Revisiting Anticoagulants: Why Dual Pathway Inhibition is Not Ready?

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below. These relationships may lead to bias in my presentation.

Affiliation/Financial Relationship	Company
• Grant/Research Support (Institutional)	• The Medicines Co., AZ, BMS, Lilly/Daiichi Sankyo
• Advisory Board	• Janssen (J+J),
• Consulting Fees/Honoraria	• Janssen (J+J), Maya Medical,

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Patient with chronic atrial fibrillation who needs DAPT for DES

Triple Therapy: The Scope of the Problem

Clinical Scenarios for Triple Therapy

Stent-assisted PCI +

- Atrial fibrillation with $CHADS_2$ score ≥2
- History of arterial embolism
- Mechanical valve
- VTE
- LV thrombus
- Coagulation disorders requiring OAK

Risk Assessment

- Risk of embolism
- Risk of stent thrombosis
- Risk of bleeding

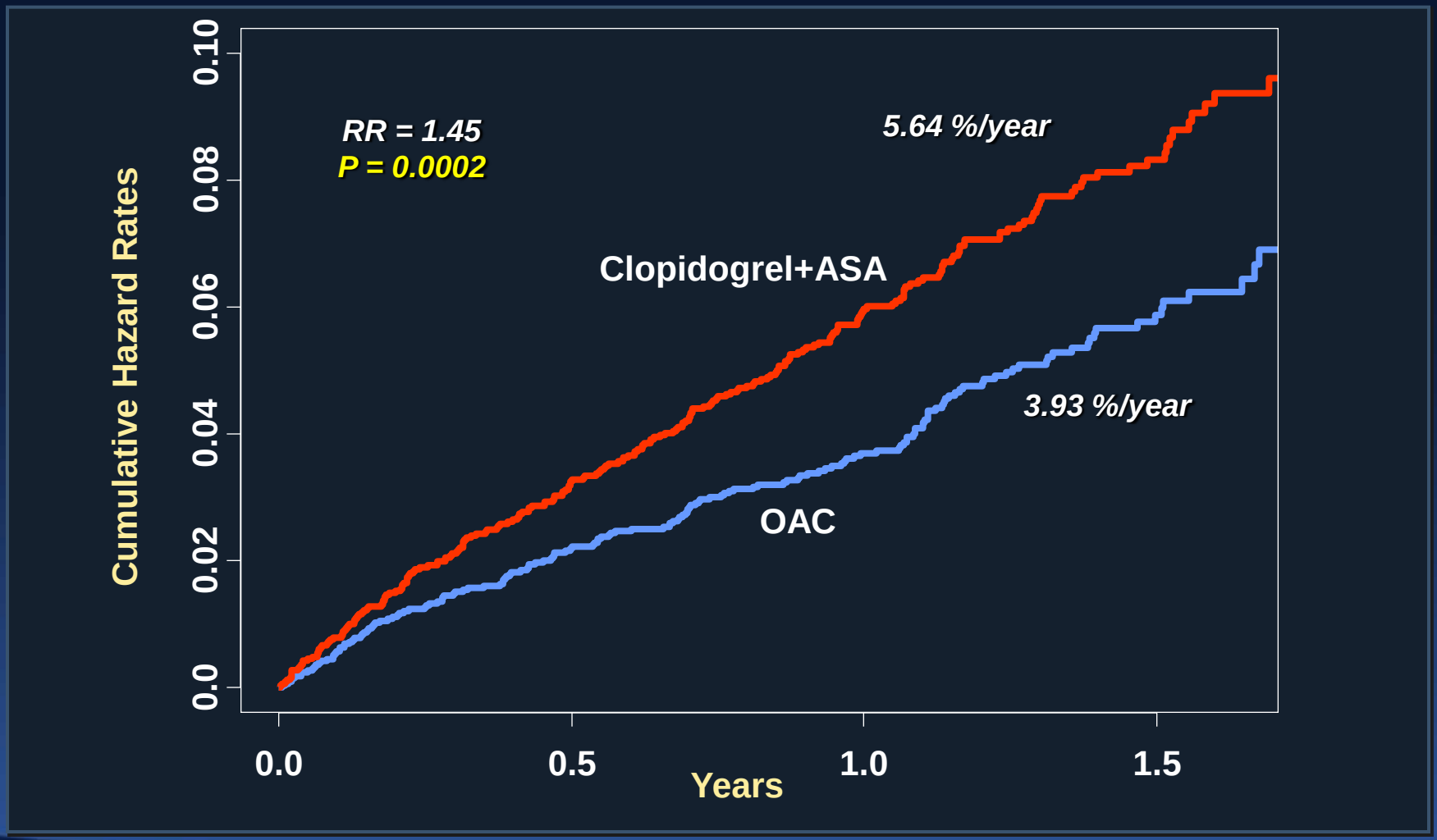
Therapeutic dilemmas

- Type of stent (BMS vs DES)
- Duration of therapy
- INR levels (2.0-2.5)
- Home-monitoring (INR self-testing)
- ASA dosage (<100 mg)
- Compliance with therapy
- CABG?
- OAK + single antiplatelet agent (Warfarin + Clopidogrel)

