



Amicale des Cardiologues de la Côte d'Azur

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LA JOURNEE D'ACTUALITESTHERAPEUTIQUES 2018

FA chez le coronarien

Dr Laurent Drogoul
Saint Laurent Du Var



Conflits d'intérêts.

Medtronic : Proctoring TAVI

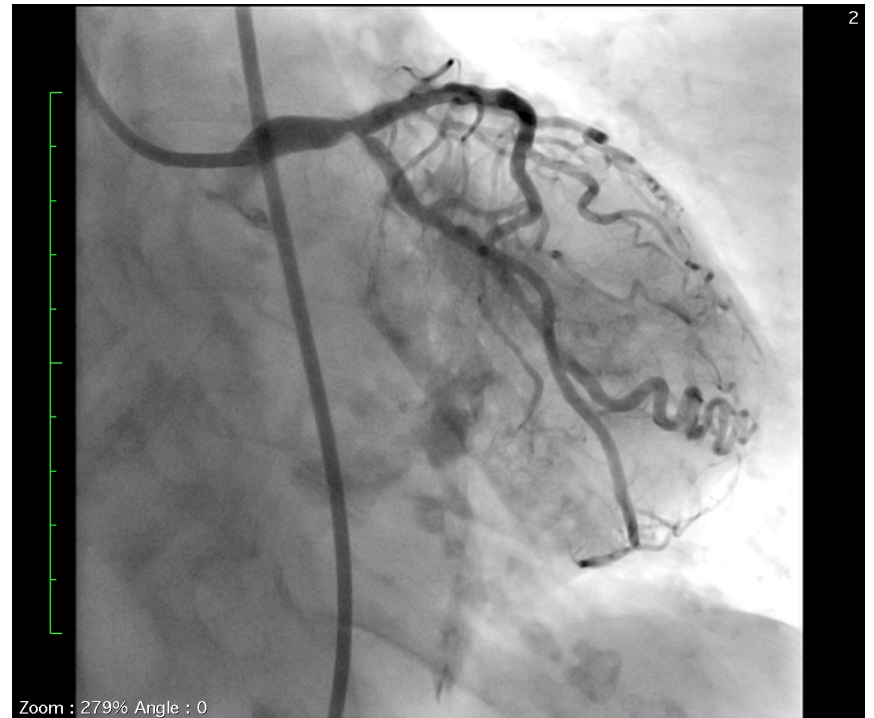
Abbott : proctoring CTO

Biosensor : proctoring CTO

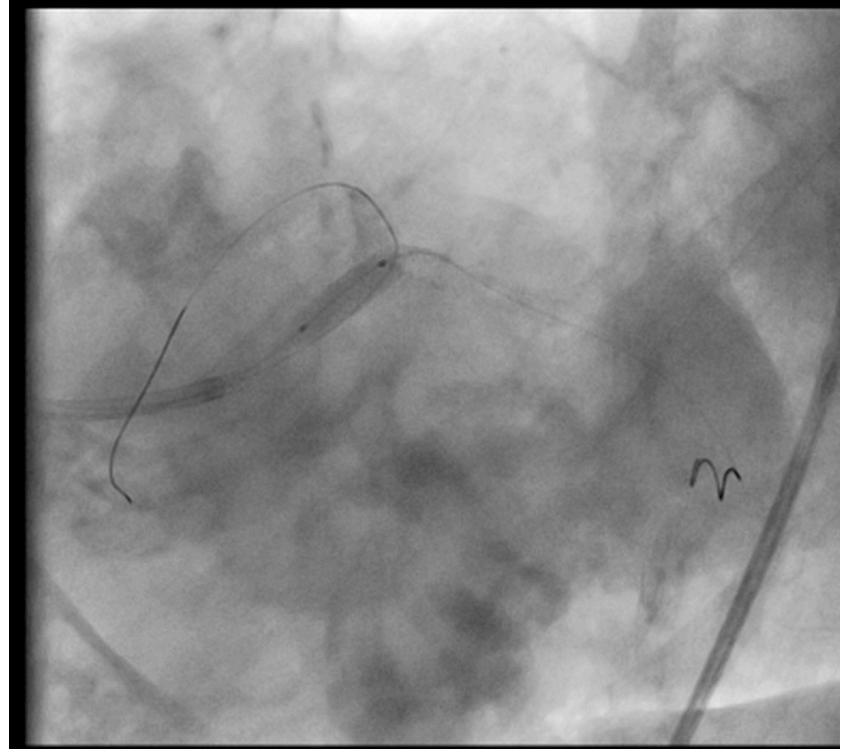
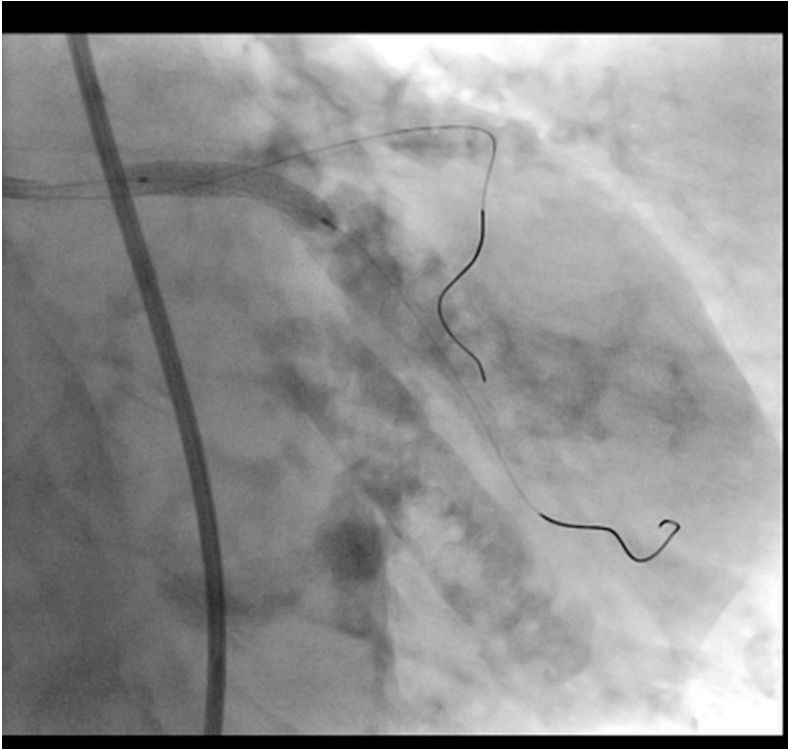
- Mme L. , 76 ans
- Admise en USIC pour accès de fibrillation atriale compliquée de douleurs thoraciques
- ATCD: HTA, Dyslipidemie, Surcharge pondérale
- TRT : PRADAXA 150 mg/j, BISOPROLOL 1,25 mg/j ,
CRESTOR 5 mg/j, RAMIPRIL 5m g/j, LASILIX 40 mg/j

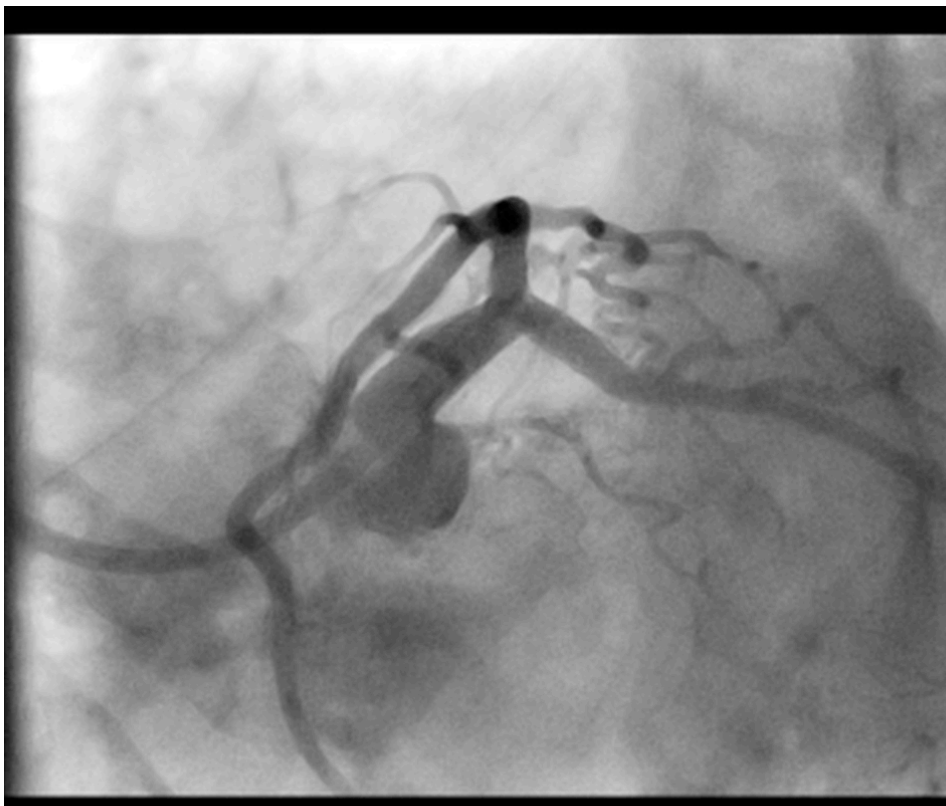
- ECG initial : Fibrillation atriale – Freq ventr: 140 bpm
- ECG H24 : sous decalage diffus de ST V1-V6
- Biologie H24 :
 - élévation de troponine à 0,43 UI/L
 - Hb=13,6 g/dl ; Leucocytes : 13 G/L ; Plaquettes :231 G/L
 - Creatininemie : 73 $\mu\text{mol/L}$ > Clairance 68 mL/min/1.73 m²
- Decision de coronarographie

Baseline Angiography



STENT ONYX 4.0*18 and POT side POT





CHA₂DS₂-VASc score: 5

HAS-BLED score : 3

QUELLE EST VOTRE STRATEGIE
D'ANTICOAGULATION / ANTIAGREGATION ?

PATIENTS AVEC FA

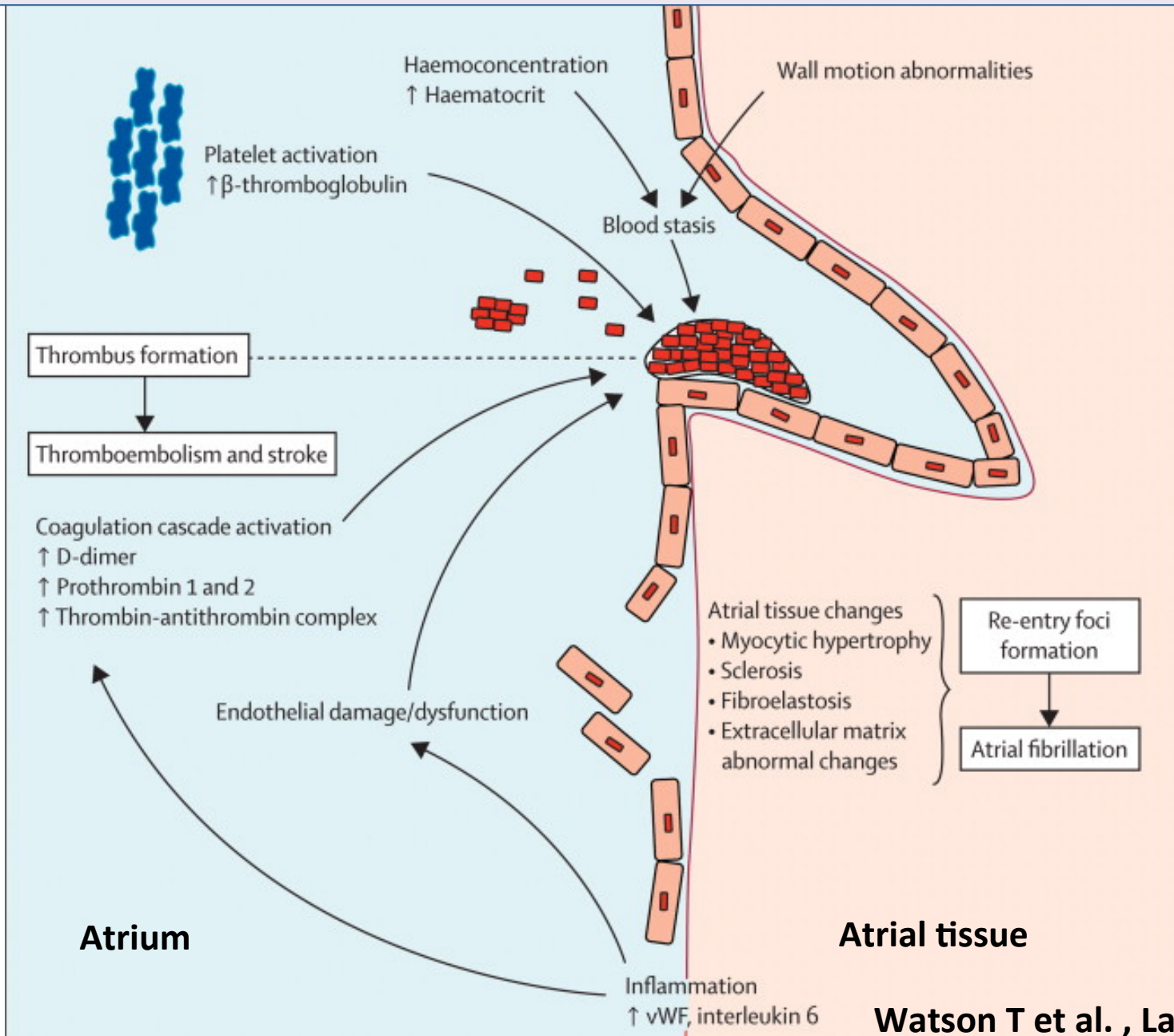
The diagram consists of three concentric circles. The outermost circle is light blue and represents 'PATIENTS AVEC FA'. Inside it is a light orange circle representing 'CORONAROPATHIE: 17-46%'. Inside the orange circle is a green circle representing 'ANGIOPLASTIE CORONAIRE: 5-15%'. The circles overlap, indicating that the group of patients with coronary angioplasty is a subset of those with coronary artery disease, which is a subset of all patients with atrial fibrillation.

