Acute coronary syndromes and stable angina pectoris

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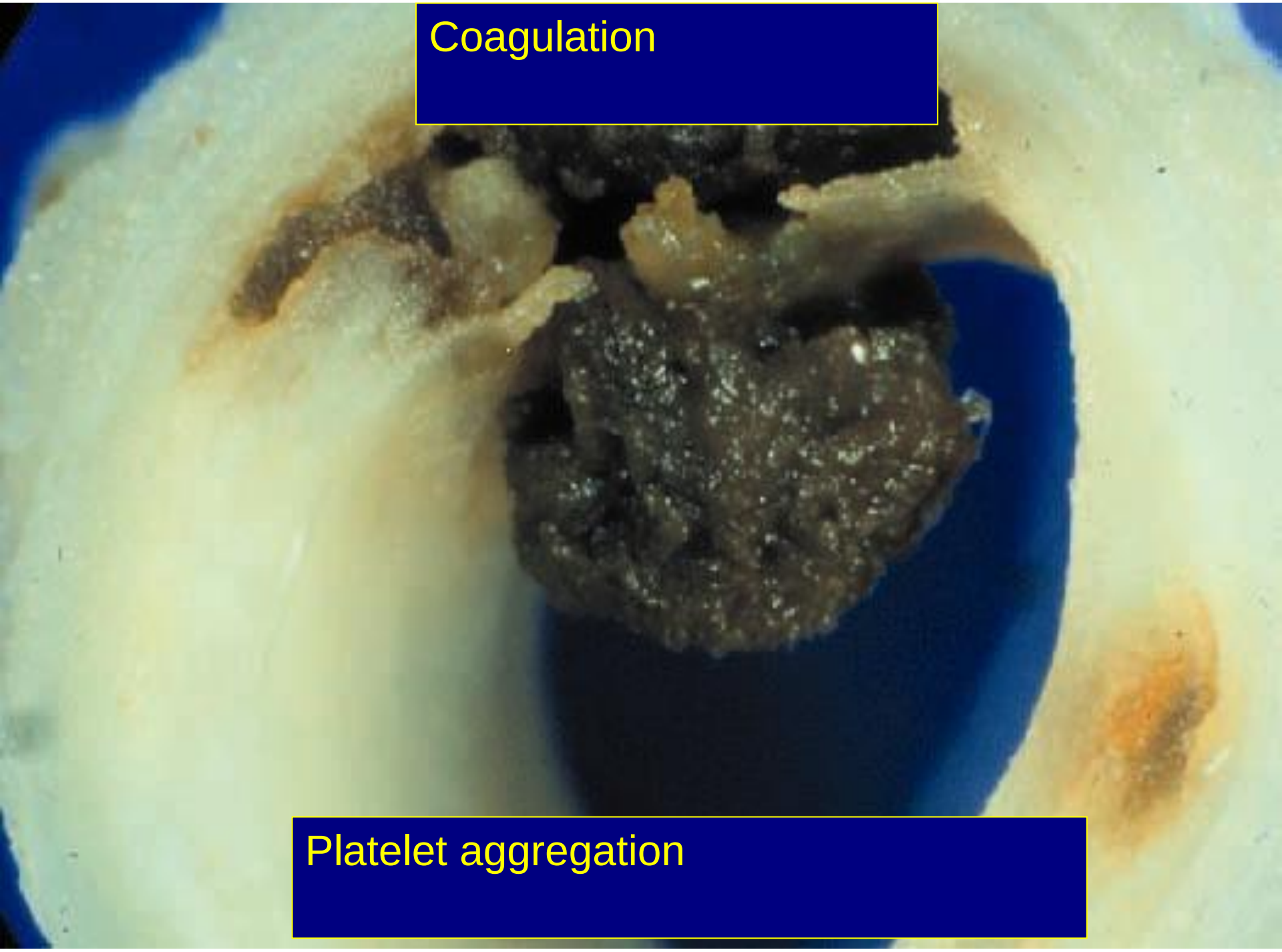
Department of Cardiology

COI

- Speakers fee: Aspen, AZ, Bayer, BMS/Pfizer
- Departmental research grant (THEMIS): AZ

Outline

- Which drugs are available?
- When to start dual antiplatelet therapy?
- When to stop dual antiplatelet therapy?
- Triple therapy
- Secondary prevention in stable cardiovascular disease


Coagulation
Platelet aggregation

Targets for antithrombotic

Anticoagulant drugs

Rivaroxaban

Fondaparinux

LMWH
UFH

Antithrombin

Bivalirudin

Tissue Factor

Plasma clotting cascade

Prothrombin

Factor Xa

Thrombin

Fibrinogen

Fibrin

Antiplatelet drugs

Aspirin

ADP

Cangrelor
Clopidogrel
Prasugrel
Ticagrelor

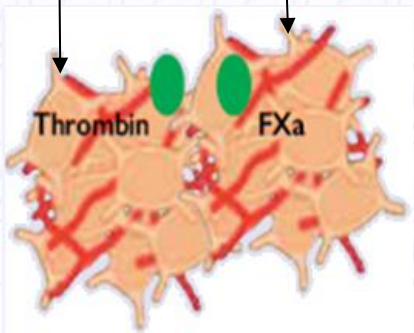
TXA_2

Conformational activation of GPIIb/IIIa

GPIIb/IIIa inhibitors

Vorapaxar

- PAR-1 receptor
- Soluble mediators (ADP, TXA_2, Ca^{++}, serotonin)
- GPIIb/IIIa receptor
- Collagen
- Clot-bound thrombin/factor Xa



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, EHJ

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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		

Recommendations for anticoagulants

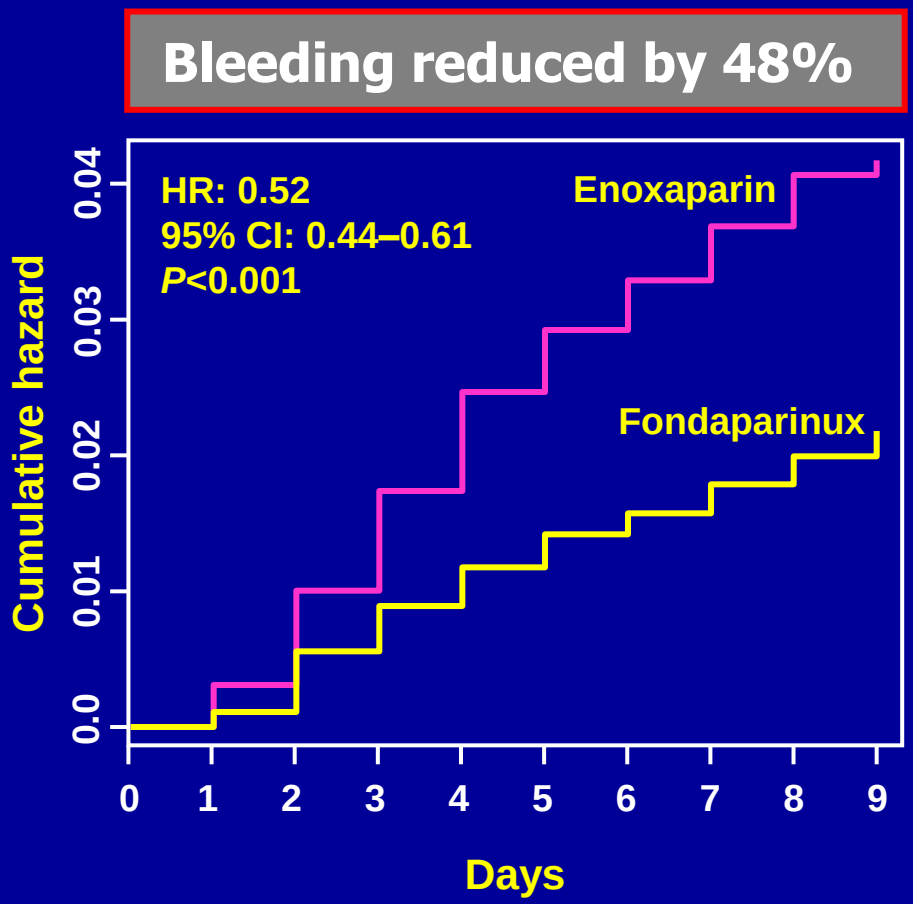
1. **Anticoagulation should be tailored according to the risk of bleeding (I-A)**
2. **Recommendations for the use of anticoagulants: choice between 4:**
   - **Bivalirudin**
   - **Enoxaparin**
   - **Fondaparinux**
   - **UFH**

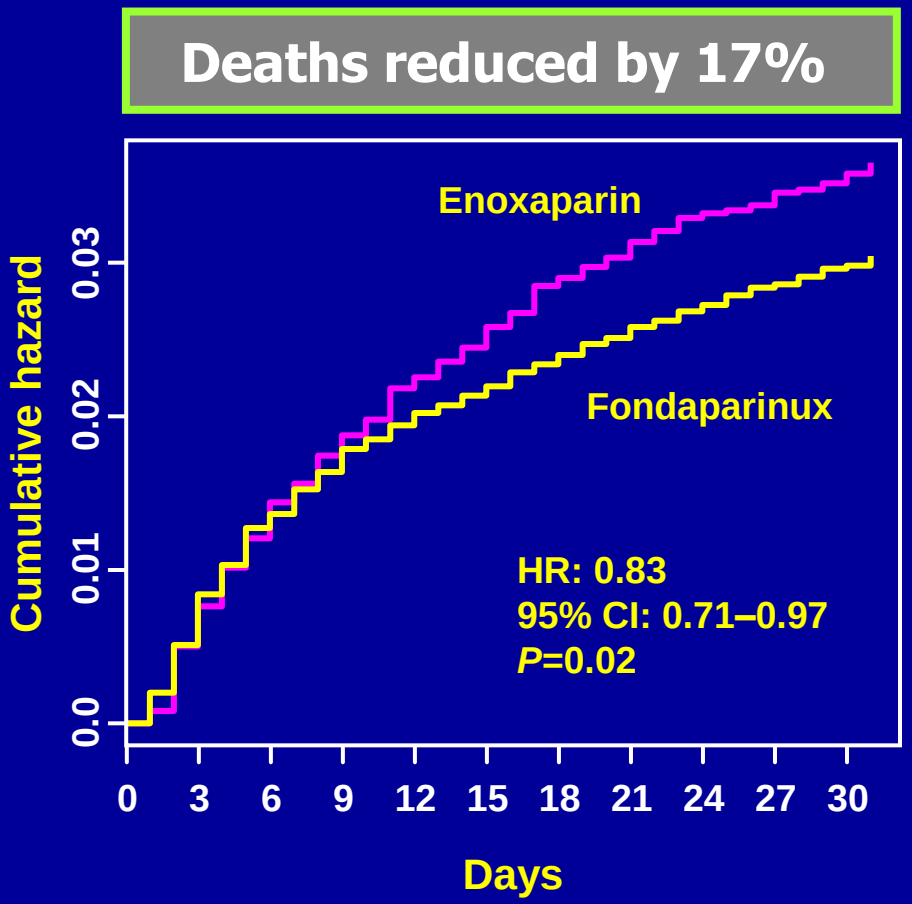
   depends on initial strategy (conservative vs early invasive) and on bleeding risk

UFH = unfractionated heparin.

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

OASIS-5
Less bleeding = fewer deaths





HR = hazard ratio.

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

- Emphasis on Fondaparinux
- Rivaroxaban is an additional option

Recommendations for anticoagulation in NSTE-ACS		
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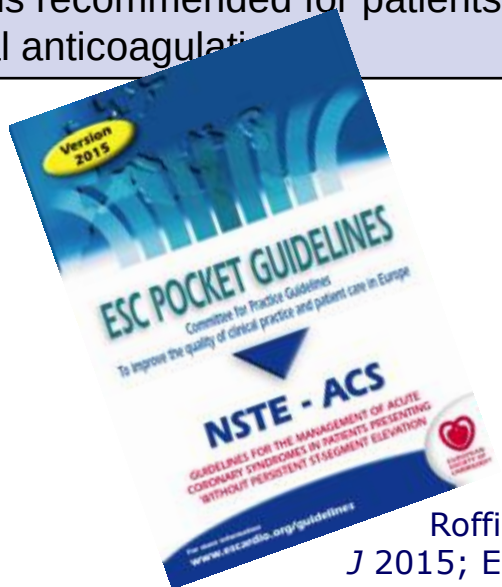
Discontinuation of anticoagulation should be considered after PCI, unless otherwise indicated.	IIa	C
Crossover between UFH and LMWH is not recommended.	III	B
In NSTEMI patients with no prior stroke/TIA and at high ischaemic risk as well as low bleeding risk receiving aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily for approximately one year) may be considered after	**IIb**	**B**

Recommendations for platelet inhibition in NSTE-ACS 2015

Recommendations	Class	Level
Oral antiplatelet therapy		
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
• **Ticagrelor** (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications[d], 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
• **Prasugrel** (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.	I	B
• Clopidogrel (300–600 mg loading dose, 75 mg daily dose) is recommended for patients who cannot receive ticagrelor or prasugrel or who require oral anticoagulati	I	B



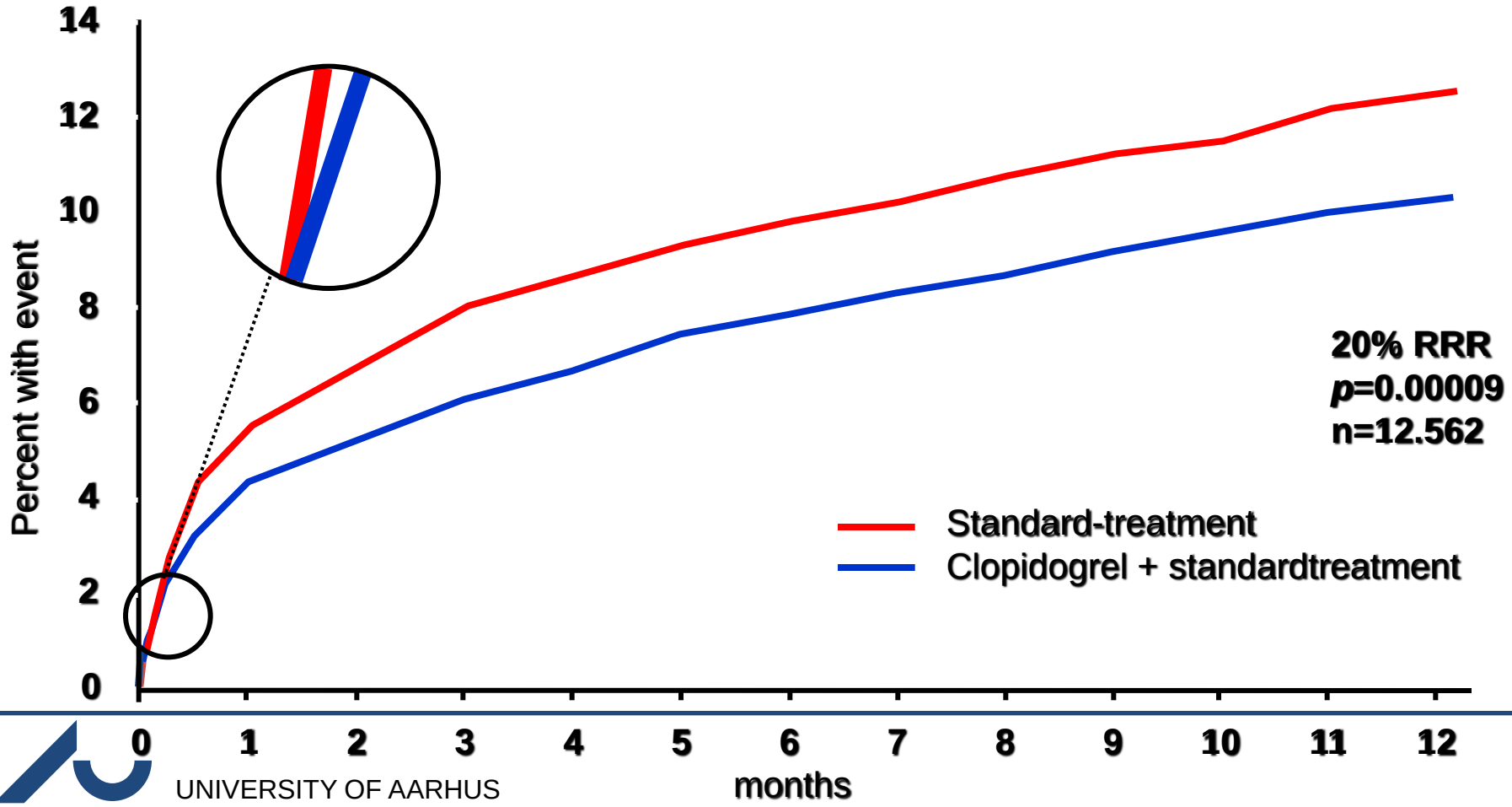
Roffi M, *et al. Eur Heart J* 2015; Epub ahead of print.

