Update su Anticoagulanti e Sanguinamento.
Case-Load & Case-Mix al Pronto Soccorso
Convegno Nazionale SIMEU 2016

NSTE-ACS sanguinamento…e Fondaparinux

Alberto Conti
Medicina d'Urgenza & PS
ASL Nord-Ovest, Massa, SSN Toscana

Milestones in ACS Management

Anti-Thrombin Rx

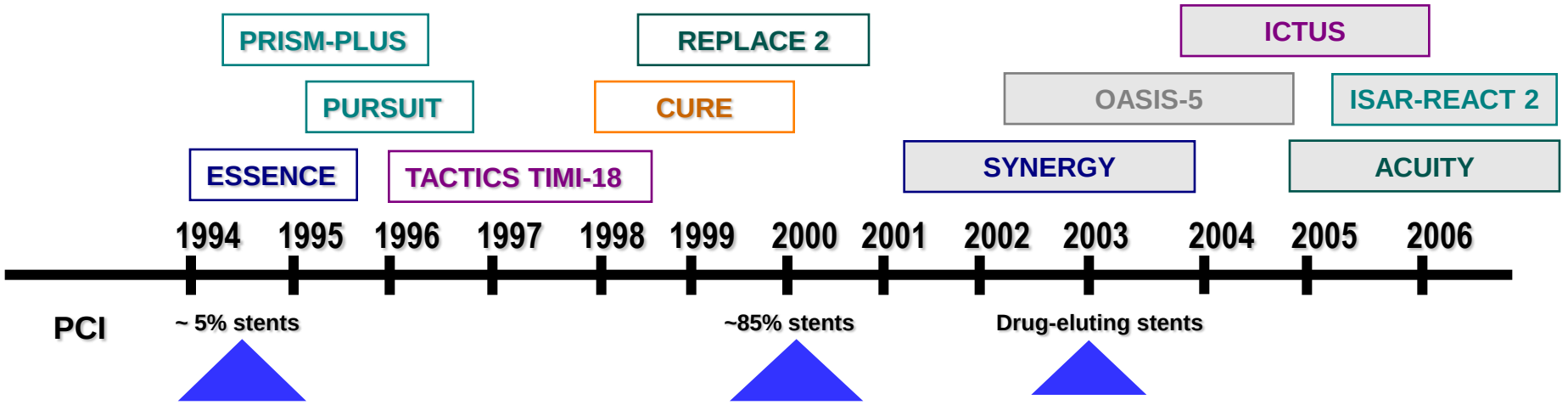
Heparin — LMWH — Bivalirudin — [Fondaparinux]

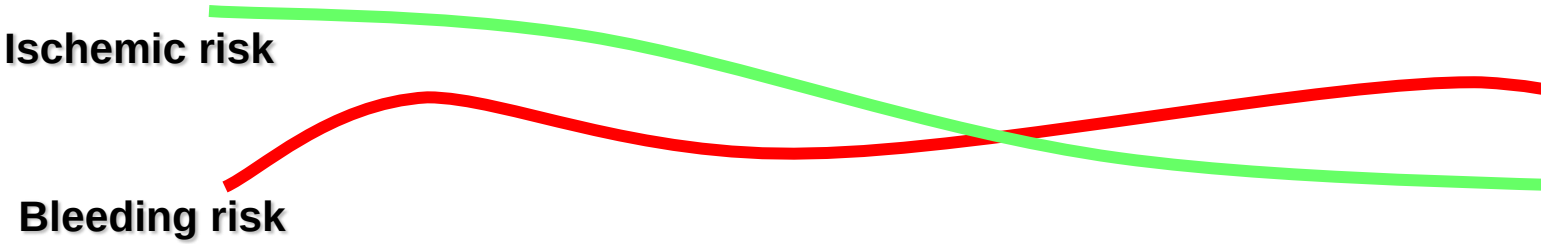
Anti-Platelet Rx

Aspirin — GP IIb/IIIa blockers — Clopidogrel

Treatment Strategy

Conservative — Early invasive



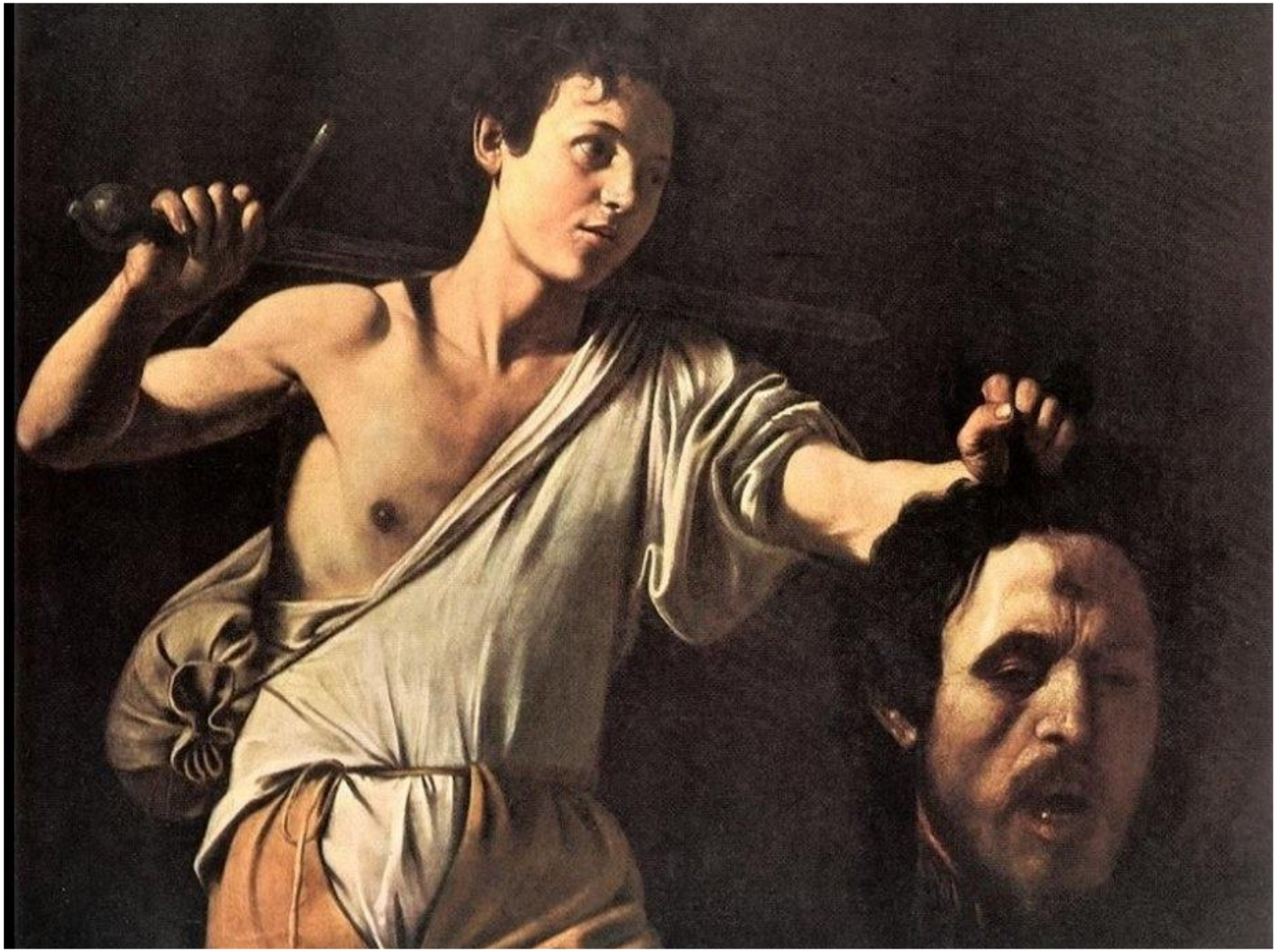


S Manukian 2010

Michelangelo Merisi (Caravaggio)
ritrasse numerose volte “la decapitazione”

La Testa della Medusa
David e Goliath
Salome con la testa di Giovanni Battista
La decapitazione di Holofernes da parte di Judith
La decapitazione di Giovanni Battista

Testa della Medusa. Caravaggio (1598 ca.)
Galleria degli Uffizi, Firenze



David e Goliath. Caravaggio (1606)
Kunsthistorisches Museum, Vienna

Salome con la testa di San Giovanni Battista. Caravaggio (1607)
National Gallery London

Judith decapita Holofernes. Caravaggio (1610).
Museo Palazzo Barberini, Roma

Decollazione San Giovanni Battista. Caravaggio (1608)

La Valletta, Malta Cattedrale di San Giovanni.

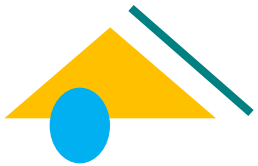
Decollazione San Giovanni Battista. Caravaggio (1608)

La Valletta, Malta Cattedrale di San Giovanni.

Sangue e Sanguinamenti

Giovanni di Paolo

Con l'immagine porta l'informazione,
degli aspetti della circolazione arteriosa



Giovanni di Paolo e Grazia. Siena 1450 ca

Giovanni di Paolo e Grazia. Siena 1450 ca

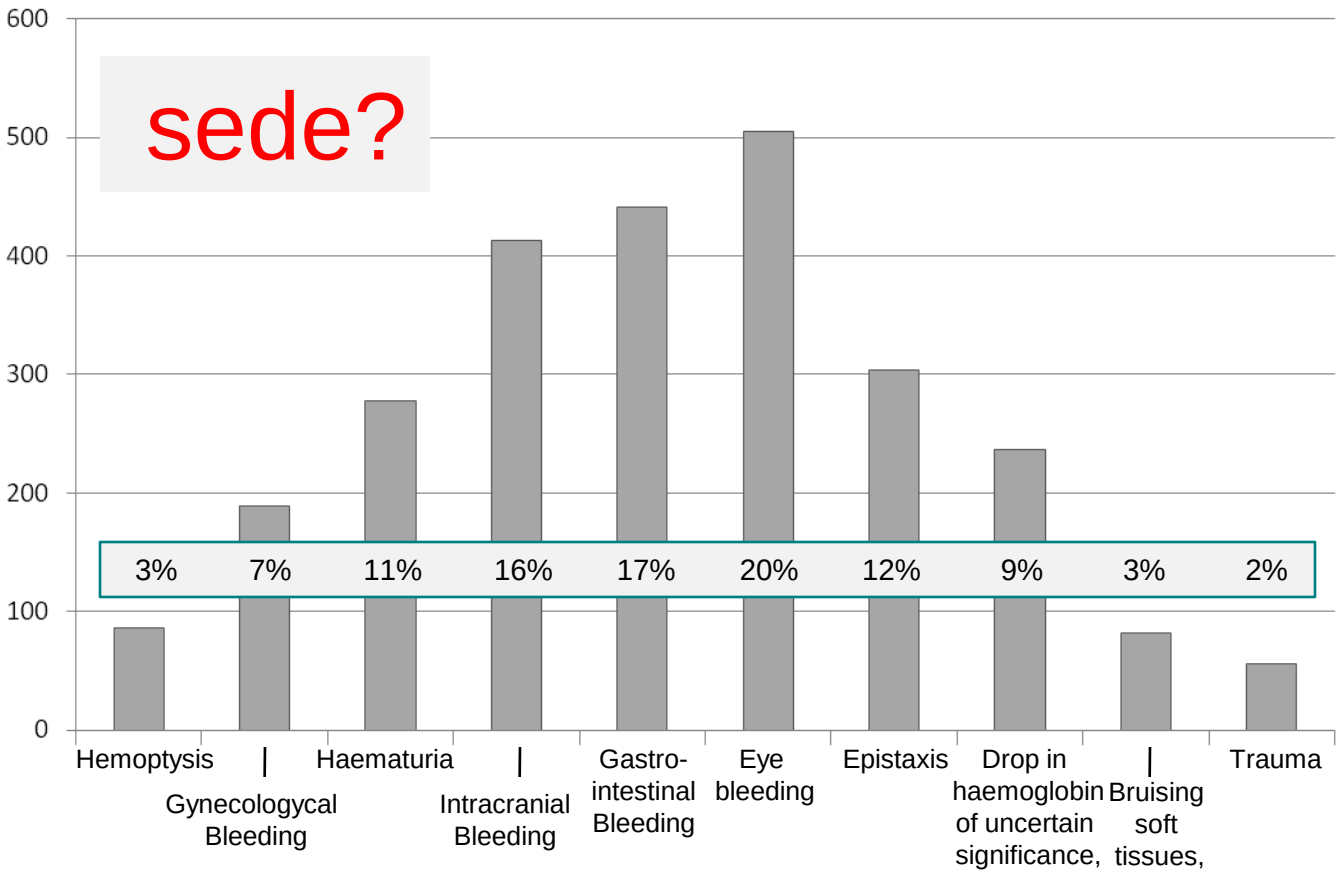
SIMEU Toscana

Bleeding at the Emergency Department

Survey Regione Toscana
3 Ospedali Universitari e 6 di Comunità

2.592 pazienti
Survey 3 mesi
aprile-maggio-giugno 2016

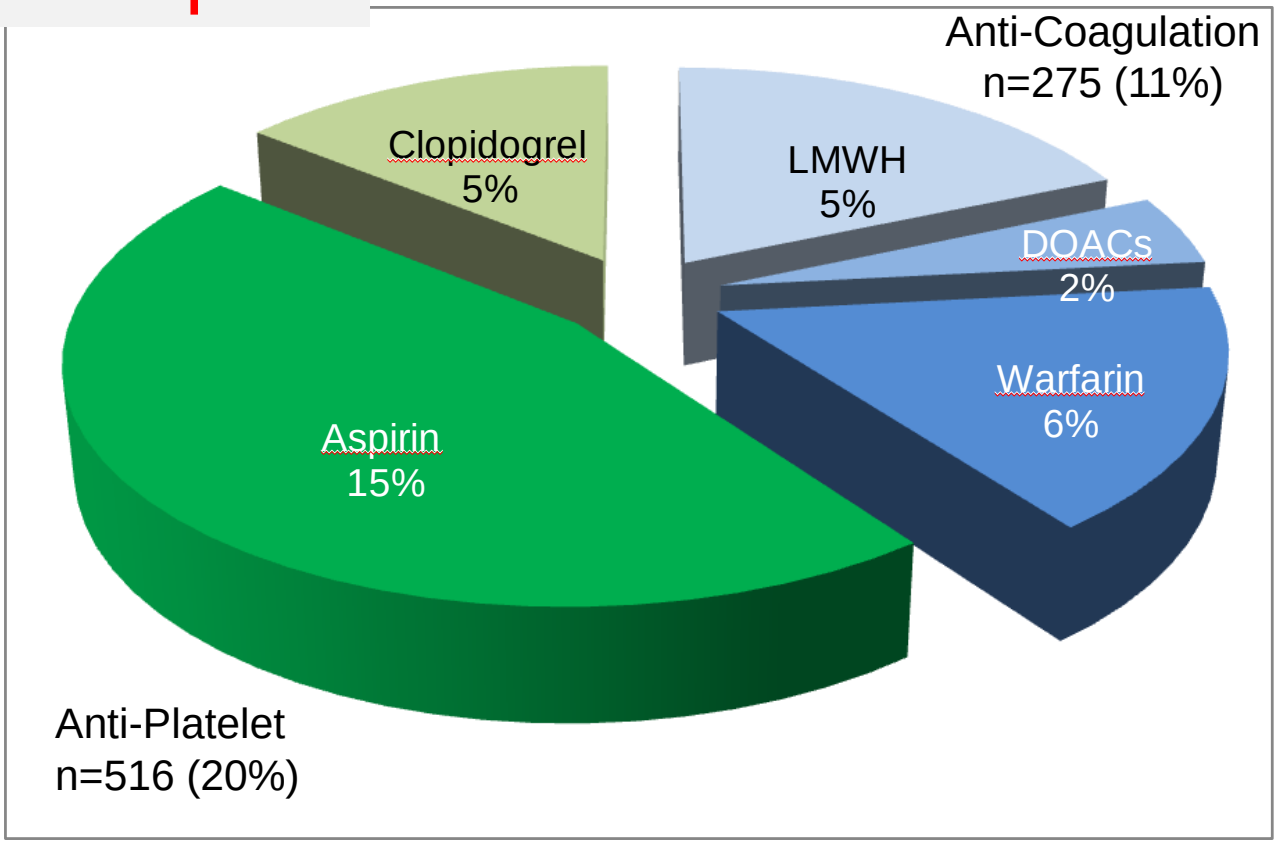
Bleeding at the Emergency Department (SIMEU Survey Regione Toscana; n=2592, 3-month survey 2016)