**CORONAROPATHIE:
17-46%**

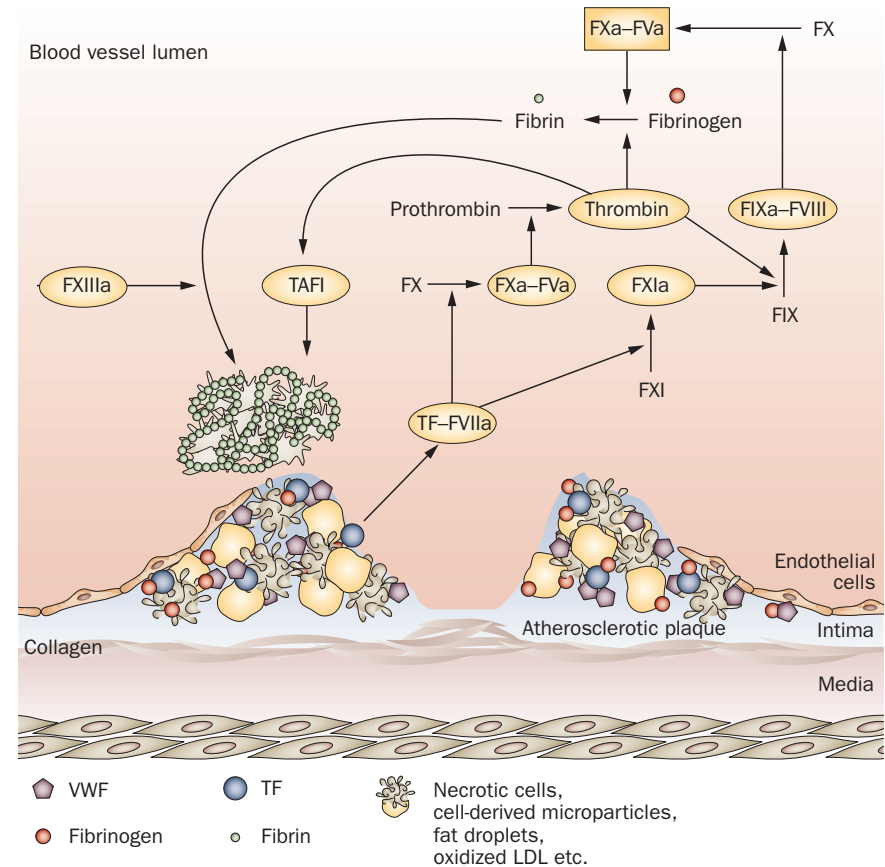
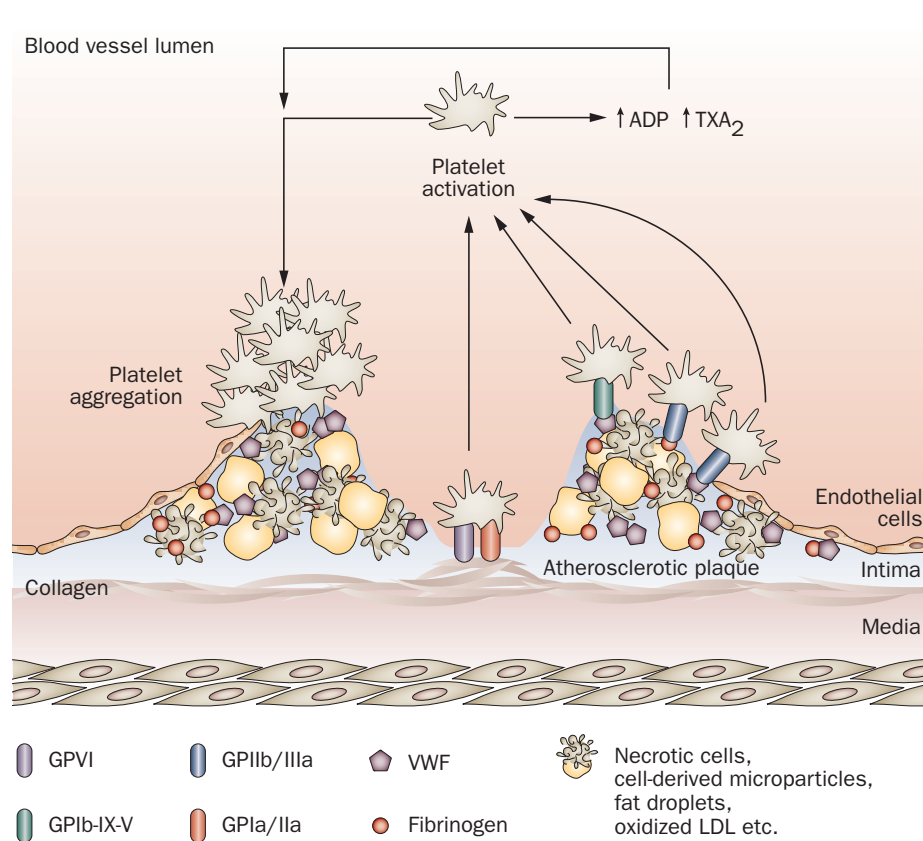
**ANGIOPLASTIE
CORONAIRE:
5-15%**

	PREVALENCE DE LA FA
CORONAROPATHIE STABLE	0.2-5 %
CORONAROPATHIE INSTABLE	6-21%
ANGIOPLASTIE CORONAIRE	5-8%

Mécanismes de thrombose atriale dans la FA



Mécanismes de thrombose dans l'athérosclérose



Facteurs de risques événements thromboemboliques patients en FA

Age (years)	
<65	1.0 (Reference)
65–74	2.97 (2.54–3.48)
≥75	5.28 (4.57–6.09)
Female sex	1.17 (1.11–1.22)
Previous ischaemic stroke	2.81 (2.68–2.95)
Intracranial bleeding	1.49 (1.33–1.67)
Vascular disease (any)	1.14 (1.06–1.23)
• Myocardial infarction	1.09 (1.03–1.15)
• Previous CABG	1.19 (1.06–1.33)
• Peripheral artery disease	1.22 (1.12–1.32)
Hypertension	1.17 (1.11–1.22)
Heart failure (history)	0.98 (0.93–1.03)
Diabetes mellitus	1.19 (1.13–1.26)
Thyroid disease	1.00 (0.92–1.09)
Thyrotoxicosis	1.03 (0.83–1.28)

Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation Cohort study. Eur Heart J 2012;33:1500–1510

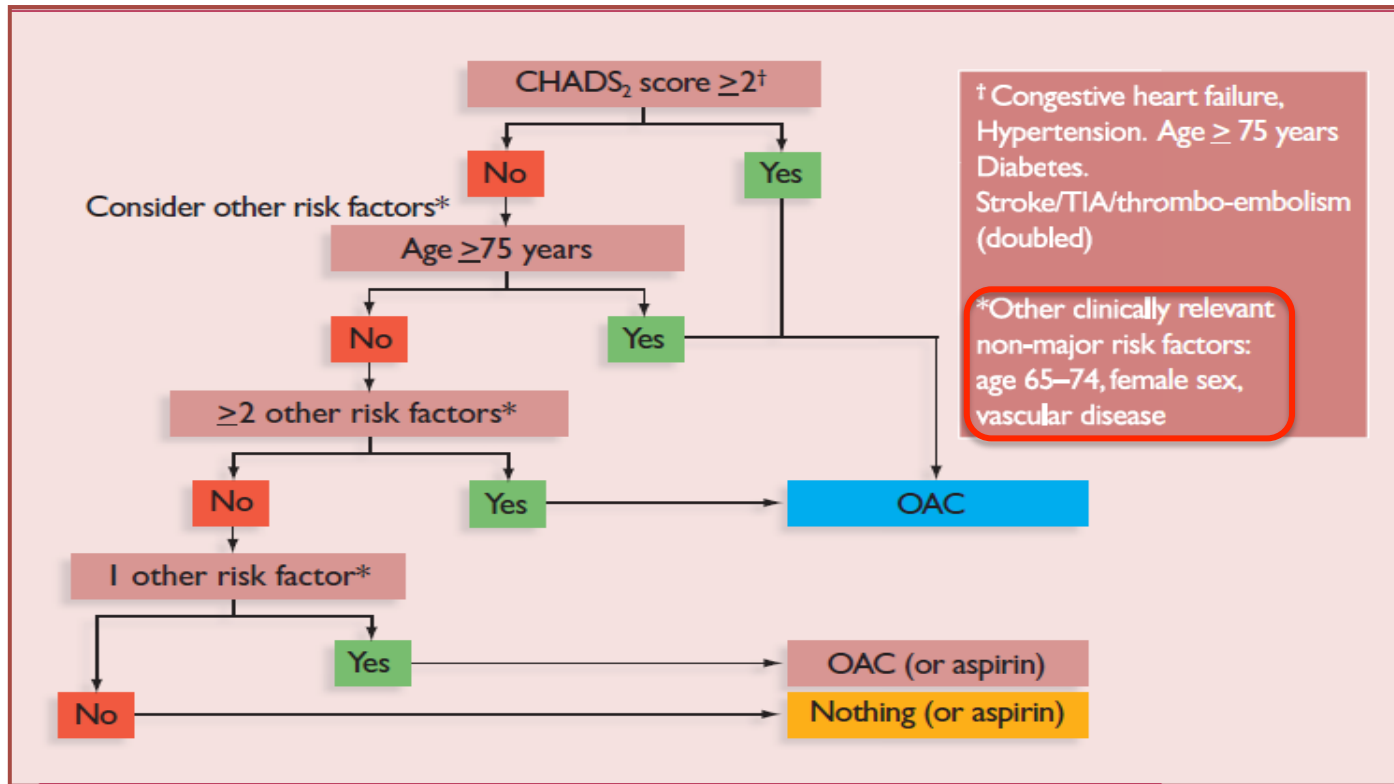
Coronaropathie = changement potentiel de score

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease ^a	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	9

^aPrior myocardial infarction, peripheral artery disease, aortic plaque.

Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation Cohort study. Eur Heart J 2012;33:1500–1510

*...Et donc de traitement préventif
avec potentiellement passage de l'aspirine à OAC*

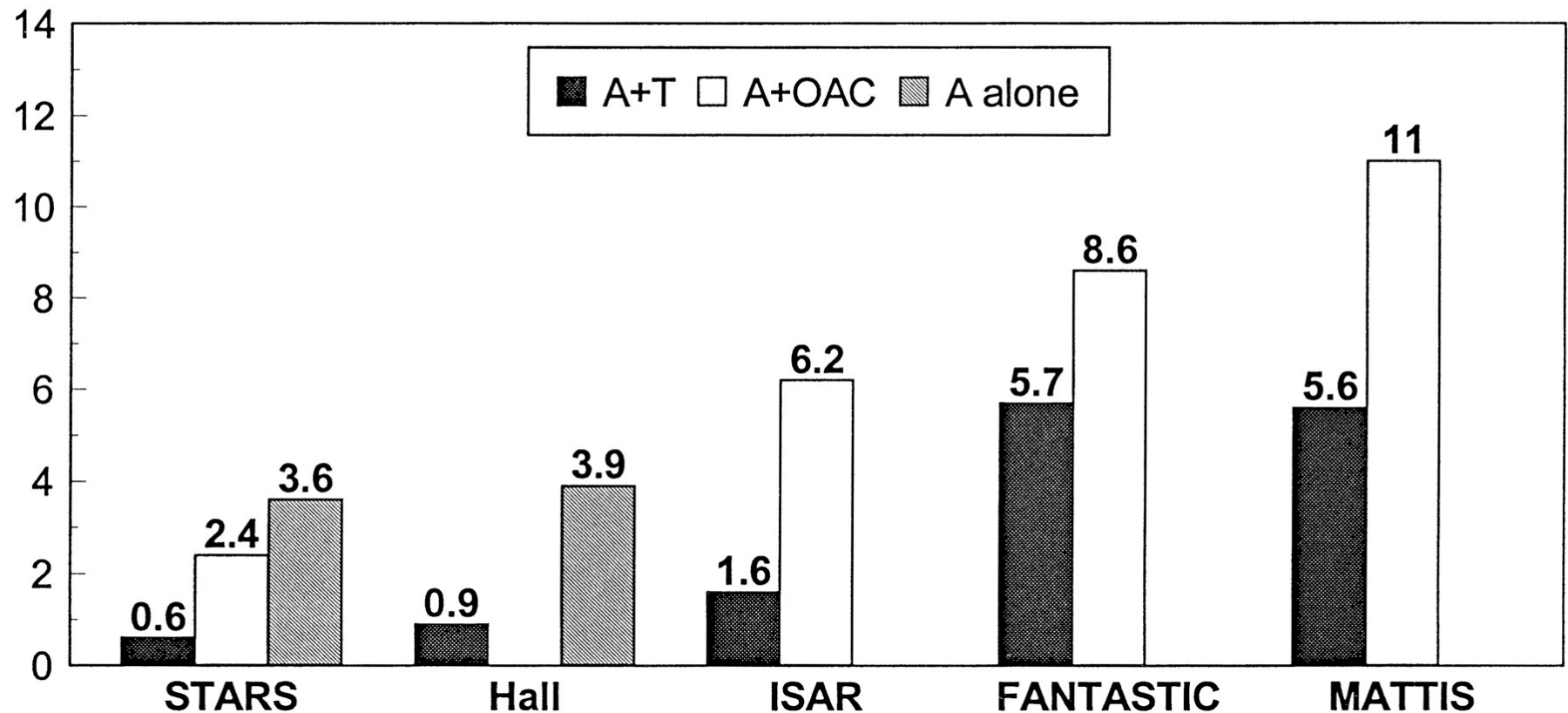


Friberg L, Rosenqvist M, Lip GY. Evaluation of risk stratification schemes for ischaemic stroke and bleeding in 182 678 patients with atrial fibrillation: the Swedish Atrial Fibrillation Cohort study. Eur Heart J 2012;33:1500–1510

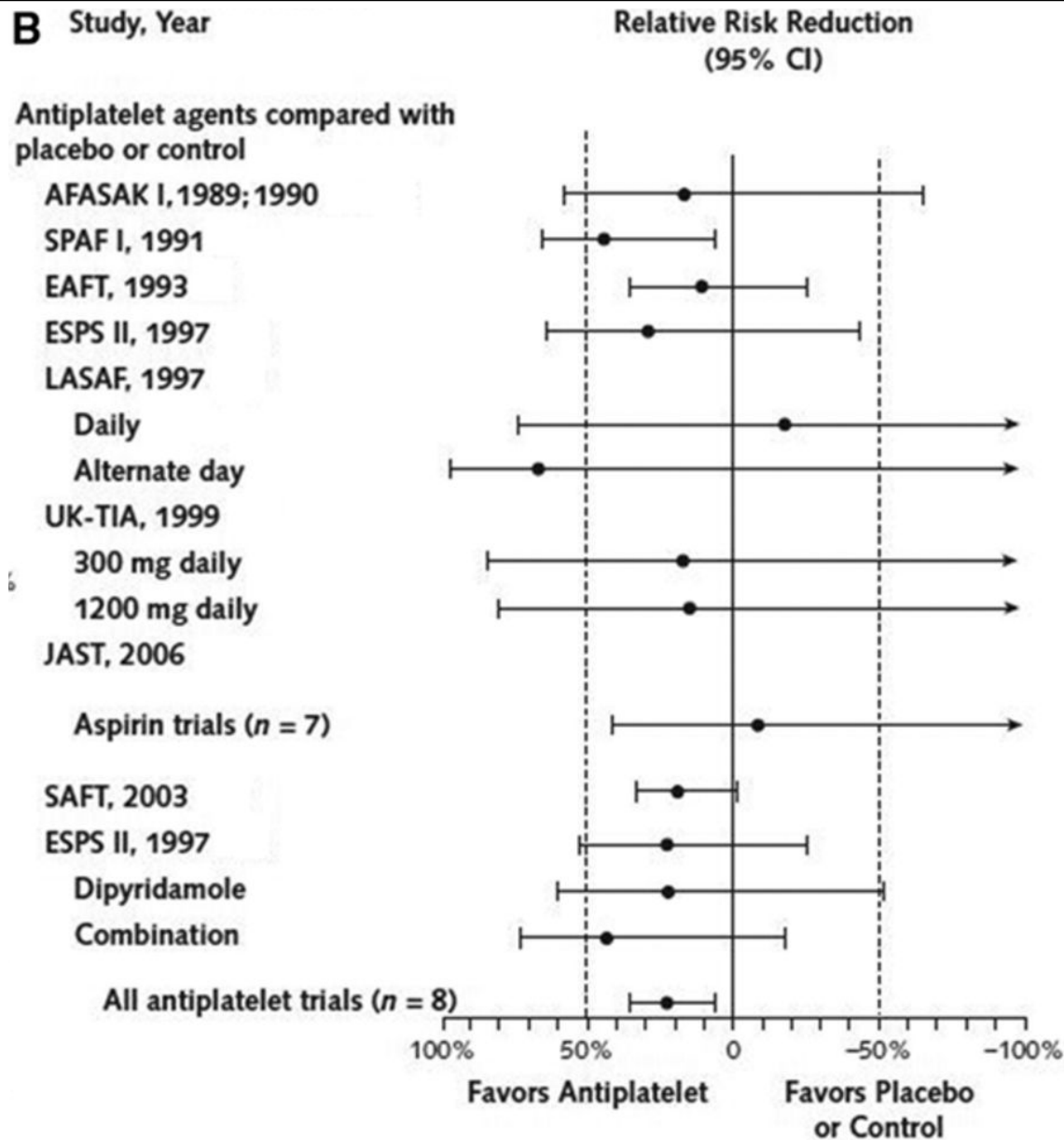
Les OAC ne protègent pas aussi bien que les AAP contre le risque d'év. secondaires après ATC

