Gemelli
Fondazione Policlinico Universitario A. Gemelli
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Forum sulla gestione post - dimissione della terapia antitrombotica

La triplice dopo SCA o PCI: tra miti e realtà

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NO FREE LUNCH

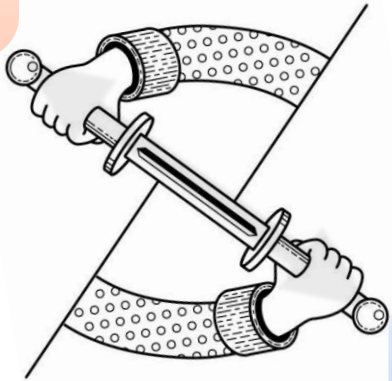
PCI

DAPT
(ASA + P2Y12 inhibitor)

Stronger

Recurrent ischemic events
+ stent thrombosis

Weaker



Weaker

Stroke

Stronger

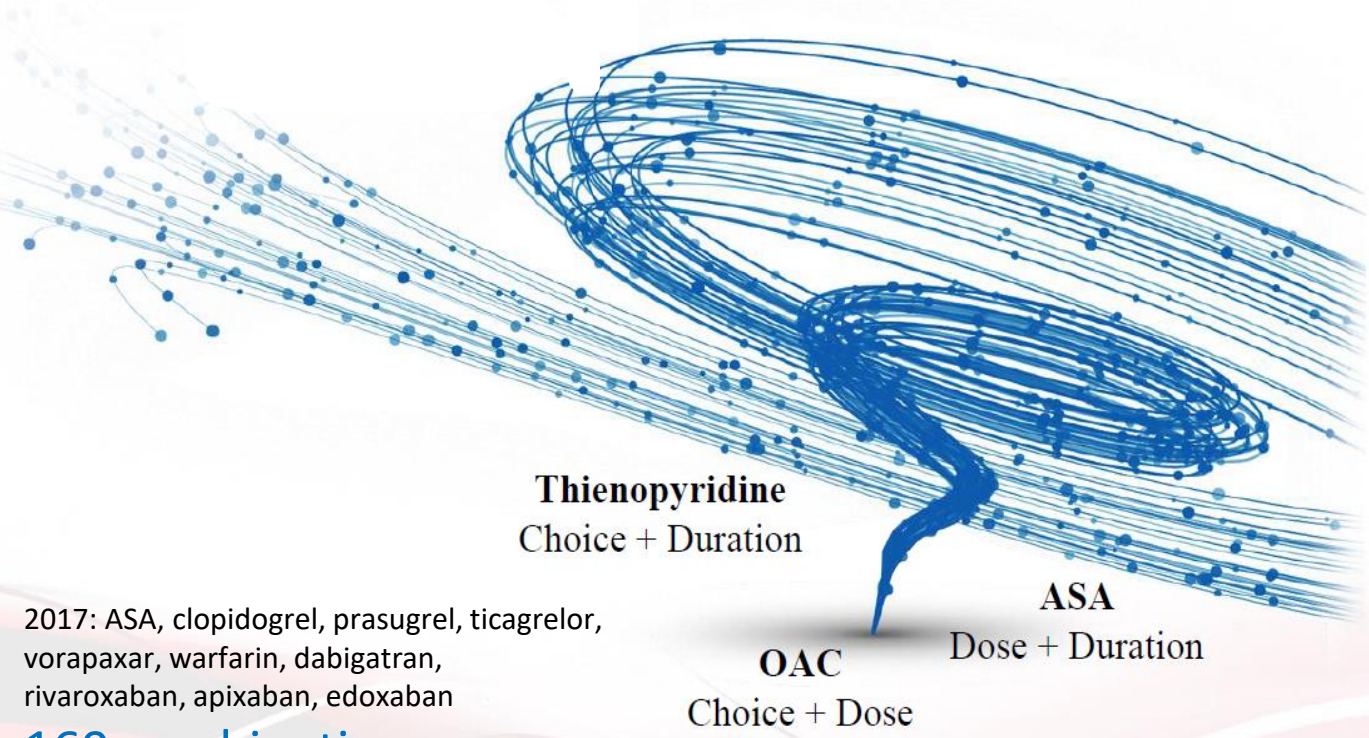
OAC

AF

Modified from Rubboli A

COMPLEXITY IN ANTITHROMBOTIC THERAPY

2009: ASA, clopidogrel, warfarin. 8 combinations

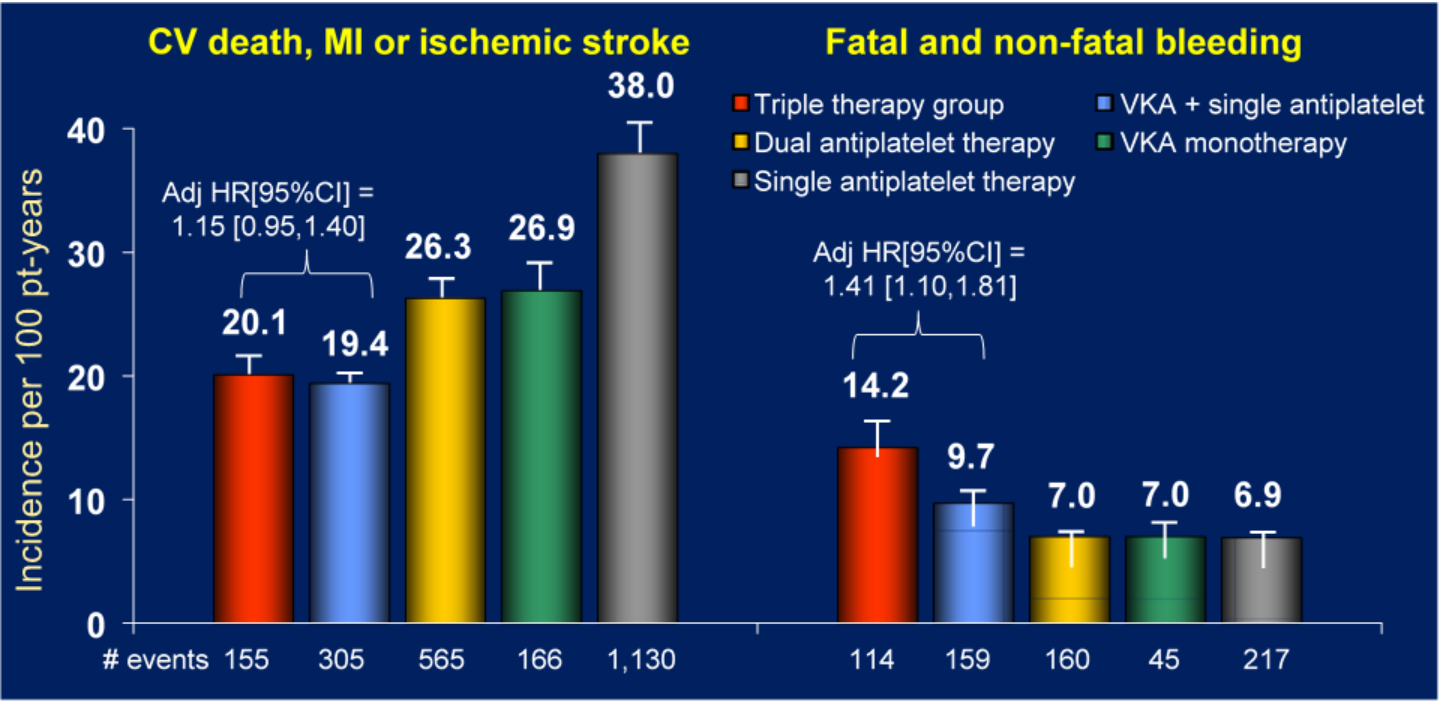


