ACTION Study Group
Institute of Cardiology
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AAP, anticoagulants et stenting coronaire

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Ensemble, imaginons la cardiologie de demain

www.action-cœur.org

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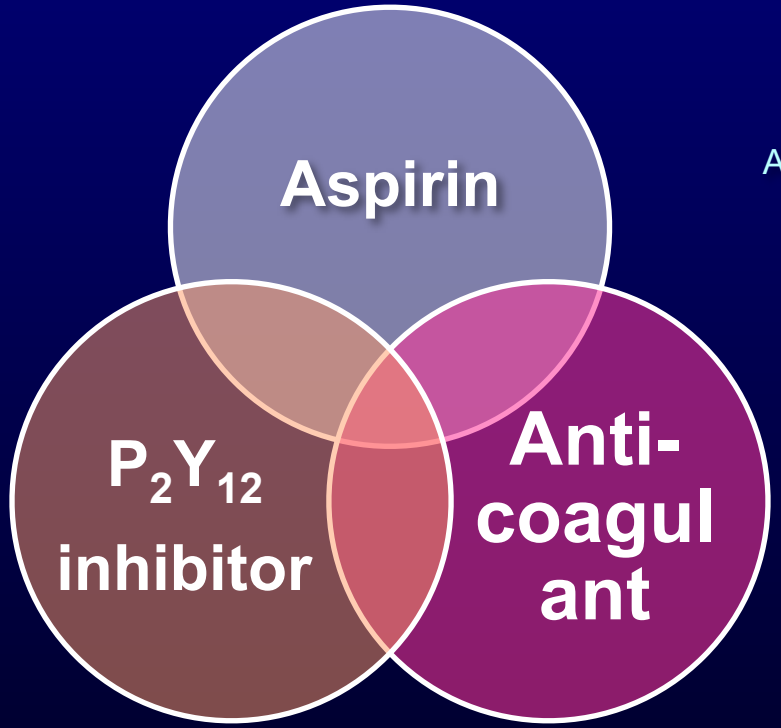
Antithrombotic Therapy

The Challenge of Combining Agents

Indication for Antiplatelet Therapy

ACS

Stent



Indication for Anticoagulation

AF

VHD

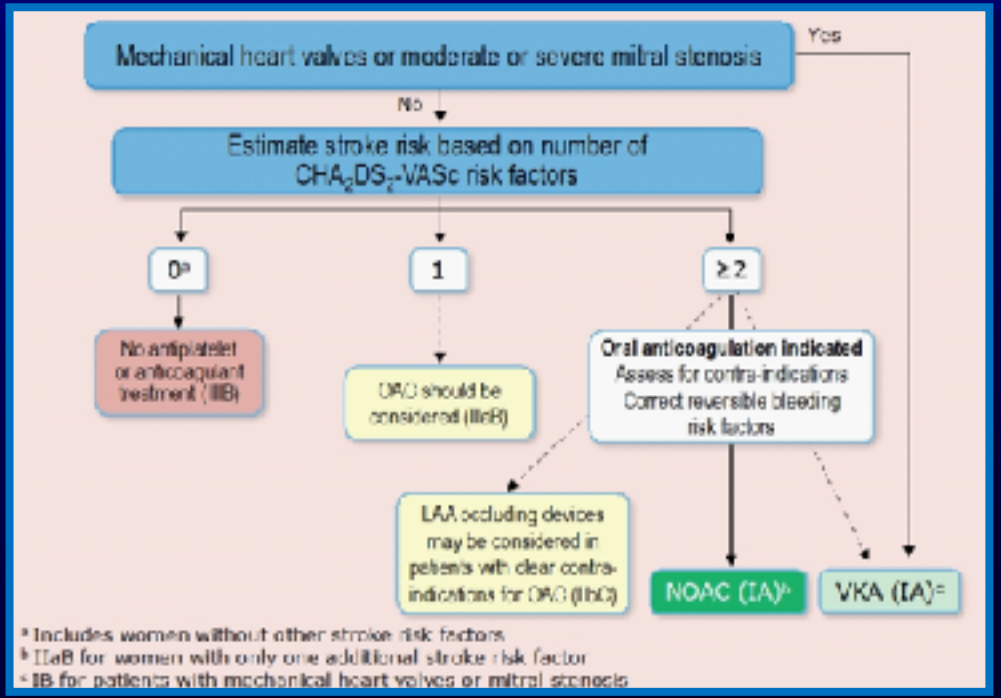
DVT/PE

1st solution: avoid anticoagulation

No anticoagulation in low risk AFib patients

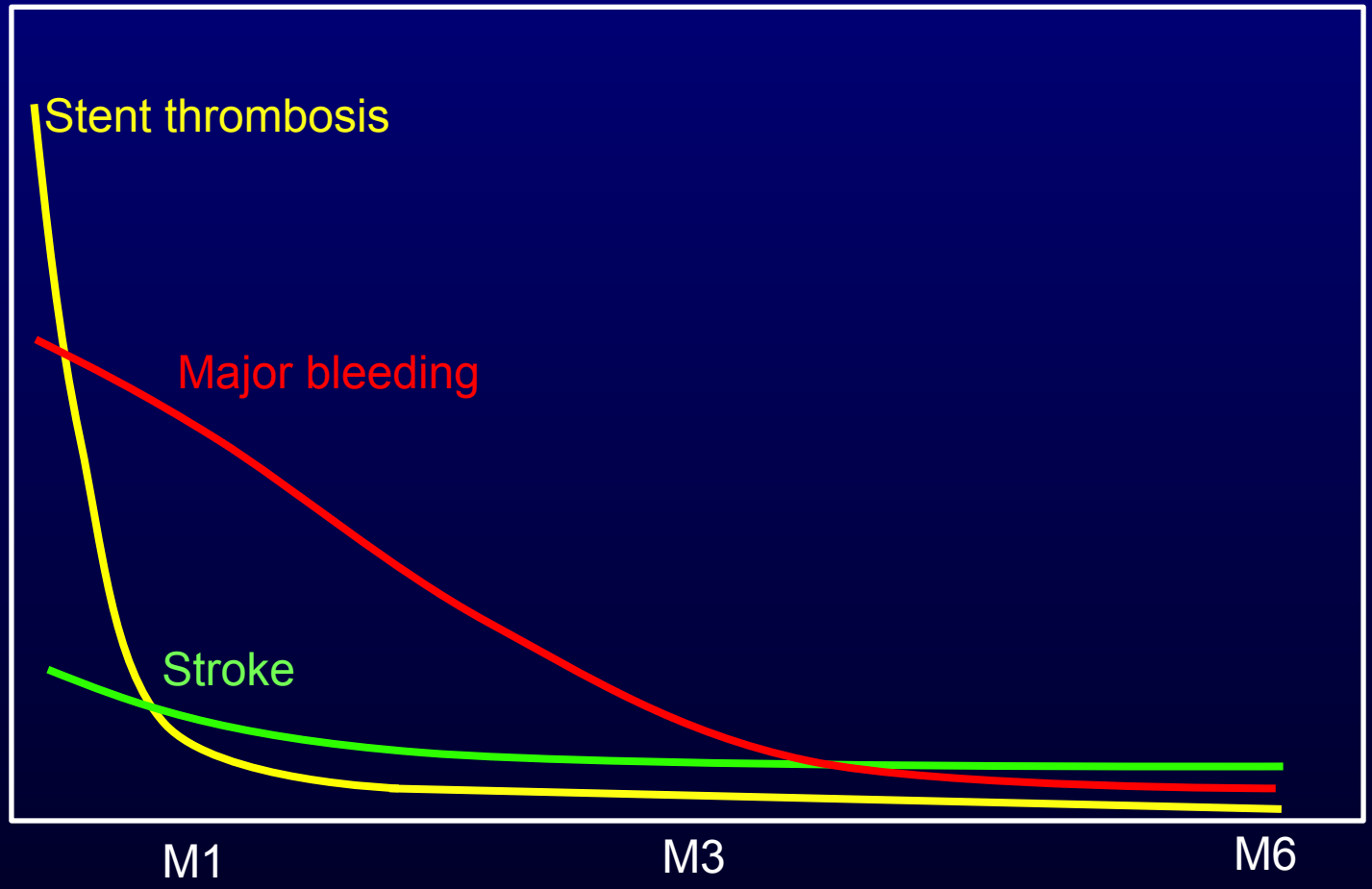
CHA_2DS_2-VASc risk factor	Points
Congestive heart failure Signs/symptoms of heart failure or objective evidence of reduced left-ventricular ejection fraction	1
Hypertension Resting blood pressure >140/90 mmHg on at least two occasions or current antihypertensive treatment	1
Age 75 years or older	2
Diabetes mellitus Fasting glucose >125 mg/dL (7 mmol/L) or treatment with oral hypoglycaemic agent and/or insulin	1
Previous stroke, transient ischaemic attack, or thromboembolism	2
Vascular disease Previous myocardial infarction, peripheral artery disease, or aortic plaque	1
Age 65–74 years	1
Sex category (female)	1

Recommendations	Class	Level
Oral anticoagulation therapy to prevent thromboembolism is recommended for all male AF patients with a CHA_2DS_2-VASc score of 2 or more.	I	A
Oral anticoagulation therapy to prevent thromboembolism is recommended in all female AF patients with a CHA_2DS_2-VASc score of 3 or more.	I	A
Oral anticoagulation therapy to prevent thromboembolism should be considered in male AF patients with a CHA_2DS_2-VASc score of 1, considering individual characteristics and patient preferences.	IIa	B
Oral anticoagulation therapy to prevent thromboembolism should be considered in female AF patients with a CHA_2DS_2-VASc score of 2, considering individual characteristics and patient preferences.	IIa	B

