The protection dilemma for patients with an acute coronary event : how do current anticoagulation and antiplatelet therapies address it?

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Disclosures

- Aspen, AstraZeneca, Bayer, BMS/Pfizer: lecture fees

ESC Guidelines

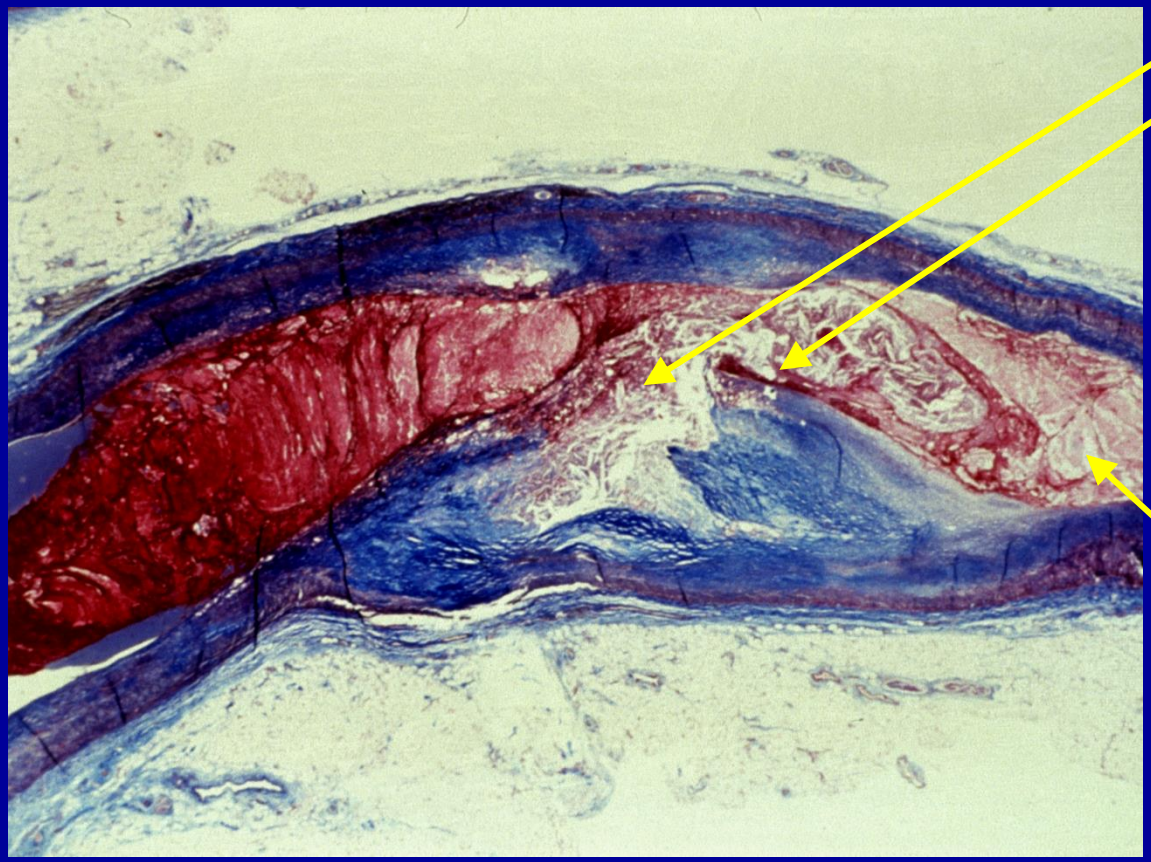
Interventional cardiologist working in a high volume PCI centre

ESC = European Society of Cardiology; PCI = percutaneous coronary intervention

DENMARK

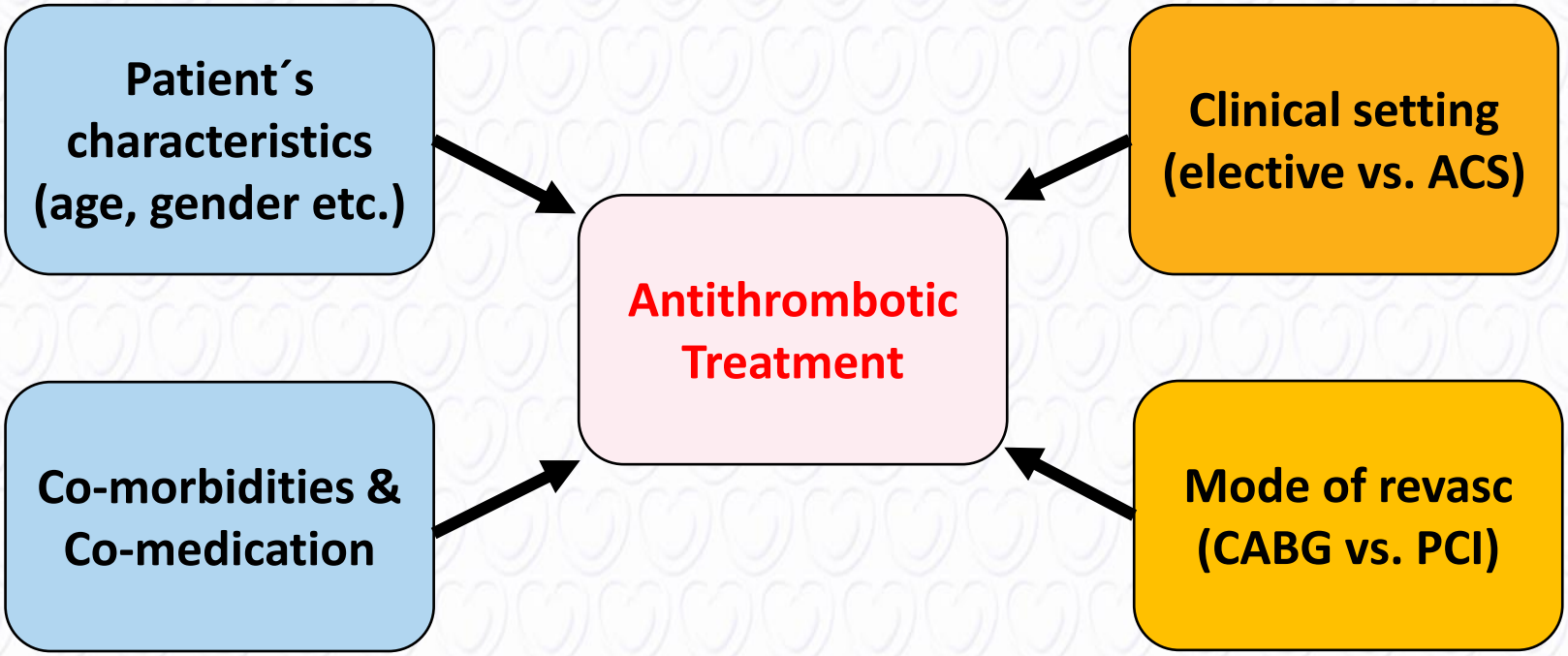
- 5.5 mill inhabitants
- 44000 square km
- 4 Primary PCI centres

Acute MI: coronary thrombus



Kristensen SD. Personal communication;
Falk E, *et al. Br Heart J* 1983; **50**:127–34;
Falk E, *et al. Circulation* 1985; **71**:699–708.

Preamble



- **Choice of treatment should balance ischemic and bleeding risk!**

2018 ESC/EACTS Guidelines on myocardial revascularisation
European Heart Journal (2018) 00, 1-96 - doi:10.1093/eurheartj/ehy394

Antithrombotic therapy in ACS

Risk factors ischaemic events

Risk factors for bleeding

ACS = acute coronary syndromes.

Kristensen SD. Personal communication.

Antithrombotics

Antiplatelets

- Aspirin
- $P2Y_{12}$ inhibitors
  - Clopidogrel
  - Prasugrel
  - Ticagrelor
  - Cangrelor
- GP IIb/IIIa
  - Abciximab
  - Eptifibatide
  - Tirofiban

PAR-1: vorapaxar

Antithrombins

- Heparin
- LMWH
  - Dalteparin
  - Enoxaparin
  - Nadroparin
- Pentasaccharide
  - Fondaparinux
- DTI
  - Lepirudin
  - Bivalirudin
  - Argatroban
  - Dabigatran

DTI = direct thrombin inhibitors; GP = glycoprotein;
LMWH = low molecular weight heparin; PAR-1 = protease-activated receptor-1.

Kristensen SD. Personal communication.

STEMI/NSTEMI PCI

Anticoagulation

NSTEMI = non-ST-segment elevation myocardial infarction;
PCI = percutaneous coronary intervention;
STEMI = ST-elevation myocardial infarction.

2007: A new concept is born

1. **Bleeding carries a high risk of death, MI and stroke**
2. **Prevention of bleeding is equally as important as prevention of ischaemic events**
3. **Risk stratification for bleeding should be part of the decision-making process**

MI = myocardial infarction;
NSTE-ACS = non-ST-segment elevation acute coronary syndromes.

Bassand JP, *et al. Eur Heart J* 2007; **28**:1598–1660.

NSTEMI: Recommendations for anticoagulants

1. **Anticoagulation should be tailored according to the risk of bleeding (I-A)**
2. **Recommendations for the use of anticoagulants: choice between 4:**
   - **Bivalirudin**
   - **Enoxaparin**
   - **Fondaparinux**
   - **UFH**

   depends on initial strategy (conservative vs early invasive) and on bleeding risk

UFH = unfractionated heparin.

Anderson JL, *et al. Circulation* 2007; **116**:e148–e304;
Bassand JP, *et al. Eur Heart J* 2007; **28**:1598–1660.

ACCF/AHA ACS Guidelines

2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention

A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions

2012 ACCF/AHA Focused Update of the Guideline for the Management of Patients With Unstable Angina/ Non–ST-Elevation Myocardial Infarction (Updating the 2007 Guideline and Replacing the 2011 Focused Update)

A Report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines

2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction

A Report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines

ACCF = American College of Cardiology Foundation;
AHA = American Heart Association;
SCAI = Society for Cardiovascular Angiography and Interventions.

Levine G, *et al. J Am Coll Cardiol* 2011; **58**:e44–122;
Jneid H, *et al. J Am Coll Cardiol* 2012; **60**:645–681;
O'Gara PT, *et al. J Am Coll Cardiol* 2013; **61**:e78–140.

2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC)

Authors/Task Force Members: Marco Roffi* (Chairperson) (Switzerland), Carlo Patrono* (Co-Chairperson) (Italy), Jean-Philippe Collet† (France), Christian Mueller† (Switzerland), Marco Valgimigli† (The Netherlands), Felicita Andreotti (Italy), Jeroen J. Bax (The Netherlands), Michael A. Borger (Germany), Carlos Brotons (Spain), Derek P. Chew (Australia), Baris Gencer (Switzerland), Gerd Hasenfuss (Germany), Keld Kjeldsen (Denmark), Patrizio Lancellotti (Belgium), Ulf Landmesser (Germany), Julinda Mehilli (Germany), Debabrata Mukherjee (USA), Robert F. Storey (UK), and Stephan Windecker (Switzerland)

ESC Committee for Practice Guidelines,
Review Coordinators, Reviewers, ESC staff
Roffi M, *et al. Eur Heart J* 2015; ePub ahead of print

EUROPEAN SOCIETY OF CARDIOLOGY®

Selection of NSTE-ACS treatment strategy and timing according to initial risk stratification

(2011: primary/
secondary high-risk criteria)

Ongoing ischaemia

↓

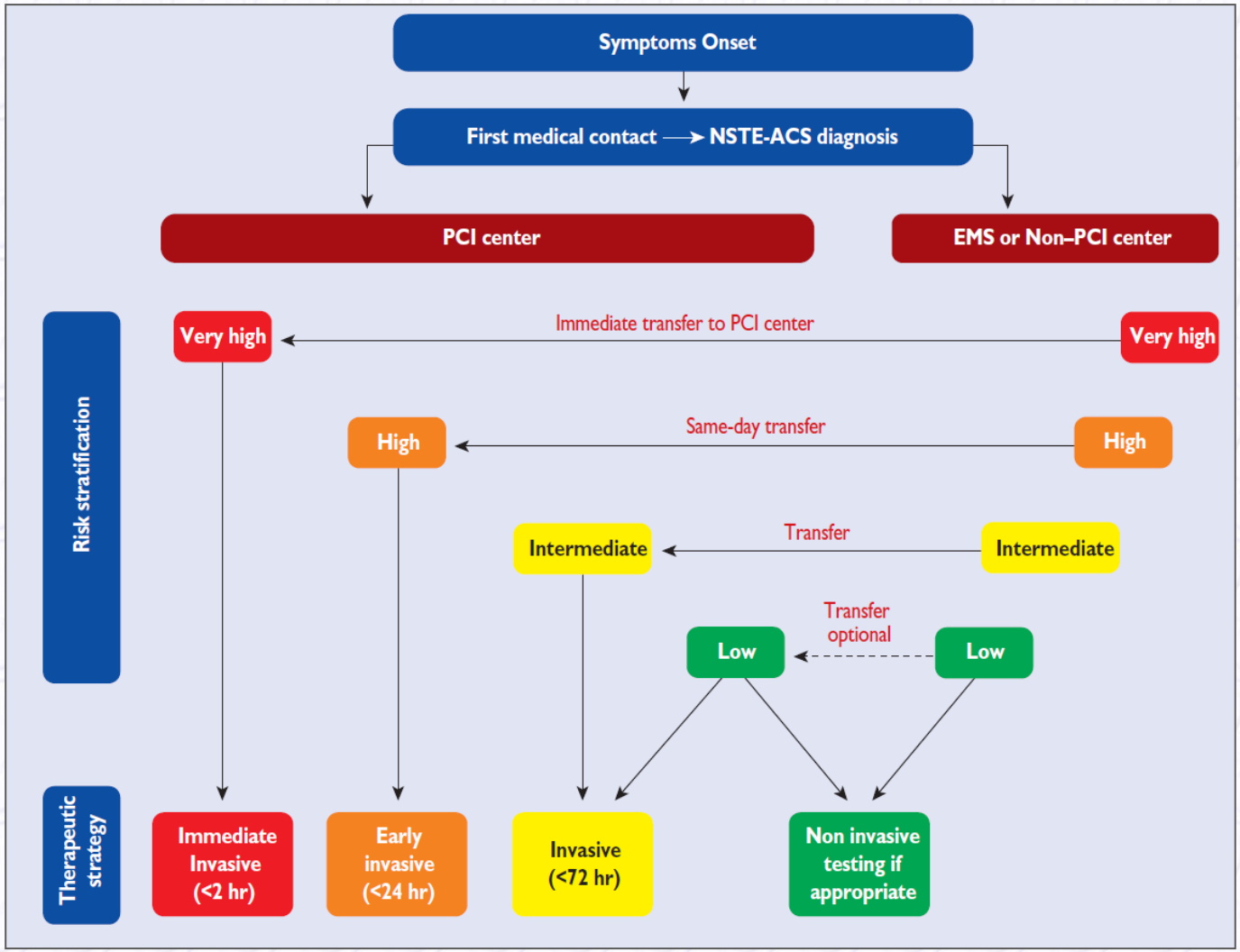
Immediate action

Very-high-risk criteria
• Haemodynamic instability or cardiogenic shock
• Recurrent or ongoing chest pain refractory to medical treatment
• Life-threatening arrhythmias or cardiac arrest
• Mechanical complications of MI
• Acute heart failure
• Recurrent dynamic ST-T wave changes, particularly with intermittent ST-elevation
High-risk criteria
• Rise or fall in cardiac troponin compatible with MI
• Dynamic ST- or T-wave changes (symptomatic or silent)
• GRACE score >140
Intermediate-risk criteria
• Diabetes mellitus
• Renal insufficiency (eGFR <60 mL/min/1.73 m²)
• LVEF <40% or congestive heart failure
• Early post-infarction angina
• Prior PCI
• Prior CABG
• GRACE risk score >109 and <140
Low-risk criteria
• Any characteristics not mentioned above

Roffi M, et al. Eur Heart J 2015; Epub ahead of print.

