# IS THERE A PLACE FOR THE NEW OAC AFTER ACS
## Bleeding risk related to triple antithrombotic therapy

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**UH „City clinic“, Sofia**

# При ОКС няма лесни антитромботични схеми. Защото няма и ясни отговори базирани на резултати от проучвания.

- Пациентите с ОКС и ПМ са обикновено по-възрастни, с по-висока честота на диабет, с по-комплексна коронарна анатомия.
- **Какво да правим с широко използваните вече празугрел или тикагрелор?**
- **Можем ли да избираме свободно VKA или NOAC?**
- **Нуждаем ли се от Аспирин винаги?**
- Как да балансираме между ползи, риск от кървене и риск от стент тромбоза?

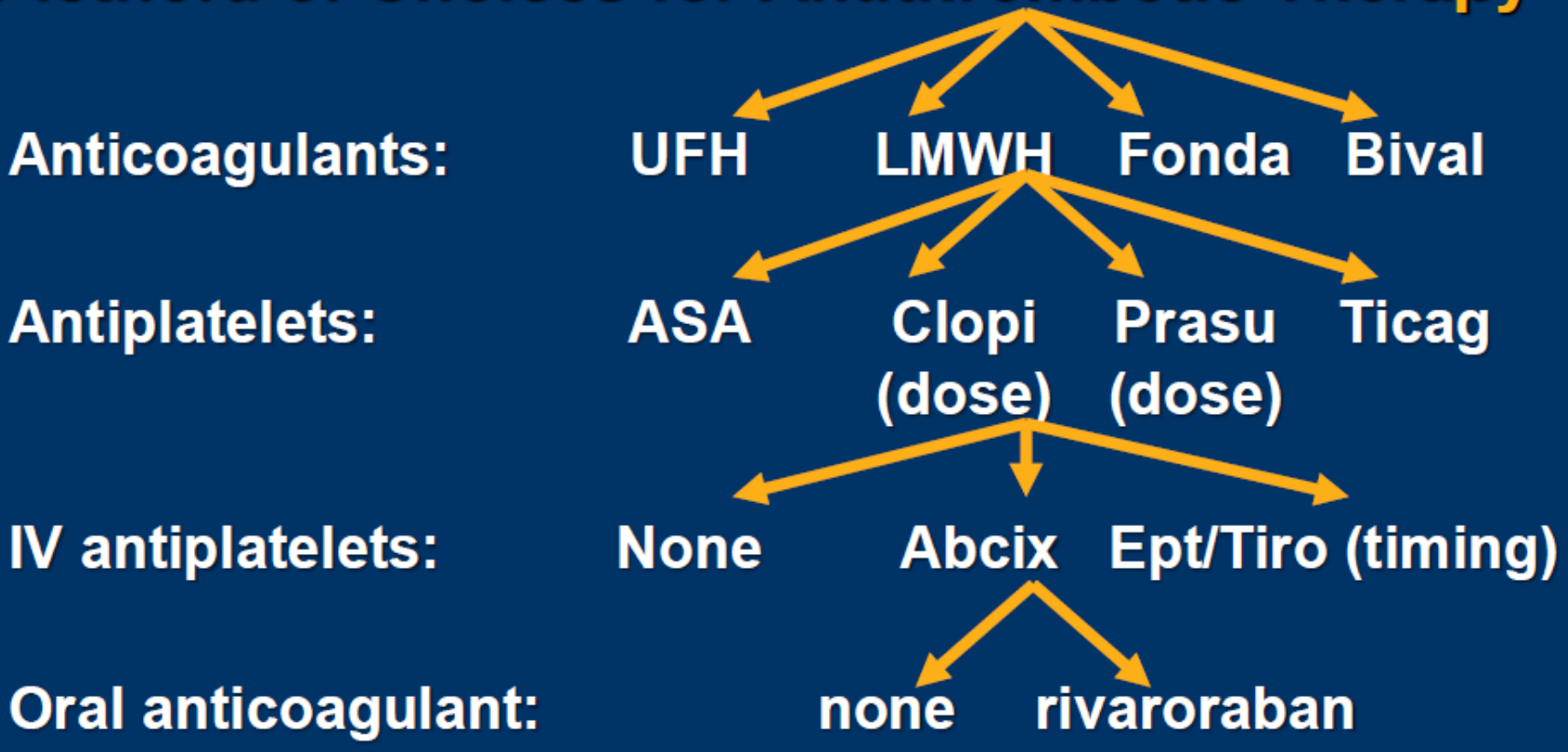
# Cardiac conditions requiring anticoagulant therapy

- Atrial fibrillation
- Deep venous thromboembolism
- Pulmonary embolism
- Mechanical valve surgery

On the other hand

**Acute coronary syndrome** or **coronary stent implantation** require **"dual-anti-platelet therapy"**

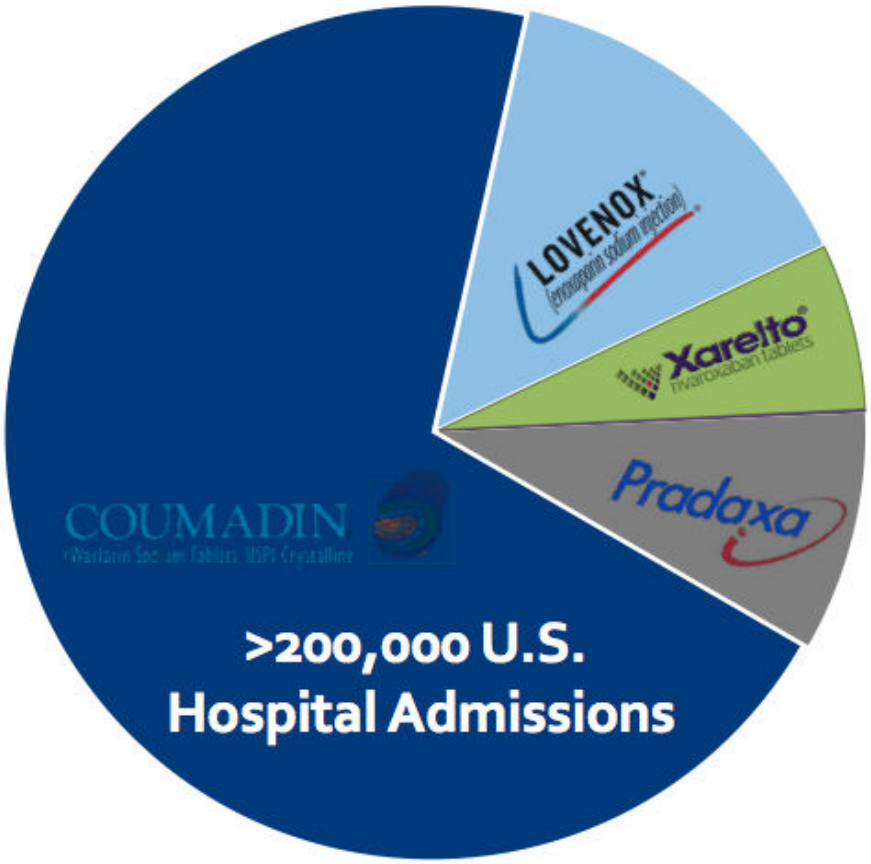
# Plethora of Choices for Antithrombotic Therapy




**96 Different Combinations!**

Risk:

# Картината на кървенето при лечение с някои антикоагуланти в САЩ /2013/




U.S. Admissions for Bleeding Event

- Lovenox 33,000
- XARELTO 14,500
- Eliquis 148
- Pradaxa 22,000
- Coumadin 150,000

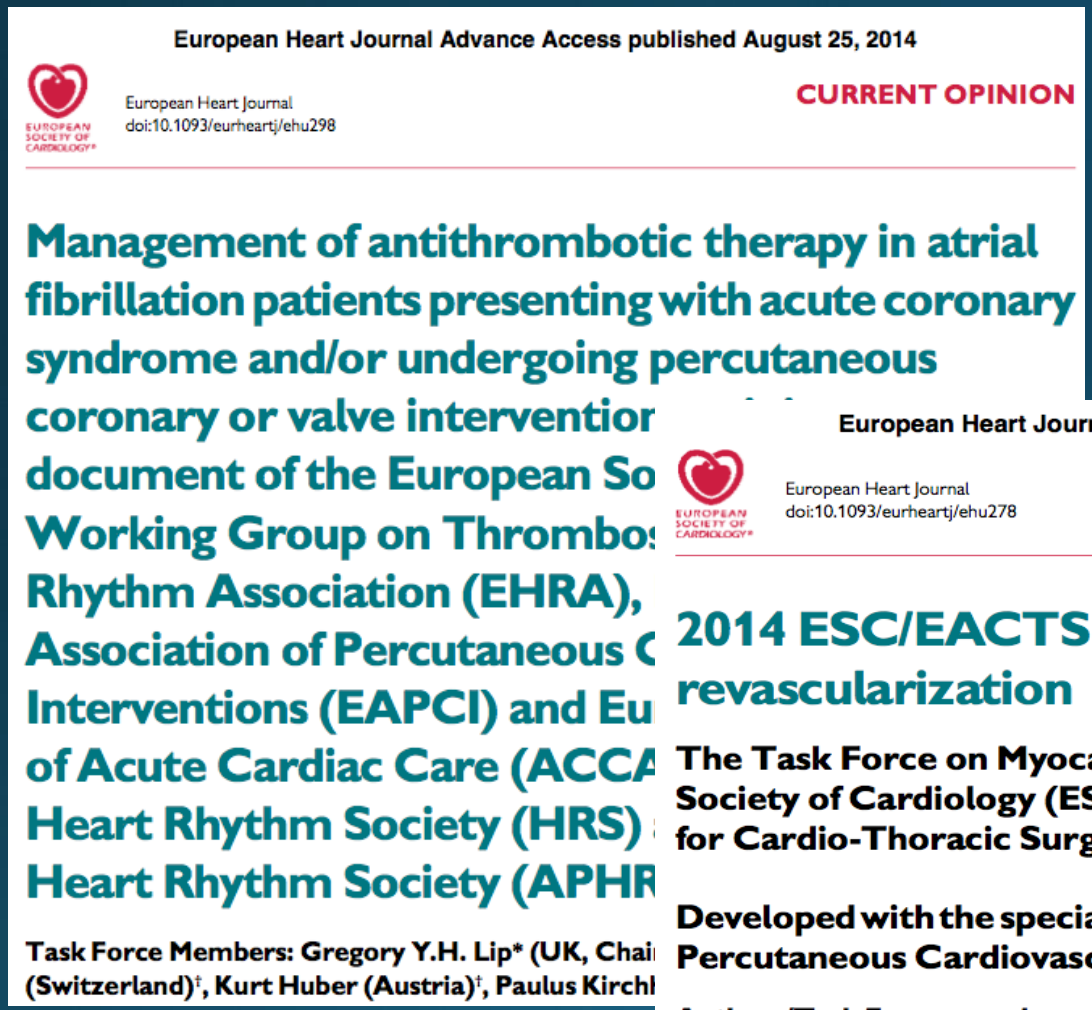
Implications of admissions

- Morbidity (LOS = 7 days +/- 10 days)
- Mortality (15 to 20% @30 days)
- Cost (top 15% > $100K/event)

>500,000 patients may benefit from antidote by 2020

Truven MARKETSCAN® Commercial, Medicare Supplemental and Medicaid Database (12 months ending June 2013)

# 2014 Guidelines on myocardial revascularization



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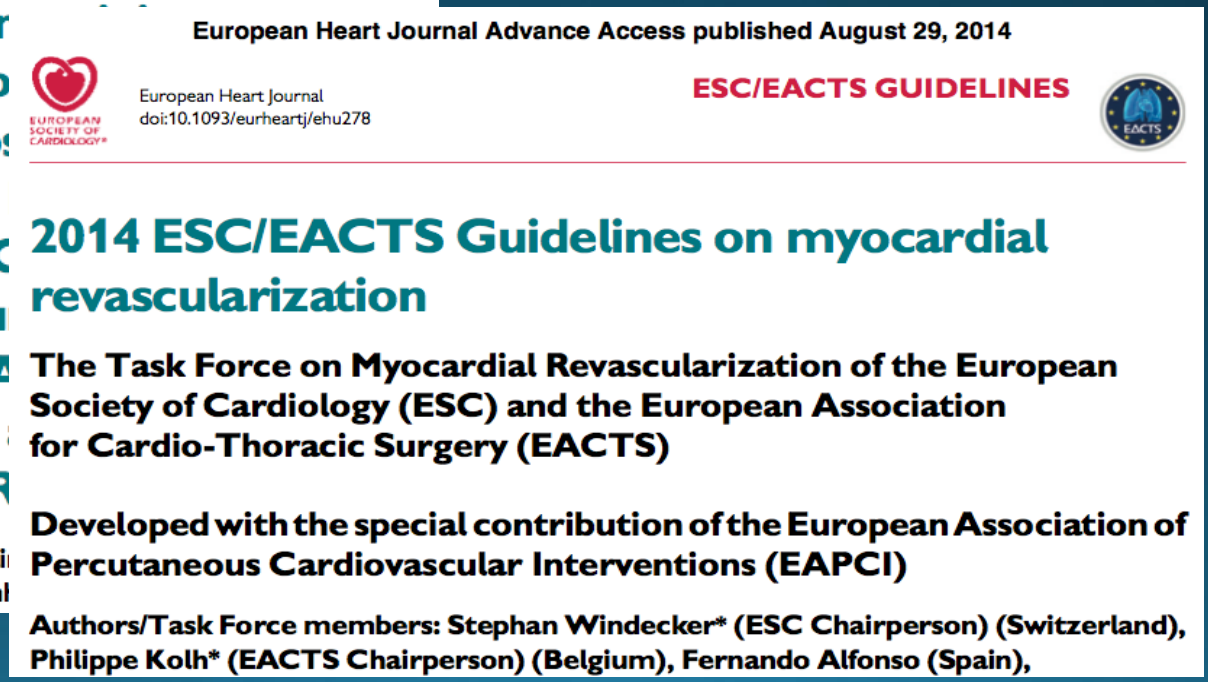
CURRENT OPINION

**Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventio**
**document of the European So**
**Working Group on Thrombos**
**Rhythm Association (EHRA),**
**Association of Percutaneous C**
**Interventions (EAPCI) and Eu**
**of Acute Cardiac Care (ACCA**
**Heart Rhythm Society (HRS)**
**Heart Rhythm Society (APHR**

Task Force Members: Gregory Y.H. Lip* (UK, Chai
(Switzerland)†, Kurt Huber (Austria)†, Paulus Kirchl



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ESC/EACTS GUIDELINES

**2014 ESC/EACTS Guidelines on myocardial revascularization**

**The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)**

**Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI)**

Authors/Task Force members: Stephan Windecker* (ESC Chairperson) (Switzerland), Philippe Kolh* (EACTS Chairperson) (Belgium), Fernando Alfonso (Spain),

# Antithrombotic therapy: triple therapy or triple threat?

*Jessica Mega[1] and Edward T. Carreras[1]*

*[1]Brigham and Women's Hospital and Harvard Medical School, Boston, MA*

**Table 3. Major outcomes in the RE-LY,[6] ROCKET AF,[7] and ARISTOTLE[8] trials**

| | RE-LY (dabigatran 110 mg BID) RR (95% CI) | RE-LY (dabigatran 150 mg BID) RR (95% CI) | ROCKET-AF (rivaroxaban 20 mg QD) HR (95% CI) | ARISTOTLE (apixaban 5 mg BID) HR (95% CI) |
|---|---|---|---|---|
| Ischemic stroke | 1.11 (0.89-1.40) | 0.76 (0.60-0.98) | 0.94 (0.75-1.17) | 0.92 (0.74-1.13) |
| Hemorrhagic stroke | 0.31 (0.17-0.56) | 0.26 (0.14-0.49) | 0.59 (0.37-0.93) | 0.51 (0.35-0.75) |
| Mortality | 0.91 (0.80-1.03) | 0.88 (0.77-1.00) | 0.85 (0.70-1.02) | 0.89 (0.80-0.998) |
| Major bleeding | 0.80 (0.69-0.93) | 0.93 (0.81-1.07) | 1.04 (0.90-1.20) | 0.69 (0.60-0.80) |

Comparisons are made with warfarin. ROCKET-AF efficacy presented with the on-treatment analysis.
RR indicates relative risk.