Recommendations for Patients with AF Undergoing Stenting

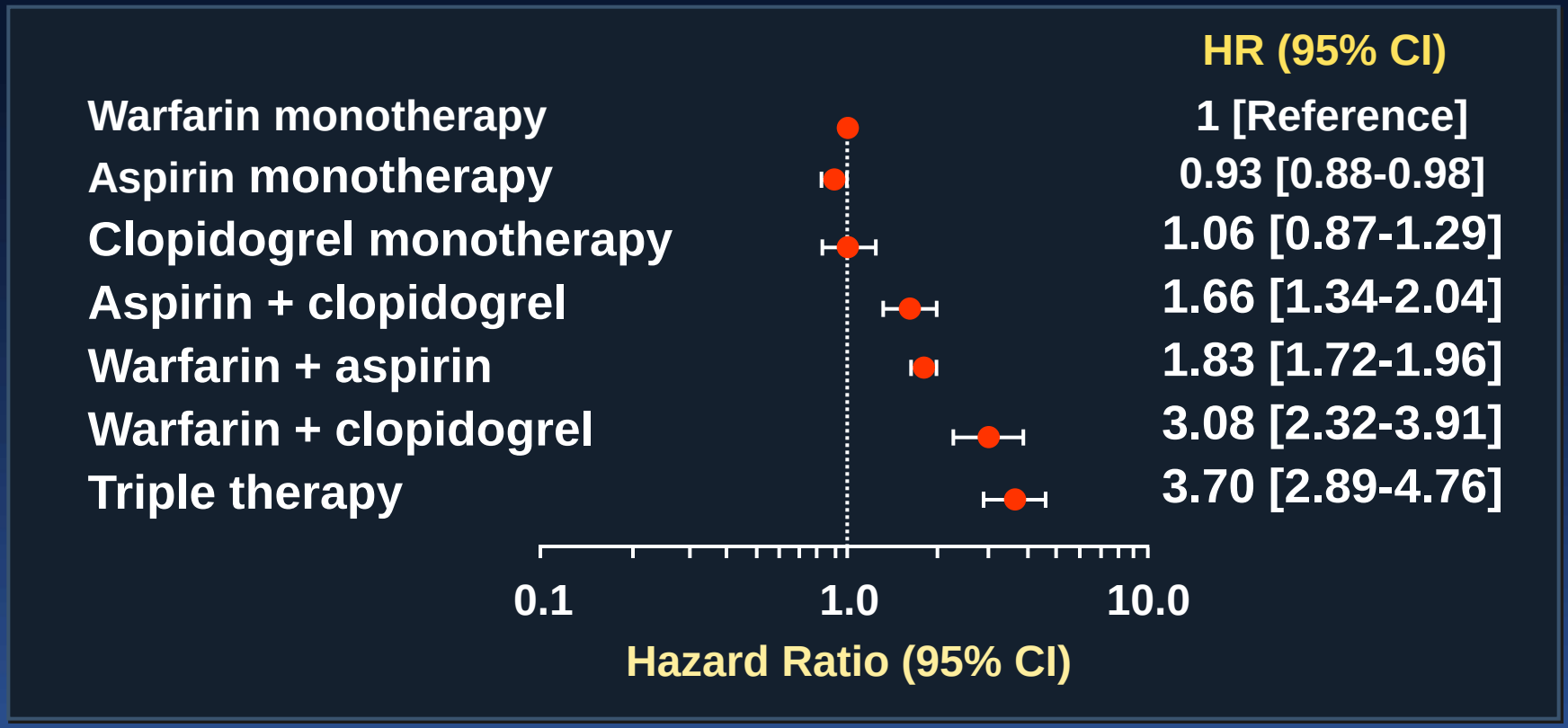
- Assess the risk for stent thrombosis, ischemic events, and thromboembolism, and adjust the need or degree of anticoagulation to the risk

ACTIVE W: Stroke, Non-CNS Systemic Embolism, MI & Vascular Death



Lancet 2006 Jun 10;367(9526):1903-12.

Bleeding Associated with Warfarin, Aspirin, Clopidogrel in Patients with AF n=82,854

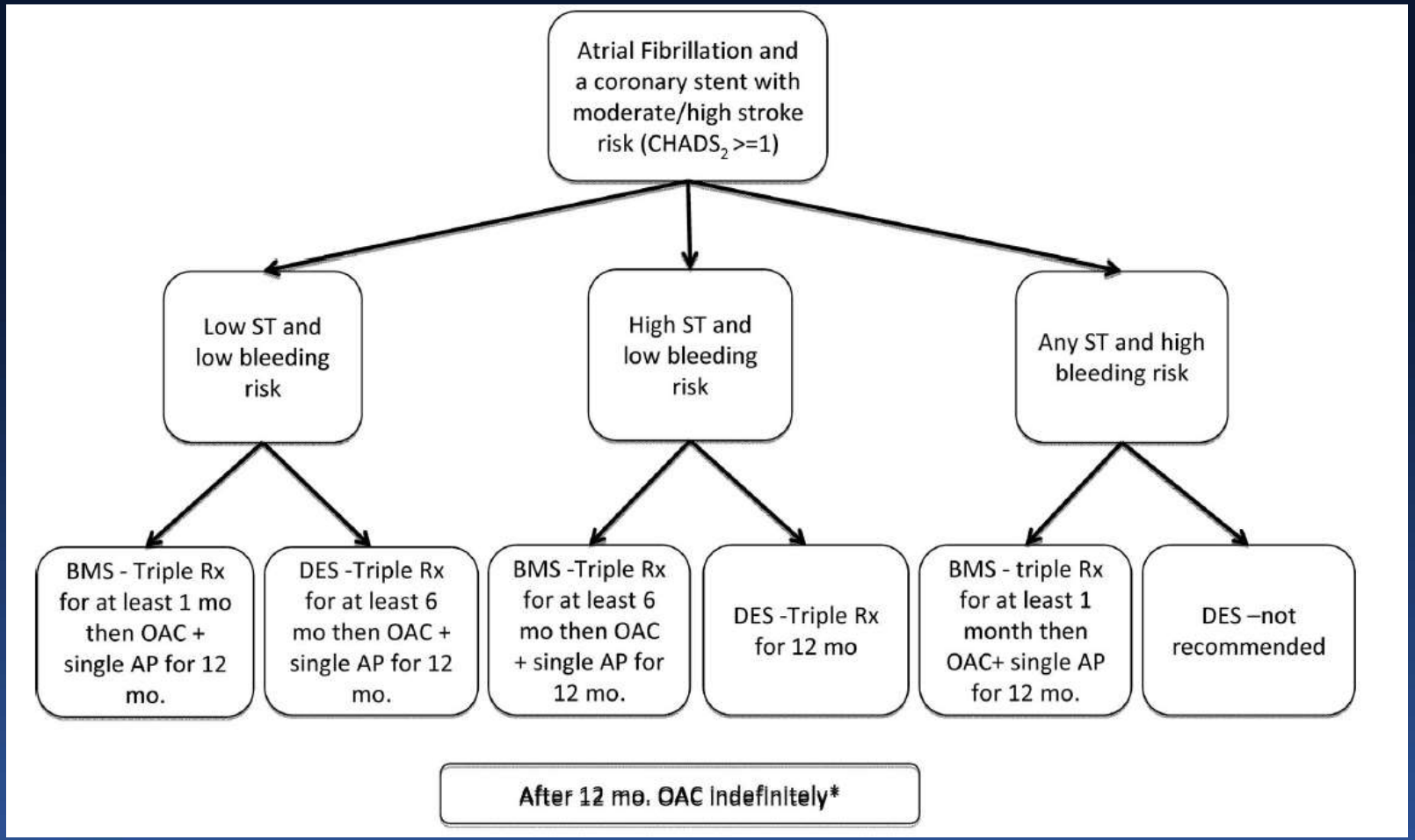


Hansen et al, *Arch Intern Med*, 2010;170:1433-1441

North American Consensus Statement Regarding Antithrombotic Therapy in Atrial Fibrillation Requiring a Stent

