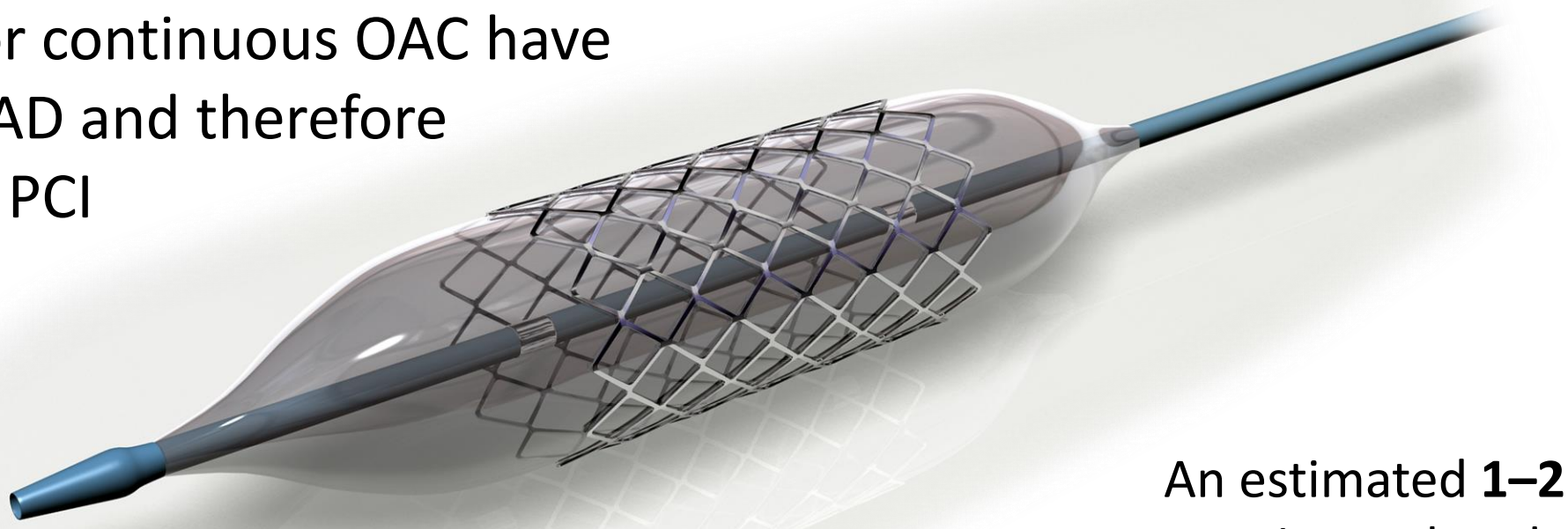
UNIVERSITÀ
POLITECNICA
DELLE MARCHE

Medical management of AF following PCI

Dr. Federico Guerra
Cardiology and Arrhythmology Clinic
Ancona, Italy

AF and PCI

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

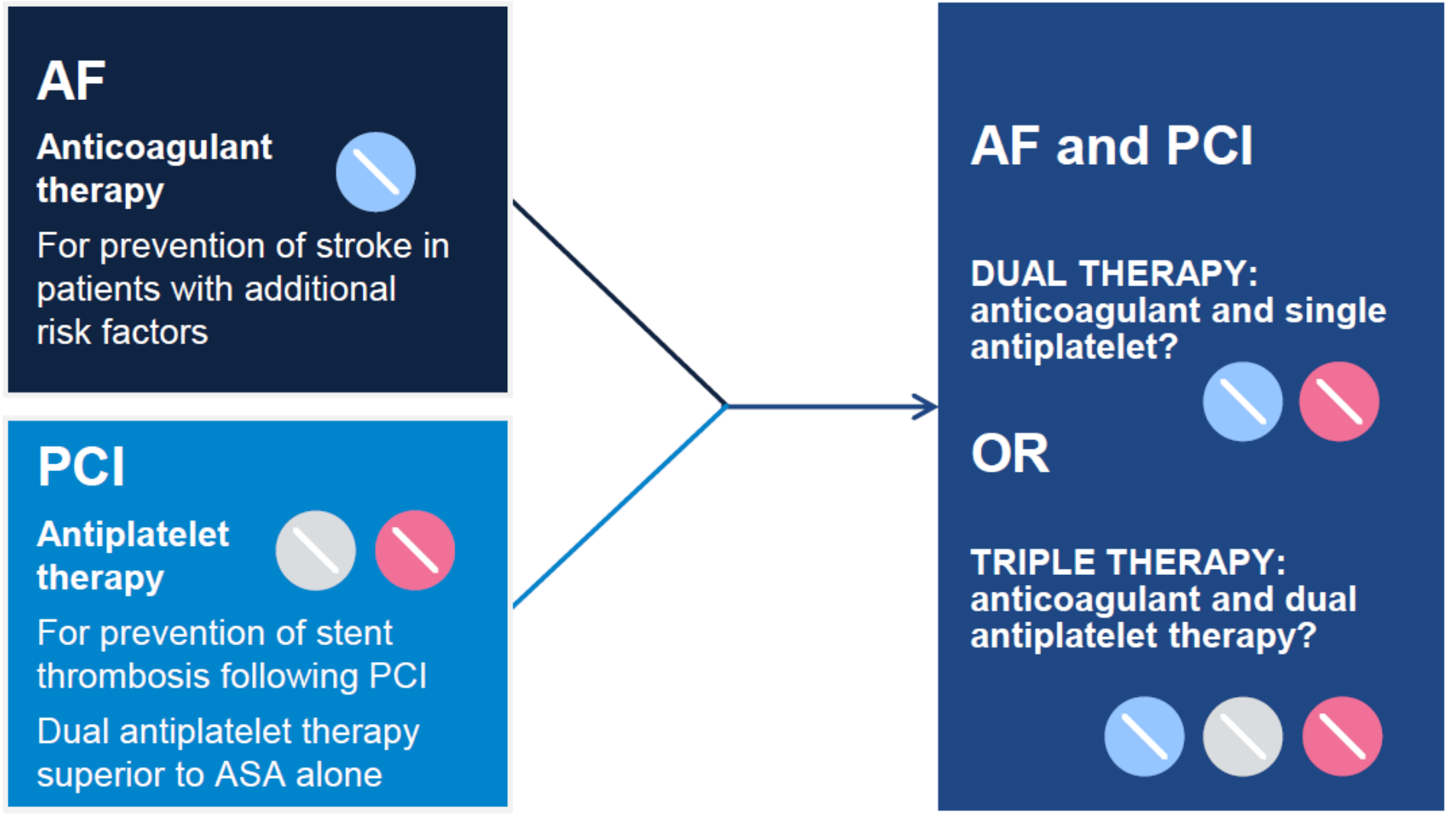


An estimated **1–2 million** anticoagulated patients in Europe are candidates for PCI procedures

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

Lip et al. Thromb Haemost 2010

Medical management



Kirchhof et al. Eur Heart J 2016; Lip et al. Eur Heart J 2014

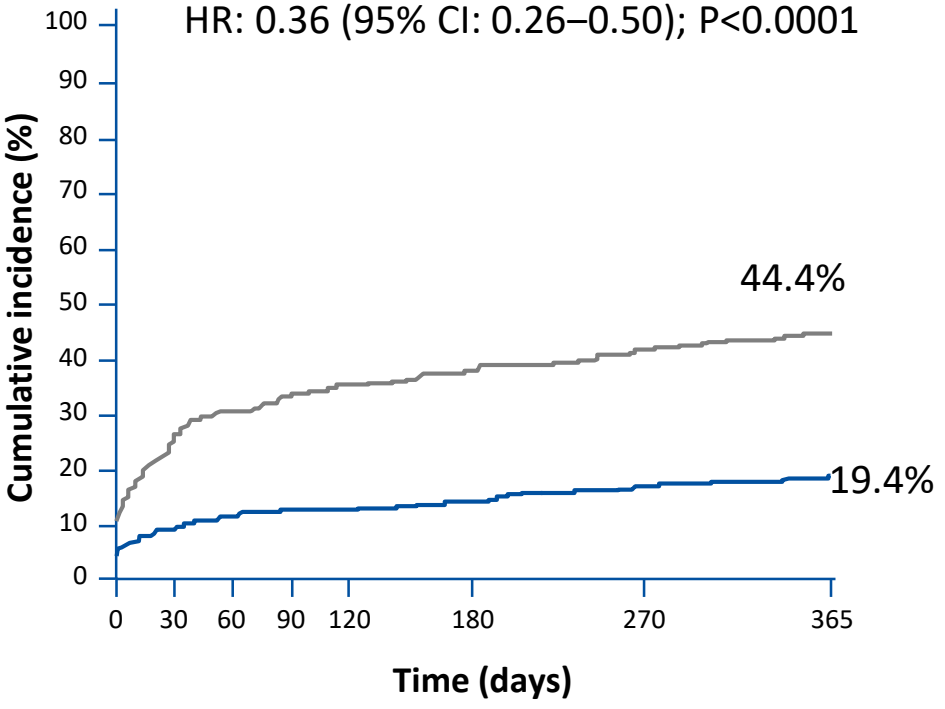
Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial

Triple therapy group (VKA + clopidogrel + ASA)

Double therapy group (VKA + clopidogrel)

