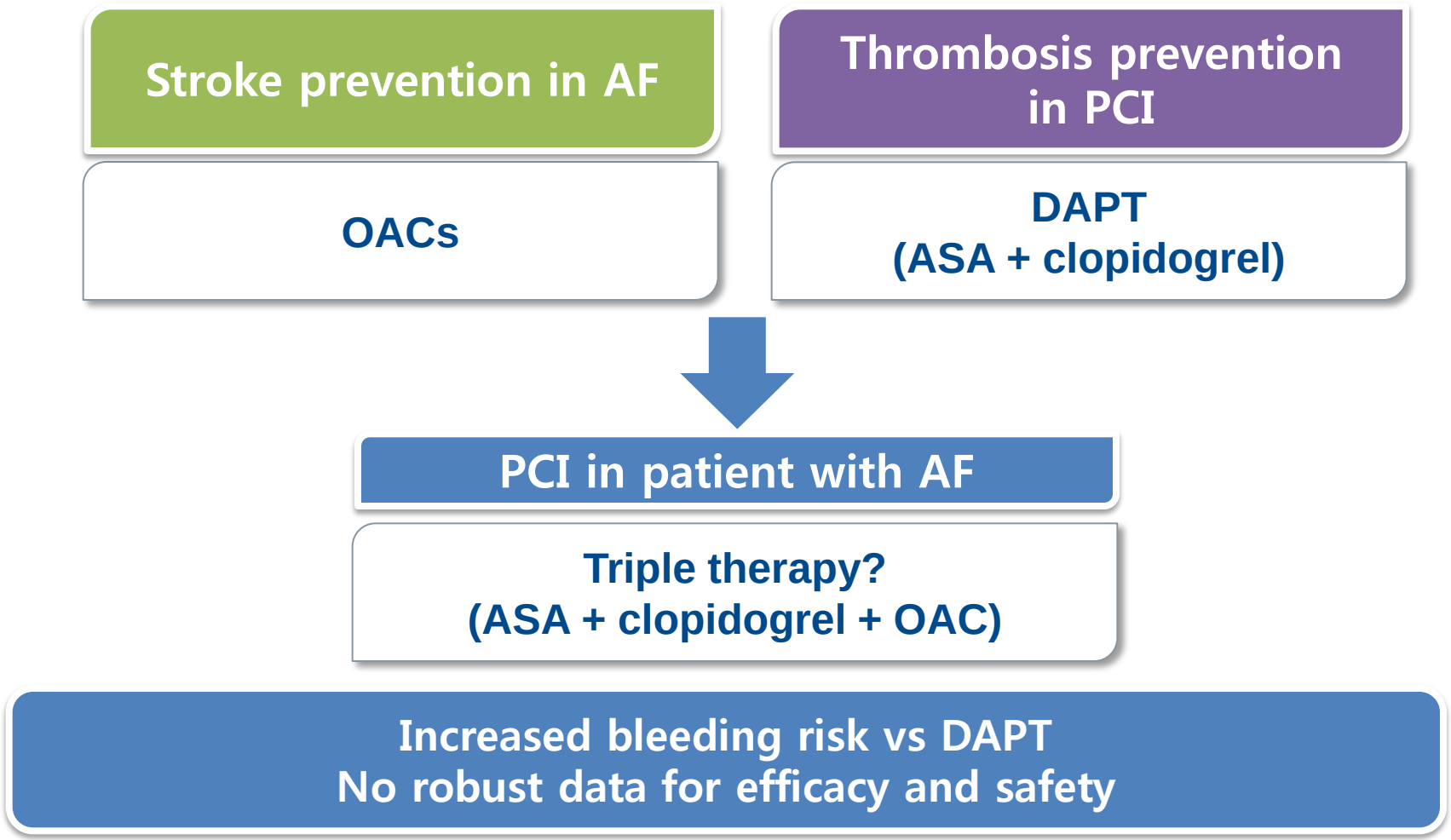
The Optimal Antithrombotic Strategy in Patients with AF and ACS: Focusing on the AUGUSTUS Trial

Kyung Woo Park, MD, PhD, MBA

Seoul National University Hospital, Seoul, Korea

Our Dilemma



ASA = acetylsalicylic acid; DAPT = dual antiplatelet therapy

Coppens M and Eikelboom JW. Circ Cardiovasc Interv 2012;5:454–5

Let’s start on the same page …..

Antiplatelet therapy: Inhibition of Platelet activation

Anticoagulation: Inhibition of coagulation cascade

Antithrombotic therapy : AntiPLT + Anticoagulation

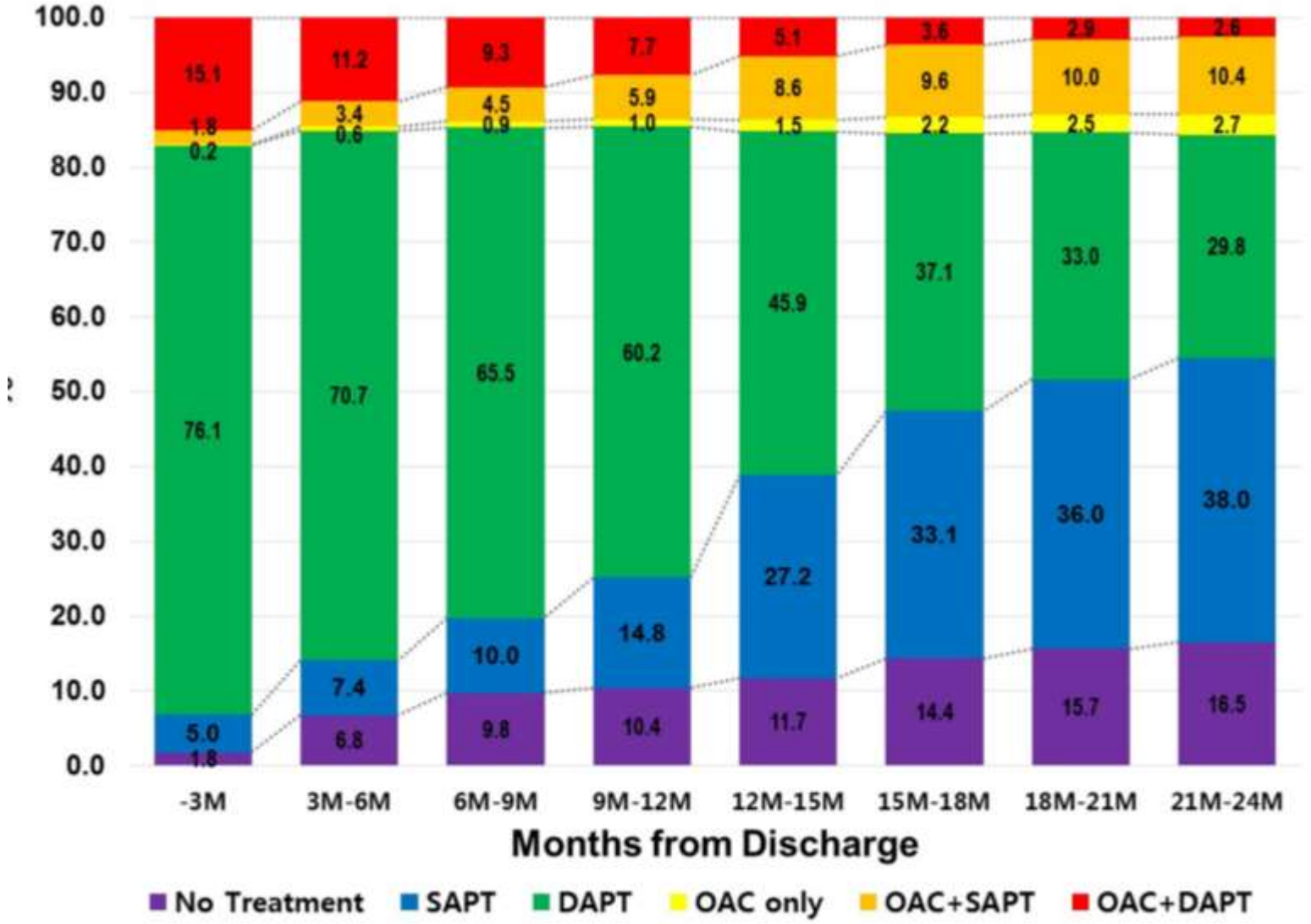
Triple Oral Antithrombotic Therapy (TOAT)

= DAPT + OAC

***DOAT* = Single antiplatelet therapy + OAC**

Prescription Pattern after PCI of AF patients

(National Health Insurance Data)

