Antithrombotic Management of AF and PCI

How to account for ischemic, thromboembolic and bleeding risks and for gender?

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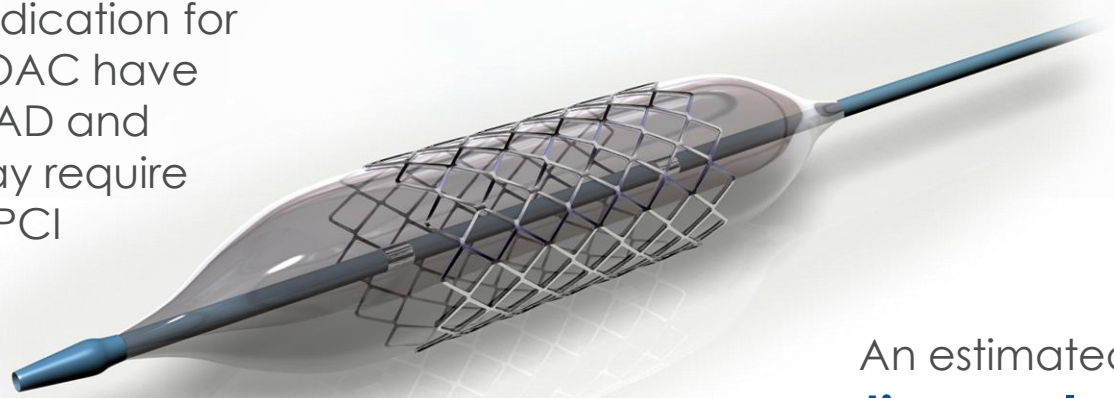
Conflict of interest

I, Ran Kornowski, MD, have no COI concerning the content of this presentation and I have not received any personal or institutional grant or sponsorship or financial compensation for this lecture.

There is an unmet need in the management of PCI in patients with AF

20–30% of patients with AF and an indication for continuous OAC have coexisting CAD and therefore may require undergoing PCI

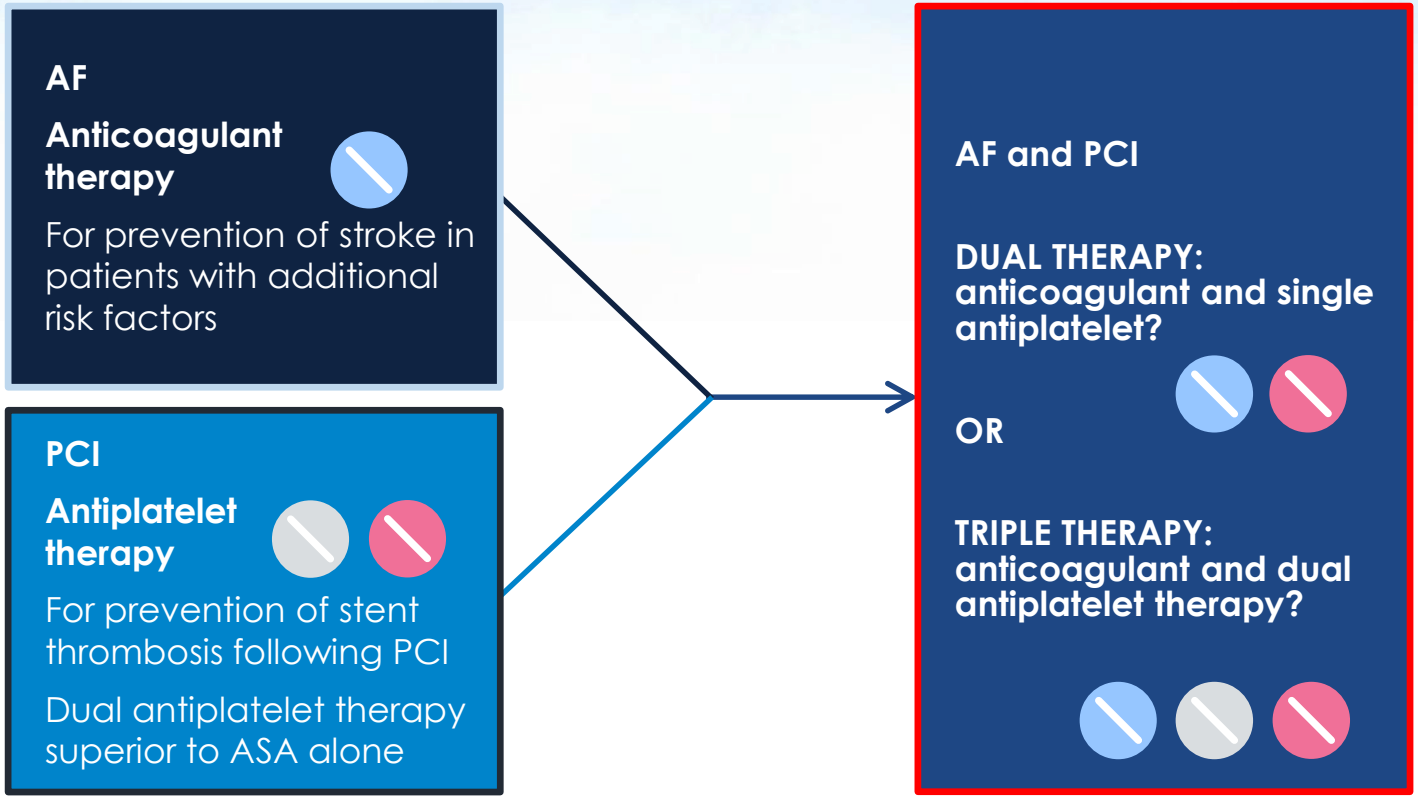


An estimated **1–2 million anticoagulated patients** in Europe are candidates for PCI procedures

Stenting requires follow-up treatment with antiplatelets, which puts anticoagulated patients at **higher risk of bleeding**

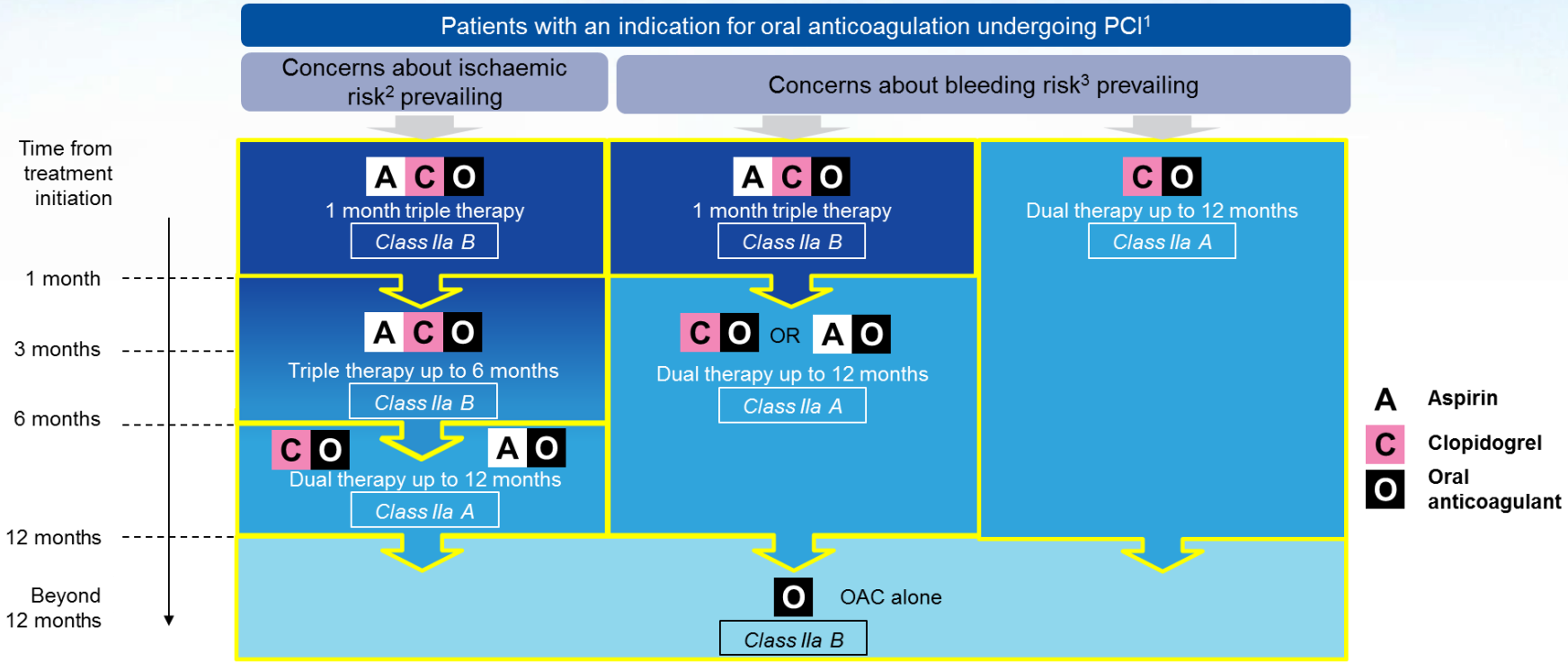
CAD; coronary artery disease; PCI, percutaneous coronary intervention
Lip et al. Thromb Haemost 2010

What combination of therapy is optimal for patients with AF undergoing PCI?