2017: ASA, clopidogrel, prasugrel, ticagrelor, vorapaxar, warfarin, dabigatran, rivaroxaban, apixaban, edoxaban

160 combinations

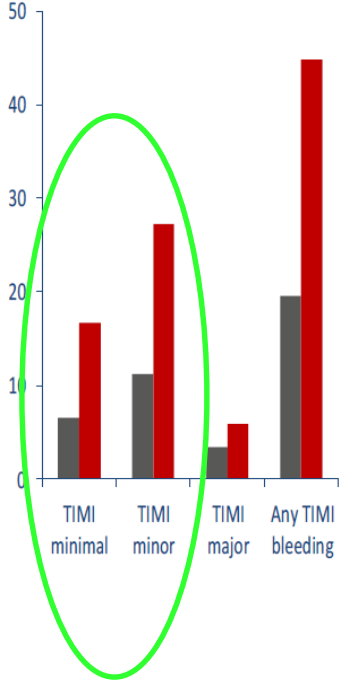
11,480 PTS WITH NVAF IN DENMARK ADMITTED FOR MI (76.4%) OR PCI (23.6%)

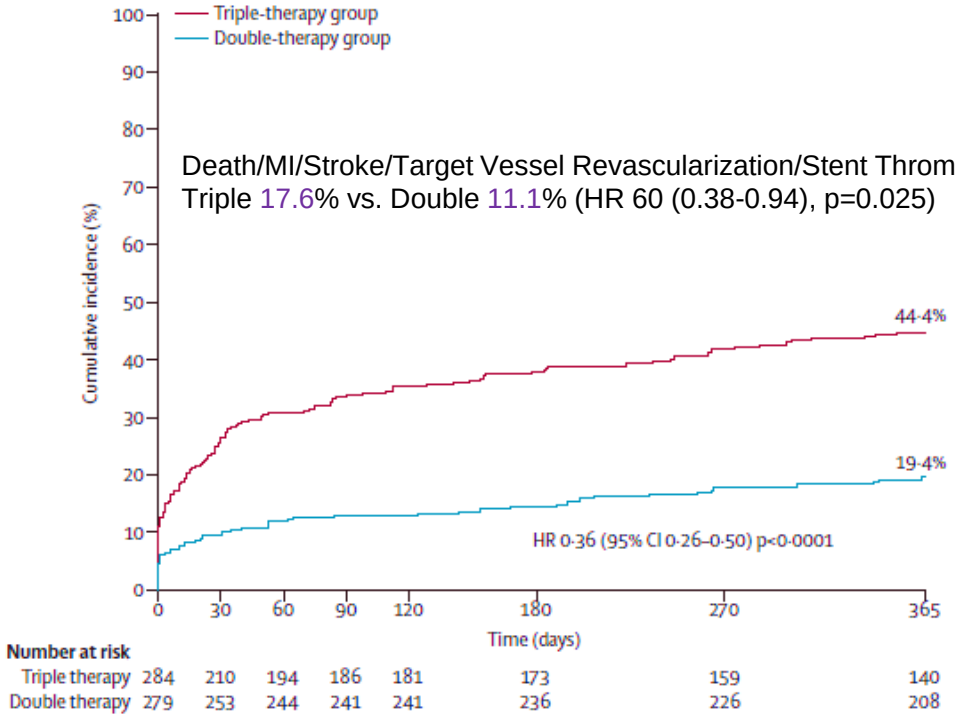
Discharge meds: aspirin (n=3,388), clopidogrel (n=768), VKA (n=848), DAPT (n=3,144), C + VKA (n=527), DAPT + VKA (n=1,495)



Lamberts M et al. *Circulation*. 2012;126:1185-1193

«Drop the aspirin» (with VKA)



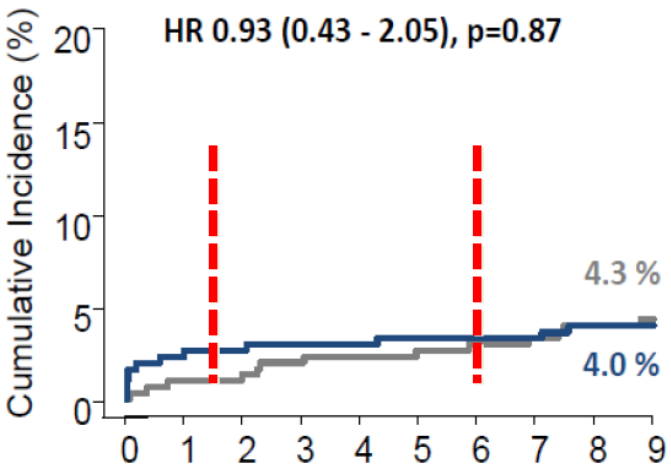


Death/MI/Stroke/Target Vessel Revascularization/Stent Thrombosis
Triple 17.6% vs. Double 11.1% (HR 60 (0.38-0.94), p=0.025)