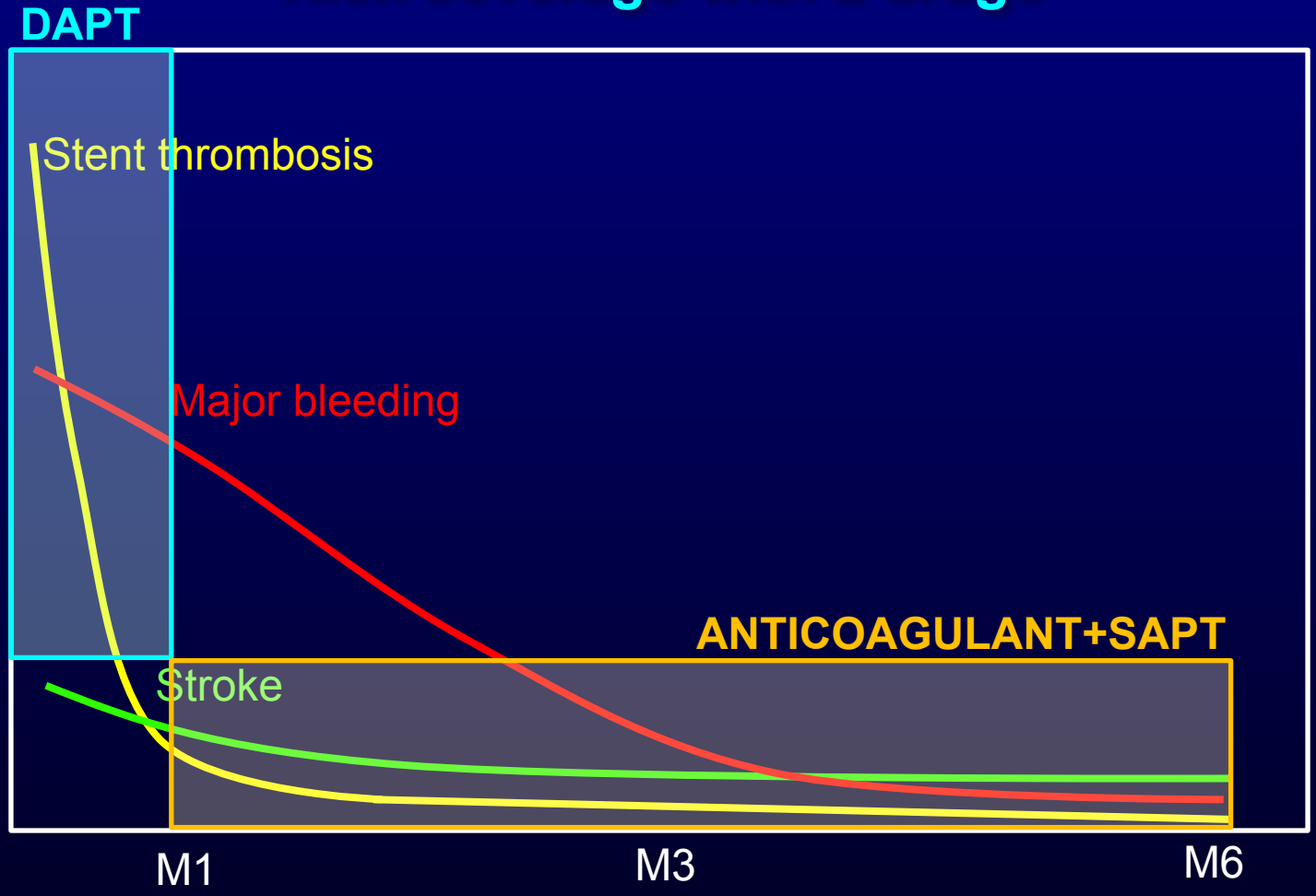


Kirchoff et al. Eur Heart J 2016

Risk evolution



Risk coverage with 2 drugs



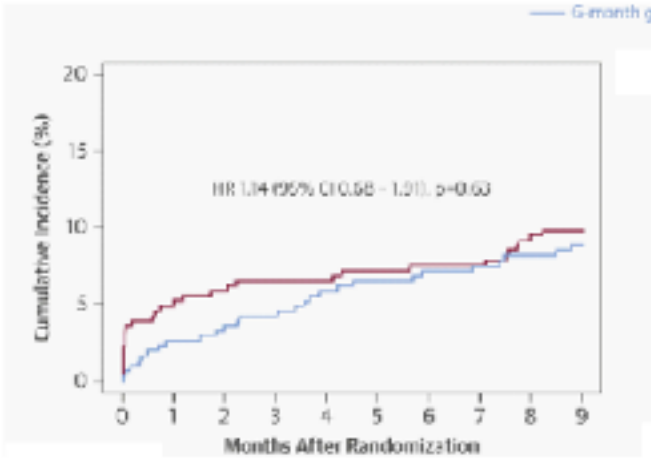
2nd solution: shorten duration of triple treatment

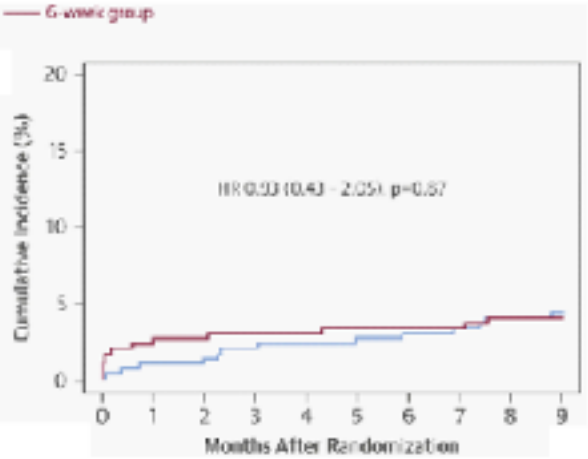
Short triple treatment: ISAR-TRIPLE

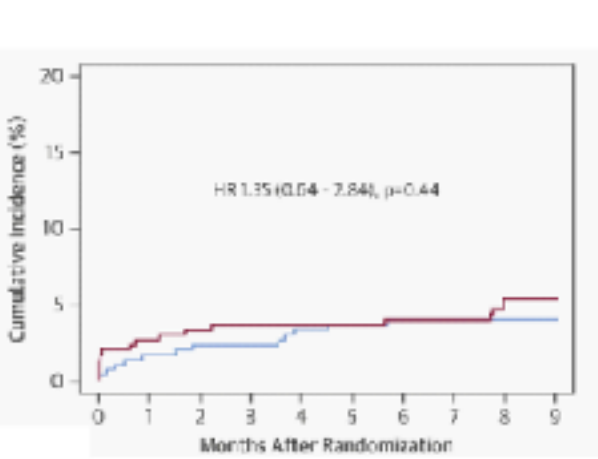
1° EP: death, MI, stent thrombosis, stroke or TIMI major bleeding

2° EP: cardiac death, MI, stent thrombosis or isch. stroke

TIMI major bleeding



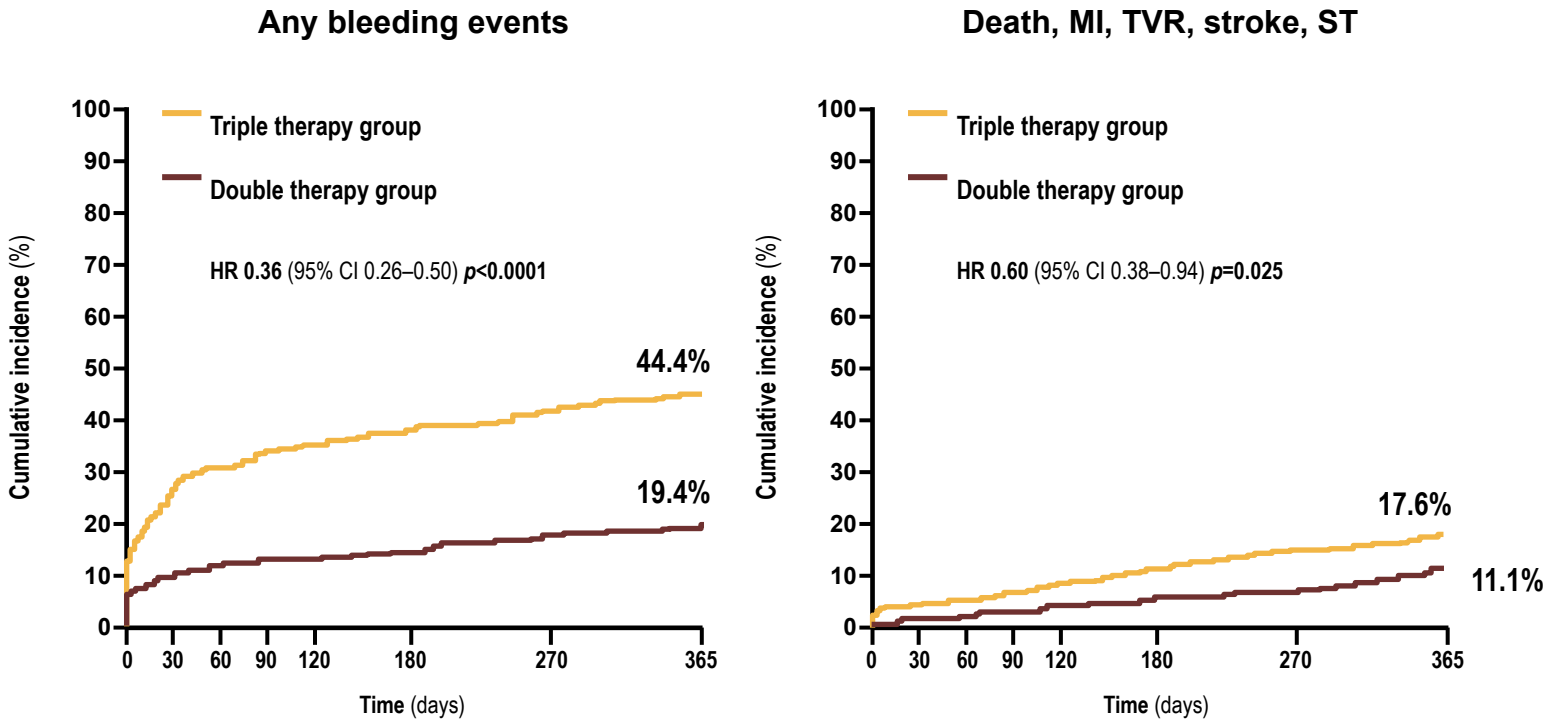




Fiedler et al. J Am Coll Cardiol. 2015

3rd solution: avoid triple treatment

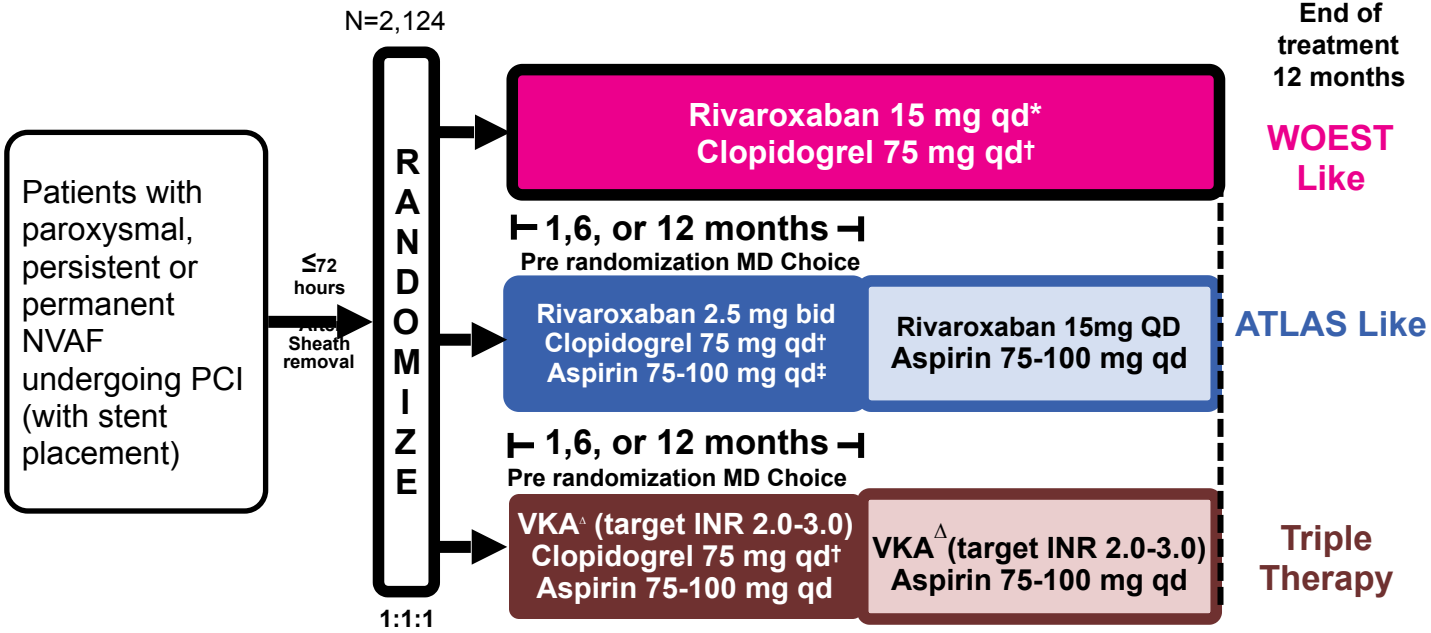
No aspirin (and VKA): WOEST



MI, myocardial infarction; OAC, oral anticoagulant; PCI, percutaneous coronary intervention; ST, stent thrombosis; TVR, target vessel revascularisation

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

No aspirin (and Rivaroxaban): PIONEER



- **Primary endpoint: TIMI major + minor + bleeding requiring medical attention**
- **Secondary endpoint: CV death, MI, and stroke**

*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.

†Alternative $P2Y_{12}$ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.