ASA, acetylsalicylic acid; PCI, percutaneous coronary intervention
Kirchhof et al. Eur Heart J 2016; Lip et al. Eur Heart J 2014

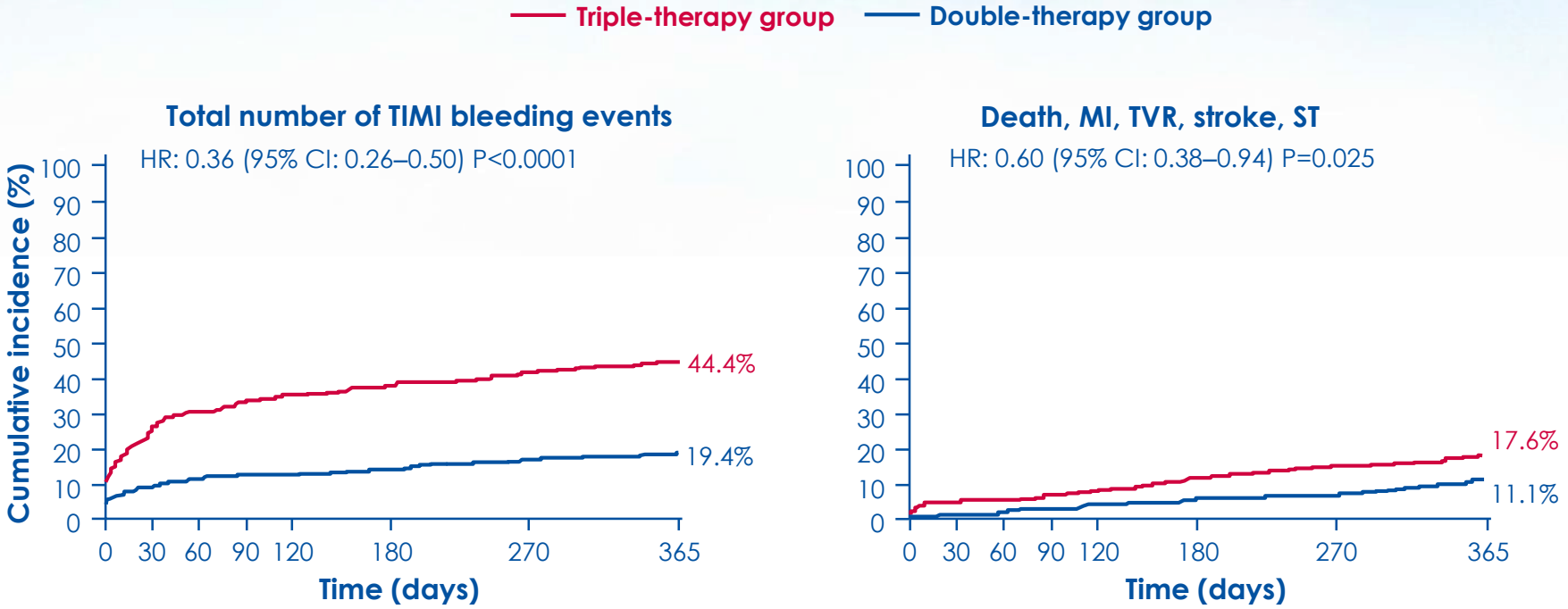
New ESC focused update on dual antiplatelet therapy in coronary artery disease



1. Periprocedural administration of aspirin and clopidogrel during PCI is recommended irrespective of the treatment strategy; 2. High ischaemic risk is considered as an acute clinical presentation or anatomical/procedural features which might increase the risk for myocardial infarction; 3. Bleeding risk can be estimated by HAS-BLED or ABC score.

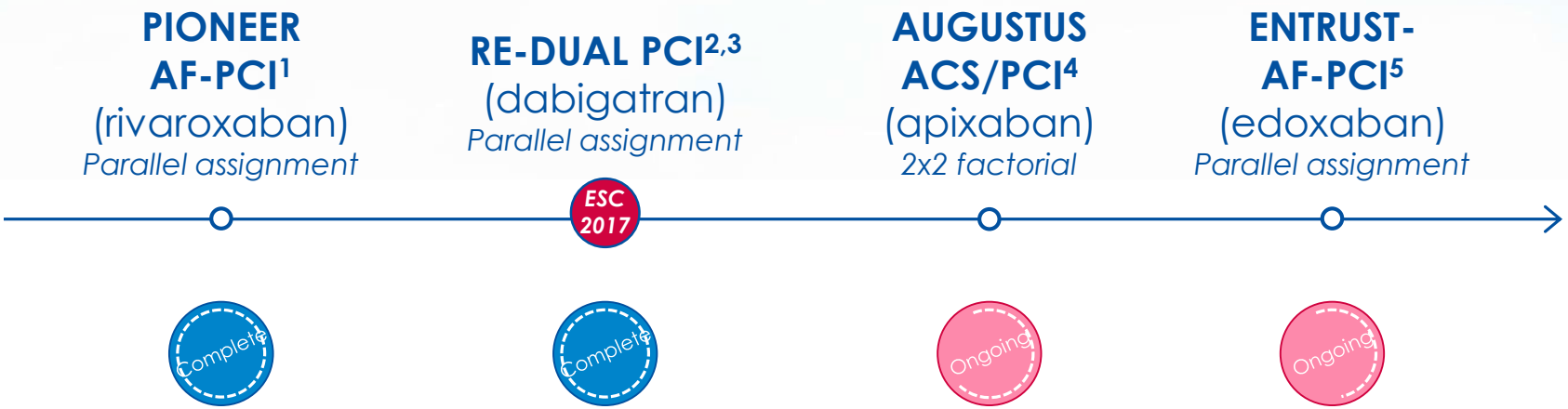
Valgimigli et al. Eur J Cardiothorac Surg 2017

WOEST: dual thx with VKA + clopidogrel (excluding ASA) reduces bleeding risk vs triple thx without compromise on efficacy



573 patients receiving OAC and undergoing PCI in open-label, randomized WOEST trial
PCI, percutaneous coronary intervention; ST, stent thrombosis; TIMI, Thrombolysis In Myocardial Infarction; TVR, target vessel revascularisation. Dewilde et al. Lancet 2013