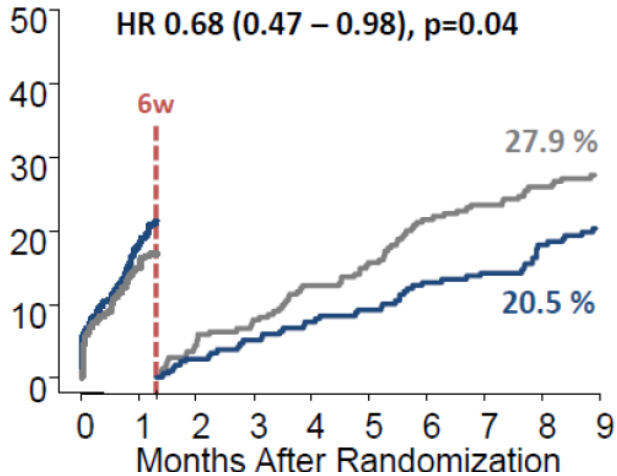
DeWilde W. et al. Lancet 2013;381:1107–15 The WOEST Trial

Shortening Triple Therapy (with VKA)

Cardiac death, myocardial infarction, stent thrombosis or ischemic stroke



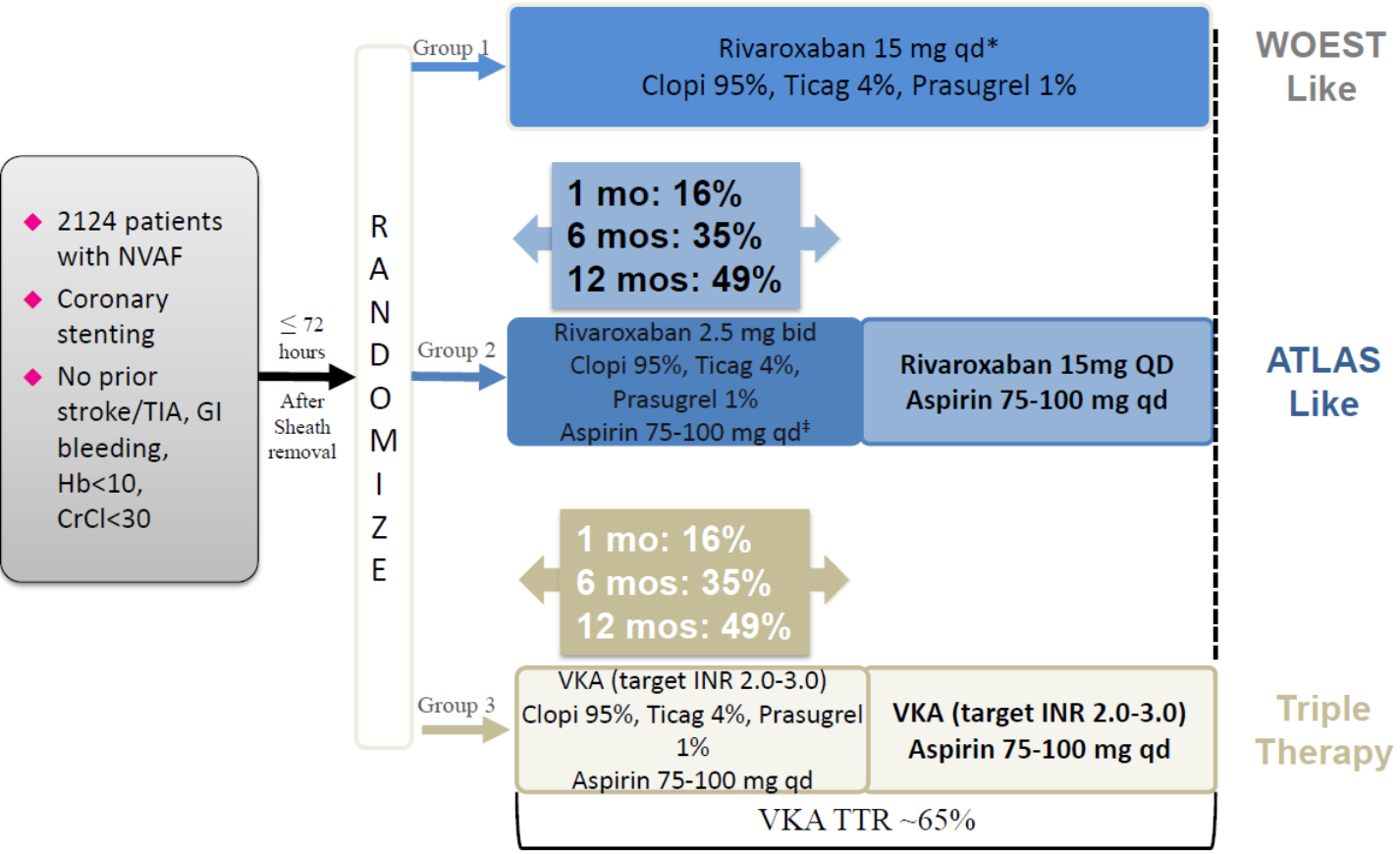
Post-hoc landmark analysis of any BARC Bleeding before and after 6 weeks (6w)