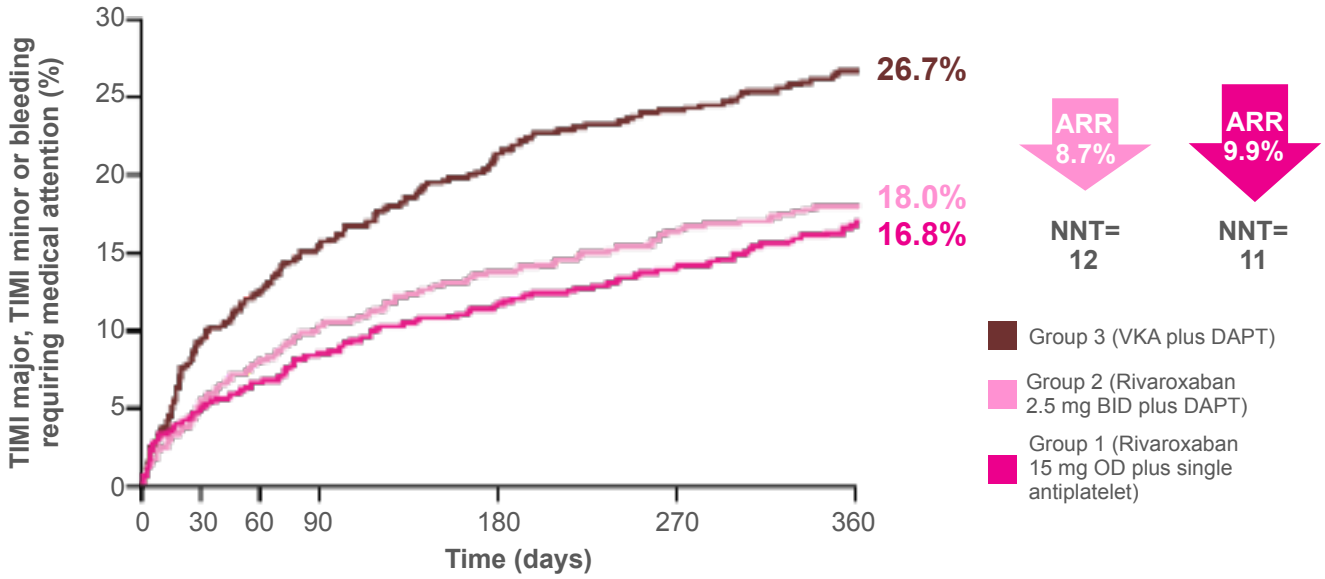
‡Low-dose aspirin (75-100 mg/d). Δ Open label VKA

Gibson CM et al, *New Engl J Med* 2016; doi: 10.1056/NEJMoa1611594

Significantly Improved Safety vs the VKA Strategy

Rivaroxaban 15 mg OD plus single antiplatelet 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

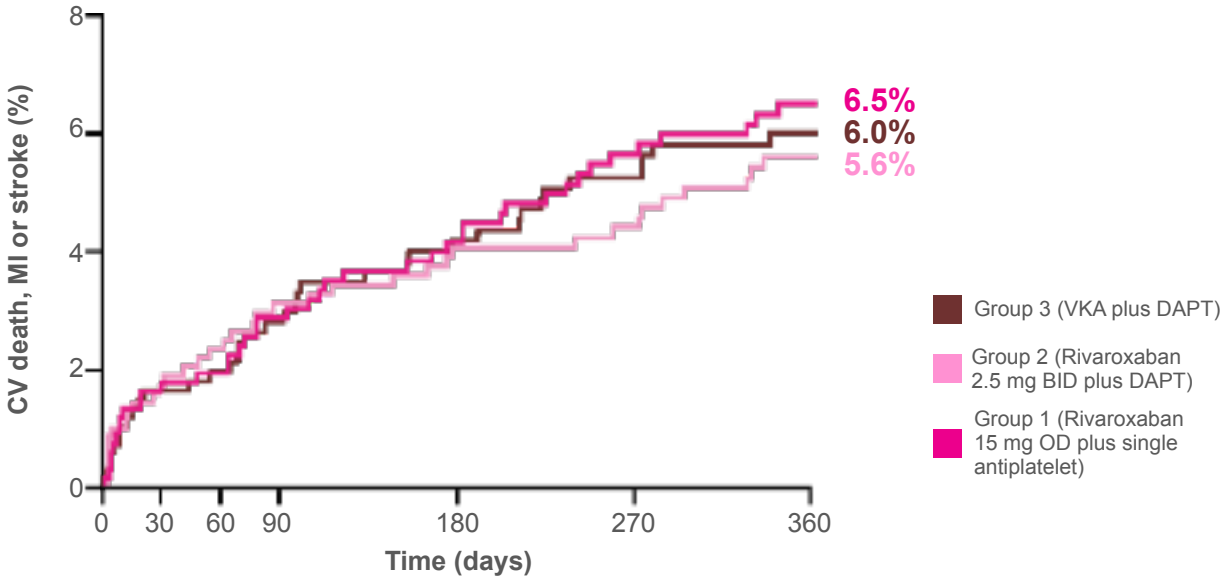


Gibson CM et al, *New Engl J Med* 2016; doi: 10.1056/NEJMoa1611594

Efficacy was Comparable

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=1.08; (95% CI 0.69–1.68); *p*=0.75

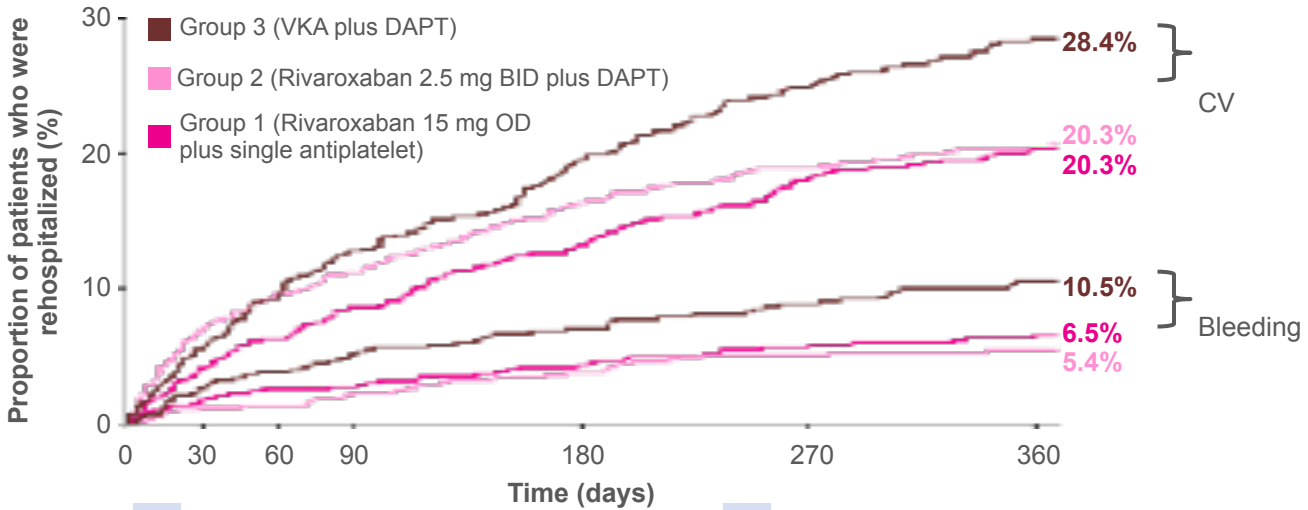
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.93 (95% CI 0.59–1.48); *p*=0.76



*Trial not powered to definitively demonstrate either superiority or non-inferiority for efficacy endpoints (if so, a total of 40,794 patients across groups will be needed, with at least 13,598 patients in each arms)

Gibson CM et al, *New Engl J Med* 2016; doi: 10.1056/NEJMoa1611594

Re-hospitalization Due to CV Events and Bleeding



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

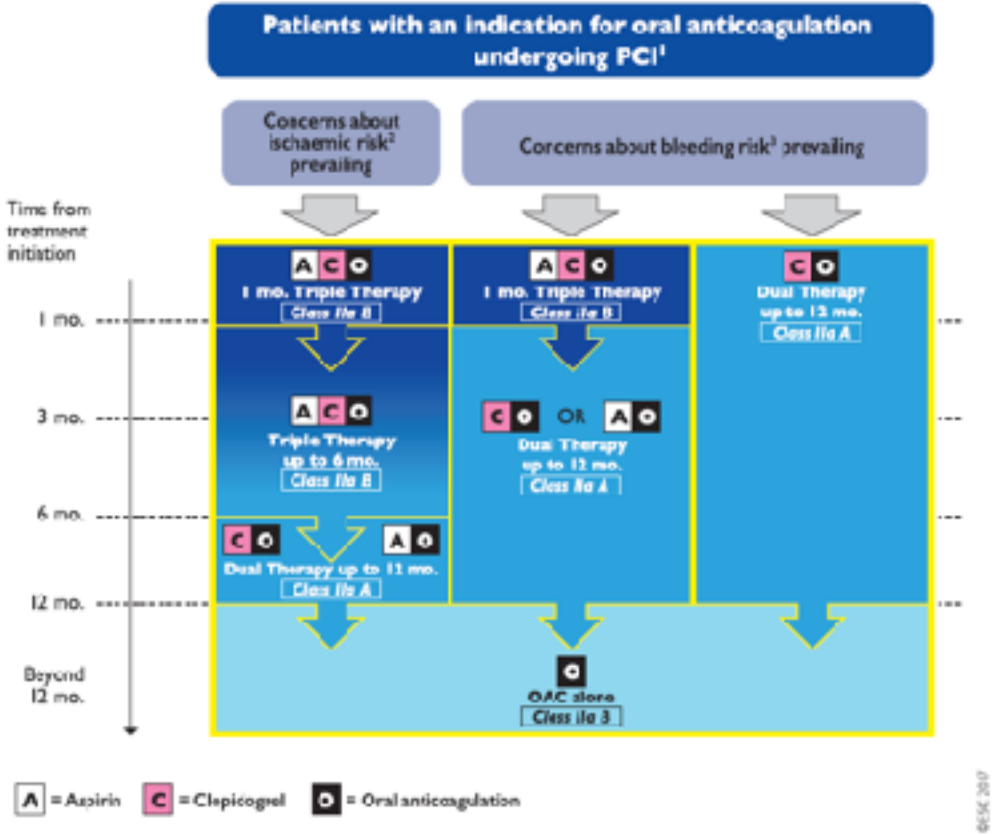
Group 1 vs Group 3:
HR=0.61; (95% CI 0.41–0.90); *p*=0.012
ARR=4.0%; NNT=25

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 hospitalization were classified by consensus panel blinded to treatment group as potentially related to either bleeding, CV or other causes; Re-hospitalizations do not include the index event and include the first re-hospitalization after the index event.

