

# Prise en charge du patient en fibrillation atriale et syndrome coronarien aigu

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*IMCVO Décembre 2021*

# Disclosures

**Speaker:** Nicolas Meneveau

I have the following potential conflicts of interest to declare:

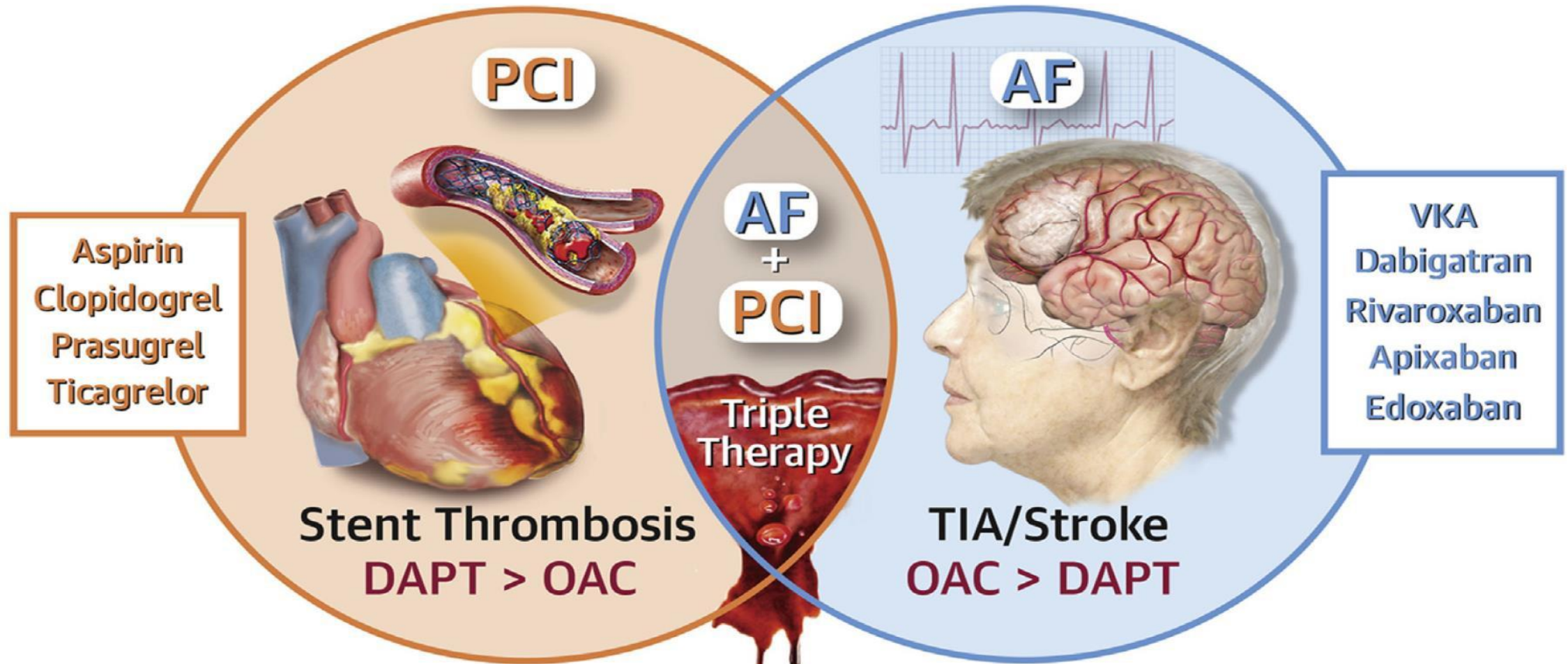
**Consultant:**

Abbott, Alliance BMS/Pfizer, Bayer, Bayer Healthcare, Edwards Lifesciences, Sanofi Regeneron, Terumo

**Honoraria:**

AstraZeneca

# Clinical challenge in patients with atrial fibrillation undergoing PCI

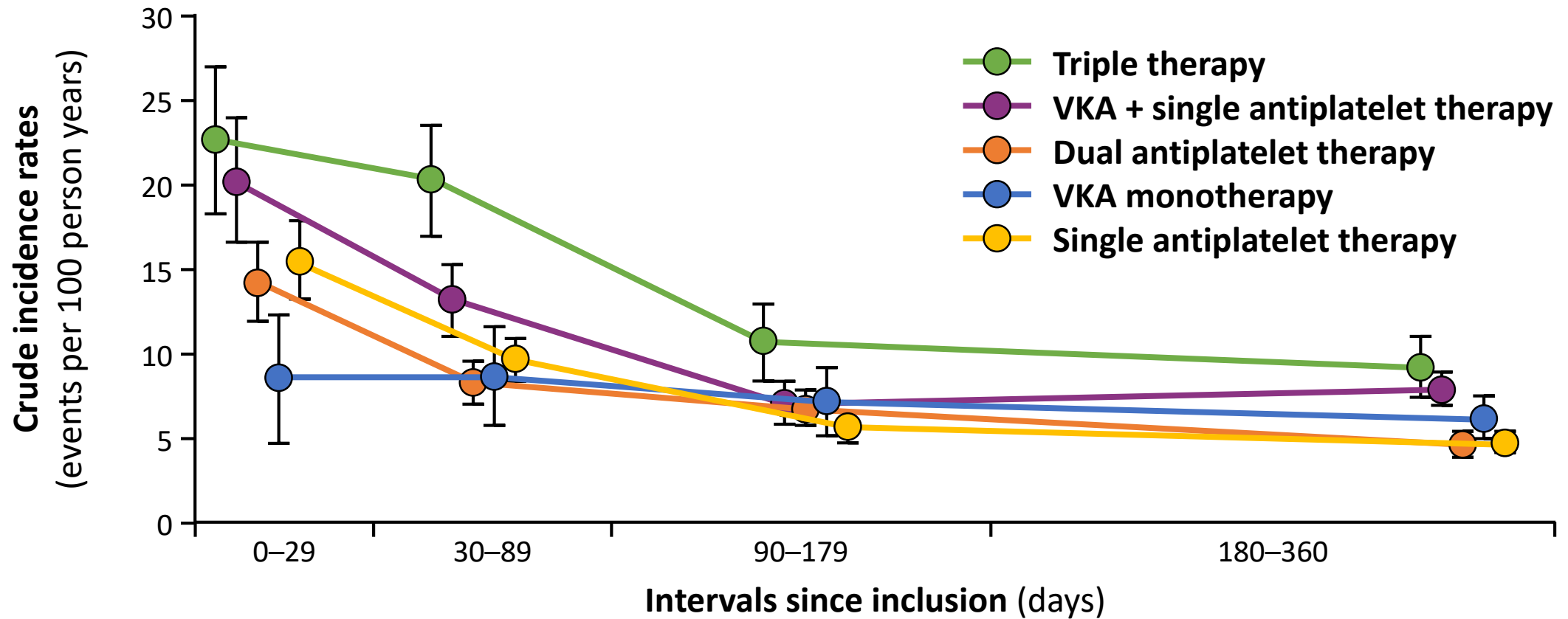


Schömig et al. NEJM 1996. Connolly et al Lancet 2006.

Capodanno D, Angiolillo DJ. JACC: Cardiovascular Interventions 2017.

# Bleeding and triple therapy after ACS/PCI in patients with atrial fibrillation

A nationwide cohort study

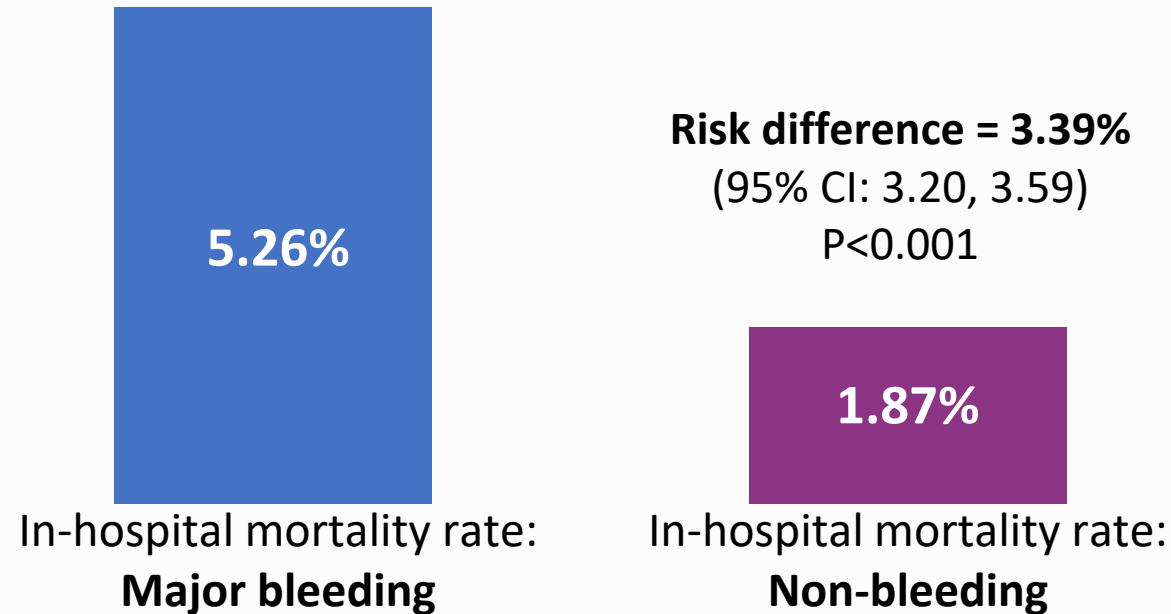


Lamberts, et al. Circulation 2012;126:1185-93.

# For patients undergoing PCI, major bleeding is associated with increased in-hospital mortality

Data from 3,386,688 procedures in the CathPCI Registry in the US 2004-2011

Bleeding represents the most common non-cardiac complication of PCI



**12.1% of deaths related to bleeding complications**

# Combinations of antiplatelet and antithrombotic agents in patients with AF and stent placement

2.8 million different combinations!

ASA dose	None	Low	High				2	1+8 = 9
ASA duration, months	1	3	6	12			4	ASA
Thienopyridine	None	Clop	Ticlo	Pras	Ticag		4	1+16 = 17
Thienopyridine duration, months	1	3	6	12			4	Thieno
AC	None	Warf	Dabi	Riva	Apix	Edox	5	1+10 = 11
AC INR/dose		Low	High				2	ACs

Permutations of single, dual or triple therapy as **early initial therapy (0, 1, 3, 6 months)** following ACS: **9 x 17 x 11 = 1,683**

Permutations of single or dual therapy **late after early therapy (0, 1, 3, 6, 12 months)** following ACS: **1,683**

**Total permutations *throughout one year*: 2.8 million**

# Triple therapy with aspirin, prasugrel and VKA after DES implantation

377 consecutive pts (2009–2011) with an indication for OAC treated with a 6-month regimen of aspirin and either prasugrel (N=21) or clopidogrel (N=356)

Death, MI, stroke or ST

TIMI bleeding

(%) 50 p=0.61

bleeding (%) 50 p<0.001

ESC Recommendations – DAPT 2017

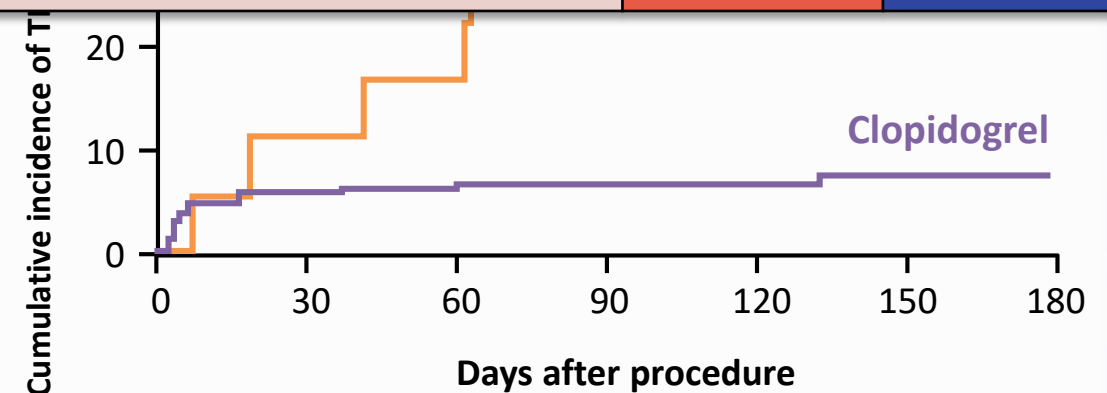
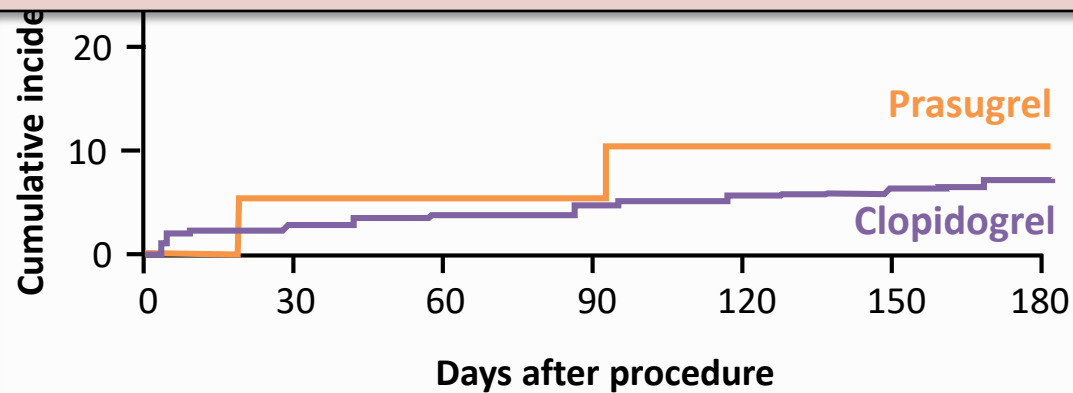
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC

Class

Level

III

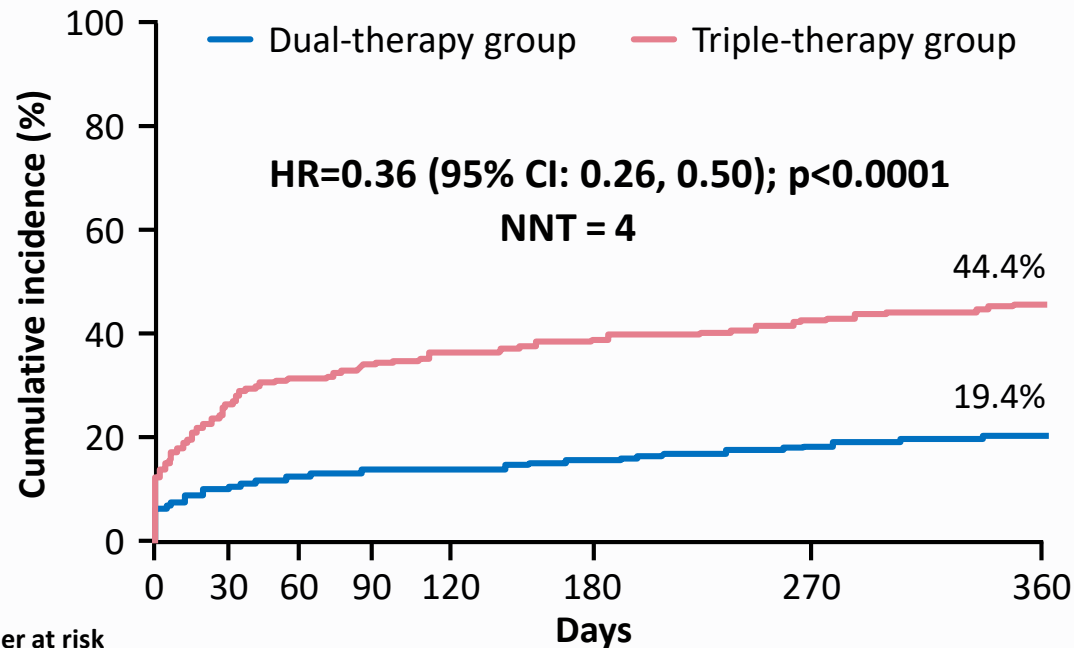
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# WOEST : Trial results

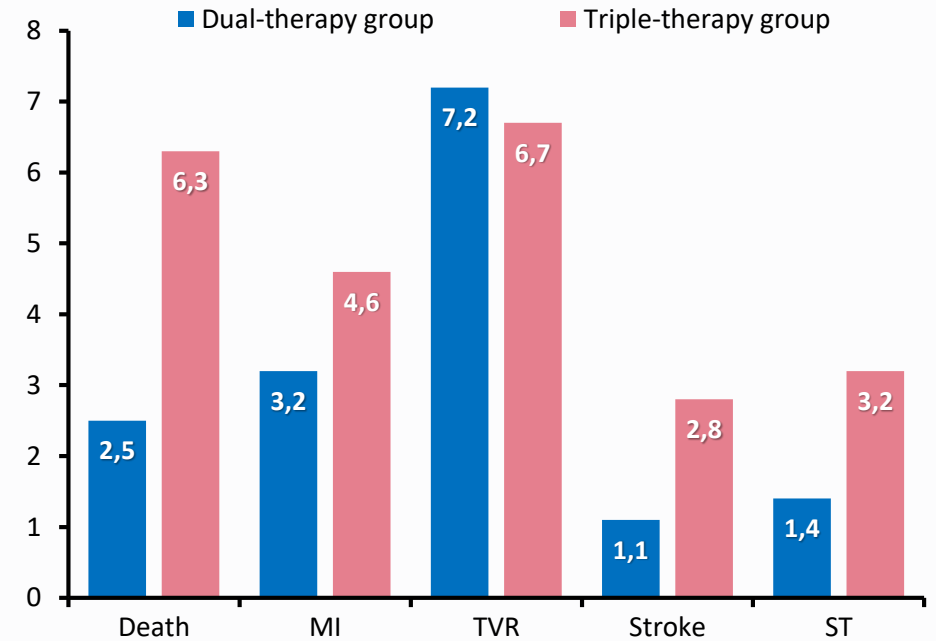
**573 patients** on OAC undergoing stent (DES/BMS) implantation received oral anticoagulants\* + clopidogrel 75 mg qd\*\* and randomised 1:1 to also receive aspirin 80 mg OR aspirin placebo qd

## Primary endpoint: any bleeding



Number at risk	0	30	60	90	120	180	270	360
Triple therapy	284	210	194	186	181	173	159	140
Double therapy	279	253	244	241	241	236	226	208

## Secondary endpoint: ischaemic events

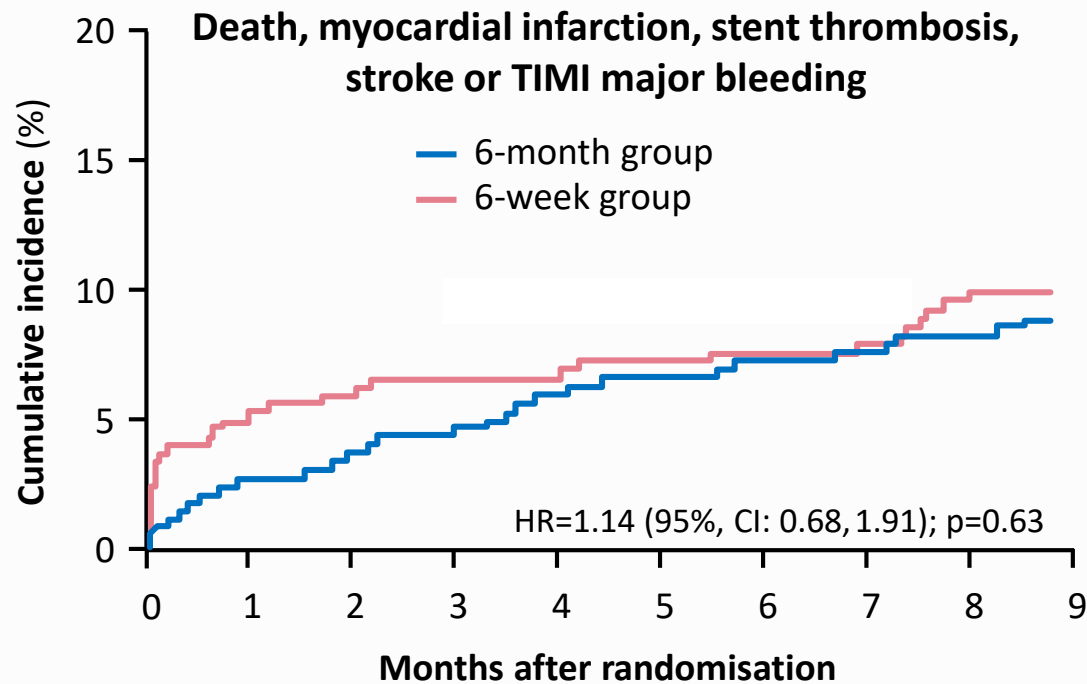




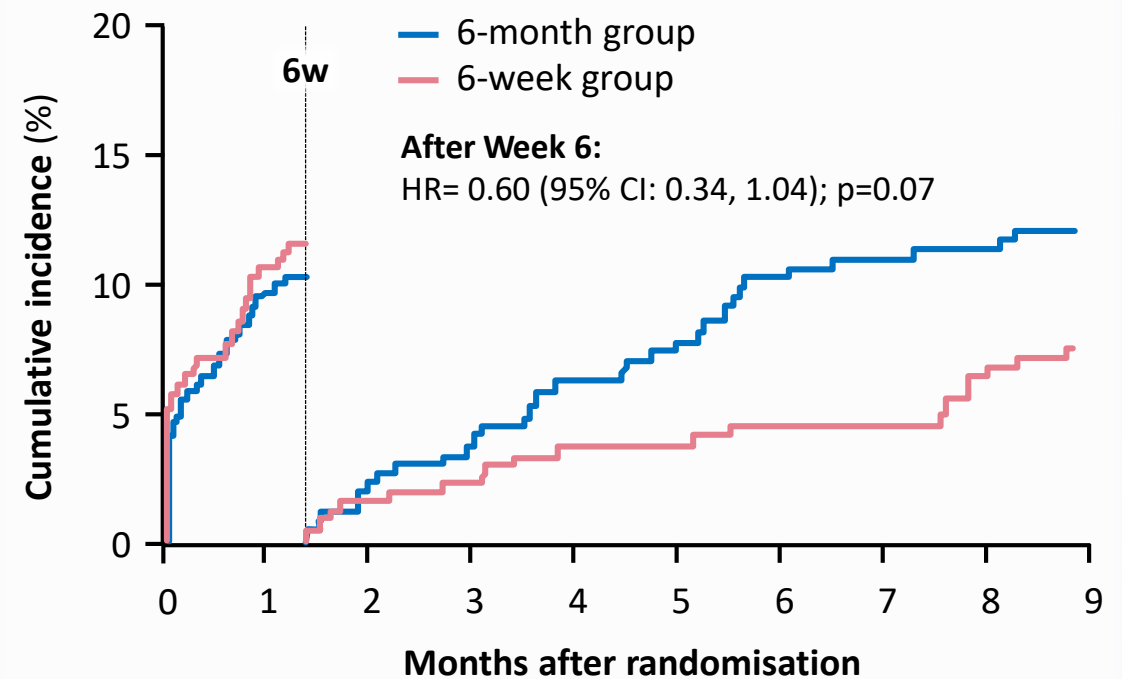
# ISAR-TRIPLE : Trial results

**Duration of triple therapy in 600 Pts requiring oral anticoagulation after DES implantation**  
**6-week vs 6-month triple therapy (1:1 randomisation)**

