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Atrial Fibrillation and ischemic heart disease

- Interaction between atrial fibrillation and myocardial ischemia. Double trouble!
- Translating trials to clinical practice: *is dual therapy the new standard of care for AF patients and ACS/PCI?*



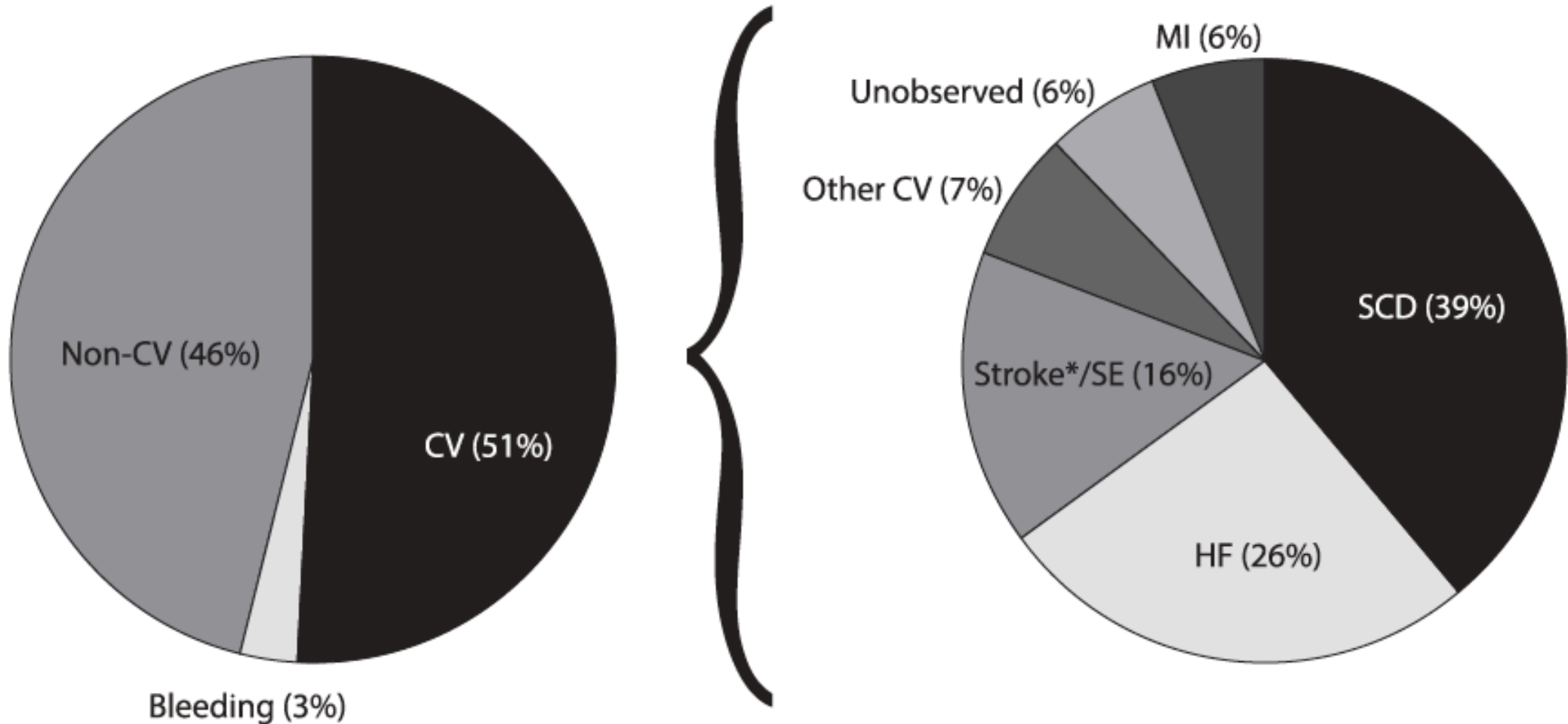
Atrial fibrillation and ischemic heart disease

A Fatal Attraction

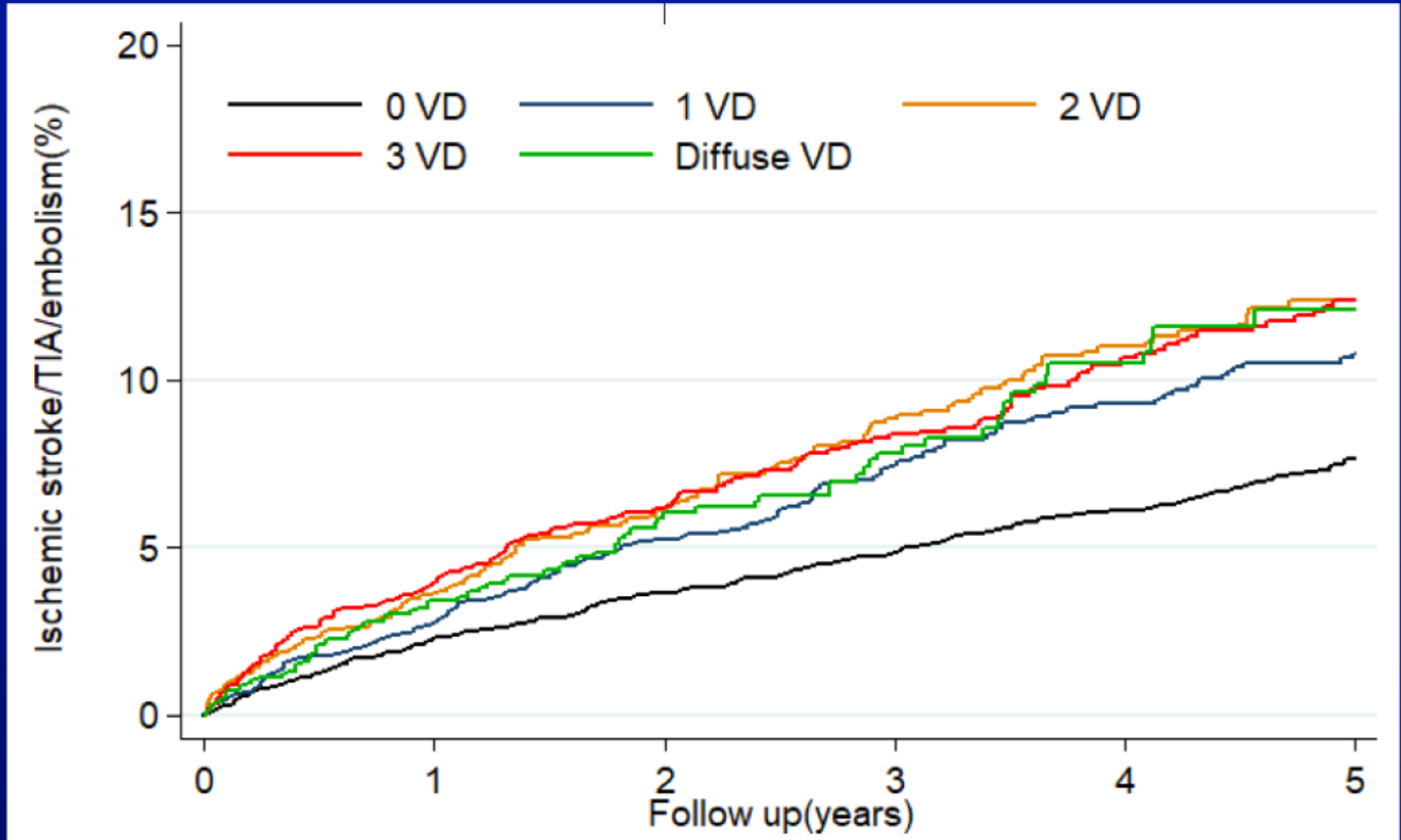
- **AF and CAD share the same risk factors**
- **Given their high prevalence and similar risk factor profile, AF and CAD often coincide in an individual patient**
- **Myocardial ischemia may induce atrial fibrillation**
- **Atrial fibrillation may induce myocardial ischemia**



Among anticoagulated patients with AF and CV risk factors, stroke or systemic embolism is not the most common cause of death!