Gibson CM *et al*, *Circulation* 2016; doi:10.1161/CIRCULATIONAHA.116.025783

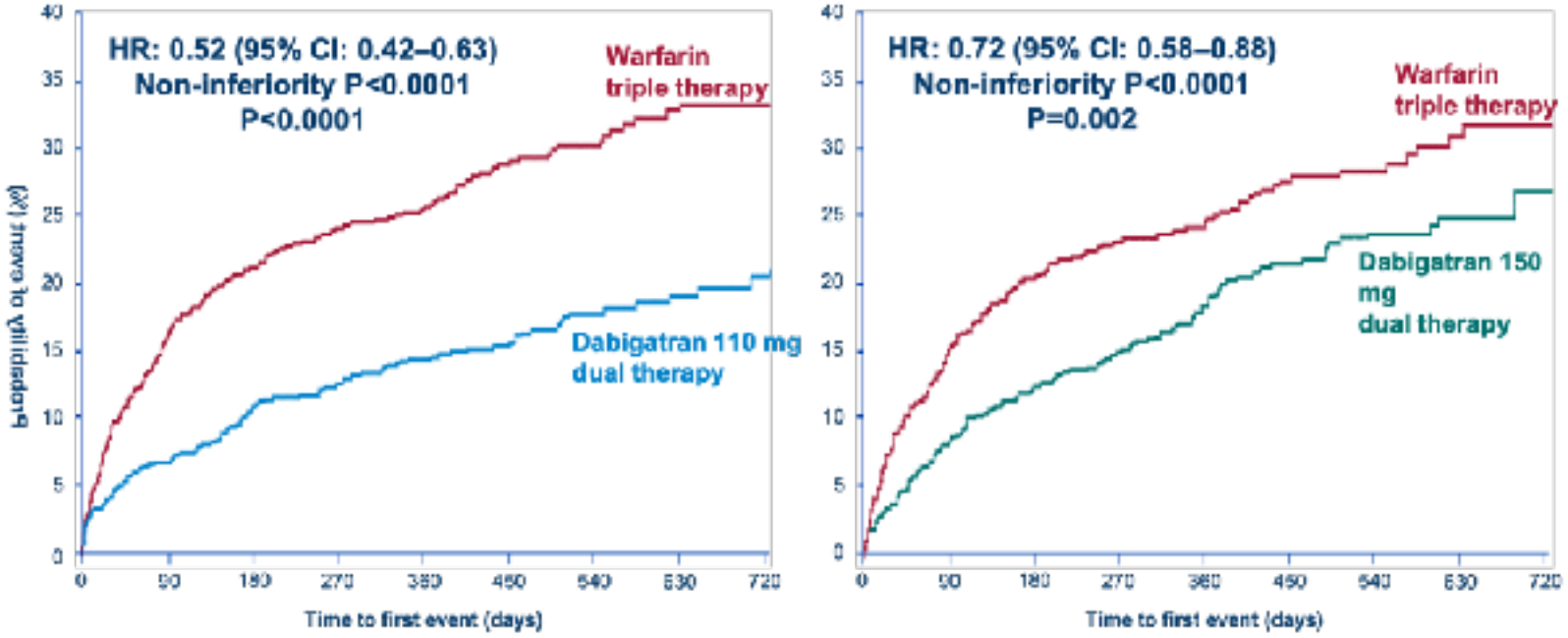
2017 ESC Guidelines on A Fib



European Heart Journal (2017) 0, 1–48

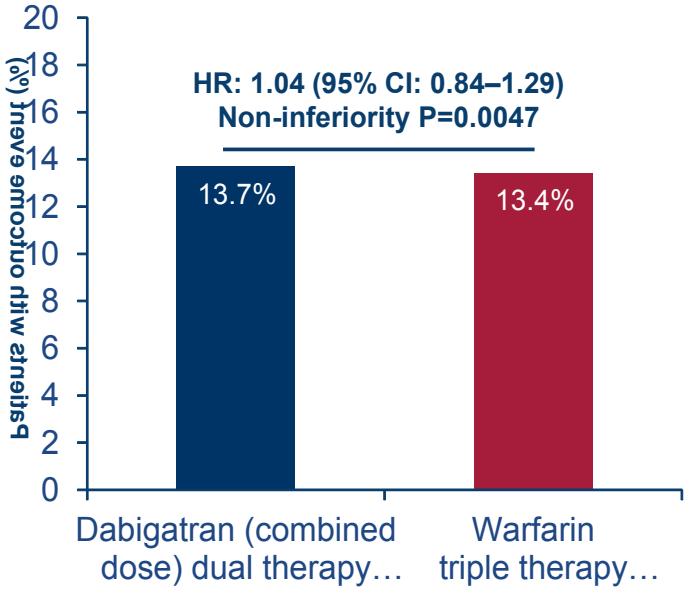
No aspirin (and dabigatran): RE-DUAL

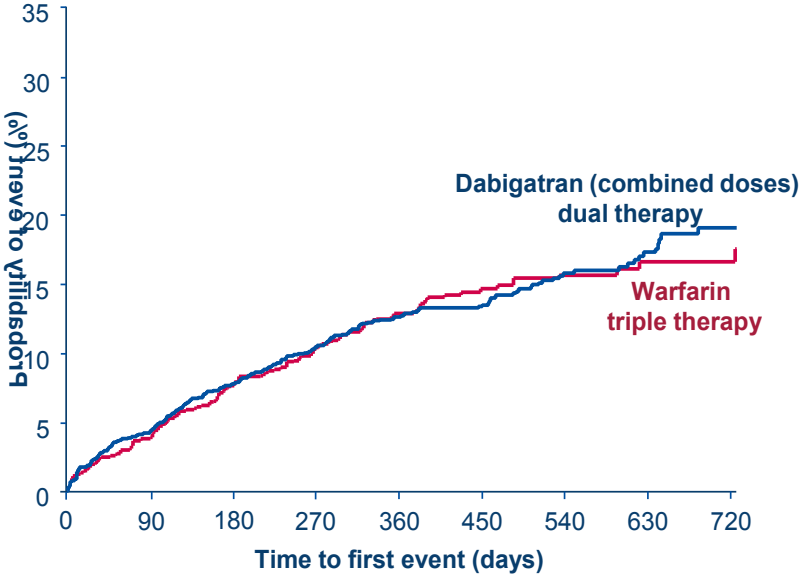
ISTH bleeding event



Full analysis set presented. HRs and Wald CIs from Cox proportional-hazard model. For the dabigatran 110 mg vs warfarin comparison, the model is stratified by age, non-elderly vs elderly (<70 or ≥70 in Japan and <80 or ≥80 years old elsewhere). For the dabigatran 150 mg vs warfarin comparison, an unstratified model is used, elderly patients outside the USA are excluded. Non-inferiority P value is one sided (alpha=0.025). Wald two-sided P value from (stratified) Cox proportional-hazard model (alpha=0.05)

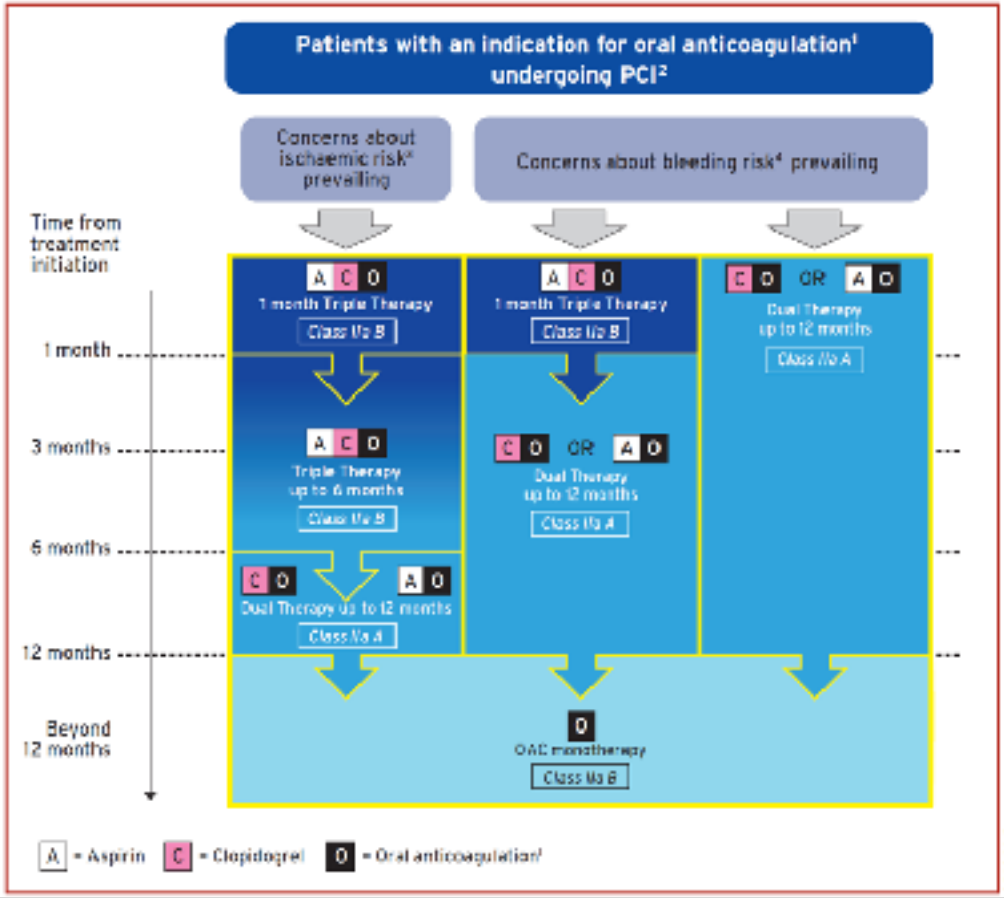
No aspirin (and dabigatran) : death or thromboembolic event, or unplanned revascularization





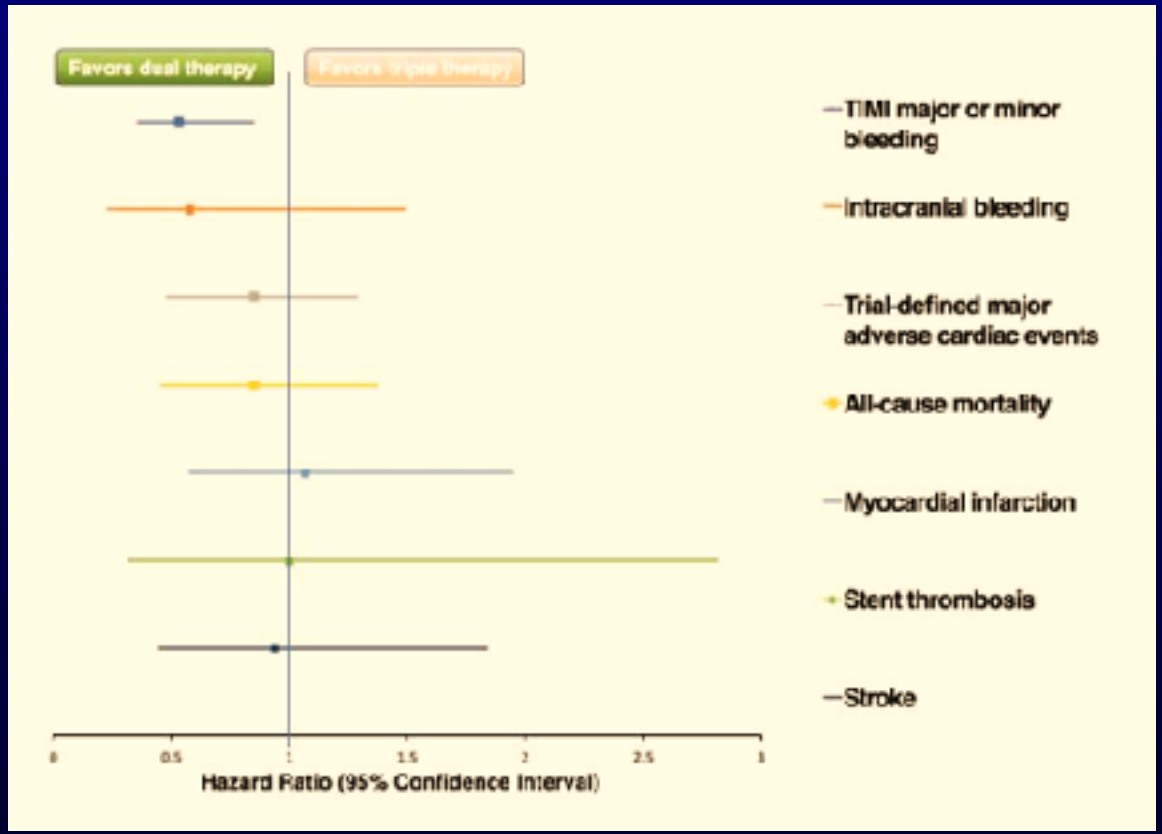
Non-inferiority P value is one sided (alpha=0.025). Results presented are Step 3 of hierarchical testing procedure, testing non-inferiority of dabigatran dual therapy (combined doses) to warfarin triple therapy in death or thromboembolic event and unplanned revascularization

