Managing clinical challenges in patients with NVAF

: Pleiotropic Effect of NOACs *vs.* VKA, especially on Vascular Protection

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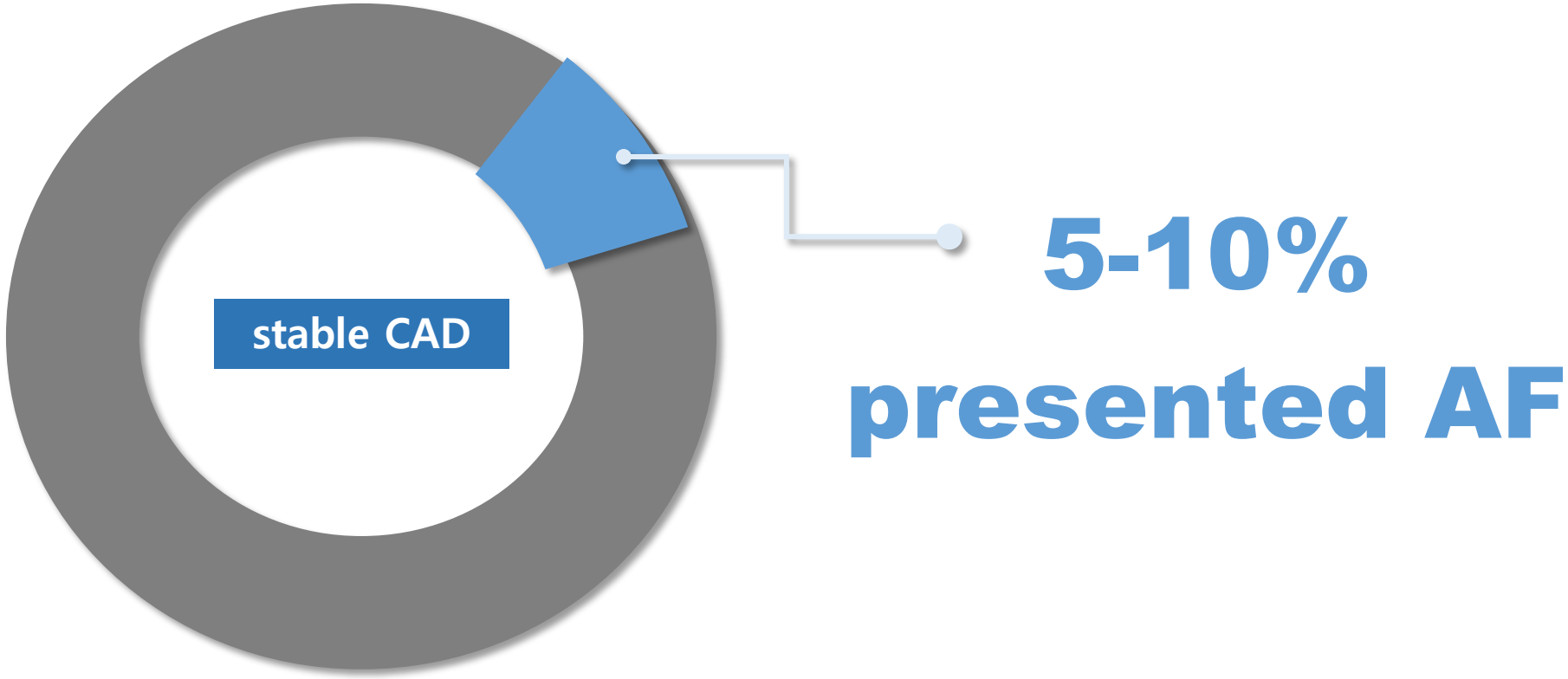
Comorbid of AF in stable CAD patients

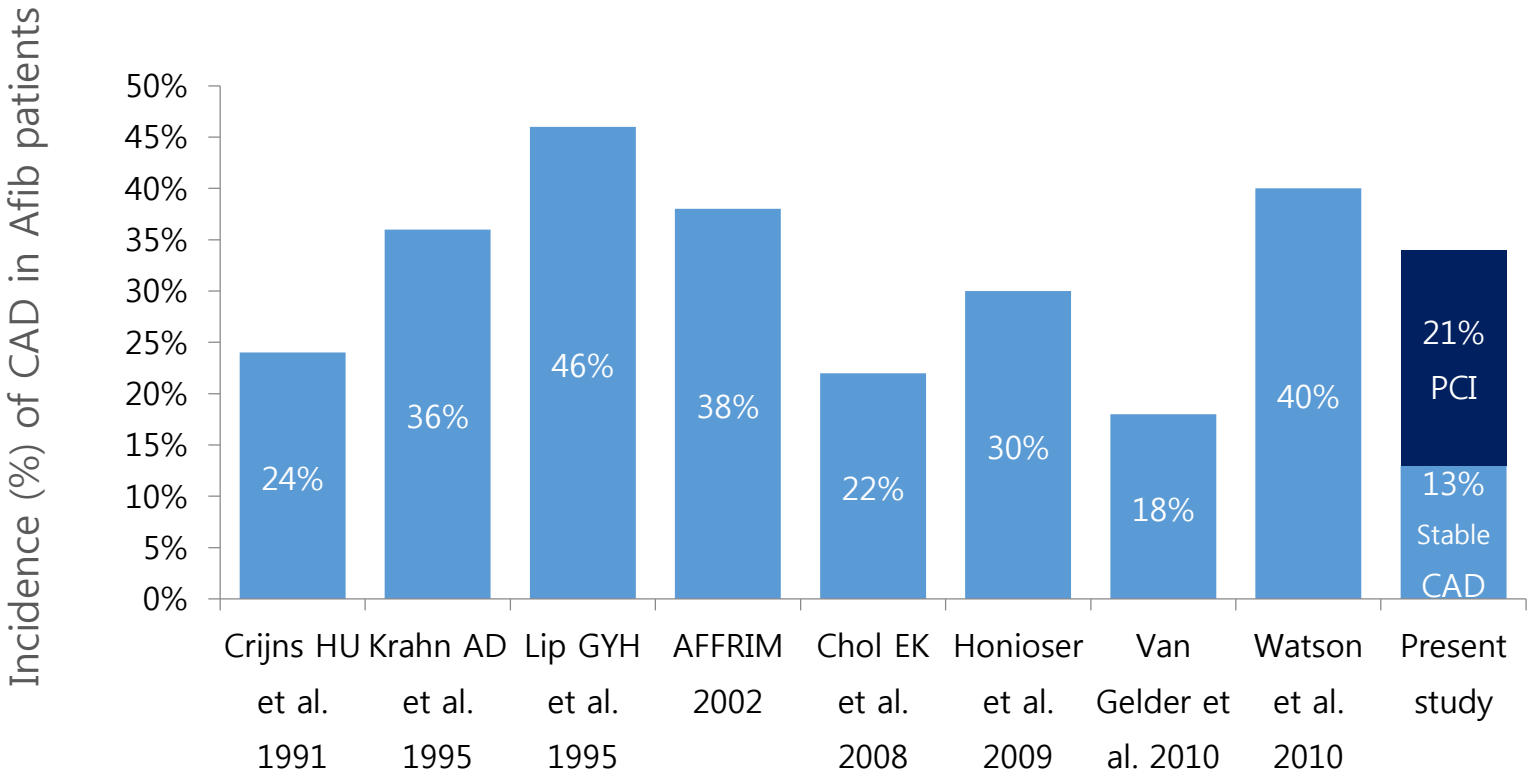
◆ AF presented in 5-10% of patients with stable coronary artery disease (CAD) (varying according to comorbidities)



AF, atrial fibrillation; CAD, coronary artery disease.
Rohla M, et al. Int J Cardiology 2015;184:108–114. Pilgrim T, et al. EuroIntervention. 2013;8:1061-1071.

Comorbid of CAD in AF patients

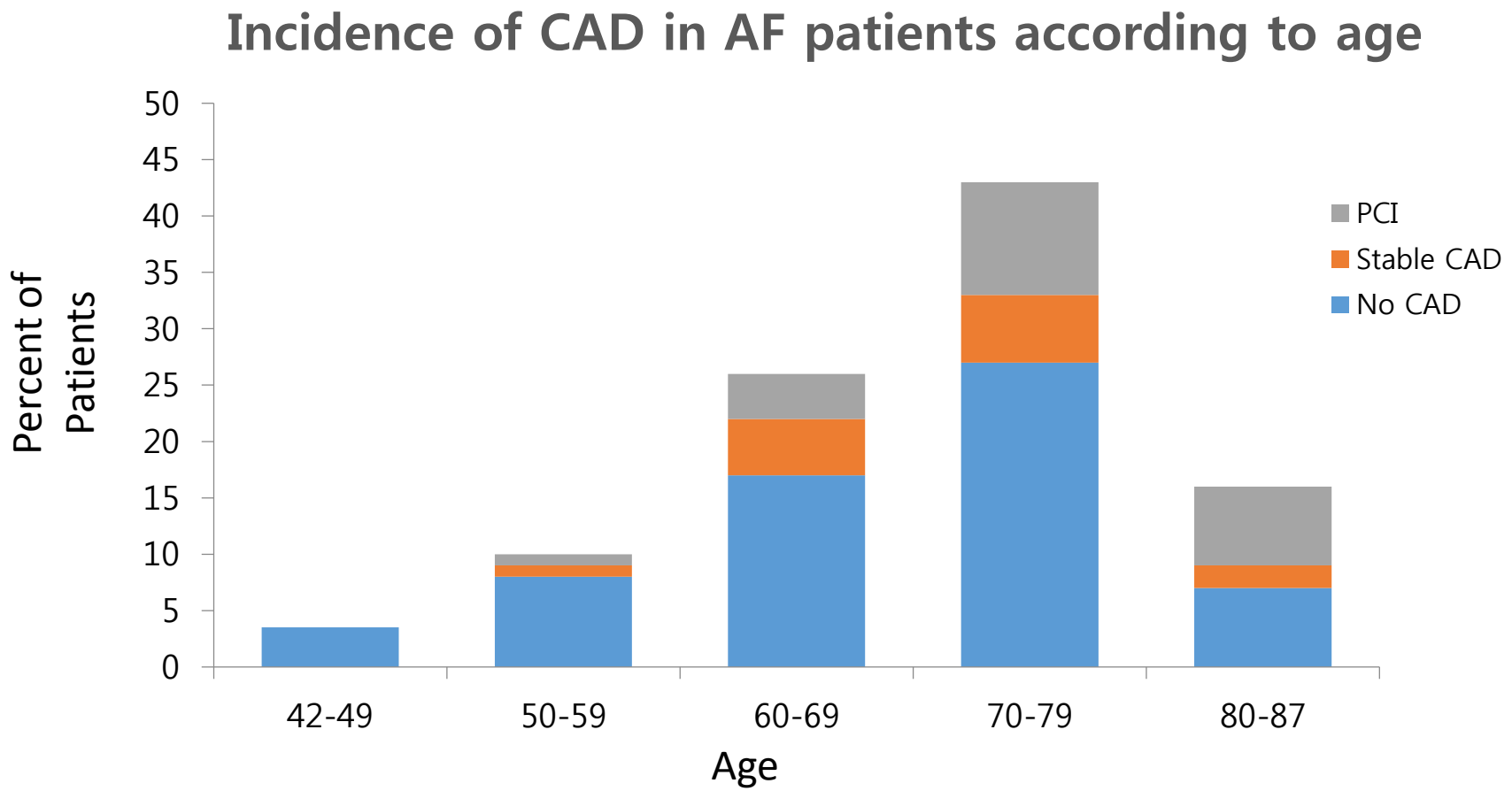
- High CAD prevalence of **18%~46.5%** in AF Patients



CAD, coronary artery disease; PCI, percutaneous coronary intervention.
PLoS ONE 6(9): e24964