CABG = coronary artery bypass graft; eGFR = estimated glomerular flow rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndromes; PCI = percutaneous coronary intervention.

Selection of NSTE-ACS treatment strategy and timing according to initial risk stratification



Roffi M, *et al. Eur Heart J* 2015; Epub ahead of print.

Mortality in hospital and at 6 months according to the GRACE risk score

Risk category (tertile)	GRACE risk score	In-hospital death (%)
Low	≤ 108	< 1
Intermediate	109-140	1-3
High	> 140	> 3
Risk category (tertile)	**GRACE risk score**	**Post- discharge to 6-month death (%)**
Low	≤ 88	< 3
Intermediate	89-118	3-8
High	> 118	> 8

Hamm C, *et al. Eur Heart J* 2011; 32:2999–3054.

CRUSADE score of in-hospital major bleeding

Predictor	Score
Baseline haematocrit, %	
< 31	9
31-33.9	7
34-36.9	3
37-39.9	2
≥ 40	0
Creatinine clearance, mL/min	
≤ 15	39
> 15-30	35
> 30-60	28
> 60-90	17
> 90-120	7
> 120	0

Predictor	Score
Heart rate (b.p.m.)	
≤ 70	0
71-80	1
81-90	3
91-100	6
101-110	8
111-120	10
≥ 121	11
Male	0
Female	8
Sex	
Male	0
Female	8
Signs of CHF at presentation	
No	0
Yes	7

Predictor	Score
Prior vascular disease	
No	0
Yes	6
Diabetes mellitus	
No	0
Yes	6
Systolic blood pressure, mmHg	
≤ 90	10
91-100	8
101-120	5
121-180	1
181-200	3
≥ 201	5

www.crusadebleedingscore.org

CHF = Congestive Heart Failure

Hamm C, *et al. Eur Heart J* 2011; 32:2999–3054;
b.p.m. = beats per minute; CHF = congestive heart failure.

Recommendations for diagnosis and risk stratification

Recommendations	Class[a]	Level[b]
It is recommended to base the diagnosis and initial short-term ischaemic and bleeding risk stratification on a combination of clinical history, symptoms, vital signs, other physician findings, ECG and laboratory results.	I	A
It is recommended to obtain a 12-lead ECG within 10 min after first medical contact and to have it immediately interpreted by an experienced physician. It is recommended to obtain and additional 12-lead ECG in case of recurrent symptoms or diagnostic uncertainty.	I	B
Additional ECG leads (V_{3R},V_{4R}, V_7–V_9) are recommended if ongoing ischaemia is suspected when standard leads are inconclusive.	I	C
It is recommended to use established risk scores for prognosis estimation.	I	B
The use of the CRUSADE score may be considered in patients undergoing coronary angiography to quantify bleeding risk.	IIb	B

Roffi M, et al. *Eur Heart J* 2015; Epub ahead of print.

EGC = electrocardiogram; NSTE-ACS = non-ST-segment elevation acute coronary syndromes.

Recommendations for anticoagulation in NSTE-ACS

Recommendations	Class[a]	Level[b]
Parenteral anticoagulation is recommended at the time of diagnosis according to both ischaemic and bleeding risks.	I	B
Fondaparinux (2.5 mg s.c. daily) is recommended as having the most favourable efficacy–safety profile regardless of the management strategy.	I	B
Bivalirudin (0.75 mg/kg i.v. bolus, followed by 1.75 mg/kg/hour for up to 4 hours after the procedure) is recommended as alternative to UFH plus GPIIb/IIIa inhibitors during PCI.	I	A
UFH 70–100 IU/kg i.v. (50–70 IU/kg if concomitant with GPIIb/IIIa inhibitors) is recommended in patients undergoing PCI who did not receive any anticoagulant.	I	B
In patients on fondaparinux (2.5 mg s.c. daily.) undergoing PCI, a single i.v. bolus of UFH (70–85 IU/kg, or 50–60 IU/kg in the case of concomitant use of GPIIb/IIIa inhibitors) is recommended during the procedure.	I	B
Enoxaparin (1 mg/kg s.c. twice daily) or UFH are recommended when fondaparinux is not available.	I	B
Enoxaparin should be considered as anticoagulant for PCI in patients pretreated with s.c. enoxaparin.	IIa	B
Additional ACT-guided i.v. boluses of UFH may be considered following initial UFH treatment.	IIb	B
Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated.	IIa	C
Crossover between UFH and LMWH is not recommended.	III	B
In NSTEMI patients with no prior stroke/TIA and at high ischaemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately one year) may be considered after discontinuation of parenteral anticoagulation.	IIb	B

- Emphasis on Fondaparinux

Roffi M, et al. *Eur Heart J* 2015; Epub ahead of print.

ESC NSTEMI Guidelines 2015

'Overall, fondaparinux is considered to be the parenteral anticoagulant with the most favourable efficacy–safety profile and is recommended regardless of the management strategy, unless the patient is scheduled for immediate coronary angiography.'

Roffi M, et al. *Eur Heart J* 2015; Epub ahead of print.

ESC = European Society of Cardiology; NSTEMI = non-ST-segment elevation myocardial infarction.

The OASIS-5 Study

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes

The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators*

Yusuf S, *et al. N Engl J Med* 2006; **354**:1464–1476.

OASIS-5: A randomised, double-blind, double-dummy trial

OASIS-5

20,078 patients with NSTE-ACS, chest discomfort < 24 hours
2 of 3: Age > 60, ST segment Δ, ↑ cardiac markers

Exclude
Age < 21
Any contra-indicated to enoxaparin
Haem stroke < 12 months
Creatinine > 3 mg/dL/265 µmol/L

Aspirin, clopidogrel, GPIIb/IIIa inhibitor, planned cath/PCI as per local practice

Randomization

Fondaparinux

2.5 mg subcut daily up to 8 days or hospital discharge

Mean treatment : 5.4 days
Mean time to PCI: 2.4 days

Enoxaparin

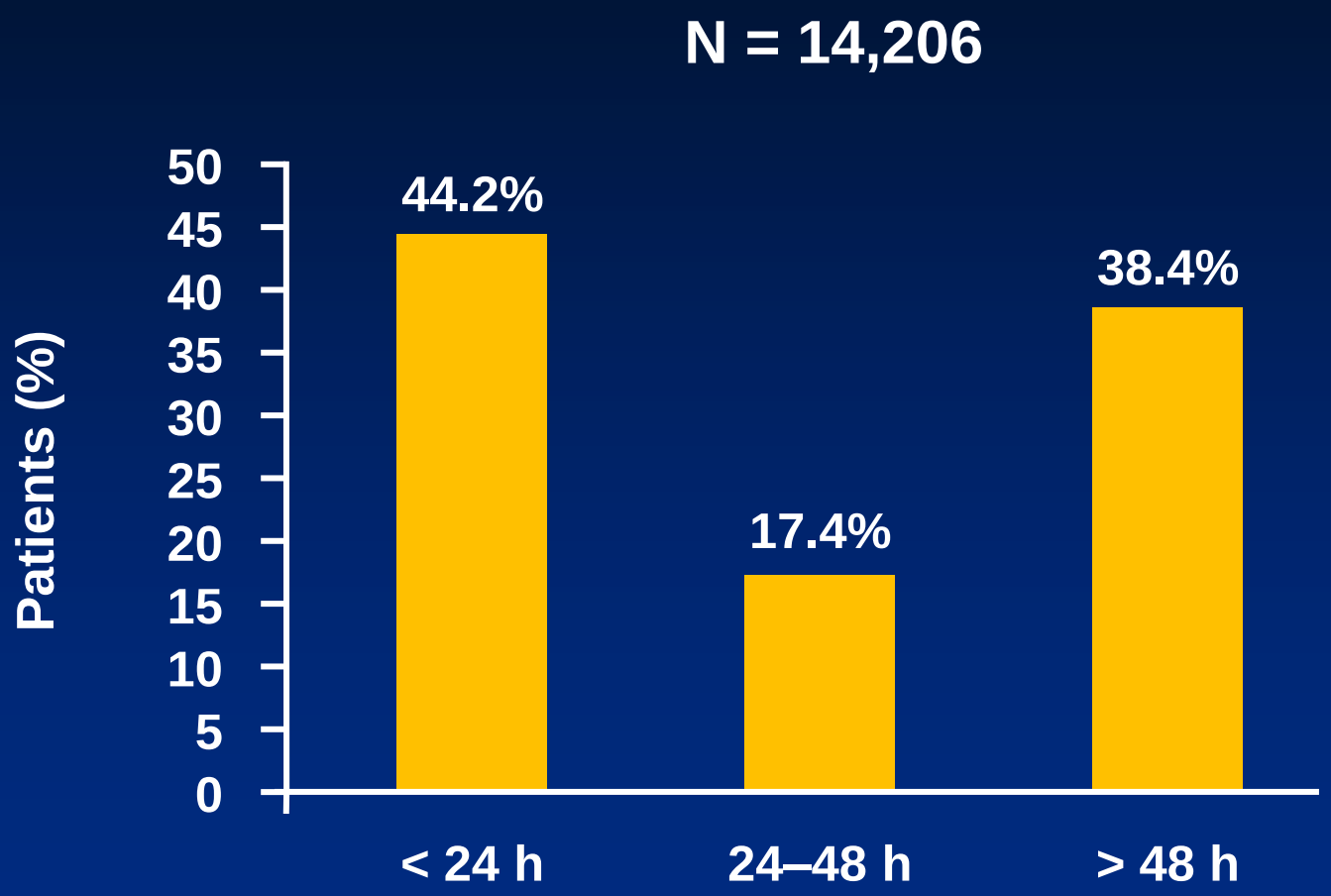
1 mg/kg subcut bid for 2–8 days
1 mg/kg subcut daily if CrCl < 30mL/min

Mean treatment : 5.2 days
Mean time to PCI: 2.6 days

CrCl = creatinine clearance; NSTE-ACS = non-ST elevation acute coronary syndrome; PCI = percutaneous coronary intervention; Subcut = subcutaneous.

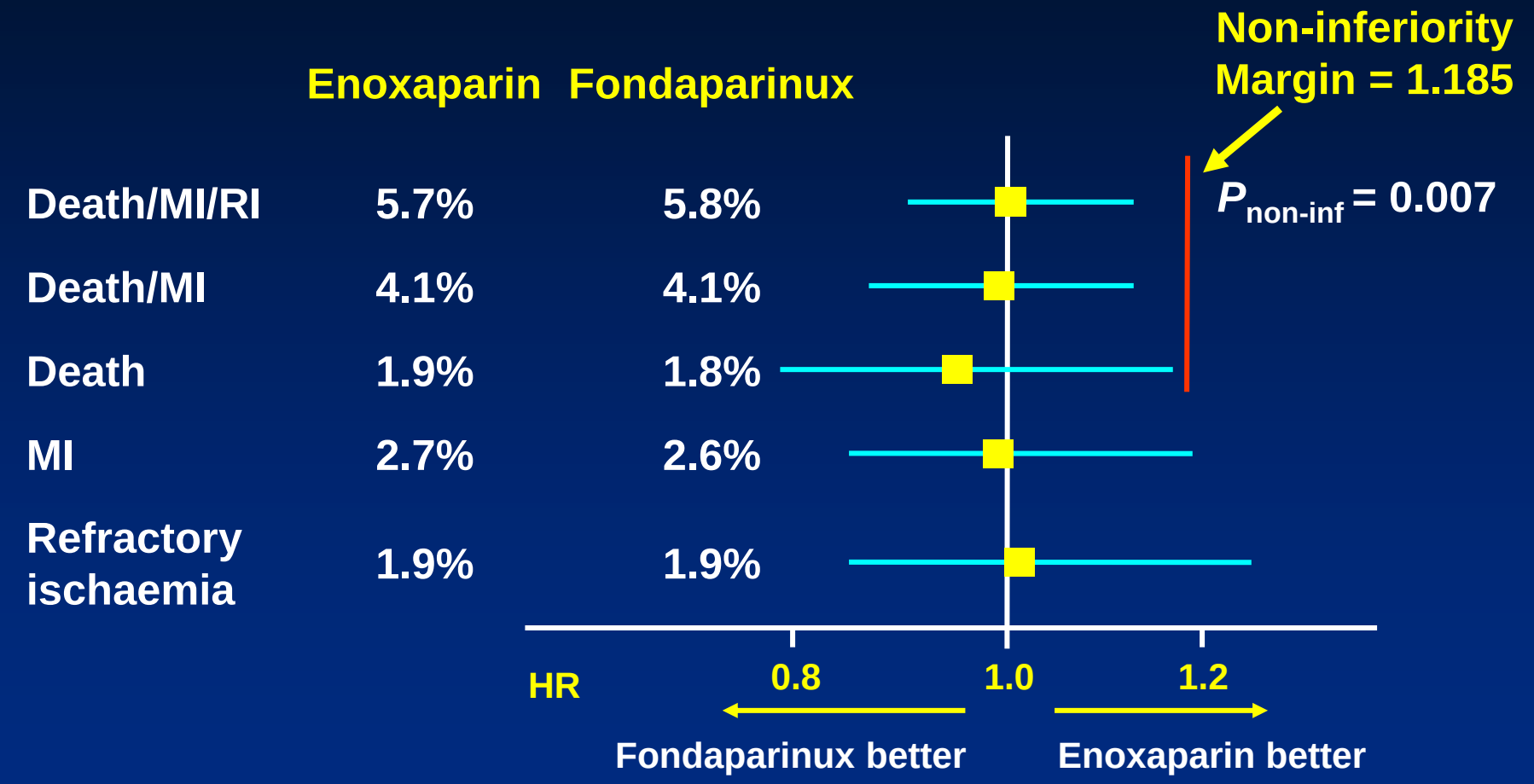
Mehta SR, *et al. Am Heart J* 2005; **150**:1107(e1-.e10);
Yusuf S, *et al. N Engl J Med* 2006; **354**:1464–1476.

OASIS-5: Majority of patients underwent early invasive strategy



Mehta SR, *et al. J Am Coll Cardiol* 2007; **50**:1742–1751.