Randomized controlled trials of pharmacological treatment after coronary stent implantation (BMS)

% of cardiac events at 30 days



Les AAP ne protègent pas aussi bien que les OAC contre le risque embolique dans la FA



Les AAP ne protègent pas aussi bien que les OAC contre le risque embolique dans la FA

C Study, Year

Relative Risk Reduction
(95% CI)

Adjusted-dose warfarin compared
with antiplatelet agents

AFASAK I, 1989;1990

AFASAK II, 1998

Chinese ATAFS, 2006

EAFIT, 1993

PATAF, 1999

SPAF II, 1994

Age ≤ 75 y

Age > 75 y

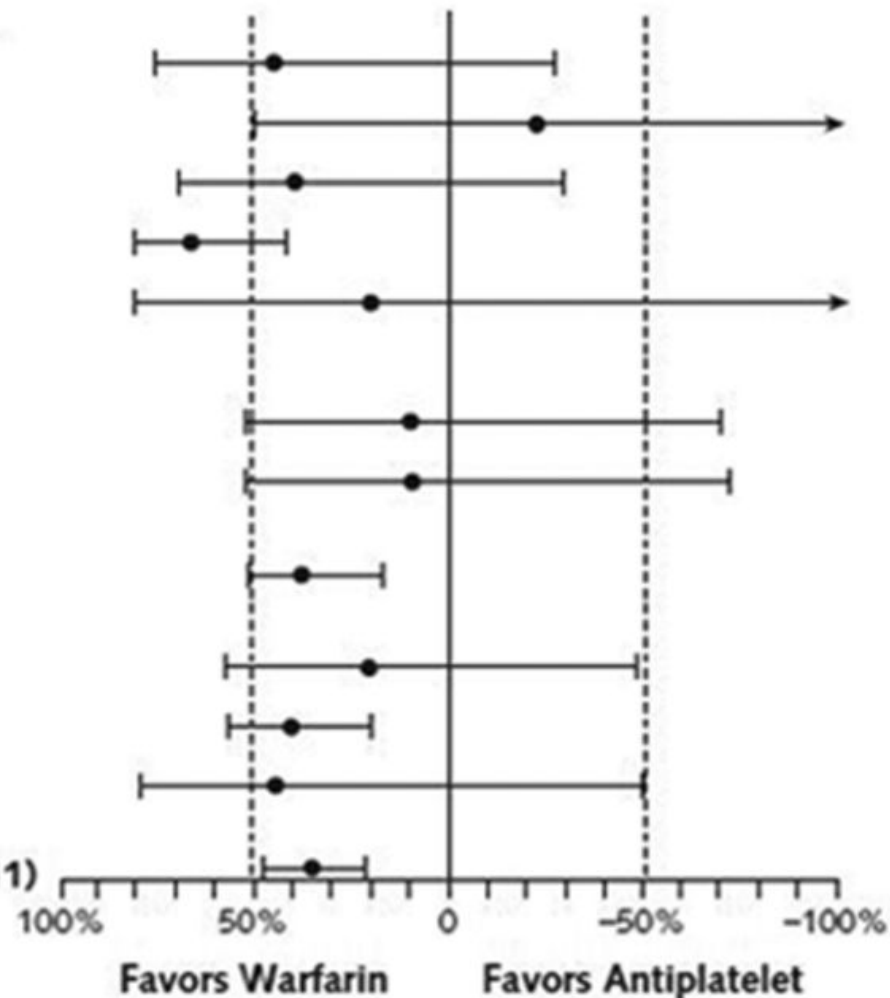
Aspirin trials ($n = 8$)^{*}

SIFA, 1997

ACTIVE-W, 2006

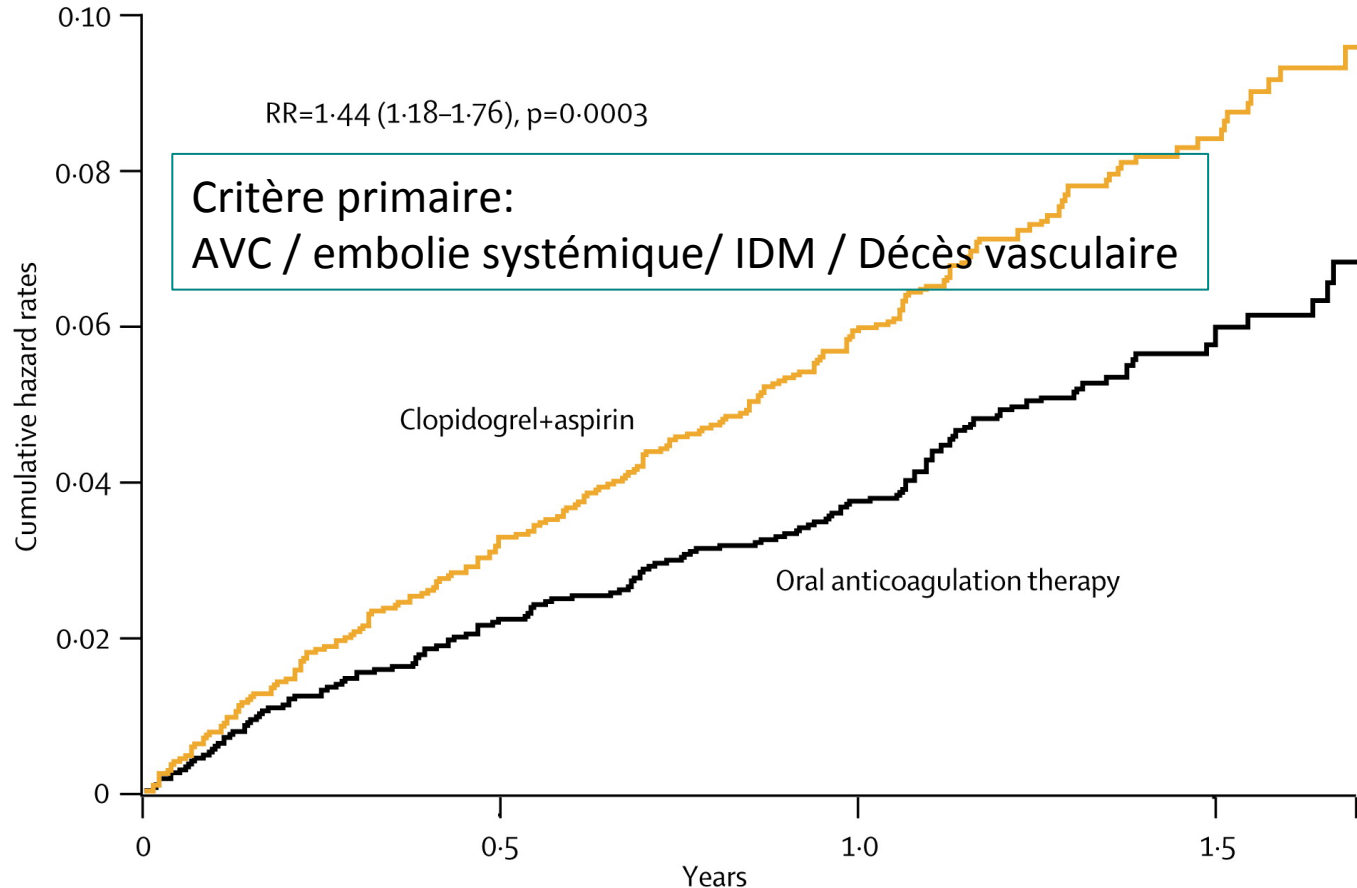
NASPEAF, 2004

All antiplatelet trials ($n = 11$)



Les AAP ne protègent pas aussi bien que les OAC contre le risque embolique dans la FA

ACTIVE-W : AVK vs. DAPT dans la prévention des complications emboliques dans la FA



Number at risk

Clopidogrel +aspirin	3335	3152	2389	927
Oral anticoagulation therapy	3371	3221	2458	924

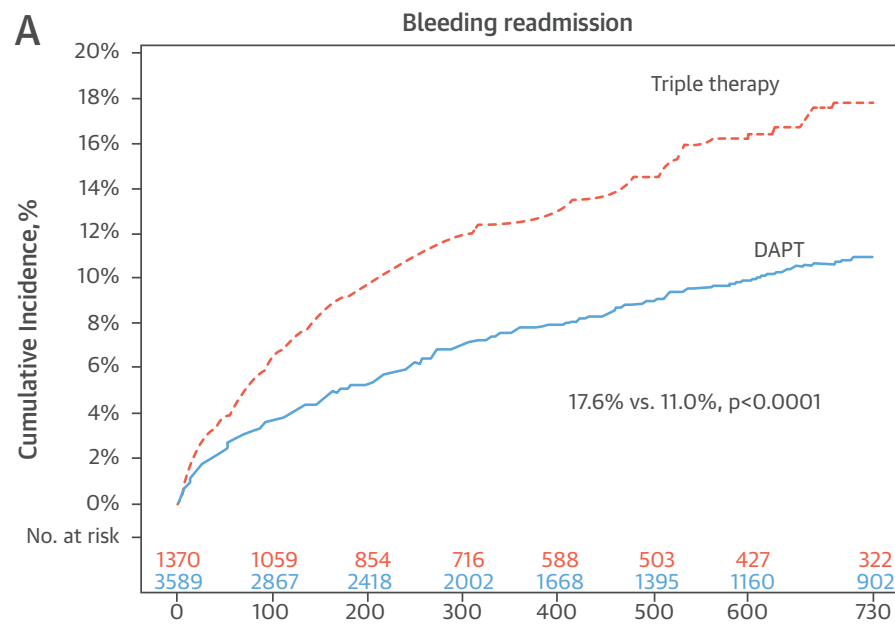
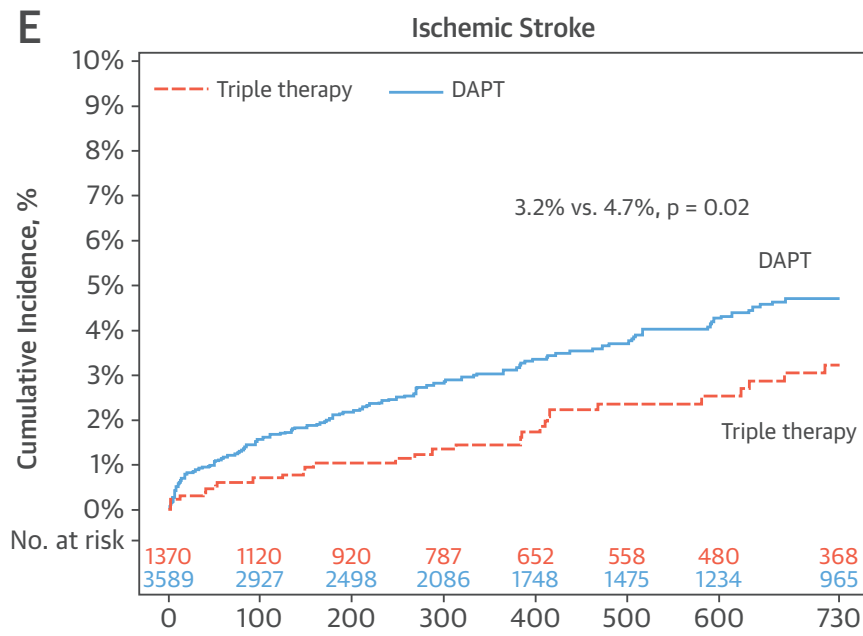
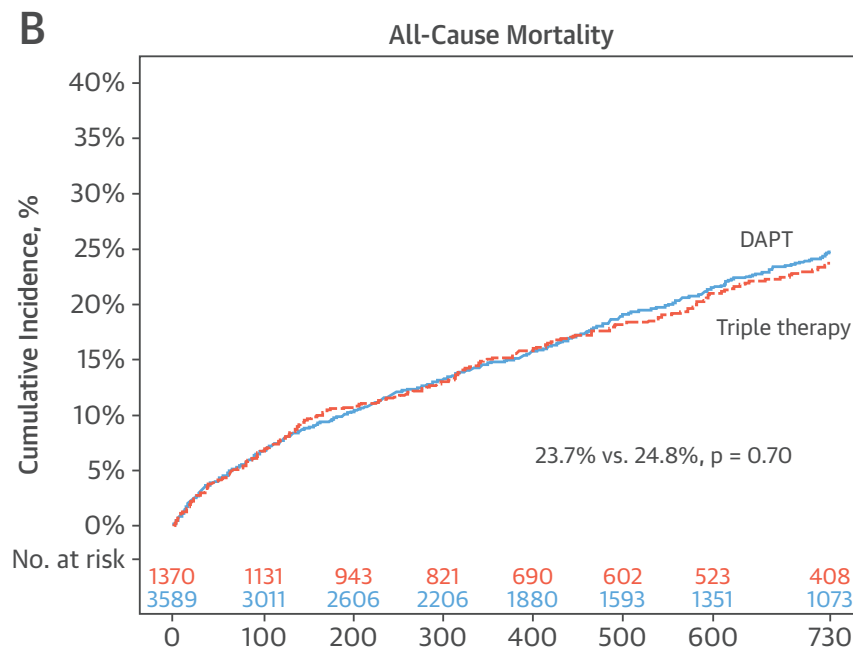
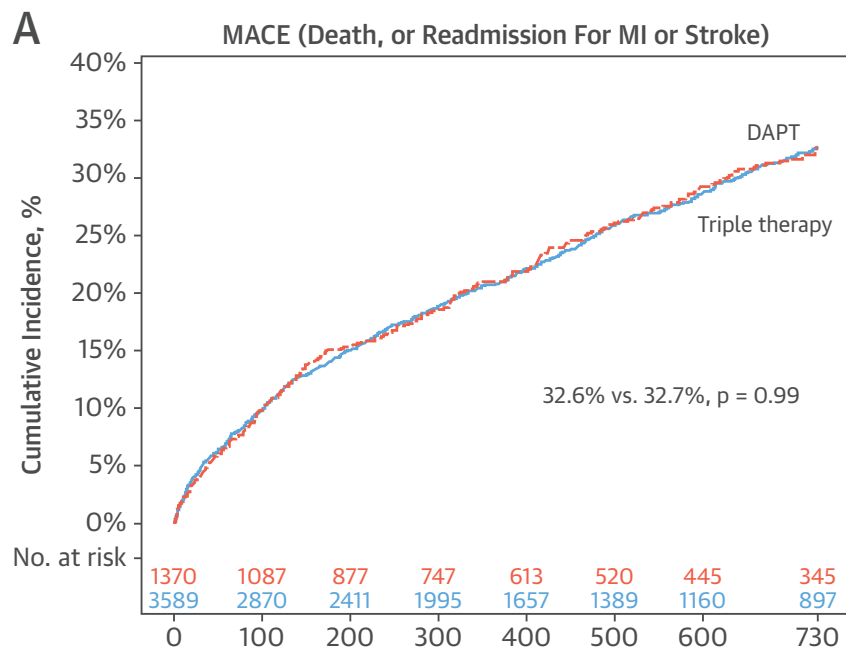
ACTIVE INVESTIGATORS, Lancet 2006

La triple thérapie est elle la bonne solution ?