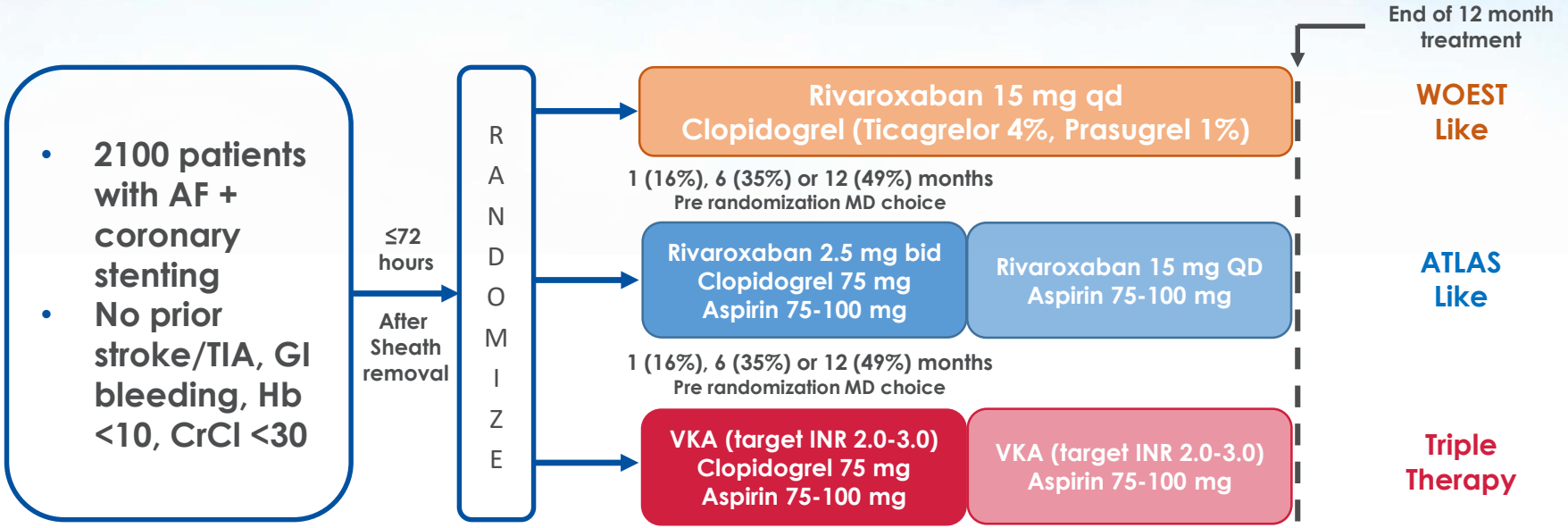
Antithrombotic therapy in patients with NVAF after PCI/post-ACS: a hot topic for research



*Patients receiving OAC + antiplatelet

1. Gibson et al. N Engl J Med 2016; 2. Cannon et al. Clin Cardiol 2016; 3. ClinicalTrials.gov: NCT02164864;
4. ClinicalTrials.gov: NCT02415400; 5. ClinicalTrials.gov: NCT02866175

PIONEER AF-PCI compared regimens of rivaroxaban with single or dual antiplatelet therapy versus triple therapy with VKA

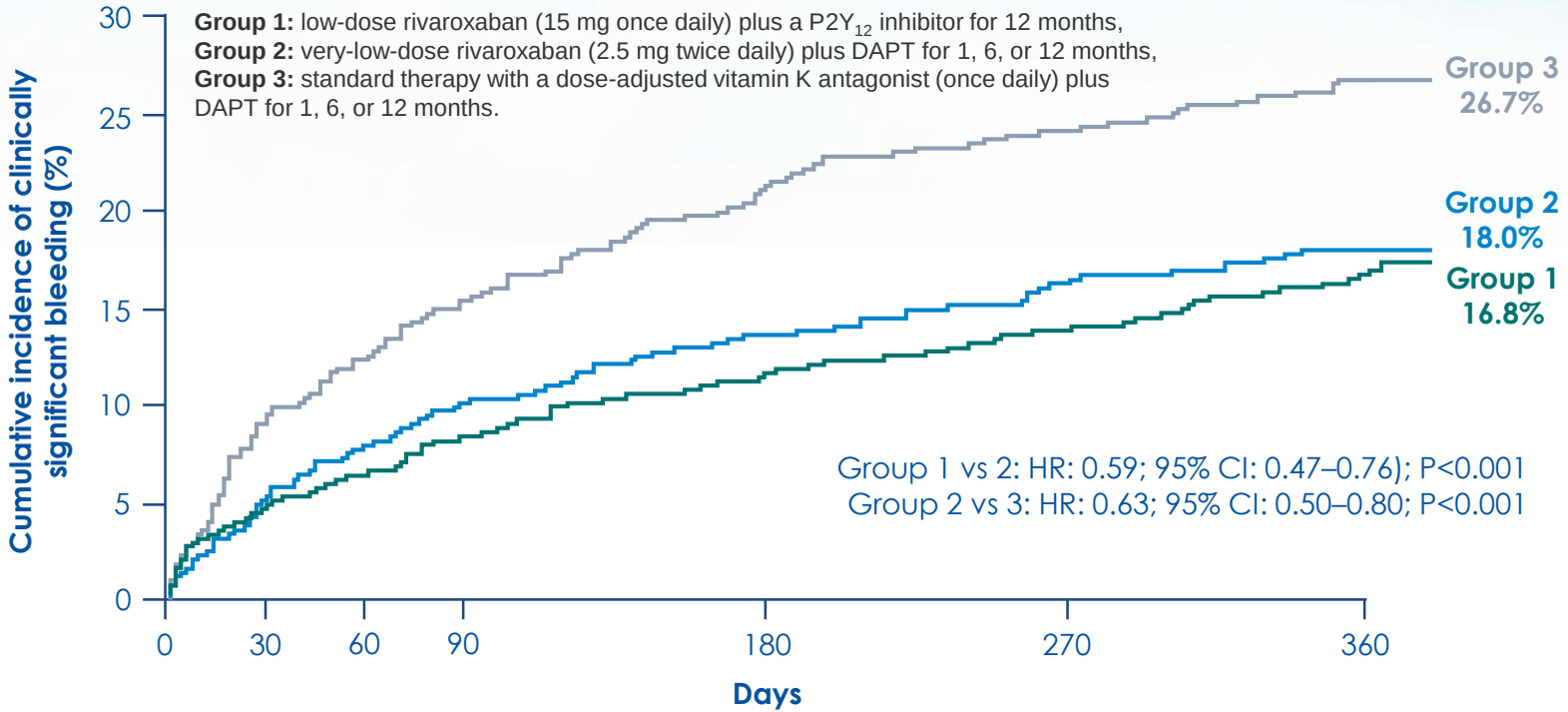


- Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke

Gibson CM et al. N Engl J Med 2016; Gibson CM et al. Circulation 2016

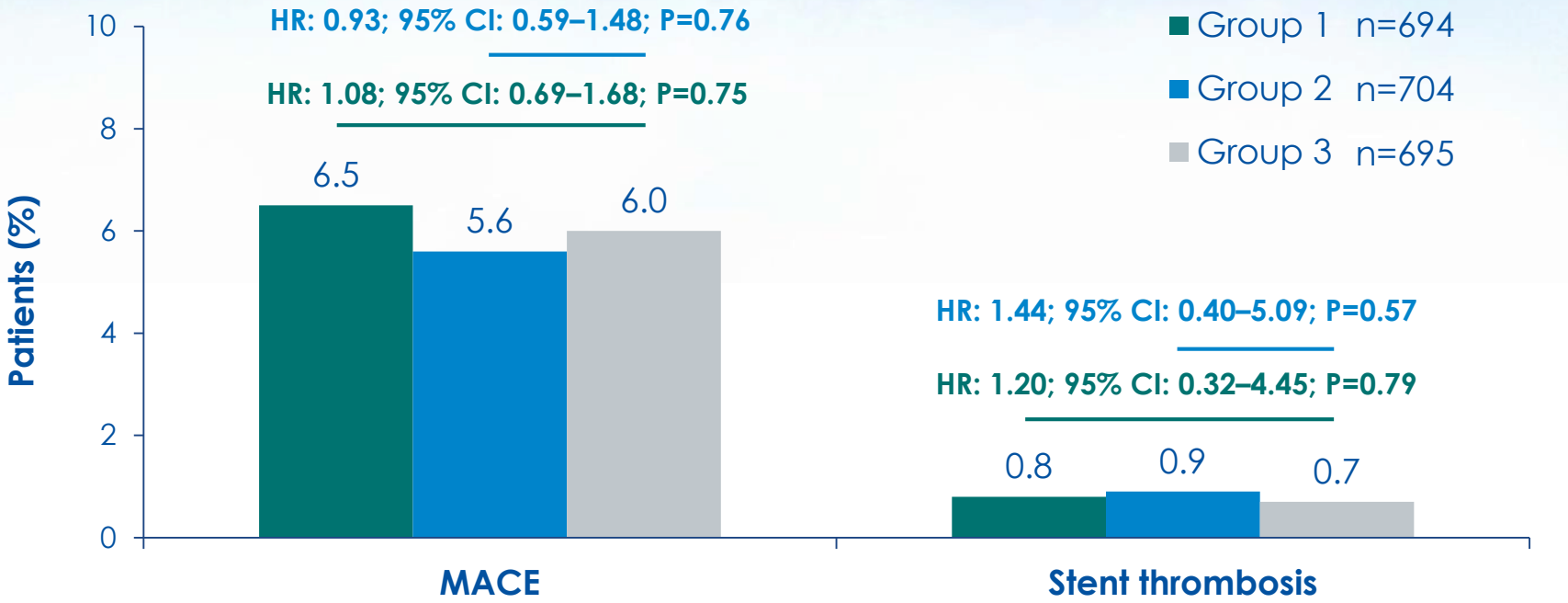
PIONEER AF-PCI: first occurrence of clinically significant bleeding events