2018 ESC Guidelines on Myocardial Revascularization



European Heart Journal (2018) **00**, 1–96

Metaanalysis of 4 RCTs



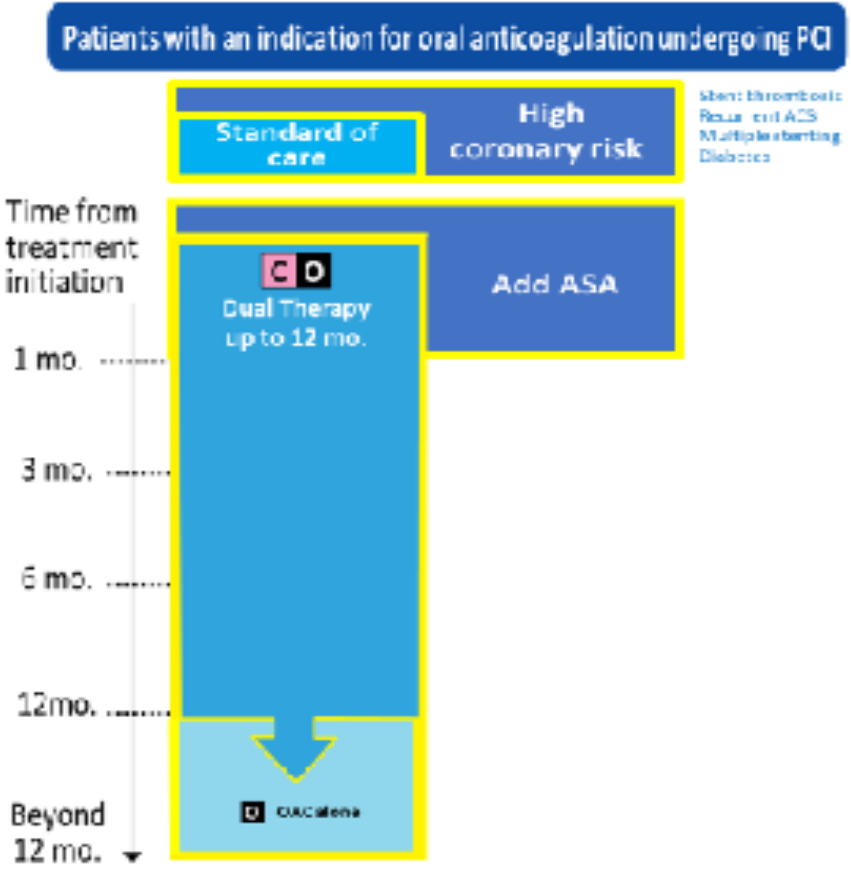
Golwala et al. EHJ 2018

ESC European Society of Cardiology
European Heart Journal (2018) 0, 1–4
doi:10.1093/eurheartj/ehy216

EDITORIAL

The times they are a changin

Nadjib Hammoudi and Gilles Montalescot*



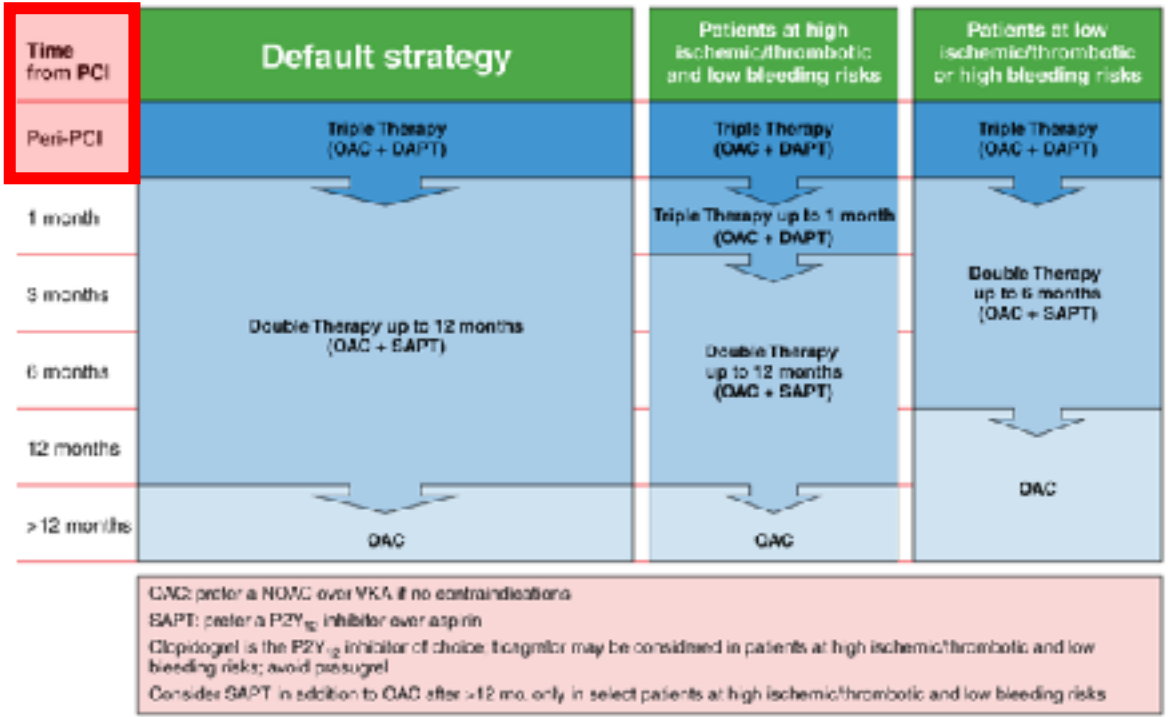
Circulation

WHITE PAPER

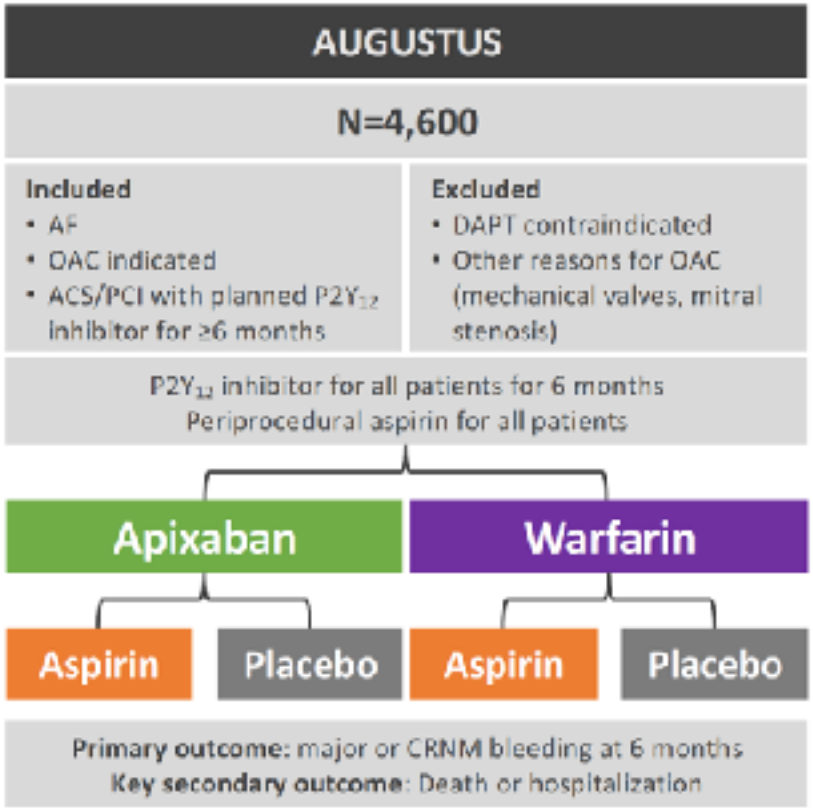
Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention

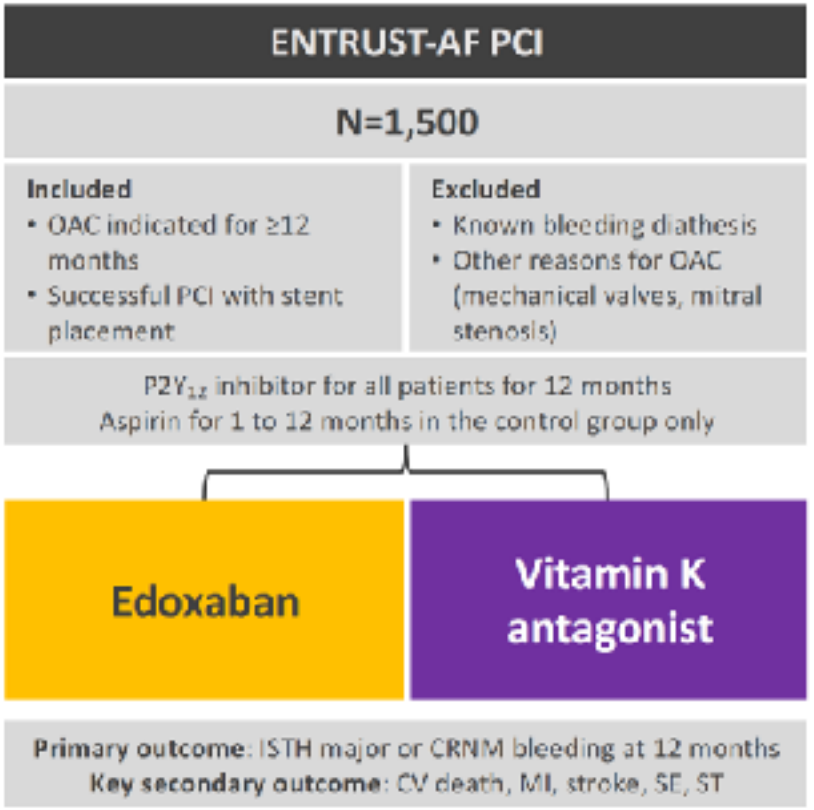
A North American Perspective–2018 Update

Circulation. 2018;138:527–536. DOI: 10.1161/CIRCULATIONAHA.118.034722



Other studies





Two Independent Hypotheses

In patients with AF and ACS or PCI on a $P2Y_{12}$ inhibitor

1. Apixaban is non-inferior to VKA for International Society on Thrombosis and Haemostasis (ISTH) major or clinically relevant non-major (CRNM) bleeding
2. Aspirin is inferior to placebo for ISTH major or CRNM bleeding in patients on oral anticoagulation (OAC)

Primary Outcome

- **ISTH major bleeding**
  - Results in death
  - Occurs in critical area or organ
  - Results in hemoglobin drop ≥2 g/dL
  - Requires transfusion of ≥2 units of whole blood or packed red blood cells
- **Clinically relevant non-major bleeding**
  - Results in hospitalization
  - Requires medical / surgical evaluation or intervention
  - Requires physician-directed change in antithrombotic regimen

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

Statistical Analysis—Hierarchical Testing

Apixaban vs. VKA:

- Major / CRNM Bleeding[NI then Sup]
- Death / Hospitalization[Sup]
- Death / Ischemic Events[Sup]

Placebo vs. Aspirin:

- Major / CRNM Bleeding[Sup]
- Death / Hospitalization[Sup]
- Death / Ischemic Events[Sup]

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

NI = non-inferiority; Sup = superiority

Baseline Characteristics

ACTION CŒUR

	Total (N=4614)
Age, median (25th, 75th), years	70.7 (64.2, 77.2)
Female, %	29.0
CHA_2DS_2-VASc score, mean (SD)	3.9 (1.6)
HAS-BLED score, mean (SD)	2.9 (0.9)
Prior OAC, %	49.0
$P2Y_{12}$ inhibitor, %	
Clopidogrel	92.6
ACS and PCI	
ACS and no PCI	23.9
Elective PCI	38.8

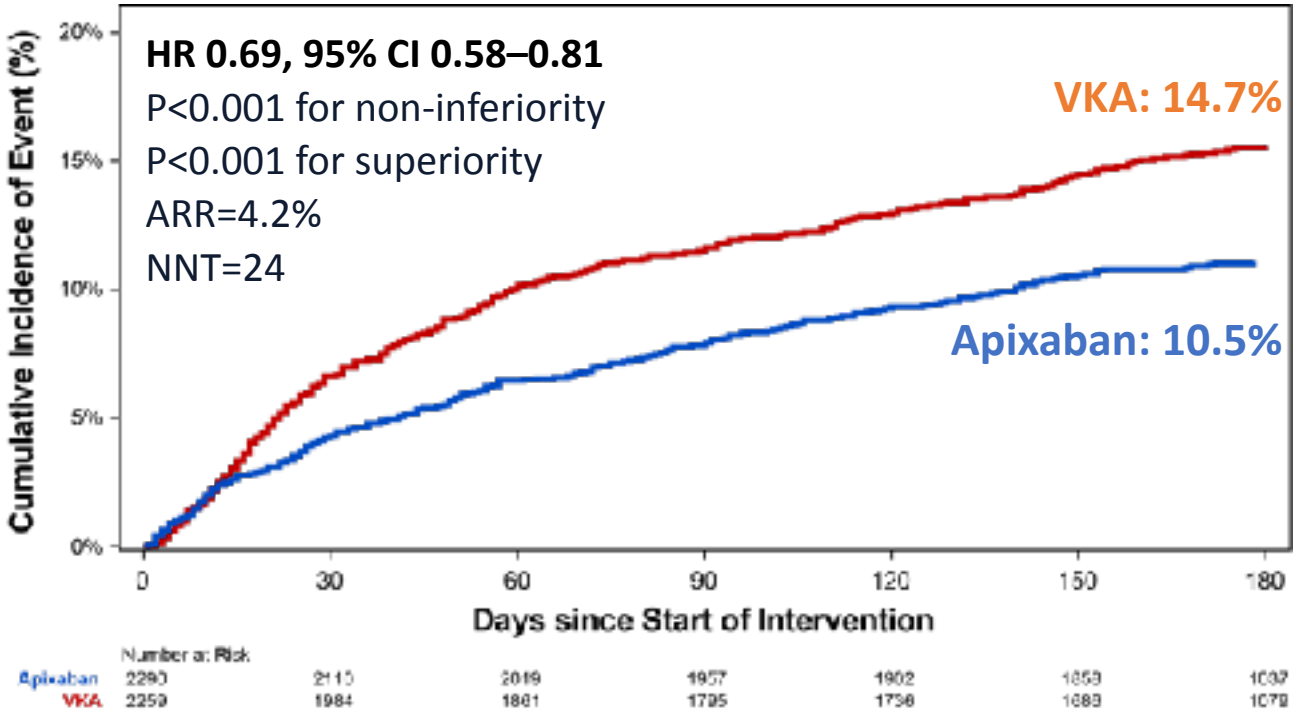
No Significant Interactions Between Randomization Factors