$P2Y_{12}$ inhibitors

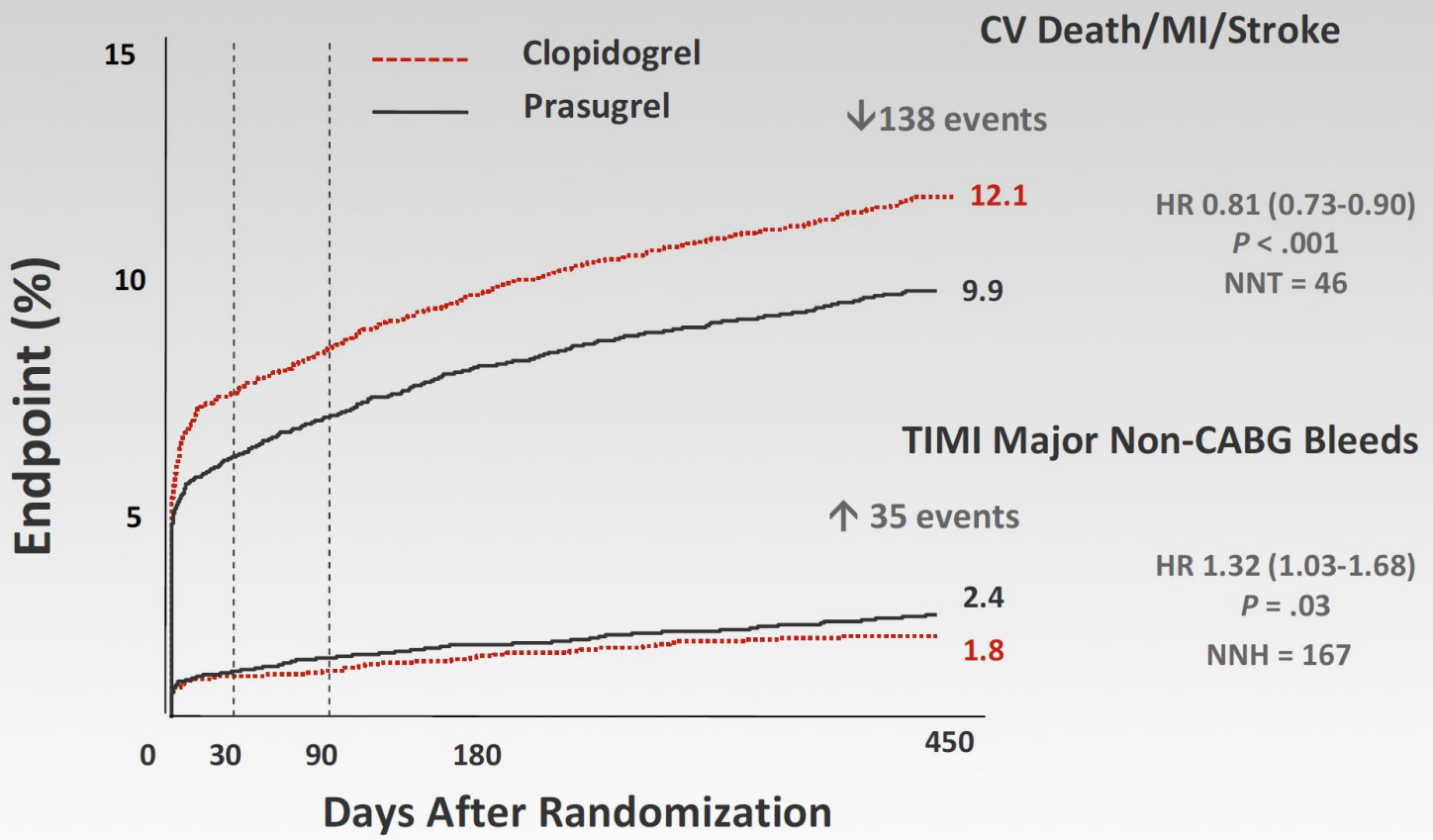
	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, limited by metabolization	Prodrug, not limited by metabolization	Active drug
Onset of effect[a]	2–4 h	30 min	30 min
Duration of effect	3–10 days	5–10 days	3–4 days
Withdrawal before major surgery	5 days	7 days	5 days

www.escardio.org/guidelines

CURE: Primary endpoint
Cardiovascular death, MI or stroke



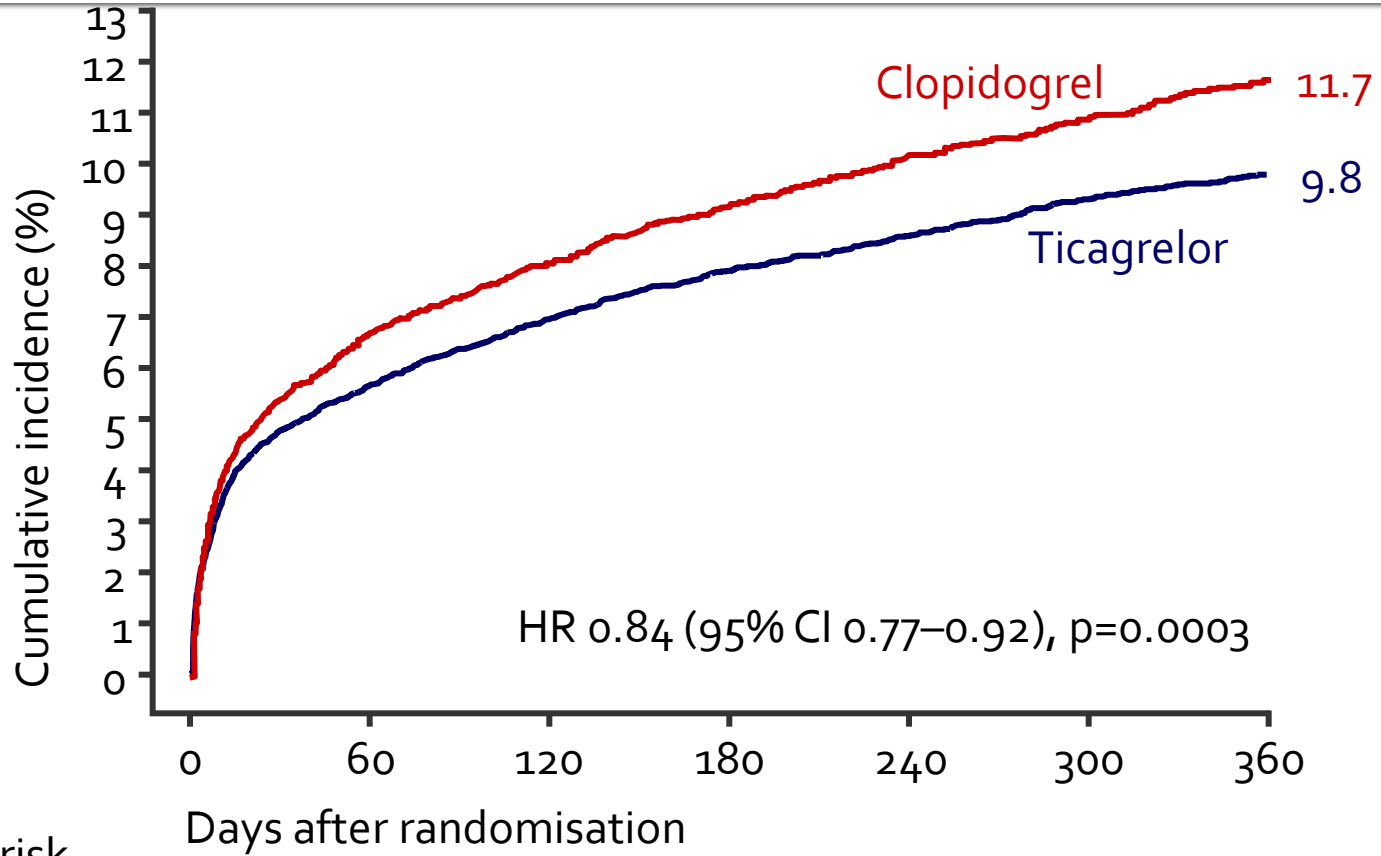
TRITON-TIMI 38 (n = 13 608)



Wiviott SD, et al. N Engl J Med 2007; 357: 2001-15.

PLATO: primary efficacy endpoint

(Composite of CV death, MI or stroke)



No. at risk

Ticagrelor	9,333	8,628	8,460	8,219	6,743	5,161	4,147
Clopidogrel	9,291	8,521	8,362	8,124	6,743	5,096	4,047

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

Personalized options for DAPT duration

More limited role for GPIIb/IIIa inhibitors

Cangrelor is a new option for i.v. therapy

Recommendations for platelet inhibition in NSTE-ACS		
Recommendations	**Class** [a]	**Level** [b]
Oral antiplatelet therapy		
Aspirin is recommended for all patients without contra-indications at an initial oral loading dose[c] of 150–300 mg (in aspirin-naïve patients) and a maintenance dose of 75–100 mg daily long-term regardless of treatment strategy.	I	A
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
• Ticagrelor (180 mg loading dose, 90 mg twice daily) is recommended, in the absence of contraindications[d], 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
• Prasugrel (60 mg loading dose, 10 mg daily dose) is recommended in patients who are proceeding to PCI if no contraindication.[d]	I	B
• 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
$P2Y_{12}$ 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
It is not recommended to administer prasugrel in patients in whom coronary anatomy is not known.	III	B
Intravenous antiplatelet therapy		
GPIIb/IIIa inhibitors during PCI should be considered for bailout situations or thrombotic complications.	IIa	C
Cangrelor may be considered in $P2Y_{12}$ inhibitor-naïve patients undergoing PCI.	IIb	A
It is not recommended to administer GPIIb/IIIa inhibitors in patients in whom coronary anatomy is not known.	III	A

Outline

- Which drugs are available?
- When to start dual antiplatelet therapy?
- When to stop dual antiplatelet therapy?
- Triple therapy
- Secondary prevention in stable cardiovascular disease

Timing of $P2Y_{12}$ Inhibitor Initiation

- 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.

2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease developed in collaboration with the EACTS*

*: European Association for Cardio-Thoracic Surgery

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History of dual antiplatelet therapy (DAPT) in patients with coronary artery disease

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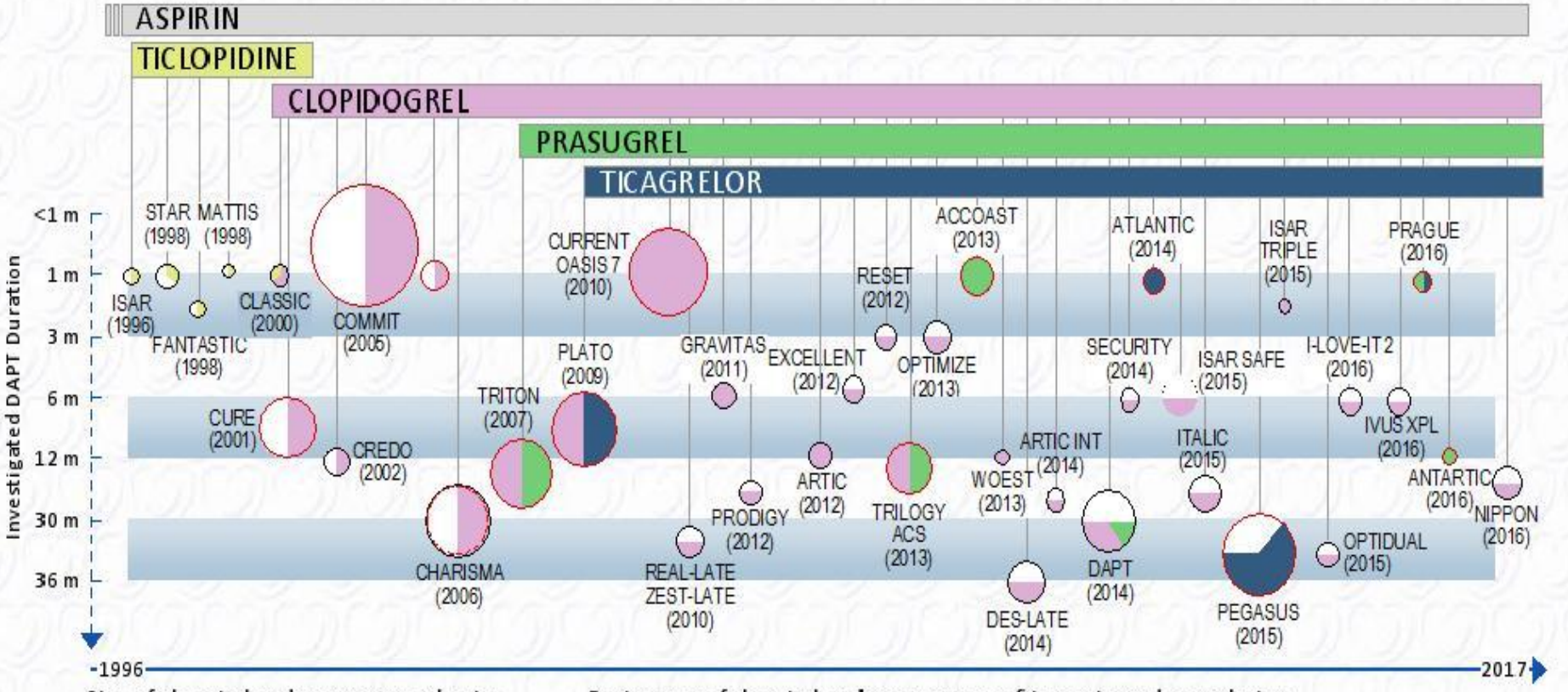


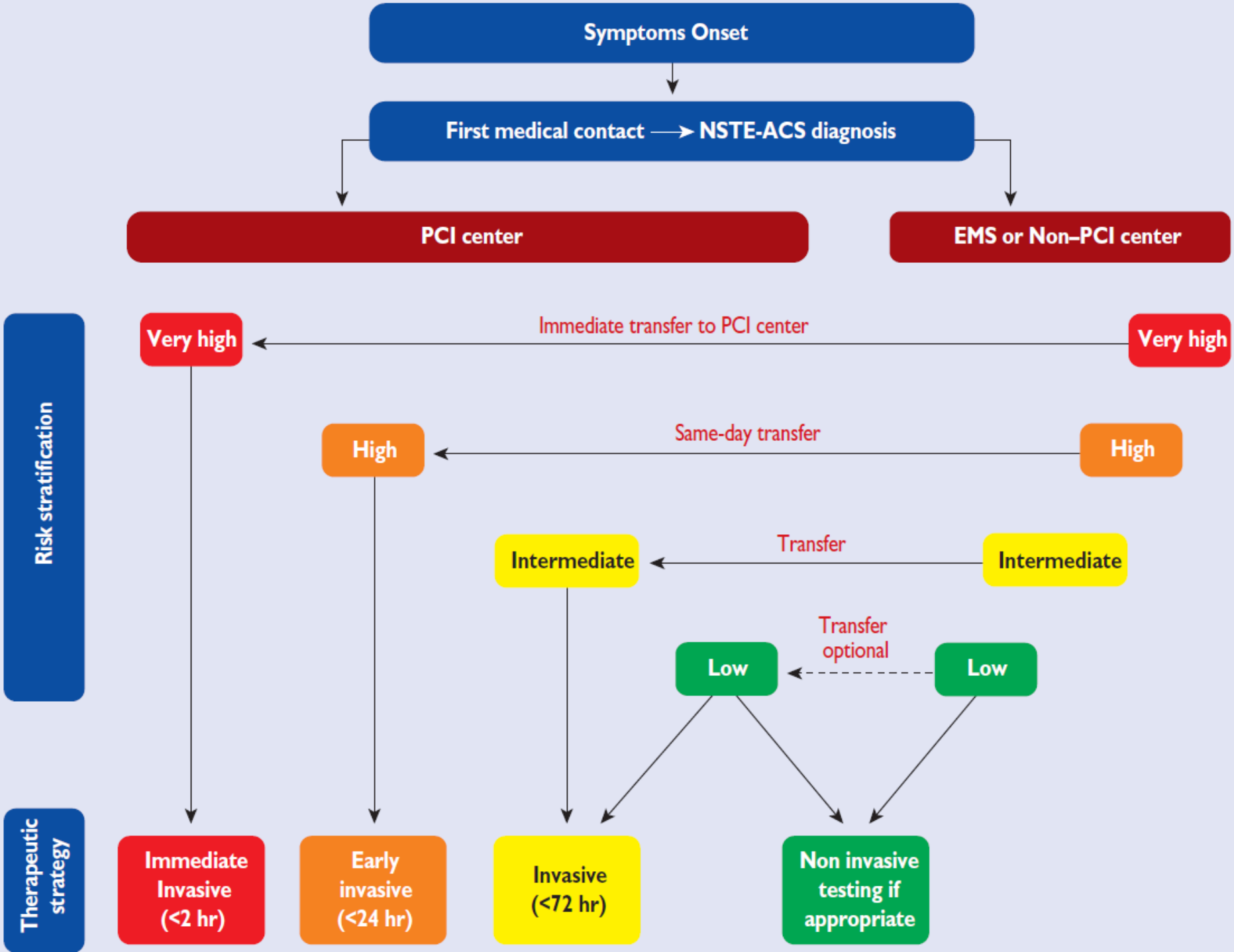
Size of the circles denotes sample size

2 5 10 20 K pts

Perimeter of the circles denotes type of investigated population

- Mixed clinical presentation at the time of stent implantation
- Acute coronary syndrome at presentation
- DAPT initiated in patients with prior myocardia infarction
- DAPT for primary prevention

www.escardio.org/guidelines 2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)


Symptoms Onset
First medical contact → NSTE-ACS diagnosis
PCI center
EMS or Non–PCI center
Risk stratification
Very high
Immediate transfer to PCI center
Very high
High
Same-day transfer
High
Intermediate
Transfer
Intermediate
Transfer optional
Low
Low
Therapeutic strategy
Immediate Invasive (<2 hr)
Early invasive (<24 hr)
Invasive (<72 hr)
Non invasive testing if appropriate

NSTEMI - pretreatment

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

$P2Y_{12}$ inhibitor selection and timing *(continued)*

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Recommendations	Class	Level
Pre-treatment with a $P2Y_{12}$ inhibitor is generally recommended in patients in whom coronary anatomy is known and the decision to proceed to PCI is made as well as in patients with STEMI.	I	A
In patients with NSTE-ACS undergoing invasive management, ticagrelor administration (180 mg loading dose, 90 mg twice daily), 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
In patients with stable CAD pre-treatment with clopidogrel may be considered if the probability of PCI is high.	IIb	C

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prehospital Ticagrelor in ST-Segment Elevation Myocardial Infarction

Gilles Montalescot, M.D., Ph.D., Arnoud W. van 't Hof, M.D., Ph.D., Frédéric Lapostolle, M.D., Ph.D., Johanne Silvain, M.D., Ph.D., Jens Flensted Lassen, M.D., Ph.D., Leonardo Bolognese, M.D., Warren J. Cantor, M.D., Ángel Cequier, M.D., Ph.D., Mohamed Chettibi, M.D., Ph.D., Shaun G. Goodman, M.D., Christopher J. Hammett, M.B., Ch.B., M.D., Kurt Huber, M.D., Magnus Janzon, M.D., Ph.D., Béla Merkely, M.D., Ph.D., Robert F. Storey, M.D., D.M., Uwe Zeymer, M.D., Olivier Stibbe, M.D., Patrick Ecollan, M.D., Wim M.J.M. Heutz, M.D., Eva Swahn, M.D., Ph.D., Jean-Philippe Collet, M.D., Ph.D., Frank F. Willems, M.D., Ph.D., Caroline Baradat, M.Sc., Muriel Licour, M.Sc., Anne Tsatsaris, M.D., Eric Vicaut, M.D., Ph.D., and Christian W. Hamm, M.D., Ph.D., for the ATLANTIC Investigators*

ABSTRACT

BACKGROUND

The direct-acting platelet $P2Y_{12}$ receptor antagonist ticagrelor can reduce the incidence of major adverse cardiovascular events when administered at hospital admission to patients with ST-segment elevation myocardial infarction (STEMI). Whether prehospital administration of ticagrelor can improve coronary reperfusion and the clinical outcome is unknown.