# Contents

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  - Darexaban
- Comparison of $P2Y_{12}$ inhibitors with new oral anticoagulants
- Summary: Role of oral anticoagulants in the treatment of patients with ACS

# Drug treatment categories in ACS

## Anti-ischaemic

- E.g. beta blockers, nitrates, calcium channel blockers

## Anticoagulant

- E.g. UFH, enoxaparin, bivalirudin, rivaroxaban

## Antiplatelet

- E.g. ASA, thienopyridines, CPTPs, glycoprotein IIb/IIIa inhibitors

## Lipid-lowering

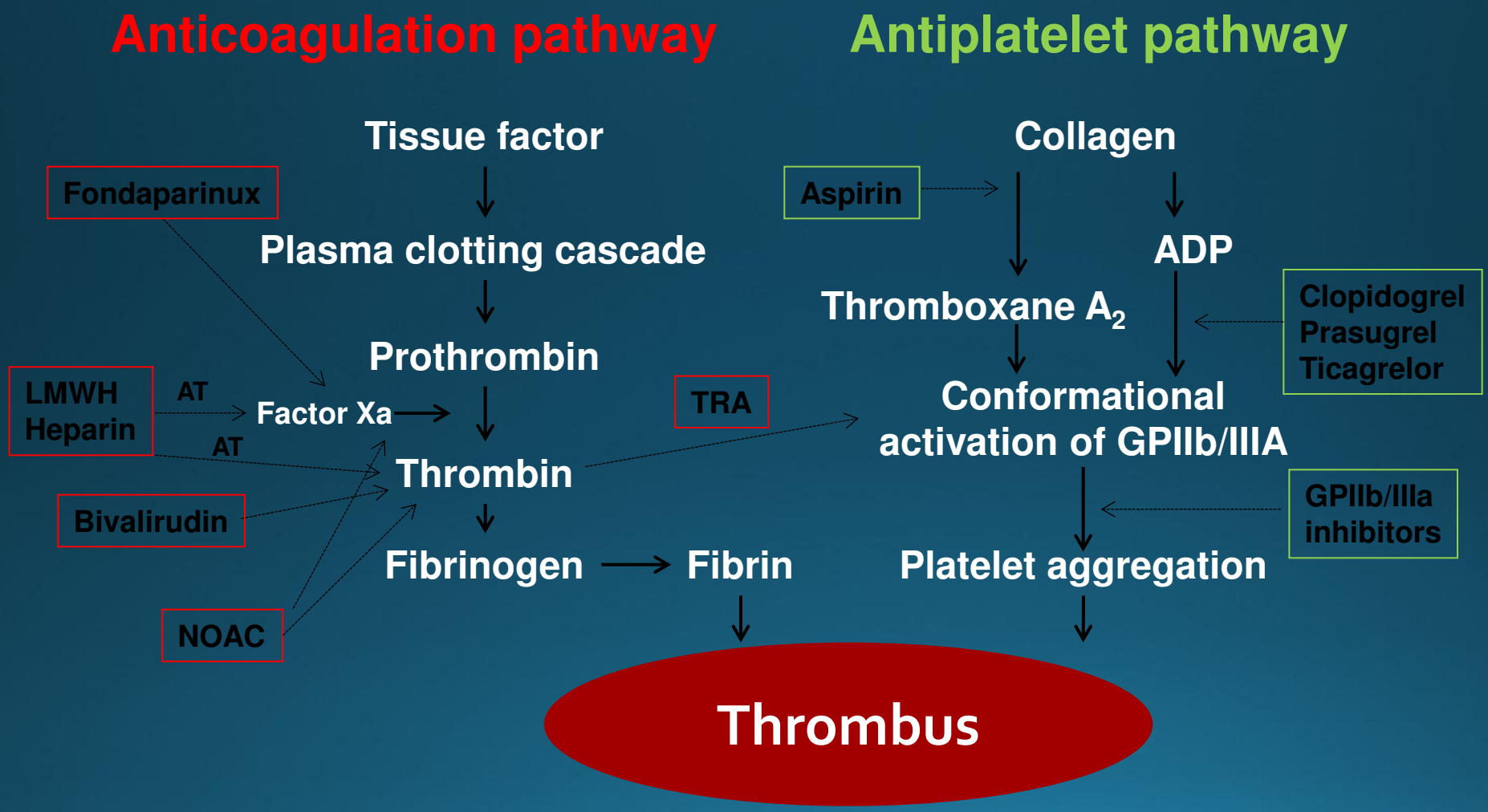
- Statins

**Four categories of drugs are used in the medical management of ACS**

ACS, acute coronary syndromes; ASA, acetylsalicylic acid; CPTP, cyclopentyltriazolopyrimidine; UFH, unfractionated heparin.

Hamm CW, et al. *Eur Heart J* 2011;32:2999–3054;
Steg G, et al. *Eur Heart J* 2012;33:2569–2619.

# Anticoagulation and antiplatelet pathways




ADP, adenosine diphosphate; AT, antithrombin; GP, glycoprotein; LMWH, low molecular weight heparin; TRA, thrombin receptor antagonist.
Hamm CW, et al. *Eur Heart J* 2011;32:2999–3054.

# Antiagregants used in triple therapy
# Tha place of ticagrelor and prasugrel

| Recommendations | Class[a] | Level[b] | Ref[c] |
|---|---|---|---|
| In patients with a firm indication for oral anticoagulation (e.g. atrial fibrillation with $CHA_2DS_2$-VASc score ≥2, venous thromboembolism, LV thrombus, or mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy. | I | C | |
| New-generation DES are preferred over BMS among patients requiring oral anticoagulation if bleeding risk is low (HAS-BLED ≤2). | IIa | C | |
| In patients with SCAD and atrial fibrillation with $CHA_2DS_2$-VASc score ≥2 at low bleeding risk (HAS-BLED ≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of at least one month after BMS or new-generation DES followed by dual therapy with (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months. | IIa | C | |
| DAPT should be considered as alternative to initial triple therapy for patients with SCAD and atrial fibrillation with a $CHA_2DS_2$-VASc score ≤1. | IIa | C | |
| In patients with ACS and atrial fibrillation at low bleeding risk (HAS-BLED≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 6 months irrespective of stent type followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months. | IIa | C | |
| In patients requiring oral anticoagulation at high bleeding risk (HAS BLED ≥3), triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of one month followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) irrespective of clinical setting (SCAD or ACS) and stent type (BMS or new-generation DES). | IIa | C | |
| Dual therapy of (N)OAC and clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients. | IIb | B | 865,870 |
| The use of ticagrelor and prasugrel as part of initial triple therapy is not recommended | III | C | |
| **Anticoagulation therapy after PCI in ACS patient** | | | |
| In selected patients who receive ASA and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered in the setting of PCI for ACS if the patient is at low bleeding risk. | IIb | B | 855 |
| **Anticoagulation during PCI in patients on oral anticoagulation** | | | |
| It is recommended to use additional parenteral anticoagulation, regardless of the timing of the last dose of (N)OAC. | I | C | |
| Periprocedural parenteral anticoagulants (bivalirudin, enoxaparin or UFH) should be discontinued immediately after primary PCI. | IIa | C | |

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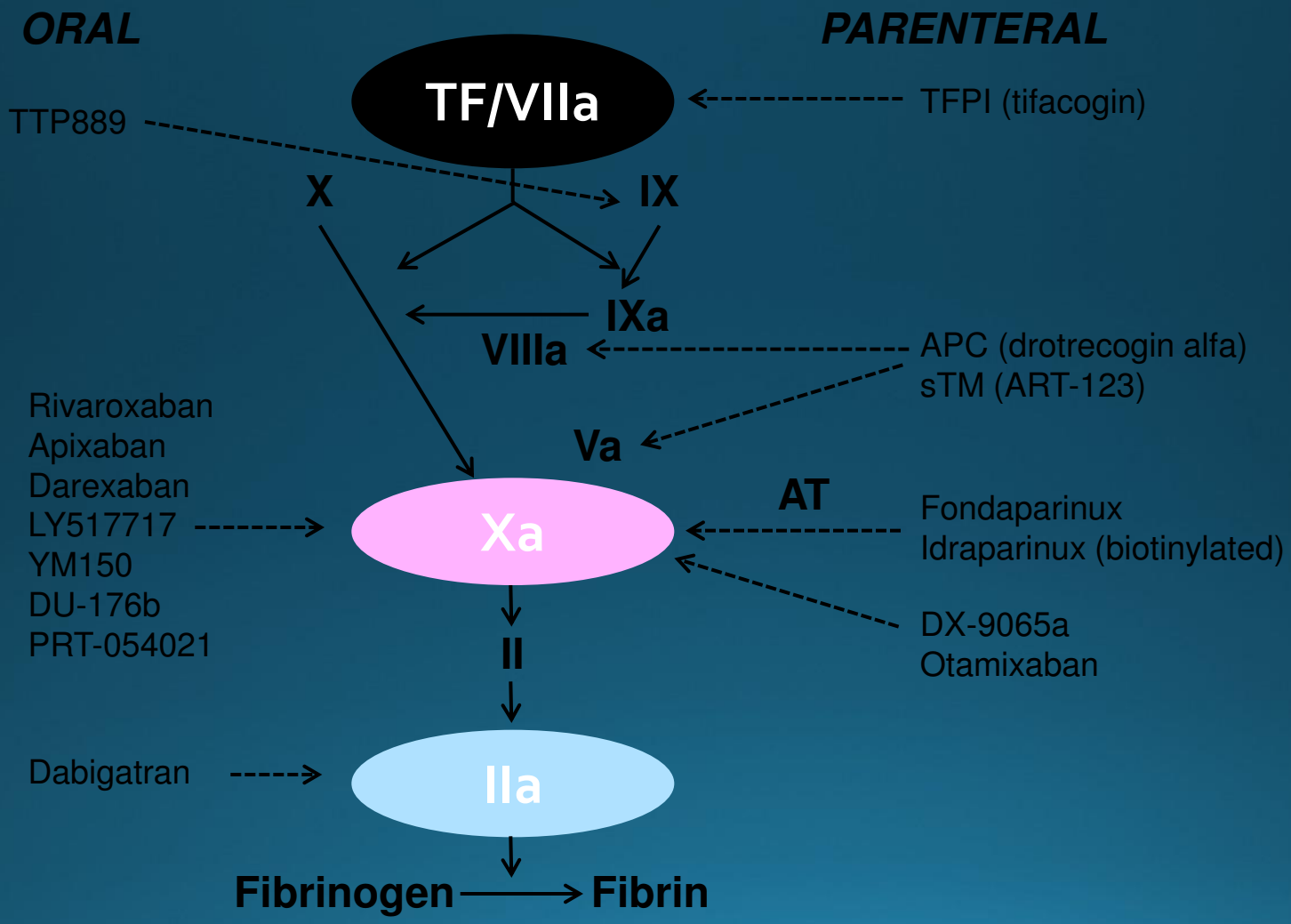
# Anticoagulants: Overview

- Established anticoagulants used in patients with ACS:
  - Heparin (inhibits thrombin by accelerating activity of antithrombin III)[Hirsch 1995]
    - Low molecular weight heparins; unfractionated heparin
  - Vitamin K antagonists (reduces activity of vitamin K-dependent factors II, VII, IX and X)[Ansell 2008]
  - Fondaparinux* (binds reversibly to antithrombin, potentiating its neutralising effect on factor Xa)[Garcia 2012]
- A number of new oral anticoagulants are in Phase II/III trials or approved for use in patients with ACS[Hamm 2011; Steg 2012]
  - Rivaroxaban (factor Xa inhibitor)†
  - Apixaban (factor Xa inhibitor)‡
  - Dabigatran (thrombin inhibitor)
  - Darexaban (factor Xa inhibitor)

*Not approved for the treatment of ACS; †Approved in Europe for the treatment of patients with ACS; ‡Phase III study terminated due to increased risk of bleeding in the absence of counterbalancing reduction in ischaemic events.
ACS, acute coronary syndromes.
Ansell J, et al. *Chest* 2008;133:160S–198S; Garcia D, et al. *Chest* 2012;141:e24S–e43S; Hamm CW, et al. *Eur Heart J* 2011;32:2999–3054; Hirsch J, et al. *Chest* 1995;108(Suppl. 4):258S–275S; Steg G, et al. *Eur Heart J* 2012;33:2569–2619.

# New anticoagulants and targets in the coagulation pathway




TF, tissue factor.
Adapted from Weitz JI, Bates SM. *J Thromb Haemost* 2005;3:1843–1853.

# Limitations of traditional anticoagulants

- The use of traditional agents is limited by various factors:
  - Altered drug metabolism due to genetic polymorphisms[Eikelboom 2010]
  - Narrow therapeutic window[Ansell 2008]
  - Interactions with drugs and diet[Eikelboom 2010]
  - Potential for accumulation in patients with renal impairment[Eikelboom 2010]
  - Lack of standardised aPTT monitoring[Hirsh 2004]
- New oral anticoagulants possess a number of advantages over established therapies:[Eikelboom 2010]
  - Rapid onset of action
  - Predictable anticoagulant effect
  - Low potential for drug and food interactions
  - No need for dose bridging
  - No need for routine coagulation monitoring

aPTT, activated partial thromboplastin time.

Ansell J, et al. *Chest* 2008;133:160S–198S; Eikelboom J, Weitz J. *Circulation* 2010;121:1523–1532; Hirsch J, Raschke R. *Chest* 2004;126:188S–203S.

# Recommended use of anticoagulants in ACS

## Class I, LOE A–C

- In NSTEMI patients:
  - Anticoagulation is recommended in all patients in addition to antiplatelet therapy
- In STEMI patients:
  - Must be implemented in addition to antiplatelet therapy in patients with clear indication for anticoagulation†

## Class II, LOE B

- In UA/NSTEMI patients:
  - Adjunctive warfarin may be administered in those with an indication for anticoagulation

## Class I, LOE C

- In STEMI patients:
  - UFH is recommended in those undergoing PCI

LOE, level of evidence; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina; UFH, unfractionated heparin.

Hamm CW, et al. *Eur Heart J* 2011;32:2999–3054; Jneid H, et al. *Circulation* 2012;126:875–910; O'Gara PT, et al. *Circulation* 2013;127:e362–e425; Steg G, et al. *Eur Heart J* 2012;33:2569–2619.

# New oral anticoagulants investigated in patients with ACS

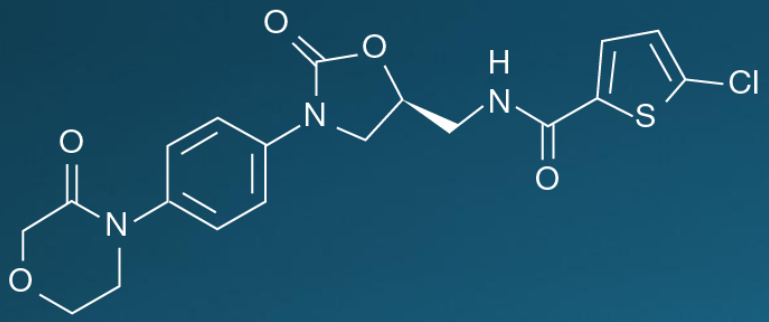
- Rivaroxaban
- Apixaban
- Dabigatran
- Darexaban

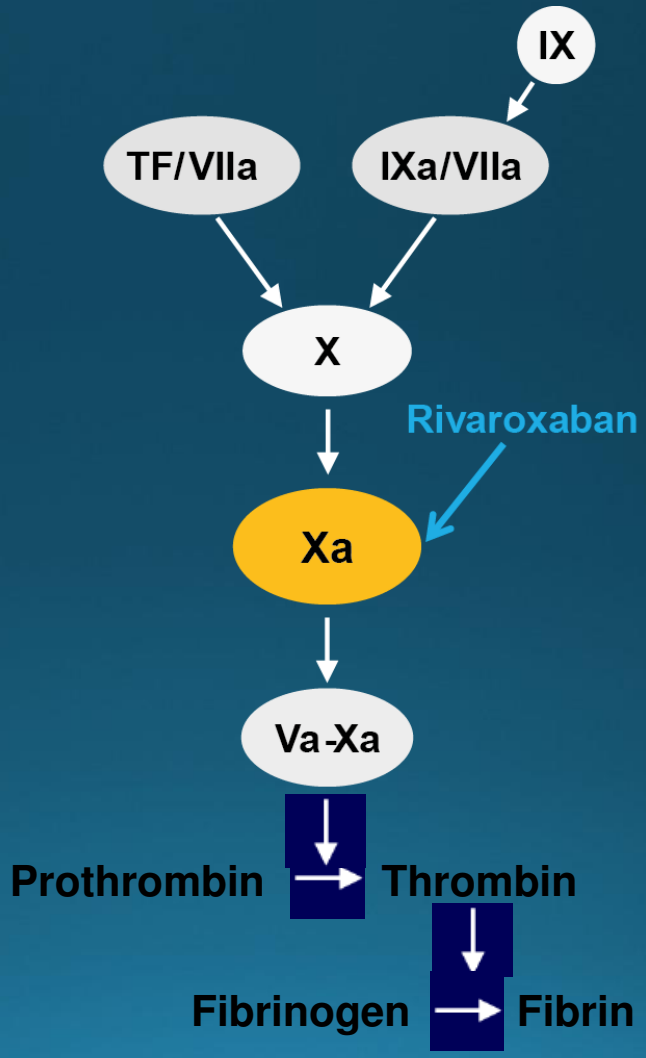
# New oral anticoagulants approved in patients with acute coronary syndromes

- Rivaroxaban

# Rivaroxaban: Mechanism of action

- Rivaroxaban is a highly selective, direct, factor Xa inhibitor



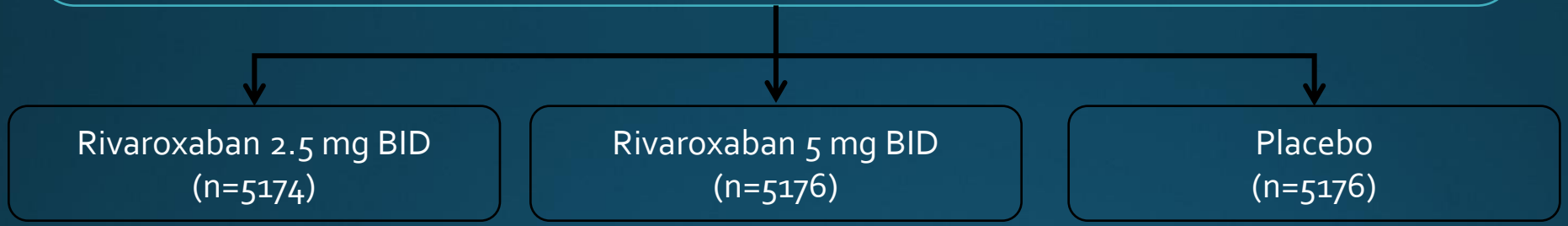

TF, tissue factor.

XARELTO® [Summary of product characteristics] Berlin, Germany. Bayer 2013.

# ATLAS ACS 2-TIMI 51: Study design

Patients with recent ACS (STEMI, NSTEMI or UA) stabilised 1–7 days post-index event (n=15,526)*

Exclusion criteria: Increased bleeding risk, ICH, prior stroke if taking ASA + a thienopyridine




Up to 31 months of treatment

*Mean duration 13.1 months*

Primary efficacy endpoint: Composite of CV death, MI or stroke

Primary safety endpoint: Non-CABG-related TIMI major bleeding

*ATLAS ACS 2 TIMI-51 was not an acute study. Mean time of 4.7 days from index event to enrolment.

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; BID, twice daily; CABG, coronary artery bypass graft; CV, cardiovascular; ICH, intracranial haemorrhage; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; UA, unstable angina.