Apixaban / VKA vs. Aspirin / Placebo

- Major / CRNM Bleeding: $P_{interaction} = 0.64$
- Death / Hospitalization: $P_{interaction} = 0.21$
- Death / Ischemic Events: $P_{interaction} = 0.28$

Major / CRNM Bleeding

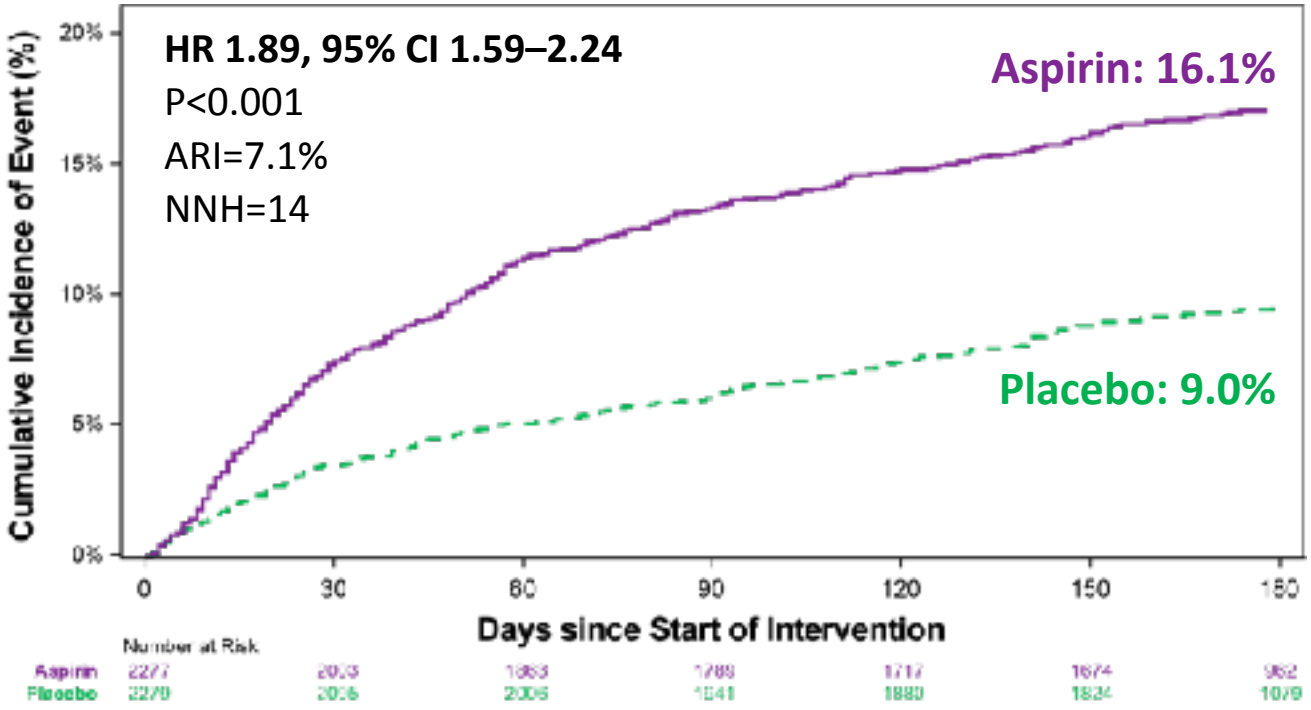
Apixaban vs. VKA



ARR: absolute risk reduction
NNT: number needed to treat

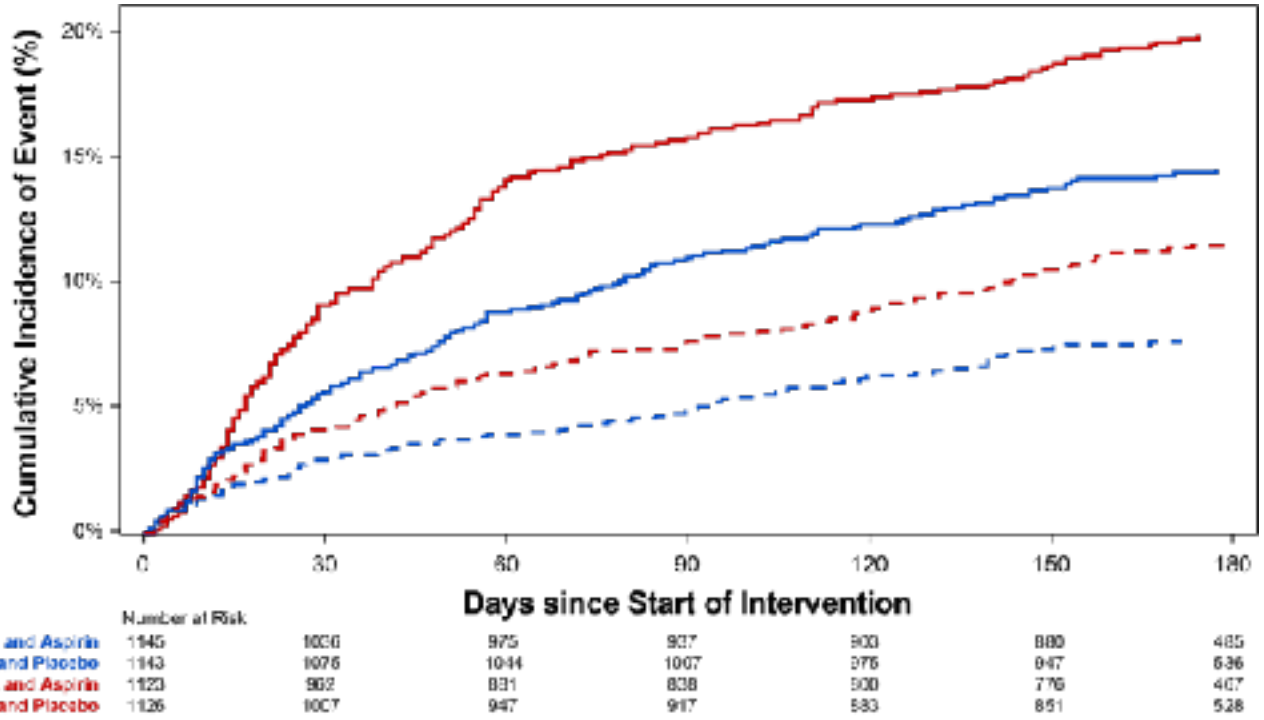
Major / CRNM Bleeding

Aspirin vs. Placebo



ARI: absolute risk increase
NNH: number needed to harm

Major / CRNM Bleeding



VKA + Aspirin (18.7%)

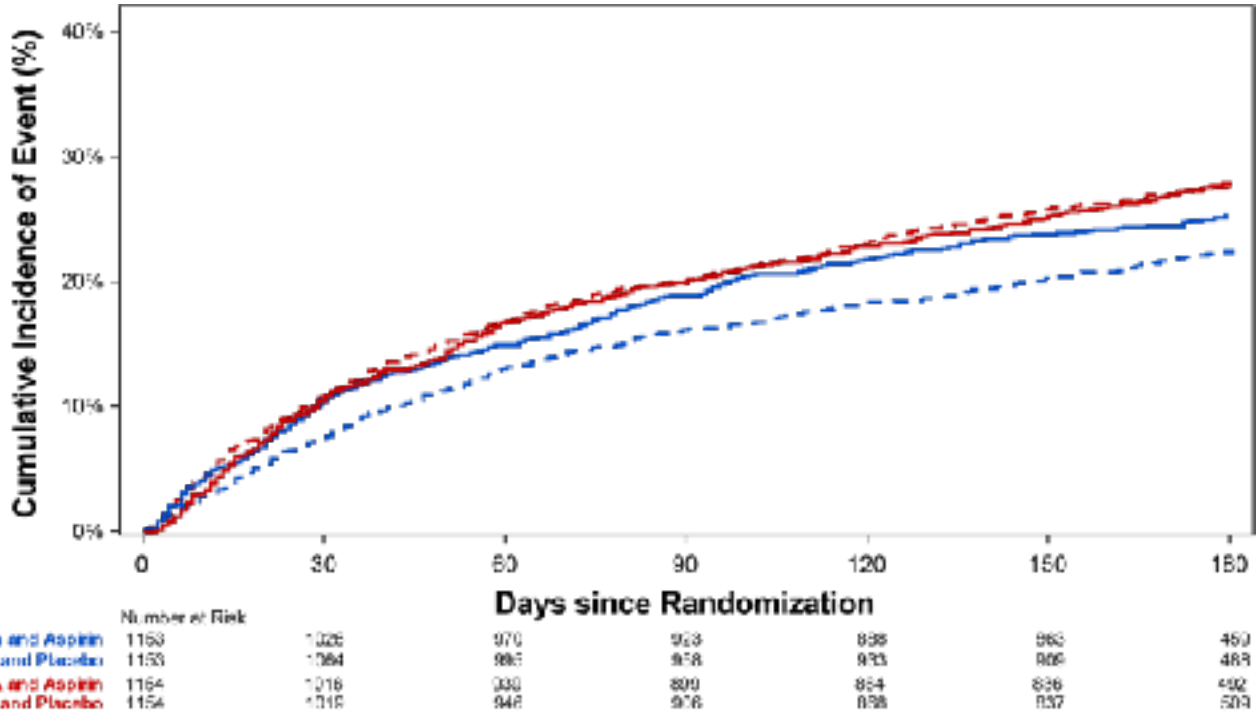
Apixaban + Aspirin (13.8%)

VKA + Placebo (10.9%)

Apixaban + Placebo (7.3%)

Apixaban + Placebo vs. VKA + Aspirin: 11.4% absolute risk reduction (NNT=9)

Death / Hospitalization



VKA + Aspirin (27.5%)
VKA + Placebo (27.3%)
Apixaban + Aspirin (24.9%)
Apixaban + Placebo (22.0%)

