USING EVIDENCE AND GUIDELINES - TREAT ***YOUR PATIENTS***

Non-ST-segment elevation acute coronary syndrome

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RISK STRATIFICATION AND CHOOSING STRATEGY

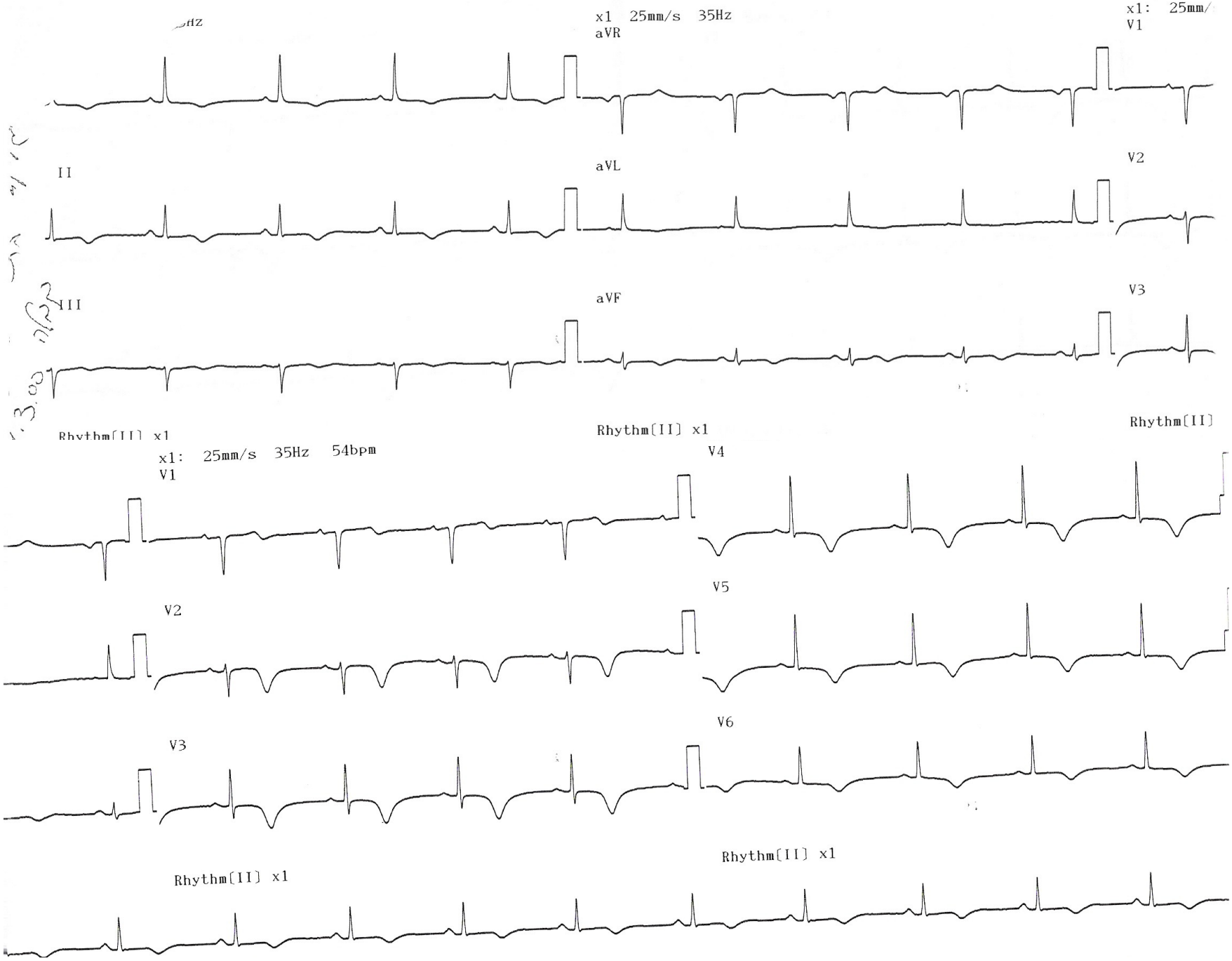
- 1. Integral prerequisite to decision making
  - a) Intensive initial assessment
  - b) Continuous clinical assessment
  - c) Targeted ECG and marker data
- 2. Risk based on contingent probabilities
  - a) Probability of obstructive CAD causing ischemia
  - b) Risk given presence of obstructive CAD
- 3. Risk scores should be a routine part of
  - assessment throughout the hospital course and periodically after discharge

Case 1

- During Saturday eve (erev shishi) dinner 60 y old hypertensive and diabetic male complained of 30 minute squeezing sub-sternal chest pain.
- Emergency mobile service (Magen David Adom) treated him with aspirin 300mg sublingual, nitroglycerin sublingual and nasal oxygen.
- The pain relieved.
- He was transferred to ER at our hospital.
- Current medications:
  - Aspirin (micropirin) 100mgX1;
  - Atenolol (normiten) 25mgX1;
  - Enalapril (enaladex) 20mgx1
  - Metformin (glucophage) 850mgx2.

Case-1(cont')

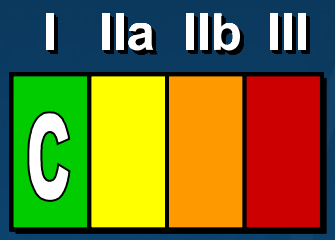
- Physical examination
  - Comfortable.
  - Weight 65 kg, BP – 130/75 mmHg, HR – 72, regular, T- 36.6^{o}C. SaO_2-99% (nasal O_2).
  - No JVD, Chest and lung clear.
  - Regular heart rhythm, no gallop or murmurs.
  - Peripheral pulses – normal.
  - No leg edema.


x1 25mm/s 35Hz
aVR
x1: 25mm/
V1
II
aVL
V2
III
aVF
V3
Rhythm[II] x1
Rhythm[II] x1
Rhythm[II]
x1: 25mm/s 35Hz 54bpm
V1
V4
V2
V5
V3
V6
Rhythm[II] x1
Rhythm[II] x1

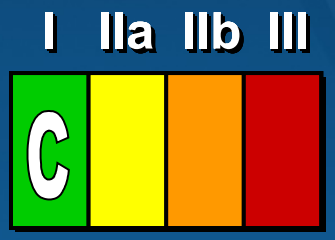
Labs

- Troponin-T on admission – 0.03 (n<0.01ng/dl, cutoff for MI >0.1ng/dl)
- CK – 110 (n<180)
- Glucose 105
- Creatinine – 1.31
- K-3.9
- Na- 139
- HB 14.8
- PLT – 285000
- WBC – 11200 (n<10000)

Early Risk Stratification



A rapid clinical determination of the likelihood risk of obstructive CAD (i.e., high, intermediate, or low) should be made in all patients with chest discomfort or other symptoms suggestive of an ACS and considered in patient management.



