Challenges in NVAF Patient with Undergoing PCI

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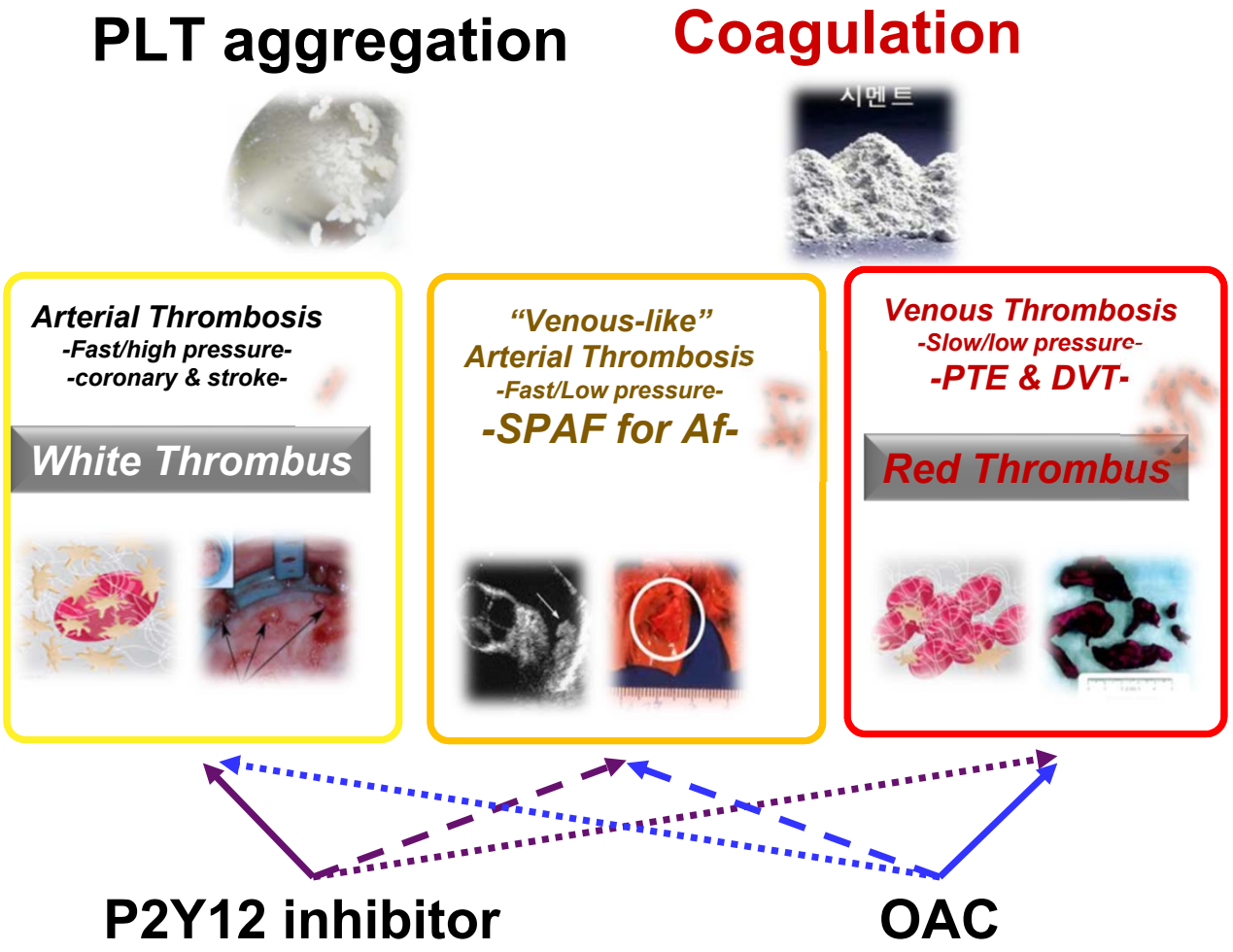
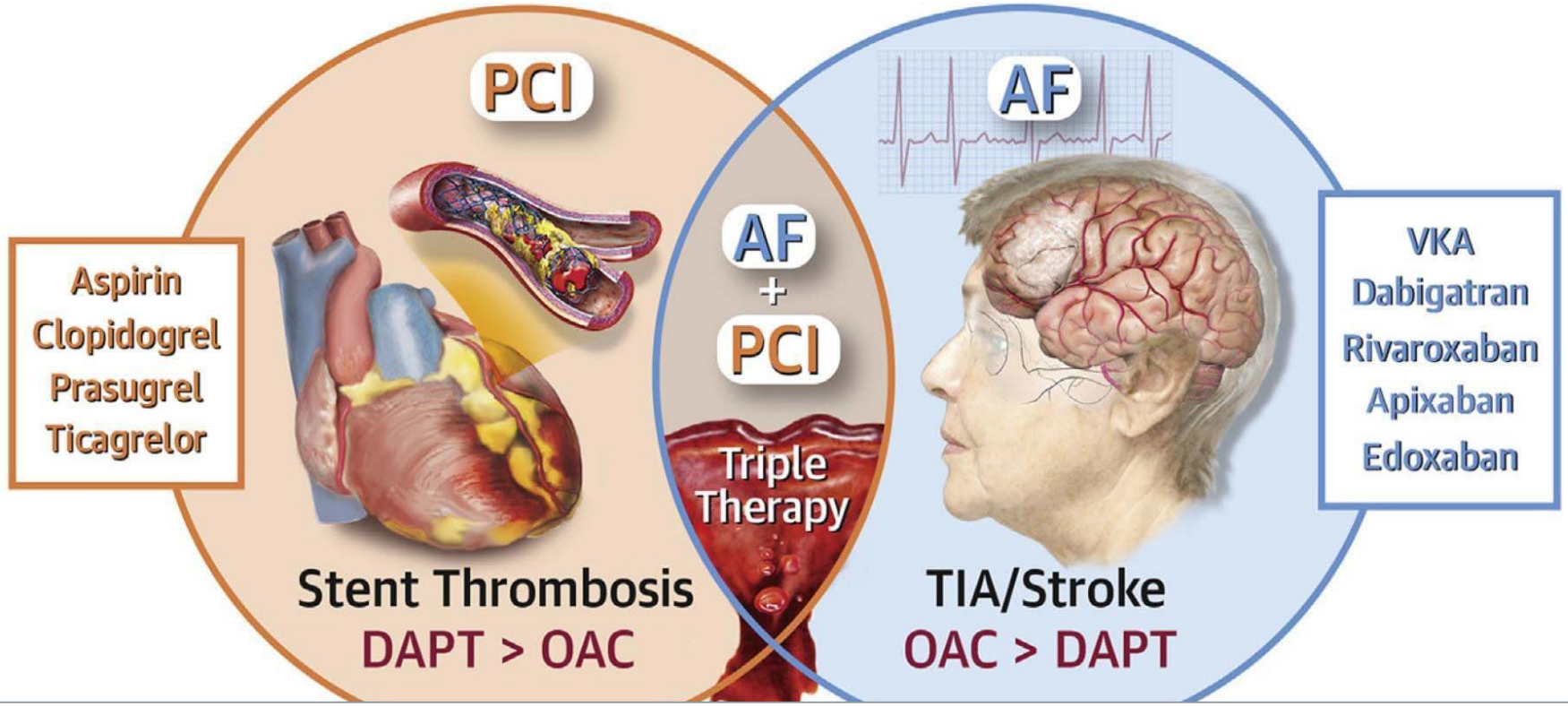
Blood Clot: Complicated – Platelet + Coagulation



Clinical Challenge in AF Patients Undergoing PCI



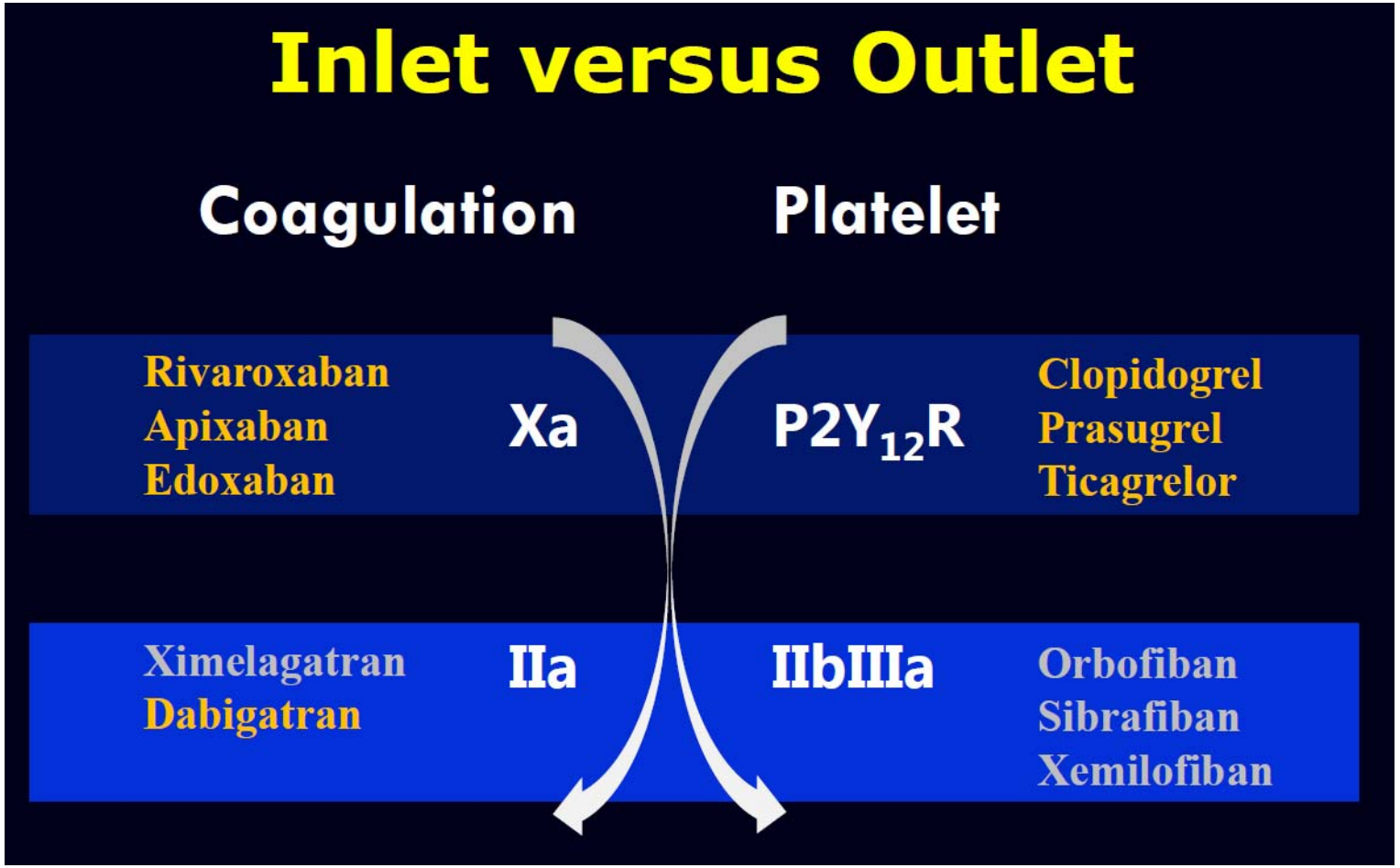
Triple therapy?: ASA + clopidogrel + OAC