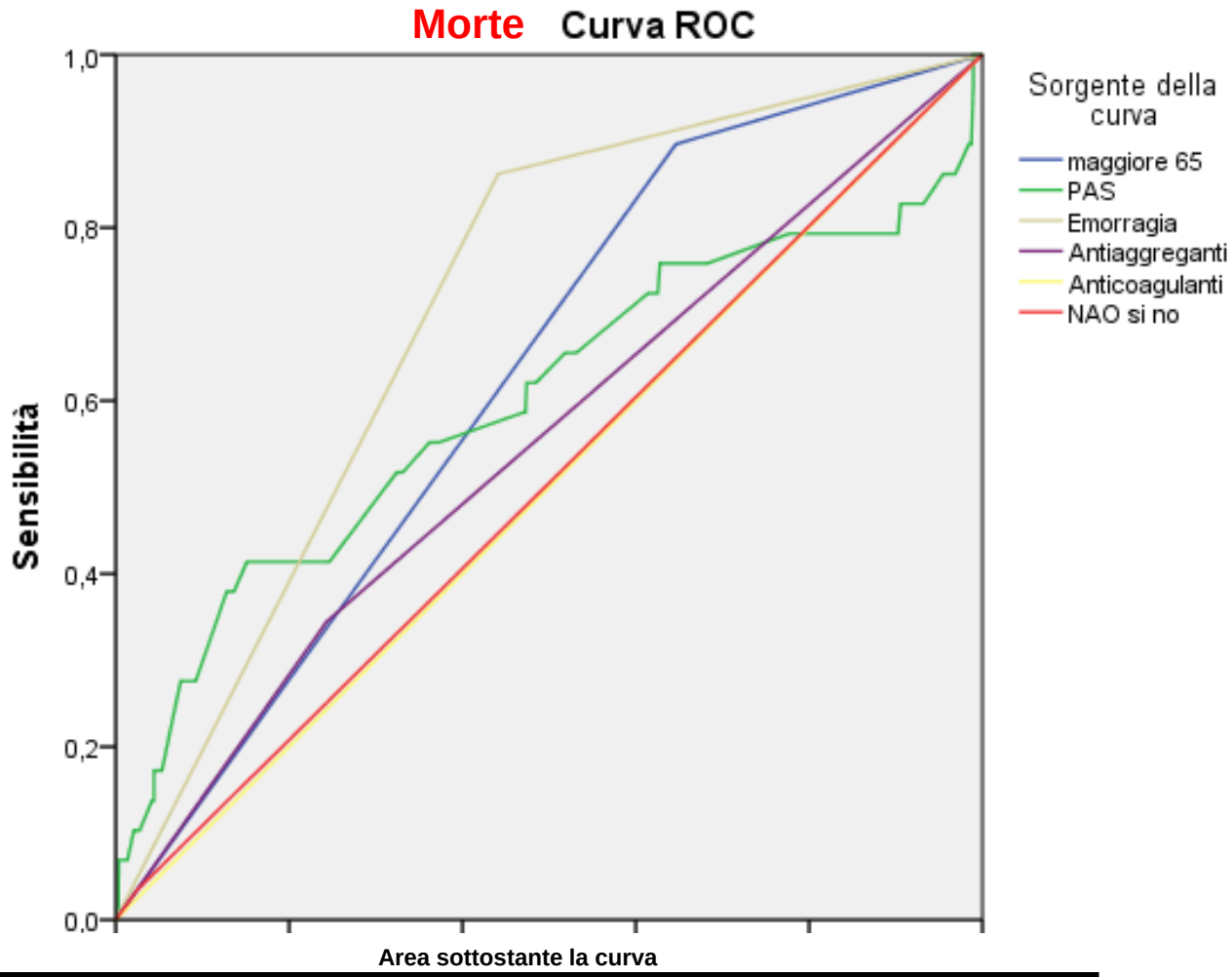
Data on file: Medicina d'Urgenza ASL Nord-Ovest Massa-Carrara

Bleeding at the ED based on pharmacological treatment (SIMEU Survey Regione Toscana; n=2592, 3-month survey 2016)

Terapia?



Death as the Primary Endpoint in Bleeding pts at the ED (n=2592, 3-month survey 2016)



Variabili del risultato del test	Area	Errore std[a]	Sig. asintotica[b]	Intervallo di confidenza al 95% asintotico	
				Limite inferiore	Limite superiore
maggiore 65	,625	,045	,021	,538	,713
PAS	,598	,066	,071	,470	,726
Emorragia	,710	,041	,000	,630	,791
Antiaggreganti	,551	,056	,350	,441	,661
Anticoagulanti	,500	,054	,999	,394	,606
NAO si no	,505	,055	,928	,398	,612

CHEST PAIN

2000, NEJM Evaluation of the patient with chest pain.
2002, Eur Heart J Task force on the management of chest pain.

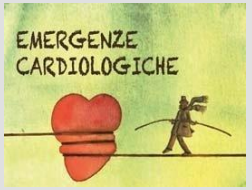
ACS

2012, Eur Heart J ESC Guidelines for the management of AMI in patients presenting with ST-segment elevation.
2015, Eur Heart J ESC Guidelines for the management of ACS in patients presenting without persistent ST-s-E.

CHEST PAIN

2015, Circulation. The Heart Pathway RCT: ED patients with chest pain for early discharge
2016, NICE Guidelines. Chest pain of recent onset (in development:GID-CGWAVE0774)
2016, Circulation. State of the Art Evaluation of ED patients with potential ACS

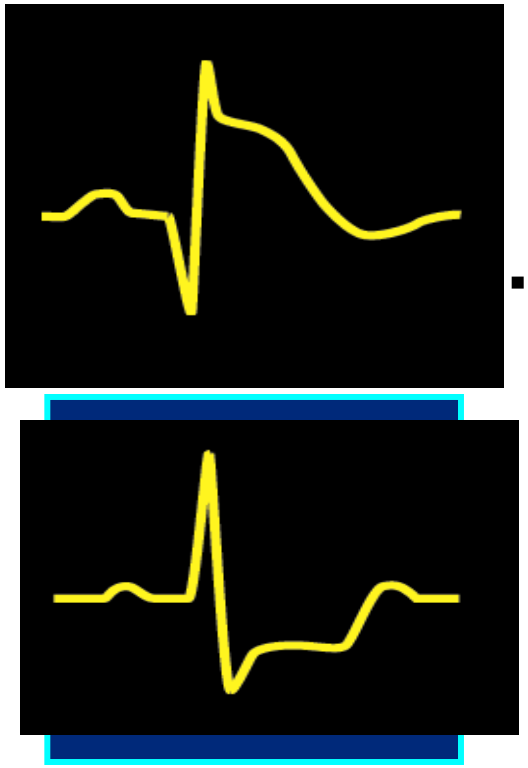
Napoli. Piazza del Plebiscito nell'800



ECG: chiave della stratificazione del rischio

Lab. Emodinamica o UCIC

Osservazione Breve in DEA



Δ ST

ECG: normale
o non diagnostico

alto rischio
>70%

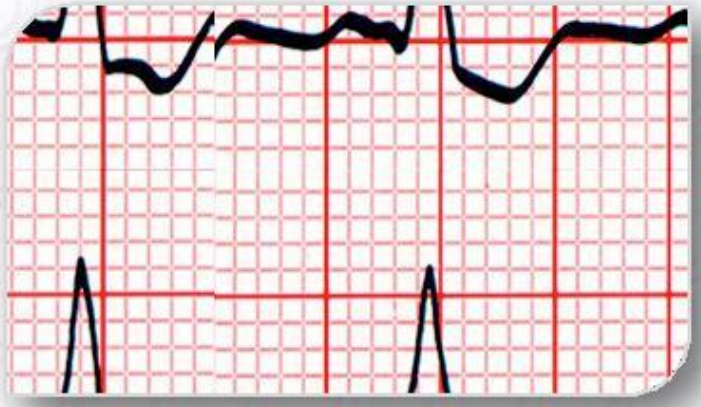
basso rischio
<5-20%

Criteria for Non-ST Segment Elevation

New horizontal or down-sloping ST segment depression ≥ 0.05 mV in 2 contiguous leads,

or

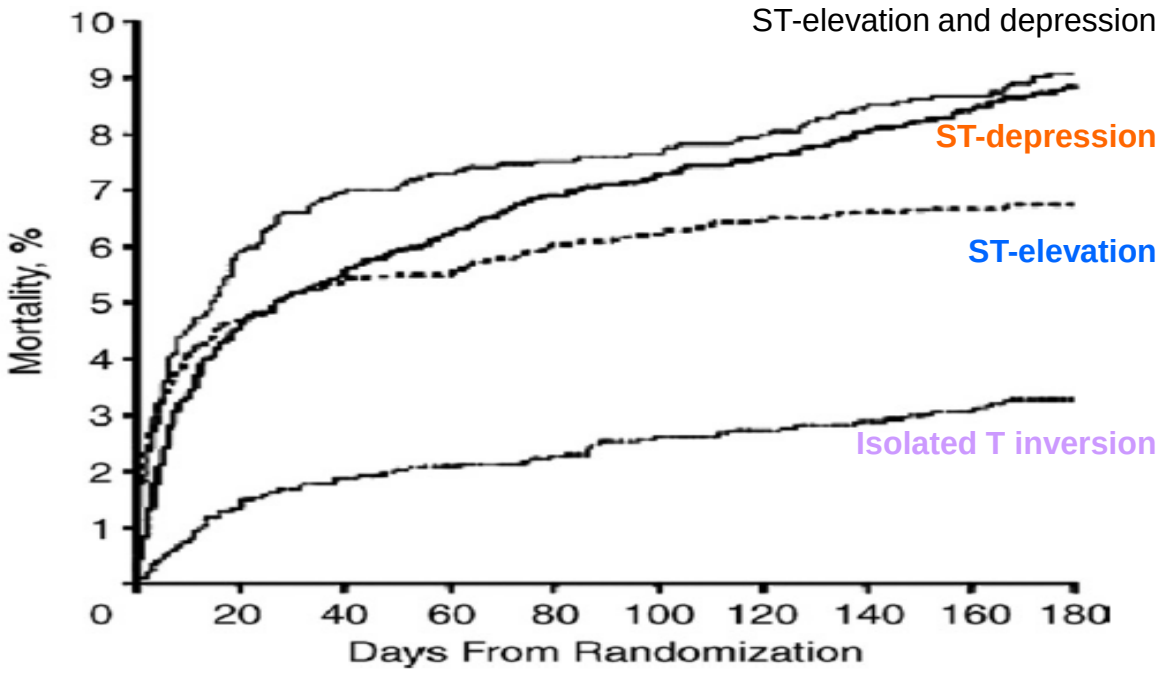
T inversion ≥ 0.1 mV in 2 contiguous leads with prominent R wave or R/S ratio > 1.



2012 ESC Guidelines for the Management of STEACS Eur Heart J doi:10.1093/euroheartj/ehv215; Eur Heart J 2012, 33

NSTE-ACS e mortalità: **1.5-4% (breve-termine); 5-11% (medio-termine: 6-mesi).**

ACC/AHA stat. update 1999; PRAIS-UK, Eur Heart J 2000.



Savonitto JAMA 1999.

Classificazione basata su Troponina

NSTE-ACS

- Angina instabile: con troponina normale.
- NSTEMI: con troponina elevata.

Oggi

NSTEACS basso rischio

NSTEACS alto rischio

Napoli. Palazzo reale: Scala d'Ingresso

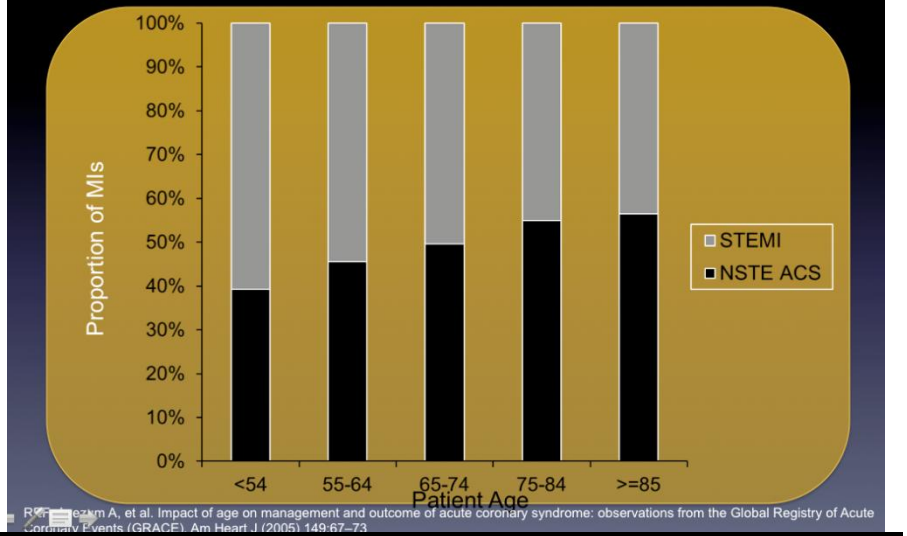
Peters RJ, NSTEACS. BMJ. 2007 Jun 16;334(7606):1265-9.
Management of NSTEACS, ESC (2011)

NSTEACS: risk criteria for invasive strategy

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

Type of MI by Age

Older adults with MI are more likely to have non-ST segment elevation ACS.



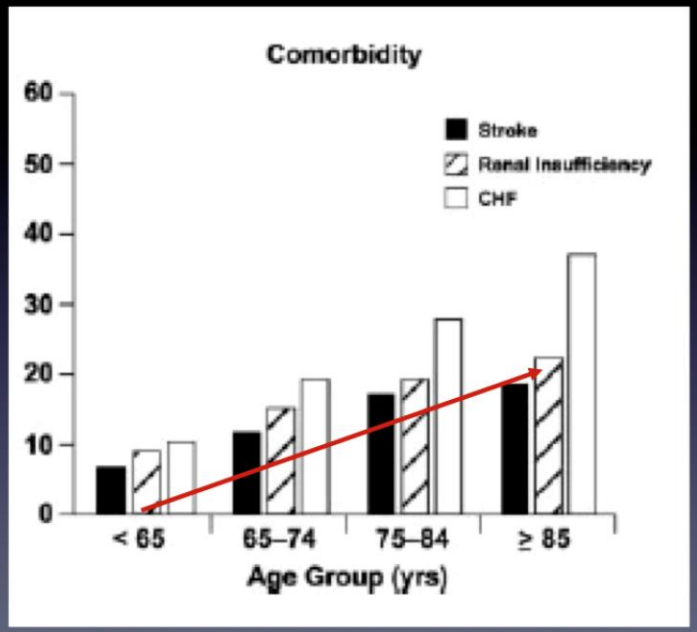
Rogers WJ, Canto JG, Lambrew CT, et al. Impact of age on management and outcome of acute coronary syndrome: observations from the Global Registry of Acute Coronary Events (GRACE). Am Heart J (2005) 149:67–73

Complexity of NSTEMI Pts
STEMI vs. NSTEMI Characteristics

Variable	CRUSADE STEMI (n = 8,011)	CRUSADE NSTEMI (n = 180,842)
Mean age ± SD (yrs)	62 ± 12	69 ± 14
Female sex (%)	31	40
Diabetes mellitus (%)	22	33
Prior MI (%)	18	30
Prior CHF (%)	6	18
Prior PCI (%)	17	21
Prior CABG (%)	7	19

CRUSADE through June 30, 2007

NSTE-ACS: ETA' & Comorbilità



NSTE-ACS:

Pazienti più anziani, più fragili ed affetti da un maggior numero di copatologie

Terapia?