Comorbid of CAD in AF patients

- Incidence of CAD in > 70 years of AF was even 41%



CAD, coronary artery disease; PCI, percutaneous coronary intervention.
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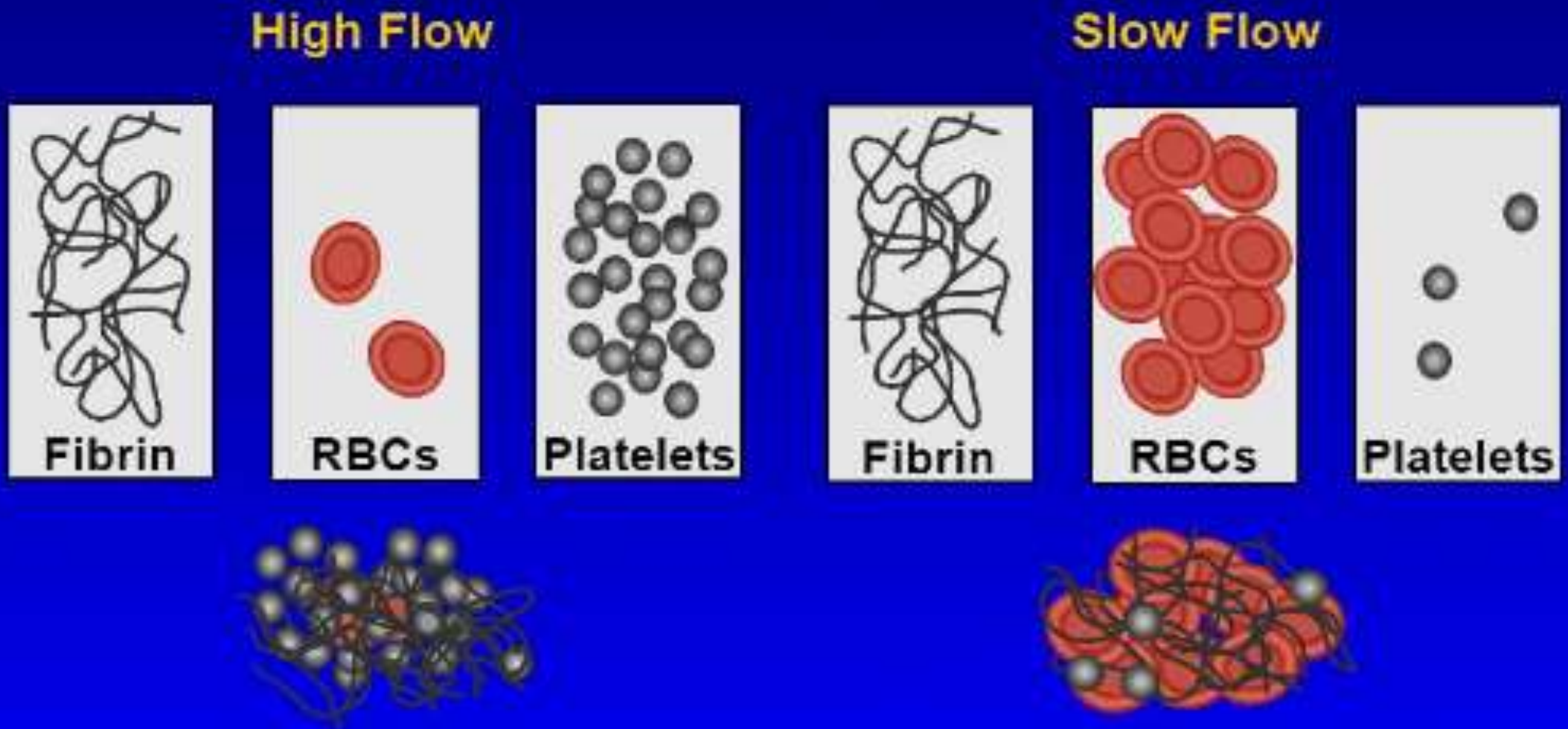
Platelets: Role in Thrombosis



RBCs, red blood cells.

What is the optimal treatment for AF and CAD?

OAC alone *vs.* OAC + Antiplatelet strategy

Major complications in AF	Major clinical events associated with CAD
Stroke and SEE	MI and CV death

OAC

More effective for **moderate-to-high risk AF to prevent stroke and SEE.**

Antiplatelet

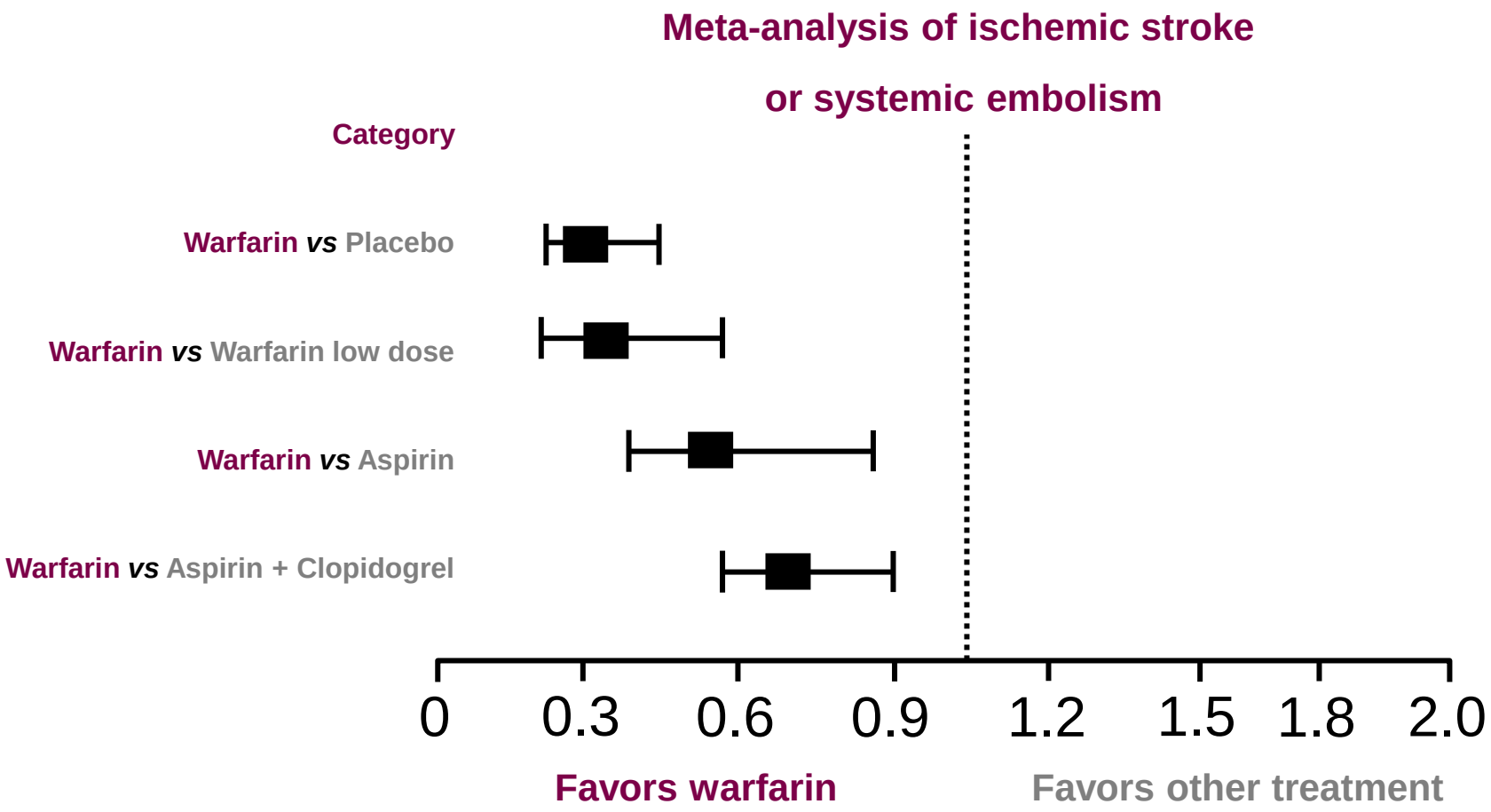
The standard management for CAD **to reduce the risk of coronary events.**

CAD, coronary artery disease; AF, atrial fibrillation; SEE, systemic embolic events; MI, myocardial infarction; CV, cardiovascular; OAC, oral anticoagulation.

PLoS ONE 6(9): e24964; http://www.acc.org/latest-in-cardiology/articles/2014/07/18/15/34/antithrombotic-therapy-for-patients-with-both-stable-cad-and-afib

AF Trials

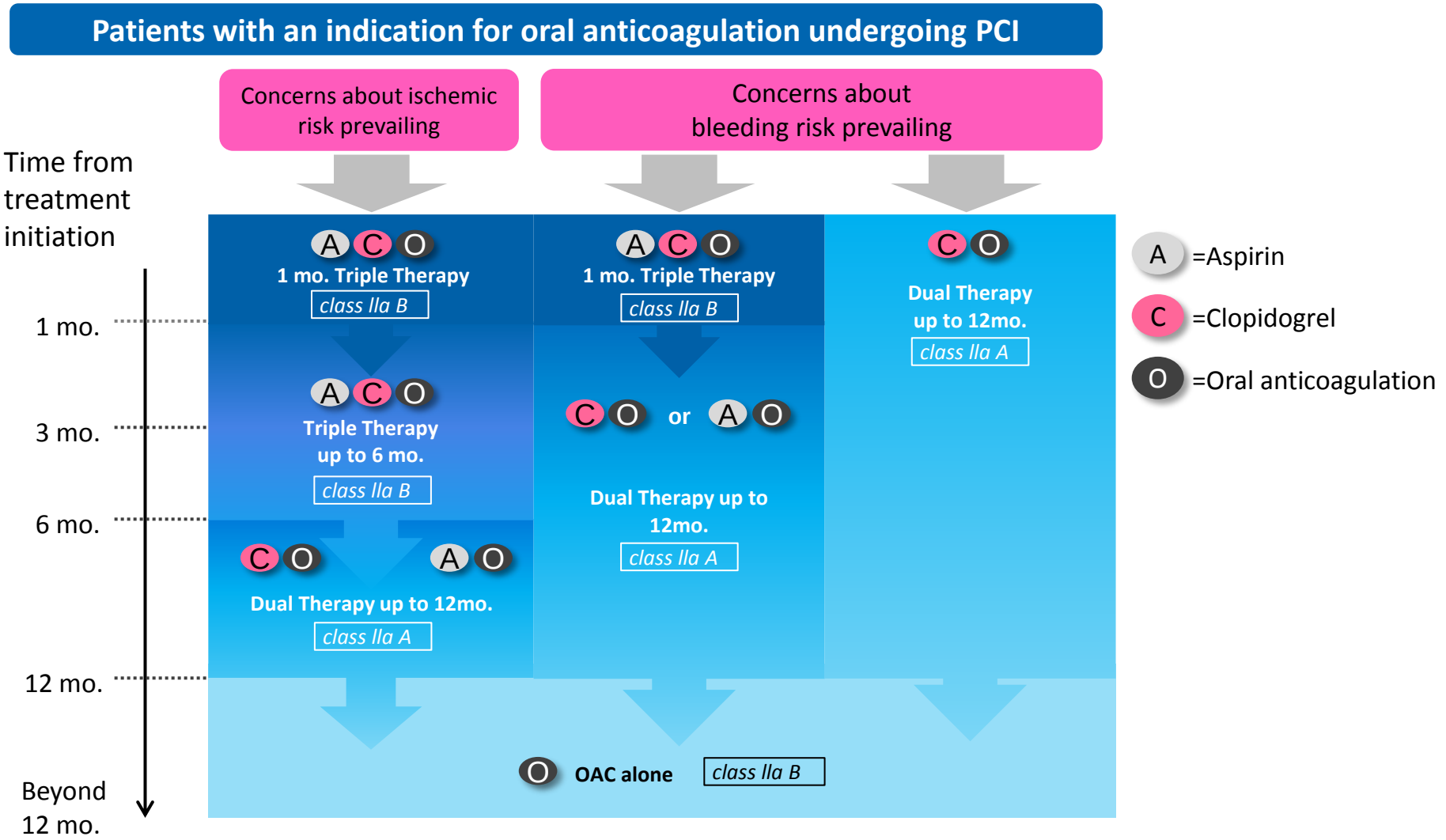
Warfarin (Vitamin K OAC) *vs.* Anti-platelets