CAD is an independent risk factor for stroke



Steensig K et al. *J Am Coll Cardiol* 26 August 2018



The modified CHA₂DS₂-VASc score

CHA ₂ DS ₂ -VASc risk factor	Points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left ventricular ejection fraction	+1
Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	+1
Age 75 years or older	+2
Diabetes mellitus Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin	+1
Previous stroke, transient ischaemic attack, or thromboembolism	+2
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque <u>and coronary artery disease</u>	+1
Age 65–74 years	+1
Sex category (female)	+1

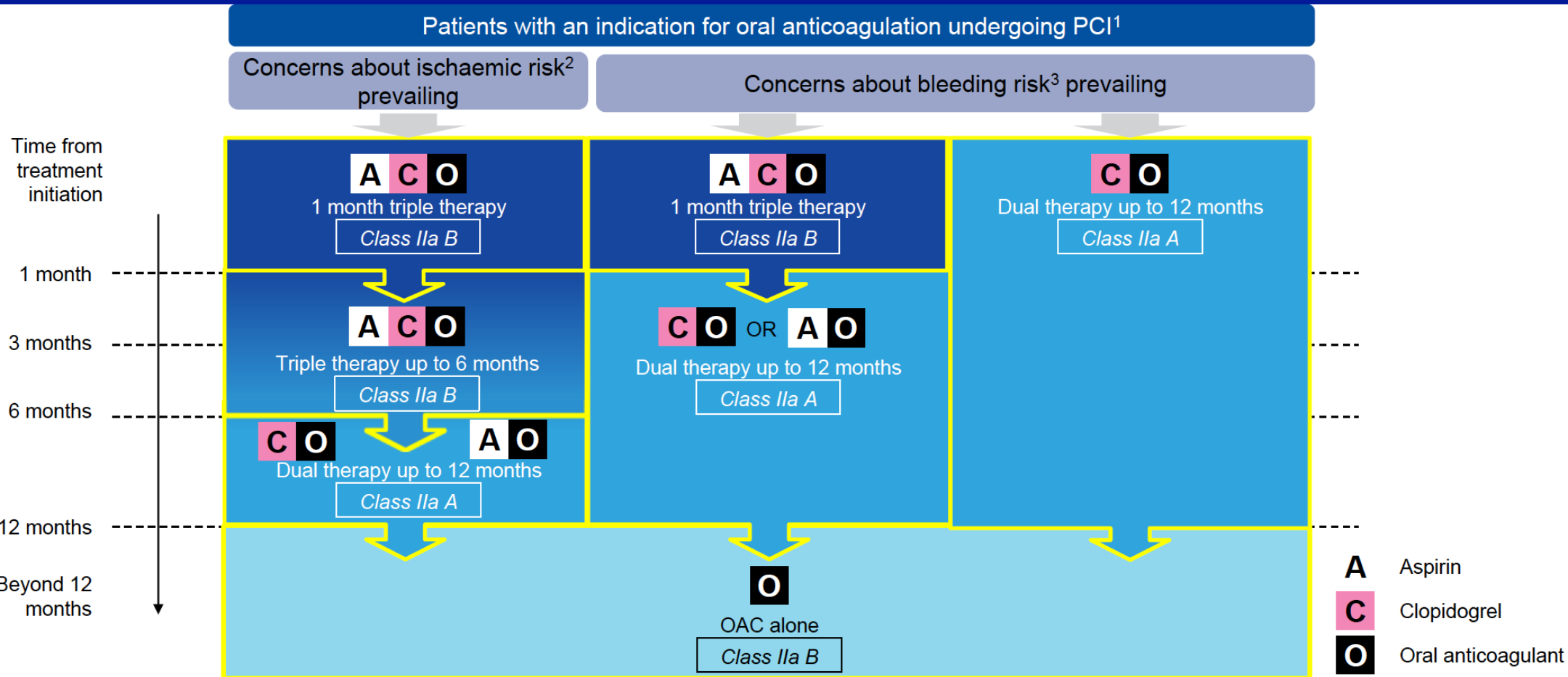


Atrial Fibrillation and ischemic heart disease

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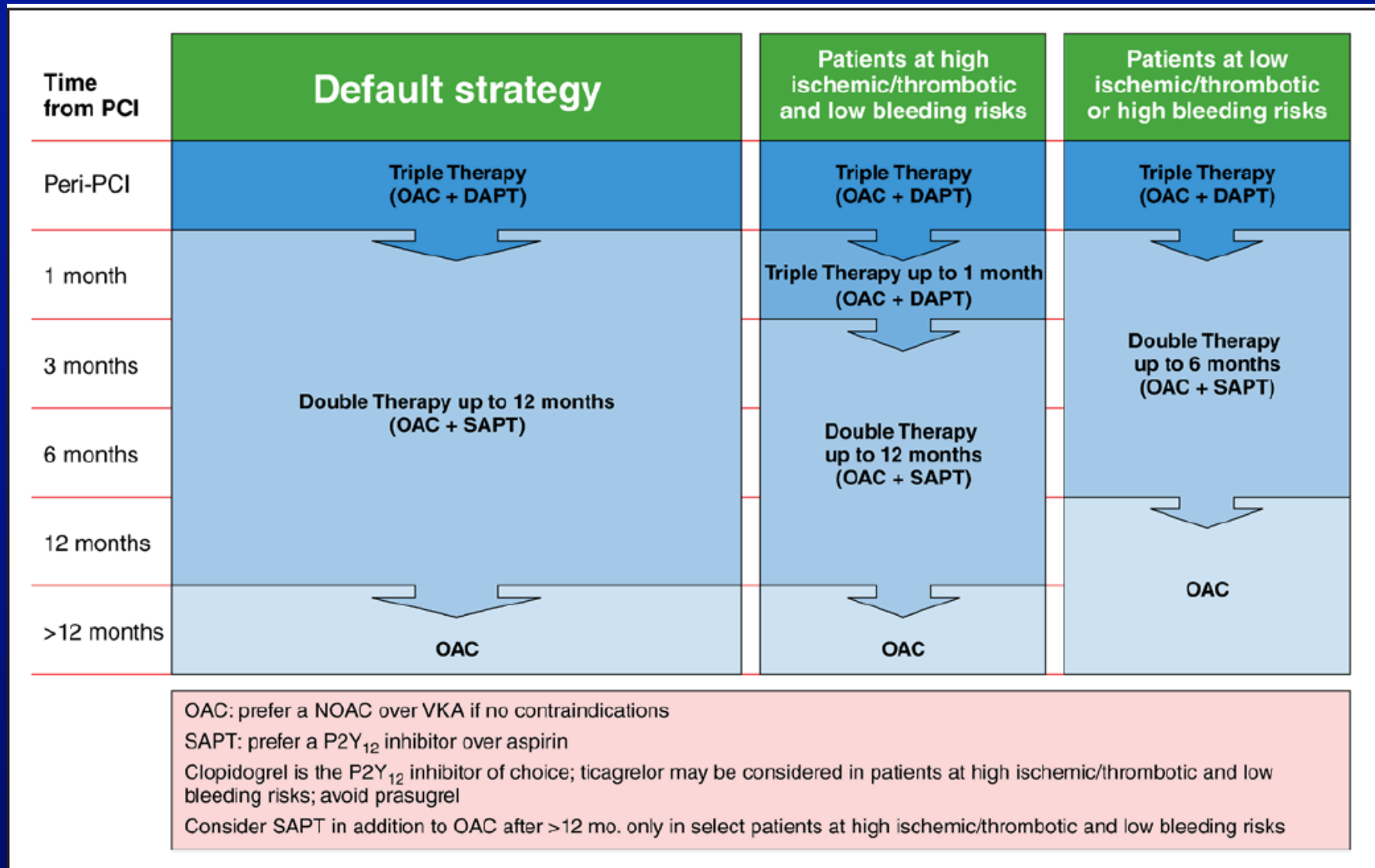


