NAVIGATING THROMBOSIS AND BLEEDING AT THE INTERSECTION OF ATRIAL FIBRILLATION AND CORONARY STENTING

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Objectives

- Design an evidence-based antithrombotic regimen in a patient with atrial fibrillation (AF) and acute coronary syndrome (ACS)
- Analyze the risks of bleeding and thrombosis in patients with AF and ACS based on published literature
- Discuss the current guideline recommendations for using antithrombotic therapy in patients with AF and ACS

Patient Case

- BA is a 63-year-old man who presents with worsening chest pain over the past week.
- At PCP office – ECG suggestive of ischemia
- Transferred to emergency department
  - Troponin T: 0.12 ng/mL
- Admitted or NSTEMI and possible PCI
- PMH and Medications:
  - Dyslipidemia: Atorvastatin 40 mg daily
  - Hypertension: Losartan 100 mg daily, Amlodipine 5 mg daily
  - Diabetes: Metformin 1000 mg BID, Aspirin 81 mg daily
  - Atrial Fibrillation: Warfarin, INR: 2.3

Patient Case

- Following morning, BA is taken for cardiac catheterization
  - Found to have 80% stenosis in his mid-LAD
    - Stented with Drug-eluting stent (DES)

- How do we manage his long-term antithrombotic therapy?
  - ACS + PCI with DES to mid-LAD
  - AF: previously taking warfarin

Which of the following would you recommend for AF stroke prevention therapy for BA?

a) Oral anticoagulation with Warfarin
b) Oral anticoagulation with a DOAC
c) Dual Antiplatelet Therapy (DAPT)
d) Aspirin monotherapy

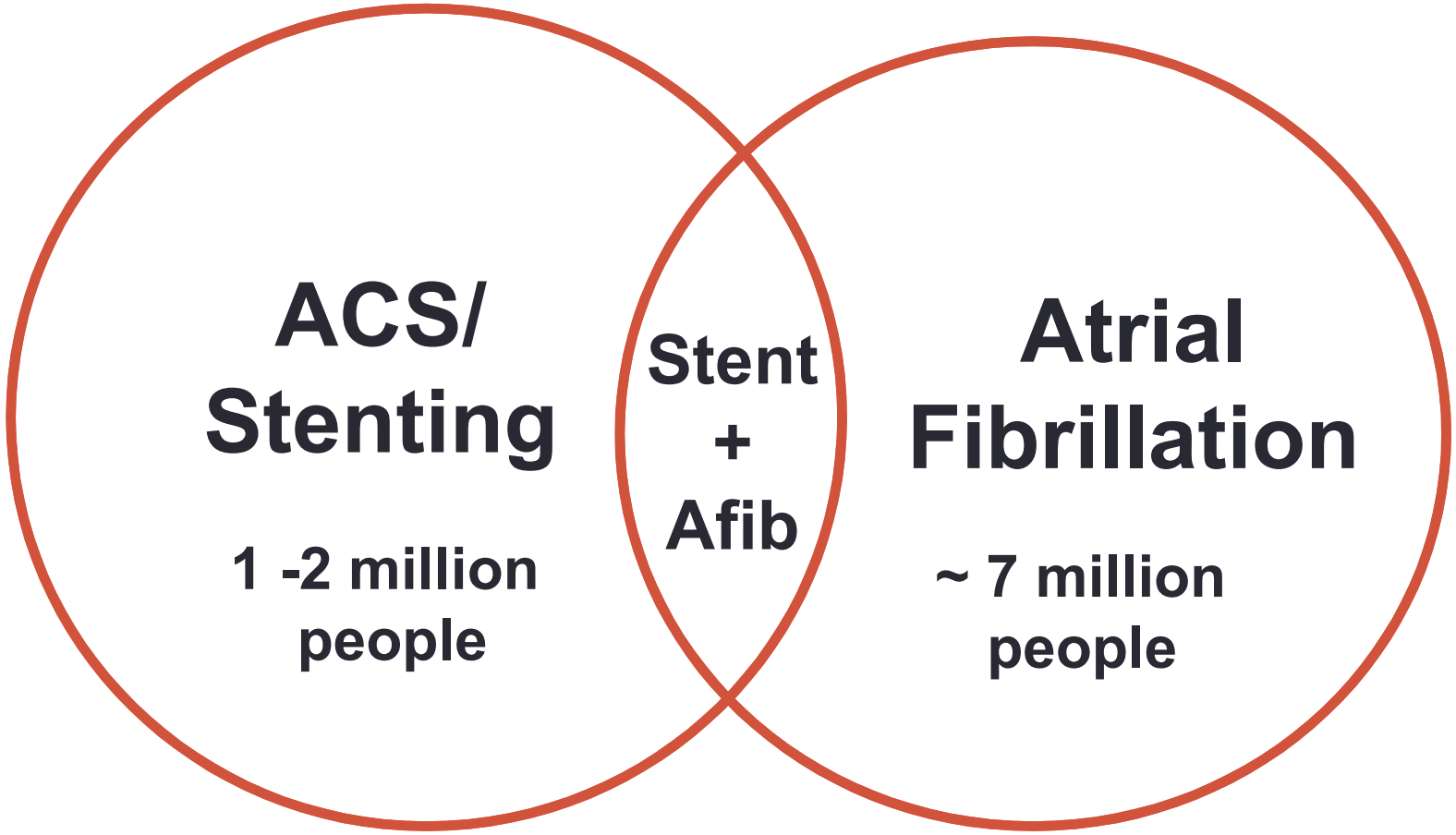
Which of the following would you recommend for preventing recurrent MI and stent thrombosis for BA's DES?

a) Aspirin monotherapy
b) Oral anticoagulation monotherapy
c) Aspirin + Oral anticoagulation
d) Aspirin + $P2Y_{12}$ inhibitor

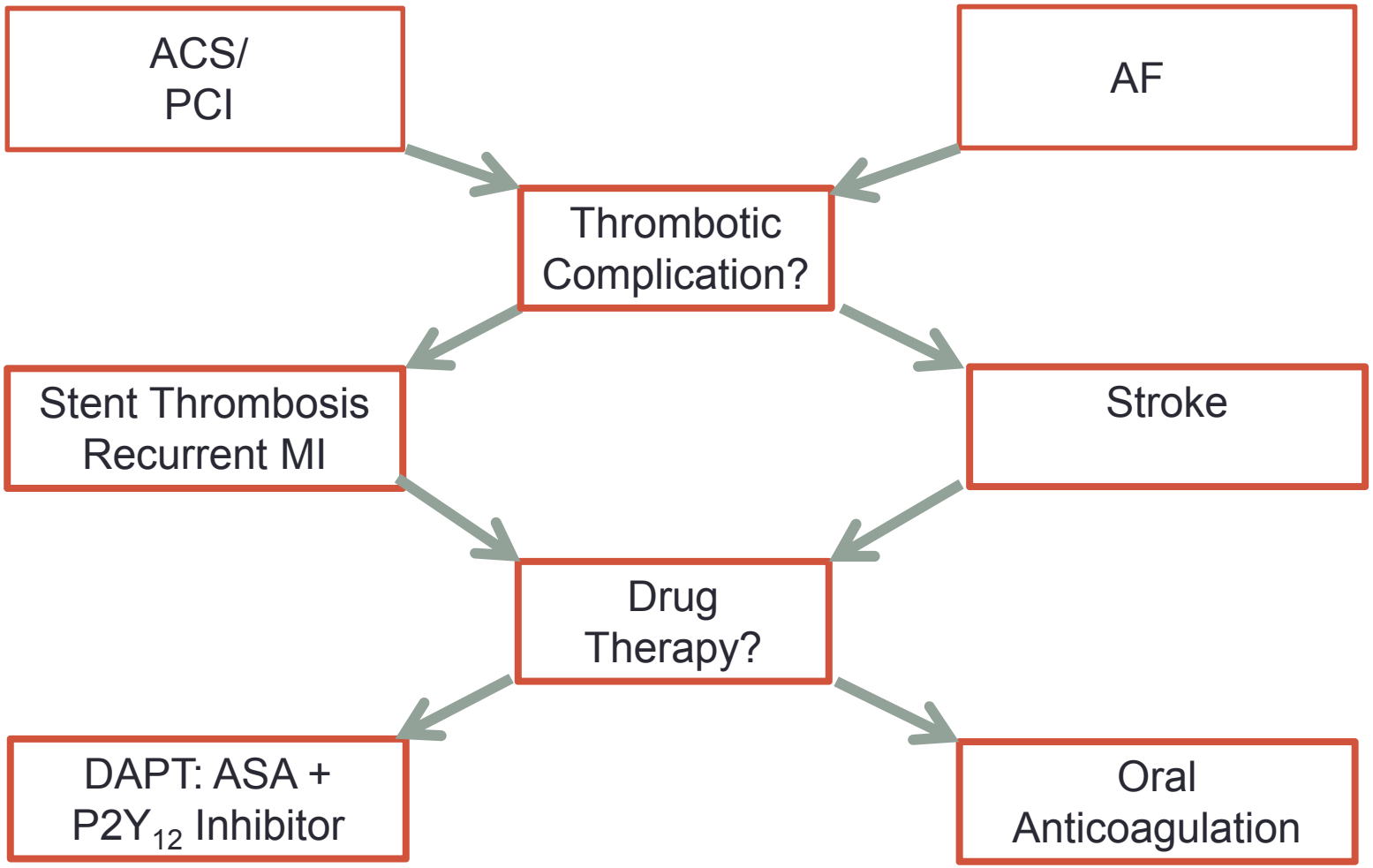
How would you manage his overall antithrombotic therapy?

a) Aspirin 81 mg daily + Clopidogrel 75 mg daily + Warfarin
b) Aspirin 81 mg daily + Prasugrel 10 mg daily + Warfarin
c) Aspirin 81 mg daily + Rivaroxaban 20 mg daily
d) Clopidogrel 75 mg daily + Dabigatran 150 mg BID

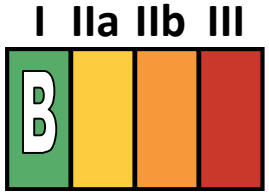
The AF and ACS Cross Over



What's the Antithrombotic Challenge?