JAMA 2001;2864:2870

2017 ESC Guideline

- Algorithm for dual antiplatelet therapy (DAPT) in patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention(PCI)



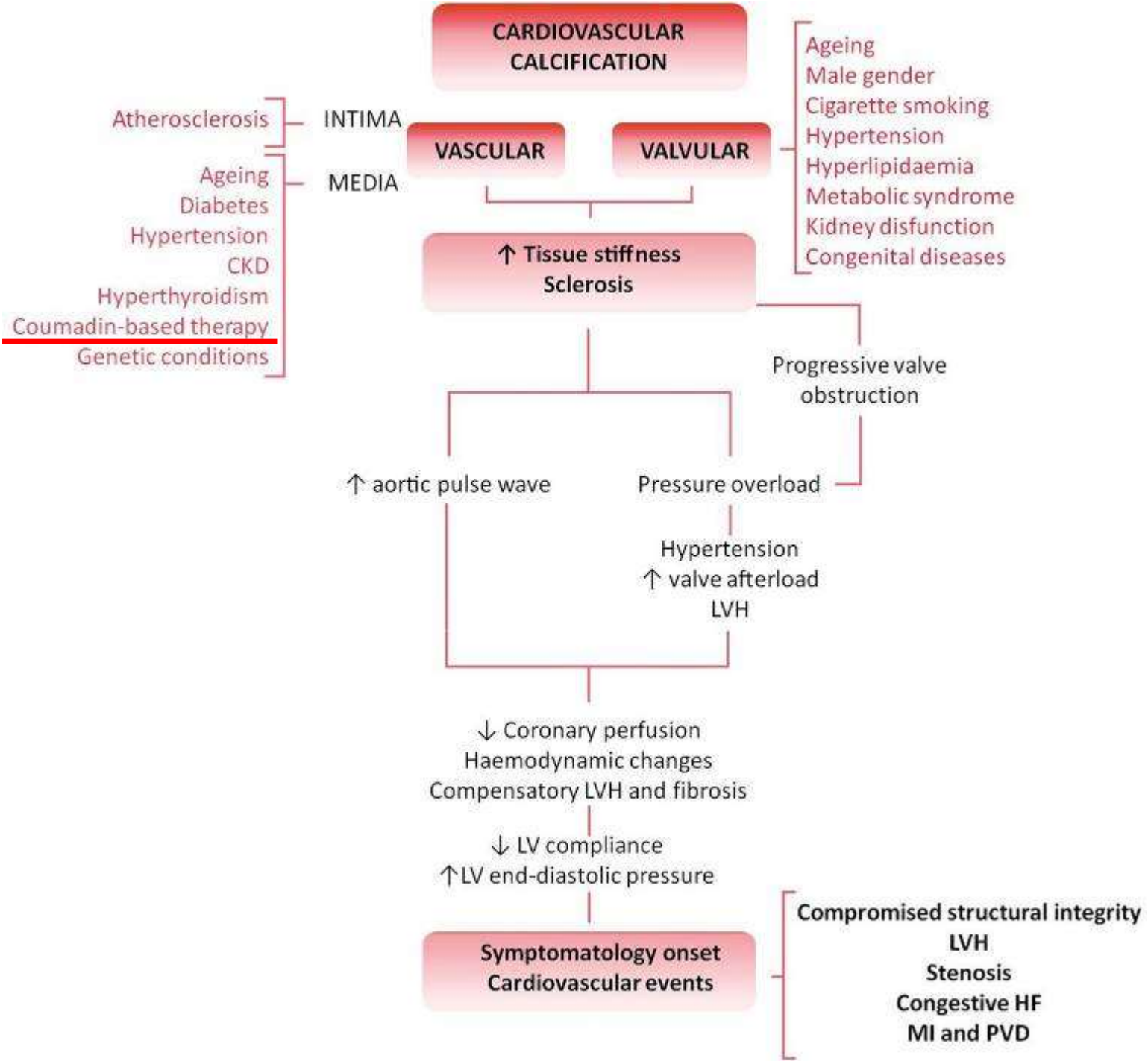
2017 ESC Focused Update on DAPT in Coronary Artery Disease, developed in collaboration with EACTS
(European Heart Journal 2017 –doi: 10.1093/eurheartj/ehx419

Table 4. Guideline recommendations for anticoagulant and antiplatelet therapy for patients with atrial fibrillation after coronary stenting or acute coronary syndrome.

Recent ACS/ CS	ESC guideline [36]	ACC/AHA guidelines
ACS	*Bleeding risk low*: TT for up to 6 months [IIaB], followed by OAC + platelet inhibitor (aspirin or clopidogrel) for up to 6 months [IIaA] *Bleeding risk high*: TT for 1 month[a] [IIaB], followed by OAC + platelet inhibitor (aspirin or clopidogrel) for up to 11 months [IIaA]	*NSTE-ACS* [42]: The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor in patients with NSTE-ACS should be minimized to the extent possible to limit the risk of bleeding [IC]. *STEMI* [43]: The duration of triple antithrombotic therapy with a vitamin K antagonist, aspirin, and a $P2Y_{12}$ receptor inhibitor should be minimized to the extent possible to limit the risk of bleeding [IC]. DES [25]: In patients with ACS treated with DAPT after DES implantation who develop a high risk of bleeding (e.g. treatment with oral anticoagulant therapy), discontinuation of $P2Y_{12}$ inhibitor therapy after 6 months may be reasonable [IIbC].
Elective CS	*Bleeding risk low*: TT for 1 month (IIaB)[a], followed by OAC + platelet inhibitor (aspirin or clopidogrel) for up to 11 months [IIaA]. *Bleeding risk high*: TT for 1 month [IIaB], followed by OAC + platelet inhibitor for up to 11 months (aspirin or clopidogrel) [IIaA]. Dual therapy with OAC + clopidogrel for up to 12 months [IIaA] is an alternative if the bleeding risk outweighs the ischemic risk	DES [25]: In patients with SIHD treated with DAPT after DES implantation who develop a high risk of bleeding (e.g. treatment with oral anticoagulant therapy), are at high risk of severe bleeding complication (e.g. major intracranial surgery), or develop significant overt bleeding, discontinuation of $P2Y_{12}$ inhibitor therapy after 3 months may be reasonable. [IIbC]
Stable CAD (one year after CS/ ACS)	OAC monotherapy[a] [IIaB]	Warfarin should be administered [IA] (Note: Patients receiving low-dose aspirin for atherosclerosis should continue to receive it) [44,45].

Squared brackets indicate class of recommendation and level of evidence as defined by the guidelines.
[a]TT can be extended for up to 6 months if the ischemic risk is increased (e.g. due to anatomical/procedural features).
ESC: European Society of Cardiology; ACC/AHA: American College of Cardiology/American Heart Association; ACS: acute coronary syndrome; CS: coronary stenting; TT: triple therapy; OAC: oral anticoagulant; NSTE-ACS: non-ST-elevation-acute coronary syndrome; STEMI: ST-elevation myocardial infarction; DES: drug-eluting stent; SIHD: stable ischemic heart disease; DAPT: dual antiplatelet therapy; CAD: coronary artery disease.

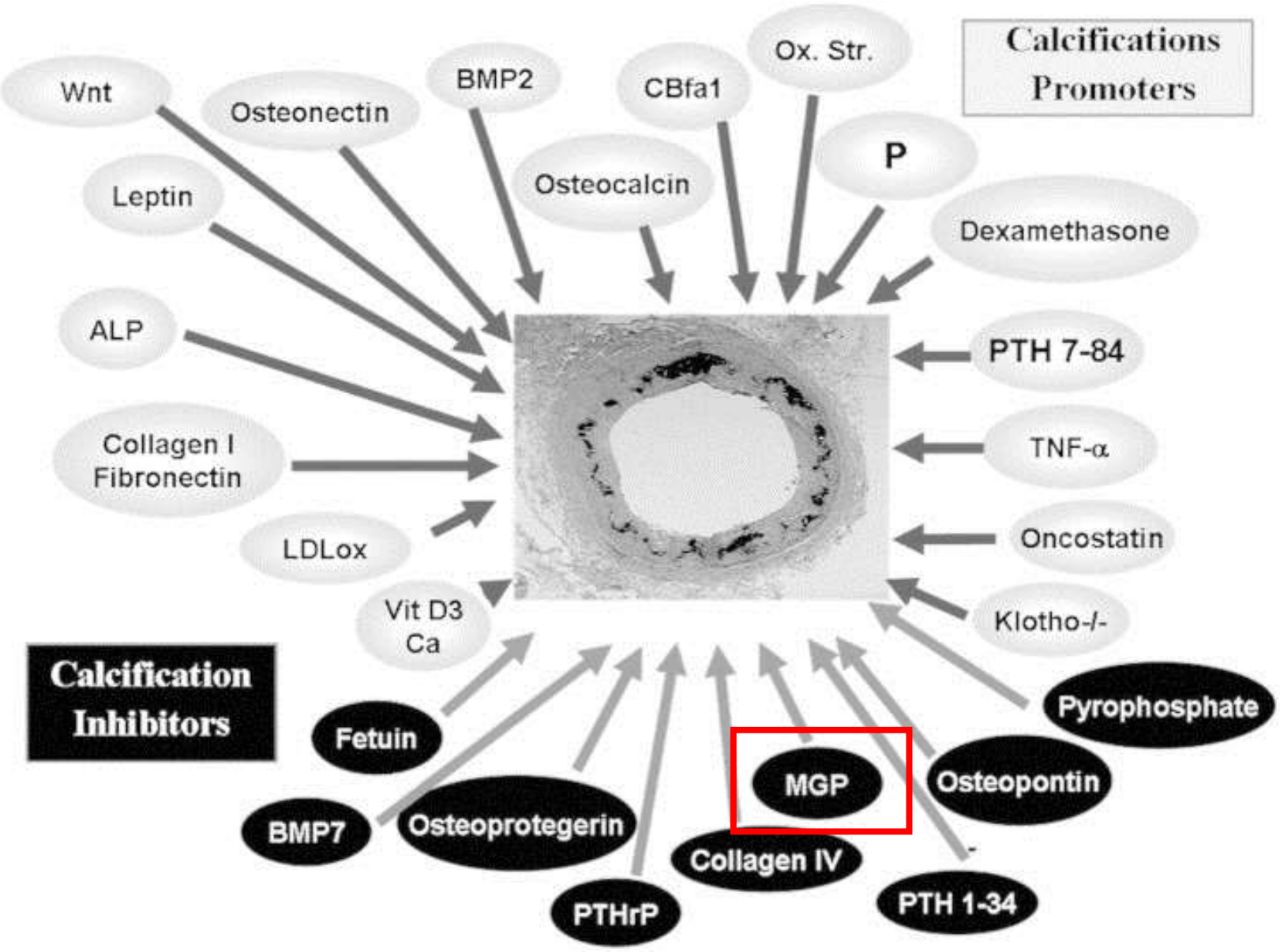
Effect of long-term treatment of VKA (Warfarin) on vascular structure



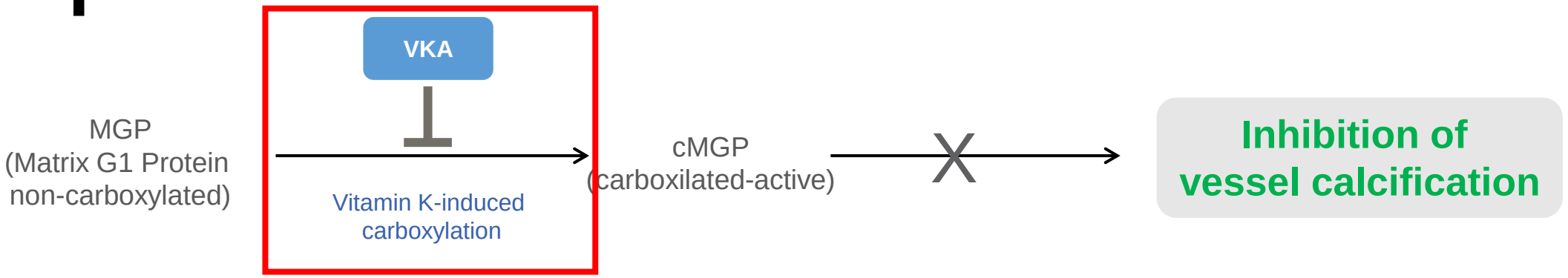
Differential pathology and clinical impact of valvular *vs.* vascular calcification flowchart.