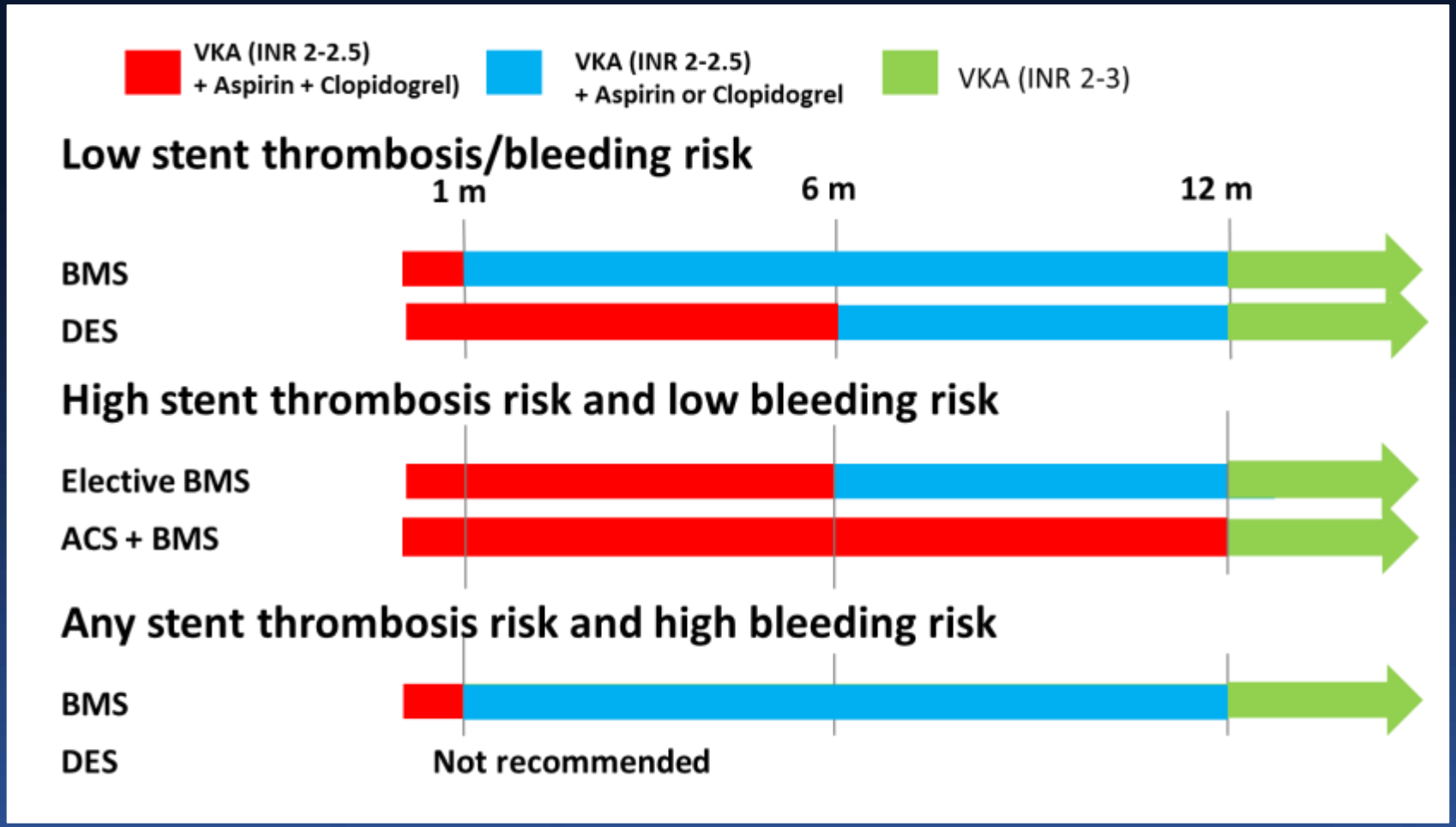
- Low dose aspirin (<100 mg per day)
- Clopidogrel is preferred in combination with aspirin and warfarin
- **Prasugrel and ticagrelor cannot be recommended**
- Warfarin dose adjusted INR between 2 and 2.5
- Not unreasonable to use dabigatran in place of warfarin based on the PETRO trial (dabigatran 50, 150, 300 mg BID with or without aspirin vs warfarin)

North American Consensus Statement Regarding Antithrombotic Therapy in Atrial Fibrillation Requiring a Stent



Adapted from Faxon D, *Thrombosis & Hemostasis* 2011;106(3):522-34

North American Consensus Statement Regarding Antithrombotic Therapy in Atrial Fibrillation Requiring a Stent



Adapted from Faxon D, *Thrombosis & Hemostasis* 2011;106(3):522-34

Dual vs. Triple Antiplatelet Therapy Prospective Studies

- **ISAR–Triple Trial: 6 months vs 6 weeks of clopidogrel after DES in patients on aspirin and warfarin**
- **WOEST (What is the Optimal antiplatElet and anticoagulant in patients with oral anticoagulants and StenTing study): warfarin + clopidogrel 75 mg/day vs warfarin + clopidogrel + aspirin (80 mg/day)**

The WOEST Trial: First Randomized 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= What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing (clinicaltrials.gov NCT00769938)

WOEST Study Design

Inclusion criteria
- Indication for OAC for ≥1 year
- PCI of a single coronary lesion

1:1 Randomization:

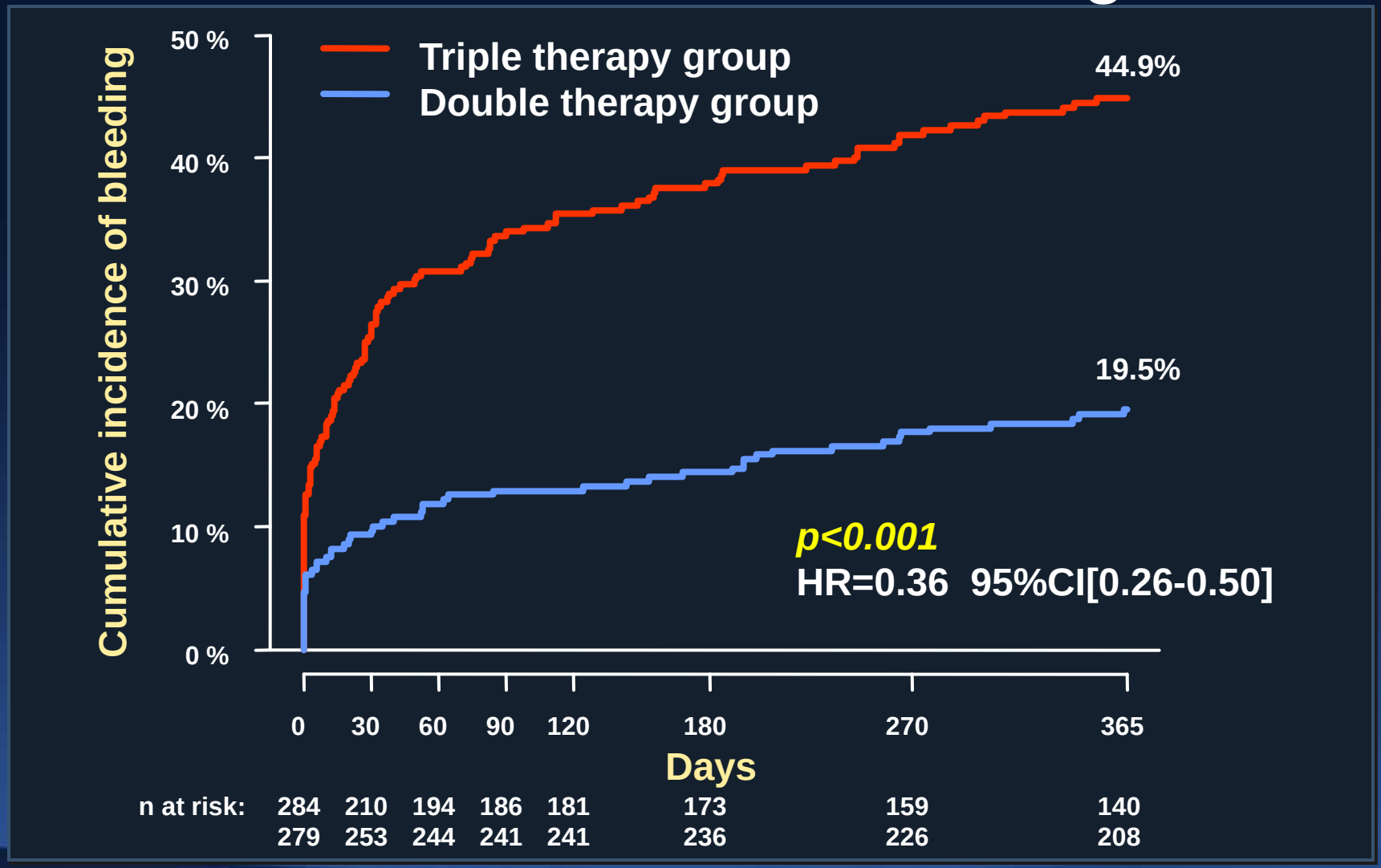
Double therapy group:	Triple therapy group
OAC + 75mg Clopidogrel qd	OAC + 75mg Clopidogrel qd + 80mg Aspirin qd
1 month minimum after BMS	1 month minimum after BMS
1 year after DES	1 year after DES