New ESC focused update on dual antiplatelet therapy in coronary artery disease

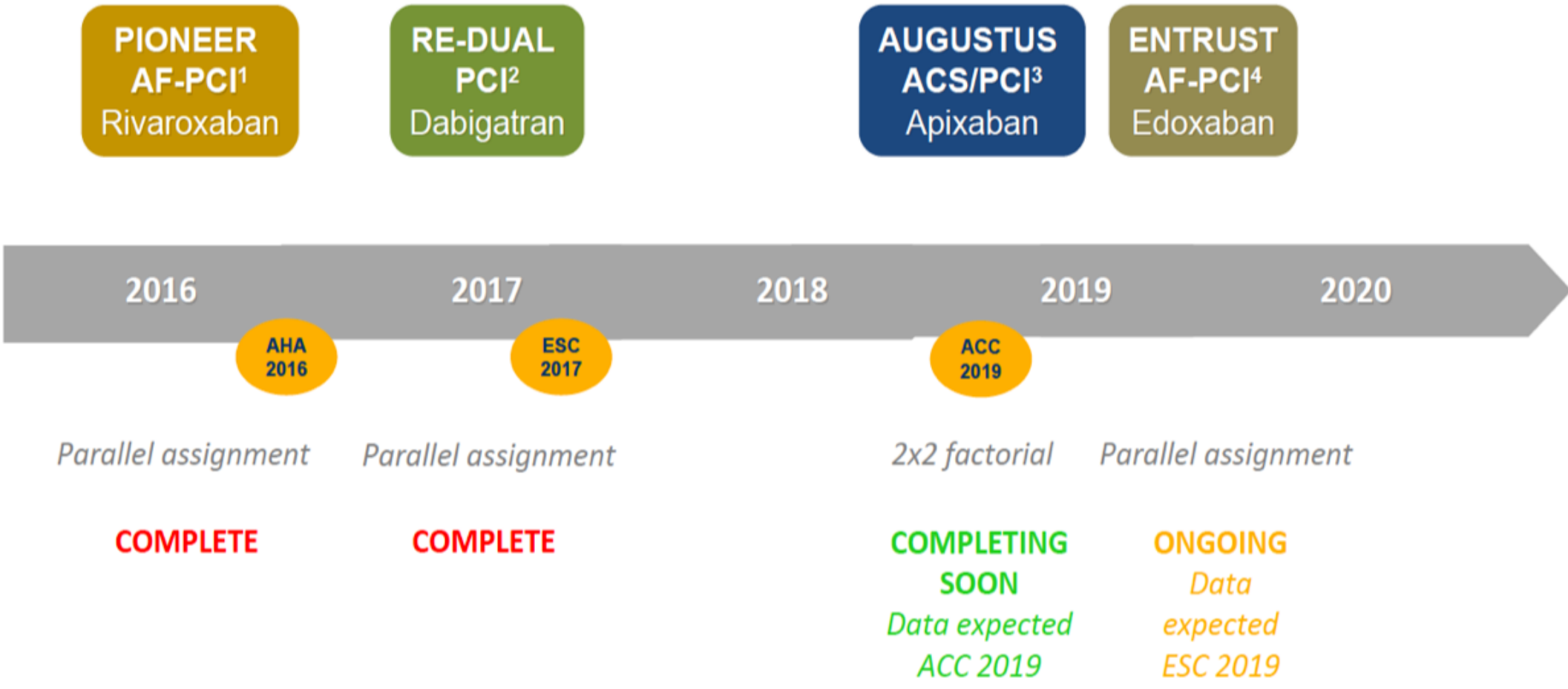


Valgimigli et al. Eur Heart J 2018

A North American Perspective–2018 Update



What evidence is there for NOACs in AF + ACS/PCI?



1. Gibson CM, et al. N Engl J Med 2016;375:2423–34.; 2. Cannon CP, et al. N Engl J Med 2017;377:1513–24;
 3. Lopes RD, et al. Am Heart J 2018;200:17–23; 4. Vranckx P, et al. Am Heart J 2018;196:105–12.

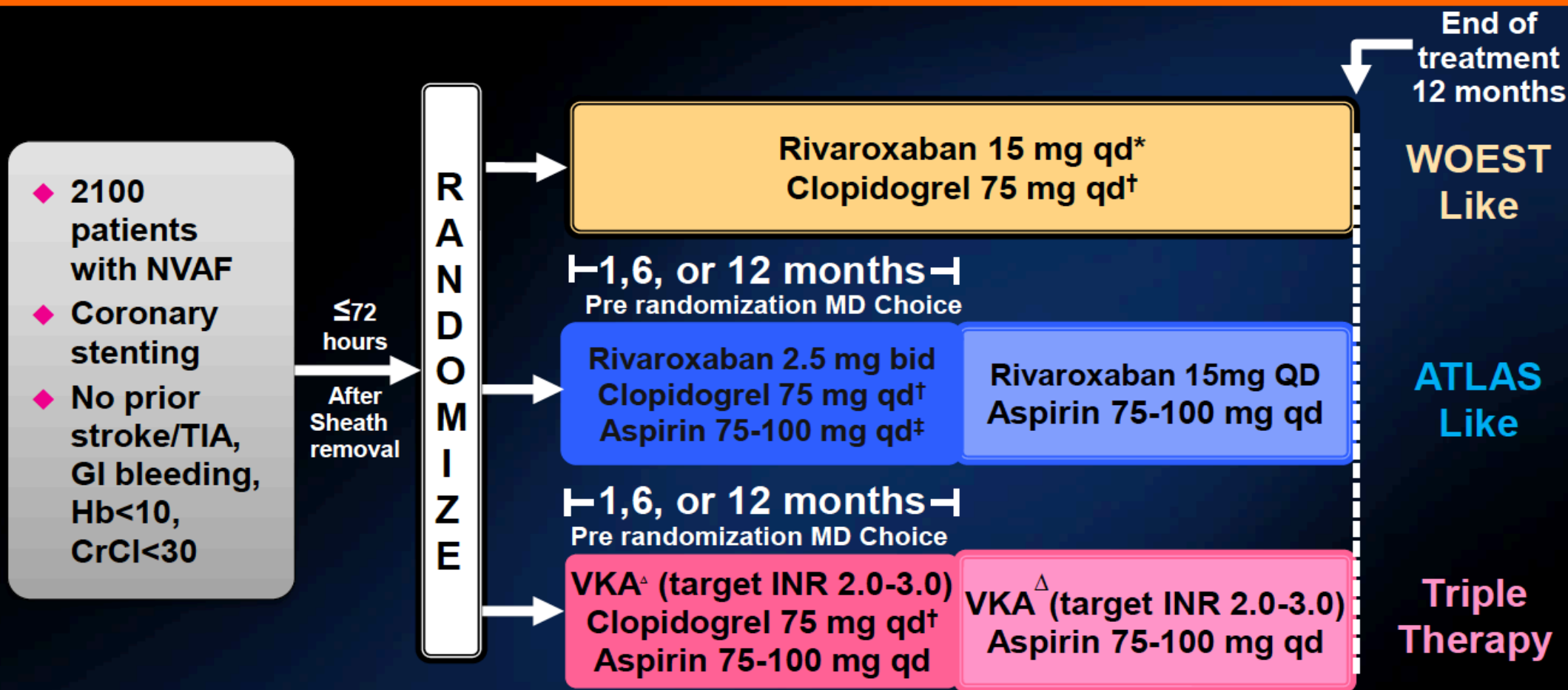


Afib PCI trials

Trial	Primary endpoint	Randomization	Expected event rate	Sample size
PIONEER	TIMI major or minor bleeding	Rivaroxaban 15 mg od+P2Y ₁₂ inhibitor Rivaroxaban 2.5 bid mg+DAPT VKA+ASA+Clop	16%	2,100
REDUAL PCI	Major or clinically relevant bleeding	VKA+ASA+Clop Dabigatran 150 mg bid+P2Y ₁₂ inhibitor Dabigatran 110 mg bid+P2Y ₁₂ inhibitor	14%	2,725

