Acute coronary syndromes: treatment considerations in 2014

Anticoagulation and PCI: a triple threat?

Leonardo Bolognese
Cardiovascular Department, Arezzo, Italy

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Anticoagulation therapy as the optimal strategy to prevent fibrin-centric thrombotic events

- Patients with mechanical heart valves
- Pulmonary embolism/deep vein thrombosis
- Atrial fibrillation

Atrial Fibrillation, Coronary Artey Disease and PCI

- ≈70% to 80% of all patients with AF have an indication for OAC, and coronary artery disease coexists in 20% to 30% of them [1,2]
- With an estimated prevalence of AF in 1% to 2% of the population[3], it may be projected that ≈1 to 2 million patients on OAC in both the United States and Europe are candidates for coronary revascularization, often in the form of percutaneous coronary interventions

1. Nieuwlaat R et al. Eur Heart J. 2005;26:2422–2434
2. Nabauer M et al. Europace 2009;11:423–434
3. Go Aset al. JAMA. 2001;285:2370–2375

Relevant Clinical Scenarios

- Patients with paroxysmal, persistent, long-standing, or permanent AF on OAC who experience an ACS, or undergo elective PCI

- New-onset AF occuring within 7 days during or after hospitalization of patients after an ACS or PCI (≈6% to 8%)

The Optimal Management of Atrial Fibrillation and ACS and/or PCI Differ

Atrial Fibrillation (ACTIVE W)[1]: The combination of aspirin and clopidogrel is not as effective as *warfarin* in patients with AF [1]

However

Stenting (STARS)[2]: The combination of *aspirin and clopidogrel* is more effective than warfarin in patients with coronary stents [2]

1. Lancet 2006; 367:1903-12
2. N Engl J Med 1998; 339:1665-71

Finding the Best Cocktail of an Anticoagulant With Antiplatelets

- VKAs Plus Antiplatelet Therapy With Aspirin and/or P2Y12 Receptor Inhibitors
- NOACs Plus Single or Dual Antiplatelet Therapy
- OACs Plus new P2Y12 Receptor Inhibitors

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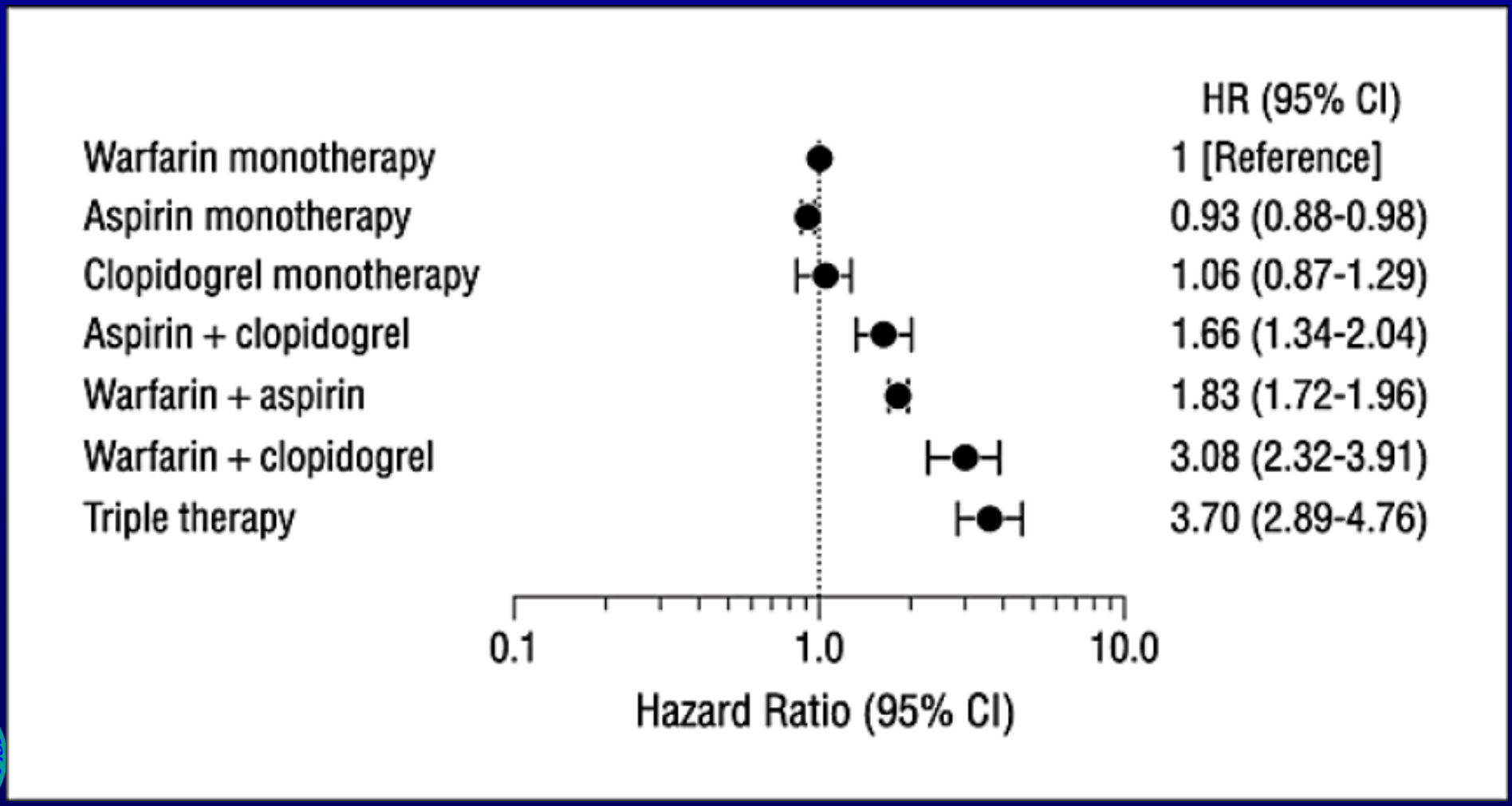
Bleeding associated with warfarin, aspirin, clopidogrel in patients with AF

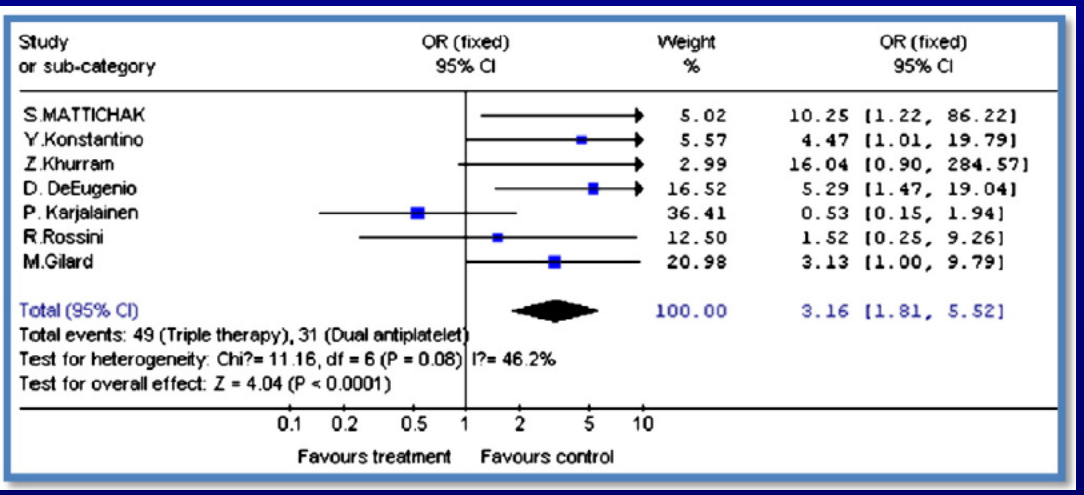
n=82,854

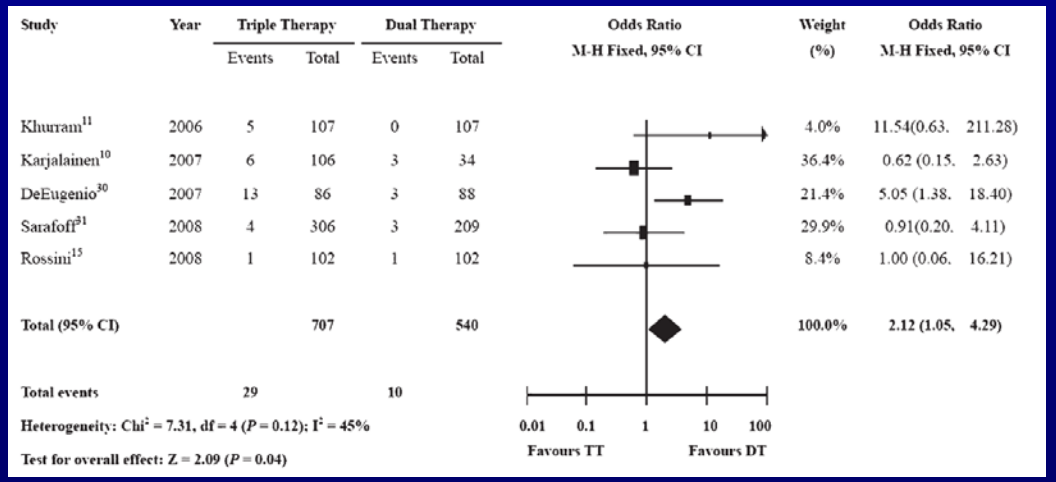


Hansen et al. Arch Intern Med 2010;170:1433-1441

Meta-analysis of the combination of warfarin and dual antiplatelet therapy after coronary stenting in pts with indications for chronic oral anticoagulation

