ESC Guidelines for the Management of Non-ST Segment Elevation Acute Coronary Syndromes

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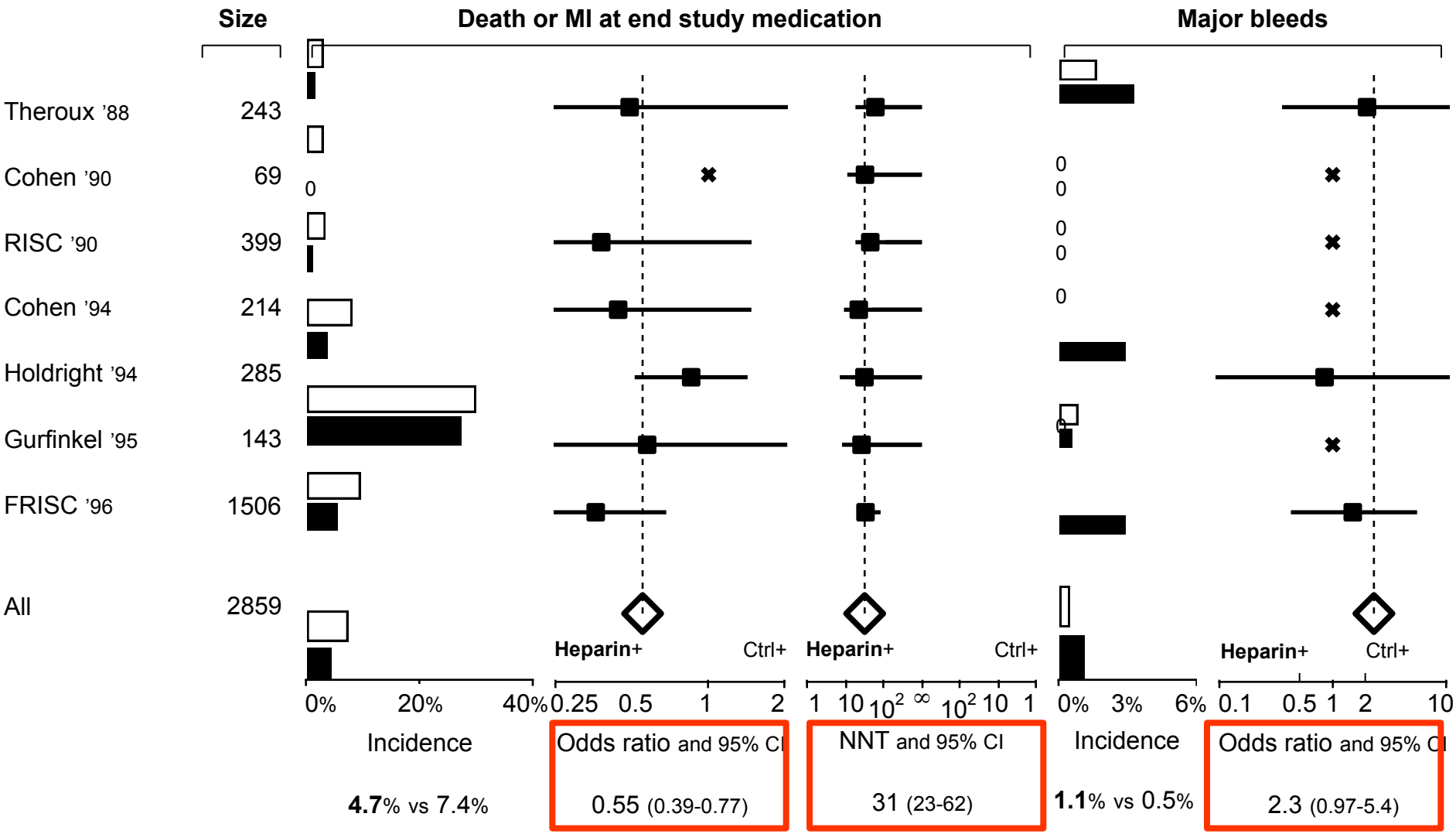
Eur Heart J 2007;28(13):1598-660

Methods

1- Cost/benefit and cost/risk ratios in the terms of
  - Number Needed to Treat

2 - Class III re-introduced in the level of recommendations
  - Class III = contra-indication (it goes without saying, but it's better to say it !)

Randomized trials of UFH/LMWH (dark bars) vs Control (open bars)



Methods

1- Cost/benefit and cost/risk ratios in the form of
  - Number Needed to Treat

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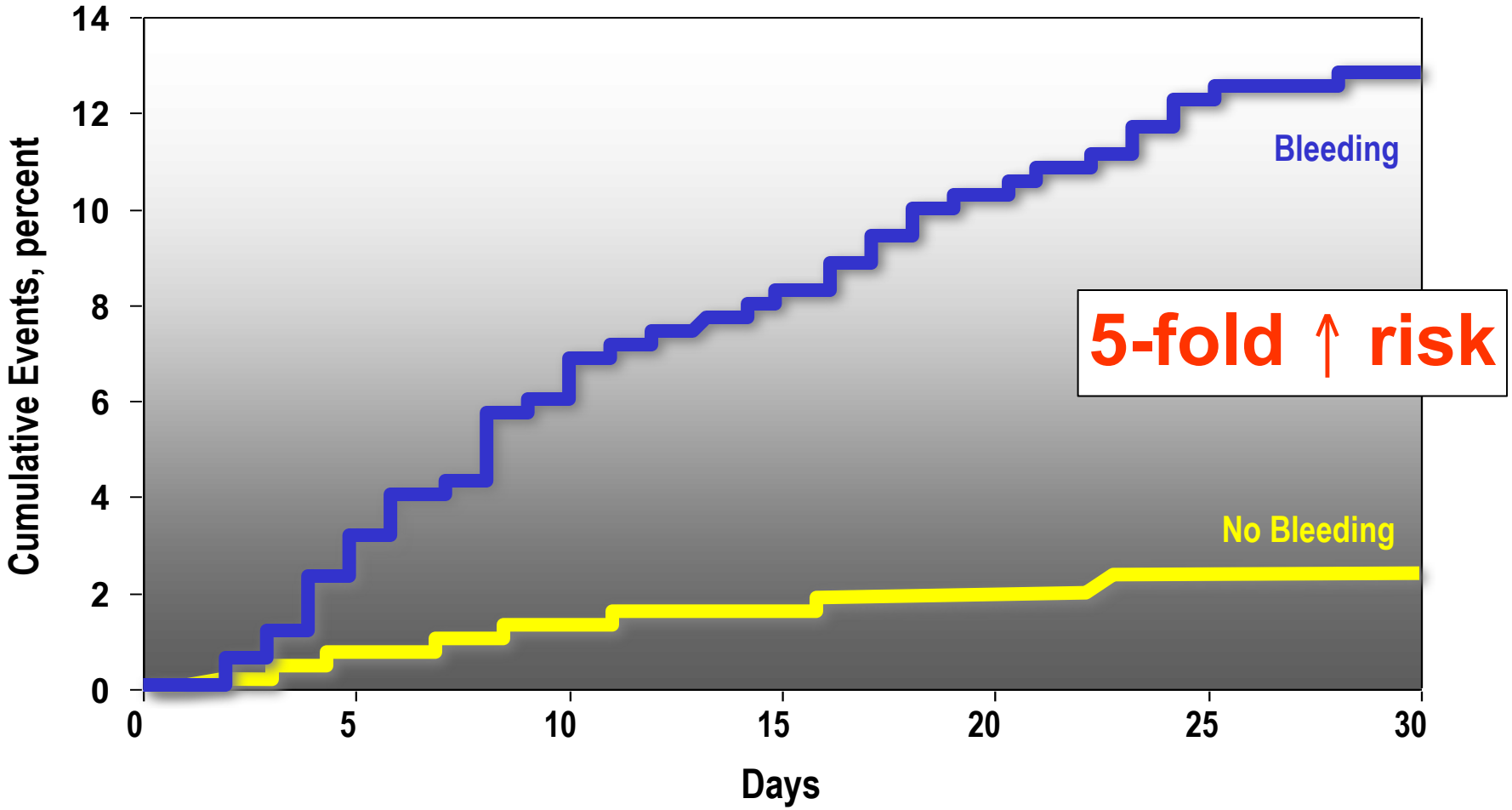
Methods