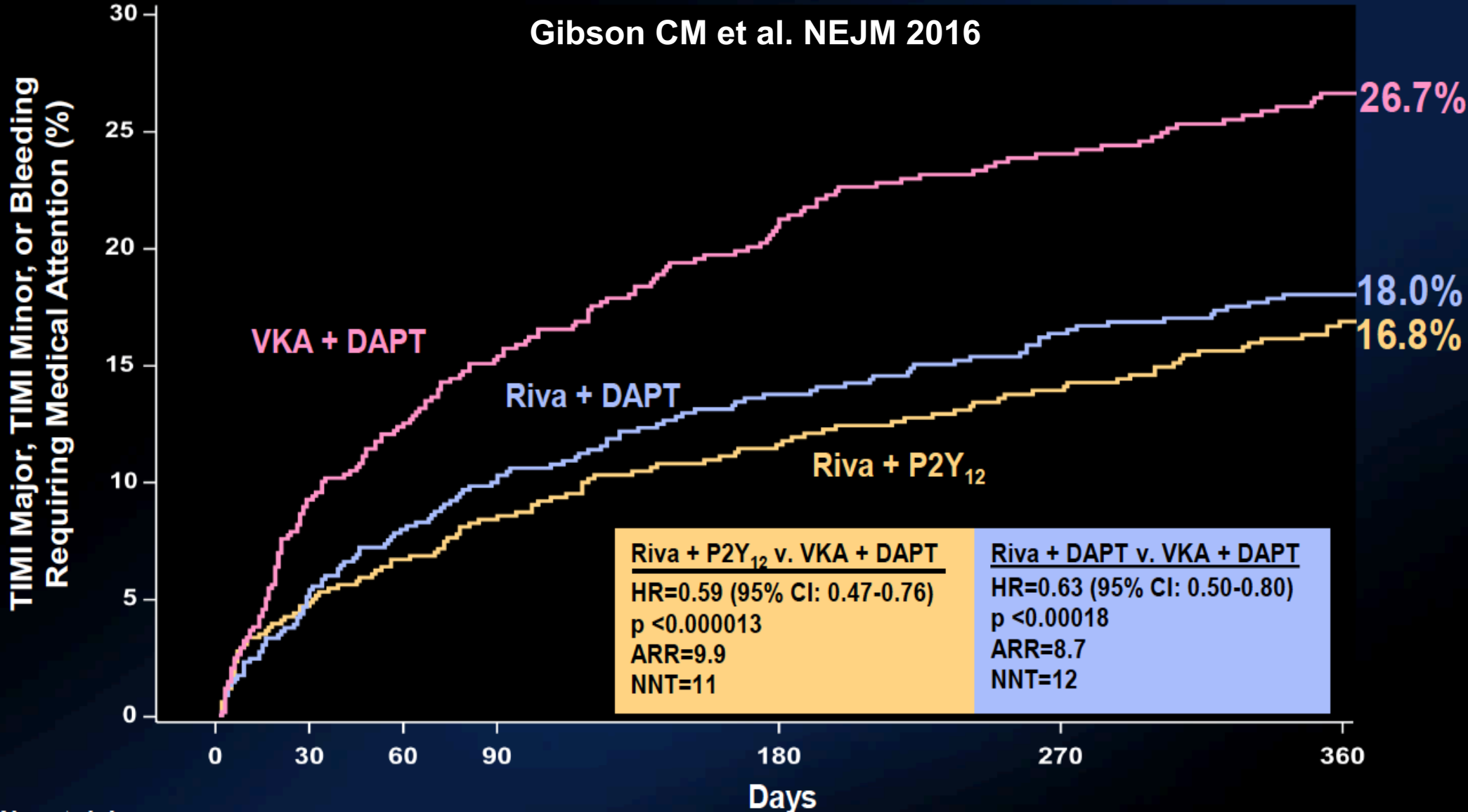


Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI



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

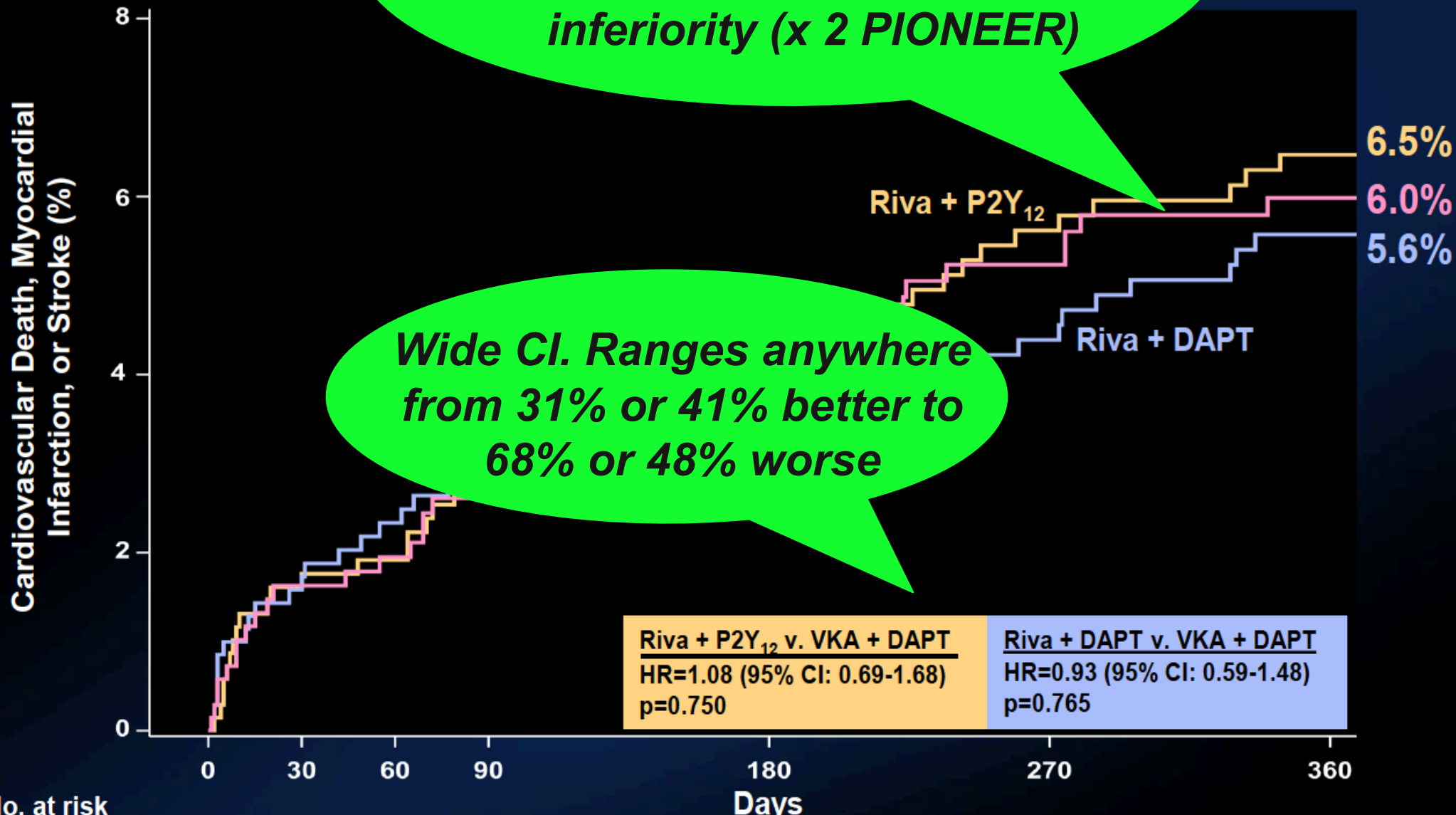
Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events



Optimal Management of First Stroke

With a 6% control event rate, NIM=2%, $\beta=90\%$; $\alpha=0.05$, 4,824 pts would be needed to show non-inferiority (x 2 PIONEER)

Wide CI. Ranges anywhere from 31% or 41% better to 68% or 48% worse



No. at risk

PIONEER AF PCI: an important trial but should we change practice?