- Registre ACTION - GWTG
- N=4959 patients > 65 ans avec FA et SCA traités par ATC
- N= 1370 patients sortis sous triple thérapie (27.6%)
- N=3589 patients sortis sous DAP (72.4%)

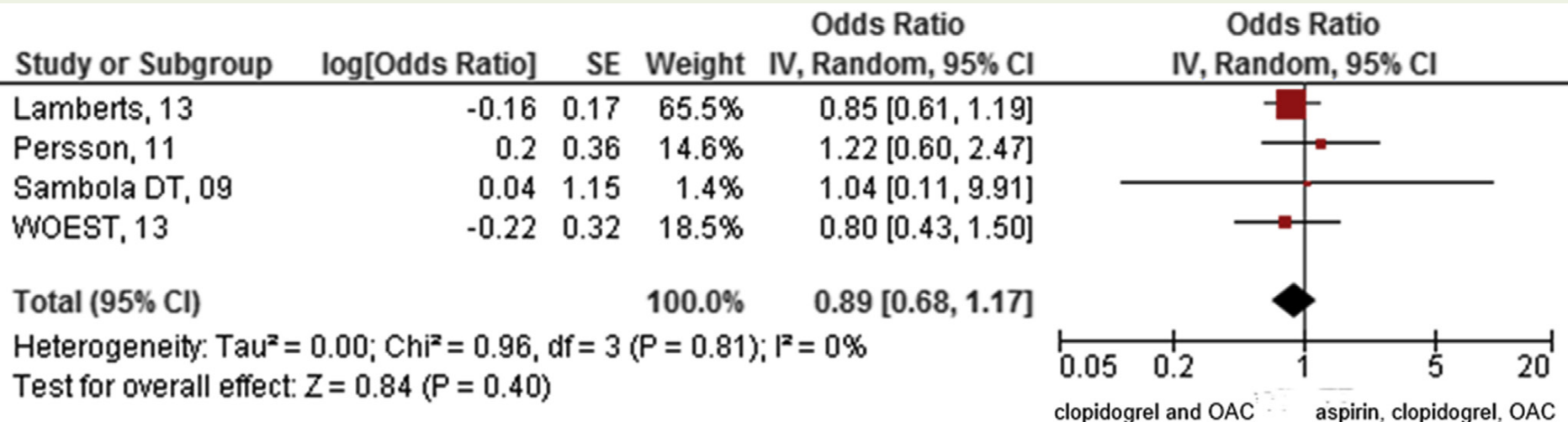
	DAPT (n = 3,589)	Triple Therapy* (n = 1,370)	p Value
Patient features			
Age, yrs	78.0 (72.0-84.0)	77.0 (72.0-82.0)	<0.01
Female	1,602 (44.6)	505 (36.9)	<0.01
Body mass index, kg/m ²	26.6 (23.6-30.5)	27.7 (24.6-31.6)	<0.01
Hypertension	2,911 (81.1)	1,145 (83.6)	0.04
Dyslipidemia	2,226 (62.0)	922 (67.3)	<0.01
Diabetes	1,075 (30.0)	486 (35.5)	<0.01
Prior MI	991 (27.6)	431 (31.5)	<0.01
Prior HF	606 (16.9)	337 (24.6)	<0.01
Prior CABG	730 (20.3)	362 (26.4)	<0.01
Prior PCI	1,014 (28.3)	424 (31.0)	<0.01
AF/flutter in previous 2 weeks	1,014 (39.7)	586 (60.8)	<0.01
Prior stroke	369 (10.3)	175 (12.8)	0.01
Peripheral arterial disease	466 (13.0)	211 (15.4)	0.03

La triple thérapie est elle la bonne solution ?

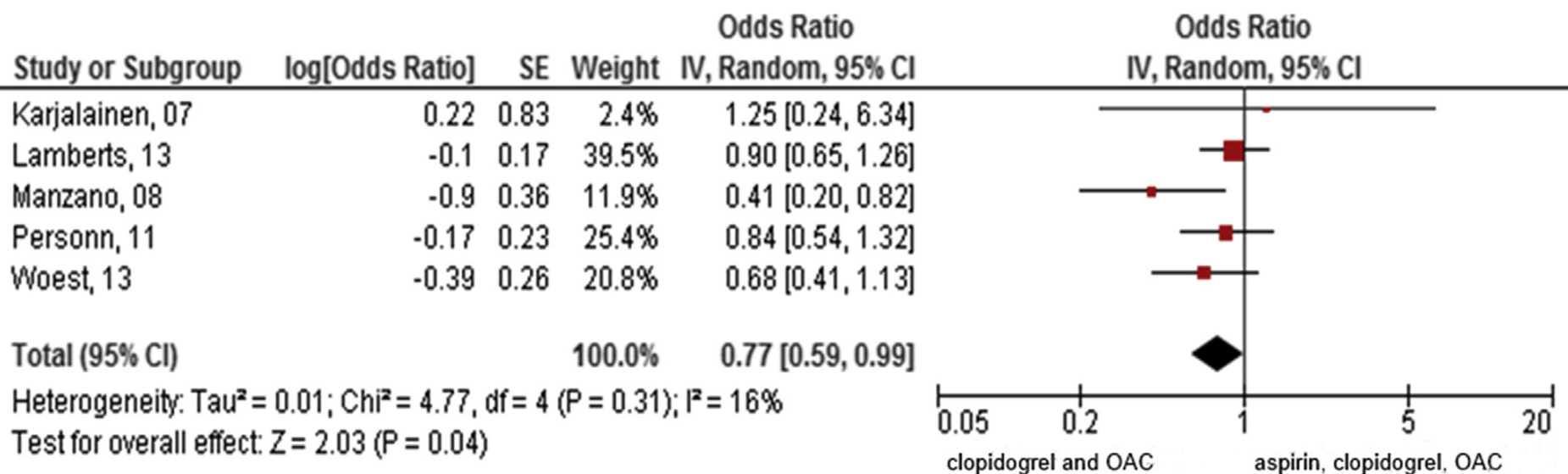


La triple thérapie est elle la bonne solution ?

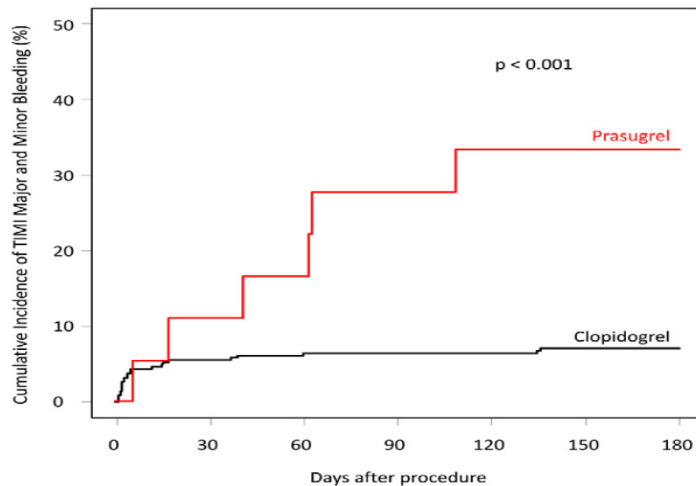
METAANALYSE DE D'ASCENZIO : RISQUE DE DECES/ IDM/ AVC/ THROMBOSE DE STENT



METAANALYSE DE D'ASCENZIO : RISQUE DE SAIGNEMENTS MAJEURS



Triple thérapie avec Prasugrel/Tica?



Triple Therapy: OAC+ASA+P2Y12 blockers
N=21 prasugrel* et N=356 Clopidogrel

The use of ticagrelor and prasugrel as part of initial triple therapy is not recommended



Sarafoff et al, JACC Vol. 61, No. 20, 2013



Peut-on faire plus simple?

WOEST - *Méthodologie*

Étude multicentrique ouverte (15 centres en Belgique et Pays-Bas) randomisée comparant 2 stratégies anti-thrombotiques après stenting (actifs 2/3 nus 1/3) :

Groupe “double thérapie”

AVK + Clopidogrel 75 mg

durée :

1 mois min pour un stent nu

12 mois pour un stent actif

Groupe “triple thérapie”

AVK + Clopidogrel 75 mg + Aspirine 80 mg

durée :

1 mois min pour un stent nu

12 mois pour un stent actif

Suivi : 12 mois

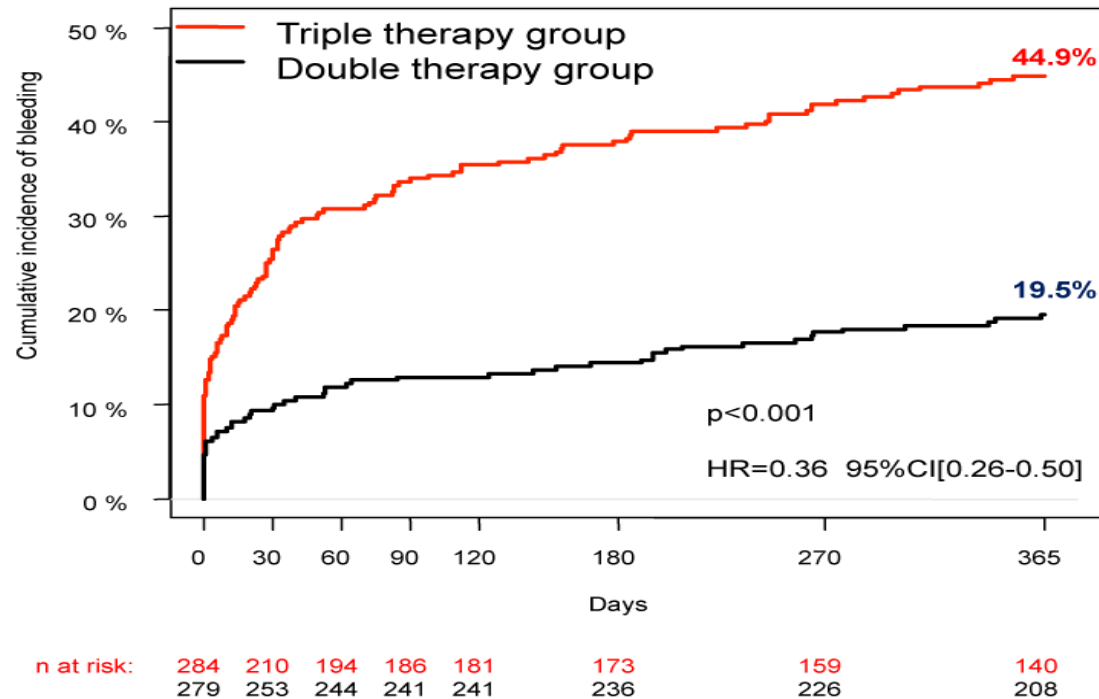
Critère primaire de jugement : survenue de tout type de saignement (critères TIMI)

Critères secondaires de jugement :

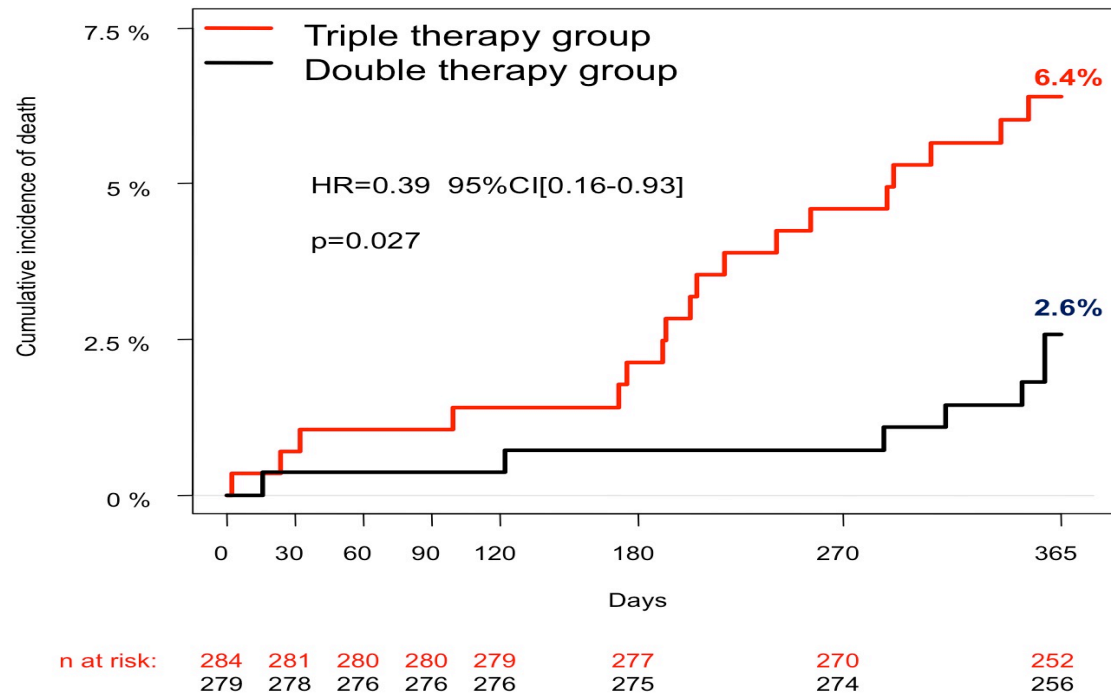
- combinaison d'AVC, décès, nécrose myocardique, thrombose de stent et revascularisation artère coupable
- tous critères

WOEST - Résultats - critère primaire

(incidence cumulée des saignements)



WOEST - *Mortalité toutes causes*



Registre Danois

12 165 patients fibrillation atriale,
hospitalisés pour infarctus et/ou angiostenting coronaire entre 2001 et 2009.
médiane CHADS2 de $1,9 \pm 1,2$,
score de risque hémorragique HAS-BLED de $2,0 \pm 0,9$