Napoli. Panorama del Golfo

2015 ESC Guidelines for the Management of NSTEACS Eur Heart J

Dolore toracico: NSTEACS

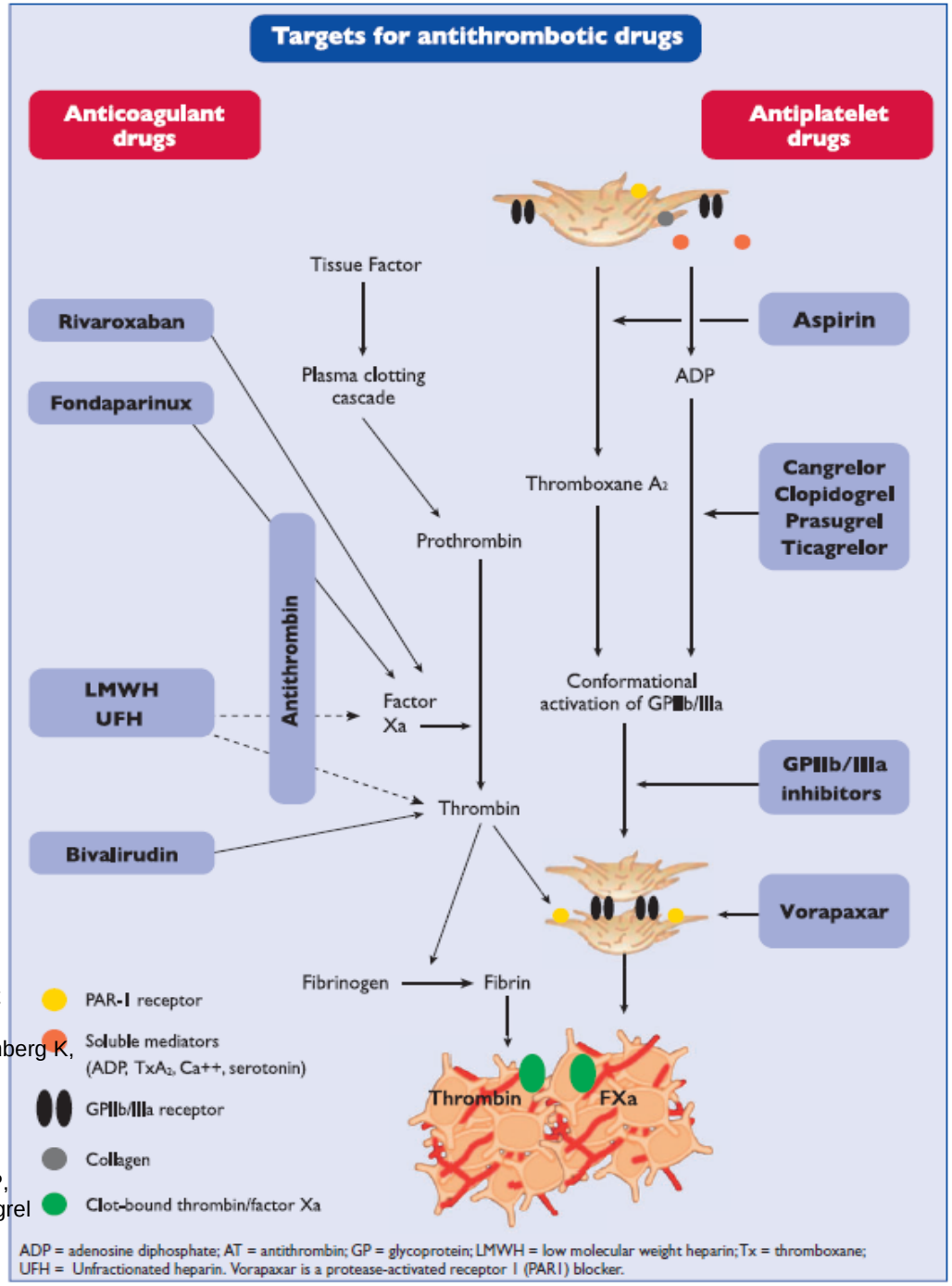
Recommendations	Class[a]	Level[b]	Ref.[c]
Oral antiplatelet therapy			
Aspirin is recommended for all patients without contraindications at an initial oral loading dose[d] of 150–300 mg (in aspirin-naive patients) and a maintenance dose of 75–100 mg/day long-term regardless of treatment strategy.	I	A	129–132
A $P2Y_{12}$ inhibitor is recommended, in addition to aspirin, for 12 months unless there are contraindications such as excessive risk of bleeds.	I	A	137, 148, 153
• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications,[e] for all patients at moderate-to-high risk of ischaemic events (e.g. elevated cardiac troponins), regardless of initial treatment strategy and including those pretreated with clopidogrel (which should be discontinued when ticagrelor is started).	I	B	153
• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.[e]	I	B	148, 164
• Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulation.	I	B	137
$P2Y_{12}$ inhibitor administration for a shorter duration of 3–6 months after DES implantation may be considered in patients deemed at high bleeding risk.	IIb	A	187–189, 192

Aspirin reduces MI or death in UA up to 46%
Oral loading dose 150-300 mg; 150 mg iv recomm.
No differences 325 mg versus 100 mg on long-term

128. Patrono C, Andreotti F, Arnesen H, Badimon L, Baigent C, Collet JP, De Caterina R, Gulba D, Huber K, Husted S, Kristensen SD, Morais J, Neumann FJ, Rasmussen LH, Siegbahn A, Steg PG, Storey RF, Van deWerf F, Verheugt F. Antiplatelet agents for the treatment and prevention of atherothrombosis. Eur Heart J 2011;32:2922–2932.
129. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. The RISC group. Lancet 1990;336:827–830.
130. Lewis HD Jr, Davis JW, Archibald DG, Steinke WE, Smitherman TC, Doherty JE 3rd, SchnaperHW, LeWinterMM, Linares E, Pouget JM, Sabharwal SC, Chesler E, DeMots H. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration cooperative study. N Engl J Med 1983;309:396–403.
131. Theroux P, Ouimet H, McCans J, Latour JG, Joly P, Levy G, Pelletier E, Juneau M, Stasiak J, deGuise P, Pelletier GB, Rinzler D,Waters DD. Aspirin, heparin, or both to treat acute unstable angina. N Engl J Med 1988;319:1105–1111.
132. Cairns JA, Gent M, Singer J, Finnie KJ, Froggatt GM, Holder DA, Jablonsky G, Kostuk WJ, Melendez LJ, Myers MG, Sackett DL, Sealey BJ, Tanser PH. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. N Engl J Med 1985;313:1369–1375.
133. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71–86.
134. Mehta SR, Bassand JP, Chrolavicius S, Diaz R, Eikelboom JW, Fox KA, Granger CB, Jolly S, Joyner CD, Rupprecht HJ, Widimsky P, Afzal R, Pogue J, Yusuf S. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med 2010;363:930–942.

DAPT reduces CE in NSTEACS

However 10% of pts will have CE
and 2% stent thrombosis
due to key gene polymorphisms

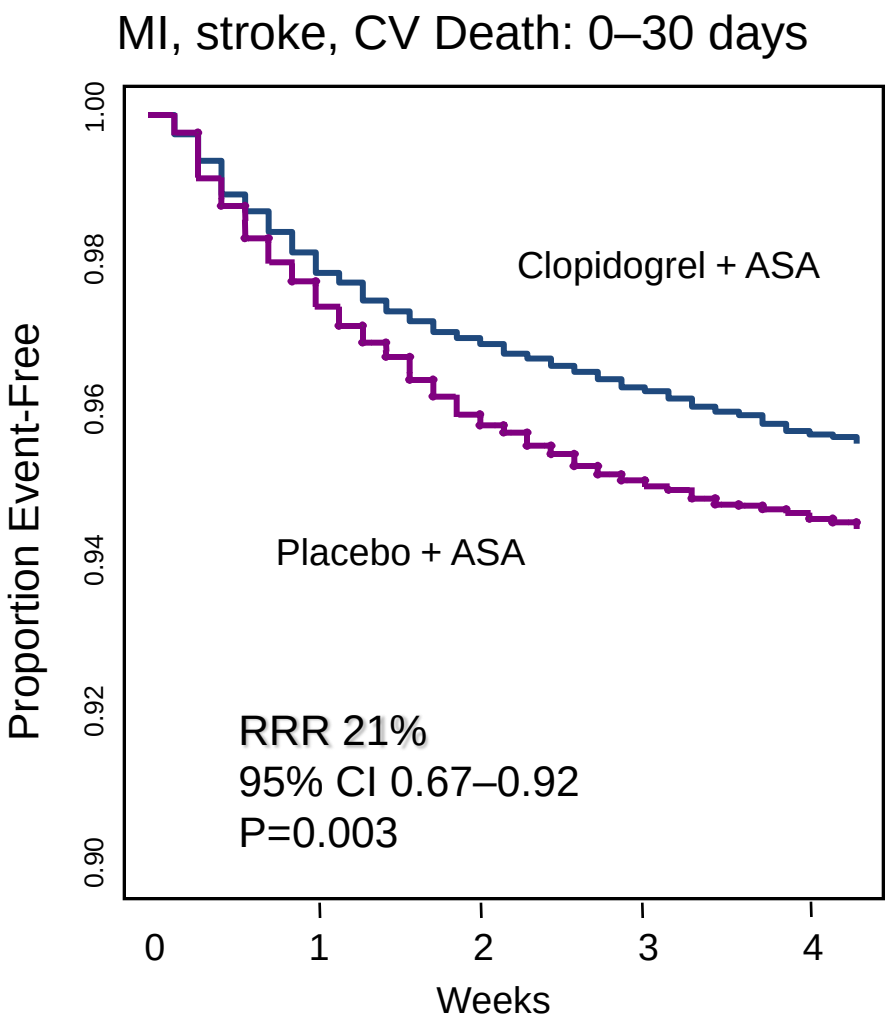


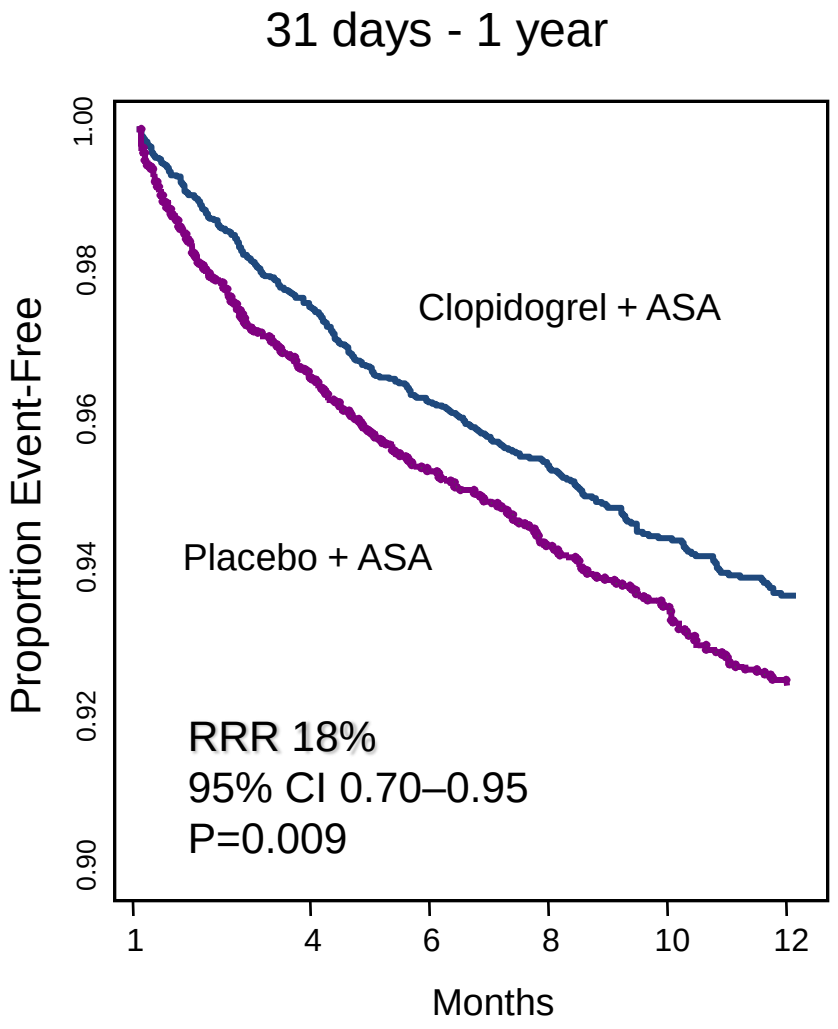
137. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrelin addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001;345:494–502.

138. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, Malmberg K, Rupprecht H, Zhao F, Chrolavicius S, Copland I, Fox KA. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet 2001;358: 527–533.

139. Parodi G, Marcucci R, Valenti R, Gori AM, Migliorini A, Giusti B, Buonamici P, Gensini GF, Abbate R, Antoniucci D. High residual platelet reactivity after clopidogrel loading and long-term cardiovascular events among patients with acute coronary syndromes undergoing PCI. JAMA 2011;306:1215–1223.