Duration of DAPT per PCI Guideline



$P2Y_{12}$ inhibitor therapy should be **given for at least 1 year** to post PCI patients treated with coronary stents for ACS, using the following maintenance doses:

- Clopidogrel 75 mg daily; or
- Prasugrel 10 mg daily; or
- Ticagrelor 90 mg twice a day

Continuation of DAPT beyond 12 months may be considered in patients undergoing DES placement

Clopidogrel should given to patients receiving drug-eluting stents for a non-ACS indication for at least 12 months if the patients are not at high risk of bleeding; or in patients receiving bare metal stents for a non-ACS indication for a minimum of 1 month, but ideally for 12 months

- If the patient received a bare metal stent and is at increased risk of bleeding then clopidogrel should be given for a minimum of 2 weeks

Levine G, et al. *J Am Coll Cardiol.* 2011;58:e44-122

2018 Chest Guidelines: Antithrombotic Therapy for AF

- CHADS-VASc = 0 (1 in females): No Therapy
- CHADS-VASc = 1 (2 in females): Oral Anticoagulation preferred over ASA, DAPT
- CHADS-VASc = 2 (≥ 3 in females): Oral Anticoagulation preferred over ASA, DAPT

*** Prefer DOACs over Warfarin***

** When using warfarin: goal TTR ≥ 70%

Lip GY et al. **CHEST (2018), doi: 10.1016/j.chest.2018.07.040.**

ASPIRIN AND WARFARIN IN ACS

Aspirin and Warfarin in ACS

MACE, %						
	Subjects, n	ASA alone	Warfarin alone	ASA + Warfarin	HR (95%)	p
CHAMP†	5059	31.4		30.9	1.01 (0.9-1.14)	NS
ASPECT-2†	993	9	5	5	0.52 (0.28-0.98)	
APRICOT-2*	274	34		14		<0.01
WARIS-II†	3630	20	16.7	15	0.71 (0.6-0.83)	0.001

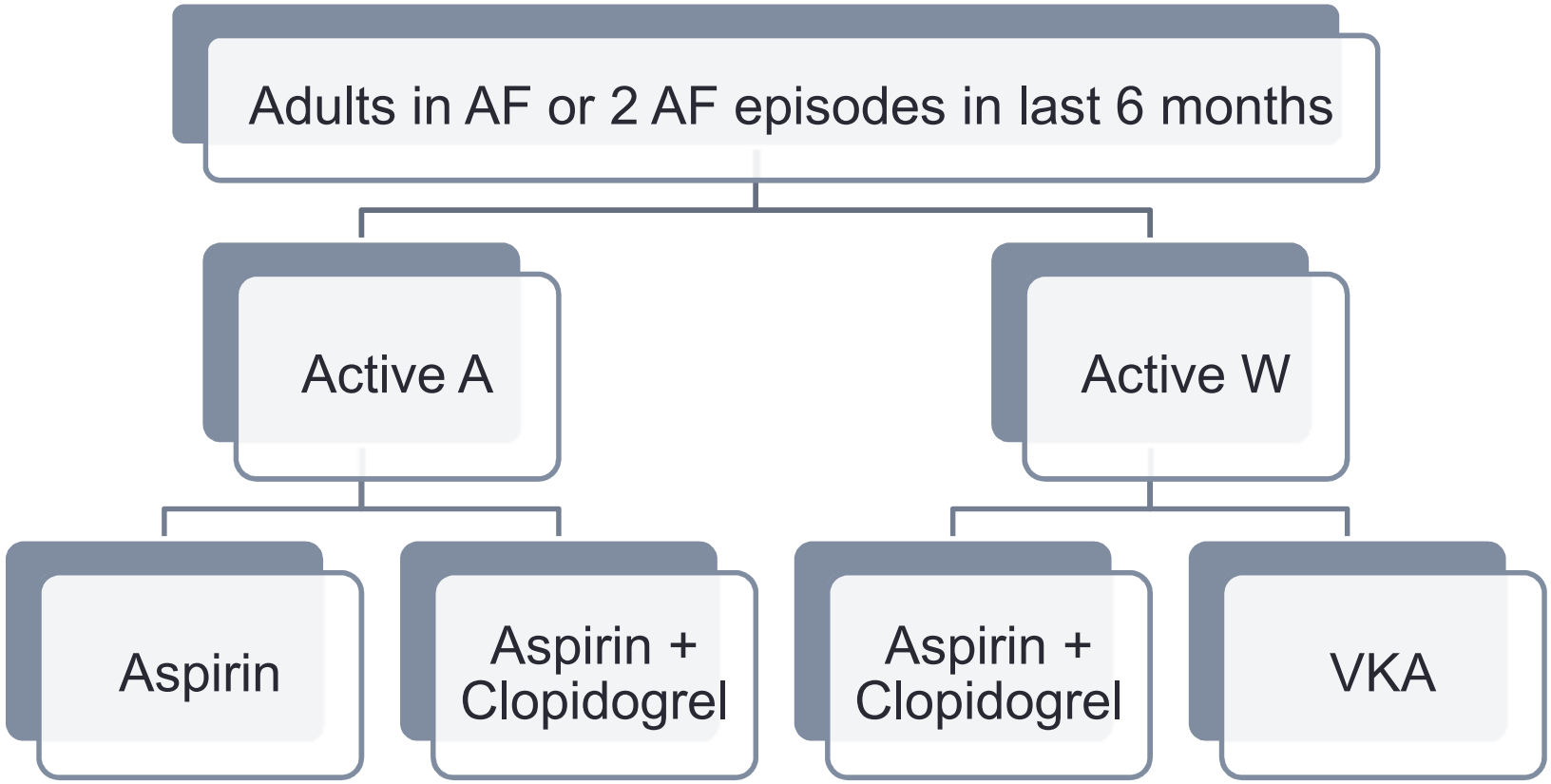
WARIS-II: Major bleeding was 0.62% for warfarin vs. 0.17% for Aspirin (p<0.001)
Minor bleeding was 2.14% for warfarin vs. 0.84% for Aspirin
-Target INR 2.8 – 4.2 in the warfarin alone group

†= death, MI, or stroke; *= Death, reinfarction, revascularization

Fiore LD, et al. Circulation, 2002; 105: 557-63. Van Es RF, et al. Lancet 2002; 360: 109-13
Brouwer MA, et al. Circulation. 2002; 106: 659-65 Hurlen M, et al. NEJM, 2002; 347(13): 969-74

DAPT IN ATRIAL FIBRILLATION

ACTIVE Trials



1° Outcome: Composite of stroke, non-CNS systemic embolism, MI, CV death

2° Outcome: Stroke; individual outcomes of composite, bleeding, net clinical benefit

Connolly SJ, et al. NEJM 2009; 360: 2066-78
Connolly SJ, et al. Lancet 2006; 367: 1903-12

ACTIVE-W

	Clopidogrel/ASA n (%/yr)	Warfarin n (%/yr)	RR (95%)	P-Value
Ischemic events				
Primary Outcome	234 (5.6)	165 (3.93)	1.44 (1.18-1.76)	0.0003
Stroke	100 (2.39)	59 (1.4)	1.72 (1.24-2.37)	0.001
MI	36 (0.86)	23 (0.55)	1.58 (0.94-2.67)	0.09
Non-CNS embolism	18 (0.43)	4 (0.1)	4.66 (1.58-13.8)	0.005
Death	159 (3.8)	158 (3.76)	0.93 (0.45-1.94)	0.85
Bleeding Events				
Major	101 (2.42)	93 (2.21)	1.10 (0.83-1.45)	0.53
Minor	568 (13.58)	481 (11.45)	1.23 (1.09-139)	0.0009
Any Bleeding	644 (15.40)	555 (13.21)	1.21 (1.08-1.35)	0.001
Net clinical benefit	316 (7.56)	229 (5.45)	1.41 (1.19-1.67)	<0.0001

Connolly SJ, et al. Lancet 2006; 367: 1903-12

Triple Therapy

- Triple therapy is defined as dual-antiplatelet therapy (DAPT) with concomitant oral anticoagulation.

- Commonly used in patients who have indications for both DAPT and OAC
  - Atrial Fibrillation (AF)
  - ACS and/or PCI with stenting

Triple Therapy: Risks

- Major bleeding is higher!

- Numerous published data have demonstrated that compared with dual therapies:
  - Patients with DAPT + OAC have much higher rates of major bleeding

Danish National Patient Registry

	Patients treated for AF		Patients treated for MI	
	Incidence (% per person-yr)	Unadjusted risk ratio (95% CI)	Incidence (% per person-yr)	Unadjusted risk ratio (95% CI)
ASA alone	3.7	0.96 (0.95 – 0.96)	2.6	Reference
Clopidogrel Alone	5.6	1.45 (1.22 – 1.66)	4.6	1.75 (1.75 – 1.76)
VKA alone	3.9	Reference	4.3	1.63 (1.62 – 1.65)
ASA/Clopidogrel	7.4	1.91 (1.59 – 2 21)	3.7	1.43 (1.43 – 1.43)
ASA/VKA	6.9	1.75 (1.71 – 1.79)	5.1	1.94 (1.94 – 1.95)
Clopidogrel/VKA	13.9	3.57 (2.88 – 4.22)	12.3	4.68 (4.64 – 4.74)
Triple Therapy	15.7	4.03 (3.22 – 4.78)	12.0	4.57 (4.55 – 4.61)

Risk of Bleeding Event – includes admissions for bleeding diagnoses, nonfatal bleeding episodes, or bleeding listed as cause of death

Sorensen R, et al. Lancet. 2009; 374: 1967-74. Hansen ML, et al. Arch Intern Med. 2010; 170(10): 1433-41

WOEST: Can we do better?