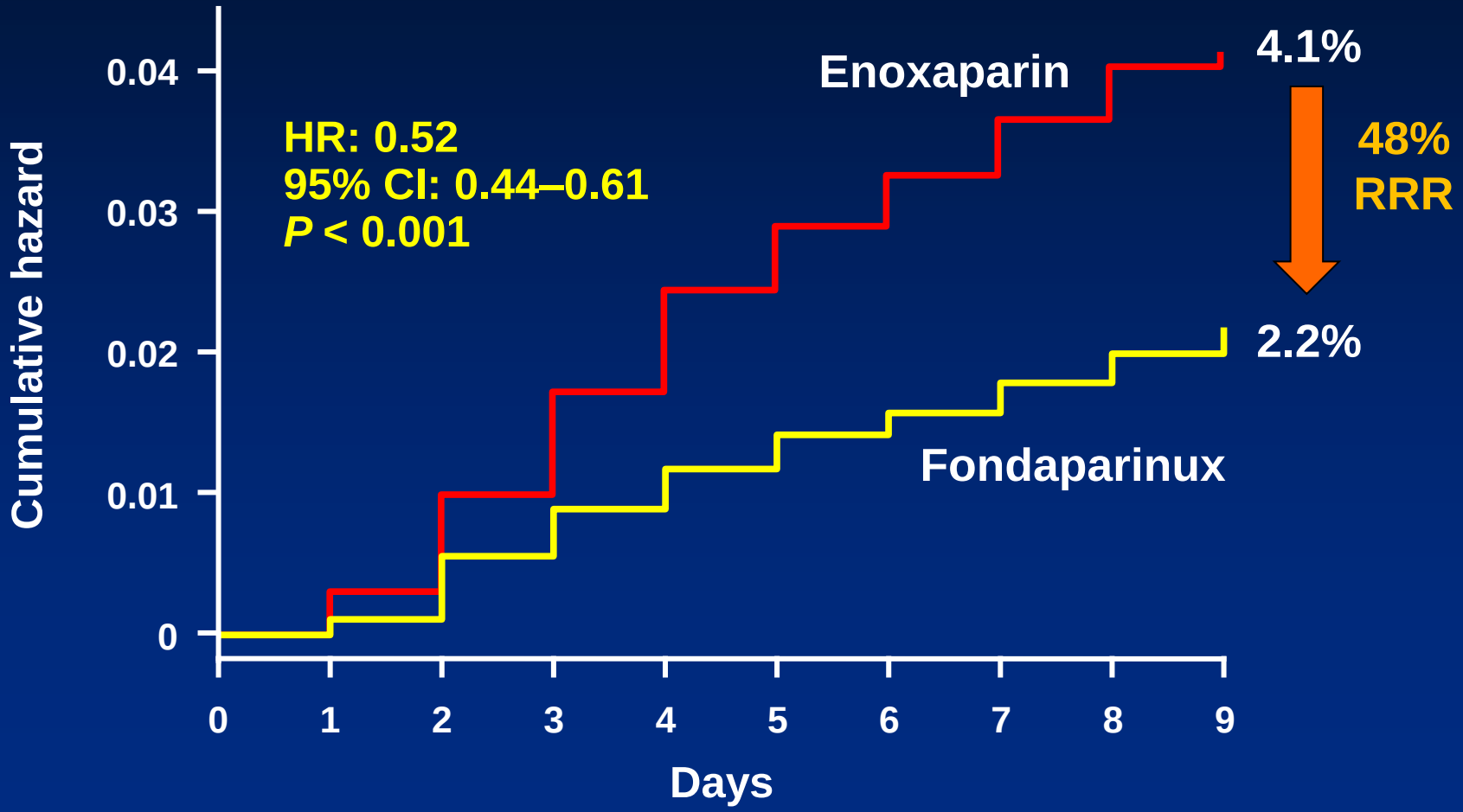
OASIS-5: Similar efficacy outcome rates in both groups at Day 9



HR = hazard ratio; MI = myocardial infarction; RI = refractory ischaemia.

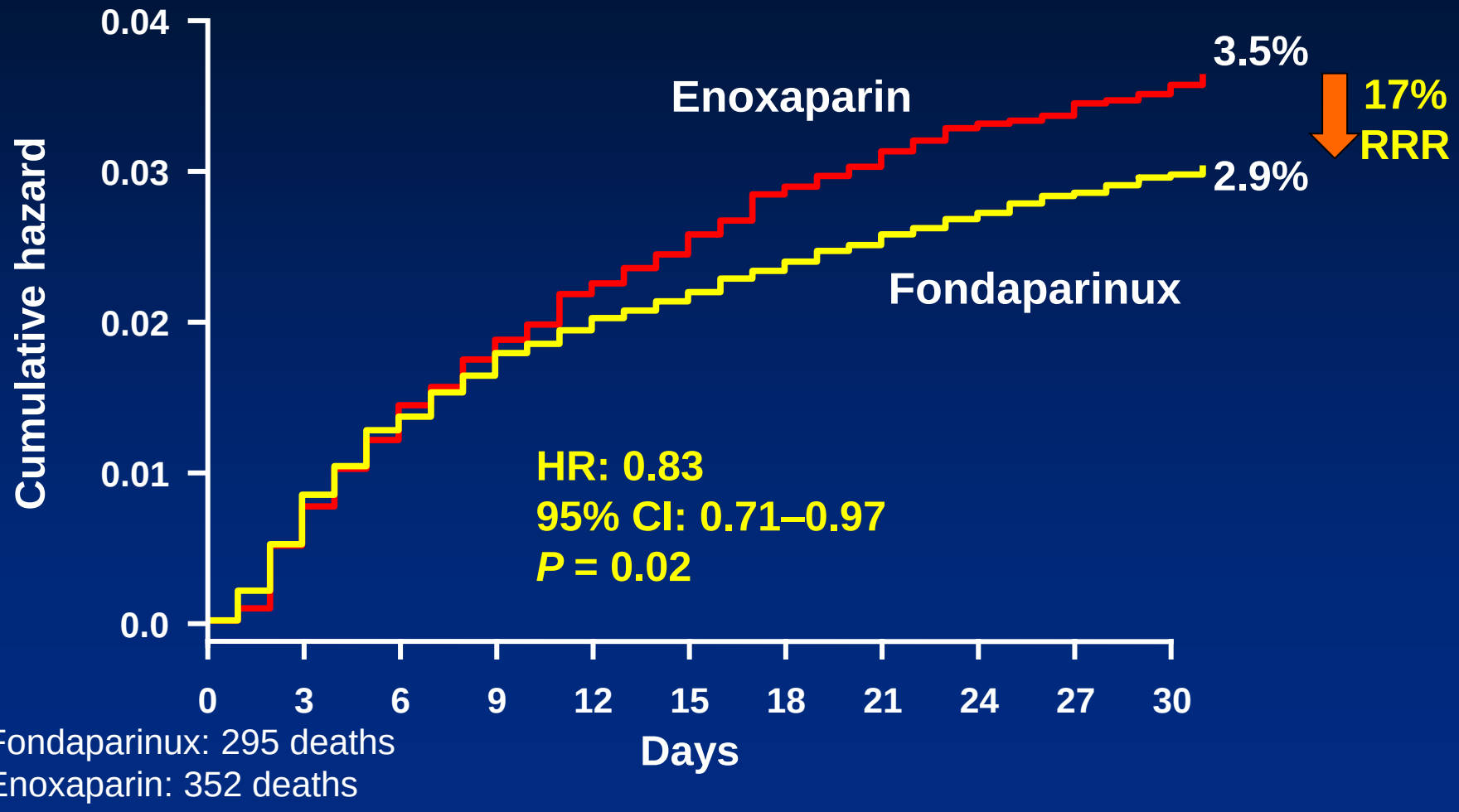
Yusuf S, *et al. N Engl J Med* 2006; **354**:1464–1476.

Fondaparinux substantially reduced major bleeding vs enoxaparin at Day 9



Yusuf S, *et al. N Engl J Med* 2006; **354**:1464–1476.

OASIS-5: Fondaparinux significantly reduced mortality vs enoxaparin at Day 30

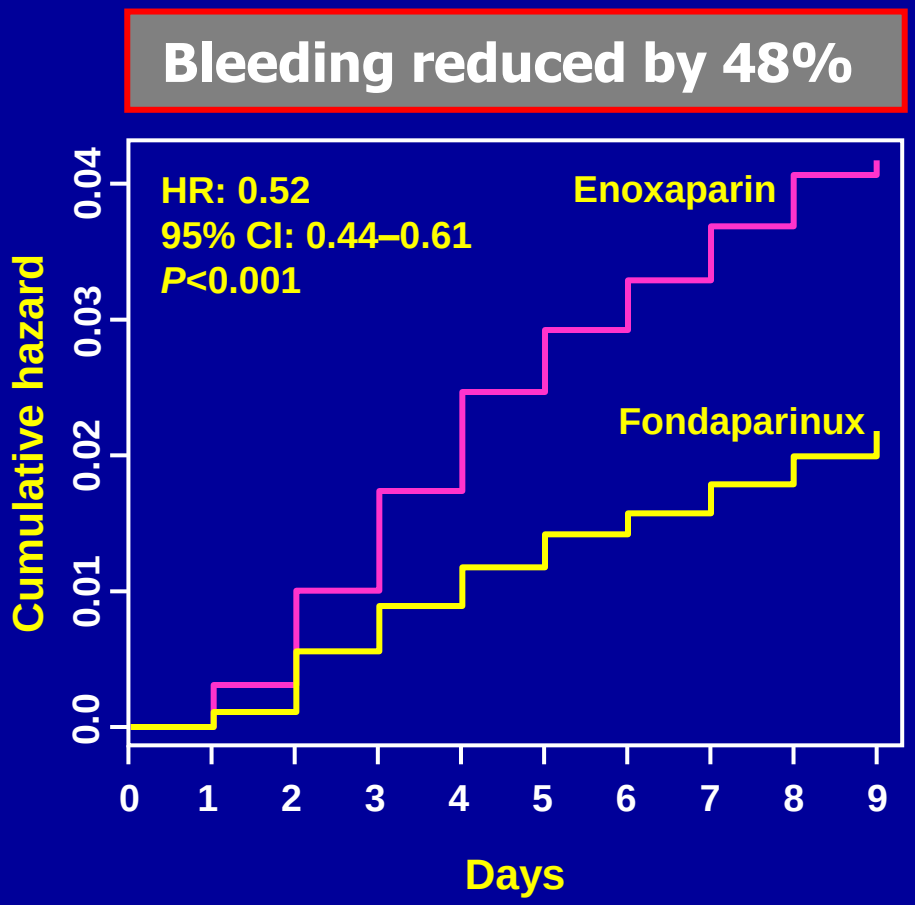


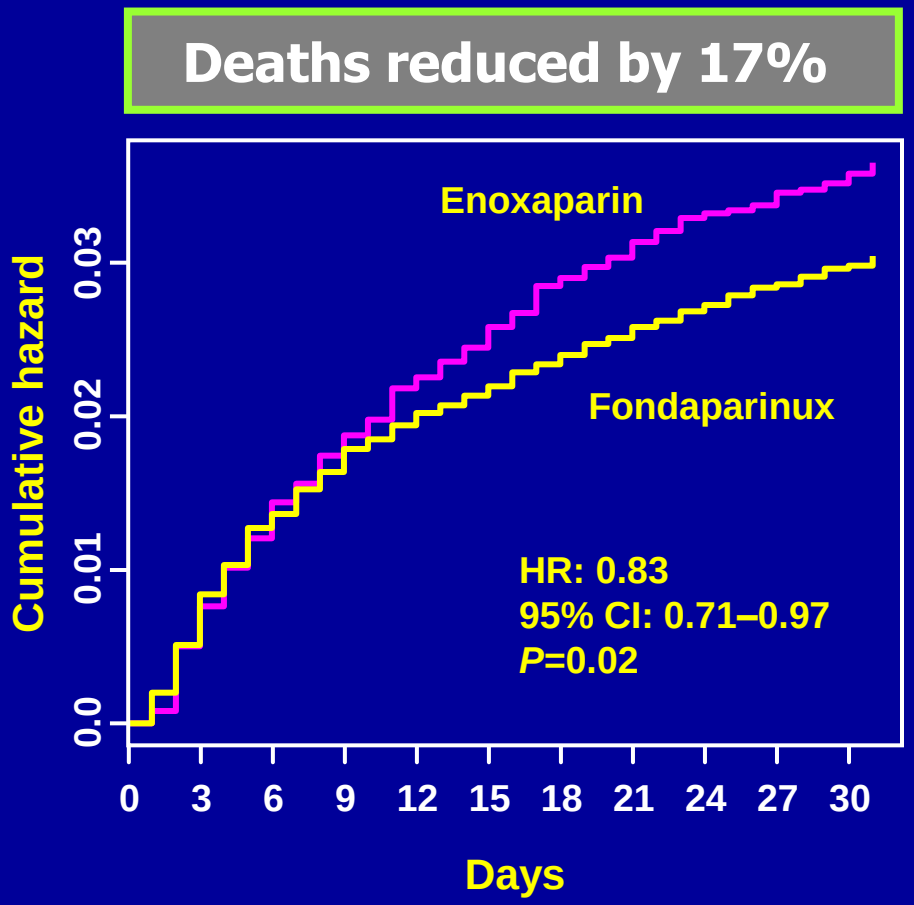
Fondaparinux: 295 deaths
Enoxaparin: 352 deaths

CI = confidence interval; HR = hazard ratio; RRR = relative risk reduction.

Yusuf S, *et al. N Engl J Med* 2006; **354**:1464–1476.

OASIS-5
Less bleeding = fewer deaths

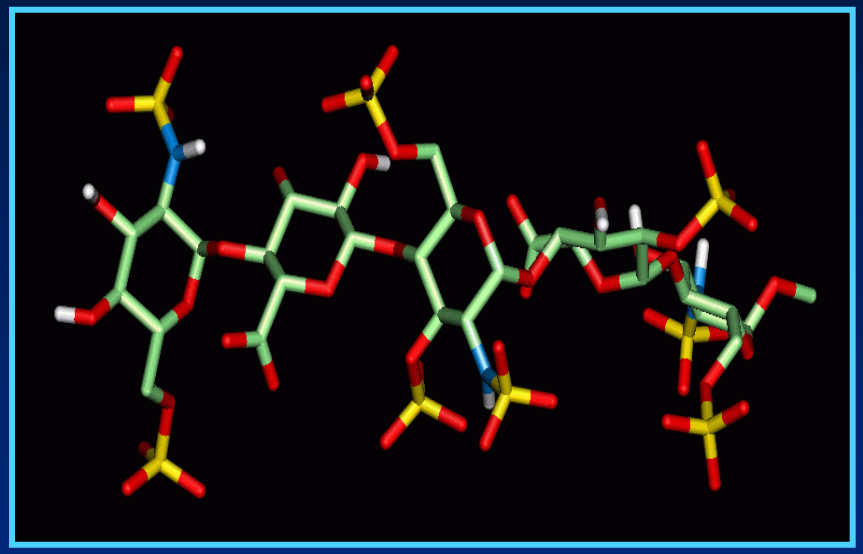




HR = hazard ratio.