CURE: Benefit of Clopidogrel Therapy at Over first year

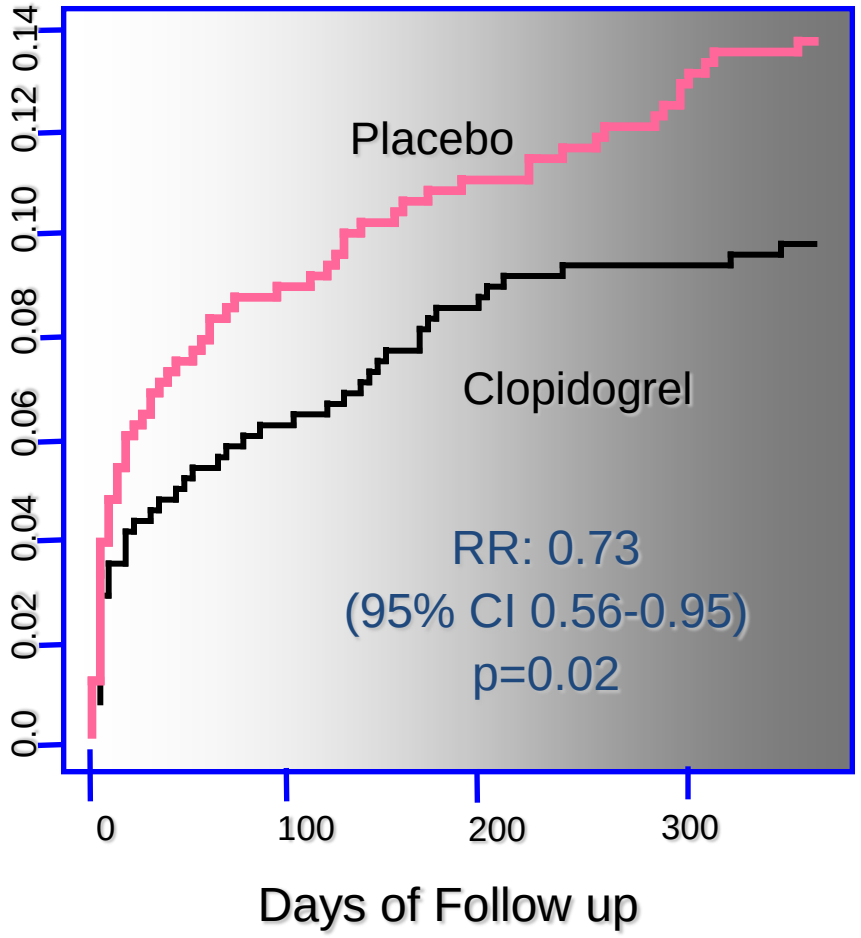




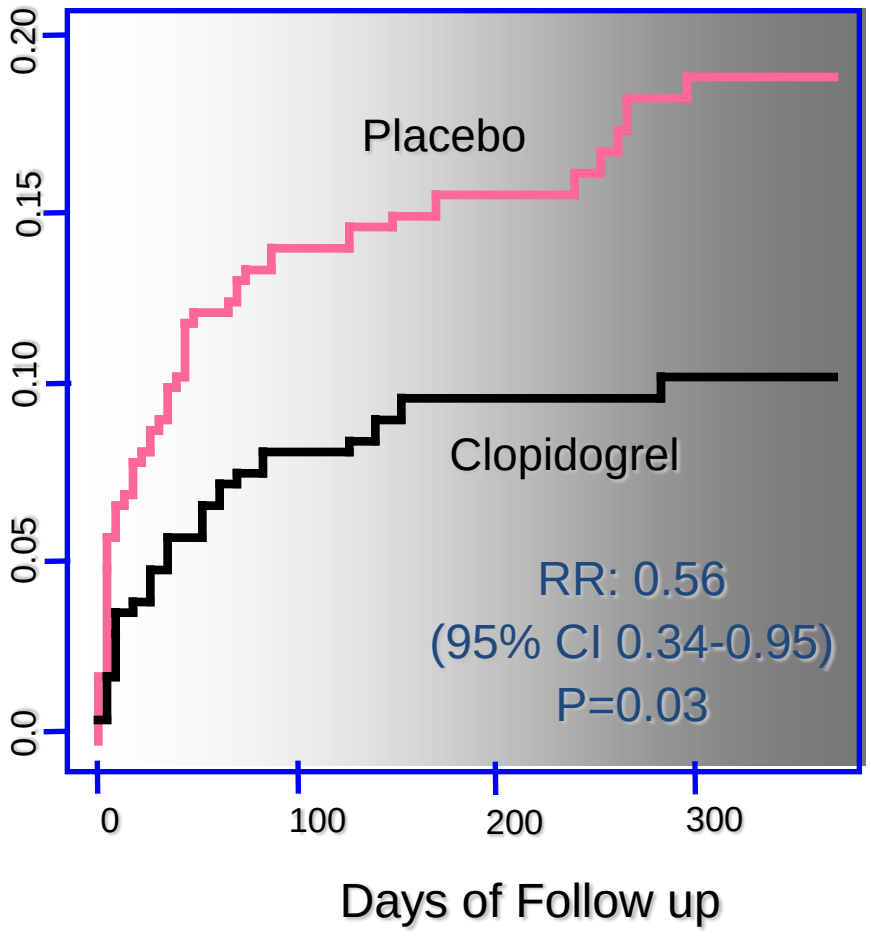
Yusuf, S. et al for THE CURE Trial Investigators. Circ. 2003;107:966-972.

PCI-Cure. Benefit of Clopidogrel in PCI With and Without a Stent

CV Death/MI STENT



CV Death/MI NO STENT



Mehta SR. ACC 2003

NSTEACS and P2Y12-inhibitors

P2Y12 inhibitor has been recommended irrespective of mgmt strategy

-Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, Caso P, Dude Gielen S, Huber K, Ohman M, Petrie MC, Sonntag F, Uva MS, Storey RF, Wijns Zahger D. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: the Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011;32:2999–3054.
- Bellemain-Appaix A, Brieger D, Beygui F, Silvain J, Pena A, Cayla G, Bartheler Collet JP, Montalescot G. New P2Y12 inhibitors versus clopidogrel in percutaneo coronary intervention: a meta-analysis. J Am Coll Cardiol 2010;56:1542–1551.

Argument for or against pretreatment with P2Y12 inh. in NSTEACS pts have been discussed and the topic remains controversial

-Collet JP, Silvain J, Bellemain-Appaix A, Montalescot G. Pretreatment with P2Y12 inhibitors in non-ST-segment-elevation acute coronary syndrome: an outdated and harmful strategy. Circulation 2014;130:1904–1914.
-Valgimigli M. Pretreatment with P2Y12 inhibitors in non-ST-segment-elevation acute coronary syndrome is clinically justified. Circulation 2014;130:1891–1903.

	Clopidogrel	Prasugrel	Ticagrelor	Cangrelor
Chemical class	Thienopyridine	Thienopyridine	Cyclopentyl-triazolopyrimidine	Stabilized ATP analogue
Administration	Oral	Oral	Oral	Intravenous
Dose	300–600 mg orally then 75 mg a day	60 mg orally then 10 mg a day	180 mg orally then 90 mg twice a day	30 μg/kg bolus a… 4 μg/kg/m…
Dosing in CKD				
• Stage 3 (eGFR 30–59 mL/min/1.73m²)	No dose adjustment	No dose adjustment	No dose adjus…	
• Stage 4 (eGFR 15–29 mL/min/1.73m²)	No dose adjustment	No dose adjustment		
• Stage 5 (eGFR <15 mL/min/1.73m²)	Use only for selected indications (e.g. stent thrombosis prevention)	Not recom…		…o dose adjustment
Binding reversibility	Irreversible			Reversible
Activation	Prodrug, with variable liver metab…		…g with additional active metabolite	Active drug
Onset of loading dose effect[a]			30 min[b]	2 min
Duration of effect		…10 days	3–5 days	1–2 hours
Withdrawal before surgery		7 days[c]	5 days[c]	1 hour
Plasma half-life of active $P2Y_{12}$ inhibitor[d]		30–60 min[e]	6–12 hours	5–10 min
Inhibition of adenosine reuptake	No	No	Yes	Yes ('inactive' metabolite only)

Concertazione con cardiologo-emodinamista di riferimento

NSTEACS and Aticoagulants

Anticoagulants are used to inhibit thrombin generation, thereby reducing thrombus-related events in NSTEACS; the combination with PLT inhibitotors is more effective

Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS, Yusuf S. Unfractionatedheparin and low-molecular-weight heparin in ACS without ST elevation: a meta-analysis. Lancet 2000;355:1936–1942.

UFH remains a widely used anticoagulant in NSTEACS in the context of short delay to cath lab and short hospital stay despite consistent evidence for greater bleeding risk compared with other strategies

Silvain J, Beygui F, Barthelemy O, Pollack C Jr, Cohen M, Zeymer U, Huber K, Goldstein P, Cayla G, Collet JP, Vicaut E, Montalescot G. Efficacy and safety of Enoxaparin versus unfractionated heparin during percutaneous coronary intervention: systematic review and meta-analysis. BMJ 2012;344:e553.

LMWH has a more predictable dose-effect relationship than UFH. The most widely used agent is enoxaparin (1 mg/kg sc twice daily; once daily if GFR < 30 ml/min1.73 m2).

Drug	Recommendations		
	Normal renal function or stage 1–3 CKD (eGFR ≥30 mL/min/1.73m²)	Stage 4 CKD (eGFR 15–29 mL/min/1.73m²)	Stage 5 CKD (eGFR <15 mL/min/1.73m²)
Unfractionated heparin	• Prior to coronary angiography: 60–70 IU/kg i.v. (max 5000 IU) and infusion (12–15 IU/kg/h) (max 1000 IU/h), target aPTT 1.5–2.5x control • During PCI: 70-100 IU/kg i.v. (50–70 IU/kg if concomitant with GPIIb/IIIa inhibitors)	No dose adjustment	No dose adjustment
Enoxaparin	1 mg/kg s.c. twice a day	1 mg/kg s.c. once a day	Not recommended
Fondaparinux	2.5 mg s.c. once a day	Not recommended if eGFR <20 mL/min/1.73m²	Not recommended

-Collet JP, Montalescot G, Lison L, Choussat R, Ankri A, Drobinski G, Sotirov I, Thomas D. Percutaneous coronary intervention after subcutaneous enoxaparin pretreatment in patients with UA. Circulation 2001;103:658–663.
- Martin JL, Fry ET, Sanderink GJ, Atherley TH, Guimart CM, Chevalier PJ, Ozoux ML, Pensyl CE, Bigonzi F. Reliable anticoagulation with enoxaparin in patients undergoing percutaneous coronary intervention: the pharmacokinetics of enoxaparin in PCI (PEPCI) study. Catheter Cardiovasc Interv 2004;61:163–170.

2015 ESC Guidelines for the Management of NSTEACS Eur Heart J doi:10.1093/euroheartj/ehv320

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- Martin JL, Fry ET, Sanderink GJ, Atherley TH, Guimart CM, Chevalier PJ, Ozoux ML, Pensyl CE, Bigonzi F. Reliable anticoagulation with enoxaparin in patients undergoing percutaneous coronary intervention: the pharmacokinetics of enoxaparin in PCI (PEPCI) study. Catheter Cardiovasc Interv 2004;61:163–170.

2015 ESC Guidelines for the Management of NSTEACS Eur Heart J doi:10.1093/euroheartj/ehv320

ACUITY

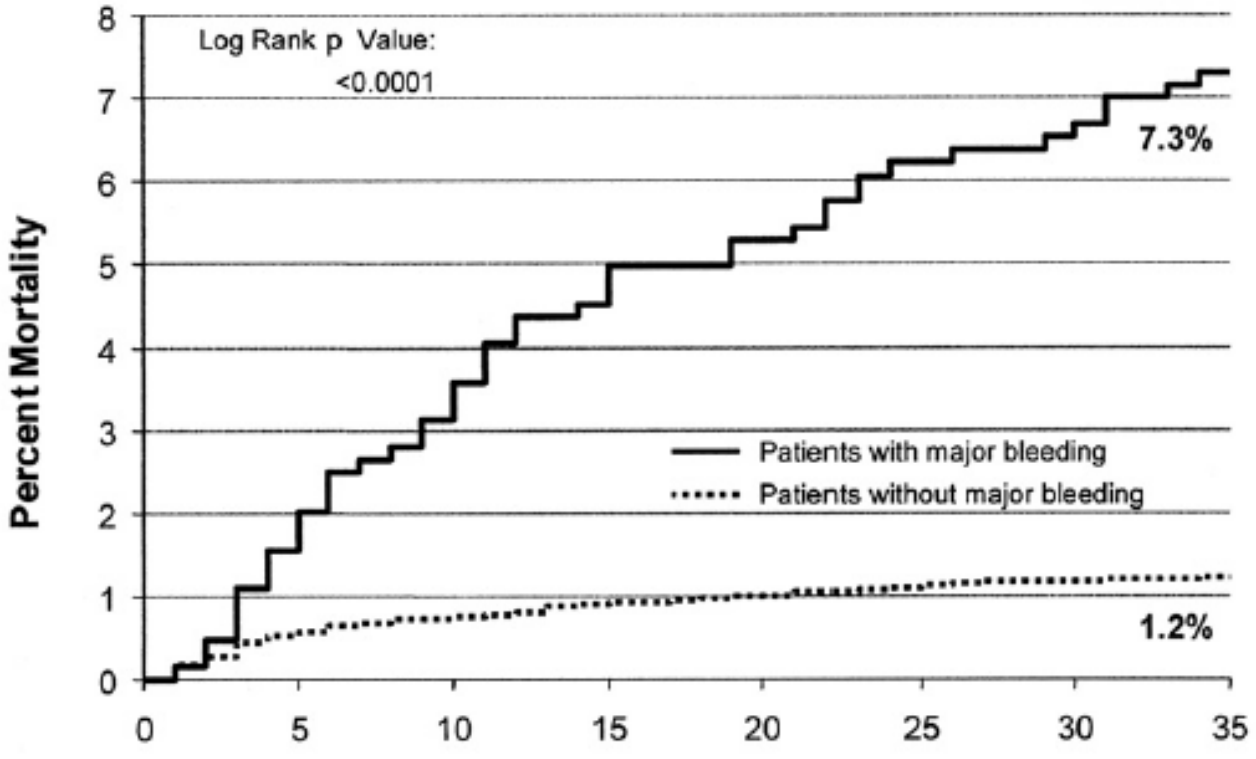
Impact of Major Bleeding on 30-Day Mortality and Clinical Outcomes in Patients With Acute Coronary Syndromes

An Analysis From the ACUITY Trial

Steven V. Manoukian, MD, FACC,* Frederick Feit, MD, FACC,† Roxana Mehran, MD, FACC,‡
Michele D. Voeltz, MD,* Ramin Ebrahimi, MD, FACC,§ Martial Hamon, MD,‖
George D. Dangas, MD, PHD, FACC,‡ A. Michael Lincoff, MD, FACC,¶
Harvey D. White, DSC, FACC# Jeffrey W. Moses, MD, FACC,‡ Spencer B. King III, MD, MACC**
E. Magnus Ohman, MD, FACC,†† Gregg W. Stone, MD, FACC‡

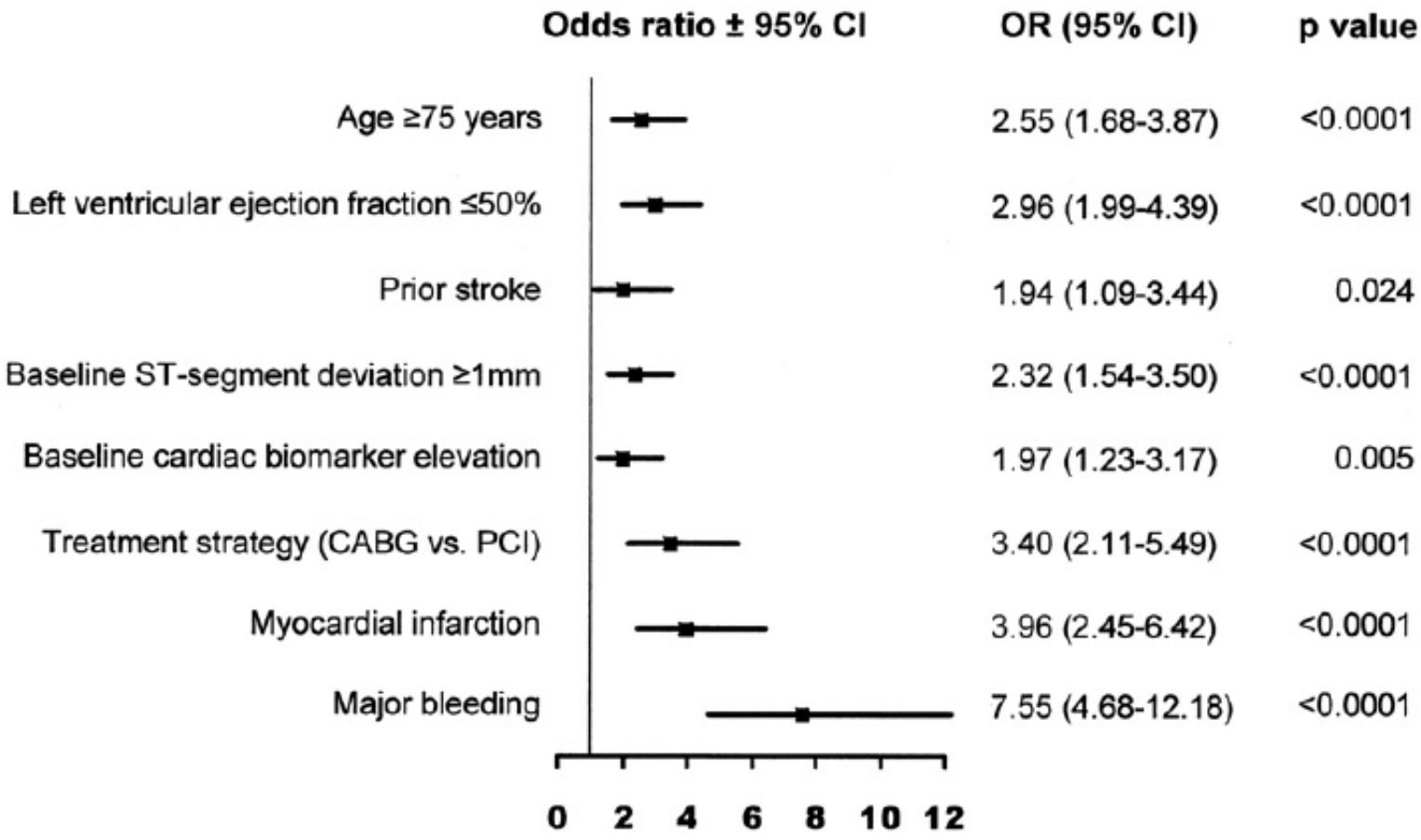
Atlanta, Georgia; Los Angeles, California; New York, New York; Caen, France; Cleveland, Ohio; Auckland, New Zealand; and Durham, North Carolina