1. the primary endpoint was mainly driven by bleedings requiring medical attention, whereas the rate of TIMI major or minor bleedings was not significantly different between the groups

Cohort and End Point	Group 1	Group 2	Groups 1 and 2		Group 3	Group 1 vs. Group 3		Group 2 vs. Group 3		Groups 1 and 2 vs. Group 3	
			No. of Participants with Events (Kaplan–Meier Event Rate)			Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
All participants — no.	696	706	1402		697						
Clinically significant bleeding	109 (16.8)	117 (18.0)	226 (17.4)		167 (26.7)	0.59 (0.47–0.76)	<0.001	0.63 (0.50–0.80)	<0.001	0.61 (0.50–0.75)	<0.001
Major bleeding	14 (2.1)	12 (1.9)	26 (2.0)		20 (3.3)	0.66 (0.33–1.31)	0.23	0.57 (0.28–1.16)	0.11	0.61 (0.34–1.09)	0.09
Minor bleeding	7 (1.1)	7 (1.1)	14 (1.1)		13 (2.2)	0.51 (0.20–1.28)	0.14	0.50 (0.20–1.26)	0.13	0.51 (0.24–1.08)	0.07
Bleeding requiring medical attention	93 (14.6)	102 (15.8)	195 (15.2)		139 (22.6)	0.61 (0.47–0.80)	<0.001	0.67 (0.52–0.86)	0.002	0.64 (0.51–0.80)	<0.001

PIONEER AF PCI: an important trial but should we change practice?

2. The RVRX regimens used reduced doses

- The RVRX dose was reduced to either 15 mg daily with P₂Y₁₂ or to 2.5 mg bid with DAPT
- These doses were neither tested nor approved in the SPAF indication
- Thus, reduced bleeding when compared to full dose VKA is not surprising
- The real question is: does this preserve the efficacy of anticoagulation to prevent stroke?



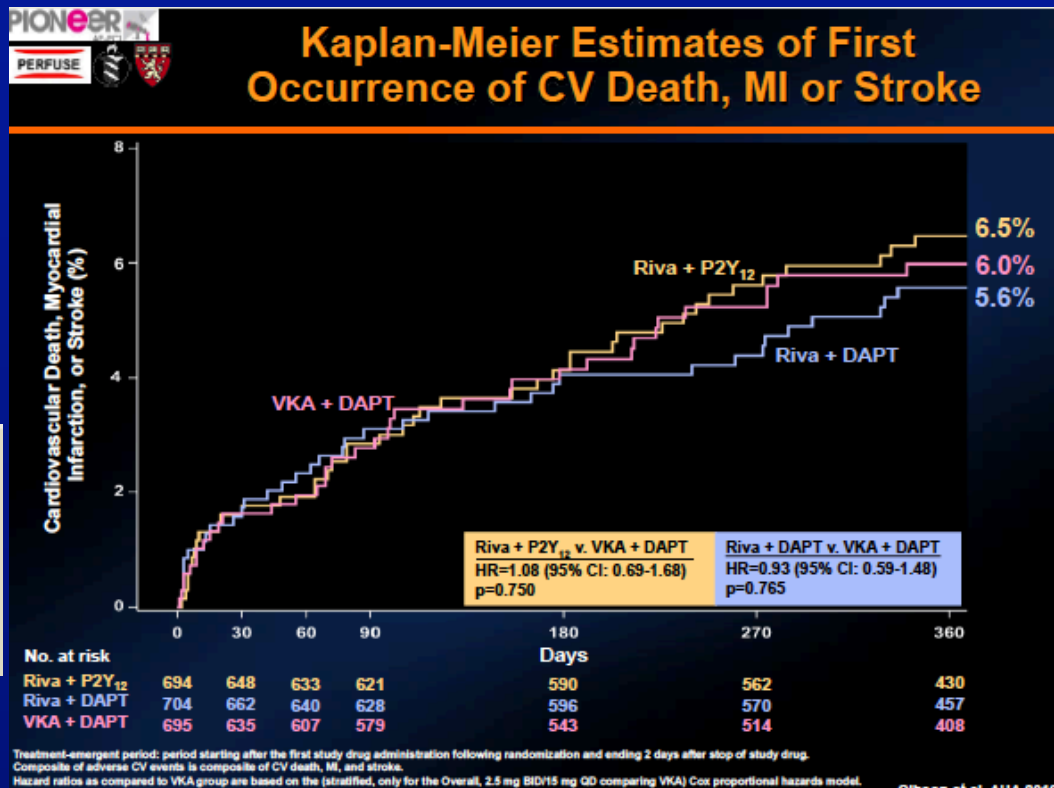
PIONEER AF PCI: an important trial but should we change practice?

3. This trial did not established (or even test) noninferiority of RVRX-based strategies vs VKA+DAPT for stroke prevention

HR (95% CI) for stroke

Riva + P2Y₁₂ vs. VKA + DAPT : 1.07 (0.39-2.96) p=0.891

Riva + DAPT vs. VKA + DAPT : 1.36 (0.52-3.58) p=0.530

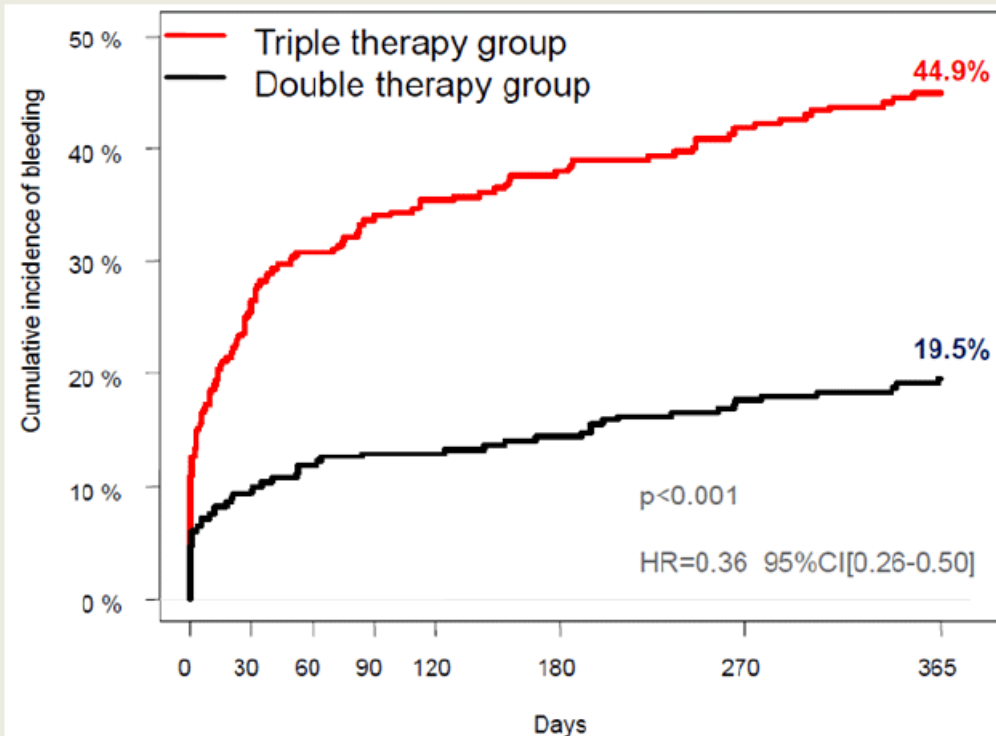


Participants assigned to DAPT for 6 mo — no.	248	243		
Major adverse cardiovascular event	16 (7.0)	9 (4.3)	1.72 (0.76–3.88)	0.19
Death from cardiovascular causes	6 (2.8)	4 (1.9)	1.45 (0.41–5.12)	0.57
Myocardial infarction	7 (3.0)	6 (2.9)	1.13 (0.38–3.37)	0.82
Stroke	6 (2.7)	0		0.02
Stent thrombosis	4 (1.7)	1 (0.4)	3.91 (0.44–35.02)	0.19

PIONEER AF PCI: an important trial but should we change practice?