Mega J, et al. *N Engl J Med* 2012;366:9–19.

# ATLAS ACS 2-TIMI 51: Inclusion/exclusion criteria

## Inclusion criteria

- ≥18 years of age
- Symptoms suggestive of an ACS and in whom a STEMI, NSTEMI or UA was diagnosed
- Patients under 55 years of age had either diabetes mellitus or a previous MI in addition to the index event

## Key exclusion criteria

- Platelet count of <90,000 $mm^3$ OR haemoglobin level of <10 g/dL OR CrCl <30 mL/min at screening
- Clinically significant GI bleeding within 12 months before randomisation
- Previous intracranial haemorrhage
- Previous ischaemic stroke or TIA in patients who were taking both ASA and a thienopyridine

ACS, acute coronary syndrome; ASA, acetylsalicylic acid; CrCl, creatinine clearance; GI, gastrointestinal; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischaemic attack; UA, unstable angina.

Mega J, et al. *N Engl J Med* 2012;366:9–19.

# ATLAS ACS 2-TIMI 51: Baseline characteristics

| Characteristic | Rivaroxaban | | Placebo (n=5176) |
|---|---|---|---|
| | 2.5 mg BID (n=5174) | 5 mg BID (n=5176) | |
| Mean age, years (SD) | 61.8 (9.2) | 61.9 (9.0) | 61.5 (9.4) |
| Male, n (%) | 3875 (74.9) | 3843 (74.2) | 3882 (75.0) |
| Race, n (%) | | | |
| White | 3798 (73.4) | 3815 (73.7) | 3796 (73.3) |
| Black | 34 (0.7) | 34 (0.7) | 39 (0.8) |
| Asian | 1099 (21.2) | 1055 (20.4) | 1075 (20.8) |
| Other | 243 (4.7) | 272 (5.3) | 266 (5.1) |
| Index diagnosis, n (%) | | | |
| STEMI | 2601 (50.3) | 2584 (49.9) | 2632 (50.9) |
| NSTEMI | 1321 (25.5) | 1335 (25.8) | 1323 (25.6) |
| UA | 1252 (24.2) | 1257 (24.3) | 1221 (23.6) |

BID, twice daily; NSTEMI, non-ST-segment elevation myocardial infarction; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

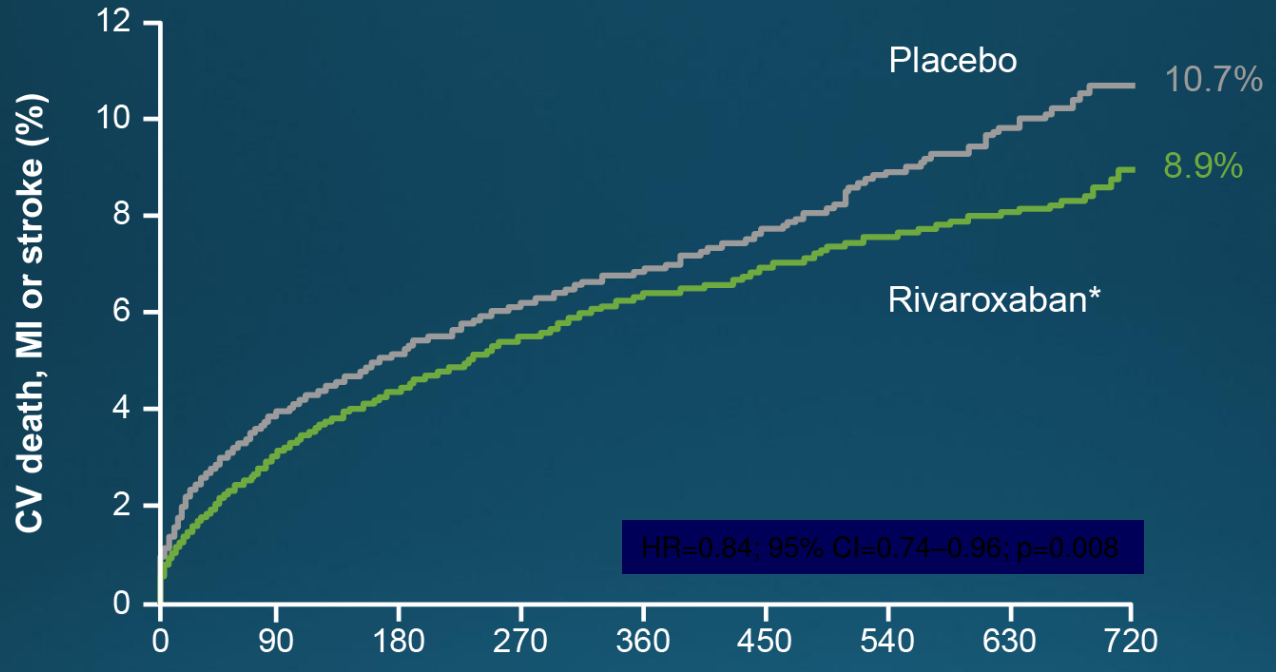
Mega J, et al. *N Engl J Med* 2012;366:9–19.

# ATLAS ACS 2-TIMI 51: Baseline characteristics (cont'd)

| Characteristic | Rivaroxaban | | Placebo (n=5176) |
|---|---|---|---|
| | 2.5 mg BID (n=5174) | 5 mg BID (n=5176) | |
| Medications, n (%) | | | |
| ASA | 5105 (98.7) | 5099 (98.5) | 5108 (98.7) |
| Thienopyridine | 4790 (92.6) | 4812 (93.0) | 4811 (92.9) |
| Beta-blocker | 3426 (66.2) | 3394 (65.6) | 3444 (66.5) |
| ACE inhibitor or ARB | 2022 (39.1) | 1977 (38.2) | 2050 (39.6) |
| Statin | 4304 (83.2) | 4342 (83.9) | 4321 (83.5) |
| Calcium channel blocker | 820 (15.8) | 742 (14.3) | 764 (14.8) |

ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BID, twice daily.
Mega J, et al. *N Engl J Med* 2012;366:9–19.

# ATLAS ACS 2-TIMI 51: Primary efficacy endpoint




| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 5113 | 4437 | 3974 | 3253 | 2664 | 2059 | 1460 | 878 | 421 |
| Rivaroxaban | 10,229 | 8817 | 7797 | 6324 | 5137 | 3967 | 2830 | 1747 | 831 |

**Rivaroxaban* significantly reduced the rate of CV death, MI or stroke compared with placebo (p=0.008)**

*Combined 2.5 mg and 5 mg. Rivaroxaban 2.5 mg is indicated for the treatment of ACS in the EU.
ACS, acute coronary syndrome; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
Mega J, et al. *N Engl J Med* 2012;366:9–19.

# ATLAS ACS 2-TIMI 51: Safety endpoints

| Safety event | Rivaroxaban 2.5 mg BID* (n=5114) | Placebo (n=5113) | HR (95% CI) | p value |
|---|---|---|---|---|
| TIMI major bleeding not associated with CABG | 65 (1.8) | 19 (0.6) | 3.46 (2.08–5.77) | <0.001 |
| TIMI minor bleeding | 32 (0.9) | 20 (0.5) | 1.62 (0.92–2.82) | 0.09 |
| TIMI bleeding requiring medical attention | 492 (12.9) | 282 (7.5) | 1.79 (1.55–2.07) | <0.001 |
| Intracranial haemorrhage | 14 (0.4) | 5 (0.2) | 2.83 (1.02–7.86) | 0.04 |
| Fatal bleeding | 6 (0.1) | 9 (0.2) | 0.67 (0.24–1.89) | 0.45 |

**Patients with ACS treated with 2.5 mg BID rivaroxaban experienced a significantly higher rate of TIMI major bleeding compared with placebo (p<0.001)**

*Rivaroxaban 2.5 mg is indicated for the treatment of ACS in the EU.
ACS, acute coronary syndromes; BID, twice daily; CABG, coronary artery bypass graft; CI, confidence interval; HR, hazard ratio; TIMI, thrombolysis in myocardial infarction.
Mega J, et al. *N Engl J Med* 2012;366:9–19.

# Rivaroxaban: Approved indication in patients with ACS

- In the EU, rivaroxaban is indicated for the prevention of atherothrombotic events in adult patients after an ACS with elevated cardiac biomarkers,
  co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine

- For the prevention of atherothrombotic events in patients with ACS, the recommended dose of rivaroxaban is 2.5 mg twice daily

- Rivaroxaban is NOT approved for use in the US in patients with ACS

ACS, acute coronary syndrome; ASA, acetylsalicylic acid.

XARELTO® [Summary of product characteristics] Berlin, Germany. Bayer 2013;
XARELTO® [Prescribing information] Titusville, USA. Janssen Pharmaceuticals 2011.

# Rivaroxaban: Contraindications

- Use is not recommended in patients:
  - With severe renal impairment (CrCl <15 mL/min)
  - With hepatic disease associated with coagulopathy and clinically relevant bleeding risk
  - With clinically significant active bleeding
  - With a lesion or condition at significant risk of major bleeding
  - Receiving any other anticoagulant agent (except under the circumstances of switching treatment to or from rivaroxaban)
  - With a prior stroke or TIA receiving antiplatelet therapy for ACS
  - Who are pregnant or breast feeding
  - With severe hypersensitivity to rivaroxaban or any of the excipients
  - Receiving concomitant P-gp and strong CYP3A4 inhibitors or inducers

ACS, acute coronary syndrome; CrCl, creatinine clearance; TIA, transient ischaemic attack.

XARELTO® [Summary of product characteristics] Berlin, Germany. Bayer 2013;
XARELTO® [Prescribing information] Titusville, USA. Janssen Pharmaceuticals 2011.

# New oral anticoagulants investigated in patients with acute coronary syndromes

Apixaban, dabigatran, darexaban

# New oral anticoagulants investigated in patients with ACS: Overview

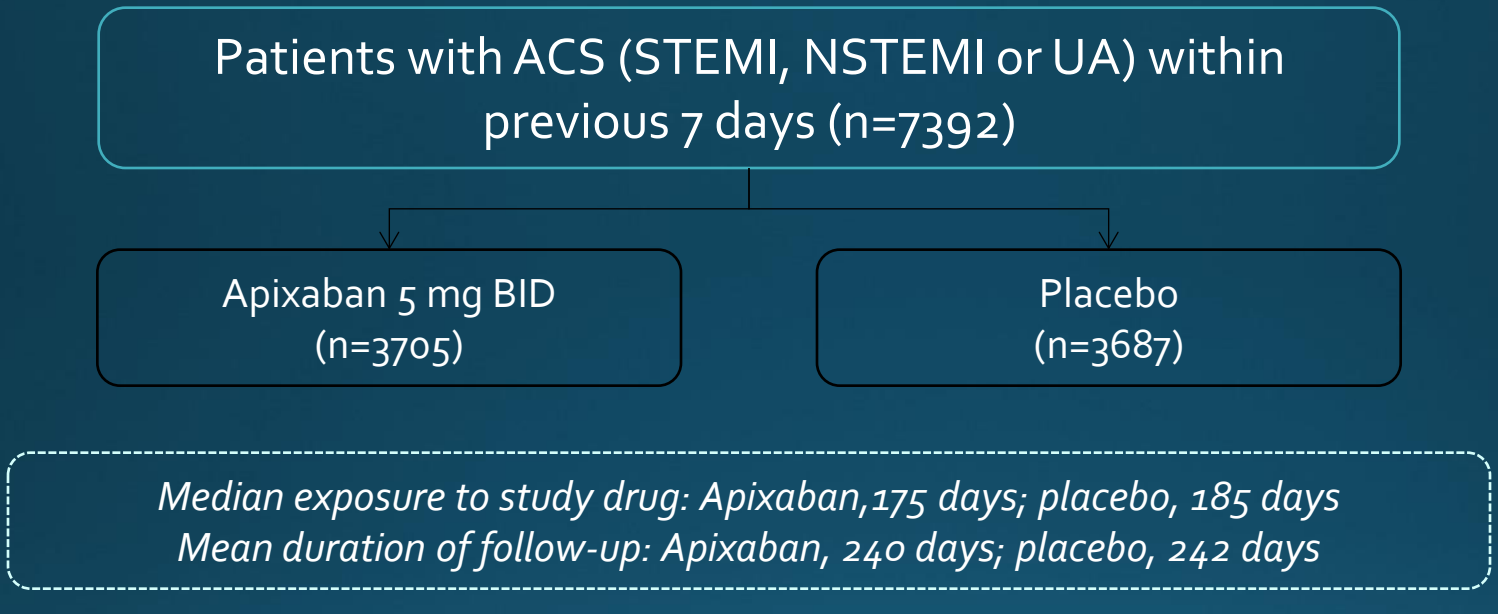
| Characteristic | Apixaban[ELIQUIS 2012] | Dabigatran[PRADAXA 2013] | Darexaban[Steg 2011] |
|---|---|---|---|
| Mechanism of action | Reversible, active site, factor Xa inhibitor | Direct thrombin inhibitor | Direct factor Xa inhibitor |
| $T_{1/2}$ | ~12 hours | 12–17 hours | 14–18 hours |
| Protein binding | ~87% | ~35% | Not available |
| Development phase | Phase III study terminated early[Alexander 2011] | Phase III study in patients with ACS completed[Oldgren 2011] | Phase II |
| ACS indication | No | No | No |

ACS, acute coronary syndromes; $T_{1/2}$, half life.

Alexander J, et al. *N Engl J Med* 2011;365:699–708; ELIQUIS® [Prescribing information] 2012;
Oldgren J, et al. *Eur Heart J* 2011;32:2781–2789; PRADAXA® [Prescribing information] 2013;
Steg G, et al. *Eur Heart J* 2011;32:2541–2554.

# Apixaban

# APPRAISE-2: Study design




ACS, acute coronary syndromes; BID, twice daily; CV, cardiovascular; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis in Myocardial Infarction; UA, unstable angina.

Alexander J, et al. *N Engl J Med* 2011;365:699–708.

# APPRAISE-2: Inclusion/exclusion criteria

## Inclusion criteria

- Clinically stable patients diagnosed with ACS receiving standard of care therapy
  - Standard of care included ASA or ASA plus any $P2Y_{12}$-receptor antagonist
- Two or more of the following high-risk characteristics
  - Age of ≥65 years; diabetes mellitus; MI within previous 5 years; cerebrovascular disease, peripheral vascular disease, clinical heart failure or a LVEF of <40% in association with the index event; impaired renal function (CrCl <60 mL/min); no revascularisation after the index event

## Exclusion criteria

- Severe hypertension
- Active bleeding or high risk for major bleeding
- Haemoglobin <9 g/dL

ACS, acute coronary syndromes; ASA, acetylsalicylic acid; CrCl, creatinine clearance; LVEF, left ventricular ejection fraction; MI, myocardial infarction.
Alexander J, et al. *N Engl J Med* 2011;365:699–708;
http://clinicaltrials.gov/show/NCT00831441 Accessed August 2013.

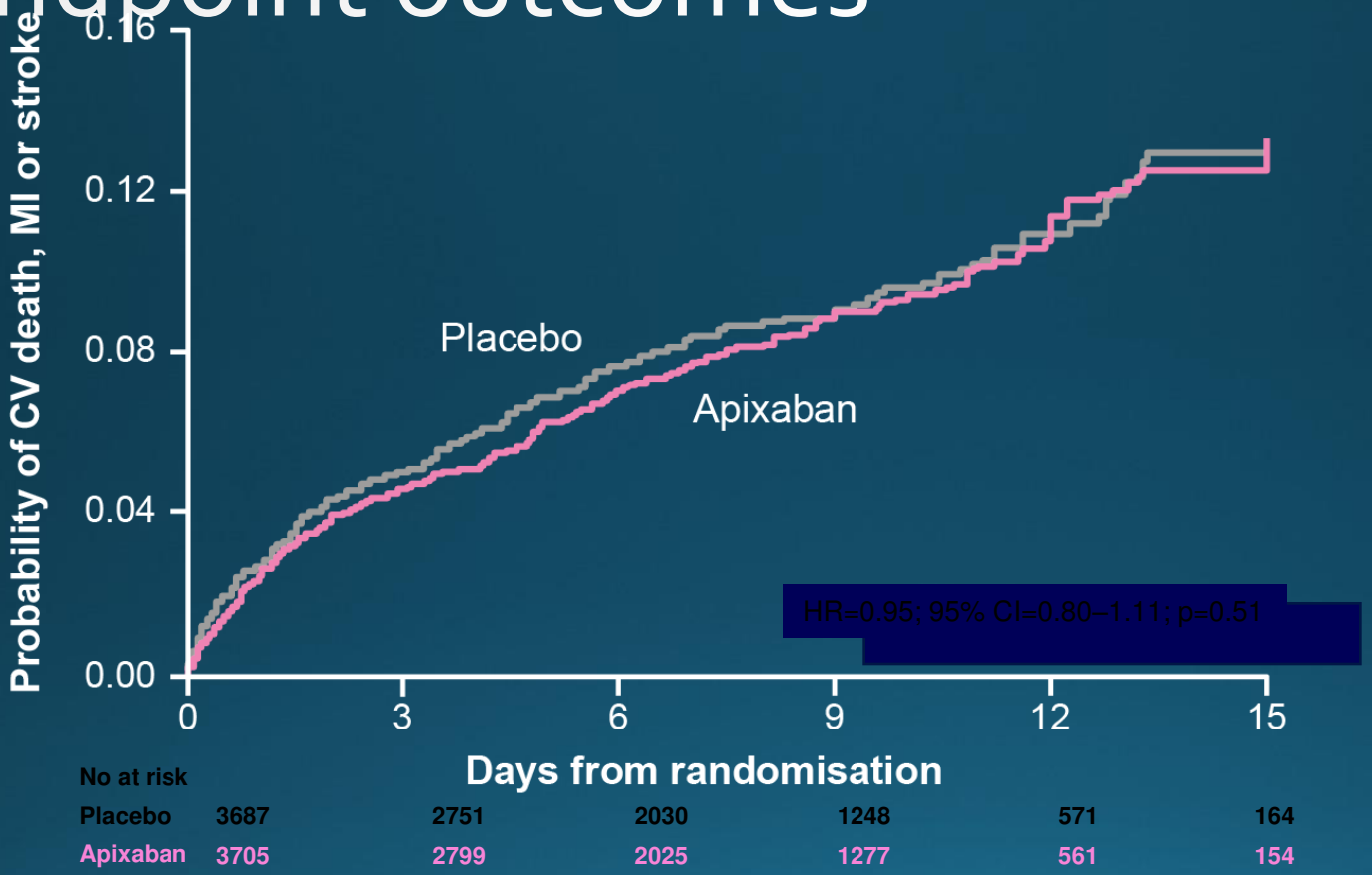
# APPRAISE-2: Baseline characteristics

| Characteristic | Apixaban (n=3705) | Placebo (n=3687) |
|---|---|---|
| Median age, years (range) | 67 (59–73) | 67 (58–74) |
| Female, n (%) | 1209 (32.6) | 1169 (31.7) |
| Index ACS event, n (%) | | |
| STEMI | 1474 (39.8) | 1453 (39.4) |
| NSTEMI | 1533 (41.4) | 1541 (41.8) |
| UA | 673 (18.2) | 667 (18.1) |
| Management of index event | | |
| Coronary angiography | 1923 (51.9) | 1927 (52.3) |
| PCI | 1624 (43.8) | 1631 (44.2) |
| CABG | 22 (0.6) | 23 (0.6) |
| Medical therapy | 2061 (55.6) | 2034 (55.2) |

ACS, acute coronary syndromes; CABG, coronary artery bypass graft; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; UA, unstable angina.