3- Quality level of trials taken into account

- Double blind, randomised design
- Use of hard endpoints in the primary endpoint
  - death and MI
  - death / MI / stroke and bleeding as net clinical benefit
- Adequate sample size calculations
- Contemporary adjunctive treatments (stents, clopidogrel, IIb/IIIa inhibitors…)

4- Efficacy / safety profile of drugs / treatments taken into account for the gradation of recommendations

30 Day Death According to Bleeding
OASIS Registry, OASIS-2, CURE



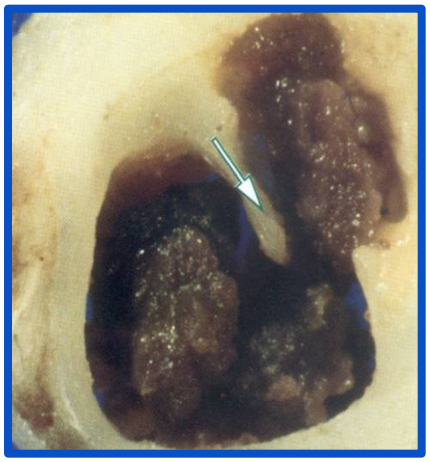
Eikelboom Circulation 2006;114: 774 - 782

A New Concept is Born

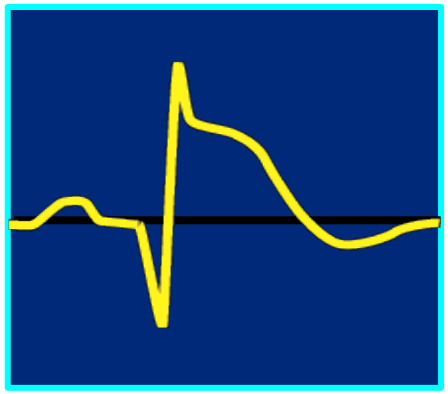
1. Bleeding carries a high risk of death, MI and stroke
2. Rate of major bleeding is as high as the rate of death at the acute phase of NSTE-ACS
3. Prevention of bleeding is equally as important as prevention of ischemic events and results in a significant risk reduction for death, MI and stroke
4. Risk stratification for bleeding should be part of the decision making process

Pathophysiology

ACS with persistent ST-segment elevation

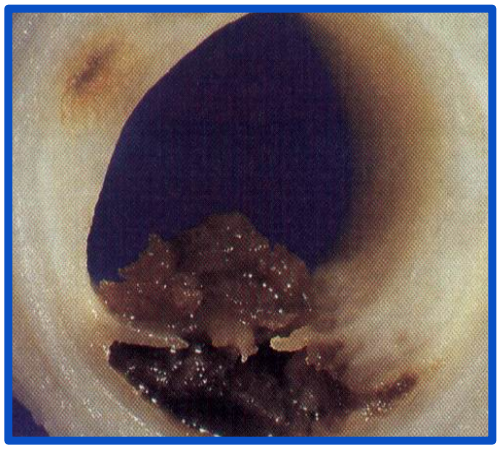


Adapted from Michael Davies



Troponin elevated

ACS without persistent ST-segment elevation



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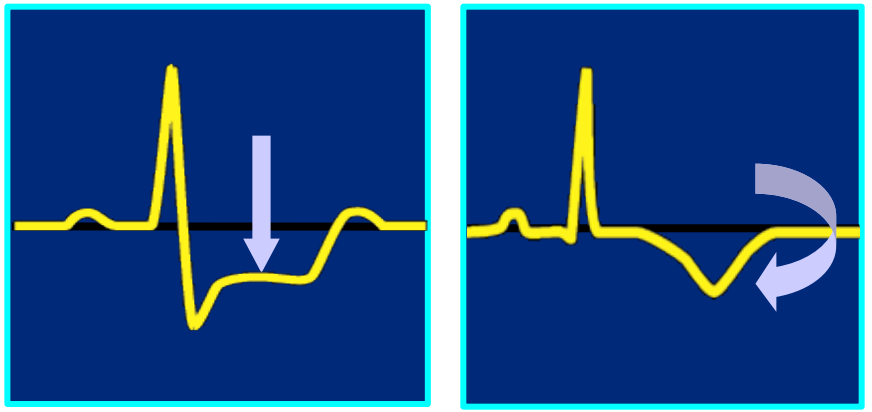
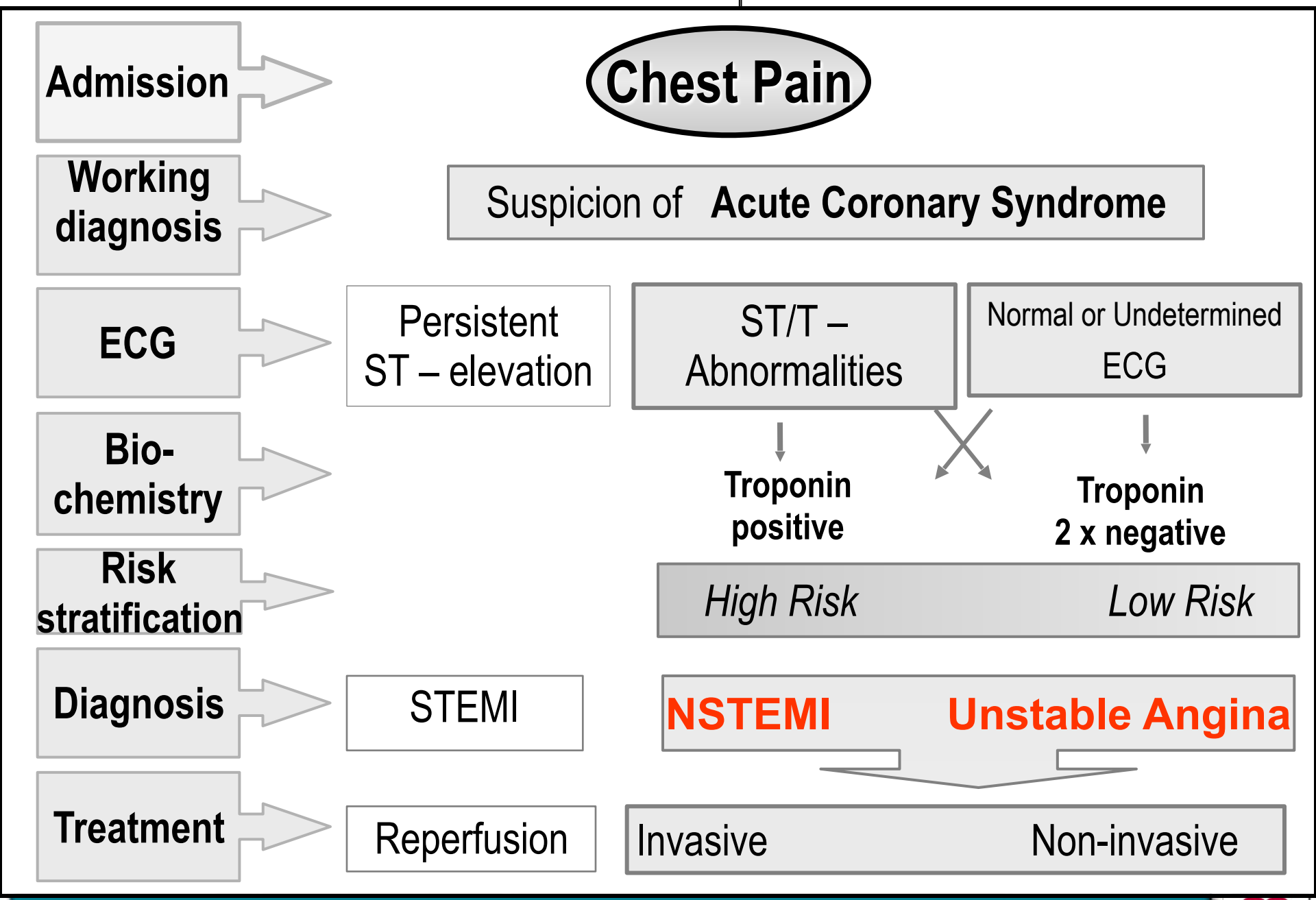


