Coronaropathies et Anticoagulants

Journée d'Actualités Thérapeutiques ACCA Nice
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Disclosures

Speaker: Nicolas Meneveau

☑ I have the following potential conflicts of interest to declare:

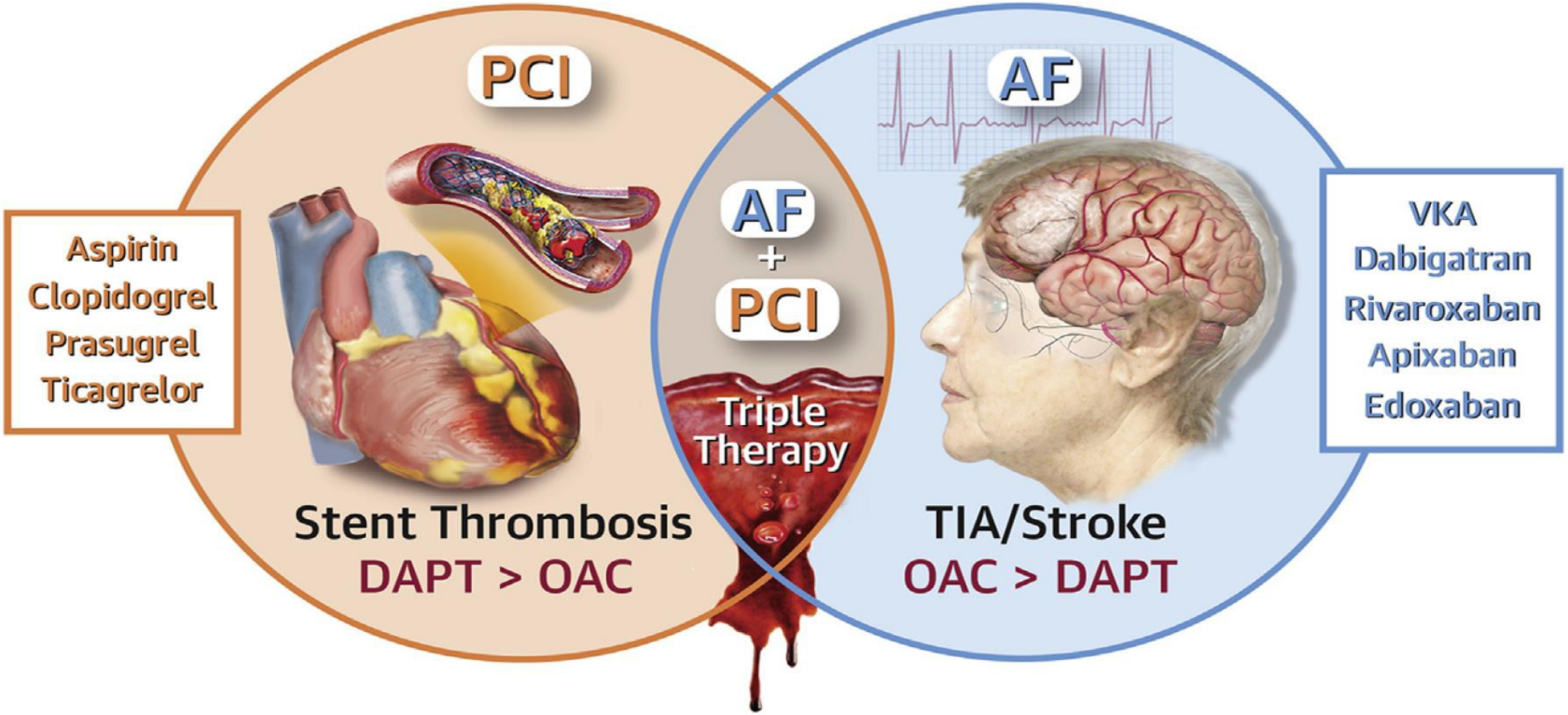
Consultant:

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

Honoraria:

AstraZeneca

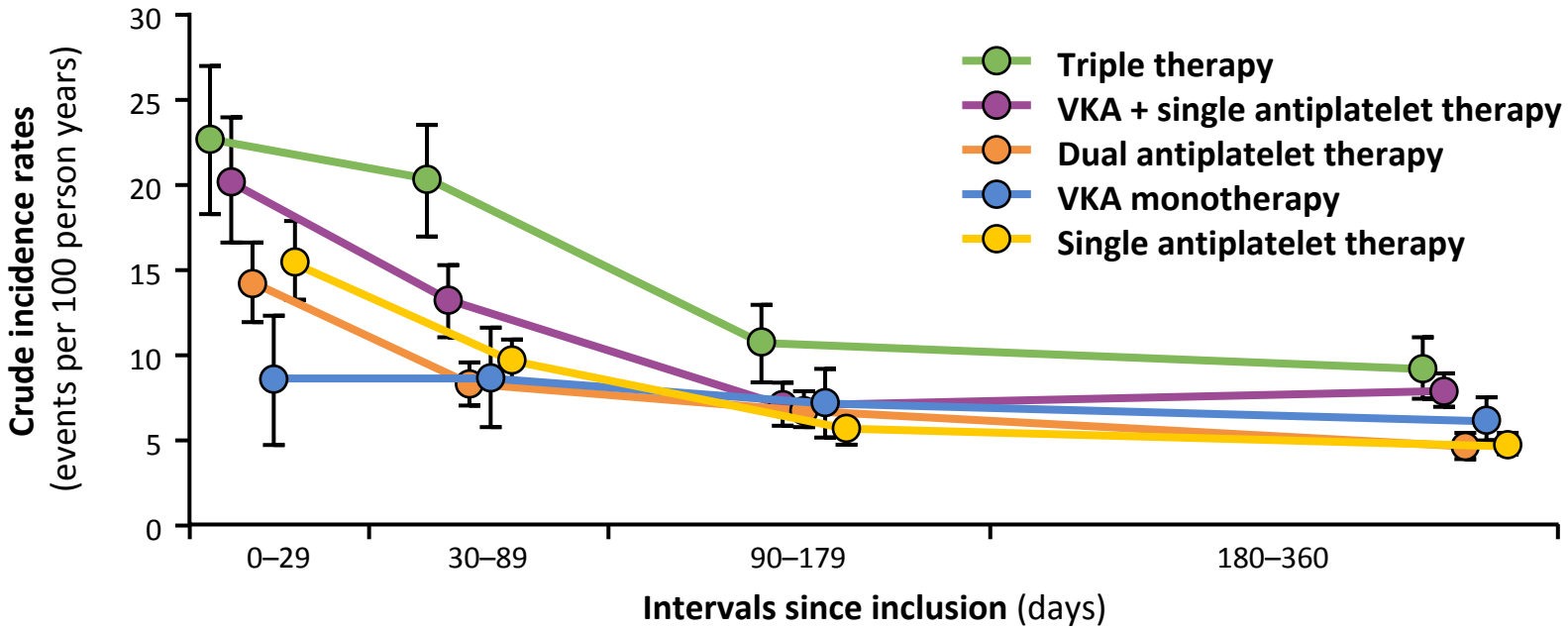
Clinical challenge in patients with atrial fibrillation undergoing PCI



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



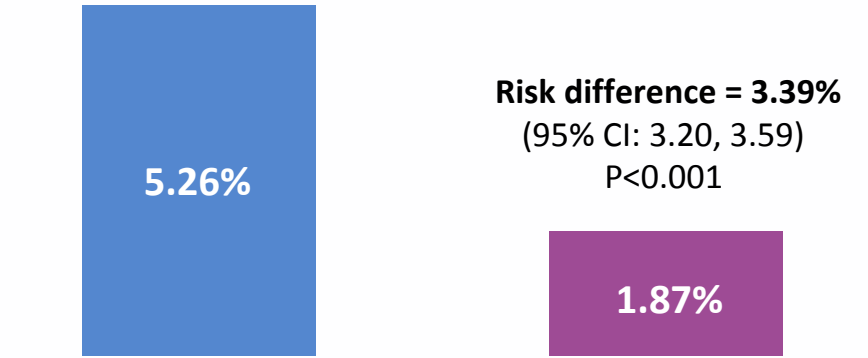
Graph shows crude incidence of fatal and nonfatal bleeding according to antithrombotic regimen in time following inclusion.
Triple therapy includes aspirin, clopidogrel, and VKAs; VKA + single APT includes VKA + aspirin or clopidogrel; dual APT includes aspirin and clopidogrel; VKA monotherapy includes only VKA; single APT includes aspirin or clopidogrel.
APT, antiplatelet therapy; MI, myocardial infarction; VKA, vitamin K antagonist.

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

CI, confidence interval; PCI, percutaneous coronary intervention.

Chatriwalla AK, et al. JAMA 2013;309:1022–9.