Risk of major bleeding with TT vs DAPT





Gao F et al. Int J Cardiol. 2011;148:96–101

Zhao HJ et al .Chest. 2011;139:260–270

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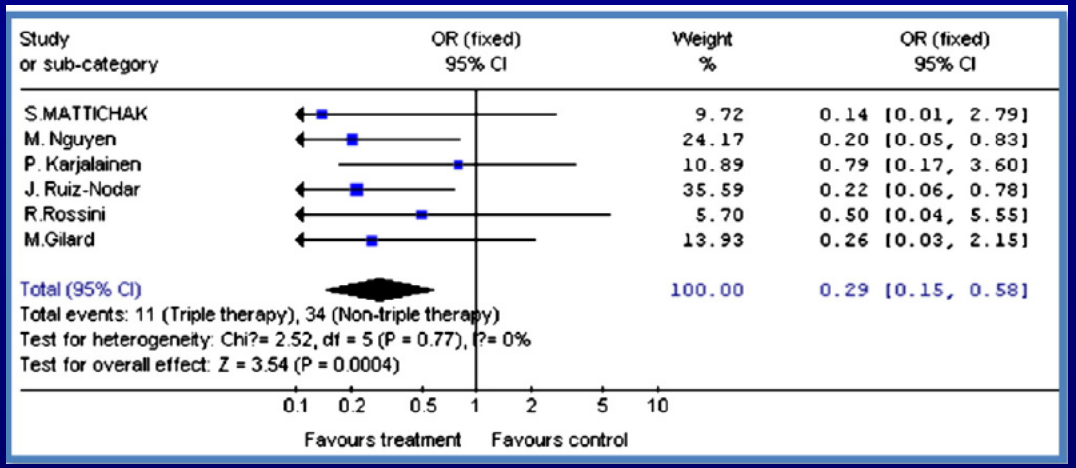
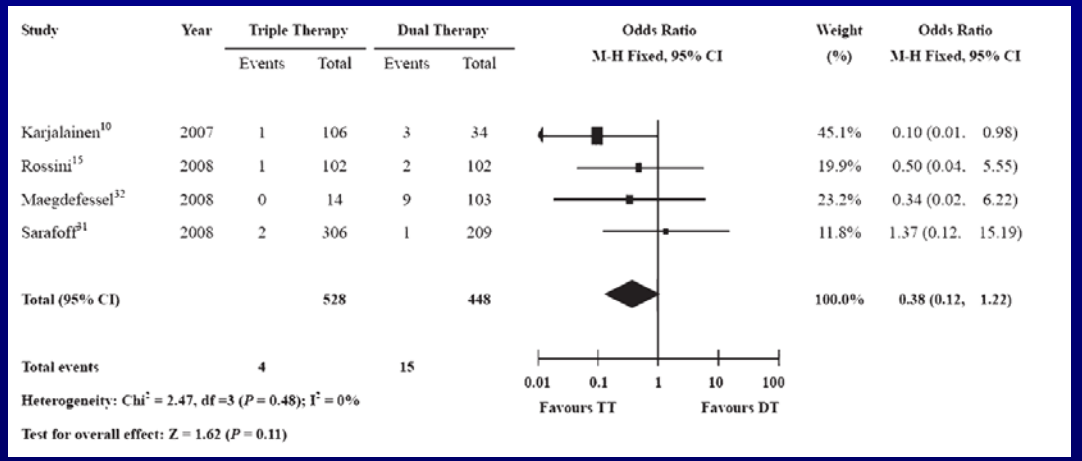
Meta-analyses of the combination of warfarin and dual antiplatelet therapy after coronary stenting in pts with indications for chronic oral anticoagulation

Risk of ischemic stroke in patients receiving TT or DT





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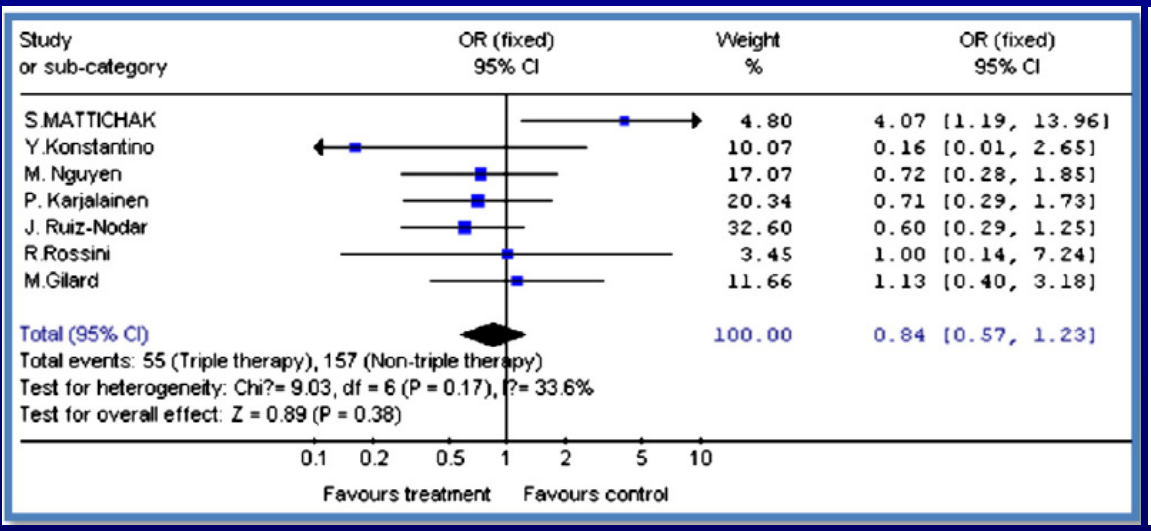
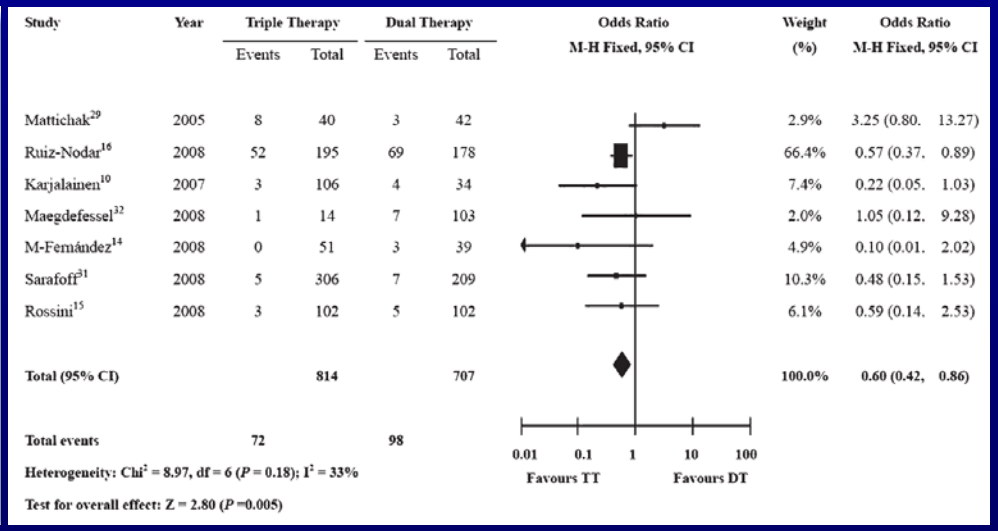
Meta-analysis of the combination of warfarin and dual antiplatelet therapy after coronary stenting in pts with indications for chronic oral anticoagulation

Risk of MI with TT vs DAPT



Gao F et al. Int J Cardiol. 2011;148:96–101

Risk of MACE with TT vs DAPT



Zhao HJ et al. Chest. 2011;139:260–270

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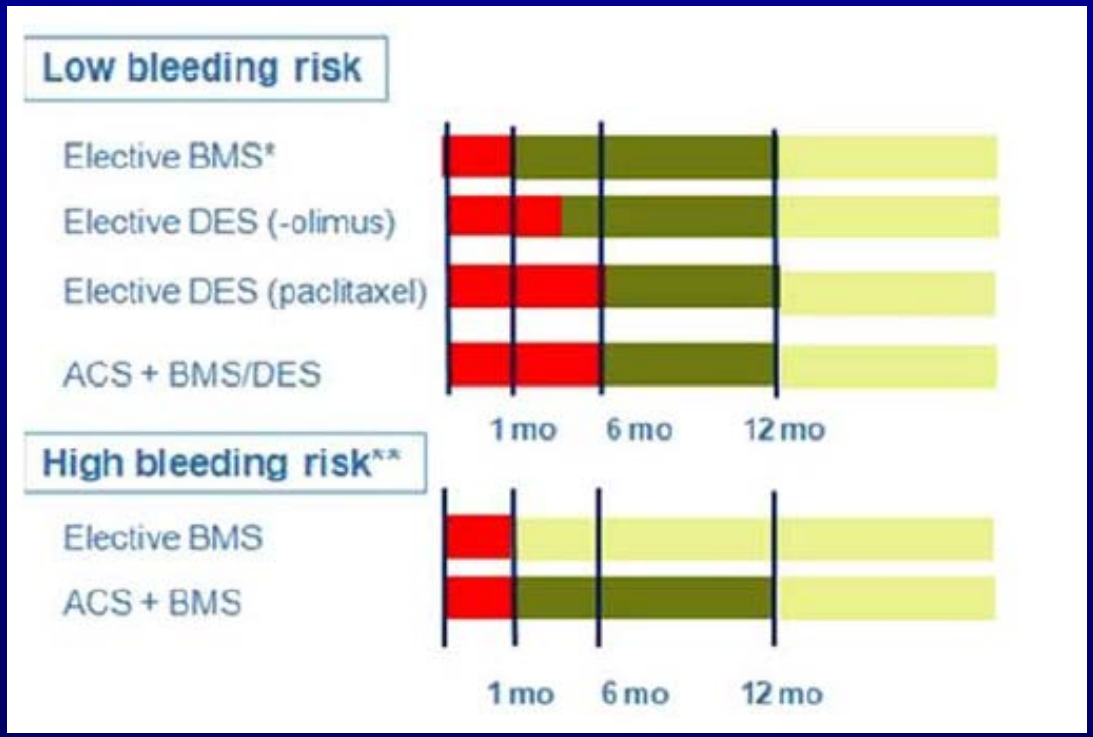
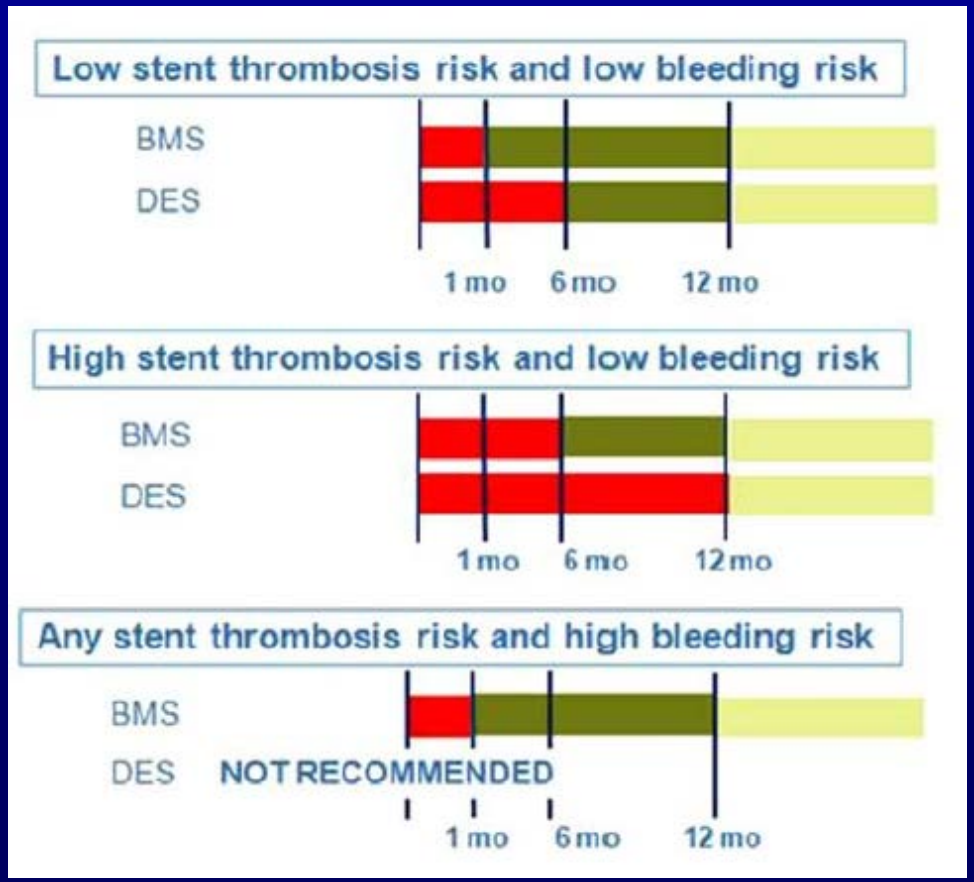
Recommendations for Combined Anticoagulant and Antiplatelet Therapy After PCI in Atrial Fibrillation

Lip GYH et al. Eur Heart J. 2010;31:1311–1318.
Faxon DP et al.Circ Cardiovasc Interv. 2011;4:522–534.