Troponins elevated or not

Diagnosis & Risk Assessment



Therapeutic Options

- Anti-ischaemic agents
- Anti-coagulants
  - UFH or LMWHs
  - Fondaparinux
  - Bivalirudin
- Anti-platelet agents
  - ASA
  - Clopidogrel
  - IIbIIIa Inhibitors
- Revascularisation

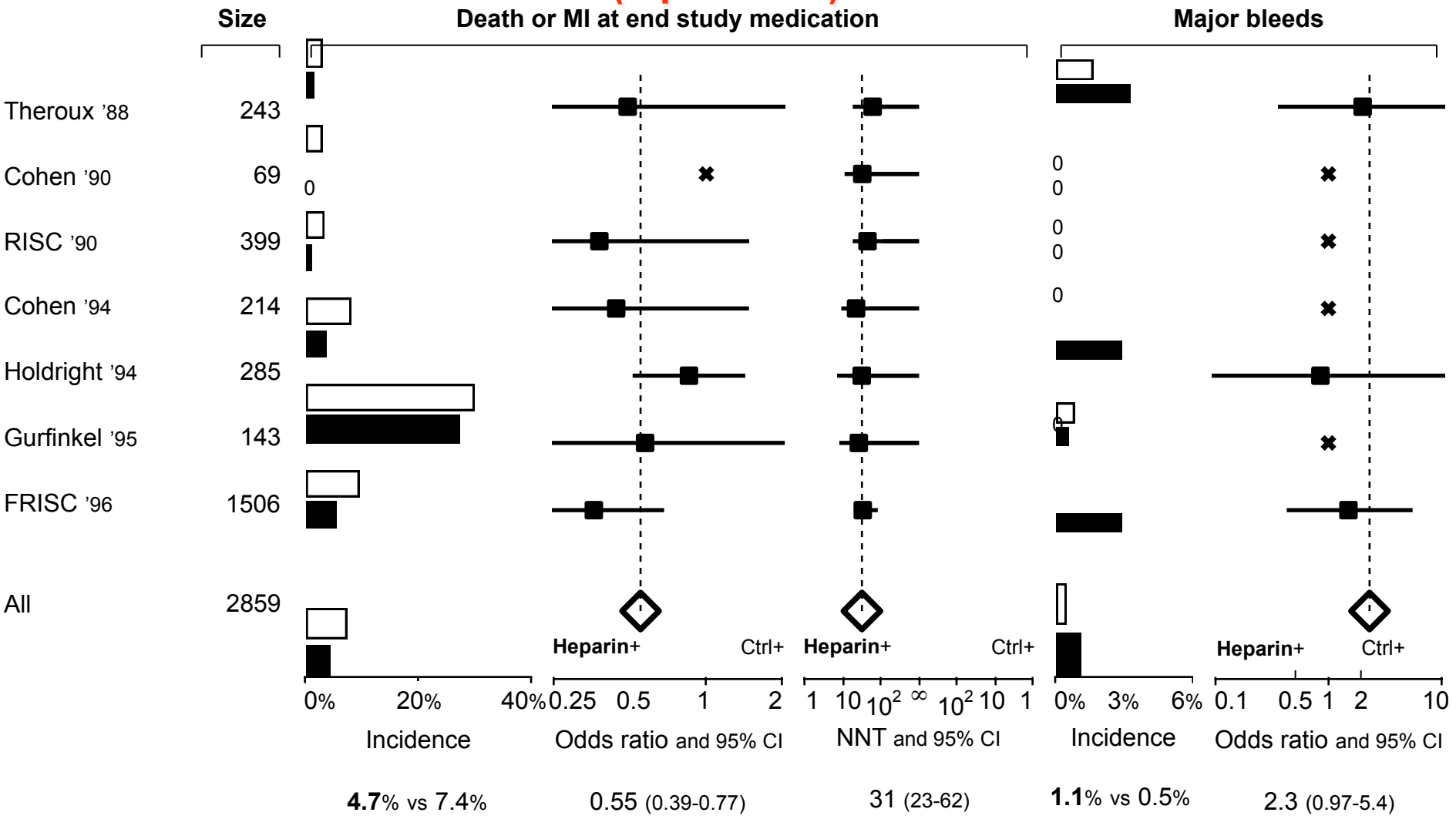
Recommendations for Anti-ischaemic Drugs

- Beta-blockers are recommended in the absence of contraindications, particularly in patients with hypertension or tachycardia (I-B).
- Intravenous or oral nitrates are effective for symptom relief in the acute management of anginal episodes (I-C).
- Calcium channel blockers provide symptom relief in patients already receiving nitrates and beta-blockers; they are useful in patients with contraindications to beta-blockade, and in the subgroup of patients with vaso-spastic angina (I-B).
- Nifedipine, or other dihydropyridines, should not be used (III-B), unless combined with beta-blockers (IIa-B)