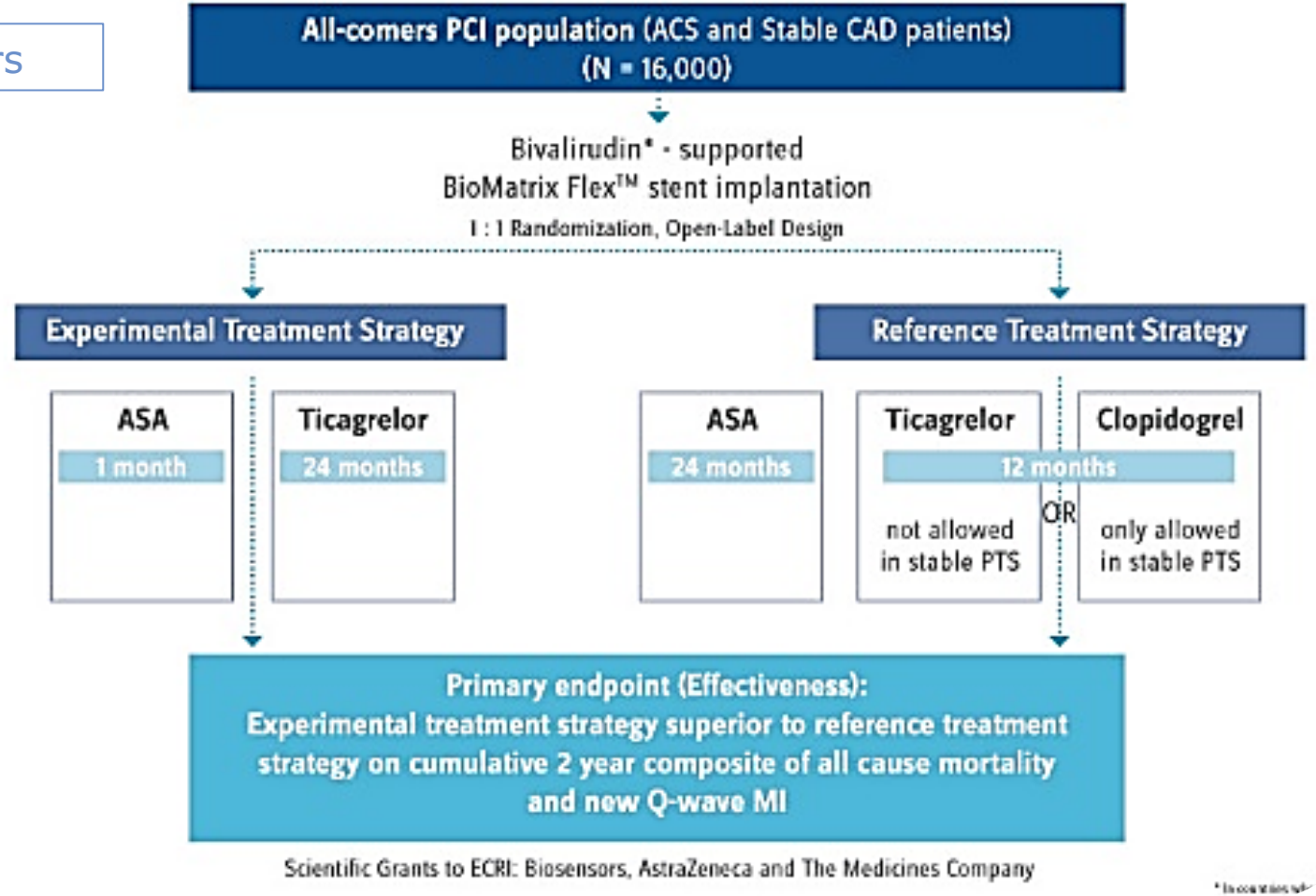
Apixaban + Placebo vs. VKA + Aspirin: 5.5% absolute risk reduction (NNT=18)

Ischemic Outcomes
Aspirin vs. Placebo

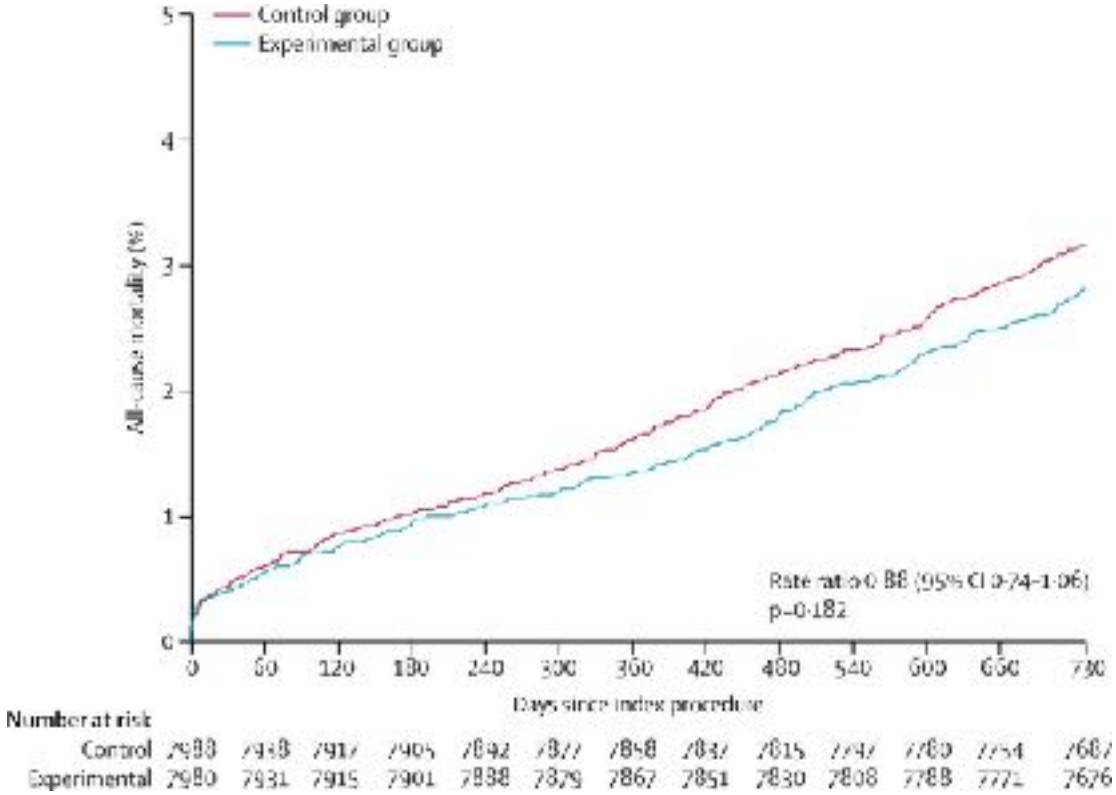
Endpoint	Aspirin (N=2307)	Placebo (N=2307)	HR (95% CI)
Death / Ischemic Events (%)	6.5	7.3	0.89 (0.71–1.11)
Death (%)	3.1	3.4	0.91 (0.66–1.26)
CV Death (%)	2.3	2.5	0.92 (0.63–1.33)
Stroke (%)	0.9	0.8	1.06 (0.56–1.98)
Myocardial Infarction (%)	2.9	3.6	0.81 (0.59–1.12)
Definite or Probable Stent Thrombosis (%)	0.5	0.9	0.52 (0.25–1.08)
Urgent Revascularization (%)	1.6	2.0	0.79 (0.51–1.21)
Hospitalization (%)	25.4	23.4	1.10 (0.98–1.24)

Removing ASA after PCI?

Global-leaders



Global-leaders



	Experimental treatment group (N=7980)	Control group (N=7988)	Rate ratio (95% CI)	p value
All-cause mortality or new Q-wave myocardial infarction	304 (3·81%)	349 (4·37%)	0·87 (0·75–1·01)	0·073
All cause mortality	224 (2·81%)	253 (3·17%)	0·88 (0·74–1·06)	0·182
New Q-wave myocardial infarction*	83 (1·04%)	103 (1·29%)	0·80 (0·60–1·07)	0·14
Composite of all-cause mortality, stroke, or new Q-wave myocardial infarction	362 (4·54%)	416 (5·21%)	0·87 (0·76–1·00)	0·055
Myocardial infarction	248 (3·11%)	250 (3·13%)	1·00 (0·84–1·19)	0·98
Stroke				
Overall	80 (1·00%)	82 (1·03%)	0·98 (0·72–1·33)	0·90
Ischaemic	63 (0·79%)	68 (0·85%)	0·93 (0·66–1·31)	0·68
Haemorrhagic	13 (0·16%)	9 (0·11%)	1·45 (0·62–3·35)	0·39
Undetermined	6 (0·08%)	5 (0·06%)	1·21 (0·37–3·95)	0·76
Revascularisation	719 (9·26%)	793 (9·93%)	0·91 (0·84–1·00)	0·17
Target vessel revascularisation	381 (4·77%)	442 (5·54%)	0·88 (0·77–1·01)	0·068
Definite stent thrombosis	64 (0·82%)	64 (0·82%)	1·00 (0·71–1·42)	0·98
BARC				
BARC 3 or 5 bleeding	163 (2·04%)	169 (2·12%)	0·97 (0·78–1·20)	0·77
BARC 5 bleeding				
Any	22 (0·28%)	24 (0·30%)	0·92 (0·52–1·64)	0·78
5b bleeding	15 (0·19%)	18 (0·23%)	0·84 (0·42–1·66)	0·61
5a bleeding	7 (0·09%)	6 (0·08%)	1·17 (0·38–3·49)	0·78
BARC 3 bleeding				
Any	150 (1·88%)	159 (1·99%)	0·95 (0·76–1·18)	0·63
3c bleeding	35 (0·44%)	25 (0·31%)	1·41 (0·84–2·35)	0·19
3b bleeding	53 (0·66%)	74 (0·93%)	0·72 (0·52–1·02)	0·065
3a bleeding	77 (0·96%)	70 (0·88%)	1·10 (0·80–1·53)	0·55

*Shown are the first event per event type for each patient only. Multiple events of the same type within the same patient are disregarded. Data were censored 730 days after index percutaneous coronary intervention. BARC=Bleeding Academic Research Consortium. †New Q-wave or equivalent left bundle branch block (n=3) as adjudicated by the core laboratory.

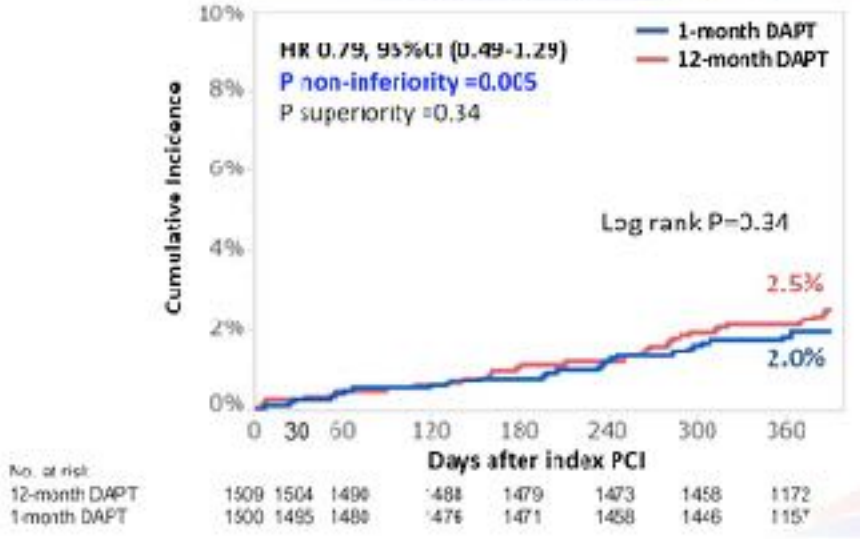
Table 3: Primary and prespecified secondary outcomes

Vranckx P et a. Lancet 2018

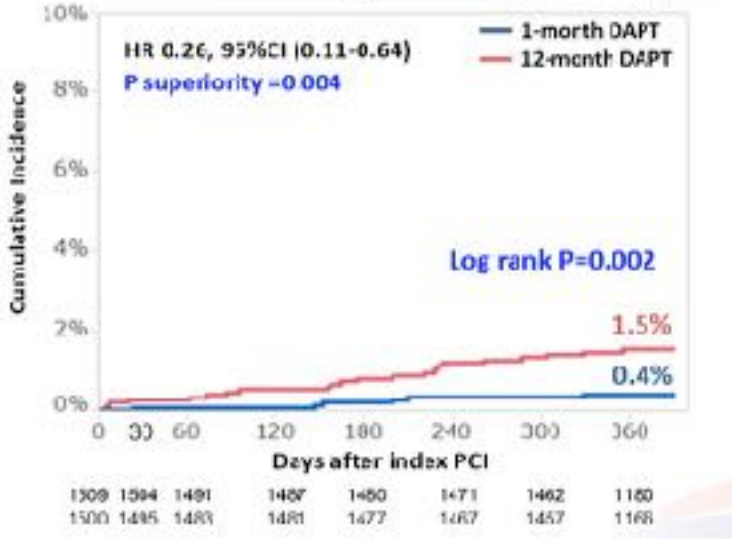
STOP-DAPT-2

3009 low-risk scheduled PCI patients – ASA stopped – **1° EP (NCB): 3.7% 12 mths vs. 2.4% 1 mth, p=0.04**