Yusuf S, *et al. N Engl J Med* 2006; **354**:1464–1476.

Fondaparinux: A synthetic inhibitor of Factor Xa



- Once-daily administration
- Rapid onset ($C_{max}/2$ = 25 min)
- Half-life: 15–18 h
- No liver metabolism
- No protein binding (other than AT)
- No risk of pathogen contamination
- No dose adjustment necessary in elderly
- Anticoagulant effect can be normalised with administration of activated factor VII

AT = antithrombin; C_{max} = maximum concentration.

Herbert JM, *et al. Cardiovasc Drug Rev* 1997; **15**:1–26;
van Boeckel CAA, *et al. Angew Chem Int Ed Engl* 1993; **32**:1671–1690;
Bijsterveld NR, *et al. Circulation* 2002; **106**:2550–2554.

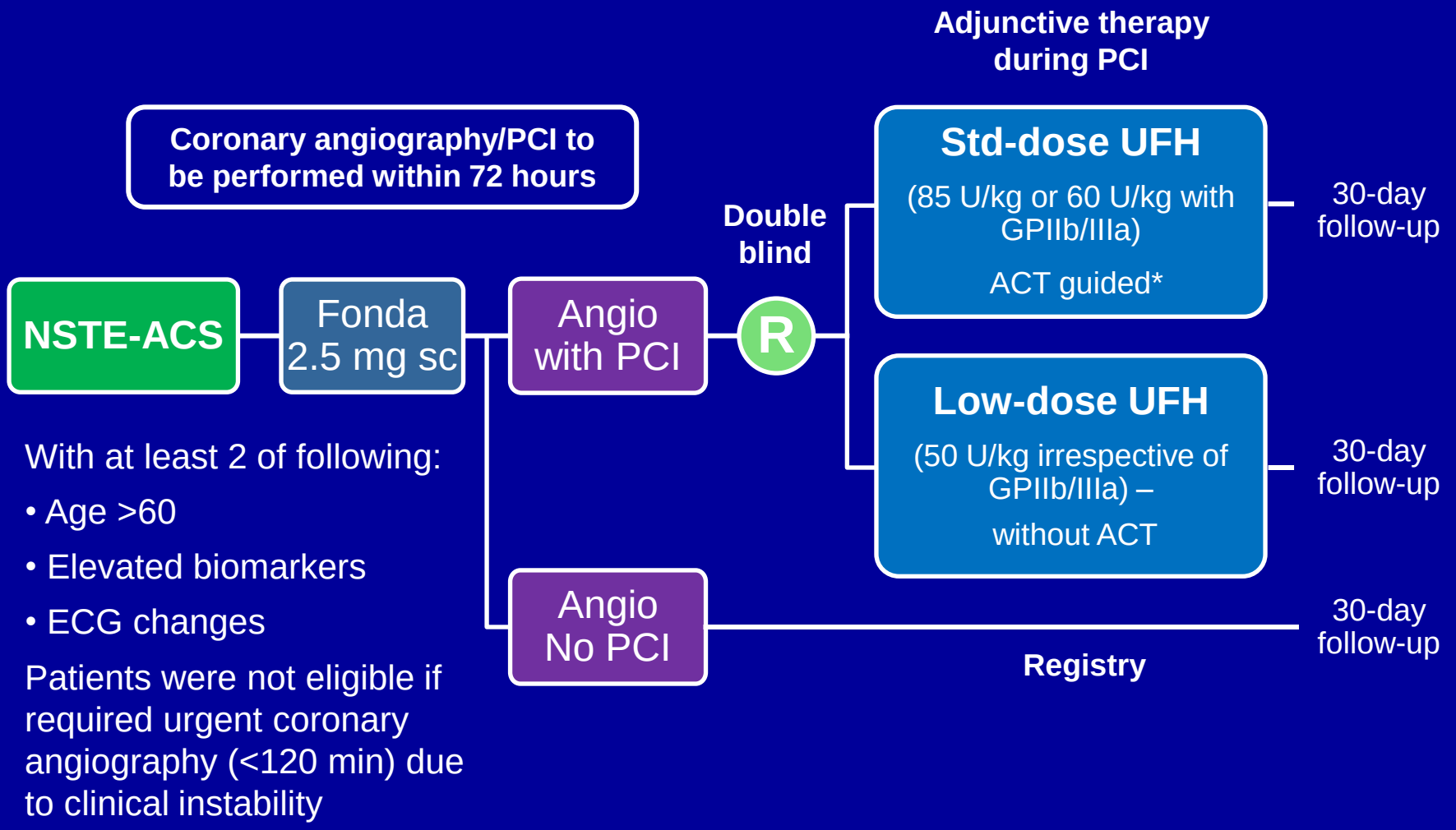
Fondaparinux and PCI: Avoiding catheter thrombus

In patients on fondaparinux (2.5 mg s.c. daily) undergoing PCI, a single i.v. bolus of UFH (70–85 IU/kg, or 50–60 IU/kg in the case of concomitant use of GPIIb/IIIa inhibitors) is recommended during the procedure

Roffi M, et al. *Eur Heart J* 2015; Epub ahead of print.

GP = glycoprotein; PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

Study design

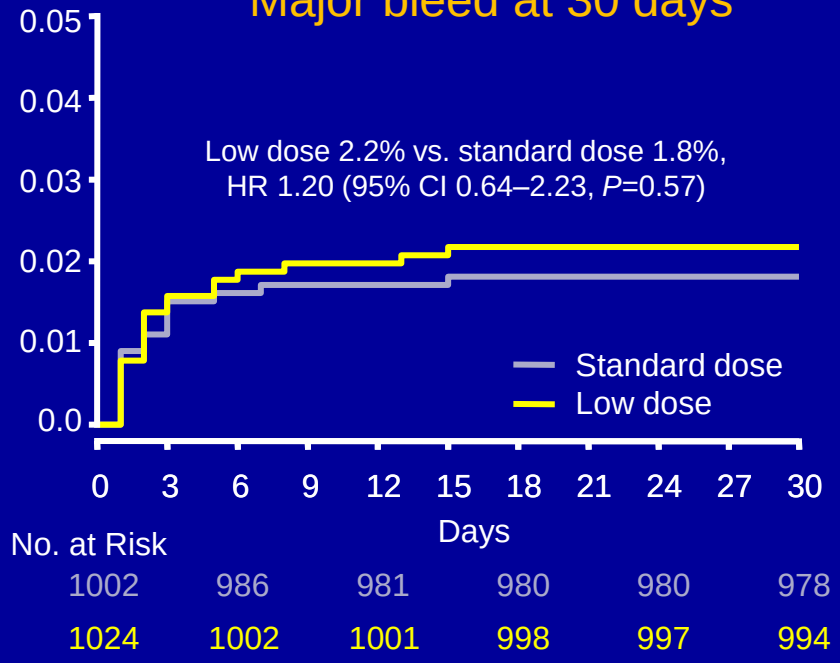


*ACT targets consistent with current guidelines.
ACT = activated clotting time; ECG = electrocardiogram;
GP = glycoprotein; NSTE-ACS = non-ST-segment elevation acute coronary syndromes;
PCI = percutaneous coronary intervention; UFH = unfractionated heparin.

The FUTURA/OASIS-8 Trial Group. *JAMA.* 2010; **304**:1339–1349.

Outcomes to 30 days

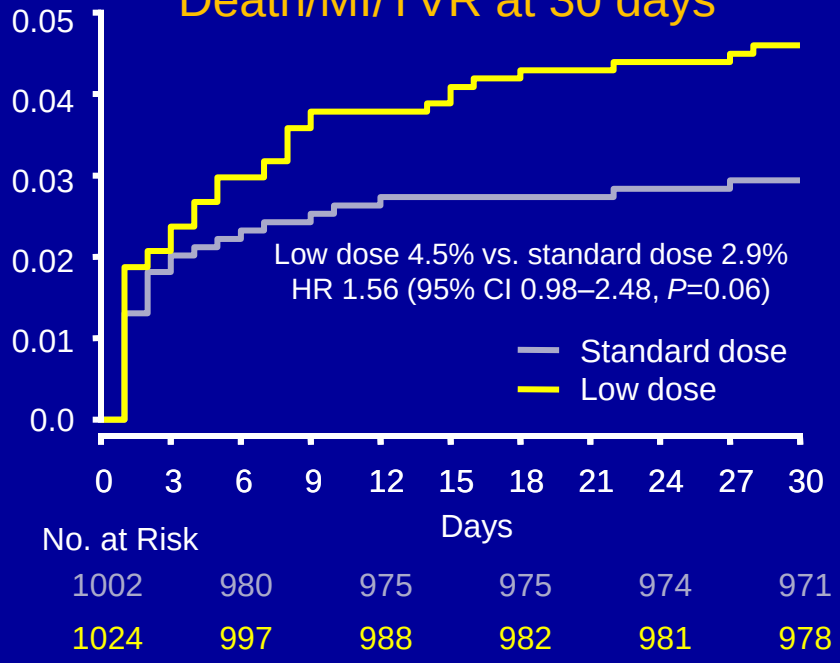
Major bleed at 30 days



No. at Risk

1002	986	981	980	980	978
1024	1002	1001	998	997	994

Death/MI/TVR at 30 days



No. at Risk

1002	980	975	975	974	971
1024	997	988	982	981	978

Subgroup analysis showed consistent results for primary outcome and for death/MI/TVR for pre-specified subgroups of: age, sex, GPIIb/IIIa, BMI, CrCl, arterial access site

BMI = body mass index; CI = confidence interval;
CrCl = creatinine clearance; GP = glycoprotein; HR = hazard ratio;
MI = myocardial infarction; TVR = target vessel revascularisation.

The FUTURA/OASIS-8 Trial Group. *JAMA.* 2010; **304**:1339–1349.

Recommendations for anticoagulation in NSTE-ACS

Recommendations	Class[a]	Level[b]
Parenteral anticoagulation is recommended at the time of diagnosis according to both ischaemic and bleeding risks.	I	B
Fondaparinux (2.5 mg s.c. daily) is recommended as having the most favourable efficacy–safety profile regardless of the management strategy.	I	B
Bivalirudin (0.75 mg/kg i.v. bolus, followed by 1.75 mg/kg/hour for up to 4 hours after the procedure) is recommended as alternative to UFH plus GPIIb/IIIa inhibitors during PCI.	I	A
UFH 70–100 IU/kg i.v. (50–70 IU/kg if concomitant with GPIIb/IIIa inhibitors) is recommended in patients undergoing PCI who did not receive any anticoagulant.	I	B
In patients on fondaparinux (2.5 mg s.c. daily.) undergoing PCI, a single i.v. bolus of UFH (70–85 IU/kg, or 50–60 IU/kg in the case of concomitant use of GPIIb/IIIa inhibitors) is recommended during the procedure.	I	B
Enoxaparin (1 mg/kg s.c. twice daily) or UFH are recommended when fondaparinux is not available.	I	B
Enoxaparin should be considered as anticoagulant for PCI in patients pretreated with s.c. enoxaparin.	IIa	B
Additional ACT-guided i.v. boluses of UFH may be considered following initial UFH treatment.	IIb	B
Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated.	IIa	C
Crossover between UFH and LMWH is not recommended.	III	B
In NSTEMI patients with no prior stroke/TIA and at high ischaemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately one year) may be considered after discontinuation of parenteral anticoagulation.	IIb	B

Roffi M, et al. *Eur Heart J* 2015; Epub ahead of print.

Implications

- ACS patients treated with fondaparinux can undergo PCI safely with unfractionated heparin
- No evidence to depart from guideline-recommended standard-dose regimen of unfractionated heparin during PCI
- Adding unfractionated heparin during PCI to fondaparinux preserves the benefits and safety of fondaparinux (i.e. reduced bleeding) while minimising catheter thrombus

PCI = percutaneous coronary intervention.

Jolly S, *et al. JAMA* 2010; **304**:1339–1349.

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Roffi M, et al. *Eur Heart J* 2015; Epub ahead of print.

Recommendations for a purely conservative strategy

'In a purely conservative strategy, anticoagulation should be maintained up to hospital discharge (I-A)'

Hamm C, *et al. Eur Heart J* 2011; 32:2999–3054.

Fondaparinux in NSTEMI: our daily routine

- We treat NSTEMI-ACS patients with aspirin and fondaparinux when the diagnosis is made.
- Patients that undergo PCI are given UHF iv during the procedure.
- Fondaparinux is stopped after the intervention.
- Some patients are pretreated with oral P2Y12- inhibitors (ticagrelor).

What is new in antithrombotic therapy?

- **Antithrombotic treatment**
  - Timing of $P2Y_{12}$ inhibitor administration in patients scheduled for early invasive strategy (pretreatment)
  - Duration of dual antiplatelet therapy
  - Antiplatelet agents and CABG (Web addenda)
  - Managing oral antiplatelet agents in patients requiring long-term oral anticoagulants (vitamin K antagonists, non-vitamin K antagonist oral anticoagulants): rivaroxiban
  - New agents: cangrelor and vorapaxar
- **Management of acute bleeding events (Web addenda)**
  - In patients on antiplatelet agents, vitamin K antagonists, non-vitamin K antagonist oral anticoagulants
- **Special populations and conditions (Web addenda)**
  - NSTE-ACS and atrial fibrillation

Roffi M, *et al. Eur Heart J* 2015; Epub ahead of print;
Roffi, *et al.* ESC NSTE-ACS guidelines 2015 – Web addenda.
Available at: www.escardio.org