European



American



VKA + ASA + Clopidogrel
VKA + Clopidogrel (or ASA)
VKA

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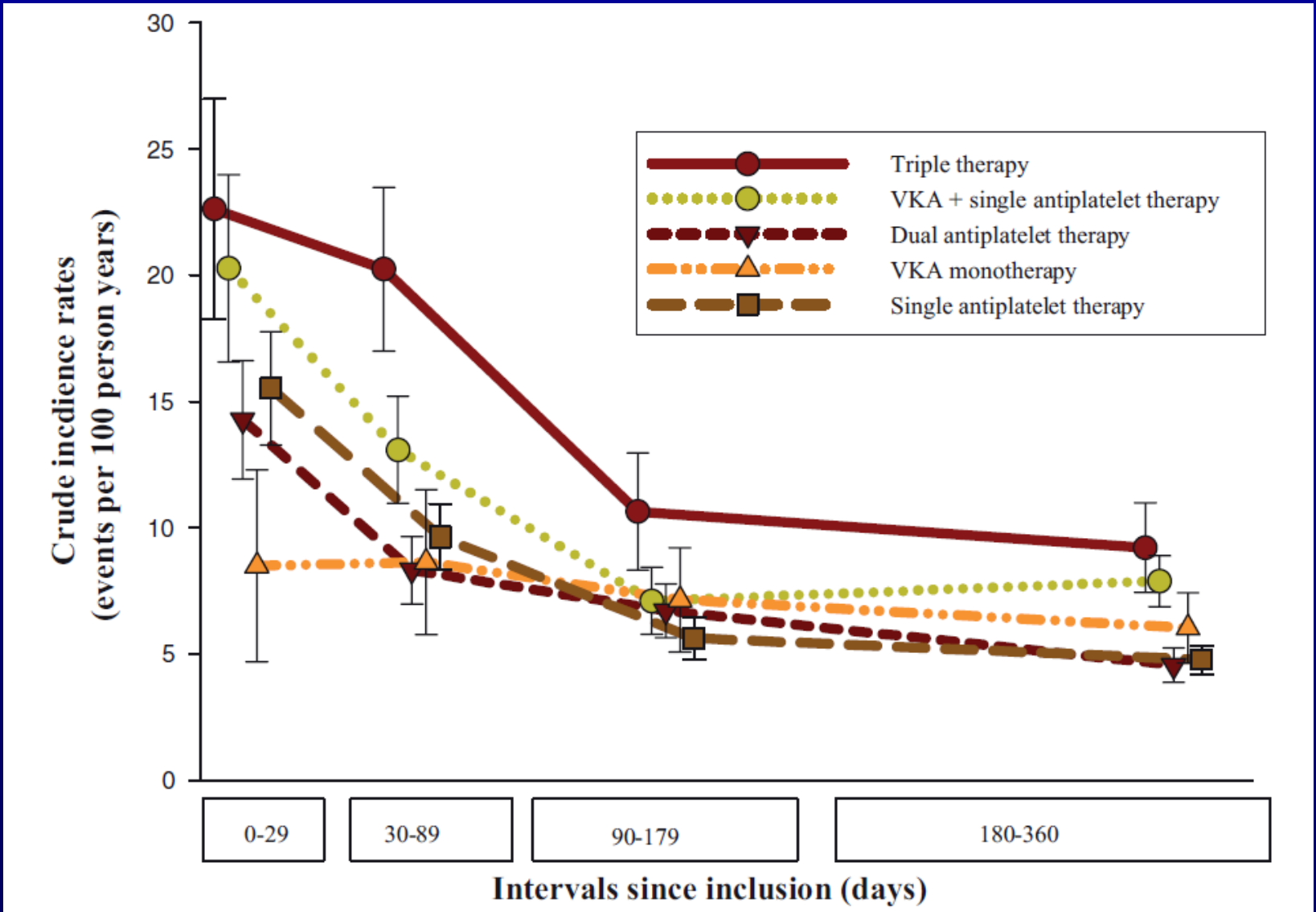
Synthesis of Recommendations

- Triple therapy should be used depending on the balance of ischemic and bleeding risk, favoring a combination of:
  - low-dose aspirin (plus proton pump inhibitor),
  - clopidogrel as the P2Y12 inhibitor of choice, and
  - OAC with warfarin, targeting an INR between 2.0 and 2.5.
- Avoidance of the use of drug-eluting stents in patients with high bleeding risk
- In Europe, a short course of DAPT (1 month) in elective stenting with a BMS is advised for pts on OAC, whereas American recommendations suggest 1 month of DAPT followed by single antiplatelet therapy (aspirin or clopidogrel) for 12 months

What is new since the 2011 consensus documents?

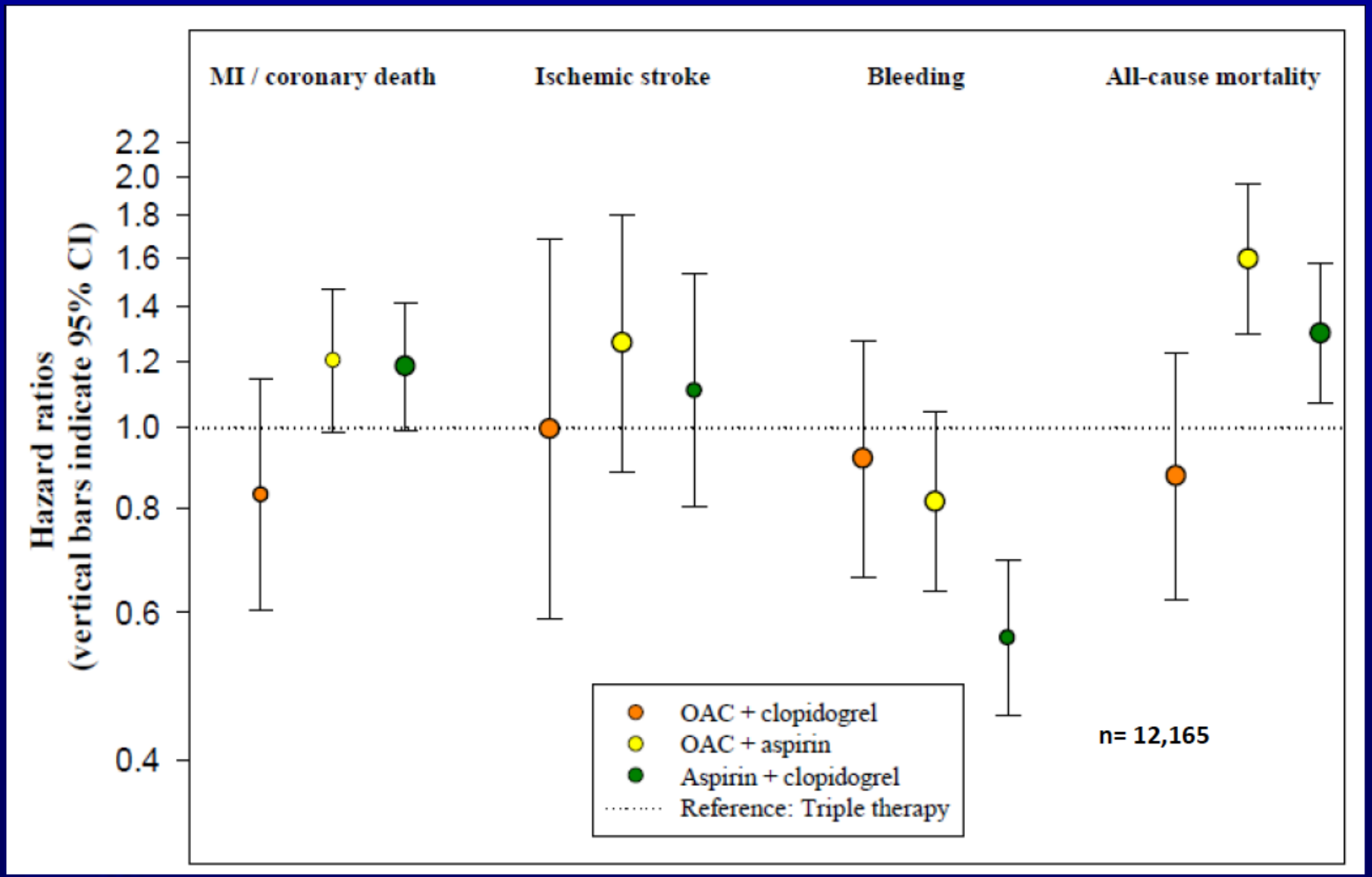
- **Additional observational published data challenging guidelines (*Danish nationwide registry*)**
- **NEW RCTs: WOEST Trial – ISAR TRIPLE Trial**
- **New generation Drug Eluting Stents: *less thrombogenic*.**
- **Introduction of non VKA oral anticoagulants (NOACs).**

Timing and Risk of Bleeding



Lamberts M Circulation 2012;126:1185-93

Dual vs Triple Therapy in AF after PCI for MI



Lamberts M J Am Coll Cardiol 2013; 62:981-989

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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 1 year after DES	1 month minimum after BMS 1 year after DES

