ inhibitor therapy to patients with STEMI undergoing balloon angioplasty alone according to the recommendations listed for BMS. (*LOE: C*).

Adjunctive Antithrombotic Therapy to Support Reperfusion With Primary PCI (cont.)

	COR	LOE
IV GP IIb/IIIa receptor antagonists in conjunction with UFH or bivalirudin in selected patients		
• Abciximab: 0.25-mg/kg IV bolus, then 0.125 mcg/kg/min (maximum 10 mcg/min)	IIa	A
• Tirofiban: (high-bolus dose): 25-mcg/kg IV bolus, then 0.15 mcg/kg/min • In patients with CrCl <30 mL/min, reduce infusion by 50%	IIa	B
• Eptifibatide: (double bolus): 180-mcg/kg IV bolus, then 2 mcg/kg/min; a second 180-mcg/kg bolus is administered 10 min after the first bolus • In patients with CrCl <50 mL/min, reduce infusion by 50% • Avoid in patients on hemodialysis	IIa	B
• Pre-catheterization laboratory administration of IV GP IIb/IIIa receptor antagonist	IIb	B
• Intracoronary abciximab 0.25-mg/kg bolus	IIb	B

Adjunctive Antithrombotic Therapy to Support Reperfusion With Primary PCI (cont.)

	COR	LOE
Anticoagulant therapy		
• UFH:		
• With GP IIb/IIIa receptor antagonist planned: 50- to 70-U/kg IV bolus to achieve therapeutic ACT‡	I	C
• With no GP IIb/IIIa receptor antagonist planned: 70- to 100-U/kg bolus to achieve therapeutic ACT§	I	C
• Bivalirudin: 0.75-mg/kg IV bolus, then 1.75–mg/kg/h infusion with or without prior treatment with UFH. An additional bolus of 0.3 mg/kg may be given if needed. • Reduce infusion to 1 mg/kg/h with estimated CrCl <30 mL/min	I	B
• Preferred over UFH with GP IIb/IIIa receptor antagonist in patients at high risk of bleeding	IIa	B
• Fondaparinux: not recommended as sole anticoagulant for primary PCI	III: Harm	B

‡The recommended ACT with planned GP IIb/IIIa receptor antagonist treatment is 200 to 250 s.
§ The recommended ACT with no planned GP IIb/IIIa receptor antagonist treatment is 250 to 300 s (HemoTec device) or 300 to 350 s (Hemochron device).

Adjunctive Antithrombotic Therapy to Support Reperfusion With Fibrinolytic Therapy

	COR	LOE
Antiplatelet therapy		
Aspirin		
• 162- to 325-mg loading dose	I	A
• 81- to 325-mg daily maintenance dose (indefinite)	I	A
• 81 mg daily is the preferred maintenance dose	IIa	B
$P2Y_{12}$ receptor inhibitors		
• Clopidogrel:	I	A
• Age ≤75 y: 300-mg loading dose	I	A (14 d) C (up to 1 y)
• Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding		
• Age >75 y: no loading dose, give 75 mg	I	A
• Followed by 75 mg daily for at least 14 d and up to 1 y in absence of bleeding	I	A (14 d) C (up to 1 y)

Adjunctive Antithrombotic Therapy to Support Reperfusion With Fibrinolytic Therapy (cont.)

	COR	LOE
Anticoagulant therapy		
• UFH:		
• Weight-based IV bolus and infusion adjusted to obtain aPTT of 1.5 to 2.0 times control for 48 h or until revascularization. IV bolus of 60 U/kg (maximum 4000 U) followed by an infusion of 12 U/kg/h (maximum 1000 U) initially, adjusted to maintain aPTT at 1.5 to 2.0 times control (approximately 50 to 70 s) for 48 h or until revascularization	I	C
• Enoxaparin:	I	A
• If age <75 y: 30-mg IV bolus, followed in 15 min by 1 mg/kg subcutaneously every 12 h (maximum 100 mg for the first 2 doses) • If age ≥75 y: no bolus, 0.75 mg/kg subcutaneously every 12 h (maximum 75 mg for the first 2 doses) • Regardless of age, if CrCl <30 mL/min: 1 mg/kg subcutaneously every 24 h • Duration: For the index hospitalization, up to 8 d or until revascularization		
• Fondaparinux:	I	B
• Initial dose 2.5 mg IV, then 2.5 mg subcutaneously daily starting the following day, for the index hospitalization up to 8 d or until revascularization • Contraindicated if CrCl <30 mL/min		