## Primary endpoint

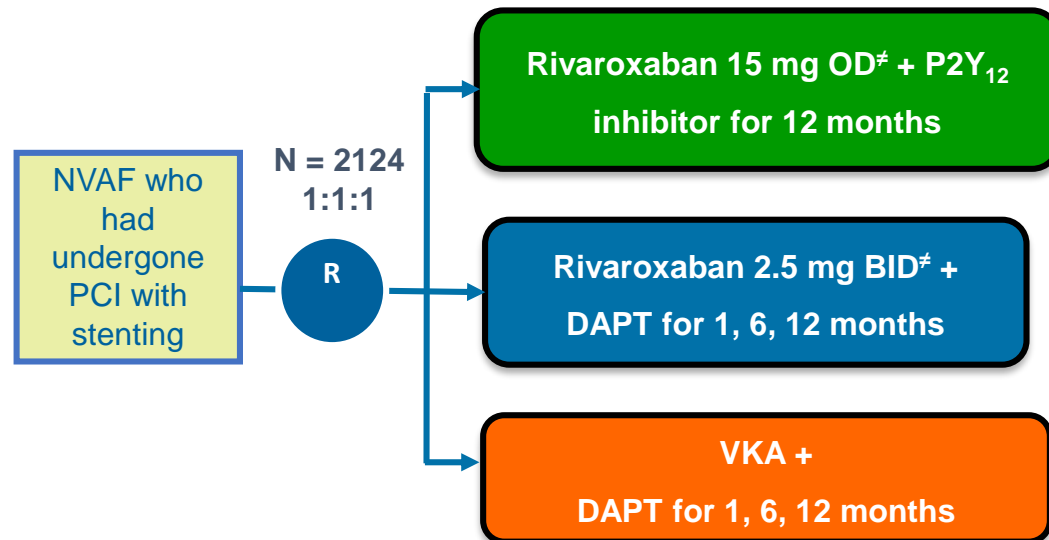


## BARC $\geq 2$



# Safety and efficacy of dual vs. triple antithrombotic therapy in patients with AF following PCI

## PIONEER AF-PCI<sup>1</sup>

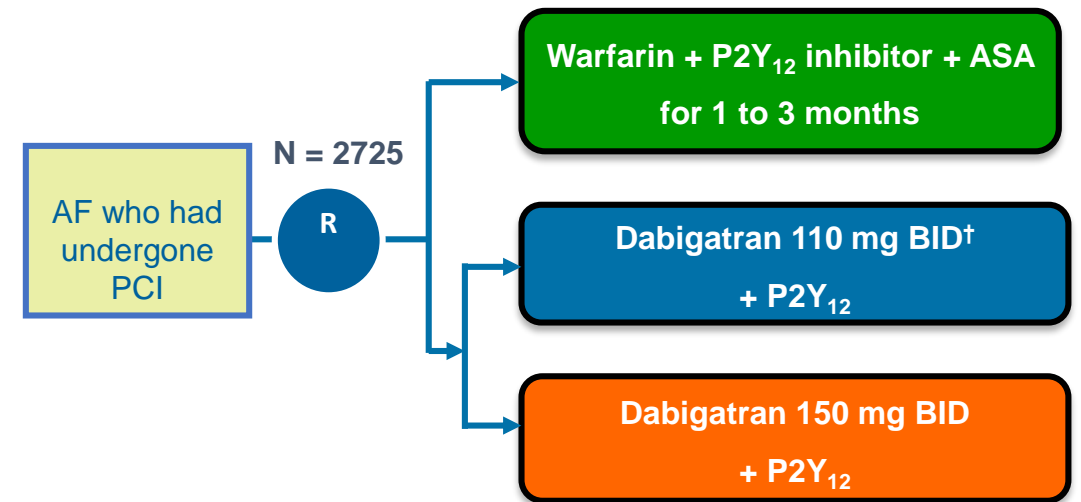


In PIONEER AF-PCI<sup>2</sup> P2Y<sub>12</sub> = clopidogrel, prasugrel, or ticagrelor

**PIONEER AF-PCI<sup>1</sup> demonstrated significantly less bleeding in either rivaroxaban containing arm compared to VKA plus DAPT.**

In patients where DAPT (ASA + P2Y<sub>12</sub>) was received for < 12 months SAPT (ASA) was given instead

## RE-DUAL PCI<sup>2</sup>



In RE-DUAL<sup>3</sup> P2Y<sub>12</sub> = clopidogrel or ticagrelor

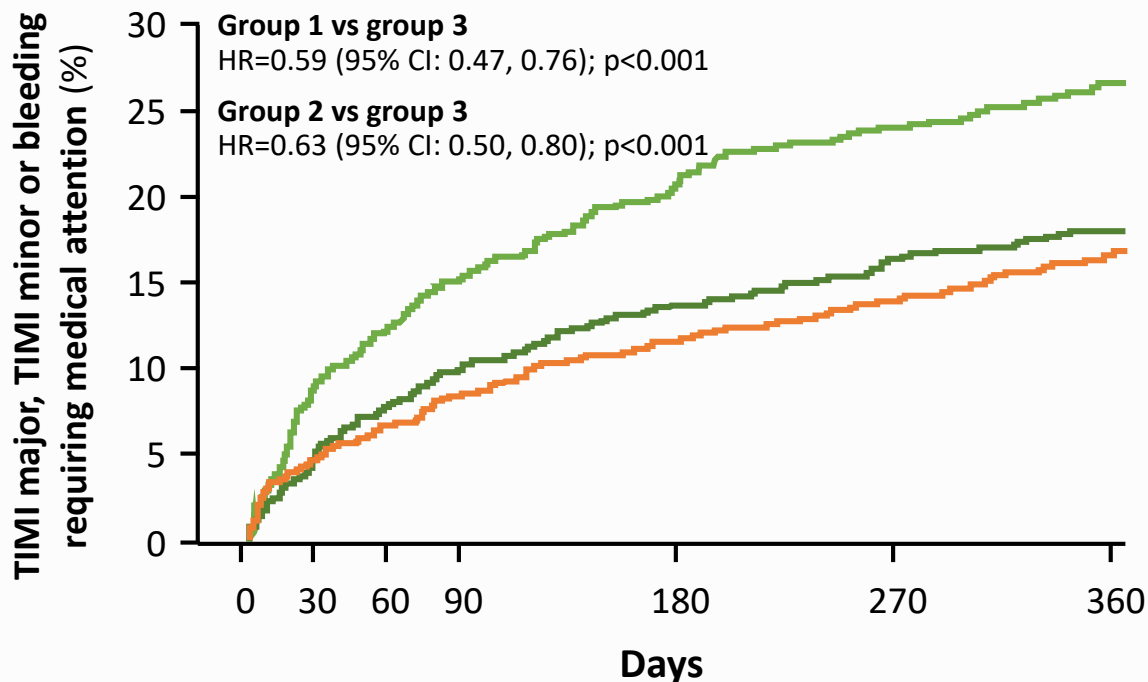
**RE-DUAL PCI<sup>2</sup> demonstrated significantly less major or CRNM bleeding in each of the dabigatran strategies compared to the VKA strategy.**

1. Adapted from Gibson CM et al. *N Engl J. Med.* 2016;375:2423-2434
2. Adapted from Cannon CP et al. *N Engl J. Med.* 2017;377:1513-1524

# Pioneer AF-PCI : Primary safety and secondary efficacy endpoints

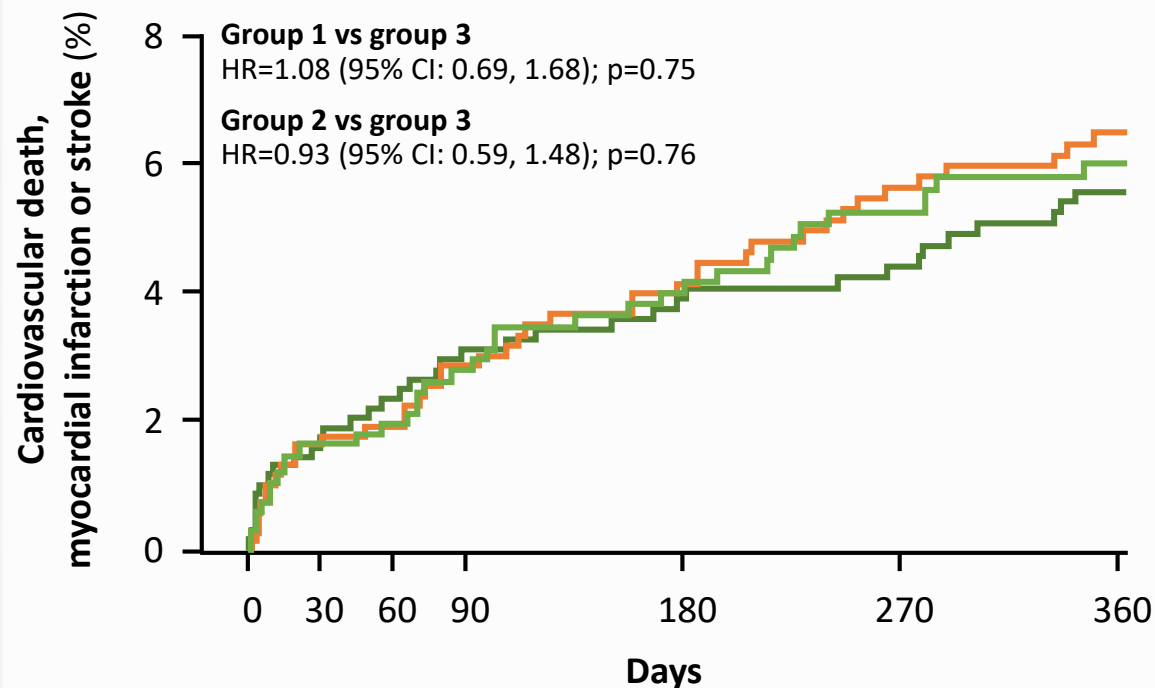
## Primary safety endpoint

**Clinically relevant TIMI bleeding**  
(major, minor bleeds requiring medical attention)



## Secondary efficacy endpoint

**CV death, MI or stroke**



— Group 1 : VKA + DAPT — Group 2 : Rivaroxaban + DAPT — Group 3 : Rivaroxaban + P2Y<sub>12</sub>

# PIONEER :

## Cumulative incidence of secondary outcomes

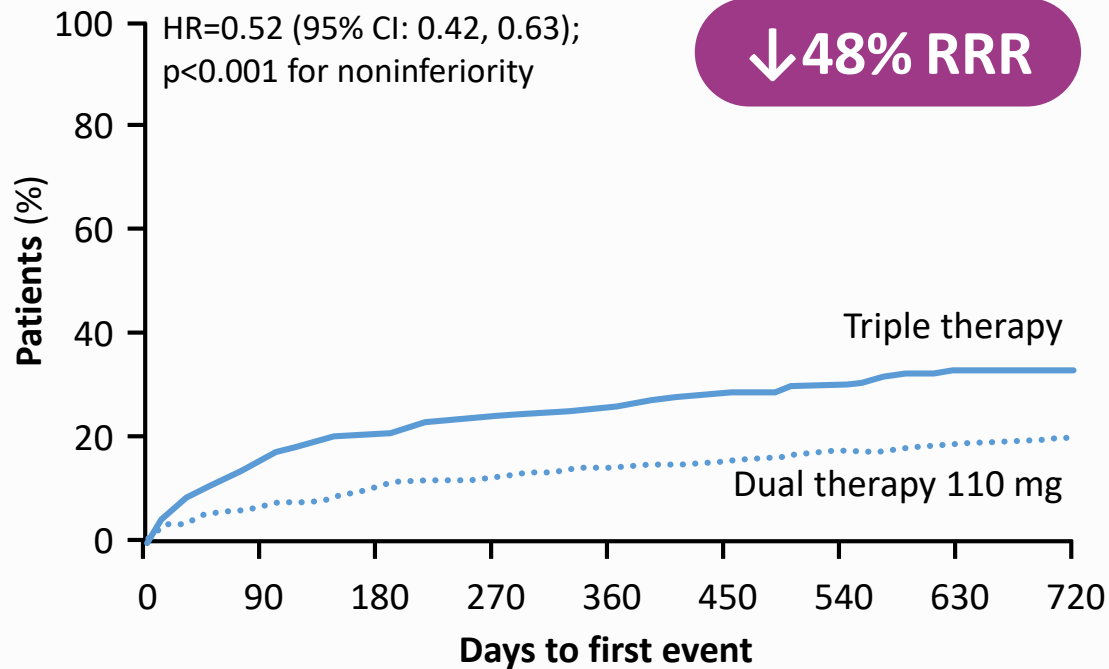
	Riva 15 mg + P2Y <sub>12</sub> inh (grp1) N = 694	Riva 2.5 mg + DAPT (grp 2) N = 704	Warfarin + DAPT (grp3) N = 695	Group 1 vs Group 3	Group 2 vs Group 3
	N (%)	N (%)	N (%)	HR (95% CI)	HR (95% CI)
<b>CV death</b>	15 (2.4)	14 (2.2)	11 (1.9)	1.29 (0.59–2.8)	1.19 (0.54–2.62)
<b>Stroke</b>	8 (1.3)	10 (1.5)	7 (1.2)	1.07 (0.39–2.96)	1.36 (0.52–3.58)
<b>MI</b>	19 (3.0)	17 (2.7)	21 (3.5)	0.86 (0.46–1.59)	0.75 (0.40–1.42)
<b>Stent thrombosis</b>	5 (0.8)	6 (0.9)	4 (0.7)	1.20 (0.32–4.45)	1.44 (0.40–5.09)