CV death, MI, Stent thrombosis, stroke



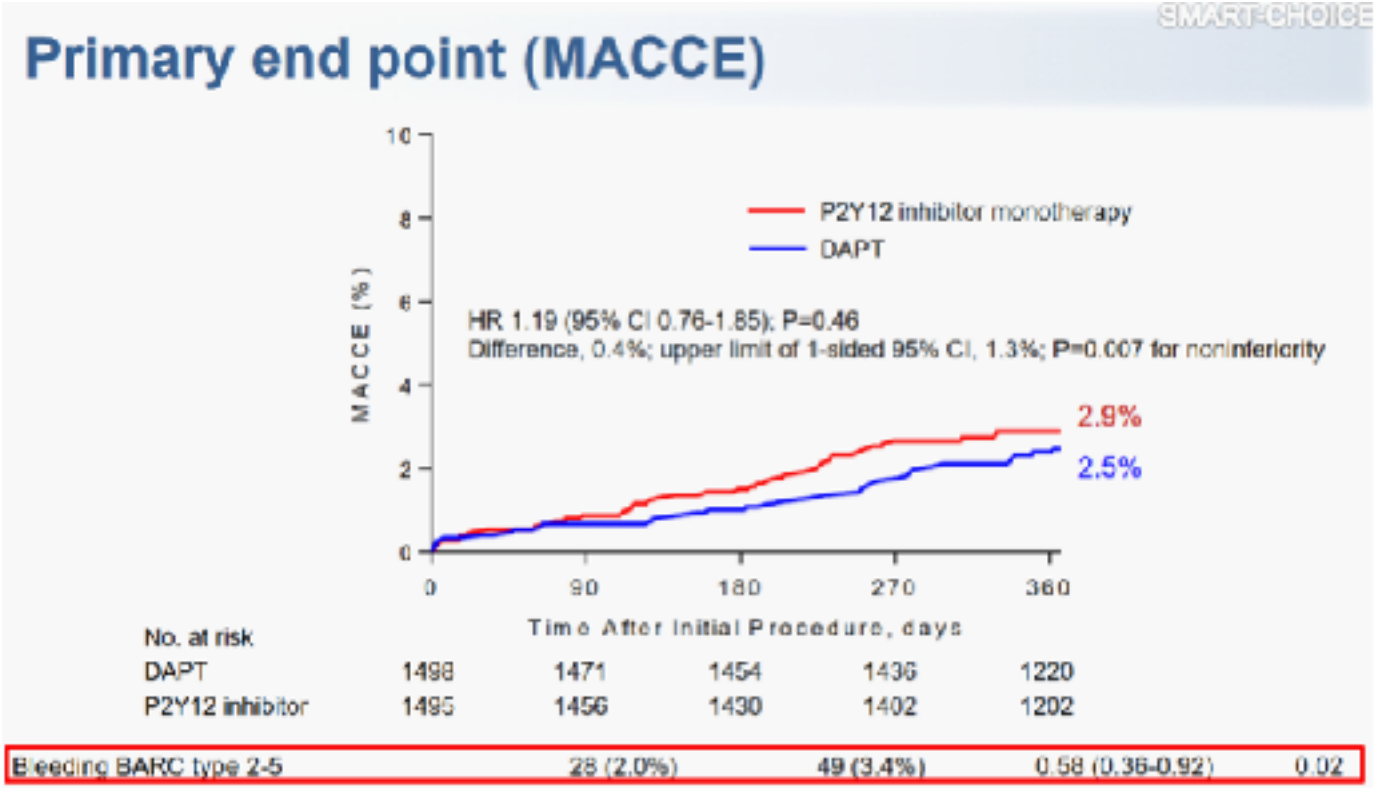
TIMI major or minor bleeding



Hirotoshi Watanabe, MD, PhD (Kyoto University) ACC2019

SMART-CHOICE

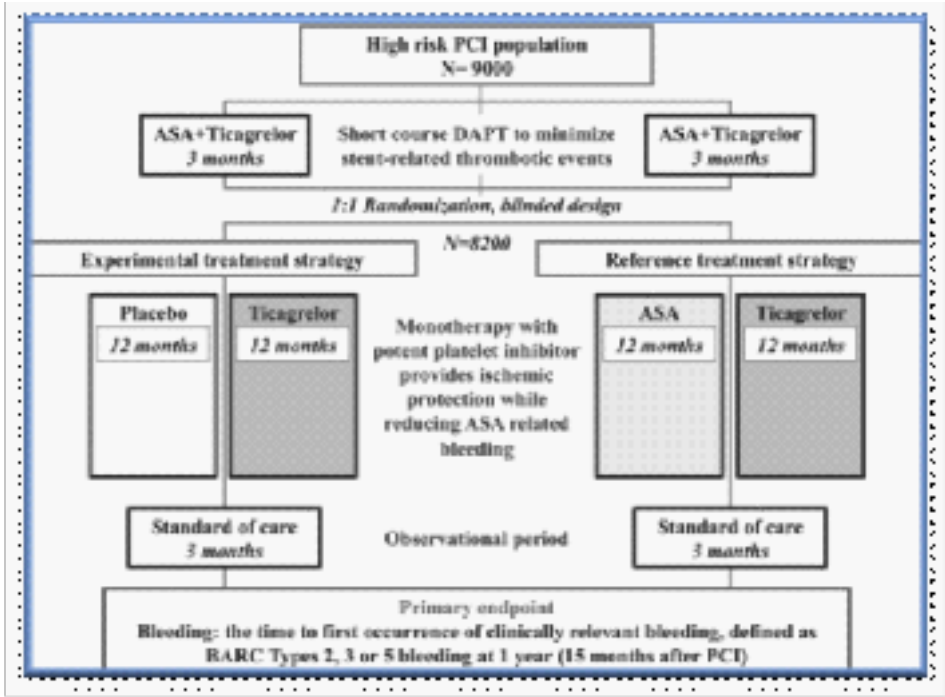
2993 scheduled PCI patients – ASA stopped – 1° EP = MACCE (NI)



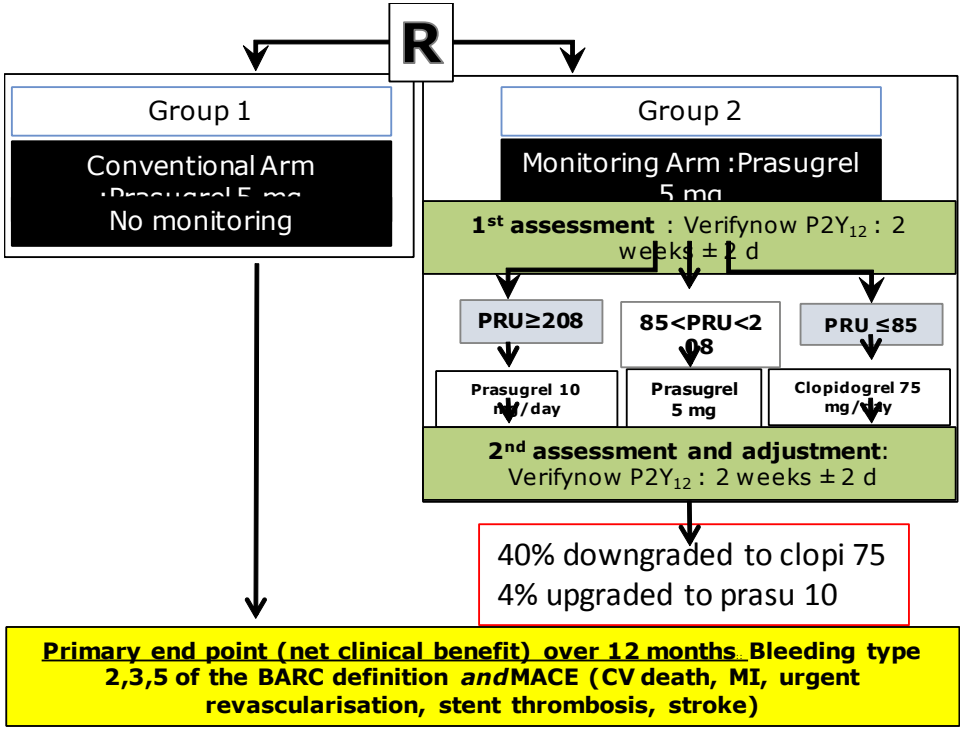
JY Hahn – ACC 2019

TWILIGHT

GLOBAL-LEADERS	16,000	ticagrelor
TWILIGHT	9,000	ticagrelor
TICO	3,056	ticagrelor
SMART-CHOICE	3,000	clopidogrel
STOPDAPT-2	3,045	clopidogrel

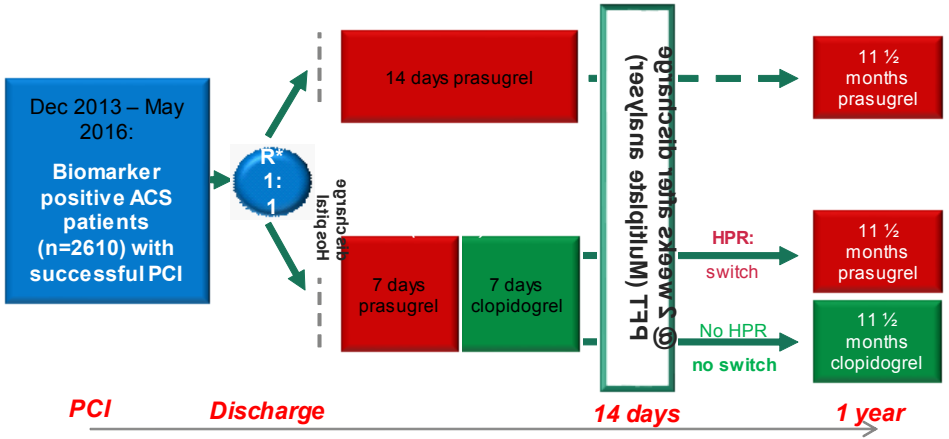


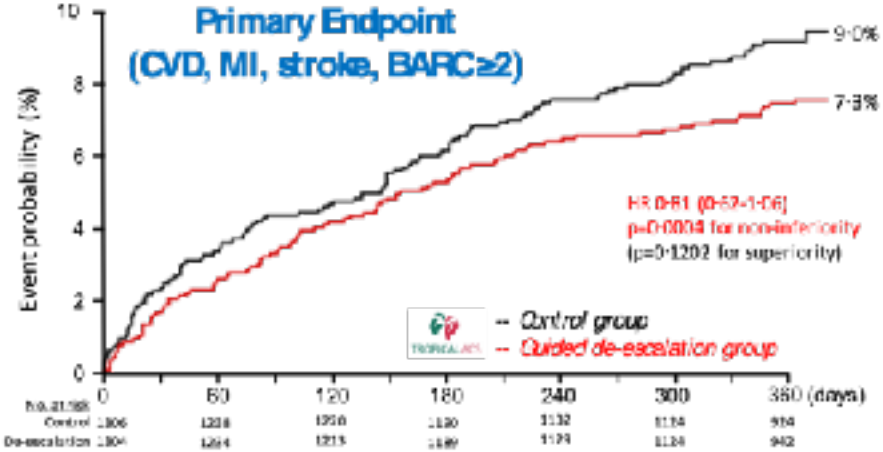
ANTARCTIC



Cayla G. for the ANTARCTIC investigators. Lancet 2016

TROPICAL ACS





Sibbing, Aradi et al., Lancet 2017;390:1747-1757 .

Conclusions

1. Evaluate bleeding risk → often high!

2. Avoid triple treatment after cath lab → Stop ASA

3. Prefer NOAC (low dose?) over VKA

4. Prefer clopidogrel over ticagrelor, except high risk ACS/PCI

5. High ischemic risk and HBR, HBR prevails: consider DAPT first 2-4 weeks, then SAPT+NOAC