Age 18-80 years old with an indication for PCI and a clear need for ≥ one year oral anticoagulation

- Warfarin, Clopidogrel , ASA
- Warfarin and Clopidogrel

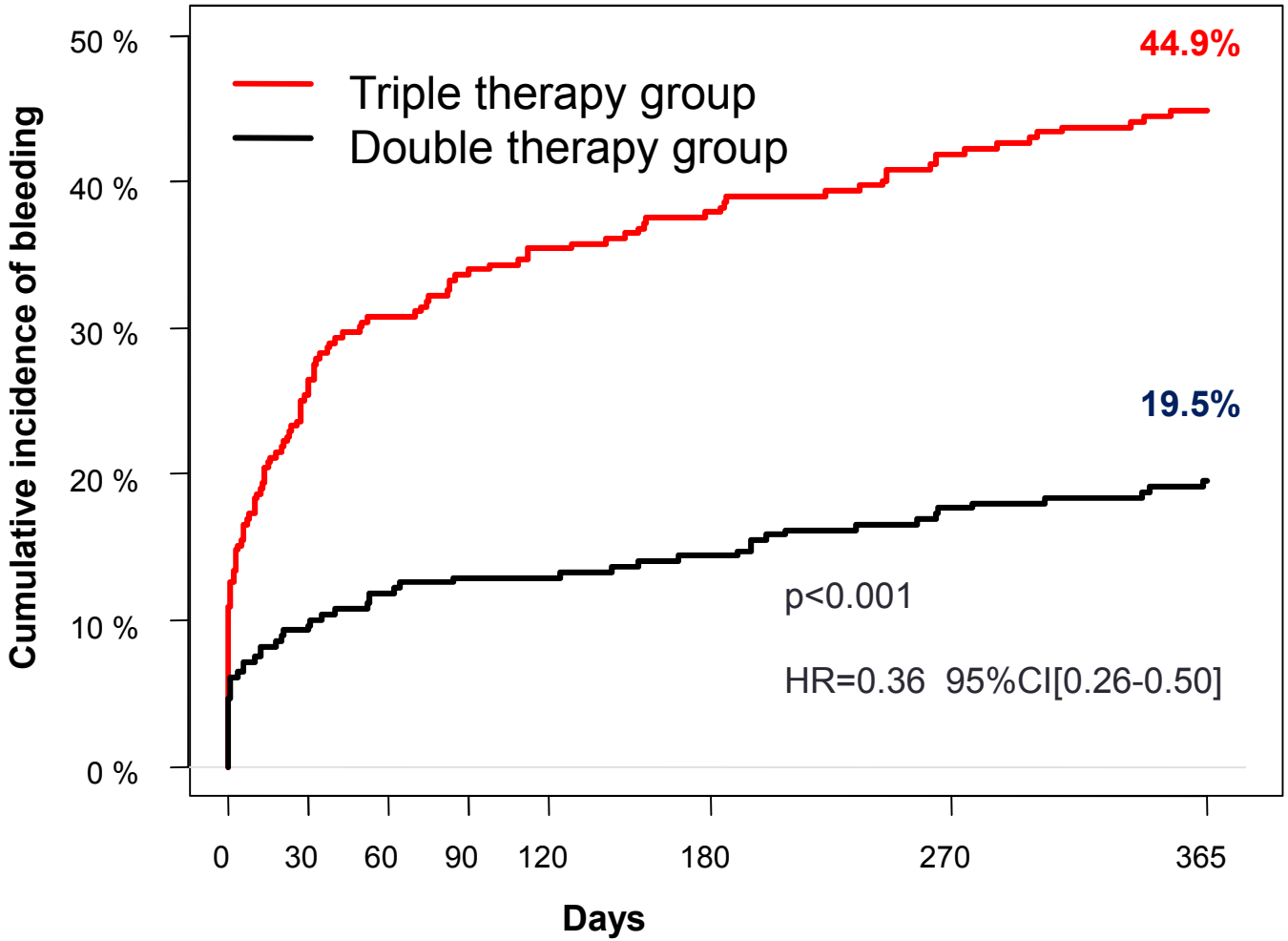
Dewilde, et al. Lancet, 2013; 381: 1107-15

WOEST

- Primary Endpoint:
  - Bleeding rates (TIMI, GUSTO, BARC)
- Secondary Endpoint:
  - Composite of death, MI, stroke, target vessel revascularization, and stent thrombosis
  - Each item individually

Dewilde, et al. Lancet, 2013; 381: 1107-15

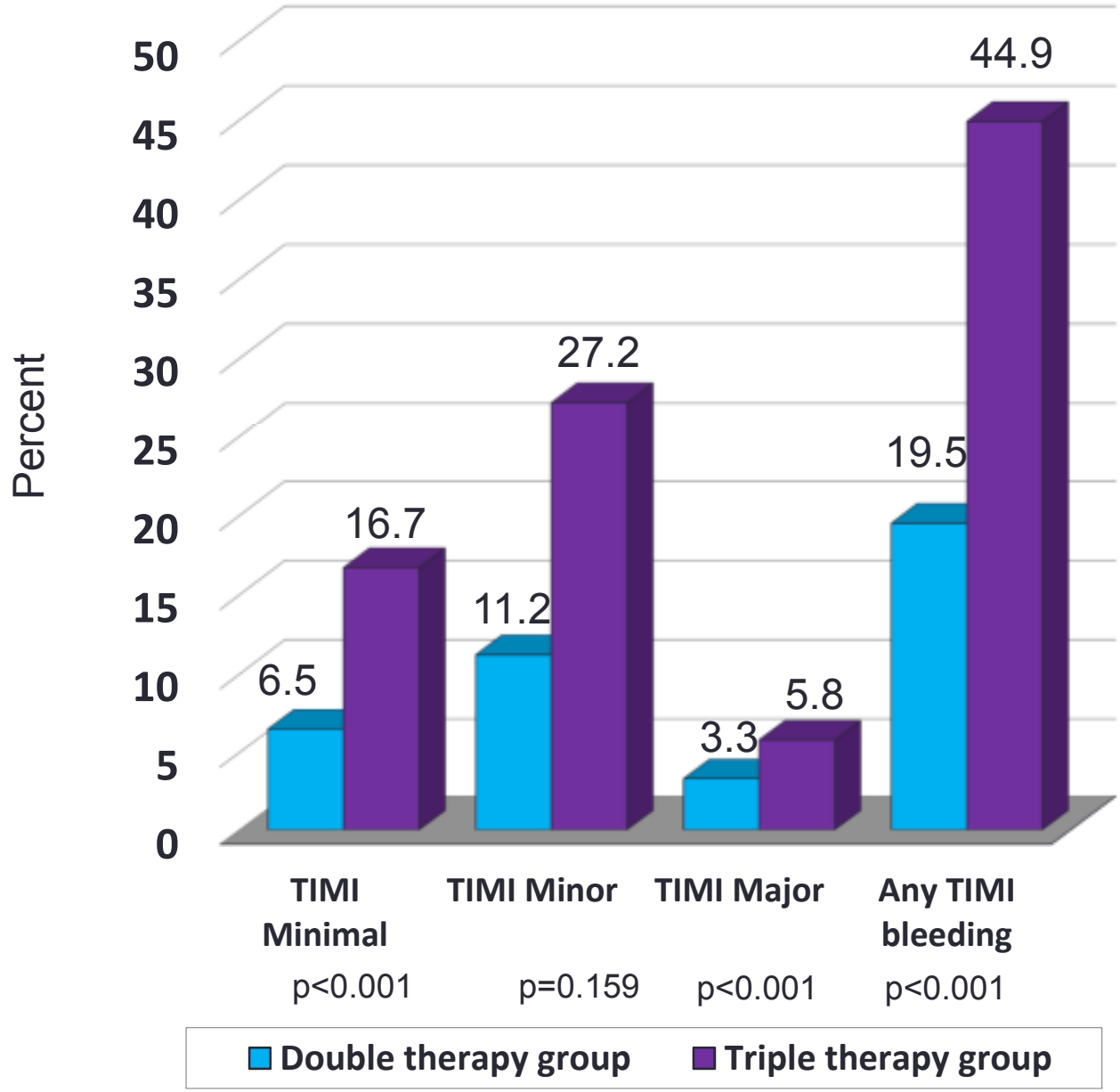
Primary Endpoint:
Total number of TIMI bleeding events