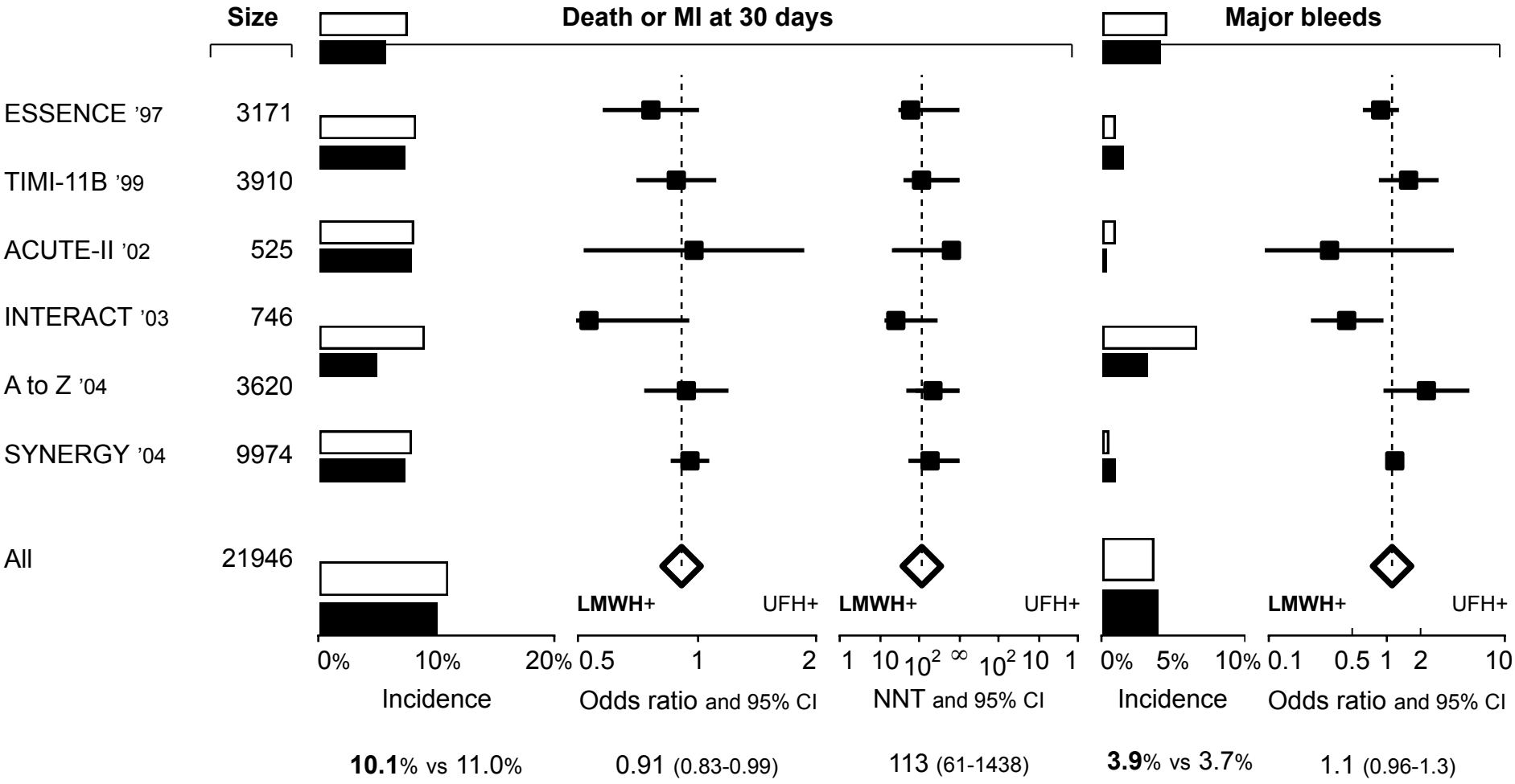
Anticoagulants – New Comers

- **Fondaparinux**
  - Unequivocal benefit over enoxaparin
  - Significant RR of both bleeding and ischaemic risks
  - Closes the loop – Shift in the paradigm
  - Catheter thrombi issue
  - Bleeding risk issue with UFH 'on top' of fonda. in PCI patients
- **Bivalirudin**
  - Not double blind trial
  - Non inferiority margin issue
  - Biased comparison of the different regimens
  - No impact of bleeding risk reduction on outcome at short and long term FU

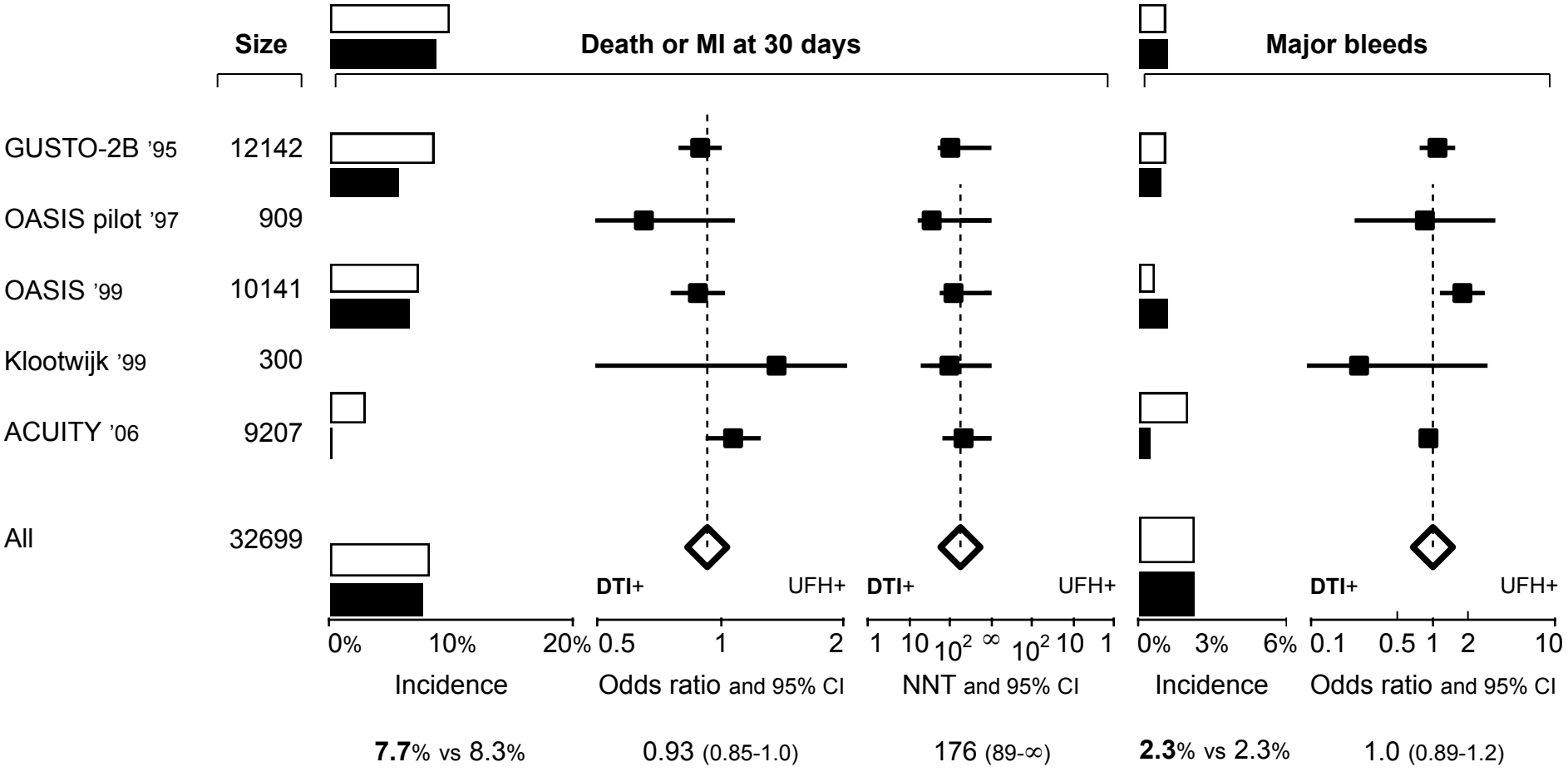
Randomized trials of UFH/LMWH (dark bars) vs Control (open bars)