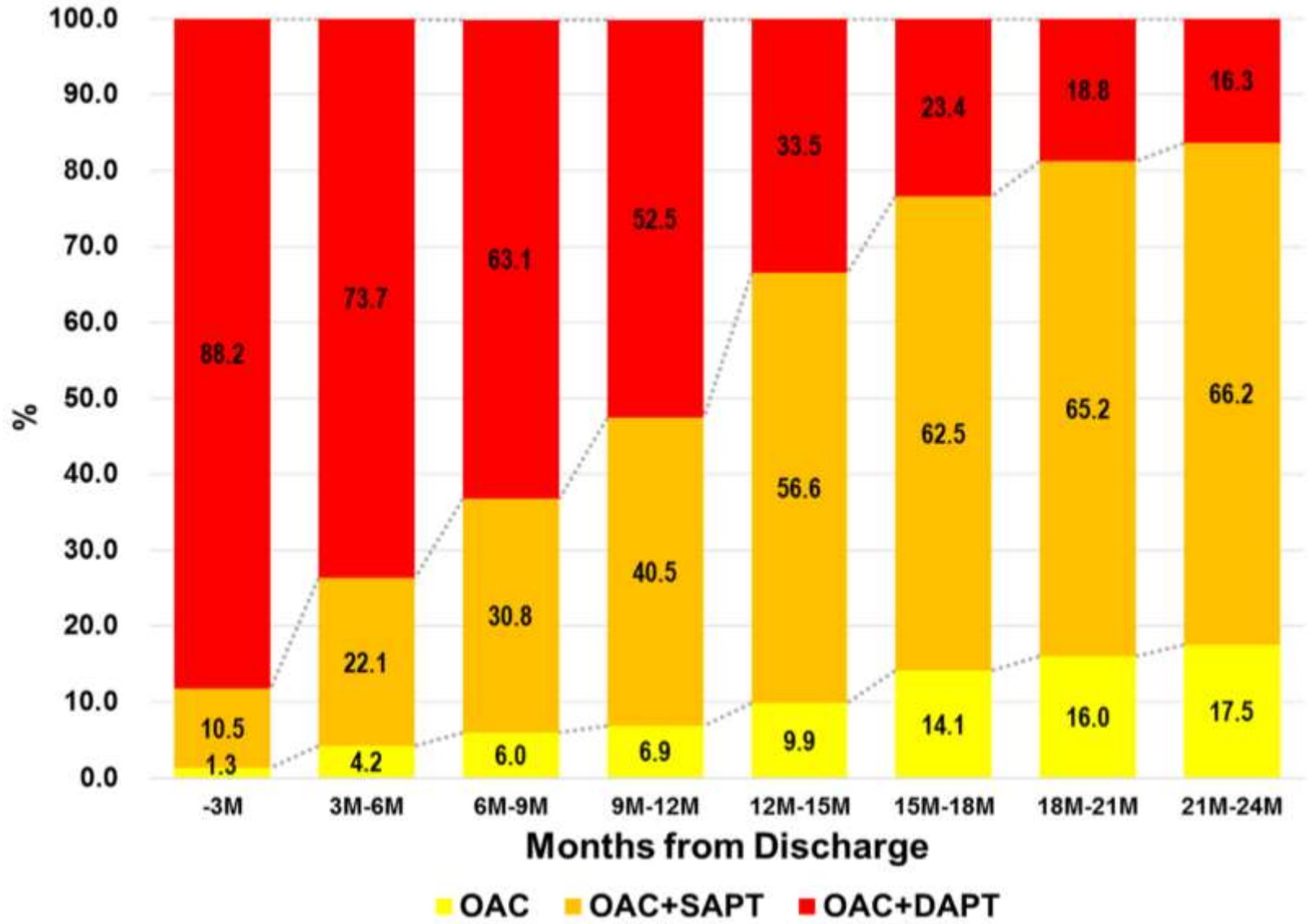


SNUH 서울대학교병원

Park JS, Park KW, Choi EK et al. Am J Cardiol 2019

Prescription Pattern of those Receiving OAC

(National Health Insurance Data)

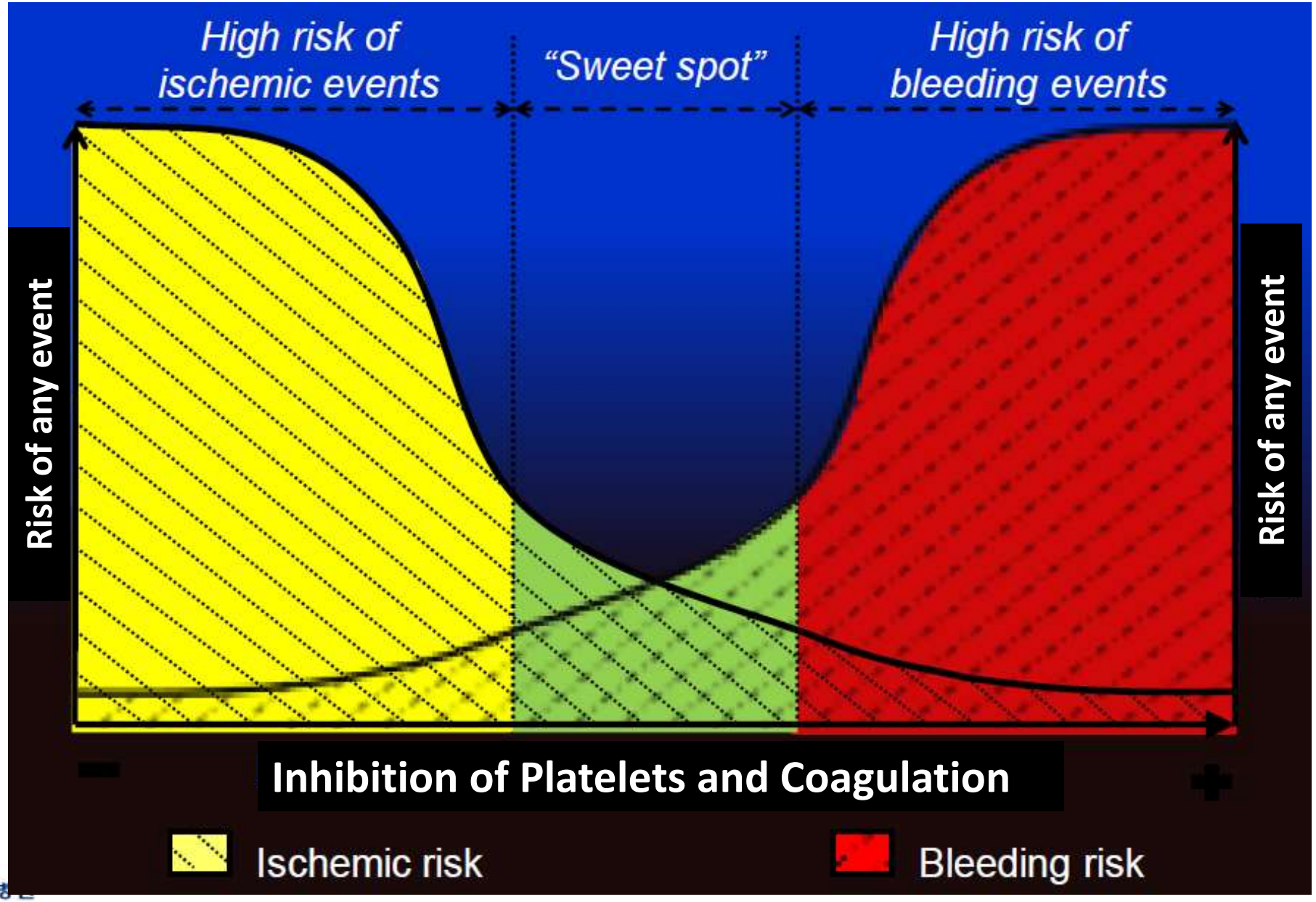


Park JS, Park KW, Choi EK et al. Am J Cardiol 2019

What kind of patients are we talking about?

1. Patient with AF presenting with an ACS (+/- PCI)
2. Patient with AF undergoing PCI
3. Patient with a history of ACS/PCI and new onset AF

The Balancing Act



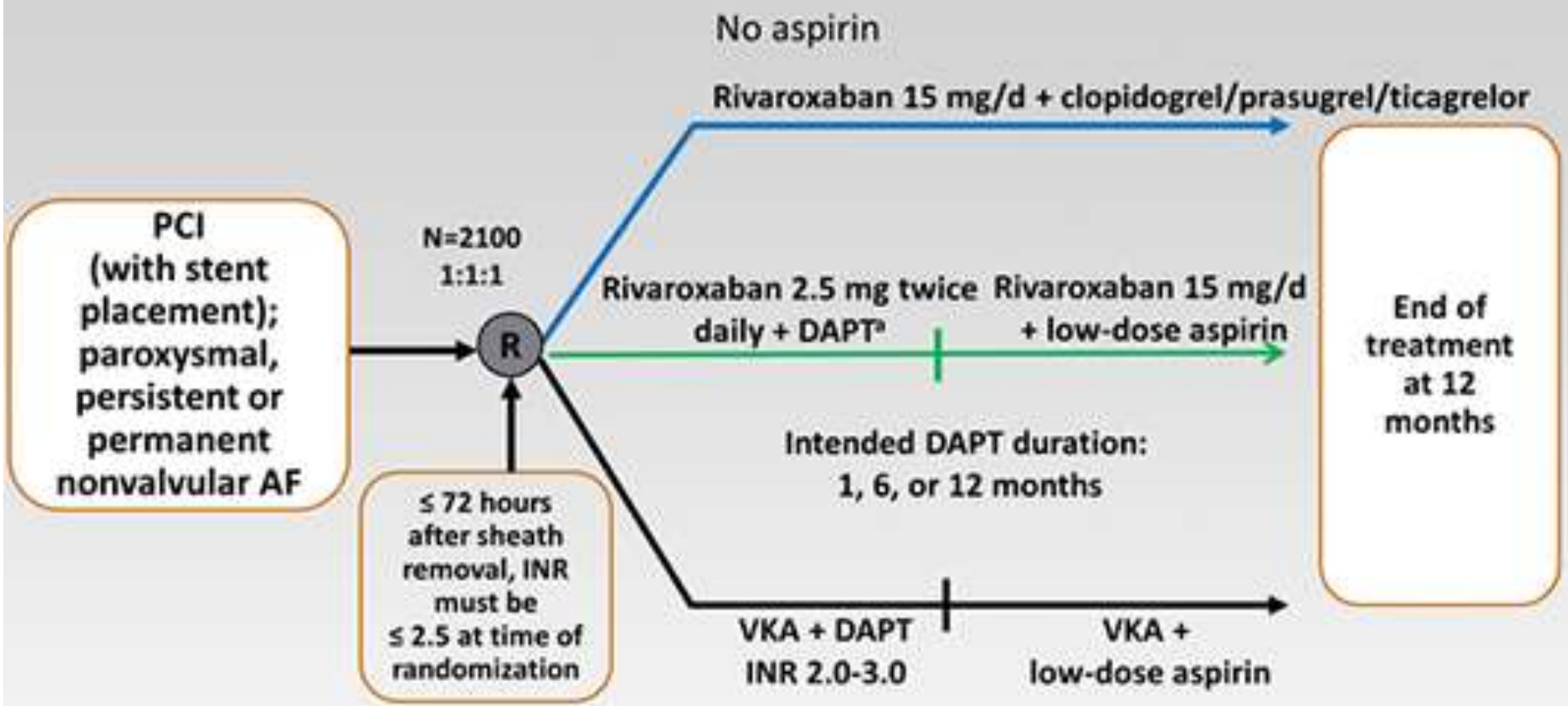
NOAC (DOAC)… in AF Patients has been shown….