Alexander J, et al. *N Engl J Med* 2011;365:699–708.

# APPRAISE-2: Primary efficacy endpoint outcomes




**In patients with recent* ACS, there was no significant difference between rates of the primary endpoint of CV death, MI or stroke in the apixaban group compared with placebo (p=0.51)**

*Within 7 days.

ACS, acute coronary syndromes; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.

Alexander J, et al. *N Engl J Med* 2011;365:699–708.

# APPRAISE-2: Primary safety endpoint outcomes

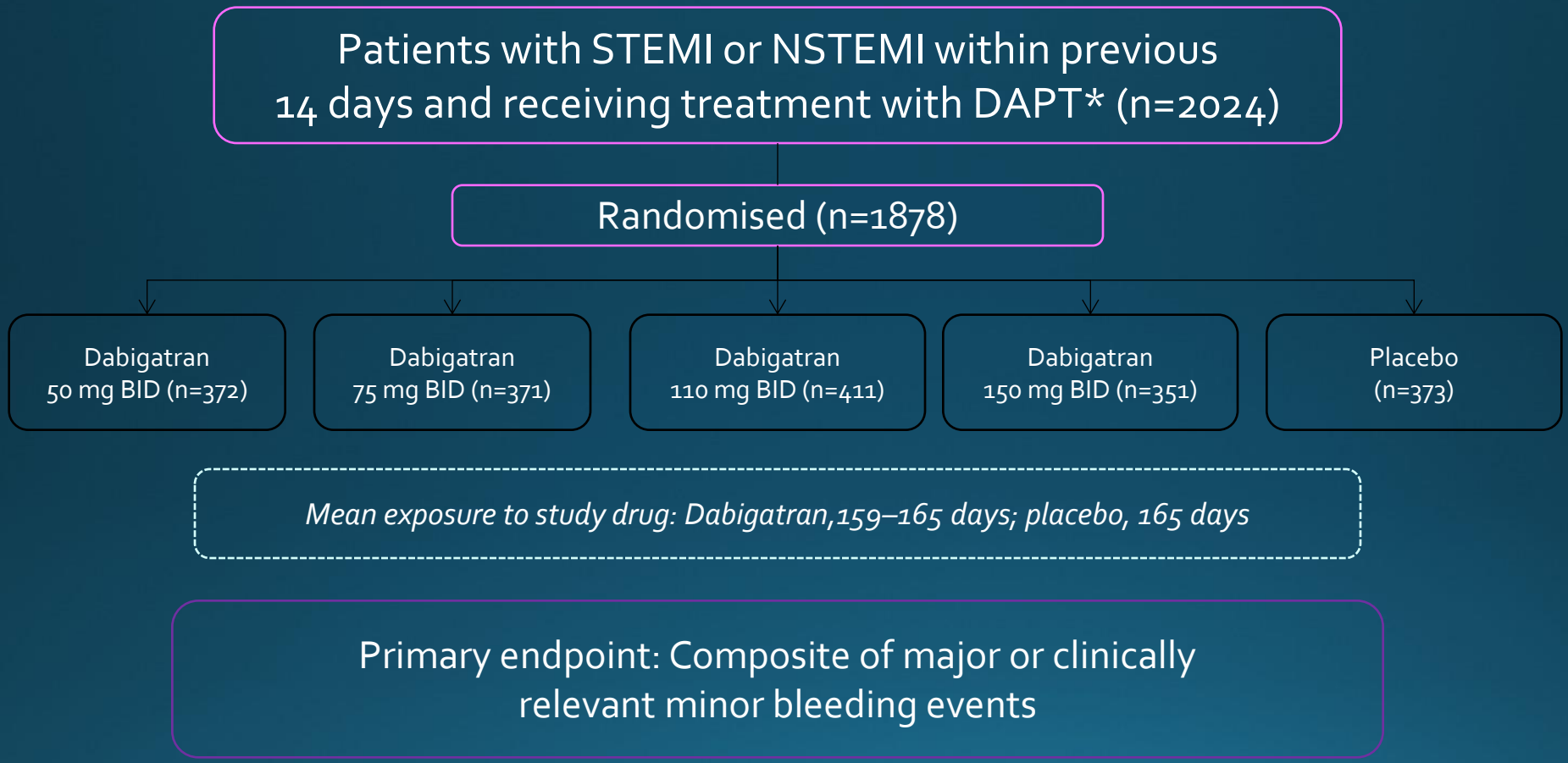
| Safety event | Apixaban 5 mg BID (n=3705) | Placebo (n=3687) | HR (95% CI) | p value |
|---|---|---|---|---|
| TIMI major bleeding | 46 (1.3) | 18 (0.5) | 2.59 (1.50–4.46) | 0.001 |
| TIMI major or minor bleeding | 80 (2.2) | 29 (0.8) | 2.79 (1.83–4.27) | <0.001 |

**Apixaban was associated with a significant increase in bleeding events with no concurrent decrease in recurrent ischaemic events – consequently, the study was terminated early**

BID, twice daily; CI, confidence interval; HR, hazard ratio; TIMI, thrombolysis in myocardial infarction.
Alexander J, et al. *N Engl J Med* 2011;365:699–708.

# Dabigatran

# RE-DEEM: Study design




*ASA plus a thienopyridine.
ASA, acetylsalicylic acid; BID, twice daily; DAPT, dual antiplatelet therapy; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.
Oldgren J, et al. *Eur Heart J* 2011;32:2781–2789.

# RE-DEEM: Key inclusion/exclusion criteria

## Inclusion criteria

- STEMI or NSTEMI within the last 14 days, receiving DAPT of ASA plus a thienopyridine
- At least one risk factor for subsequent CV complications:
  - Age ≥65 years; diabetes mellitus on treatment; previous MI; LBBB; congestive heart failure requiring treatment or LVEF <40%; PAD; moderate renal insufficiency (CrCl ≥30–60 mL/min); no revascularisation for the index event

## Exclusion criteria

- Ongoing or planned treatment with vitamin K antagonists
- Severely disabling stroke within previous 6 months or any stroke within the previous 14 days
- Conditions associated with an increased risk of bleeding

ASA, acetylsalicylic acid; CrCl, creatinine clearance; CV, cardiovascular; DAPT, dual antiplatelet therapy; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; STEMI, ST-segment elevation myocardial infarction.

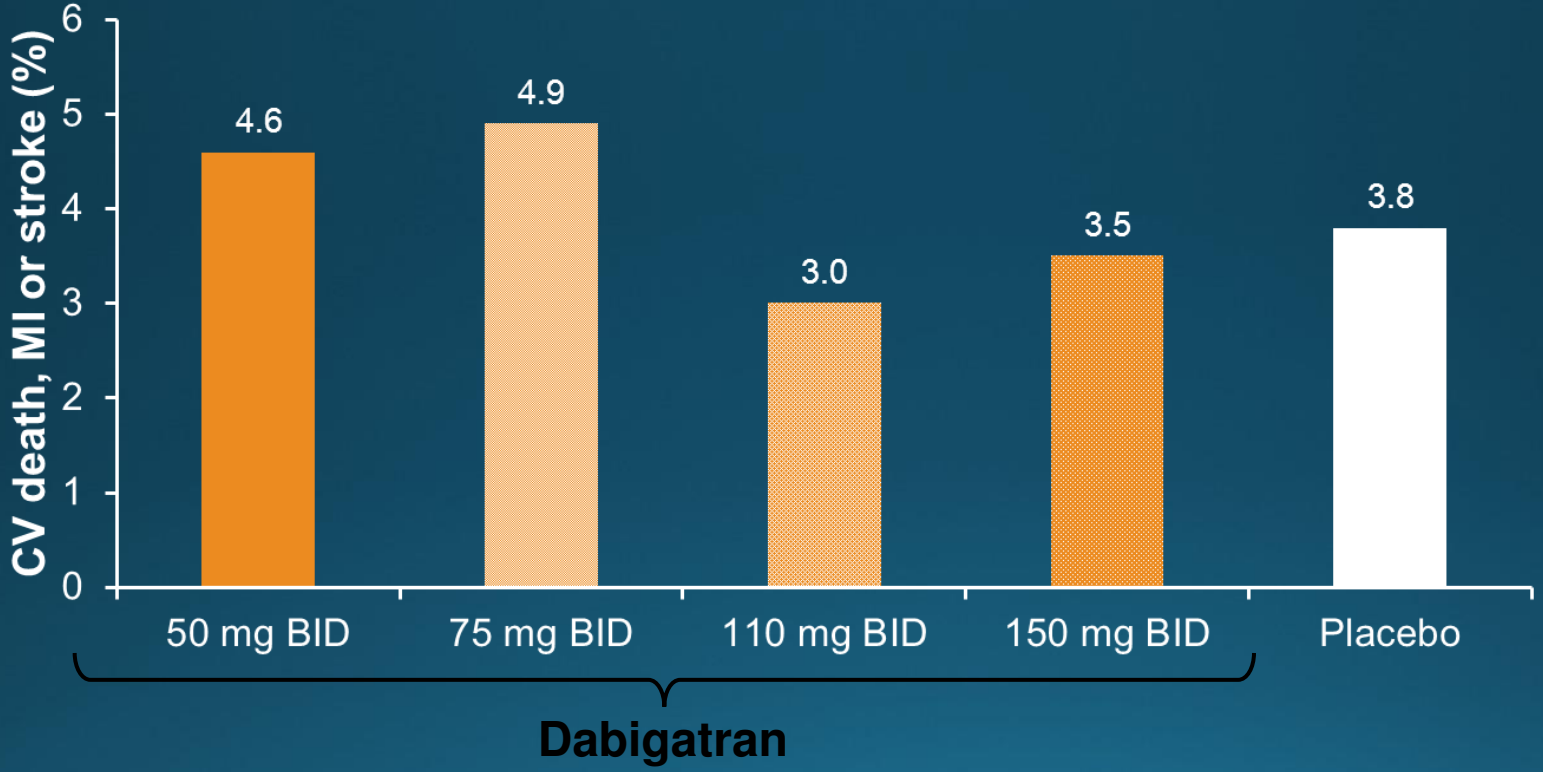
Oldgren J, et al. *Eur Heart J* 2011;32:2781–2789.

# RE-DEEM: Baseline characteristics

| Characteristic | Dabigatran | | | | Placebo (n=371) |
|---|---|---|---|---|---|
| | 50 mg BID (n=369) | 75 mg BID (n=368) | 110 mg BID (n=406) | 150 mg BID (n=347) | |
| Age, mean (SD) | 61.9 (12.3) | 60.9 (11.5) | 62.3 (11.2) | 62.3 (10.8) | 61.5 (11.3) |
| Male, % | 77.2 | 79.9 | 71.2 | 73.2 | 78.4 |
| Index event, % | | | | | |
| STEMI | 56.9 | 61.1 | 62.1 | 57.9 | 61.7 |
| NSTEMI | 43.1 | 38.9 | 37.9 | 42.1 | 38.3 |
| PCI* | 52.6 | 58.4 | 52.2 | 55.3 | 54.2 |

*Including PCI for STEMI.
BID, twice daily; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; SD, standard deviation; STEMI, ST-segment elevation myocardial infarction.
Oldgren J, et al. *Eur Heart J* 2011;32:2781–2789.

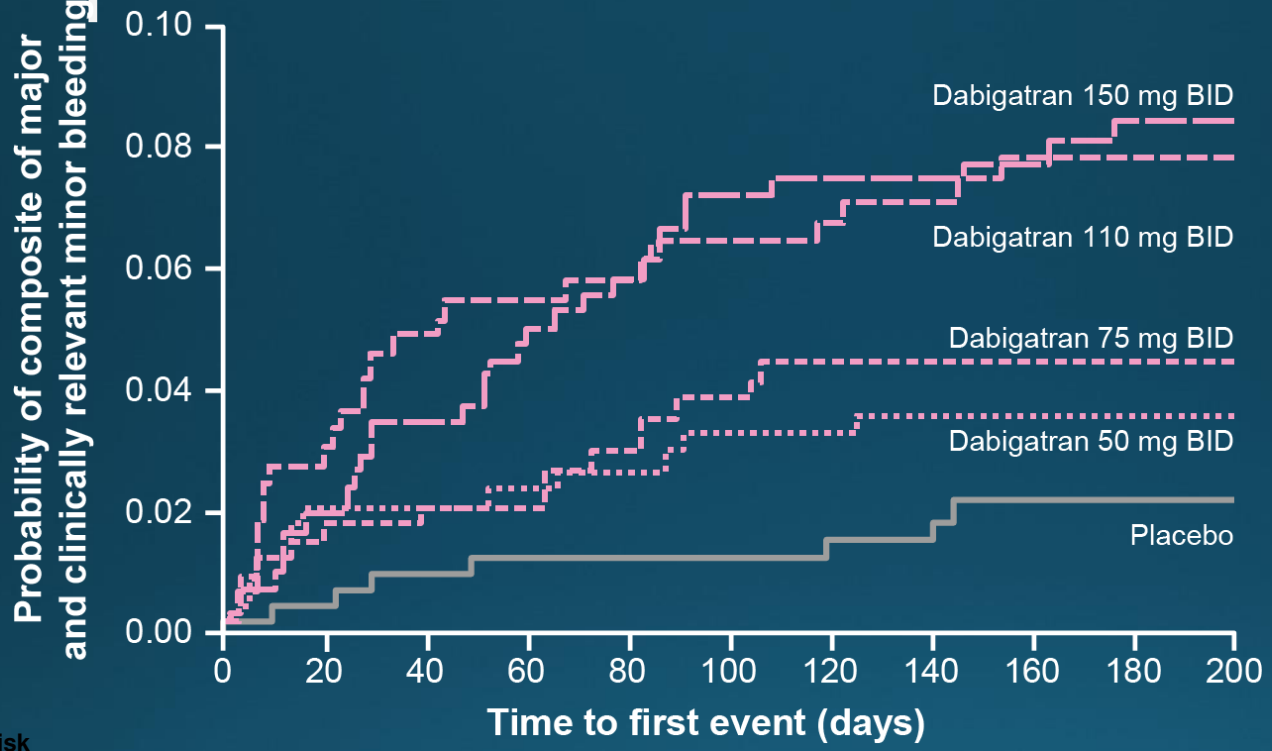
# RE-DEEM: Efficacy endpoint outcomes




**In this dose-escalation study, dabigatran 110 mg BID and 150 mg BID were associated with numerically lower rates of CV death, MI or stroke compared with lower doses**

BID, twice daily; CV, cardiovascular; MI, myocardial infarction.
Oldgren J, et al. *Eur Heart J* 2011;32:2781–2789.

# RE-DEEM: Primary safety endpoint outcomes




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Placebo | 371 | 351 | 341 | 338 | 330 | 326 | 322 | 319 | 314 | 246 | 0 |
| Dabigatran 50 mg BID | 369 | 339 | 330 | 322 | 314 | 305 | 300 | 296 | 290 | 239 | 0 |
| Dabigatran 75 mg BID | 368 | 348 | 338 | 334 | 327 | 320 | 316 | 313 | 309 | 251 | 0 |
| Dabigatran 110 mg BID | 406 | 380 | 362 | 352 | 344 | 336 | 330 | 324 | 319 | 261 | 0 |
| Dabigatran 150 mg BID | 347 | 318 | 305 | 301 | 295 | 287 | 285 | 282 | 278 | 200 | 0 |

**Dabigatran was associated with a dose-dependent increase in major or clinically relevant minor bleeding**

BID, twice daily.

Oldgren J, et al. *Eur Heart J* 2011;32:2781–2789.

# Darexaban

# RUBY-1: Study design

Patients with NSTEMI and high-risk features or STEMI within 7 days of index event (n=1370)

Randomised (n=1279)

- Darexaban 5 mg BID (n=160)
- Darexaban 10 mg QD (n=163)
- Darexaban 15 mg BID (n=161)
- Darexaban 30 mg QD (n=158)
- Darexaban 30 mg BID (n=158)
- Darexaban 60 mg QD (n=155)
- Placebo (n=324)

*Median exposure to study drug: 26 weeks*

Primary endpoint: Major and clinically relevant non-major bleeds*
Secondary endpoint: TIMI major bleeding events, composite of all-cause mortality, non-fatal MI, non-fatal stroke and severe recurrent ischaemia

*According to a modified version of the International Society on Thrombosis and Haemostasis definition.
BID, twice daily; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; QD, once daily; STEMI, ST-segment elevation myocardial infarction.
Steg G, et al. *Eur Heart J* 2011;32:2541–2554.