Randomized trials
Enoxaparin (dark bars) vs UFH (open bars)



Randomized trials
Direct thrombin inhibitors (DTIs) (dark bars) vs UFH/LMWH (open bars)



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 (I-B) (see section Management Strategy).
- 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

- Loading dose 600mg vs 300mg clopidogrel : unsettled issue
- New ADP receptor antagonists under development (TRITON, PLATO, CHAMPION: 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).

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)

Recommendations for GP IIb/IIIa Inhibitors (2)

- In high risk patients not pretreated with GP IIb/IIIa inhibitors and proceeding to PCI, abciximab is recommended immediately following angiography. (I-A) The use of eptifibatide or tirofiban in this setting is less well established (IIa-B).
- GP IIb/IIIa inhibitors must be combined with an anticoagulant (I-A).
- Bivalirudin may be used as an alternative to GP IIb/IIIa inhibitors plus UFH/LMWH. (IIa-B)
- When anatomy is known and PCI planned to be performed within 24 hours with GP IIb/IIIa inhibitors, most secure evidence is for abciximab (IIa-B)

Treatment

Coronary revascularisation

Invasive vs. Conservative Strategies

1. New data coming from long-term follow-up of RITA-3, FRISC-2 and Mehta meta-analysis show significant risk reduction for death and death & MI at long-term follow-up
2. Early hazard shown in ICTUS trial (excess of death & MI observed within 1st month after revascularisation in immediate invasive group)
3. Early hazard shown in Mehta meta-analysis

ICTUS Lancet 2007;369:827
RITA-3 Lancet 2005;366:914
FRISC 2 Lancet 2000;356:9-16
Mehta JAMA 2005:293:2908

Timing of Intervention

1. Few studies have shown superiority of very early intervention vs deferred intervention.
   - ISAR-COOL (small sample size) *JAMA 2003;290:1593*
2. 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*
3. Timing of intervention recommended on the basis of risk stratification *Arch Intern Med 2006;166:2027*

Pharmacological Environment of PCI

1. 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
3. Triple antiplatelet therapy
   - Recommended on the basis of ISAR-REACT-2

JAMA 2006;295:1531

Recommendations for invasive evaluation and revascularisation (1)

- Urgent coronary angiography is recommended in patients with refractory or recurrent angina associated with dynamic ST deviation, heart failure, life threatening arrhythmias or haemodynamic instability (I - C).

- Early (< 72 hours) coronary angiography followed by revascularisation (PCI or CABG) in patients with intermediate to high-risk features is recommended (I - A).

- Routine invasive evaluation of patients without intermediate to high risk features is not recommended (III-C), but non-invasive assessment of inducible ischaemia is advised (I - C).

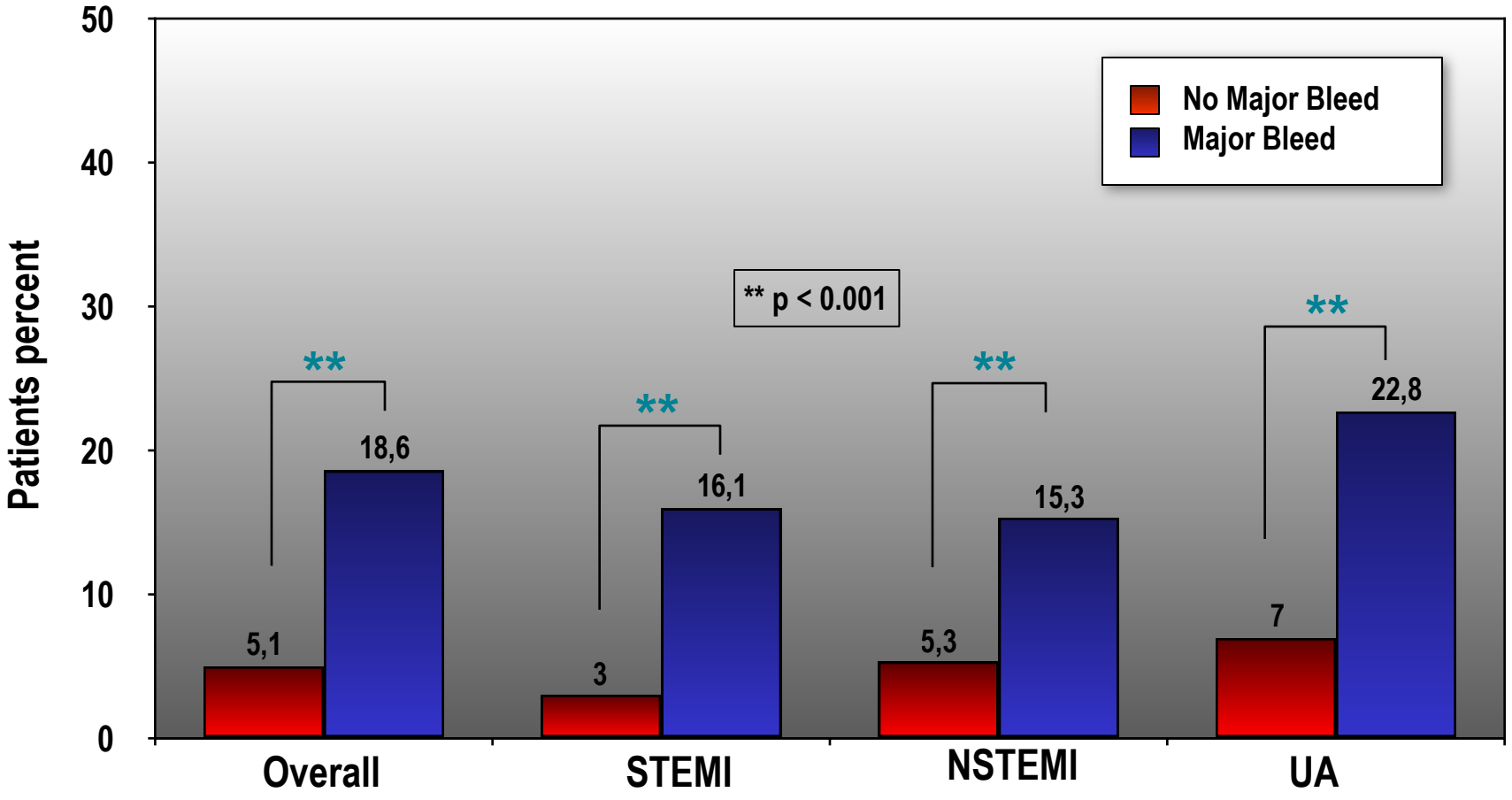
Recommendations for invasive evaluation and revascularisation (2)

- PCI of non-significant lesions by angiography is not recommended (III - C).