Delayed Invasive Management

Antiplatelet Therapy to Support PCI After Fibrinolytic Therapy

Antiplatelet Therapy to Support PCI After Fibrinolytic Therapy

I IIa IIb III
A

After PCI, aspirin should be continued indefinitely.

I IIa IIb III
C

Clopidogrel should be provided as follows:

a. A 300-mg loading dose should be given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI within 24 hours of receiving fibrinolytic therapy;
b. A 600-mg loading dose should be given before or at the time of PCI to patients who did not receive a previous loading dose and who are undergoing PCI more than 24 hours after receiving fibrinolytic therapy; and
c. A dose of 75 mg daily should be given after PCI.

Antiplatelet Therapy to Support PCI After Fibrinolytic Therapy

After PCI, it is reasonable to use 81 mg of aspirin per day in preference to higher maintenance doses.

Prasugrel, in a 60-mg loading dose, is reasonable once the coronary anatomy is known in patients who did not receive a previous loading dose of clopidogrel at the time of administration of a fibrinolytic agent, but prasugrel should not be given sooner than 24 hours after administration of a fibrin-specific agent or 48 hours after administration of a non–fibrin-specific agent.

Prasugrel, in a 10-mg daily maintenance dose, is reasonable after PCI.

Antiplatelet Therapy to Support PCI After Fibrinolytic Therapy

Harm

Prasugrel should not be administered to patients with a history of prior stroke or transient ischemic attack.

Delayed Invasive Management

Anticoagulant Therapy to Support PCI After Fibrinolytic Therapy

Adjunctive Antithrombotic Therapy to Support PCI After Fibrinolytic Therapy

	COR	LOE
Antiplatelet therapy		
Aspirin		
• 162- to 325-mg loading dose given with fibrinolytic agent (before PCI). (Section 5.1.4.1 and Table 7)	I	A
• 81- to 325-mg daily maintenance dose after PCI (indefinite)	I	A
• 81 mg daily is the preferred daily maintenance dose	IIa	B
$P2Y_{12}$ receptor inhibitors		
Loading doses		
For patients who received a loading dose of clopidogrel with fibrinolytic therapy:		
• Continue clopidogrel 75 mg daily without an additional loading dose	I	C
For patients who have not received a loading dose of clopidogrel:		
• If PCI is performed ≤24 h after fibrinolytic therapy: clopidogrel 300-mg loading dose before or at the time of PCI	I	C
• If PCI is performed >24 h after fibrinolytic therapy: clopidogrel 600-mg loading dose before or at the time of PCI	I	C
• If PCI is performed >24 h after treatment with a fibrin-specific agent or >48 h after a non–fibrin-specific agent: prasugrel 60 mg at the time of PCI	IIa	B
For patients with prior stroke/TIA: prasugrel	III: Harm	B

Adjunctive Antithrombotic Therapy to Support PCI After Fibrinolytic Therapy (cont.)

	COR	LOE
$P2Y_{12}$ receptor inhibitors		
Maintenance doses and duration of therapy		
DES placed: Continue therapy for at least 1 y with:		
• Clopidogrel: 75 mg daily	I	C
• Prasugrel: 10 mg daily	IIa	B
BMS placed: Continue therapy for at least 30 d and up to 1 y with:*		
• Clopidogrel: 75 mg daily	I	C
• Prasugrel: 10 mg daily	IIa	B

*Balloon angioplasty without stent placement may be used in selected patients. It might be reasonable to provide $P2Y_{12}$ inhibitor therapy to patients with STEMI undergoing balloon angioplasty after fibrinolysis alone according to the recommendations listed for BMS. (*Level of Evidence: C*)

Adjunctive Antithrombotic Therapy to Support PCI After Fibrinolytic Therapy (cont.)