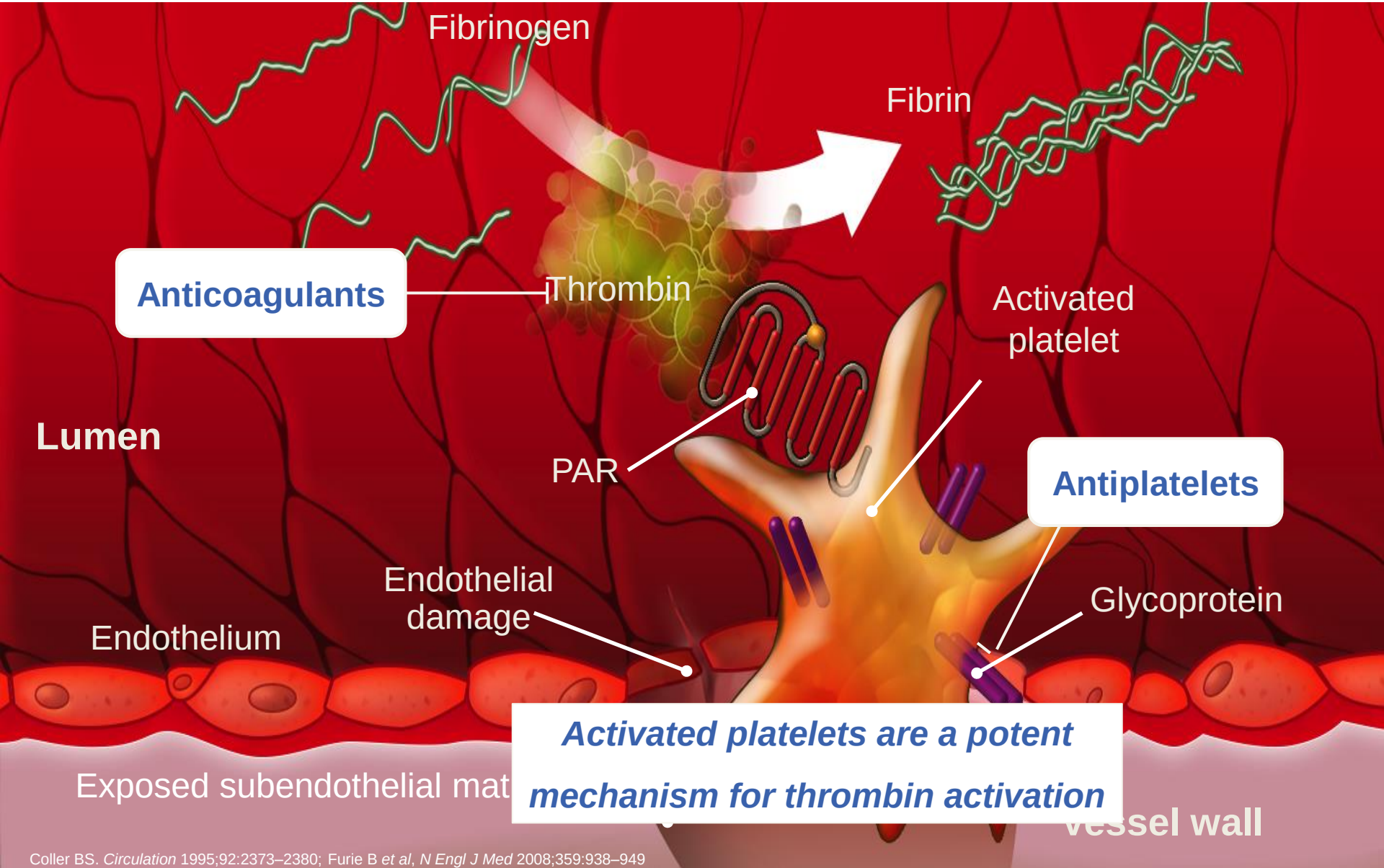
CABG = coronary artery bypass graft; NSTE-ACS = non-ST-segment elevation acute coronary syndromes.

Timing of $P2Y_{12}$ Inhibitor Initiation: NSTEMI GL

- As the optimal timing of ticagrelor or clopidogrel administration in NSTE-ACS patients scheduled for an invasive strategy has not been adequately investigated, no recommendation for or against pretreatment with these agents can be formulated. Based on the ACCOAST results, pretreatment with prasugrel is not recommended.

Two Pathways for Platelet Activation

Contact with the Exposed Vessel Wall and Direct Activation by Thrombin



Coller BS. *Circulation* 1995;92:2373–2380; Furie B *et al*, *N Engl J Med* 2008;359:938–949

Antithrombotic treatment in patients with NSTE-ACS undergoing PCI

NSTE-ACS

Recommendations	Class	Level
Pre-treatment and antiplatelet therapy		
Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150-300 mg (or 75-250 mg i.v.), and at a maintenance dose of 75-100 mg daily long-term.	I	A
A $P2Y_{12}$ inhibitor is recommended in addition to aspirin, maintained over 12 months unless there are contraindications such as an excessive risk of bleeding. Options are:	I	A
• **Prasugrel** in $P2Y_{12}$-inhibitor naïve patients who proceed to PCI (60 mg loading dose, 10 mg daily dose).	I	B
• **Ticagrelor** irrespective of the preceding $P2Y_{12}$ inhibitor regimen (180 mg loading dose, 90 mg b.i.d.).	I	B

NO CHANGE

∑: Aspirin plus potent $P2Y_{12}$ receptor inhibitor

2018 ESC/EACTS Guidelines on myocardial revascularisation
European Heart Journal (2018) 00, 1-96 - doi:10.1093/eurheartj/ehy394

Antithrombotic treatment in patients with NSTE-ACS undergoing PCI

NSTE-ACS

Recommendations	Class	Level
•Clopidogrel (600 mg loading dose, 75 mg daily dose) only when prasugrel or ticagrelor are not available or are contraindicated.	I	B
GP IIb/IIIa antagonists should be considered for bail-out if there is evidence of no-reflow or a thrombotic complication.	IIa	C
For **pre-treatment** in patients with NSTE-ACS undergoing invasive management, **ticagrelor administration** (180 mg loading dose, 90 mg b.i.d.), **or clopidogrel** (600 mg loading dose, 75 mg daily dose) if ticagrelor is not an option, should be considered as soon as the diagnosis is established.	IIa	C
Cangrelor may be considered in $P2Y_{12}$-inhibitor naïve patients undergoing PCI.	IIb	A

Class III for prasugrel (ACCOAST)

NEW: CHAMPION

2018 ESC/EACTS Guidelines on myocardial revascularisation
European Heart Journal (2018) 00, 1-96 - doi:10.1093/eurheartj/ehy394

Antithrombotic treatment in patients with ST-elevation myocardial infarction undergoing PCI

STEMI

Recommendations	Class	Level
Pre-treatment and antiplatelet therapy		
Aspirin is recommended for all patients without contraindications at an initial oral loading dose of 150–300 mg (or 75–250 mg i.v.), and at a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months, unless there are contra-indications such as excessive risk of bleeding.	I	A
GP IIb/IIIa inhibitors should be considered for bail-out if there is evidence of no-reflow or a thrombotic complication.	IIa	C

NO CHANGE

∑: Aspirin plus potent P2Y12 receptor inhibitor

2018 ESC/EACTS Guidelines on myocardial revascularisation
European Heart Journal (2018) 00, 1-96 - doi:10.1093/eurheartj/ehy394

Antithrombotic treatment in patients with ST-elevation myocardial infarction undergoing PCI

STEMI

Recommendations	Class	Level
Cangrelor may be considered in $P2Y_{12}$-inhibitor naïve patients undergoing PCI.	IIb	A
GP IIb/IIIa antagonists may be considered in $P2Y_{12}$-inhibitor naïve patients undergoing PCI.	IIb	C

NEW: CHAMPION

2018 ESC/EACTS Guidelines on myocardial revascularisation
European Heart Journal (2018) 00, 1-96 - doi:10.1093/eurheartj/ehy394

New potent oral P2Y12-inhibitors

- **Pretreatment?**
- **Onset of action in STEMI is delayed**

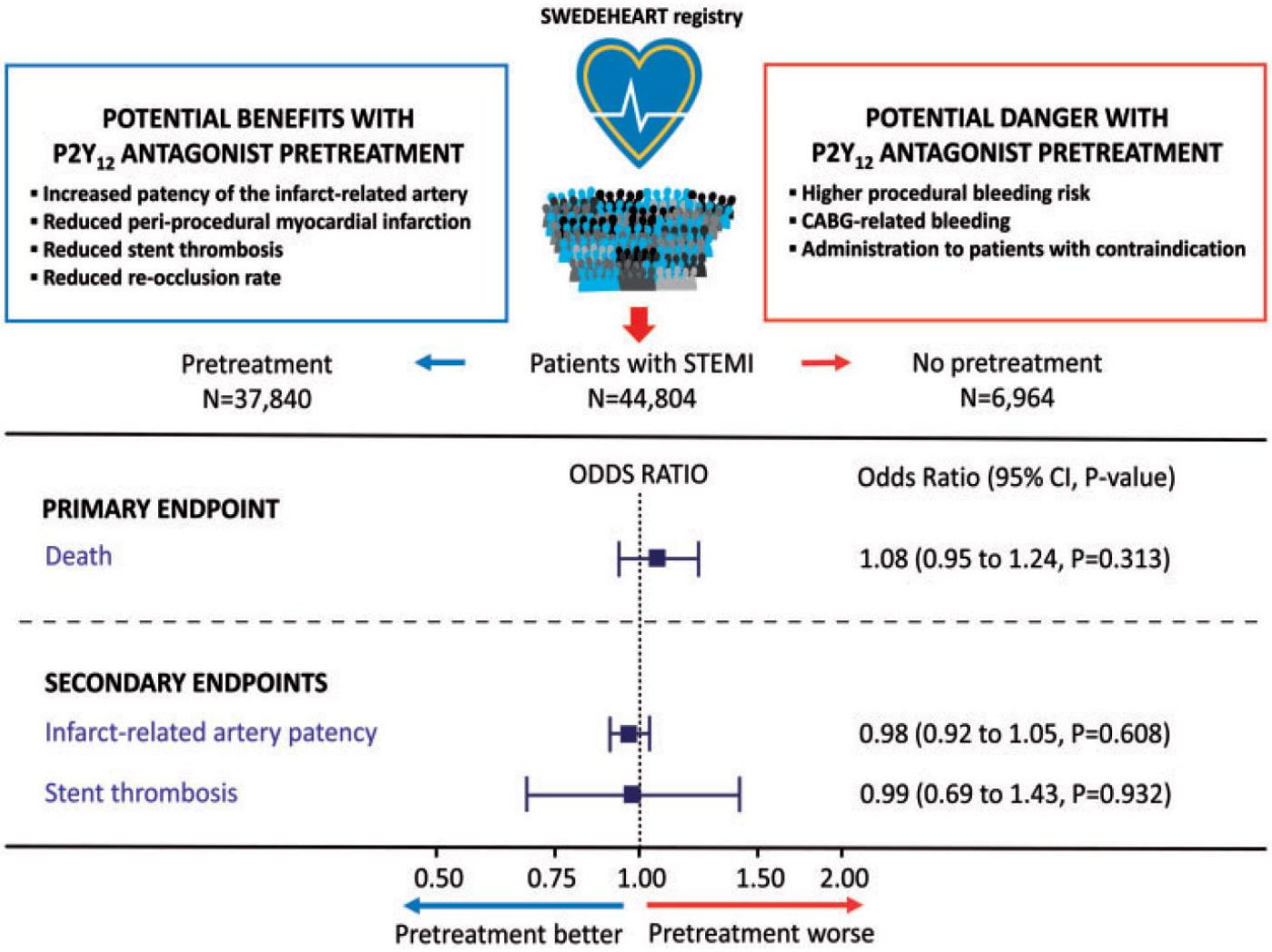
ESC European Society of Cardiology

European Heart Journal (2019) **40**, 1202–1210
doi:10.1093/eurheartj/ehz069

CLINICAL RESEARCH
Acute coronary syndromes

Pretreatment with $P2Y_{12}$ receptor antagonists in ST-elevation myocardial infarction: a report from the Swedish Coronary Angiography and Angioplasty Registry

Bjorn Redfors[1], Christian Dworeck[1], Inger Haraldsson[1], Oskar Angerås[1], Jacob Odenstedt[1], Dan Ioanes[1], Petur Petursson[1], Sebastian Völz[1], Per Albertsson[1], Truls Råmunddal[1], Jonas Persson[2], Sasha Koul[3], David Erlinge[3], and Elmir Omerovic[1]*



Take home figure Illustration of potential benefits and danger with pretreatment with P2Y12, and the pretreatment-associated propensity score adjusted risks of the primary and secondary endpoints among the 44 804 patients who underwent acute coronary angiography due to ST-elevation myocardial infarction in Sweden between 1 January 2005 and 1 November 2016.

Redfors et al, EHJ ”019

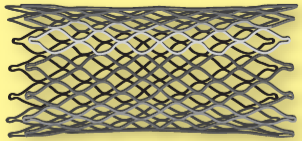
ESC European Society of Cardiology
European Heart Journal (2019) **40**, 1211–1213
doi:10.1093/eurheartj/ehz058

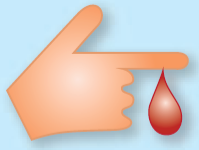
EDITORIAL

Pre-treatment with a $P2Y_{12}$ antagonist before PCI in STEMI: why should we wait?

Jeremie Abtan[1,2] and P. Gabriel Steg[1,2,3]*

[1]DHU (Département Hospitalo-Universitaire)-FIRE (Fibrosis, Inflammation, REmodelling), Hôpital Bichat, AP-HP (Assistance Publique-Hôpitaux de Paris), Université Paris-Diderot, Sorbonne-Paris Cité, Paris France; [2]FACT (French Alliance for Cardiovascular clinical Trials), an F-CRIN network, INSERM U-1148, Paris, France; and [3]NLHI, ICMS, Royal Brompton Hospital, Imperial College, London, UK





Time to full antiplatelet efficacy in STEMI		Theoretical Benefit	Safety	Cost-effectiveness
Clopidogrel	>12 hours	No demonstration of improved clinical outcomes Possible reduction in stent thrombosis with early ticagrelor	No excess bleeding	Identical drug No additional cost
Ticagrelor	4 to 6 hours			
Crushed Ticagrelor	4 to 6 hours			
GPIIbIIIa inhibitors	<2 hours	Improved clinical outcomes (but old Studies)	Important increase in bleeding	Modest additional cost
Cangrelor	<2 hours	Improved clinical outcomes	Modest increase in bleeding	Substantial additional cost

NSTEMI and STEMI – pretreatment with P2Y12 inhibitors

- **Patient**
- **Time to catheterization**
- **Setting – organization – invasive strategy**

Antithrombotics

Antiplatelets

- Aspirin
- $P2Y_{12}$ inhibitors
  - Clopidogrel
  - Prasugrel
  - Ticagrelor
  - Cangrelor
- GP IIb/IIIa
  - Abciximab
  - Eptifibatide
  - Tirofiban

PAR-1: vorapaxar

Antithrombins

- Heparin
- LMWH
  - Dalteparin
  - Enoxaparin
  - Nadroparin
- Pentasaccharide
  - Fondaparinux
- DTI
  - Lepirudin
  - Bivalirudin
  - Argatroban
  - Dabigatran

DTI = direct thrombin inhibitors; GP = glycoprotein;
LMWH = low molecular weight heparin; PAR-1 = protease-activated receptor-1.

Kristensen SD. Personal communication.