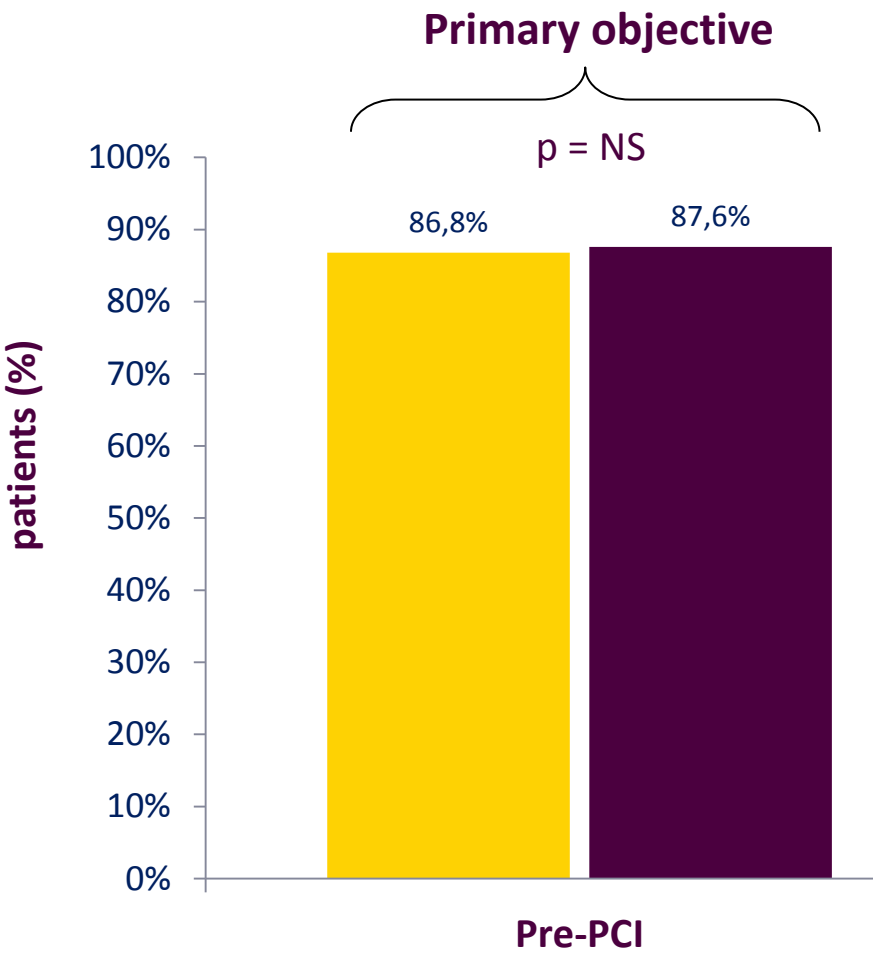
METHODS

We conducted an international, multicenter, randomized, double-blind study involv-

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Montalescot at the Allies in Cardiovascular Trials Initiatives and Organized Networks (ACTION) Study Group, Institut de Cardiologie, Centre Hospitalier Universitaire Pitié–Salpêtrière, 47 Blvd. de l'Hôpital, 75013 Paris, France, or at gilles.montalescot@psl.aphp.fr.

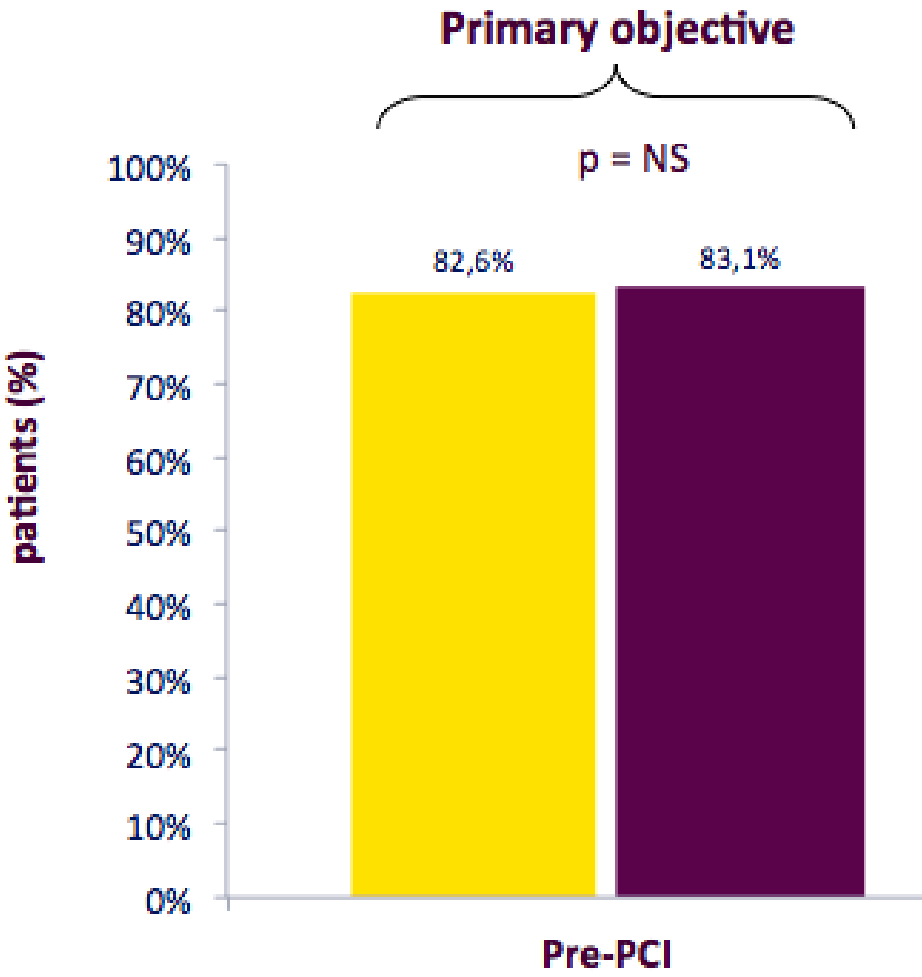
1st Co-primary endpoint

No ST-segment resolution (≥70%)



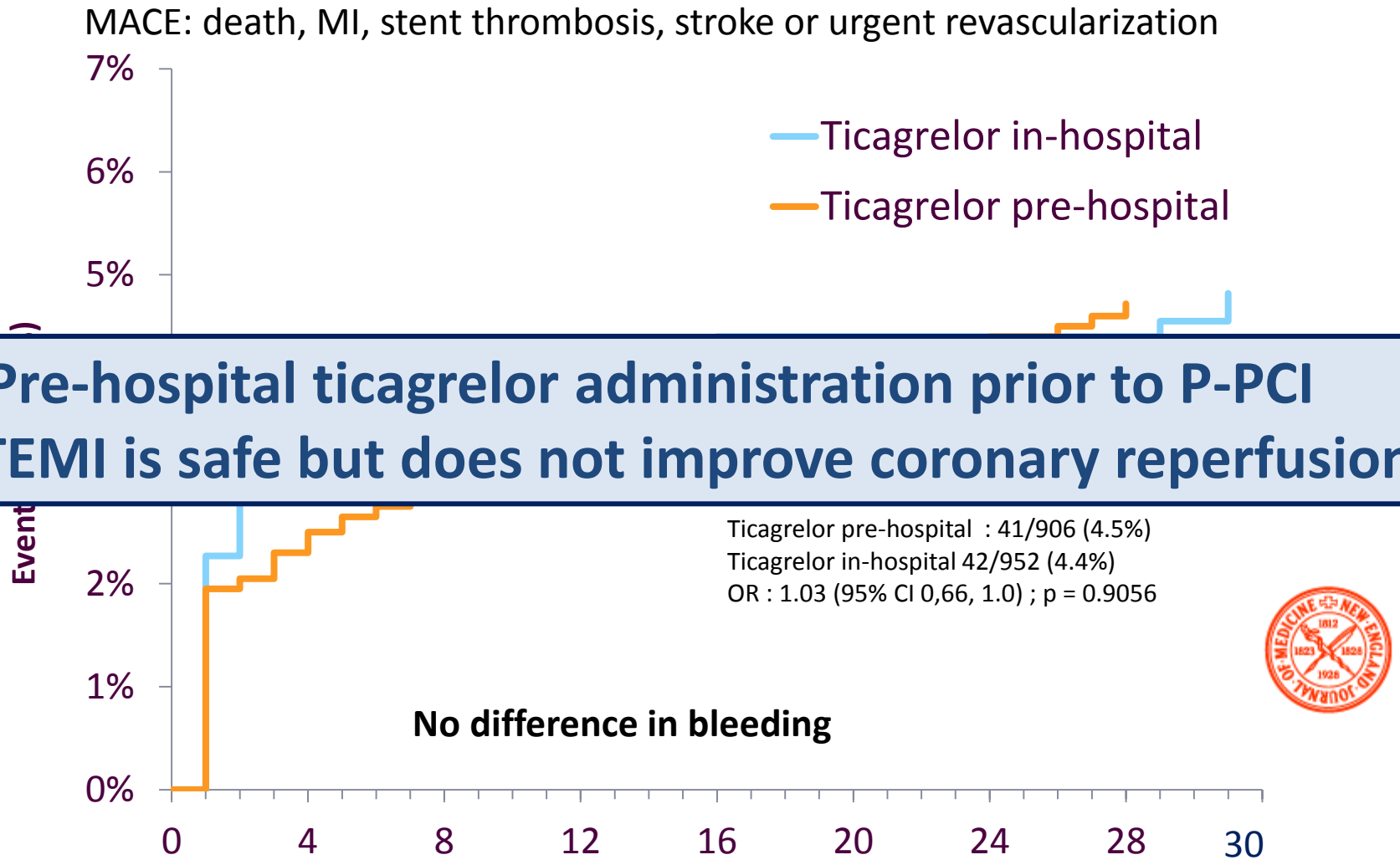
2nd Co-primary endpoint

No TIMI 3 flow in infarct-related artery



G. Montalescot, FR, 4025

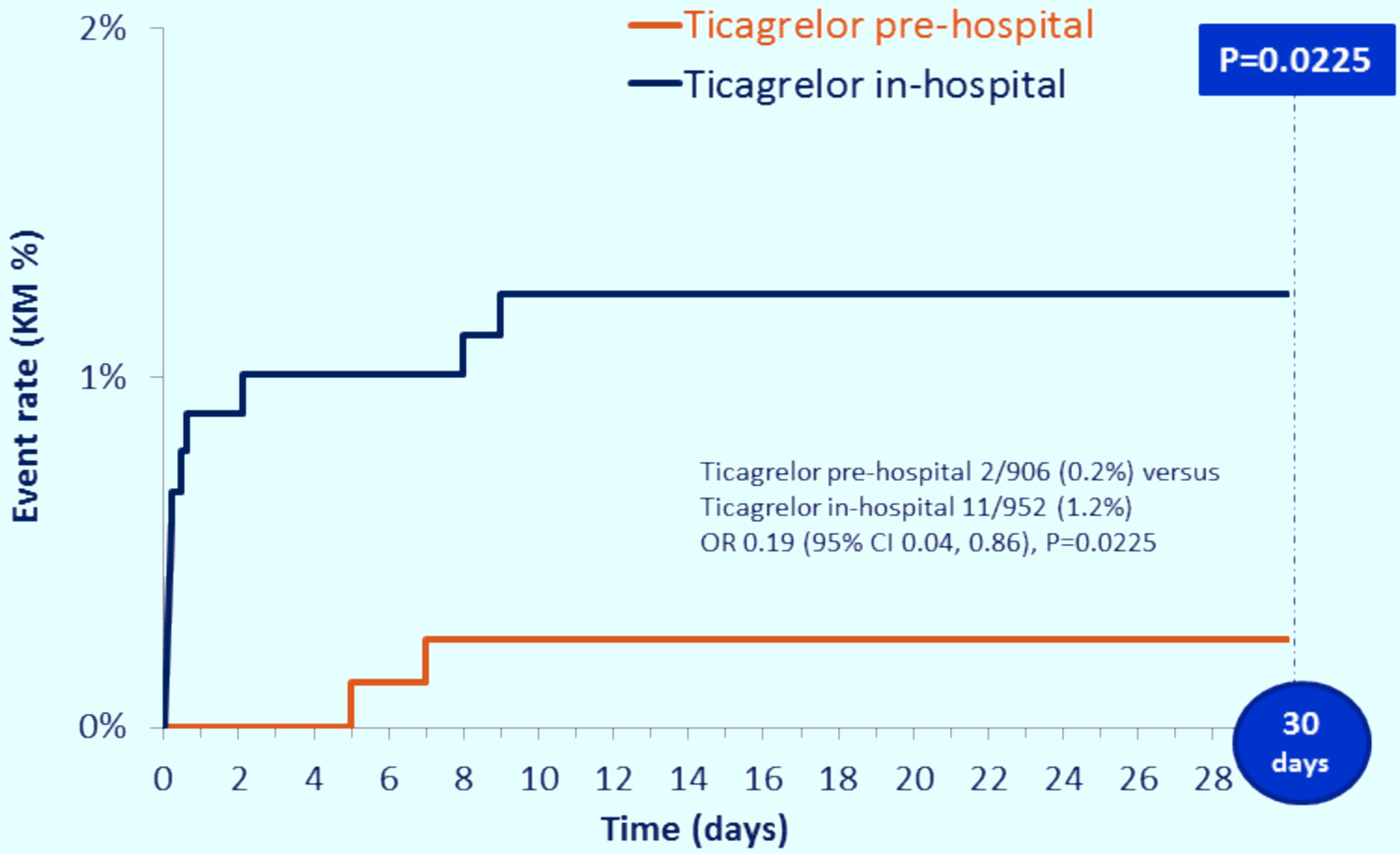
Secondary Endpoint: 30-Day MACE



Pre-hospital ticagrelor administration prior to P-PCI in STEMI is safe but does not improve coronary reperfusion

G. Montalescot, FR, 4025

Definite stent thrombosis up to 30 days



Should we use ticagrelor in the prehospital setting?

- We use it if we believe that the STEMI diagnosis is clear.

Our STEMI protocol: 2017

- Aspirin bolus orally (300 mg) or i.v. 250 mg
- Ticagrelor 180 mg or Clopidogrel 600 mg or no P2Y12 inhibitor if the diagnosis is clear and transport is rather long.
- Heparin 5000-10000 IU i.v.

Periprocedural and postprocedural antithrombotic therapyc in patients undergoing primary percutaneous coronary intervention

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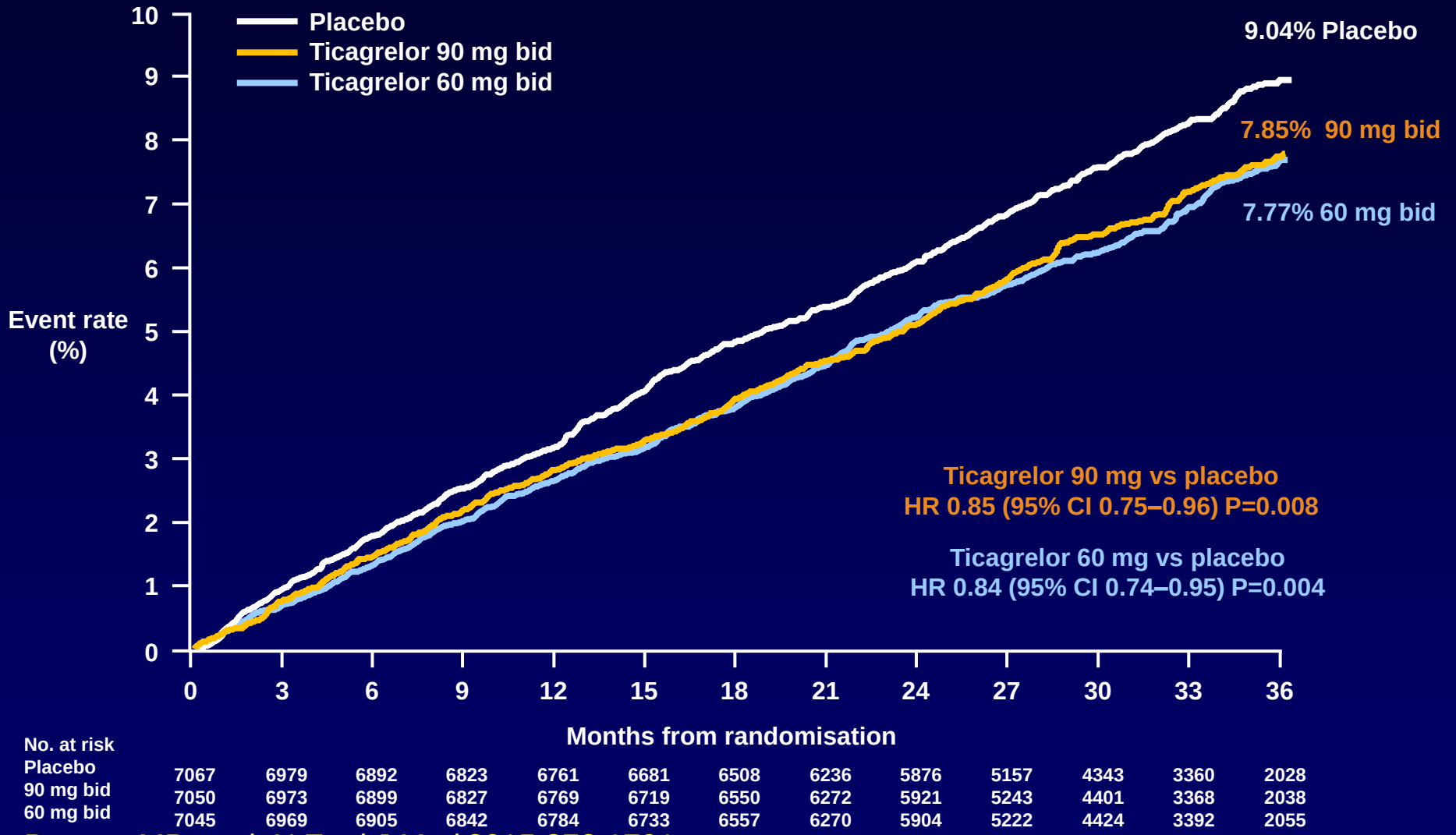
Recommendations	Class	Level
Antiplatelet therapy		
A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contra-indicated, is recommended before (or at latest at the time of) PCI and maintained over 12 months unless there are contra-indications such as excessive risk of bleeding.	I	A
Aspirin (oral or i.v, if unable to swallow) is recommended as soon as possible for all patients without contra-indications.	I	B
GP IIb/IIIa inhibitors should be considered for bailout if there is evidence of no-reflow or a thrombotic complication.	IIa	C
Cangrelor may be considered in patients who have not received $P2Y_{12}$ receptor inhibitors.	IIb	A