6-month group
6-week group

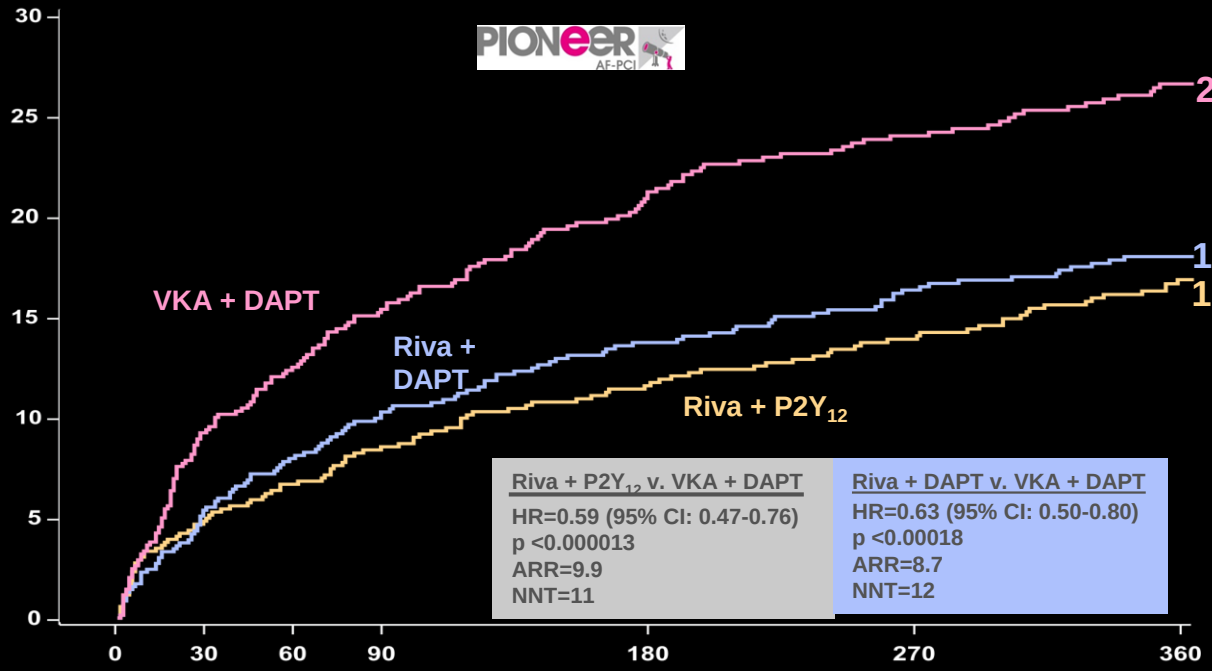
ISAR-TRIPLE Trial Bhatt DL. J Am Coll Cardiol. 2015;65:1630-2

PRE-RANDOMIZATION CHOICE OF DURATION OF DAPT & THIENOPYRIDINE: PIONEER AF-PCI



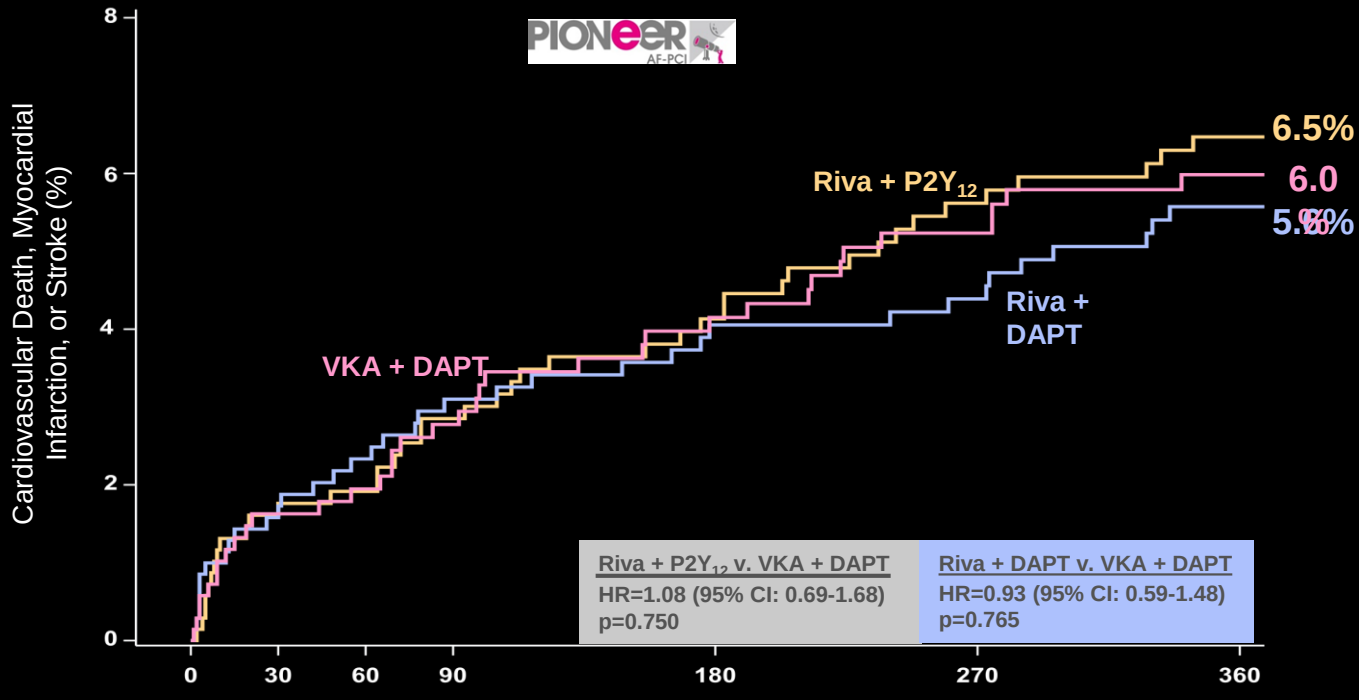
PRIMARY ENDPOINT: CLINICALLY SIGNIFICANT BLEEDING

PIONEER AF-PCI



Riva + P2Y12	696	628	606	585	543	510	389
Riva + DAPT	697	598	566	529	501	426	329
VKA + DAPT	697	593	555	521	461	426	329