1. To mostly reduce fatal and major bleeding compared with warfarin (VKA)….
2. To be at least non-inferior to warfarin in terms of stroke and systemic embolization….
3. To be able to effectively and coveniently maintain a stable anticoagulation…

Thus, DOACs have become the standard therapy for stroke prevention in treatment of patients with Atrial Fibrillation…..

How about patients receiving PCI that require DAPT

PIONEER AF-PCI [DOAT (FR) vs TOAT (BR or Warfarin)]



Primary outcome measures: clinically significant bleeding (composite of TIMI major, minor bleeding, and bleeding) requiring medical attention.
Secondary outcome measures: composite of CV death, MI, and stroke

a. DAPT = low-dose aspirin + clopidogrel, prasugrel, or ticagrelor

ClinicalTrials.gov website.[8]

HCRI
HARVARD CLINICAL RESEARCH INSTITUTE

RE-DUAL PCI™

Study in NVAF patients undergoing PCI

Boehringer Ingelheim

Worldwide Event Driven Trial

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

Run in period*

R

T1

- Dabigatran 150mg BID + P2Y12 inhibitor¥
- Dabigatran 110mg BID + P2Y12 inhibitor¥
- Warfarin (INR 2.0-3.0) + P2Y12 inhibitor¥ + ASA ‡

‡ 1° EP

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

0-2 days post-PCI (stratified randomization)**

Complex patients†: initiation of TAT or DATΔ with Dabigatran 150 or 110 mg BID + P2Y12 inhibitor¥ + ASA vs. TAT with Warfarin (INR 2.0-3.0) + P2Y12 inhibitor¥ + ASA

Non-Complex patients†: initiation of DAT with Dabigatran 150 or 110 mg BID + P2Y12 inhibitor¥ (with d/c of ASA) vs. TAT with Warfarin (INR 2.0- 3.0) + P2Y12 inhibitor¥ + ASA

initated TAT discontinue ASA and initiate DAT regimen in D110/D150 arms

Non-Complex patients: Maintenance of DAT regimen in D110/D150 arms

n = 2818 patients per arm (total = 8454 patients)

TAT: triple antithrombotic therapy
DAT: dual antithrombotic therapy

* Run in: pre-assessment of the patient high-risk vs. non-high risk characteristics (bridging therapy during the procedure [LMWH, Bivalirudin , UFH, etc.] at the discretion of practicing physician)

** Randomization can be done immediately after PCI and up to 72 hours post-PCI; study drug can be started within 6 hours (stable patients) or within 12 hours (complex patients) after sheath removal an hemostasis assured and up to 72 hours post-PCI

† Complex criteria: patient's clinical presentation (ACS vs. non-ACS) and lesion/procedure characteristics (e.g. left main, etc.) → DAPT Study Complexity Criteria

Δ Initiation of TAT or DAT in Complex patients randomized to receive dabigatran is left at the discretion of the practicing physician

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

∏ Follow up visits at month 1, 3, 6, 9, 12, 15 and 18, 24 and 30 post-randomization