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

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**

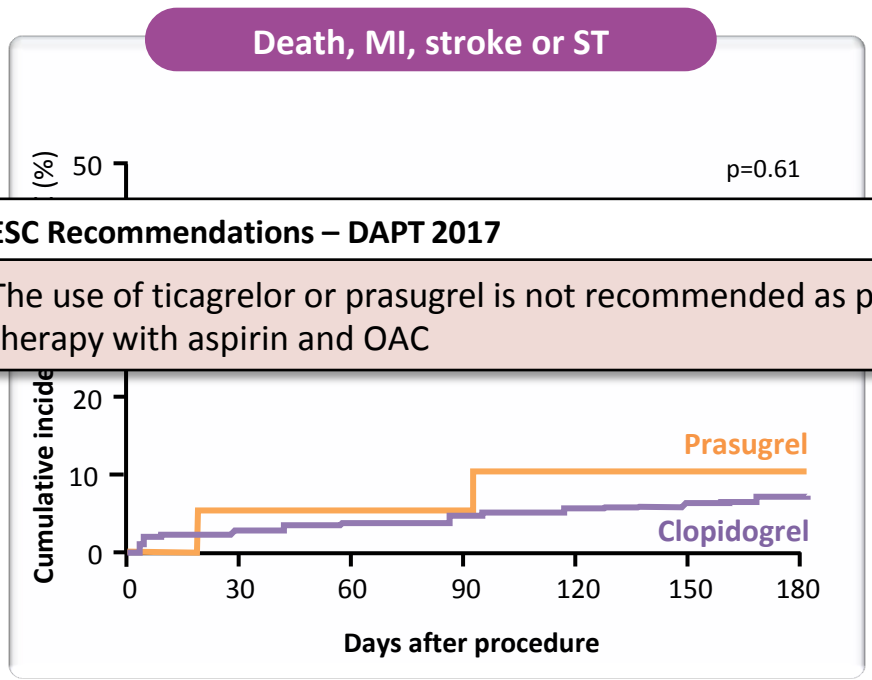
Total permutations *throughout one year:* 2.8 million

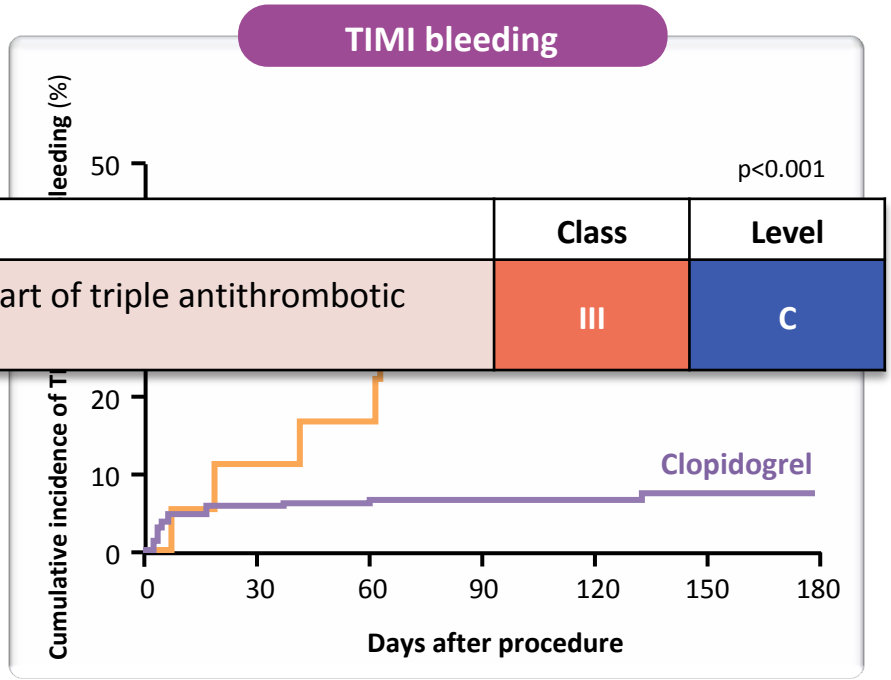
AC, anticoagulant; ASA, acetylsalicylic acid; INR, international normalised ratio.

Gibson CM. JACC 2017;69:172–5.

Triple therapy with aspirin, prasugrel and vitamin K antagonists after DES implantation

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





ESC Recommendations – DAPT 2017	Class	Level
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC	III	C

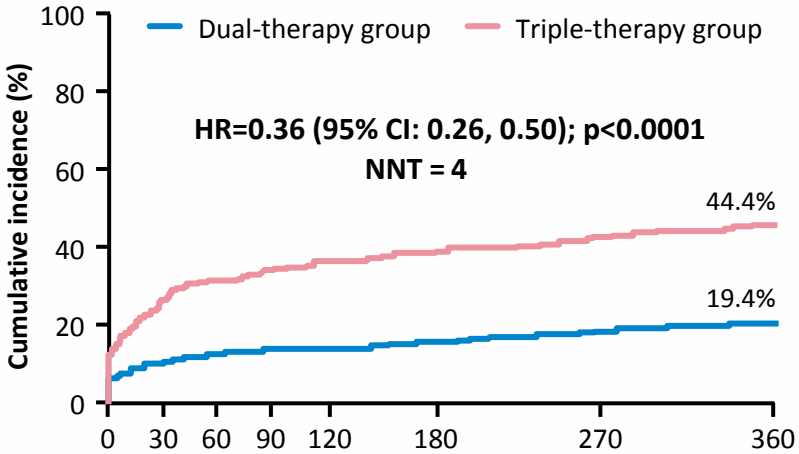
MACCE, major adverse cardiovascular and cerebrovascular ischaemic event(s).

Sarafoff N, et al. J Am Coll Cardiol 2013;61:2060–6.

WOEST : Trial results

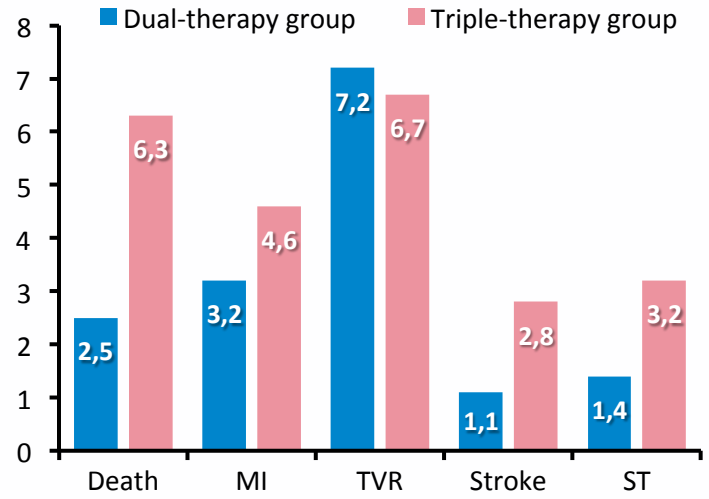
573 patients on OAC undergoing stent (DES/BMS) implantation received oral anticoagulants* + clopidogrel 75 mg qd** and randomised 1:1 to also receive aspirin 80 mg OR aspirin placebo qd

Primary endpoint: any bleeding



Number at risk								
Triple therapy	284	210	194	186	181	173	159	140
Double therapy	279	253	244	241	241	236	226	208

Secondary endpoint: ischaemic events



*INR as originally indicated; **BMS: 1 month; DES and/or ACS:1 year.
BMS, bare-metal stent; DES, drug eluting stent implantation; qd; once daily; ST, stent thrombosis; TVR, target-vessel revascularisation.

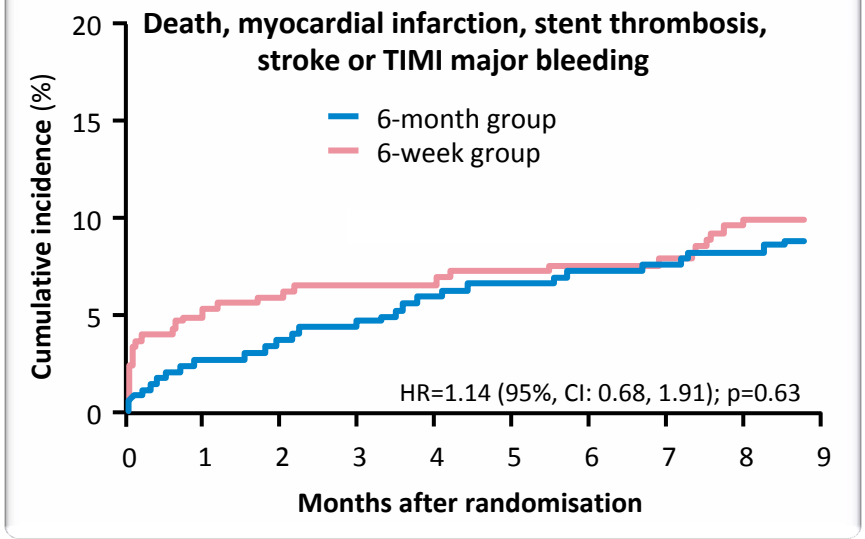
Dewilde W, et al. Lancet 2013;381:1107–15.