**Use of NOACs was not associated with increased cardiovascular outcomes compared with VKA**

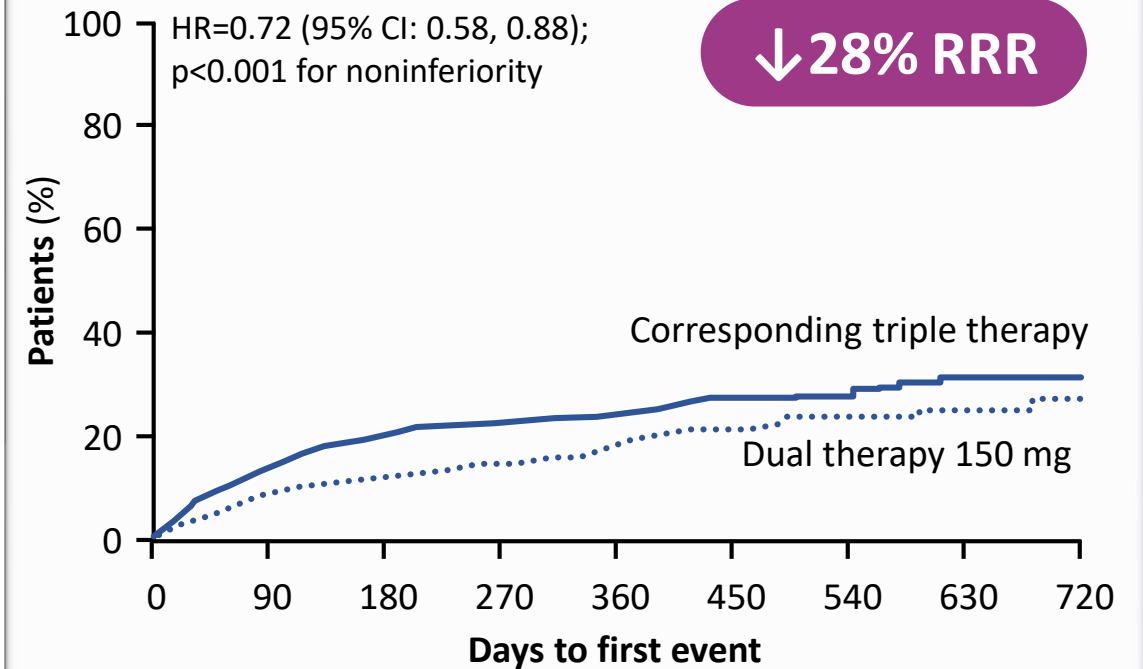
# RE-DUAL PCI : Major or clinically relevant bleeding

2,725 patients with atrial fibrillation undergoing PCI

## Dual therapy (110 mg) vs triple therapy

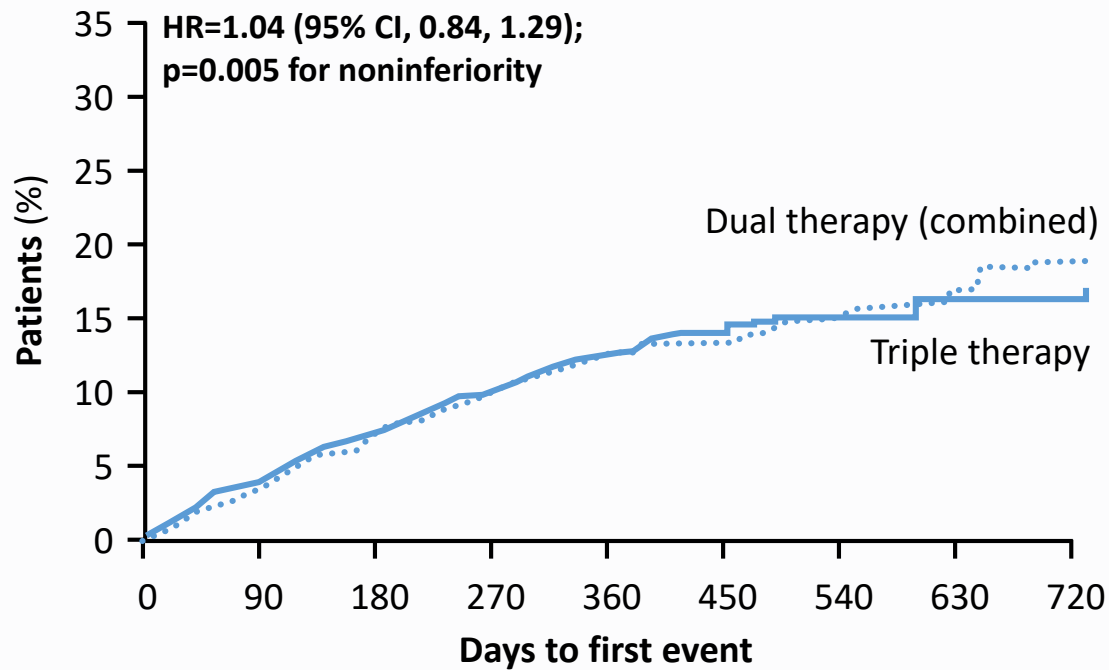


## Dual therapy (150 mg) vs triple therapy

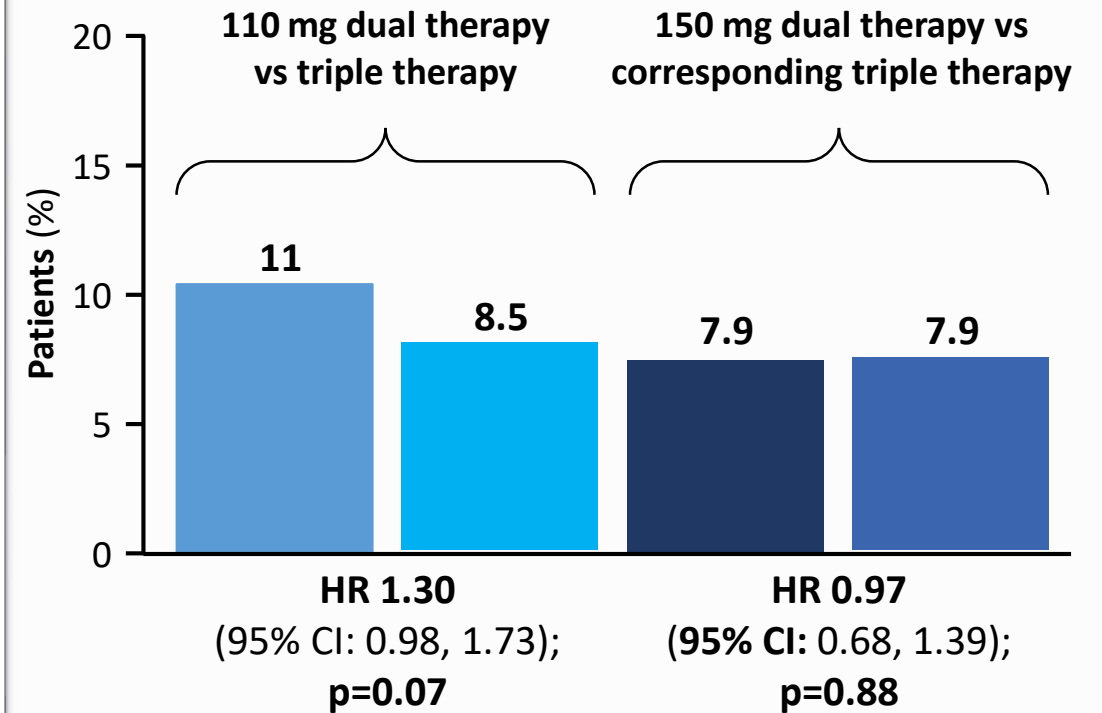


# RE-DUAL PCI : Secondary efficacy endpoints

**Thromboembolic events  
(MI, stroke, systemic embolism),  
death or unplanned revascularisation**



**Thromboembolic events  
(MI, stroke, systemic embolism)  
or death**



# RE-DUAL : What about MACEs ?

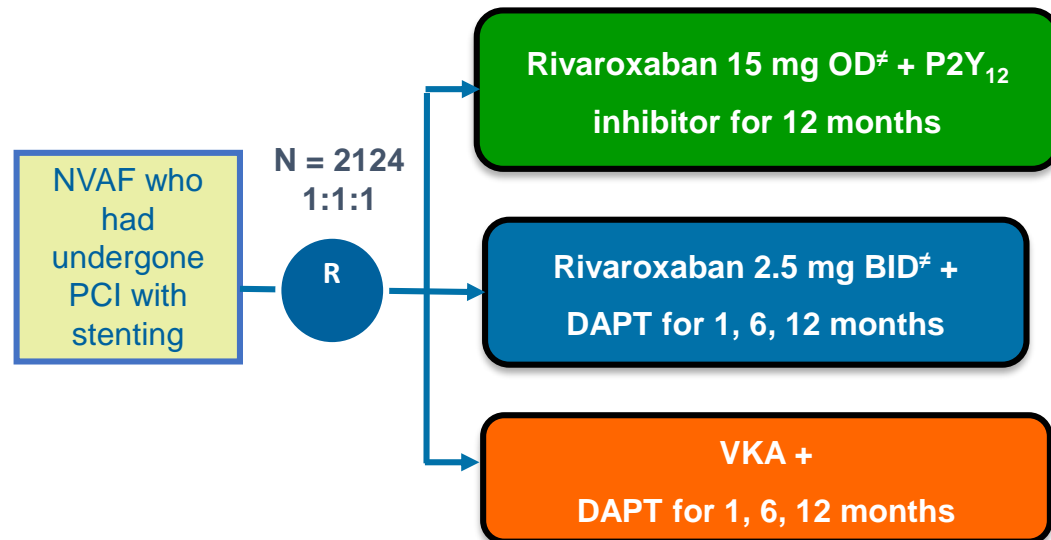
## Incidence of selected secondary efficacy outcomes

	Dual therapy with dabigatran (110 mg) vs triple therapy with warfarin			Dual therapy with dabigatran (150 mg) vs triple therapy with warfarin		
	110 mg dual therapy N=981	Triple therapy N=981	HR (95% CI)	150 mg dual therapy N=763	Triple therapy N=764	HR (95% CI)
	N (%)	N (%)		N (%)	N (%)	
<b>Death</b>	55 (5.6)	48 (4.9)	1.12 (0.76–1.65)	30 (3.9)	35 (4.6)	0.83 (0.51–1.34)
<b>Stroke</b>	17 (1.7)	13 (1.3)	1.30 (0.63–2.67)	9 (1.2)	8 (1.0)	1.09 (0.42–2.83)
<b>MI</b>	44 (4.5)	29 (3.0)	1.51 (0.94–2.41)	26 (3.4)	22 (2.9)	1.16 (0.66–2.04)
<b>Definite stent thrombosis</b>	15 (1.5)	8 (0.8)	1.86 (0.79–4.40)	7 (0.9)	7 (0.9)	0.99 (0.35–2.81)

The absolute number of stent thrombosis was low

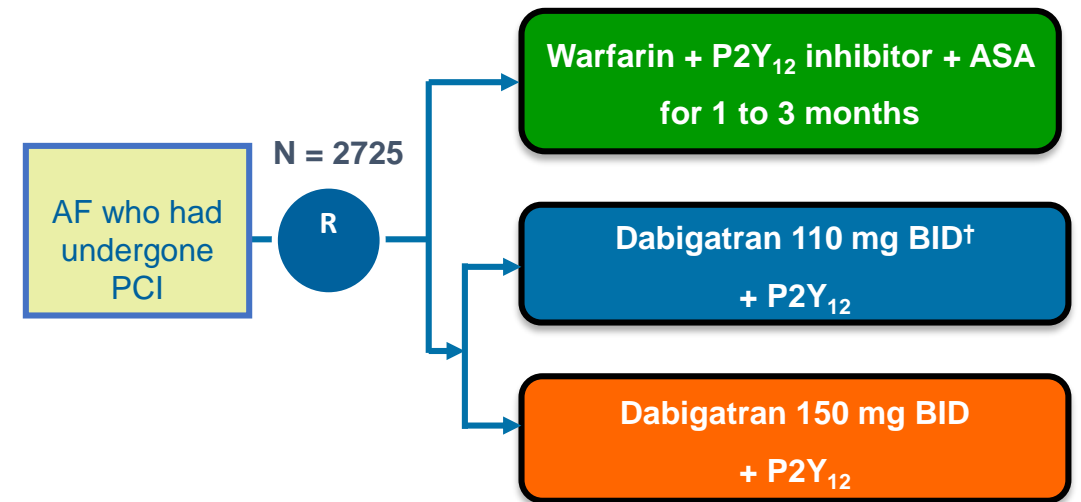
# Safety and efficacy of dual vs. triple antithrombotic therapy in patients with AF following PCI

## PIONEER AF-PCI<sup>1</sup>



In PIONEER AF-PCI<sup>2</sup> P2Y<sub>12</sub> = clopidogrel, prasugrel, or ticagrelor

## RE-DUAL PCI<sup>2</sup>



In RE-DUAL<sup>3</sup> P2Y<sub>12</sub> = clopidogrel or ticagrelor

**These trials were not powered or designed to assess whether the bleeding reduction was due to the use of a NOAC or the removal of aspirin from the post-PCI oral antithrombotic strategy.<sup>1</sup>**

In patients where DAPT (ASA + P2Y<sub>12</sub>) was received for < 12 months DAPT (ASA) was given instead

1. Adapted from Gibson CM et al. *N Engl J. Med.* 2016;375:2423-2434
2. Adapted from Cannon CP et al. *N Engl J. Med.* 2017;377:1513-1524



# AUGUSTUS : Study design

## INCLUSION

- Atrial fibrillation (prior, persistent, >6 hr)
  - Physician decision for OAC
- Acute coronary syndrome or PCI
  - Planned P2Y<sub>12</sub> inhibitor for ≥6 months