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

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

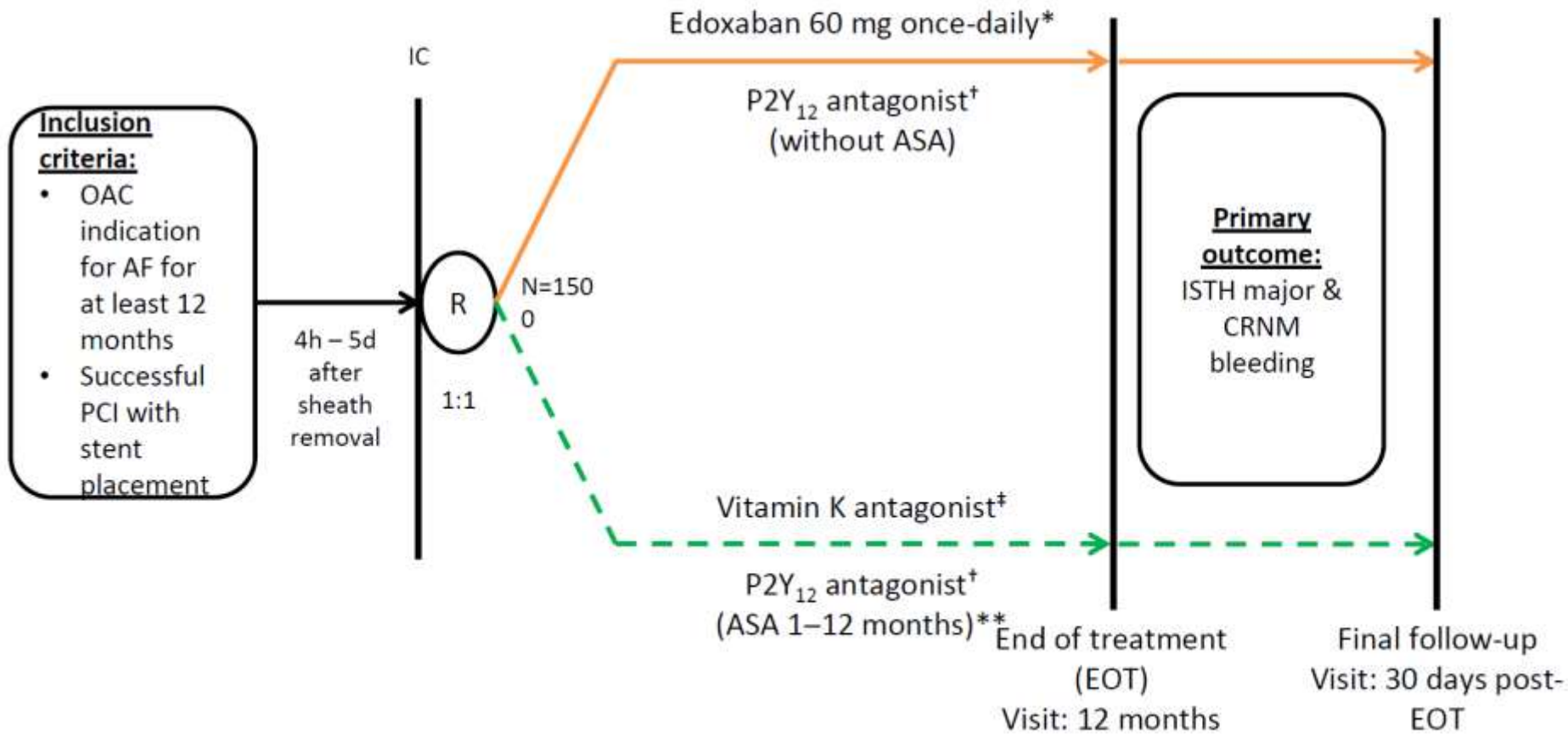
placebo

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

Secondary objective: Death, MI, stroke, stent thrombosis

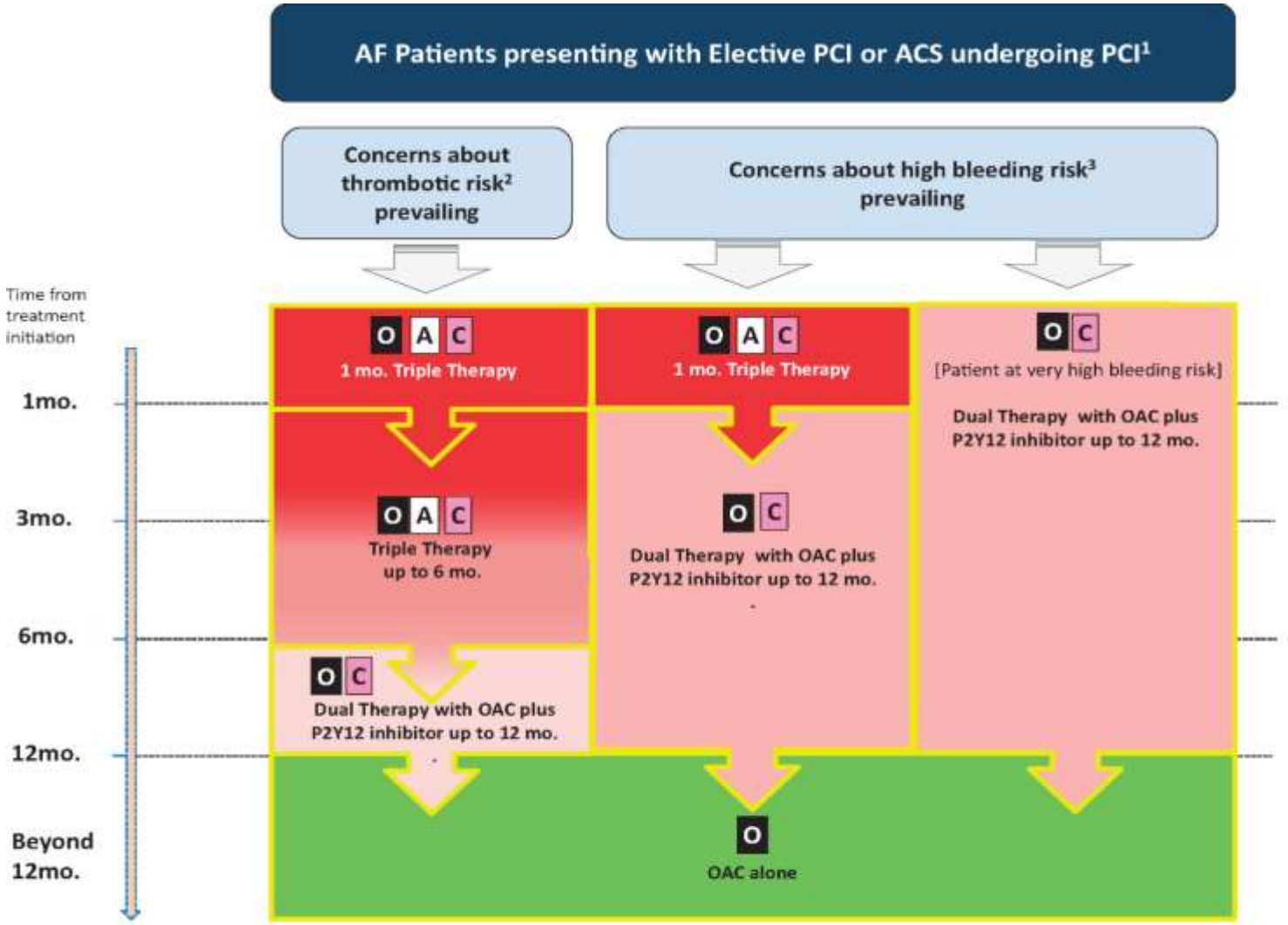
ENTRUST-AF PCI Trial

EDOXABAN TREATMENT VERSUS VKA IN PATIENTS WITH AF UNDERGOING PCI – ENTRUST-AF PCI



Drug [Trial]	Standard Treatment	Active Tx 1	Active Tx 2
Ribaroxaban [PIONEER AF-PCI] : **W-TOAT vs. TOAT** **W-TOAT vs. DOAT**	TOAT (with warfarin) + Early discontinuation of P2Y12 inhibitor	TOAT (with Riba low dose) + Early discount of P2Y12 inh (Riba conventional dose)	DOAT with P2Y12 inh
Dabigatran [RE-DUAL PCI]: **W-TOAT vs. DOAT**	TOAT (with warfarin) + Early discontinuation of P2Y12 inhibitor	DOAT with NOAC (low dose) and P2Y12 inh	DOAT with NOAC (high dose) and P2Y12 inh
Apixaban [AUGUSTUS]: **W-TOAT vs. TOAT** **W-DOAT vs. DOAT**	TOAT with Warfarin	DOAT vs. TOAT	NOAC vs. Warfarin
Edoxaban [ENTRUST-AF] **W-TOAT vs. DOAT**	TOAT with Warfarin	DOAT with NOAC and P2Y12 inh	

2018 ESC consensus statement



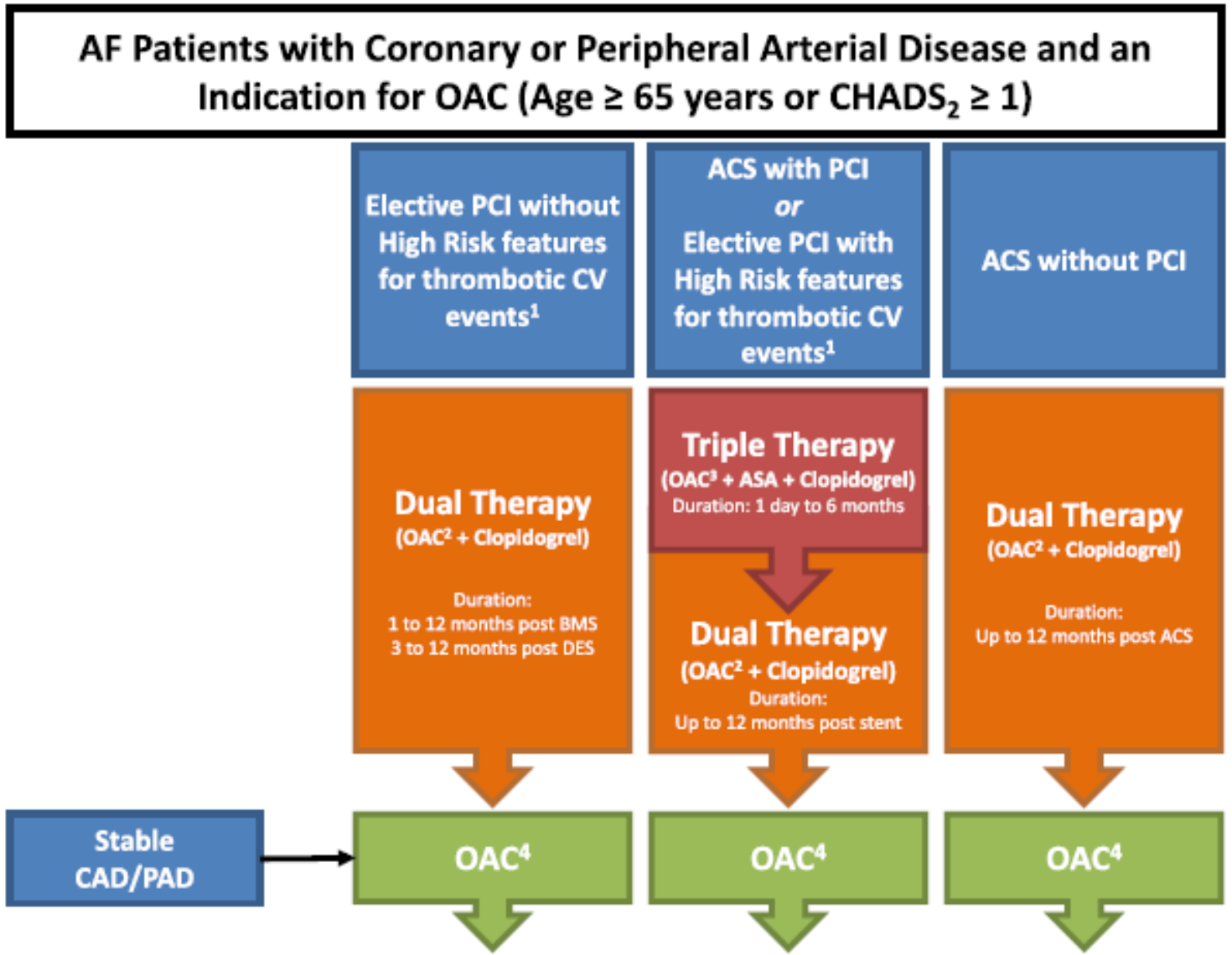
[1]:Periprocedural administration of aspirin and clopidogrel during PCI is recommended irrespective of the treatment strategy; as dual therapy, potent P2Y12 inhibitors (ticagrelor) may be combined with dabigatran

[2]: High atherothrombotic risk (For Elective PCI, use SYNTAX score; for ACS, GRACE score >140; stenting of the left main, proximal LAD, proximal bifurcation; recurrent MIs; stent thrombosis etc.) and low bleeding risk

[3]: Bleeding risk can be estimated using the HAS-BLED score; correct modifiable bleeding risk factors

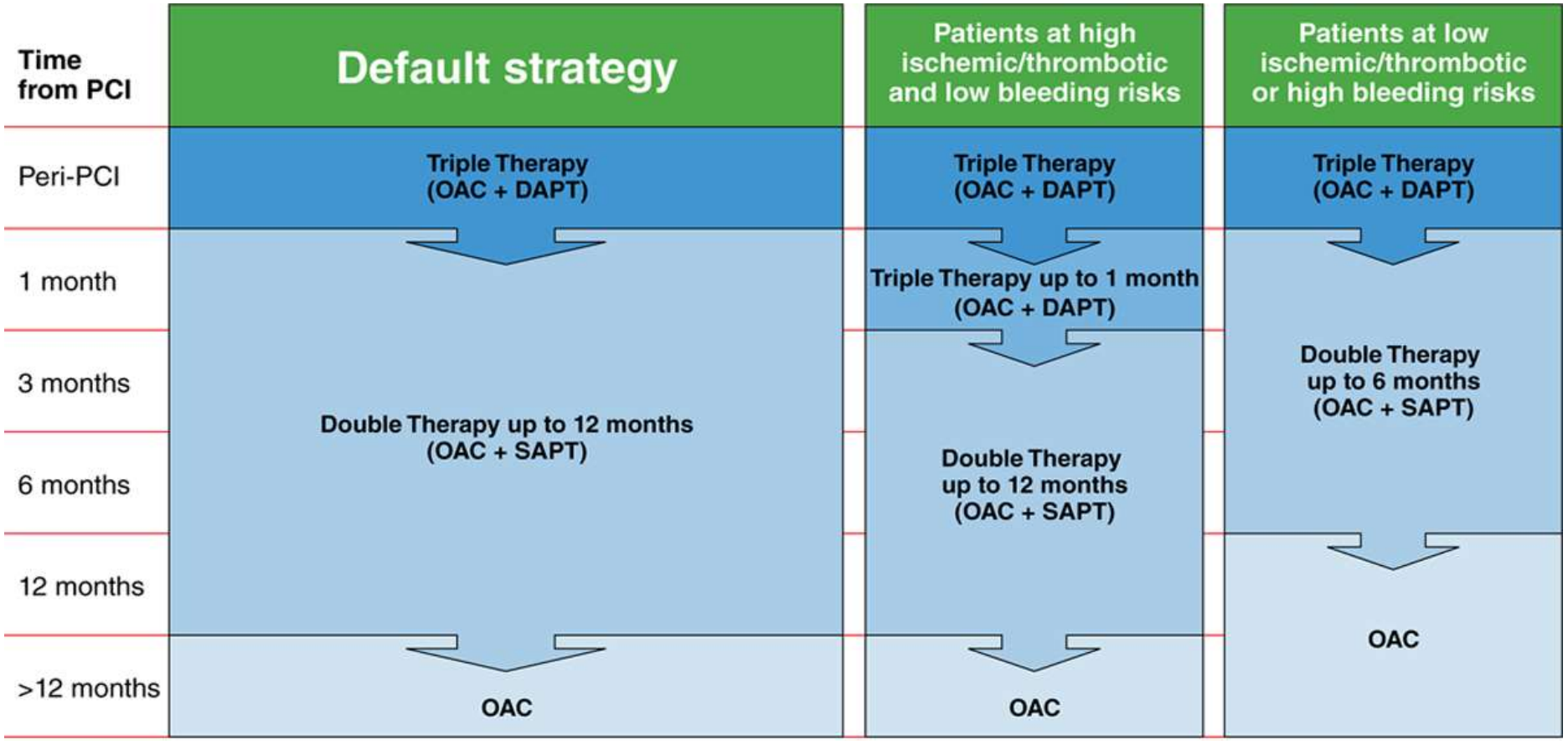
Lip G et al, Europace. Published online July 21, 2018. doi:10.1093/europace/euy174

2018 Focused Update of Canadian Cardiovascular Society Guidelines



Andrade *et al*, *Can J Cardiol* 2018;34:1371–1392

2018 North American Expert Consensus Update



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)

What do we want to know fundamentally from AF PCI Trials?