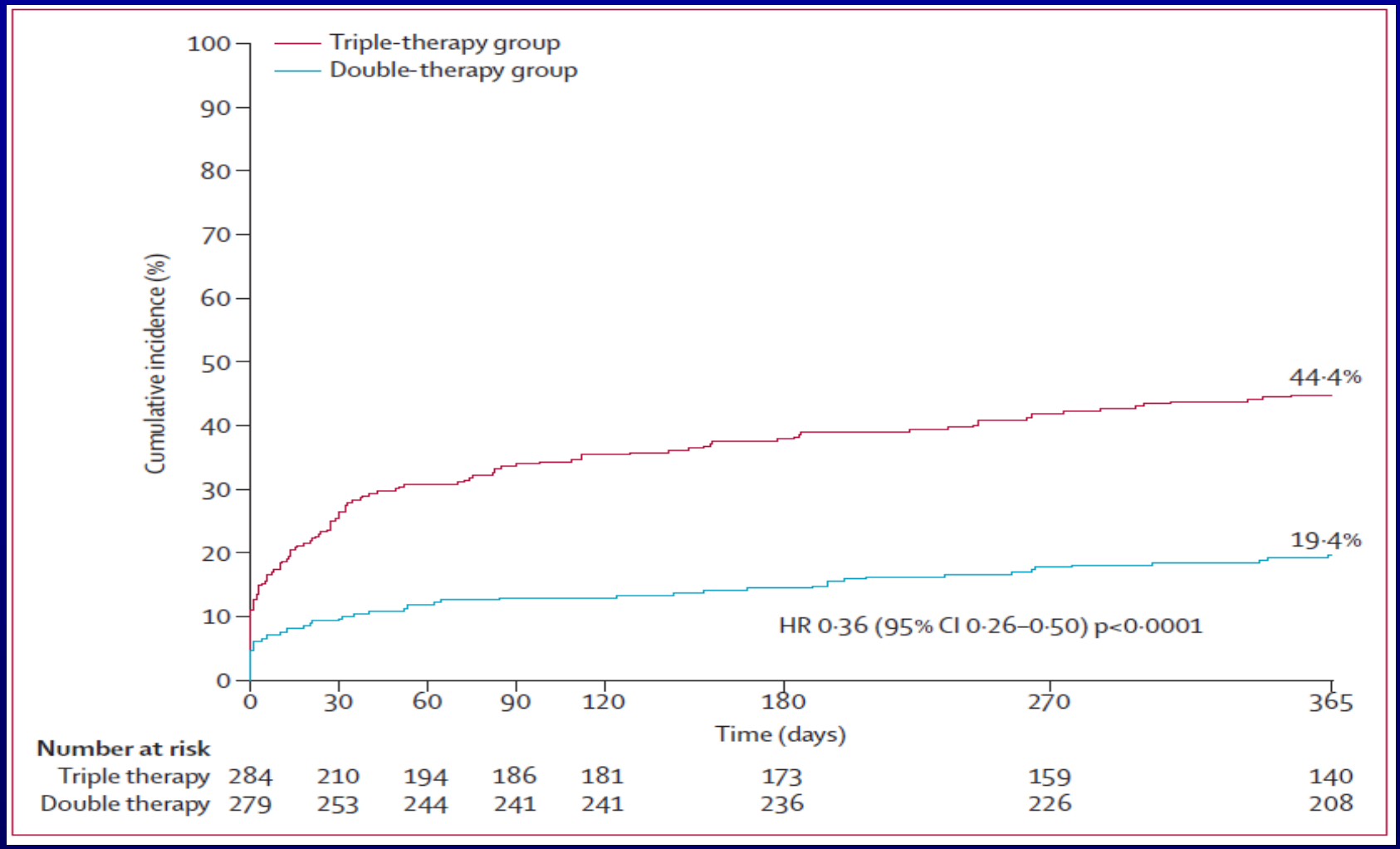
Follow up: 1 year

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

WOEST Primary Endpoint (Any bleeding)



Dewilde WJ et al. Lancet. 2013;381:1107–1115

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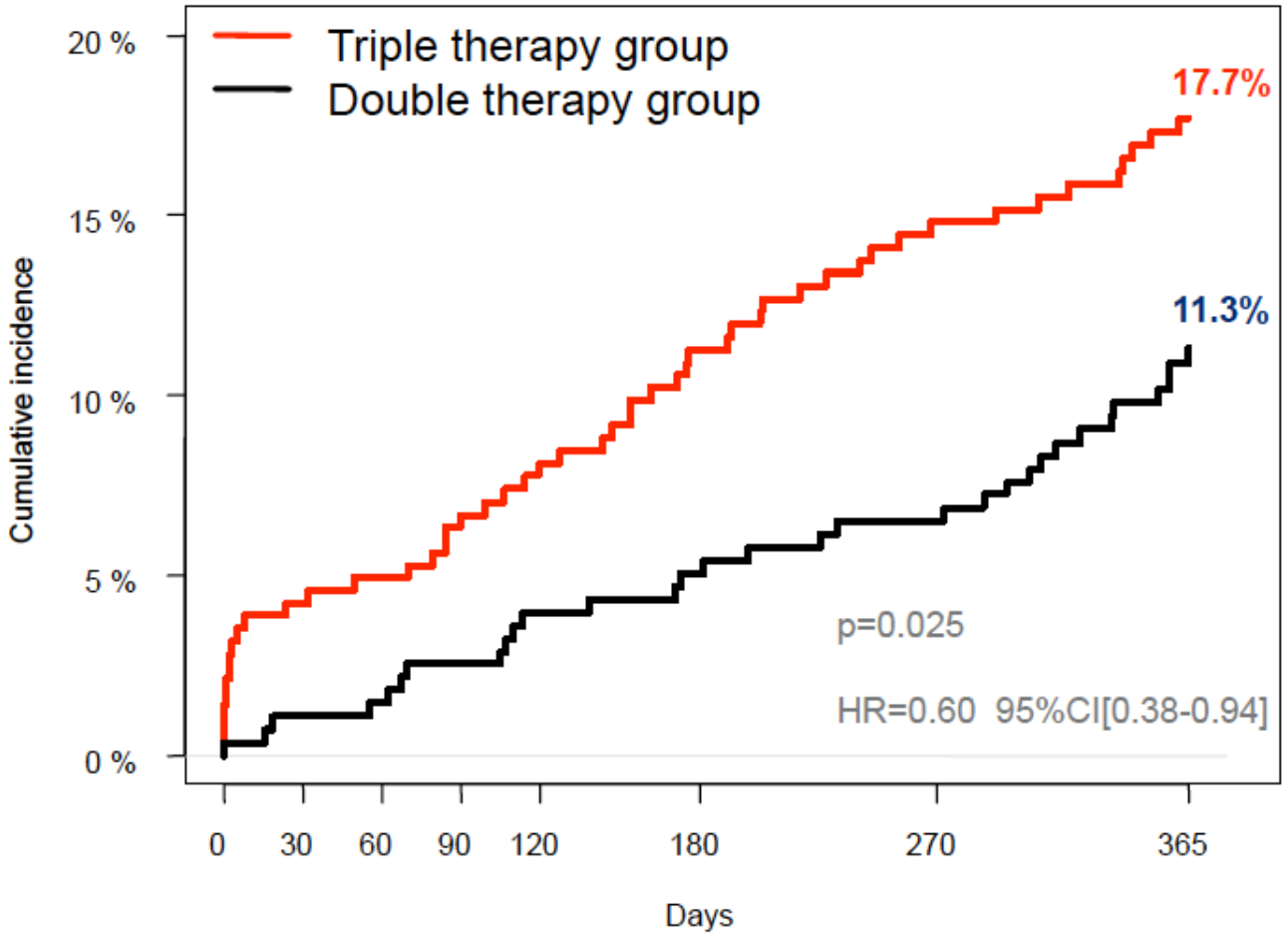
WOEST

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



Dewilde WJ et al. Lancet. 2013;381:1107–1115

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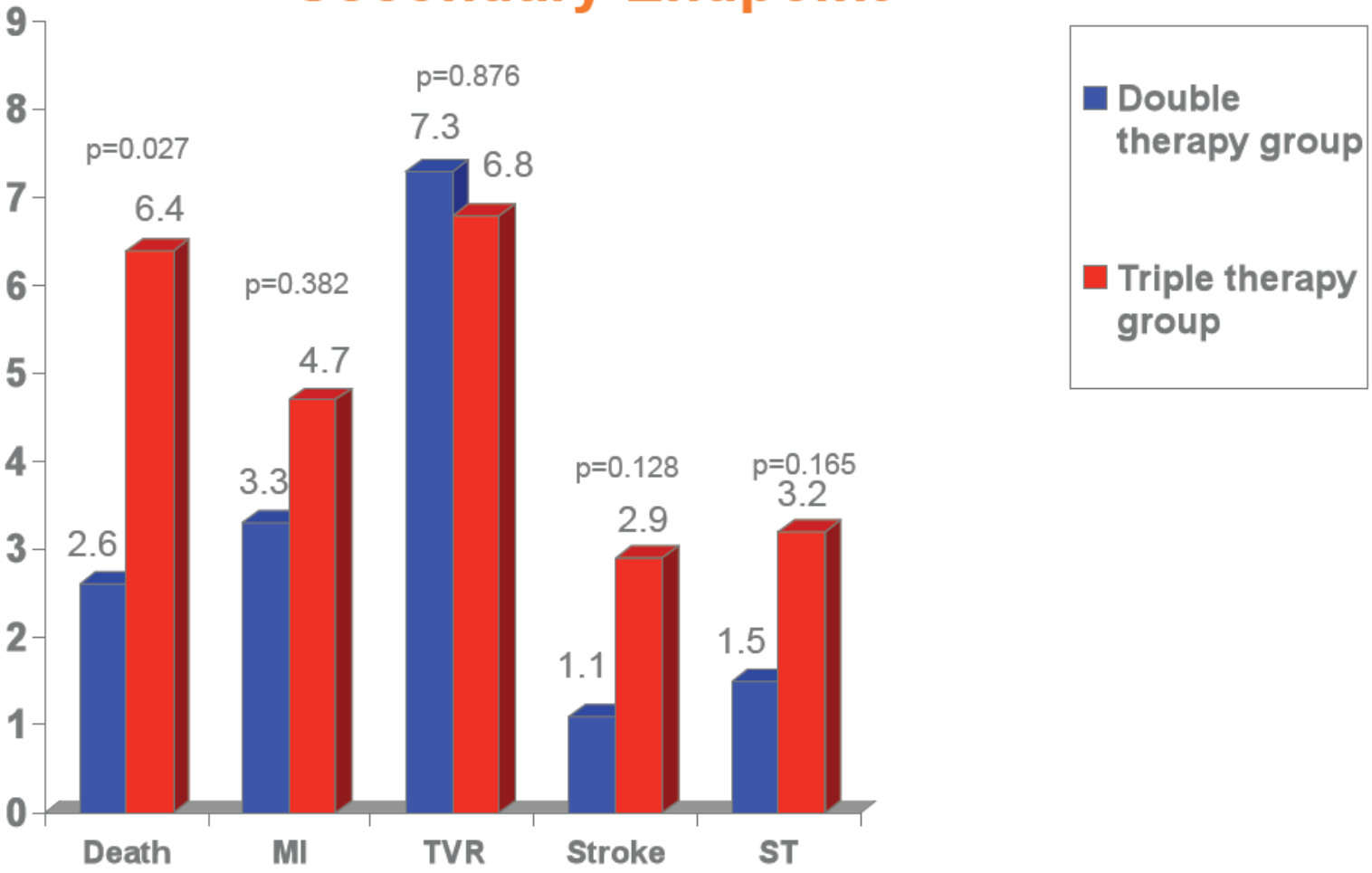
WOEST

Secondary Endpoint



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

ZIEKENHUIS ST ANTONIUS

Dewilde WJ et al. Lancet. 2013;381:1107–1115

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WOEST Limitations

- The study was powered to show superiority on the primary bleeding endpoint, but not to show non-inferiority on the secondary endpoint
- Open label trial design with its inherent bias
- The difference in bleeding rate is mainly driven by minor bleedings
- Kaplan-Meier curves for bleeding diverge up to 30 days and then parallel

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ISAR-TRIPLE: Study Organization

TEST HYPOTHESES:

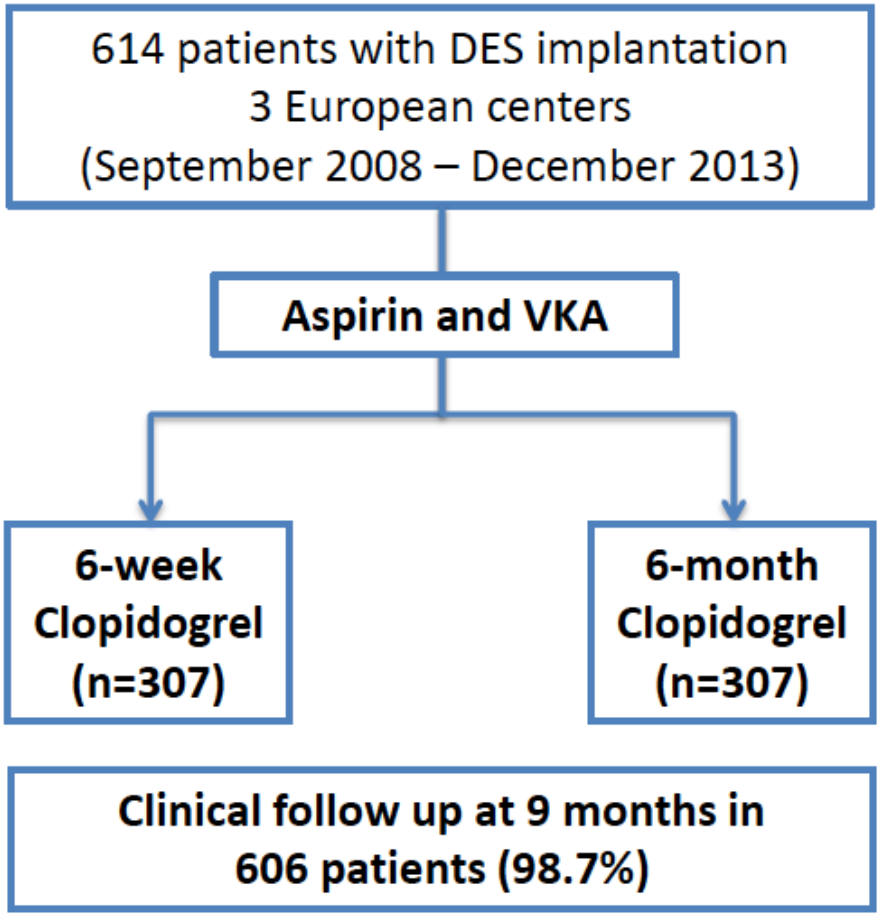
6-week superior to 6-month therapy; Primary Endpoint 10%, Risk reduction 60% with 6-week therapy; Power = 80%, alpha = 0.05; 283 patients per group

PRIMARY ENDPOINT:

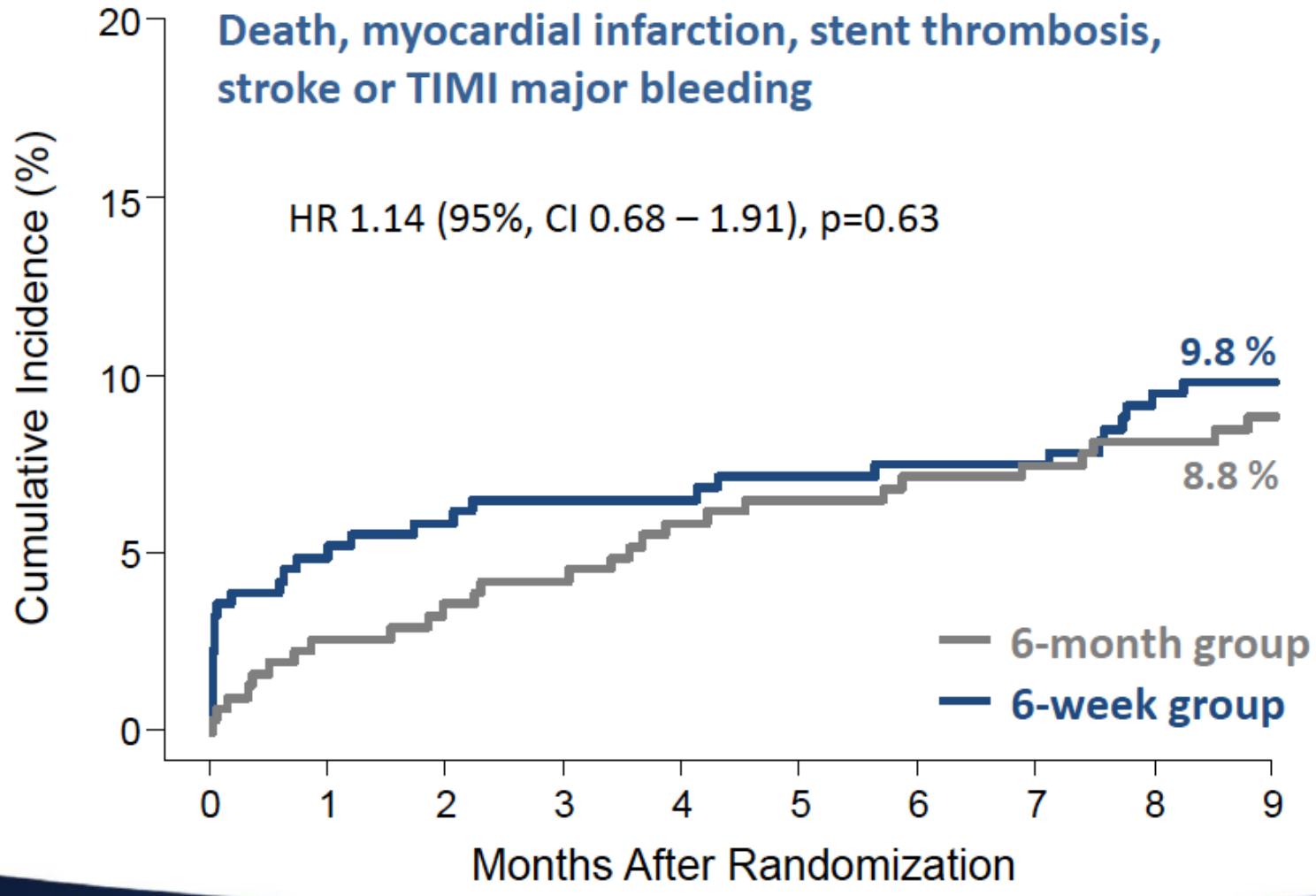
- Death, myocardial infarction, definite stent thrombosis, stroke or TIMI major bleeding at 9 months

SECONDARY ENDPOINTS:

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

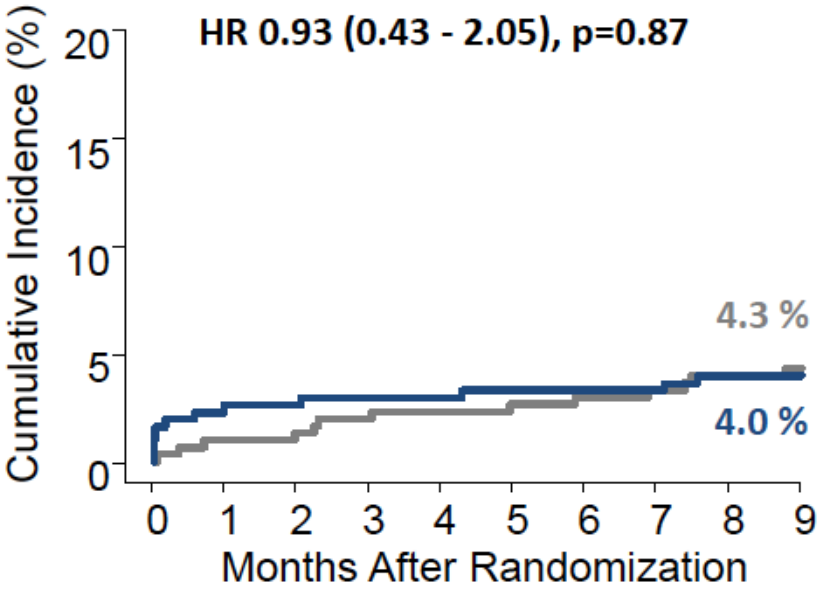


Primary Endpoint

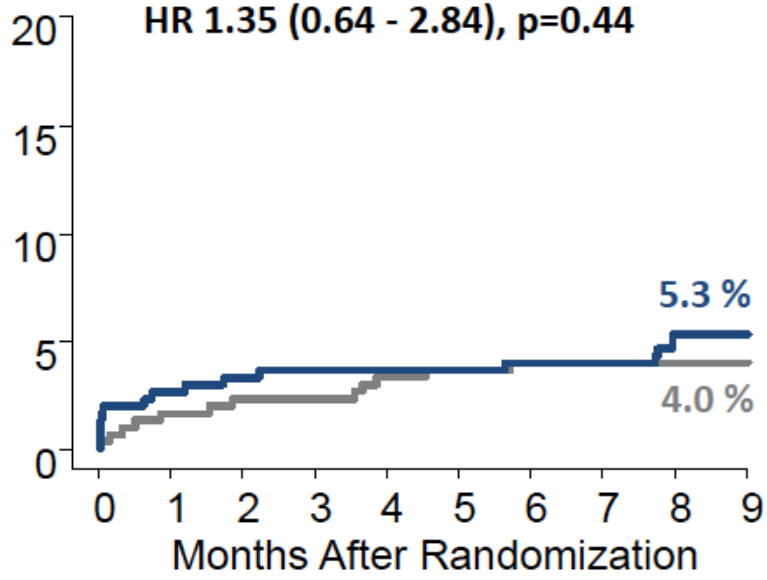


Secondary Endpoints

Cardiac death, myocardial infarction, stent thrombosis or ischemic stroke



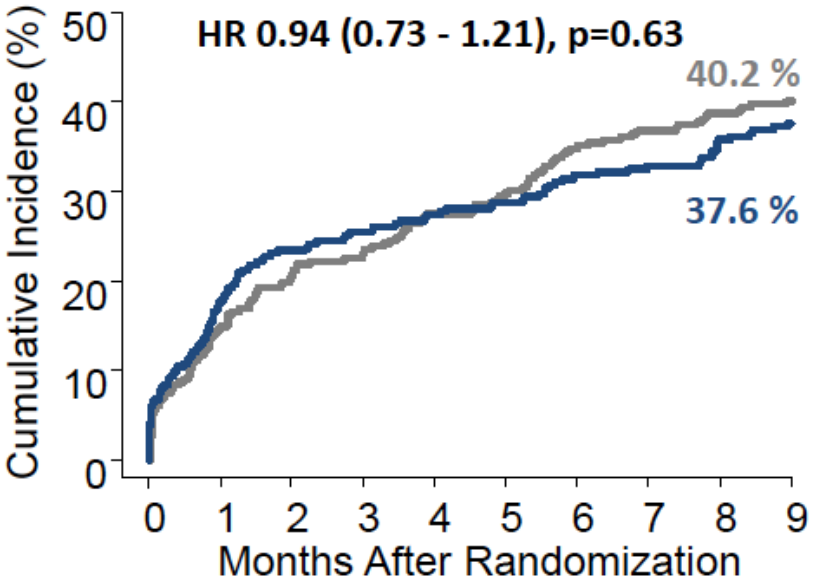
TIMI major bleeding



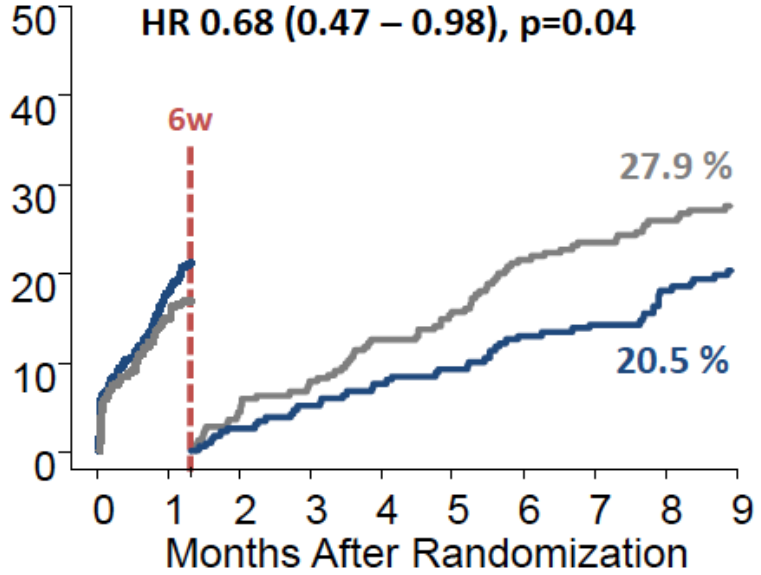
6-month group
6-week group

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

TCT 2014

Conclusion

- The main finding was that a 6-week triple therapy is not superior to a 6-month triple therapy with regard to net clinical outcomes