ISAR-TRIPLE : Trial results

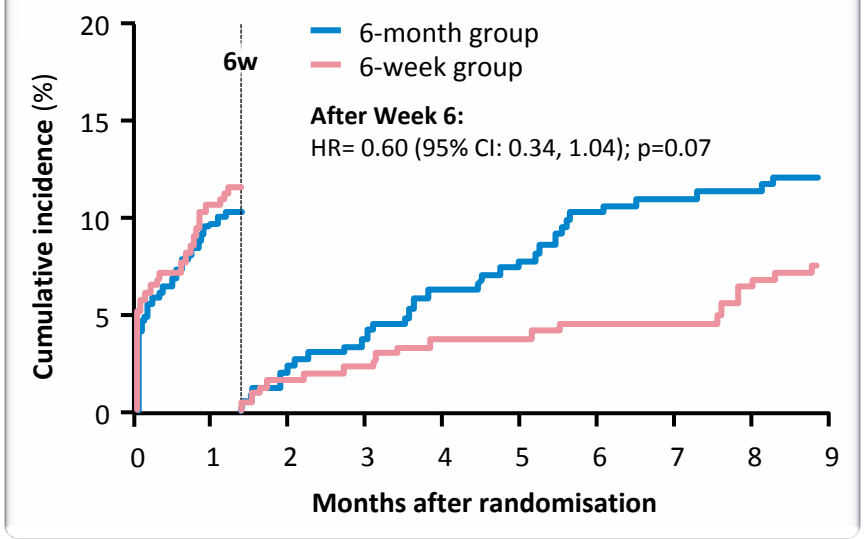
Duration of triple therapy in 600 Pts requiring oral anticoagulation after DES implantation

6-week vs 6-month triple therapy (1:1 randomisation)

Primary endpoint



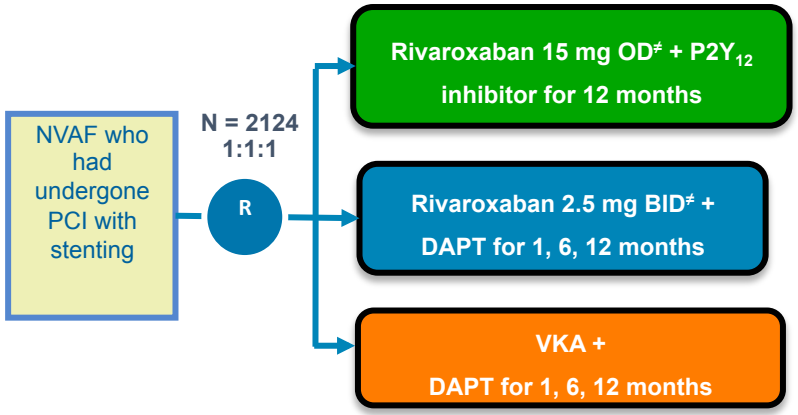
BARC ≥2



Fiedler KA, et al. J Am Coll Cardiol 2015;65:1619–29.

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

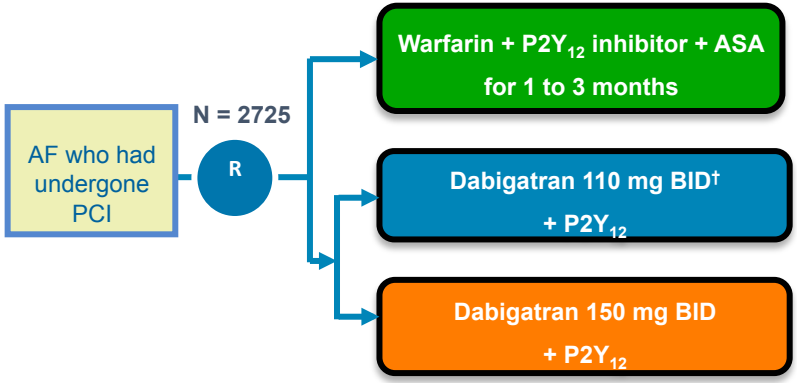
PIONEER AF-PCI[2]



In PIONEER AF-PCI[2] $P2Y_{12}$ = clopidogrel, prasugrel, or ticagrelor

PIONEER AF-PCI[2] demonstrated significantly less bleeding in either rivaroxaban containing arm compared to VKA plus DAPT.

RE-DUAL PCI[3]



In RE-DUAL[3] $P2Y_{12}$ = clopidogrel or ticagrelor

RE-DUAL PCI[3] demonstrated significantly less major or CRNM bleeding in each of the dabigatran strategies compared to the VKA strategy.

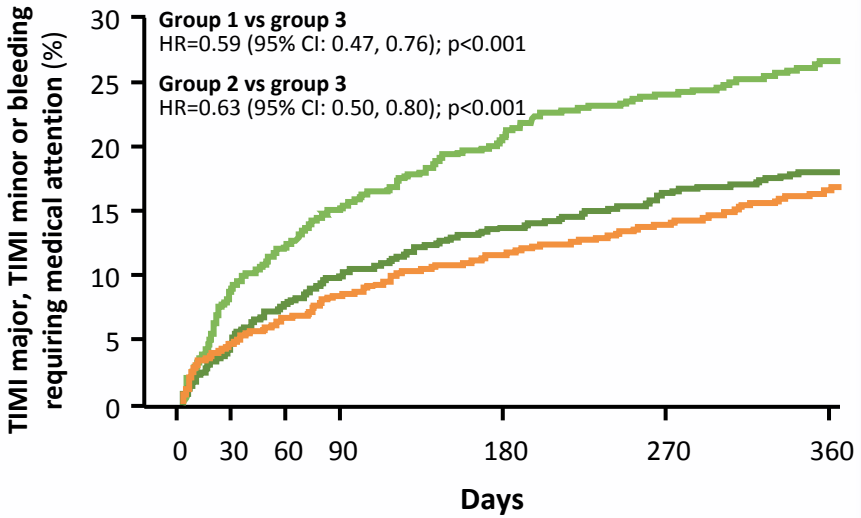
In patients where DAPT (ASA + $P2Y_{12}$) was received for < 12 months SAPT (ASA) was given instead

1. Lopes RD et al. *Am Heart J.* 2018;200:17-23
2. Adapted from Gibson CM et al. *N Engl J. Med.* 2016;375:2423-2434
3. Adapted from Cannon CP et al. *N Engl J. Med.* 2017;377:1513-1524
4. Rivaroxaban US labeling package insert available at www.accessdata.fda.gov/scripts/cder/daf/ accessed April 2018
5. Rivaroxaban SmPC available at www.ema.europa.eu accessed April 2018

Pioneer AF-PCI: Primary safety and secondary efficacy endpoints

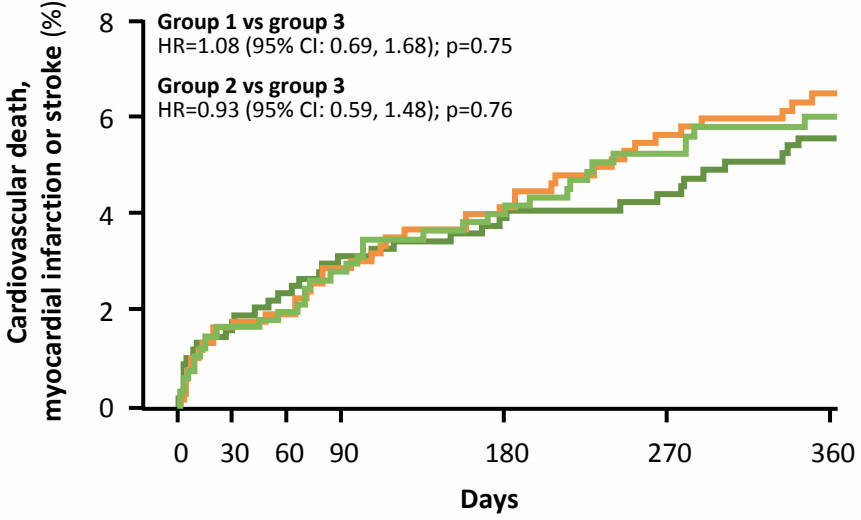
Primary safety endpoint

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 + $P2Y_{12}$

Gibson CM, et al. N Engl J Med 2016;375:2423–34.

PIONEER:
Cumulative incidence of secondary outcomes

	Riva 15 mg + $P2Y_{12}$ 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)
CV death	15 (2.4)	14 (2.2)	11 (1.9)	1.29 (0.59–2.8)	1.19 (0.54–2.62)
Stroke	8 (1.3)	10 (1.5)	7 (1.2)	1.07 (0.39–2.96)	1.36 (0.52–3.58)
MI	19 (3.0)	17 (2.7)	21 (3.5)	0.86 (0.46–1.59)	0.75 (0.40–1.42)
Stent thrombosis	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

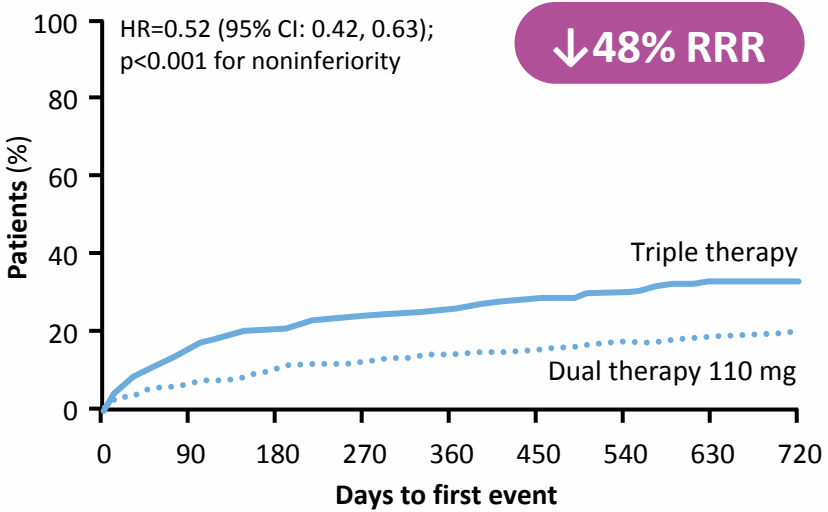
CV, cardiovascular; DAPT, dual antiplatelet therapy; MI, myocardial infarction.