Patients who present with chest discomfort or other ischemic symptoms should undergo early risk stratification for the risk of cardiovascular events (e.g., death or [re]MI) that focuses on history, including anginal symptoms, physical findings, ECG findings, and biomarkers of cardiac injury, and results should be considered in patient manage

Anderson et al., ACC/AHA NSTEMI guidelines, 2007

Likelihood of ACS Secondary to CAD

Feature	High Likelihood *Any below:*	Intermediate Likelihood *No high likelihood features but any below:*	Low Likelihood *No high- or intermediate likelihood features but may have:*
History	**Typical angina** **Known hx of CAD, including MI**	**Probable angina** **Age >70 y** **Male, DM**	**Atypical symptoms**
Examination	**CHF**	**PVD, CVA**	**Pain on palpation**
ECG	**New ECG changes**	**Known ECG abnormalities**	**Normal ECG**
Cardiac Markers	**Positive**	**Normal**	**Normal**

Anderson et al., ACC/AHA NSTEMI guidelines, 2007

TIMI Risk Score for NSTEMI

- Age ≥ 65 years
- At least 3 risk factors for CAD
- Prior coronary stenosis of ≥ 50%
- ST-segment deviation on ECG presentation
- At least 2 anginal events in prior 24 hours
- Use of aspirin in prior 7 days
- Elevated serum cardiac biomarkers

The TIMI risk score is determined by the sum of the presence of the above 7 variables at admission. 1 point is given for each variable. Primary coronary stenosis of 50% or more remained relatively insensitive to missing information and remained a significant predictor of events. Antman EM, et al. *JAMA* 2000;284:835–42.

TIMI = Thrombolysis in Myocardial Infarction.

TIMI Risk Score

TIMI Risk Score	All-Cause Mortality, New or Recurrent MI, or Severe Recurrent Ischemia Requiring Urgent Revascularization Through 14 Days After Randomization %	
0-1	4.7	Intermediate risk
2	8.3	
3	13.2	High Risk
4	19.9	
5	26.2	
6-7	40.9	

The TIMI risk calculator is available at www.timi.org. Anderson JL, et al. *J Am Coll Cardiol* 2007;50:e1–e157, Table 8. TIMI =

Risk Scoring According to TIMI

Case 1

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- Emergency mobile service (Magen David Adom) treated him with aspirin 300mg sublingual, nitroglycerin sublingual and nasal oxygen.
- The pain relieved.
- Current medications:
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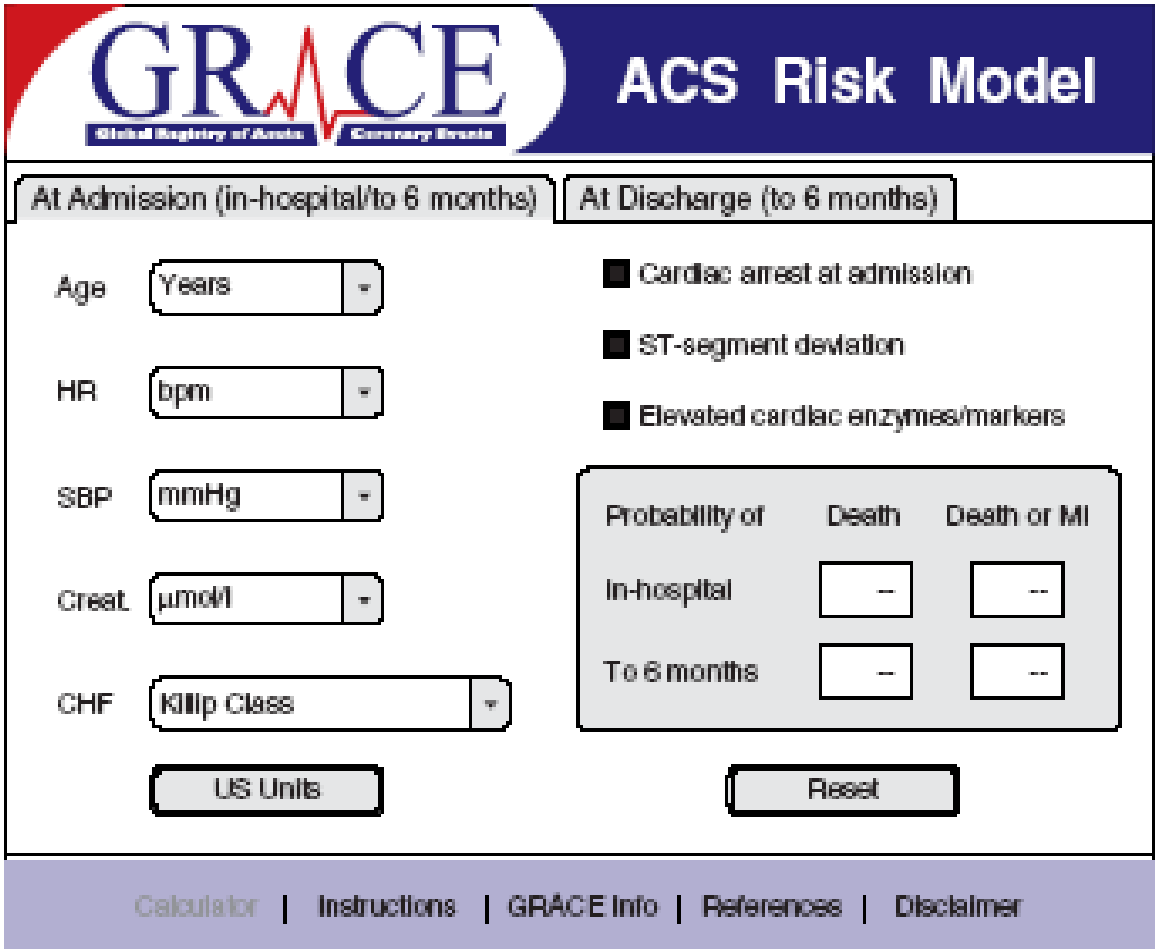
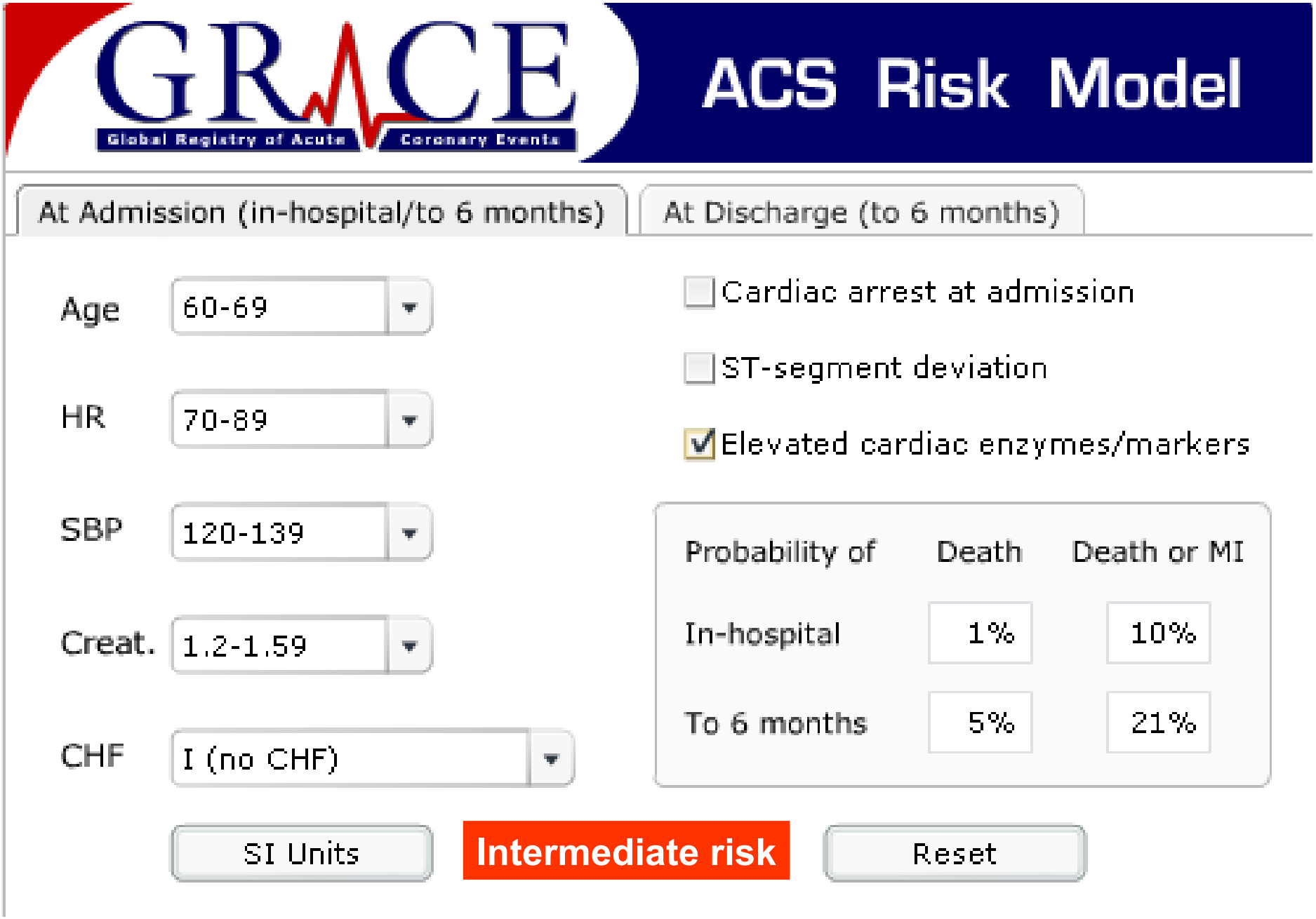
  - Atenolol (normiten) 25mgX1;
  - Enalapril (enaladex) 20mgx1
  - Metformin (glucophage) 85[illegible]