Composite of bleeding events*



*Composite of major bleeding or minor bleeding according to TIMI criteria or bleeding requiring medical attention; †Trial not powered to definitively establish superiority or noninferiority. TIMI, Thrombolysis in Myocardial Infarction;
Gibson et al. N Engl J Med 2016

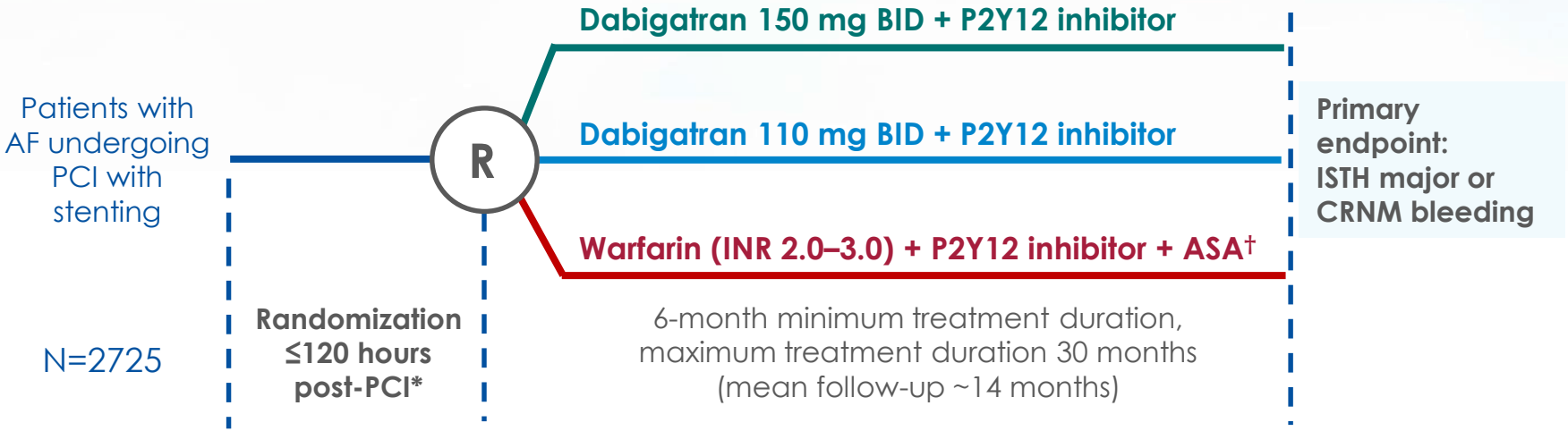
PIONEER AF-PCI: similar rates of thromboembolic events across treatment groups, with low power to demonstrate efficacy



The study was not powered to show superiority or non-inferiority between treatments in efficacy endpoints

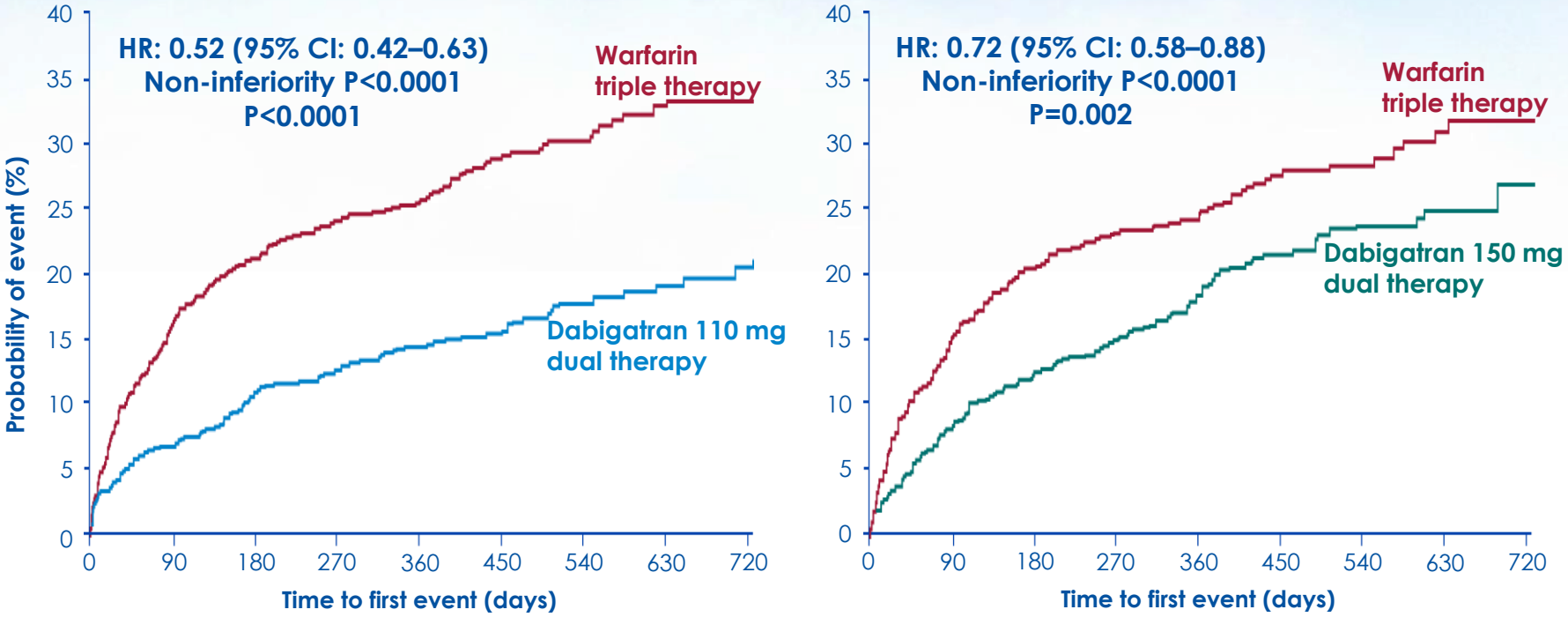
MACE, major adverse cardiac event (composite of CV death, MI, and stroke); Gibson et al. N Engl J Med 2016

RE-DUAL PCI tested the safety and efficacy of two regimens of dual therapy with dabigatran without ASA vs triple therapy with warfarin



*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; Cannon et al. N Engl J Med 2017