CV DEATH, MI OR STROKE: PIONEER AF-PCI



PIONEER AF-PCI: SOME NOTES

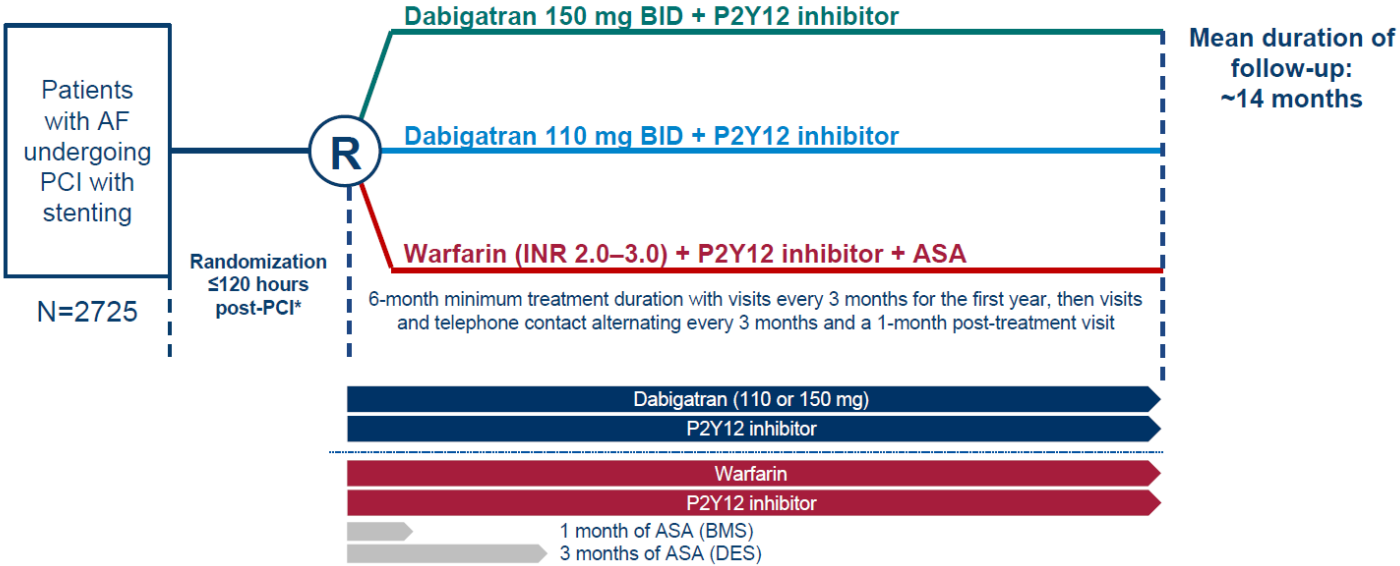
Table S1

Sample size and power calculation of major adverse cardiovascular events required to detect a ≥ 15% risk reduction at a two-sided significance level of 0.05

Endpoint	Event rate	No. per group to attain 90% power	Power with 700 subjects per group
Overall			
Adverse CV event	6.0%	13,598	11.4%
CV death	1.8%	47,196	6.8%
MI	3.5%	23,883	8.6%
Stroke	1.2%	71,195	6.2%
Stent thrombosis	0.7%	122,620	5.7%

Study Design: Multicenter, randomized, open-label trial following a PROBE design

Study in NVAF patients undergoing PCI



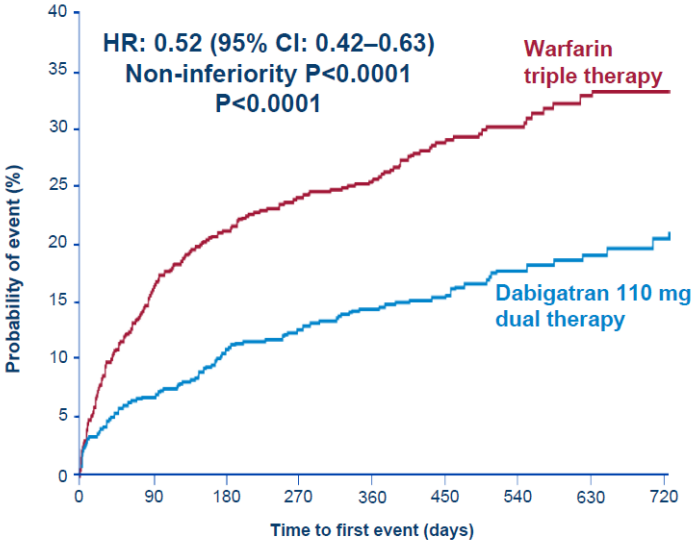
***Study drug should be administered 6 hours after sheath removal and no later than ≤120 hrs post-PCI (≤72 hrs is preferable).** PROBE, prospective, randomized, open, blinded end-point; R, randomization; BMS, bare metal stent; DES, drug-eluting stent. ClinicalTrials.gov: NCT02164864; Cannon et al. Clin Cardiol 2016

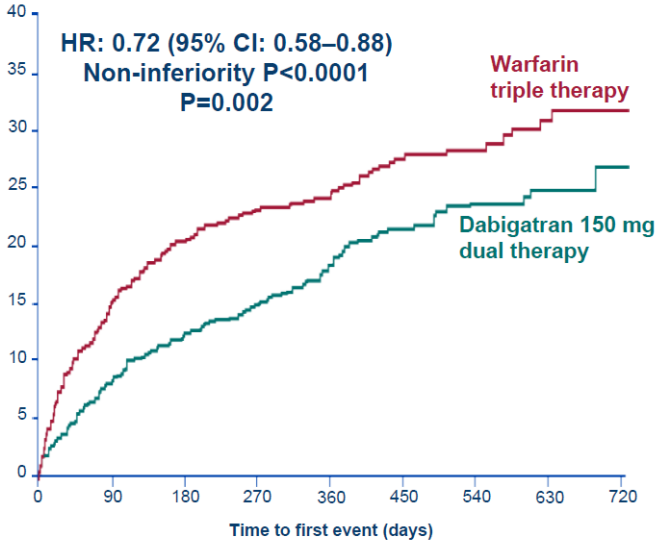
Baseline characteristics

	Dabigatran 110 mg dual therapy (n=981)	Warfarin triple therapy (n=981)	Dabigatran 150 mg dual therapy (n=763)	Corresponding Warfarin triple therapy (n=764)
Age, years, mean	71.5	71.7	68.6	68.8
≥80 (US, ROW), ≥70 (Japan), %	22.9	22.9	1.0	1.0
<80 (US, ROW), <70 (Japan), %	77.1	77.1	99.0	99.0
Male, %	74.2	76.5	77.6	77.7
Baseline CrCl, mL/min, mean	76.3	75.4	83.7	81.3
Diabetes mellitus, %	36.9	37.8	34.1	39.7
CHA_2DS_2-VASc score (mean)	3.7	3.8	3.3	3.6
Modified HAS-BLED score at baseline (mean)	2.7	2.8	2.6	2.7
ACS indication for PCI, %	51.9	48.4	51.2	48.3
DES only, %	82.0	84.2	81.4	83.5