Increased bleeding risk vs DAPT
No robust data for efficacy and safety

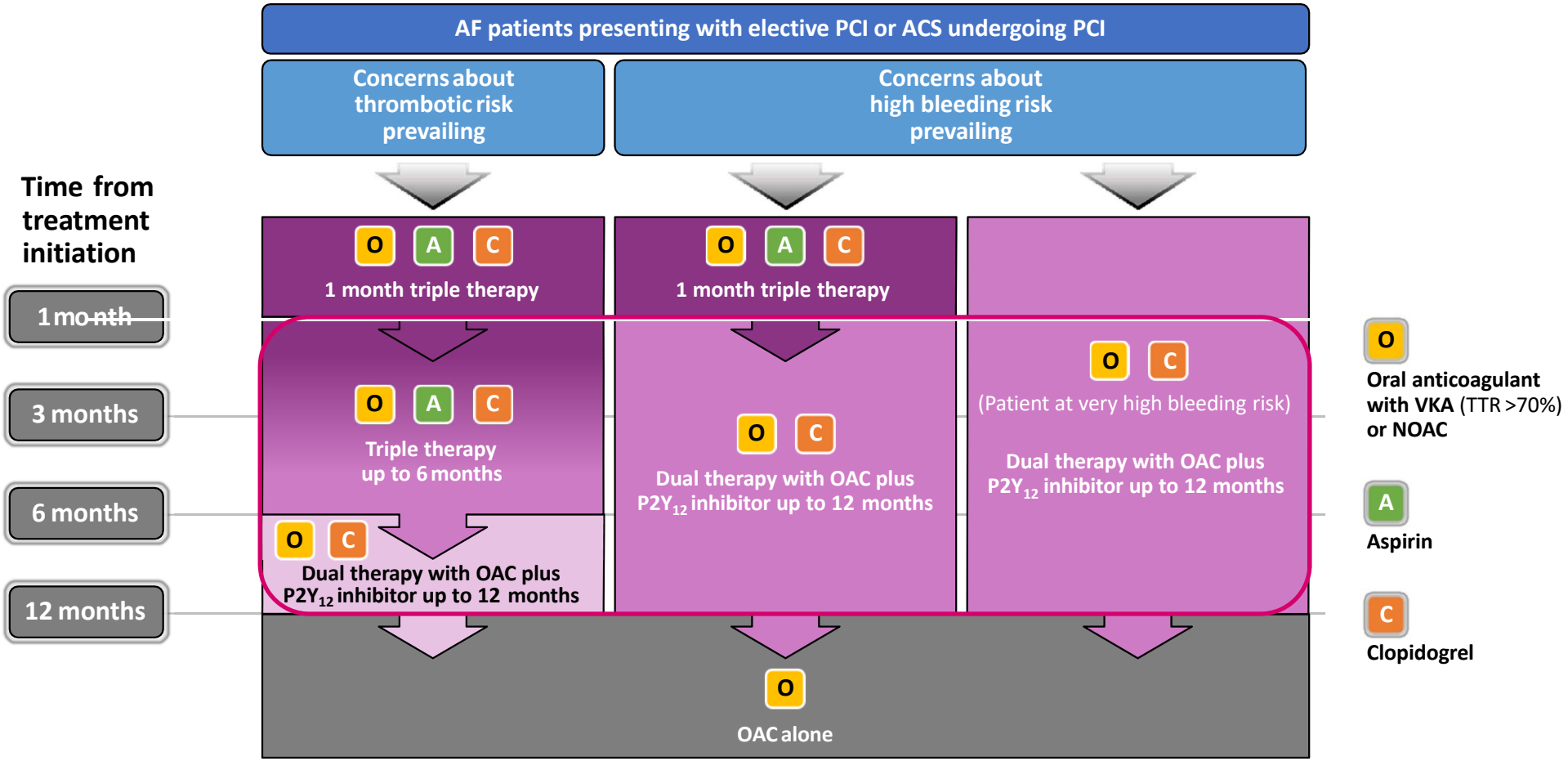
Capodanno D, Angiolillo DJ. JACC: Cardiovascular Interventions 2017;10:1086–8.

Best Combo in High-risk ASCVD patients (**Atrial Fibrillation**): Dual Coagulation + Platelet Inhibition

"Balance between Efficacy and Safety" is most important



ESC 2018 Joint European consensus, endorsed by AP Heart Rhythm Society



1. Periprocedural administration of aspirin and clopidogrel during PCI is recommended irrespective of the treatment strategy; as dual therapy, potent $P2Y_{12}$ 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.

ESC, European Society of Cardiology; NOAC, non-VKA oral anticoagulant; TTR = Time in Therapeutic Range.

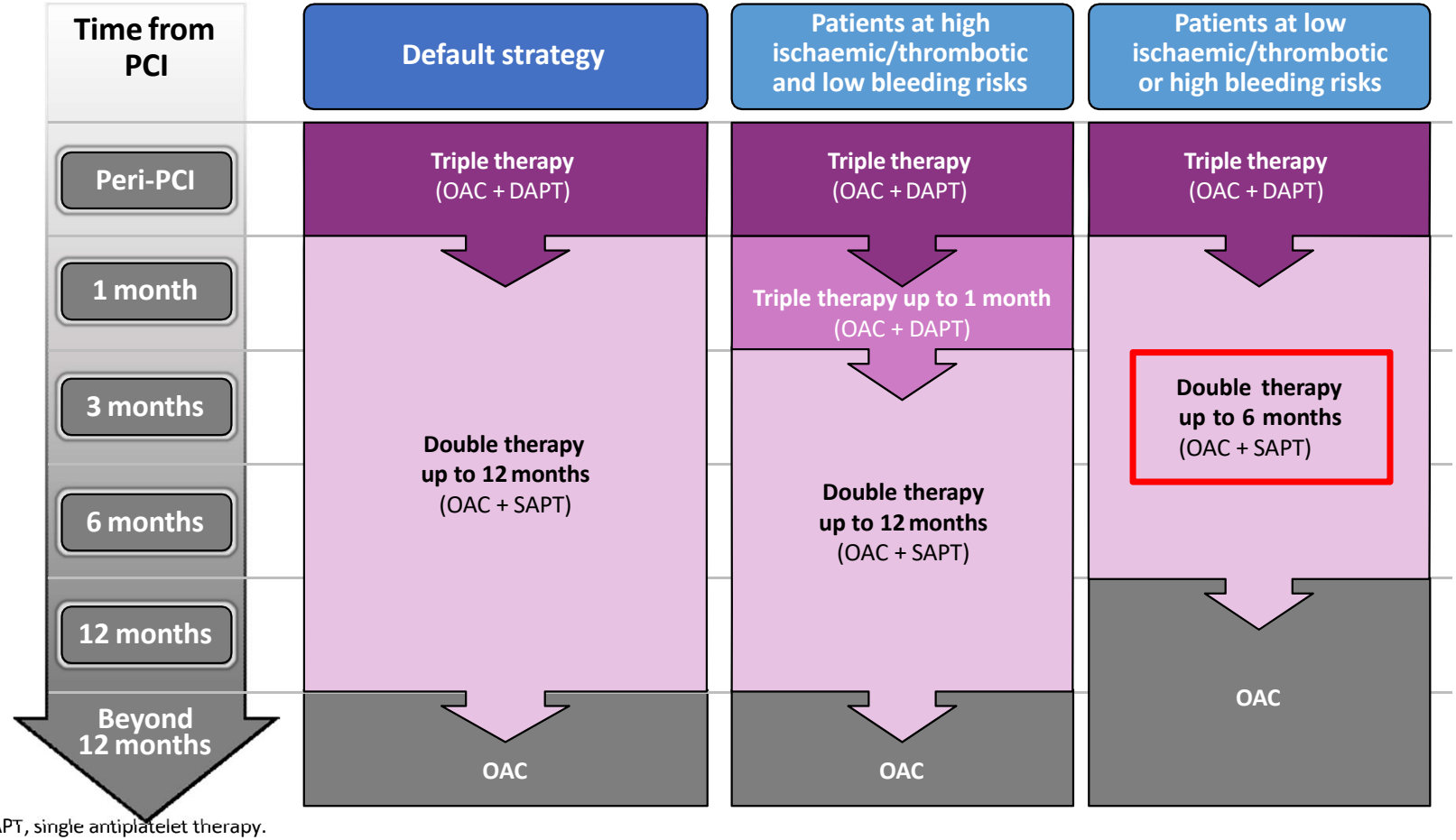
Lip GYH, et al. Europace 2019;21:192–193

ESC 2019 Guideline for Management of CCS

Antithrombotic therapy in post-PCI patients with AF or another indication for an OAC		
It is recommended that peri-procedural aspirin and clopidogrel are administered to patients undergoing coronary stent implantation.	I	C
In patients who are eligible for a NOAC, it is recommended that a NOAC (apixaban 5 mg b.i.d., dabigatran 150 mg b.i.d., edoxaban 60 mg o.d., or rivaroxaban 20 mg o.d.)[f] is used in preference to a VKA in combination with antiplatelet therapy.[300,301,308,310,311]	I	A
When rivaroxaban is used and concerns about high bleeding risk[d] prevail over concerns about stent thrombosis[h] or ischaemic stroke,[g] rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant single or dual antiplatelet therapy.[300,301,308,310]	IIa	B
When dabigatran is used and concerns about high bleeding risk[d] prevail over concerns about stent thrombosis[h] or ischaemic stroke,[g] dabigatran 110 mg b.i.d. should be considered in preference to dabigatran 150 mg b.i.d. for the duration of concomitant single or dual antiplatelet therapy.[300,301,308]	IIa	B
After uncomplicated PCI, early cessation (≤1 week) of aspirin and continuation of dual therapy with an OAC and clopidogrel should be considered if the risk of stent thrombosis[h] is low, or if concerns about bleeding risk prevail over concerns about the risk of stent thrombosis,[h] irrespective of the type of stent used.[301,308–310]	IIa	B
Triple therapy with aspirin, clopidogrel, and an OAC for ≥1 month should be considered when the risk of stent thrombosis[h] outweighs the bleeding risk, with the total duration (≤6 months) decided according to assessment of these risks and clearly specified at hospital discharge.	IIa	C
In patients with an indication for a VKA in combination with aspirin and/or clopidogrel, the dose intensity of the VKA should be carefully regulated with a target international normalized ratio in the range of 2.0–2.5 and with time in therapeutic range >70%.[300,301,308–310]	IIa	B

Knuuti J, et al. Eur Heart J 2019;e-pub.