- After critical evaluation of the risk to benefit ratio, and depending on known co-morbidities and potential need for non-cardiac surgery in the short/ medium term (e.g. planned intervention or other conditions) requiring temporary withdrawal of dual antiplatelet therapy, consideration should be given to the type of stent to be implanted (BMS or DES) (I-C).

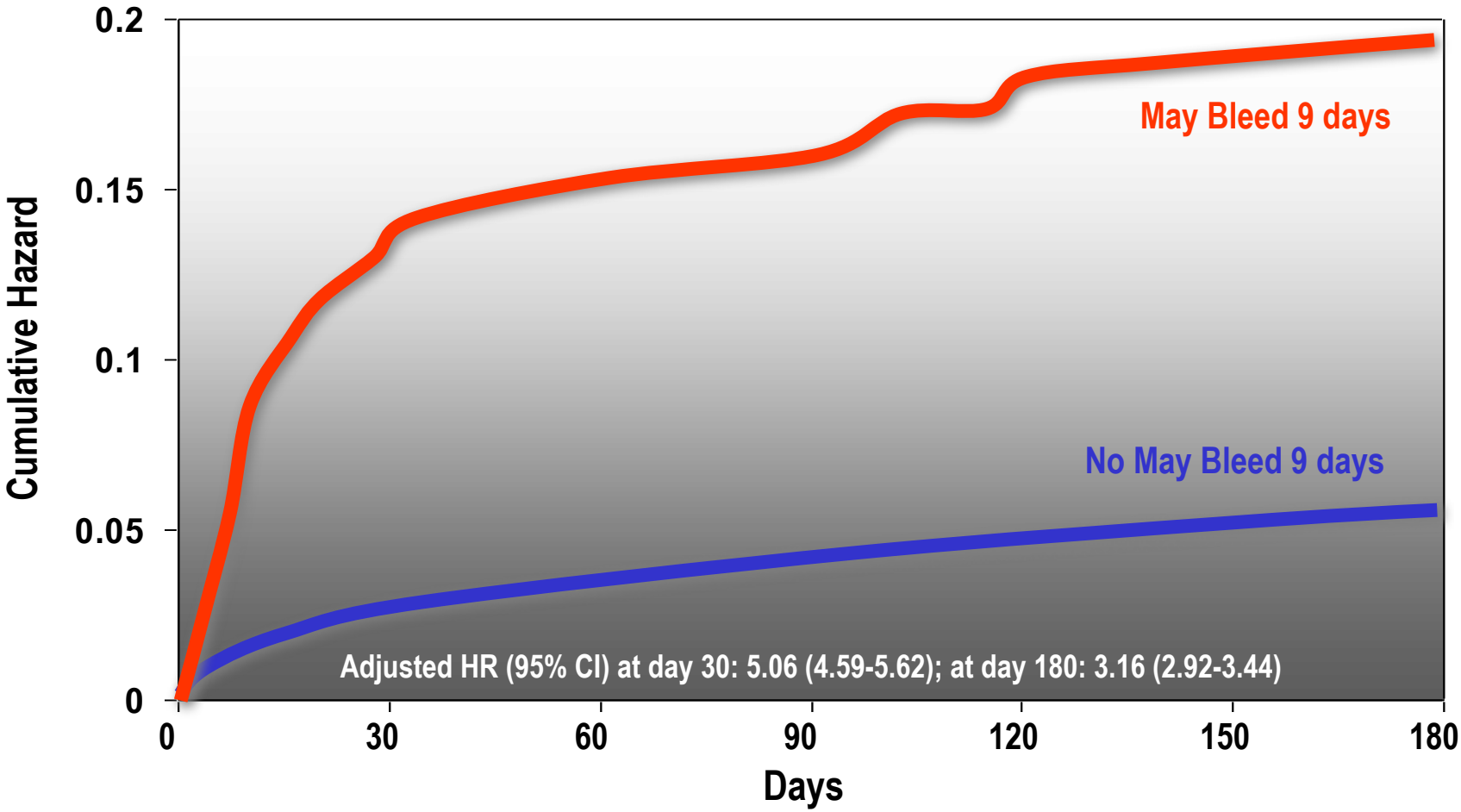
Complications and their management
Bleeding
Thrombocytopenia

In-Hospital Death Rates in Patients According to Major Bleeding



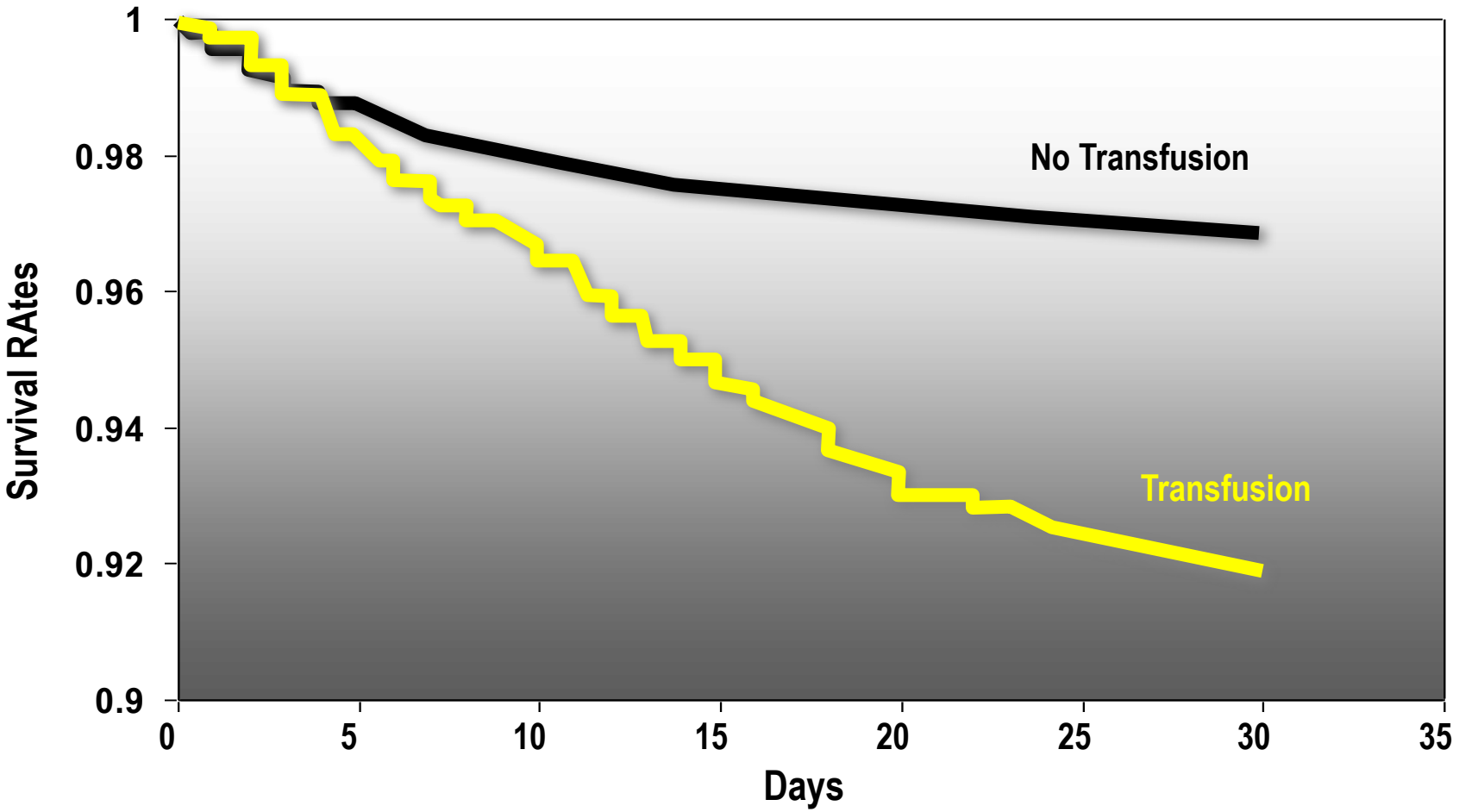
Moscucci M et al. Eur Heart J 2003;24:1815-23.