# RUBY-1: Key inclusion/exclusion criteria

## Key inclusion criteria

- Clinically stable patients with STEMI or NSTEMI as index event
- Elevated cardiac biomarkers
- For NSTEMI patients, at least one of the following risk factors:
  - Age ≥65 years; ST deviation on ECG; previous ACS <12 months prior to randomisation; multi-vessel CAD; ischaemic stroke or TIA ≥12 months prior to randomisation; type 2 diabetes mellitus; PAD

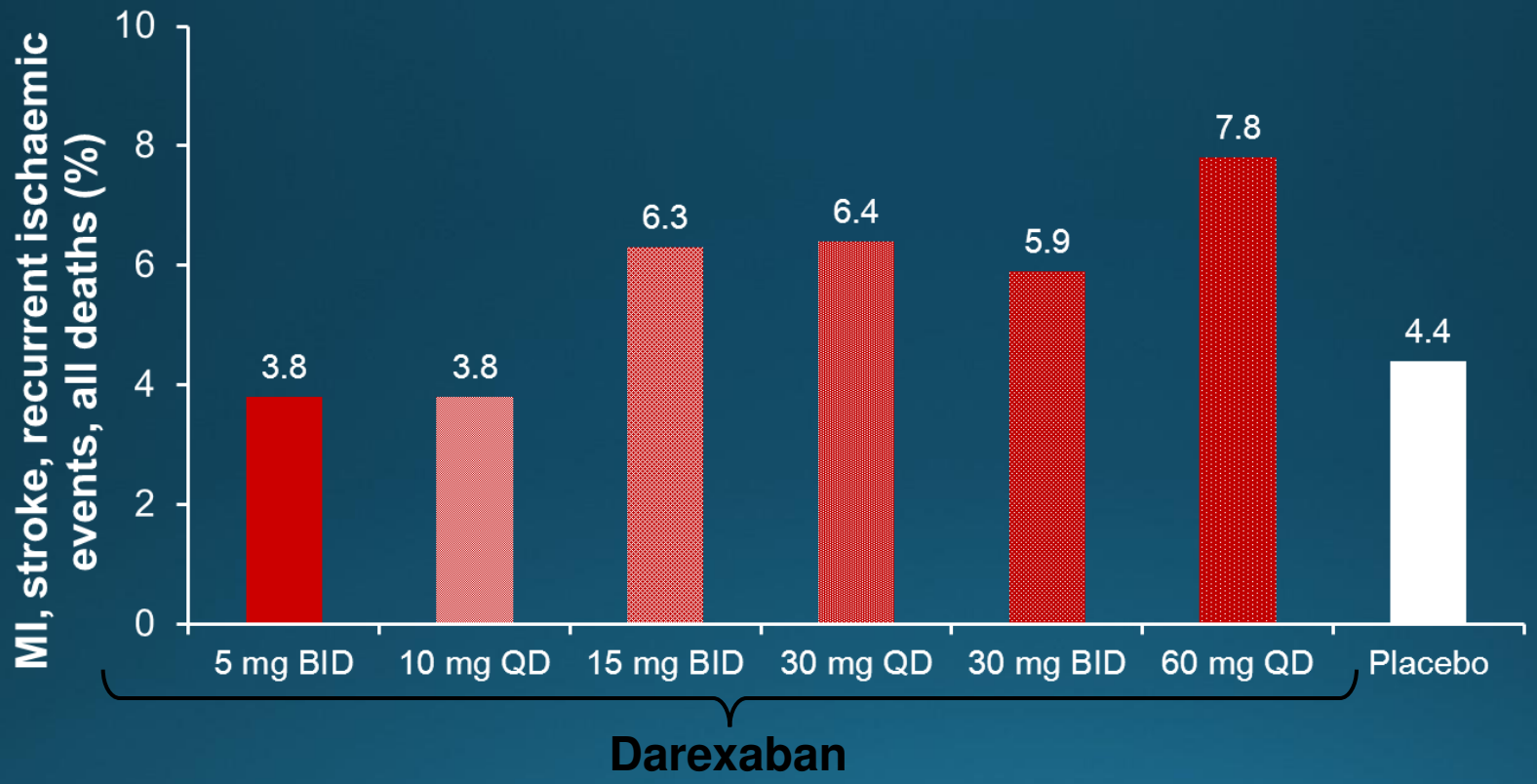
## Key exclusion criteria

- Need for ongoing therapy with parenteral or oral anticoagulants
- Patient planned for myocardial revascularisation or other invasive procedure with increased risk for bleeding within 60 days
- Recent stroke or TIA <12 months prior to index event
- Renal CrCl of <60 mL/min

ACS, acute coronary syndromes; CAD, coronary artery disease; CrCl, creatinine clearance; ECG, electrocardiography; NSTEMI, non-ST-segment elevation myocardial infarction; PAD, peripheral artery disease; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischaemic attack.

Steg G, et al. *Eur Heart J* 2011;32:2541–2554.

# RUBY-1 trial: Primary efficacy endpoint outcomes

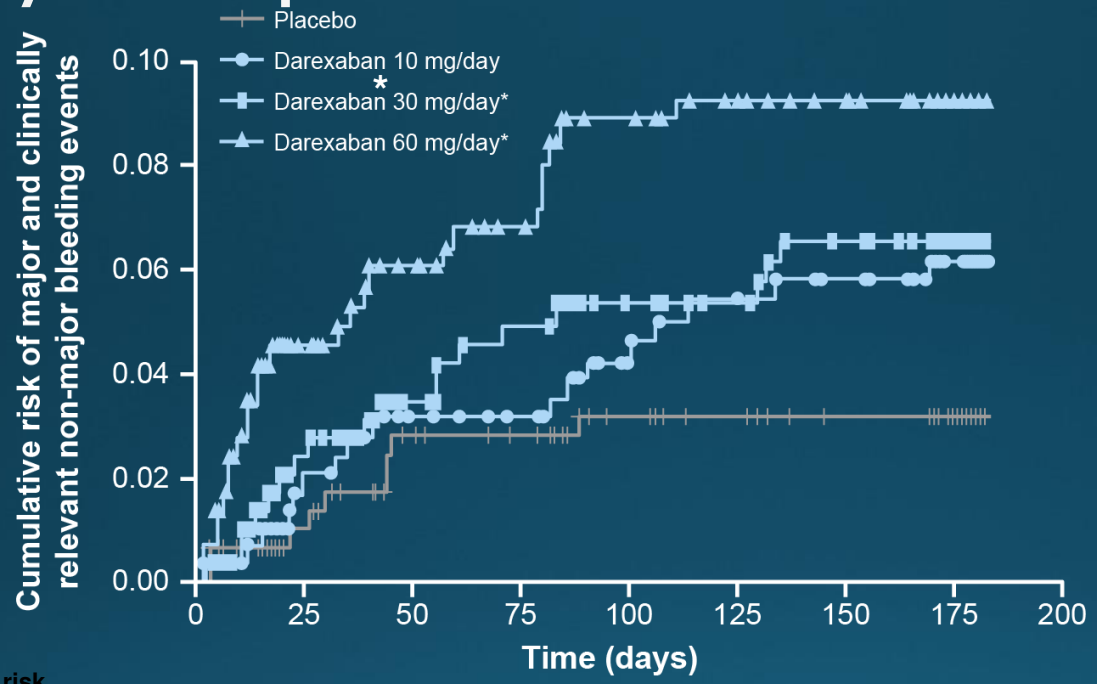



**No decrease in CV events with darexaban compared with placebo at Month 6 in patients with STEMI and NSTEMI**

BID, twice daily; CV, cardiovascular; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; QD, once daily; STEMI, ST-segment elevation myocardial infarction.

Steg G, et al. *Eur Heart J* 2011;32:2541–2554.

# Darexaban RUBY-1 trial: Primary safety endpoint outcomes




| No. at risk | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 319 | 283 | 269 | 264 | 255 | 251 | 243 | 238 |
| Darexaban 10 mg | 318 | 278 | 266 | 261 | 249 | 242 | 237 | 223 |
| Darexaban 30 mg | 315 | 280 | 260 | 253 | 240 | 234 | 224 | 212 |
| Darexaban 60 mg | 306 | 257 | 241 | 232 | 218 | 212 | 207 | 194 |

**Bleeding rates were numerically higher in all darexaban treatment arms compared with placebo with a dose-response relationship observed**

*QD and BID combined.
BID, twice daily; QD, once daily.
Steg G, et al. *Eur Heart J* 2011;32:2541–2554.

# Comparison of $P2Y_{12}$ inhibitors with new oral anticoagulants

- At present there are no head-to-head trials of ticagrelor or prasugrel in combination with new oral anticoagulants in ACS patients (i.e. triple therapy)

- The PIONEER AF-PCI study is currently investigating triple therapy with rivaroxaban in patients with AF who have undergone PCI
  - Open-label, randomised, controlled study
  - Patients randomised to:
    - Rivaroxaban 2.5 mg twice daily plus ASA and a $P2Y_{12}$ inhibitor*
    - Rivaroxaban 15 mg once daily and a P2Y12 inhibitor*
    - Vitamin K antagonist once daily plus ASA and a $P2Y_{12}$ inhibitor*
  - Primary outcome measure: Number of patients with clinically significant bleeding at Month 12

- Only a small number of patients in the PIONEER AF-PCI study will receive $P2Y_{12}$ inhibitors, therefore outcomes will provide limited information about the potential benefits of triple therapy with different $P2Y_{12}$ inhibitors

*Clopidogrel 75 mg once daily or prasugrel 10 mg once daily or ticagrelor 90 mg twice daily.
ACS, acute coronary syndromes; AF, atrial fibrillation; ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention.
http://clinicaltrials.gov/show/NCT01830543 Accessed August 2013.

# Summary: Role of oral anticoagulants in the treatment of patients with ACS

- New oral anticoagulants were developed to improve CV clinical management limited by the disadvantages of traditional agents[Eikelboom 2010]
- Rivaroxaban, apixaban, dabigatran and darexaban target factor Xa or thrombin, key enzymes in the coagulation pathway[Eikelboom 2010; PRADAXA 2013]
- Only rivaroxaban 2.5 mg is approved for use in patients with ACS in Europe[XARELTO® 2013]
  - A Phase III study with apixaban was terminated early due to increased bleeding events with no concurrent reduction in CV events[Alexander 2011]
  - A large Phase III study of low dose darexaban is required to determine its utility in preventing CV events in patients after ACS
  - It is currently unknown whether a Phase III trial will be initiated with dabigatran
- Given the potential for a higher risk of bleeding, triple therapy with the newer $P2Y_{12}$ inhibitors plus a new oral anticoagulant in patients with ACS is still controversial

ACS, acute coronary syndromes; CV, cardiovascular.

Alexander J, et al. *N Engl J Med* 2011;365:699–708; Eikelboom J, Weitz J. *Circulation* 2010;121:1523–1532; PRADAXA® [Prescribing information] 2013; XARELTO® [Summary of product characteristics] Berlin, Germany. Bayer 2013.

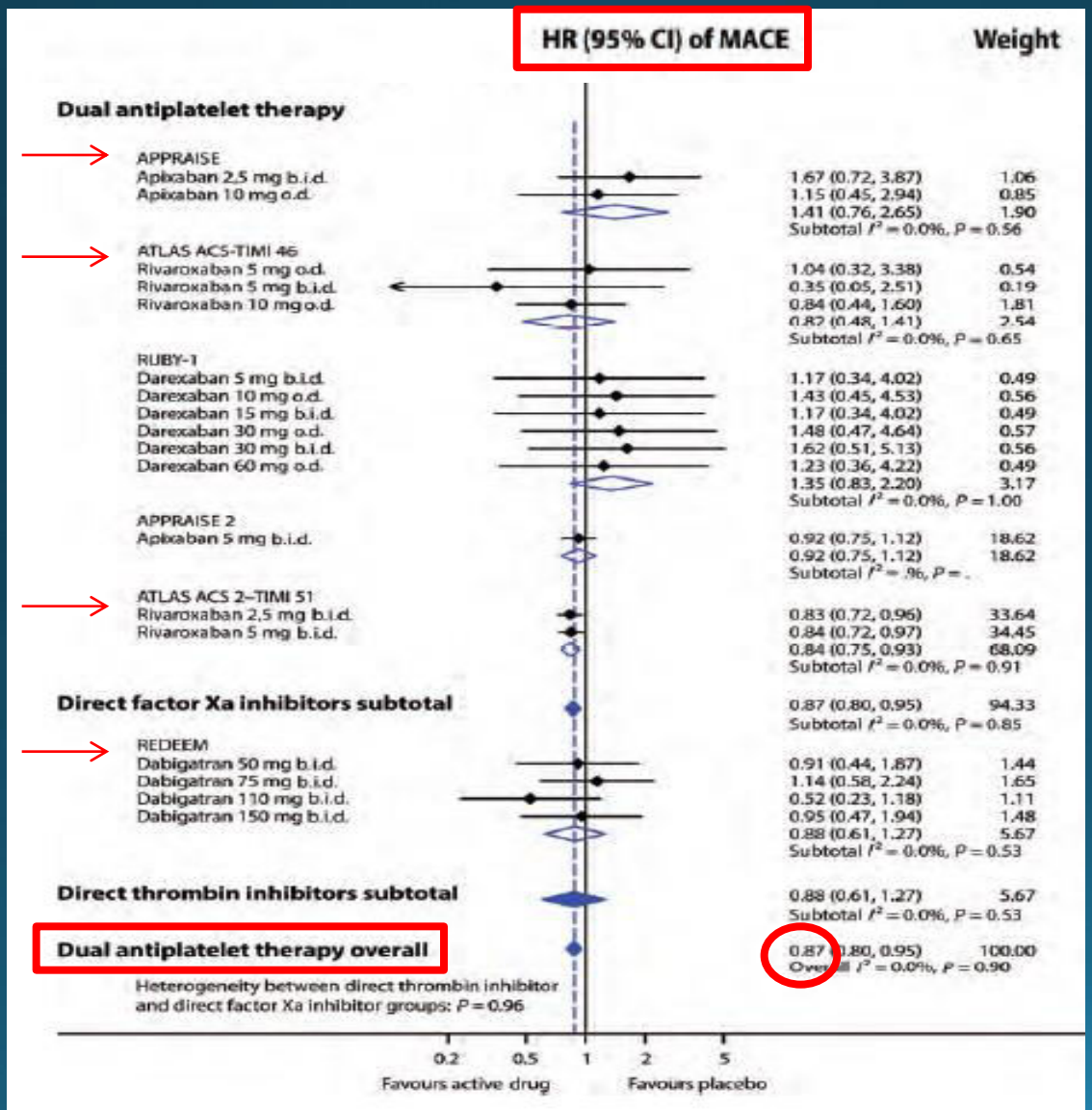
European Heart Journal (2013) 34, 1670–1680
doi:10.1093/eurheartj/eht049

CLINICAL RESEARCH
*Acute coronary syndromes*

# New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis

**Jonas Oldgren[1,2]*, Lars Wallentin[1,2], John H. Alexander[3], Stefan James[1,2], Birgitta Jönelid[1], Gabriel Steg[4,5,6], and Johan Sundström[1,2]**

[1]Department of Medical Sciences, Uppsala University, Uppsala, Sweden; [2]Uppsala Clinical Research Center, Uppsala, Sweden; [3]Duke Clinical Research Institute, Duke University Medical Center, Durham, NC, USA; [4]INSERM U-698, Paris, France; [5]Université Paris-Diderot, Sorbonne Paris Cité, Paris, France; and [6]AP-HP, Hôpital Bichat, Paris, France



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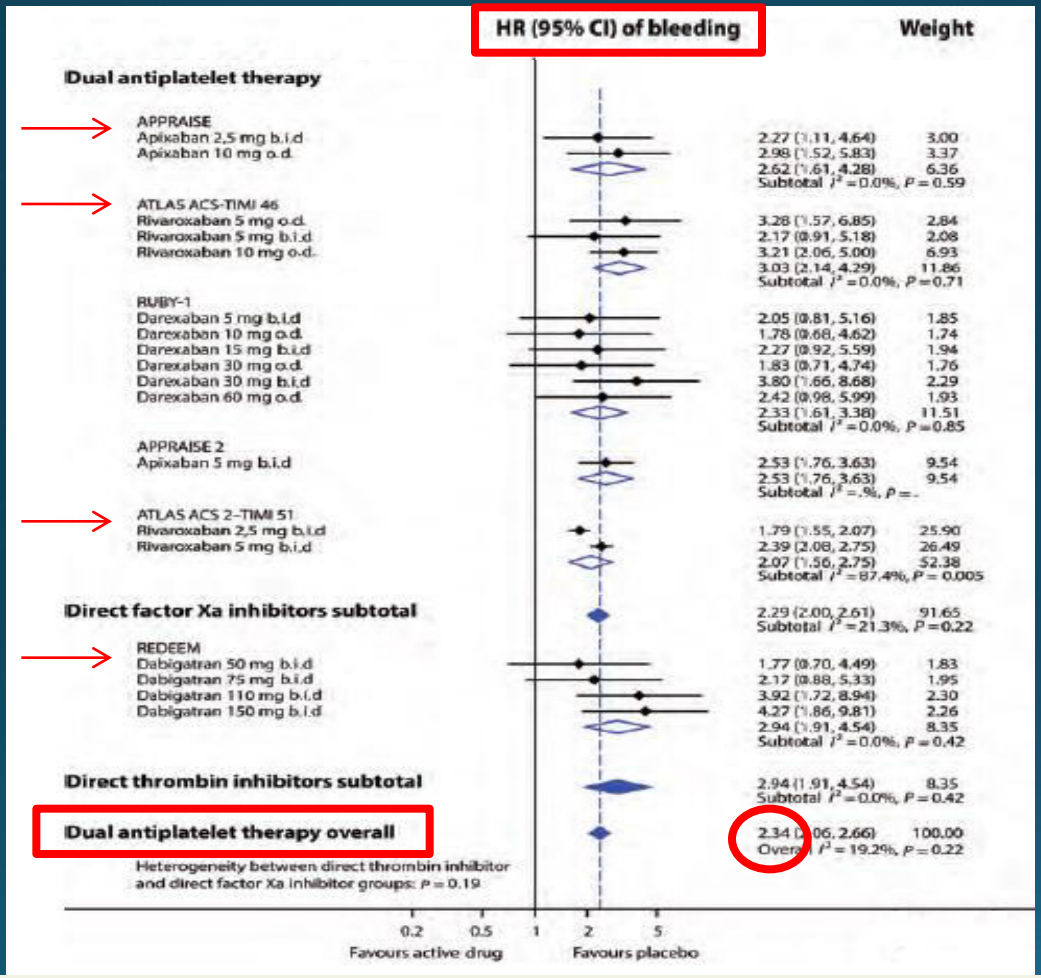



**Conclusion** In patients with a recent acute coronary syndrome, the addition of a new oral anticoagulant to antiplatelet therapy results in a modest reduction in cardiovascular events but a substantial increase in bleeding, most pronounced when new oral anticoagulants are combined with dual antiplatelet therapy.