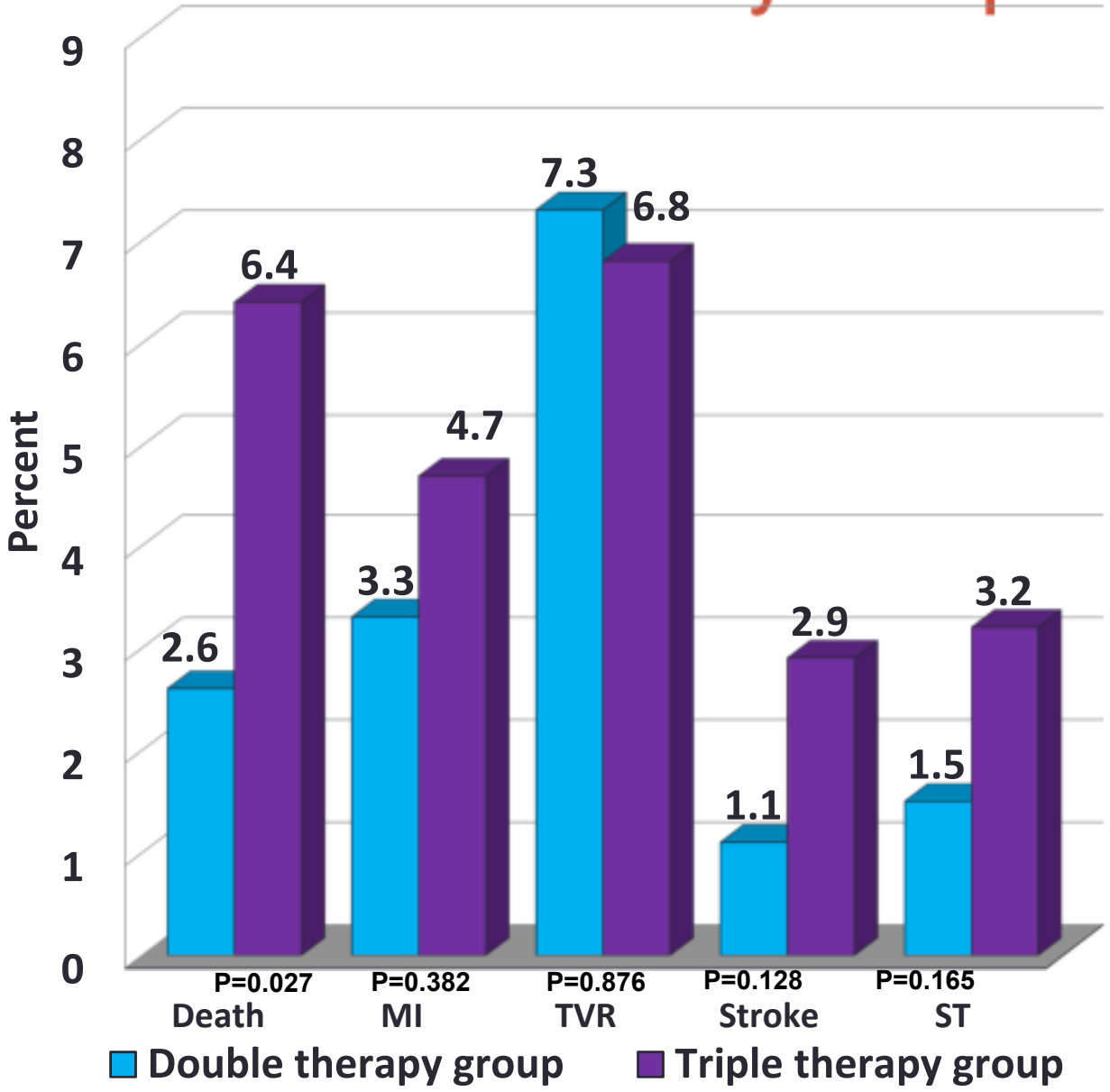
NNH=4

Dewilde, et al. Lancet, 2013; 381: 1107-15

Primary Endpoint: Bleeding events TIMI classification



WOEST: Secondary Endpoint



WOEST: Conclusions

- First randomized trial to address the optimal antiplatelet therapy in patients on OAC undergoing coronary stenting
  - OAC plus clopidogrel causes less bleeding than triple antithrombotic therapy
  - Secondary endpoint was met: with double therapy there is no excess of thrombotic/thromboembolic events
  - Less all-cause mortality with double therapy
- The study was powered to show superiority on the primary bleeding endpoint, but not to show non-inferiority on the secondary endpoint

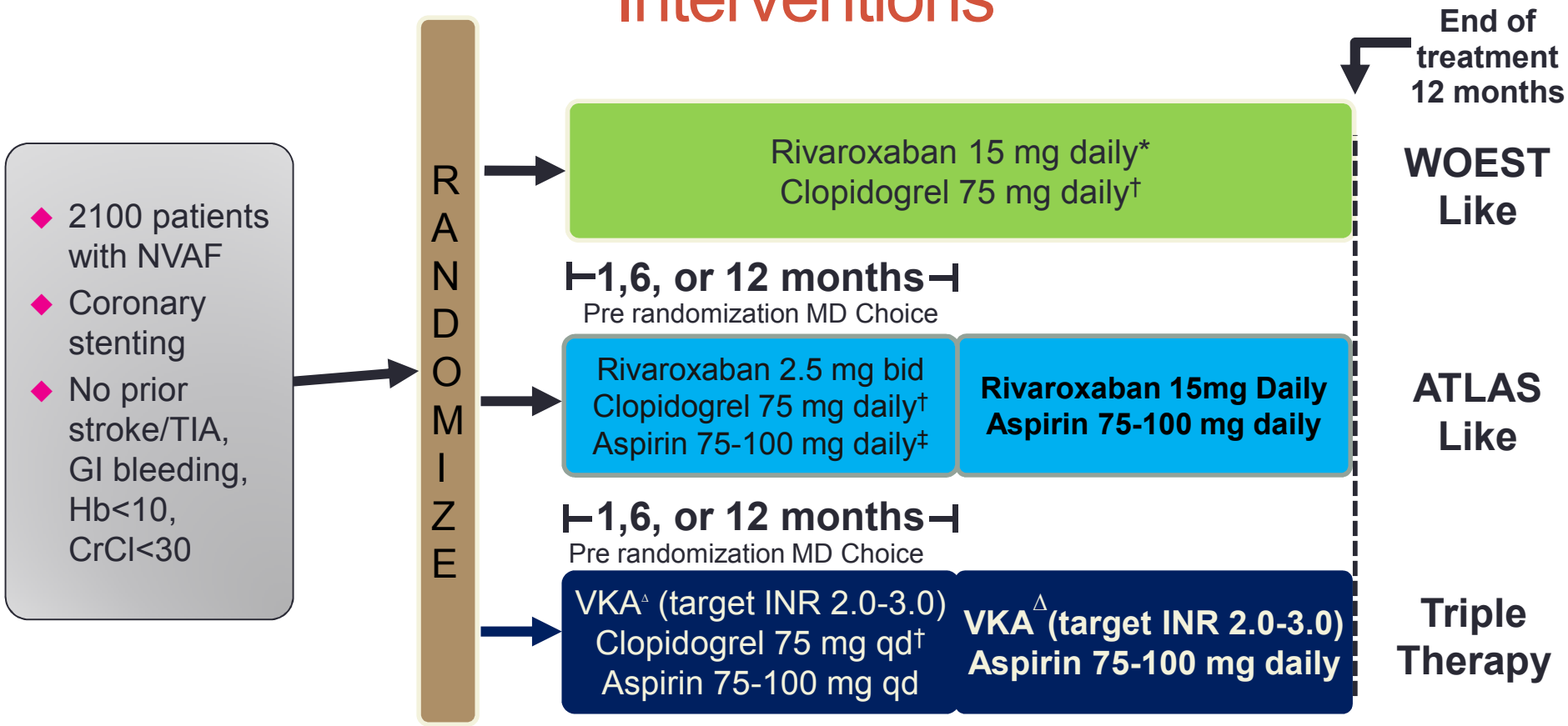
PREVENTION OF BLEEDING IN PATIENTS WITH ATRIAL FIBRILLATION UNDERGOING PCI: PIONEER AF-PCI

Gibson CM, Mehran R, Bode C et al.
N Engl J Med 2016;375:2423-34.

Pioneer AF-PCI: Objectives

- To evaluate the risks and benefits of using 2 different Rivaroxaban dosing strategies in patients with AF who present for coronary stent placement

PIONEER AF-PCI: Trial Design + Interventions



- Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

*Rivaroxaban 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). ∆ Open label VKA

Pioneer AF-PCI: Inclusion and Exclusion

Inclusion Criteria

- Men and Women aged 18 years or older
- Patients with AF who required OAC
- PCI with stent placement

Exclusion Criteria

- Pts with a h/o Stroke or TIA
- Clinically significant GI Bleeding within 12 months of randomization
- CLcr < 30 mL/min
- Anemia: Hgb < 10 g/dL

PIONEER AF-PCI: Endpoints

- Primary Endpoint: SAFETY
  - 1st occurrence of clinically significant bleeding
    - Composite of TIMI major or minor bleeding
- Secondary Endpoints:
  - Incidence of bleeding for the individual components of bleeding
  - Major Adverse Cardiovascular Events (MACE)
    - Composite: Death, MI, Stroke