Follow up: 1 year

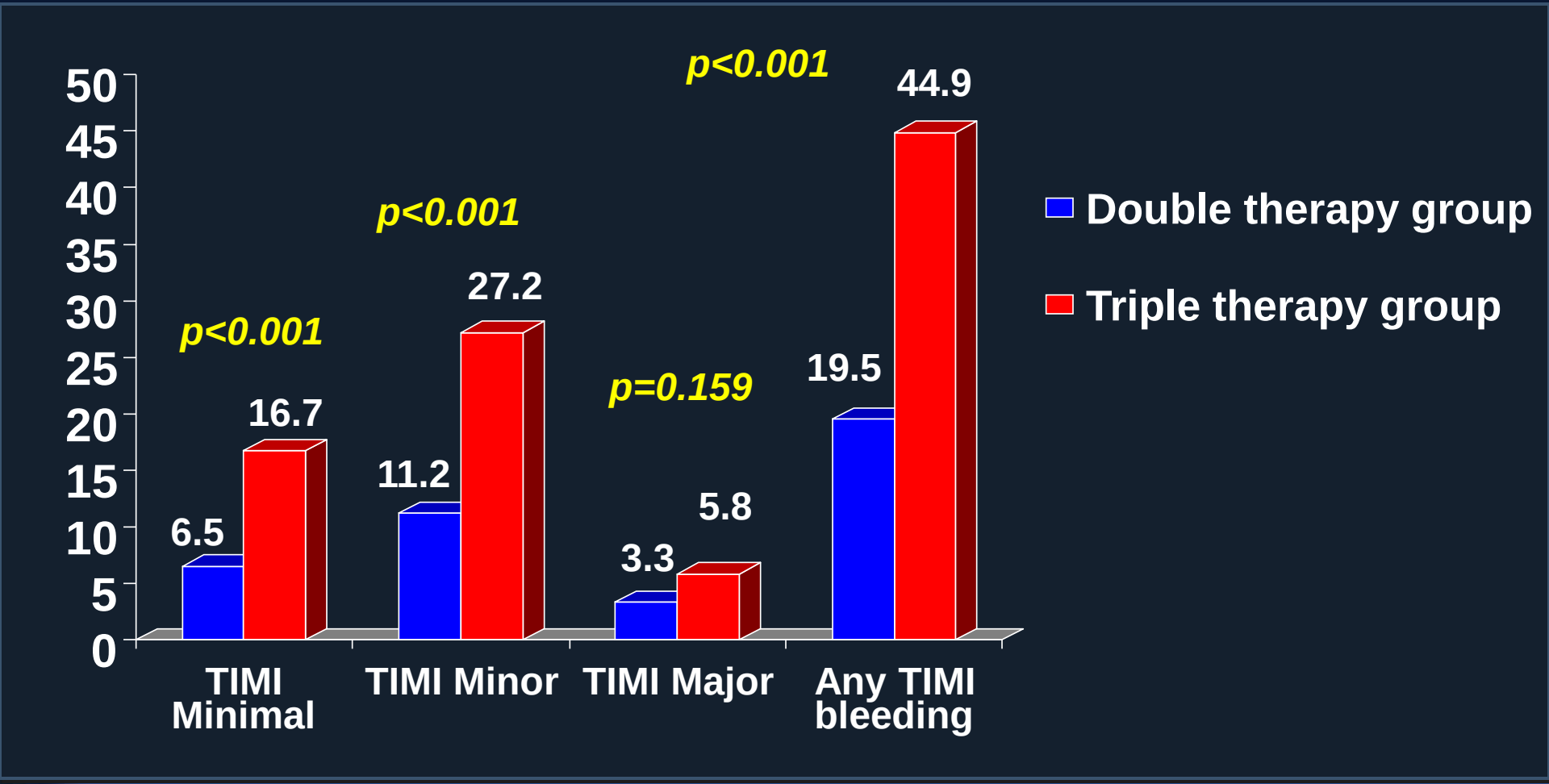
Primary Endpoint: The occurence of all bleeding events (TIMI criteria) (powered for a reduction from 12% to 5%)