TIMI risk score for NSTEMI=2

GRACE Risk Stratification



Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, Goodman SG, Granger CB, Steg PG, Gore JM, Budaj A, Avezum A, Flather MD, Fox KA. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA* 2004; 291:2727-2733


GRACE
Global Registry of Acute Coronary Events
ACS Risk Model
At Admission (in-hospital/to 6 months)
At Discharge (to 6 months)
Age
60-69
HR
70-89
SBP
120-139
Creat.
1.2-1.59
CHF
I (no CHF)
Cardiac arrest at admission
ST-segment deviation
Elevated cardiac enzymes/markers
Probability of
Death
Death or MI
In-hospital
1%
10%
To 6 months
5%
21%
SI Units
Intermediate risk
Reset

Mortality In-hospital and at 6 Months In Low, Intermediate and High Risk Categories in Registry Populations According to the GRACE Risk Score

Risk category (tertiles)	GRACE Risk Score	In-hospital deaths (%)
Low	<=108	<1
Intermediate	109-140	1-3
High	>140	>3
Risk category (tertiles)	**GRACE Risk Score**	**Post-discharge to 6 months deaths (%)**
Low	<=88	<3
Intermediate	89-118	3-8
High	>118	>8

Http://Www.Outcomes.Org/Grace

Feature	High Risk *At least 1 of the following features must be present:*	Intermediate Risk *No high-risk feature, but must have 1 of the following:*	Low Risk *No high- or intermediate-risk feature but may have any of the following features:*
History	Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease, or CABG; prior aspirin use	
Character of pain	Prolonged ongoing (greater than 20 min) rest pain	Prolonged (greater than 20 min) rest angina, now resolved, with moderate or high likelihood of CAD Rest angina (greater than 20 min) or relieved with rest or sublingual NTG Nocturnal angina New-onset or progressive CCS class III or IV angina in the past 2 weeks without prolonged (greater than 20 min) rest pain but with intermediate or high likelihood of CAD (see Table 6)	Increased angina frequency, severity, or duration Angina provoked at a lower threshold New onset angina with onset 2 weeks to 2 months prior to presentation
Clinical findings	Pulmonary edema, most likely due to ischemia New or worsening MR murmur S_3 or new/worsening rales Hypotension, bradycardia, tachycardia Age greater than 75 years	Age greater than 70 years	
ECG	Angina at rest with transient ST-segment changes greater than 0.5 mm Bundle-branch block, new or presumed new Sustained ventricular tachycardia	T-wave changes Pathological Q waves or resting ST-depression less than 1 mm in multiple lead groups (anterior, inferior, lateral)	Normal or unchanged ECG
Cardiac markers	Elevated cardiac TnT, TnI, or CK-MB (e.g., TnT or TnI greater than 0.1 ng per ml)	Slightly elevated cardiac TnT, TnI, or CK-MB (e.g., TnT greater than 0.01 but less than 0.1 ng per ml)	Normal

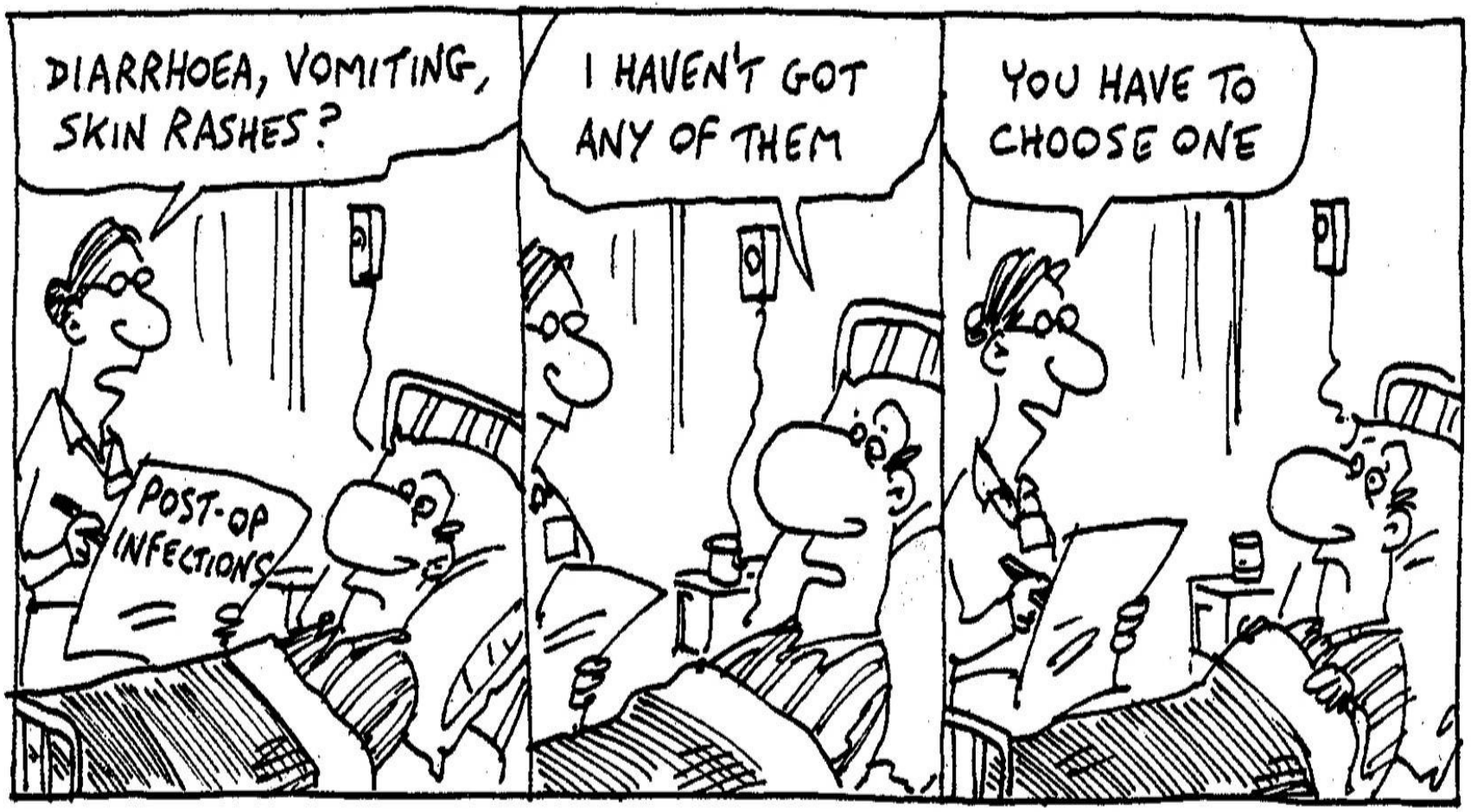
*Estimation of the short-term risks of death and nonfatal cardiac ischemic events in UA (or NSTEMI) is a complex multivariable problem that cannot be fully specified in a table such as this; therefore, this table is meant to offer general guidance and illustration rather than rigid algorithms. Adapted from AHCPR Clinical Practice Guidelines No. 10, Unstable Angina: Diagnosis and Management, May 1994 (28).

CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; CCS = Canadian Cardiovascular Society; CK-MB = creatine kinase, MB fraction; ECG = electrocardiogram; MI = myocardial infarction; MR = mitral regurgitation; NTG = nitroglycerin; TnI = troponin I; TnT = troponin T; UA/NSTEMI = unstable angina/non–ST-elevation myocardial infarction.

Question 1

- How to classify this patient –
  - A. High risk
  - B. Intermediate risk
  - C. Low risk
  - D. There is insufficient information for risk stratification

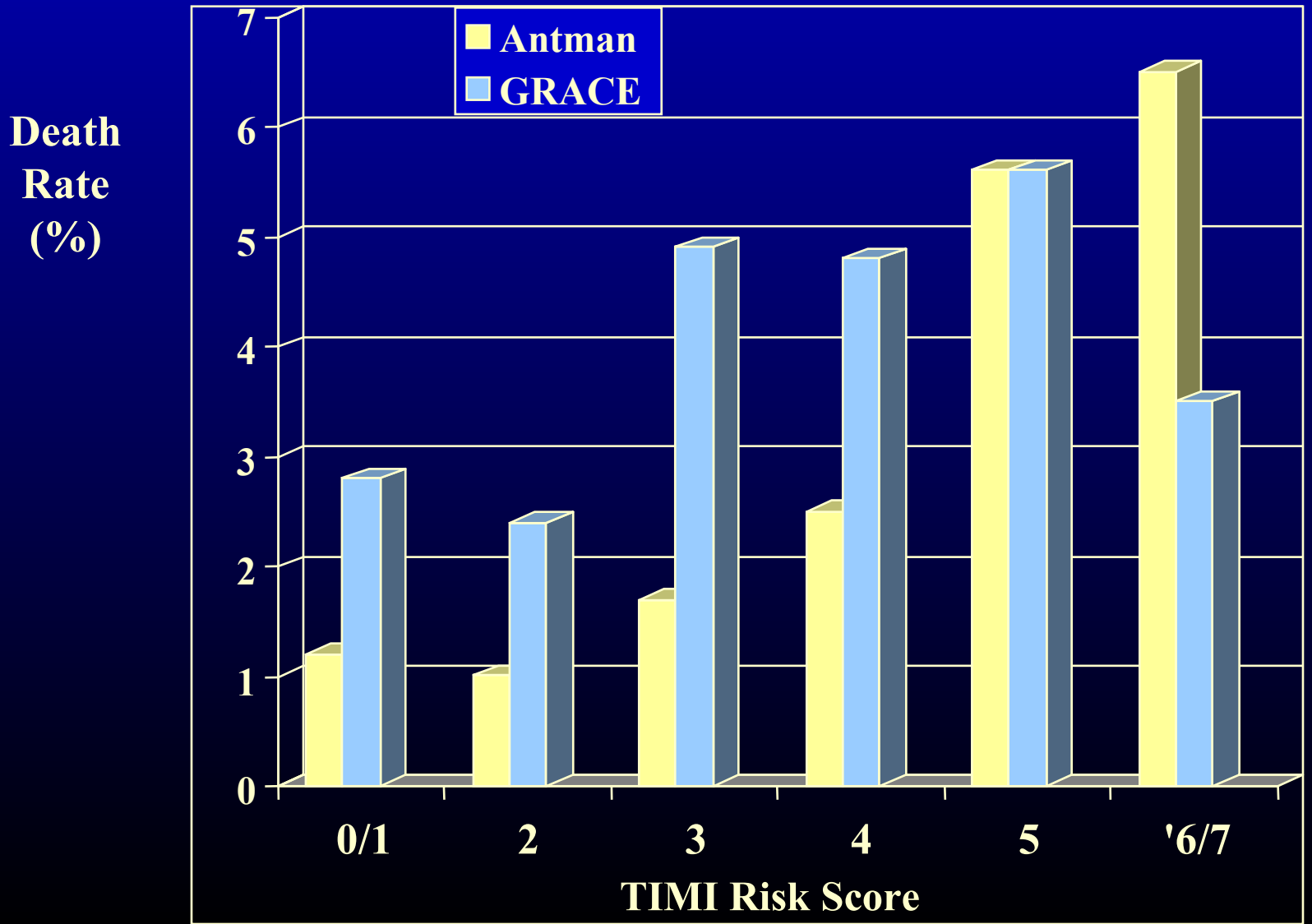
Risk Scores


DIARRHOEA, VOMITING, SKIN RASHES?
POST-OP INFECTIONS
I HAVEN'T GOT ANY OF THEM
YOU HAVE TO CHOOSE ONE

Question 1

- How to classify this patient –
  - A. High risk
  - B. Intermediate risk
  - C. Low risk
  - D. There is insufficient information for risk stratification