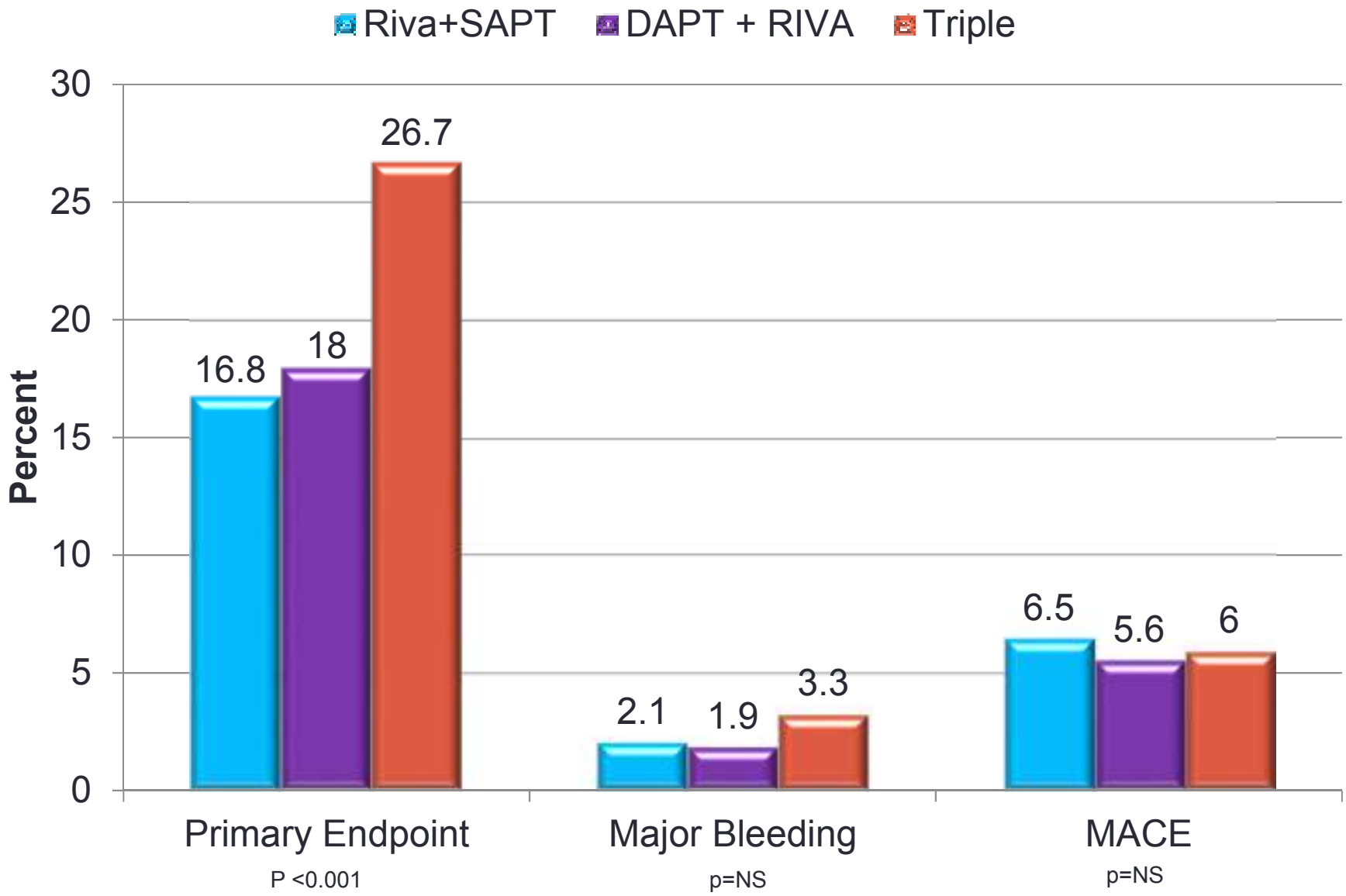
PIONEER AF-PCI: Points to consider

- How is TIMI Major and Minor bleeding defined?
  - TIMI Major:
    - Any symptomatic intracranial hemorrhage
    - Clinically overt signs of hemorrhage (including imaging) associated with a drop in hemoglobin of ≥ 5 g/dL, -or-
    - Absolute drop in hematocrit of ≥ 15%
  - TIMI Minor:
    - Clinically overt sign of hemorrhage (including imaging) with a fall in hemoglobin concentration of 3 to < 5 g/dL, -or-
    - Drop in hematocrit of 9 - < 15%

PIONEER AF-PCI: Baseline Characteristics

	Riva + SAPT (N=709)	Riva + DAPT (N=709)	Triple Therapy (N=706)
Age, mean ± SD	70.4 ± 9.1	70.0 ± 9.1	69.9 ± 8.7
Sex, female, n (%)	181 (25.5%)	174 (24.5%)	188 (26.6%)
Diabetes Mellitus, n (%)	204 (28.8%)	199 (28.1%)	221 (31.1%)
Type of Index Event, n (%)			
NSTEMI	130 (18.5%)	129 (18.4%)	123 (17.8%)
STEMI	86 (12.3%)	97 (13.8%)	74 (10.7%)
Unstable Angina	145 (20.7%)	148 (21.1%)	164 (23.7%)
Stable Angina	340 (48.5%)	329 (46.8%)	330 (47.8%)
Drug-eluting stent, n (%)	464 (65.4%)	471 (66.8%)	468 (66.5%)
Type of Atrial Fibrillation, n (%)			
Persistent	146 (20.6%)	146 (20.6%)	149 (21.1%)
Permanent	262 (37.0%)	238 (33.6%)	243 (34.5%)
Paroxysmal	300 (42.4%)	325 (45.8%)	313 (44.4%)

PIONEER AF-PCI: Results



PIONEER AF-PCI: Conclusions

- Compared with triple therapy:
  - RIVA + SAPT was associated with a significant reduction in bleeding
  - RIVA + SAPT did not appear to be associated with an increased risk of MACE

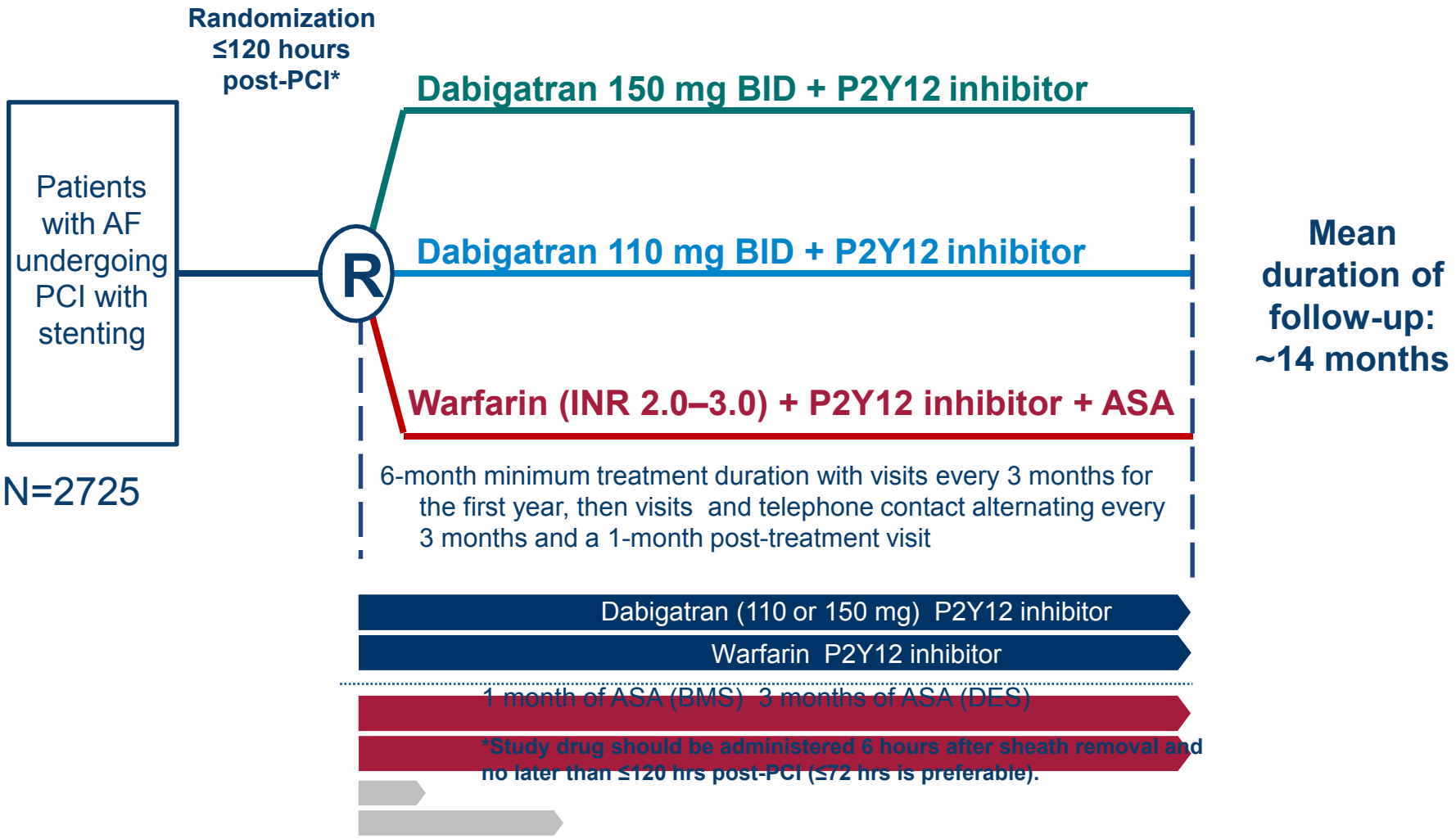
PIONEER AF-PCI: Additional Thoughts

- PIONEER and WOEST differ in some key ways:
  - WOEST had 69% AF patients vs. 100% in PIONEER
  - WOEST had 66% of patients receive triple therapy for 1 year
    - PIONEER had 22%
  - Even with these differences, the safety difference is impressive in PIONEER
  - PIONEER mimics WOEST in the overall impression that for 1 year, OAC + SAPT ($P2Y_{12}$ inhibitor) appears to be safer without compromising efficacy

RE-DUAL PCI: dual antithrombotic therapy with dabigatran after percutaneous coronary intervention in patients with atrial fibrillation

Cannon CP et al. N Engl J Med 2017;377:1513-24.