Cardiovascular calcification is an active and degenerative bone-like process affecting the cardiovascular tissues. Both vessels and valves show an athero-inflammatory background and, despite the commonalities and overlap of several risk factors (such as aging, hyperlipidaemia or kidney disease), both atherosclerosis and calcific VHD are two independent pathologic entities. The biological progression of the disease, tissue characteristics and clinical impact stand those differences. The result is the independent plaque rupture primary outcome found in the progression of VHD. An increased stiffness or sclerosis induces an increased aortic pulse wave, triggering hypertension, and a reduction in coronary perfusion. Besides, the pressure overload caused by a sclerotic pre-stadium and observed in the progression of the VHD leads to LV structural and hemodynamic changes. Symptomatology onset and calcification burden are poor prognosis predictors associated with multiple adverse cardiovascular complications, such as left ventricular hypertrophy (LVH), aortic valve stenosis, congestive heart failure (HF), ascending aorta aneurysm, myocardial infarction (MI), and peripheral vascular disease (PVD).

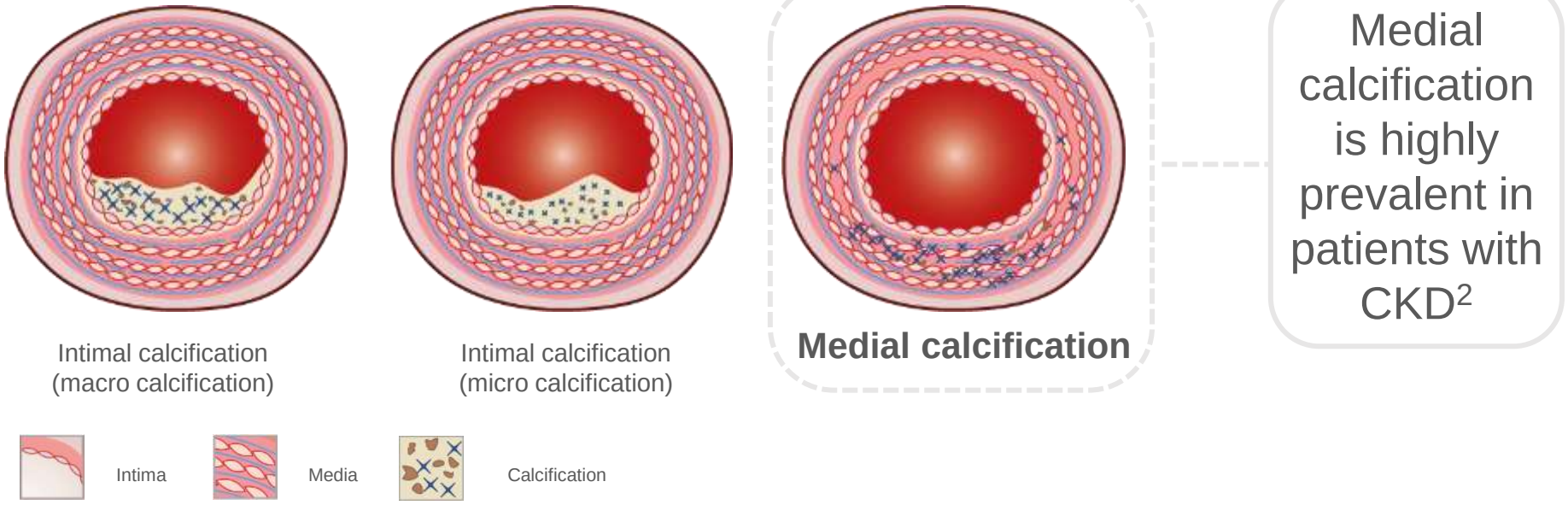
Medial and Intimal Vascular Calcification



MGP prevents Medial and Intimal Calcification



MGP is the main inhibitor of vascular calcification, and vitamin K is required for full activity of MGP[1]

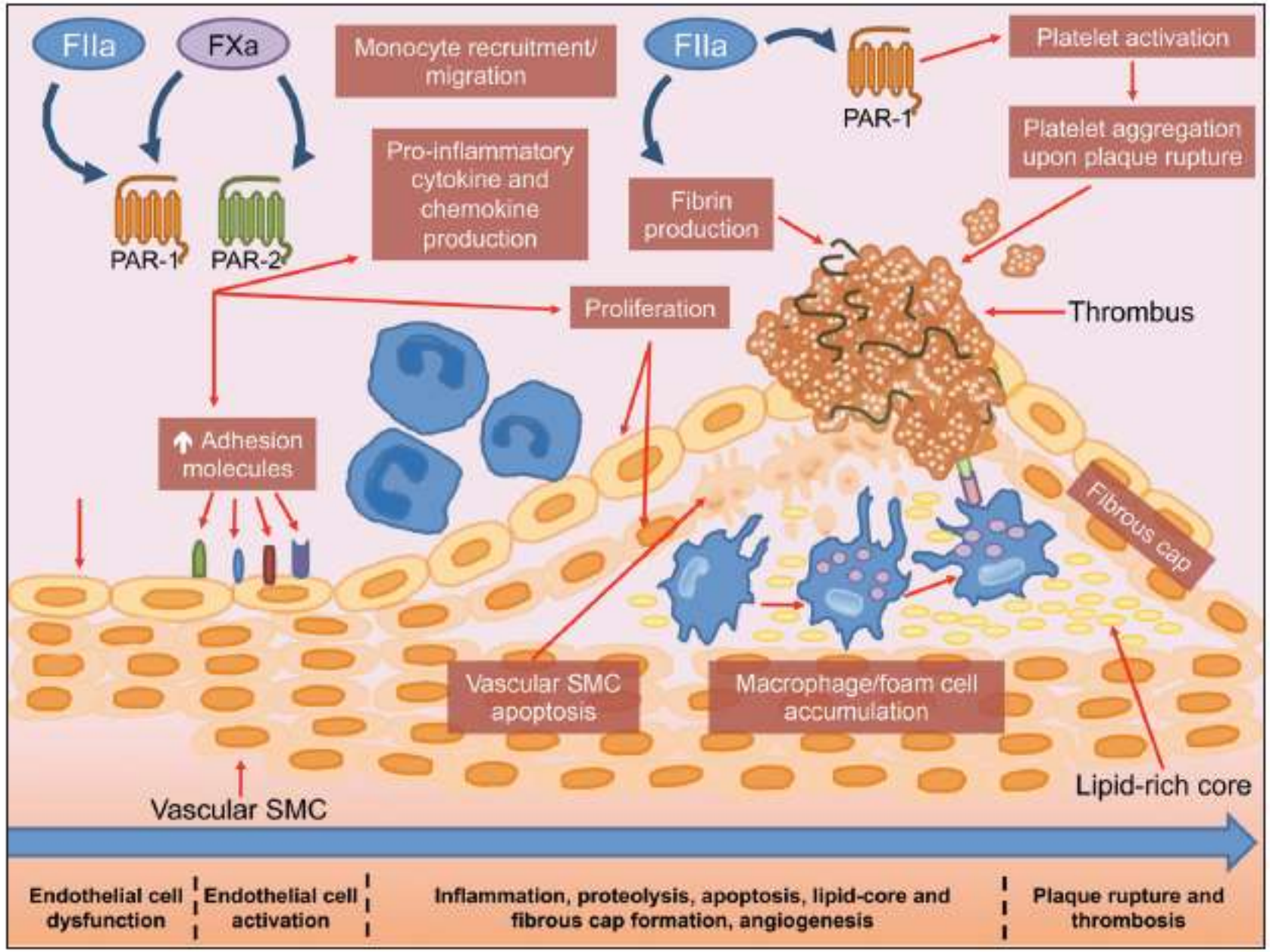


Medial calcification is highly prevalent in patients with CKD[2]

1. Van Gorp RH, Schurgers LJ. *Nutrients* 2015;7:9538–9557; 2. Willems BAG et al. *Mol Nutr Food Res* 2014;58:1620–1635.

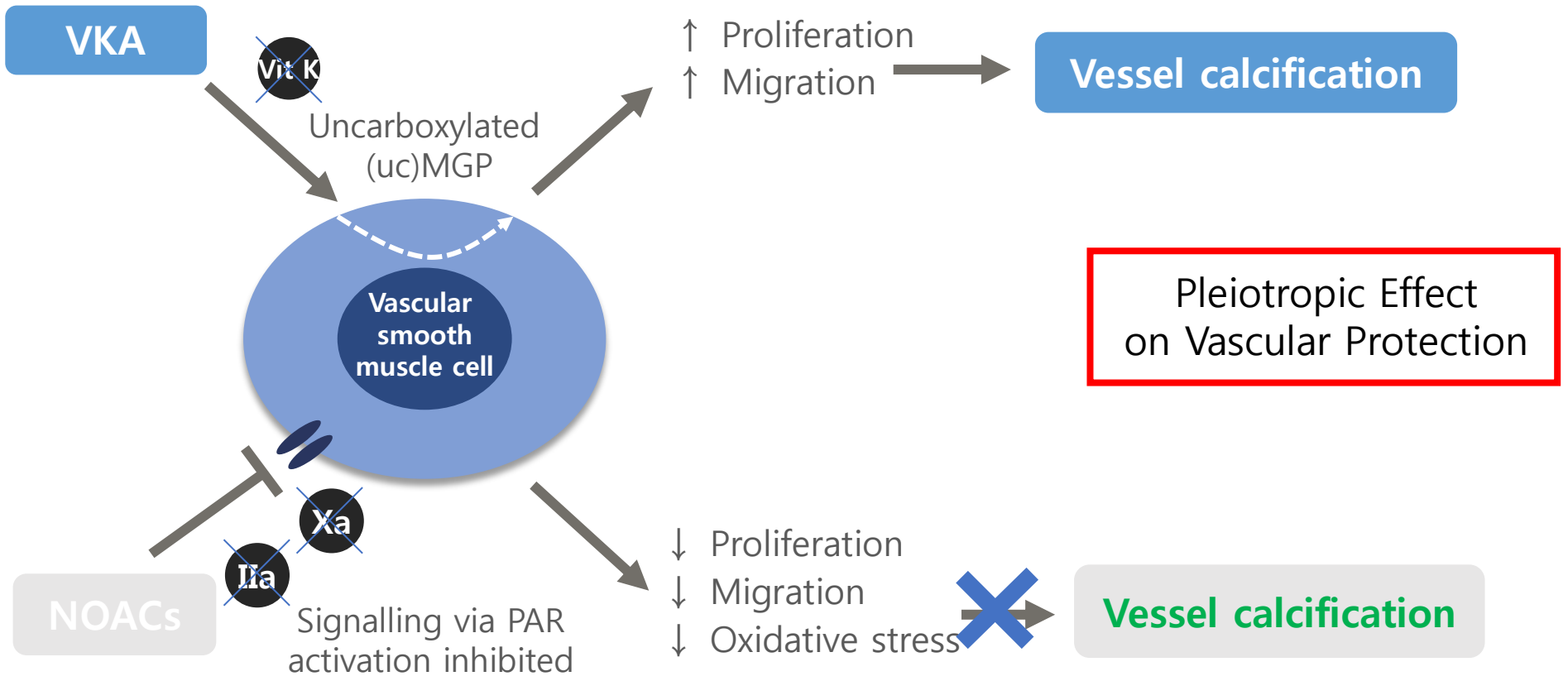
Pleiotropic effect of NOACs on vascular structure

Figure 4: Overview of pathophysiology of atherothrombosis and the role of factor Xa and thrombin. Dysregulation of endothelial cells forms the basis for the initial development of atherosclerosis and plaques develop through the accumulation of lipid deposits and foam cells. Increased expression of adhesion molecules and release of pro-inflammatory cytokines by activated endothelial cells promotes recruitment of blood cells. The sustained inflammation reduces plaque stability and promote plaque rupture. Both factor Xa and thrombin contribute to the development of atherothrombosis. F, factor; PAR, proteinase-activated receptor; SMC, smooth muscle cell.