- Shortening the duration of triple therapy neither reduced the incidence of major bleeding nor increased the incidence of ischemic events

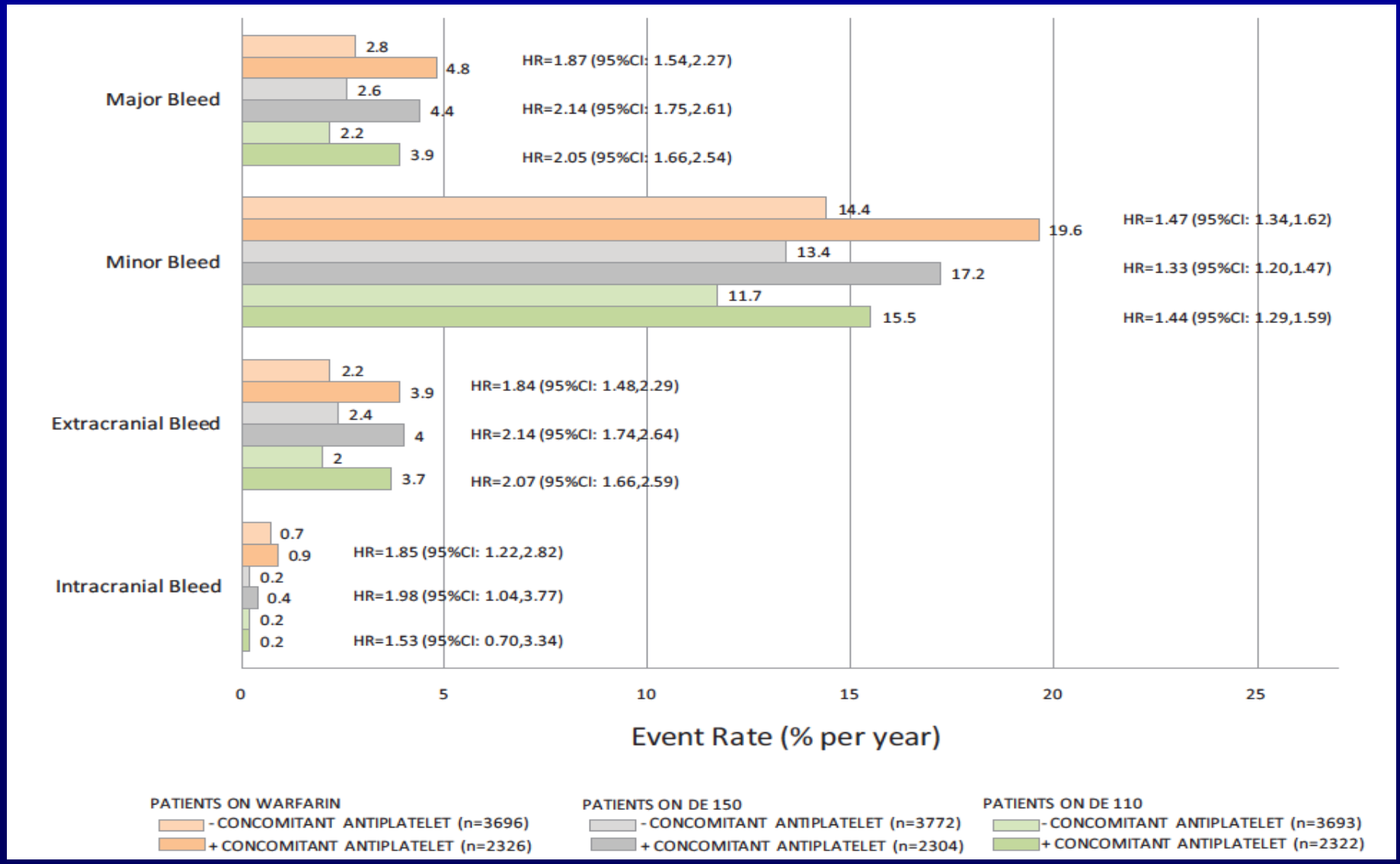
Finding the Best Cocktail of an Anticoagulant With Antiplatelets

- VKAs Plus Antiplatelet Therapy With Aspirin and/or P2Y12 Receptor Inhibitors
- **NOACs Plus Single or Dual Antiplatelet Therapy**
- OACS Plus new P2Y12 Receptor Inhibitors

NOACs Plus Single or Dual Antiplatelet Therapy

- Currently available data on oral antiplatelet agents (mostly aspirin alone) in addition to NOACs are scarce and limited to relatively small subgroups of patients from trials of dabigatran or apixaban
- Of the 4 pivotal phase III AF trials of NOACs, 3 (rivaroxaban, apixaban, and edoxaban) did not allow the inclusion of pts with concomitant clopidogrel use
- The only phase III AF trial that allowed concomitant use of clopidogrel was the one of dabigatran

Concomitant Use of Antiplatelet Therapy with Dabigatran or Warfarin in the RELY Trial



Dans AL et alCirculation. 2013;127:634–640

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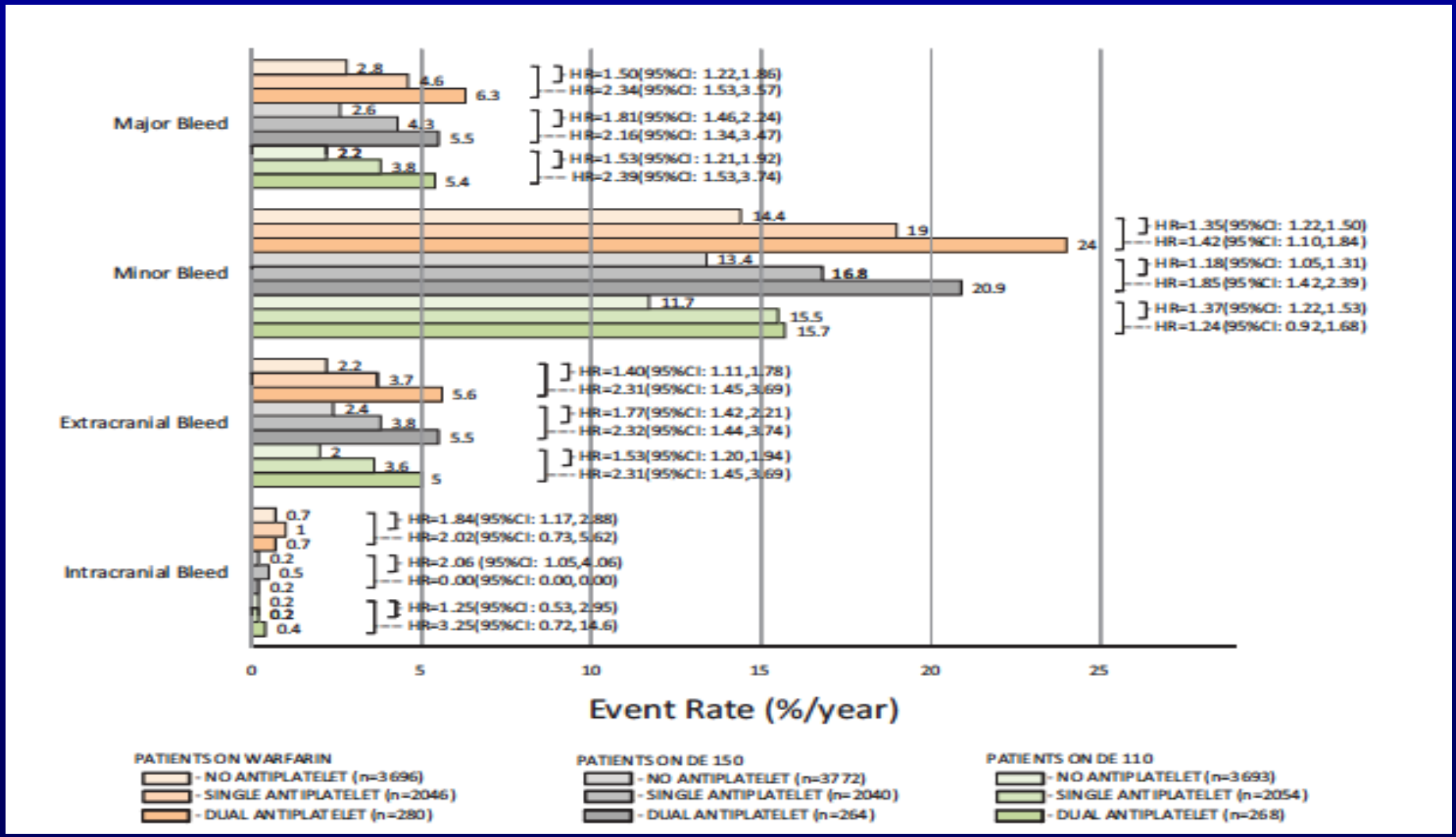
Rates of various forms of bleeding in the 3 treatment groups (warfarin, DE150, and DE110), comparing pts without concomitant antiplatelets on single and on dual antiplatelets



Dans AL et alCirculation. 2013;127:634–640

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Dabigatran 110mg may be a safer alternative to warfarin in patients requiring antiplatelet therapy

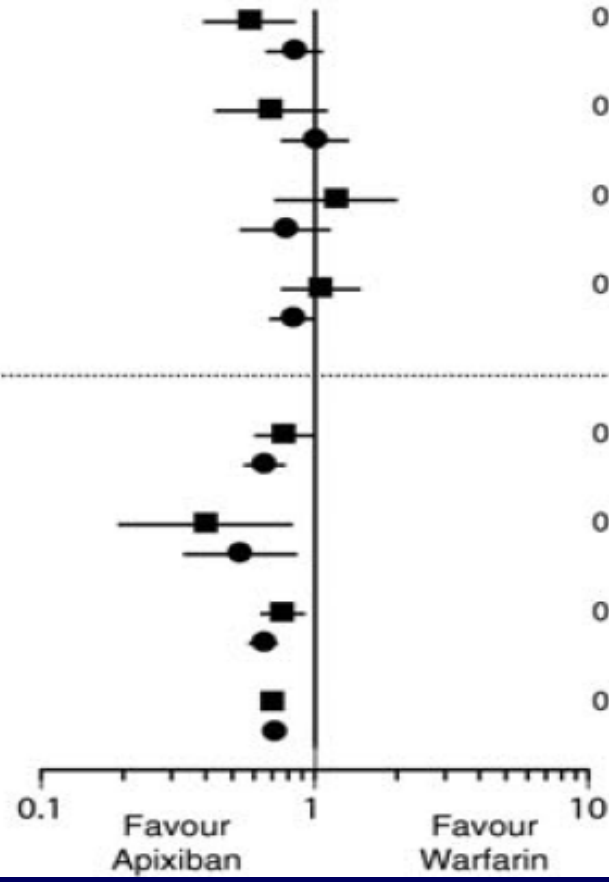
- Post hoc analysis: use of antiplatelet therapy was not randomized or stratified.
- Antiplatelet therapy left at the discretion of the physician.
- Most patients were taking ASA (80mg *or more*), 1,9% Clopidogrel, 4,5% DAPT (median duration, *66% of the study period*).
- Adding a single anti-platelet drug ***increased the risk of major bleeding by 60%***.