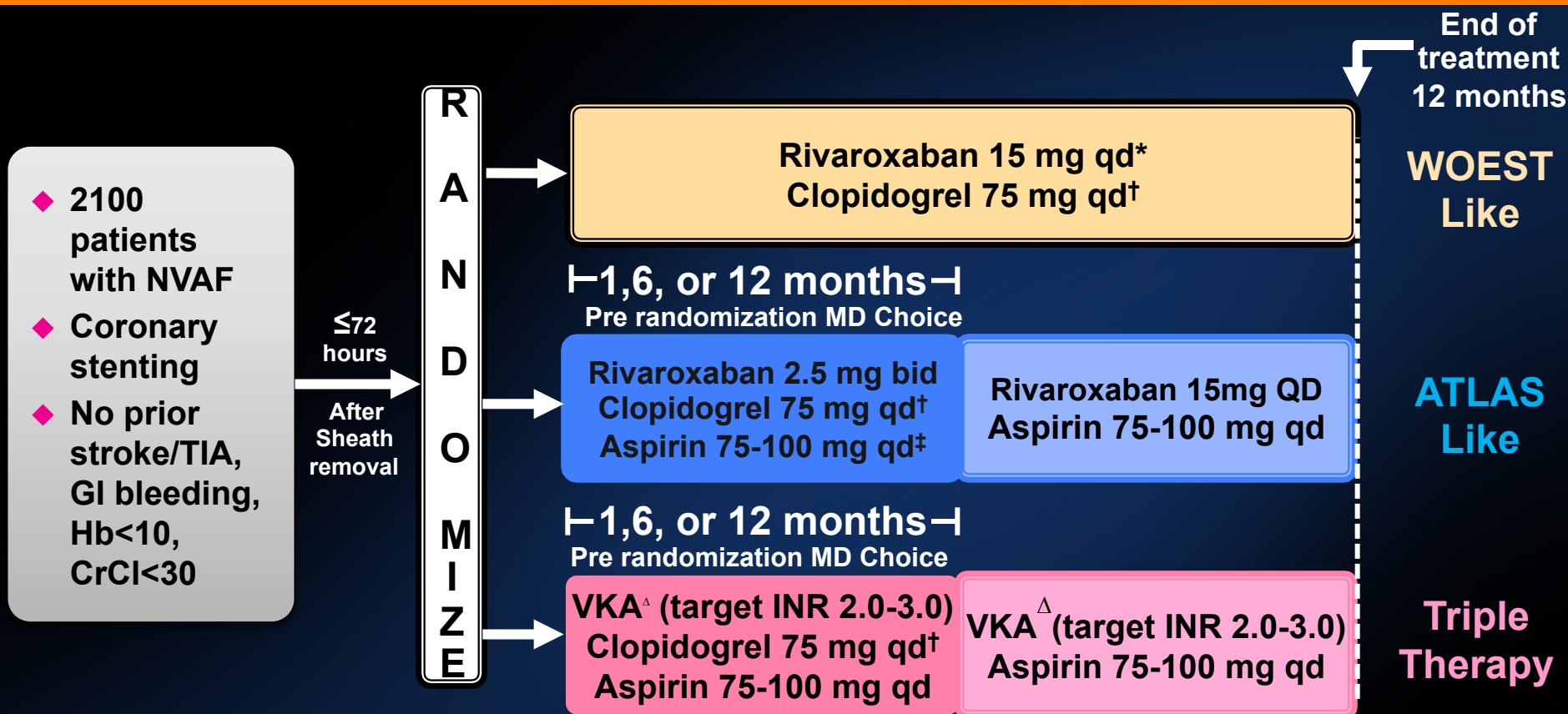
- -40% : *monothérapie: AVK, ou aspirine ou clopidogrel ;*
- -50% : *bithérapie : AVK/clopidogrel, AVK/aspirine ou aspirine/clopidogrel ;*
- -15% : *trithérapie : AVK + clopidogrel + aspirine.*

**Association AVK/clopidogrel plus favorable.
Trithérapie moins d'efficacité et majore le risque de complications
hémorragiques**

AVK/clopidogrel vs trithérapie RR=0,78 ; IC95% [0,55-1,12]

Oldgren J, Budaj A, Granger CB, Khder Y, Roberts J, Siegbahn A et al. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J 2011;32:2781–9.

Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI



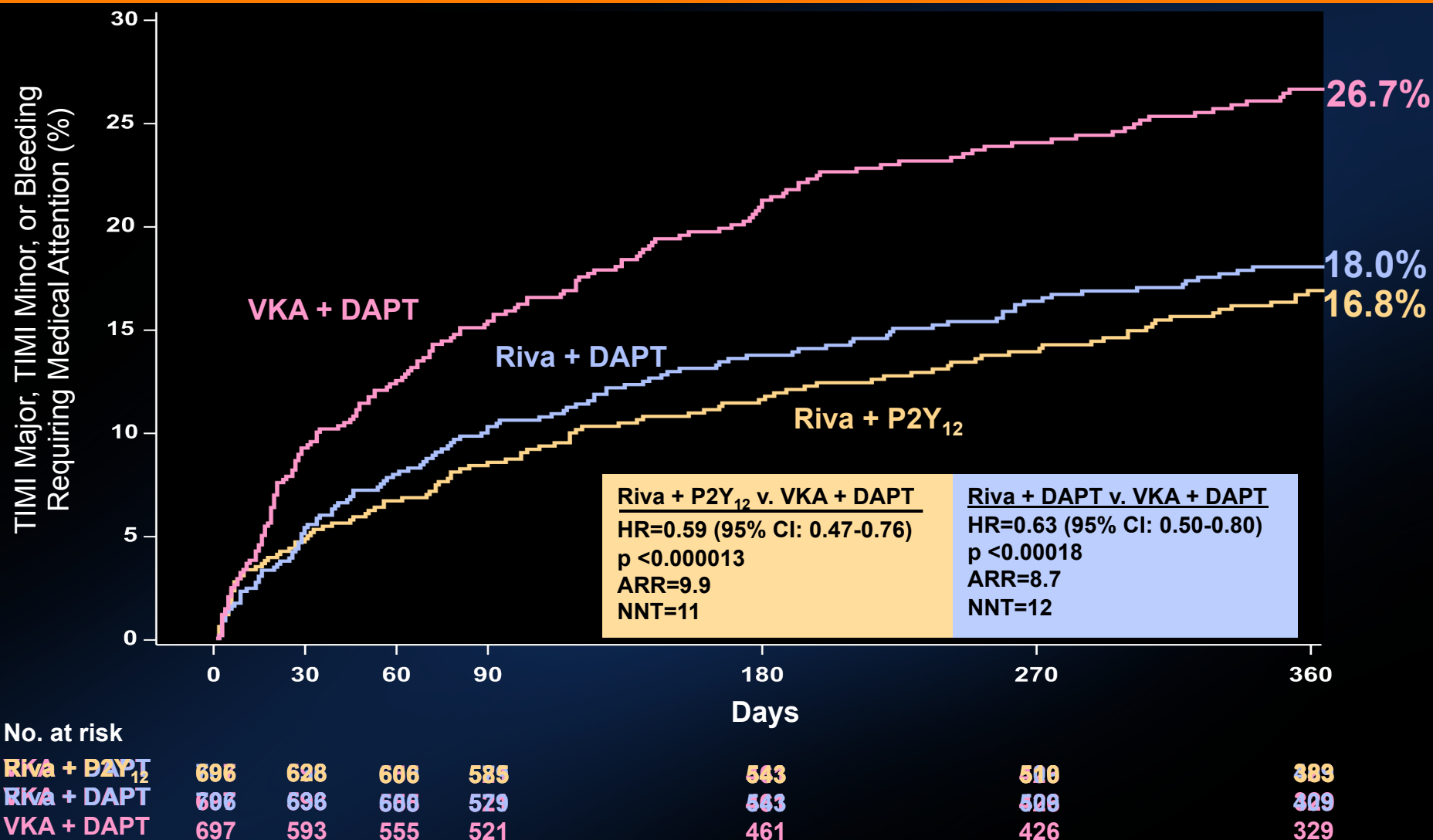
- **Primary endpoint:** TIMI major + minor + bleeding requiring medical attention
- **Secondary endpoint:** CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

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

†Alternative P2Y₁₂ inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.

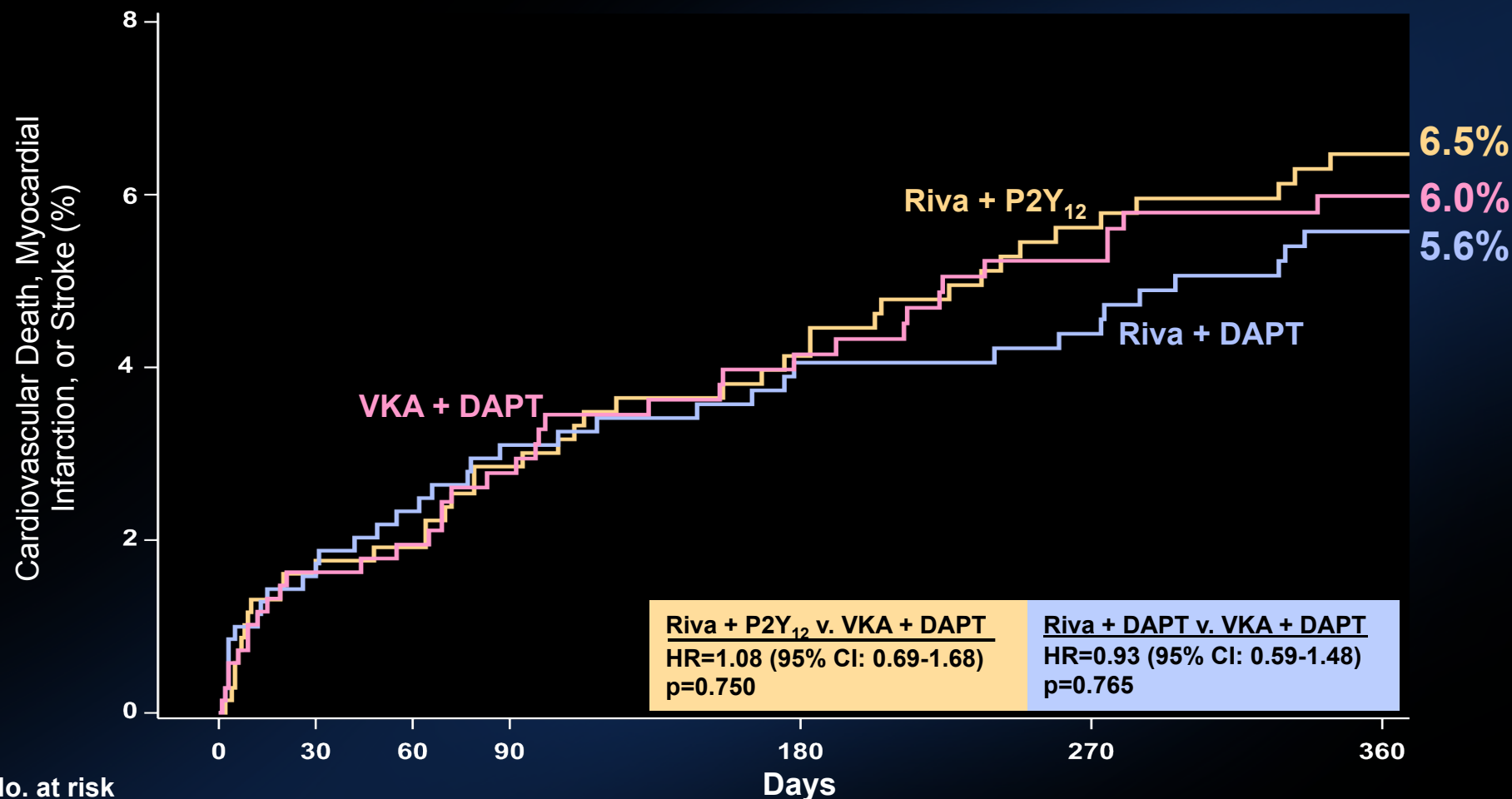
‡Low-dose aspirin (75-100 mg/d). ^Δ Open label VKA

Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events



Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.
Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA.
Hazard ratios as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.
Log-Rank P-values as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

Kaplan-Meier Estimates of First Occurrence of CV Death, MI or Stroke



No. at risk

Riva + P2Y ₁₂	694	648	633	621	590	562	430
Riva + DAPT	704	662	640	628	596	570	457
VKA + DAPT	695	635	607	579	543	514	408

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

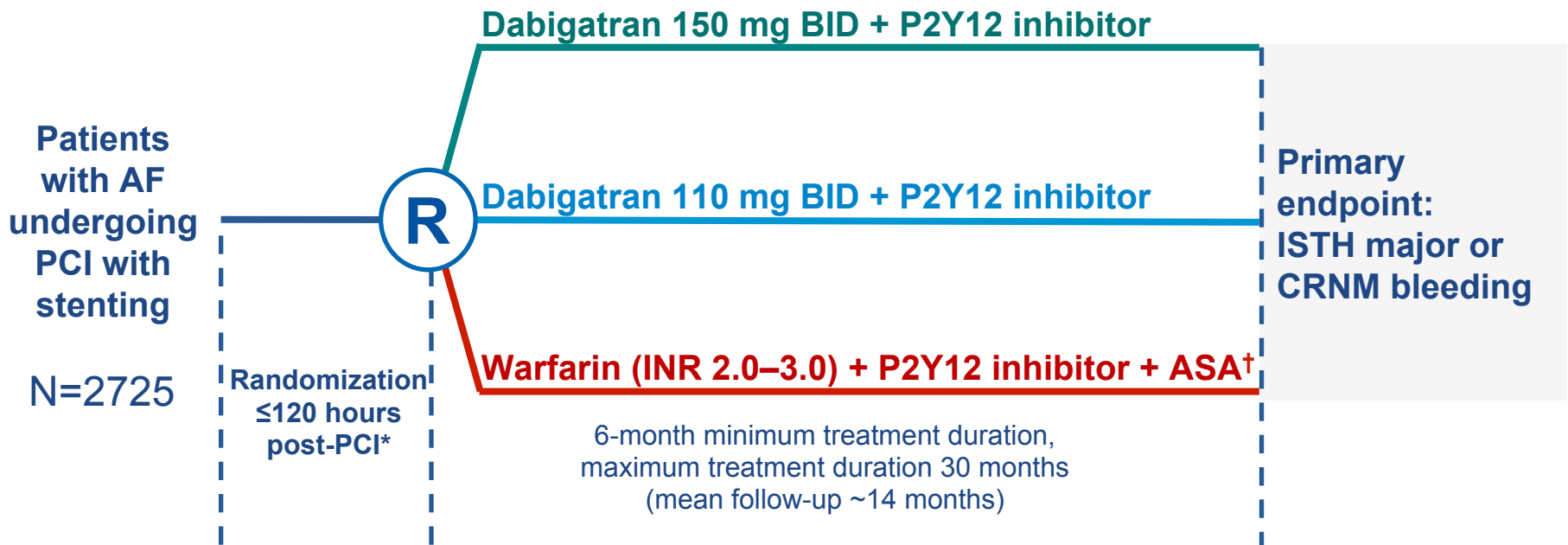
Composite of adverse CV events is composite of CV death, MI, and stroke.

Hazard ratios as compared to VKA group are based on the (stratified, only for the Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.