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

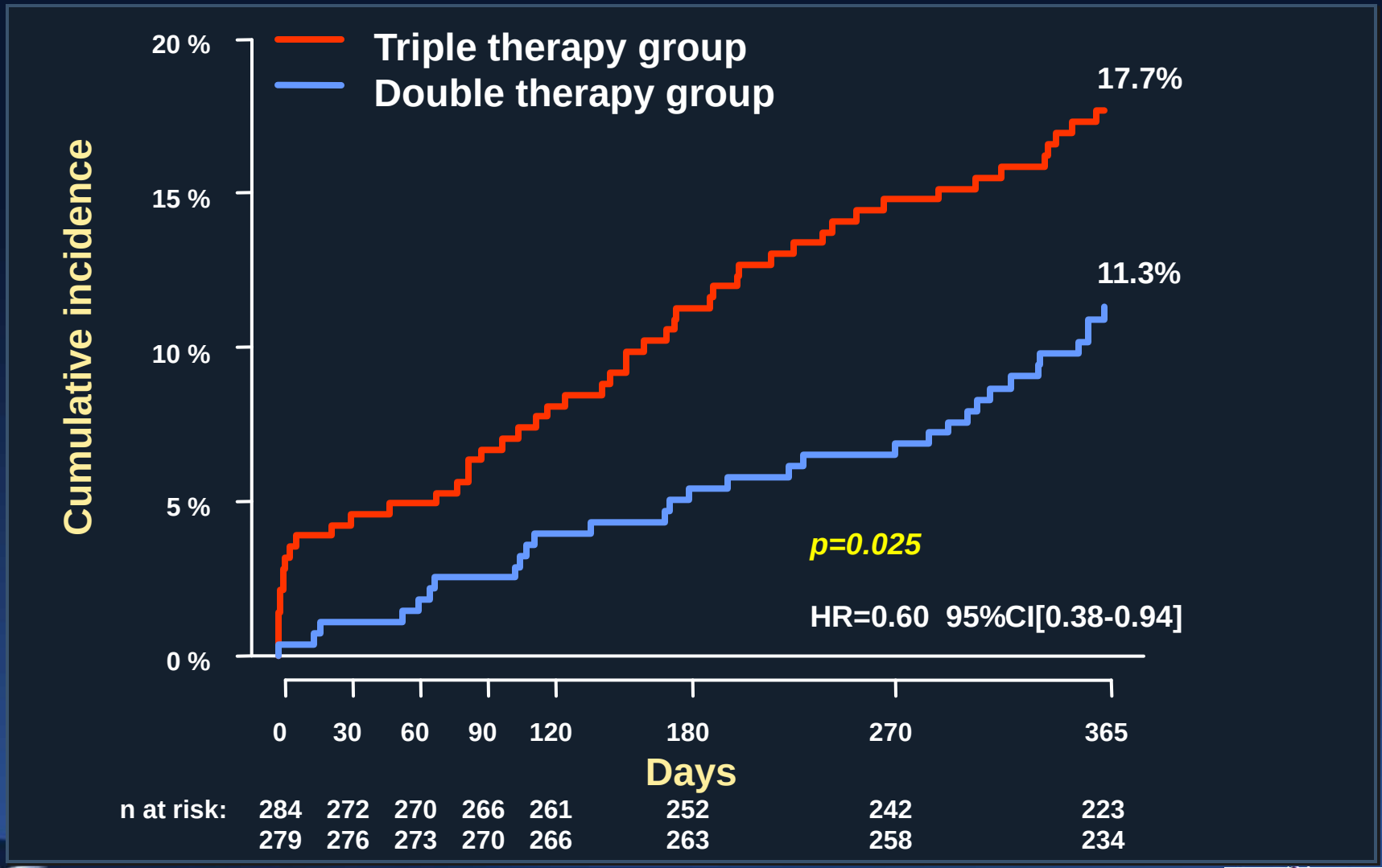
WOEST Primary Endpoint: TIMI Major or Minor or Minimal Bleeding



WOEST Primary Endpoint: Bleeding Events TIMI Classification



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



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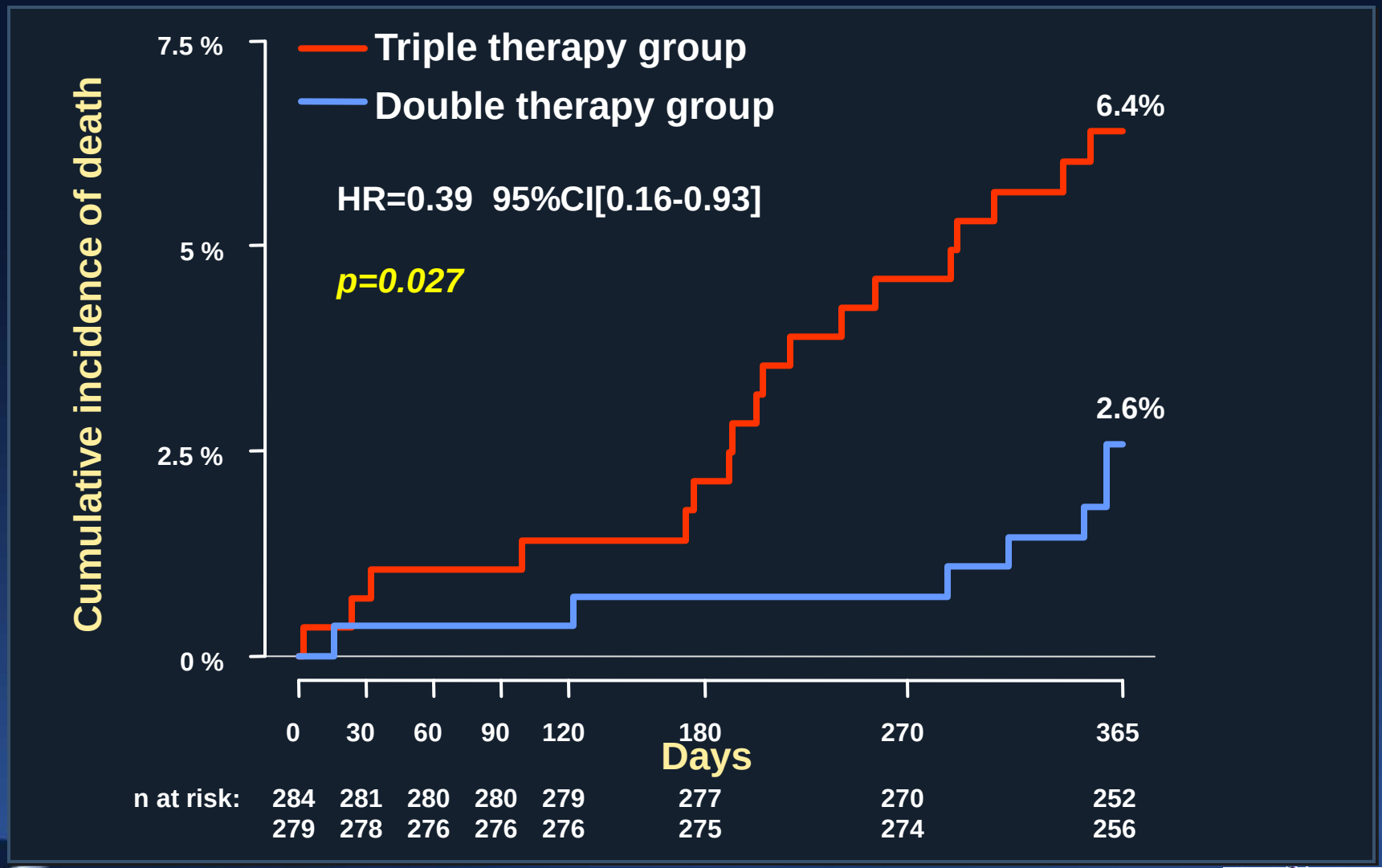
WOEST All-Cause Mortality



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

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ISAR-TRIPLE: Study Organization

TEST HYPOTHESES:

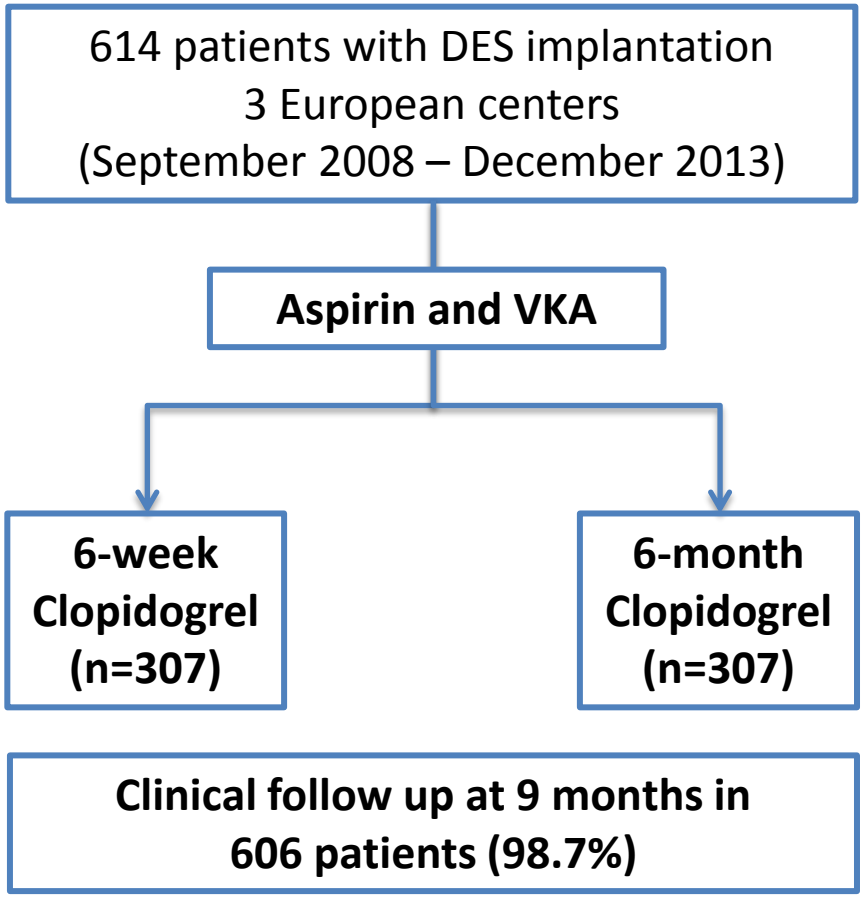
6-week superior to 6-month therapy; Primary Endpoint 10%, Risk reduction 60% with 6-week therapy; Power = 80%, alpha = 0.05; 283 patients per group

PRIMARY ENDPOINT:

- Death, myocardial infarction, definite stent thrombosis, stroke or TIMI major bleeding at 9 months

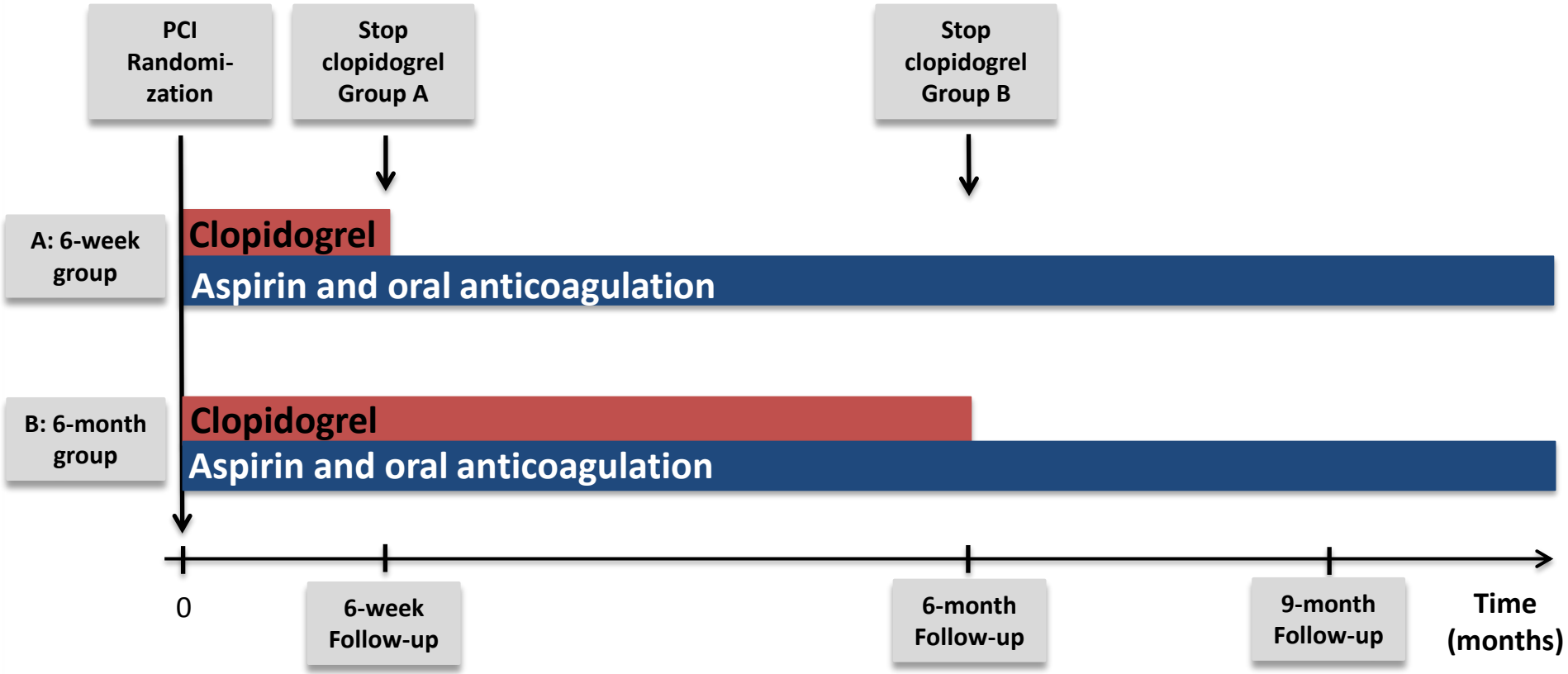
SECONDARY ENDPOINTS:

- Ischemic complications: Cardiac death, myocardial infarction, definite stent thrombosis or ischemic stroke
- Bleeding complications (TIMI major)