ACUITY



Patients at Risk								
Patients with major bleeding:	644	633	623	614	609	602	599	589
Patients without major bleeding:	13169	13009	12975	12951	12933	12911	12864	12761

ACUITY


Odds ratio ± 95% CI
OR (95% CI)
p value
Age ≥75 years
2.55 (1.68-3.87)
<0.0001
Left ventricular ejection fraction ≤50%
2.96 (1.99-4.39)
<0.0001
Prior stroke
1.94 (1.09-3.44)
0.024
Baseline ST-segment deviation ≥1mm
2.32 (1.54-3.50)
<0.0001
Baseline cardiac biomarker elevation
1.97 (1.23-3.17)
0.005
Treatment strategy (CABG vs. PCI)
3.40 (2.11-5.49)
<0.0001
Myocardial infarction
3.96 (2.45-6.42)
<0.0001
Major bleeding
7.55 (4.68-12.18)
<0.0001
0 2 4 6 8 10 12

Sanguinamenti maggiori, trasfusioni, re-infarto miocardico …e rischio di mortalità

Studio ACUITY

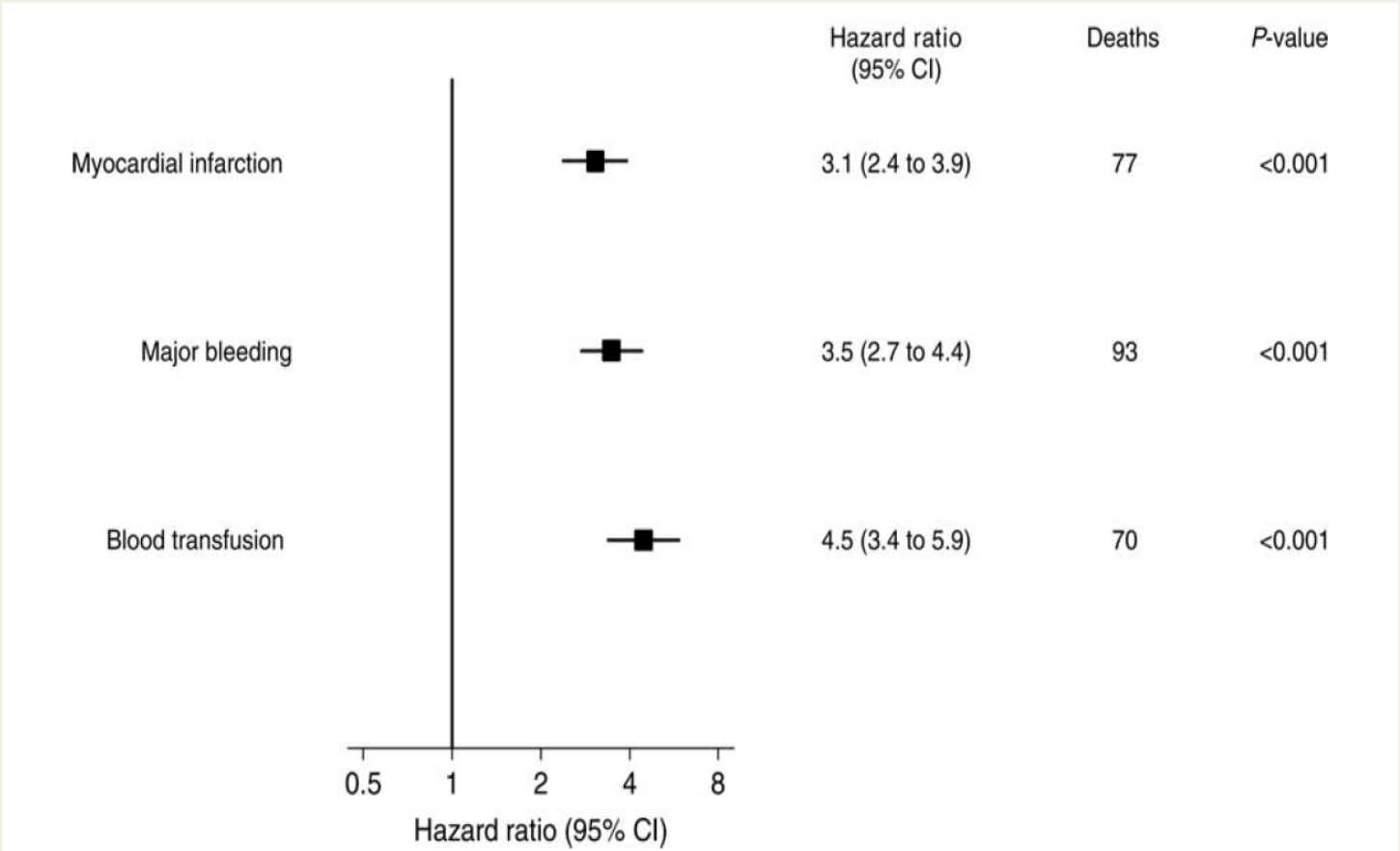


Figure 3 Influence of recurrent MI, major bleed, and non-CABG related blood transfusion on mortality to 1 year [three Cox model with MIs, bleeds, and transfusions as time-updated covariates (pre-/post-event) adjusted for baseline predictors]. When included as a time-updated covariate in the Cox model, major bleeding and blood transfusion within 30 days of randomization had similar or slightly greater risk of 1-year mortality compared with MI within 30 days.

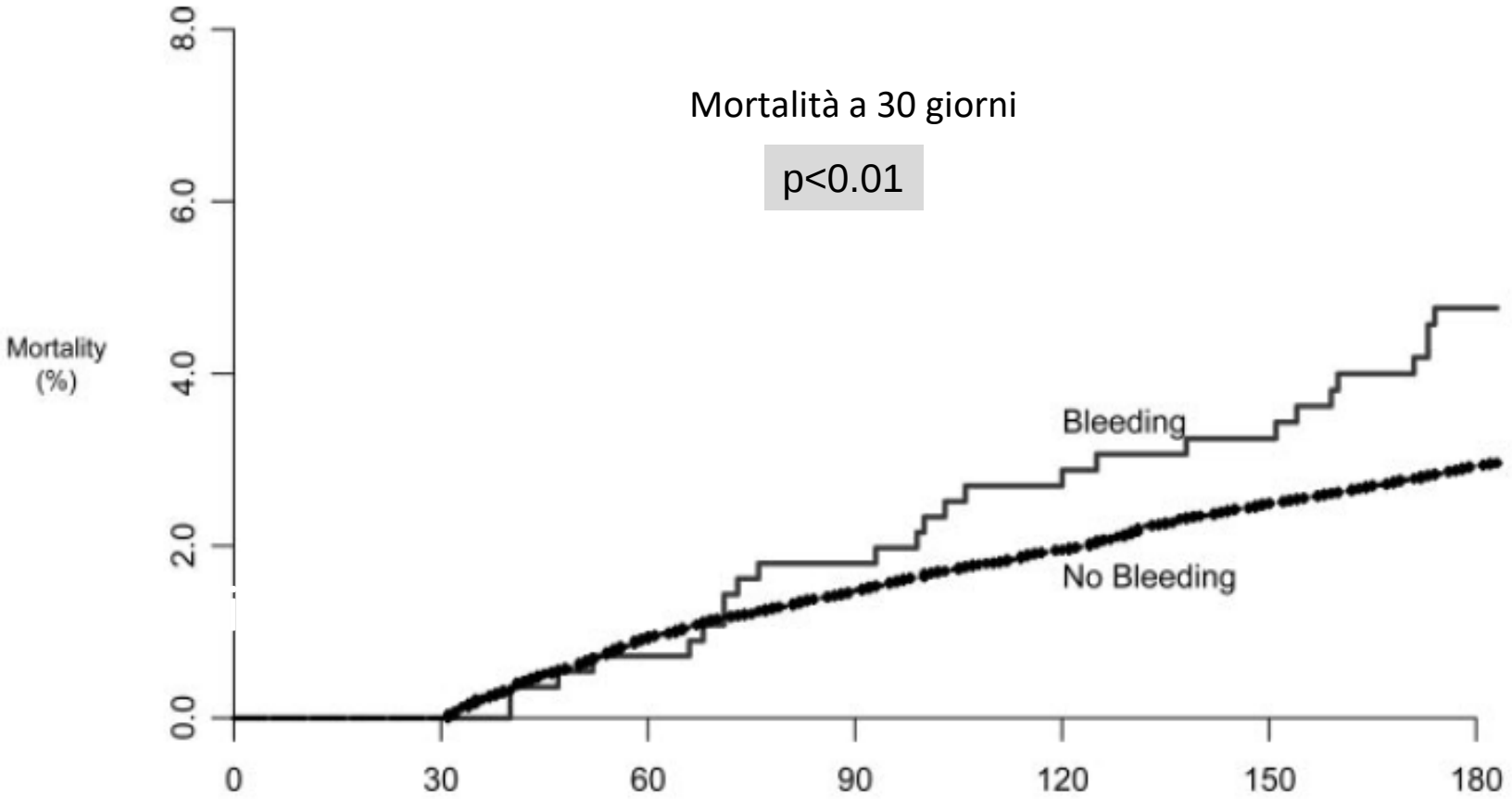
Mehran, R. et al. Eur Heart J 2009 30:1457-1466

Adverse Impact of Bleeding on Prognosis in Patients With Acute Coronary Syndromes

by John W. Eikelboom, Shamir R. Mehta, Sonia S. Anand, Changchun Xie, Keith A.A. Fox, and Salim Yusuf

Mortalità a 30 giorni

p<0.01



Quale strategia di prevenzione per il sanguinamento in ACS ?

Milestones in ACS Management

Anti-Thrombin Rx

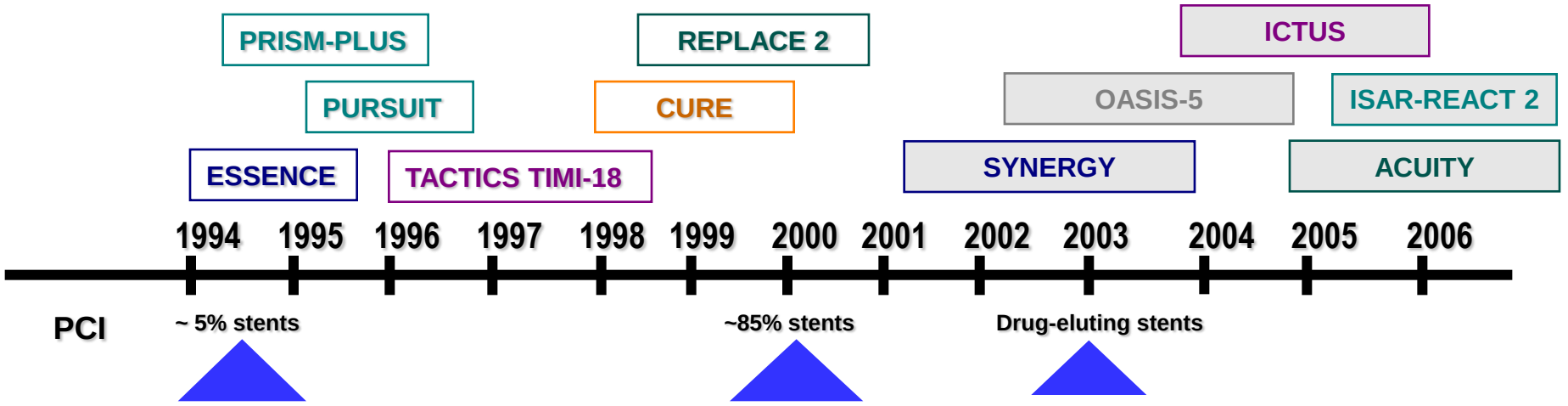
Heparin — LMWH — Bivalirudin — [Fondaparinux]