2018 North American expert consensus document



'A **double therapy** approach (OAC + $P2Y_{12}$ inhibitor) should represent the **default strategy** for most patients…'

'An NOAC (rather than VKA) should generally be preferred…'

'If ticagrelor is chosen as the $P2Y_{12}$ agent, concomitant aspirin should not be given (i.e. avoid triple therapy), as was done in the RE-DUAL PCI trial'

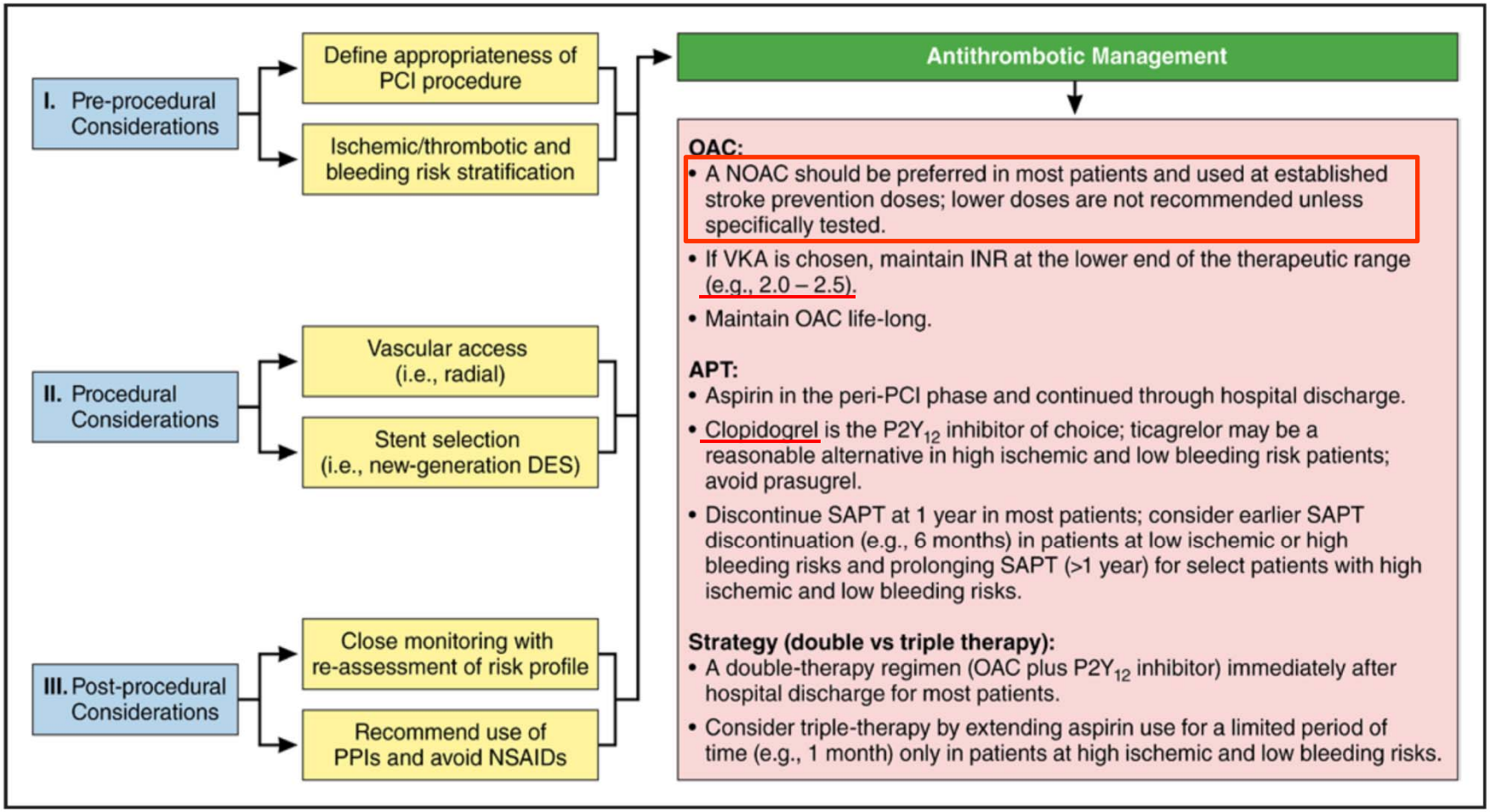
SAPT, single antiplatelet therapy.

OAC: prefer a NOAC over VKA if no contraindications; SAPT: prefer a $P2Y_{12}$ inhibitor over aspirin.

Clopidogrel is the $P2Y_{12}$ inhibitor of choice; ticagrelor may be considered in patients at high ischaemic/thrombotic and low bleeding risks; avoid prasugrel. Consider SAPT in addition to OAC after >12 months only in select patients at high ischaemic/thrombotic and low bleeding risks.

Angiolillo, et al. Circulation 2018;138:527–36.

2018 North American expert consensus document



Angiolillo, et al. Circulation 2018;138:527–36.

AF-PCI Trials: PIONEER AF-PCI, RE-DUAL, AUGUSTUS, ENTRUST AF-PCI

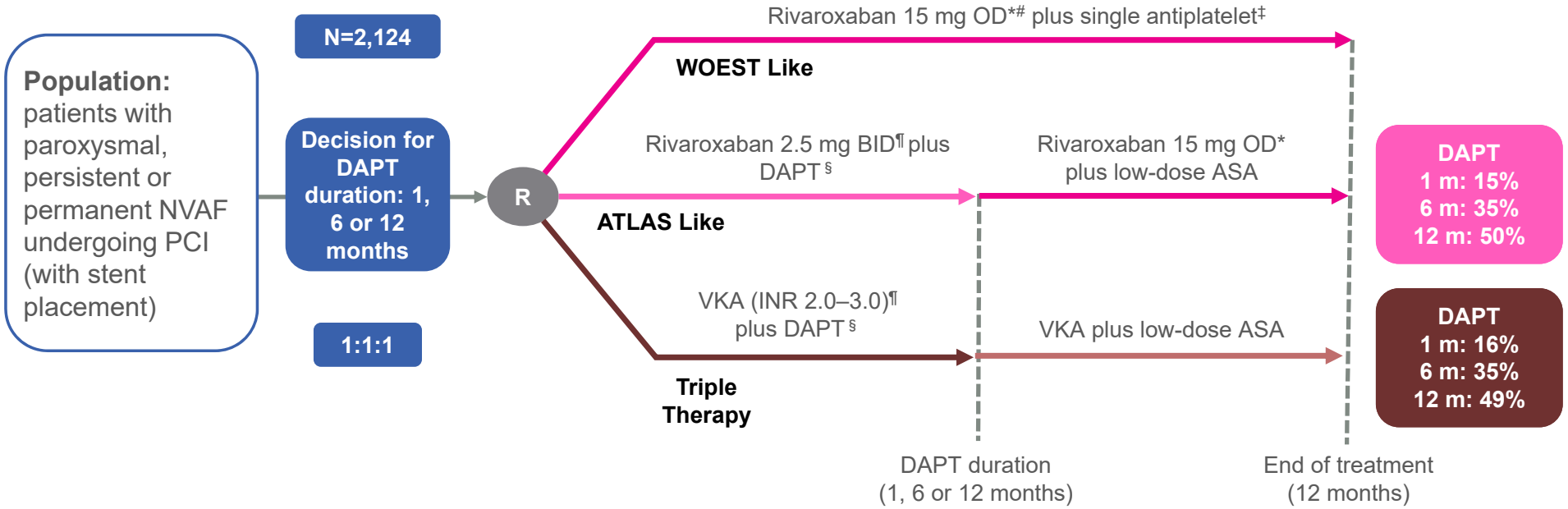
	PIONEER AF – PCI (Rivaroxaban)	RE-DUAL PCI (Dabigatran)	AUGUSTUS (Apixaban)	ENTRUST AF – PCI (Edoxaban)
Design	• An International, multi-center, randomized, open-label • VKA+ASA+$P2Y_{12}$ inhibitor vs. rivaroxaban 2.5mg twice daily+ASA+$P2Y_{12}$ inhibitor **vs. rivaroxaban 15mg(or 10mg) daily+$P2Y_{12}$ inhibitor**	• An International, Multicenter, randomized, open-label • VKA+ASA+$P2Y_{12}$ inhibitor vs. dabigatran 110mg twice daily+$P2Y_{12}$ inhibitor vs. dabigatran 150mg twice daily+$P2Y_{12}$ inhibitor(No Prasugrel)	• An International, multicenter, two-by-two factorial, randomized, open-label (apixaban vs. VKA), double-blind (ASA vs. placebo) • VKA±ASA+$P2Y_{12}$inhibitor vs. apixaban 5mg(or 2.5mg) twice daily±ASA+$P2Y_{12}$ inhibitors	• An International, multicenter, randomized, open-label, non-inferiority phase 3b trial • VKA+ASA+$P2Y_{12}$ inhibitor vs. edoxaban 60mg (or 30mg) once daily + $P2Y_{12}$ inhibitor
Bleeding endpoint	TIMI major or minor bleeding or requiring medical attention	ISTH major or clinically relevant bleeding	ISTH major or clinically relevant bleeding	ISTH major or clinically relevant non-major (CRNM) bleeding
Efficacy Endpoints	Cardiac death, MI or stroke	Death, MI, stroke, systemic thromboembolism or unplanned revascularization	Death or hospitalization, composite of death, MI, stroke, stent thrombosis, or urgent revascularization	Composite of cardiovascular death, stroke, systemic embolic events, MI, definite stent thrombosis

Please note this information is from separate, independent studies and the studies are not directly comparable owing to different study design. Therefore it should be carefully interpreted.