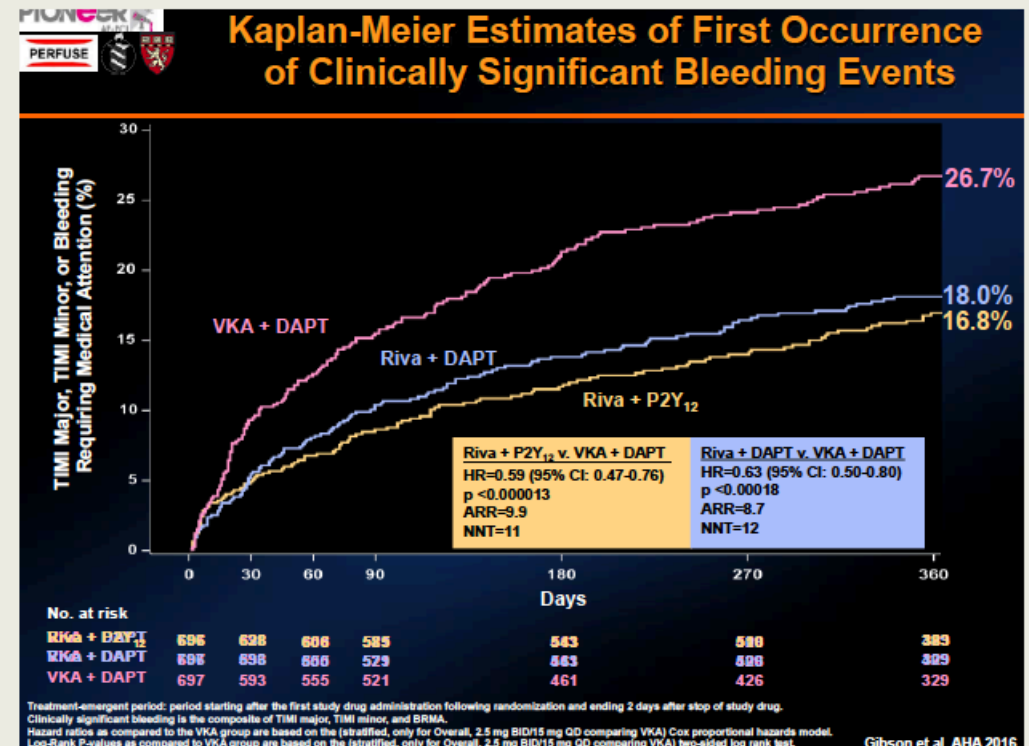
4. The RVRX strategies were not compared to the WOEST” strategy of VKA+clopidogrel alone