## EXCLUSION

- Contraindication to DAPT
- Other reason for VKA (prosthetic valve, moderate/severe mitral stenosis)

**Randomise**  
N=4,614 patients

Open  
label

**Apixaban 5 mg BID**

Apixaban 2.5 mg BID in selected patients

**VKA**

(INR 2–3)

*P2Y<sub>12</sub> inhibitor for ≥6 months  
Aspirin for all on the day of ACS and/or PCI  
Aspirin versus placebo after randomisation*

**Aspirin**

Double  
blind

**Placebo**

**Aspirin**

Double  
blind

**Placebo**

**Primary outcome:** ISTH major/CRNM bleeding

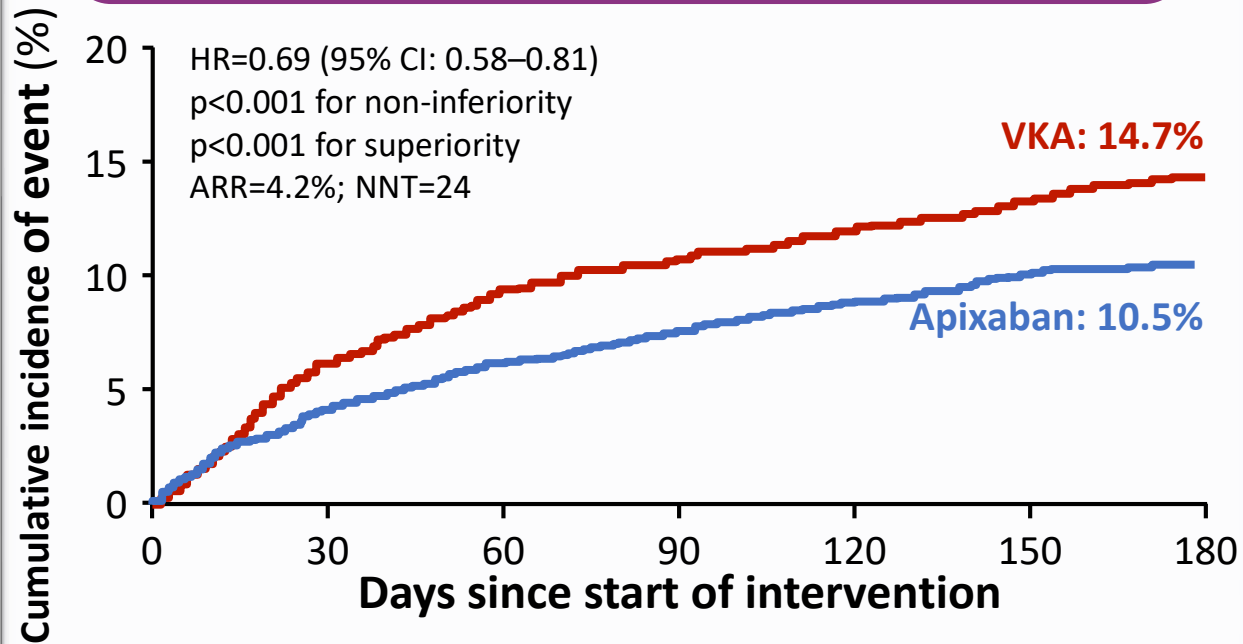
**Secondary outcome(s):** death/hospitalisation, death/ischaeamic events