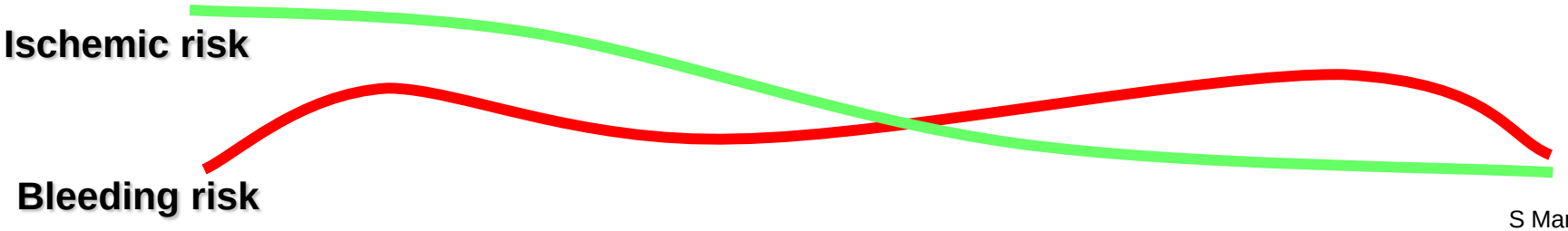
Anti-Platelet Rx

Aspirin — GP IIb/IIIa blockers — Clopidogrel

Treatment Strategy

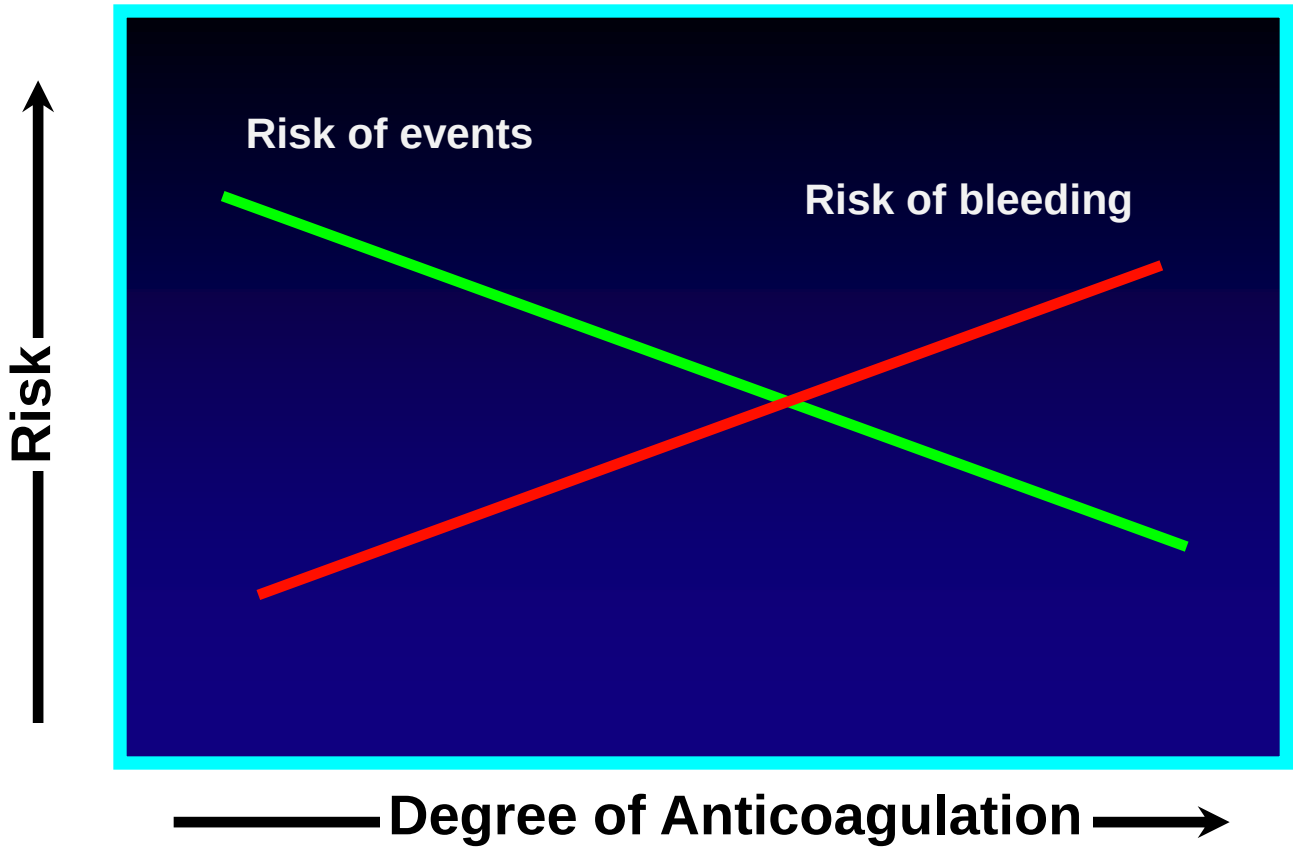
Conservative — Early invasive





S Manukian 2010

Bilancing Events and Bleeding

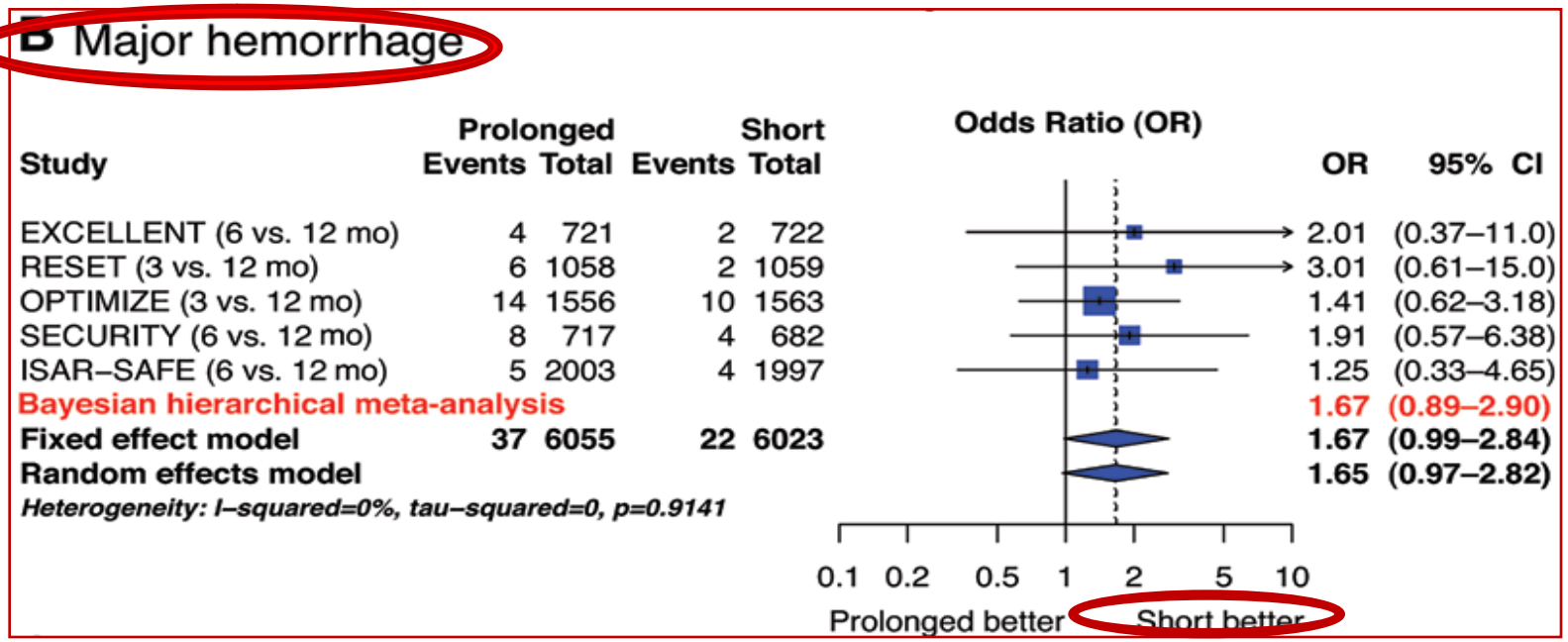


Hemostasis ⟷ **Thrombosis**

Two sides of the same coin

Duration of Dual Antiplatelet Therapy: A Systematic Review for the 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease

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



Circulation. 2016;134:e156–e178. DOI: 10.1161/CIR.0000000000000405

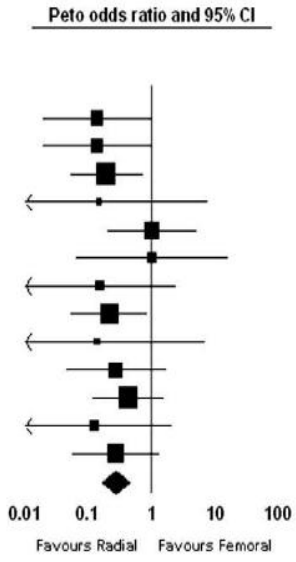
Radial versus femoral access for coronary angiography or intervention and the impact on major bleeding and ischemic events: A systematic review and meta-analysis of randomized trials

Sanjit S. Jolly, MD,[a] Shoaib Amlani, MD,[a] Martial Hamon, MD,[b] Salim Yusuf, MBBS, D Phil,[a] and Shamir R. Mehta, MD, MSc[a] *Hamilton, Ontario, Canada; and Caen, France*

1

A) **Major Bleeding**

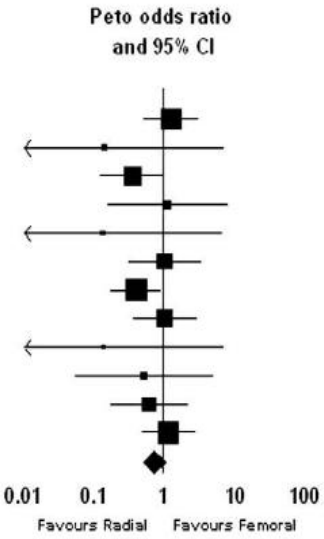
Study name	Radial	Femoral	Peto odds ratio
ACCESS	0 / 300	4 / 300	0.13
Achenbach	0 / 152	4 / 155	0.14
Bodi	3 / 666	7 / 332	0.19
BRAFE	0 / 50	1 / 55	0.15
FARMI	3 / 57	3 / 57	1.00
Gorge	1 / 214	1 / 216	1.01
Mann 1998	0 / 68	2 / 77	0.15
OCTOPLUS	1 / 192	7 / 185	0.21
OUTCLAS	0 / 322	1 / 322	0.14
RADIAL AMI	1 / 25	4 / 25	0.27
RADIAMI	3 / 50	7 / 50	0.41
TEMPURA	0 / 77	2 / 72	0.12
Vazquez-Rodriguez	1 / 217	5 / 222	0.27
	13 / 2390	48 / 2068	0.27



OR 0.27 (95% CI 0.16, 0.45) $P < .001$

B) **Death, MI or stroke**

Study name	Radial	Femoral	Peto odds ratio
ACCESS	11 / 300	9 / 300	1.23
Achenbach	0 / 152	1 / 155	0.14
Bodi	7 / 666	9 / 332	0.35
BRAFE	2 / 50	2 / 55	1.10
Cooper	0 / 101	1 / 99	0.13
FARMI	6 / 57	6 / 57	1.00
OCTOPLUS	7 / 192	17 / 185	0.40
OUTCLAS**	7 / 322	7 / 322	1.00
RADIAL AMI	0 / 25	1 / 25	0.14
RADIAMI	1 / 50	2 / 50	0.51
TEMPURA*	4 / 77	6 / 72	0.61
Vazquez-Rodriguez	11 / 217	10 / 222	1.13
	56 / 2209	71 / 1874	0.71



OR 0.71 (95% CI 0.49, 1.01) $P = .058$

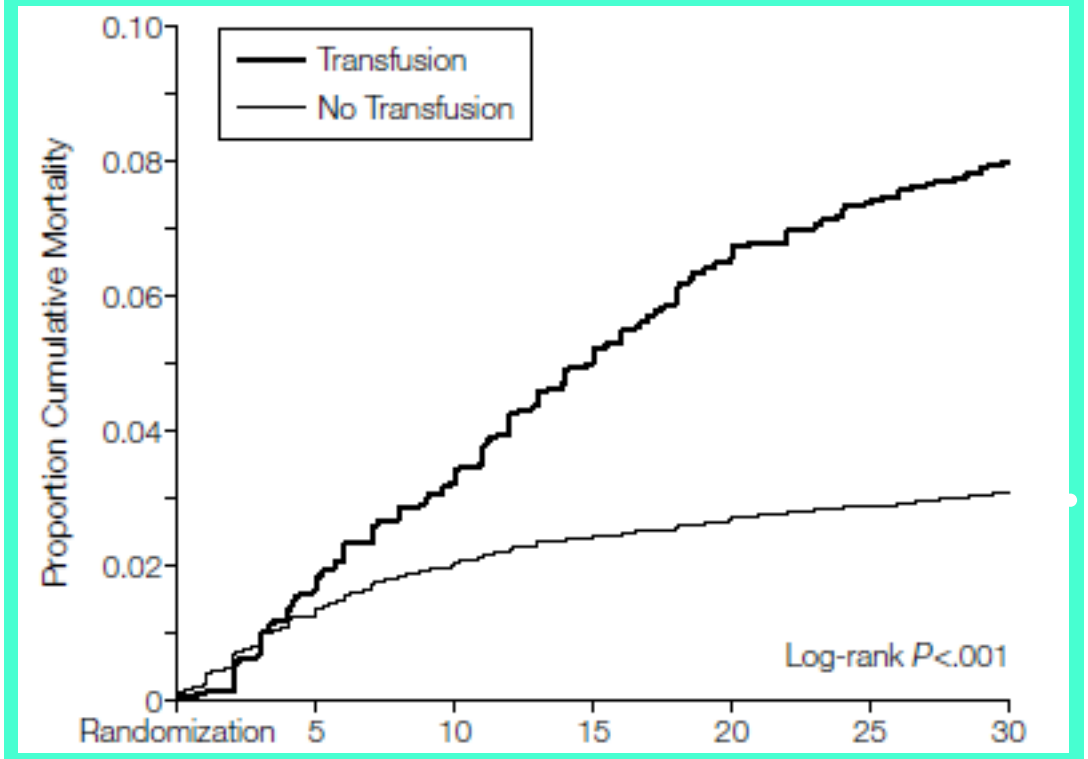
2

Blood Transfusion

If bleeding kills…

Can blood transfusion save lives?

Trasfusioni e mortalità



24000 pts with ACS analyzed from GUSTO IIb, PURSUIT and PRAGON.

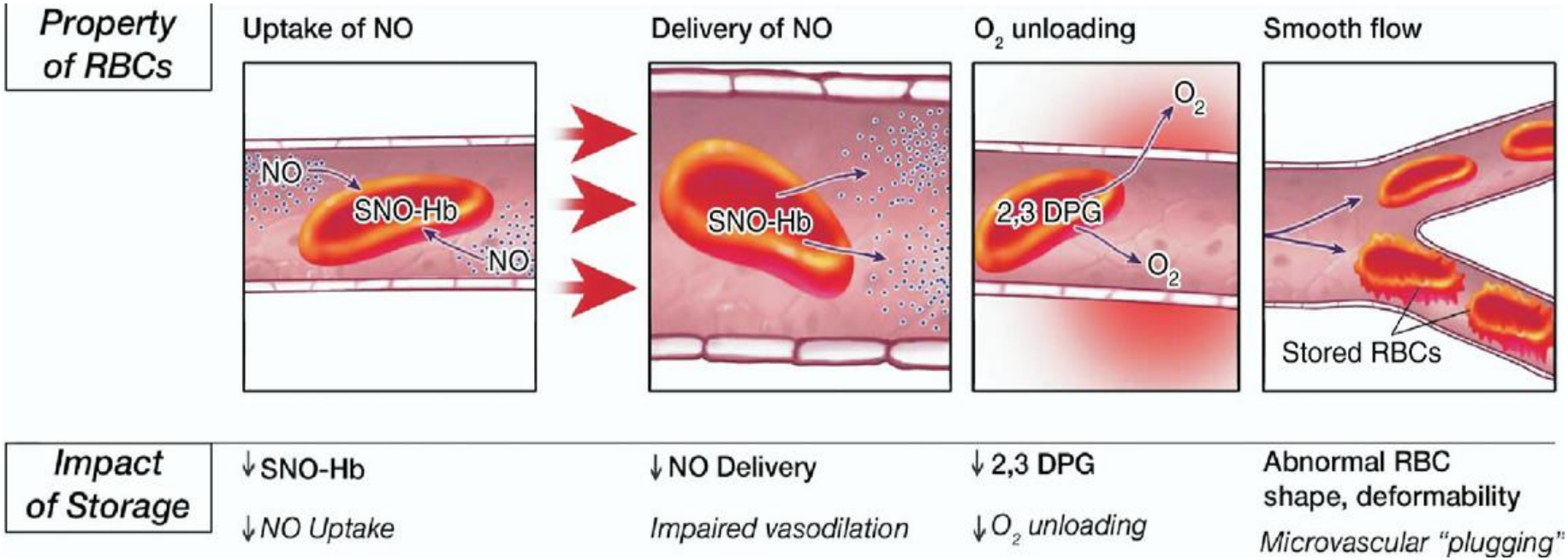
10% underwent transfusion.

Transfusion was associated with HR of 3.94 [CI 3.26-4.75] of death.