ROW, rest of world

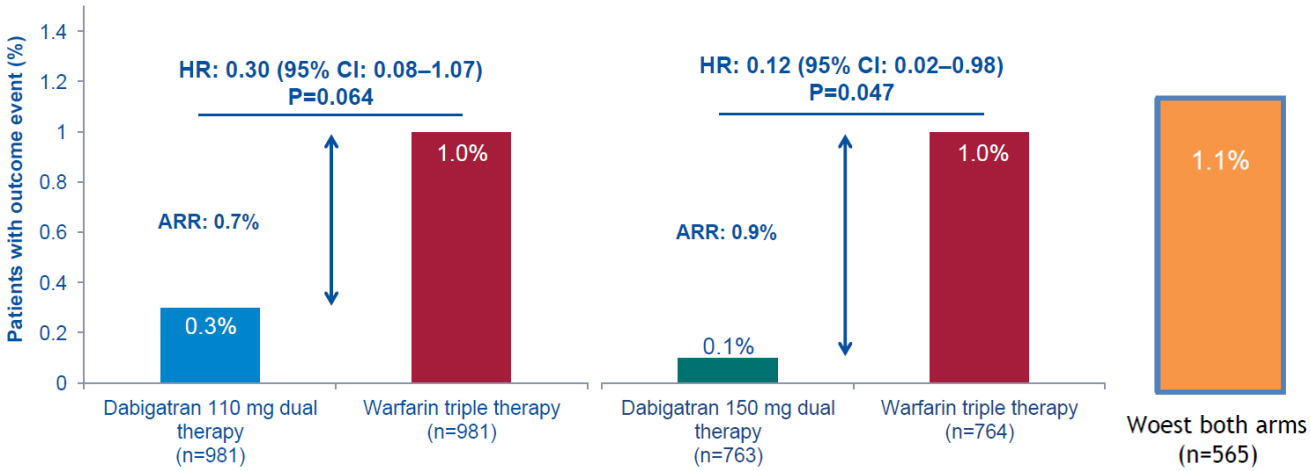
Primary Endpoint: Time to first ISTH major or clinically relevant non-major bleeding event





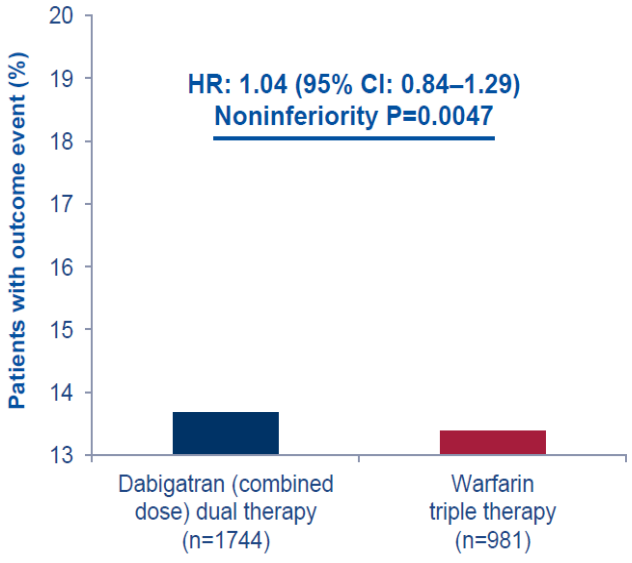
Full analysis set presented. HRs and Wald CIs from Cox proportional-hazard model. For the dabigatran 110 mg vs warfarin comparison, the model is stratified by age, non-elderly vs elderly (<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere). For the dabigatran 150 mg vs warfarin comparison, an unstratified model is used, elderly patients outside the USA are excluded. Non-inferiority P value is one sided (alpha=0.025). Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05)

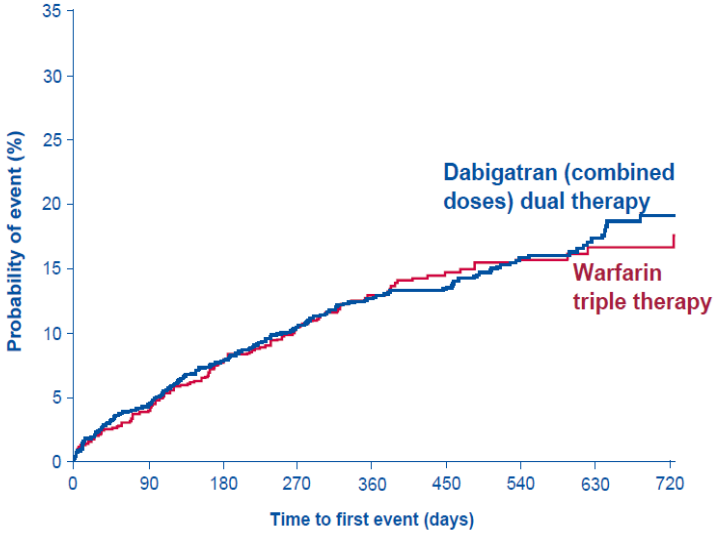
Rate of intracranial haemorrhage



Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05)

Dabigatran dual-therapy was non-inferior to warfarin triple therapy in the composite efficacy endpoint





Noninferiority P-value is one sided (alpha=0.025). Results presented are Step 3 of hierarchical testing procedure testing noninferiority of dabigatran dual therapy (combined doses) to warfarin triple therapy in death or thromboembolic event and unplanned revascularisation. Cannon et al. ESC 2017

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RE-DUAL PCI
Study in NVAF patients undergoing PCI

March 2014

The dual primary endpoints for this trial are a composite endpoint of efficacy and a safety endpoint:

1. Time to death or first thrombotic event (DTE) (all death, MI, stroke/SE)
2. Time to first ISTH Major Bleeding Event (MBE)

The secondary endpoints of efficacy are (all time to event endpoints):

1. Individual outcome events:
   - All death
     - Cardiovascular death
     - Non-cardiovascular death
     - Undetermined
   - MI
   - Stroke
   - SE
   - Stent thrombosis
2. Composite endpoint of death + MI + stroke
3. Repeated revascularisation by PCI/CABG

2840 patients in each treatment group (i.e. 8520 randomised patients in total).