# Which stent in which patient regarding OAC treatment

| Recommendations | Class[a] | Level[b] | Ref[c] |
|---|---|---|---|
| In patients with a firm indication for oral anticoagulation (e.g. atrial fibrillation with $CHA_2DS_2$-VASc score ≥2, venous thromboembolism, LV thrombus, or mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therapy. | I | C | |
| New-generation DES are preferred over BMS among patients requiring oral anticoagulation if bleeding risk is low (HAS-BLED ≤2). | IIa | C | |
| In patients with SCAD and atrial fibrillation with $CHA_2DS_2$-VASc score ≥2 at low bleeding risk (HAS-BLED ≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of at least one month after BMS or new-generation DES followed by dual therapy with (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months. | IIa | C | |
| DAPT should be considered as alternative to initial triple therapy for patients with SCAD and atrial fibrillation with a $CHA_2DS_2$-VASc score ≤1. | IIa | C | |
| In patients with ACS and atrial fibrillation at low bleeding risk (HAS-BLED≤2), initial triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 6 months irrespective of stent type followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months. | IIa | C | |
| In patients requiring oral anticoagulation at high bleeding risk (HAS BLED ≥3), triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of one month followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) irrespective of clinical setting (SCAD or ACS) and stent type (BMS or new-generation DES). | IIa | C | |
| Dual therapy of (N)OAC and clopidogrel 75 mg/day may be considered as an alternative to initial triple therapy in selected patients. | IIb | B | 865,870 |
| The use of ticagrelor and prasugrel as part of initial triple therapy is not recommended | III | C | |
| **Anticoagulation therapy after PCI in ACS patient** | | | |
| In selected patients who receive ASA and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered in the setting of PCI for ACS if the patient is at low bleeding risk. | IIb | B | 855 |
| **Anticoagulation during PCI in patients on oral anticoagulation** | | | |
| It is recommended to use additional parenteral anticoagulation, regardless of the timing of the last dose of (N)OAC. | I | C | |
| Periprocedural parenteral anticoagulants (bivalirudin, enoxaparin or UFH) should be discontinued immediately after primary PCI. | IIa | C | |

**HAS-BLED≤2 – new generation DES, ≥3 – BMS.**

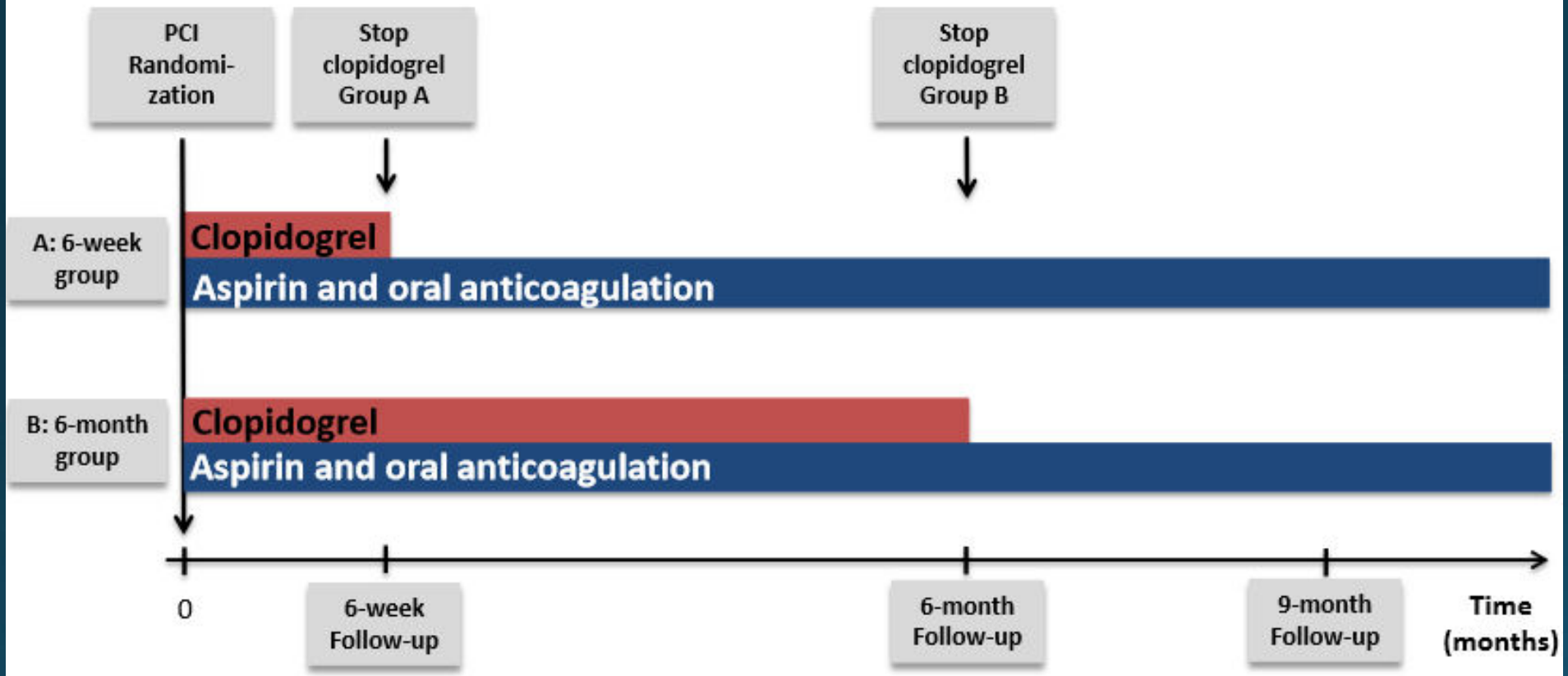
European Heart Journal

# Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation (ISAR-TRIPLE Trial)

**Katrin A. Fiedler, Michael Maeng, Julinda Mehilli, Stefanie Schulz, Robert A. Byrne, Dirk Sibbing, Petra Hoppmann, Simon Schneider, Massimiliano Fusaro, Ilka Ott, Steen D. Kristensen, Tareq Ibrahim, Steffen Massberg, Heribert Schunkert, Karl-Ludwig Laugwitz, Adnan Kastrati and Nikolaus Sarafoff**

Deutsches Herzzentrum, Technische Universität, Munich, Germany; Aarhus University Hospital, Aarhus, Denmark; Klinikum der Ludwig Maximilians Universität, Munich, Germany; Klinikum rechts der Isar, Technische Universität, Munich, Germany

# Randomization






Fiedler et al. Am Heart J. 2014; 167(4):459-465

# Antithrombotic therapy

**ASPIRIN:**
75-200 mg per day
**CLOPIDOGREL:**
75 mg per day
**PHENPROCOUMON or WARFARIN:**
Target INR 2.0 or 2.5 in patients with mechanical valves

| Compliance | 6-week FU | 6-month FU | 9-month FU |
|---|---|---|---|
| **Aspirin*** | 97 % | 95 % | 96 % |
| **OAC*** | 94 % | 91 % | 88 % |
| **INR (median)*** | 2.2 | 2.3 | 2.3 |
| **Time in therapeutic range *** | 64 % | 69 % | 66 % |
| **Clopidogrel 6-week group** | 97 % P=0.56 | 26 % P<0.001 | 23 % P<0.001 |
| **Clopidogrel 6-month group** | 98 % | 87 % | 35 % |

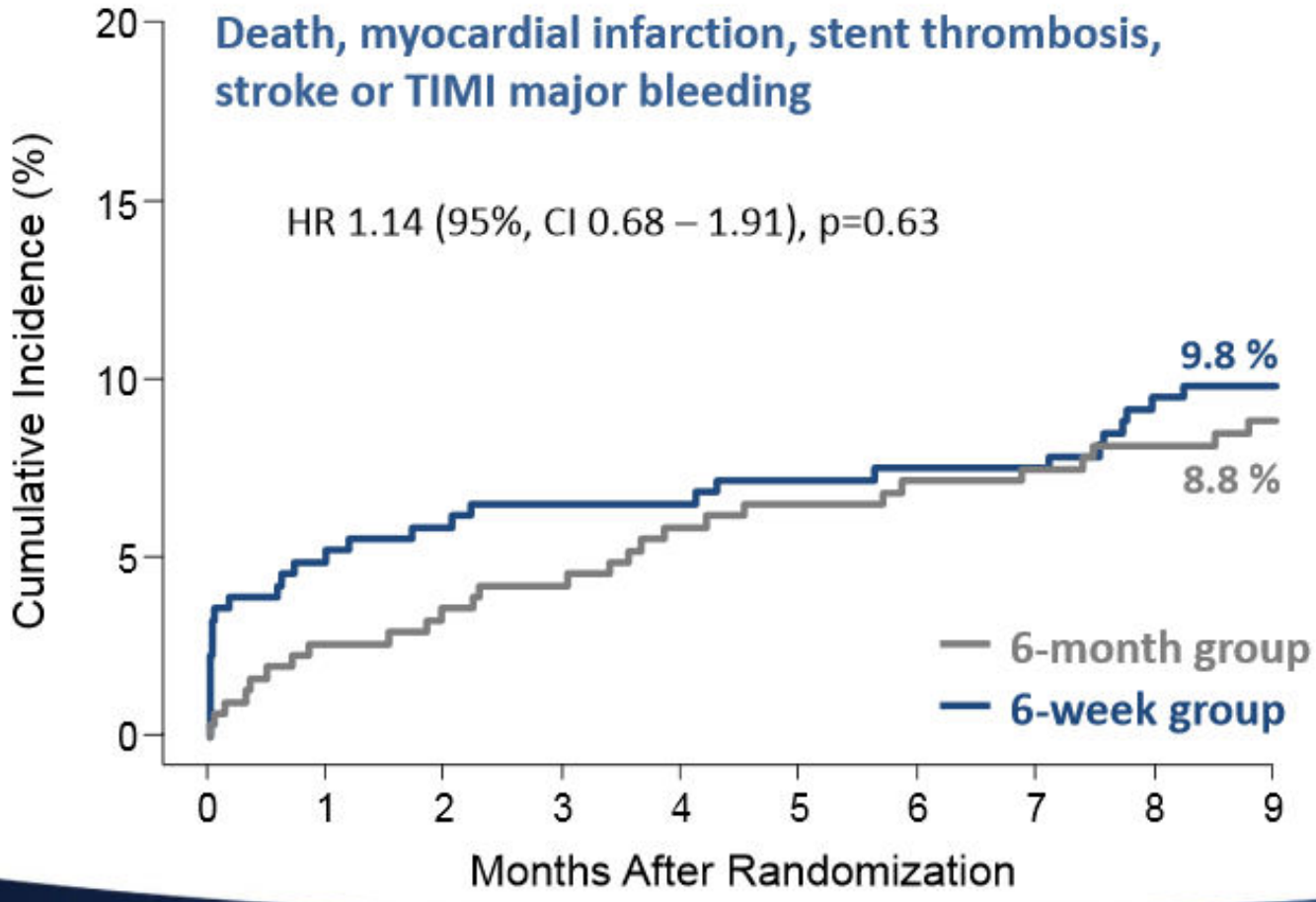
*No significant differences between groups; FU= Follow Up time point

# Stent type

| | 6-week group (417 lesions) | 6-month group (409 lesions) |
|---|---|---|
| 2nd gen. permanent polymer DES | 203 (48.7) | 206 (50.4) |
| Biodegradable polymer DES | 131 (31.4) | 134 (32.8) |
| Polymer free DES | 45 (10.8) | 46 (11.2) |
| 1st gen. permanent polymer DES | 29 (6.9) | 16 (3.9) |
| BVS | 4 (1.0) | 3 (0.7) |
| BMS* | 2 (0.5) | 0 |
| DEB/PTCA** | 3 (0.7) | 4 (1.0) |

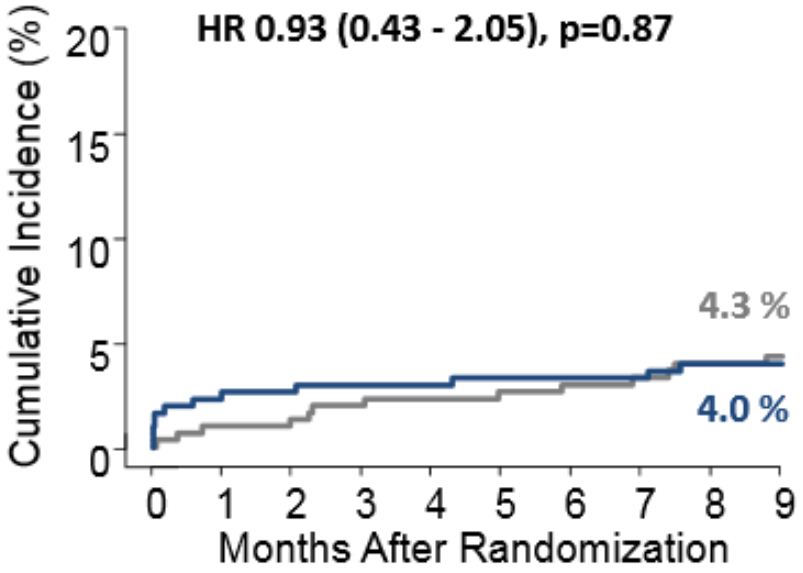
DES = Drug-eluting stent; BMS = Bare-metal stent; BVS = Bioresorbable vascular scaffold; DEB = Drug-eluting balloon; *One patient had 1 DES and 1 BMS and 1 patient had 1 BMS only. ** These patients were treated with drug eluting balloons (DEB) except for 1 patient in the 6-week group and 1 patient in the 6-month group.

# Primary Endpoint

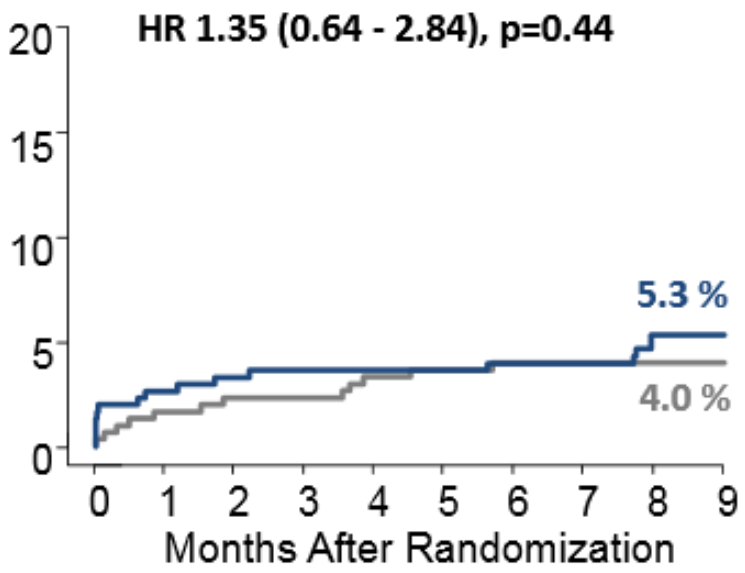


# Secondary Endpoints

## Cardiac death, myocardial infarction, stent thrombosis or ischemic stroke




## TIMI major bleeding




6-month group
6-week group

# Results

| | 6-week group (n=307) | 6-month group (n=307) | Hazard ratio (95% CI) | p value |
|---|---|---|---|---|
| Death | 12 (4.0) | 16 (5.2) | 0.75 (0.35 -1.59) | 0.45 |
| Cardiac death | 5 (1.7) | 9 (3.0) | 0.56 (0.19 - 1.66) | 0.29 |
| Myocardial infarction | 6 (2.0) | 0 | - | 0.03 |
| Definite stent thrombosis | 2 (0.7) | 0 | - | 0.50 |
| Stroke | 4 (1.3) | 6 (2.0) | 0.67 (0.14 - 2.78) | 0.75 |
| Ischemic stroke | 3 (1.0) | 4 (1.3) | 0.75 (0.11 - 4.40) | 0.99 |

**Temporal distribution of MIs in 6-week group:**

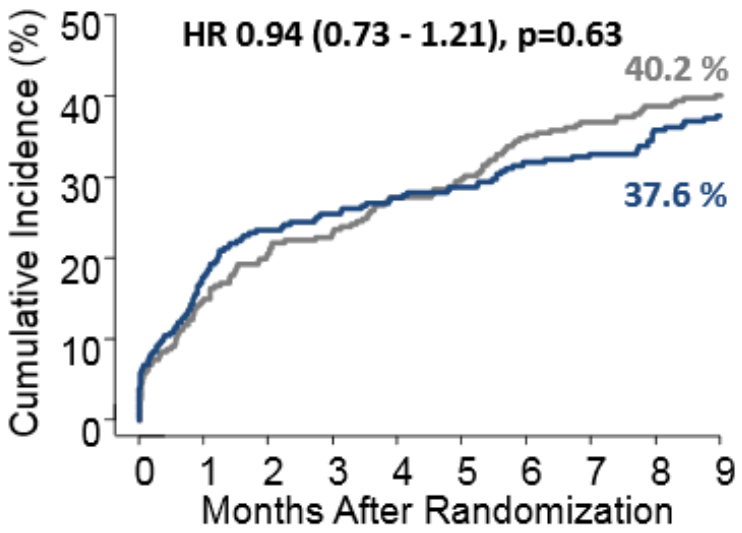
4 within 24h of PCI } Both groups on triple therapy