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

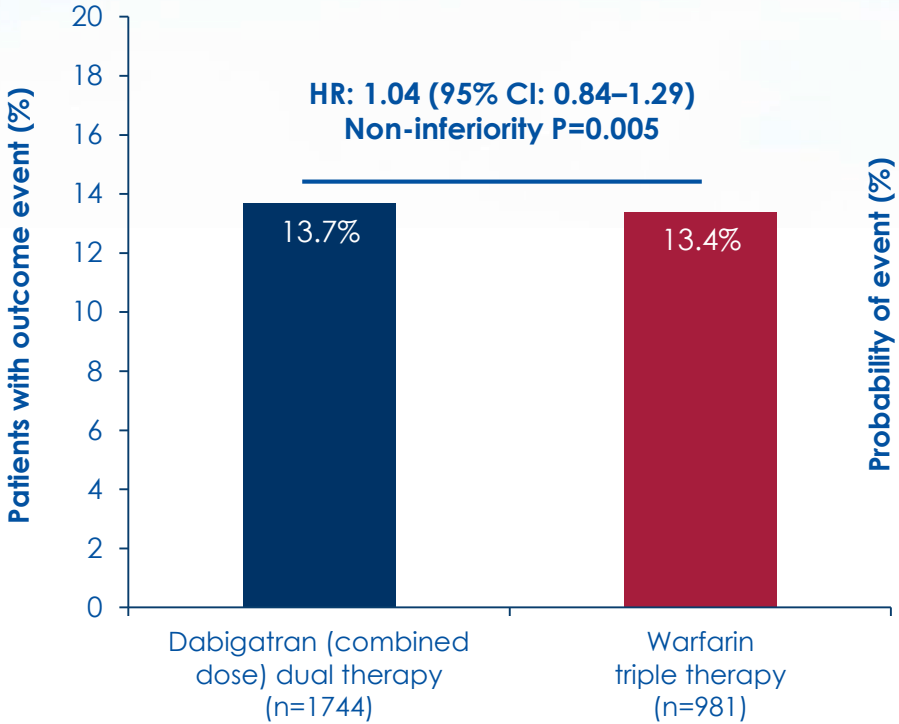


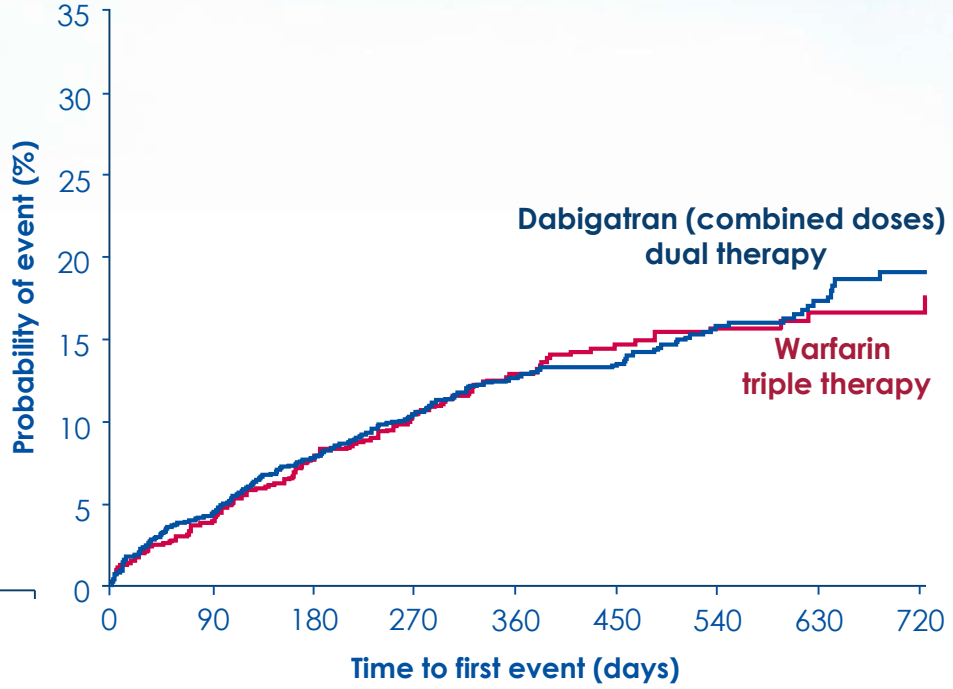
For the dabigatran 150 mg vs warfarin comparison, elderly patients outside the USA (≥80 years) and Japan (≥70 years) are excluded. Full analysis set presented

CRNMBE, clinically relevant non-major bleeding event; ISTH, International Society on Thrombosis and Haemostasis; Cannon et al. N Engl J Med 2017

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

Composite endpoint of death or thromboembolic event (MI, stroke or systemic embolism) or unplanned revascularization (PCI/CABG)

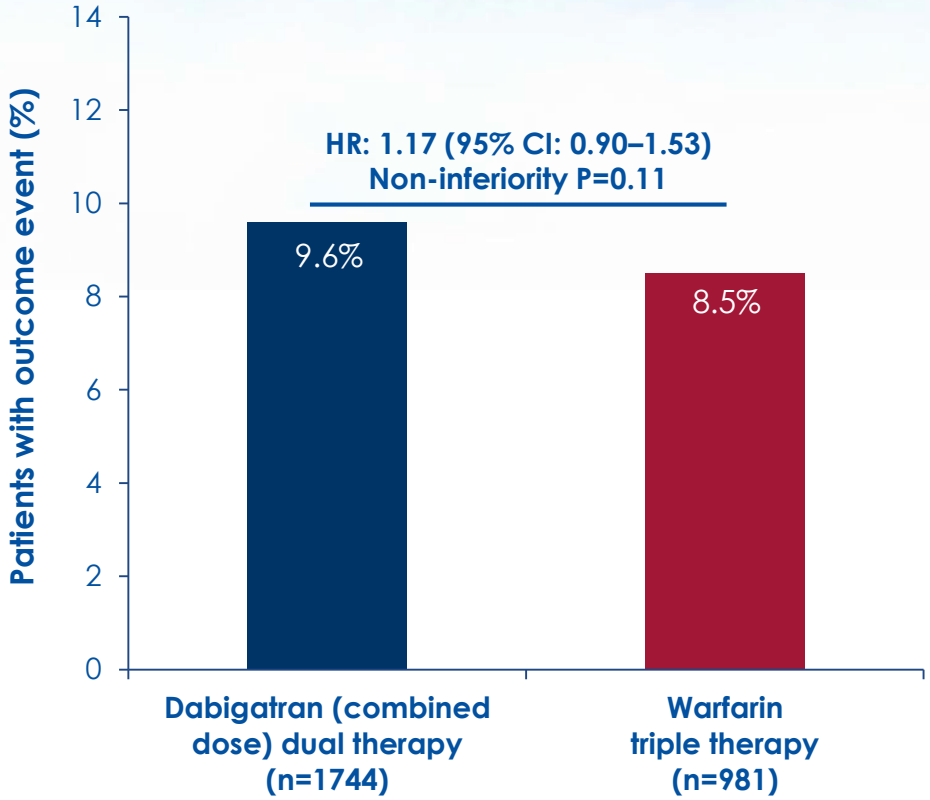




CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention

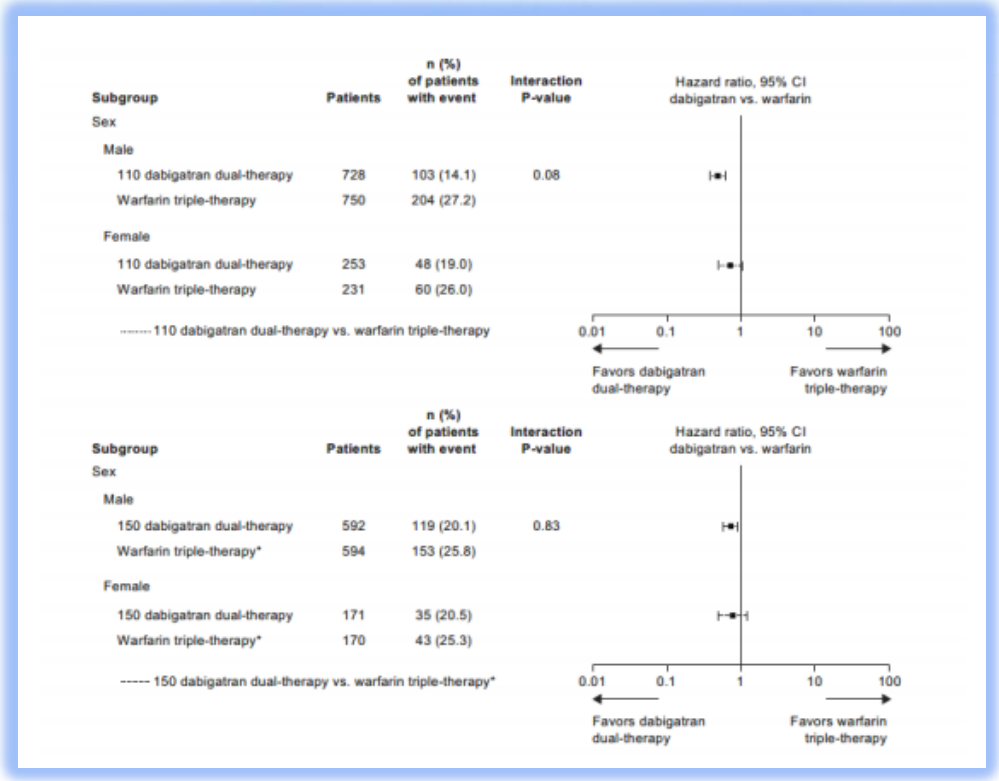
Cannon et al. N Engl J Med 2017

Secondary endpoint: time to death or thromboembolic event (death, MI, stroke or SE)