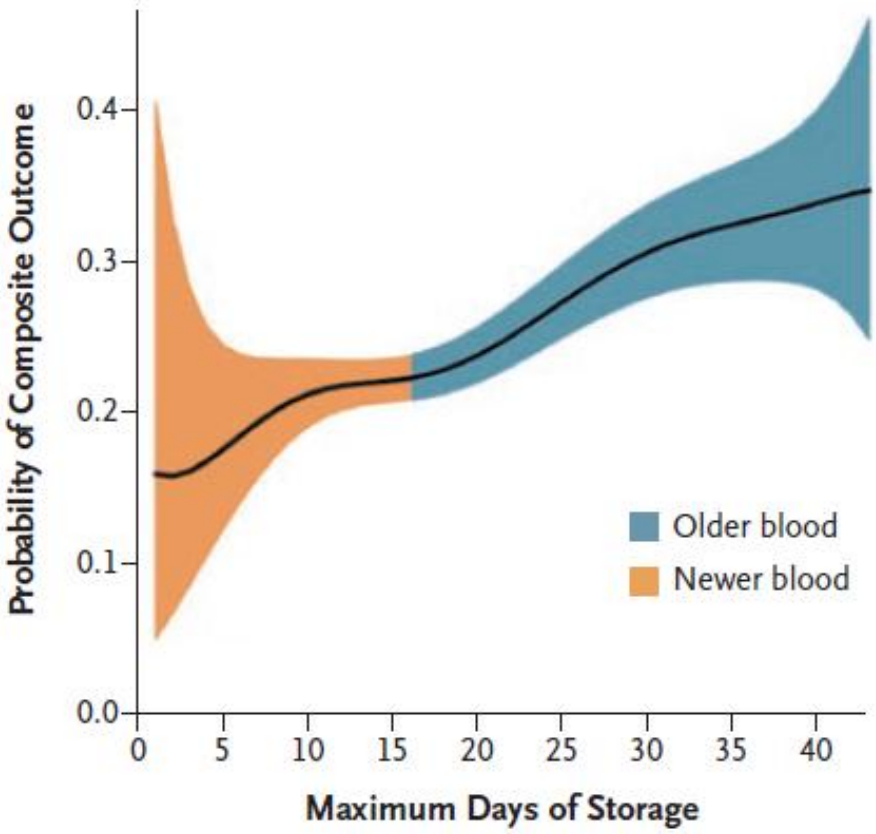
Se trasfusi la mortalità è 4 volte maggiore

Rao et al. JAMA. 2004;292:1555-1562

Transfusion > Mortality



Older blood > higher mortality



- Red cell transfusion in post-CABG and valve pts was studied.
- 3000 pts were given old blood (> 2 weeks) and 3000 pts were given new blood (< 2 weeks).
- At 1 year, mortality was significantly less in pts given new blood (7.4% vs 11%, $p < 0.001$).

NSTEACS and Aticoagulants

The parenteral selective factor Xa inhibitor fondaparinux is a synthetic pentasaccaride that binds reversibly and non-covalenty to antithrombin with high affinity, thereby preventing thrombin generation.
T/2 17 hours allowing once-daily dosing.
No dose adjustments are required

-Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, Granger CB, Budaj A, Peters RJ,Bassand JP, Wallentin L, Joyner C, Fox KA. Comparison of fondaparinux and enoxaparinin acute coronary syndromes. N Engl J Med 2006;354:1464–1476.

3

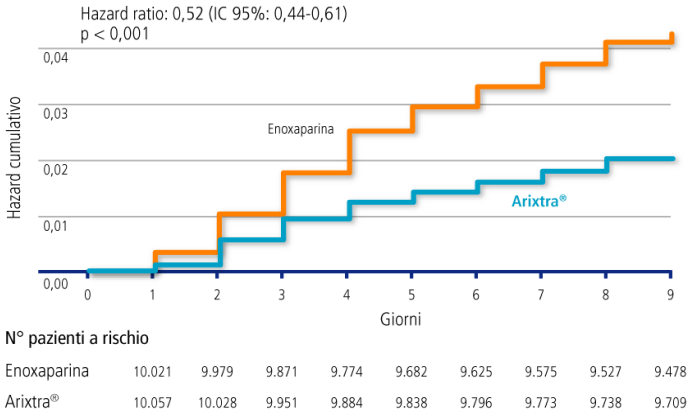
Fondaparinux is not-inferior to enoxaparin
and has minor bleeding risk

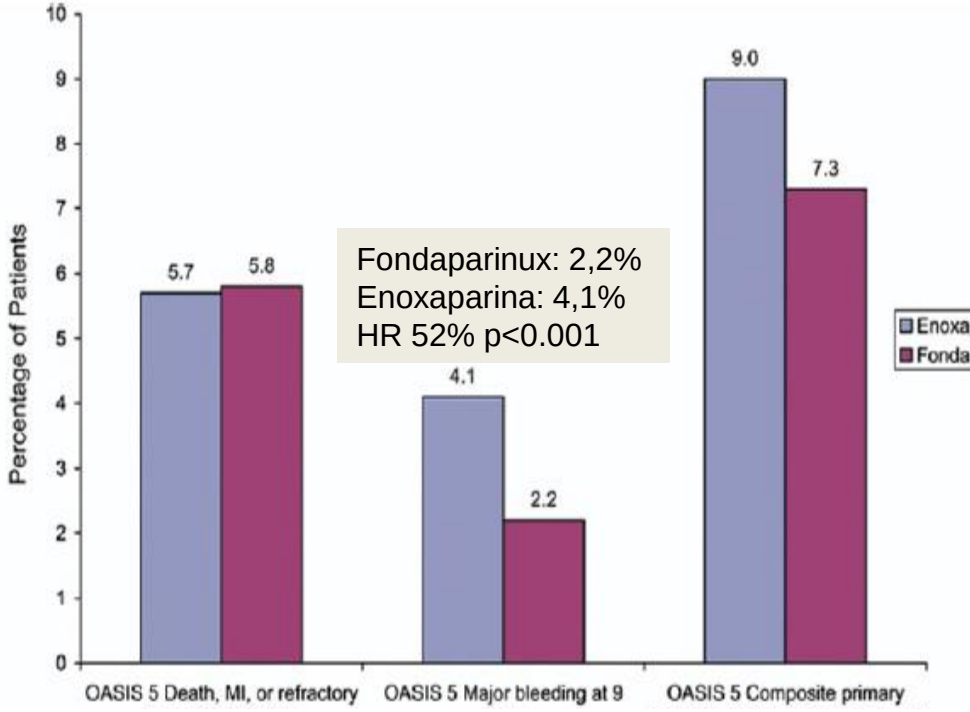
Drug	Recommendations		
	Normal renal function or stage 1–3 CKD (eGFR ≥30 mL/min/1.73m²)	Stage 4 CKD (eGFR 15–29 mL/min/1.73m²)	Stage 5 CKD (eGFR <15 mL/min/1.73m²)
Unfractionated heparin	• Prior to coronary angiography: 60–70 IU/kg i.v. (max 5000 IU) and infusion (12–15 IU/kg/h) (max 1000 IU/h), target aPTT 1.5–2.5x control • During PCI: 70–100 IU/kg i.v. (50–70 IU/kg if concomitant with GPIIb/IIIa inhibitors)	No dose adjustment	No dose adjustment
Enoxaparin	1 mg/kg s.c. twice a day	1 mg/kg s.c. once a day	Not recommended
Fondaparinux	2.5 mg s.c. once a day	Not recommended if eGFR	Not recommended

Jolly SS, Faxon DP, Fox KA, Afzal R, Boden WE, Widimsky P, Steg PG, Valentin V, Budaj A, Granger CB, Joyner CD, Chrolavicius S, Yusuf S, Mehta SR. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes treated with glycoprotein IIb/IIIa inhibitors or thienopyridines: results from the OASIS 5 (Fifth Organization to Assess Strategies in Ischemic Syndromes) trial. J Am Coll Cardiol 2009;54:468–476.

2015 ESC Guidelines for the Management of NSTEACS Eur Heart J doi:10.1093/euroheartj/ehv320

Fondaparinux





1.The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators
"Comparison of fondaparinux and enoxaparin in acute coronary syndromes" N Engl J Med 2006; 354: 1464-1476
1.Bassand J.P., Richard-Lordereau I., Cadray Y. "Efficacy and safety of fondaparinux in patients with acute coronary syndromes" Expert Rev Cardiovasc Ther 2007; 5 (6): 1013-1026

OASIS 5

Recommendations for anticoagulation in NSTE-ACS

	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

Alfonso Ross Terres et al. BMC Cardiovascular Disorders (2015) 15:180
DOI 10.1186/s12872-015-0175-1

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Cost-effectiveness of fondaparinux versus enoxaparin in non-ST-elevation acute coronary syndrome in Canada (OASIS-5)

Jorge Alfonso Ross Terres[1,2,4*], G. Lozano-Ortega[2,4], R. Kendall[2,4] and M. J. Sculpher[3,4]

Results: The trial data showed that fondaparinux is protective against all clinical events observed in the trial. The model showed that: over 180 days, fondaparinux dominates enoxaparin, producing similar estimates of QALYs gained and saving $439; over a patient's lifetime, fondaparinux yields an ICER of $4293/QALY. Based on PSA, the probabilities that fondaparinux dominates enoxaparin (less costly and more effective) and that is cost-effective at a $50,000 threshold were 42 % and 96 %, respectively.

Conclusions: In the Canadian hospital setting, fondaparinux is cost-effective when compared to enoxaparin for the treatment of NSTE-ACS. This result holds both in the immediate post-event period and over the lifetimes of patients.

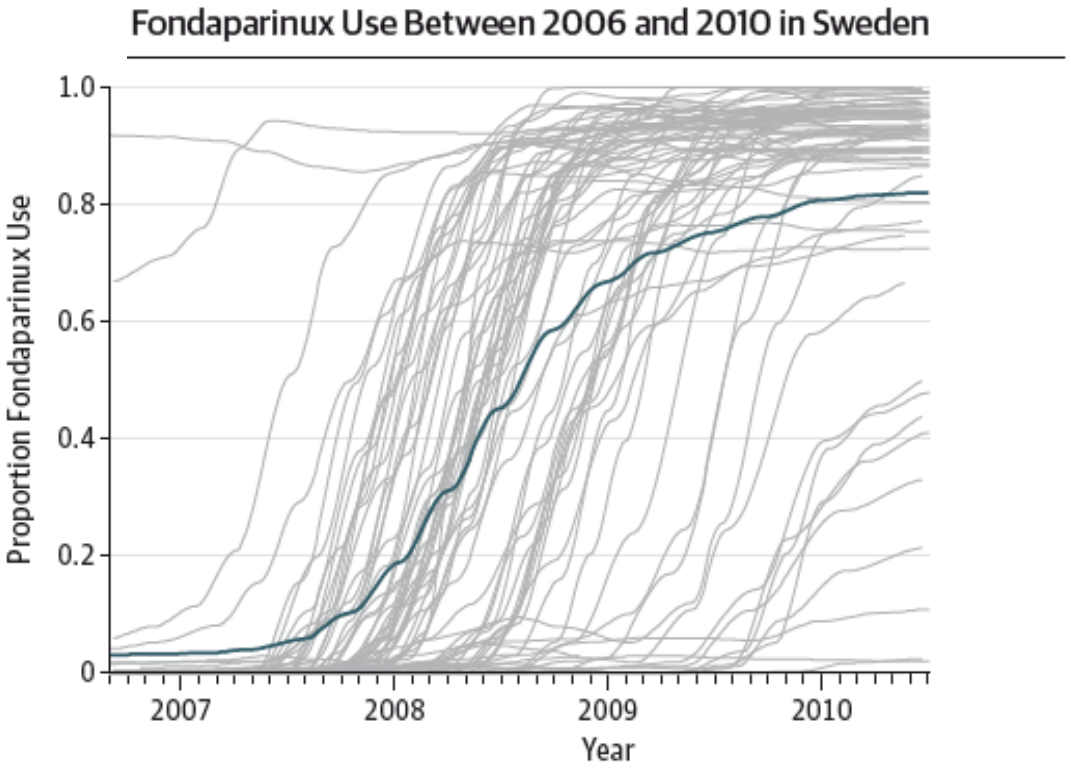
Fondaparinux uptake

Incremento uso di

Fondaparinux

da 0.7 dal 2006

a 84.8% del 2010



Proportion of patients per hospital treated with fondaparinux instead of low-molecular-weight heparin (LMWH) between September 2006 and June 2010 (74 units with ≥100 patients treated are presented of the 86 participating units). The bold line represents all patients treated and entered in the registry.

72 Ospedali Svedesi
40.616 pazienti
(Fondaparinux - 36.4%
Enoxaparina - 63.6%)

Szummer C. Association Between the Use of Fondaparinux vs Low-Molecular-Weight Heparin and Clinical Outcomes In Patients With Non–ST-Segment Elevation Myocardial Infarction et al. JAMA. 2015;313(7):707-716

NSTEACS and anti-ischaemic drugs

If following treatment the pt does not become free of ischaemic signs or symptoms immediate cath-lab (independently of ECG and cTnI)

Oxigen should be administered when O2 sat. is <90% or if the patient is in respiratory distress

- Stub D, Smith K, Bernard S, Nehme Z, Stephenson M, Bray JE, Cameron P, Barger B, Ellims AH, Taylor AJ, Meredith IT, Kaye DM. Air versus oxygen in ST-segment-elevation myocardial infarction. Circulation 2015;131:2143–2150.

Opiate administration when symptoms are not relieved by nitrates and b-blockers with the caveat that morphine may slow intestinal absorption of oral PLT inhib.

Nitrates iv are more effective than s.l. Beyond symptom control there is no indication for nitrates.

Pay attention to sildenafil

-Borzak S, Cannon CP, Kraft PL, Douthat L, Becker RC, Palmeri ST, Henry T, Hochman JS, Fuchs J, Antman EM, McCabe C, Braunwald E. Effects of prior aspirin and anti-ischemic therapy on outcome of patients with unstable angina. TIMI 7 Investigators. Thrombin inhibition in myocardial ischemia. Am J Cardiol 1998;81: 678–681.

- Schwartz BG, Kloner RA. Drug interactions with phosphodiesterase-5 inhibitors used for the treatment of erectile dysfunction or pulmonary hypertension. Circulation 2010;122:88–95.

Recommendations	Class[a]	Level[b]	Ref.[c]
Early initiation of beta-blocker treatment is recommended in patients with ongoing ischaemic symptoms and without contraindications.	I	B	119
It is recommended to continue chronic beta-blocker therapy, unless the patient is in Killip class III or higher.	I	B	126
Sublingual or i.v. nitrates are recommended to relieve angina;[d] i.v. treatment is recommended in patients with recurrent angina, uncontrolled hypertension or signs of heart failure.	I	C	
In patients with suspected/confirmed vasospastic angina, calcium channel blockers and nitrates should be considered and beta-blockers avoided.	IIa	B	127

2015 ESC Guidelines for the Management of NSTEACS Eur Heart J doi:10.1093/euroheartj/ehv320

NSTEACS and anti-ischaemic drugs

B-blockers reduce incidence of death up to 13% ,
Yusuf S, Wittes J, Friedman L. Overview of results of randomized clinical trials in heart disease. I. Treatments following myocardial infarction. JAMA 1988;260: 2088–2093.

Meta Analysis of 73000 pts with ACS 8% reduction of in-hospital death with no increase in cardiogenic shock
Chatterjee S, Chaudhuri D, Vedanthan R, Fuster V, Ibanez B, Bangalore S, Mukherjee D. Early intravenous beta-blockers in patients with acute coronary syndrome—a meta-analysis of randomized trials. Int J Cardiol 2013;168:915–921.

A registry study of 23000 pts found that patients at risk of cardiogenic shock (HR>110 b/in,PAS<120 mmHg, age>70 y. increase incidence of cardiogenic shock when treated with b-blockers within 24 hours
-Kontos MC, Diercks DB, Ho PM, Wang TY, Chen AY, Roe MT. Treatment and outcomes in patients with myocardial infarction treated with acute beta-blocker therapy: results from the American College of Cardiology's NCDRw. Am Heart J 2011;161:864–870.