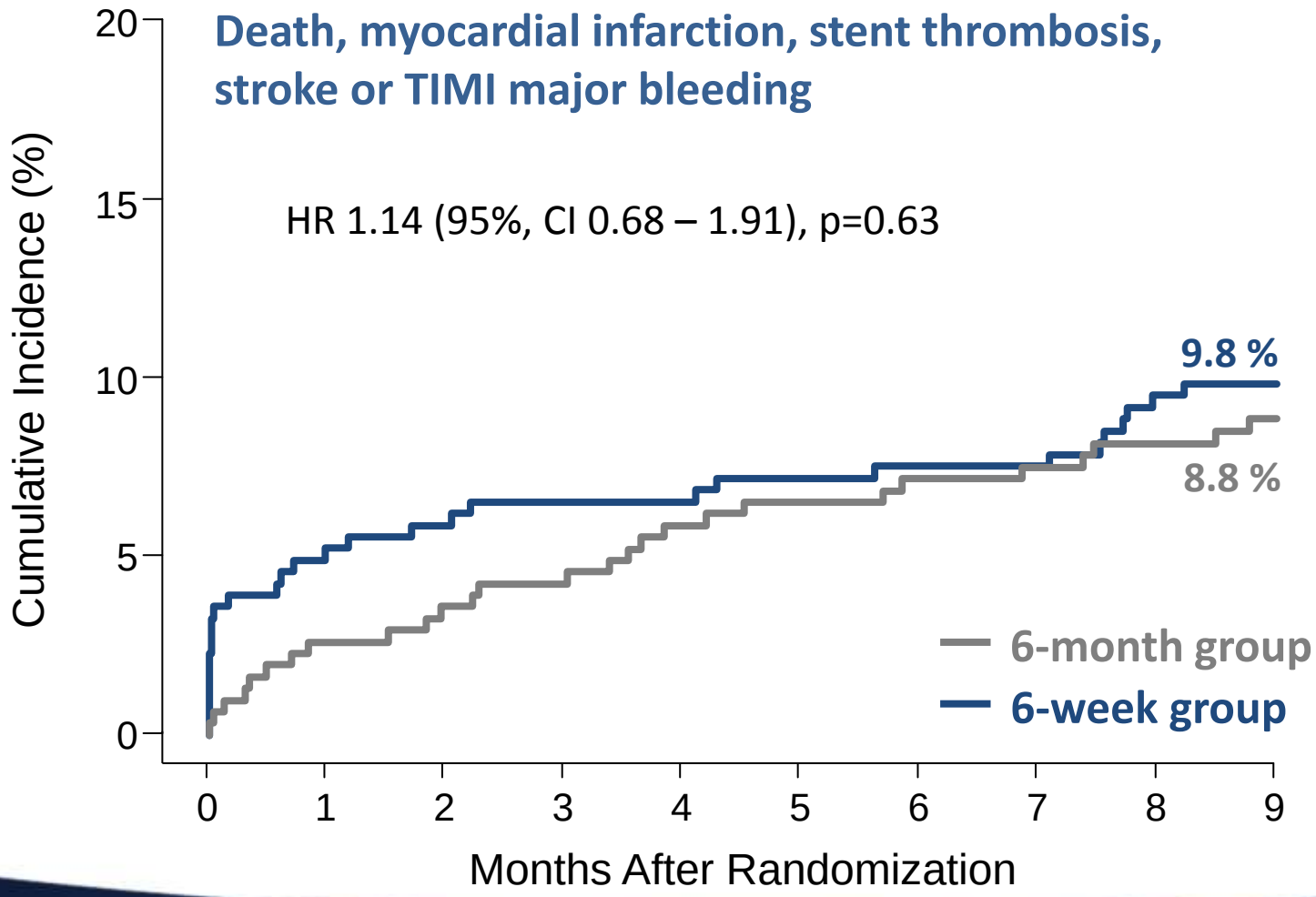
VKA: Vitamin K Antagonist

Randomization



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

Primary Endpoint



Ischemic Outcomes

	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:

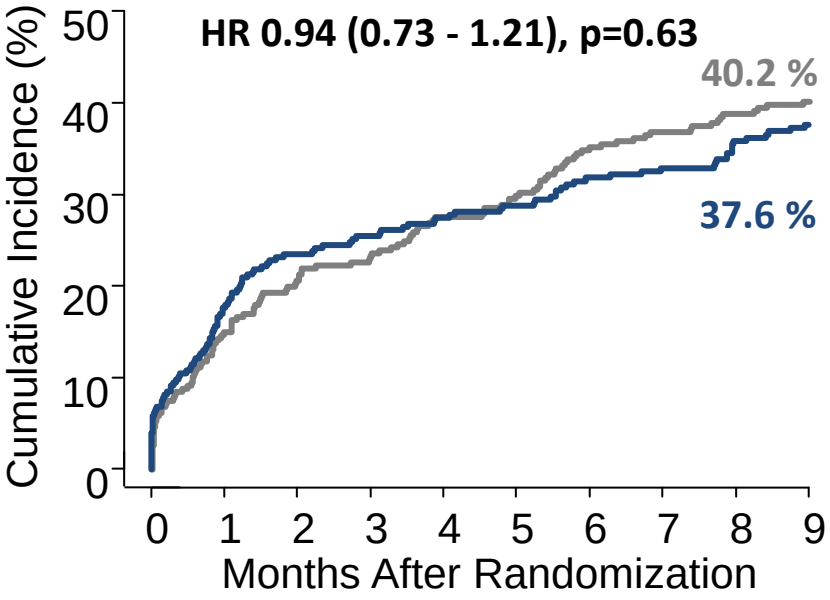
4 within 24h of PCI } Both groups on triple therapy

1 at 2.5 weeks

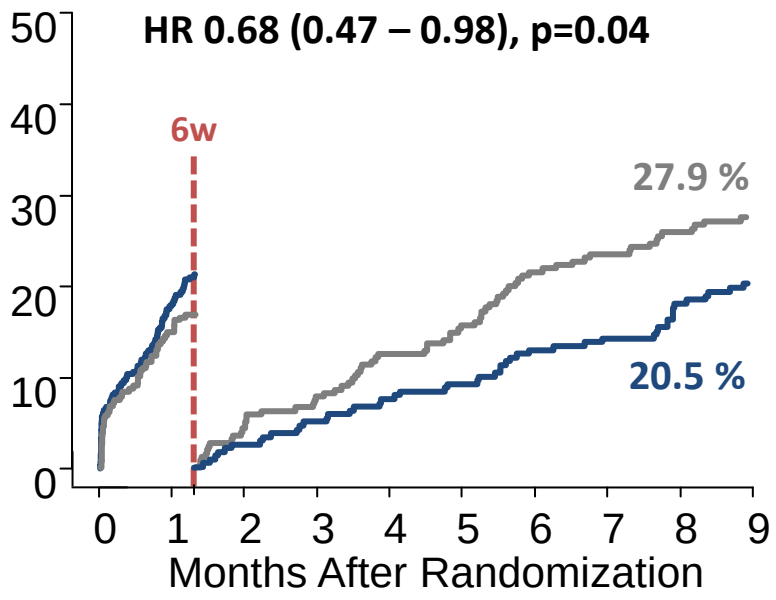
1 at 7 months } Both groups on aspirin and OAC

Any BARC Bleeding (type 1-5)