Apixaban vs. warfarin with concomitant aspirin in pts with atrial fibrillation: insights from the ARISTOTLE trial

A Overall

Aspirin
No Aspirin

Outcome	Apixaban	Warfarin	HR (95% CI)	Interaction P-value
Stroke or systemic embolism	41 (1.12) 127 (1.11)	67 (1.91) 149 (1.32)	0.58 (0.39 – 0.85) 0.84 (0.66 – 1.07)	0.10
Ischaemic stroke	29 (0.79) 95 (0.83)	40 (1.14) 94 (0.83)	0.69 (0.43 – 1.11) 1.00 (0.75 – 1.33)	0.19
Myocardial infarction	33 (0.90) 46 (0.40)	26 (0.74) 58 (0.51)	1.20 (0.71 – 2.00) 0.78 (0.53 – 1.14)	0.19
Death	71 (1.93) 188 (1.64)	64 (1.82) 223 (1.97)	1.05 (0.75 – 1.47) 0.83 (0.68 – 1.00)	0.23
Major bleeding	114 (3.10) 211 (1.82)	138 (3.92) 317 (2.78)	0.77 (0.60 – 0.99) 0.65 (0.55 – 0.78)	0.29
Haemorrhagic stroke	10 (0.27) 25 (0.22)	24 (0.68) 47 (0.42)	0.40 (0.19 – 0.83) 0.53 (0.33 – 0.86)	0.52
Major or CRNM bleeding	199 (5.54) 410 (3.59)	246 (7.18) 620 (5.58)	0.76 (0.63 – 0.92) 0.65 (0.57 – 0.73)	0.15
Any bleeding	682 (22.64) 1657 (16.61)	859 (32.84) 2180 (23.72)	0.70 (0.63 – 0.77) 0.71 (0.67 – 0.76)	0.70



Alexander JH et al. Eur Heart J 2014; 35: 224–232

Finding the Best Cocktail of an Anticoagulant With Antiplatelets

- Combining antiplatelets and anticoagulants increases bleeding risk. This appears to be the case also when an antiplatelet agent is added to a new OAC in AF pts
- Dabigatran appears to maintain its overall favorable profile compared with warfarin in pts on antiplatelets
- No interaction was observed in terms of safety with aspirin use at the time of randomization in AF pts in the ROCKET AF (Rivaroxaban) and ARISTOTLE (Apixaban) trials, but there is currently no information on bleeding risk during prolonged use. In addition, DAPT was an exclusion criterion in ARISTOTLE and ROCKET-AF

2014 ESC/EACTS Guidelines on myocardial revascularization

Recommendations for antithrombotic treatment in patients undergoing PCI who require oral anticoagulation

Recommendations	Class[a]	Level[b]
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 1 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 1 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

2014 ESC/EACTS Guidelines on myocardial revascularization

Recommendations for antithrombotic treatment in patients undergoing PCI who require oral anticoagulation

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

Although the trial was too small to assess ischaemic outcomes, dual therapy with clopidogrel and oral anticoagulants may be considered as an alternative to triple therapy in patients with high bleeding risk.

Finding the Best Cocktail of an Anticoagulant With Antiplatelets

- VKAs Plus Antiplatelet Therapy With Aspirin and/or P2Y12 Receptor Inhibitors
- NOACs Plus Single or Dual Antiplatelet Therapy
- OACS Plus new P2Y12 Receptor Inhibitors

Novel P2Y12 inhibitors and OAC

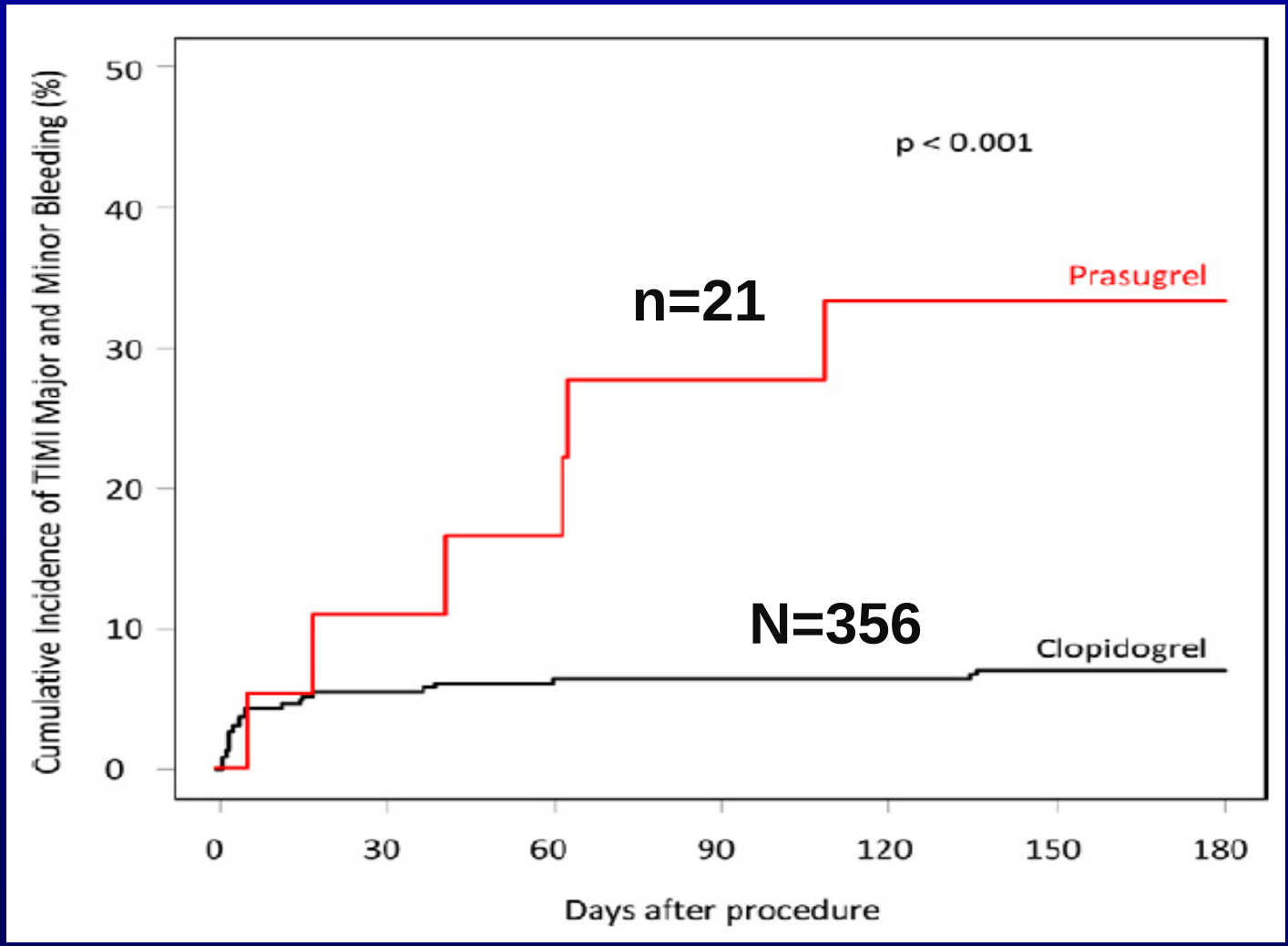
- TRITON-TIMI 38, TRILOGY-ACS, PLATO, PEGASUS-TIMI 54 (ongoing) patients were not enrolled if they were on OAC
- Both prasugrel and tocagrelor are associated with potent platelet inhibition and increased risk of bleedings (including fatal intracranial hemorrhage), raising concerns if concomitantly used with OAC (in line with the product label)

Recommendations on the Management of Patients on Oral Anticoagulation With ACS and/or Undergoing PCI

DAPT with clopidogrel and aspirin. Prasugrel and ticagrelor should be avoided in patients concomitantly treated with OAC

Lip GYH et al. Eur Heart J. 2010;31:1311–1318.
Faxon DP et al.Circ Cardiovasc Interv. 2011;4:522–534.

Triple Therapy With Aspirin, Prasugrel, and Vitamin K Antagonists in Patients With DES Implantation and an Indication for Oral Anticoagulation



Sarafoff N et al. J Am Coll Cardiol 2013;61:2060–6.

2014 ESC/EACTS Guidelines on myocardial revascularization

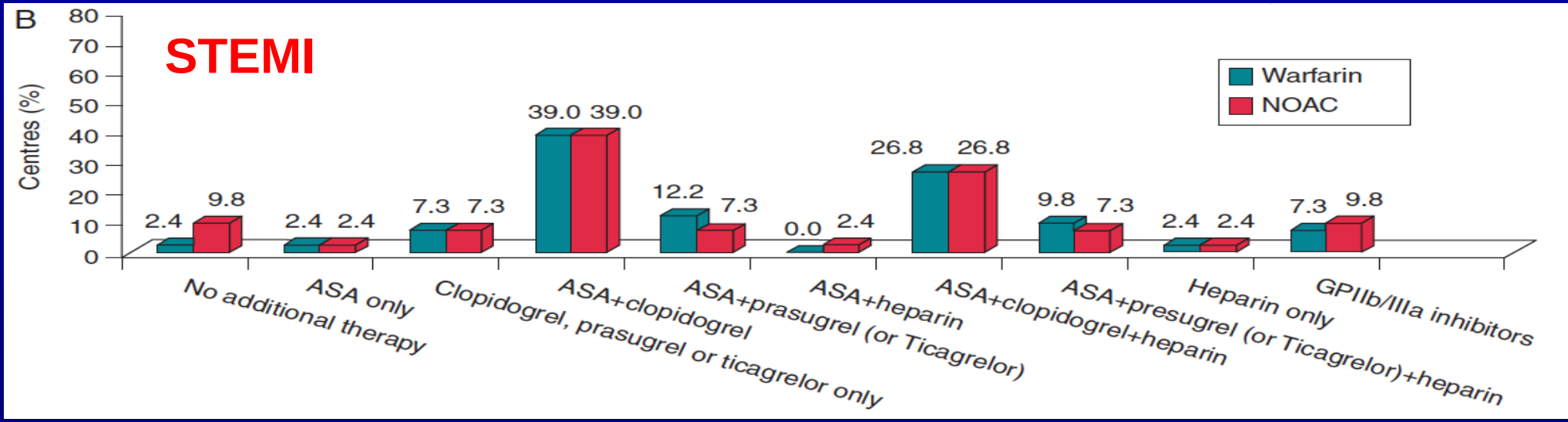
Recommendations for antithrombotic treatment in patients undergoing PCI who require oral anticoagulation