Recommendations for platelet inhibition in NSTE-ACS (continued)		
Recommendations	**Class[a]**	**Level[b]**
Long-term $P2Y_{12}$ inhibition		
$P2Y_{12}$ inhibitor administration in addition to aspirin beyond 1 year may be considered after careful assessment of the ischaemic and bleeding risks of the patient.	**IIb**	**A**
General recommendations		
A proton pump inhibitor in combination with DAPT is recommended in patients at higher than average risk of gastrointestinal bleeds (i.e. with a history of gastrointestinal ulcer/haemorrhage, anticoagulant therapy, chronic NSAID/corticosteroid use or two or more among age ≥65 years, dyspepsia, gastro-oesophageal reflux disease, *Helicobacter pylori* infection, and chronic alcohol use).	**I**	**B**
In patients on $P2Y_{12}$ inhibitors who need to undergo non-emergency major non-cardiac surgery[e], postponing surgery for at least 5 days after cessation of ticagrelor or clopidogrel, and for 7 days for prasugrel, should be considered if clinically feasible and unless the patient is at high risk of ischaemic events,.	**IIa**	**C**
In case of a non-cardiac surgical procedure that cannot be postponed or a bleeding complication, discontinuation of the $P2Y_{12}$ inhibitor may be considered after a minimum of 1 and 3 months from PCI with BMS and new-generation DES, respectively.	**IIb**	**C**

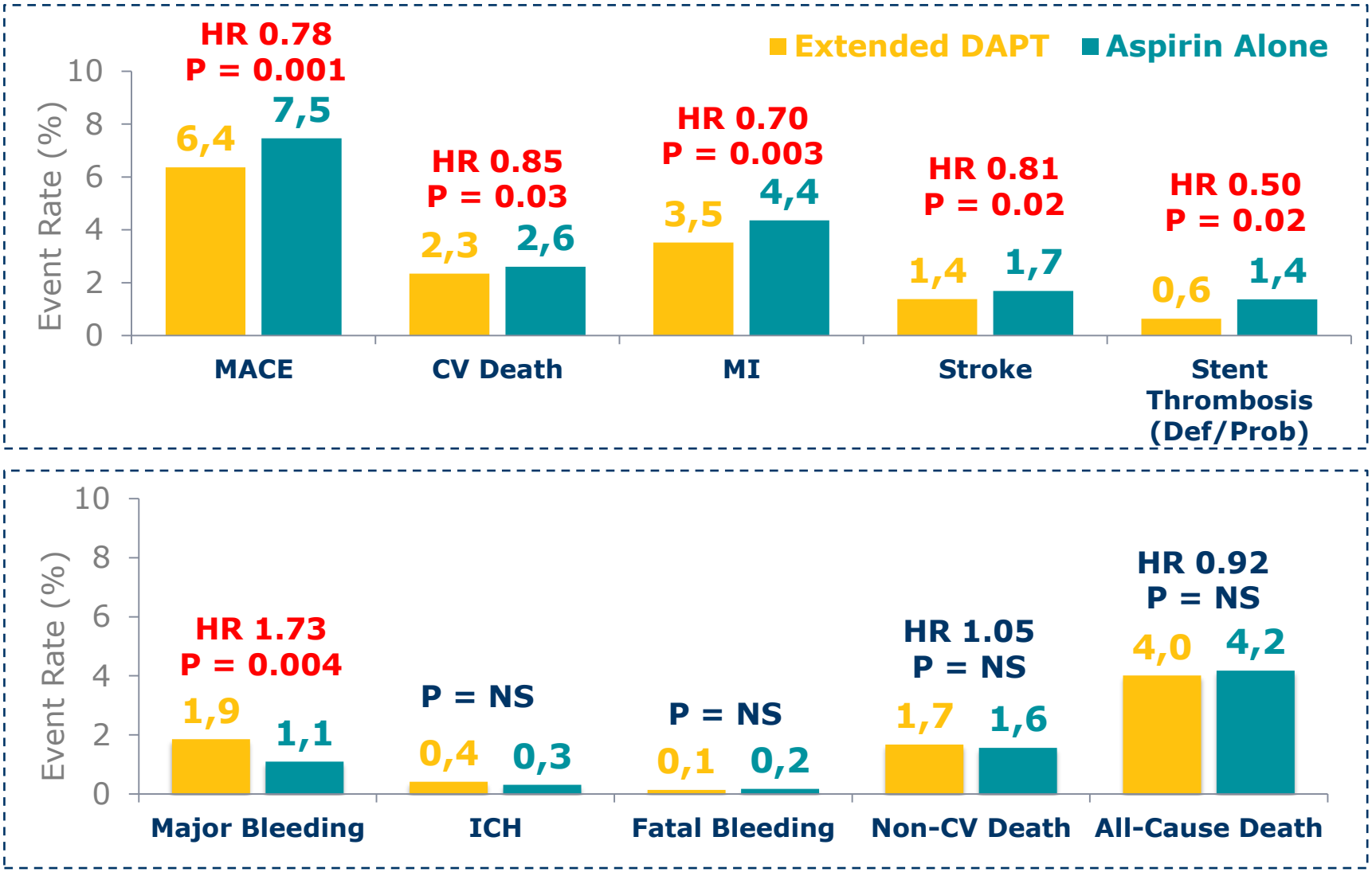
PEGASUS-TIMI 54: Primary Endpoint



No. at risk													
Placebo	7067	6979	6892	6823	6761	6681	6508	6236	5876	5157	4343	3360	2028
90 mg bid	7050	6973	6899	6827	6769	6719	6550	6272	5921	5243	4401	3368	2038
60 mg bid	7045	6969	6905	6842	6784	6733	6557	6270	5904	5222	4424	3392	2055

Bonaca MP *et al. N Engl J Med* 2015;372:1791-800.

INDIVIDUAL CV AND BLEEDING ENDPOINTS: metaanalysis



J. Udell (Toronto, CA) FP3913

NBV: Stabil CAD - elektiv PCI

- Aspirin 75 mg
- Clopidogrel 75 mg

Stenting

- (BMS)
- DES (old and new-generation)
- BVS (resorbable stents)

Dual antiplatelet therapy duration and related stent choices in patients with stable coronary artery disease treated with percutaneous coronary intervention

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Recommendations	Class	Level
In patients with stable CAD treated with coronary stent implantation, DAPT consisting of clopidogrel in addition to aspirin is generally recommended for 6 months, irrespective of the stent type.	I	A
Irrespective of the intended DAPT duration, DES is the preferred treatment option.	I	A
In patients with stable CAD considered at high bleeding risk (e.g. PRECISE-DAPT ≥25), DAPT for 3 months should be considered*.	IIa	B
In patients with stable CAD treated with drug-coated balloon, DAPT for 6 months should be considered.	IIa	B

*:The evidence supporting this recommendation comes from two studies where zotarolimus-eluting Endeavour sprint stent has been investigated in conjunction with a 3-month DAPT regimen.

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Dual antiplatelet therapy duration and related stent choices in patients with stable coronary artery disease treated with percutaneous coronary intervention *(continued)*

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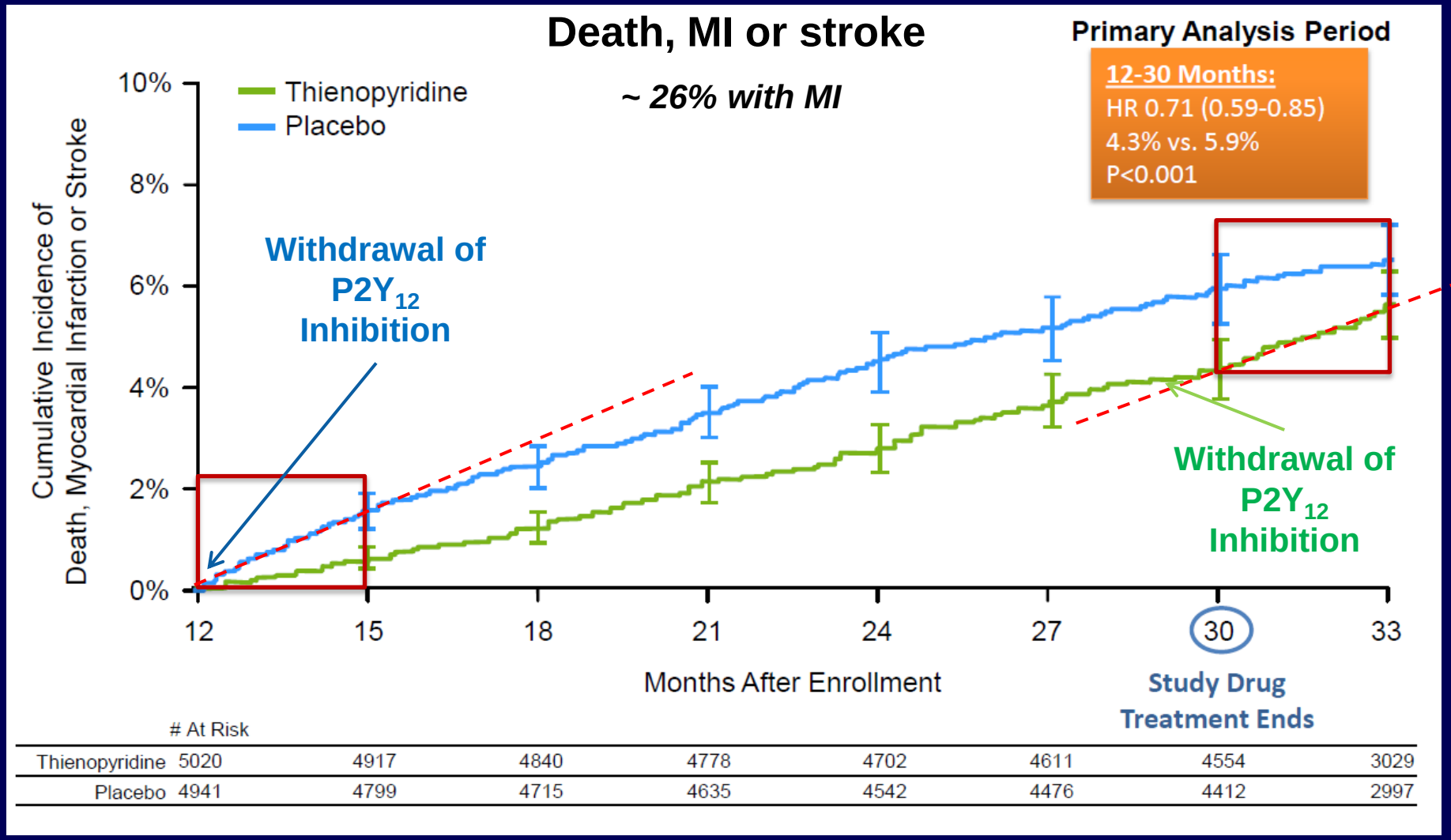
Recommendations	Class	Level
In patients with stable CAD treated with bioresorbable vascular scaffolds, DAPT for at least 12 months should be considered.	IIa	C
In patients with stable CAD who have tolerated DAPT without a bleeding complication and who are at low bleeding but high thrombotic risk, continuation of DAPT with clopidogrel for >6 months and ≤30 months may be considered.	IIb	A
In patients with stable CAD in whom 3-month DAPT poses safety concerns, DAPT for 1 month may be considered*.	IIb	C

*;1-month DAPT after implantation of zotarolimus-eluting Endeavour sprint stent or drug coated stent reduced risks of reintervention, myocardial infarction and inconsistently of stent thrombosis compared to bare-metal stent under similar DAPT duration. It is unclear if this evidence applies to other contemporary DES.

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

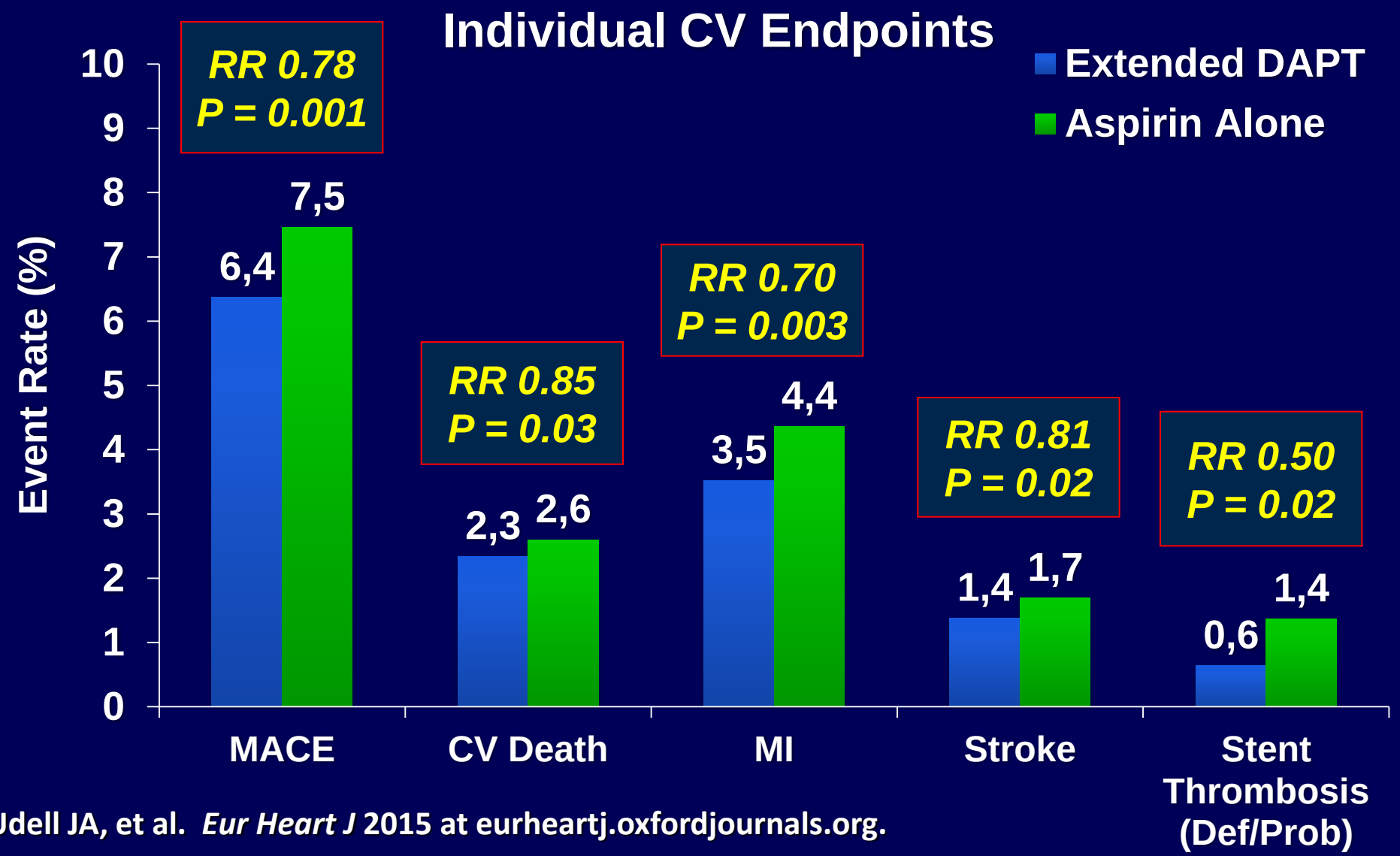
DAPT study: Continuation or withdrawal of thienopyridine 12 months after coronary stenting



# At Risk								
Thienopyridine	5020	4917	4840	4778	4702	4611	4554	3029
Placebo	4941	4799	4715	4635	4542	4476	4412	2997

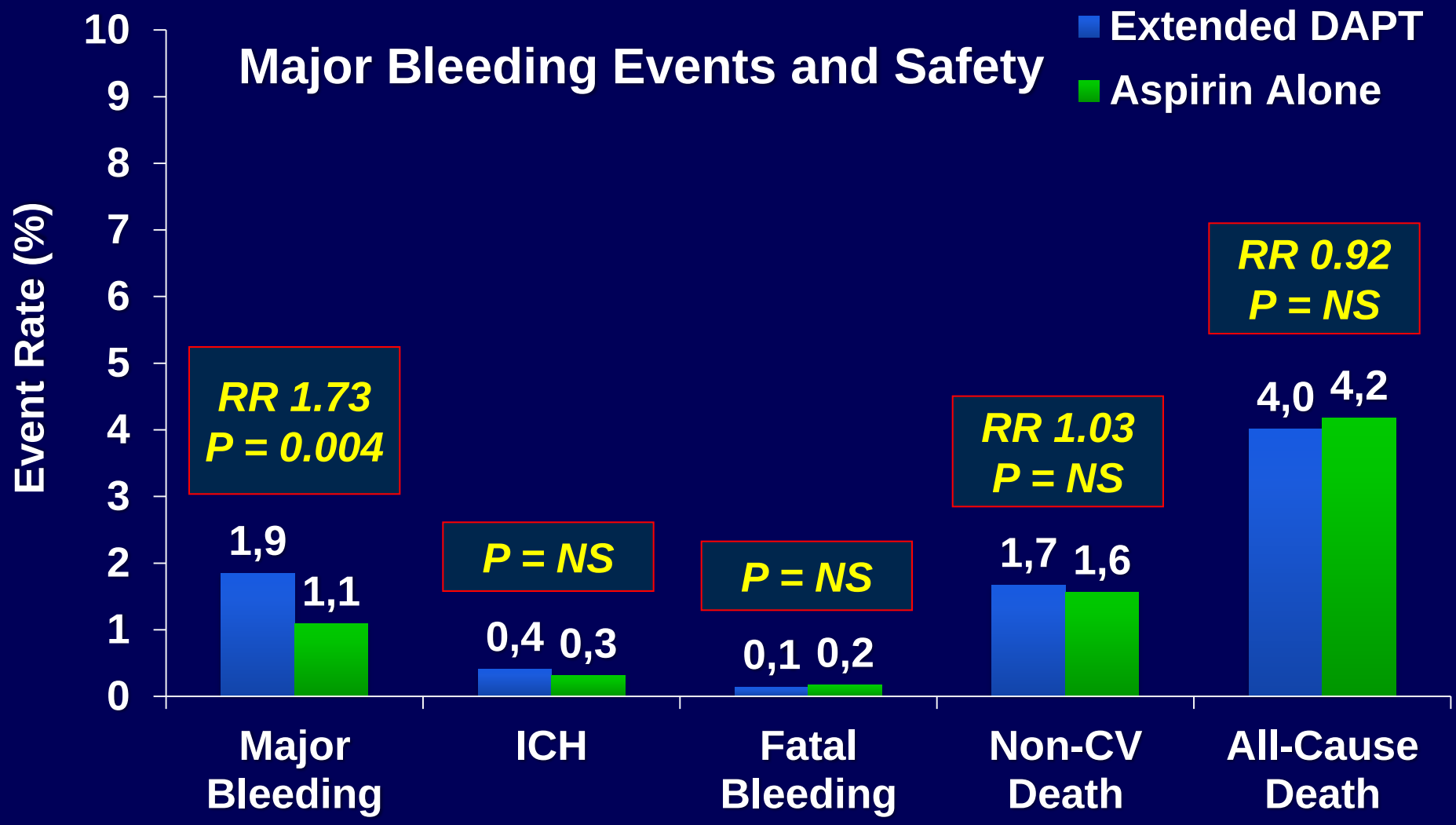
Mauri et al. NEJM 2014

Long-term DAPT post MI: meta-analysis (n=33,435)



Udell JA, et al. *Eur Heart J* 2015 at eurheartj.oxfordjournals.org.