WOEST
VKa + clopidogrel



Dewilde W et al. *Lancet* 2013

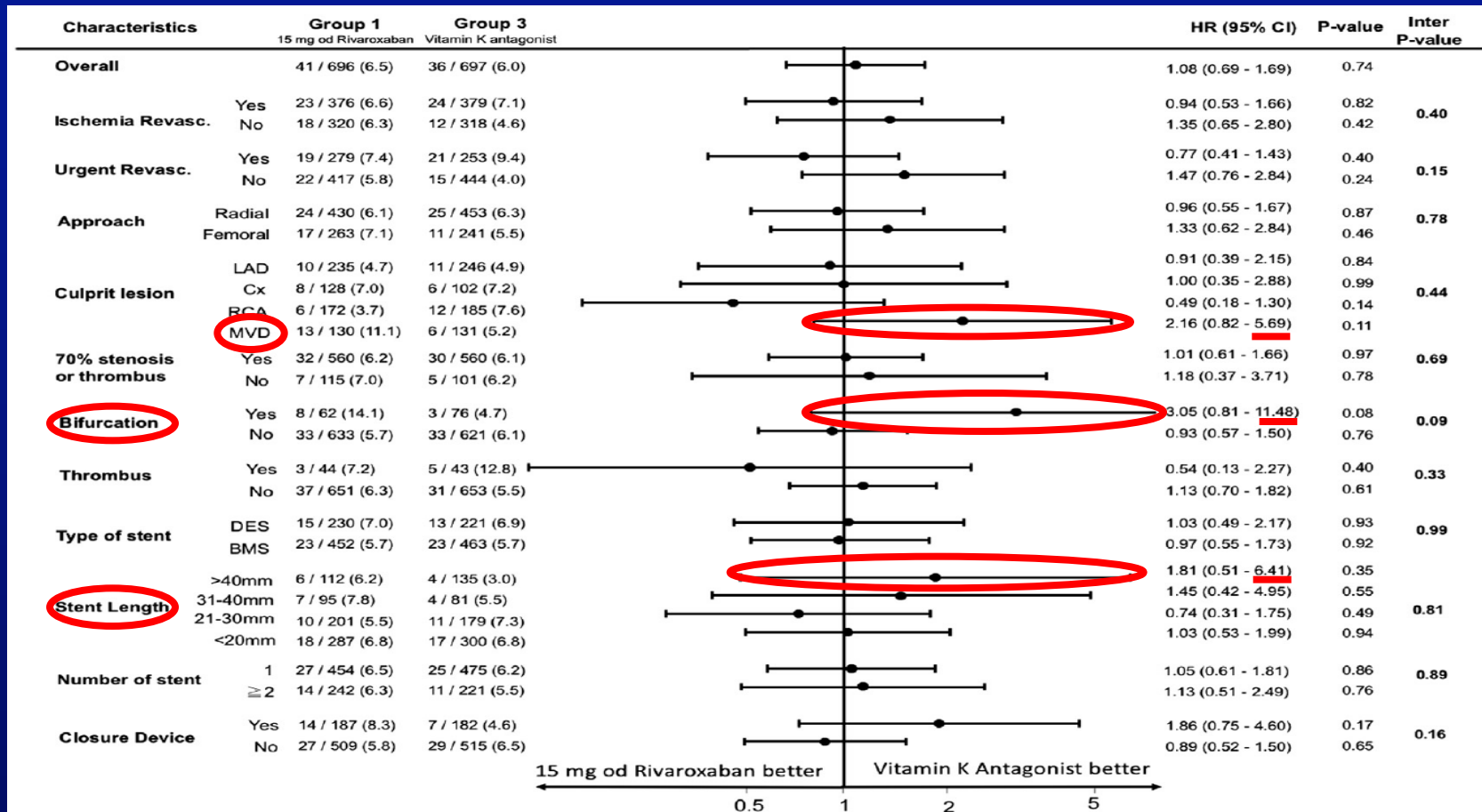
PIONEER AF-PCI
RVRX reduced dose + APT



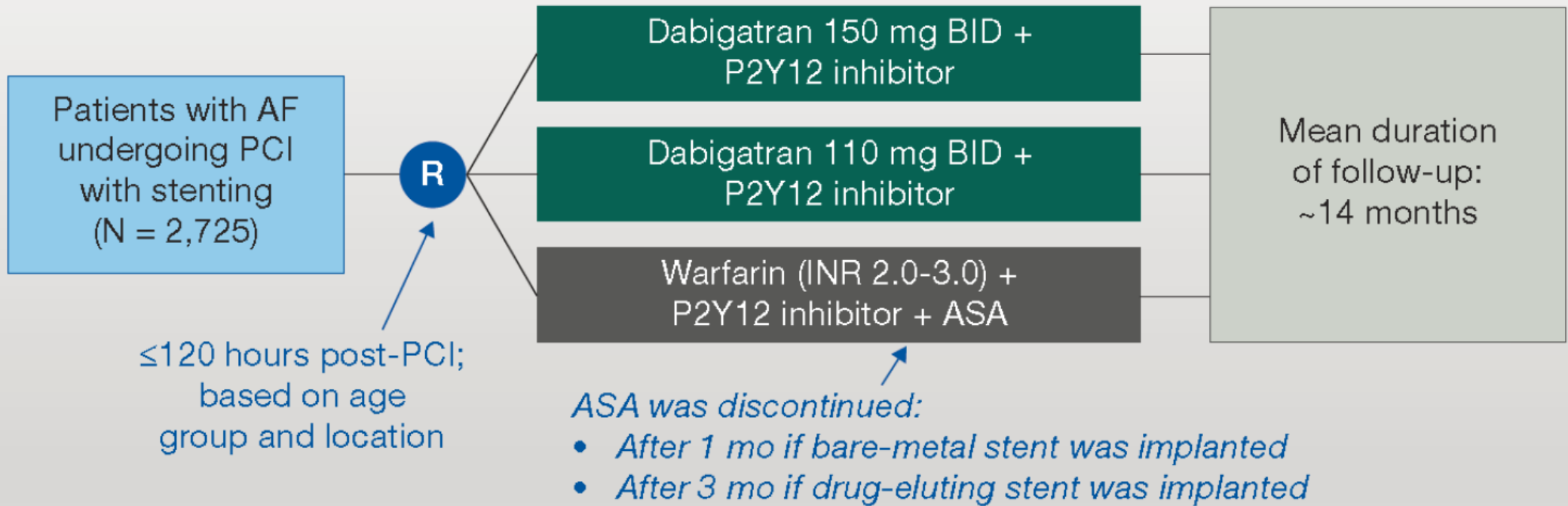
Gibson CM et al. *NEJM* 2016

PIONEER AF PCI: an important trial but should we change practice?

5. The point estimates for some procedural characteristics known to be associated with a higher risk of ST suggest the possibility of increased risk ischemic events



RE-DUAL PCI: Dabigatran-Based Dual Therapy vs Standard Triple Therapy



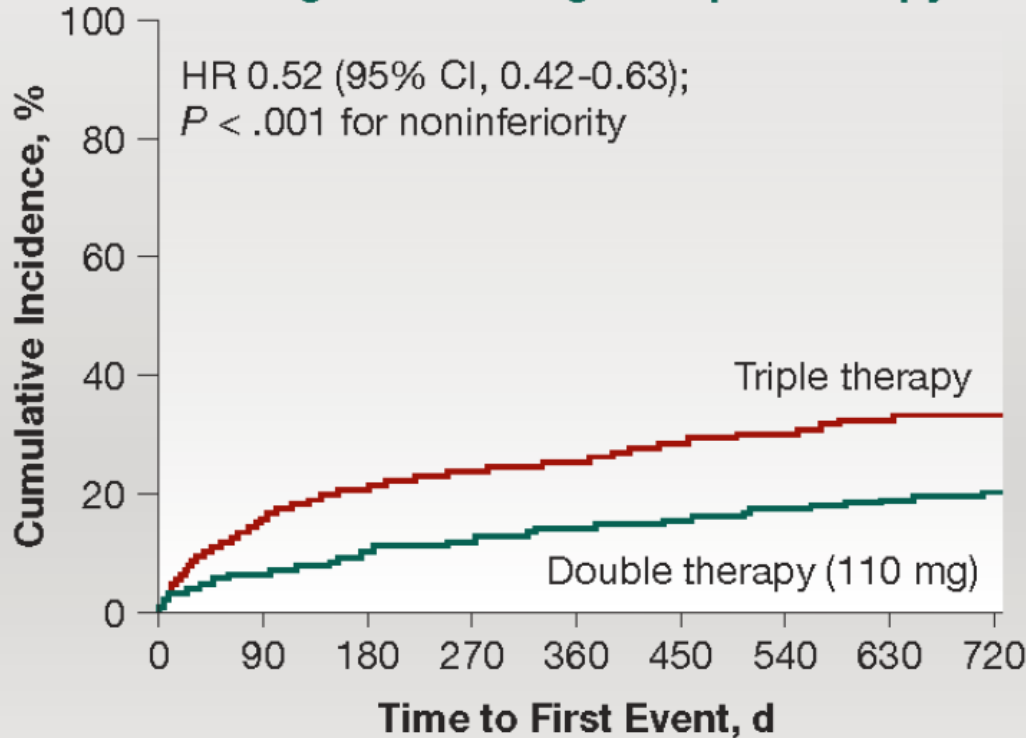
- **Primary outcome measures:** Time to first ISTH major or CRNM bleeding
- **Secondary outcome measures:** Composite of all-cause death or thrombotic event (MI or stroke/SE) and unplanned revascularisation (PCI/CABG); death or thrombotic event; individual outcome events; composite endpoint of death, MI, or stroke; and unplanned revascularisation by PCI/CABG



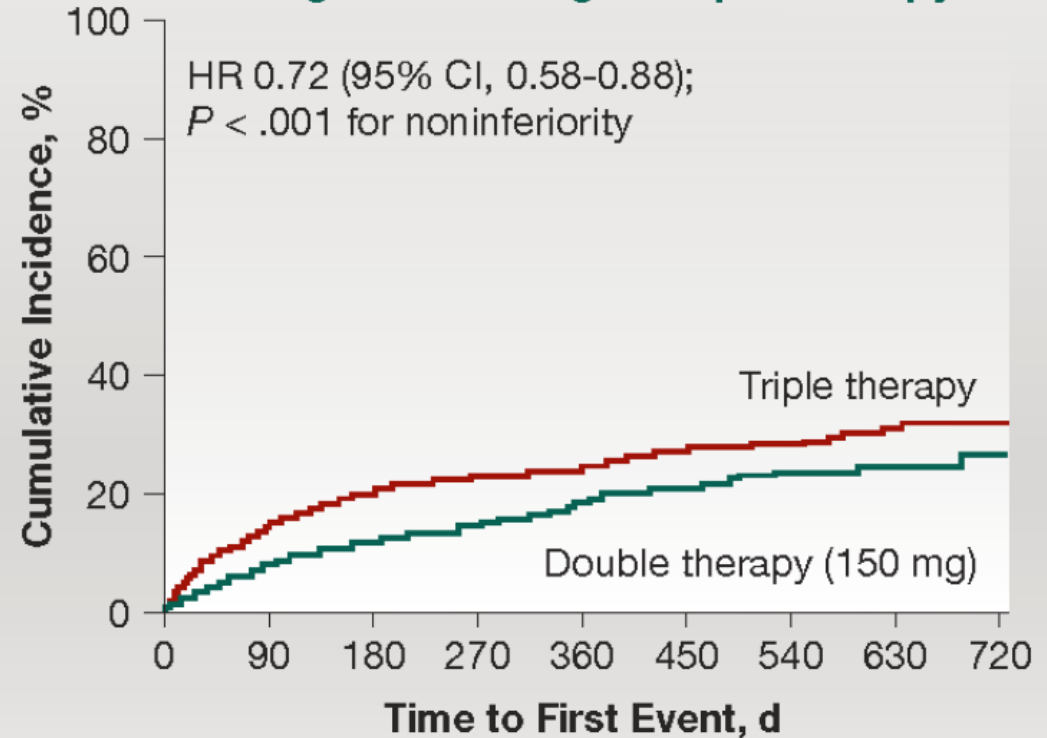
Cannon CP et al. N Engl J Med 2017; 377: 1513-24

RE-DUAL PCI: Time to First ISTH Major or Clinically Relevant Nonmajor Bleeding in Patients Receiving Dual Therapy vs Triple Therapy