1. Gibson CM et al, New Engl J Med 2016; doi: 10.1056/NEJMoa1611594 2. Christopher PC et al, New Engl J Med 2017; 377:1513-1524
3. Lopes RD et al, New Engl J Med 2019; DOI: 10.1056/NEJMoa1817083 4. Vranckx P et al, American Heart Journal. 2018;196:105-112

Rivaroxaban is the First NOAC to Provide Data From a Dedicated RCT in AF-PCI

Design: An open-label, randomized, controlled phase IIIb safety study



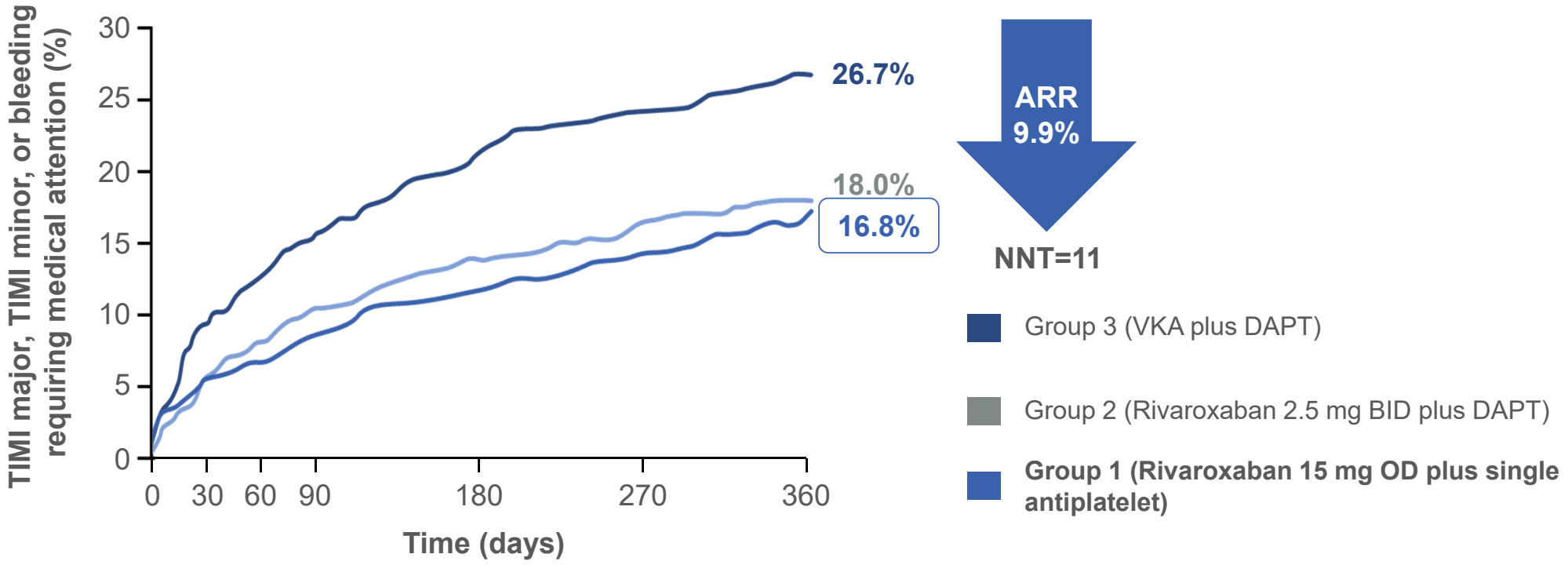
*CrCl 30–49 ml/min: 10 mg OD; #first dose 72–96 hours after sheath removal; ‡clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%); §ASA (75–100 mg daily) plus clopidogrel (75 mg daily) (alternative use of prasugrel or ticagrelor allowed, but capped at 15%);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

1. Janssen Scientific Affairs, LLC. 2016. https://clinicaltrials.gov/ct2/show/NCT01830543 [accessed 10 Oct 2016];
2. Gibson CM *et al*, *Am Heart J* 2015;169:472–478e5; 3. Gibson CM et al, *New Engl J Med* 2016; doi: 10.1056/NEJMoa1611594

Rivaroxaban 15mg Strategies Were Associated with Significantly Improved Safety

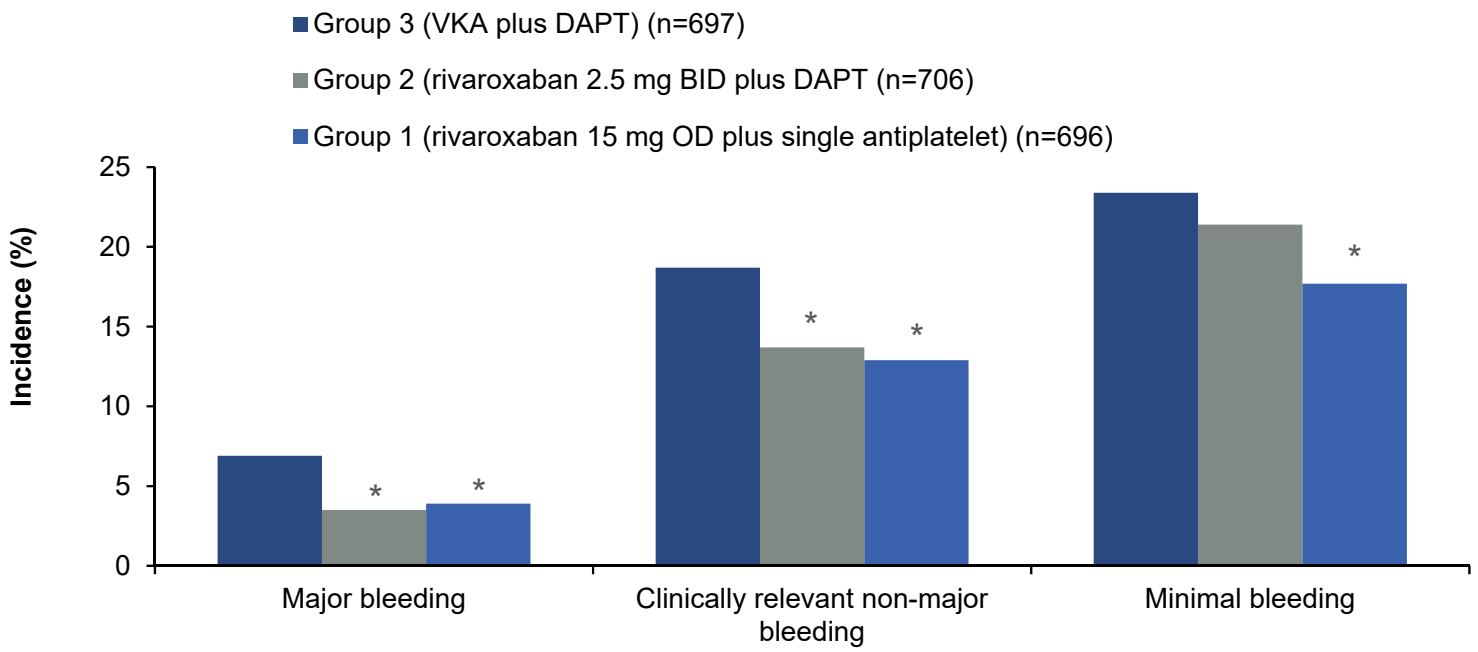
Rivaroxaban 15 mg OD plus SAPT vs VKA plus DAPT: HR=0.59; (95% CI 0.47–0.76); *p*<0.001

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, N Engl J Med* 2016;375:2423–2434

ISTH Major Bleeding Significantly Reduced with Rivaroxaban Strategies Versus VKA



Incidence of fatal bleeding: 0.3% in group 1, 0.3% in group 2, 0.9% in group 3

Both rivaroxaban strategies associated with significant reduction in ISTH major and clinically relevant non-major bleeding vs the VKA plus DAPT strategy

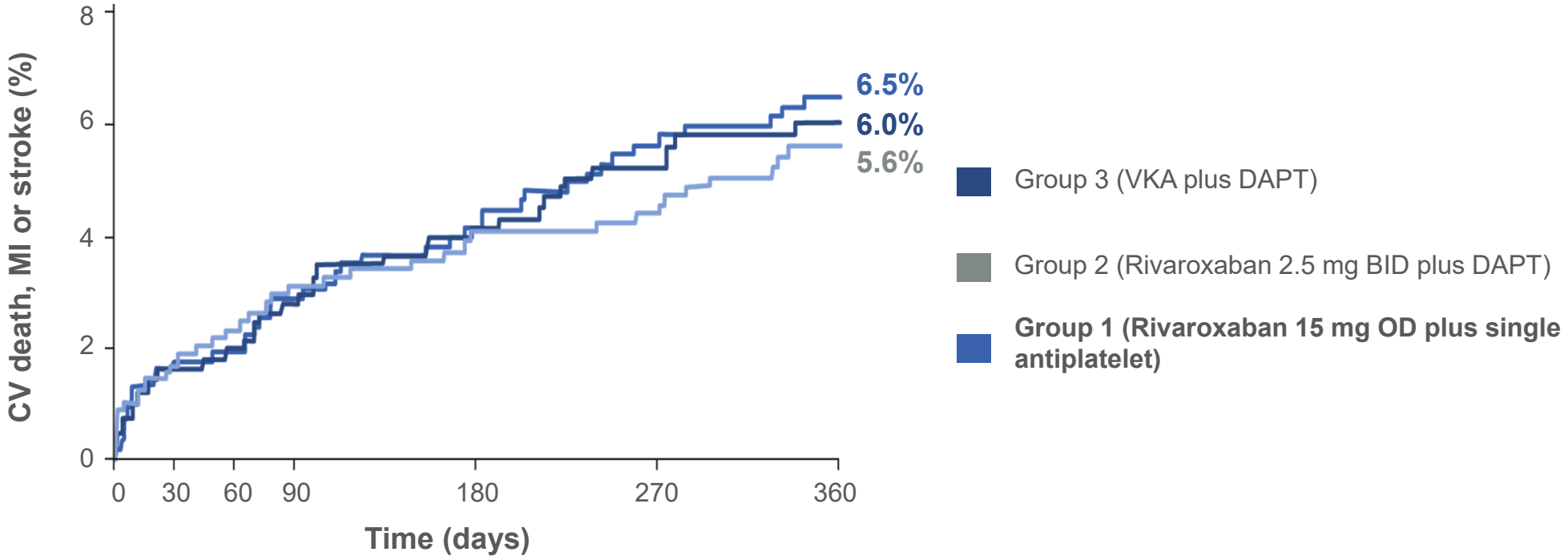
*p<0.05 vs Group 3.