Gibson et al. N Engl J Med 2016;375:2423–34.

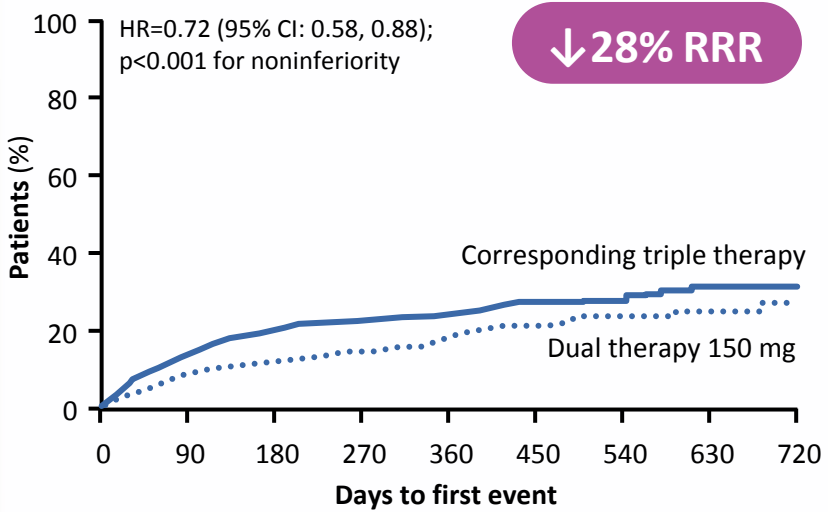
RE-DUAL PCI:
Major or clinically relevant bleeding

2,725 patients with atrial fibrillation undergoing PCI

Dual therapy (110 mg) vs triple therapy



Dual therapy (150 mg) vs triple therapy

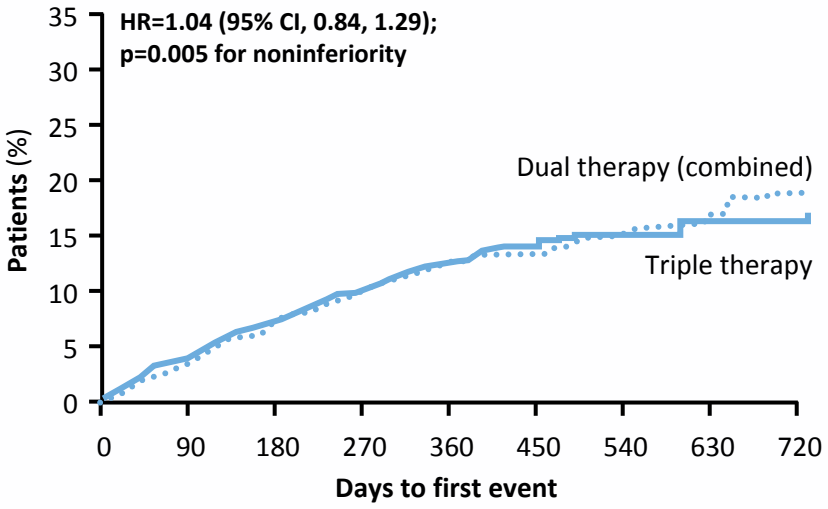


RRR, relative risk reduction.

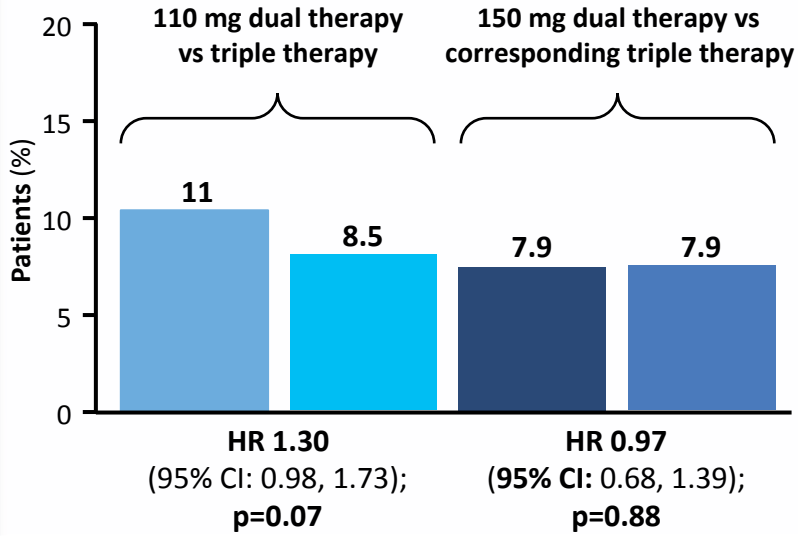
Cannon C, et al. N Engl J Med 2017;377:1513–24.

RE-DUAL PCI: Secondary efficacy endpoints

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



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



Cannon C, et al. N Engl J Med 2017;377:1513–24.

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 (%)	
Death	55 (5.6)	48 (4.9)	1.12 (0.76–1.65)	30 (3.9)	35 (4.6)	0.83 (0.51–1.34)
Stroke	17 (1.7)	13 (1.3)	1.30 (0.63–2.67)	9 (1.2)	8 (1.0)	1.09 (0.42–2.83)
MI	44 (4.5)	29 (3.0)	1.51 (0.94–2.41)	26 (3.4)	22 (2.9)	1.16 (0.66–2.04)
Definite stent thrombosis	15 (1.5)	8 (0.8)	1.86 (0.79–4.40)	7 (0.9)	7 (0.9)	0.99 (0.35–2.81)

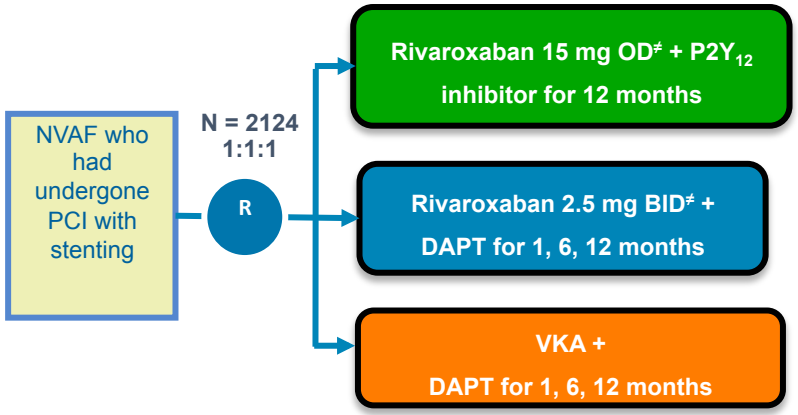
The absolute number of stent thrombosis was low

CV, cardiovascular; DAPT, dual antiplatelet therapy; MI, myocardial infarction.

Cannon C, et al. N Engl J Med 2017;377:1513–24.

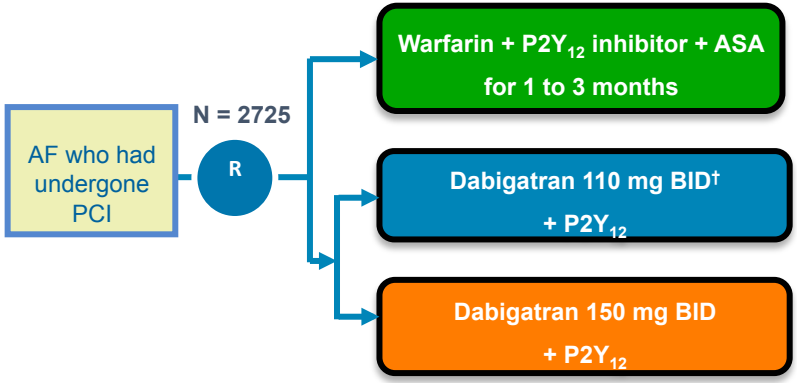
Safety and efficacy of dual vs. triple antithrombotic therapy in patients with AF following PCI

PIONEER AF-PCI[2]



In PIONEER AF-PCI[2] $P2Y_{12}$ = clopidogrel, prasugrel, or ticagrelor

RE-DUAL PCI[3]



In RE-DUAL[3] $P2Y_{12}$ = 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.[1]

In patients where DAPT (ASA + $P2Y_{12}$) was received for < 12 months SAPT (ASA) was given instead