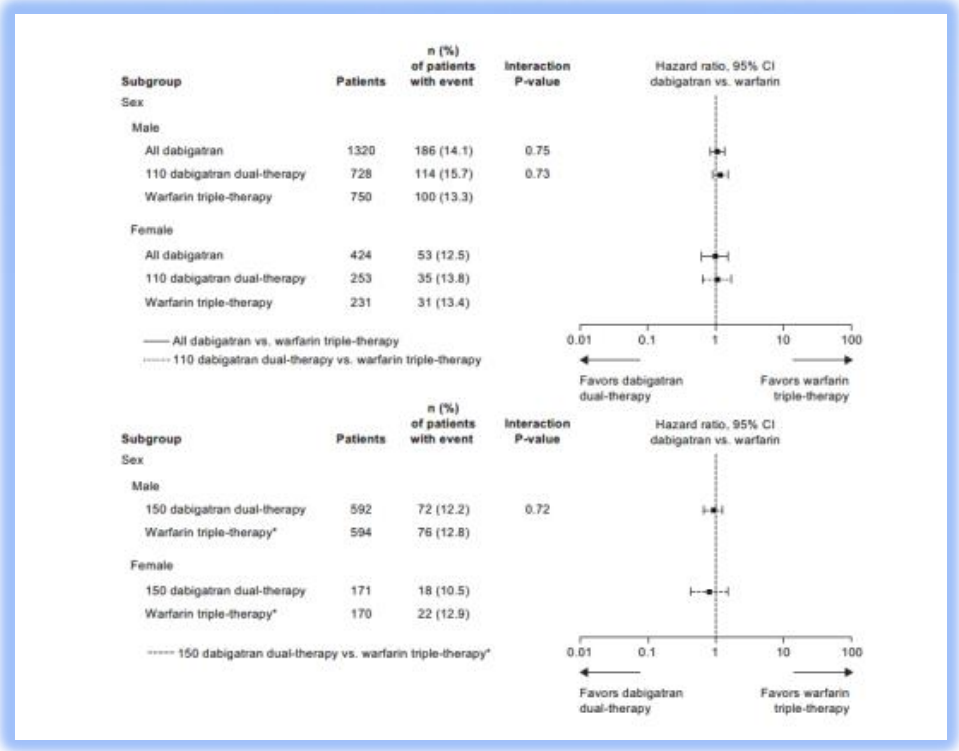
Cannon et al. N Engl J Med 2017

Primary ISTH bleeding endpoint according to gender: no sex-related interaction in RE-DUAL PCI



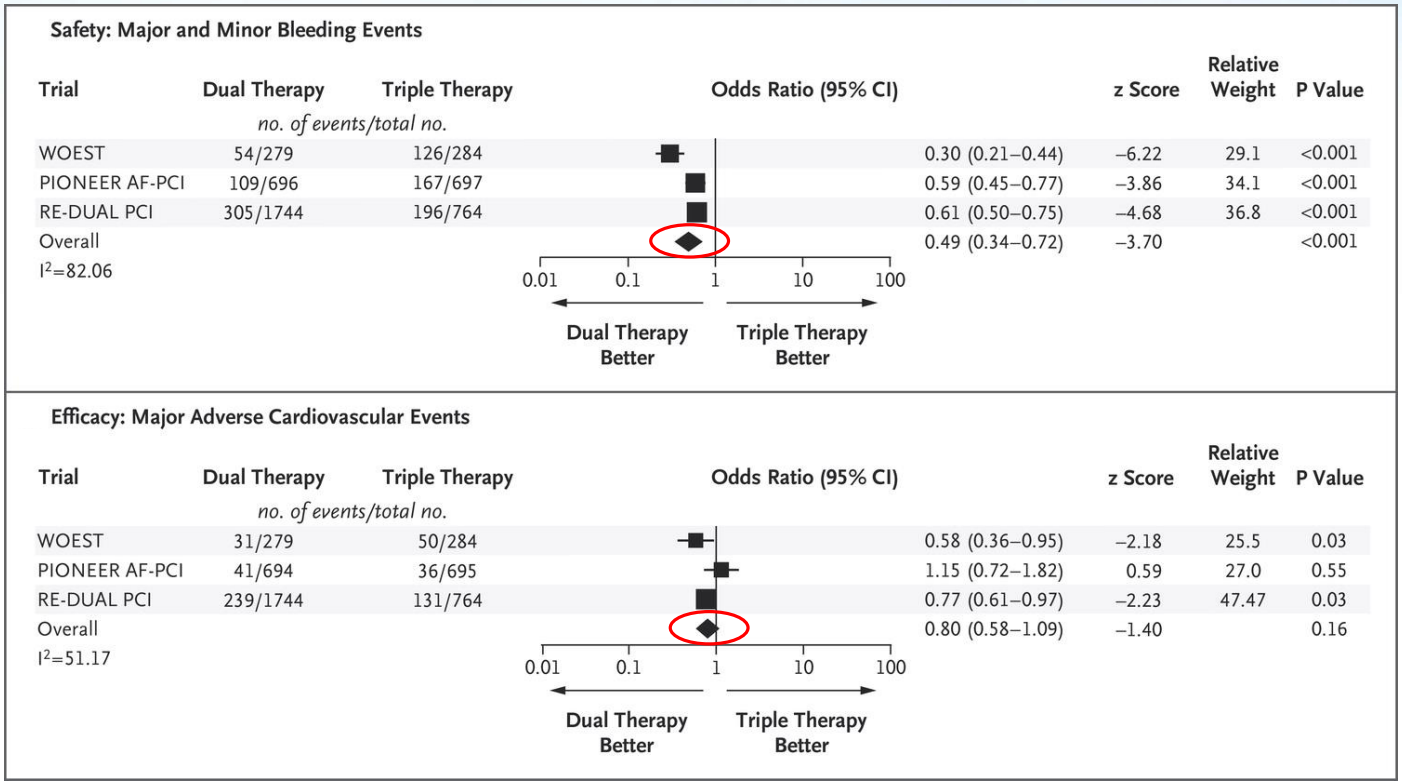
Cannon et al. N Engl J Med 2017

Secondary efficacy endpoint according to gender:
Thromboembolic Events or Death or Unplanned Revascularization by Subgroup.



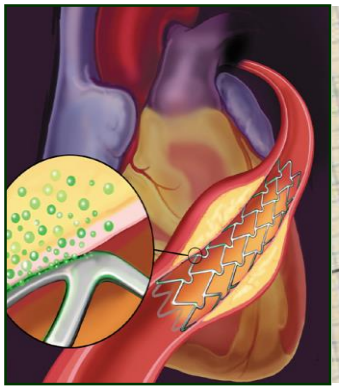
Cannon et al. N Engl J Med 2017

Antithrombotic therapy in AF patients after PCI: Meta-analysis of results from WOEST, PIONEER AF-PCI and RE-DUAL PCI trials



Piccini JP, Jones WS. N Engl J Med 2017

How to implement the data to current clinical practice?



Assessing thromboembolic stroke risk: CHA_2DS_2-VASc

CHA_2DS_2-VASc criteria	Score
CHF/LV dysfunction	1
Hypertension	1
Age ≥75 yrs	**2**
Diabetes mellitus	1
Stroke/TIA/TE	**2**
Vascular disease	1
Age 65–74 yrs	1
Sex **c**ategory (i.e. female gender)	1

CHF=congestive heart failure; LV=left ventricular; TE=thromboembolism;
TIA=transient ischaemic attack - Lip GY et al. Chest 2010; Lip GY et al. Stroke 2010

Total score	Annual stroke rate N=1084[1]	Annual stroke rate N=73,538[2]
0	1	0.0
1	422	1.3
2	1230	2.2
3	1730	3.2
4	1718	4.0
5	1159	6.7
6	679	9.8
7	294	9.6
8	82	6.7
9	14	15.2

1. Lip G et al. Chest 2009;
2. Olesen JB et al. BMJ 2011

Assessing bleeding risk: HAS-BLED Score

HAS-BLED is a scoring system developed to assess 1-year risk of major bleeding in patients taking anticoagulants with atrial fibrillation.