Gibson CM *et al, N Engl J Med* 2016;375:2423–2434

Efficacy Was Comparable Between All Three Treatment Strategies*

Rivaroxaban 15 mg OD plus SAPT vs VKA plus DAPT: HR=1.08; (95% CI 0.69–1.68); *p*=0.750

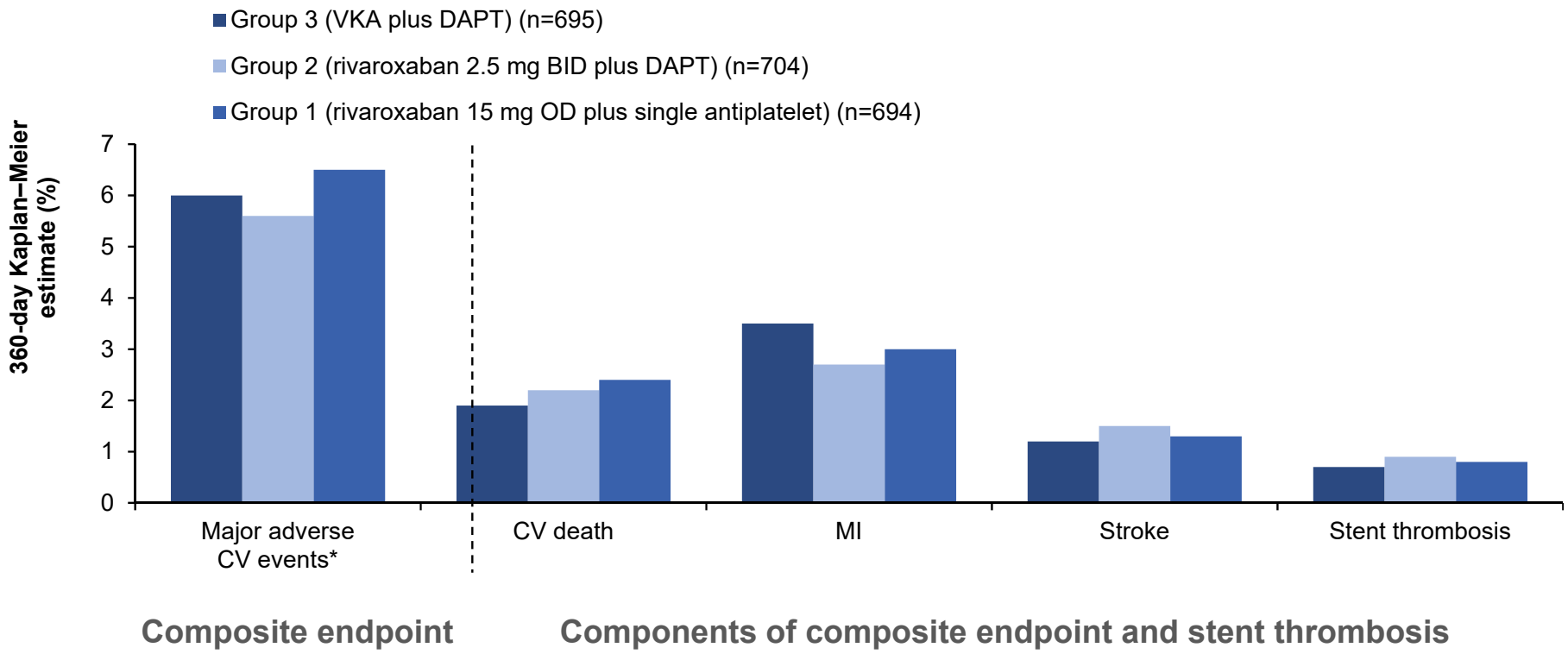
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.93 (95% CI 0.59–1.48); *p*=0.765



*Trial not powered to definitively demonstrate either superiority or non-inferiority for efficacy endpoints.

Gibson CM *et al, N Engl J Med* 2016;375:2423–2434

Comparable Efficacy with Rivaroxaban Strategies Versus VKA plus DAPT

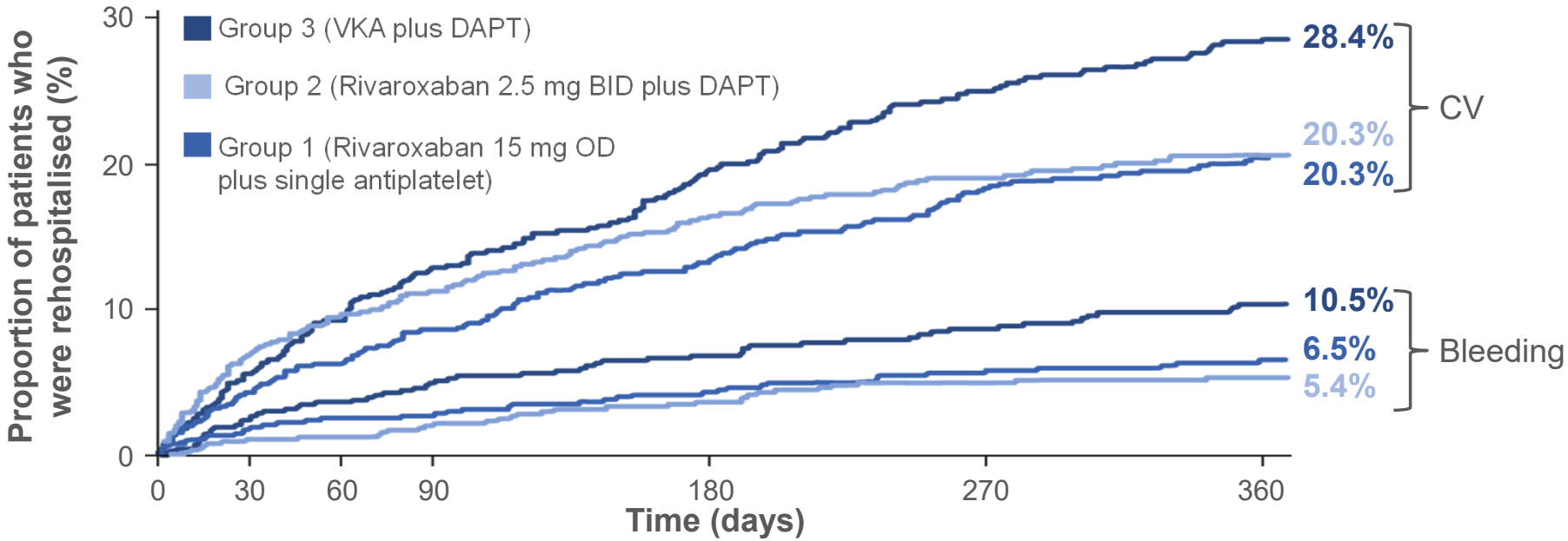


Incidence of major adverse CV events was comparable between all three treatment strategies; however, the trial was not powered for efficacy

*Composite of CV death, MI, and stroke.

Gibson CM *et al, N Engl J Med* 2016;375:2423–2434

Rehospitalisation Due to CV Events and Bleeding Were Both Reduced with the Rivaroxaban Strategies



CV

Group 1 vs Group 3:
HR=0.68; (95% CI 0.54–0.85); *p*<0.001
ARR=8.1%; NNT=13
Group 2 vs Group 3:
HR=0.73 (95% CI 0.58–0.91); *p*=0.005
ARR=8.1%; NNT=13

Bleeding

Group 1 vs Group 3:
HR=0.61; (95% CI 0.41–0.90); *p*=0.012
ARR=4.0%; NNT=25
Group 2 vs Group 3:
HR=0.51 (95% CI 0.34–0.77); *p*=0.001
ARR=5.1%; NNT=20

Adverse events leading to hospitalisation were classified by consensus panel blinded to treatment group as potentially related to either bleeding, CV, or other causes. Re hospitalisations do not include the index event and include the first rehospitalisation after the index event.

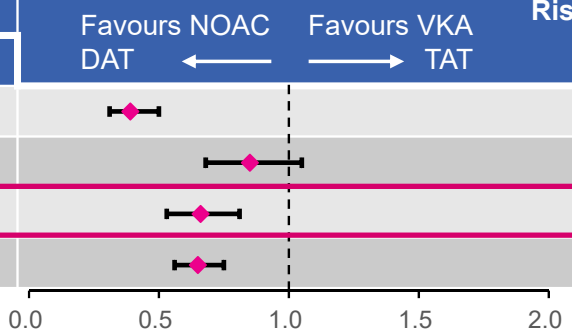
Gibson CM *et al, Circulation* 2017;135:323–333

Result Comparison of NOAC AF PCI Trials for Bleeding Outcomes

Comparative NOAC AF PCI Trials for Outcomes Defined by Each NOAC AF PCI Trials

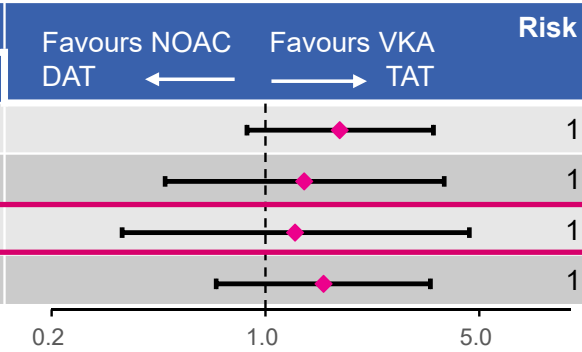
Safety Outcome (ISTH Major or Clinically Relevant Non-major Bleeding)

Study or Subgroup	NOAC DAT		VKA TAT		Risk Ratio, 95 % CI
	Events	Total	Events	Total	
AUGUSTUS	84	1143	210	1123	0.39 (0.31, 0.50)
ENTRUST AF-PCI	128	751	152	755	0.85 (0.68, 1.05)
PIONEER AF-PCI	117	696	178	697	0.66 (0.53, 0.81)
RE-DUAL PCI	305	1744	264	981	0.65 (0.56, 0.75)



Efficacy Outcome (Stent Thrombosis)

Study or Subgroup	NOAC DAT		VKA TAT		Risk Ratio, 95 % CI
	Events	Total	Events	Total	
AUGUSTUS	21	1153	12	1154	1.75 (0.87, 3.54)
ENTRUST AF-PCI	8	751	6	755	1.34 (0.47, 3.84)
PIONEER AF-PCI	5	694	4	695	1.25 (0.34, 4.64)
RE-DUAL PCI	22	1744	8	981	1.55 (0.69, 3.46)