1. Lopes RD et al. *Am Heart J.* 2018;200:17-23
2. Adapted from Gibson CM et al. *N Engl J. Med.* 2016;375:2423-2434
3. Adapted from Cannon CP et al. *N Engl J. Med.* 2017;377:1513-1524
4. Rivaroxaban US labeling package insert available at www.accessdata.fda.gov/scripts/cder/daf/ accessed April 2018
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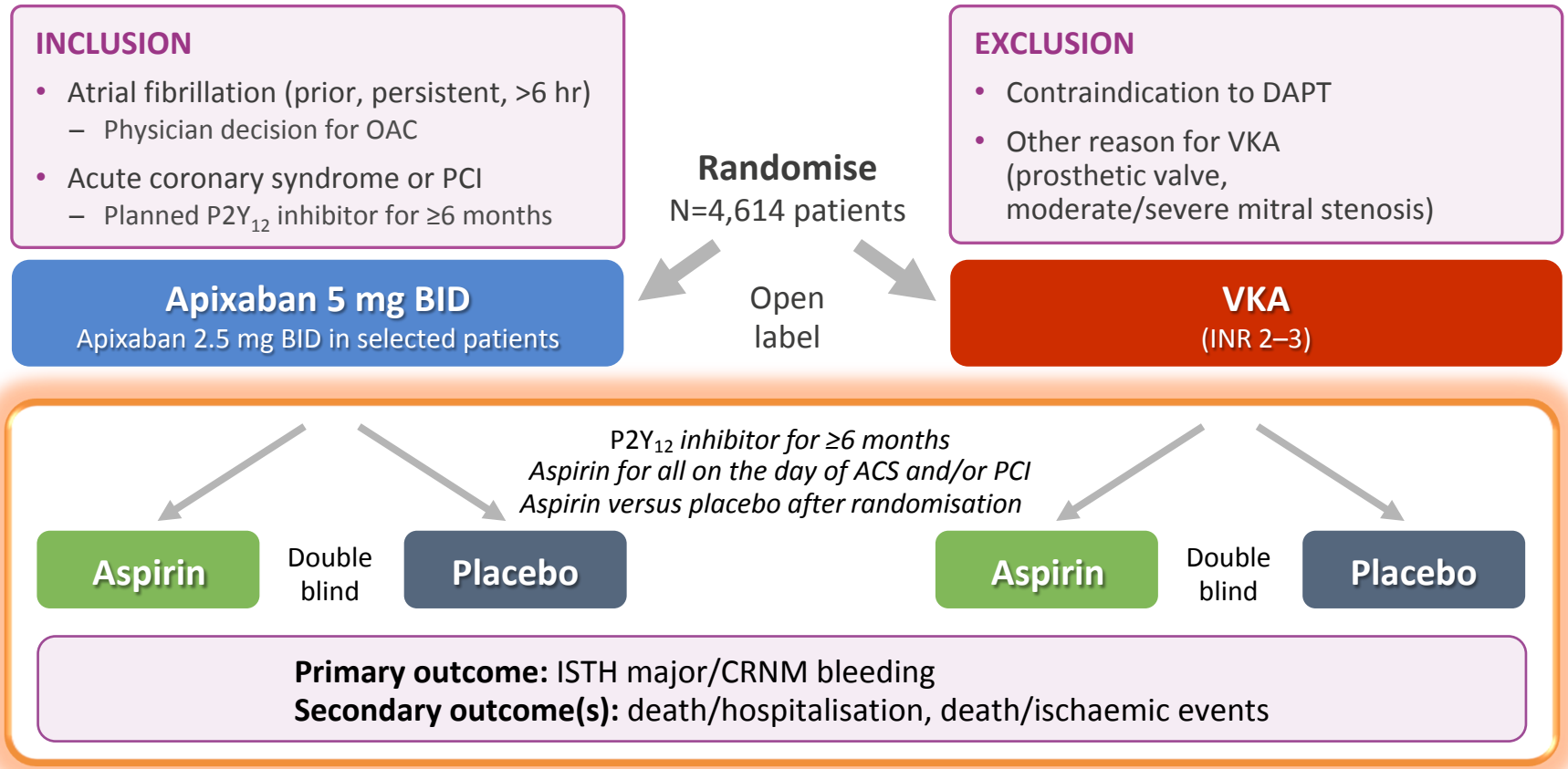
AUGUSTUS : Study design

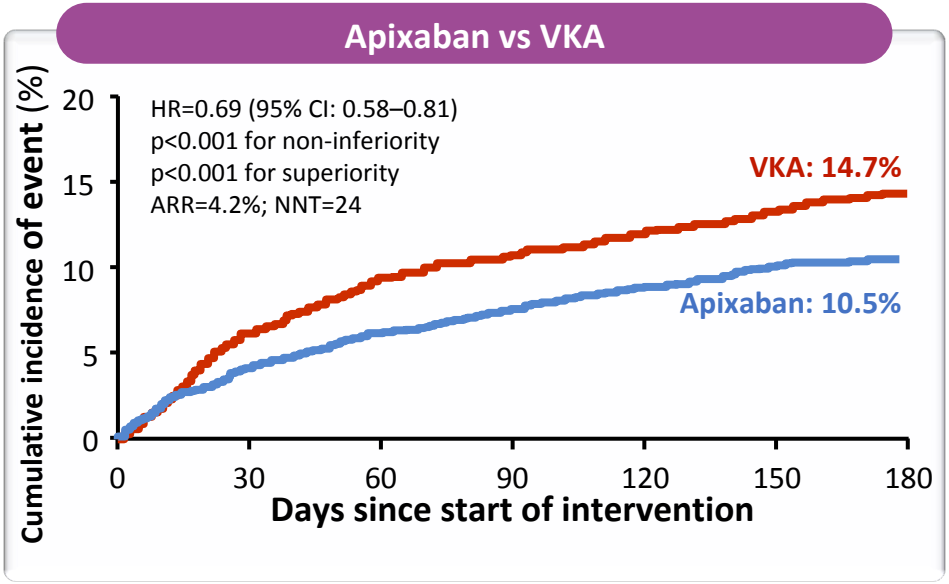


BID, twice daily; INR, international normalised ratio.

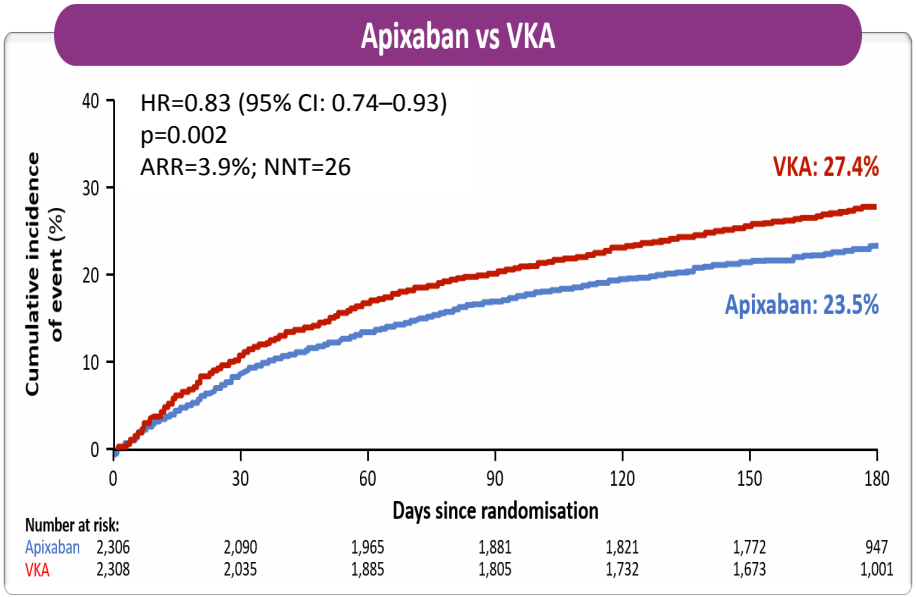
Lopes RD, et al. Am Heart J 2018;200:17-23.

AUGUSTUS primary Outcome : Apixaban vs VKA

ISTH major or CRNM bleeding



Death or hospitalization



ARR, absolute risk reduction; CI, confidence interval; HR, hazard ratio; NNT, number needed to treat.

Lopes RD, et al. N Engl J Med 2019;doi:10.1056/NEJMoa1817083;
Lopes RD. Final-AUGUSTUS-Main-Results-ACC19-PRESENTATION-17-March-2019.