# AUGUSTUS primary Outcome : Apixaban vs VKA

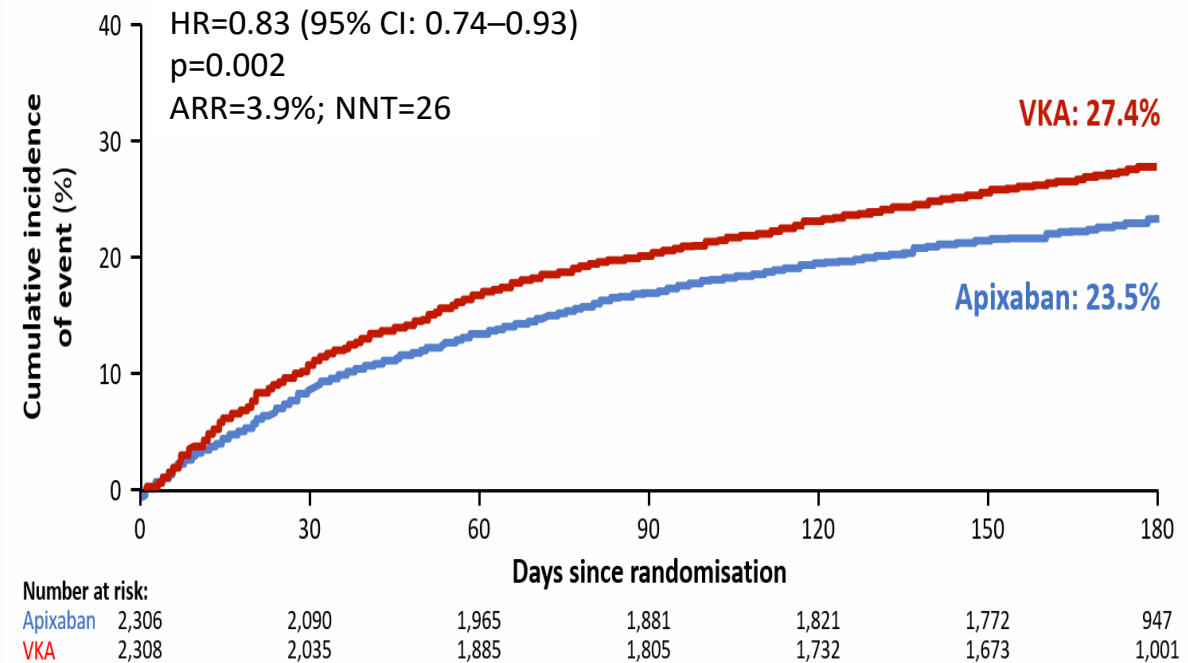
## ISTH major or CRNM bleeding

## Death or hospitalization

Apixaban vs VKA



Apixaban vs VKA

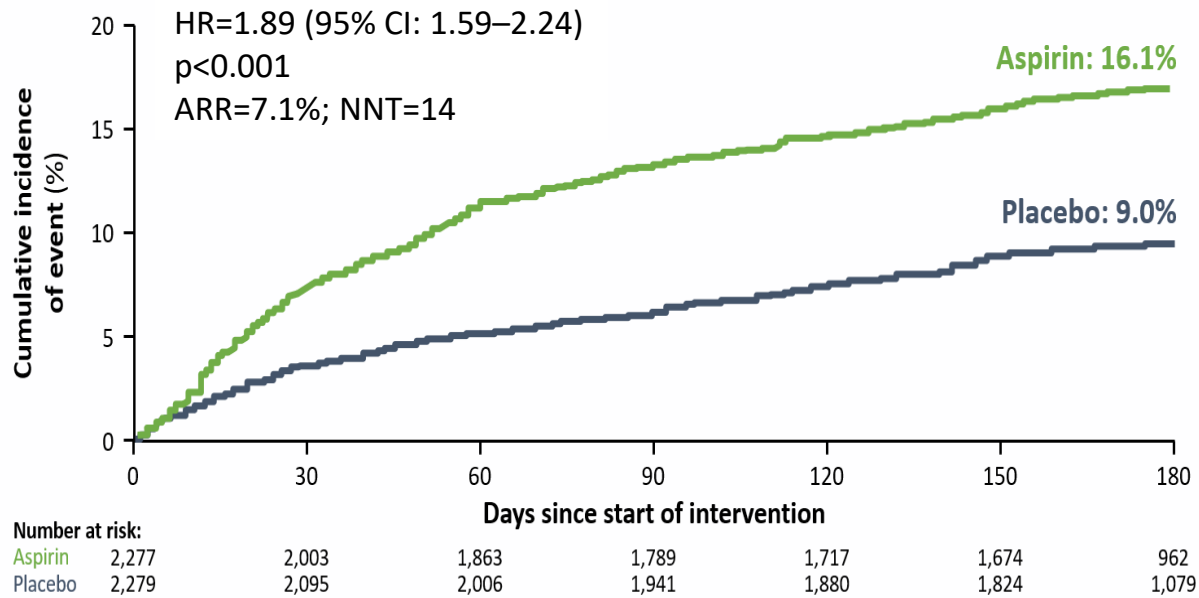


# AUGUSTUS primary Outcome : aspirin vs placebo

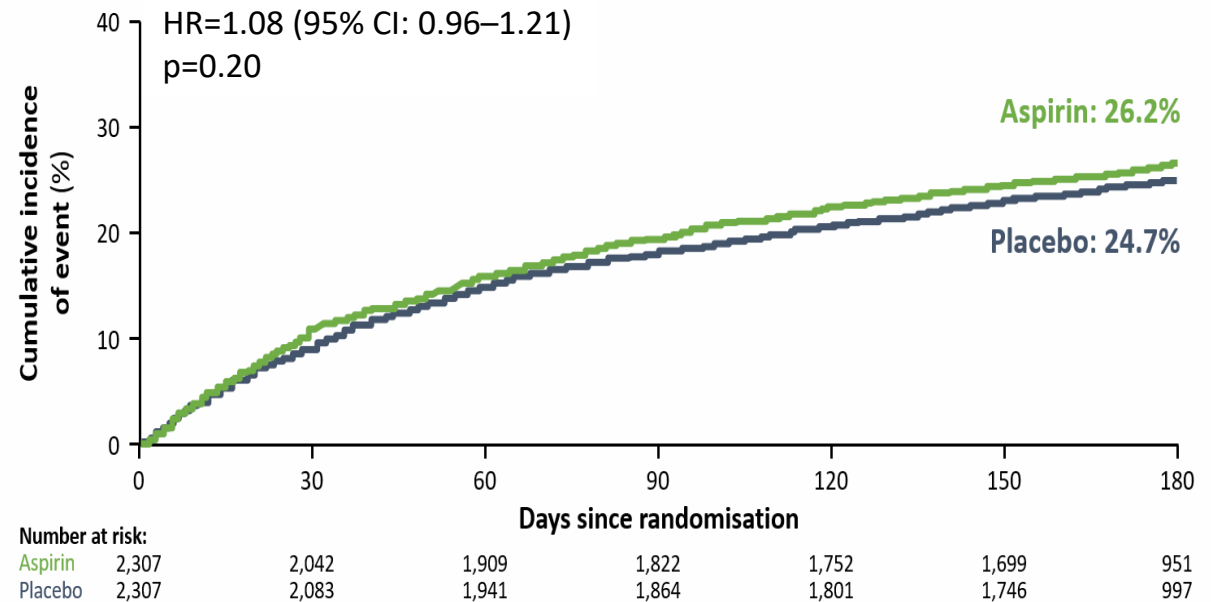
## ISTH major or CRNM bleeding

## Death or hospitalization

Aspirin vs aspirin placebo



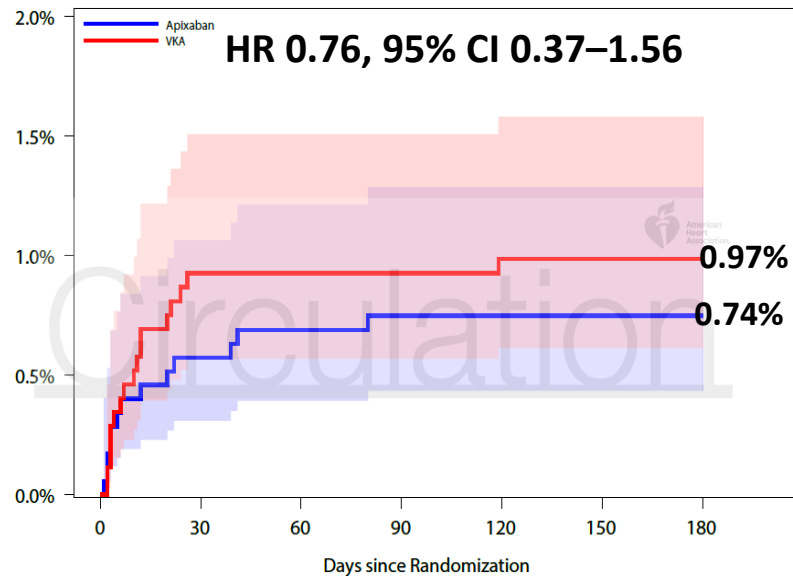
Aspirin vs aspirin placebo



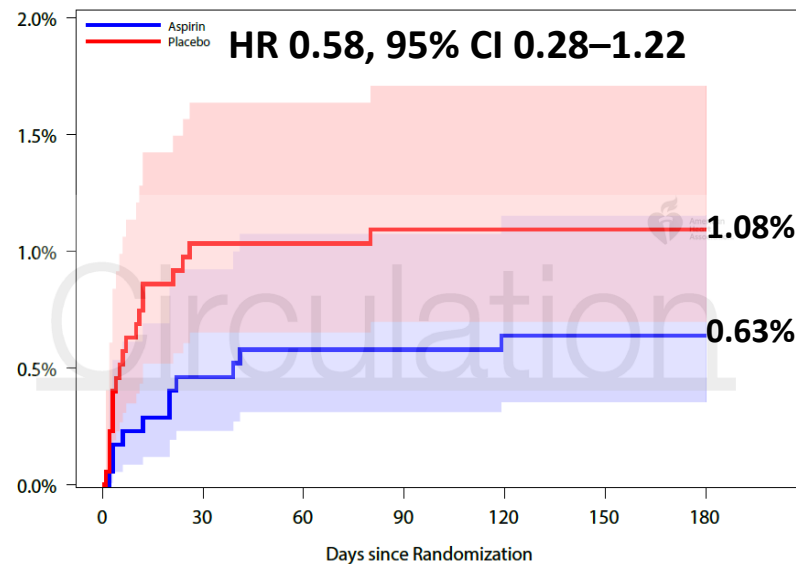
# AUGUSTUS : Stent Thrombosis

## Definite/Probable Stent Thrombosis

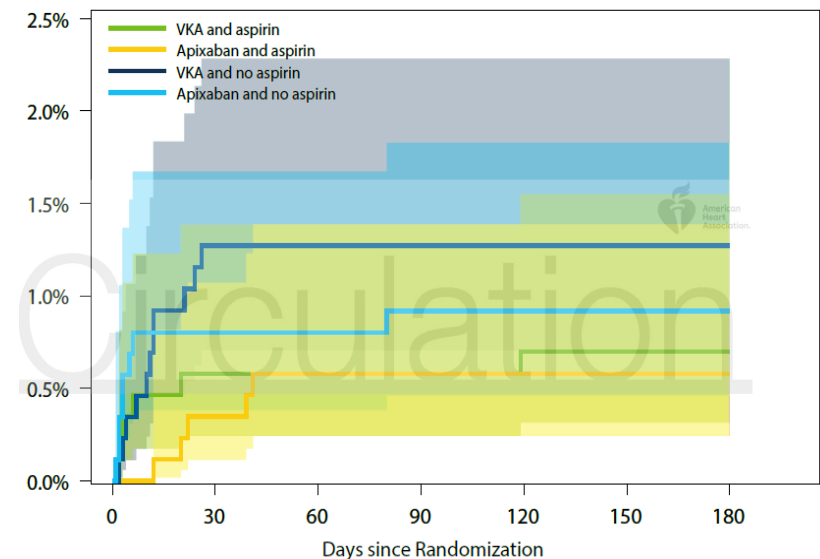
### Apixaban vs VKA



### Aspirin vs placebo



### Intervention combination

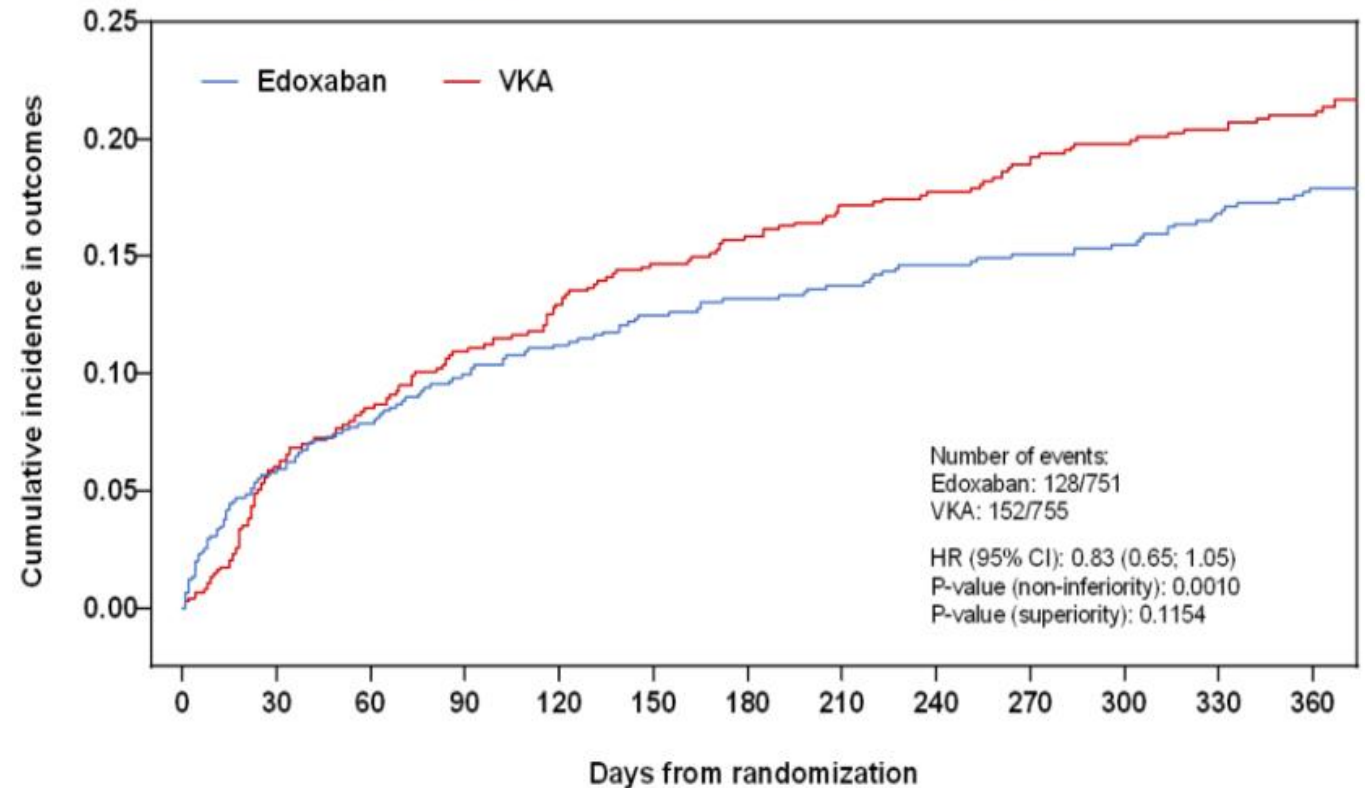
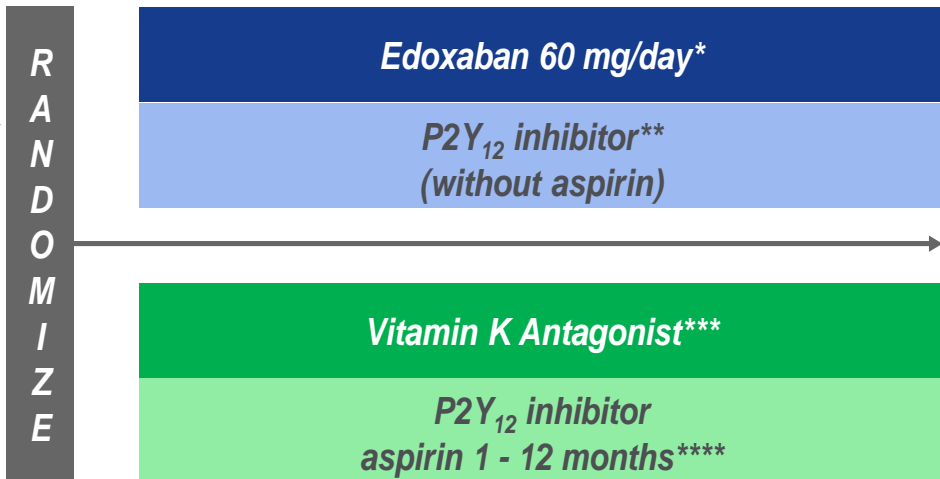


The number needed to treat (NNT) to avoid 1 stent thrombosis event for aspirin versus placebo at 6 months is 222 and the number need to harm (NNH) to cause 1 major bleeding event is 41.

# Safety and efficacy of dual vs. triple antithrombotic therapy in patients with AF following PCI : **ENTRUST-AFPCI**



## Primary Study Endpoint ITT Analysis (N=1506), overall study period



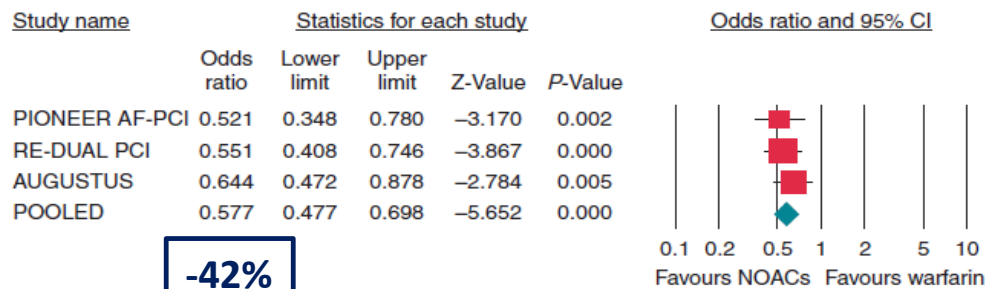
Vranckx P et al. Lancet 2019.12;394:1335-1343.

# Meta-analysis of pooled data from CRT : Bleeding : NOAC better than VKA

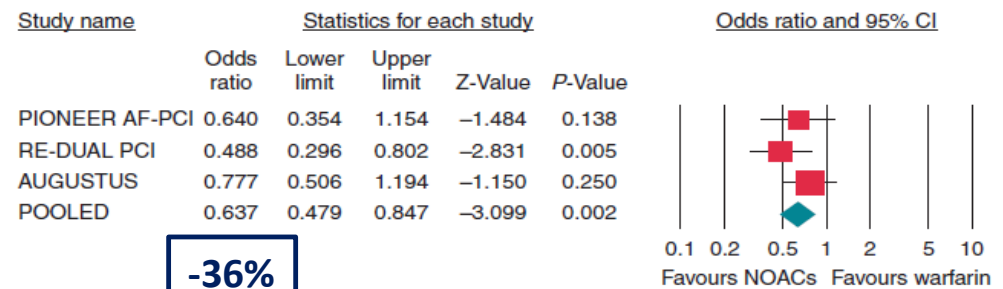
**NOAC-based regimens associated with significantly less bleeding than VKA-based regimens**