PAR: proteinase-activated receptor

NOACs have vascular protection effect



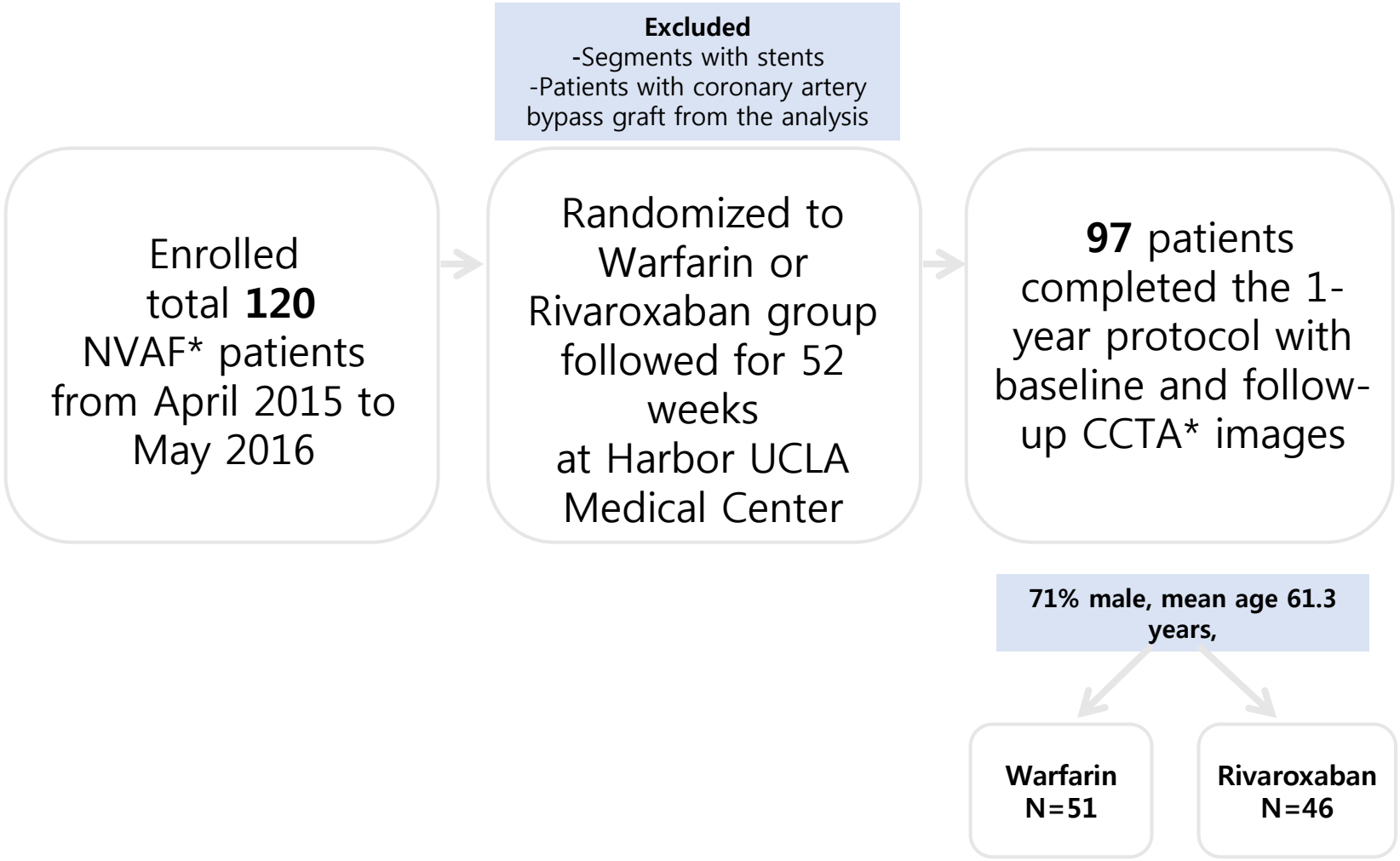
In pre-clinical study, it was found that factor Xa inhibitors may have anti-inflammatory effects by inhibiting PAR2-mediated pro-inflammatory signaling pathway. However, further studies are needed to confirm the mechanisms responsible for these renal outcomes of NOAC.

1. Van Gorp RH, Schurgers LJ. *Nutrients* 2015;7:9538–9557.

Randomized trial of Rivaroxaban *vs.* warfarin in the evaluation of progression of coronary atherosclerosis

Am Heart J 2018;127–130

Study Design



NVAF: non valvular atrial fibrillation; CCTA: coronary computed tomography angiography

Am Heart J 2018;127–130.

Baseline characteristics

	Warfarin (n = 51)	Rivaroxaban (n = 46)	P value
Age, y	60.2 ± 11.7	62.5 ± 10.5	0.294
Male, n (%)	39 (76.5%)	30 (65.2%)	0.222
BMI*, kg/m^2	32.3 ± 7.6	33.6 ± 7.2	0.401
Hypertension, n (%)	49 (96.1%)	40 (87.0%)	0.145
Diabetes mellitus, n (%)	22 (43.1%)	14 (30.4%)	0.196
Dyslipidemia, n (%)	37 (72.5%)	31 (67.4%)	0.580
Current smoking, n (%)	4 (7.8%)	6 (13%)	0.510
Statin use, n (%)	31 (60.8%)	30 (65.2%)	0.652
Family history, n (%)	21 (41.2%)	23 (50.0%)	0.383
Laboratory finding			
Creatinine, mg/dL	1.3 ± 1.3	1.1 ± 0.8	0.289
Total cholesterol, mg/dL	145.9 ± 40.7	154.3 ± 42.5	0.385
High-density lipoprotein,mg/dL	41.2 ± 11.6	41.8 ± 10.7	0.786
Low-density lipoprotein,mg/dL	78.8 ± 42.8	71.6 ± 45.8	0.426
Triglyceride, mg/dL	136.9 ± 87.4	171.7 ± 102.6	0.075
INR*	2.52 ± 0.98	-	-

BMI; body mass index INR: international normalized ratio;

Am Heart J 2018;127–130.

Results

Difference in plaque volumes between baseline and follow-up between Warfarin and Rivaroxaban groups

	Warfarin (n = 51)	Rivaroxaban (n = 46)	P value
Absolute PV* change (mm^3)			
Total □	40.5 (9.6-97.3)	26.3 (4.5-61.5)	.123
Noncalcified □	30.1 (2.3-72.3)	20.1 (0.3-45.5)	.259
Fibrous □	**13.9 (0-48.4)**	**0.2 (−13.4 to 29.3)**	**.035**
Fibrous fatty □	2.9 (0-23.6)	9.8 (0-26.8)	.582
Low attenuation □	0.2 (0-4.2)	1.2 (−0.2 to 10.6)	.475
Calcified □	3.9 (0-29.2)	0.8 (0-9.8)	.220
Normalized PV change (mm^3)			
Total □	51.1 (12.1-94.7)	26.9 (5.4-62.8)	.120
Noncalcified □	30.1 (2.2-74.6)	19.0 (0.2-57.5)	.236
Fibrous □	**14.6 (0-55.0)**	**0.2 (−14.5 to 26.3)**	**.035**
Fibrous fatty □	3.6 (0-19.3)	8.0 (0-27.3)	.633
Low attenuation □	0.2 (0-4.4)	1.1 (−0.2 to 10.2)	.460
Calcified □	3.6 (0-29.0)	0.8 (0-12.0)	.203

Data are presented as median (interquartile range)

PV: plaque volume;

Am Heart J 2018;127–130.

Risk of Myocardial Infarction in Anticoagulated Patients With Atrial Fibrillation

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ABSTRACT

BACKGROUND Evidence is conflicting as to the efficacy of direct oral anticoagulation (DOAC) and vitamin K antagonist (VKA) for prevention of myocardial infarction (MI).

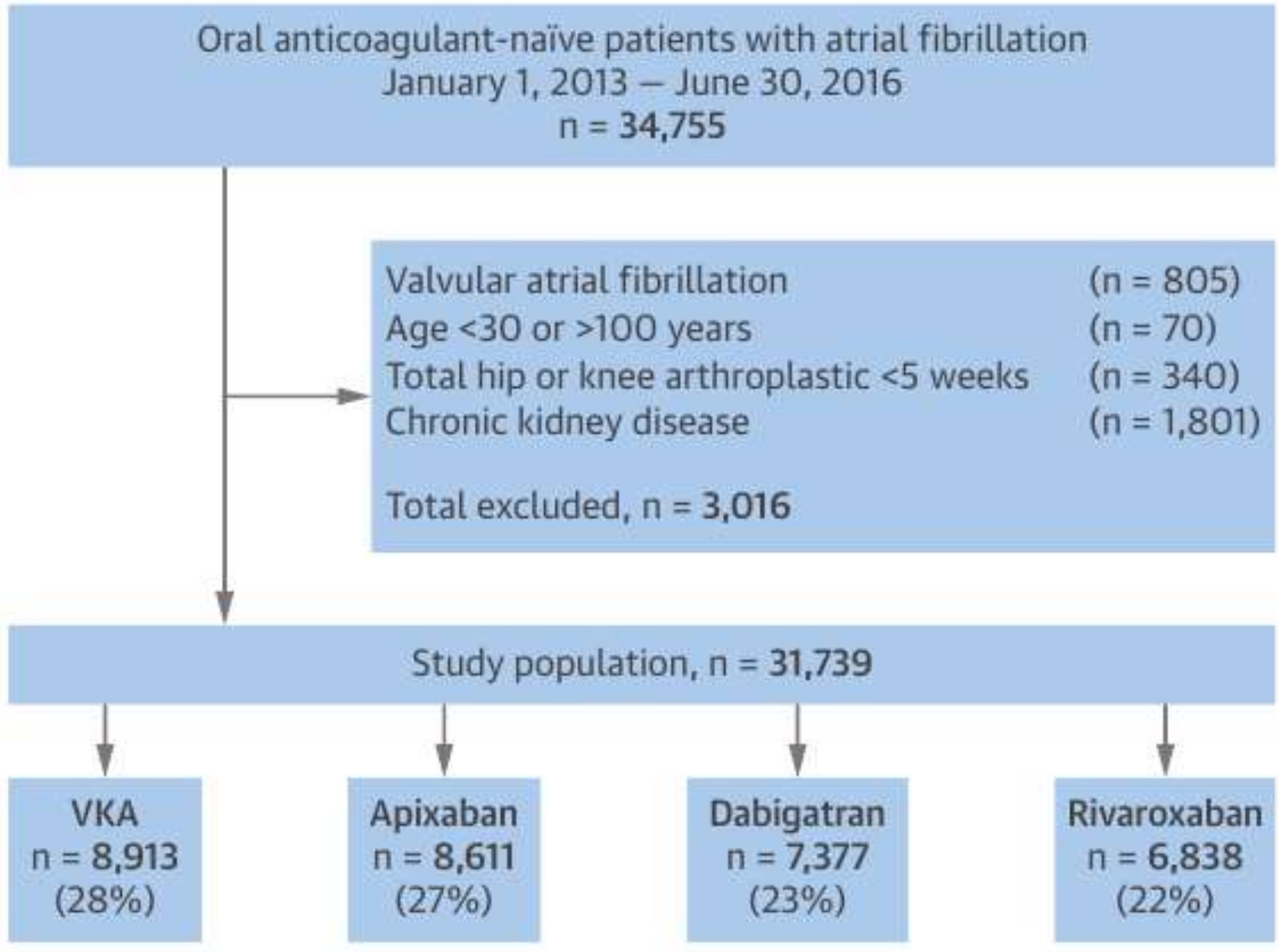
OBJECTIVES This study aimed to investigate the risk of MI associated with the use of apixaban, dabigatran, rivaroxaban, and VKA in patients with atrial fibrillation.