1. TOAT vs. DOAT: What is superior? Most likely DOAT will have less bleeding….
2. If DOAT significantly reduces major bleeding compared with TOAT, what about ischemic or embolic outcomes?
3. What about VKA vs. DOAC? If DOAT is superior in terms of bleeding, is this due to the effect of DOAC? Or because 3 has been reduced to 2?

The AUGUSTUS Trial: Two Independent Hypotheses

In patients with AF and ACS or PCI on a $P2Y_{12}$ inhibitor

1. **Apixaban is non-inferior to VKA for International Society on Thrombosis and Haemostasis** (ISTH) **major or clinically relevant non-major** (CRNM) **bleeding**

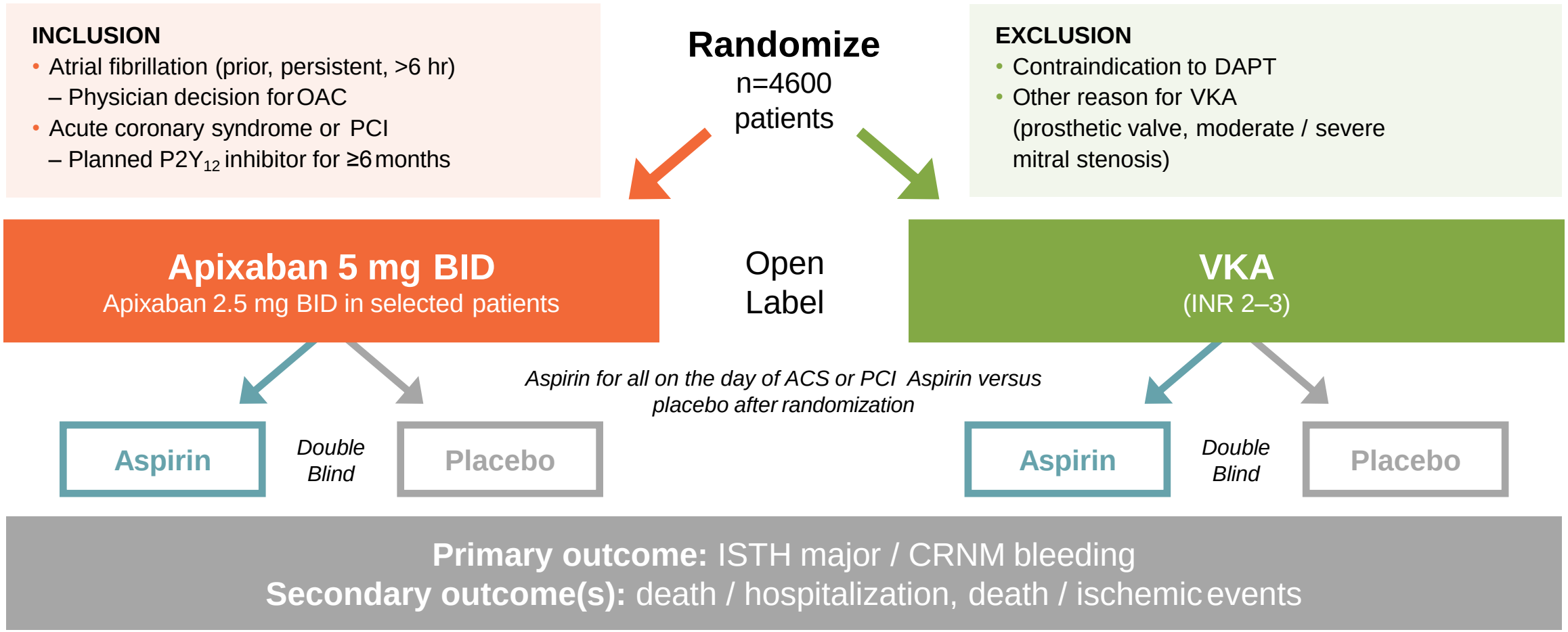
VKA vs. NOAC (DOAC)

2. **Aspirin is inferior to placebo for ISTH major or CRNM bleeding in patients on oral anticoagulation** (OAC)

DOAT vs. TOAT

Lopes RD, et al. N Engl J Med 2019; 380:1509-1524

The AUGUSTUS Trial: Design



Lopes RD, et al. N Engl J Med 2019; 380:1509-1524

Trial Organization

EXECUTIVE COMMITTEE

- John Alexander (Chair)
- Renato Lopes (PI)
- Roxana Mehran (USA)
- Christopher Granger (USA)
- Shaun Goodman (Canada)
- Harald Darius (Germany)
- Stephan Windecker (Switzerland)
- Ronald Aronson (BMS)

DATA SAFETY MONITORING BOARD

- Lars Wallentin (Chair)
- Robert Harrington
- Stuart Pocock
- Statistical Support—Uppsala Clinical Research

CLINICAL EVENTS CLASSIFICATION(CEC) COMMITTEE

- Duke Clinical Research Institute

ACADEMIC COORDINATING CENTER

- Duke Clinical Research Institute

CONTRACT RESEARCH ORGANIZATION

- Pharmaceutical Product Development (PPD)

SPONSORS

- Bristol-Myers Squibb/ Pfizer

Lopes RD, et al. N Engl J Med 2019; 380:1509-1524

Participating Countries and Number of Patients

Lopes RD, et al. N Engl J Med 2019; 380:1509-1524

Primary Outcome

ISTH major bleeding

- Results in death
- Occurs in critical area or organ
- Results in hemoglobin drop ≥2 g/dL
- Requires transfusion of ≥2 units of whole blood or packed red blood cells

Clinically relevant non-major bleeding

- Results in hospitalization
- Requires medical / surgical evaluation or intervention
- Requires physician-directed change in antithrombotic regimen

Lopes RD, et al. N Engl J Med 2019; 380:1509-1524

Secondary Outcomes

- **Death or Hospitalization**
- **Death or Ischemic Events**
  - Stroke, myocardial infarction, stent thrombosis (definite or probable), urgent revascularization

Lopes RD, et al. N Engl J Med 2019; 380:1509-1524

Statistical Analysis—Hierarchical Testing

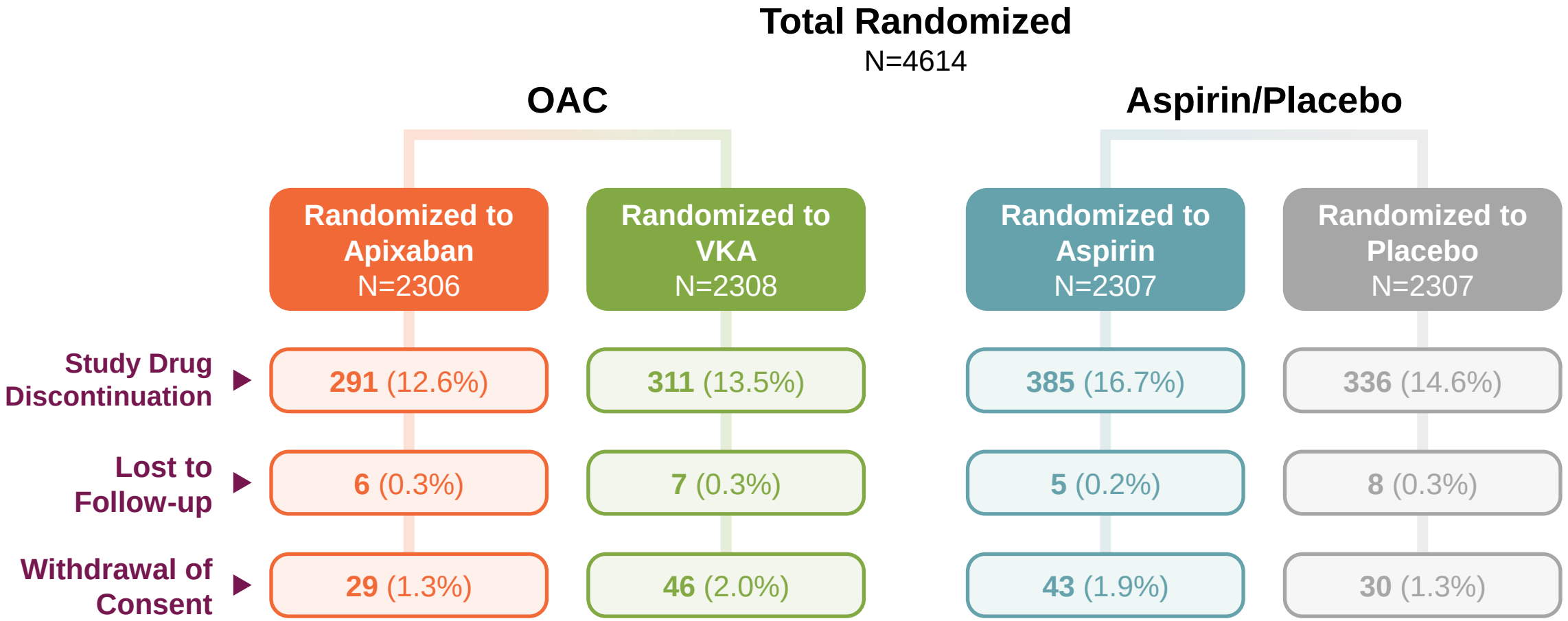
Apixaban vs. VKA:

- **Major / CRNM Bleeding**[NI then Sup]
- **Death / Hospitalization**[Sup]
- **Death / Ischemic Events**[Sup]

Placebo vs. Aspirin:

- **Major / CRNM Bleeding**[Sup]
- **Death / Hospitalization**[Sup]
- **Death / Ischemic Events**[Sup]

CONSORT Diagram



Baseline Characteristics

CHA_2DS_2-VASc score, mean (SD)	**3.9 (1.6)**
HAS-BLED score, mean (SD)	**2.9 (0.9)**
Prior OAC, %	**49.0**
$P2Y_{12}$ inhibitor, %	
▪ Clopidogrel	**92.6**

	Total (N=4,614)
Age, median (25th, 75th)**, years**	70.7 (64.2, 77.2)
Female, %	29.0
CHA_2DS_2-VASc score, mean (SD)	3.9 (1.6)
HAS-BLED score, mean (SD)	2.9 (0.9)
Prior OAC, %	49.0
$P2Y_{12}$ inhibitor, %	
▪ Clopidogrel	92.6
▪ Prasugrel	1.1
▪ Ticagrelor	6.2
Number of days from ACS/PCI to randomization, mean (SD)	6.6 (4.2)
Qualifying index event, %	
▪ ACS and PCI	37.3
▪ ACS and no PCI	23.9
▪ Elective PCI	38.8

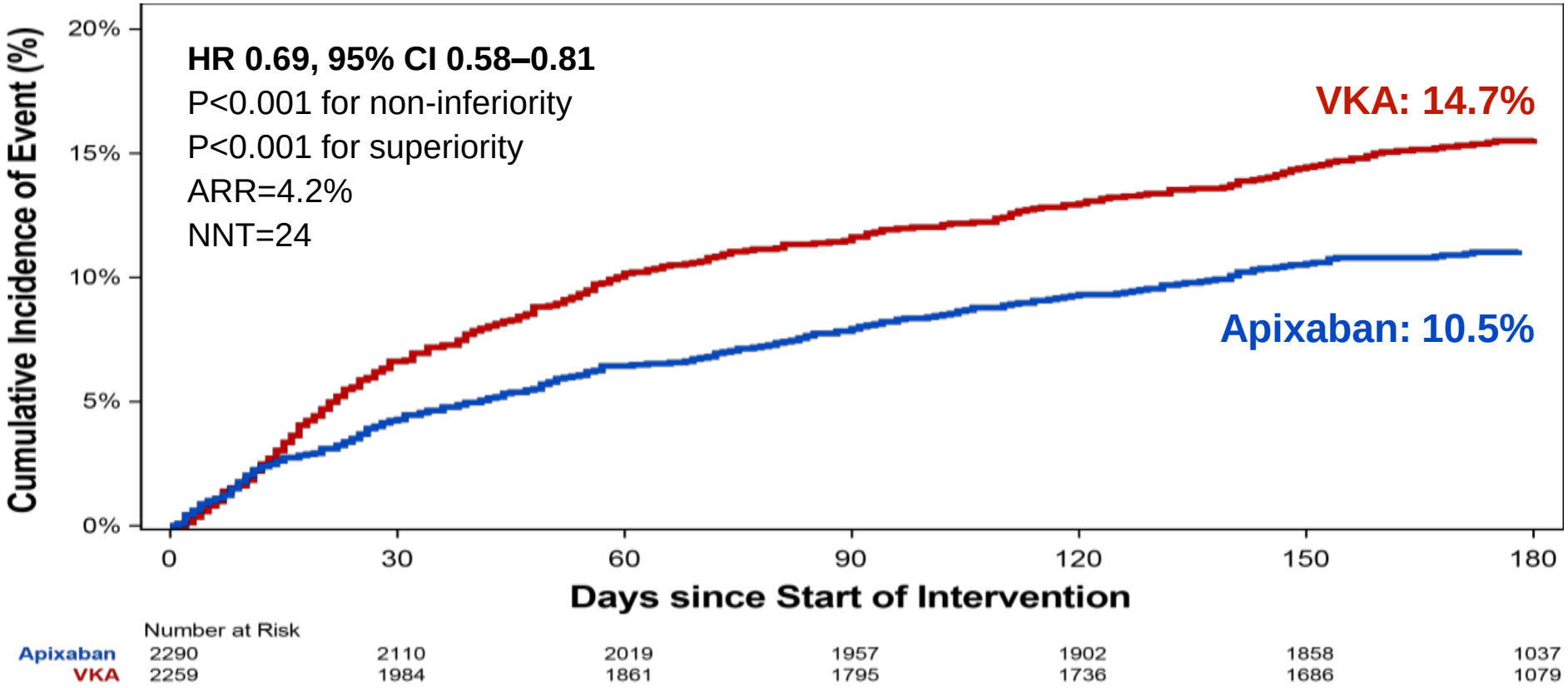
No Significant Interactions Between Randomization Factors

Apixaban / VKA vs. Aspirin / Placebo

- **Major / CRNM Bleeding** : $P_{interaction} = 0.64$
- **Death / Hospitalization** : $P_{interaction} = 0.21$
- **Death / Ischemic Events** : $P_{interaction} = 0.28$

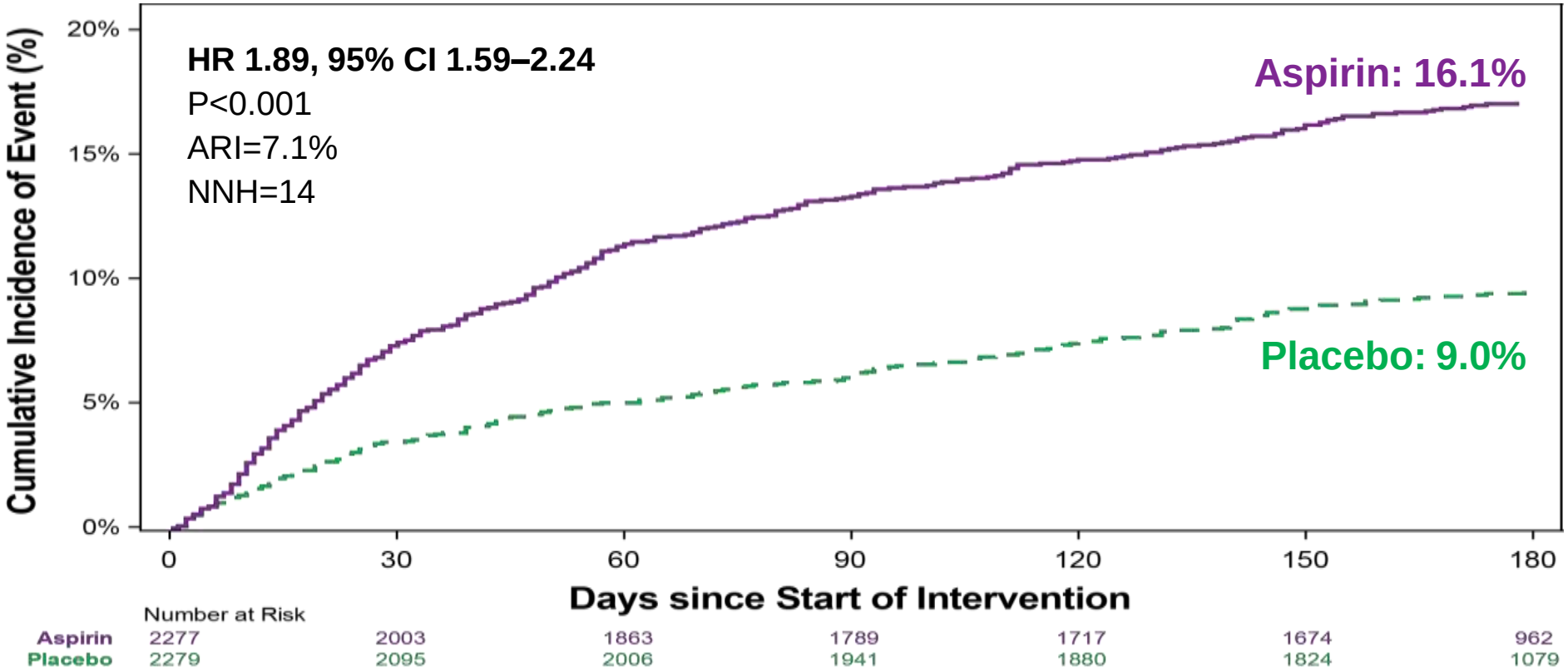
Major / CRNM Bleeding (VKA vs. NOAC)