Increased Mortality at Days 30/180 in Patients with Major Bleeds by Day 9 in OASIS 5



Budaj et al. JACC 2006;abstract 972-224

30 Day Survival by Transfusion Group
GUSTO IIb, PURSUIT, PARAGON B
(n=24,000 10% transfused)



Rao SV, JAMA 2004;292:1555

Recommendations for Bleeding Complications (1)

- Assessment of bleeding risk is an important component of the decision making process. Bleeding risk is increased with higher or excessive doses of anti-thrombotic agents, length of treatment, combinations of several anti-thrombotic drugs, switch between different anticoagulant drugs, as well as with older age, reduced renal function, low body weight, female gender, baseline haemoglobin and invasive procedures (I-B).

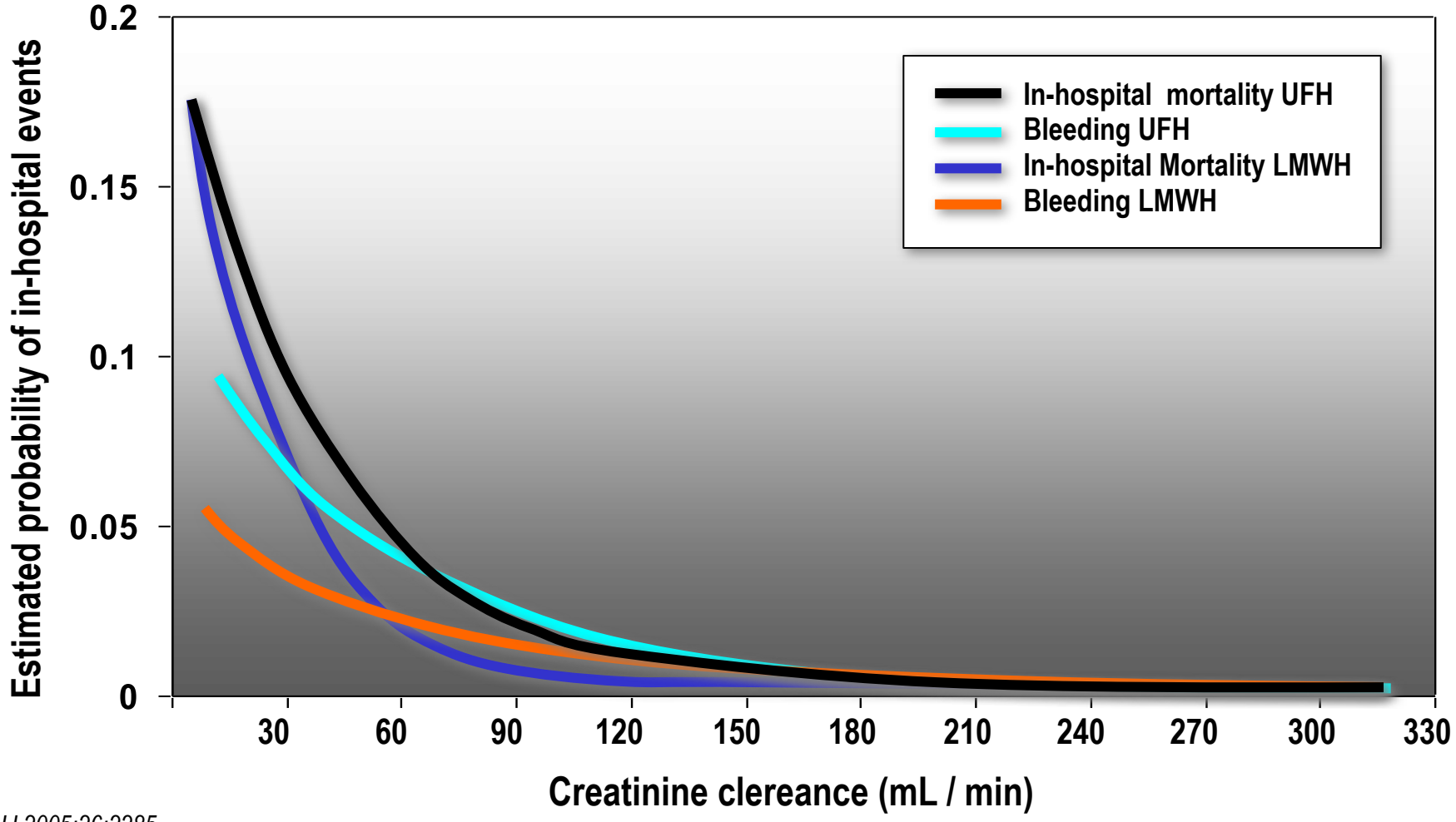
- Bleeding risk should be taken into account when deciding for a treatment strategy. Drugs, combination of drugs and non-pharmacological procedures (vascular access) known to carry a reduced risk of bleeding should be preferred in patients at high risk of bleeding (I-B)

Recommendations for Bleeding Complications (2)

- Minor bleeding should preferably be managed without interruption of active treatments (I-C).
- Major bleeding requires interruption and/or neutralisation of both anticoagulant and antiplatelet therapy, unless bleeding can be adequately controlled by specific haemostatic intervention (I-C).
- Blood transfusion may have deleterious effects on outcome, and should therefore be considered individually, but withheld in haemodynamically stable patients with haematocrit >25% or haemoglobin level > 8g/L (I-C).