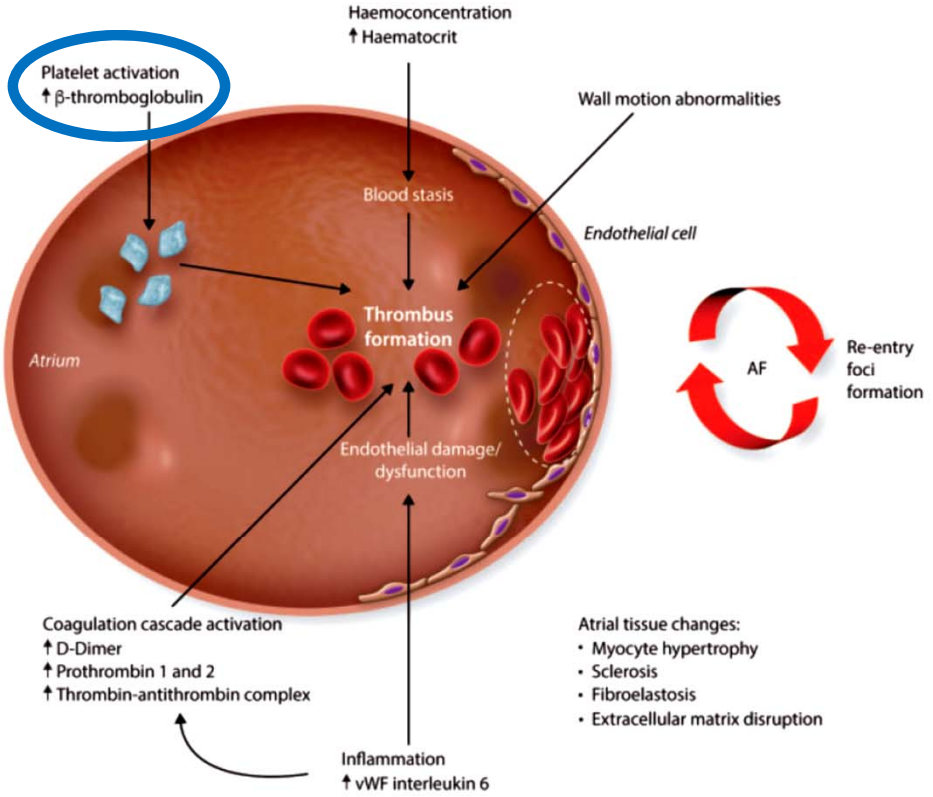


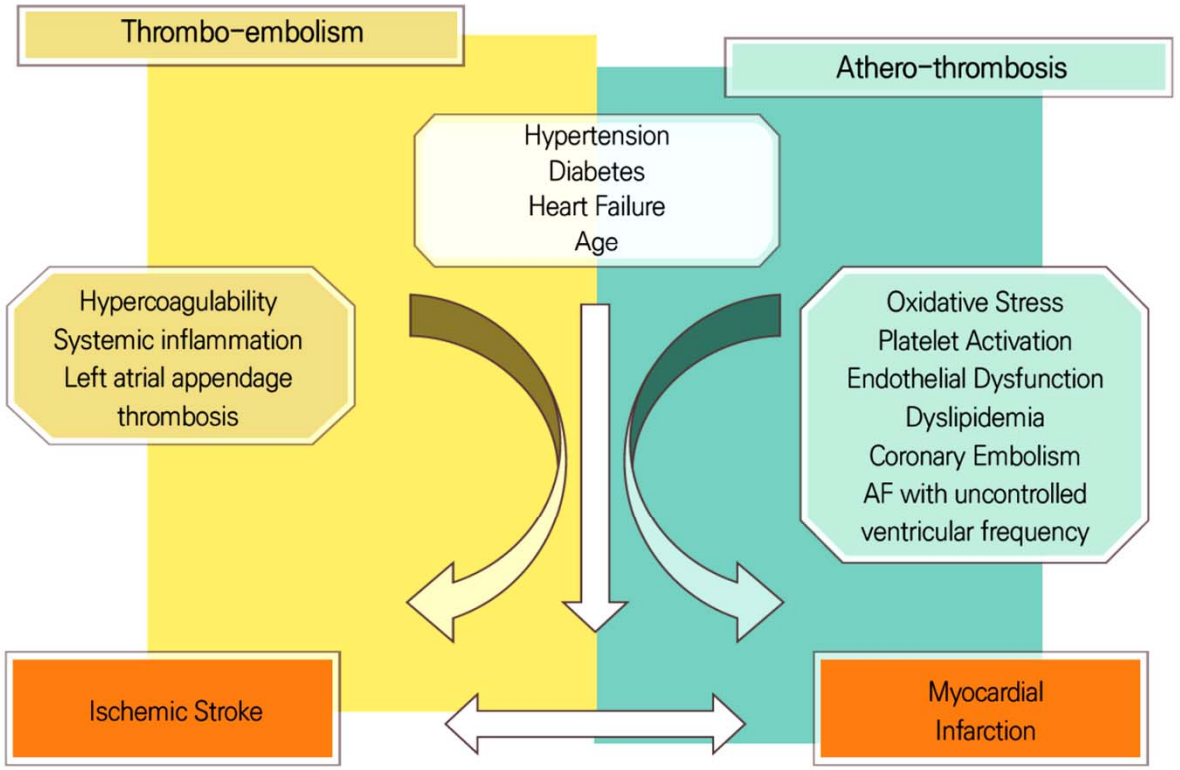
PIONEER AF-PCI provides a well-balanced safety and efficacy profile for Rivaroxaban Dual Therapy in treating AF-PCI patients

Please note this information is from separate, independent studies and the studies are not directly comparable owing to different study design. Therefore it should be carefully interpreted.

1. European Heart Journal (2019) 0, 1–11 doi:10.1093/eurheartj/ehz732

Mechanism of Thromboembolism and Atherothrombosis in AF

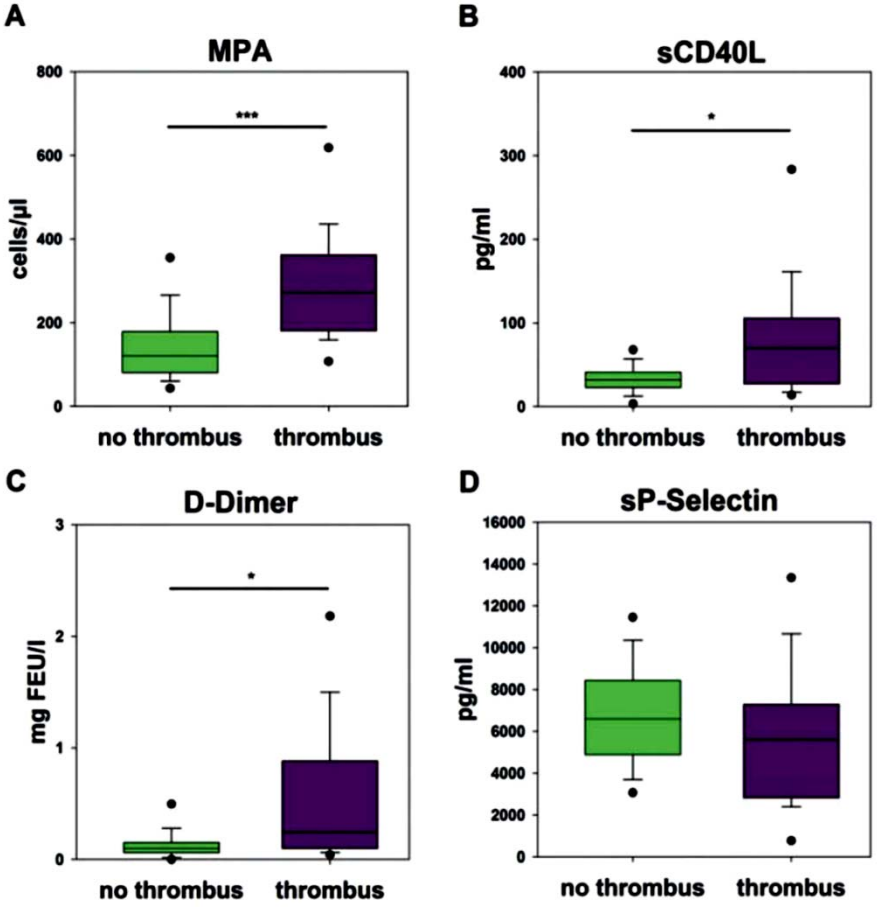




Violi F, et al. JAHA 2016;5:e003347.

Thrombotic Biomarkers by LAA Thrombus in AF

LAA thrombus in AF patients (TEE): Yes (n=28) vs. No (n=80)

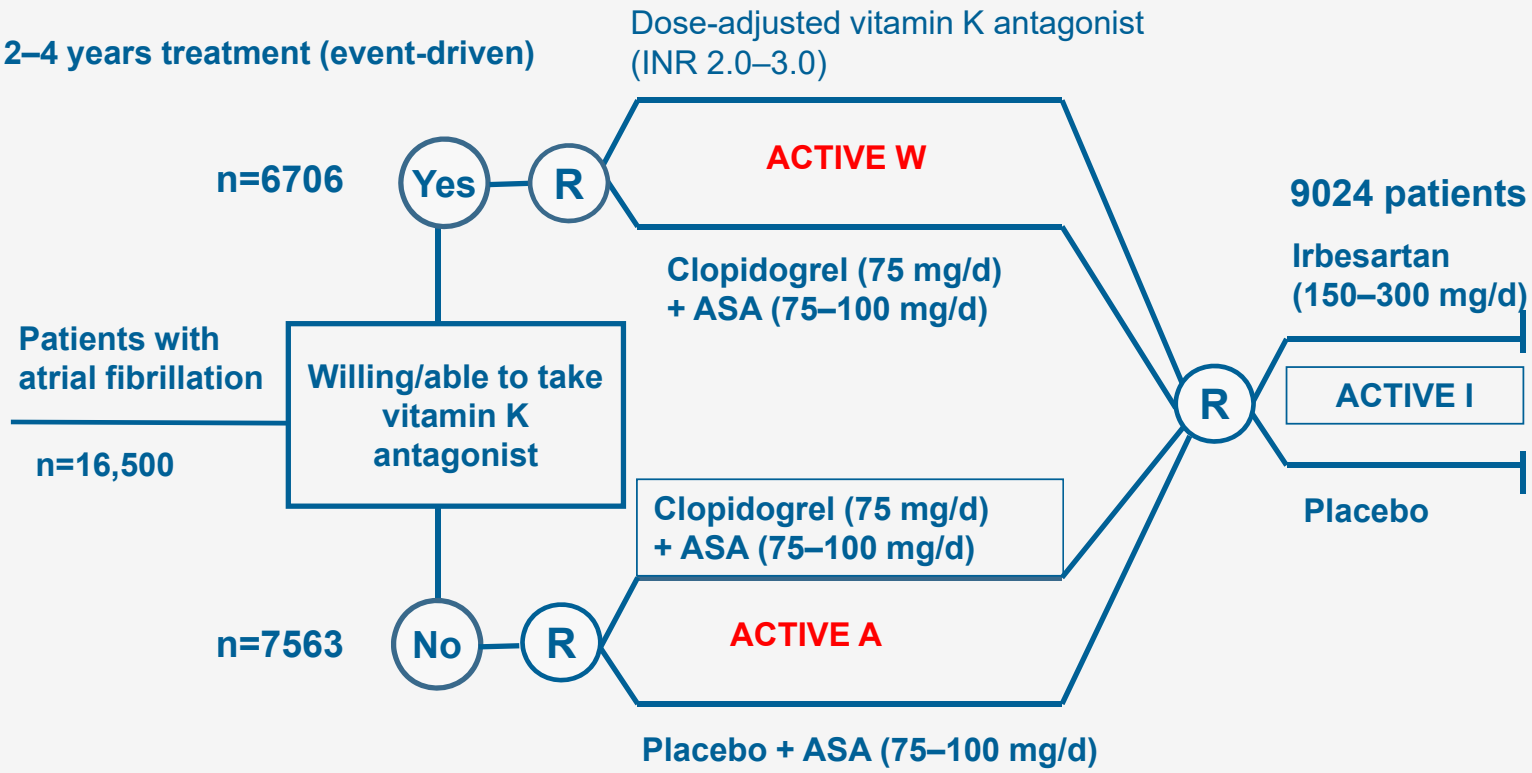


Multivariate analysis for LAA thrombus

Parameter	OR	95 % CI	*p* Value
Age	1.024	0.964–1.088	0.442
Diabetes	2.032	0.448–9.211	0.358
CAD	0.889	0.222–3.565	0.868
LVEF	0.957	0.909–1.008	0.099
LA-diameter	1.097	0.973–1.235	0.129
MPAs (cells/µl)	1.009	1.004–1.015	**0.001****
Elevated MPAs (>170 cells/µl)	61.79	6.85–557.22	**<0.001*****
sCD40L	1.037	1.012–1.063	**0.003****
Elevated sCD40L (>40 pg/ml)	7.23	2.23–23.39	**0.001****
D-dimer	51.168	1.105–2369.616	**0.044***
Elevated D-dimer (>0.5 mg FEU/l)	4.41	0.62–31.09	0.14

Tarnowski D, et al. Platelets, 2018; 29: 41–47.