RE-DUAL: Study Design



Cannon CP et al. N Engl J Med 2017;377:1513-24.

RE-DUAL: Enrollment Criteria

Key inclusion criteria

- Patients aged ≥18 years with paroxysmal, persistent or permanent NVAF
- ACS successfully treated by PCI and stenting (BMS or DES)
- Stable CAD with ≥1 lesion eligible for PCI that was successfully treated by elective PCI and stenting (BMS or DES)

Key exclusion criteria

- Cardiogenic shock during current hospitalization
- Use of fibrinolytics within 24 hrs of randomization that, in the investigator's opinion, will put patient at high risk of bleeding
- Stroke or major bleeding event within 1 month prior to screening visit
- Severe renal impairment (CrCl <30mL/min)

ACS, acute coronary syndrome; CAD, coronary artery disease; CrCl, creatinine clearance

Cannon CP et al. N Engl J Med 2017;377:1513-24.

RE-DUAL: Study objective and design

RE-DUAL PCI tests the safety and efficacy of two regimens of dual therapy with dabigatran without aspirin vs. triple therapy with warfarin

- The primary endpoint was time to first ISTH major or clinically relevant non-major bleeding
- Secondary endpoints: MACE

ISTH, International Society of Thrombosis and Haemostasis; MI, myocardial infarction Non-inferiority testing (margin 1.38)

Cannon CP et al. N Engl J Med 2017;377:1513-24.

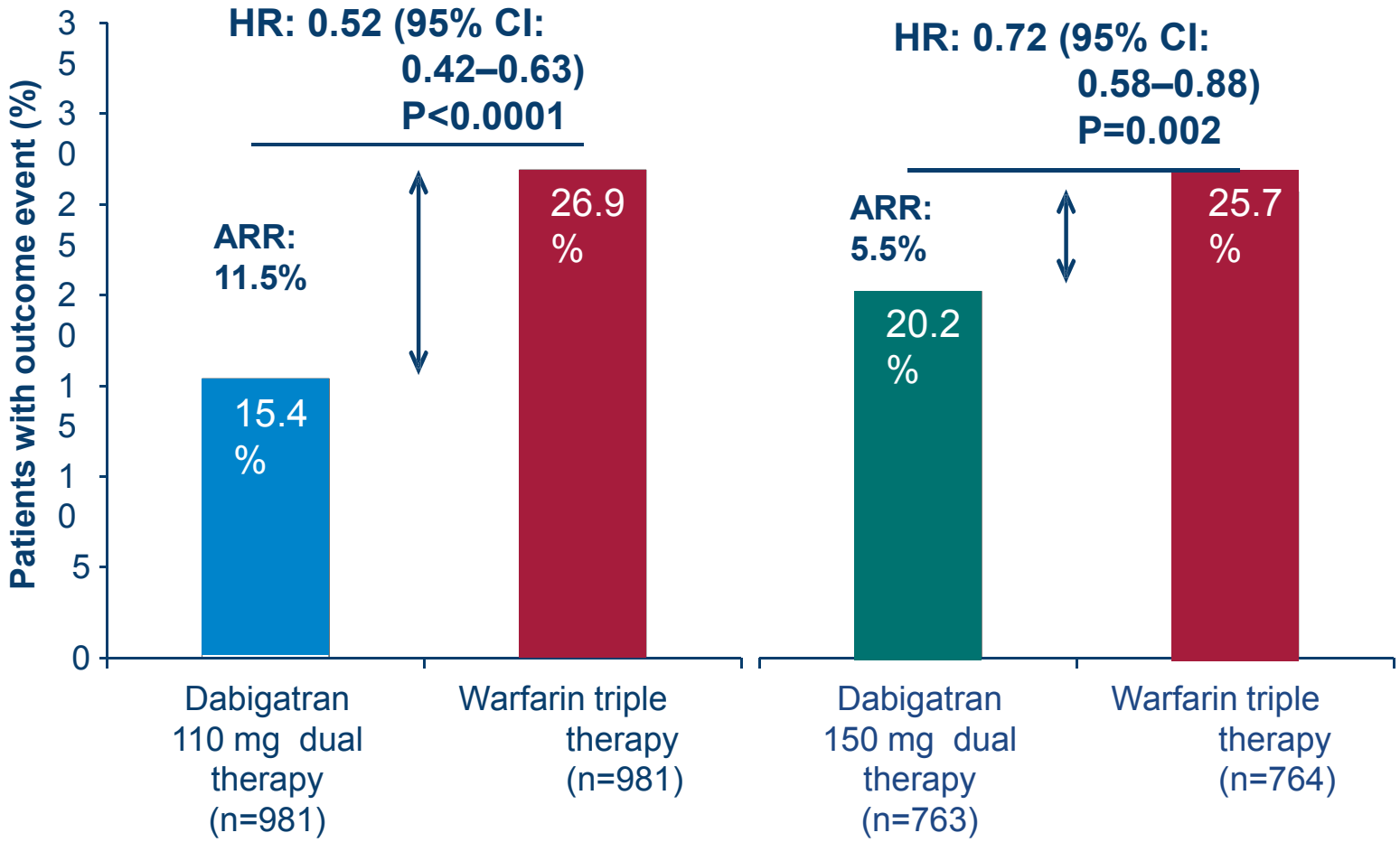
Baseline characteristics

	Dabi 110 mg dual therapy (n=981)	Warfarin triple therapy (n=981)	Dabi 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

wond

Cannon CP et al. N Engl J Med 2017;377:1513-24.

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



Cannon CP et al. N Engl J Med 2017;377:1513-24.

RE-DUAL: thromboembolic endpoints

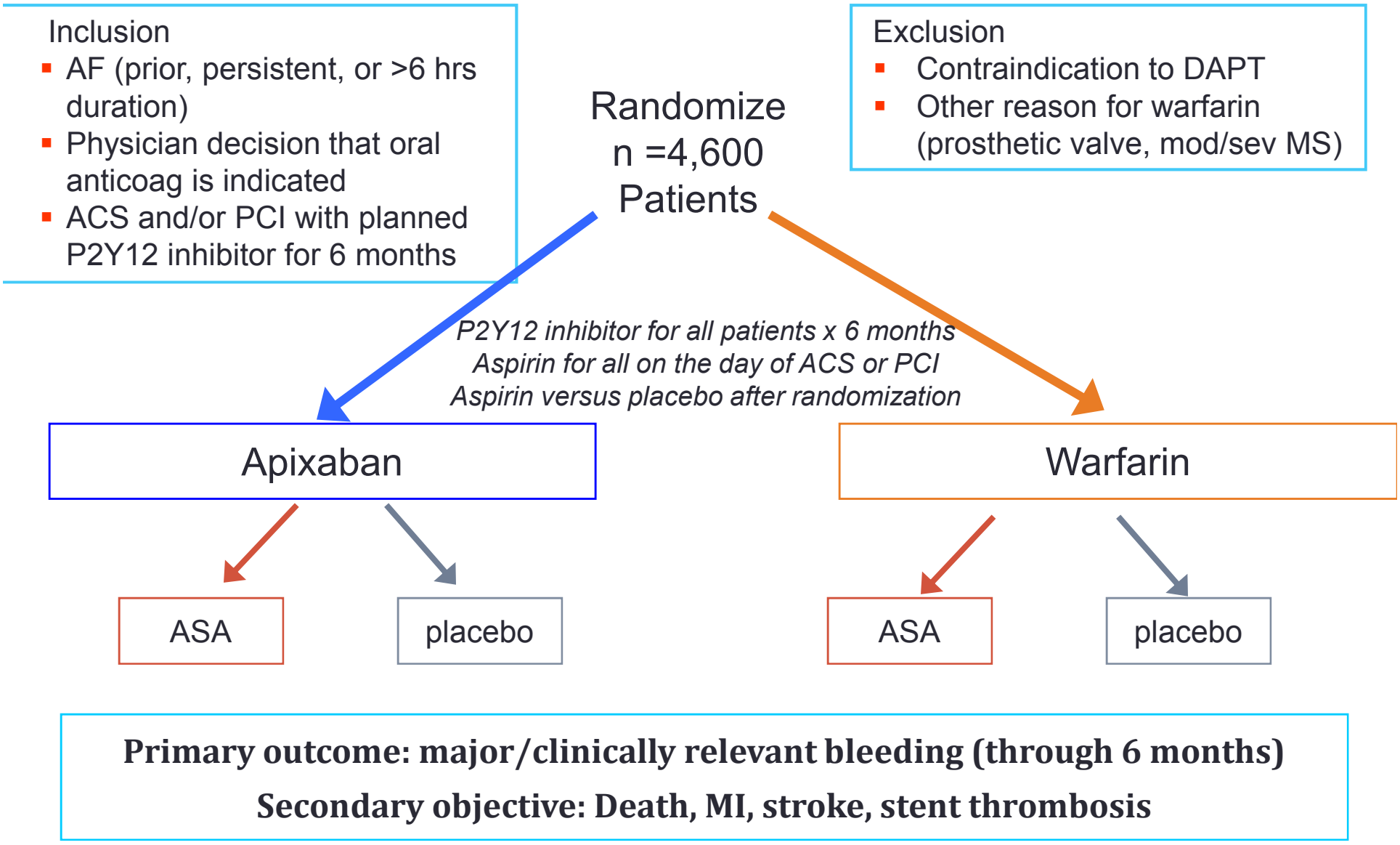
Dabigatran 110 mg dual therapy (n=981) n (%)		Warfarin triple therapy (n=981) n (%)	D110 DT vs. warfarin TT HR (95% CI)	P value	Dabigatran 150 mg dual therapy (n=763) n (%)	Warfarin triple therapy (n=764) n (%)	D150 DT vs. warfarin TT HR (95% CI)	P value
All-cause death	55 (5.6)	48 (4.9)	1.12 (0.76–1.65)	0.56	30 (3.9)	35 (4.6)	0.83 (0.51–1.34)	0.44
Stroke	17 (1.7)	13 (1.3)	1.30 (0.63–2.67)	0.48	9 (1.2)	8 (1.0)	1.09 (0.42–2.83)	0.85
Unplanned revascularization	76 (7.7)	69 (7.0)	1.09 (0.79–1.51)	0.61	51 (6.7)	52 (6.8)	0.96 (0.65–1.41)	0.83
MI	44 (4.5)	29 (3.0)	1.51 (0.94–2.41)	0.09	26 (3.4)	22 (2.9)	1.16 (0.66–2.04)	0.61
Stent thrombosis	15 (1.5)	8 (0.8)	1.86 (0.79–4.40)	0.15	7 (0.9)	7 (0.9)	0.99 (0.35–2.81)	0.98

Cannon CP et al. N Engl J Med 2017;377:1513-24.