	Condition	Points
H	Hypertension: (uncontrolled, >160 mmHg systolic)	1
A	Abnormal renal function: Dialysis, transplant, Cr >2.26 mg/dL or >200 µmol/L	1
	Abnormal liver function: Cirrhosis or Bilirubin >2x Normal or AST/ALT/AP >3x Normal	1
S	Stroke: Prior history of stroke	1
B	Bleeding: Prior Major Bleeding or Predisposition to Bleeding	1
L	Labile INR: (Unstable/high INR), Time in Therapeutic Range < 60%	1
E	Elderly: Age > 65 years	1
D	Prior Alcohol or Drug Usage History (≥ 8 drinks/week)	1
	Medication Usage Predisposing to Bleeding: (Antiplatelet agents, NSAIDs)	1

Pisters, R et al. *Chest*. 2010; 138: 1093–100.

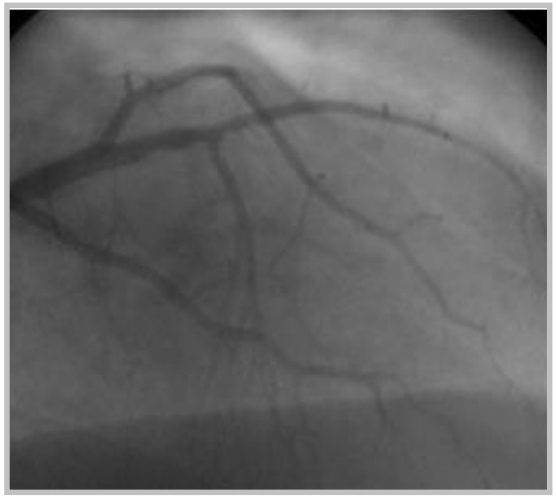
DAPT Score

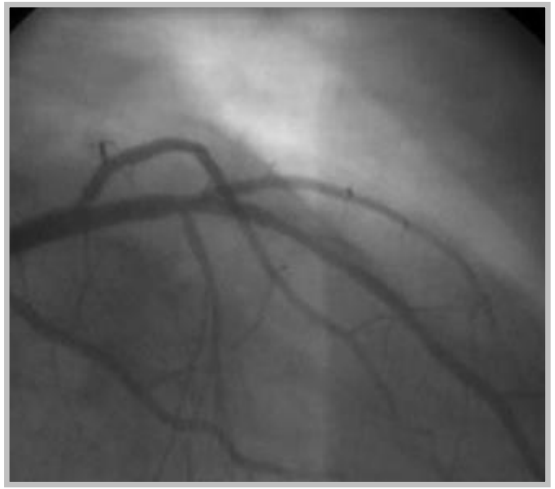
Yeh RW et al. JAMA 2016

Factors Used to Calculate a "DAPT Score"	
Variable	**Points**
Age ≥75 y	-2
Age 65 to <75 y	-1
Age <65 y	0
Current cigarette smoker	1
Diabetes mellitus	1
MI at presentation	1
Prior PCI or prior MI	1
Stent diameter <3 mm	1
Paclitaxel-eluting stent	1
CHF or LVEF <30%	2
Saphenous vein graft PCI	2

Case #1

- 62 YO male, HTN, DM, Current smoker, CKD stage III.
  - ✓Creat=1.5 / GFR = 56
- Admitted d/t recent MI
  - ✓AP for 10 days, TnT +, Q waves V1-3
- On admission ECG – AF of unknown duration.
- On angiography –mid LAD obstruction bifurcation with a large diagonal and septal branches.
- Underwent PCI to LAD (DES) and POBA to diagonal branch.





Case #1

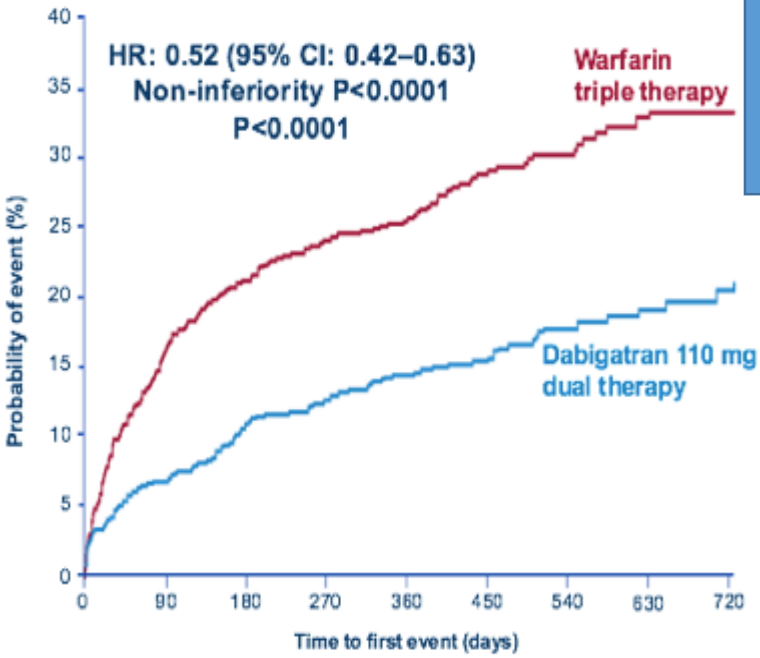
Clinical dilemma:

- High bleeding risk (HAS-BLED=3).
- High stroke risk (CHA_2DS_2 VASC=3).
- High coronary ischemic risk (DAPT score =3).
- How to maintain the most effective DAP thx?

- **What are the most relevant data?**

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

RE-DUAL PCI
Study in NVAF patients undergoing PCI

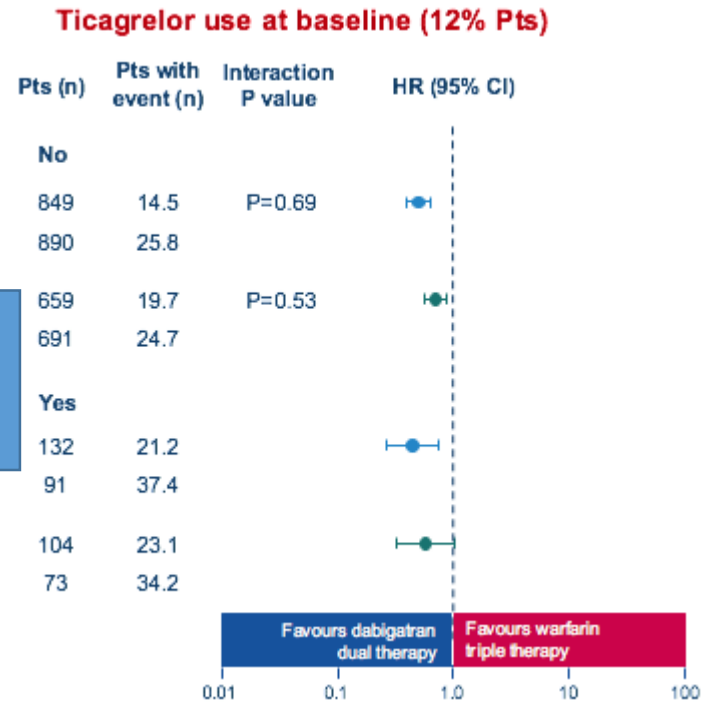


50% reduction in bleeding risk while maintaining non-inferiority for stroke risk with low dose Dabigatran

Consistent results with either Clopidogrel or Ticagrelor - potential for reduced ischemic risk (PLATO, PEGASUS)

Subgroup analysis: ticagrelor use at baseline Time to first ISTH MBE or CRNMBE

RE-DUAL PCI
Study in NVAF patients undergoing PCI



Cannon CP et al. N Engl J Med2017

Case #1

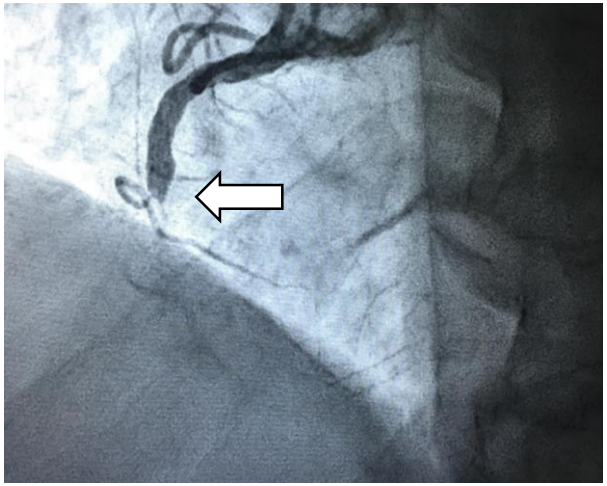
- Patient was discharged on day 5, treated with Dabigatran 110 mg BID and Plavix 75 mg QD for one year post MI and PCI.