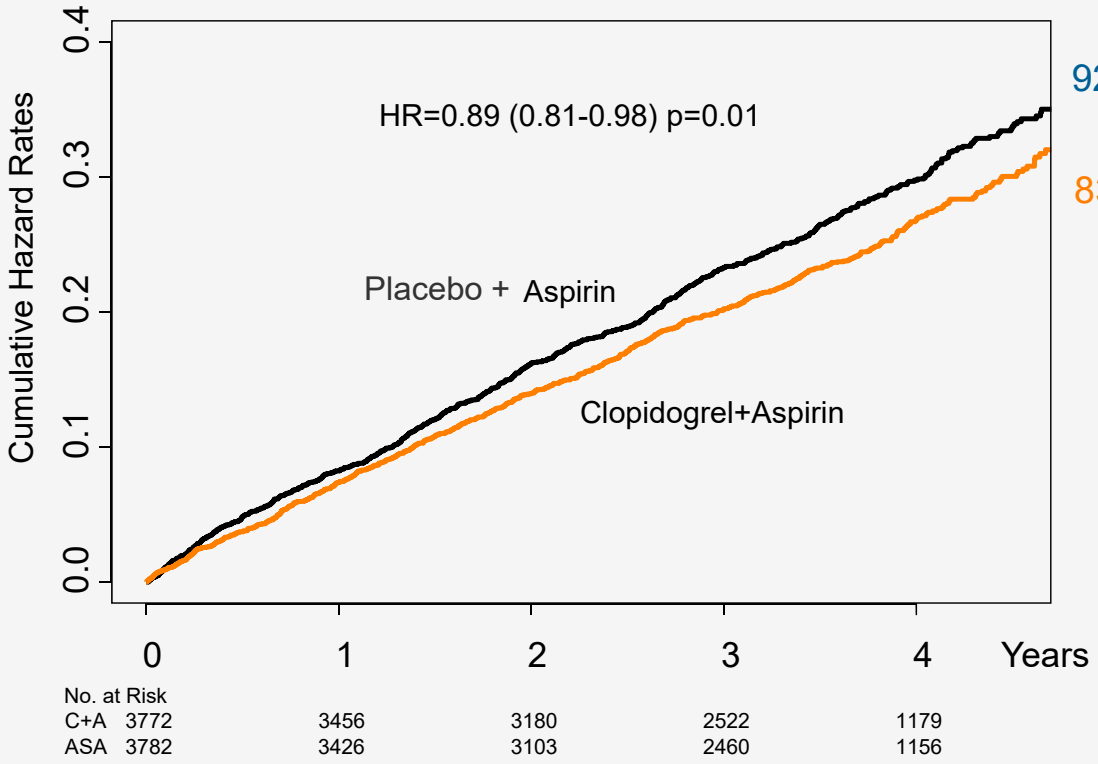
ACTIVE: A vs. AC, AC vs. WFR in AF



The ACTIVE Steering Committee. Am Heart J 2006; 151:1187-93

ACTIVE A: Primary outcome reduced by 11% (RRR)
Stroke, MI, Non-CNS systemic embolism or vascular death

The addition of clopidogrel to ASA significantly reduced vascular events with an 11% RRR compared with ASA alone



924 (7.6%/year)

832 (6.8%/year)

The ACTIVE Investigators N Engl J Med 2009;360

Primary and Secondary Outcomes

	Clopidogrel plus ASA (N=3772)		ASA (N=3782)		Clopidogrel plus ASA vs. ASA		
	Number of events	Rate per 100 patient years	Number of events	Rate per 100 patient years	Relative risk	95% confidence interval	P-value
Primary outcome (stroke, MI, non-CNS systemic embolism or vascular death)	832	6.8	924	7.6	0.89	0.81-0.98	0.01
Stroke							
All	296	2.4	408	3.3	0.72	0.62-0.83	<0.001
Ischemic	235	1.9	343	2.8	0.68	0.57-0.80	
Hemorrhagic	30	0.2	22	0.2	1.37	0.79-2.37	
Cause uncertain	41	0.3	51	0.4	0.81	0.54-1 22	
Fatal	70	0.5	93	0.7	0.75	0.55-1.03	
Stroke							
Non-disabling	107	0.9	153	1.2	0.70	0.54-0.89	0.004
Disabling/fatal	198	1.6	267	2.1	0.74	0.62-0.89	0.001
MI	90	0.7	115	0.9	0.78	0.59-1.03	0.077
Non-CNS systemic embolism	54	0.4	56	0.4	0.96	0.66-1.40	0.84
Vascular death	600	4.7	599	4.7	1.00	0.89-1.12	0.97
Total death	825	6.4	841	6.6	0.98	0.89-1.08	0.69

The ACTIVE Investigators N Engl J Med 2009;360

Overall Benefit-Risk in ACTIVE A

Primary Efficacy Endpoint vs. Primary Safety Endpoint

Disabling strokes vs. Transfusions

Ischemic/uncertain Stroke prevented (-118)
vs. hemorrhagic Stroke caused (+8)