Long-term DAPT post MI: meta-analysis (n=33,435)



Udell JA, et al. *Eur Heart J* 2015 at eurheartj.oxfordjournals.org.

Risk scores validated for dual antiplatelet therapy duration decision-making

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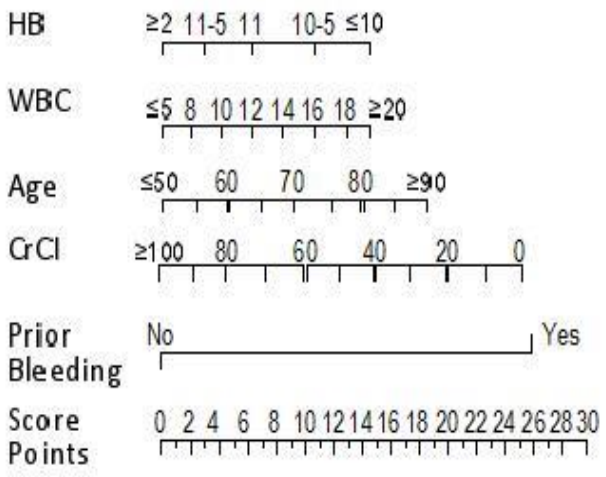
	PRECISE-DAPT score	DAPT score	
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT	
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	Standard DAPT (12 months) vs. Long DAPT (30 months)	
Score calculation		Age ≥75 65 to <75 <65 Cigarette smoking Diabetes mellitus MI at presentation Prior PCI or prior MI Paclitaxel-eluting stent Stent diameter <3 mm CHF or LVEF <30% Vein graft stent	 −2 pt −1 pt 0 pt +1 pt +1 pt +1 pt +1 pt +1 pt +1 pt +2 pt +2 pt
Score range	0 to 100 points	−2 to 10 points	
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT	
Calculator	www.precisedaptscore.com	www.daptstudy.org	

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(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Use of risk scores as guidance for the duration of dual antiplatelet therapy

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Recommendations	Class	Level
The use of risk scores designed to evaluate the benefits and risks of different DAPT durations may be considered.	IIb	A

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(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

$P2Y_{12}$ inhibitor selection and timing *(continued)*

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Recommendations	Class	Level
Ticagrelor or prasugrel on top of aspirin may be considered instead of clopidogrel in stable CAD patients undergoing PCI, taking into account the ischaemic (e.g. high SYNTAX score, prior stent thrombosis, location and number of implanted stents) and bleeding (e.g. according to PRECISE-DAPT) risks.	IIb	C
In NSTE-ACS patients in whom coronary anatomy is not known, it is not recommended to administer prasugrel.	III	B

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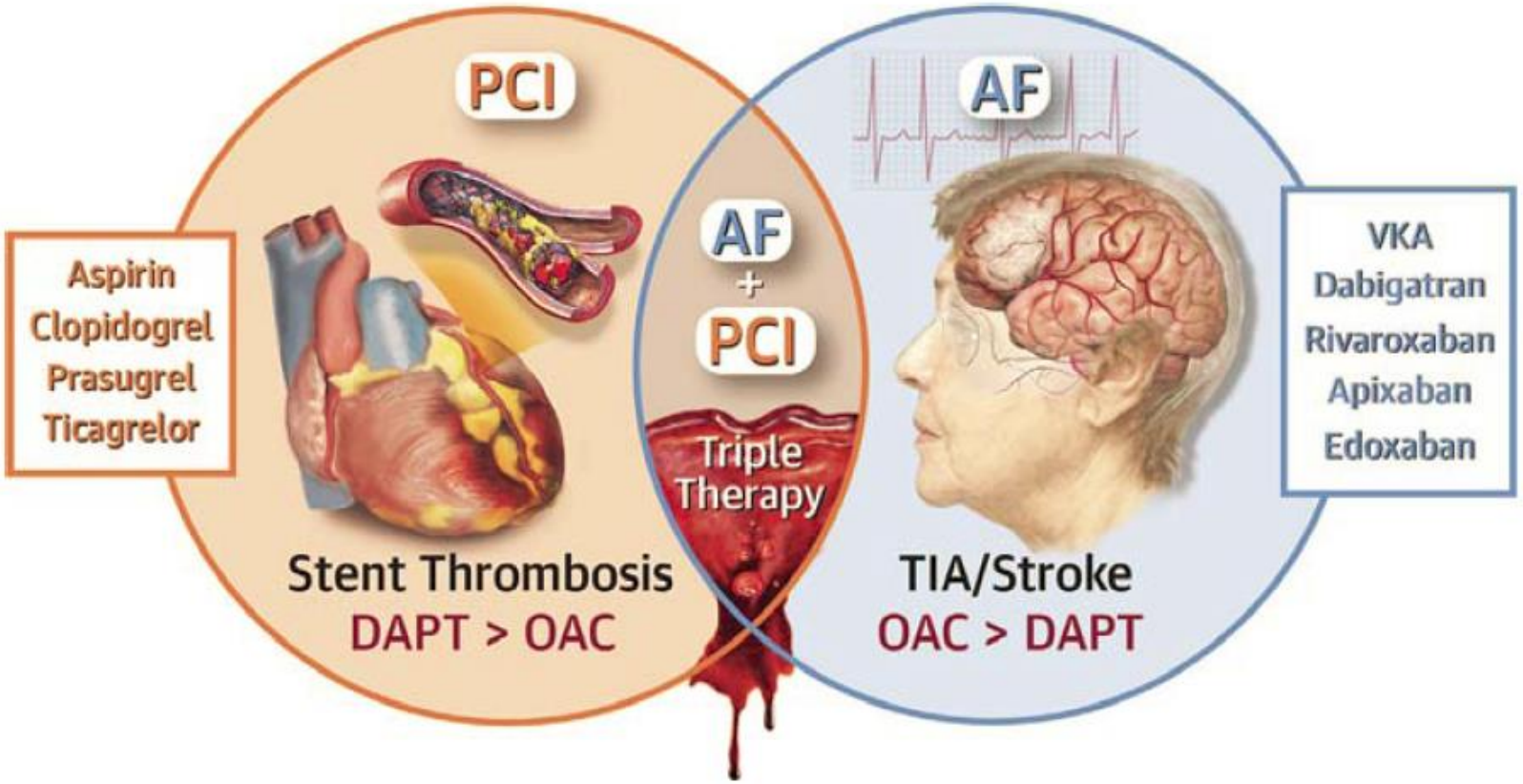
Duration and choice of DAPT

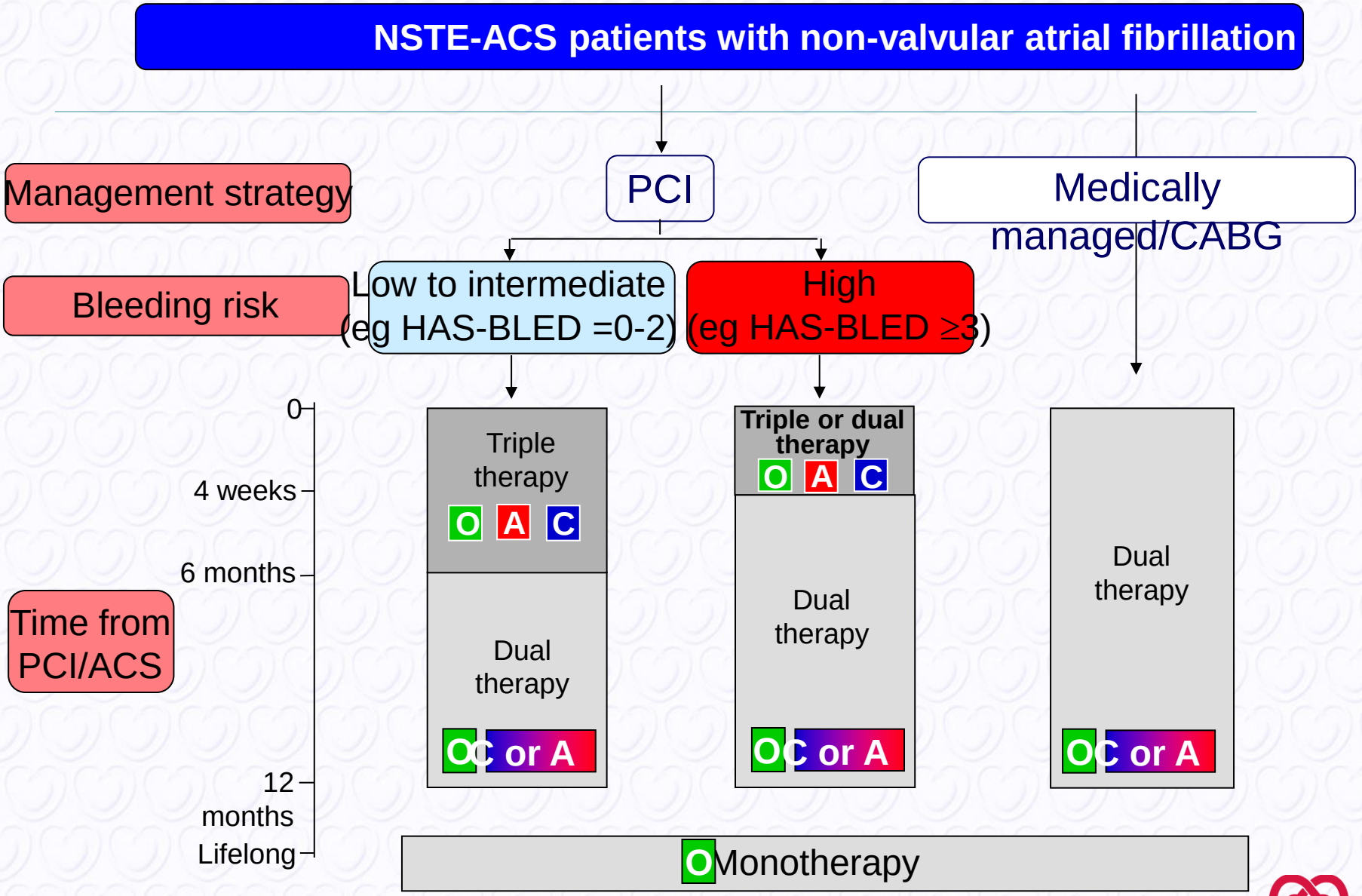
- ACS?
- Thrombotic risk?
- Bleeding risk?
- Lesion/stent risk?

Outline

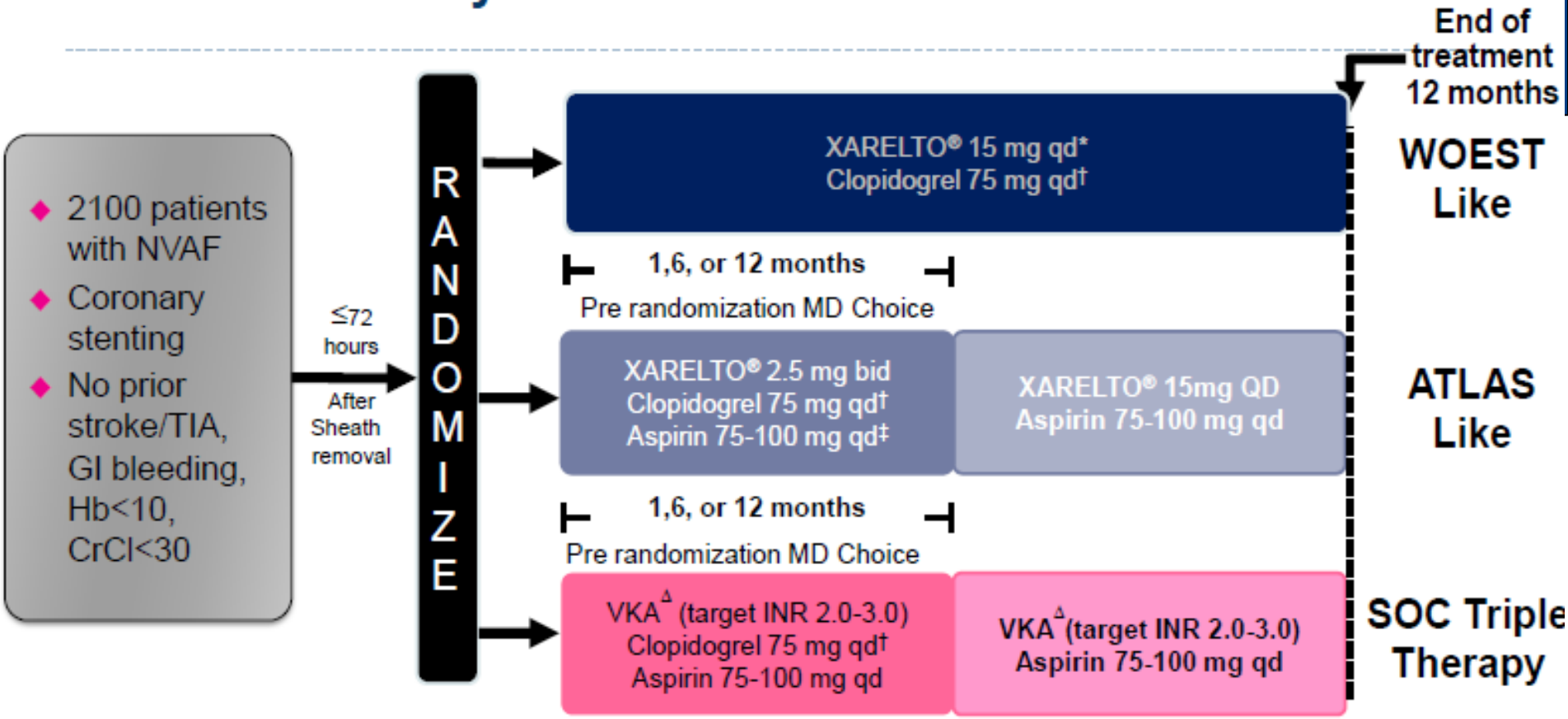
- Which drugs are available?
- When to start dual antiplatelet therapy?
- When to stop dual antiplatelet therapy?
- Triple therapy
- Secondary prevention in stable cardiovascular disease

The challenge…




NSTE-ACS patients with non-valvular atrial fibrillation
Management strategy
PCI
Medically managed/CABG
Bleeding risk
Low to intermediate (eg HAS-BLED =0-2)
High (eg HAS-BLED ≥3)
Time from PCI/ACS
0
4 weeks
6 months
12 months
Lifelong
Triple therapy
O A C
Dual therapy
O C or A
Triple or dual therapy
O A C
Dual therapy
O C or A
Dual therapy
O C or A
O Monotherapy
O Oral anticoagulation (VKA or NOACs)
A Aspirin 75-100 mg daily
C Clopidogrel 75 mg daily

Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI

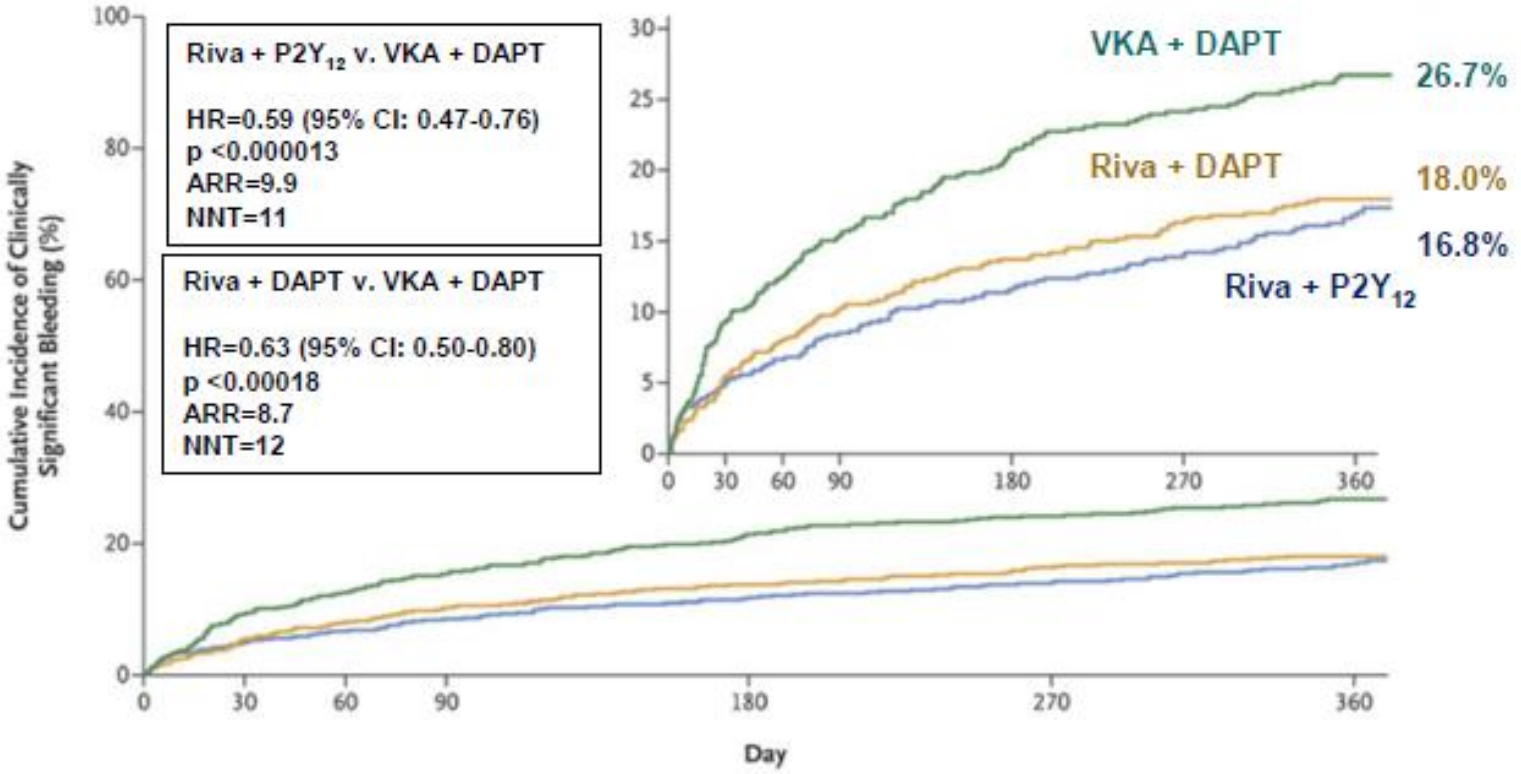


- Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.
†Alternative $P2Y_{12}$ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.
‡Low-dose aspirin (75–100 mg/d). Δ Open label VKA

Gibson CM et al. N Engl J Med 2016;375:2423–34

Rivaroxaban plus DAPT or $P2Y_{12}$ reduces clinically relevant bleeding compared with standard therapy

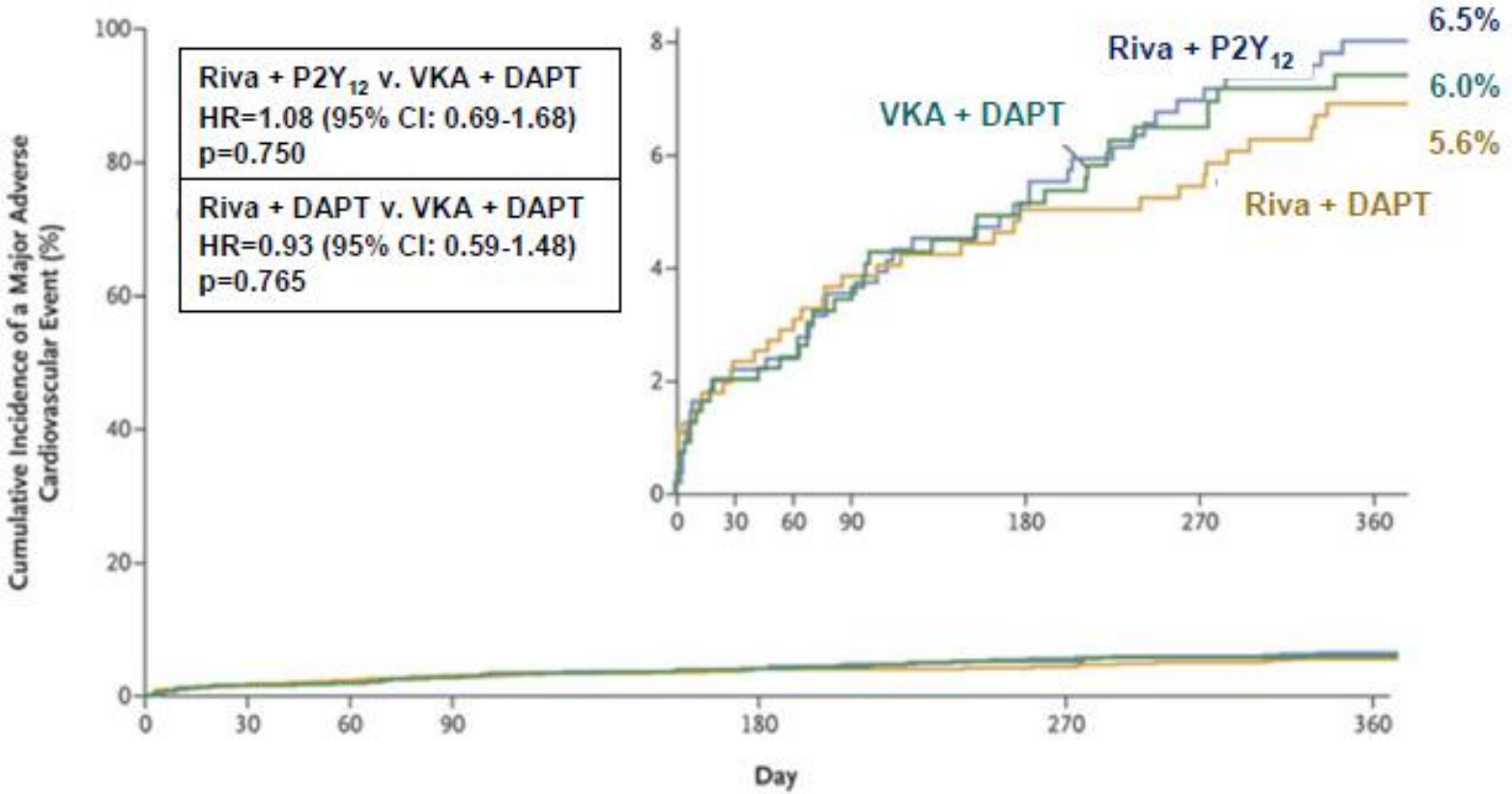


No. at Risk							
Group 1	696	628	606	585	543	510	383
Group 2	706	636	600	579	543	509	409
Group 3	697	593	555	521	461	426	329

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA.
Hazard ratios as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank P-values as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

Gibson CM et al. N Engl J Med 2016;375:2423–34

Similar incidence of MACE with rivaroxaban compared with standard therapy

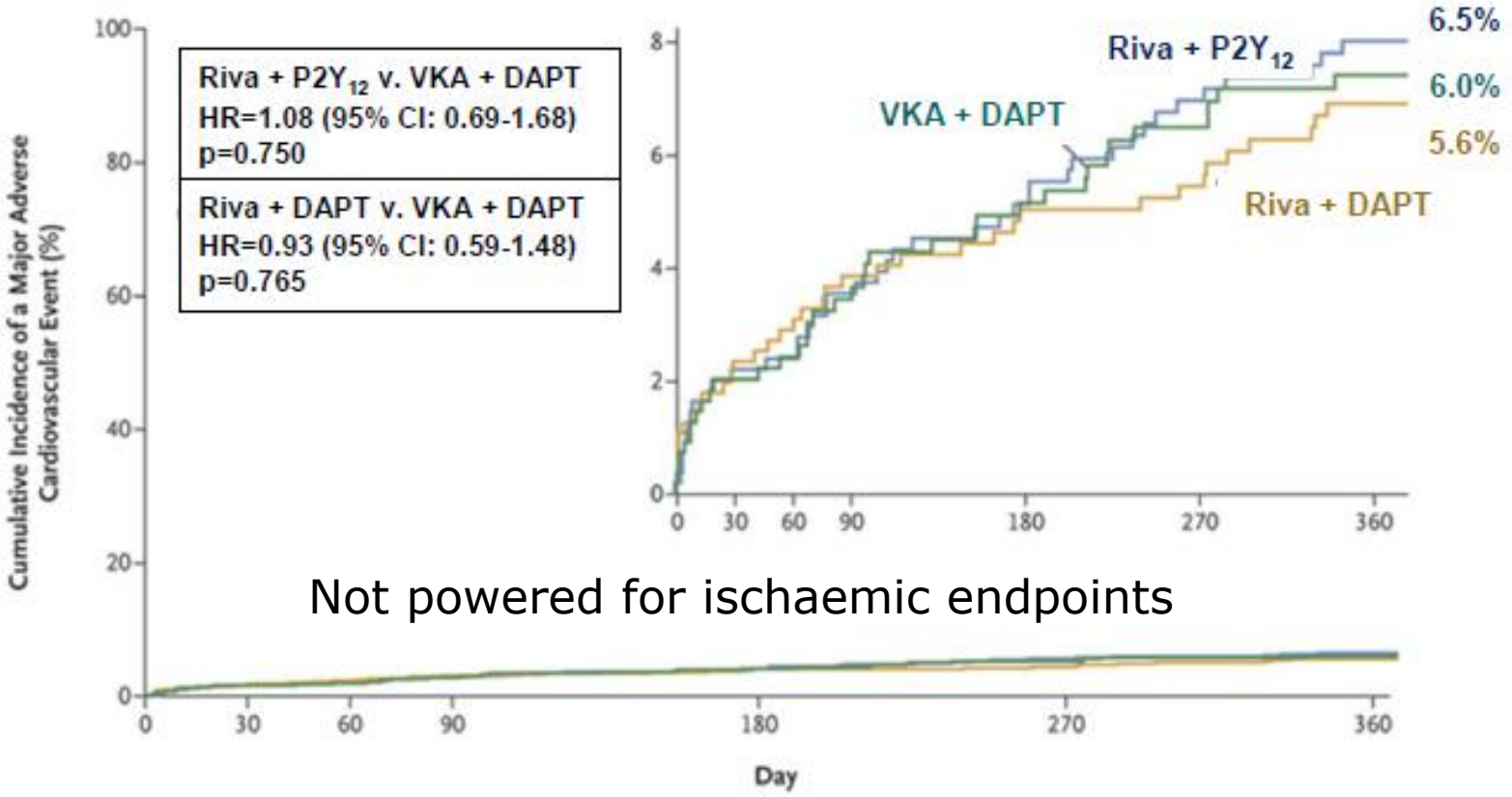


No. at Risk							
Group 1	694	648	633	621	590	562	430
Group 2	704	662	640	628	596	570	457
Group 3	695	635	607	579	543	514	408

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Composite of adverse CV events is composite of CV death, MI, and stroke.
Hazard ratios as compared to VKA group are based on the (stratified, only for the Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank P-values as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/115 mg QD comparing VKA) two-sided log rank test.

Gibson CM et al. N Engl J Med 2016;375:2423–34

Similar incidence of MACE with rivaroxaban compared with standard therapy



Not powered for ischaemic endpoints

No. at Risk							
Group 1	694	648	633	621	590	562	430
Group 2	704	662	640	628	596	570	457
Group 3	695	635	607	579	543	514	408

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
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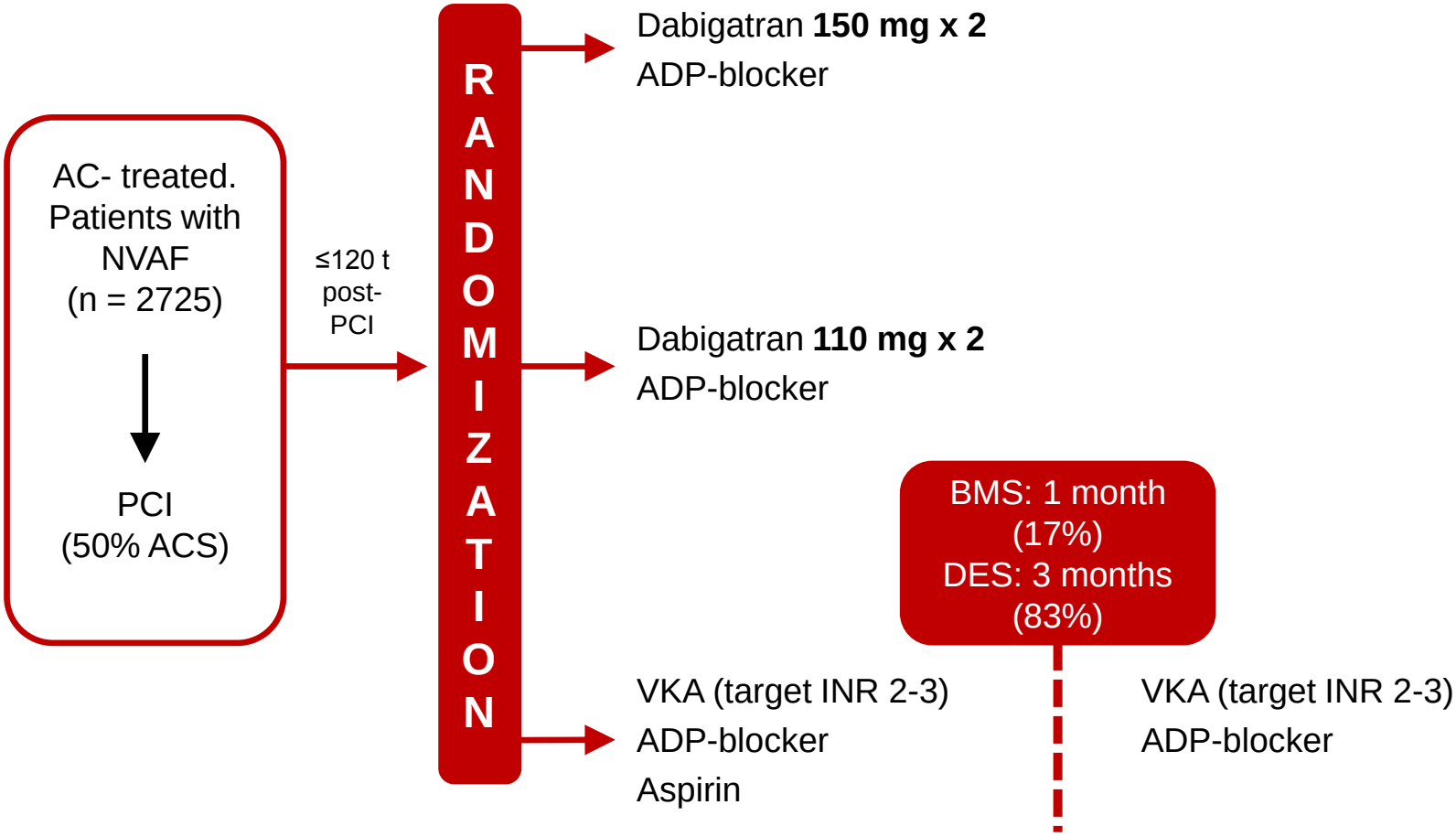
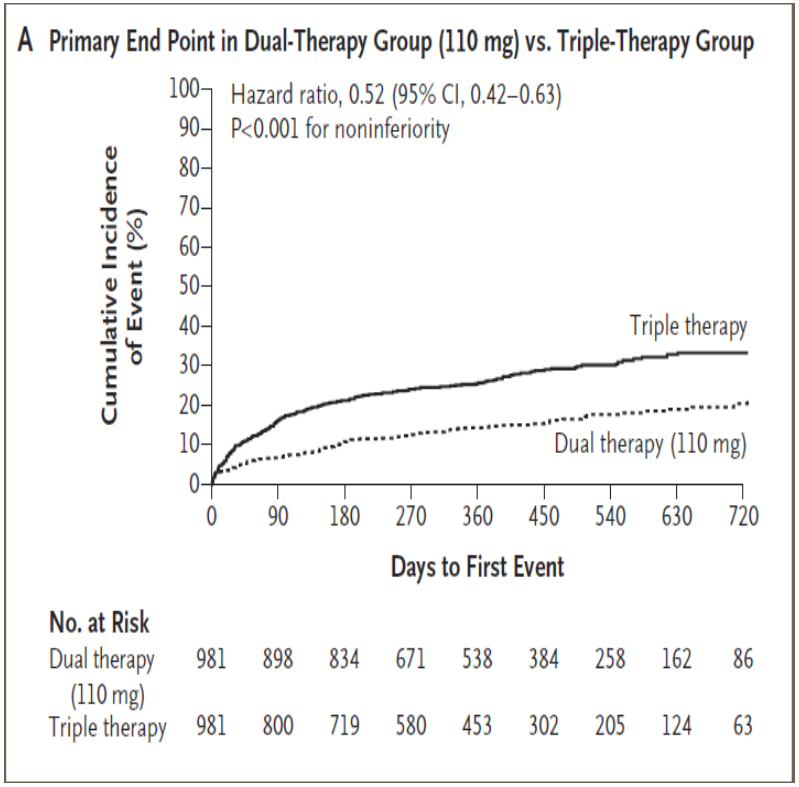
Log-Rank P-values as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/115 mg QD comparing VKA) two-sided log rank test.