Comparison of TIMI Risk Scores for Death: Antman Data Vs. GRACE Data



Comparison of TIMI Risk Scores for Death: Antman Data vs GRACE Data

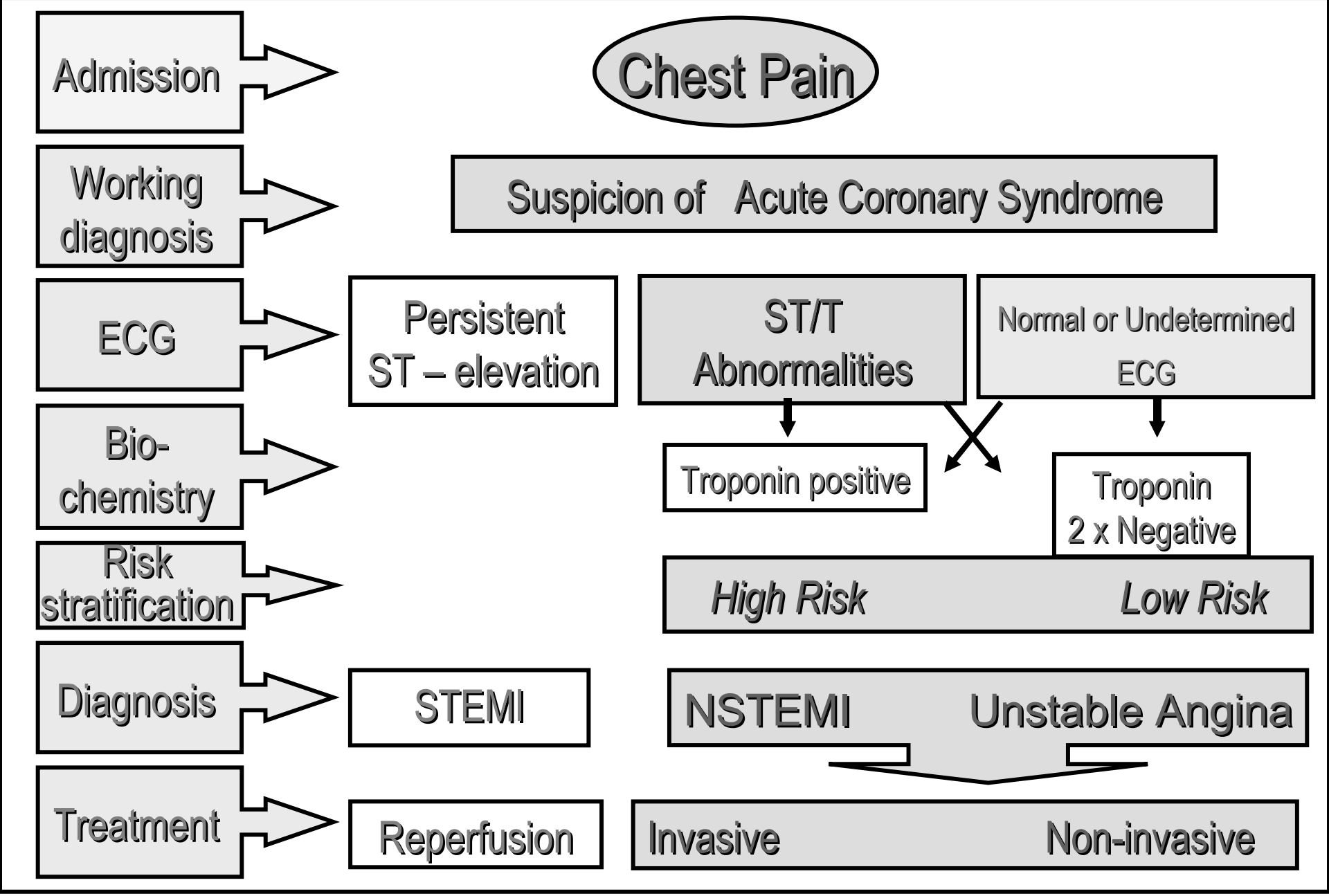
- Unselected patients reveal substantially higher event rates than those entered into recent trials
- A major challenge exists in the application of proven therapies to the full spectrum of patients with ACS

RISK SCORES

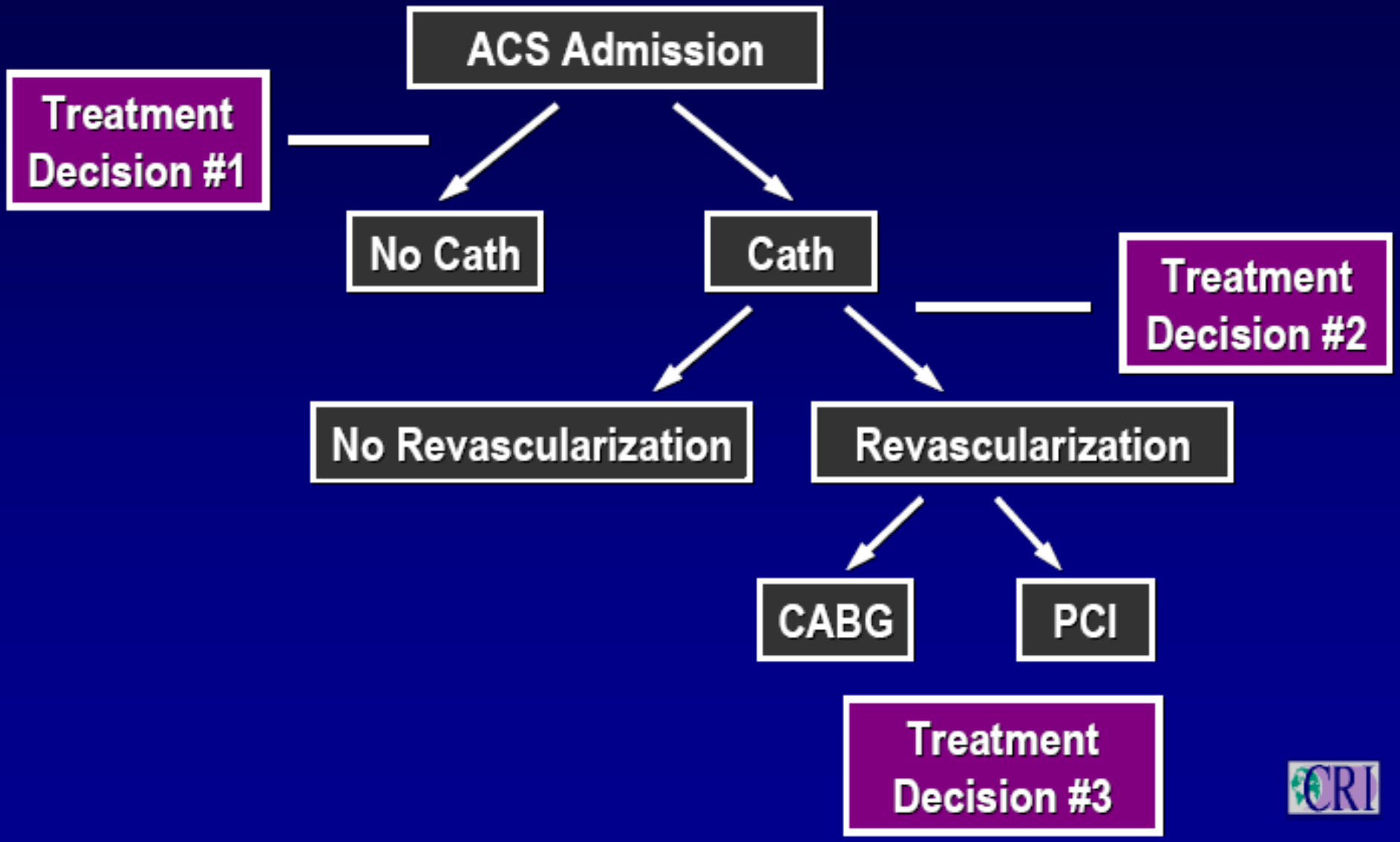
	TIMI	GRACE	Future
History	**Age, HTN, DM,Smoking, High Cholesterol, Family Hx of CAD**	**Age**	**Continuous assessment**
Presentation	**Severe angina, ASA within 7 days, Elevated biomarkers, ST-segment deviation**	**Heart rate, Systolic BP, Elevated biomarkers, heart failure, cardiac arrest, elevated markers, ST-segment deviation**	**New markers Electronic health records**

Cannon C., Using evidence and guidelines to individualize care for ACS – a case based presentation – www.theheart.org/CME

de Araujo Goncalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. *Eur Heart J* 2005; **26**:865-872.