Characteristics of Tirofiban and Abciximab

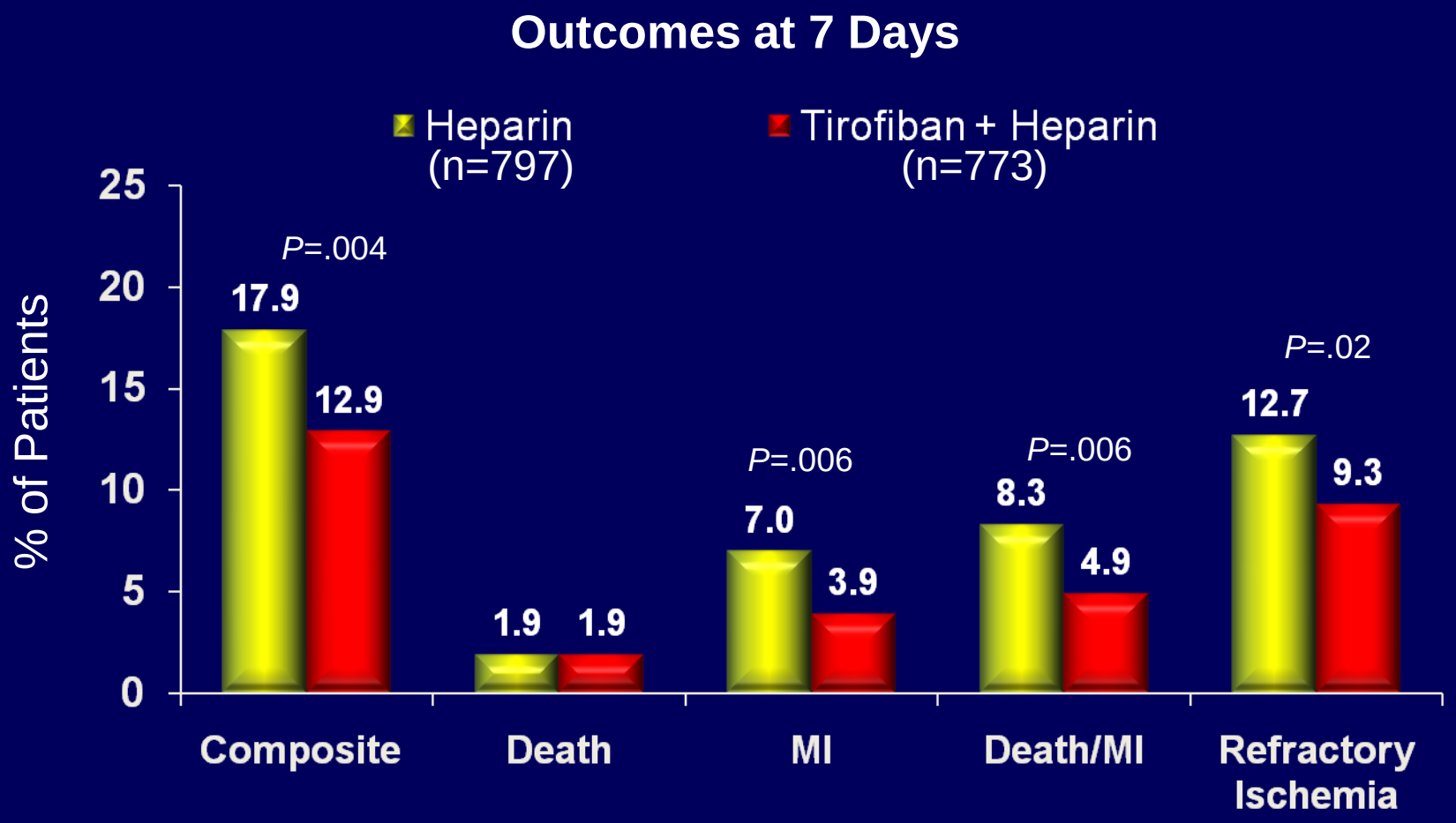
Tirofiban

- non-peptide
- 495 dalton MW
- recovery of platelet function: hours
- specific for IIb/IIIa receptor

Abciximab

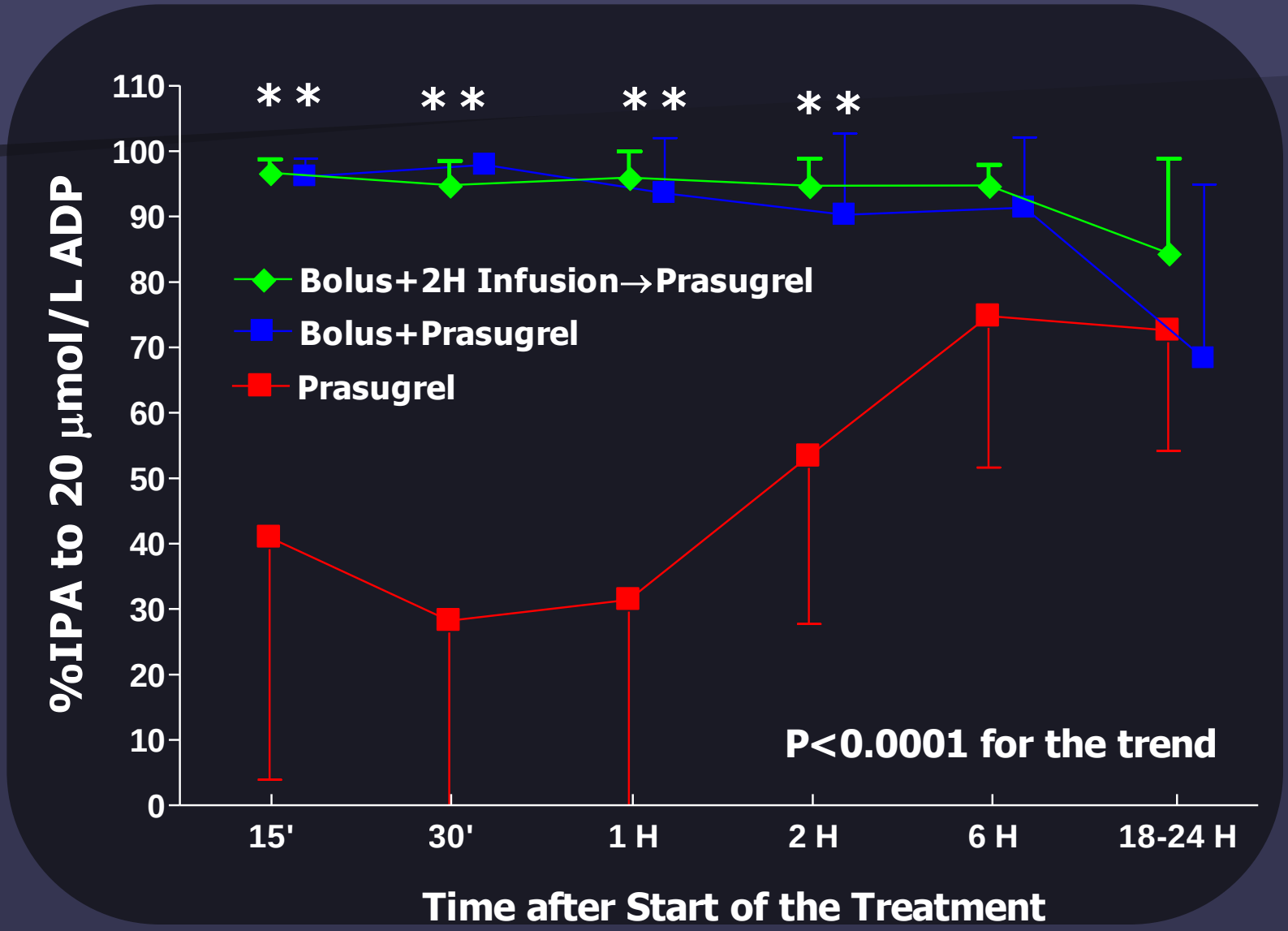
- monoclonal antibody
- 47,615 dalton MW
- recovery of platelet function: days
- binds to IIb/IIIa, MAC-1, $\alpha_v\beta_3$

PRISM PLUS: Primary Endpoint and Components (NSTEMI-ACS)



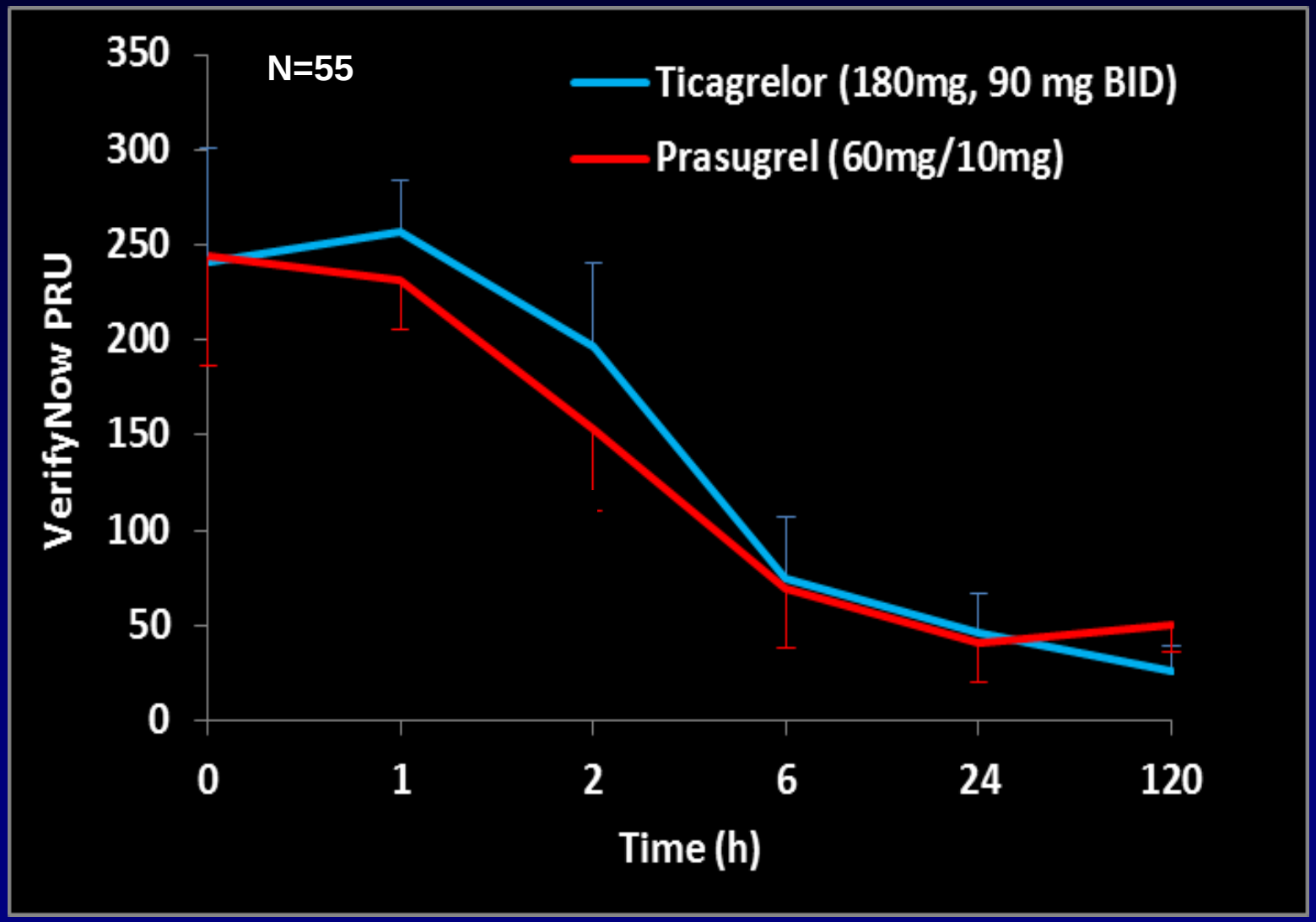
PRISM-PLUS Study Investigators. *N Engl J Med.* 1998;338(21):1488-1497.

Prasugrel vs. GPI onset of action in STEMI:



Valgimigli M et al, J Am Coll Cardiol Intv 2012;5:268–77

Prasugrel vs. Ticagrelor in STEMI



Adapted from: Xanthopoulou et al. ESC 2012, Abstract 458; Eur Heart J_2012_Abstract Suppl 41

ON-TIME -2

Acute myocardial infarction
diagnosed in ambulance or referral center
ASA + 600 mg Clopidogrel + UFH

N=984
6/2006-11/2007

Placebo		Tirofiban *
	Transportation	
Angiogram	PCI center	Angiogram
Tirofiban provisional	PCI	Tirofiban cont'd

Bolus: 25 µg/kg & 0.15 µg/kg/min infusion

Results: Primary Endpoint

Residual ST deviation at 60 min.

mean ± SD	Placebo	Tirofiban	p- value
Readable ECG	94.1%	95.5%	0.358
Residual ST - deviation (mm)	4.8 ±6.3	3.3 ± 4.3	**0.002**
normal ECG	30.2%	37.3%	**0.031**
> 3 mm ST-deviation	44.3%	36.6%	**0.026**

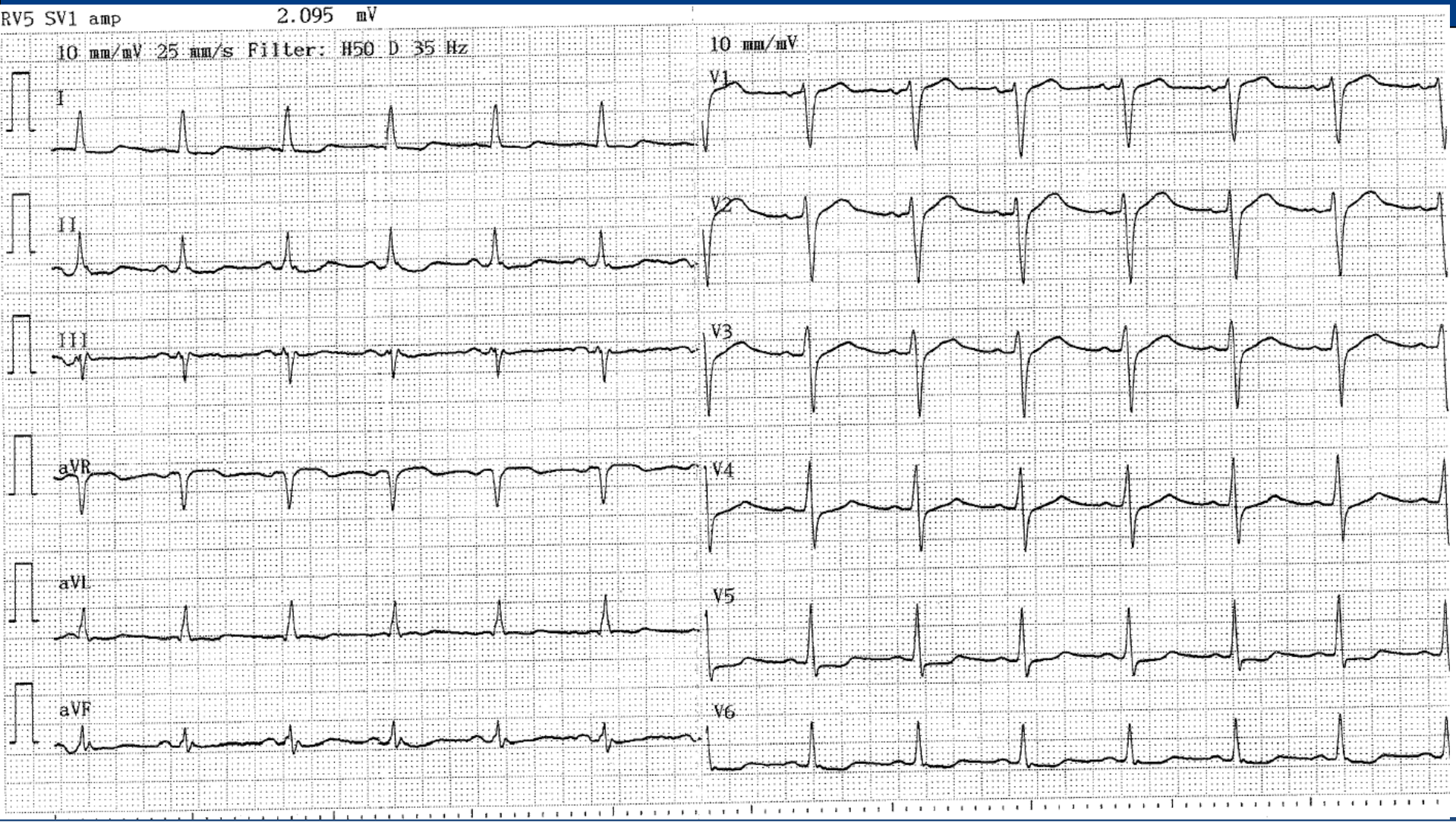
Case

84 year old lady

- Hypertension for 20 years
- Thiazide
- Amlodipine 5 mg
- Aspirin 75 mg
- Lives alone in her flat
- Takes care of herself
- Known renal failure, eGFR= 40 ml/min
- Weight= 52 kg, BMI 21

BMI, body mass index; eGFR, estimated glomerular filtration rate.