	COR	LOE
Anticoagulant therapy		
• Continue UFH through PCI, administering additional IV boluses as needed to maintain therapeutic ACT depending on use of GP IIb/IIIa receptor antagonist†	I	C
• Continue enoxaparin through PCI:	I	B
◦ No additional drug if last dose was within previous 8 h		
◦ 0.3-mg/kg IV bolus if last dose was 8 to 12 h earlier		
• Fondaparinux:	III: Harm	C
◦ As sole anticoagulant for PCI		

†The recommended ACT with no planned GP IIb/IIIa receptor antagonist treatment is 250–300 s (HemoTec device) or 300–350 s (Hemochron device).

Routine Medical Therapies

Beta Blockers

Beta Blockers

Oral beta blockers should be initiated in the first 24 hours in patients with STEMI who do not have any of the following: signs of HF, evidence of a low output state, increased risk for cardiogenic shock,* or other contraindications to use of oral beta blockers (PR interval >0.24 seconds, second- or third-degree heart block, active asthma, or reactive airways disease).

Beta blockers should be continued during and after hospitalization for all patients with STEMI and with no contraindications to their use.

*Risk factors for cardiogenic shock (the greater the number of risk factors present, the higher the risk of developing cardiogenic shock) are age >70 years, systolic BP <120 mm Hg, sinus tachycardia >110 bpm or heart rate <60 bpm, and increased time since onset of symptoms of STEMI.

Beta Blockers

Patients with initial contraindications to the use of beta blockers in the first 24 hours after STEMI should be reevaluated to determine their subsequent eligibility.

It is reasonable to administer intravenous beta blockers at the time of presentation to patients with STEMI and no contraindications to their use who are hypertensive or have ongoing ischemia.

Routine Medical Therapies

Renin-Angiotensin-Aldosterone System Inhibitors

Renin-Angiotensin-Aldosterone System Inhibitors

An ACE inhibitor should be administered within the first 24 hours to all patients with STEMI with anterior location, HF, or EF less than or equal to 0.40, unless contraindicated.

An ARB should be given to patients with STEMI who have indications for but are intolerant of ACE inhibitors.

Renin-Angiotensin-Aldosterone System Inhibitors

An aldosterone antagonist should be given to patients with STEMI and no contraindications who are already receiving an ACE inhibitor and beta blocker and who have an EF less than or equal to 0.40 and either symptomatic HF or diabetes mellitus.

ACE inhibitors are reasonable for all patients with STEMI and no contraindications to their use.

Routine Medical Therapies

Lipid Management

Lipid Management

I IIa IIb III — B

High-intensity statin therapy should be initiated or continued in all patients with STEMI and no contraindications to its use.

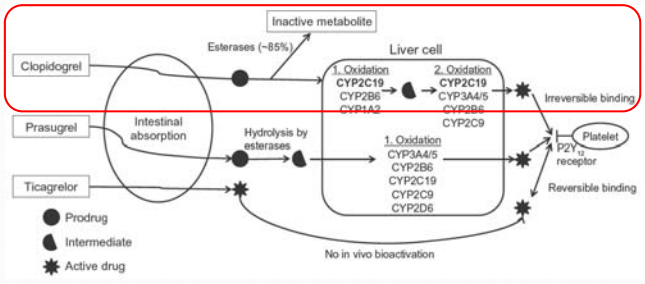
I IIa IIb III — C

It is reasonable to obtain a fasting lipid profile in patients with STEMI, preferably within 24 hours of presentation.