Admission
Chest Pain
Working diagnosis
Suspicion of Acute Coronary Syndrome
ECG
Persistent ST – elevation
ST/T Abnormalities
Normal or Undetermined ECG
Bio-chemistry
Troponin positive
Troponin 2 x Negative
Risk stratification
High Risk
Low Risk
Diagnosis
STEMI
NSTEMI
Unstable Angina
Treatment
Reperfusion
Invasive
Non-invasive

Use of Invasive Cardiac Procedures in ACS



Management

- Admission to -
  - Intensive cardiac care unit
  - Intermediate care unit
  - Medical ward
  - Troponin-T level is lower than cutoff for MI – so the patient may be discharged after non-invasive risk stratification

Management

- Aspirin?
- Clopidogrel?
- Nitroglycerin (IV, sublingual)?
- β-blocker?
- Statins?
- Heparin, bivalirudin or LMWH?
- GP IIb/IIIa antagonists?

Management

- Change in hypoglycemic regimen?
- Patient activity level?
- Any other examinations?
- Repeated cardiac biomarkers?

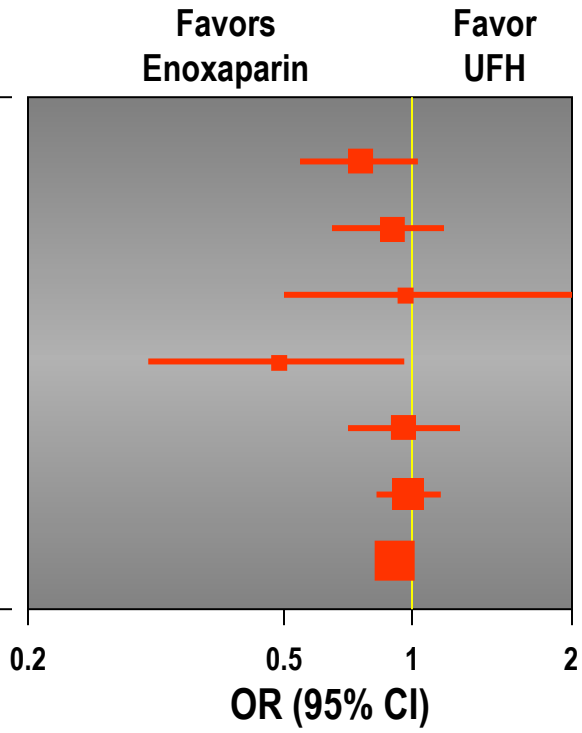
Management

- The patient received 100mg of aspirin (coated) and admitted in intensive cardiac care unit.
- He was loaded by clopidogrel 300mg and s.c. enoxaparin 1mg/kg BID was ordered.
- Another set of cardiac biomarkers with full SMA was ordered.
- Chest X-ray – normal.

Efficacy and Bleeding Complications Among Patients Randomized to Enox or UFH in NSTE-ACS

Death or MI at 30 Days

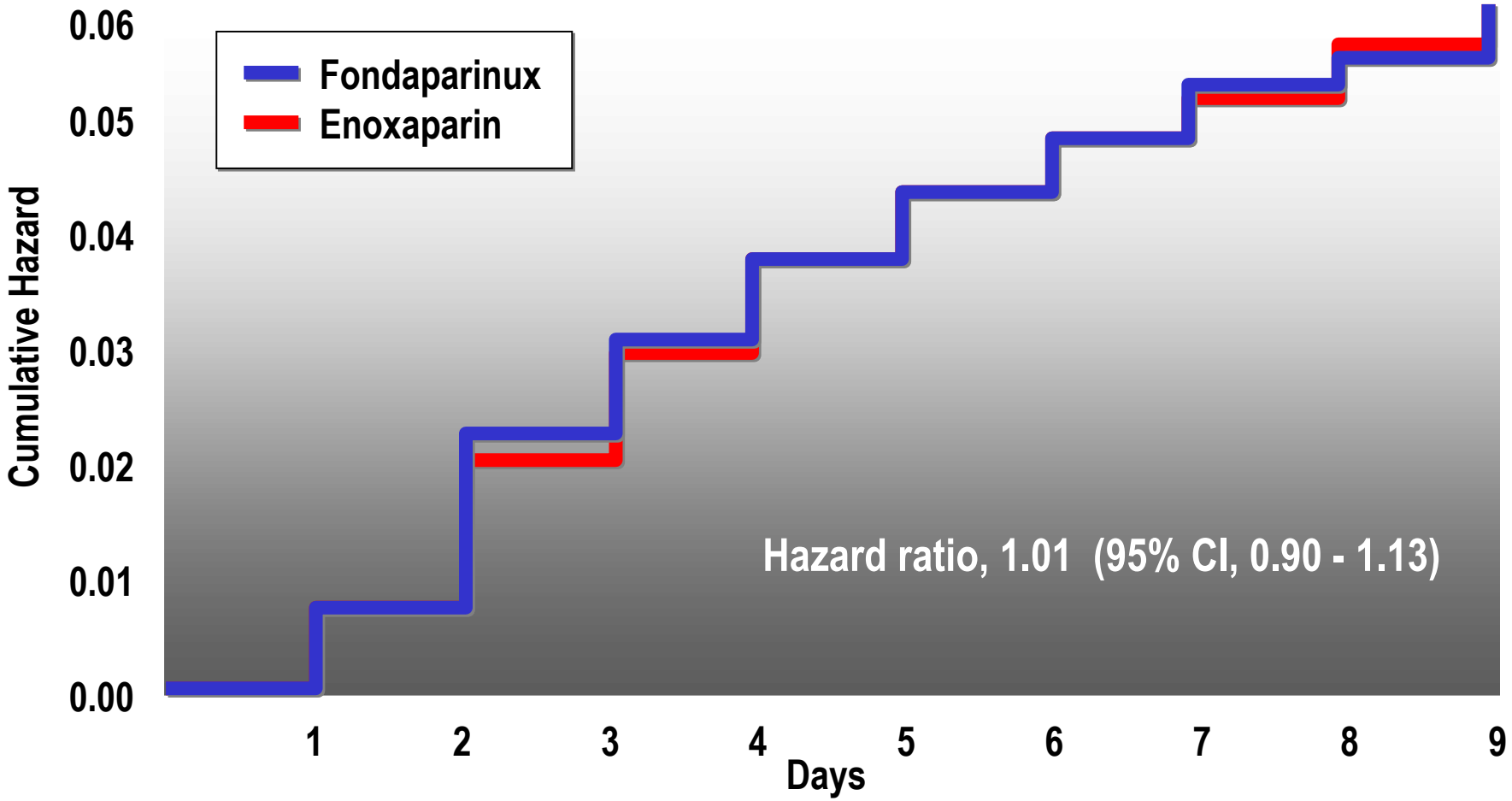
Trial	Events, No./Total (%) Enoxaparin	UHF	OR (95% CI)
ESSENCE	94/1607 (5.8)	118/1564 (7.5)	0.76 (0.58-1.01)
TIMI 11B	145/1953 (7.4)	163/1957 (8.6)	0.88 (0.70-1.11)
ACUTE II	25/315 (7.9)	17/210 (8.1)	0.97 (0.51-1.83)
INTERACT	19/380 (5.0)	33/366 (9.0)	0.54 (0.30-0.96)
A to Z	137/1852 (7.4)	139/1768 (7.9)	0.94 (0.73-1.20)
SYNERGY	696/4992 (14.0)	722/4982 (14.5)	0.96 (0.86-1.07)
OVERALL	1116/11099 (10.1)	1192/10847 (11.0)	0.91 (0.83-0.99)



Petersen. JAMA 2004;292:89–96

OASIS 5 Trial

Death, myocardial infarction or refractory ischemia through day 9



Recommendations for Anticoagulation (1)

- Anticoagulation is recommended for all patients in addition to antiplatelet therapy (I-A)
- Anticoagulation should be selected according to the risk of both ischaemic and bleeding events (I-B)
- Several anticoagulants are available, namely UFH, LMWH, fondaparinux, bivalirudin. The choice depends on the initial strategy (urgent invasive, early invasive, or conservative strategies) (I-B)
- In an urgent invasive strategy UFH (I-C), or enoxaparin (IIa-B) or bivalirudin (I-B) should be immediately started.