## (B) NOACs versus VKA

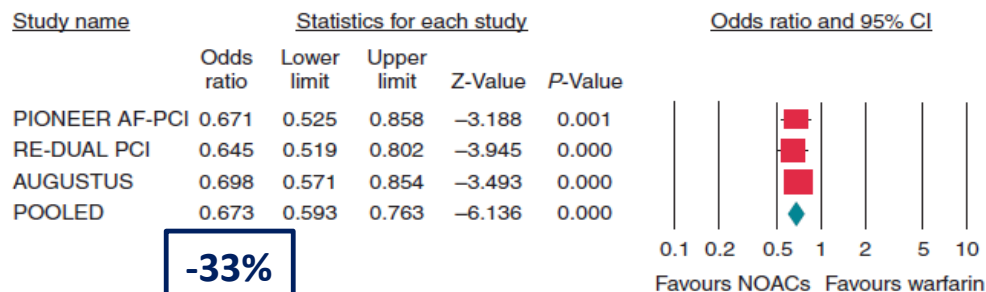
### ISTH Major bleeding



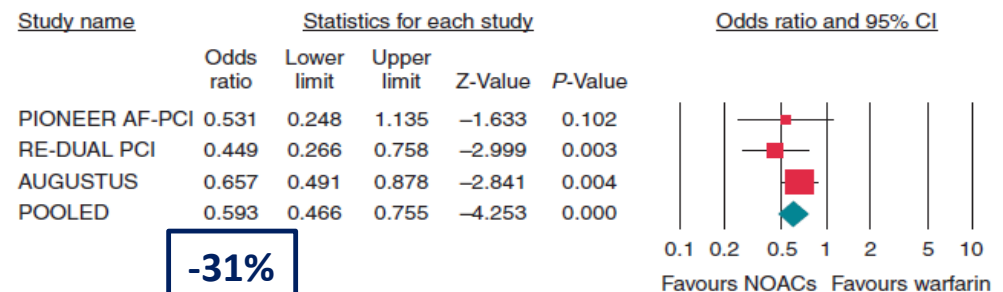
### TIMI Major bleeding



### CRNM Bleeding



### TIMI Minor bleeding

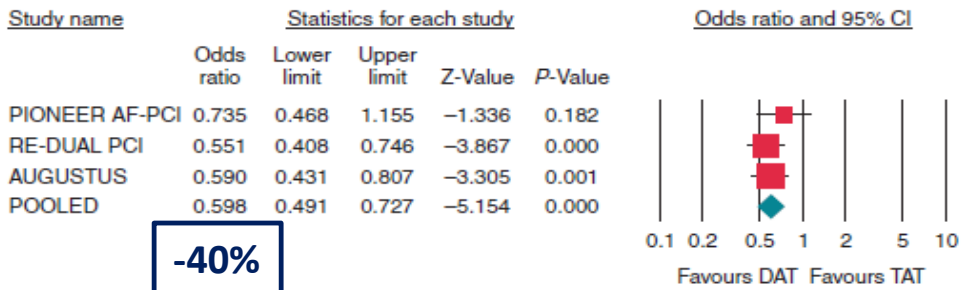


# Meta-analysis of pooled data from RCT : Bleeding : DAT better than TAT

**DAT-based regimens were associated with significantly less bleeding than TAT-based regimens**

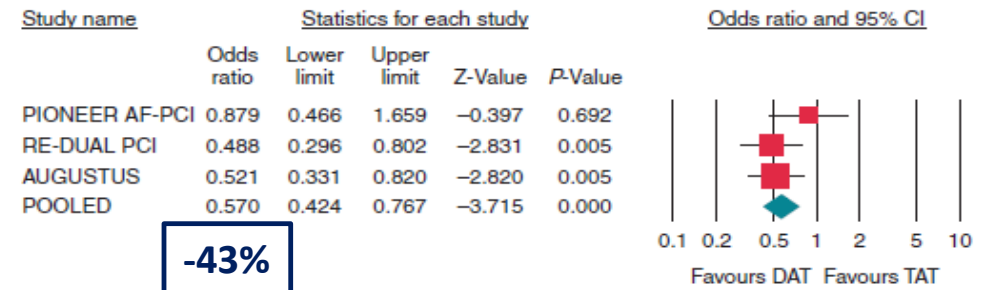
## (A) DAT versus TAT

### ISTH Major bleeding



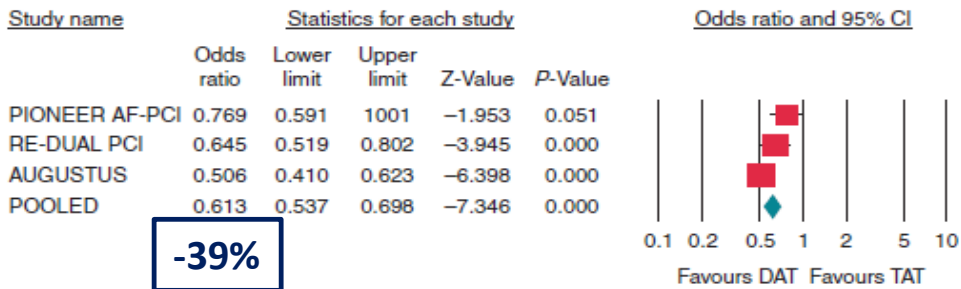
Fixed effects meta-analysis  $Q = 1.093$ ,  $P = 0.579$ ;  $I^2: 0\%$

### TIMI Major bleeding



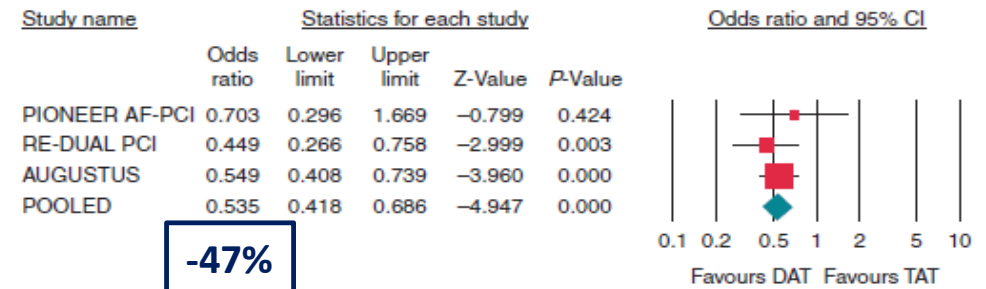
Fixed effects meta-analysis  $Q = 2.326$ ,  $P = 0.313$ ;  $I^2: 14\%$

### ISTH CRNM bleeding



Random effects meta-analysis  $Q = 6.344$ ,  $P = 0.042$ ;  $I^2: 68\%$

### TIMI Minor bleeding



Fixed effects meta-analysis  $Q = 0.842$ ,  $P = 0.656$ ;  $I^2: 0\%$

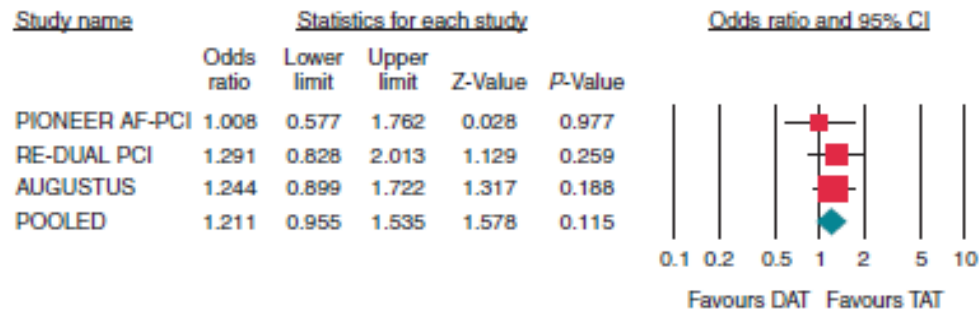
# Meta-analysis of pooled data from RCT : Myocardial infarction & stent thrombosis

**Higher rates of ST with DAT vs TAT**

**Similar rates of MI & ST with NOAC vs VKA**

(A) DAT versus TAT

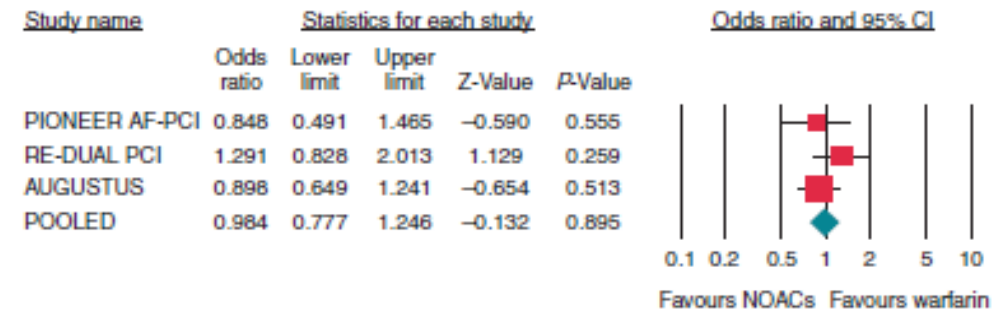
Myocardial infarction



Fixed effects meta-analysis  $Q = 0.521$ ,  $P = 0.771$ ;  $I^2: 0\%$

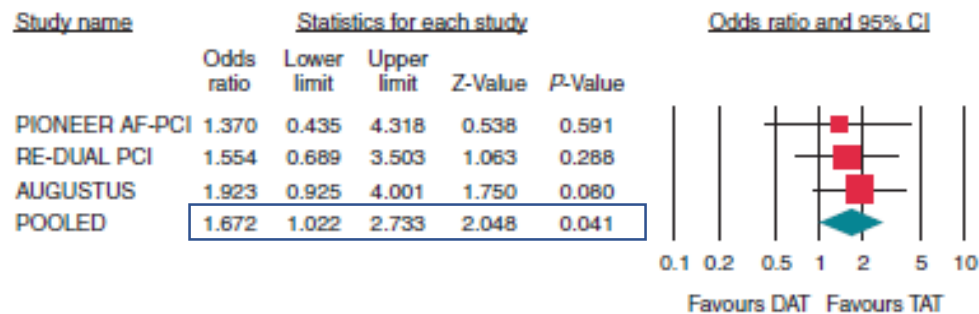
(B) NOAC versus VKA

Myocardial infarction



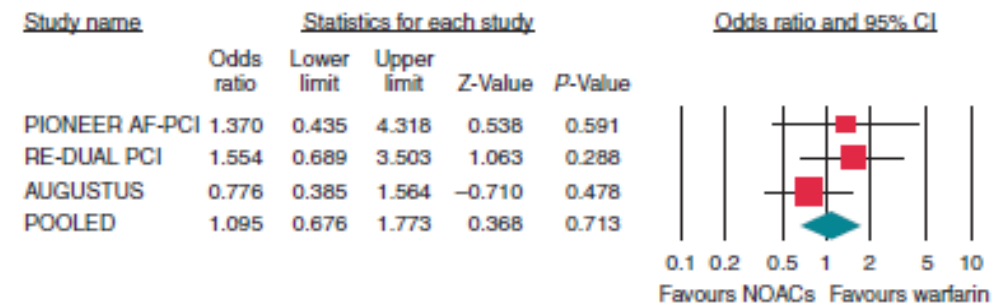
Fixed effects meta-analysis  $Q = 2.033$ ,  $P = 0.362$ ;  $I^2: 2\%$