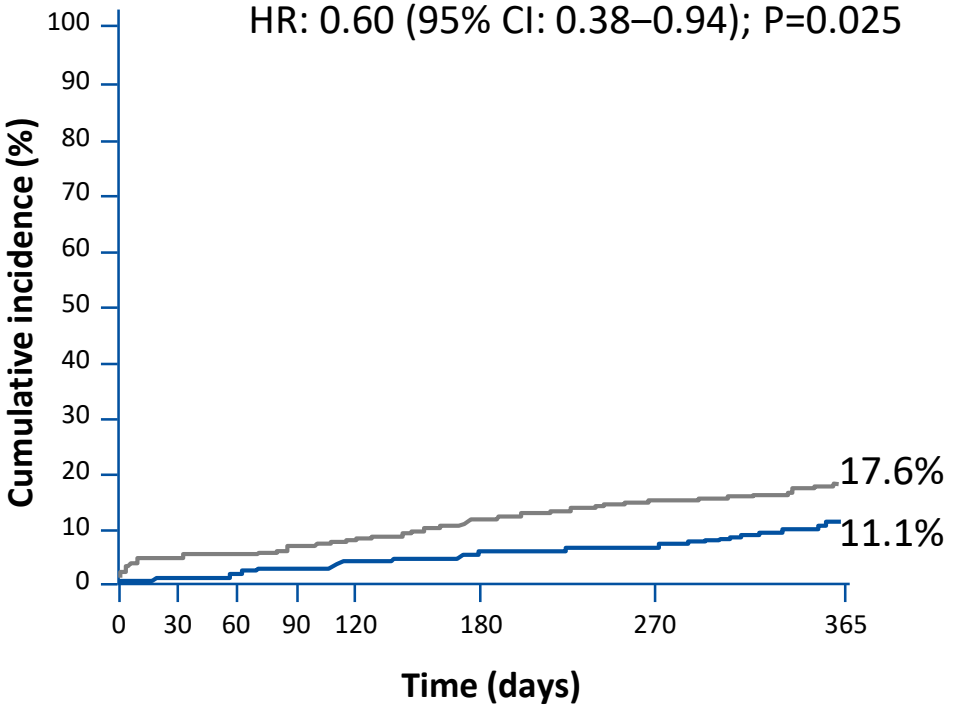
Total number of TIMI bleeding events

HR: 0.36 (95% CI: 0.26–0.50); P<0.0001



Death, MI, TVR, stroke, ST

HR: 0.60 (95% CI: 0.38–0.94); P=0.025

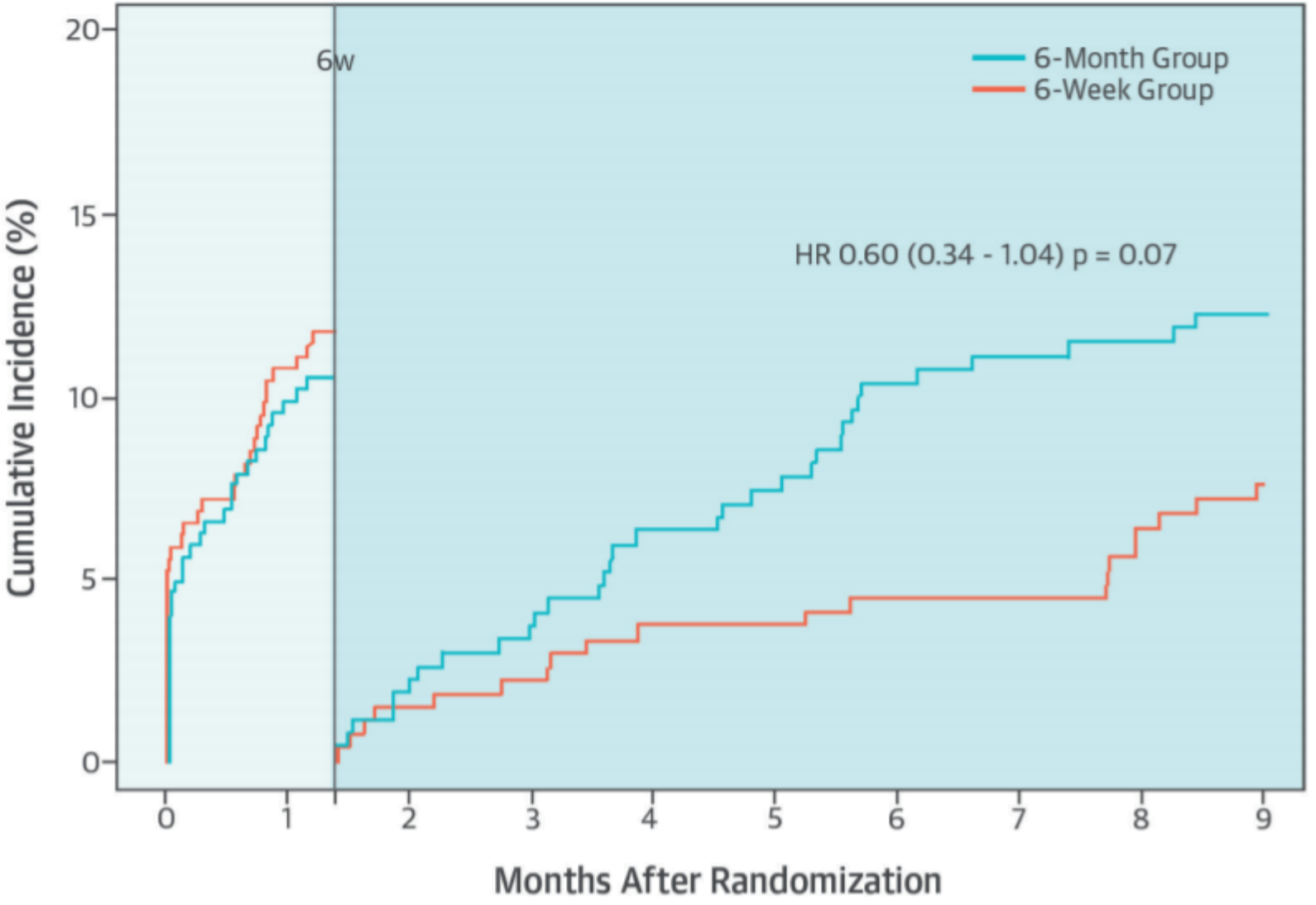


	Double therapy (n=297)	Triple therapy (n=284)	Hazard ratio (95% CI)	p value
Stent thrombosis				
Any	4 (1·4%)	9 (3·2%)	0·44 (0·14–1·44)	0·165
Definite	1 (0·4%)	3 (1·1%)	0·33 (0·03–3·22)	0·319

Dewilde et al. Lancet 2013;381:1107

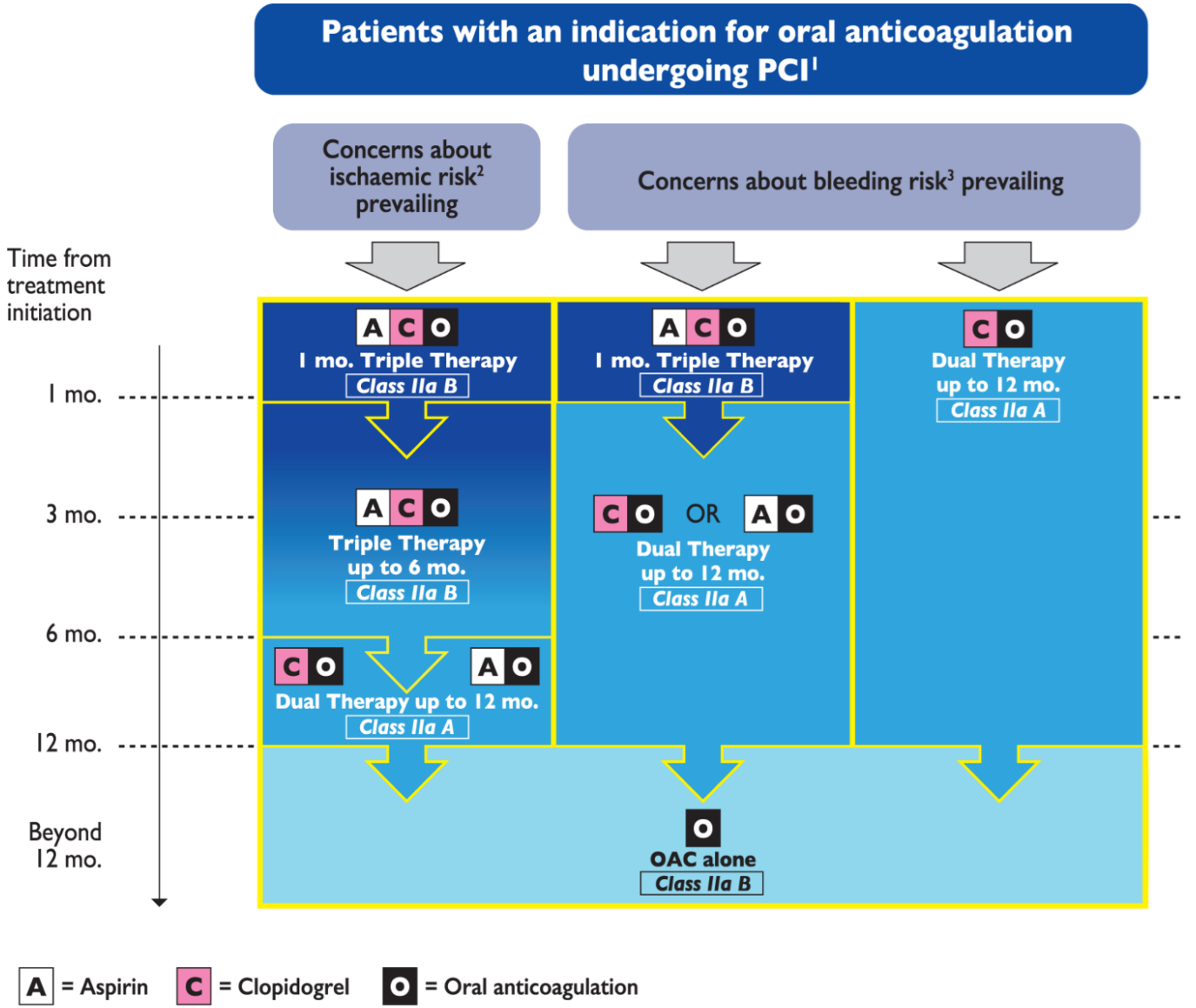
Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation

The ISAR-TRIPLE Trial



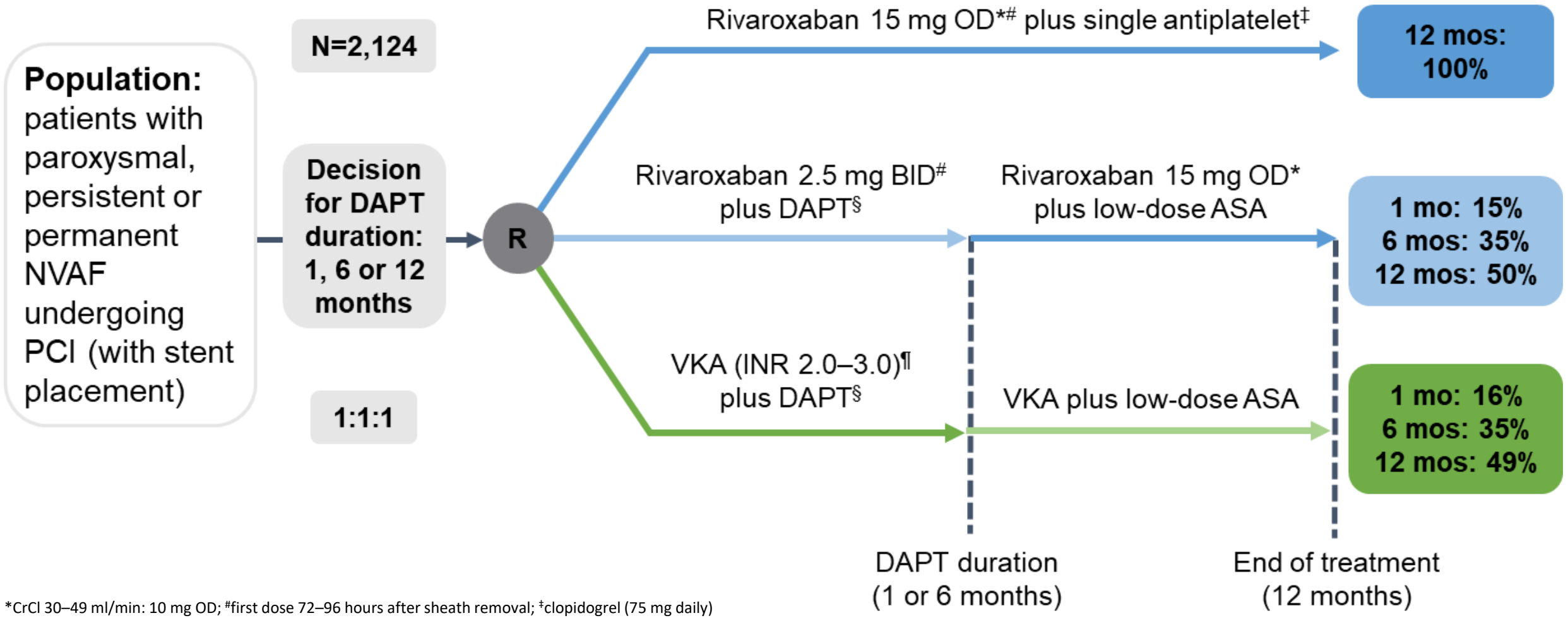
Fiedler KA et al. J Am Coll Cardiol 2015

NOAC and PCI (2017)



Vaglimigli M. et al., ESC focused update on dual antiplatelet therapy in coronary artery disease, European Heart Journal 2018

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

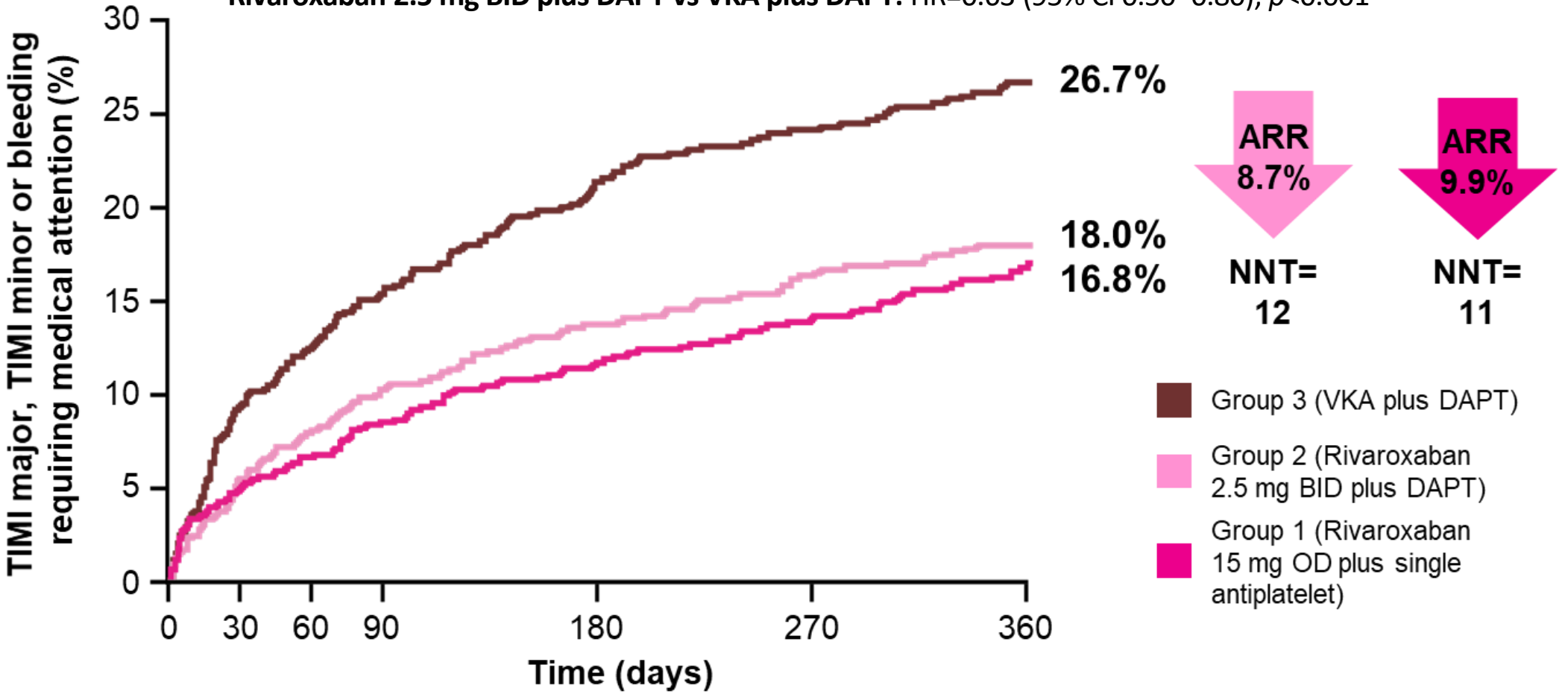


*CrCl 30–49 ml/min: 10 mg OD; #first dose 72–96 hours after sheath removal; ‡clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); §ASA (75–100 mg daily) plus clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); ¶first dose 12–72 hours after sheath removal

Gibson CM et al, NEJM 2016

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=0.59; (95% CI 0.47–0.76); *p*<0.001

Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.63 (95% CI 0.50–0.80); *p*<0.001

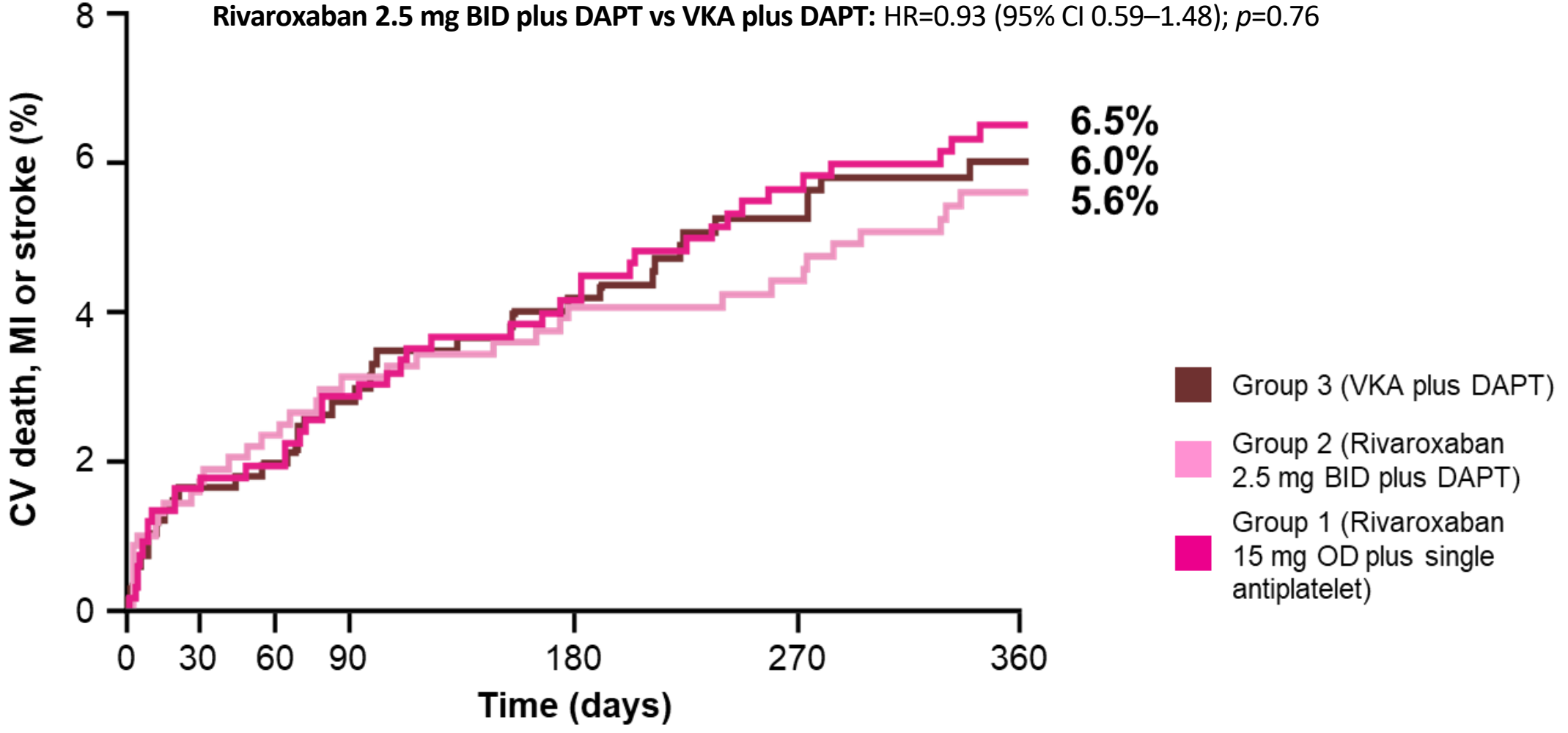


Gibson CM et al, NEJM 2016

Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=1.08; (95% CI 0.69–1.68); *p*=0.75

Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.93 (95% CI 0.59–1.48); *p*=0.76



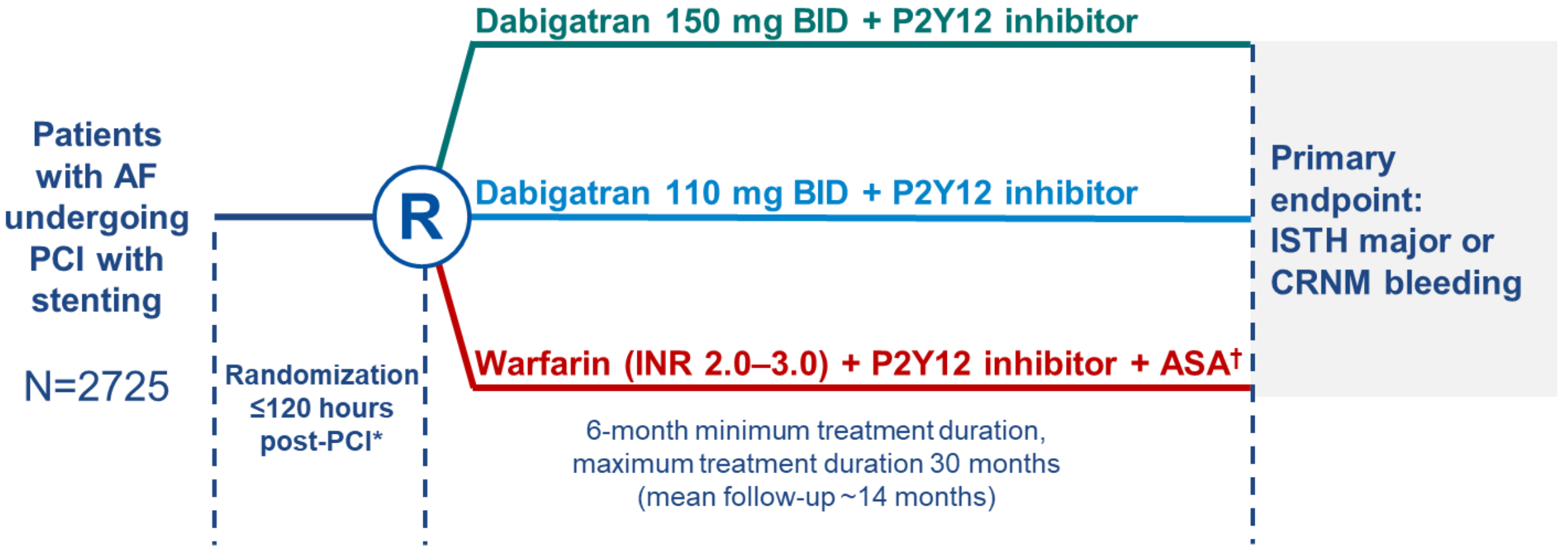
Gibson CM et al, NEJM 2016

Open issues

- 2.5 mg BID dose is not approved for AF; data on the efficacy of 15/10 mg OD in patients with AF are limited; therefore, stroke prevention of those dosages strengths tested post-PCI is unknown
- DAPT duration in each triple therapy arm was at investigators' discretion; most patients received triple therapy for ≥6 months, which is not in line with current guidelines
- Primary endpoint was driven by bleeding requiring medical attention
  only 15% were adjudicated; no hazard ratio data are available for ISTH bleeding or ICH

Gibson CM et al, NEJM 2016

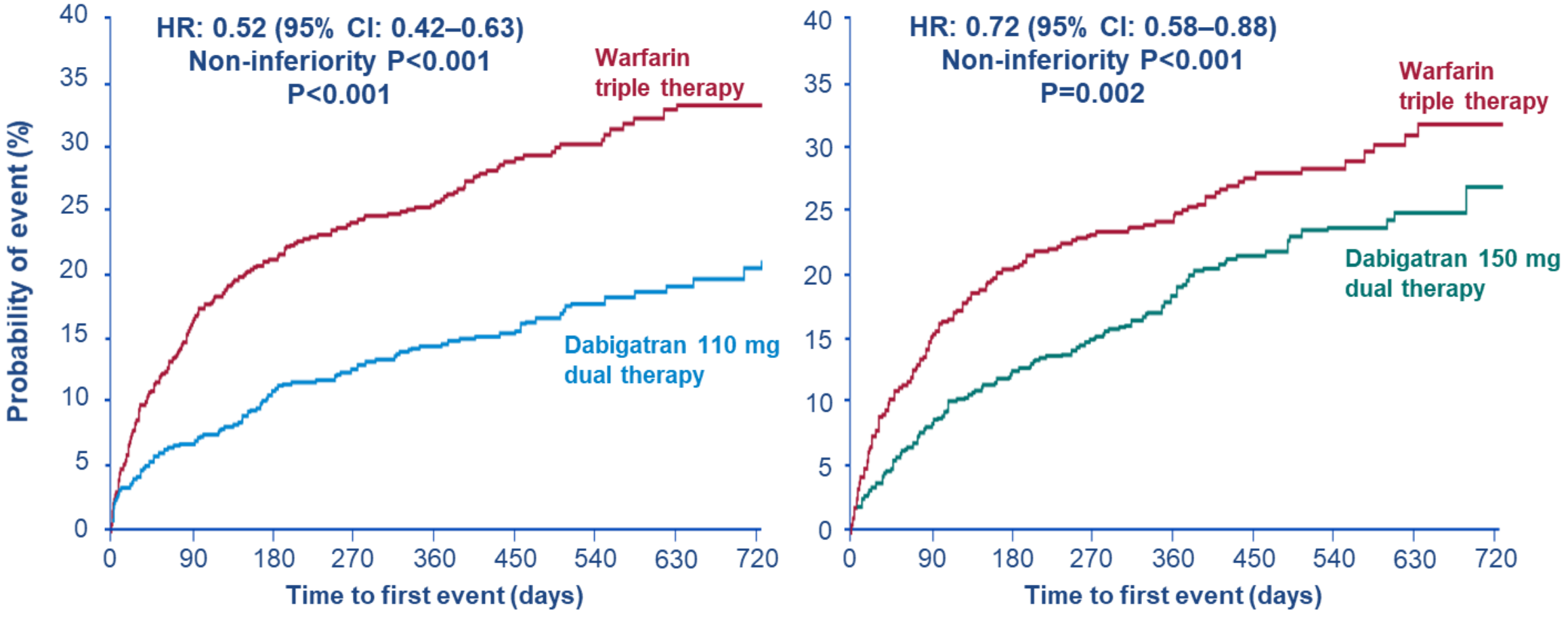
Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation



- *Study drug should be administered 6 hours after sheath removal and no later than 120 hours post-PCI (≤72 hours is preferable). †ASA discontinued after 1 month after bare-metal stent and 3 months after drug-eluting stent