AUGUSTUS secondary outcome : Composite of ischaemic events : Apixaban vs VKA

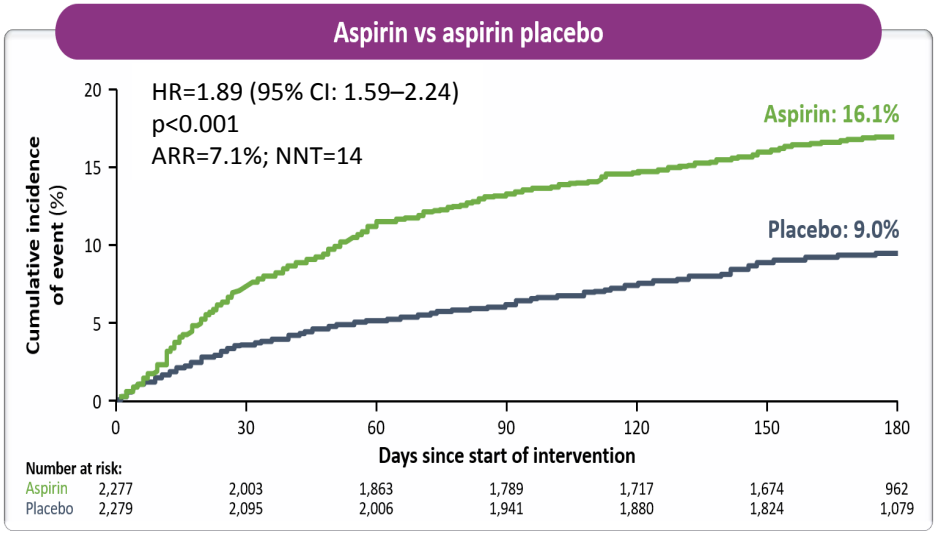
Endpoint	Apixaban (N=2306)	VKA (N=2308)	HR (95% CI)
Death/Ischaemic events (%)	6.7	7.1	0.93 (0.75–1.16)
Death (%)	3.3	3.2	1.03 (0.75–1.42)
CV death (%)	2.5	2.3	1.05 (0.72–1.52)
Stroke (%)	**0.6**	**1.1**	**0.50 (0.26–0.97)**
Myocardial infarction (%)	3.1	3.5	0.89 (0.65–1.23)
Definite or probable stent thrombosis (%)	0.6	0.8	0.77 (0.38–1.56)
Urgent revascularisation (%)	1.7	1.9	0.90 (0.59–1.38)
Hospitalisation (%)	**22.5**	**26.3**	**0.83 (0.74–0.93)**

CV, cardiovascular.

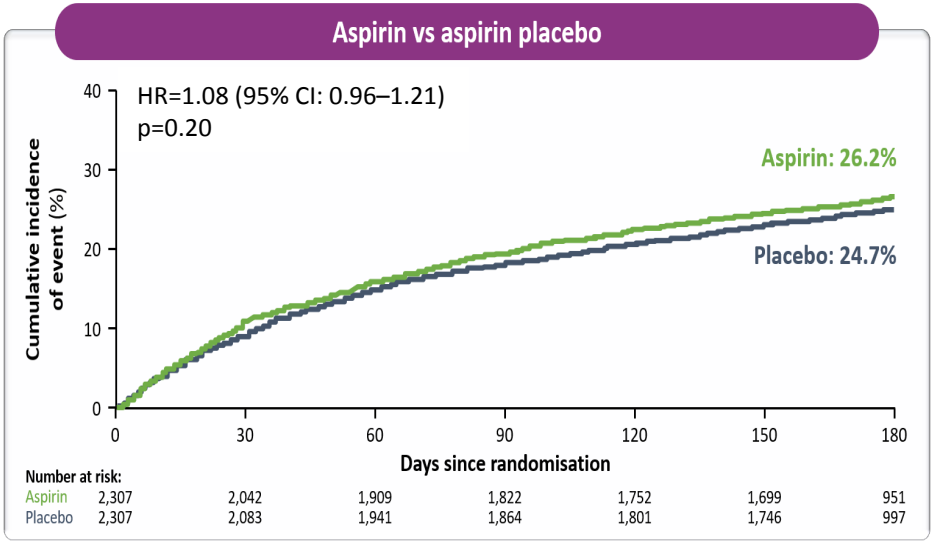
Lopes RD, et al. N Engl J Med 2019;doi:10.1056/NEJMoa1817083;
Lopes RD. Final-AUGUSTUS-Main-Results-ACC19-PRESENTATION-17-March-2019.

AUGUSTUS primary Outcome : aspirin vs placebo

ISTH major or CRNM bleeding



Death or hospitalization



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Lopes RD, et al. N Engl J Med 2019;doi:10.1056/NEJMoa1817083;
Lopes RD. Final-AUGUSTUS-Main-Results-ACC19-PRESENTATION-17-March-2019.

AUGUSTUS secondary outcome: Death or ischaemic events : aspirin vs aspirin placebo

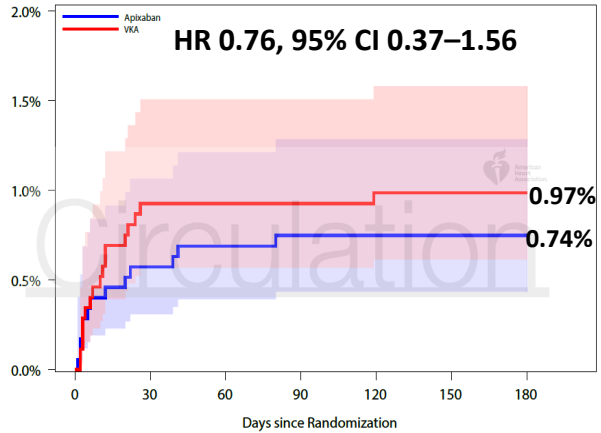
Endpoint	Aspirin (N=2,307)	Placebo (N=2,307)	HR (95% CI)
Death, n (%)	**72** (3.1)	**79** (3.4)	**0.91** (0.66–1.26)
CV death, n (%)	**53** (2.3)	**58** (2.5)	**0.92** (0.63–1.33)
Stroke, n (%)	**20** (0.9)	**19** (0.8)	**1.06** (0.56–1.98)
Myocardial infarction, n (%)	**68** (2.9)	**84** (3.6)	**0.81** (0.59–1.12)
Definite or probable stent thrombosis, n (%)	**11** (0.5)	**21** (0.9)	**0.52** (0.25–1.08)
Urgent revascularisation, n (%)	**37** (1.6)	**47** (2.0)	**0.79** (0.51–1.21)
Hospitalisation, n (%)	**585** (25.4)	**540** (23.4)	**1.10** (0.98–1.24)

Lopes RD, et al. N Engl J Med 2019; doi:10.1056/NEJMoa1817083.

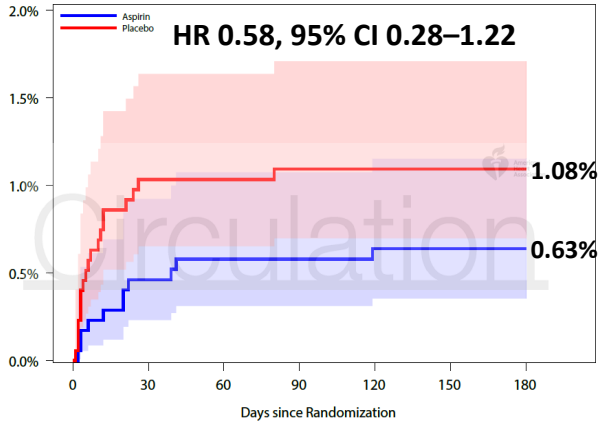
AUGUSTUS : Stent Thrombosis

Definite/Probable Stent Thrombosis

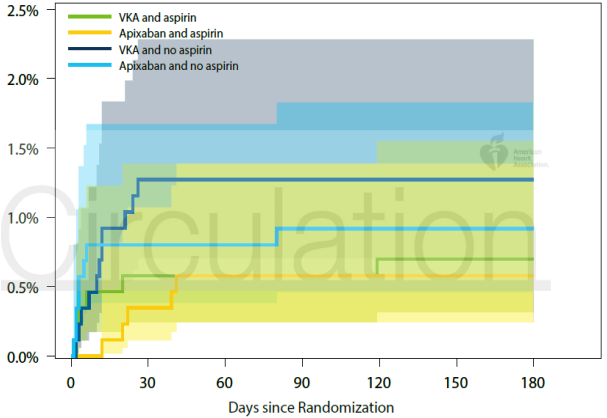
Apixaban vs VKA



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.

Lopez R et al. 10.1161/CIRCULATIONAHA.119.044584.