Log-Rank P-values as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

6 Subjects were excluded from all efficacy analyses because of violations in Good Clinical Practice guidelines

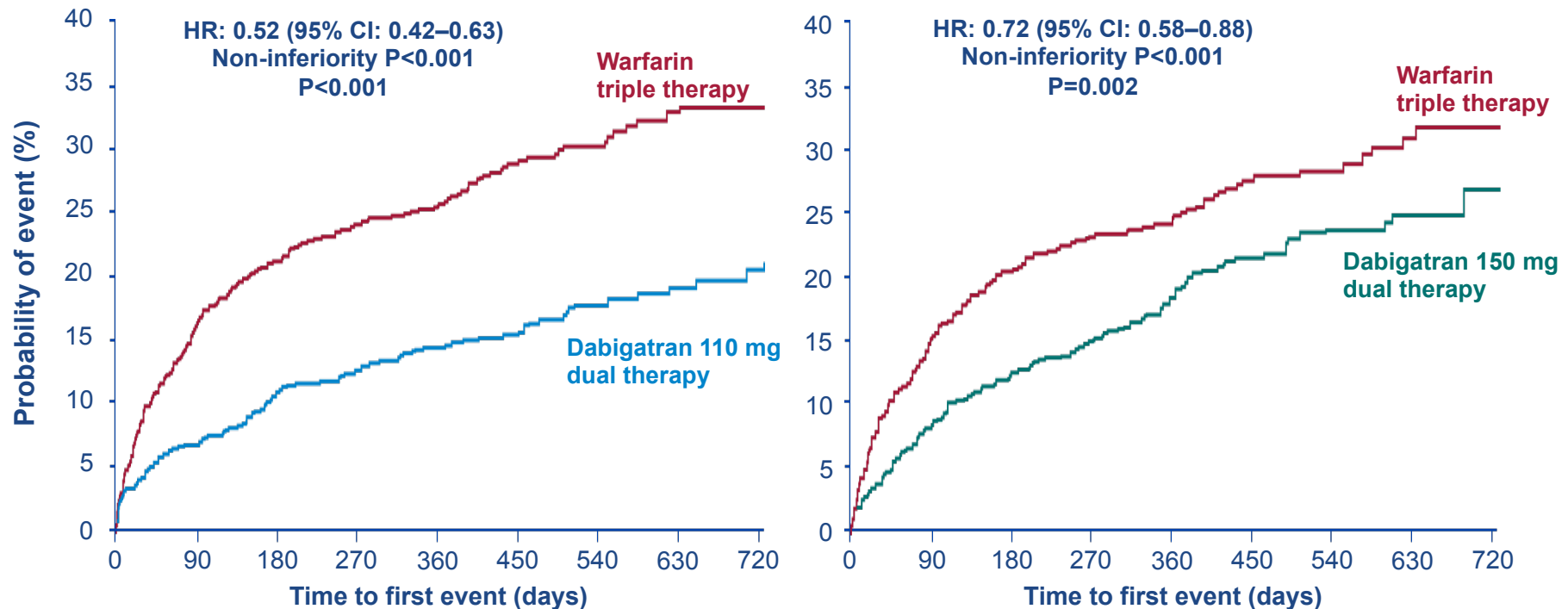
RE-DUAL PCI tested the safety and efficacy of two regimens of dual therapy with dabigatran without ASA vs triple therapy with warfarin



RE-DUAL PCI was a multicentre, open-label trial following a prospective, randomized, open, blinded end-point design;

*Study drug should be administered 6 hours after sheath removal and no later than 120 hours post-PCI (≤72 hours is preferable). [†]ASA discontinued after 1 month after bare-metal stent and 3 months after drug-eluting stent; ASA, acetylsalicylic acid; CRNM, clinically relevant non-major; R, randomization; Cannon et al. Clin Cardiol 2016; Cannon et al. N Engl J Med 2017

Significantly lower rates of ISTH major bleeding or CRNMBE with dabigatran dual therapy

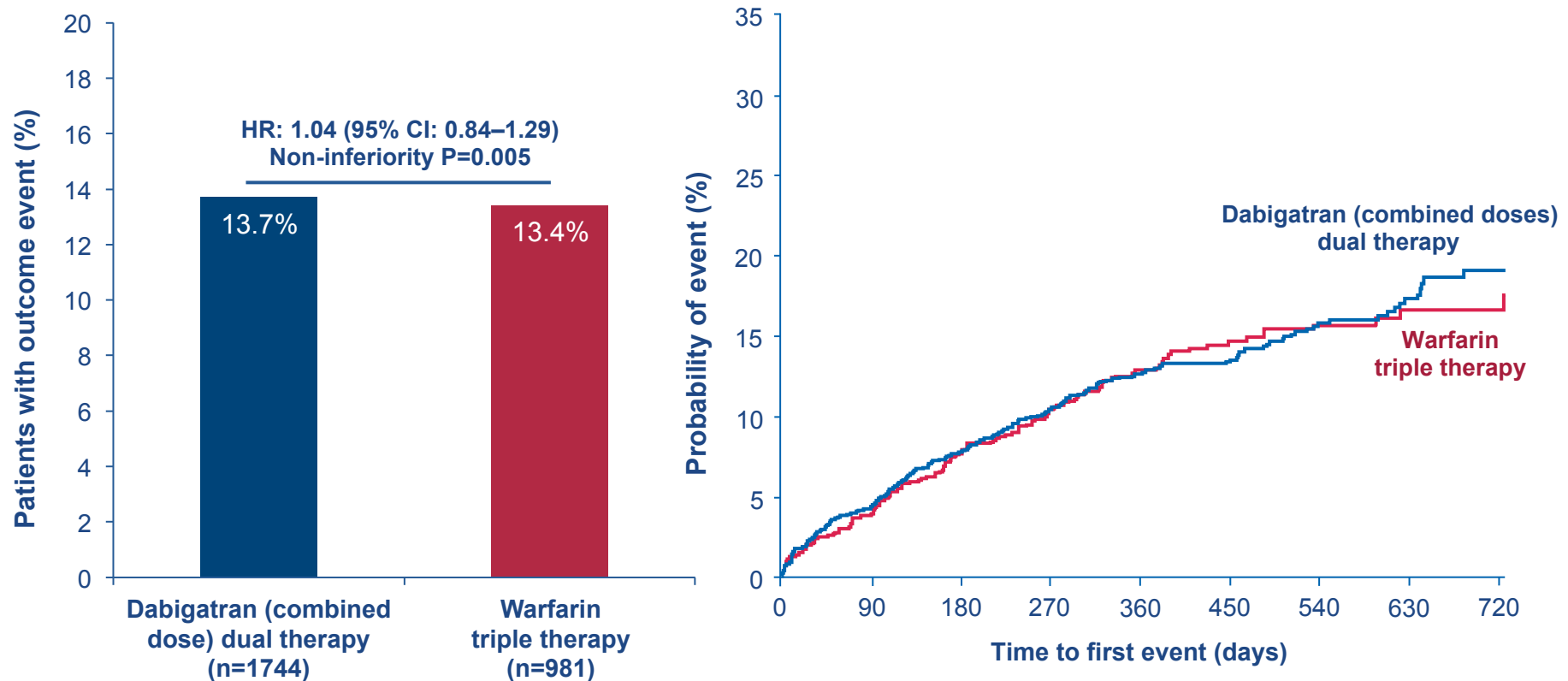


For the dabigatran 150 mg vs warfarin comparison, elderly patients outside the USA (≥ 80 years) and Japan (≥ 70 years) are excluded. Full analysis set presented

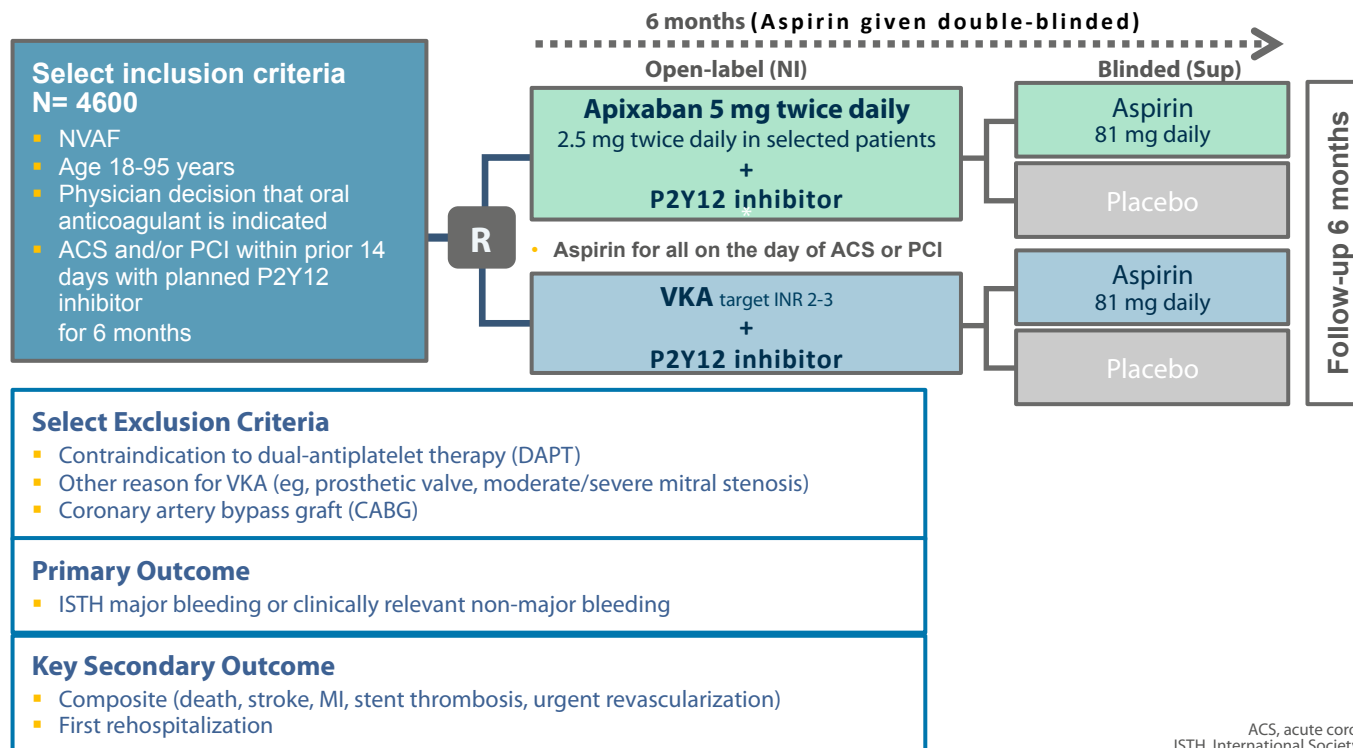
CRNMBE, clinically relevant non-major bleeding event; ISTH, International Society on Thrombosis and Haemostasis; Cannon et al. ESC 2017; Cannon et al. N Engl J Med 2017

Dabigatran dual therapy was non-inferior to warfarin triple therapy in the composite efficacy endpoint

Composite endpoint of death or thromboembolic event (MI, stroke or systemic embolism) or unplanned revascularization (PCI/CABG)



AUGUSTUS Study Design: NVAF Patients with ACS or Undergoing PCI



*Patients with ≥ 2 of the following: age ≥ 80 years, weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL ($133 \mu\text{mol/L}$).

Available from: <https://clinicaltrials.gov/ct2/show/NCT02415400>.
NLM Identifier: NCT02415400. Accessed on February 09, 2017.

ACS, acute coronary syndrome;
ISTH, International Society on Thrombosis
and Haemostasis; MI, myocardial infarction;
NVAF, non-valvular atrial fibrillation;
PCI, percutaneous coronary intervention;
R, randomization; VKA, vitamin K antagonist.

Limites de WOEST/PIONEER-AF/RE-DUAL

- Les critères de jugement primaires utilisés sont essentiellement des critères de **sécurité** (saignement).
- Les études n'ont pas cherché à mettre en évidence une différence en terme d'**efficacité** (thrombose de stent et/ou récurrence ischémique).

Que nous disent les guidelines ?

2017 ESC Focused Update on Dual Antiplatelet Therapy in Coronary Artery Disease developed in collaboration with the EACTS*

Recommendations	Class ^a	Level ^b
It is recommended to administer periprocedurally aspirin and clopidogrel in patients undergoing coronary stent implantation.	I	C
In patients treated with coronary stent implantation, triple therapy with aspirin, clopidogrel, and OAC should be considered for 1 month, irrespective of the type of stent used. ¹⁹⁵	IIa	B
Triple therapy with aspirin, clopidogrel, and OAC for longer than 1 month and up to 6 months should be considered in patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics that outweigh the bleeding risk. ¹⁹⁵	IIa	B

Dual antiplatelet therapy duration in patients with indication for oral anticoagulation (continued)

Recommendations	Class	Level
Discontinuation of antiplatelet treatment in patients treated with OAC should be considered at 12 months.	IIa	B
In patients with an indication for VKA in combination with aspirin and/or clopidogrel, the dose intensity of VKA should be carefully regulated with a target INR in the lower part of the recommended target range and a time in the therapeutic range >65–70%.	IIa	B
When a NOAC is used in combination with aspirin and/or clopidogrel, the lowest approved dose effective for stroke prevention tested in AFib trials should be considered.	IIa	C
When rivaroxaban is used in combination with aspirin and/ or clopidogrel, rivaroxaban 15 mg <i>q.d.</i> may be used instead of rivaroxaban 20 mg <i>q.d.</i>	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC.	III	C

Strategies to avoid bleeding complications in patients treated with oral anticoagulant

- Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA₂DS₂-VASc, ABC, HAS-BLED) with a focus on modifiable risk factors.
- Keep triple therapy duration as short as possible; dual therapy after PCI (oral anticoagulant and clopidogrel) to be considered instead of triple therapy.
- Consider the use of NOACs instead of VKA when NOACs are not contra-indicated.
- Consider a target INR in the lower part of the recommended target range and maximize time in therapeutic range (i.e. >65–70%) when VKA is used.
- Consider the lower NOAC regimen tested in approval studies and apply other NOAC regimens based on drug-specific criteria for drug accumulation.
- Clopidogrel is the P2Y₁₂ inhibitor of choice.
- Use low-dose (≤ 100 mg daily) aspirin.
- Routine use of PPIs.

Unfavourable patient profile for a combination of oral anticoagulant and antiplatelet therapy

• Short life expectancy.
• Ongoing malignancy.
• Poor expected adherence.
• Poor mental status.
• End stage renal failure.
• Advanced age.
• Prior major bleeding/prior haemorrhagic stroke.
• Chronic alcohol abuse.
• Anaemia.
• Clinically significant bleeding on dual antithrombotic therapy.