Recommendations for Anticoagulation (2)

- In an non-urgent situation, as long as decision between early invasive or conservative strategy is pending:
  - Fondaparinux is recommended on the basis of the most favorable efficacy/safety profile (I-A).
  - Enoxaparin with a less favourable efficacy/safety profile than fondaparinux should be used only if the bleeding risk is low (IIa-B)
  - As efficacy/safety profile of LMWH (other than enoxaparin) or UFH relative to fondaparinux is unknown; these anticoagulants cannot be recommended over fondaparinux (IIa-B)

Recommendations for Anticoagulation (3)

- At PCI procedures the initial anticoagulant should be maintained also during the procedure regardless whether this treatment is UFH (I-C), enoxaparin (IIa-B) or bivalirudin (I-B), while addititional UFH in standard dose (50-100 IU/kg bolus) is necessary in case of fondaparinux (IIa-C).
- Anticoagulation can be stopped within 24 hours after invasive procedure (IIa-C). In a conservative strategy, fondaparinux, enoxaparin or other LMWH may be maintained up to hospital discharge. (I-B)

Anti-Platelet Treatment

Pharmacological Treatment (in the ward)

- 600mg vs 300mg clopidogrel loading dose: unsettled issue
- New thienopyridines under development (TRITON, PLATO: ongoing studies)
- GP IIb/IIIa inhibitors
  - Upstream or deferred
  - ACUITY Timing – No unequivocal results

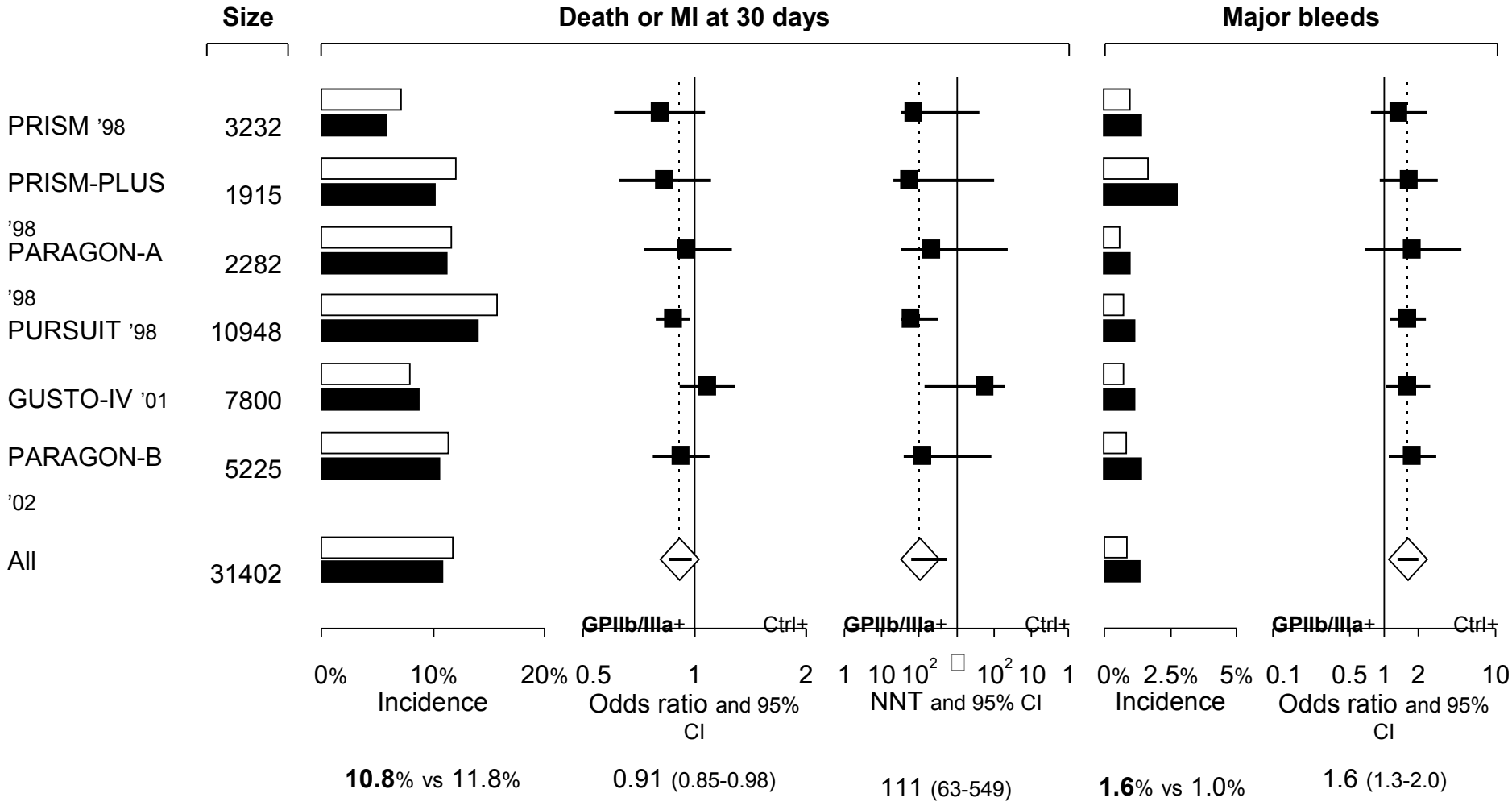
Recommendations for Oral Antiplatelet Drugs (1)

- Aspirin is recommended for all patients presenting with NSTE-ACS without contraindication at an initial loading dose of 160 - 325mg (non-enteric) (I-A), and at a maintenance dose of 75 to 100mg long-term (I-A).
- For all patients, immediate 300mg loading dose of clopidogrel is recommended, followed by 75mg clopidogrel daily (I-A). Clopidogrel should be maintained for 12 months unless there is an excessive risk of bleeding (I-A).
- For all patients with contraindication to aspirin, clopidogrel should be given instead (I-B).

Recommendations for Oral Antiplatelet Drugs (2)

- In patients considered for an invasive procedure/ PCI, a loading dose of 600mg of clopidogrel may be used to achieve more rapid inhibition of platelet function (IIa-B).
- In patients pretreated with clopidogrel who need to undergo CABG, surgery should be postponed for 5 days for clopidogrel withdrawal if clinically feasible (IIa-C).

Randomised Trials of GP IIb/IIIa Inhibitors (dark bars) vs Control (open bars)



Recommendations for GP IIb/IIIa Inhibitors (1)

- In patients at intermediate to high risk, particularly patients with elevated troponins, ST-depression, or diabetes, either eptifibatide or tirofiban for initial early treatment are recommended in addition to oral antiplatelet agents (IIa-A).
- The choice of combination of antiplatelet agents and anticoagulants should be made in relation to risk of ischaemic and bleeding events. (I-B)
- Patients who received initial treatment with eptifibatide or tirofiban prior to angiography, should be maintained on the same drug during and after PCI (IIa-B)

Management

- Simvastatin 40mg OD was ordered.
- Metformin treatment was discontinued and the patient blood glucose monitoring was ordered three times a day before meal.
- Atenolol and enalapril treatment were continued without dose changes.