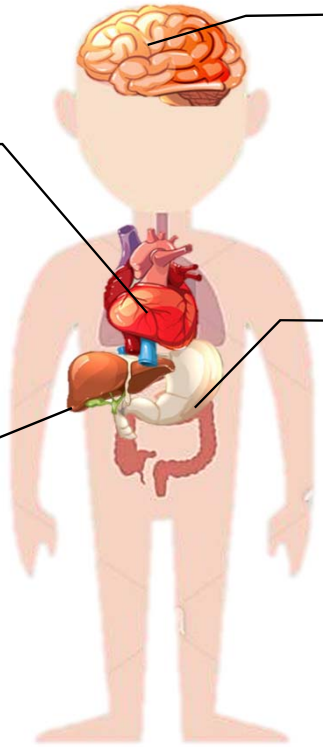
Net benefit = - 110 strokes

Unique Profiles of East Asian Population on NOAC

Bad memory for Warfarin

① ***↑ Hemorrhagic stroke***
- ↑ Lacunar infarct
- ↑ Hemorrhagic transformation

② ***↓ CAD***
≈ Ischemic stroke
↑ ↑ ICH



↑ GI bleeding (?)
- ↑ Helicobacter pylori infection
- ↑ CYP polymorphism

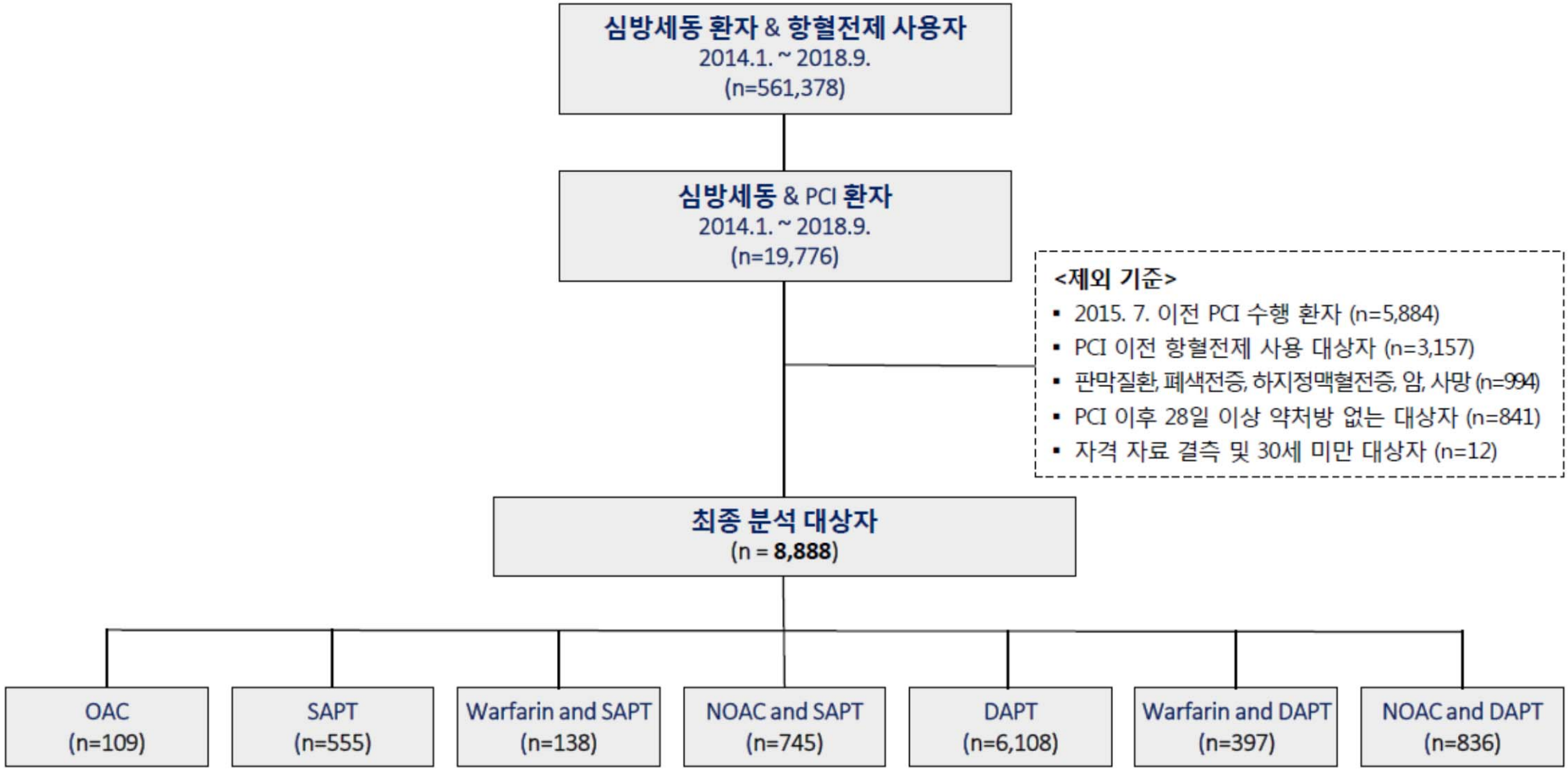
③ ***Different response to NOAC***

Rivaroxaban/dabigatran: ↑ 25~30%
Apixaban: ≈
Edoxaban: ↓ 20-25%

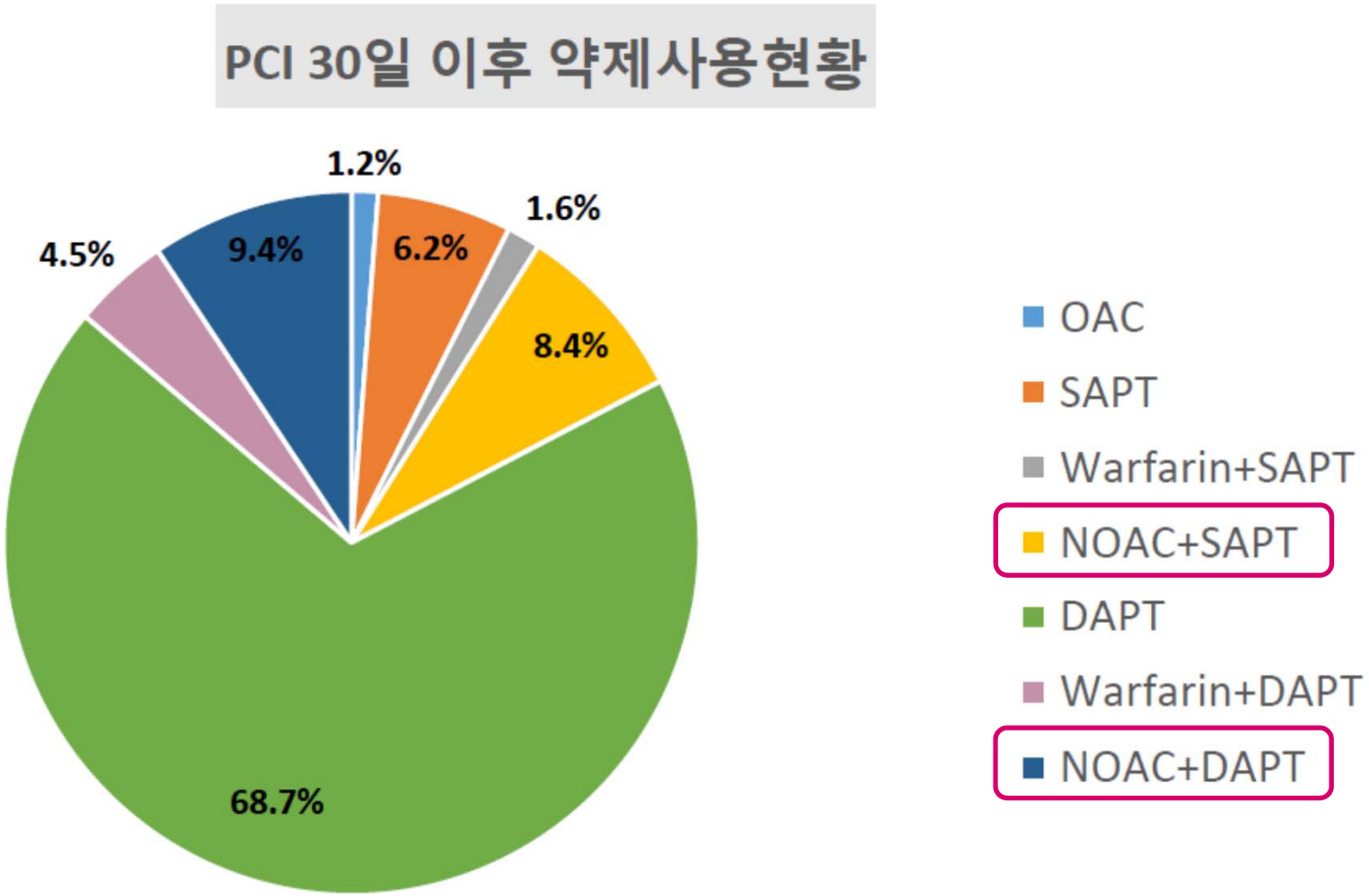
Issue in Korean data: AF Patients Undergoing PCI – ”NO OAC”

	Asan-PCI registry	Korean NHIS	KAMIR-NIH
Time interval	2003.1~2011.12	2009.1~2013.12	2011.11~2015.10
Patients category	all IHD	PCI, AF code	NSTEMI, STEMI
Publication	JACC Interv 2017	Am J Cardiol 2019	Unpublished
Number of AF (%)	711 (7.1%)	8,891 (NA)	763 (5.6%)
No OAC during 1 year	**90.5%**	**85.4%**	**83.1%**
OAC only after 1 year	NA	9.9%	21.1%

Current Status of Korea Regarding AF Patients Undergoing PCI: NECA



Antithrombotic Tx of Korea Regarding AF Patients Undergoing PCI



Antithrombotic Regimen in AF Korean Patients Undergoing PCI

Characteristics	Total (N=8,888)		Mono Therapy				Dual Therapy						Triple Therapy			
			OAC (n=109)		SAPT (n=555)		Warfarin+SAPT (n=138)		NOAC+SAPT (n=745)		DAPT (n=6,108)		Warfarin+DAPT (n=397)		NOAC+DAPT (n=836)	
Dose of NOACs																
Reduced dosage	1,187	(80.7)	54	(65.9)	–	–	–	–	533	(79.7)	–	–	–	–	600	(83.3)
Type of NOACs†																
Dabigatran	568	(33.6)	22	(20.2)	–	–	–	–	252	(33.8)	–	–	–	–	294	(35.2)
Rivaroxaban	318	(18.8)	17	(15.6)	–	–	–	–	151	(20.3)	–	–	–	–	150	(17.9)
Apixaban	540	(32.0)	34	(31.2)	–	–	–	–	243	(32.6)	–	–	–	–	263	(31.5)
Edoxaban	276	(16.3)	20	(18.3)	–	–	–	–	113	(15.2)	–	–	–	–	143	(17.1)
Type of P2Y12‡																
Clopidogrel	7,464	(84.0)	–	–	337	(60.7)	112	(81.2)	618	(83.0)	5,213	(85.3)	375	(94.5)	799	(95.6)
Prasugrel	309	(3.5)	–	–	9	(1.6)	0	(0.0)	5	(0.7)	281	(4.6)	6	(1.5)	8	(1.0)
Ticagrelor	869	(9.8)	–	–	36	(6.5)	0	(0.0)	12	(1.6)	769	(12.6)	21	(5.3)	31	(3.7)
평균 추적관찰기간(개월)																
Death, Mean (SD)	21.4	(10.5)	19.8	(10.0)	19.5	(10.5)	20.3	(11.0)	17.5	(9.8)	22.1	(10.5)	25.3	(10.6)	19.3	(9.9)
Major bleeding, Mean (SD)	20.8	(10.7)	19.4	(10.3)	18.9	(10.7)	19.5	(11.4)	17.0	(9.9)	21.5	(10.6)	24.5	(11.0)	18.8	(10.1)
Any bleeding, Mean (SD)	20.3	(10.8)	18.9	(10.6)	18.2	(10.9)	19.3	(11.4)	16.4	(9.9)	21.0	(10.7)	23.9	(11.2)	18.3	(10.2)
Ischemic stroke, Mean (SD)	20.9	(10.6)	18.8	(10.4)	19.0	(10.5)	19.6	(11.2)	17.0	(9.8)	21.7	(10.6)	24.6	(10.8)	18.9	(10.1)
MI, Mean (SD)	20.5	(10.8)	19.2	(9.9)	18.7	(10.6)	19.3	(11.2)	16.9	(9.9)	21.2	(10.8)	24.0	(11.3)	18.4	(10.1)
Composite, Mean (SD)	20.1	(10.9)	18.3	(10.3)	18.4	(10.5)	18.8	(11.3)	16.5	(9.9)	20.8	(10.9)	23.4	(11.5)	18.2	(10.2)

Values are n(%) or mean (standard deviation).

Abbreviations: BMI, body mass index; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; PPIs, proton pump inhibitors; NSAIDs, non-steroidal anti-inflammatory drug; MI, myocardial infarction.

Safety & Effectiveness Outcomes (Time-dependent COX Analysis)

Outcomes	DAPT (n=6,108)		Mono Therapy OAC (n=109)			Mono Therapy SAPT (n=555)			OAC + SAPT (n=883)			OAC + DAPT (n=1,233)		
	event		event	HR	95% CI	event	HR	95% CI	event	HR	95% CI	event	HR	95% CI
Major bleeding (n=411)	272	Ref.	4	**1.65**	**(1.06, 2.57)**	27	0.86	(0.61, 1.21)	39	**1.34**	**(1.01, 1.78)**	69	1.35	(0.97, 1.89)
Intracranial bleeding (n=136)	83	Ref.	1	**2.03**	**(1.00, 4.14)**	14	1.26	(0.74, 2.13)	13	1.17	(0.67, 2.04)	25	**2.22**	**(1.27, 3.86)**
Any bleeding (n=719)	467	Ref.	9	**1.47**	**(1.04, 2.07)**	54	0.92	(0.72, 1.19)	70	1.22	(0.98, 1.53)	119	**1.51**	**(1.17, 1.94)**
Ischemic stroke (n=240)	159	Ref.	6	0.56	(0.23, 1.39)	19	0.60	(0.36, 1.00)	25	0.67	(0.43, 1.05)	31	1.25	(0.83, 1.89)
MI (n=539)	392	Ref.	5	**0.34**	**(0.16, 0.73)**	34	**0.59**	**(0.42, 0.82)**	34	**0.52**	**(0.37, 0.72)**	74	1.21	(0.93, 1.58)
All cause mortality (n=1,213)	800	Ref.	14	1.29	(0.98, 1.71)	109	1.08	(0.89, 1.30)	117	0.85	(0.70, 1.04)	173	**1.30**	**(1.07, 1.59)**
Composite of death, MI, or stroke (n=1,777)	1,201	Ref.	23	1.03	(0.80, 1.32)	140	0.85	(0.72, 1.00)	165	**0.80**	**(0.68, 0.94)**	248	**1.28**	**(1.09, 1.50)**
Composite of death, MI, stroke or major bleeding (n=2,015)	1,363	Ref.	26	1.12	(0.89, 1.41)	155	**0.85**	**(0.73, 0.99)**	183	0.87	(0.75, 1.01)	288	**1.28**	**(1.10, 1.49)**

*Adjusted for age, sex, BMI, index MI, Ischemic stroke, CKD, CHF, DM, CCI, CHADS-VASc, HAS-BLED, smoking status, Beta blocker, CCB, ACE inhibitor or ARB, Digoxin, Statin, PPI and NSAID.