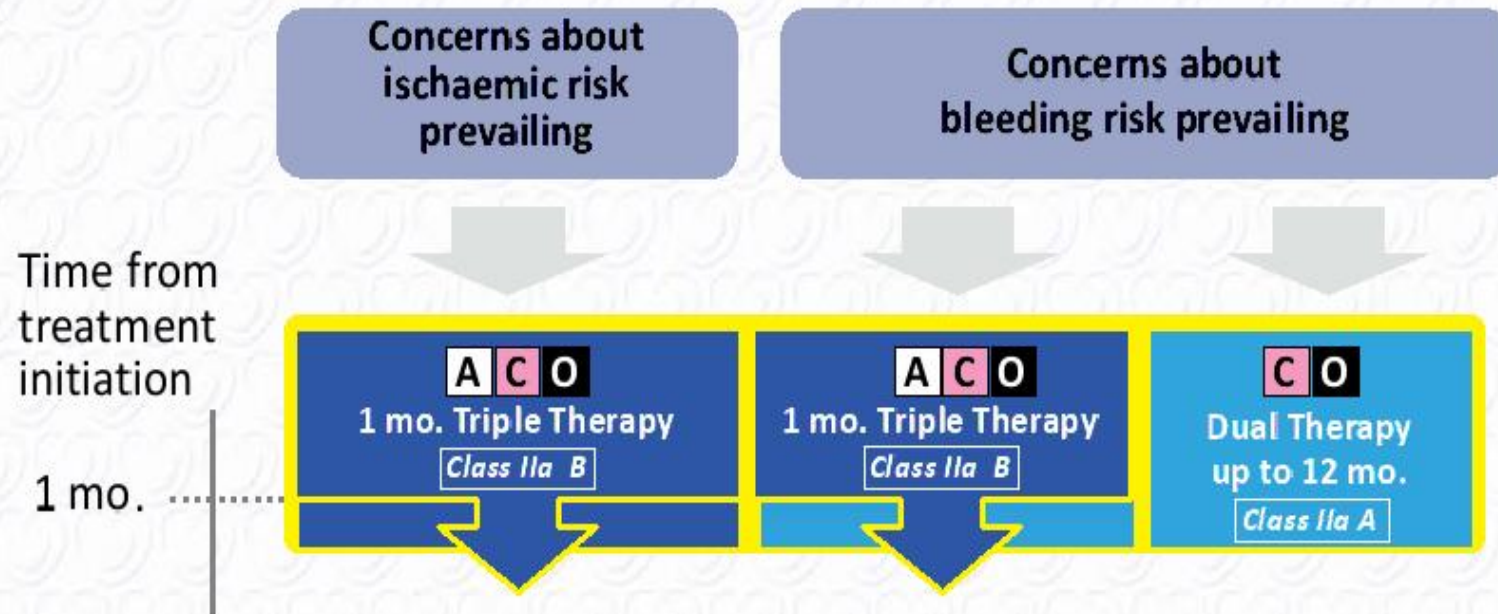
Informations disponibles AVANT la pose du stent

Dual antiplatelet therapy duration in patients with indication for oral anticoagulation

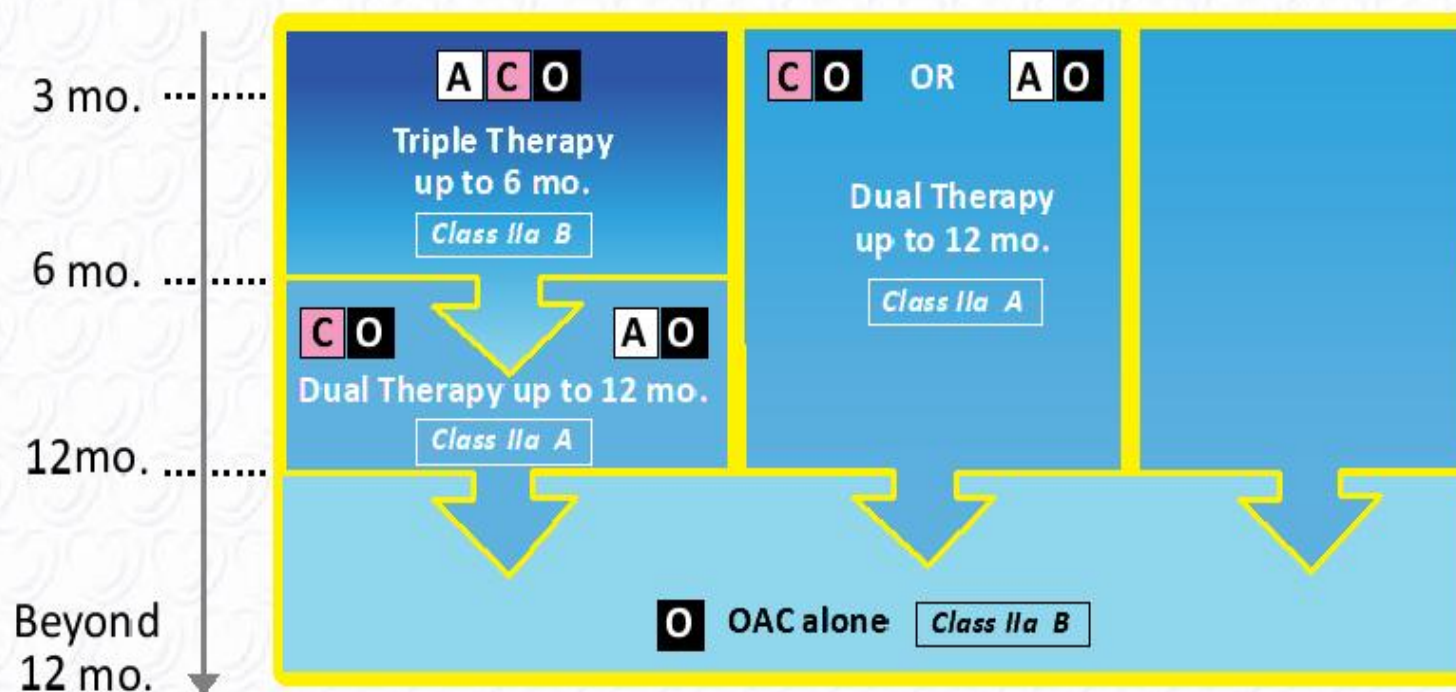
Recommendations	Class	Level
It is recommended to administer periprocedurally aspirin and clopidogrel in patients undergoing coronary stent implantation.	I	C
In patients treated with coronary stent implantation, triple therapy with aspirin, clopidogrel and OAC should be considered for 1 month, irrespective of the type of stent used.	Ila	B
Triple therapy with aspirin, clopidogrel and OAC for longer than 1 month and up to 6 months should be considered in patients with high ischaemic risk due to ACS or other anatomical/procedural characteristics, which outweigh the bleeding risk.	Ila	B

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

Patients with an indication for oral anticoagulation undergoing PCI



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



A = Aspirin **C** = Clopidogrel **O** = Oral anticoagulation

Ce qu'il faut envisager au moment du choix du traitement...

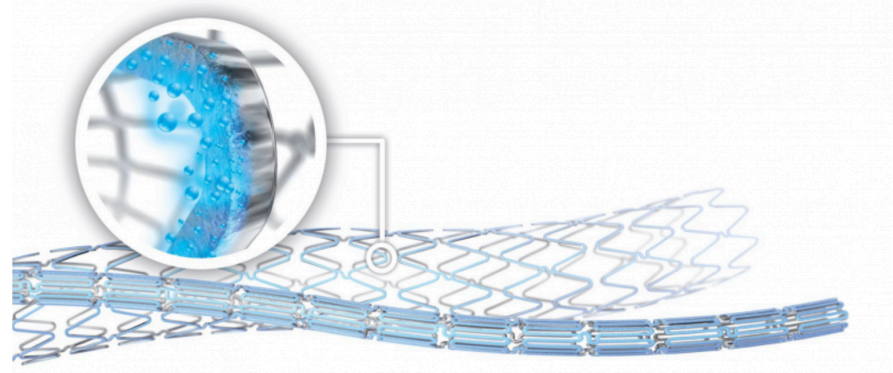
- **Le risque ischémique résiduel de la procédure
(= le risque de thrombose de stent)**
- **Le risque de saignement du patient:**
 - **Scores de risque : HAS-BLED, PRECISE-DAPT, ABC...**
 - **Profil clinique**

High-risk features of stent-driven recurrent ischaemic events

- Prior stent thrombosis on adequate antiplatelet therapy.
- Stenting of the last remaining patent coronary artery.
- Diffuse multivessel disease especially in diabetic patients.
- Chronic kidney disease (i.e. creatinine clearance <60 mL/min).
- At least three stents implanted.
- At least three lesions treated.
- Bifurcation with two stents implanted.
- Total stent length >60 mm.
- Treatment of a chronic total occlusion.

Choix du stent...

Polymer-free Drug-Coated Coronary Stents in Patients at High Bleeding Risk



Inclusion criteria — no. (%)§

Age ≥ 75 yr

Oral anticoagulation planned to continue after PCI

Hemoglobin < 11 g/liter or transfusion within 4 wk before randomization

Platelet count $< 100,000/\text{mm}^3$

Hospital admission for bleeding in previous 12 mo

Stroke in previous 12 mo

Previous intracerebral hemorrhage

Severe chronic liver disease

Creatinine clearance < 40 ml/min

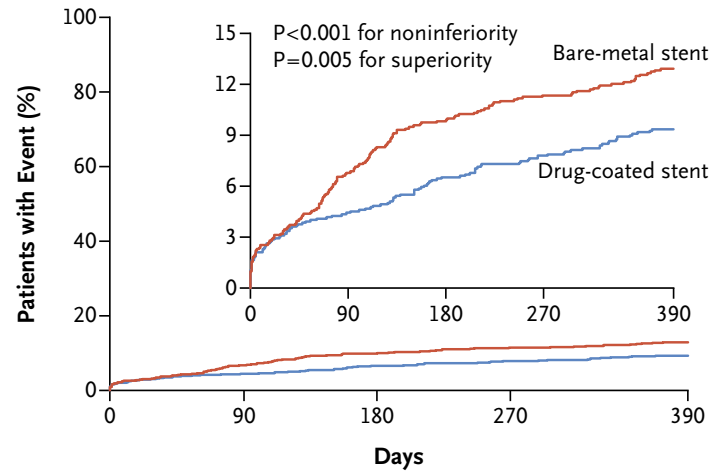
Cancer in previous 3 yr¶

Planned major surgery in next 12 mo

Glucocorticoids or NSAID planned for > 30 days after PCI

Expected nonadherence to > 30 days of dual antiplatelet therapy

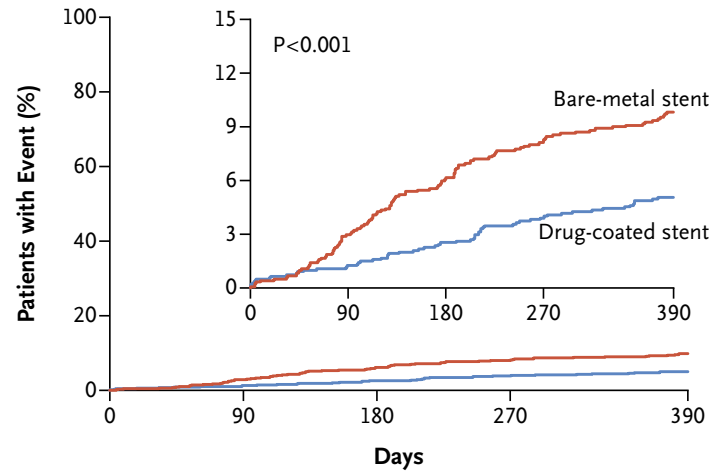
A Primary Safety End Point



No. at Risk

Drug-coated stent	1221	1146	1105	1081	1045
Bare-metal stent	1211	1115	1066	1037	1000

B Primary Efficacy End Point




No. at Risk

Drug-coated stent	1221	1167	1130	1098	1053
Bare-metal stent	1211	1131	1072	1034	984

HAS-BLED

Letter	Clinical Characteristic	Points
H	Hypertension	1
A	Abnormal Liver or Renal Function	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INR	1
E	Elderly (age > 65)	1
D	Drugs or Alcohol	1 or 2
Maximum Score		9

Haemoglobin 

unit


13.6

☒ g/dL

☐ mmol/L

Age (years)

76


White blood cells 

unit


13

☐ u/mL

☒ 10⁹/L

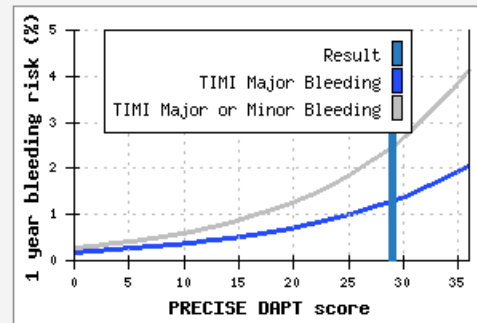
Creatinine Clearance (mL/min) 

68

Prior Bleeding  ☐

CALCULATE

RESET



RESULT:

Cluster of risk:

High

Score Calculated

29

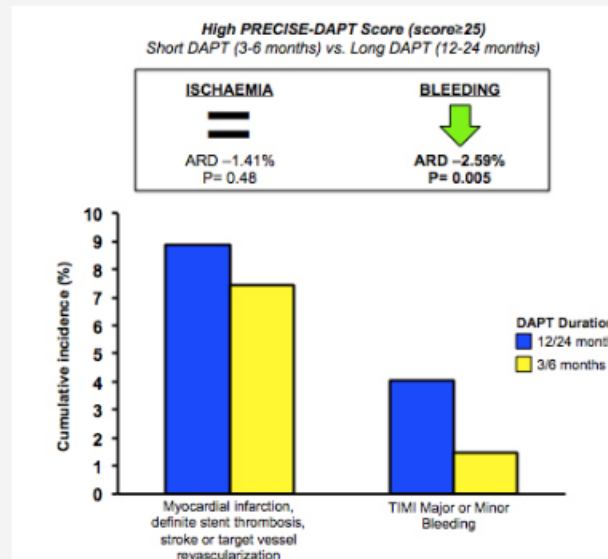
12 months risk of TIMI
major or minor
Bleeding

2.5%

12 months risk of TIMI
Major Bleeding

1.3%

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In patients with high PRECISE-DAPT score (Score ≥ 25) a short DAPT (3-6 months) as compared with a long DAPT (12-24 months) was associated with lower TIMI major and minor bleeding and similar rate of the composite ischemic endpoint.

Au total pour Mme L...