- **Apixaban vs. VKA**

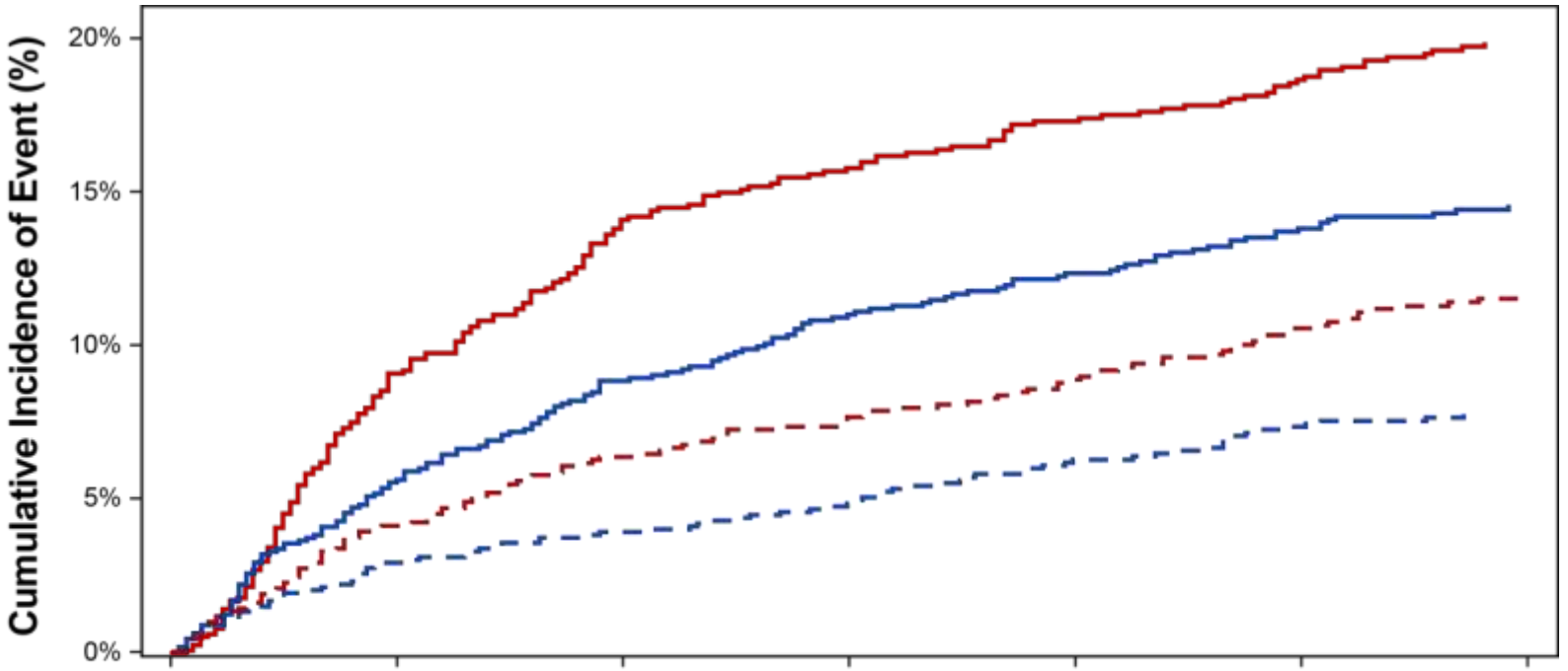


Major / CRNM Bleeding (DOAT vs. TOAT)

- **Aspirin vs. Placebo**



Major / CRNM Bleeding (NOAC based DOAT best)



Number at Risk							
Apixaban and Aspirin	1145	1036	975	937	903	880	485
Apixaban and Placebo	1143	1075	1044	1007	975	947	536
VKA and Aspirin	1123	962	881	838	800	776	467
VKA and Placebo	1126	1007	947	917	883	851	528

VKA + Aspirin (18.7%)

Apixaban + Aspirin (13.8%)

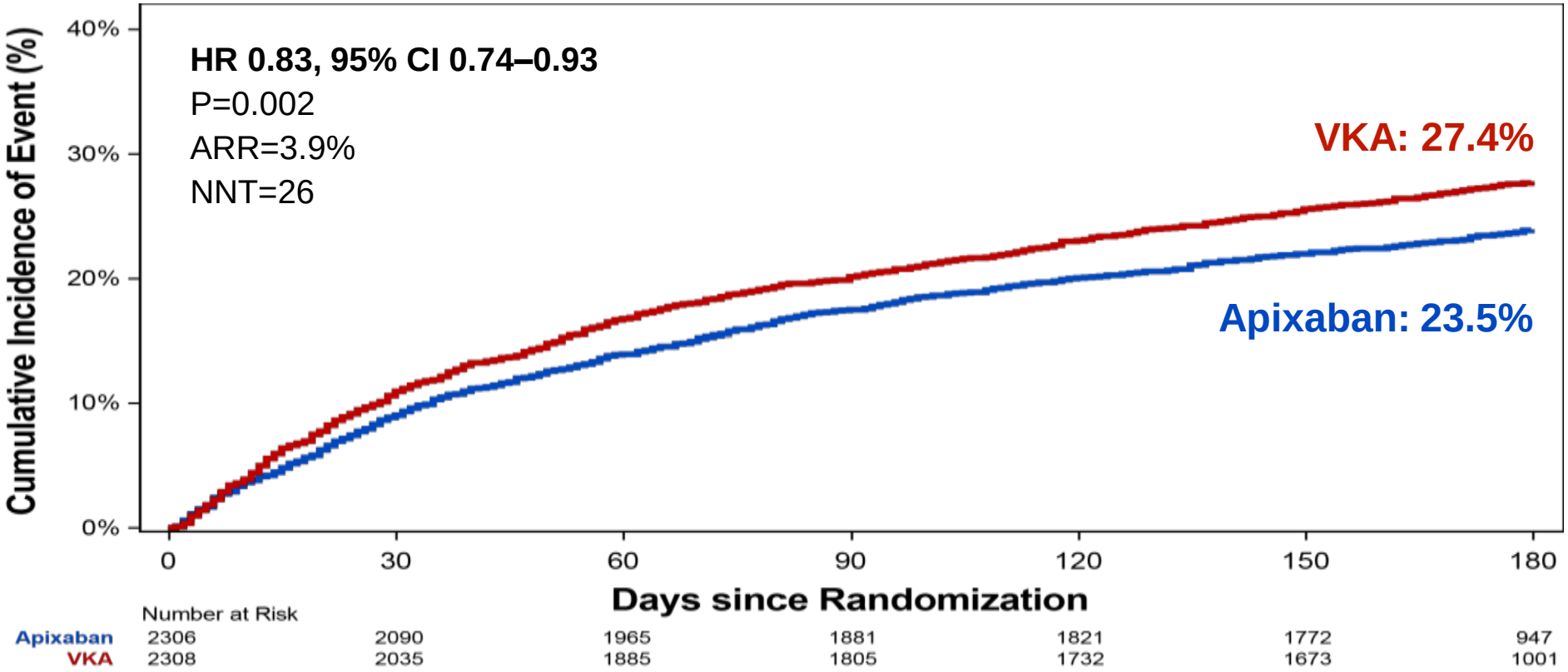
VKA + Placebo (10.9%)

Apixaban + Placebo (7.3%)

Apixaban + Placebo vs. VKA + Aspirin: 11.4% absolute risk reduction (NNT=9)

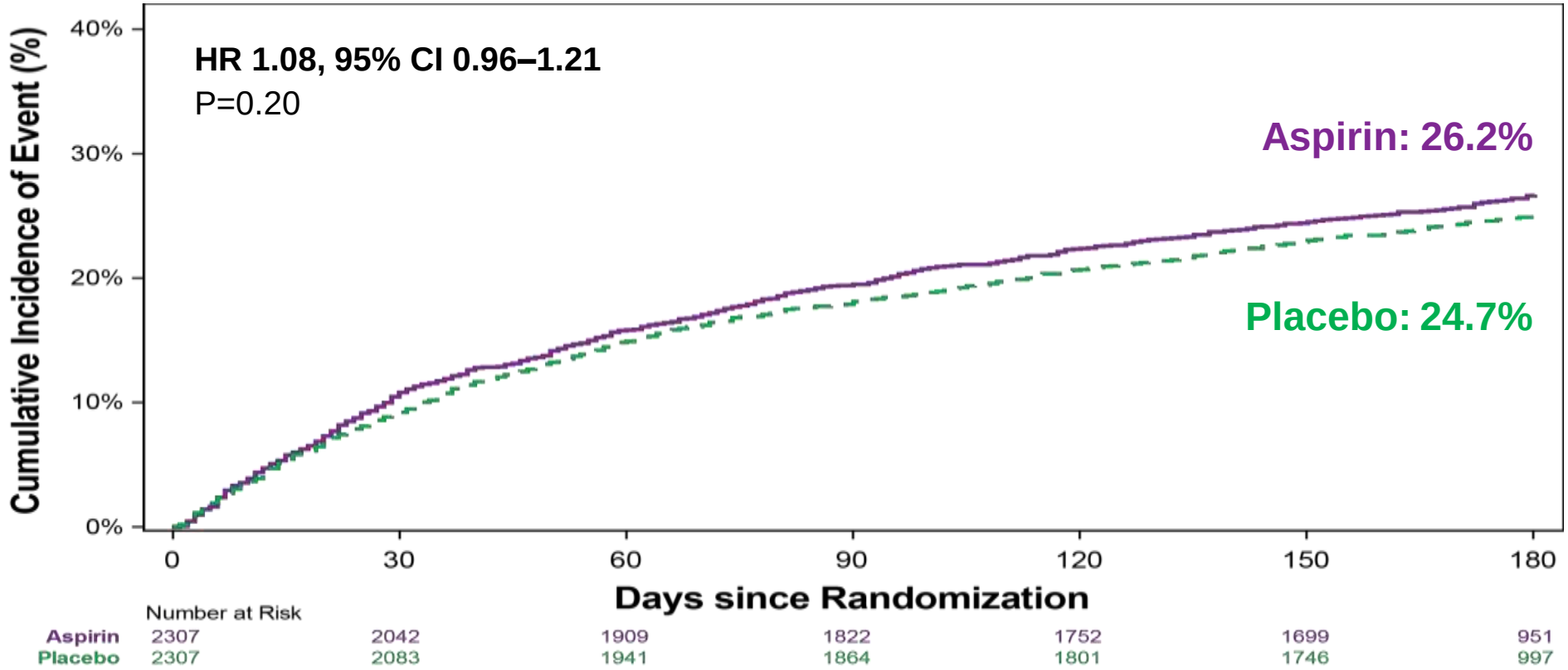
Death / Hospitalization (VKA vs. NOAC)