July 2016 (after 3 global amendments)

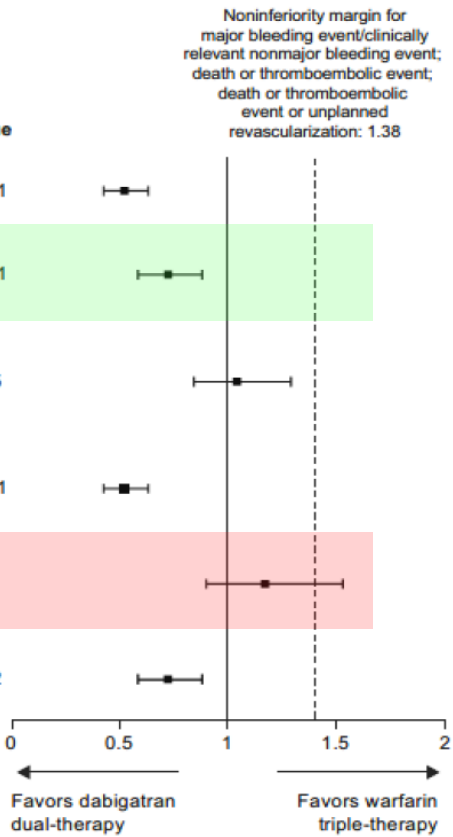
The primary endpoint for this trial is a safety endpoint. See section 5.2.1. There are no primary efficacy endpoints.

The secondary efficacy endpoints (all time to first event) are:

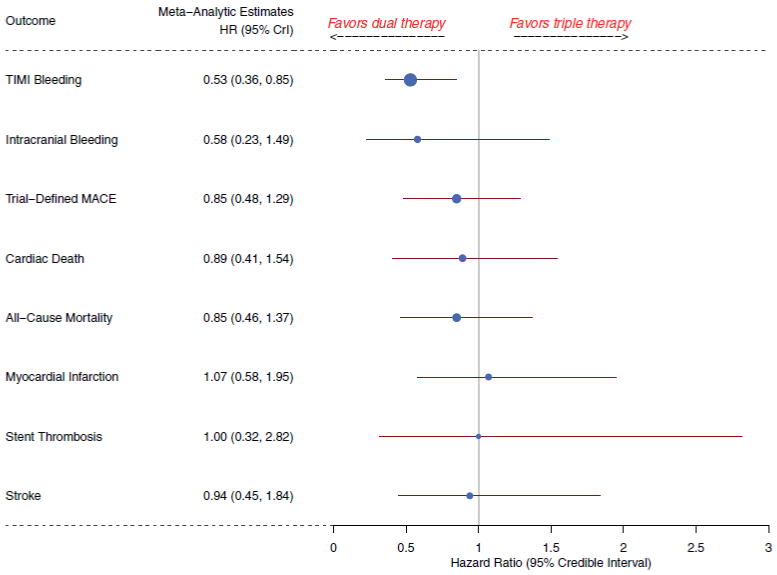
1. A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE) and unplanned revascularisation by PCI/CABG
2. A combined endpoint of thrombotic events or death (DTE: all death + MI + stroke/SE)
3. Individual outcome events:
   - All death
     - Cardiovascular death
     - Non-cardiovascular death
     - Undetermined
   - MI
   - Stroke
   - SE
   - Stent thrombosis
4. Composite endpoint of death + MI + stroke
5. Unplanned revascularisation by PCI/CABG

834 patients in each treatment group (i.e. 2502 randomised patients in total)

Step	Test	HR (95% CI)	P-value
1	Noninferiority of dabigatran 110 dual-therapy to warfarin triple-therapy in major bleeding event/ clinically relevant nonmajor bleeding event	0.52 (0.42 to 0.63)	<0.001
2	Noninferiority of dabigatran 150 dual-therapy to warfarin triple-therapy* in major bleeding event/ clinically relevant nonmajor bleeding event	0.72 (0.58 to 0.88)	<0.001
3	Noninferiority of dabigatran 150 dual-therapy and dabigatran 110 dual-therapy combined to warfarin triple-therapy in death or thromboembolic event or unplanned revascularization by PCI/CABG	1.04 (0.84 to 1.29)	0.005
4	Superiority of dabigatran 110 dual-therapy to warfarin triple-therapy in major bleeding event/ clinically relevant nonmajor bleeding event	0.52 (0.42 to 0.63)	<0.001
5	Noninferiority of dabigatran 150 dual-therapy and dabigatran 110 dual-therapy combined to warfarin triple-therapy in death or thromboembolic event	1.17 (0.90 to 1.53)	0.11
6	Superiority of dabigatran 150 dual-therapy to warfarin triple-therapy* for major bleeding event/ clinically relevant nonmajor bleeding event	0.72 (0.58 to 0.88)	0.002