METHODS Patients with atrial fibrillation were identified using Danish health care registers and stratified by initial oral anticoagulant treatment. Standardized absolute 1-year risks were estimated based on Cox regression for hazard rates of MI hospitalizations and mortality. Reported were absolute risks separately for the oral anticoagulation treatments and standardized to the characteristics of the study population.

RESULTS Of the 31,739 patients included (median age, 74 years; 47% females), the standardized 1-year risk of MI for VKA was 1.6% (95% confidence interval [CI]: 1.3 to 1.8), apixaban was 1.2% (95% CI: 0.9 to 1.4), dabigatran was 1.2% (95% CI: 1.0 to 1.5), and rivaroxaban was 1.1% (95% CI: 0.8 to 1.3). No significant risk differences were observed in the standardized 1-year risks of MI among the DOACs: dabigatran versus apixaban (0.04%; 95% CI: −0.3 to 0.4), rivaroxaban versus apixaban (0.1%; 95% CI: −0.4 to 0.3), and rivaroxaban versus dabigatran (−0.1%; 95% CI: −0.5 to 0.2). The risk differences for DOACs versus VKA were all significant: −0.4% (95% CI: −0.7 to −0.1) for apixaban, −0.4% (95% CI: −0.7 to −0.03) for dabigatran, and −0.5% (95% CI: −0.8 to −0.2) for rivaroxaban.

CONCLUSIONS No significant risk differences of MI were found in the direct comparisons of DOACs, and DOACs were all associated with a significant risk reduction of MI compared with VKA. (J Am Coll Cardiol 2018;72:17–26)

FIGURE 1 Selection of Study Cohort



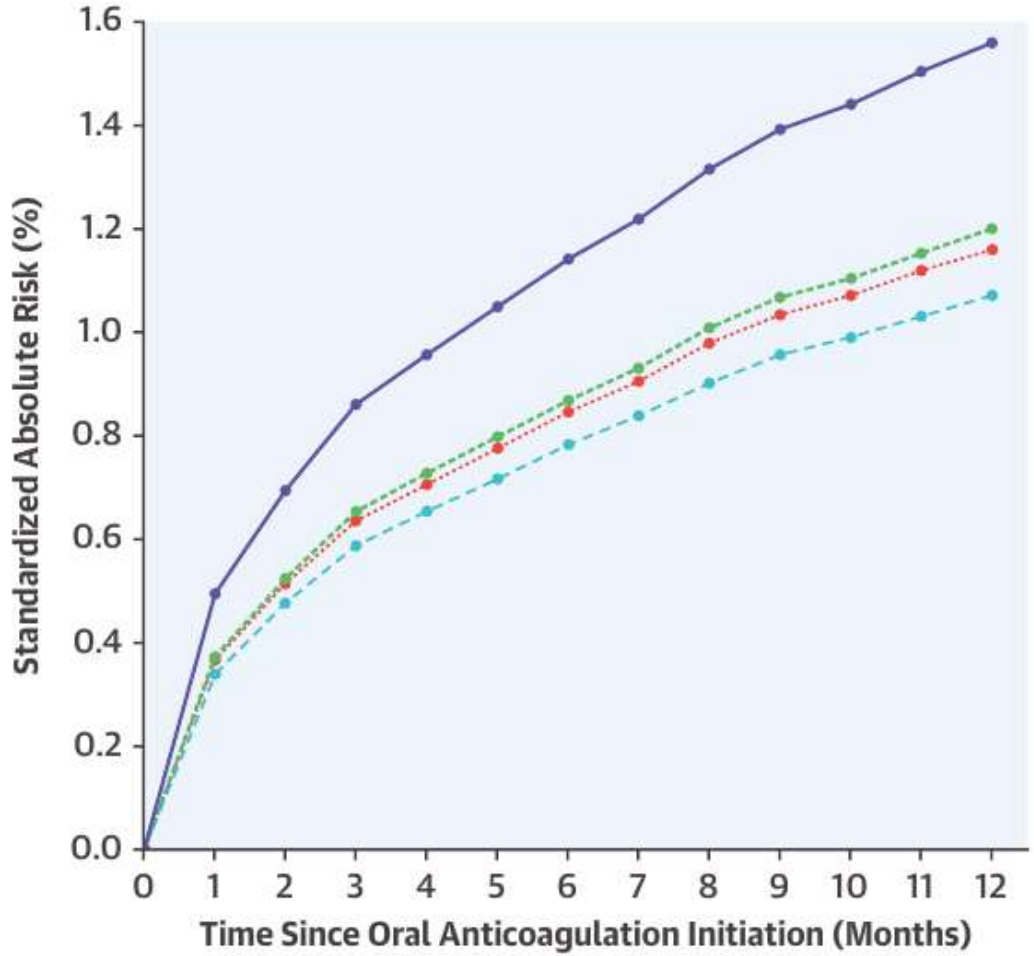
CENTRAL ILLUSTRATION Oral Anticoagulation Therapy and Risk of MI in Patients With Atrial Fibrillation

Standardized Absolute Risk of MI Within 1-Year

In patients with nonvalvular atrial fibrillation:

What is the risk of MI when treated with the following oral anticoagulants?

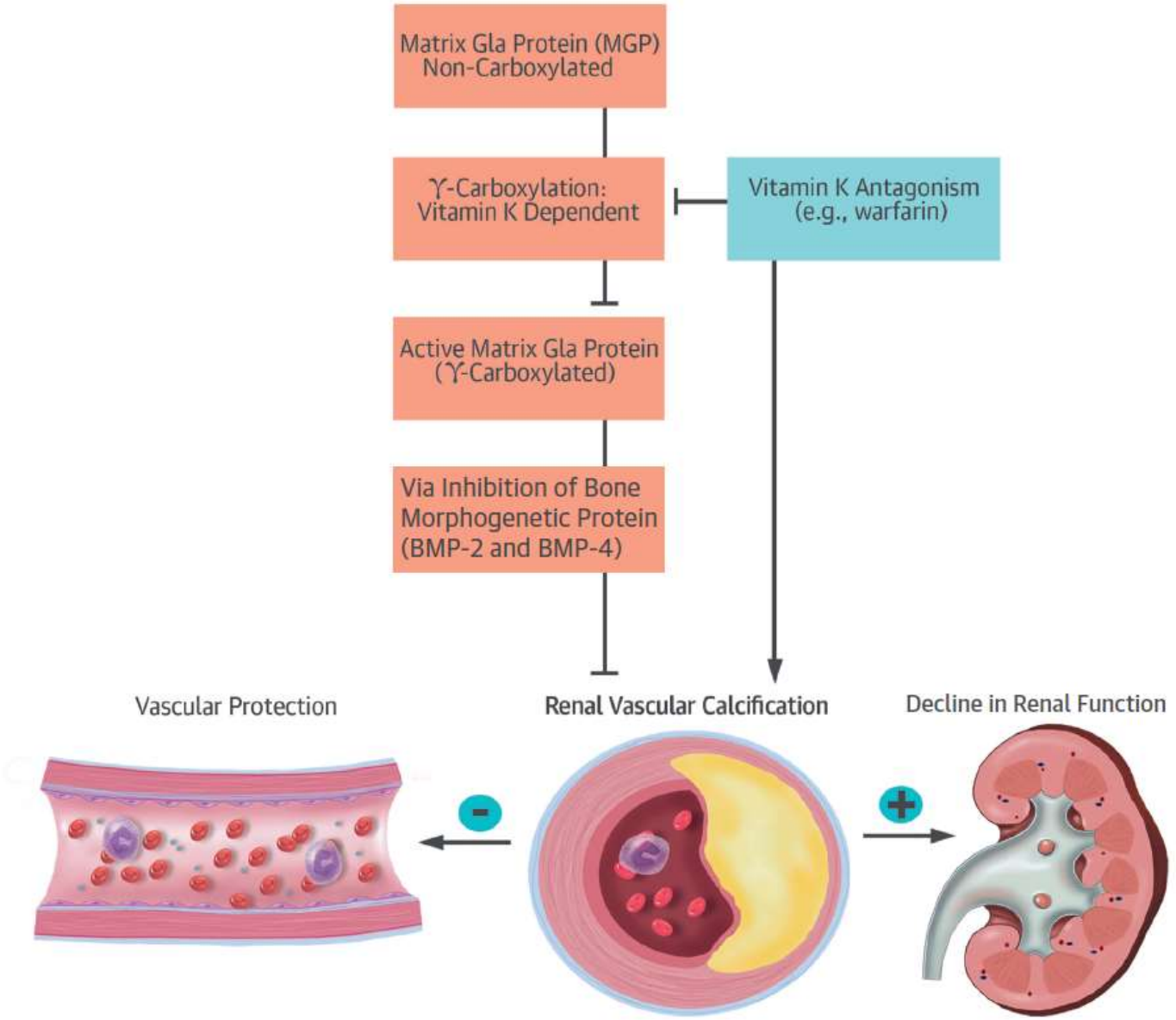
- Apixaban
- Dabigatran
- Rivaroxaban
- Vitamin K Antagonist



Lee, C.J.-Y. et al. J Am Coll Cardiol. 2018;72(1):17-26.

Patients with atrial fibrillation have a higher risk of myocardial infarction (MI), and the optimal prevention of MI with oral anticoagulative therapy is unknown. Our study finds no significant difference in the standardized absolute 1-year risk for MI in the direct comparison of the direct oral anticoagulants. Furthermore, all the direct oral anticoagulants were associated with a significantly lower standardized absolute risk of MI than vitamin K antagonists.