Any BARC Bleeding



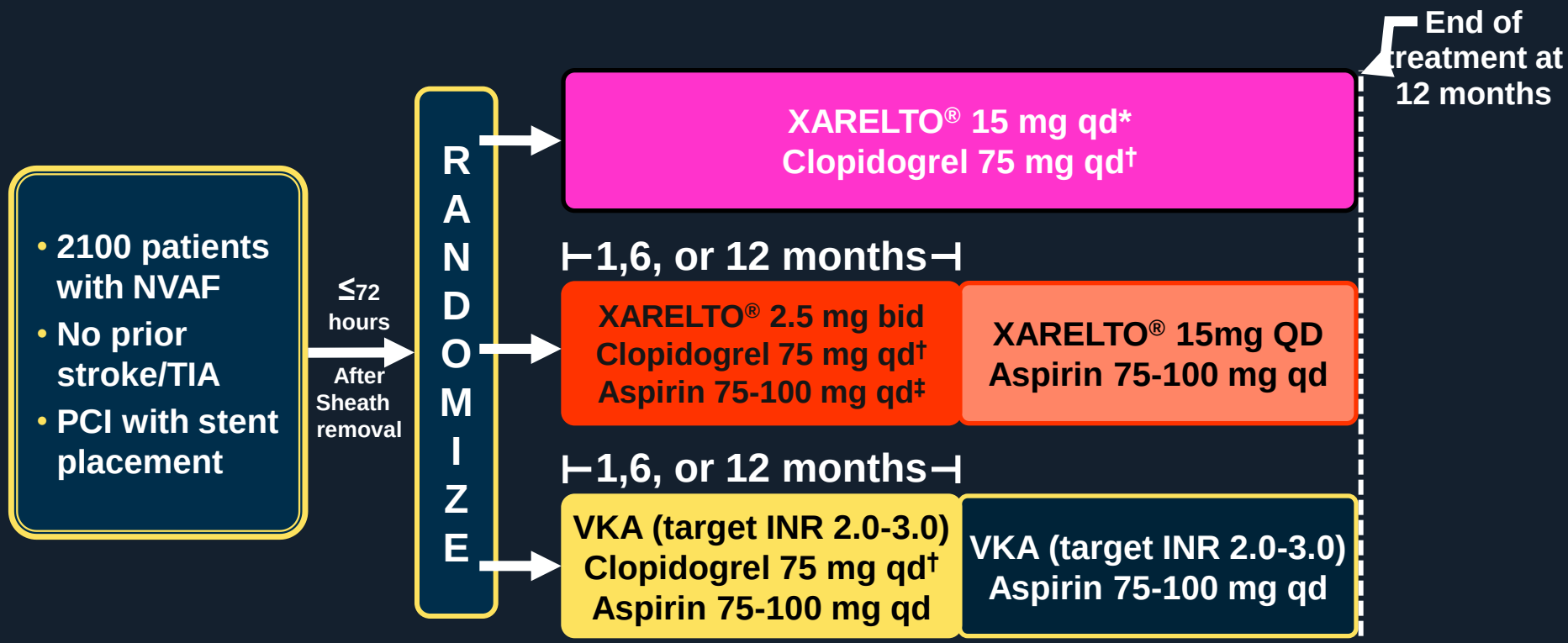
Post-hoc landmark analysis of any BARC Bleeding before and after 6 weeks (6w)



6-month group

6-week group

XARELTO® (rivaroxaban) Use in Patients With AF Undergoing PCI: PIONEER AF-PCI



- Primary endpoint: TIMI major, minor, and bleeding requiring medical attention
- Secondary endpoint: CV death, MI, stroke, and stent thrombosis

*XARELTO® 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).
Data on File. Janssen Pharmaceuticals, Inc.

RE-DUAL PCI™

Study in NVAF patients undergoing PCI

STUDY TITLE

A prospective **R**andomised, open label, blinded endpoint (PROBE) study to **E**valuate **DUAL** antithrombotic therapy with dabigatran etexilate (110mg b.i.d. and 150mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor with aspirin in patients with non valvular atrial fibrillation (NVAF) that have undergone a percutaneous coronary intervention (**PCI**) with stenting. (RE-DUAL PCI)

STUDY HYPOTHESES

D110 plus a P2Y12 inhibitor is:

Non-inferior with respect to the combined thrombotic event rate (TE: death + MI + stroke/SE)

AND

Non-inferior* with respect to clinically relevant bleeding relative to a triple combination of warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) plus ASA

D150 plus a P2Y12 inhibitor is:

Non-inferior with respect to the combined thrombotic event rate (TE: death + MI + stroke/SE)

AND

Non-inferior* with respect to clinically relevant bleeding relative to a triple combination of warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) plus ASA

Worldwide Event Driven Trial

Paroxysmal, persistent or permanent AF (PCI with stenting [BMS or DES] elective or ACS)

Screening

R

0-72 hours post-PCI

Dabigatran 150mg BID + P2Y12 inhibitor¥**

Dabigatran 110mg BID + P2Y12 inhibitor¥**

Warfarin (INR 2.0-3.0) + P2Y12 inhibitor¥ + ASA**

3M 6M 9M 12M 15M 18/24/30M or EOT

n = 2500

1° End Point

Time to first clinically relevant bleeding rate (ISTH Major)

* After establishing non-inferiority of the D110 and D150 DAT regimens, testing for superiority will be conducted

* ASA is discontinued immediately after a successful procedure in patients randomized to receive dabigatran

* ASA will be discontinued in the warfarin arm. BMS: Discontinuation of ASA at month 1 ; DES: discontinuation of ASA at month 3

¥ P2Y12 inhibitor (either Clopidogrel or Ticagrelor). The P2Y12 inhibitor can be discontinued after month 12 of follow up at the discretion of the physician

Boehringer Ingelheim

HCRI Harvard Clinical Research Institute

AFIB608904PROF

Apixaban Versus Warfarin in Patients with AF and ACS or PCI: The AUGUSTUS Trial

Inclusion
- AF (prior, persistent, or >6 hrs duration)
- Physician decision that oral anticoag is indicated
- ACS or PCI with planned P2Y12 inhibitor for 6 months

Randomize
n =4,600
Patients

Exclusion
- Contraindication to DAPT
- Other reason for warfarin (prosthetic valve, mod/sev MS)

Apixaban | **Warfarin**

P2Y12 inhibitor for all patients x 6 months
Aspirin for all on the day of ACS or PCI
Aspirin versus placebo after randomization

ASA | **placebo** | **ASA** | **placebo**

Primary outcome: major/clinically relevant bleeding (through 6 months)

Secondary objective: Death, MI, stroke, stent thrombosis

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Triple Therapy

Summary and Synthesis of Guideline, Expert Consensus Documents, and Comprehensive Review Article Recommendations on the Management of Patients Treated With Triple Therapy

- Assess ischemic and bleeding risks using validated risk predictors (e.g., CHA2DS2-VASc, HAS-BLED)
- Keep triple therapy duration as short as possible; dual therapy only (oral anticoagulant and clopidogrel) may be considered in select patients
- Consider target INR 2.0–2.5 when warfarin is used
- Clopidogrel is the $P2Y_{12}$ inhibitor of choice
- Use low dose (≤100 mg daily) aspirin
- PPI Rx should be used in patients with a history of GI bleeding and are reasonable to use in patients with increased risk of GI bleeding

Levine GN, et al. 2016 ACC/AHA Guideline Focused Update on Duration of DAPT in Patients with CAD. JACC 2016 & Circulation 2016