- **Apixaban vs. VKA**

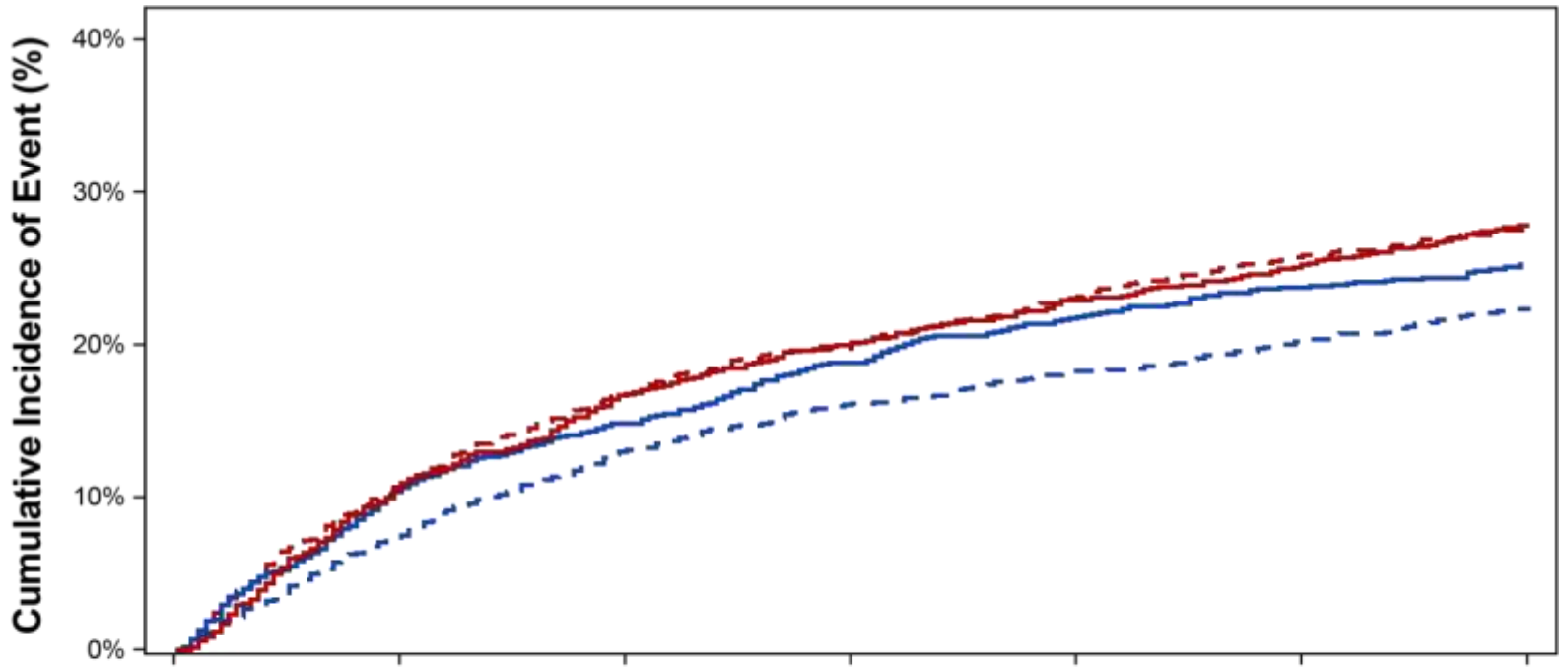


Death / Hospitalization (DOAT vs. TOAT)

- **Aspirin vs. Placebo**



Death / Hospitalization (NOAC based DOAT is best)



Number at Risk							
Apixaban and Aspirin	1153	1026	970	923	888	863	459
Apixaban and Placebo	1153	1064	995	958	933	909	488
VKA and Aspirin	1154	1016	939	899	864	836	492
VKA and Placebo	1154	1019	946	906	868	837	509

VKA + Aspirin (27.5%)
VKA + Placebo (27.3%)
Apixaban + Aspirin (24.9%)
Apixaban + Placebo (22.0%)

Apixaban + Placebo vs. VKA + Aspirin:
5.5% absolute risk reduction (NNT=18)

Ischemic Outcomes (VKA vs. NOAC)

Apixaban vs. VKA

Endpoint	Apixaban (N=2306)	VKA (N=2308)	HR (95% CI)
Death / Ischemic Events (%)	6.7	7.1	0.93 (0.75–1.16)
Death (%)	3.3	3.2	1.03 (0.75–1.42)
CV Death (%)	2.5	2.3	1.05 (0.72–1.52)
Stroke (%)	**0.6**	**1.1**	**0.50 (0.26–0.97)**
Myocardial Infarction (%)	3.1	3.5	0.89 (0.65–1.23)
Definite or Probable Stent Thrombosis (%)	0.6	0.8	0.77 (0.38–1.56)
Urgent Revascularization (%)	1.7	1.9	0.90 (0.59–1.38)
Hospitalization (%)	**22.5**	**26.3**	**0.83 (0.74–0.93)**

Ischemic Outcomes (DOAT vs. TOAT)

Aspirin vs. Placebo

Endpoint	Aspirin (N=2307)	Placebo (N=2307)	HR (95% CI)
Death / Ischemic Events (%)	6.5	7.3	0.89 (0.71–1.11)
Death (%)	3.1	3.4	0.91 (0.66–1.26)
CV Death (%)	2.3	2.5	0.92 (0.63–1.33)
Stroke (%)	0.9	0.8	1.06 (0.56–1.98)
Myocardial Infarction (%)	**2.9**	**3.6**	**0.81 (0.59–1.12)**
Definite or Probable Stent Thrombosis (%)	**0.5**	**0.9**	**0.52 (0.25–1.08)**
Urgent Revascularization (%)	**1.6**	**2.0**	**0.79 (0.51–1.21)**
Hospitalization (%)	25.4	23.4	1.10 (0.98–1.24)

The AUGUSTUS Trial: Main findings

- **In a population of 4614 patients with AF who had an ACS and/or underwent PCI (theoretical need for OAC+DAPT):**

1) Apixaban was shown to be superior to VKA on the primary outcome of bleeding complications (4.2% ARR; NNT ~24) (Apixaban >> VKA)

2) Compared with placebo, aspirin significantly increased the rates of bleeding (7.1% ARI; NNH ~14) (DOAT >> TOAT)

3) Dual therapy using apixaban+clopidogrel wins on bleeding reduction (11.4% ARR; NNT ~9) (Apixaban based DOAT was best)

4) Compared with VKA, apixaban significantly reduced the composite of death or hospitalization (NNT~24), with no differences in ischemic events (Apixaban ≥ VKA)

5) Stopping aspirin did not increase ischemic events or rates of death or hospitalization compared with placebo

The AUGUSTUS Trial: Strengths

- **The AUGUSTUS trial expands upon our current knowledge in this field, particularly with regards to the choice of OAC** (NOAC vs VKA) **and whether there is a need for aspirin on a background of OAC and a P2Y12 inhibitor. However, compared with other RCT's, it provides the most compelling data for the following reasons:**

a. The largest of currently available RCT's.

b. Used dosing regimens of a NOAC approved for stroke prevention in AF.

c. Unique study design; represents the first RCT evaluating if the reduction in bleeding truly related to a NOAC compared with a VKA.

d. The double-blind nature of aspirin versus placebo (first RCT) provides significant rigor to the study findings.

The AUGUSTUS Trial: Considerations

- **There was a numerical increase in stent thrombosis** (ST) **with omission of aspirin therapy** (0.5% vs 0.9%)**. Need for understanding of:**
  - timing of ST
  - predictors of ST
  - role for more potent P2Y12 inhibitors
  - role for very short duration of aspirin
- **Time from index event to enrollment: 1-2wks (past critical period for ST)**
- **Nearly one-quarter of patients were medically managed ACS, thus not at risk for stent thrombosis.**
- **Optimal antithrombotic therapy in AF patients 6-12 months after ACS/PCI still remains unknown.**

What do we want to know fundamentally from AF PCI Trials?

1. TOAT vs. DOAT: What is superior? Most likely DOAT will have less bleeding…. √
2. If DOAT significantly reduces major bleeding compared with TOAT, what about ischemic or embolic outcomes? √ or ?
3. What about VKA vs. DOAC? If DOAT is superior in terms of bleeding, is this due to the effect of DOAC? Or because 3 has been reduced to 2? √

Summary

1. The patient with AF that requires DAPT (AF patient receiving PCI or with ACS) poses a big dilemma for clinicians.
2. Previous studies addressing this issues (PIONEER AF, REDUAL) have suggested a benefit of DOAT over TOAT in terms of risk of major bleeding. However, neither study addressed systematically DOAT vs. TOAT and NOAC vs. VKA. AUGUSTUS is the first study to directly address this.
3. In the NOAC vs. VKA analysis, apixaban was superior to warfarin in terms of bleeding, death/ hospitalization and reduced stroke and systemic embolization.
4. In the DOAT vs. TOAT analysis, DOAT was superior to TOAT in terms of bleeding, and there were no significant differences in death/hospitalization. The numerically higher rates of ST/MI require further data.
5. In terms of ISTH major and CRNM bleeding and death/hospitalization, Apixaban based DOAT was the best.