Avoid use of b-blockers in spasm and coacaine abuse

Recommendations	Class[a]	Level[b]	Ref.[c]
Early initiation of beta-blocker treatment is recommended in patients with ongoing ischaemic symptoms and without contraindications.	I	B	119
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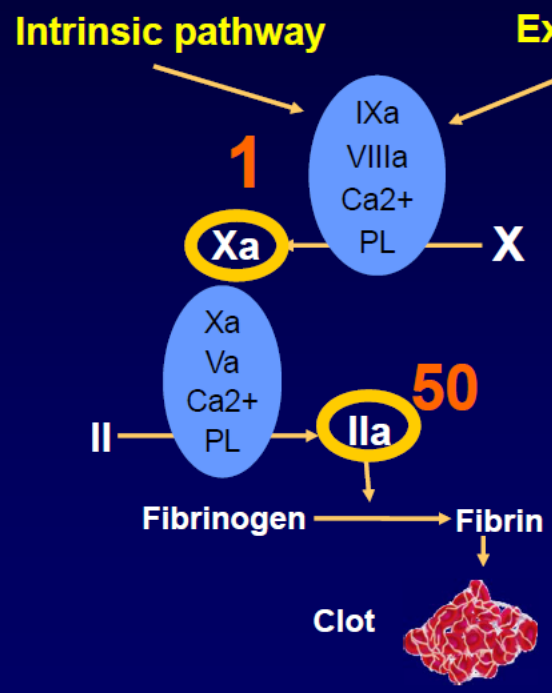
2015 ESC Guidelines for the Management of NSTEACS Eur Heart J doi:10.1093/euroheartj/ehv320

Factor Xa:
A key step in coagulation pathway



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

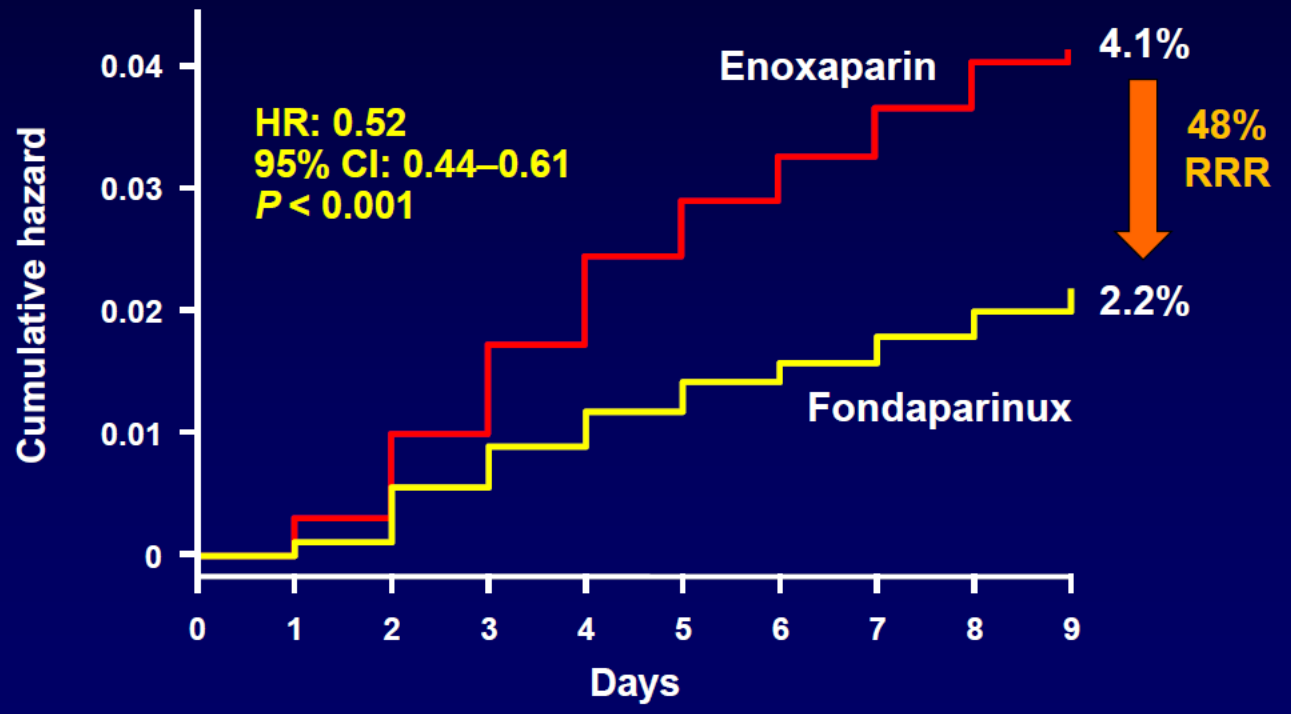
Anti-X
Fondaparinux
Rivaroxaban
Apixaban
Edoxaban

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.

OASIS 5
Fondaparinux vs Enoxaparin in NSTEACS

Fondaparinux substantially reduced major bleeding vs Enoxaparin



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

OASIS 5
Fondaparinux vs Enoxaparin in NSTEACS

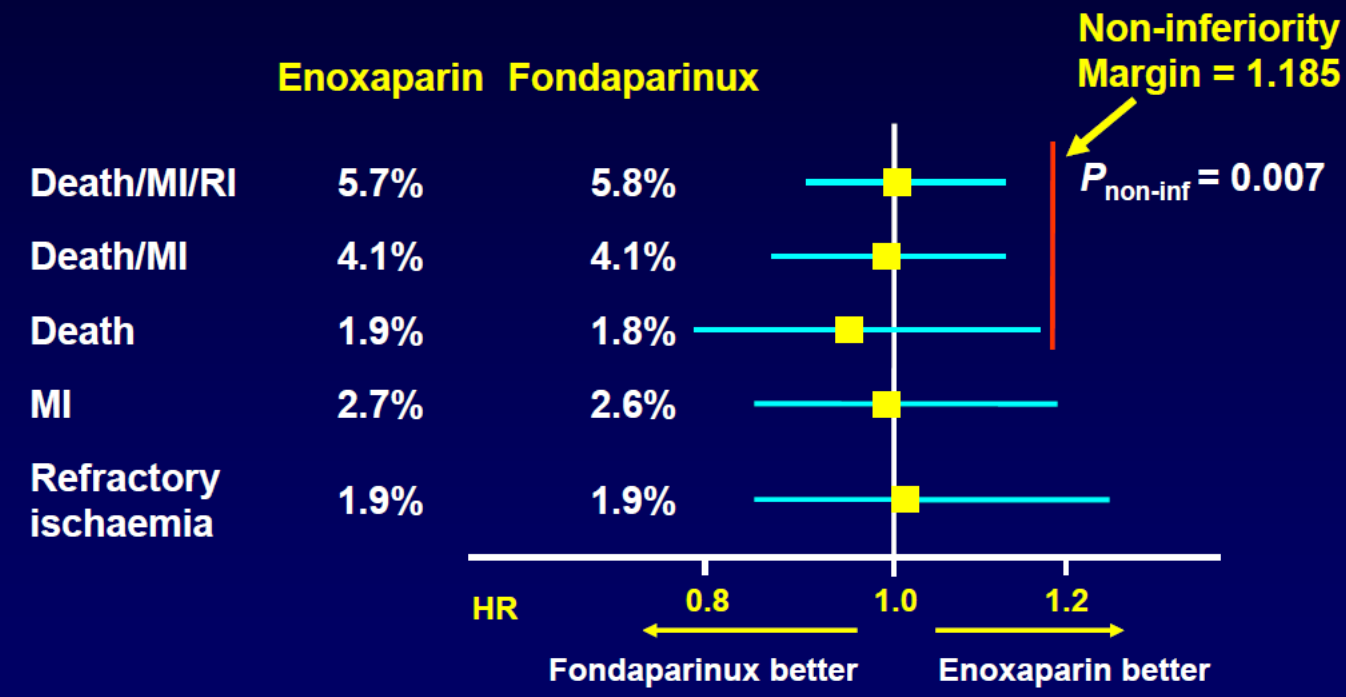
OASIS-5: Reduction in major bleeding was consistent in almost all categories

Major bleeding at Day 9	Enoxaparin, no. of patients	Fondaparinux, no. of patients	*P*-value
No. randomised	10,021	10,057	
Total major bleeds	412 (4.1%)	217 (2.2%)	< 0.001
Intracranial	7	7	NS
Requiring surgery to stop bleeding	77	41	< 0.001
Retroperitoneal	37	9	< 0.001
Transfusion	287	164	< 0.001
Associated with death at study end	79	38	< 0.001

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

OASIS 5
Fondaparinux vs Enoxaparin in NSTEACS

OASIS-5: Similar efficacy outcome rates

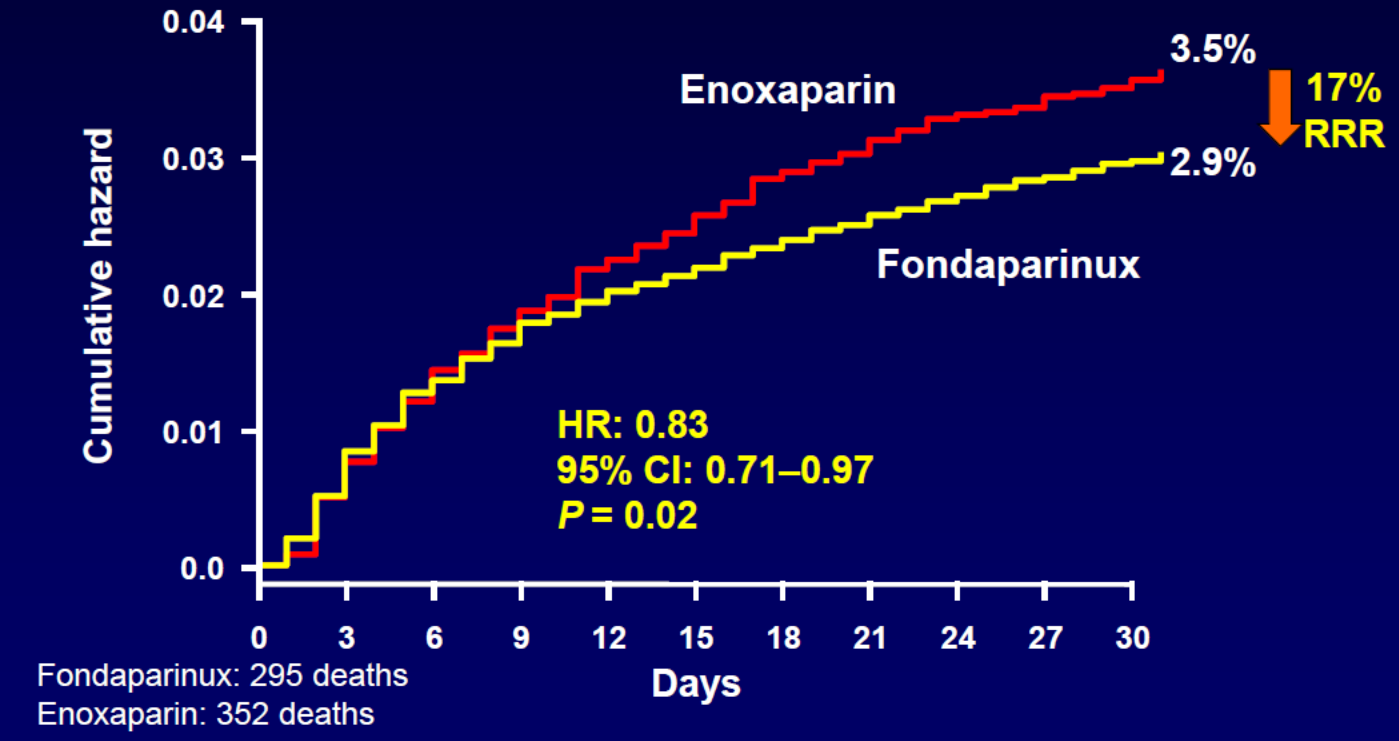


HR = hazard ratio; MI = myocardial infarction; RI = refractory ischaemia.

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

OASIS 5
Fondaparinux vs Enoxaparin in NSTEACS

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



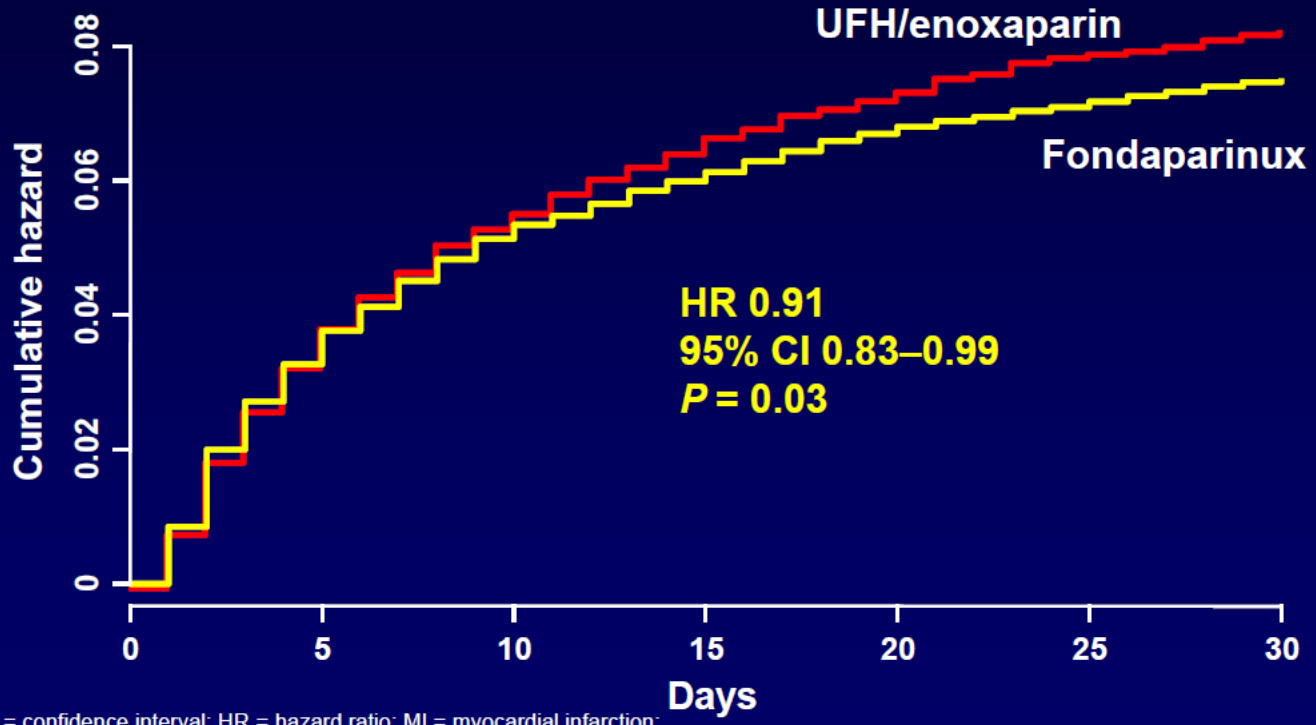
CI = confidence interval; HR = hazard ratio; RRR = relative risk reduction.

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

OASIS-5 and -6: Combined analysis

Fondaparinux superior to UFH/enoxaparin

Death/MI/stroke at 30 days



CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; UFH = unfractionated heparin.

Mehta SR,.*et al.* *Circulation* 2008; **118**:2038–2046.

Nelle NSTACS

- **Il sanguinamento è "l'altra faccia della medaglia" nella terapia antiaggregante/anticoagulante**
- **Personalizzare strategia su reale rischio ischemico/ emorragico**
- **Emotrasfusioni limitate alla stabilizzazione emodinamica**
- **Valorizzare opzioni di anticoagulazione oltre alla DAPT:**

Fondaparinux….DOACS?

x congresso nazionale
simeu
NAPOLI 18-20 NOVEMBRE 2016

Napoli. Giardini Certosa San Martino

…vi ringrazio per l’attenzione