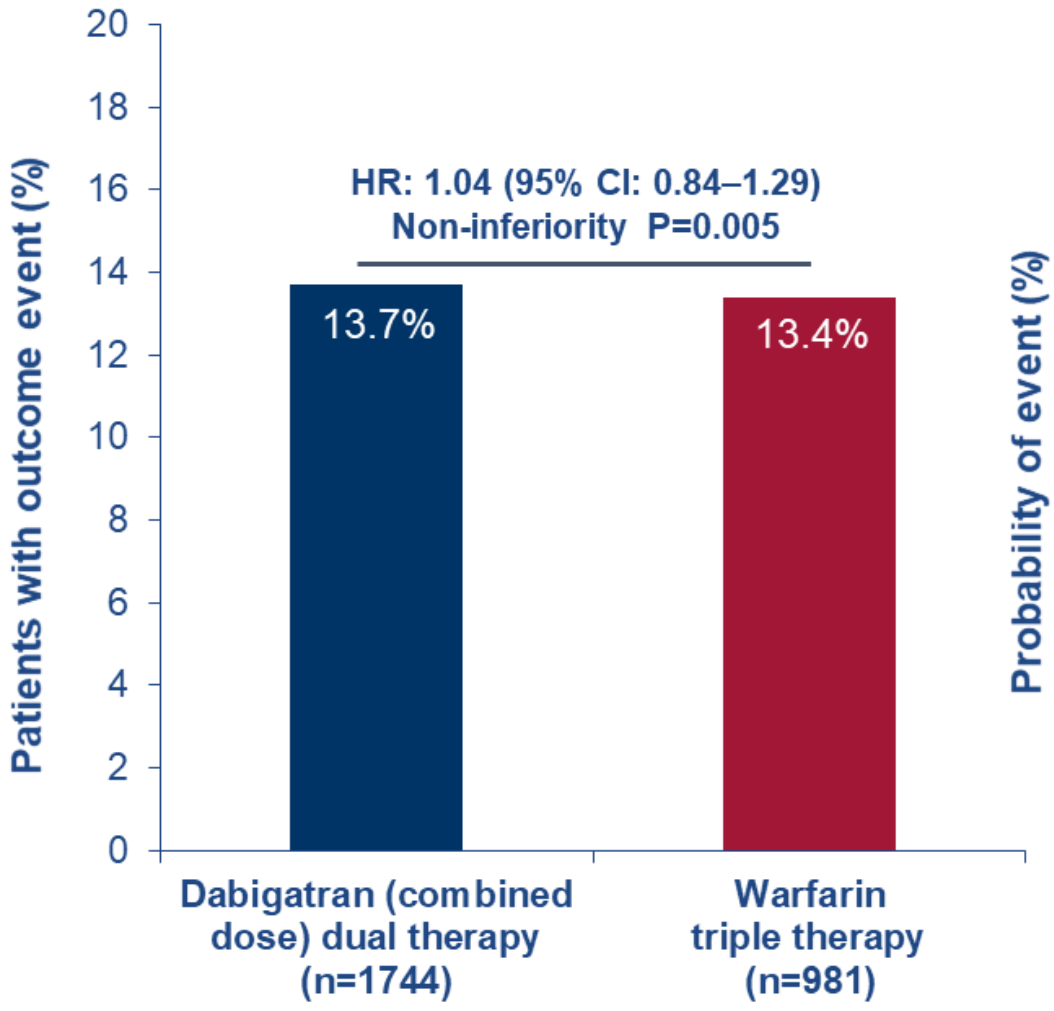
Cannon C et al, NEJM 2017

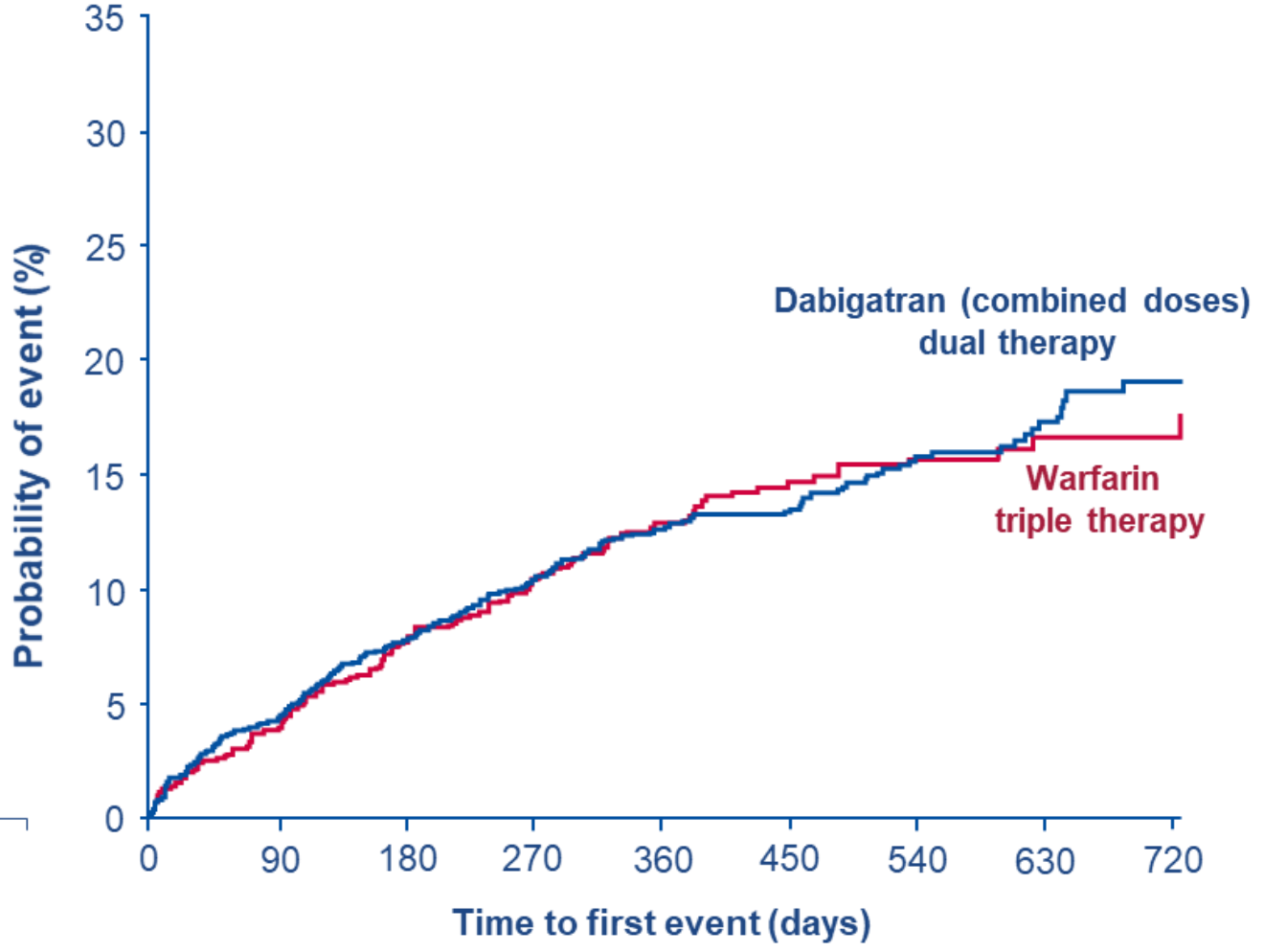
Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation



Cannon C et al, NEJM 2017

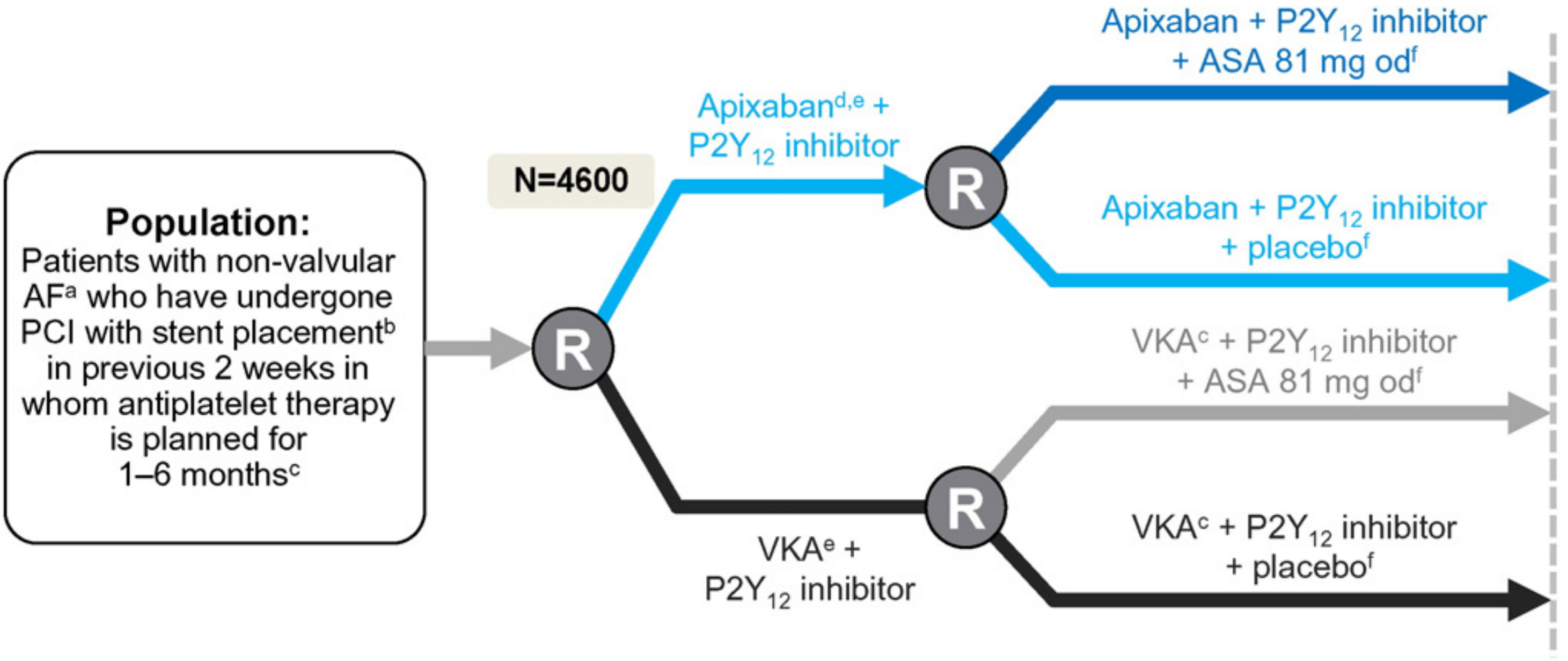
Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation





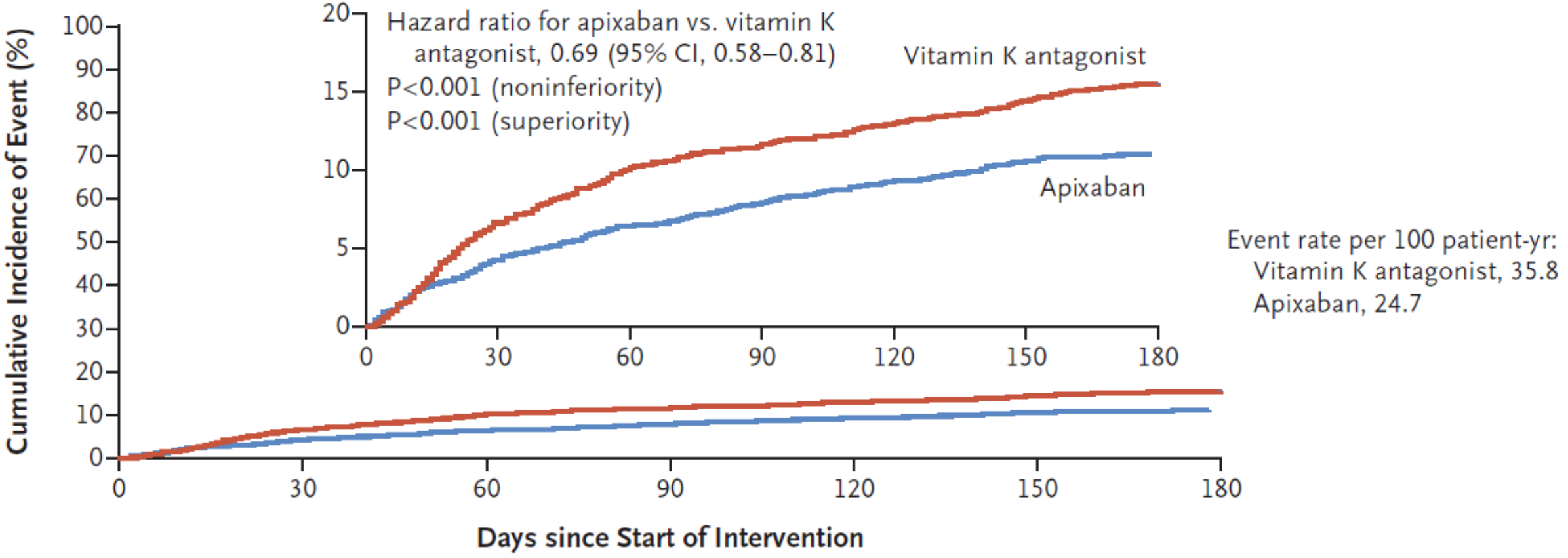
Cannon C et al, NEJM 2017

Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation



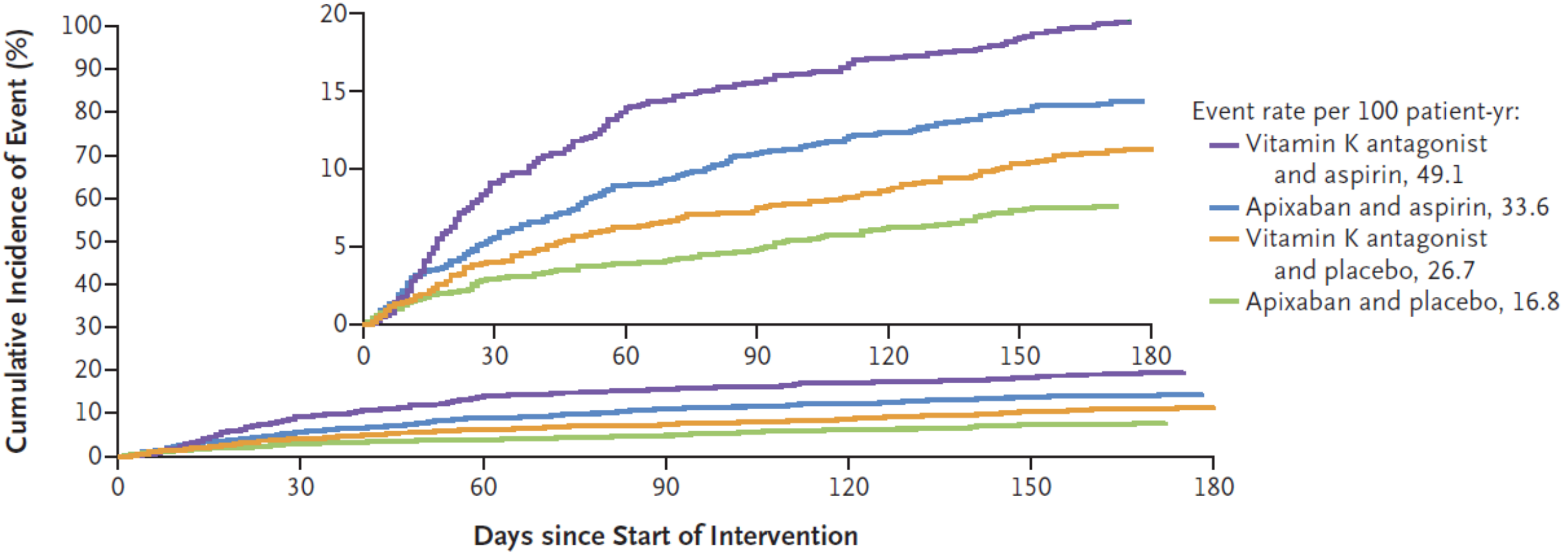
Lopes R et al., NEJM 2019

Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation



Lopes R et al., NEJM 2019

Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation



Lopes R et al., NEJM 2019

Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial

PROBE design: Prospective, Randomized, Open label, Blinded endpoint Evaluation in 1500 AF patients with ACS or stable CAD

<u>Inclusion Criteria:</u>

- 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*
- $P2Y_{12}$ inhibitor** (without aspirin)

12 m.

- Vitamin K Antagonist***
- $P2Y_{12}$ inhibitor aspirin 1 - 12 months****

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

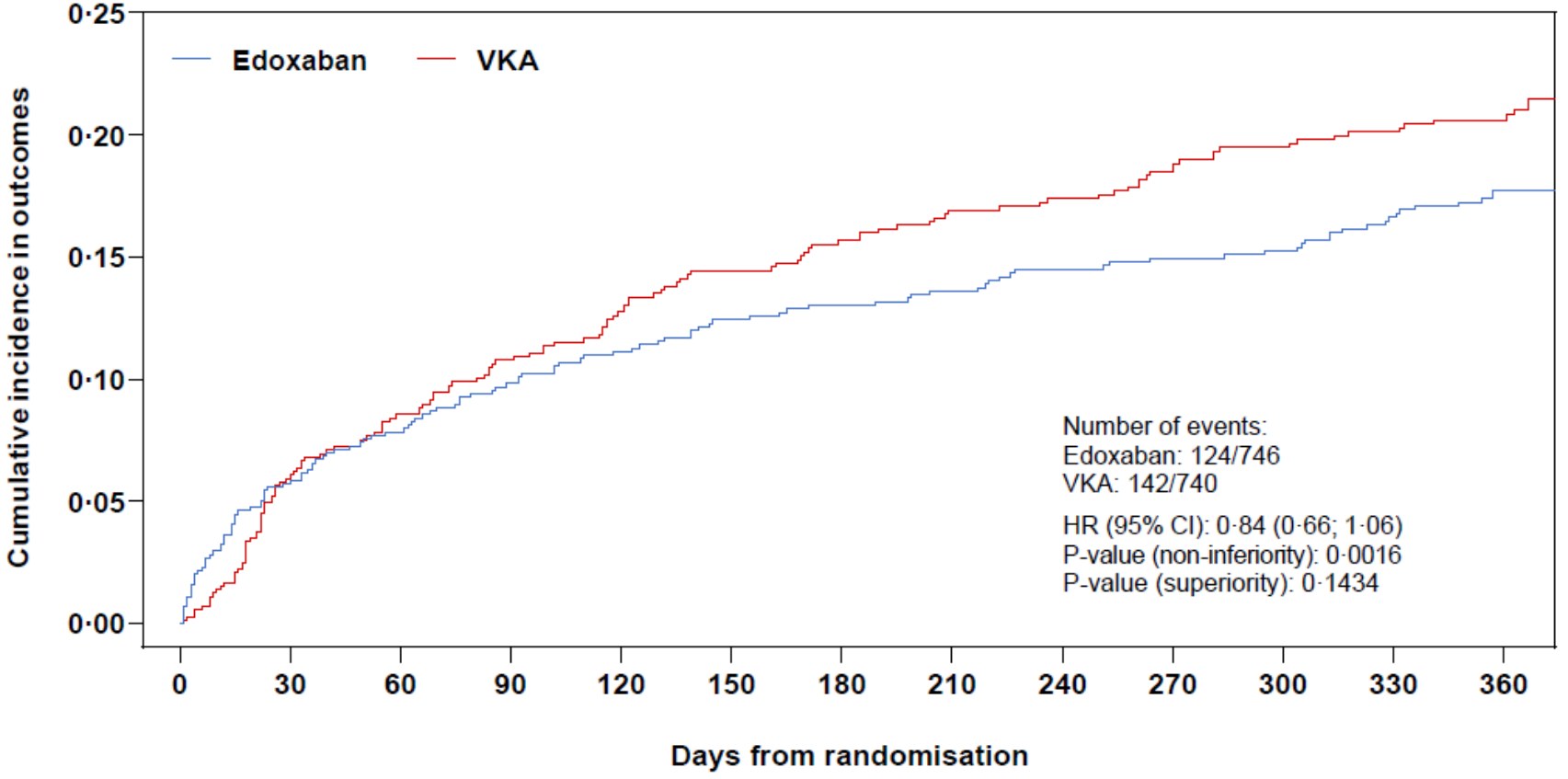
**Clopidogrel 75mg once-daily or if documented need prasugrel 5 or 10mg once-daily or ticagrelor 90mg twice-daily . Predeclared at randomization