84 year old lady



84 year old lady

- TnT: 540 ng/ml (<14 ng/l)
- eGFR: 45 ml/min

eGFR, estimated glomerular filtration rate; TnT, troponin T.

Management strategy

- Medication?
- Examinations/investigations?

Medication

- Antiplatelet therapy?
- Aspirin

- Clopidogrel?
- Ticagrelor?
- Prasugrel?

Medication

- Anticoagulation therapy?

- UF heparin?
- LMWH?
- Fondaparinux?
- Bivalirudin?

84 year old lady: management strategy

- Medication:
- Aspirin 75 mg (continued)
- Fondaparinux 2.5 mg subcutaneous daily
- Nitroglycerin intravenously

- Examinations?

Examinations

- Echo?
- CT?
- CAG?

CAG, coronary angiography; CT, computed tomography; Echo, echocardiogram.

84 year old lady: management strategy

- Medication:
- Aspirin 75 mg (continued)
- Fondaparinux 2.5 mg subcutaneous daily
- Nitroglycerin intravenously

- Examinations:
- Echo
- CAG within 24 hours

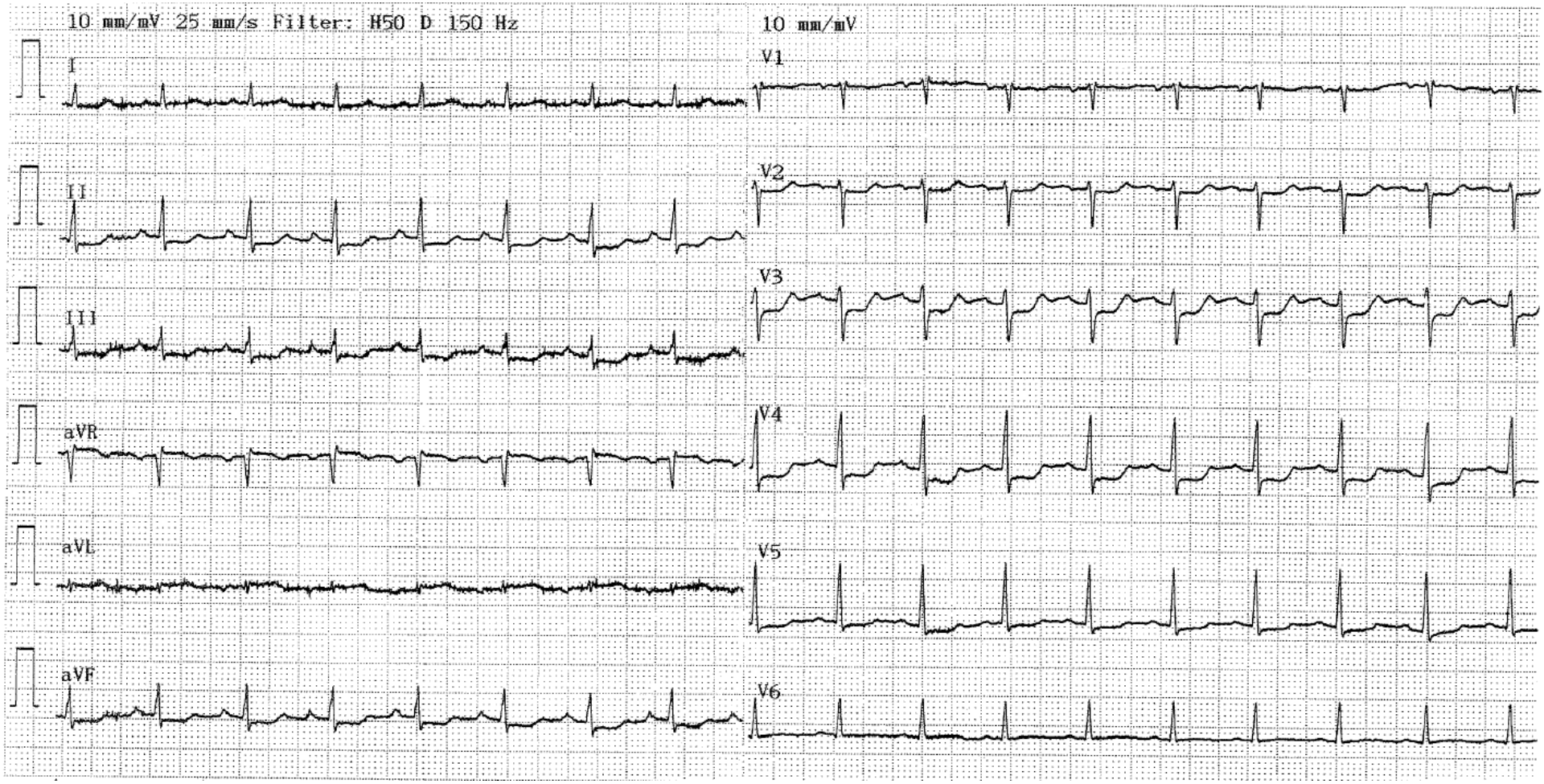
CAG, coronary angiography.

8 hours later

- More intensive pain
- Nitroglycerine dose increased
- ECG changes

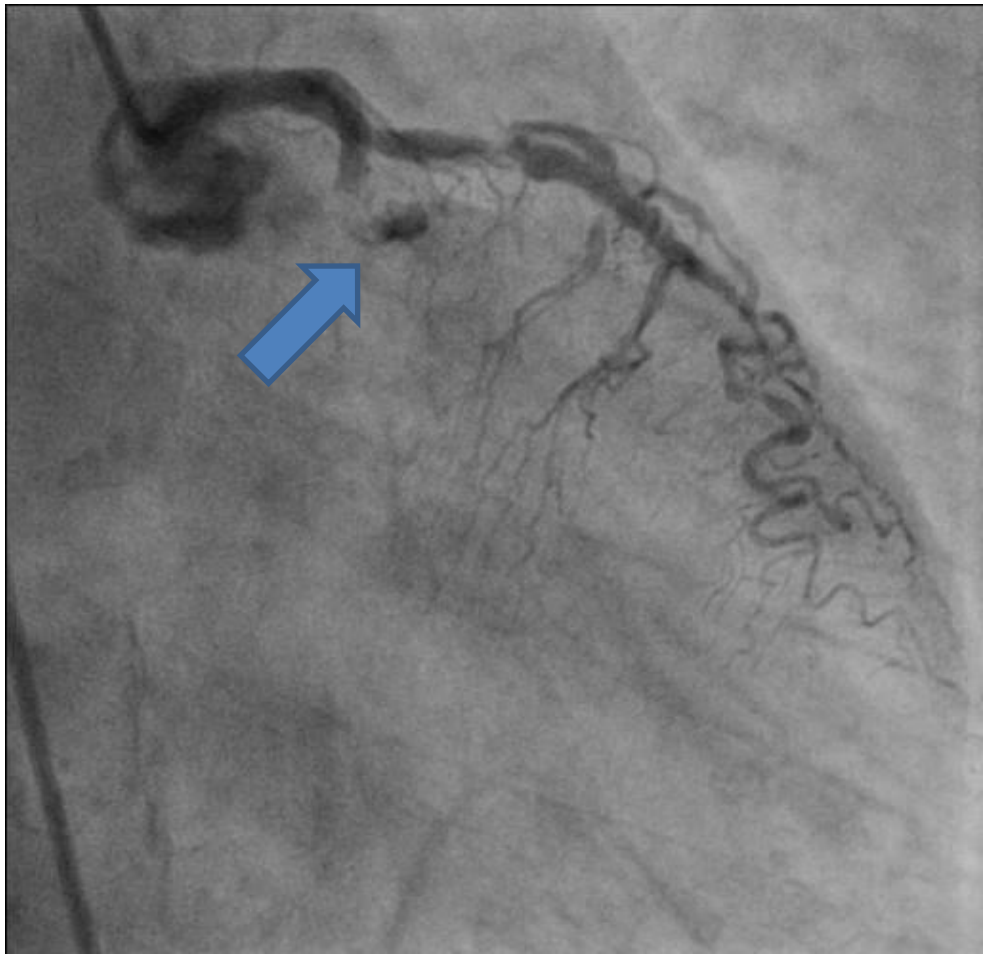
ECG, electrocardiogram.

84 year old lady



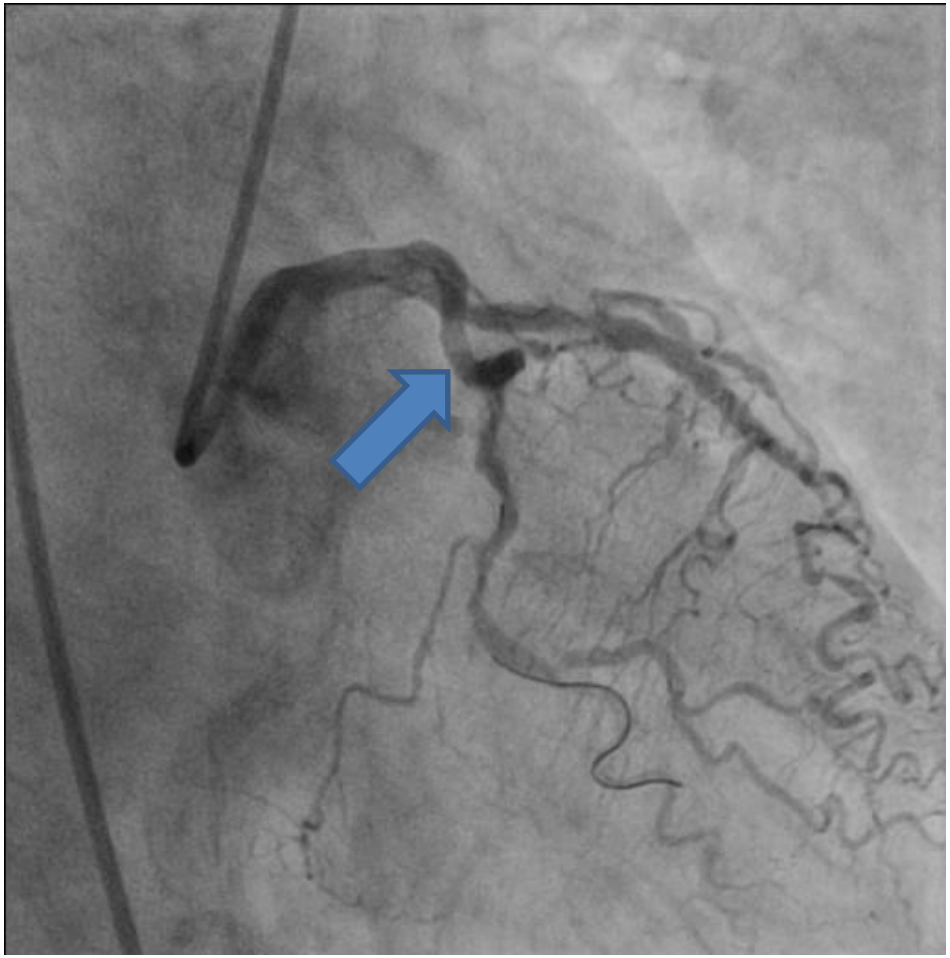
Ongoing pain - referred for acute CAG

UFH iv
Tirofiban
Ticagrelor



CAG, coronary angiography.

PCI with DES in Cx



Cx, circumflex artery; DES, drug-eluting stent; PCI, percutaneous coronary intervention.

84 year old lady: medication during/after PCI?

- Medication:

- Aspirin 75 mg life long

- Tirofiban: 25 mcg/kg bolus followed by an infusion of 0.075 mcg/kg/min (reduced dose as eGFR<60 ml/min) for 6 hours.
- Ticagrelor 90 mg bid for 12 months
- PPI – for some time

PCI, percutaneous coronary intervention; PPI, proton pump inhibitor.

Take home messages

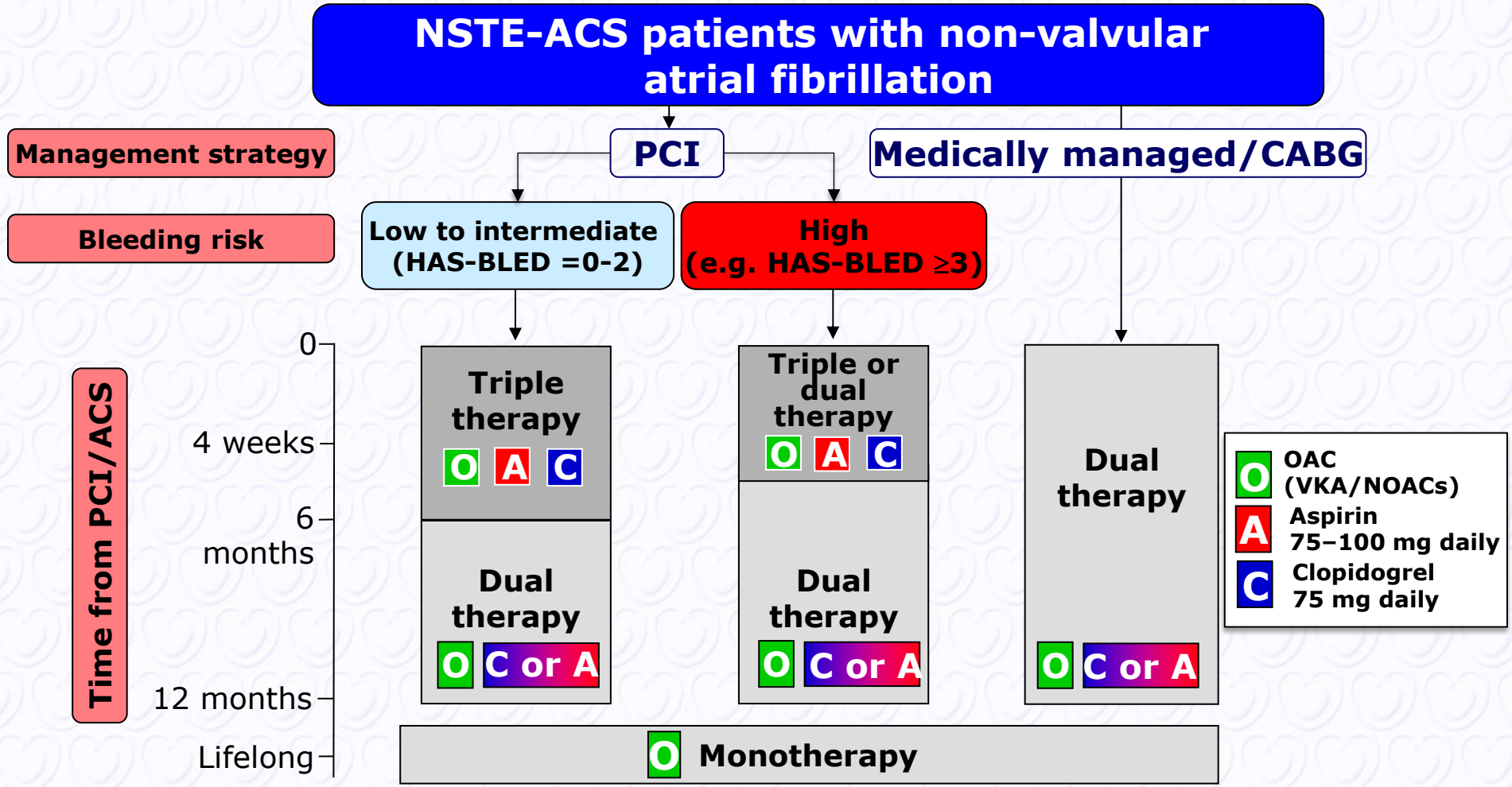
- Fondaparinux is an efficient and safe anticoagulant that is strongly recommended in NSTEMI-ACS when the diagnosis is established - in patients undergoing PCI additional UFH should be given
- GPI inhibitors should be considered in complex PCI with heavy thrombus burden and in bail out situations
- GPI inhibitors may be considered in PCI patients not pretreated with P2Y12 inhibitors

Antithrombotics in ACS/PCI

Thank you very much for your attention

Back up

ESC NSTEMI guidelines 2015



www.escardio.org Roffi M, *et al. Eur Heart J* 2015; Epub ahead of print.