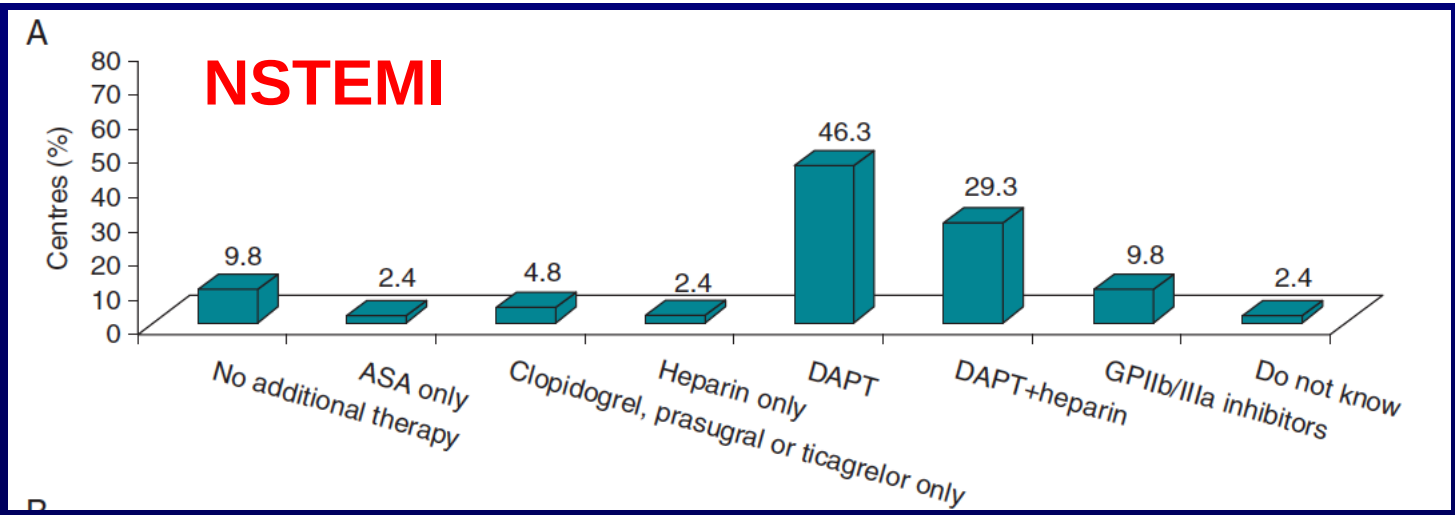
The use of ticagrelor and prasugrel as part of initial triple therapy is not recommended.	III	C

The use of prasugrel or ticagrelor as part of triple therapy should be avoided, given the lack of established benefit and the greater risk of major bleeding compared with clopidogrel (HR 4.6; 95% CI 1.9–11.4; P , 0.001) in an observational study.

Management strategies in AF patients presenting with STEMI or NSTEMI within an optimal timeframe for PCI

European Heart Rhythm Association Survey





Europace 2014; 16: 293–298

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Management strategies in AF patients presenting with STEMI or NSTEMI within an optimal timeframe for PCI

European Heart Rhythm Association Survey

STEMI: Overall, DAPT was added to warfarin in 36 centres (87.5%), or to a NOAC in 33 centres (80.5%). The combination of prasugrel or ticagrelor plus aspirin was more commonly given on top of warfarin (nine centres, 21.9%) than in addition to NOACs (six centres, 14.6%).

NSTEMI: 6 centres (19.4%) used aspirin and prasugrel or ticagrelor

U.O. MALATTIE CARDIOVASCOLARI USL 8 - AREZZO

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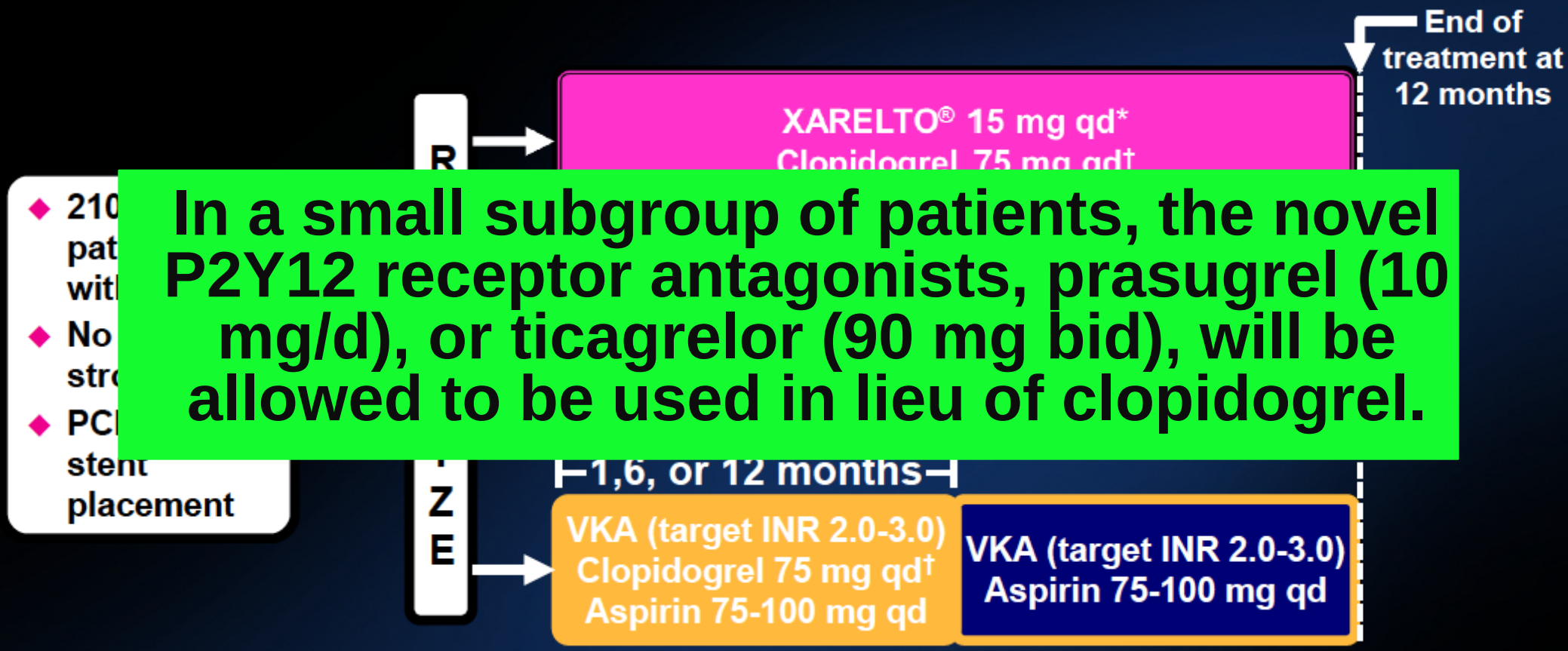
Future Directions: Ongoing Studies

- **MUSICA-2**: triple therapy vs high-dose DAPT in PCI pts with $CHADS_2 \leq 2$
- **EVOLVE**
- **RE-DUAL PCI**: dabigatran 150 or 110 mg twice-daily plus single antiplatelet therapy versus triple therapy with warfarin in PCI pts
- **PIONEER AF-PCI**

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



In a small subgroup of patients, the novel P2Y12 receptor antagonists, prasugrel (10 mg/d), or ticagrelor (90 mg bid), will be allowed to be used in lieu of clopidogrel.

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

RE-DUAL PCI™

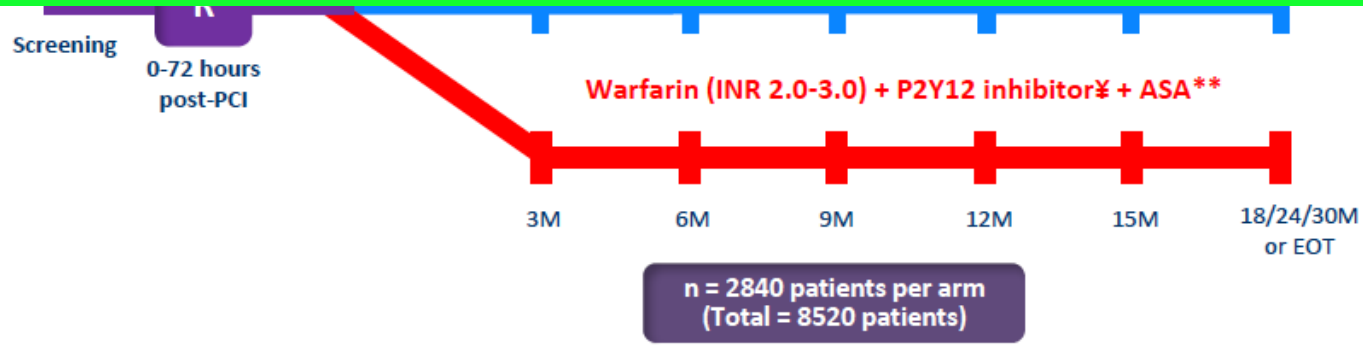
Study in NVAF patients undergoing PCI

A prospective Randomised, open label, blinded endpoint (PROBE) study to Evaluate DUAL antithrombotic therapy with dabigatran etexilate (110mg b.i.d. and 150mg b.i.d.) plus clopidogrel or

D110 plus a P2Y12 inhibitor is:
Non-inferior with respect to the combined thrombotic event rate (TE: death + MI + stroke/SE)

D150 plus a P2Y12 inhibitor is:
Non-inferior with respect to the combined thrombotic event rate (TE: death + MI + stroke/SE)

P_2Y_{12} inhibitor (either clopidogrel or *Ticagrelor*). The P_2Y_{12} inh. can be discontinued after month 12 of follow-up at the discretion of the physician



(all death, MI, Stroke/SE)

Plus

Time to first clinically relevant bleeding rate (ISTH Major)

n = 2840 patients per arm (Total = 8520 patients)

Boehringer Ingelheim

AFIB608904PROF

- 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

HCRI Harvard Clinical Research Institute

U.O. Malattie Cardiovascolari USL 8 - Arezzo

ISO 9001

Recommendations on the Management of Patients on Oral Anticoagulation With ACS and/or Undergoing PCI

- Risk stratification and balance
- Avoid unnecessary revascularization
- Use the radial access
- Use a bare metal stent whenever possible, unless in selected pts

Anticoagulation during percutaneous coronary intervention in patients on oral anticoagulation

Elective PCI

- no additional anticoag. is needed if the INR is >2.5.
- NO interruption of VKAs

Primary PCI

- Additional parenteral anticoag., regardless of the timing of the last dose of oral anticoagulant
- Bivalirudin may be preferred over UFH or enox especially when patients are exposed to dabigatran.
- Enox. should be preferred in cases of prior exposure to direct anti-Xa inhibi (rivaroxaban or apixaban) to avoid cross-over.
- GPI should be avoided

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Recommendations on the Management of Patients on Oral Anticoagulation With ACS and/or Undergoing PCI

- DAPT with clopidogrel and aspirin. Prasugrel and ticagrelor should be avoided in patients concomitantly treated with OAC
- Warfarin (targeting low-intensity OAC with an INR between 2.0 and 2.5) remains the standard of care for patients with AF who also require DAPT
- Dabigatran 110mg may be a safer alternative to warfarin in patients requiring dual antiplatelet therapy

U.O. MALATTIE CARDIOVASCOLARI USL 8 - AREZZO

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