Stent thrombosis



Fixed effects meta-analysis  $Q = 0.287$ ,  $P = 0.866$ ;  $I^2: 0\%$

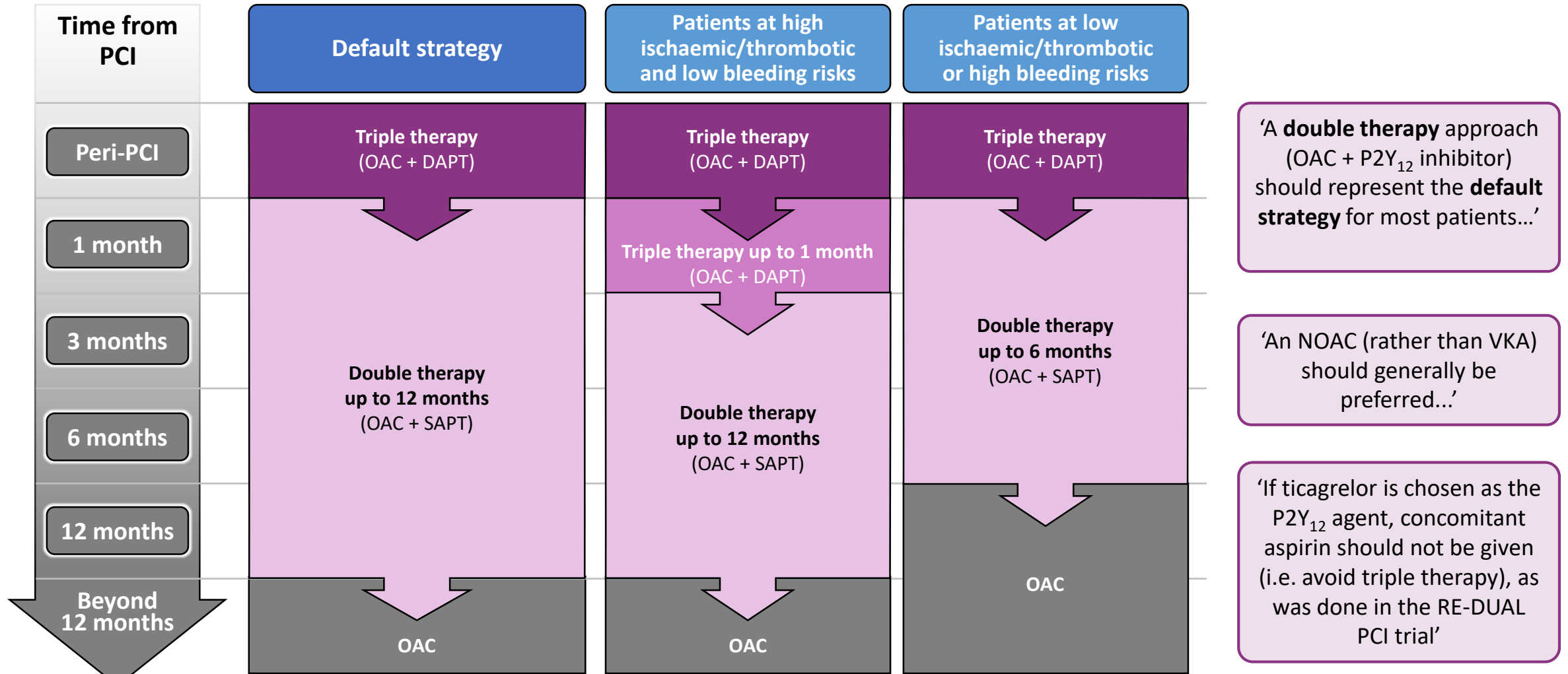
Stent thrombosis



Fixed effects meta-analysis  $Q = 1.787$ ,  $P = 0.409$ ;  $I^2: 0\%$

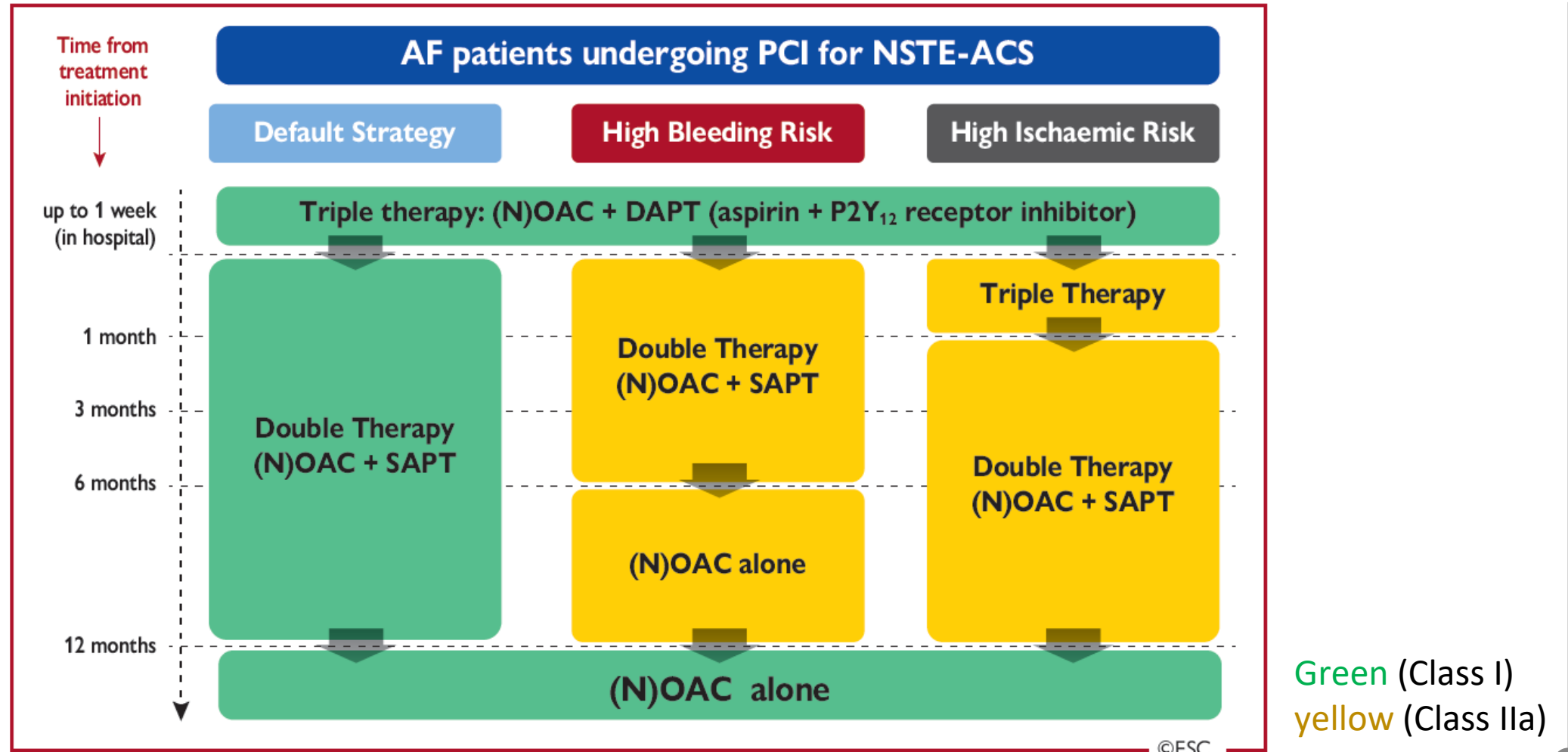


# 2018 North American expert consensus document

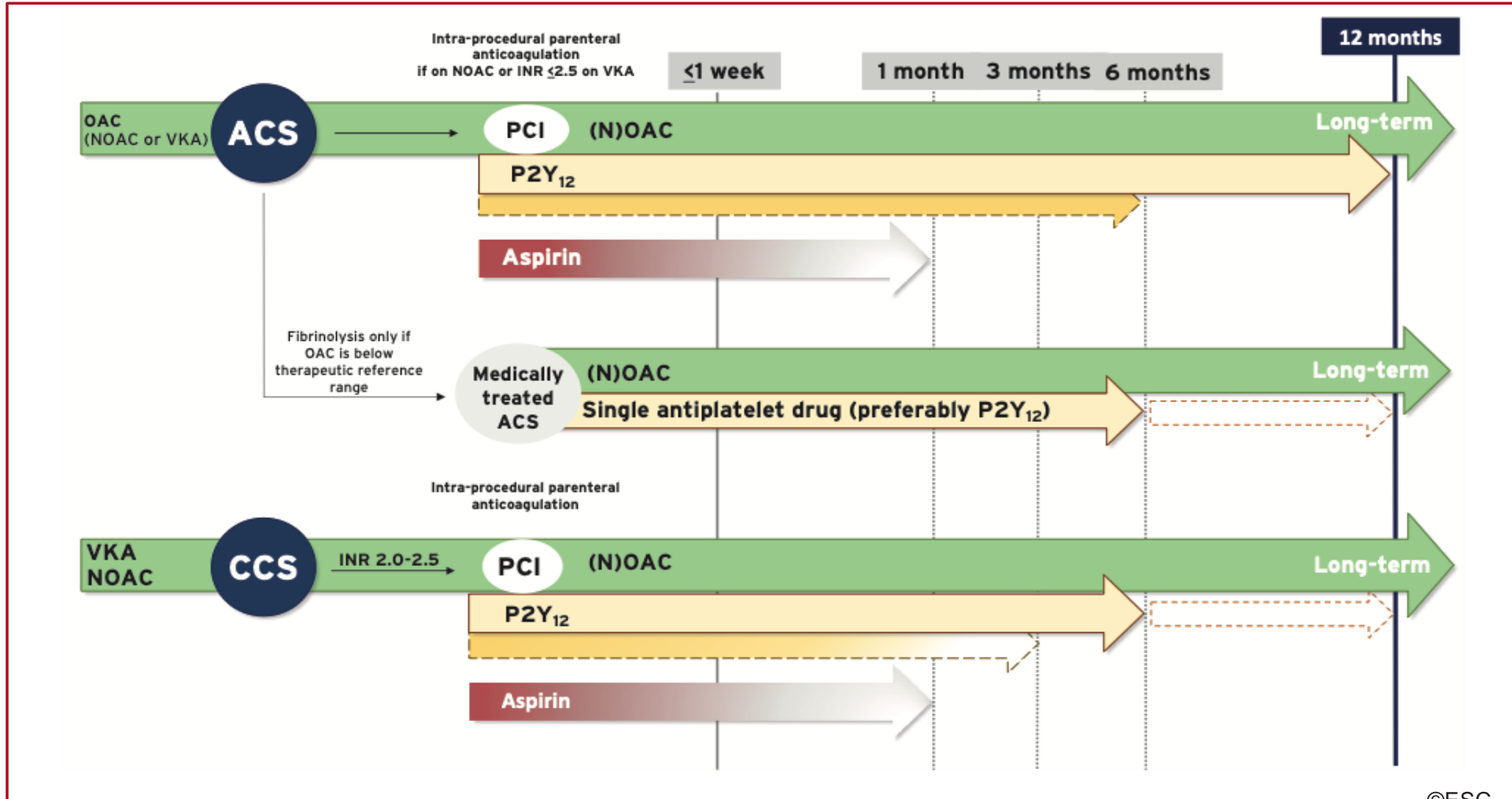


SAPT, single antiplatelet therapy.  
 OAC prefer a NOAC over VKA if no contraindications; SAPT: prefer a P2Y<sub>12</sub> inhibitor over aspirin.  
 Clopidogrel is the P2Y<sub>12</sub> inhibitor of choice; ticagrelor may be considered in patients at high ischaemic/thrombotic and low bleeding risks; avoid prasugrel.  
 Consider SAPT in addition to OAC after >12 months only in select patients at high ischaemic/thrombotic and low bleeding risks.

# 2020 ESC Guidelines : antithrombotic therapy in NSTEMI-ACS pts with AF undergoing PCI or medical management



# 2020 ESC Guidelines : post-procedural management of pts with AF and ACS/PCI



# 2020 ESC Guidelines : post-procedural management of pts with AF and ACS/PCI

## THROMBOTIC RISK FACTORS

- Diabetes mellitus requiring therapy
- Prior ACS/recurrent myocardial infarction
- Multivessel CAD
- Concomitant PAD
- Premature CAD (occurring at age of <45 y) or accelerated CAD (new lesion within 2 years)
- CKD (eGFR <60 mL/min)
- Clinical presentation (ACS)
- Multivessel stenting
- Complex revascularisation (left main stenting, bifurcation lesion stenting, chronic total occlusion intervention, last patent vessel stenting)
- Prior stent thrombosis on antiplatelet treatment
- Procedural factors (stent expansion, residual dissection, stent length, etc.)

## BLEEDING RISK FACTORS

- Hypertension
- Abnormal renal or liver function
- Stroke or ICH history
- Bleeding history or bleeding diathesis (e.g., anaemia with haemoglobin <110 g/L)
- Labile INR (if on VKA)
- Elderly (>65 years)
- Drugs (concomitant OAC and antiplatelet therapy, NSAIDs), excessive alcohol consumption

## STRATEGIES TO REDUCE BLEEDING ASSOCIATED WITH PCI

- Radial artery access
- PPIs in patients taking DAPT who are at increased risk of bleeding (e.g., the elderly, dyspepsia, gastro-oesophageal reflux disease, Helicobacter pylori infection, chronic alcohol use)
- Non-administration of unfractionated heparin in patients on VKA with INR >2.5
- Pre-treatment with aspirin only, add a P2Y<sub>12</sub> inhibitor when coronary anatomy is known or if STEMI
- GP IIb/IIIa inhibitors only for bailout or periprocedural complications
- Shorter duration of combined antithrombotic therapy

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# Recommendations for patients with AF and an ACS, PCI, or CCS (1)

Recommendations	Class	Level
<b>General recommendations for patients with AF and an indication for concomitant antiplatelet therapy</b>		
In AF patients eligible for NOACs, <u>it is recommended to use a NOAC<sup>a</sup> in preference to a VKA in combination with antiplatelet therapy.</u>	<b>I</b>	<b>A</b>
In patients at high bleeding risk ( <u>HAS-BLED <math>\geq 3</math></u> ), rivaroxaban 15 mg o.d. should be considered in preference to rivaroxaban 20 mg o.d. for the duration of concomitant single or DAPT, to mitigate bleeding risk.	<b>IIa</b>	<b>B</b>
In patients at high bleeding risk ( <u>HAS-BLED <math>\geq 3</math></u> ), 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 DAPT, to mitigate bleeding risk.	<b>IIa</b>	<b>B</b>
In AF patients with an indication for a VKA in combination with antiplatelet therapy, the VKA dosing should be carefully regulated with a target INR of 2.0–2.5 and TTR >70%.	<b>IIa</b>	<b>B</b>

# 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes

Recommendations	Class	Level
<b>Antithrombotic therapy in post-PCI patients with AF or another indication for an OAC</b>		
<u>Dual therapy with an OAC and either ticagrelor or prasugrel may be considered as an alternative to triple therapy with an OAC, aspirin, and clopidogrel in patients with a moderate or high risk of stent thrombosis,<sup>a</sup> irrespective of the type of stent used.</u>	IIb	C
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and an OAC.	III	C

<sup>a</sup> Risk of stent thrombosis encompasses (i) the risk of thrombosis occurring and (ii) the risk of death should stent thrombosis occur, both of which relate to anatomical, procedural, and clinical characteristics. Risk factors for CCS patients include stenting of left main stem, proximal LAD, or last remaining patent artery; suboptimal stent deployment; stent length >60 mm; diabetes mellitus; CKD; bifurcation with two stents implanted; treatment of chronic total occlusion; and previous stent thrombosis on adequate antithrombotic therapy.

# Conclusion : AF and acute coronary syndrome

- **Which anticoagulant treatment:** In most patients, NOACs should be preferred over VKA unless contraindicated
- **Which P2Y<sub>12</sub> inhibitor :** Clopidogrel is the first-line choice;
- **When and for Whom:**
  - **Dual**-therapy (OAC plus P2Y12 inhibitor) immediately or early after hospital discharge should be considered for most patients.
  - **Triple**-therapy (extended use of aspirin beyond hospital discharge) should be considered only for patients at high ischemic/thrombotic\* and low bleeding risks. Duration should be limited (e.g. 1 month)

\*High atherothrombotic risk as assessed by SYNTAX score (PCI), Grace score > 140 (ACS), stenting of left main or proximal LAD; proximal bifurcation, recurrent ACS, stent thrombosis....

\*Bleeding risk as assessed by HAS-BLED score, BARC Consensus