1 at 2.5 weeks

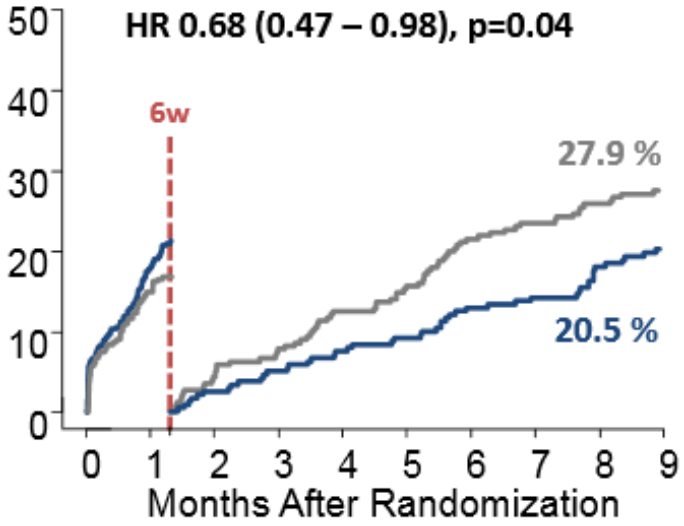
1 at 7 months } Both groups on aspirin and OAC

# Any BARC Bleeding (type 1-5)

## Any BARC Bleeding




## Post-hoc landmark analysis of any BARC Bleeding before and after 6 weeks (6w)




— 6-month group
— 6-week group

CITY CLINIC WOEST

# The WOEST Trial: First randomised trial comparing two regimens with and without aspirin in patients on oral anticoagulant therapy undergoing coronary stenting

Willem Dewilde, Tom Oirbans, Freek Verheugt, Johannes Kelder, Bart De Smet, Jean-Paul Herrman, Tom Adriaenssens, Mathias Vrolix, Antonius Heestermans, Marije Vis, Saman Rasoul, Kaioum Sheikjoesoef, Tom Vandendriessche, Carlos Van Mieghem, Kristoff Cornelis, Jeroen Vos, Guus Brueren, Nicolien Breet and Jurriën ten Berg

The WOEST Trial= **W**hat is the **O**ptimal antiplat**E**let and anticoagulant therapy in patients with oral anticoagulation and coronary **S**ten**T**ing (clinicaltrials.gov NCT00769938)

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# Aim of the study

**To test the hypothesis that in patients on OAC undergoing PCI, *clopidogrel alone* is superior to the combination *aspirin and clopidogrel* with respect to bleeding but is not increasing thrombotic risk in a multicentre two-country study (The Netherlands and Belgium)**



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# Study Design-1

**Inclusion criteria:**

1/ Indication for OAC for at least 1 year
2/ One coronary lesion eligible for PCI
3/ Age over 18

**Exclusion criteria:**

1/ History of intracranial bleeding
2/ Cardiogenic shock during hospitalisation
3/ Peptic ulcer in the previous 6 months
4/ TIMI major bleeding in the previous year
5/ Contra-indication for aspirin or clopidogrel
6/ Thrombocytopenia (platelet count less than 50,000 per ml)
7/ Pregnancy
8/ Age >80

# Study Design-2

***1:1 Randomisation:***

| Double therapy group: | Triple therapy group |
|---|---|
| OAC + 75mg Clopidogrel qd | OAC + 75mg Clopidogrel qd + 80mg Aspirin qd |
| 1 month minimum after BMS<br>1 year after DES | 1 month minimum after BMS<br>1 year after DES |

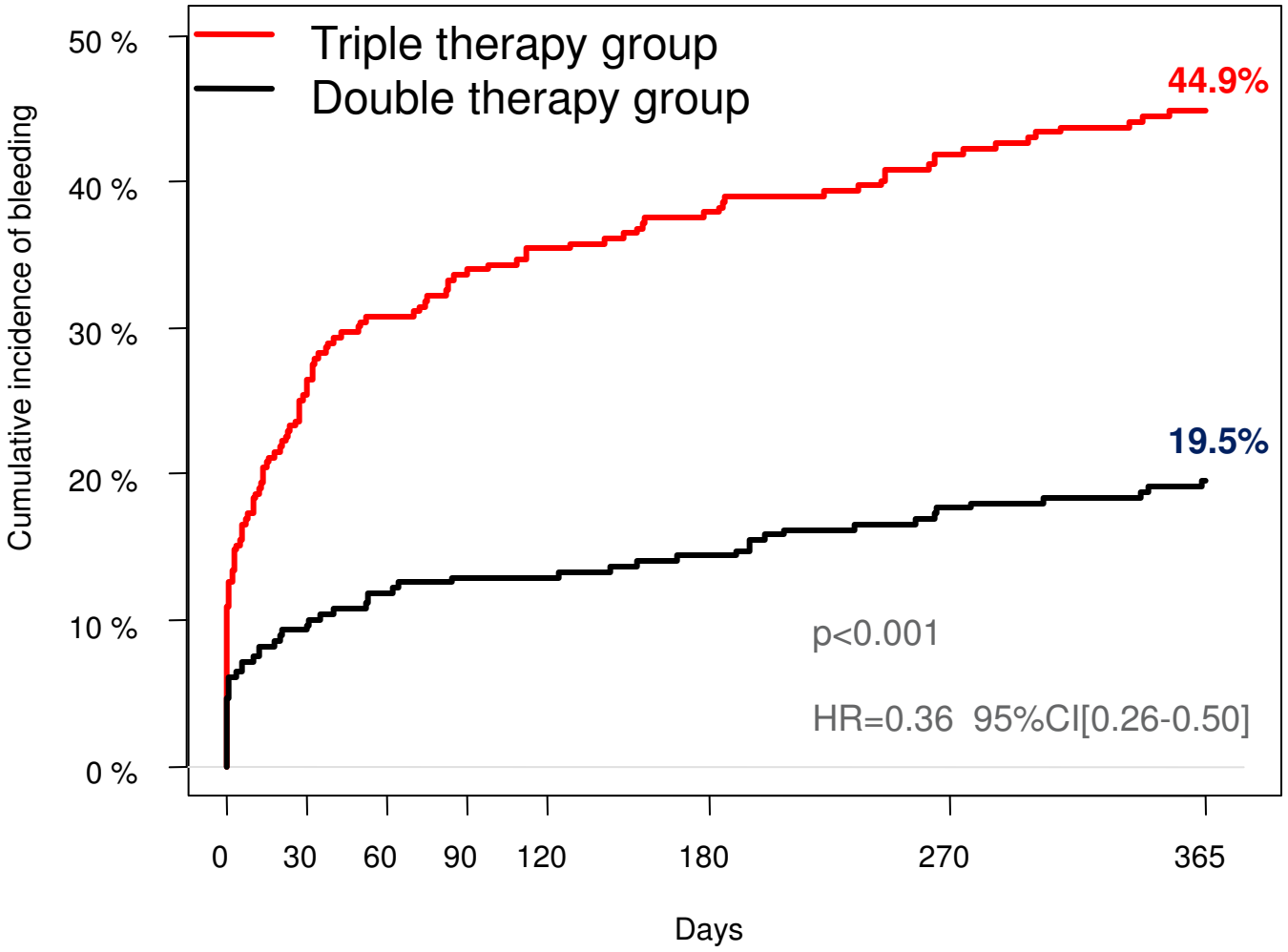
***Follow up:*** 1 year

***Primary Endpoint:*** The occurence of all bleeding events (TIMI criteria)

***Secondary Endpoints:***

- Combination of stroke, death, myocardial infarction, stent thrombosis and target vessel revascularisation
- All individual components of primary and secondary endpoints

# Primary Endpoint: Total number of TIMI bleeding events




| n at risk: | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 284 | 210 | 194 | 186 | 181 | 173 | 159 | 140 |
| | 279 | 253 | 244 | 241 | 241 | 236 | 226 | 208 |

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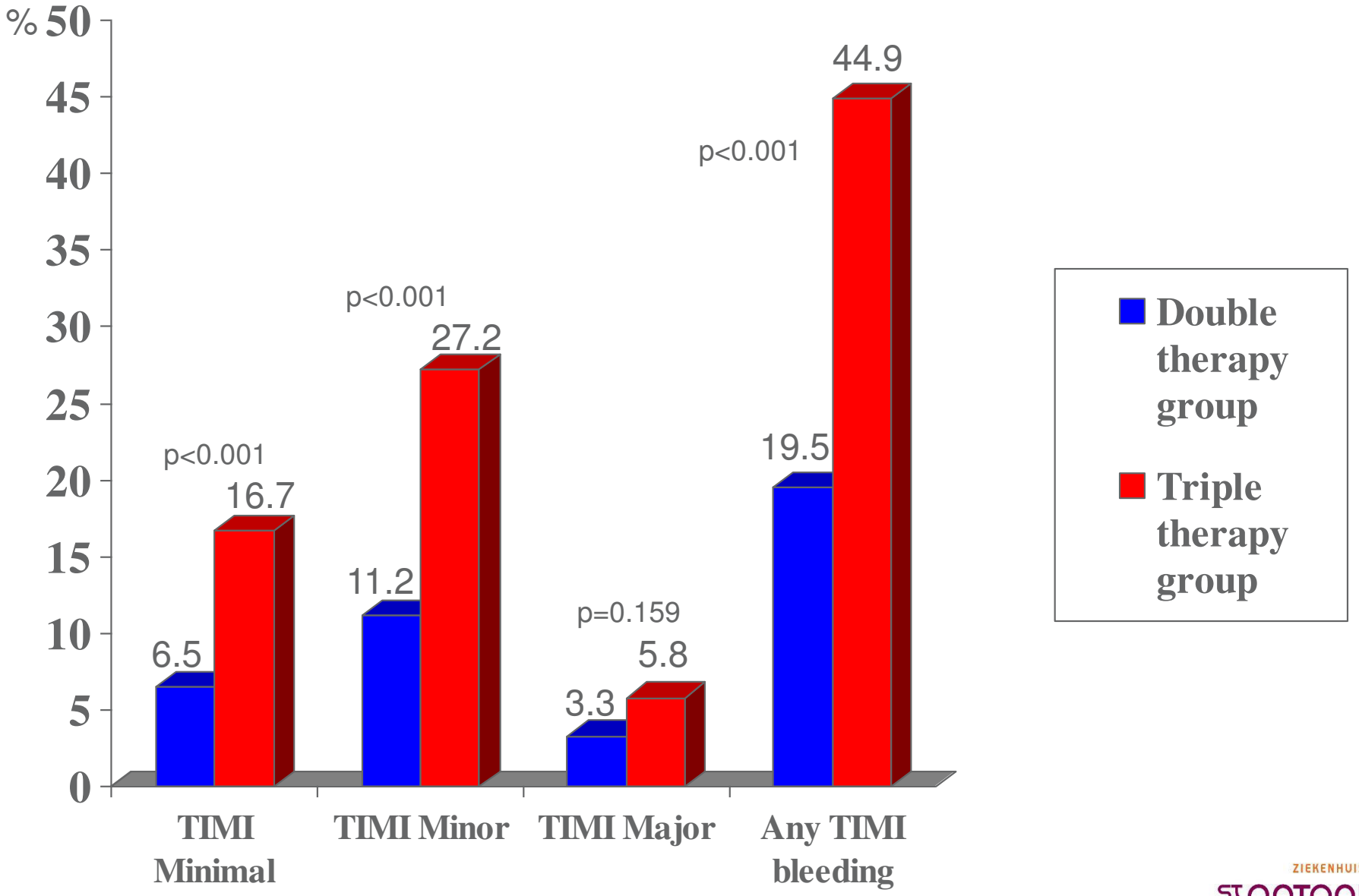
# Primary Endpoint: Bleeding events TIMI classification

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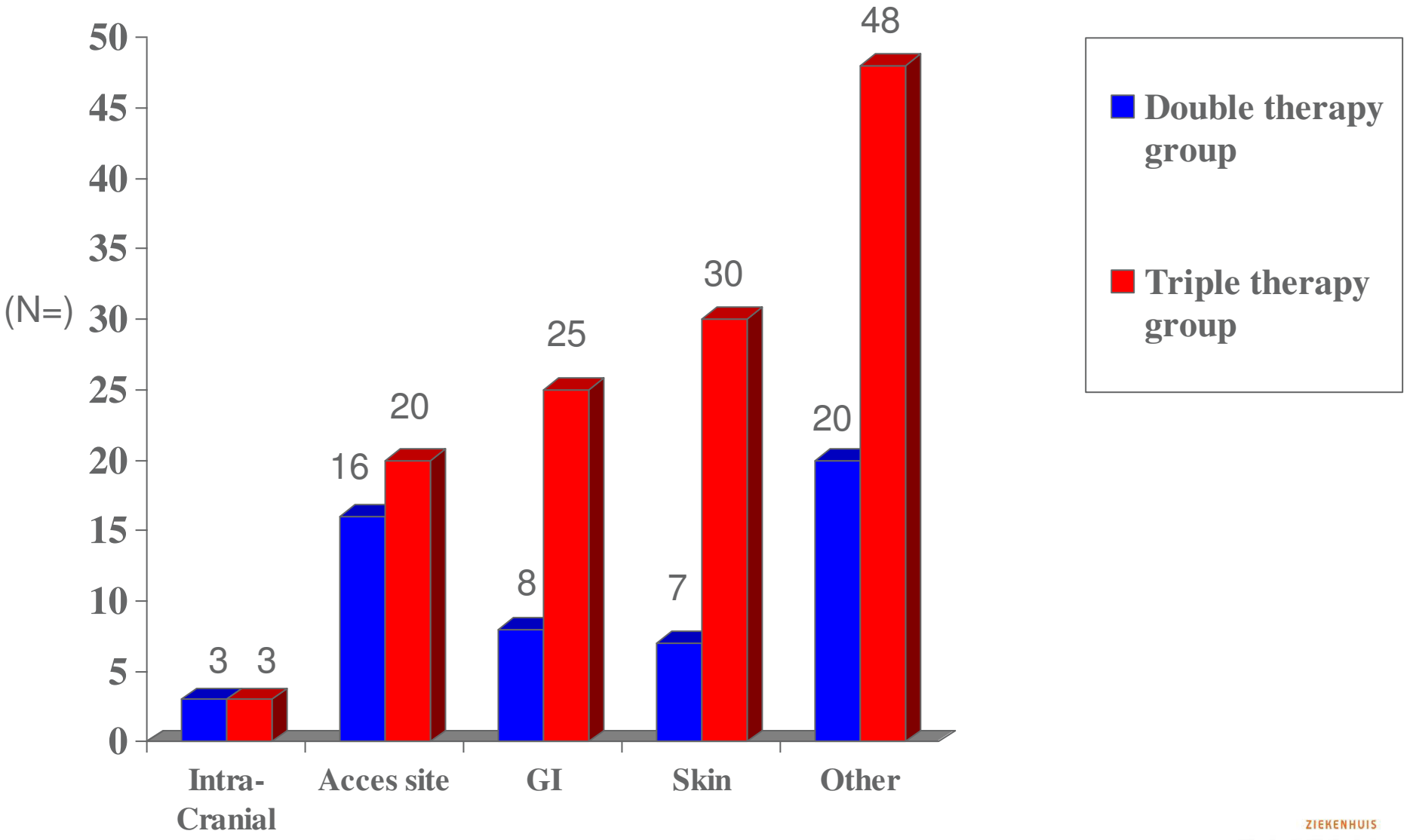
# Locations of TIMI bleeding: Worst bleeding per patient




GI=gastro intestinal; Other bleeding consists of eye, urogenital, respiratory tract, retroperitoneal, mouth, PMpocket bleeding

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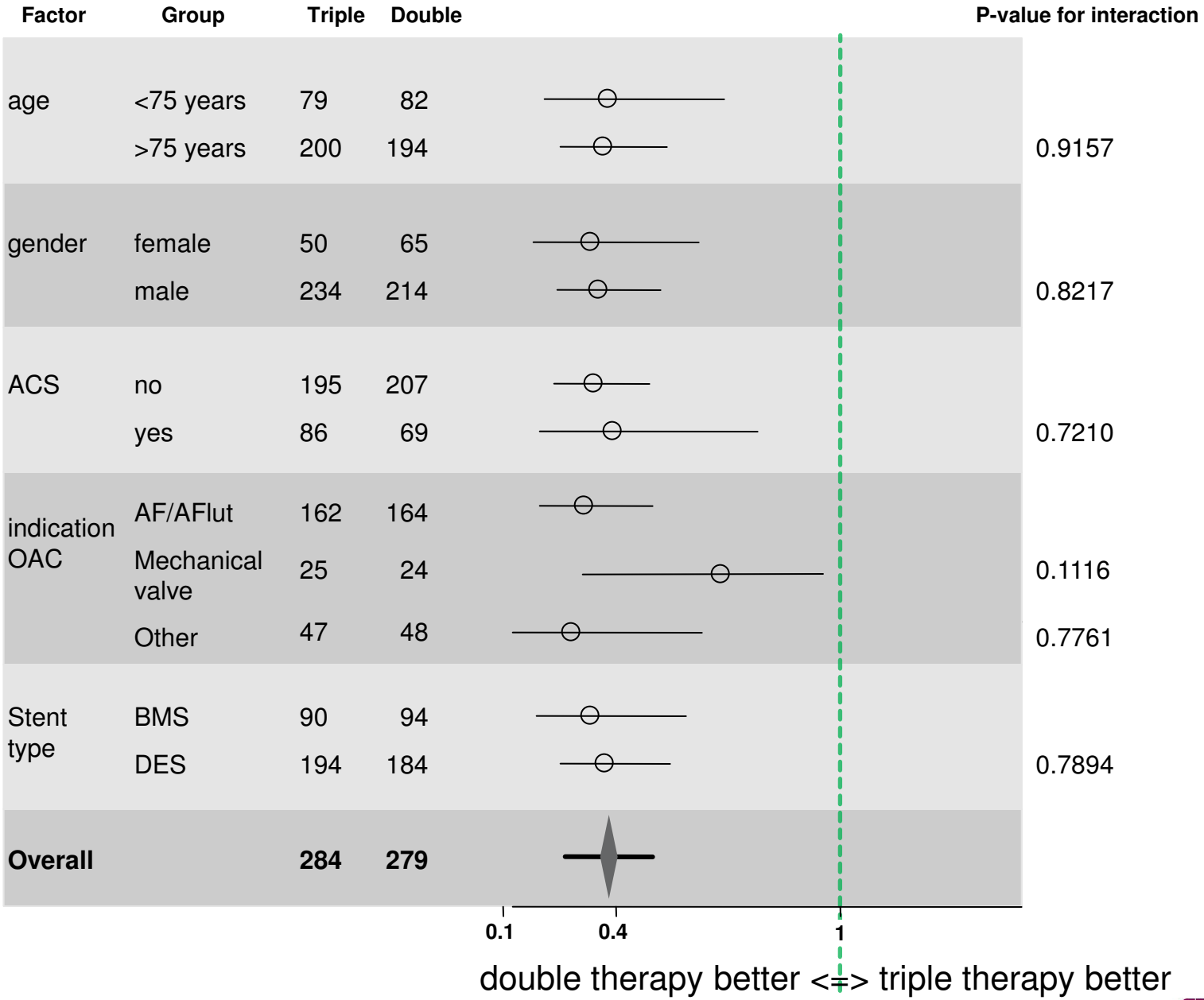
# Forest plot of primary endpoint Hazard Ratios