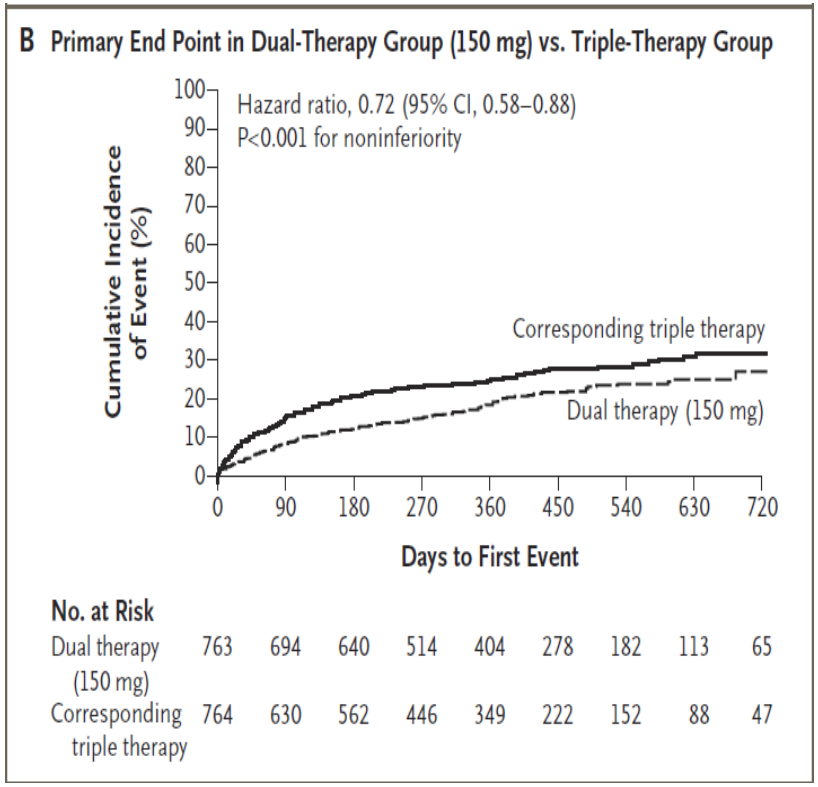
Gibson CM et al. N Engl J Med 2016;375:2423–34

REDUAL-PCI


AC- treated.
Patients with
NVAF
(n = 2725)
PCI
(50% ACS)
≤120 t
post-
PCI
RANDOMIZATION
Dabigatran **150 mg x 2**
ADP-blocker
Dabigatran **110 mg x 2**
ADP-blocker
BMS: 1 month
(17%)
DES: 3 months
(83%)
VKA (target INR 2-3)
ADP-blocker
Aspirin
VKA (target INR 2-3)
ADP-blocker

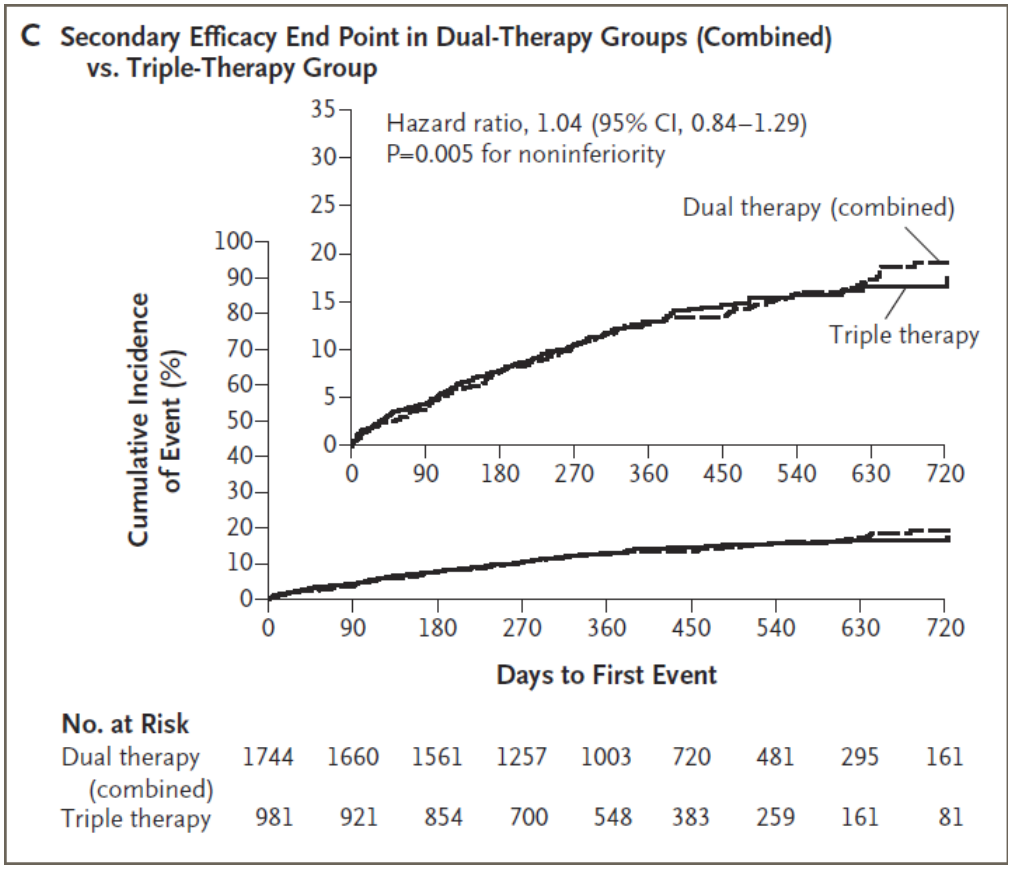
REDUAL-PCI: Safety





Cannon et al. NEJM 2017

REDUAL-PCI: Efficacy



Cannon et al. NEJM 2017

- Thromboemboli
- Death
- Revascularization

Ongoing studies

- AUGUSTUS (apixaban)
- ENTRUST (edoxaban)

Strategies to avoid bleeding complications in patients treated with oral anticoagulant

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• Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA_2DS_2-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.
• Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.
• Consider the use of NOACs instead of VKA when NOACs are not contra-indicated.
• Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. >65–70%) when VKA is used.
• Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.
• Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
• Use low-dose (≤100 mg daily) aspirin.
• Routine use of PPIs.

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(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

High-risk features of stent-driven recurrent ischaemic events

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- Prior stent thrombosis on adequate antiplatelet therapy.
- Stenting of the last remaining patent coronary artery.
- Diffuse multivessel disease especially in diabetic patients.
- Chronic kidney disease (i.e. creatinine clearance <60 mL/min).
- At least three stents implanted.
- At least three lesions treated.
- Bifurcation with two stents implanted.
- Total stent length >60 mm.
- Treatment of a chronic total occlusion.

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(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Unfavourable patient profile for a combination of oral anticoagulant and antiplatelet therapy

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• Short life expectancy.
• Ongoing malignancy.
• Poor expected adherence.
• Poor mental status.
• End stage renal failure.
• Advanced age.
• Prior major bleeding/prior haemorrhagic stroke.
• Chronic alcohol abuse.
• Anaemia.
• Clinically significant bleeding on dual antithrombotic therapy.

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Dual antiplatelet therapy duration in patients with indication for oral anticoagulation

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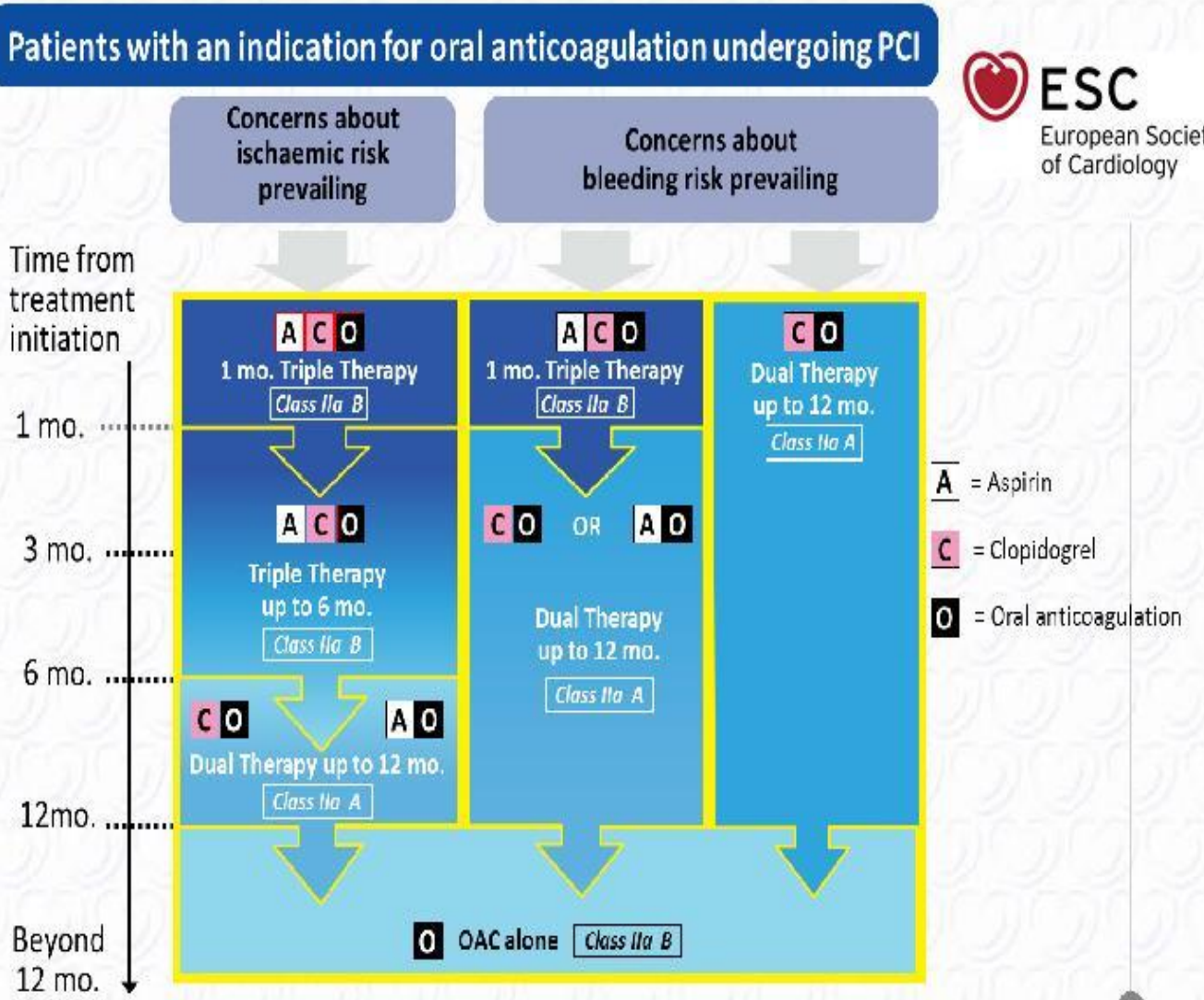
Recommendations	Class	Level
It is recommended to administer periprocedurally aspirin and clopidogrel in patients undergoing coronary stent implantation.	I	C
In patients treated with coronary stent implantation, triple therapy with aspirin, clopidogrel and OAC should be considered for 1 month, irrespective of the type of stent used.	IIa	B
Triple therapy with aspirin, clopidogrel and OAC for longer than 1 month and up to 6 months should be considered in patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics, which outweigh the bleeding risk.	IIa	B
Dual therapy with clopidogrel 75 mg/day and OAC should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk.	IIa	A

2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention (PCI)



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2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS (European Heart Journal 2017 - doi:10.1093/eurheartj/ehx419)

Outline

- Which drugs are available?

- When to start dual antiplatelet therapy?
- When to stop dual antiplatelet therapy?

- Triple therapy

- Secondary prevention in stable cardiovascular disease

Aspirin (clopidogrel)

COMPASS

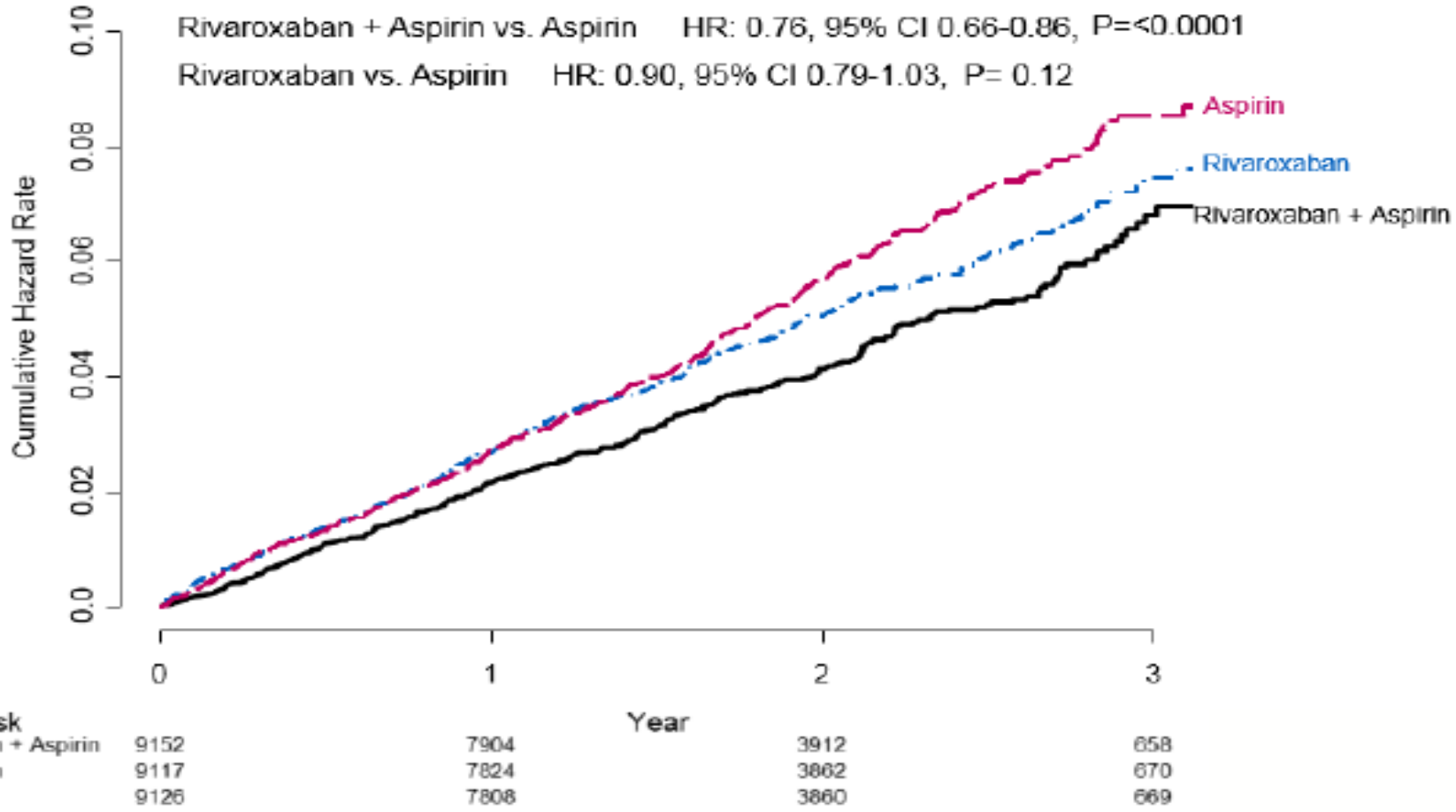
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn, S.S. Anand, P. Widimsky, M. Hori, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Probstfield, D.L. Bhatt, J. Zhu, Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A. Kakkar, K.A.A. Fox, A.N. Parkhomenko, G. Ertl, S. Störk, M. Keltai, L. Ryden, N. Pogosova, A.L. Dans, F. Lanas, P.J. Commerford, C. Torp-Pedersen, T.J. Guzik, P.B. Verhamme, D. Vinereanu, J.-H. Kim, A.M. Tonkin, B.S. Lewis, C. Felix, K. Yusoff, P.G. Steg, K.P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong, and S. Yusuf, for the COMPASS Investigators*

Primary: CV death, stroke, MI



Primary components

Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	p
CV death	160 (1.7%)	203 (2.2%)	0.78 (0.64-0.96)	0.02
Stroke	83 (0.9%)	142 (1.6%)	0.58 (0.44-0.76)	<0.0001
MI	178 (1.9%)	205 (2.2%)	0.86 (0.70-1.05)	0.14

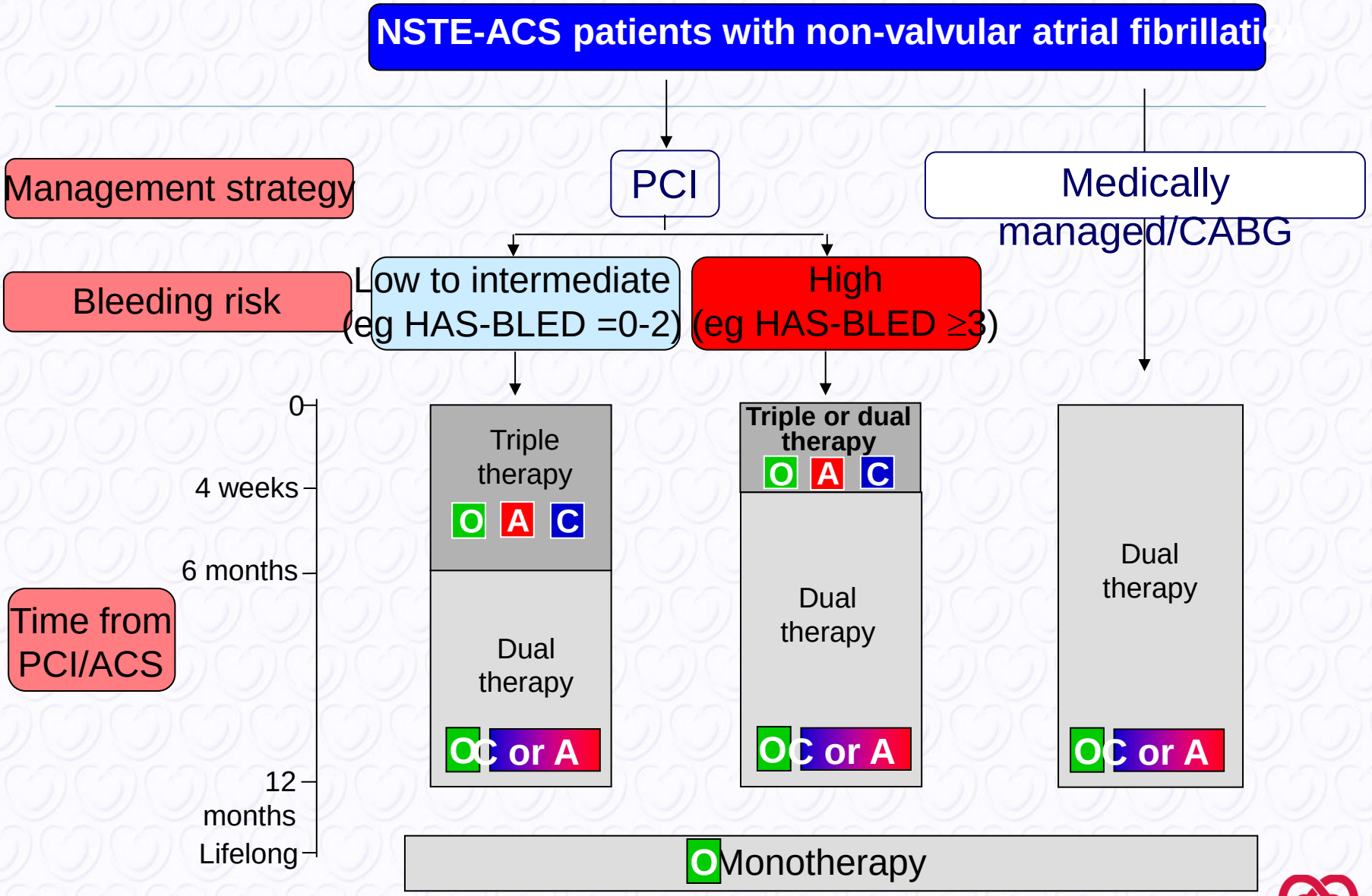
Major bleeding

Outcome	R + A N=9,152	R N=9,117	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin		Rivaroxaban vs. Aspirin	
	N (%)	N (%)	N (%)	HR (95% CI)	P	HR (95% CI)	P
Major bleeding	288 (3.1%)	255 (2.8%)	170 (1.9%)	1.70 (1.40-2.05)	<0.0001	1.51 (1.25-1.84)	<0.0001
Fatal	15 (0.2%)	14 (0.2%)	10 (0.1%)	1.49 (0.67-3.33)	0.32	1.40 (0.62-3.15)	0.41
Non fatal ICH*	21 (0.2%)	32 (0.4%)	19 (0.2%)	1.10 (0.59-2.04)	0.77	1.69 (0.96-2.98)	0.07
Non-fatal other critical organ*	42 (0.5%)	45 (0.5%)	29 (0.3%)	1.43 (0.89-2.29)	0.14	1.57 (0.98-2.50)	0.06