Management

- Echocardiogram performed by the experienced physician on duty revealed normal left ventricular systolic function with mild concentric hypertrophy and without regional wall motion abnormalities.
- Dilated left atrium – LA area 25 cm^2.
- No significant valvular problems were detected.
- Pulmonary artery systolic pressure assessed as tricuspid regurgitation systolic gradient of 40 mm Hg was reported.
- Repeated biomarkers were negative.

Questions

- Cath or no cath?
- If yes – when –
  - Immediately?
  - On the Saturday morning?
  - Wait till Sunday.

ECG Findings

ST-segment shifts and T wave changes are the ECG indicators NSTE-ACS

ST-segment depression ≥ 0.5 mm in the appropriate clinical context, is suggestive of NSTE-ACS and linked to prognosis.

Minor (0.5mm) ST depression may be difficult to measure

More relevant is ST depression of ≥ 1mm (0.1 mV) which is associated with an 11% rate of death and MI at 1 year.

ST depression of ≥ 2mm carries about a 6 fold higher mortality risk.

ST depression combined with transient ST elevation also identifies a high risk subgroup.

- **Deep inversion of the T-waves in the anterior chest leads is often related to a significant stenosis of the proximal LAD or MS**

A normal ECG does not exclude the possibility of NSTE-ACS.

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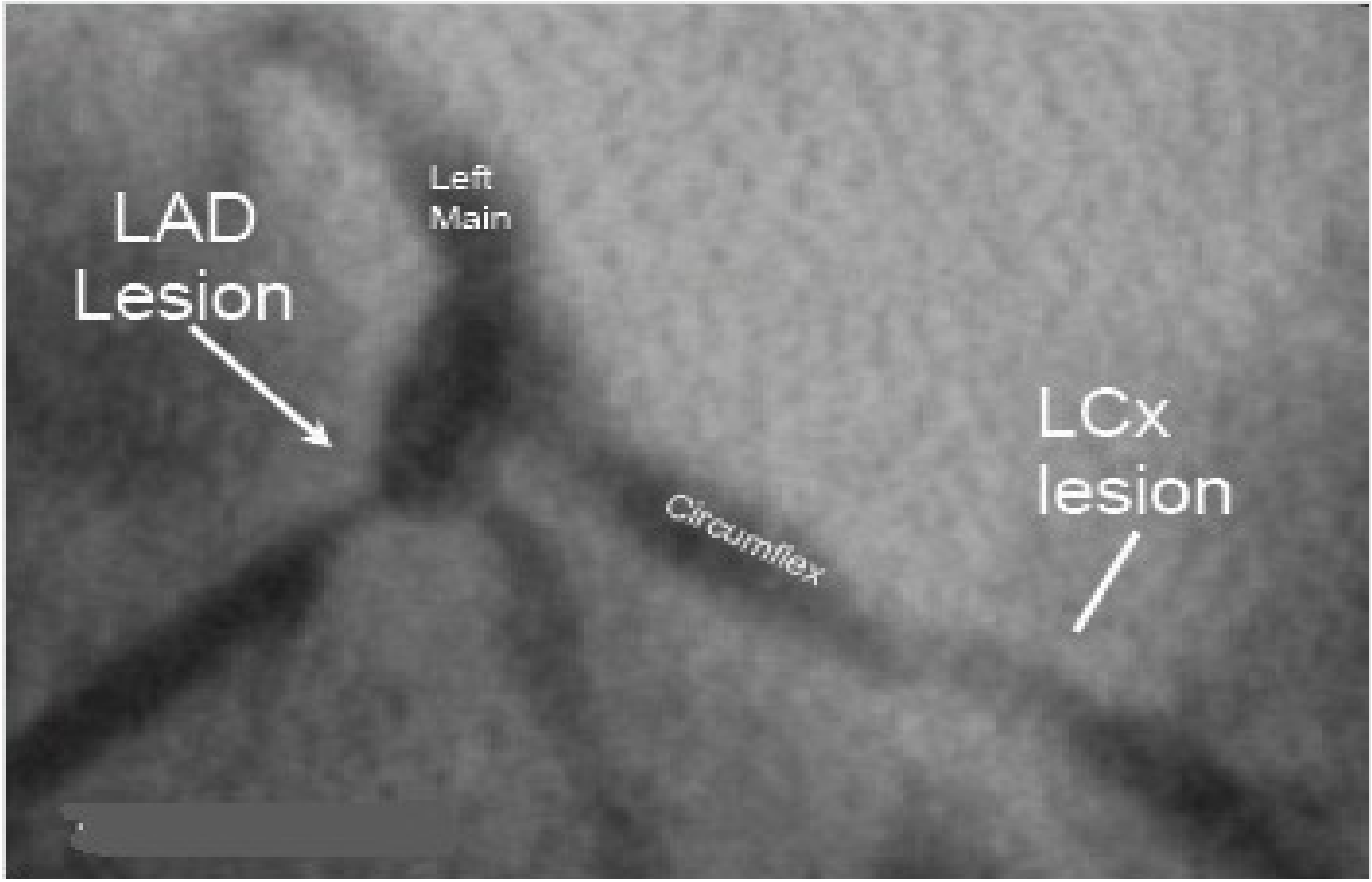
- **Deep inversion of the T-waves in the anterior chest leads is often related to a significant stenosis of the proximal LAD or MS**

A normal ECG does not exclude the possibility of NSTE-ACS.

The patient is diabetic

Coronary angiography



Timing of Intervention

- Few studies have shown superiority of very early intervention vs deferred intervention.
  - ISAR-COOL (small sample size) *JAMA 2003;290:1593*
- Many trials, registries and meta-analysis have shown early hazard with early intervention vs deferred intervention
  - ICTUS trial *NEJM 2005;353:1095*
  - Mehta Meta-analysis *JAMA 2005;293:2908*
  - GRACE & CRUSADE registries *Heart 2007;93:177* *Arch Intern Med 2006;166:2027*

3. Timing of intervention recommended on the basis of risk stratification

Pharmacological Environment of PCI

- Loading dose of clopidogrel
  - 300 vs 600mg
  - pre-treatment vs no pre-treatment

2. Anti-coagulants in the cathlab
   - UFH
   - Bivalirudin
   - Enoxaparin if started in the ward (no cross-over)
   - Fondaparinux cannot be used stand-alone
- Triple antiplatelet therapy
  - Recommended on the basis of ISAR-REACT-2

    JAMA 2006;295:1531

Management

- Eptifibatide bolus was given and LAD and LCX lesions underwent PCI with DES – Cypher in LAD and Endeavor in LCX were placed.
- The patient was discharged on the next day to home.

Your recommendations

- Treatment on discharge
  - How long plavix?
  - How long aspirin?
    - Any dose changes in future?
  - Any change in his antidiabetic regimen?
  - What is the goal of Hba1C?
  - What is the LDL-C goal?
  - What is the BP goal?
  - When back to workplace?

Your recommendations

- Treatment on discharge
  - Plavix 75mgx1 for at least one year
  - Aspirin 100mgx1 for life
    - ACC/AHA guidelines recommend 325mg for 3 months and than 100mg for life
  - Metformin can be safely re-administered if no renal deterioration was observed after 48 hours
  - Atenolol 25mgx1
  - Enaladex 20mgx1
  - Simovil 40mgx1
  - LDL-C goal less than 70 for the first year at least.
  - HBA1C goal - <7.0 or < 6.5 (ACC/AHA vs ESC)
  - Return to workplace after 10-14 days (if engaged in heavy physical activity – exercise testing is advisable before)