RIQUE ISCHEMIQUE

- **Modéré à élevé**
- **SCA**
- **Stenting du TCG distal**

RISQUE HEMORRAGIQUE

- **Faible à modéré**
- **HAS BLED=3**
- **PRECISE DAPT:28**
- **Pas d'anémie**
- **Fct rénale normale**
- **HTA contrôlée**

- **PRADAXA 110 mg + KARDEGIC 75 mg/j + PLAVIX 75 mg/ j**
- **pendant 3/6 mois**

Puis

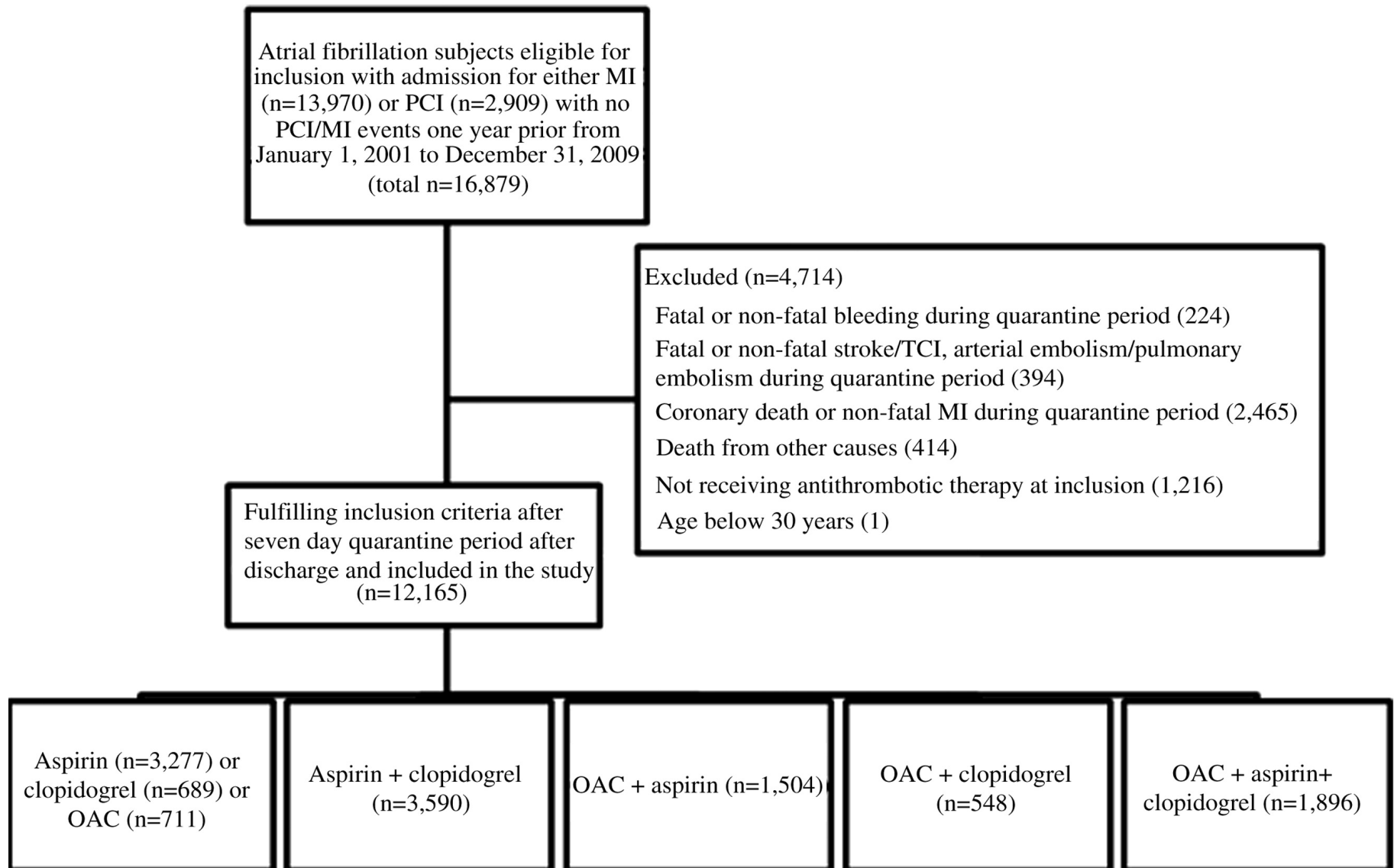
- **PRADAXA 110 mg + PLAVIX 75 mg/ j**
- **jusqu'à 1 an**

CONCLUSIONS

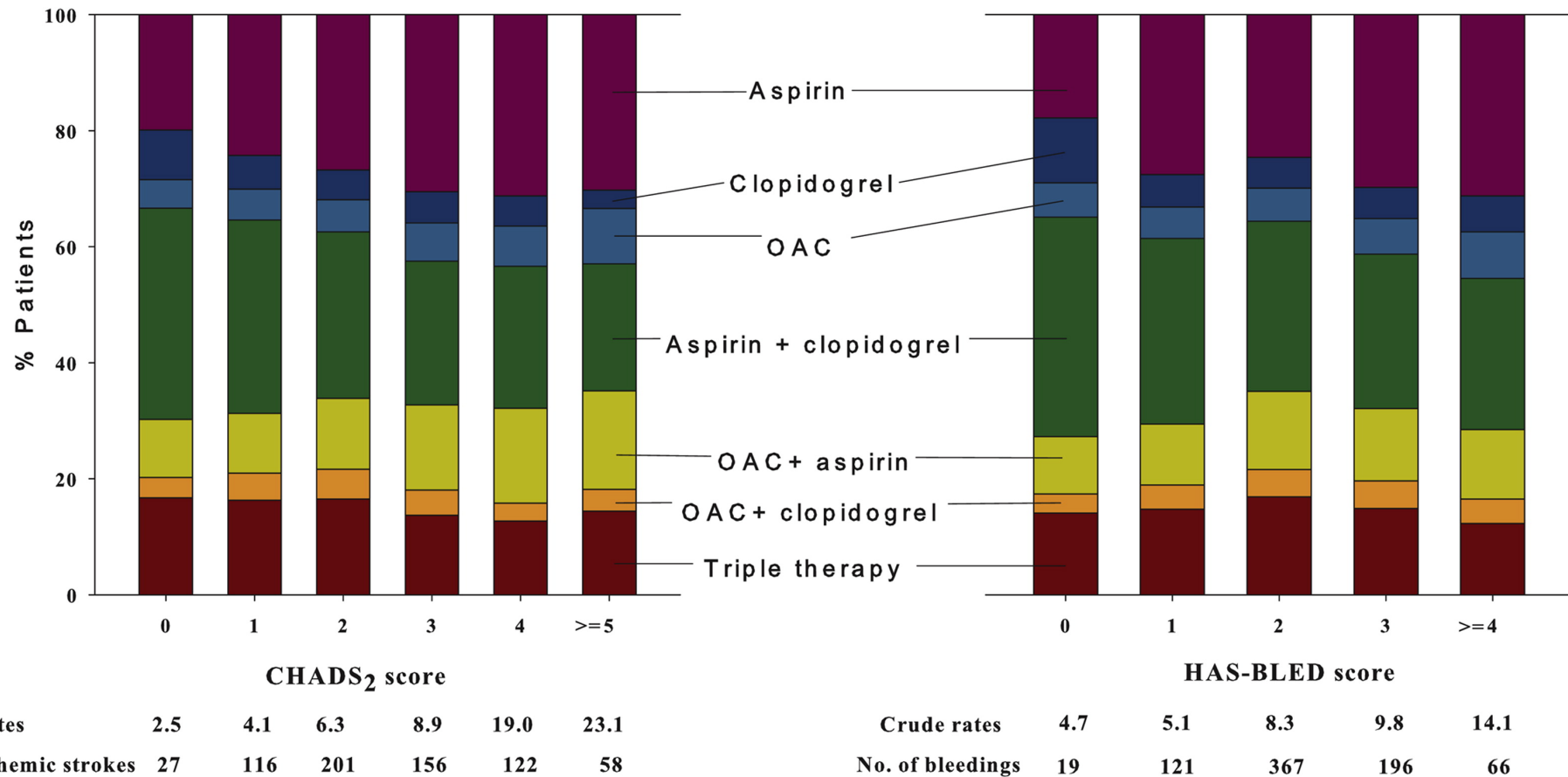
- La prise en charge médicamenteuse des patients en FA autour de d'une angioplastie est une situation fréquente et complexe.
- Plusieurs options de traitement sont possibles, la triple thérapie ACO/DAP n'est plus obligatoire (surtout avec l'amélioration des stents)
- La traitement doit être individualisé et discuté en fonction du risque ischémique et du risque hémorragique du patient.
- Les associations AOD+ clopidogrel sont prometteuses et doivent être évaluées à plus grande échelle.

Merci pour votre attention

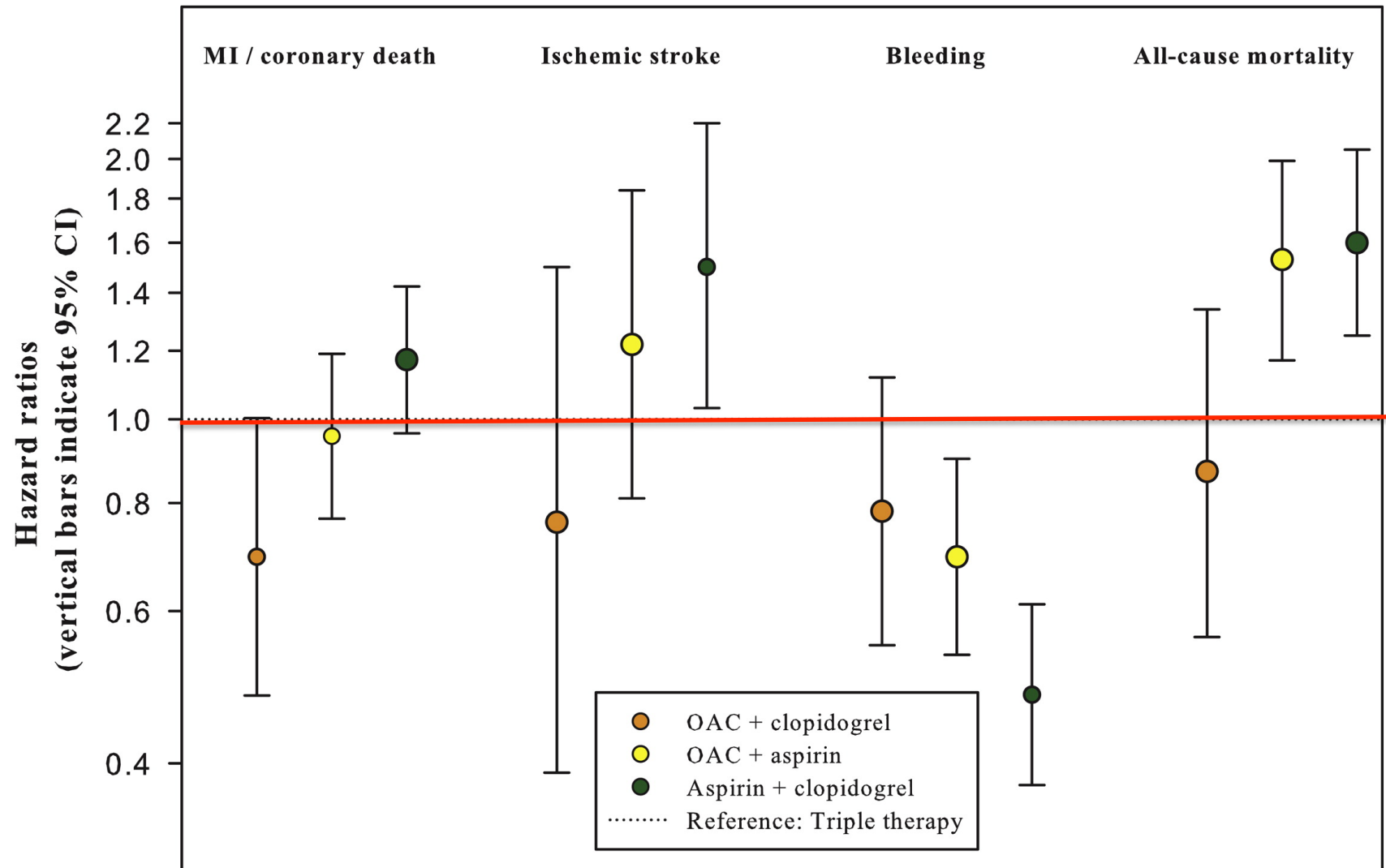
TTT vs. DAPT dans la vraie vie : le Registre Danois



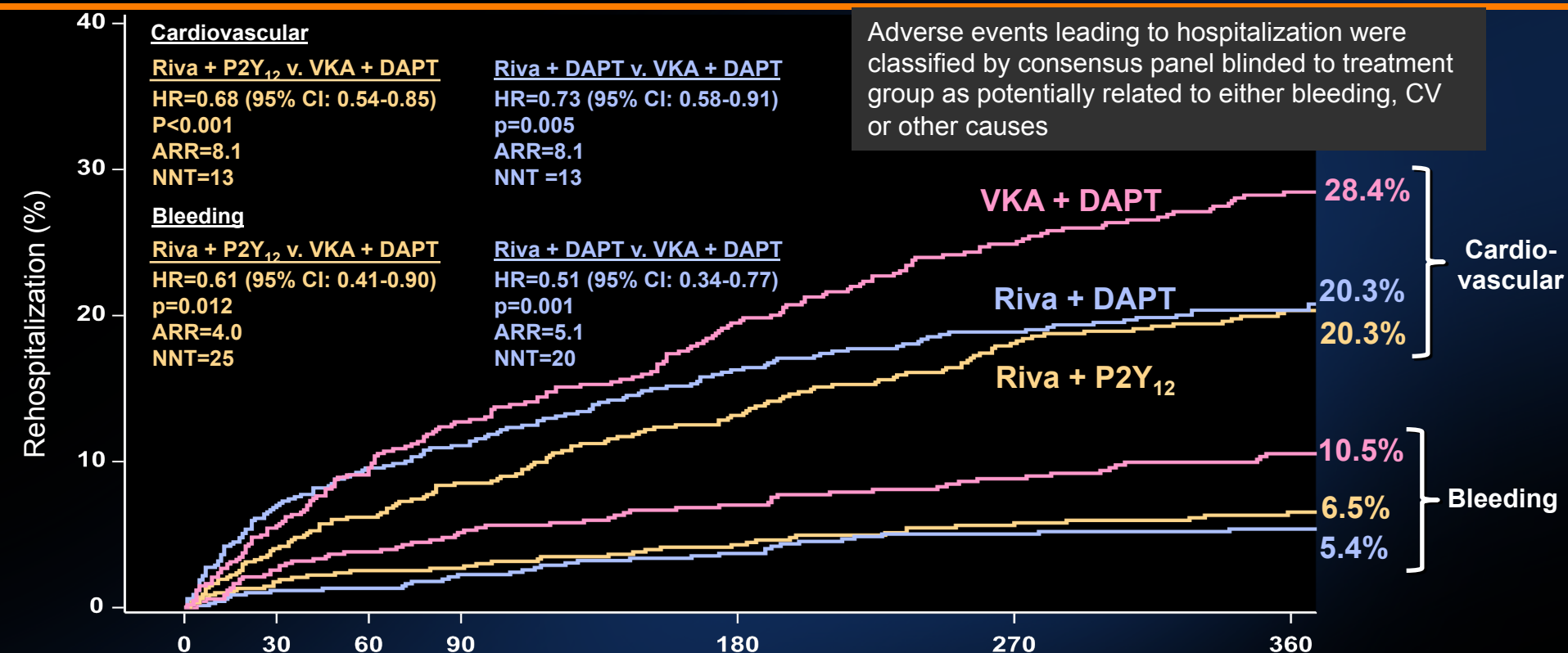
TTT vs. DAPT dans la vraie vie : le Registre Danois



TTT vs. DAPT dans la vraie vie : le Registre Danois



Hospitalization Related to Cardiovascular or Bleeding Event



No. at risk cardiovascular

	0	30	60	90	180	270	360
Riva + P2Y ₁₂	696	632	607	586	537	491	367
Riva + DAPT	706	627	595	576	525	495	400
VKA + DAPT	697	609	560	517	457	410	314

No. at risk bleeding

	0	30	60	90	180	270	360
Riva + P2Y ₁₂	696	645	630	618	585	553	421
Riva + DAPT	706	659	636	621	590	560	453
VKA + DAPT	697	630	601	568	528	494	386

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Rehospitalizations do not include the index event and include the first rehospitalization after the index event.

Hazard ratios as compared to the VKA group are based on the Cox proportional hazards model.

Log-Rank P-values as compared to VKA group are based on the two-sided log rank test.