ACS = acute coronary syndrome; CABG = coronary artery bypass graft; ESC = European Society of Cardiology; (N)OAC = (non-VKA) oral anticoagulants; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; VKA = vitamin K agonist.

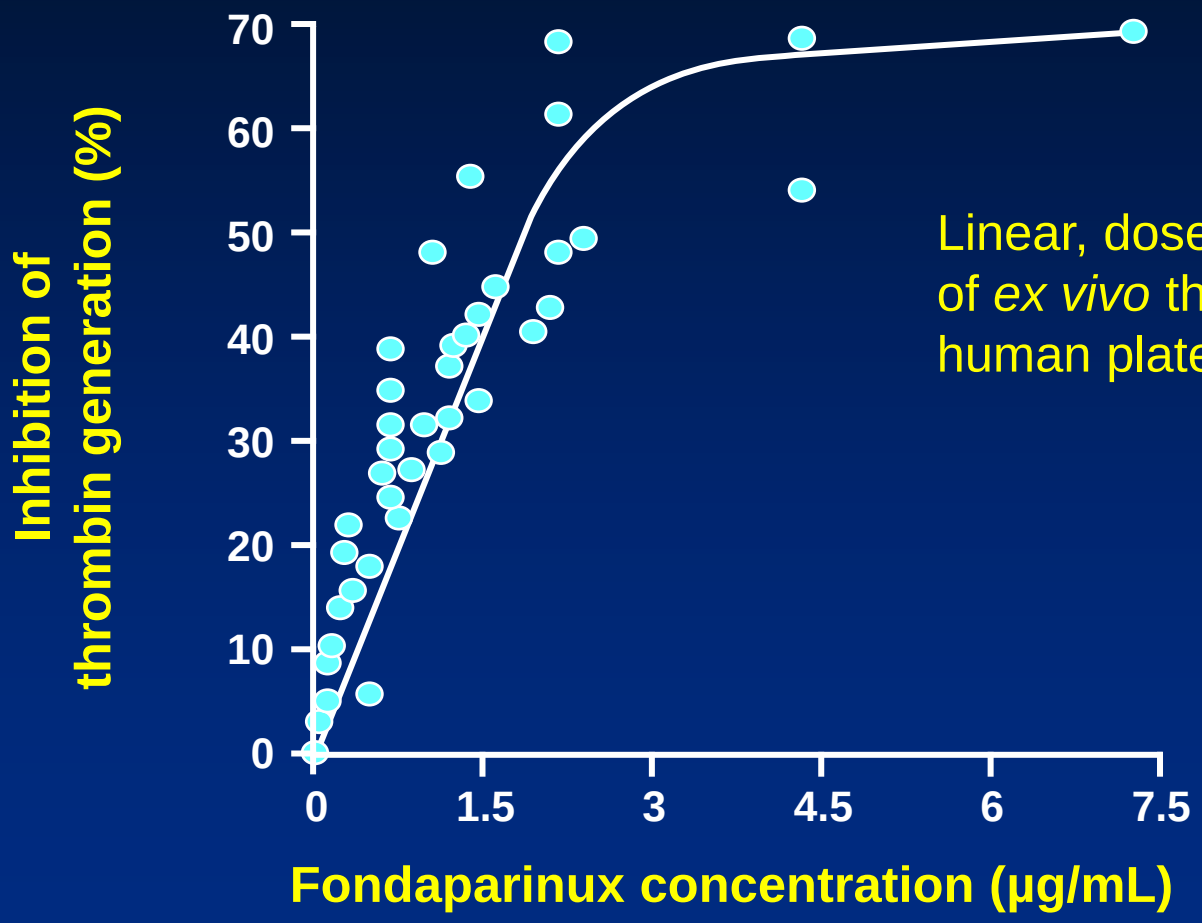
EUROPEAN SOCIETY OF CARDIOLOGY®

Summary: Evolving practices

- Sensitivity to bleeding risks
- Lowering dose of heparin (and ACT target)
- More potent, consistent, faster oral antiplatelets
- Choice of anticoagulant therapy
- Shorter procedures
- PCI goals and unique patient characteristics
- Better and smaller equipment
- Evolving PCI landscape
  - Radial access and measures to reduce bleeding
  - Impact of newer ADP-receptor antagonists

ACT = activated clotting time; ADP = adenosine diphosphate;
PCI = percutaneous coronary intervention.

Fondaparinux has highly predictable activity

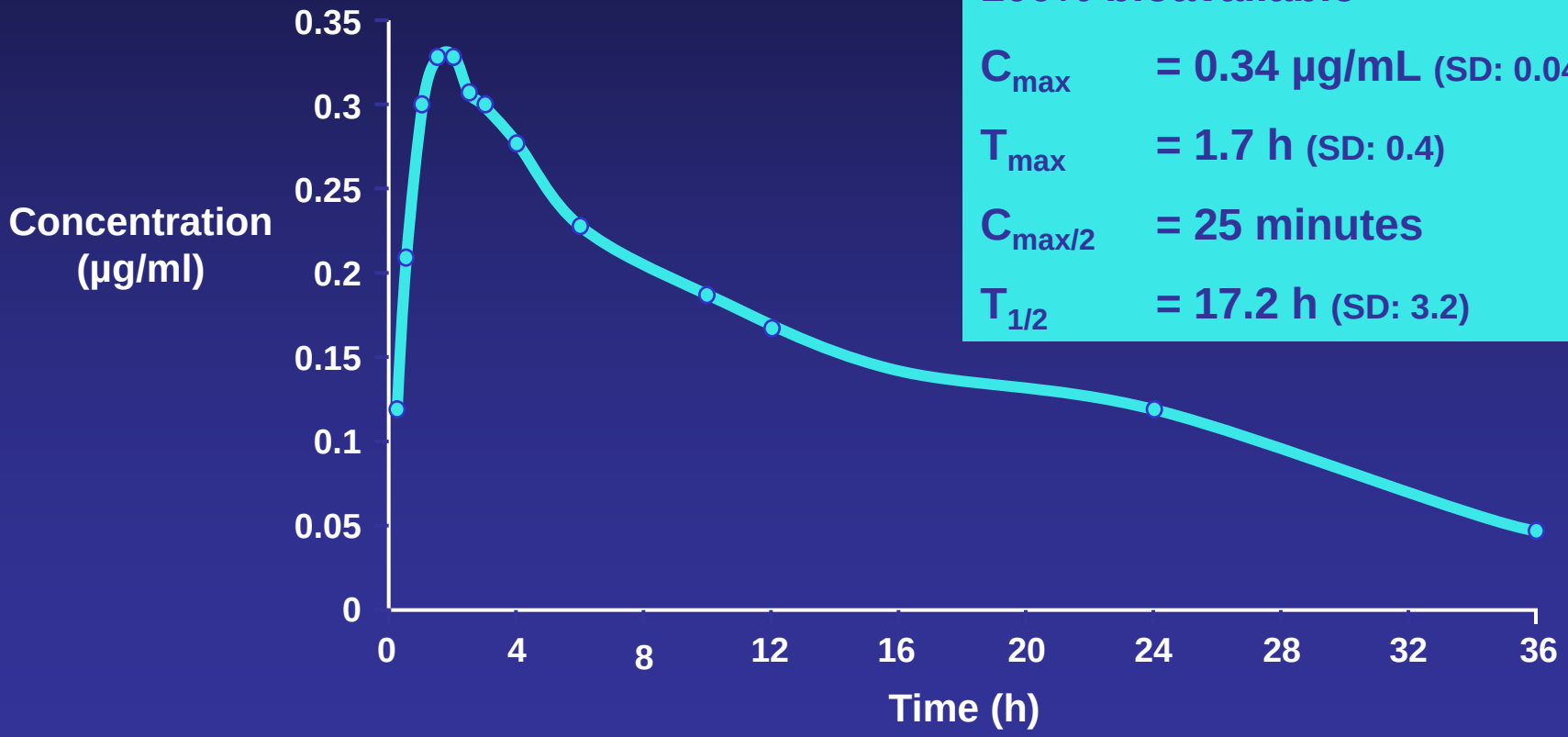


Linear, dose-dependent inhibition of *ex vivo* thrombin generation in human platelet-depleted plasma

Lormeau JC & Herault JP. *Thromb Haemost* 1995; **74**:1474–1477.

Arixtra® Pharmacokinetic Profile:

Rapid onset of action
Significant plasma levels within 25 minutes
Low variability



100% bioavailable

- C_{max} = 0.34 µg/mL (SD: 0.04)
- T_{max} = 1.7 h (SD: 0.4)
- $C_{max/2}$ = 25 minutes
- $T_{1/2}$ = 17.2 h (SD: 3.2)

Donat F, et al. Clin Pharmacokinet 2002;41 Suppl 2:1–9

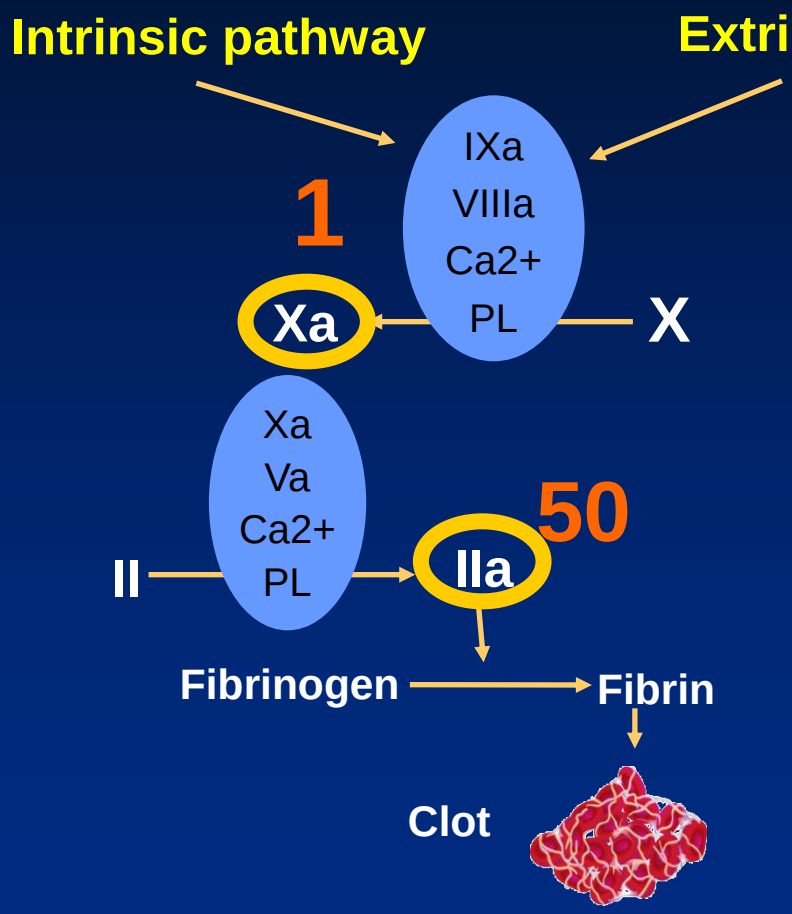
Fibrinolytic therapy

Antithrombin co-therapy with fibrinolysis		
Anticoagulation is recommended in STEMI patients treated with lytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. The anticoagulant can be:	I	A
• Enoxaparin i.v followed by s.c. (using the regimen described below) (preferred over UFH).	I	A
• UFH given as a weight-adjusted i.v. bolus and infusion.	I	C
In patients treated with streptokinase, fondaparinux i.v. bolus followed by s.c. dose 24 h later.	IIa	B

Steg PG, *et al. Eur Heart J* 2012; 33:2569–2619.

STEMI = ST-segment elevated myocardial infarction; UFH = unfractionated heparin.

Factor Xa:
A key step in coagulation pathway



Inhibition of Factor Xa can more effectively inhibit the generation of thrombin, than inhibiting thrombin itself

PL = phospholipid.

Rosenberg RD & Aird WC. *N Engl J Med* 1999; **340**:1555–1564;
Wessler S & Yin TY. *Thromb Diath Haemorrh* 1974; **32**:71–78.

Antithrombotic treatment in stable coronary artery disease patients undergoing PCI

SCAD

Recommendations	Class	Level
Peri-interventional treatment		
Aspirin is indicated before elective stenting.	I	A
An oral loading dose of aspirin (150-300 mg p.o. or 75-250 mg i.v.) is recommended if the patient is not pre-treated.	I	C
Clopidogrel (600 mg loading dose, 75 mg daily maintenance dose) is recommended for elective stenting.	I	A
Glycoprotein IIb/IIIa antagonists should be considered only for bail-out.	IIa	C
Prasugrel or ticagrelor may be considered in specific high-risk situations of elective stenting (e.g. history of stent thrombosis or left main stenting).	IIb	C

NO CHANGE

∑: Aspirin plus Clopidogrel

Option without randomized data

2018 ESC/EACTS Guidelines on myocardial revascularisation
European Heart Journal (2018) 00, 1-96 - doi:10.1093/eurheartj/ehy394