Special Conditions & Populations
Chronic Kidney Disease

In-hospital Mortality or Bleeding According to the Level of CrCl in Patients Treated with UFH or LMWH



EHJ 2005;26:2285

Recommendations for Patients with CKD (1)

- CrCl and/or GFR should be calculated for every patient hospitalised for NSTE-ACS (I-B). Elderly people, women and low body weight patients merit special attention as near normal serum creatinine levels may be associated with lower than expected CrCl and GFR levels (I-B).

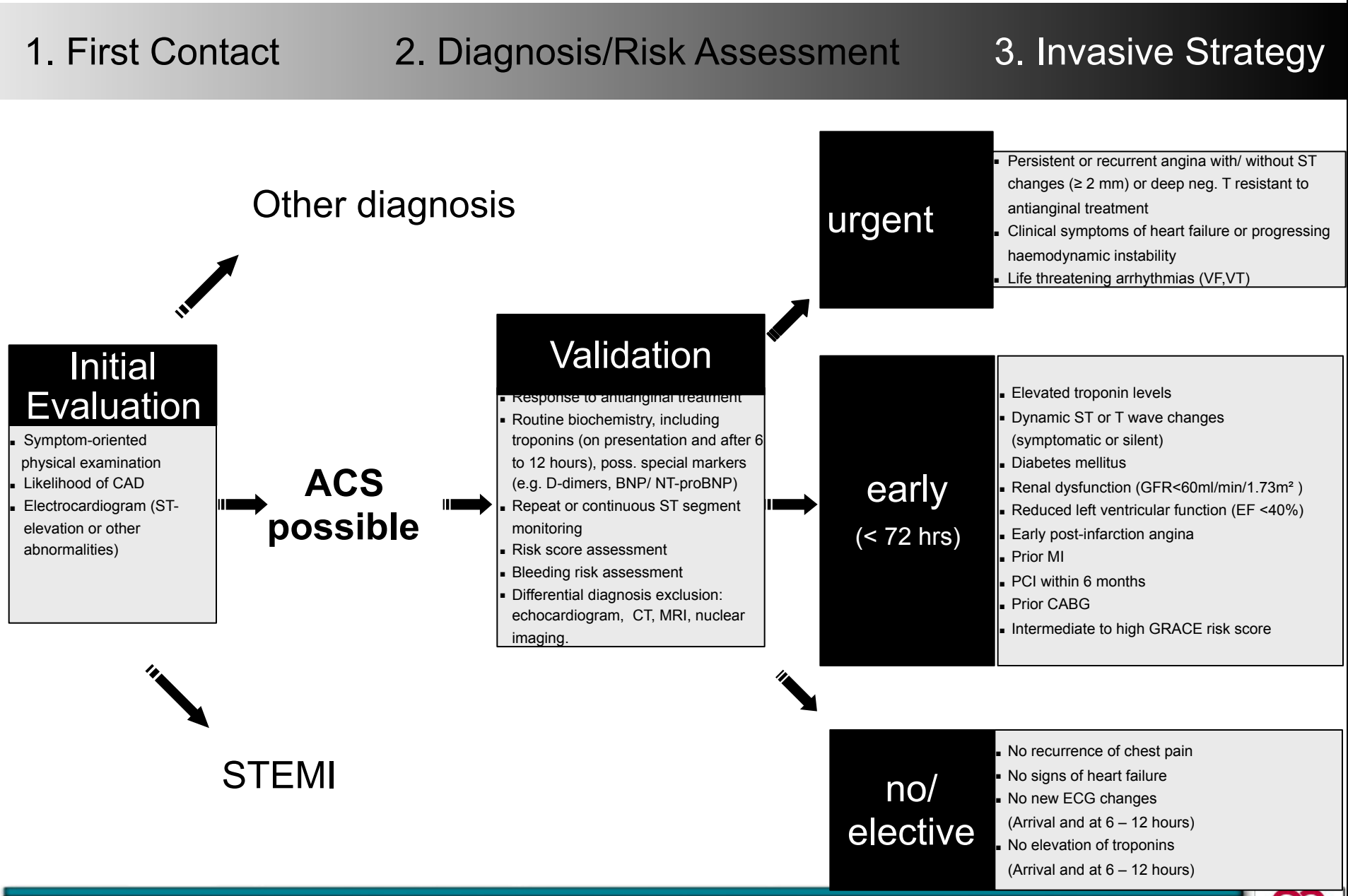
- Patients with CKD should receive the same first-line treatment as any other patient, in the absence of contra-indications (I-B).

- In patients with CrCl < 30ml/min or GFR <30ml/min/1.73m^2, a careful approach to the use of anticoagulants is recommended, since dose adjustment is necessary with some, while others are contraindicated. (I-C)

Recommendations for Patients with CKD (2)

- UFH infusion adjusted according to aPTT is recommended when CrCl < 30ml/min or GFR <30ml/min/1.73m² (I-C).
- GP IIb/IIIa inhibitors can be used in case of renal failure. Dose adaptation is needed with eptifibatide and tirofiban. Careful evaluation of the bleeding risk is recommended for abciximab (I-B).
- Patients with CKD with CrCl < 60 ml/min are at high risk of further ischaemic events and therefore should be submitted to invasive evaluation and revascularisation whenever possible (IIa-B).
- Appropriate measures are advised to reduce the risk of contrast induced nephropathy (I-B).

Management Strategy


1. First Contact
2. Diagnosis/Risk Assessment
3. Invasive Strategy
Other diagnosis
Initial Evaluation
Symptom-oriented physical examination
Likelihood of CAD
Electrocardiogram (ST-elevation or other abnormalities)
ACS possible
Validation
Response to antianginal treatment
Routine biochemistry, including troponins (on presentation and after 6 to 12 hours), poss. special markers (e.g. D-dimers, BNP/ NT-proBNP)
Repeat or continuous ST segment monitoring
Risk score assessment
Bleeding risk assessment
Differential diagnosis exclusion: echocardiogram, CT, MRI, nuclear imaging.
urgent
Persistent or recurrent angina with/ without ST changes (≥ 2 mm) or deep neg. T resistant to antianginal treatment
Clinical symptoms of heart failure or progressing haemodynamic instability
Life threatening arrhythmias (VF,VT)
early
(< 72 hrs)
Elevated troponin levels
Dynamic ST or T wave changes (symptomatic or silent)
Diabetes mellitus
Renal dysfunction (GFR<60ml/min/1.73m²)
Reduced left ventricular function (EF <40%)
Early post-infarction angina
Prior MI
PCI within 6 months
Prior CABG
Intermediate to high GRACE risk score
STEMI
no/ elective
No recurrence of chest pain
No signs of heart failure
No new ECG changes (Arrival and at 6 – 12 hours)
No elevation of troponins (Arrival and at 6 – 12 hours)
ESC Guidelines for the Management of NSTE-ACS ()
EUROPEAN SOCIETY OF CARDIOLOGY