OAC + SAPT: Questions remain

- While focusing on bleeding is important
  - Why not have MACE as the primary endpoint?
    - Stroke, MI, Stent thrombosis are also very important events
- Rivaroxaban 2.5 mg BID dose fit into practice?
  - Currently not FDA approved, but might be soon….
  - Is that “enough” OAC intensity to prevent stroke in AF chronically?
- Dabigatran 110 mg BID dose?
  - Currently not approved for stroke prevention in AF in the US
- What about the other DOACs?
- What about the more potent P2Y12 inhibitors?
  - How do those impact bleeding rates?
  - Choice of OAC

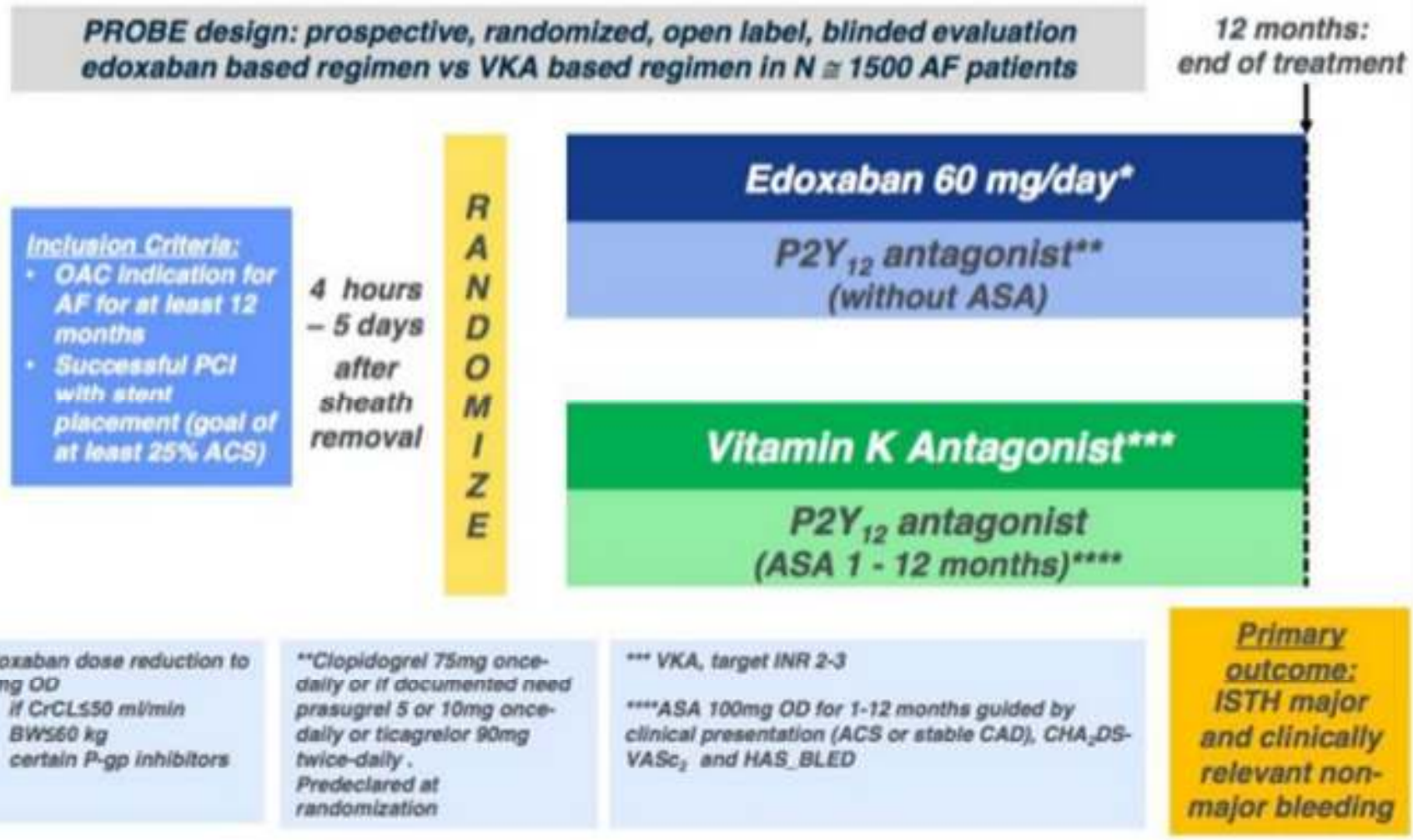
Apixaban Versus Warfarin in Patients with AF and ACS or PCI: The AUGUSTUS Trial



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

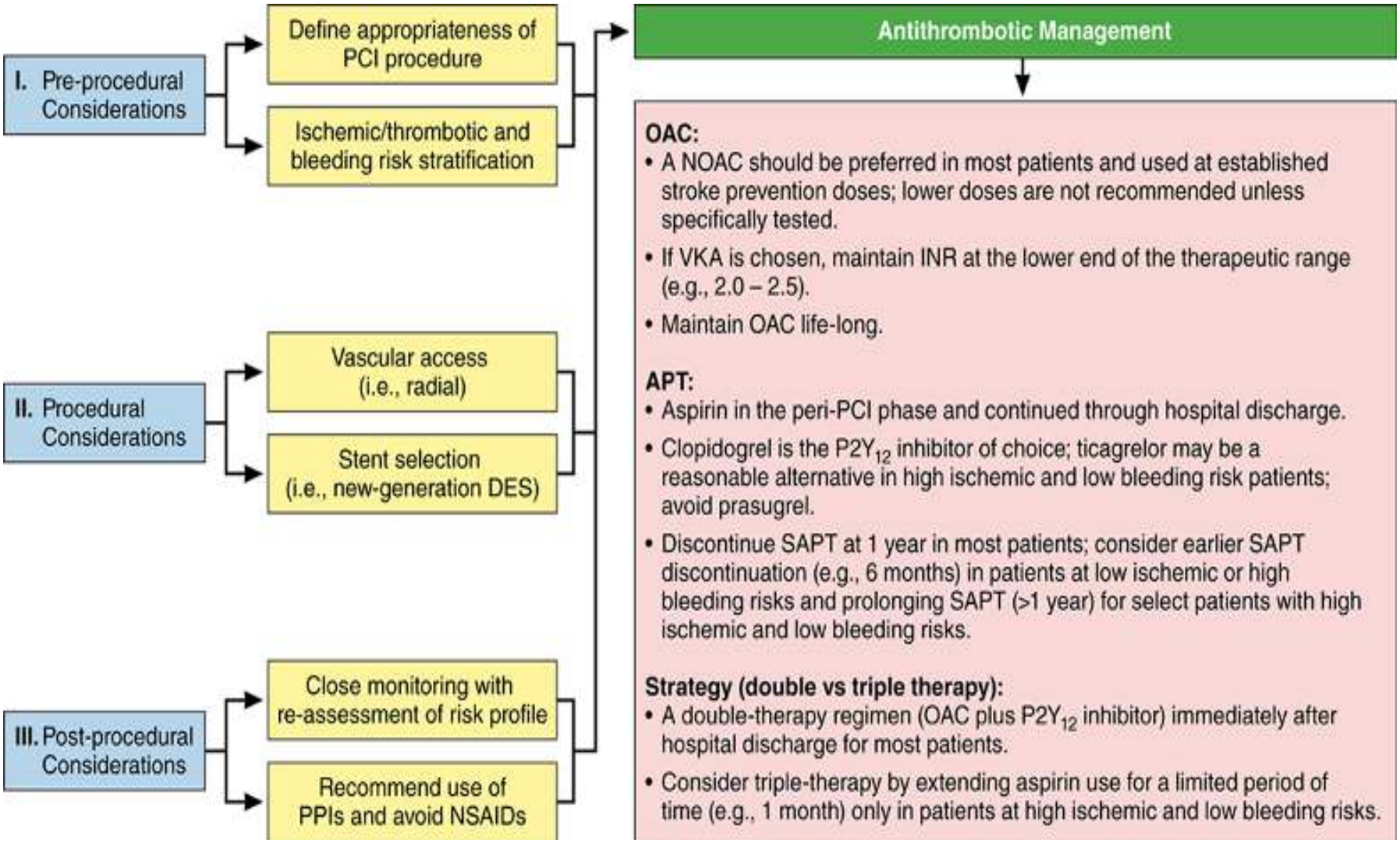
Secondary objective: Death, MI, stroke, stent thrombosis