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

ENTRUST-AFPCI

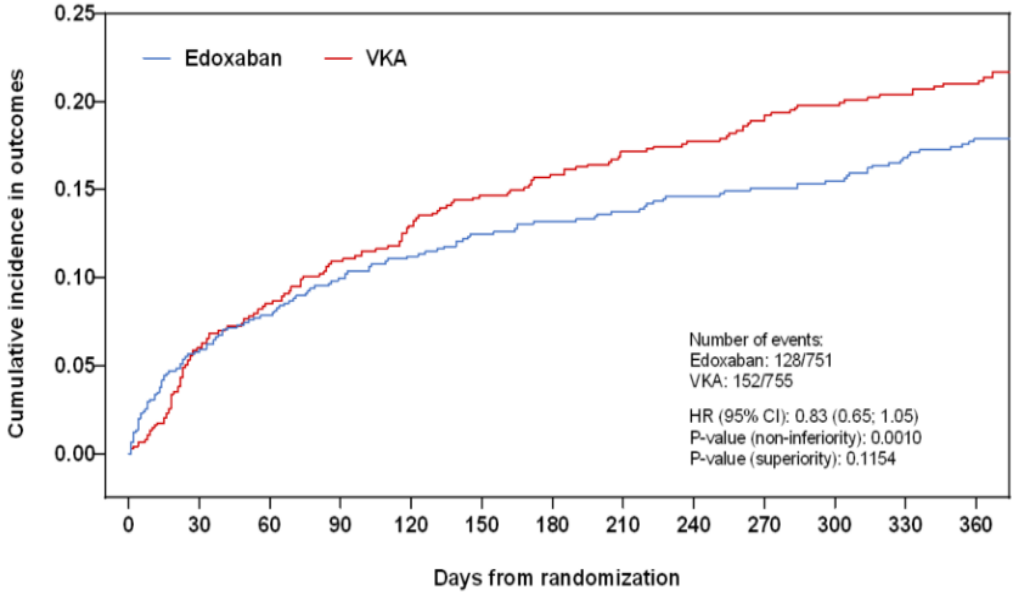
RANDOMIZE

- *Edoxaban 60 mg/day**
- *$P2Y_{12}$ inhibitor** (without aspirin)*

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

Primary Study Endpoint

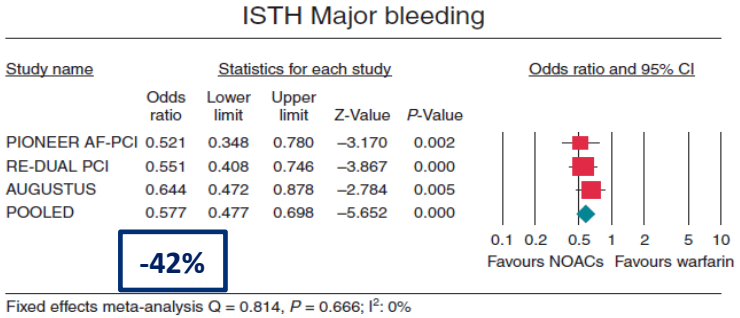
ITT Analysis (N=1506), overall study period

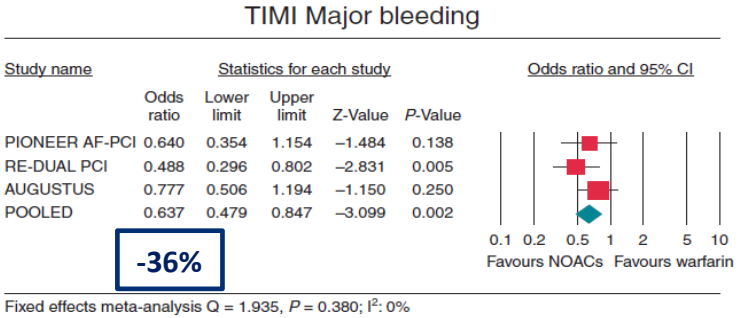


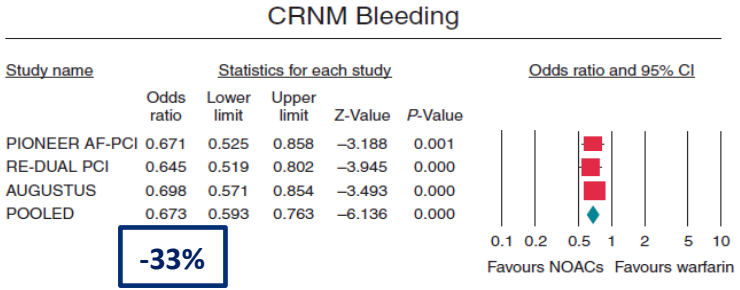
Meta-analysis of pooled data from CRT : Bleeding : NOAC better than VKA

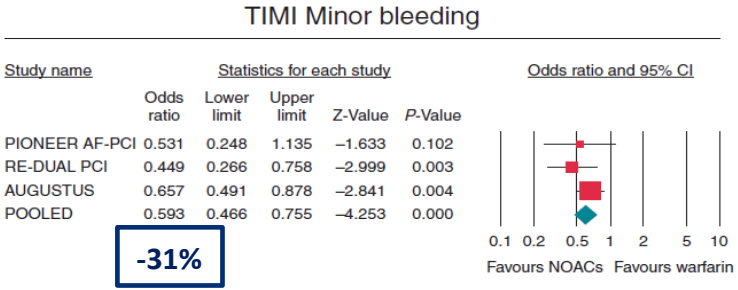
NOAC-based regimens associated with significantly less bleeding than VKA-based regimens

(B) NOACs versus VKA







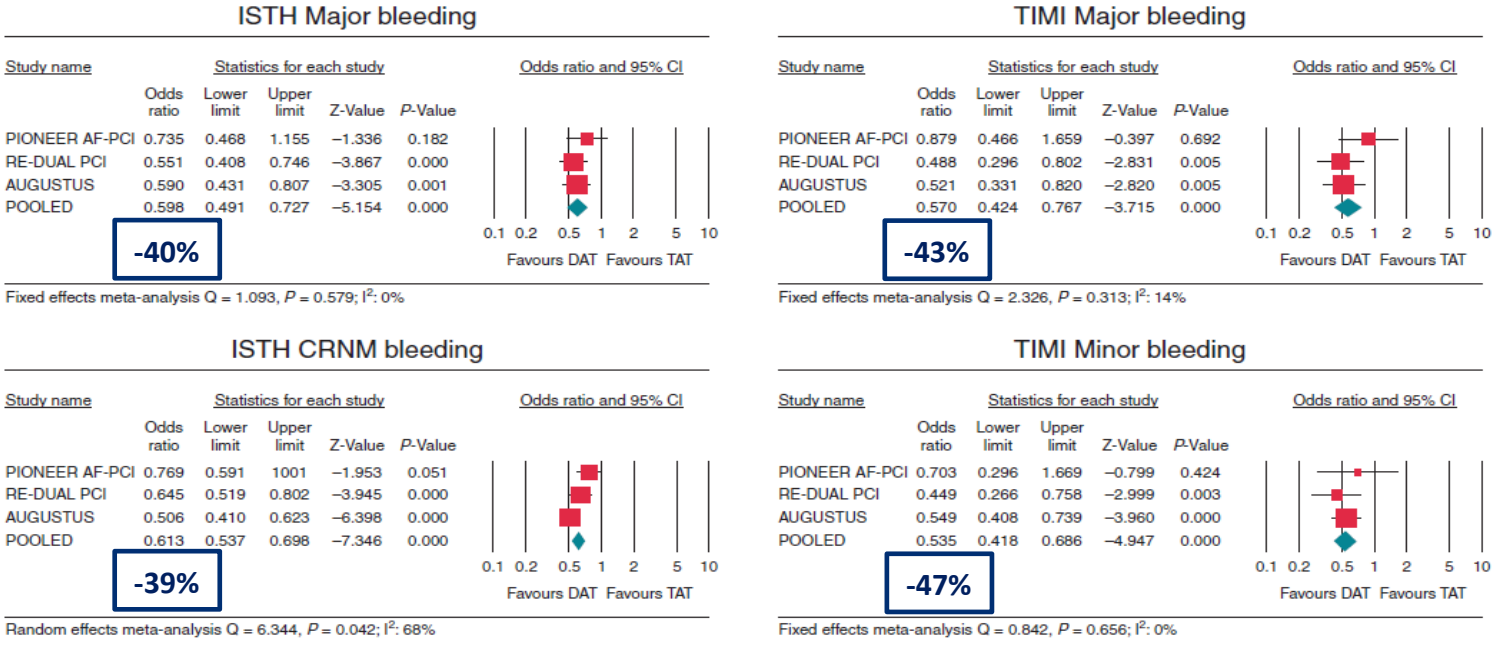


Potpara TS et al. Europace. 2020 Jan 1;22(1):33-46.

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



Potpara TS et al. Europace. 2020 Jan 1;22(1):33-46.

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

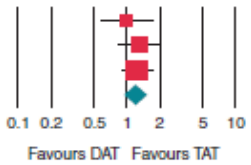
Higher rates of ST with DAT vs TAT

Similar rates of MI & ST with NOAC vs VKA

(A) DAT versus TAT

Myocardial infarction

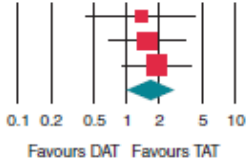
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	*p*-Value
PIONEER AF-PCI	1.008	0.577	1.762	0.028	0.977
RE-DUAL PCI	1.291	0.828	2.013	1.129	0.259
AUGUSTUS	1.244	0.899	1.722	1.317	0.188
POOLED	1.211	0.955	1.535	1.578	0.115



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

Stent thrombosis

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	*p*-Value
PIONEER AF-PCI	1.370	0.435	4.318	0.538	0.591
RE-DUAL PCI	1.554	0.689	3.503	1.063	0.288
AUGUSTUS	1.923	0.925	4.001	1.750	0.080
POOLED	1.672	1.022	2.733	2.048	0.041

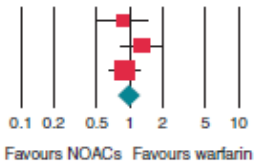


Fixed effects meta-analysis Q = 0.287, *P* = 0.866; I^2: 0%

(B) NOAC versus VKA

Myocardial infarction

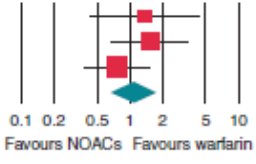
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	*p*-Value
PIONEER AF-PCI	0.848	0.491	1.465	−0.590	0.555
RE-DUAL PCI	1.291	0.828	2.013	1.129	0.259
AUGUSTUS	0.898	0.649	1.241	−0.654	0.513
POOLED	0.984	0.777	1.246	−0.132	0.895