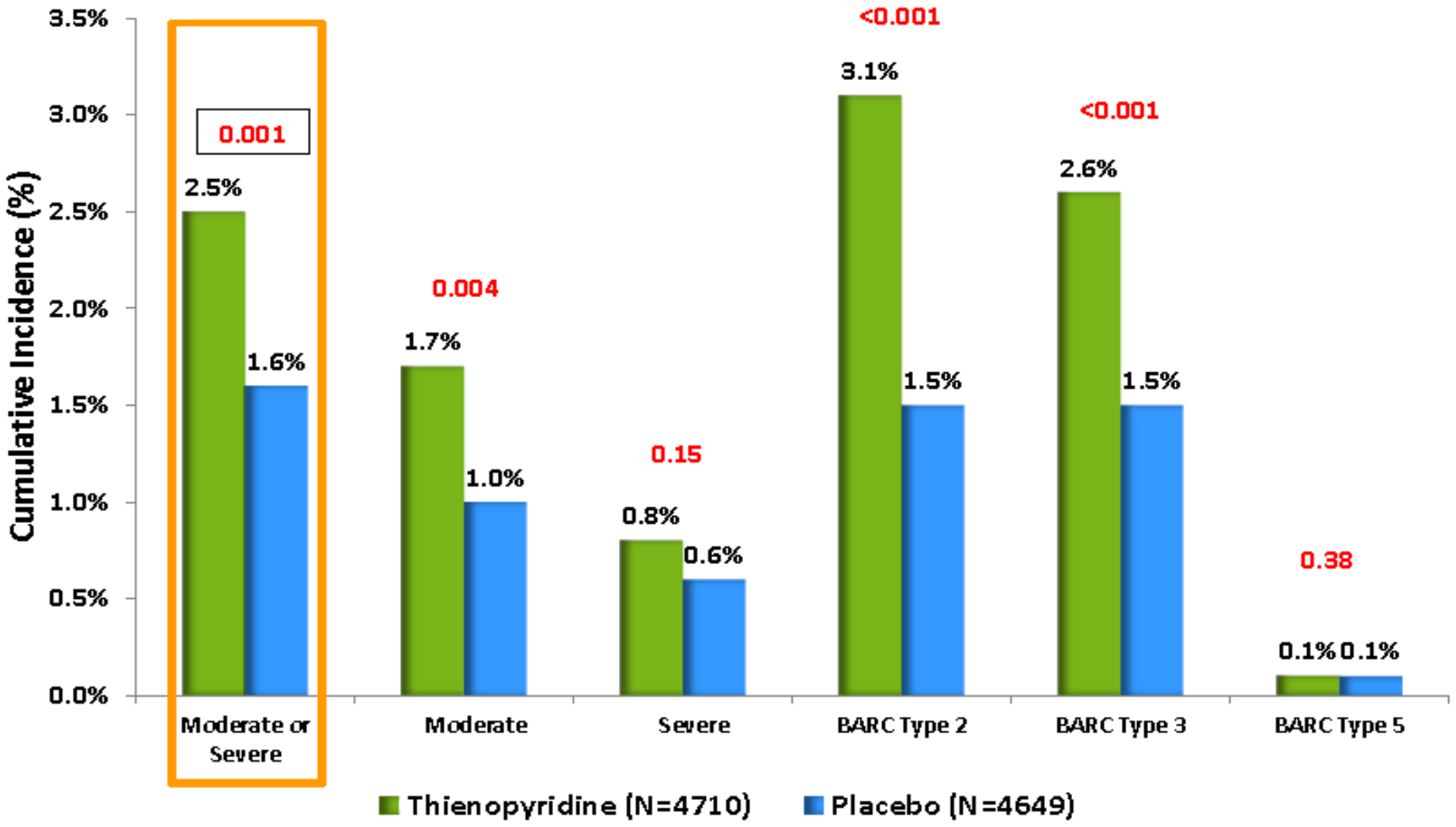
* symptomatic

Net clinical benefit

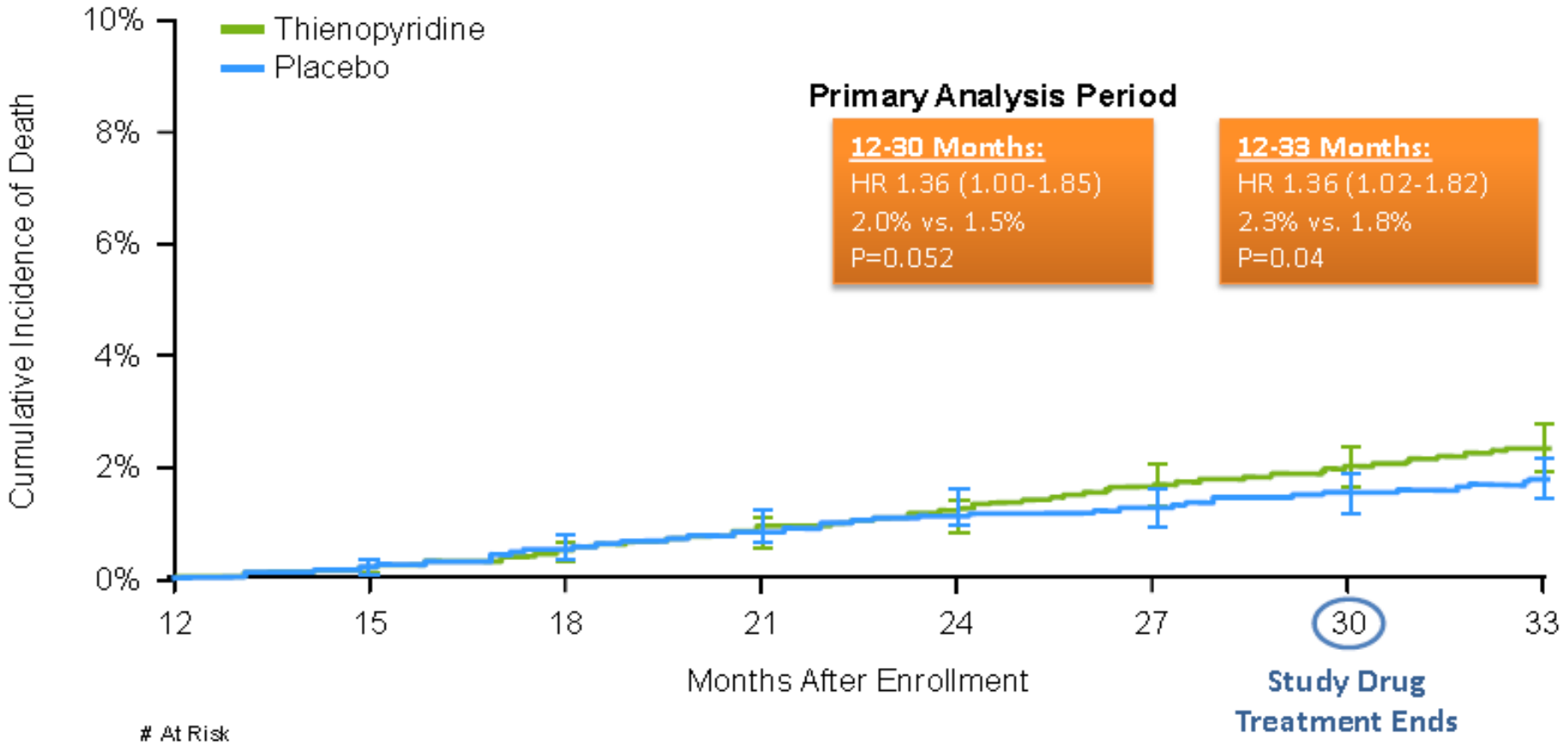
Outcome	R + A N=9,152	A N=9,126	Rivaroxaban + Aspirin vs. Aspirin	
	N (%)	N (%)	HR (95% CI)	P
Net clinical benefit (Primary + Severe bleeding events)	431 (4.7%)	534 (5.9%)	0.80 (0.70-0.91)	0.0005



Primary Safety End Point (Moderate or Severe Bleeding): 12-30 Months

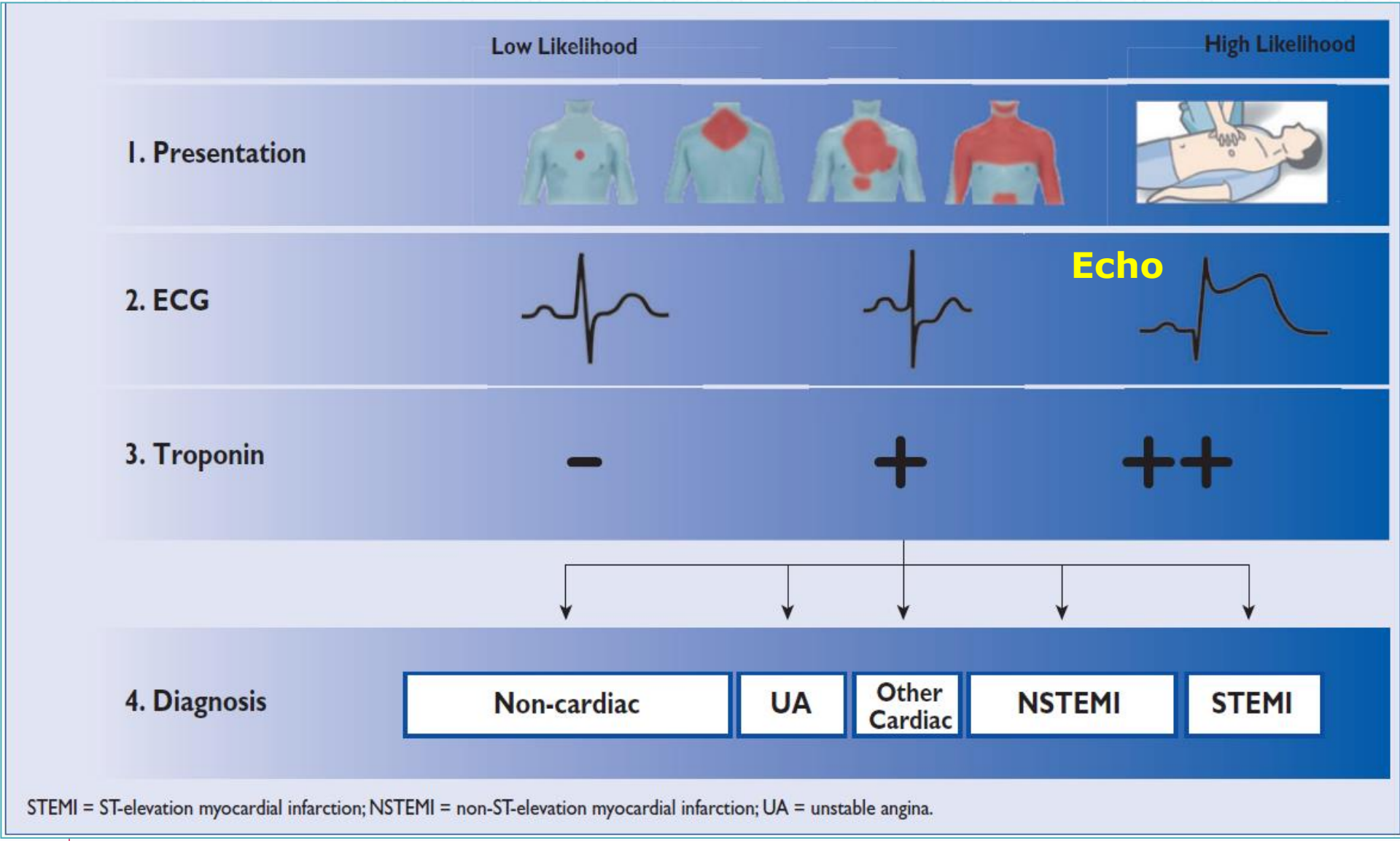


All-Cause Mortality

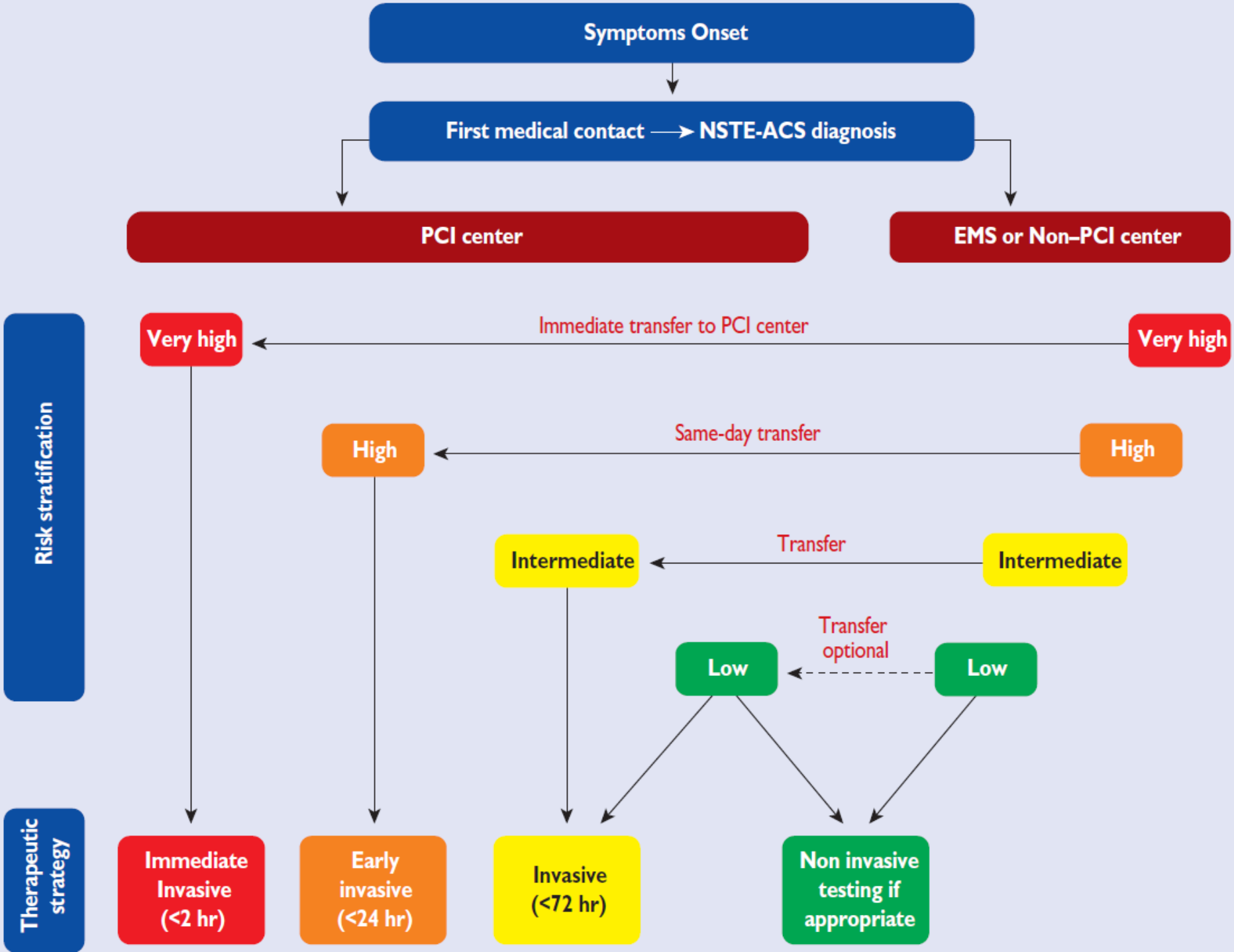


# At Risk							
Thienopyridine 5020	4936	4875	4835	4777	4703	4663	3139
Placebo 4941	4866	4805	4761	4700	4659	4618	3159

Initial assessment of patients with suspected acute coronary syndromes



STEMI = ST-elevation myocardial infarction; NSTEMI = non-ST-elevation myocardial infarction; UA = unstable angina.


Symptoms Onset
First medical contact → NSTE-ACS diagnosis
PCI center
EMS or Non–PCI center
Risk stratification
Very high
Immediate transfer to PCI center
Very high
High
Same-day transfer
High
Intermediate
Transfer
Intermediate
Transfer optional
Low
Low
Therapeutic strategy
Immediate Invasive (<2 hr)
Early invasive (<24 hr)
Invasive (<72 hr)
Non invasive testing if appropriate

NBV: Stabil CAD

- For at minimere risikoen for stenttrombose, bør patienter behandlet med PCI og BMS som minimum behandles med clopidogrel i 1 måned. Patienter behandlet med PCI og DES bør som minimum behandles med clopidogrel i 3-6 måneder. Dette har bl.a betydning for patienter, som skal opereres. Generelt anbefales dog 12 måneders behandling til alle, der har fået foretaget PCI.