ENTRUST-AF-PCI Study Design



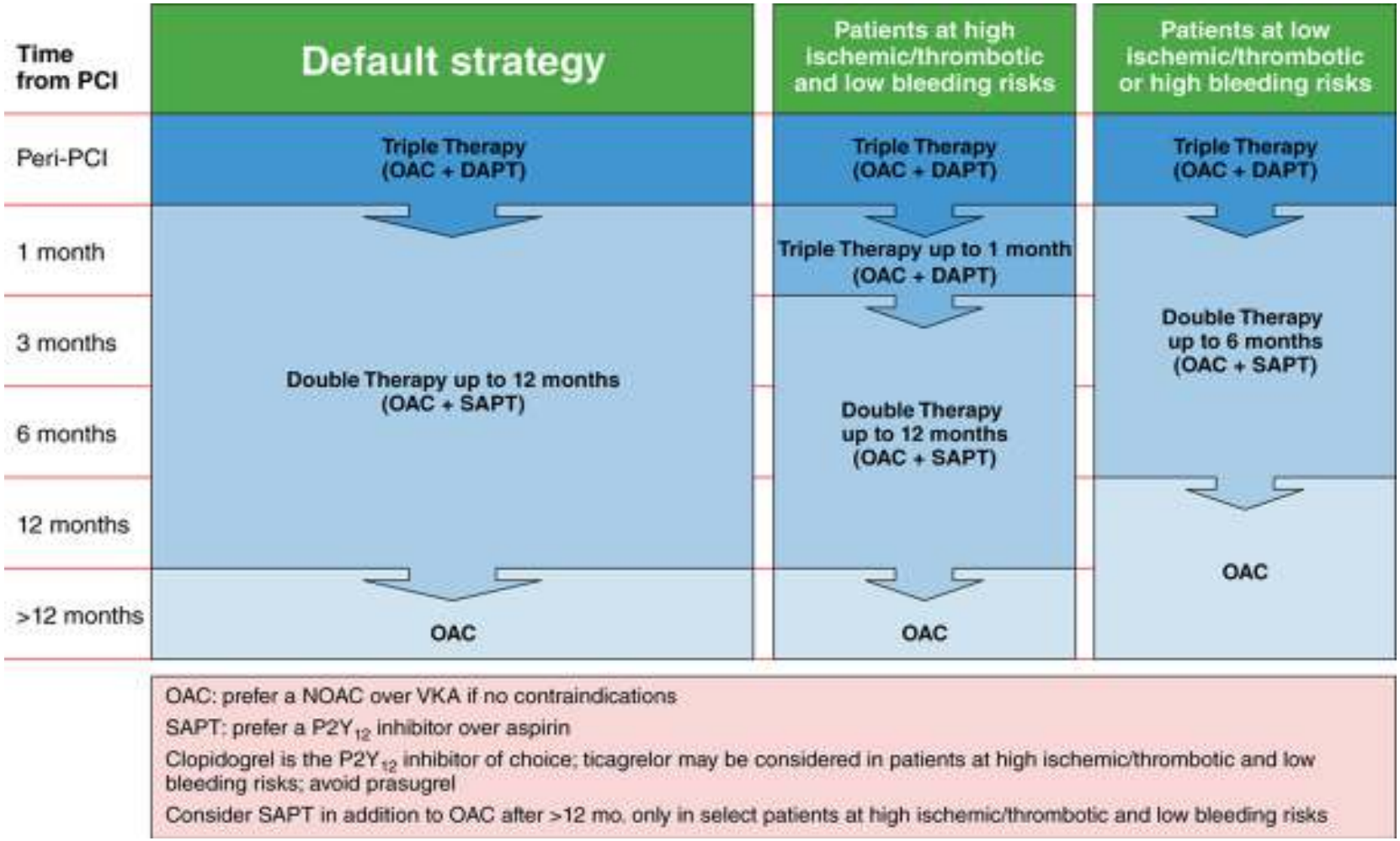
ClinicalTrials.gov Identifier: NCT02866175

North American Consensus White Paper



Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention, Volume: 138, Issue: 5, Pages: 527-536, DOI: (10.1161/CIRCULATIONAHA.118.034722)

North American Consensus White Paper



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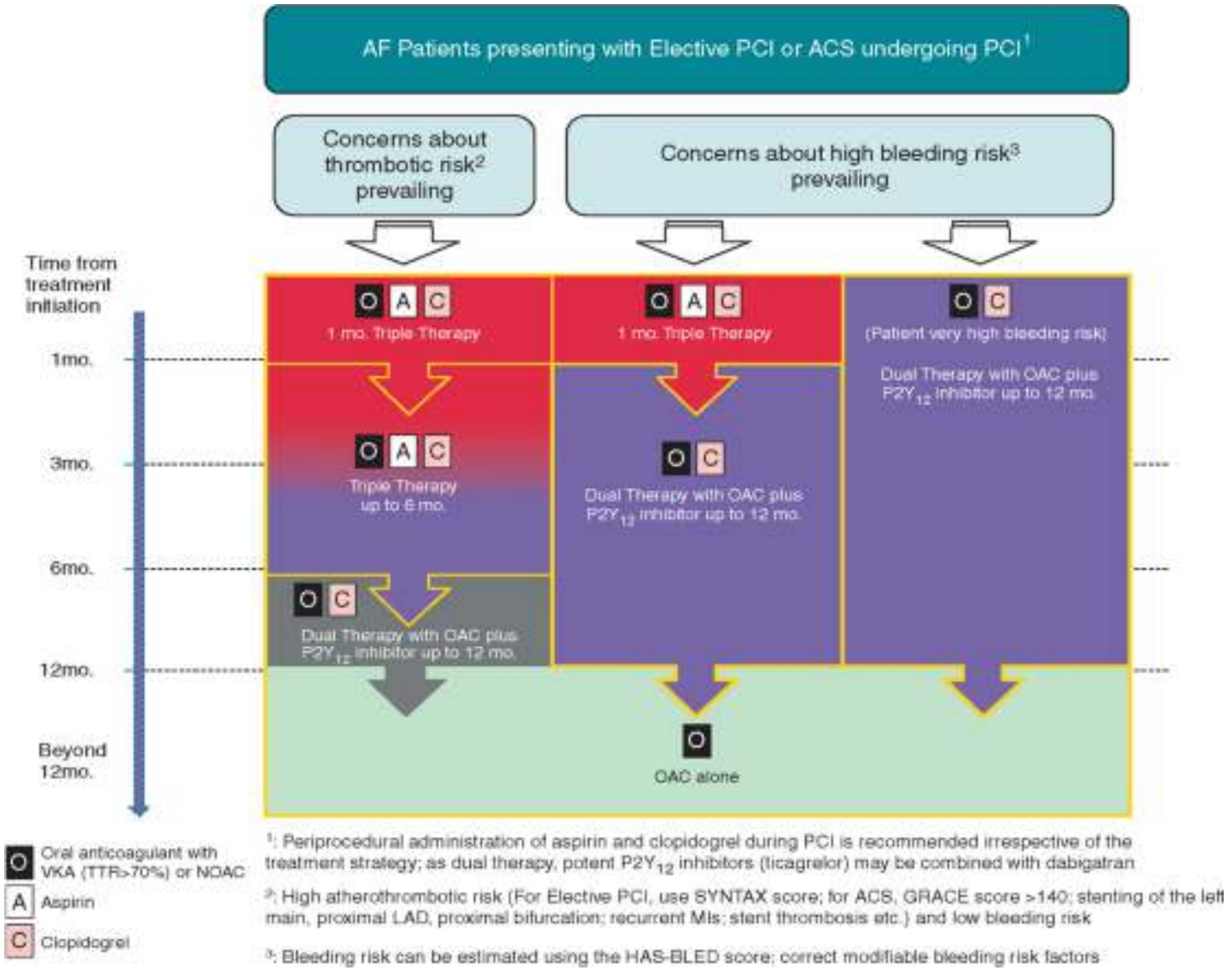

From: 2018 Joint European consensus document on the management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous cardiovascular interventionsEuropace. Published online July 21, 2018. doi:10.1093/europace/euy174

How to identify risk?

- Bleeding Risks:
  - HAS-BLED score
  - Recent or previous history of major bleeding
  - Concomitant anemia
  - Poorly controlled hypertension
- Thrombotic Risks:
  - Left-main stenting
  - Proximal LAD stenting
  - Multiple Stents
  - PCI complications
  - History of embolic events (stroke, VTE)
  - History of stent thrombosis
  - DAPT score > 2 points

Key take home points

- OAC + SAPT ($P2Y_{12}$ inhibitor) preferred over triple therapy in patients with AF + ACS
  - Clopidogrel is the preferred $P2Y_{12}$ inhibitor
    - Limited data with Ticagrelor; Prasugrel currently not recommended
  - DOACs are preferred over warfarin
    - Rivaroxaban 10 – 15 mg once daily (based on CLcr)
    - Dabigatran 150 mg BID

- Consider bleeding and thrombotic risk when considering choice of agents and duration of therapy
  - High bleeding risk = OAC + SAPT x 6 months, then OAC alone
  - High thrombotic risk = OAC + SAPT x 12 months, then OAC alone
    - Can consider triple therapy (OAC + DAPT) x 1 month

How would you manage BA's antithrombotic therapy?

a) Aspirin 81 mg daily + Clopidogrel 75 mg daily + Warfarin
b) Aspirin 81 mg daily + Prasugrel 10 mg daily + Warfarin
c) Aspirin 81 mg daily + Rivaroxaban 20 mg daily
d) Clopidogrel 75 mg daily + Dabigatran 150 mg daily
e) None of these