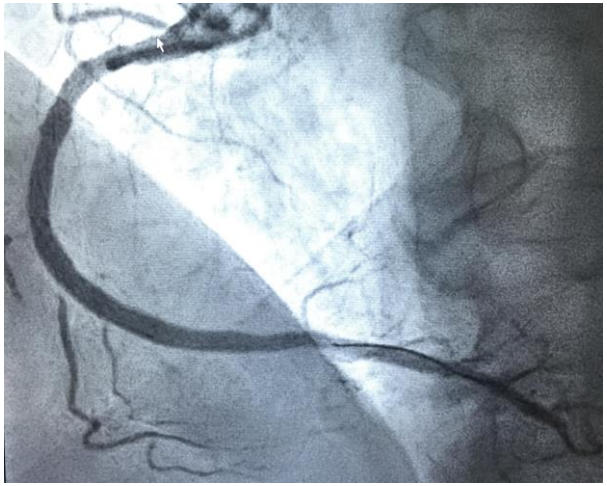
- BUT…patient also could have been treated with Dabigatran 110 mg BID and Ticagrelor 90 mg BID for one year post MI and PCI.

Now we have the confirming data!

Case #2

- 73 YO female, S/P PCI (RCA,OM2), CAF (on Warfarin) S/P TIA, low compliance to medical treatment.
- Renal function is normal (Creat. = 1.0)
- Referred for elective angiography d/t AP and a positive SPECT (large ischemia in the RCA territory).
- On angiography –In stent occlusion in the mid RCA.
- Underwent PCI with DES in the RCA.





Case #2

Clinical dilemma:

- High bleeding risk but perhaps modifiable (HAS-BLED=3, would have been 2 if compliance was not an issue).
- High stroke risk (CHA_2DS_2 VASC=5).
- Average coronary ischemic risk (DAPT score=0).

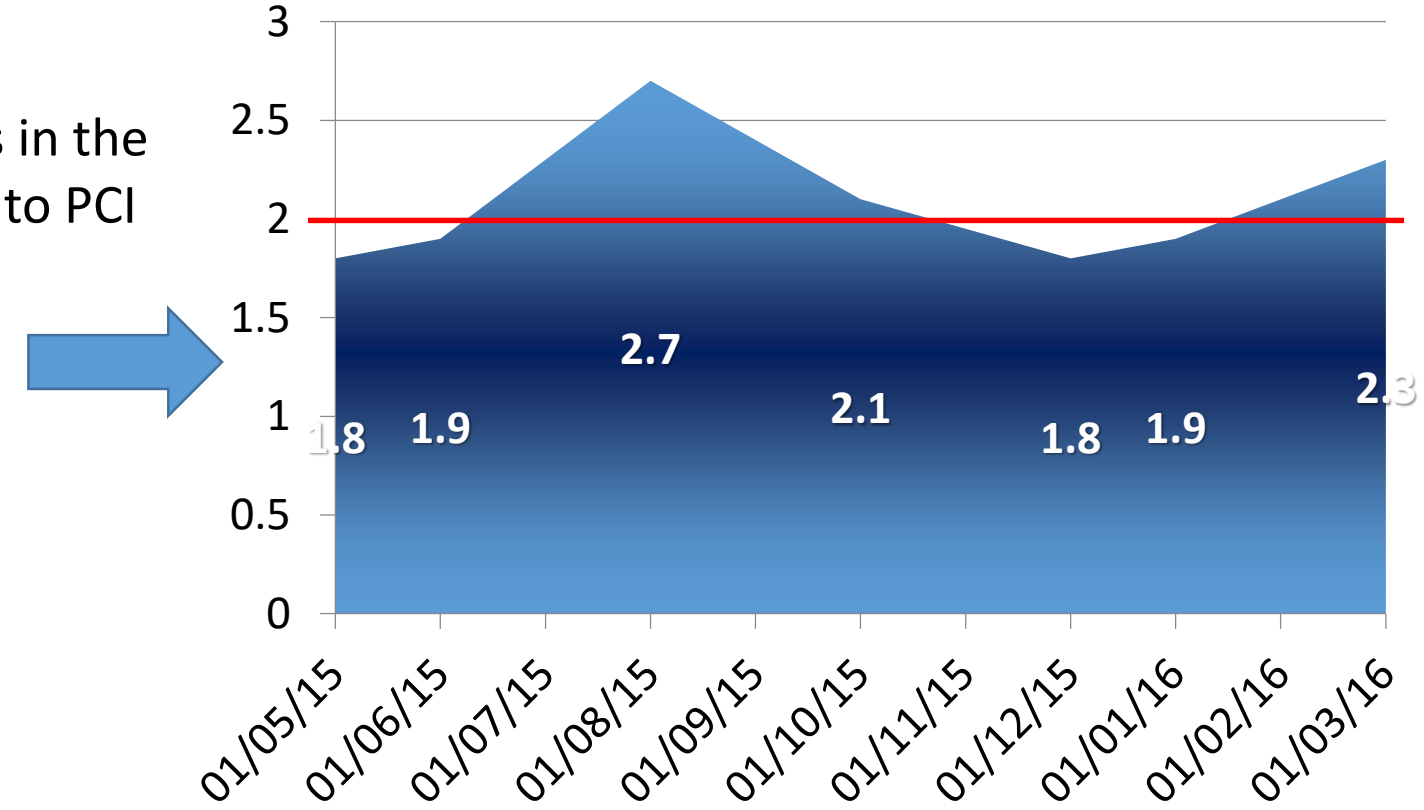
Recommendations to minimize bleeding risk

√	• Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA_2DS_2-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.
√	• Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.
√	• Consider the use of NOACs instead of VKA.
	• Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. > 65–70%) when VKA is used.
√	• Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.[a]
√	• Clopidogrel is the $P2Y_{12}$ inhibitor of choice.
	• Use low-dose (≤ 100 mg daily) aspirin.
	• Routine use of PPIs.

Valgimigli M et al, 2017 ESC Focused update on DAPT

Case #2

INR values in the year prior to PCI



RE-DUAL PCI
Study in NVAF patients undergoing PCI

Summary of patient disposition

	Dabigatran 110 mg dual therapy	Dabigatran 150 mg dual therapy	Warfarin triple therapy
Randomized patients, n	981	763	981
Patients completing study			
on study medication	756	604	686
with premature medication discontinuation	130	99	163
Premature study discontinuation	95	60	132
Adverse event	65	41	59
Protocol violation	2	4	1
Loss to follow-up	4	3	2
Consent withdrawn	21	8	56
Missing/other	3	4	14
Mean duration of follow-up, months	14.1	14.3	13.8
Total patient-years	1013	803	933
Time in target INR range 2.0–3.0,* mean	n/a	n/a	64%

Cannon CP et al. N Engl J Med2017

Case #2

- Patient was discharged with Dabigatran 150mg BID + Clopidogrel 75 mg QD according to ischemic/embolic/bleeding risk scores and RE-DUAL PCI data.
- In such a patient, treatment with Dabigatran + SAPT (Clopidogrel) should reduce the bleeding risk (HAS-BLED have changed to 2) AND provide *better protection against the significant risk of stroke*.
- The duration of Plavix should be between 6-12 months according to ESC guidelines recommendations.

Conclusion

- Managing PCI and AF is a complex clinical task!
- A carful evaluation of the cardiac ischemic risk and the hazard of stroke in addition to bleeding potential should dictate the optimal balanced pharmacotherapy among women and men patients altogether.
- Female gender increase CHA_2DS_2-VASc risk score and in some studies also the post PCI bleeding frequency, further complicating the management of those patients.