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

Stent thrombosis

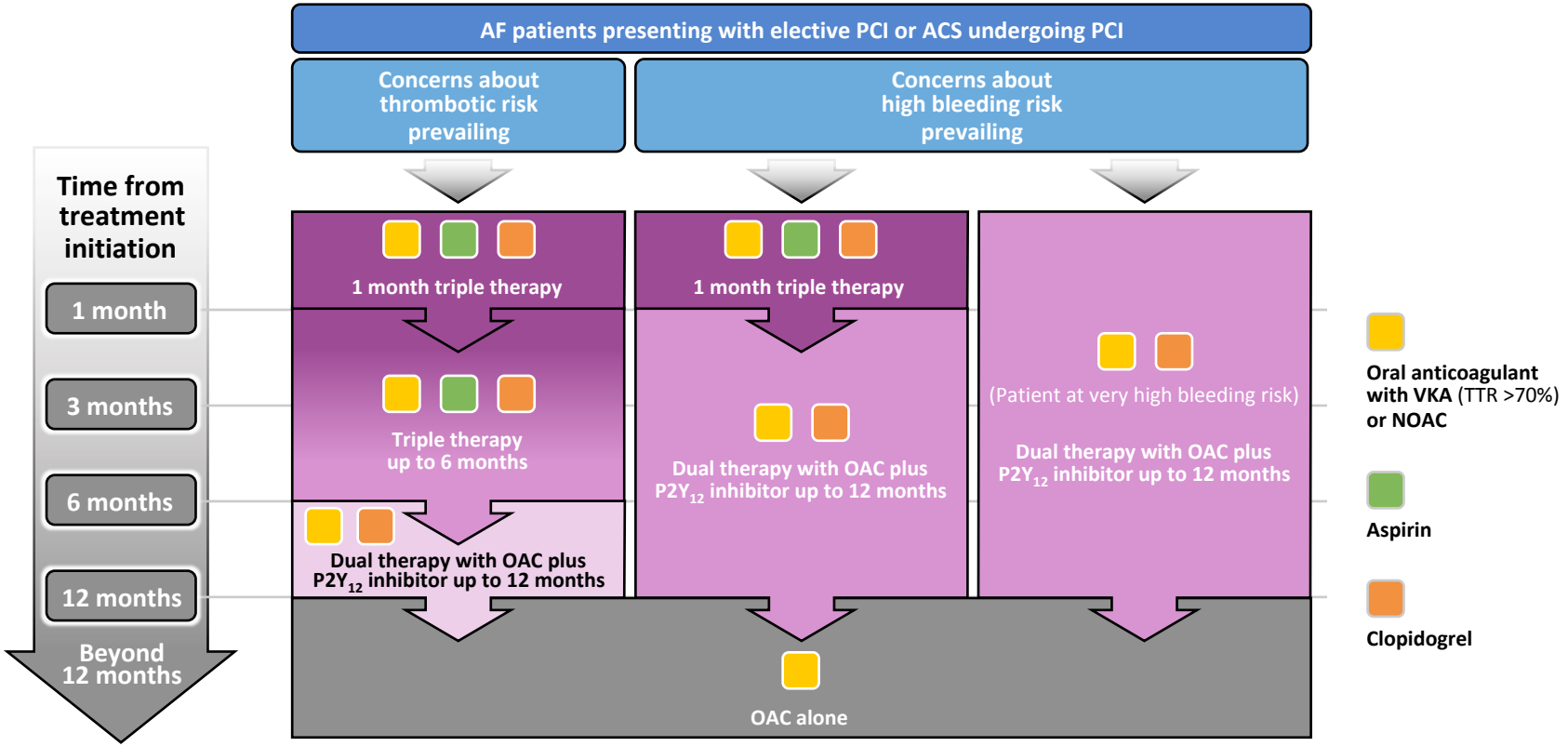
Study name	Odds ratio	Lower limit	Upper limit	Z-Value	*p*-Value
PIONEER AF-PCI	1.370	0.435	4.318	0.538	0.591
RE-DUAL PCI	1.554	0.689	3.503	1.063	0.288
AUGUSTUS	0.776	0.385	1.564	−0.710	0.478
POOLED	1.095	0.676	1.773	0.368	0.713



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

Potpara TS et al. Europace. 2020 Jan 1;22(1):33-46.

ESC 2018 Joint European consensus, endorsed by Asia Pacific Heart Rhythm Society

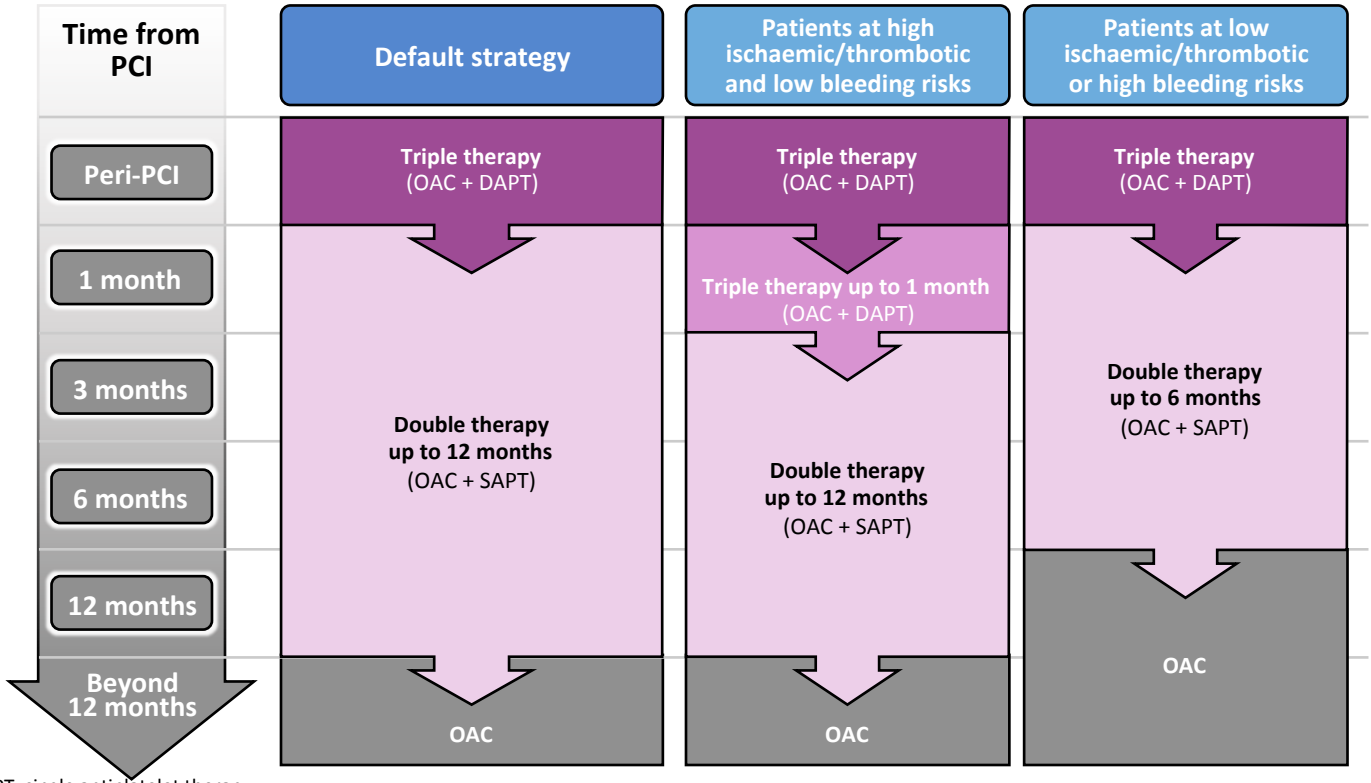


1. Periprocedural administration of aspirin and clopidogrel during PCI is recommended irrespective of the treatment strategy; as dual therapy, potent $P2Y_{12}$ inhibitors (ticagrelor) may be combined with dabigatran;
2. High atherothrombotic risk (for elective PCI, use SYNTAX score; for ACS, Grace score >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

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.

Patients with angina and/or dyspnoea and coronary artery disease - Event prevention (9)

ESC European Society of Cardiology

Recommendations	Class	Level
Antithrombotic therapy in post-PCI patients with AF or another indication for an OAC		
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[a] is low, or if concerns about bleeding risk prevail over concerns about the risk of stent thrombosis,[a] irrespective of the type of stent used.	IIa	B
Triple therapy with aspirin, clopidogrel, and an OAC for ≥1 month should be considered when the risk of stent thrombosis[a] 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%.	IIa	B

[a] 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.

Patients with angina and/or dyspnoea and coronary artery disease - Event prevention (10)

Recommendations	Class	Level
Antithrombotic therapy in post-PCI patients with AF or another indication for an OAC		
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,[a] irrespective of the type of stent used.	IIb	C
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and an OAC.	III	C

[a] 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 coronary revascularization

- Which anticoagulant treatment: In most patients, NOACs should be preferred over VKA unless contraindicated
- Which $P2Y_{12}$ inhibitor : Clopidogrel is the first-line choice; ticagrelor may be an alternative in patients at high ischemic/thrombotic and low bleeding risk; prasugrel should be avoided.
- 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