*** VKA, target INR 2-3

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

Varnckx P et al, Lancet 2019

Major bleeding: on-treatment

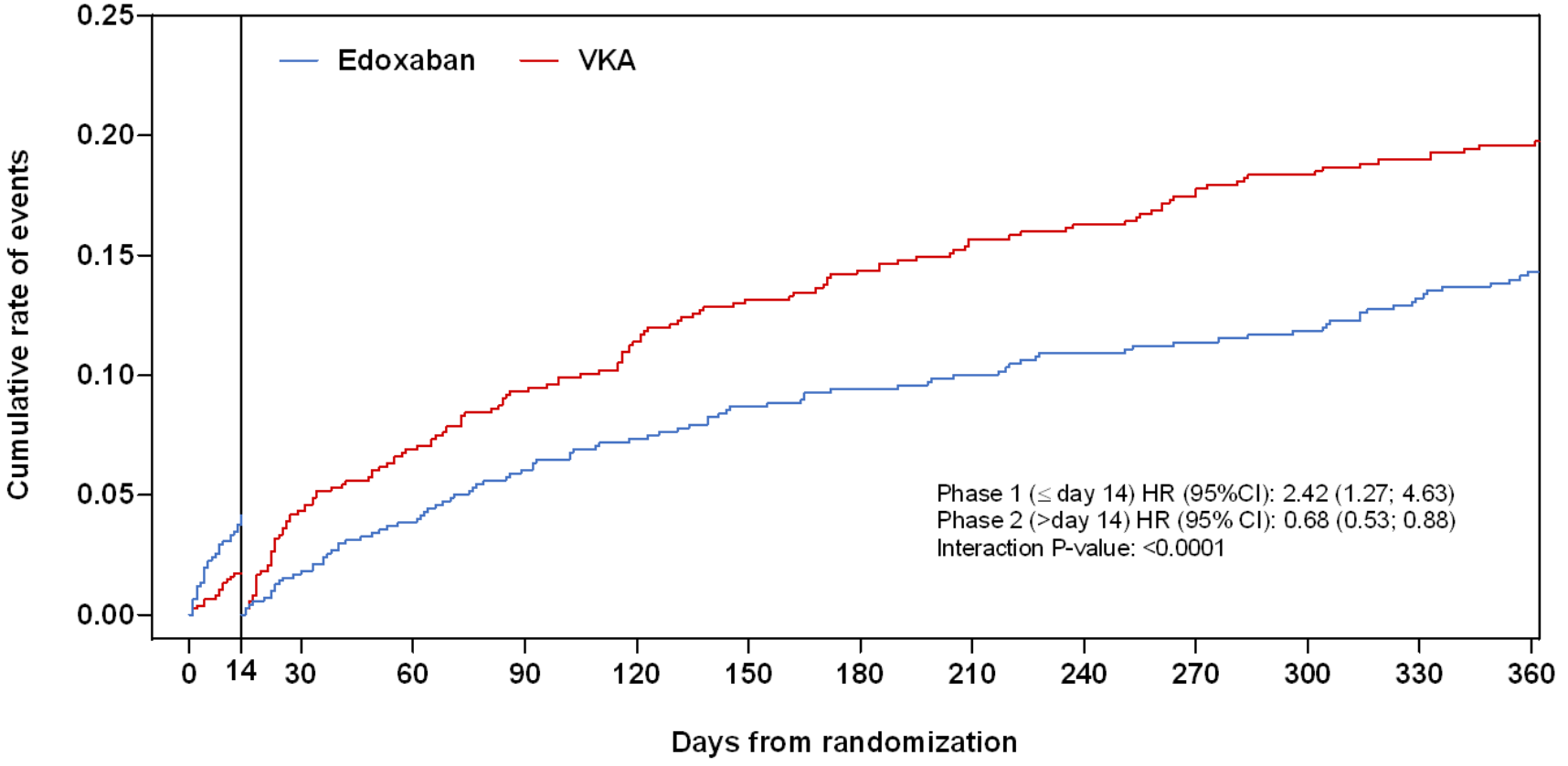


Number at risk:

EDOXABAN	746	674	651	632	614	600	590	583	573	567	554	543	471
VKA	740	653	621	594	573	554	543	529	520	510	501	492	428

Varnckx P et al, Lancet 2019

Major bleeding: post-hoc landmark KM



Number at risk:

EDOXABAN	751	707	688	665	646	629	618	609	600	590	584	575	565	506
VKA	755	721	678	648	625	603	588	578	568	561	552	543	538	485

Varnckx P et al, Lancet 2019

Why superiority was not met?

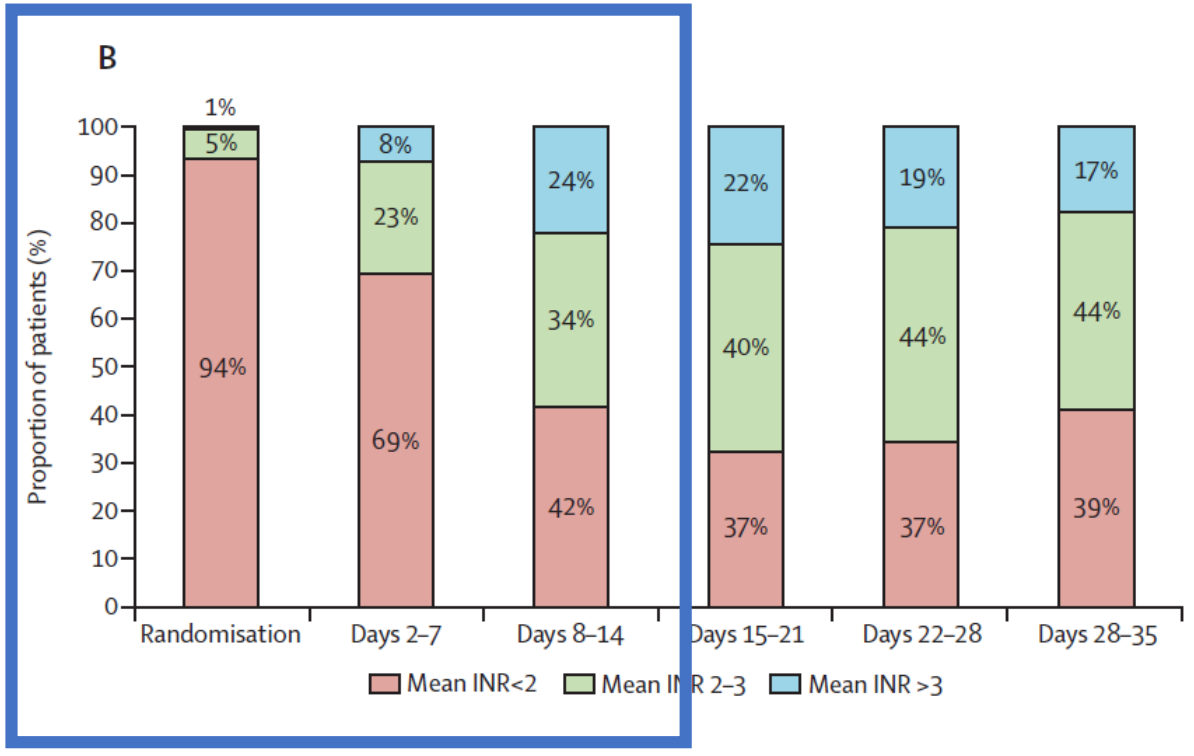
Sub-par performance of the investigational drug

- Lower safety in PCI
- High CHA2DS2-VASc (mean 4)
- Nearly 50% with ACS

Very good performance of the comparator

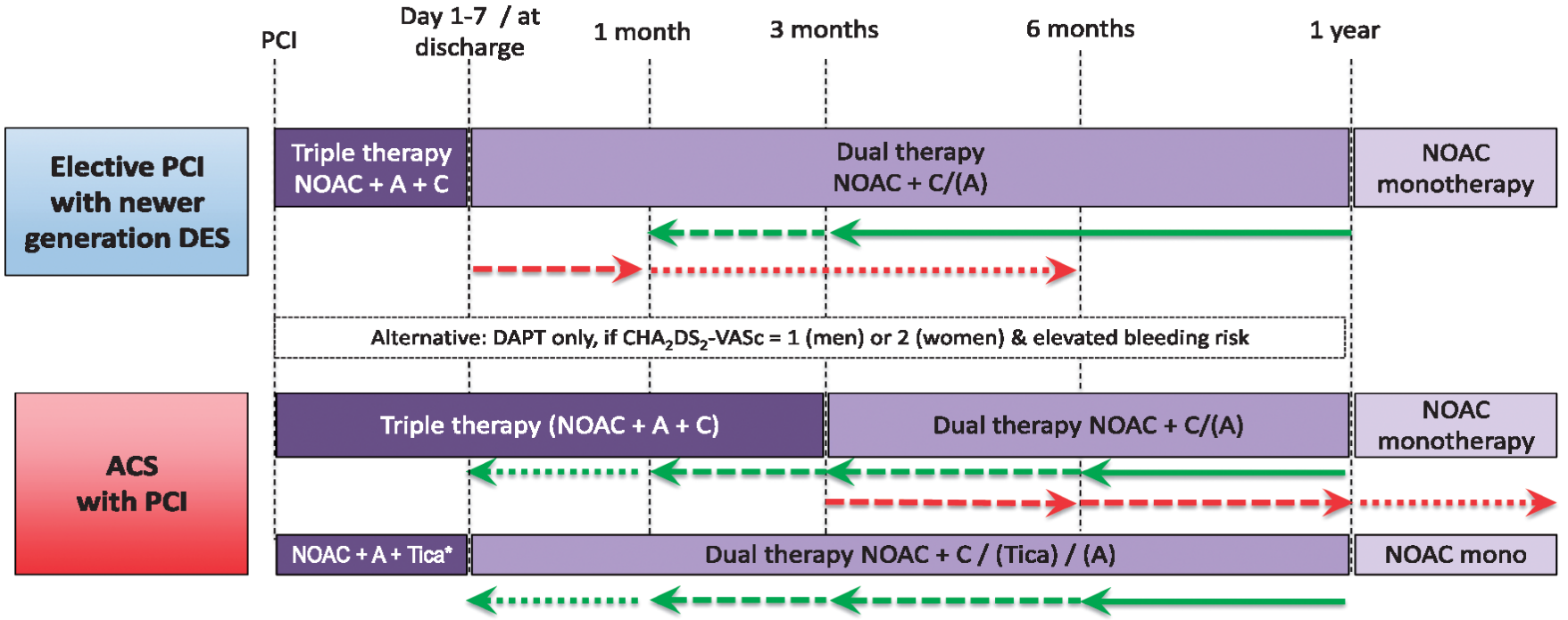
- Low TTR in the first 2 weeks
- Unexpectedly low bleeding rate with VKA, comparable to DAPT alone

	Edoxaban regimen (n=751)	VKA regimen (n=755)
Age, years	69 (63–77)	70 (64–77)
Recalculated CHA_2DS_2-VASc score	4·0 (3·0–5·0)	4·0 (3·0–5·0)
Recalculated HAS-BLED score	3·0 (2·0–3·0)	3·0 (2·0–3·0)
Clinical presentation (documented in IXRS)		
Acute coronary syndrome	388 (52%)	389 (52%)
Stable coronary artery disease	363 (48%)	366 (48%)
Type of therapy before index PCI		
VKA	232 (31%)	224 (30%)
NOAC	176 (23%)	189 (25%)
None	192 (26%)	221 (29%)
Data missing	151 (20%)	121 (16%)
Duration between end of PCI and randomisation, h	45·1 (22·3–75·6)	44·8 (22·1–76·5)