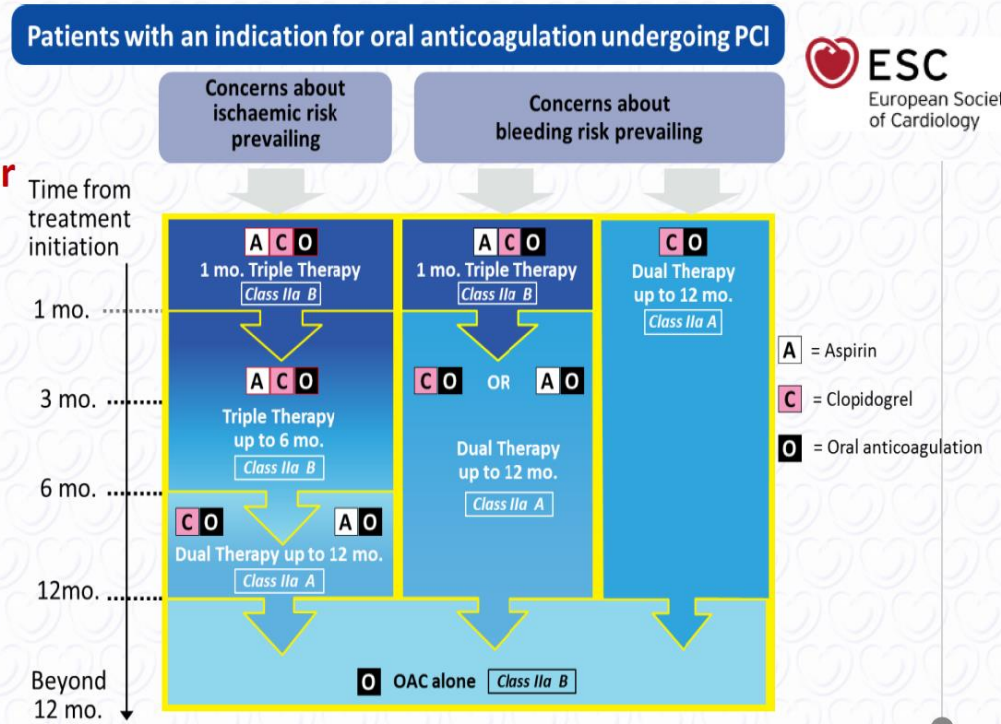
EHJ metanalysis



Take home figure Summary of bleeding and ischaemic risks for dual versus triple antithrombotic therapy.

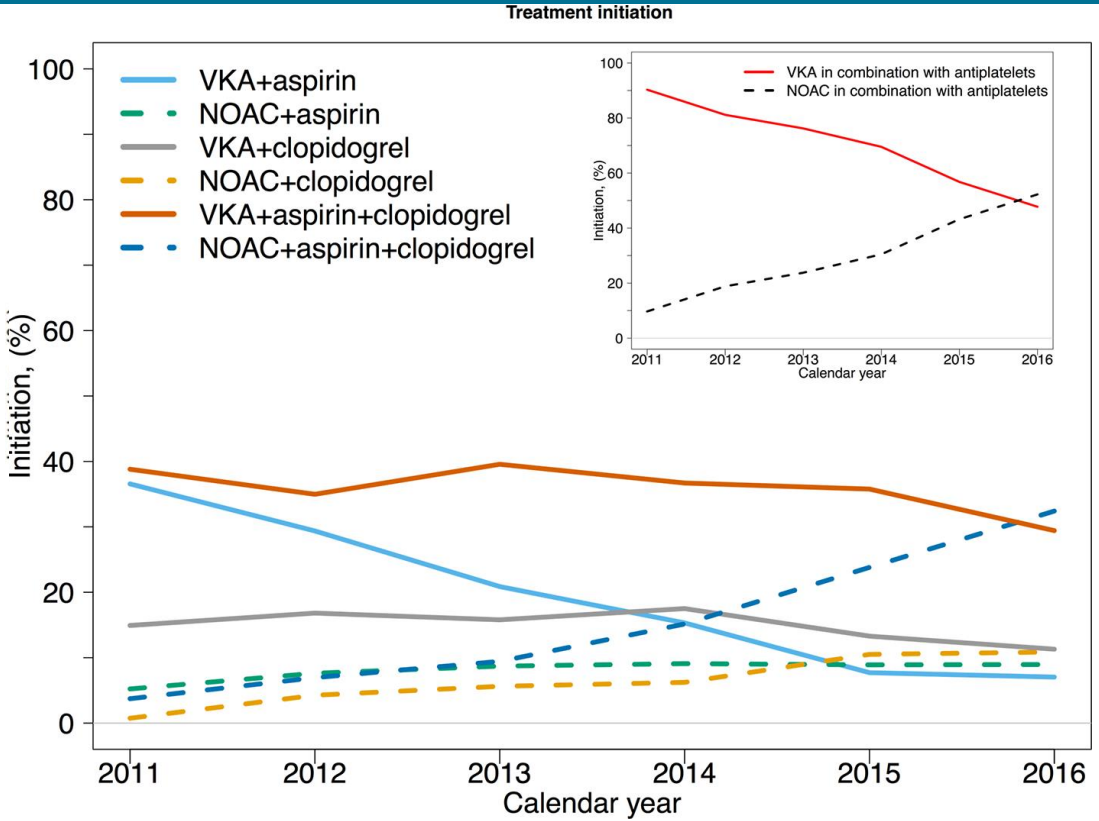
Golwala HB et al., EHJ 2018;39:1726–1735a

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



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

The reality



Sindet-Pedersen C, et al. Heart 2018;104:912–920.

ENTRUST-AF-PCI Study Design

PROBE design: prospective, randomized, open label, blinded evaluation edoxaban based regimen vs VKA based regimen in N ≅ 1500 AF patients

12 months: end of treatment

Inclusion Criteria:

- ***OAC indication for AF for at least 12 months***
- ***Successful PCI with stent placement (goal of at least 25% ACS)***

4 hours – 5 days after sheath removal

RANDOMIZE

Edoxaban 60 mg/day*

$P2Y_{12}$ antagonist** (without ASA)

Vitamin K Antagonist***

$P2Y_{12}$ antagonist (ASA 1 - 12 months)****

**Edoxaban dose reduction to 30 mg OD*
- *if CrCL≤50 ml/min*
- *BW≤60 kg*
- *certain P-gp inhibitors*

***Clopidogrel 75mg once-daily or if documented need prasugrel 5 or 10mg once-daily or ticagrelor 90mg twice-daily . Predeclared at randomization*

**** VKA, target INR 2-3*

*****ASA 100mg OD for 1-12 months guided by clinical presentation (ACS or stable CAD), CHA_2DS-$VASc_2$ and HAS_BLED*

Primary outcome: ***ISTH major and clinically relevant non-major bleeding***

ClinicalTrials.gov Identifier: NCT02866175

AUGUSTUS STUDY DESIGN

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 and/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

NEW 2017 ESC FOCUSED UPDATE

High-risk features of stent-driven recurrent ischaemic events

ESC
European Society of Cardiology

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

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

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CONCLUSIONS

- Triple therapy is not dead yet, and its lenght probably not a big issue.
- Dual therapy (in my opinion) no more that a potential alternative if high bleeding risk and no complex PCI.
- Typical patient: type II MI (with or without PCI)