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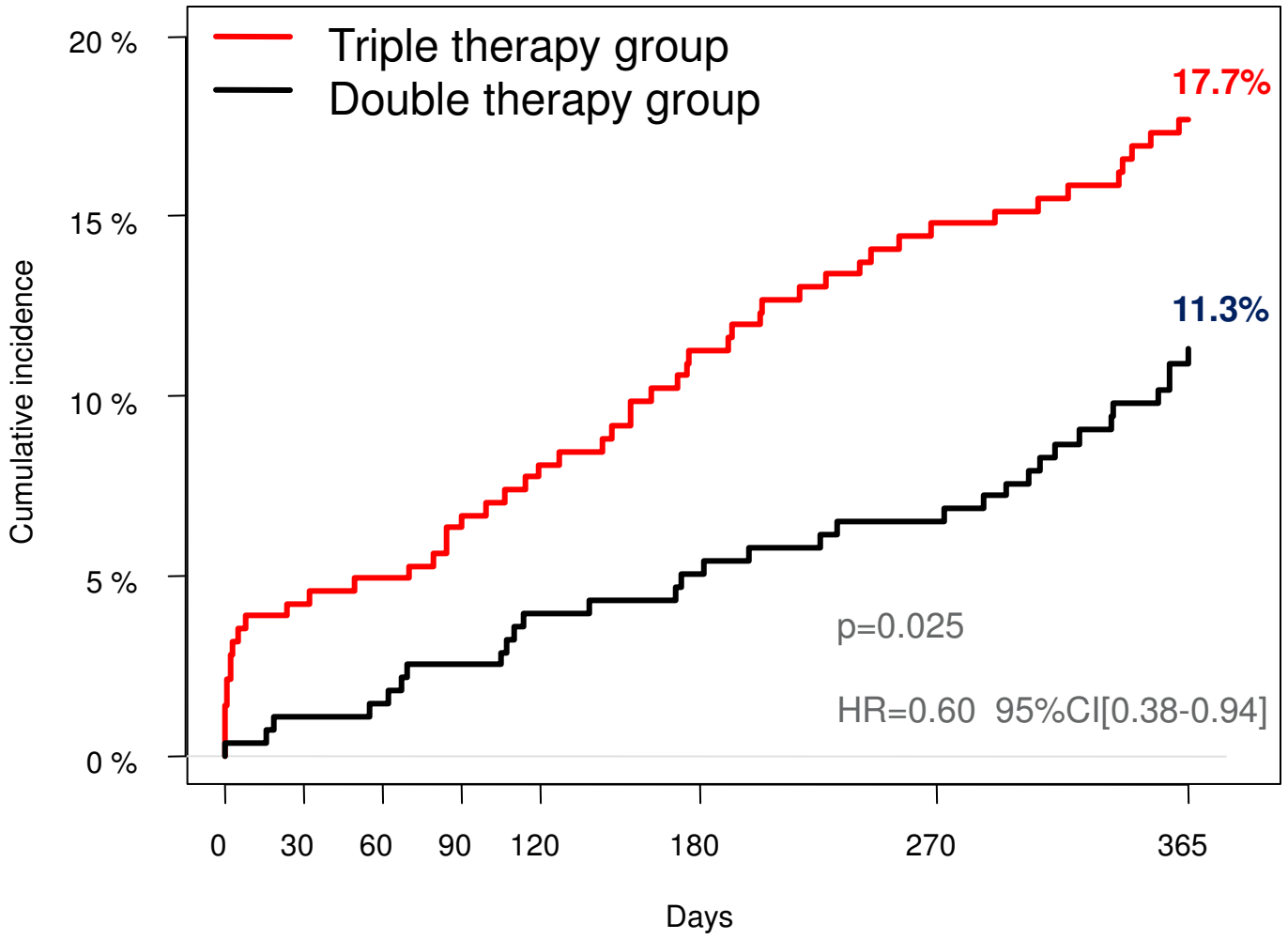
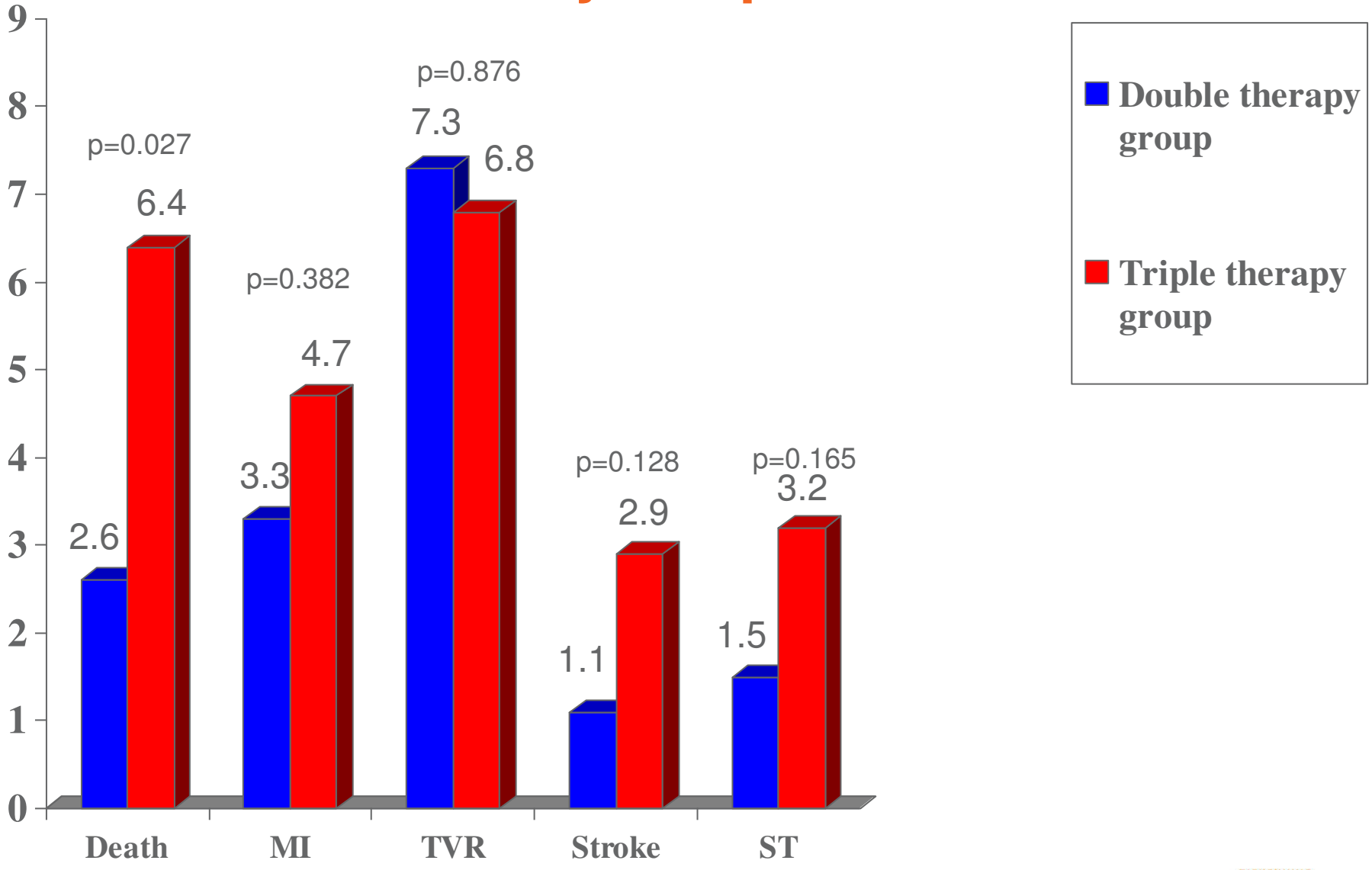
# Secondary Endpoint (Death, MI,TVR, Stroke, ST)



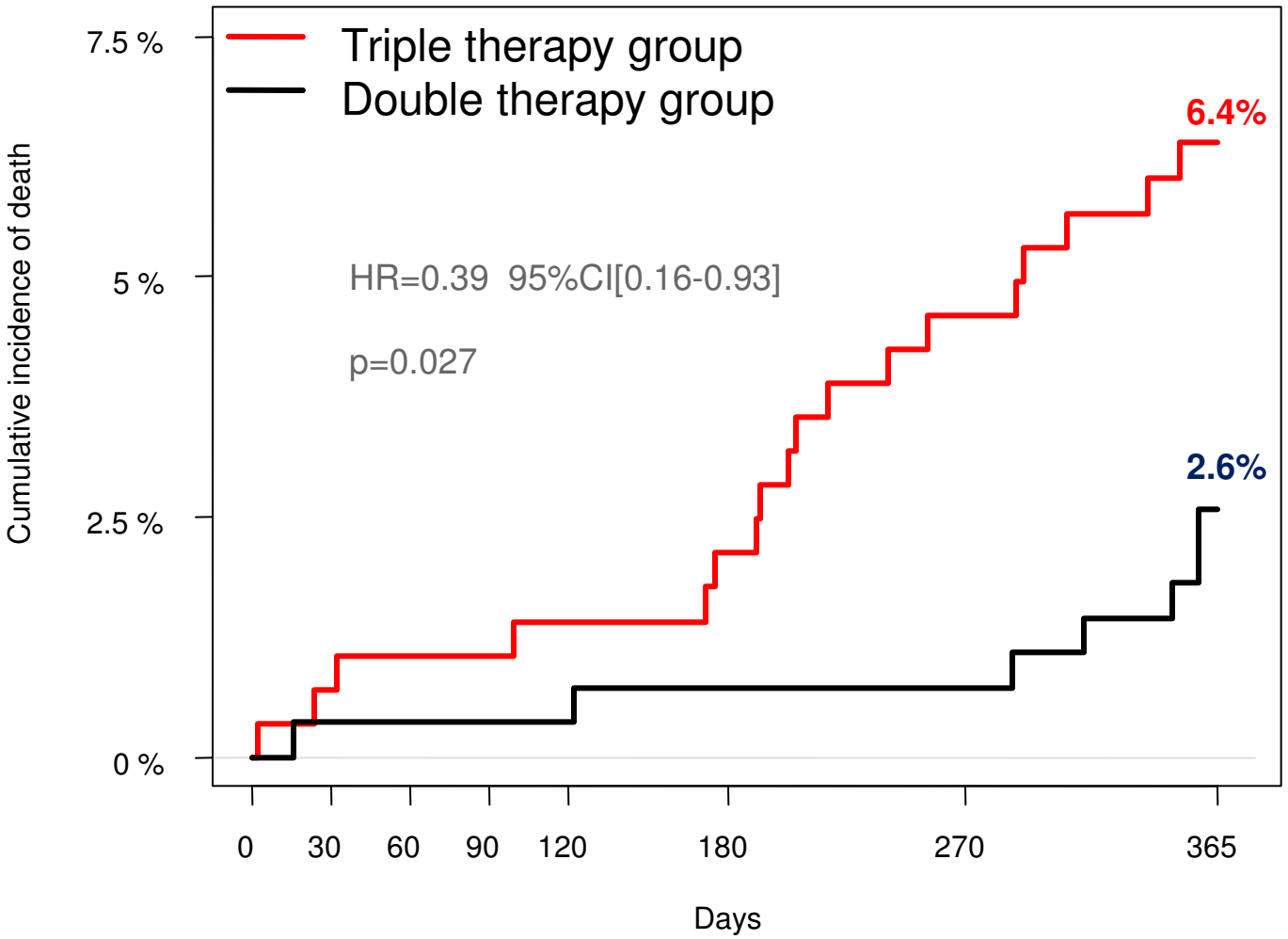

| n at risk: | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 284 | 272 | 270 | 266 | 261 | 252 | 242 | 223 |
| | 279 | 276 | 273 | 270 | 266 | 263 | 258 | 234 |

# Secondary Endpoint




MI=any myocardial infarction; TVR= target vessel revascularisation (PCI + CABG); ST= stent thrombosis

# All-Cause Mortality



# Conclusions

1. In this study which was specifically designed to detect bleeding events, the bleeding rate was higher than expected

2. Primary endpoint was met: OAC plus clopidogrel causes less bleeding than triple antithrombotic therapy, but now shown in a randomized way

3. Secondary endpoint was met: with double therapy there is no excess of thrombotic/thromboembolic events: stroke, stent thrombosis, target vessel revascularisation, myocardial infarction or death

4. Less all-cause mortality with double therapy

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# Консенсус на EHRA/EAPCI

| Haemorrhagic risk | Stroke risk | Clinical setting | Recommendations |
|---|---|---|---|
| Low or moderate (HAS-BLED 0–2) | Moderate ($CHA_2DS_2$-VASC = 1 in males) | Stable CAD | *At least 4 weeks (no longer than 6 months):* triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day[a]<br>*Up to 12th month:* OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day)[b]<br>*Lifelong:* OAC[c] |
| | High ($CHA_2DS_2$-VASC ≥2) | Stable CAD | *At least 4 weeks (no longer than 6 months):* triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day[d]<br>*Up to 12th month:* OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day)<br>*Lifelong:* OAC[c] |
| | Moderate ($CHA_2DS_2$-VASC = 1 in males) | ACS | *6 months:* triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day<br>*Up to 12th month:* OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day)<br>*Lifelong:* OAC[c] |
| | High ($CHA_2DS_2$-VASC ≥2) | ACS | *6 months:* triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day<br>*Up to 12th month:* OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day)<br>*Lifelong:* OAC[c] |
| High (HAS-BLED ≥3) | Moderate ($CHA_2DS_2$-VASC = 1 in males) | Stable CAD | *12 months:* OAC and clopidogrel 75 mg/day[b]<br>*Lifelong:* OAC[c] |
| | High ($CHA_2DS_2$-VASC ≥2) | Stable CAD | *4 weeks:* triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day[a]<br>*Up to 12th month:* OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day)<br>*Lifelong:* OAC[c] |
| | Moderate ($CHA_2DS_2$-VASC = 1 in males) | ACS | *4 weeks:* triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day[d]<br>*Up to 12th month:* OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day)<br>*Lifelong:* OAC[c] |
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- Първо изчисли скоровете!!! (HAS-BLED, CHADS-VASC)
- ASA е задължителен компонент на тройната антитромбозна терапия – Неотменна при реваскуларизация за ОКС.
- Само при нискорисковите/стабилни болни можем да си позволим да не даваме ASA
- Посланието е: Тройна антитромбозна терапия за колкото се може по-кратко! Т.е при необходимост от стент- за предпочитане са 3-та генерация DES (бърза ендотелизация)
- И по изключение, при висок HASBLED (над 3)- BMS
- NOAC не са утвърдени в рутинната практика като част от комбинираната терапия след ОКС или тройна антитромбозна терапия поради ексцесивен риск от кървене
- Очакваме резултатите от проучвания с нови дозови режими и медикаментозни комбинации

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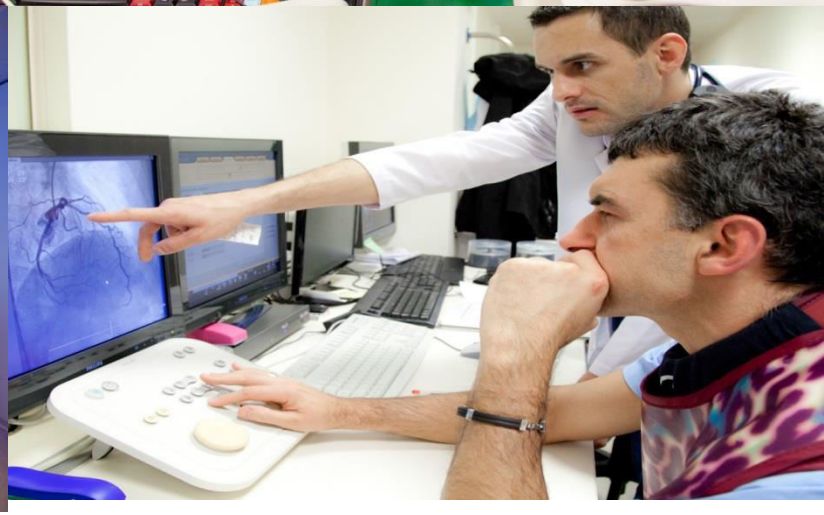
# Високите технологии в услуга на медицинския хуманизъм



Thank you very much for your attention!