Varnckx P et al, Lancet 2019

NOAC and PCI (2018)



Factors to shorten combination therapy

- (Uncorrectable) high bleeding risk
- Low atherothrombotic risk (by REACH or SYNTAX score if elective; GRACE ≥140 if ACS)

Factors to lengthen combination therapy

- First-generation DES
- High atherothrombotic risk (scores as above ; stenting of the left main, proximal LAD, proximal bifurcation; recurrent MIs; stent thrombosis etc.) and low bleeding risk

Steffel et al., EHRA Practical Guide, European Heart Journal 2018

What DO we know

- NOAC better than VKA for AF treatment in patients with recent PCI
- Dual therapy better than triple therapy in low-risk patients, and can be started at discharge
- Length of DAPT does not depend on the type of stent but on the clinical presentation (elective PCI vs. ACS)
- Clopidogrel is the only P2Y12- inhibitor with robust evidence so far, so it should be preferred in a dual therapy strategy
- No need to extend antiplatelet therapy over 1-year after PCI

What DO we NOT know

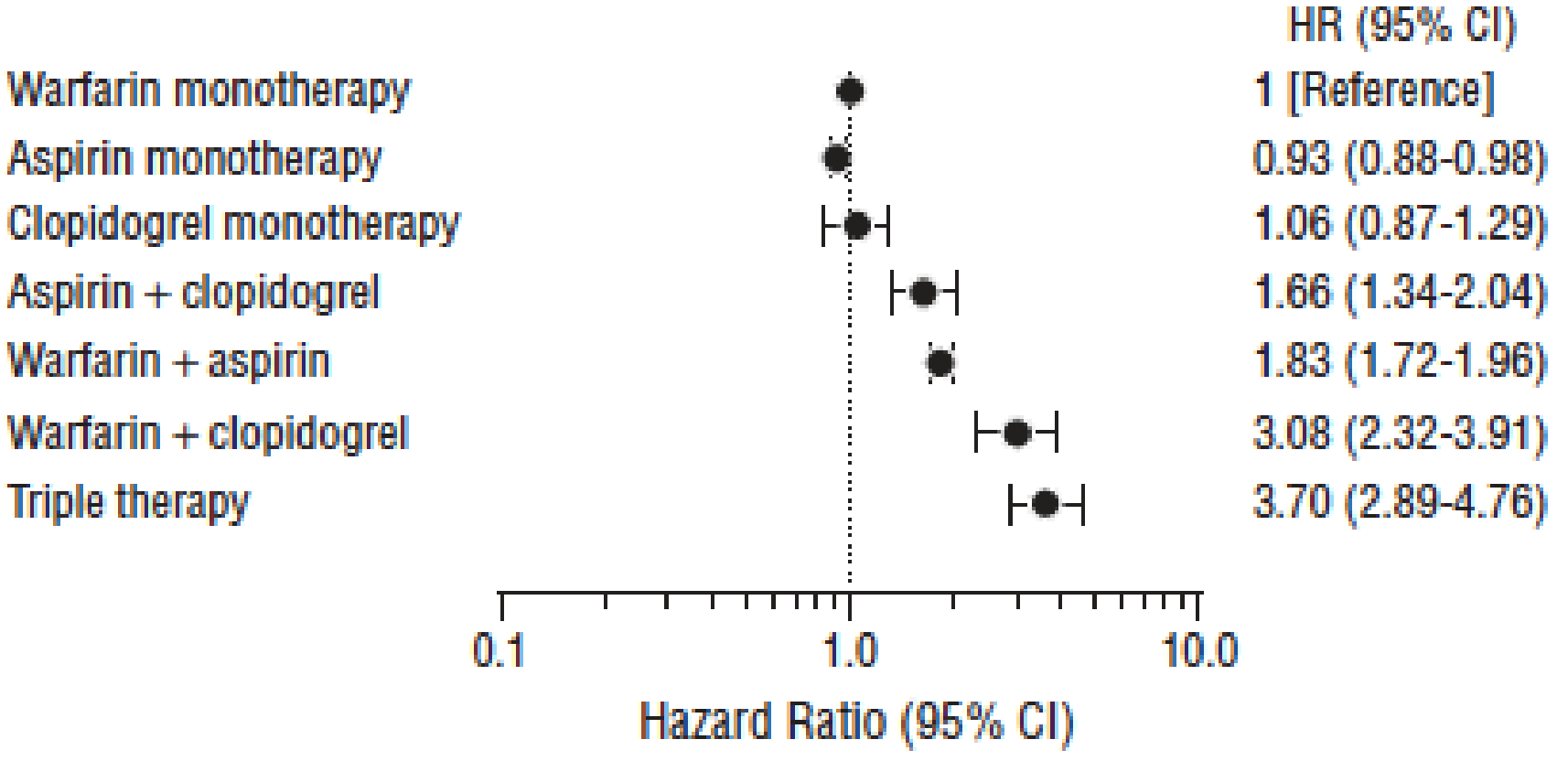
- Are PIONEER-AF PCI dosages (2.5 mg BID and 15 mg OD) effective in stroke prevention in AF patients?
- Is withdrawing aspirin safe in terms of ACS recurrence and stent thrombosis? And, if yes, when is the best time?
- What is the best P2Y12 to use in dual therapy?
- Is the lack of a superior safety in ENTRUST-AF PCI due to an intrinsic difference in edoxaban when compared to other NOACs?

UNIVERSITÀ
POLITECNICA
DELLE MARCHE

Thank you for your attention

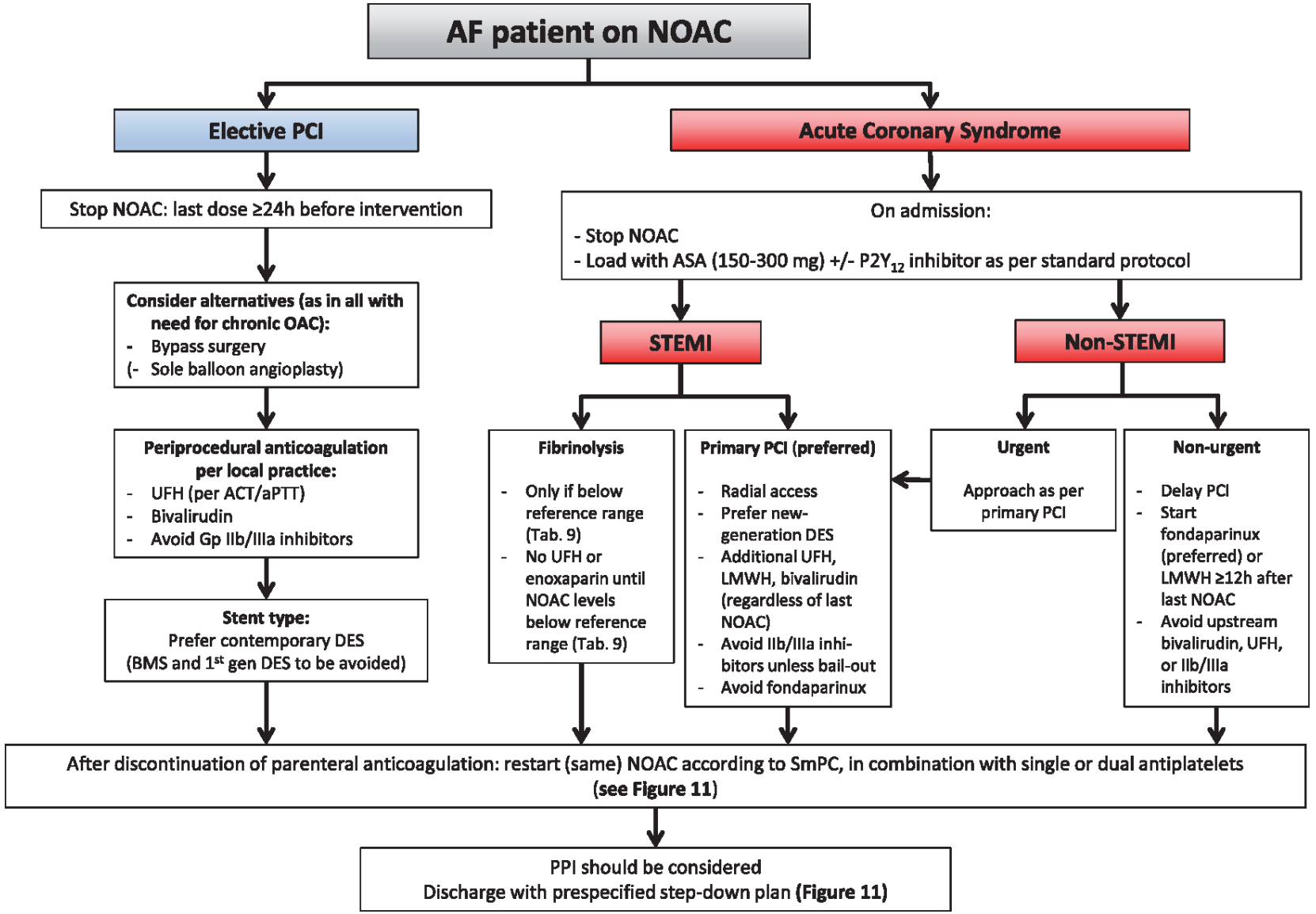
Risk of Bleeding With Single, Dual, or Triple Therapy With Warfarin, Aspirin, and Clopidogrel in Patients With Atrial Fibrillation

Nationwide registries to identify all Danish patients surviving first-time hospitalization for AF between January 1, 1997, and December 31, 2006



Hansen et al. Arch Intern Med 2010

NOAC and ACS



Steffel et al., EHRA Practical Guide, European Heart Journal 2018