NOACs can prevent progressive renal dysfunction



Adapted from Böhm M *et al*, *J Am Coll Cardiol* 2015;65:2481–2493

The risk of acute kidney injury in Asians treated with apixaban, rivaroxaban, dabigatran, or warfarin for non-valvular atrial fibrillation : A nationwide cohort study in Taiwan

Chan YH et al. *Int J Cardiol*. 2018 Aug 15;265:83-89

Result

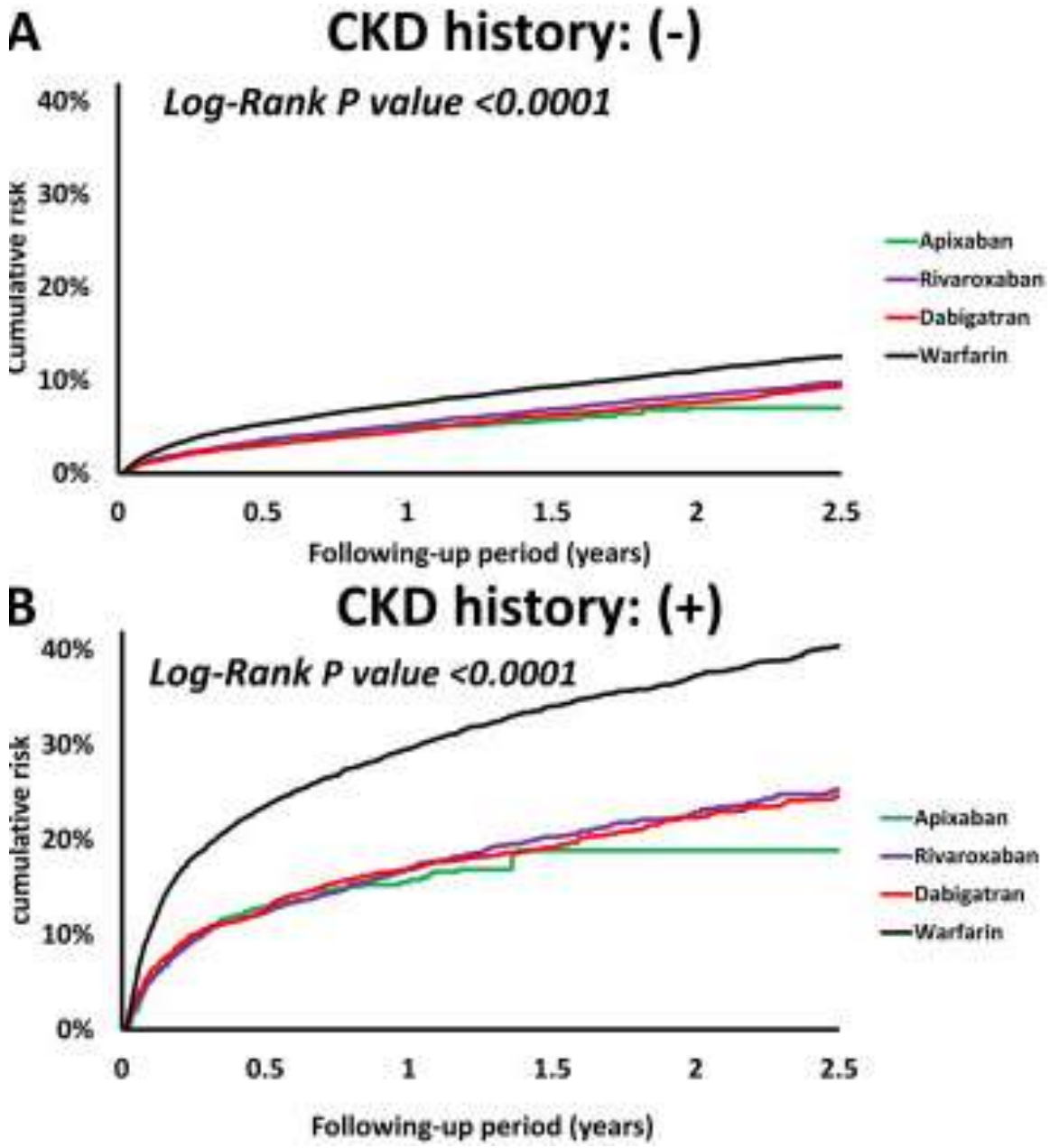
- Three NOACs were all associated with a significantly lower risk of AKI compared with warfarin for both CKD- free and CKD cohort

hazard ratio, [95% confidential interval]

- 0.65, [0.60–0.72] for apixaban
- 0.68, [0.64–0.74] for dabigatran
- **0.73, [0.68–0.79] for rivaroxaban**

and CKD cohorts

- 0.50, [0.45–0.56] for apixaban
- 0.54, [0.49–0.59] for dabigatran
- **0.53, [0.49–0.58] for rivaroxaban**



AKI, acute kidney injury; CKD, chronic kidney disease; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation

Chan YH et al. *Int J Cardiol*. 2018 Aug 15;265:83-89

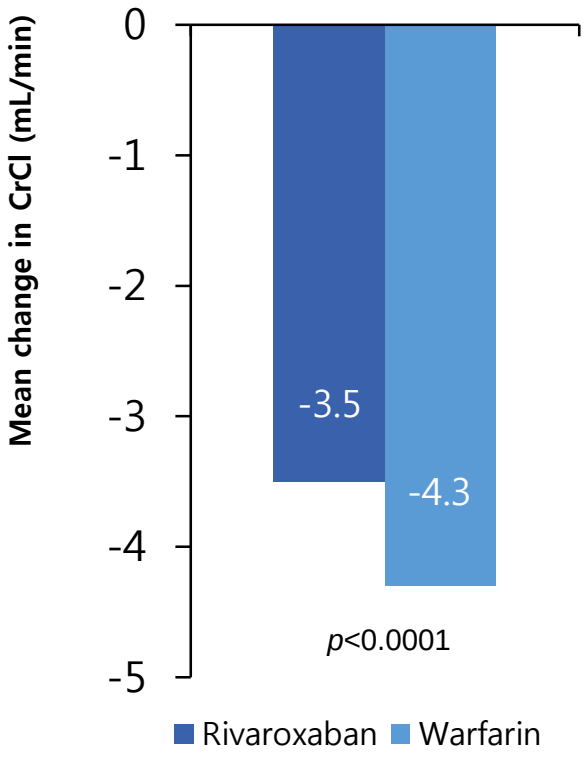
Class Effect of NOACs?

Rivaroxaban was associated with significantly less reduction in CrCl *vs.* warfarin.

ROCKET AF (n=12,612)[1]

CrCl changes over 21 months[2]

Median CrCl at baseline[1] 68 mL/min

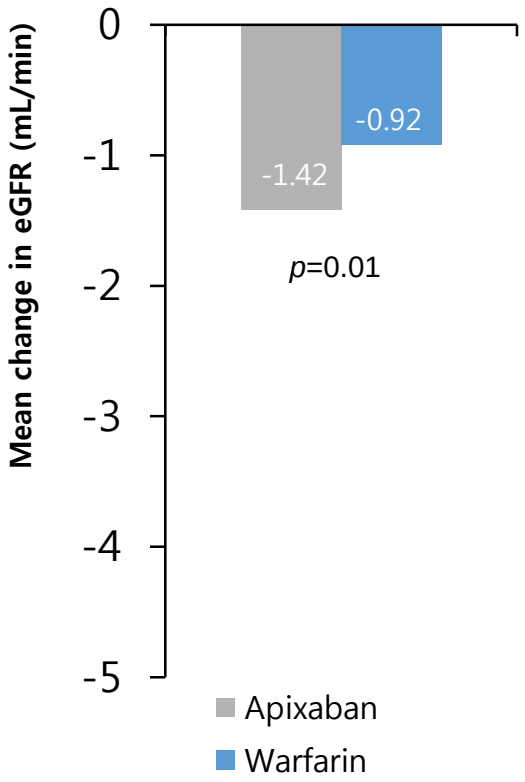


Favours rivaroxaban

ARISTOTLE (n=14,913)[3]

eGFR* changes over 12 months

eGFR at baseline NR

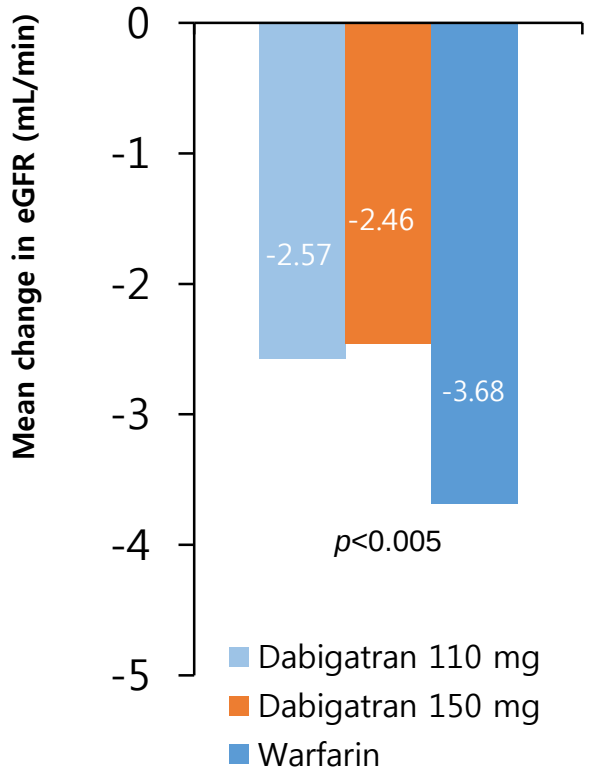


Favours warfarin

RE-LY (n=16,490)[4]

eGFR* changes over 30 months

Mean eGFR at baseline[4] 66 mL/min



Favours dabigatran

Not intended for direct comparison.
*Calculated with CKD-EPI formula.

1. Fordyce CB et al. *Circulation* 2016;134:37–47; 2. Fordyce CB et al. *Circulation* 2016;134:e532–533; 3. Hijazi Z et al. *JAMA Cardiol* 2016;1(4):451–460; 4. Böhm M et al. *J Am Coll Cardiol* 2015;65:2481–2493.

Renal Outcomes in Anticoagulated Patients with AF

Yao X *et al*, *J Am Coll Cardiol* 2017;70:2621–2632

Patient Population

- 9,769 adult patients (≥18 years of age) with NVAF who received an OAC between 1 October 2010 and 30 April 30 2016

Inclusion criteria	Exclusion criteria
◆ Patients were required to have ≥12 months of continuous enrolment in both medical and pharmacy insurance plans before treatment initiation (defined as the baseline period) ◆ Patients with linked serum creatinine results at both baseline and follow-up ◆ New users of OACs	◆ Warfarin-experienced patients ◆ Patients with valvular AF, kidney failure and other indications for NOAC use

Follow-up started from the day after treatment initiation until end of treatment, defined as the earliest date of the following: discontinuation or switch of index medication, end of enrolment in health insurance plans or end of the study period

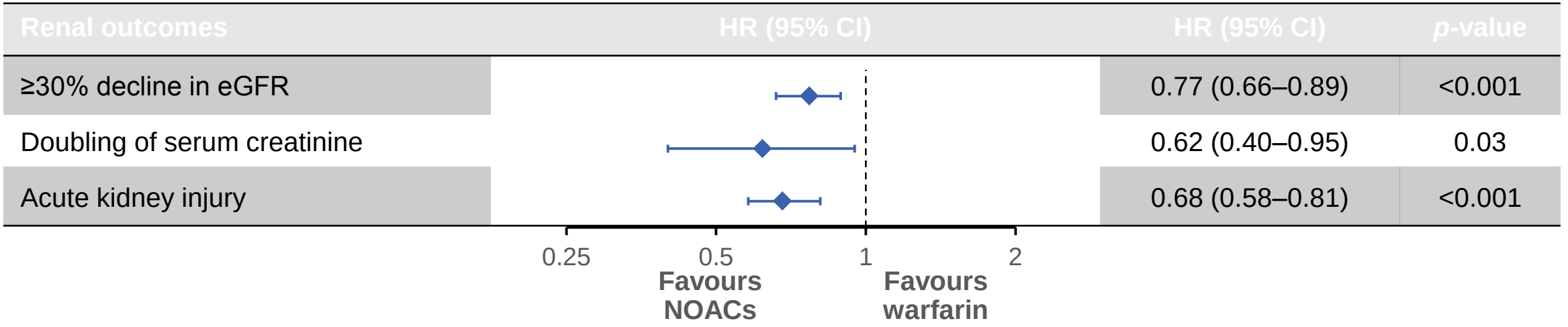
AF, atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; NVAF, non-valvular atrial fibrillation; OAC, oral anticoagulant

Yao et al., Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation. J Am Coll Cardiol. 2017 Nov 28;70(21):2621-2632.