**Primary Endpoint:
Dabigatran 110 mg vs Triple Therapy**



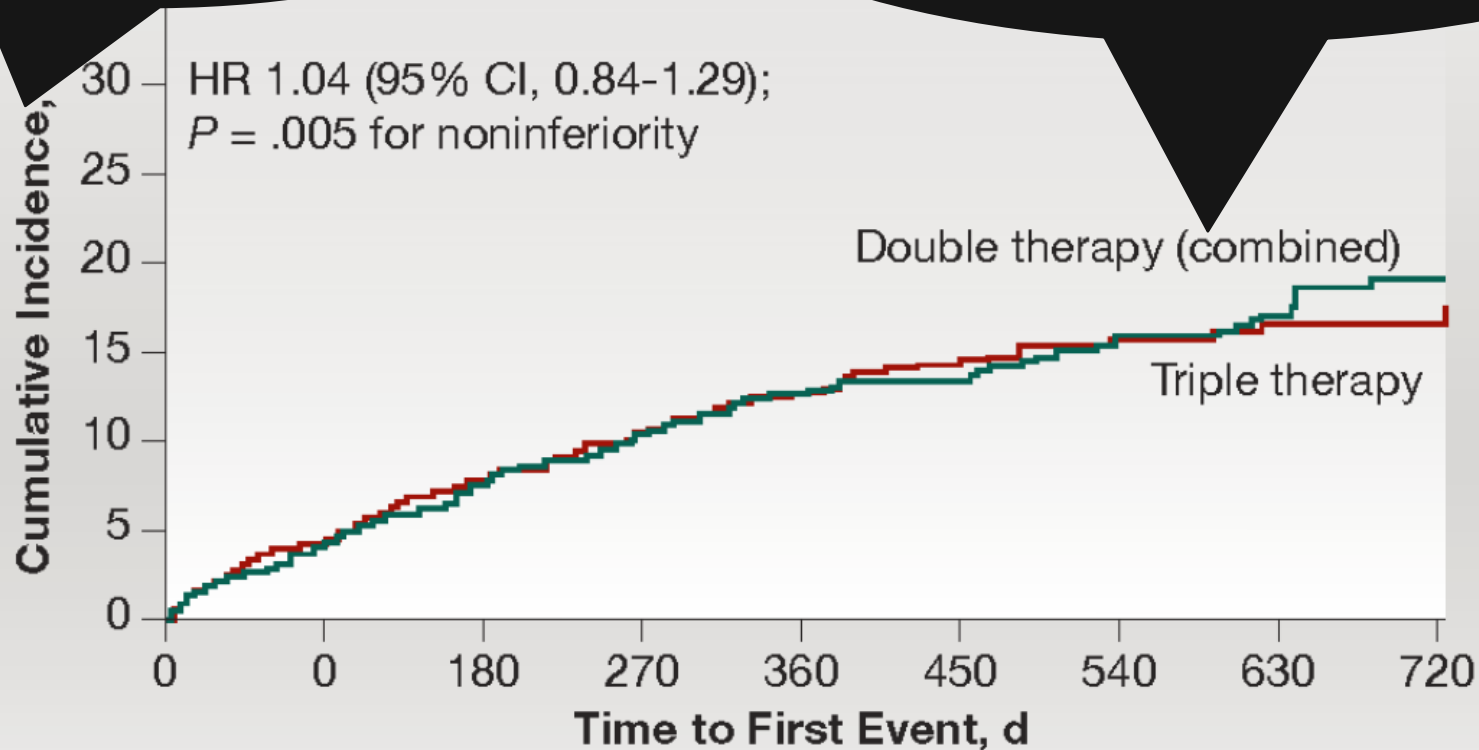
**Primary Endpoint:
Dabigatran 150 mg vs Triple Therapy**



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

Included TVR which may be unrelated with the anti-thrombotic regimen

With a 8.5% control event rate, NIM=2%, $\beta=90\%$; $\alpha=0.05$, 6,698 pts would be needed to show non-inferiority (x2 REDUAL)



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

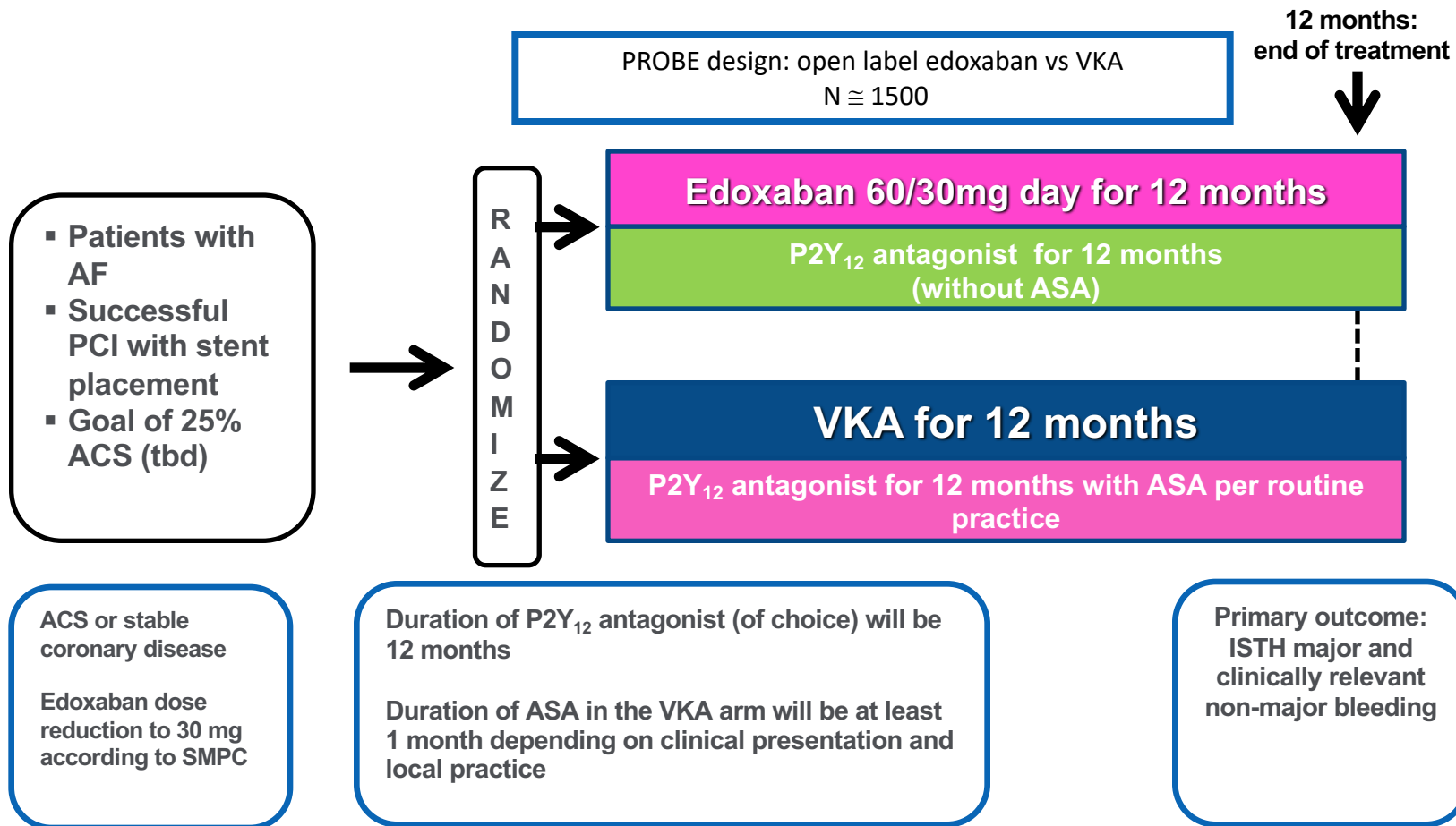
Additional individual thromboembolic endpoints

	Dabigatran 110 mg dual therapy (n=981)		D110 DT vs warfarin TT		Dabigatran 150 mg dual therapy (n=763)		D150 DT vs warfarin TT	
	n (%)	Warfarin triple therapy (n=981) n (%)	HR (95% CI)	P value	n (%)	Warfarin triple therapy (n=764) n (%)	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

ENTRUST-AF PCI Diagram



Apixaban vs 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 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



Atrial Fibrillation and ischemic heart disease

- Any type of AF can increase the risk of future ischemic events
- Consider further risk stratification for identifying atherothrombotic risk
- The optimal antithrombotic strategy for AF PCI/ACS pts undergoing PCI remain a clinical challenge
- NOACs based strategies are superior with respect to safety when compared to VKA strategies
- PIONEER AF-PCI and REDUAL PCI were underpowered to examine the impact on ischemic events
- Triple therapy with VKA may be still needed in some pts (high ischemic risk; complex PCI, poor LV function)