Question 9

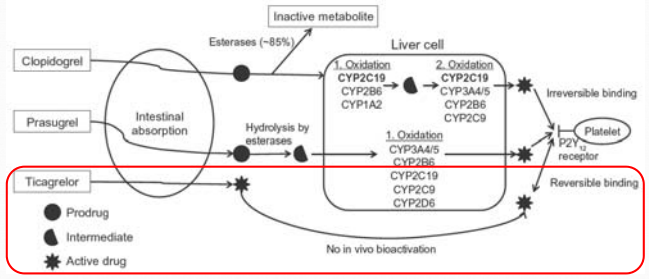
- What is the schedule of discontinuing pharmaceutical agents before urgent CABG for STEMI?

- Clopidogrel requires a two-step bioactivation by liver cell, which irreversibly binds to P2Y12 receptor, thus inhibiting platelet activation.



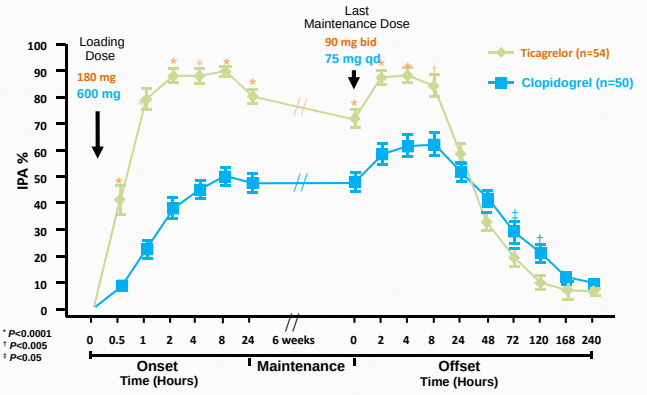
Cavallari LH,et al. Pharmgenomics Pers Med 2011;4:123-36.

- Ticagrelor is a reversible P2Y12 antagonist that does not require hepatic bioactivation.



Cavallari LH,et al. Pharmgenomics Pers Med 2011;4:123-36.

ONSET/OFFSET:
Pharmacodynamics in Stable CAD Patients



Adapted from Gurbel PA, et al. *Circulation*. 2009;120:2577–2585.

$P2Y_{12}$ inhibitors

	Plavix®	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversibility	Irreversibility	Reversibility
Activation	Prodrug	Prodrug	Active drug
Duration of effect	3-10 days	5-10 days	3-4 days
Withdraw before major surgery	5 days	7 days	5 days

Coronary Artery Bypass Graft Surgery

Timing of Urgent CABG in Patients With STEMI in Relation to Use of Antiplatelet Agents

Timing of Urgent CABG in Patients With STEMI in Relation to Use of Antiplatelet Agents

I IIa IIb III — C

Aspirin should not be withheld before urgent CABG.

I IIa IIb III — B

Clopidogrel or ticagrelor should be discontinued at least 24 hours before urgent on-pump CABG, if possible.

I IIa IIb III — B

Short-acting intravenous GP IIb/IIIa receptor antagonists (eptifibatide, tirofiban) should be discontinued at least 2 to 4 hours before urgent CABG.

Timing of Urgent CABG in Patients With STEMI in Relation to Use of Antiplatelet Agents

I IIa IIb III — B

Abciximab should be discontinued at least 12 hours before urgent CABG.

I IIa IIb III — B

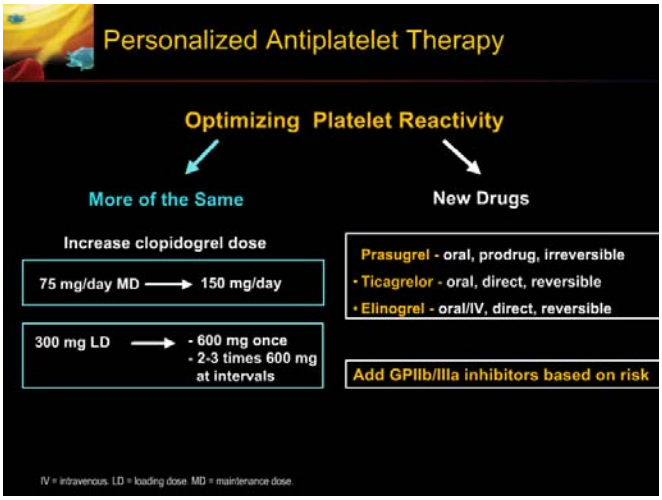
Urgent off-pump CABG within 24 hours of clopidogrel or ticagrelor administration might be considered, especially if the benefits of prompt revascularization outweigh the risks of bleeding.

I IIa IIb III — C

Urgent CABG within 5 days of clopidogrel or ticagrelor administration or within 7 days of prasugrel administration might be considered, especially if the benefits of prompt revascularization outweigh the risks of bleeding.

Question 10

- What is (are) proven to be more beneficial for ticargrelor over clopidogrel ?
  - ACS overall
  - STEMI
  - NSTEMI
  - Unstable angina
  - Stable angina



$P2Y_{12}$ inhibitors

	Plavix®	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversibility	Irreversibility	Reversibility
Activation	Prodrug	Prodrug	Active drug
Duration of effect	3-10 days	5-10 days	3-4 days
Withdraw before major surgery	5 days	7 days	5 days

PLATO study design

NSTE-ACS (moderate-to-high risk) STEMI (if primary PCI)
Clopidogrel-treated or -naive;
randomised within 24 hours of index event
(N=18,624)

Clopidogrel
If pre-treated, no additional loading dose; if naive, standard 300 mg loading dose, then 75 mg qd maintenance; (additional 300 mg allowed pre PCI)

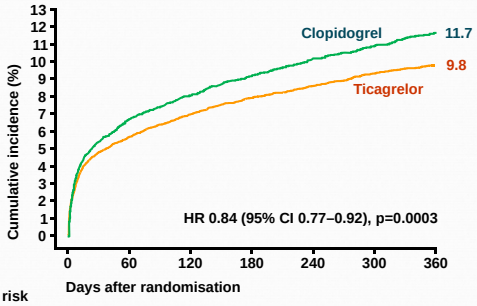
Ticagrelor
180 mg loading dose, then 90 mg bid maintenance; (additional 90 mg pre-PCI)

6-12 month exposure
Mean duration 277 days

Primary endpoint: CV death + MI + Stroke
Primary safety endpint: Total major bleeding

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.

PLATO: Primary Efficacy Endpoints

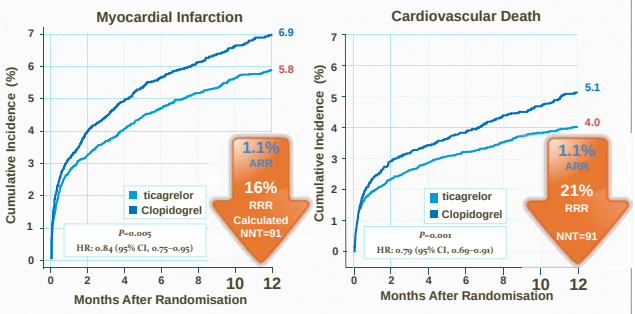


No. at risk							
Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

K-M = Kaplan-Meier; HR = hazard ratio; CI = confidence interval

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.

PLATO: Secondary Efficacy Endpoints

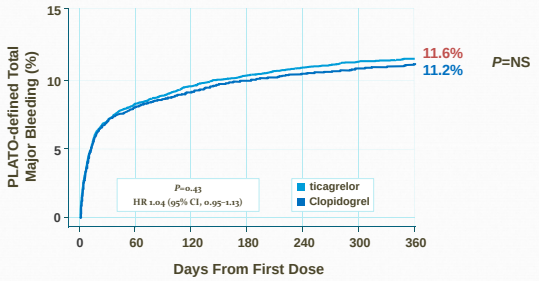


Rate of stroke for ticagrelor was not different from clopidogrel (1.3% vs 1.1%), *P*=0.225

Both groups included aspirin.

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.
Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057. Supplement

PLATO: Primary Safety Endpoint



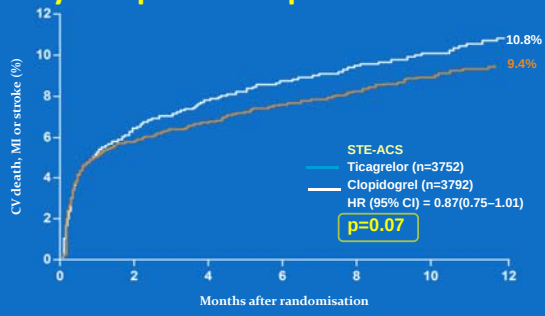
No. at risk							
ticagrelor	9,235	7,246	6,826	6,545	5,129	3,783	3,433
Clopidogrel	9,186	7,305	6,930	6,930	5,209	3,841	3,479

Both groups included aspirin.

Wallentin L, et al. *N Engl J Med*. 2009;361:1045–1057.

PLATO STE-ACS: Primary composite endpoint

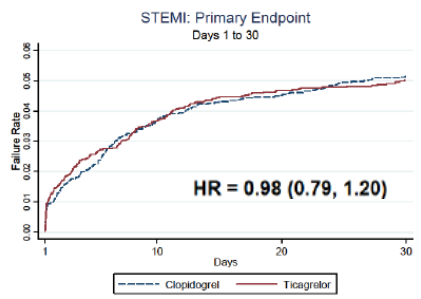
[Steg 2010:J–L]



ACS, acute coronary syndromes; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; STE, ST-segment elevation.
Steg PG, et al. *Circulation* 2010;122:2131–2141.

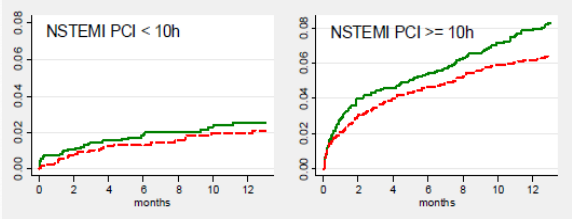
PLATO STEMI:
Primary endpoint within 30 Days

For STEMI subjects, *no* comparative benefit for ticagrelor over Plavix observed in 30-day endpoint



http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022433Orig1s000MedR.pdf, (Page 175/640)

PLATO NSTEMI with PCI < 10 hours: Mortality



FDA website: AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/UCM221383

Conclusion

Therapeutic approaches to reducing secondary events

- Aspirin for all patients
- Clopidogrel for stent (+) or NSTTEMI
- Ticagrelor(90mg) :2# stat→ 1# bid x 9 months for AMI or NSTTEMI benefit > clopidogrel
- ACEi or ARB for EF <50%
- Beta-blocker for all patients, especially metoprolol, carvedilol & bisoprolol for EF < 40%
- Aldactone Tx for CHF (+) with EF < 40%
- Statin for LDL > 100, target < 70mg/dL if DM or CAD(+)
- Post-MI with CHF →prophylactic ICD: ? Benefit in EPS (+) inducible VT/Vf

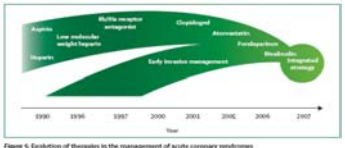
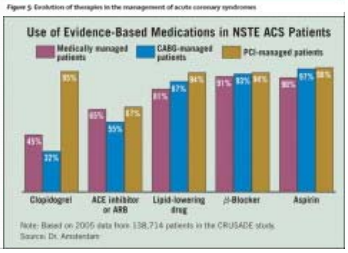


Figure 5. Evolution of therapies in the management of acute coronary syndromes



Thank for your attention