Renal Outcomes – All NOACs

- At 2 years, the cumulative risk was
  - 24.4% for ≥30% decline in eGFR
  - 4.0%, doubling of serum creatinine
  - 14.8% for AKI
  - 1.7% for kidney failure

- Compared with warfarin, the use of NOACs was associated with reduced risks of ≥30% decline in eGFR, doubling of serum creatinine and acute kidney disease

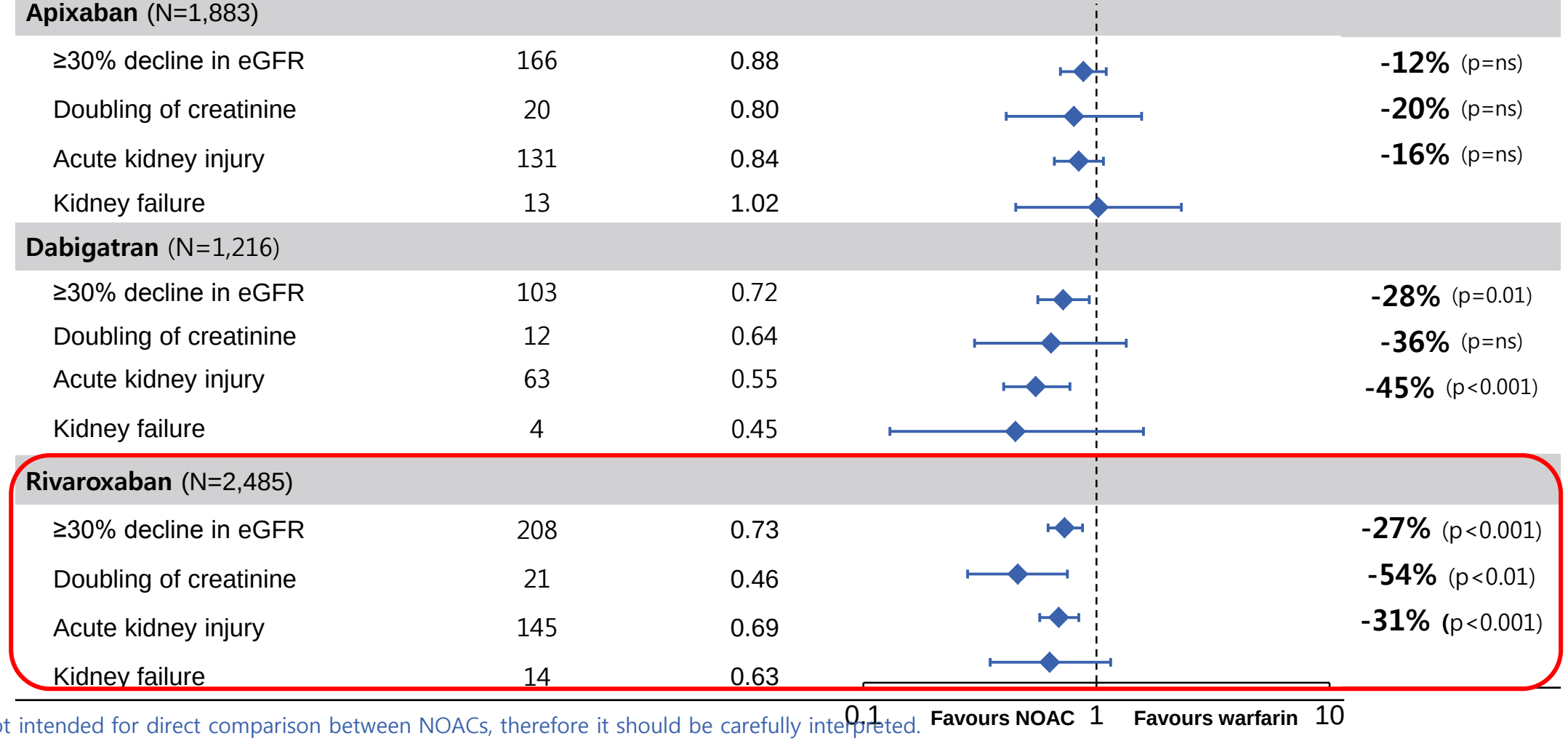


AKI, acute kidney injury; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; NOAC, non-vitamin K antagonist oral anticoagulant

Yao et al., Renal Outcomes in Anticoagulated Patients With Atrial Fibrillation. J Am Coll Cardiol. 2017 Nov 28;70(21):2621-2632.

Real-world Evidence Confirms that Renal Function is Maintained in Patients Receiving Rivaroxaban

Renal outcome	No. of events	HR	HR (95% CI)	RRR
Apixaban (N=1,883)				
≥30% decline in eGFR	166	0.88		**-12%** (p=ns)
Doubling of creatinine	20	0.80		**-20%** (p=ns)
Acute kidney injury	131	0.84		**-16%** (p=ns)
Kidney failure	13	1.02		
Dabigatran (N=1,216)				
≥30% decline in eGFR	103	0.72		**-28%** (p=0.01)
Doubling of creatinine	12	0.64		**-36%** (p=ns)
Acute kidney injury	63	0.55		**-45%** (p<0.001)
Kidney failure	4	0.45		
Rivaroxaban (N=2,485)				
≥30% decline in eGFR	208	0.73		**-27%** (p<0.001)
Doubling of creatinine	21	0.46		**-54%** (p<0.01)
Acute kidney injury	145	0.69		**-31%** (p<0.001)
Kidney failure	14	0.63		



Results are not intended for direct comparison between NOACs, therefore it should be carefully interpreted.

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; RRR, relative risk reduction

Yao X et al. *J Am Coll Cardiol* 2017;70:2621–2632.

Comparative Safety and Effectiveness of NOACs *vs.* Phenprocoumon in Patients with NVAF and Renal Disease – Results from the **RELOADED** Study

NOAC: non-VKA oral anticoagulant; NVAF: Non-Valvular Atrial Fibrillation

Bonnemeier H, Abstract AS25-066 presented at the 5th ESOC, 22-24 May 2019; https://public-poster-links.s3.amazonaws.com/ESOC-2019/ESOC-2019-AS25-066.pdf

Patient Characteristics

	Rivaroxaban		Apixaban		Edoxaban		Phenprocoumon	
	Overall N=22,339	Renal N=5,121(23%)	Overall N=16,201	Renal N=4,750(30%)	Overall N=2,828	Renal N=682(24%)	Overall N=23,552	Renal N=7,289(31%)
Mean age (SD*)	70.7 (12.0)	75.9 (9.4)	73.6 (11.6)	78.5 (9.1)	72.1 (11.4)	77.0 (9.2)	74.1 (9.9)	77.2 (8.4)
Women	41.9%	40.4%	43.9%	44.1%	40.0%	38.3%	41.9%	39.8%
Reduced dose	24.5%	43.4%	33.4%	52.8%	23.0%	42.8%	NA	NA
Mean CHA2DS2-VASc (SD)	3.6 (1.9)	4.6 (1.7)	4.1 (1.9)	5.1 (1.7)	3.7 (1.8)	4.6 (1.6)	4.1 (1.7)	4.9 (1.6)
Mean modified HAS-BLED (SD)	2.5 (1.2)	3.6 (0.9)	2.8 (1.2)	3.8 (0.9)	2.6 (1.2)	3.6 (0.8)	2.8 (1.1)	3.7 (0.8)
Diabetes mellitus	31.3%	48.2%	33.6%	49.1%	30.6%	48.7%	48.7%	50.3%
Chronic heart disease	37.0%	51.3%	39.4%	51.9%	34.7%	47.7%	46.5	59.2%
History of IS*/TIA*/SE*	13.4%	18.5%	21.1%	27.2%	11.8%	15.8%	15.6%	19.7%
History of major bleeding	3.6%	6.6%	4.3%	7.3%	2.8%	5.3%	4.3%	6.8%
Malignant diseases	15.2%	20.6%	16.6%	22.0%	15.3%	21.7%	16.0%	20.2%

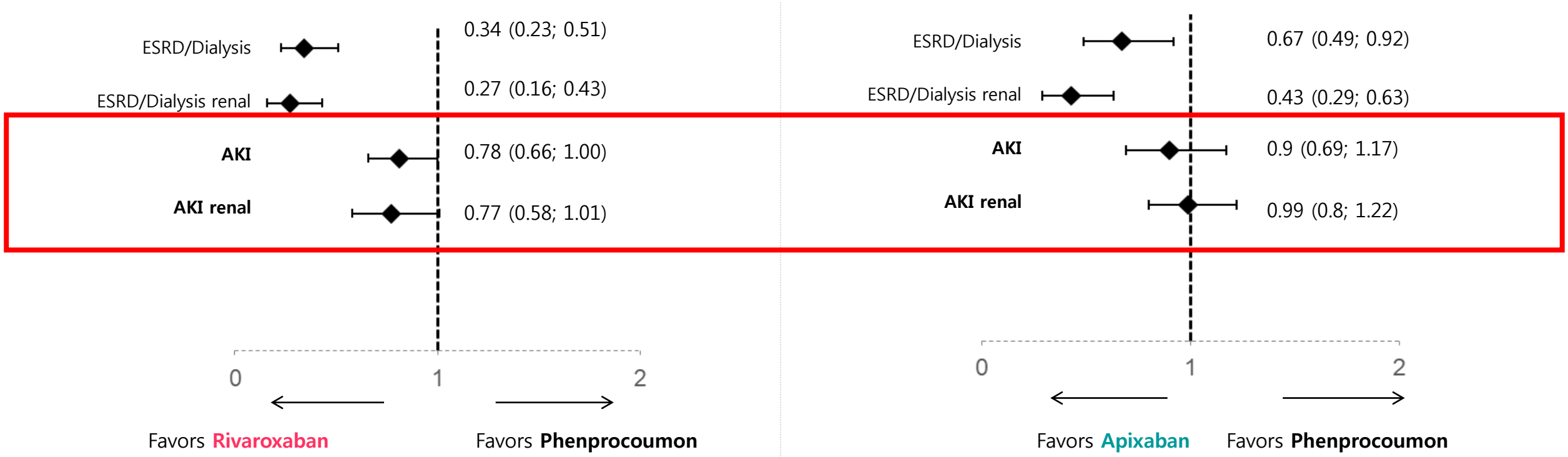
SD: standard devication; IS: ischemic stroke; TIA: transient ischemic attack; SE: systemic embolism

Bonnemeier H, Abstract AS25-066 presented at the 5th ESOC, 22-24 May 2019; https://public-poster-links.s3.amazonaws.com/ESOC-2019/ESOC-2019-AS25-066.pdf

Results

Cox Proportional-Hazard Regression Analysis-adjusted for more than 100 selected baseline covariates

NOAC *vs.* Phenprocoumon



AKI: acute kidney injury; ESRD: end-stage renal disease; ; ICH: intracranial hemorrhage; SE: systemic embolism

Bonnemeier H, Abstract AS25-066 presented at the 5th ESOC, 22-24 May 2019; https://public-poster-links.s3.amazonaws.com/ESOC-2019/ESOC-2019-AS25-066.pdf

Take Home Messages

Compared with VKA,

- **NOACs** have revealed **a significant risk reduction of AMI and AKI** in real world evidences.
- **Rivaroxaban** prevented the **progression of calcified plaque burden** in NVAF patients with stable coronary artery disease.
- **Rivaroxaban** prevented the **renal function decline over time**, however, Apixaban did not show any difference in real world evidences.

OD, once daily; NVAF, non-valvular atrial fibrillation; NOAC, non-vitamin K antagonist oral anticoagulant; CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury