GRCI 2017
France

6 AU 8 DÉCEMBRE 2017
Novotel Paris Tour Eiffel

Passion Communication Education

Antiplaquettaires et anticoagulants après stenting coronaire chez le patient en FA

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DÉCLARATION DE LIENS D'INTÉRÊT AVEC LA PRÉSENTATION

Intervenant : Patrick Ohlmann, Strasbourg

☑ Je déclare les liens d'intérêt suivants :

Affiliation/Financial Relationship	Company
• Grant/Research Support	• Abbott, Biosensor, Boston, Edwards-Lifesciences, Medtronic, Terumo,
• Consulting Fees/Honoraria	• Astra-Zeneca, Sanofi-Aventis, Zoll

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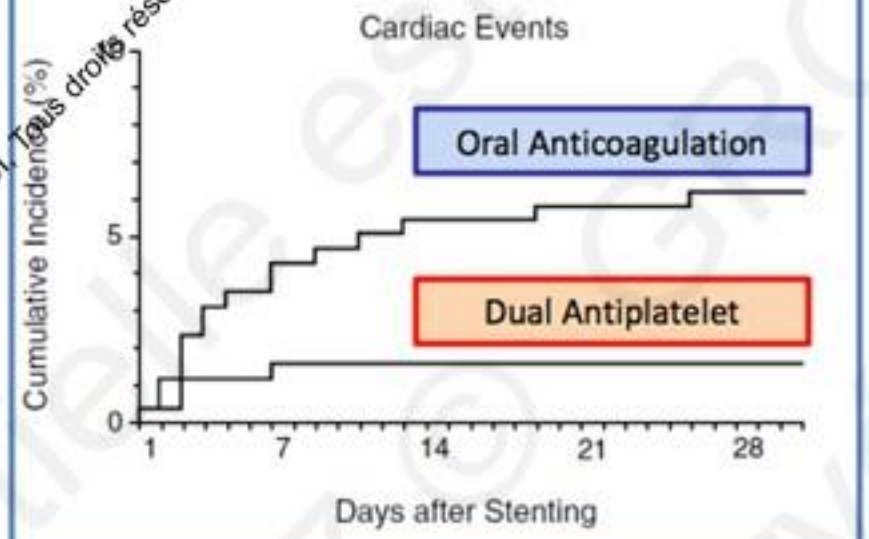
Problématique

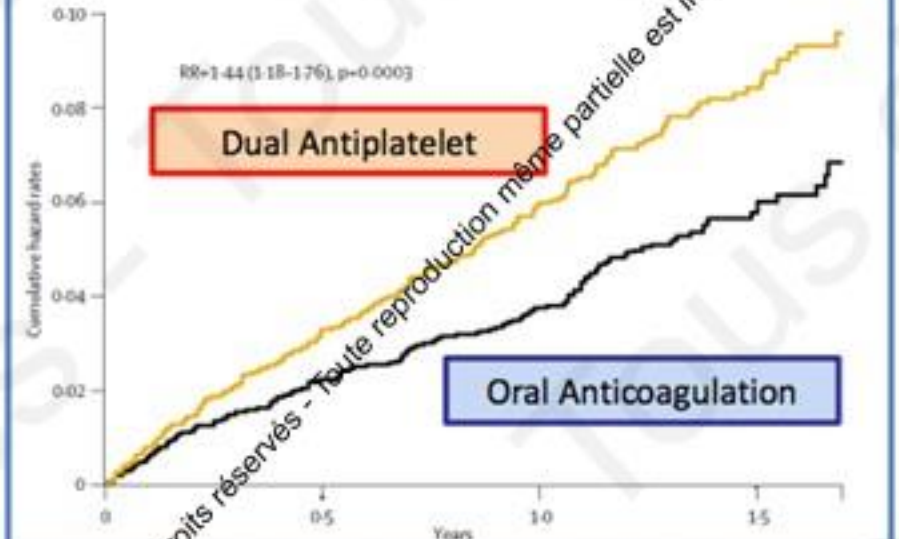
Coronary stent implantation



ISAR, NEJM 1996

+

Atrial fibrillation



ACTIVE-W Lancet 2006

= Dual Antiplatelet + Oral Anticoagulation

Stent et patient sous anticoagulation

- 6-8 % of patients avec SCA
  - FA
  - Valve mécanique
  - MTEV
- Anticoagulation FA si score CHA_2DS_2VASC
  - >1 homme
  - >2 femme
- AVK + DAPT: risque hémorragique x 2-3

Épidémiologie

- 1 milliard d'habitants US + Europe
- 20 millions en FA (1-2%)
- 16 millions sous AC (80%)
- 5 millions coronariens (20-45%)
- 1-2 millions PCI avec stents (20-25%)

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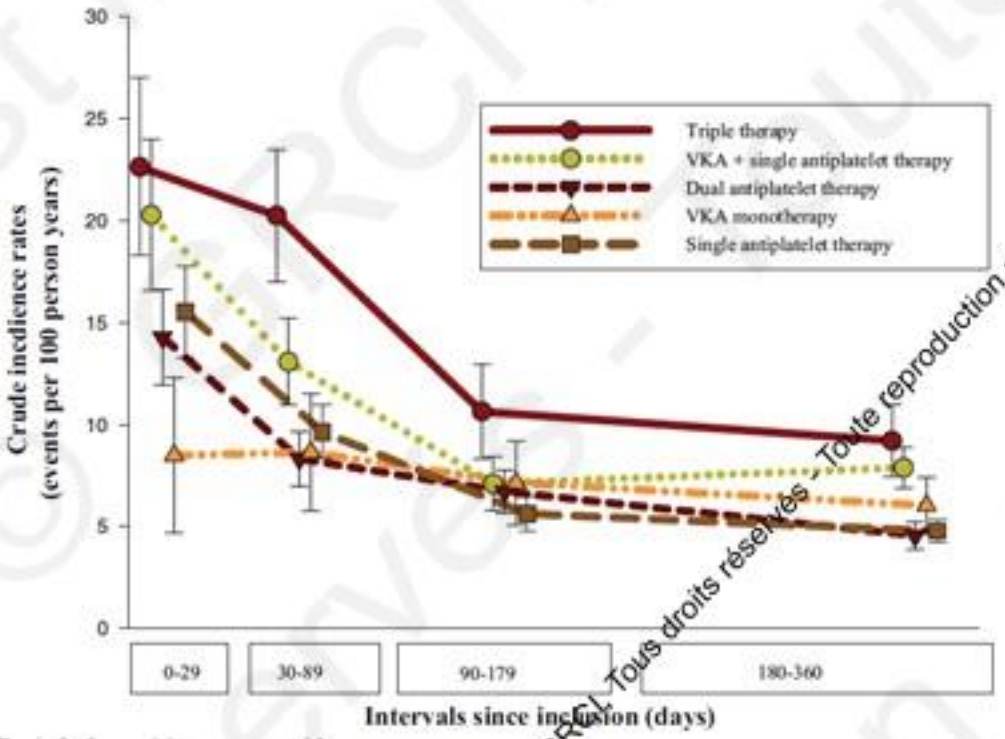
Triple vs. DAPT
risque hémorragique

Registre Danois
11480 patients



Lamberts 2012 Circulation p1185

Recommandations ESC 2017
Stratégies de réduction du risque hémorragique sous DAPT + anticoagulants

Assess ischaemic and bleeding risks using validated risk predictors (e.g. CHA_2DS_2-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 $P2Y_{12}$ inhibitor of choice.
• Use low-dose (≤100 mg daily) aspirin.
• Routine use of PPIs.

Valgimigli 2017 Focused update ESC guidelines

Scores de risque

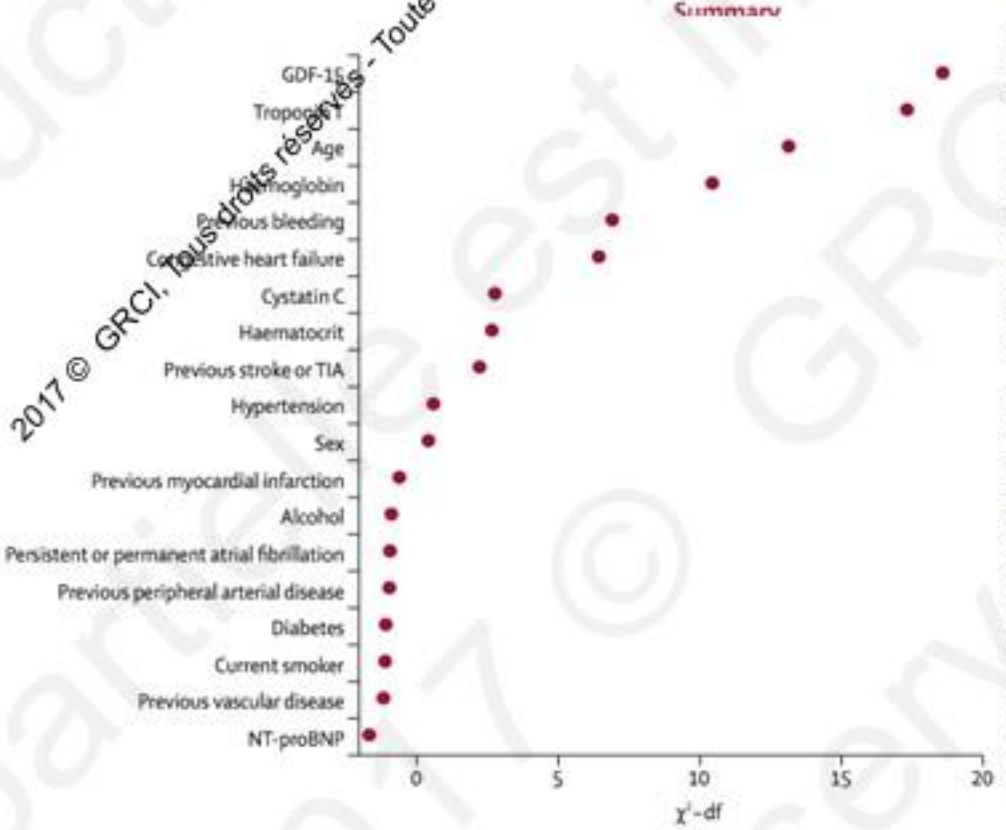
- **CHA2VAS2C**
  - Age>65 1
  - Age>75 2
  - HTA 1
  - Cardiac failure 1
  - Diabetes 1
  - Stroke 2
  - Vascular disease 1

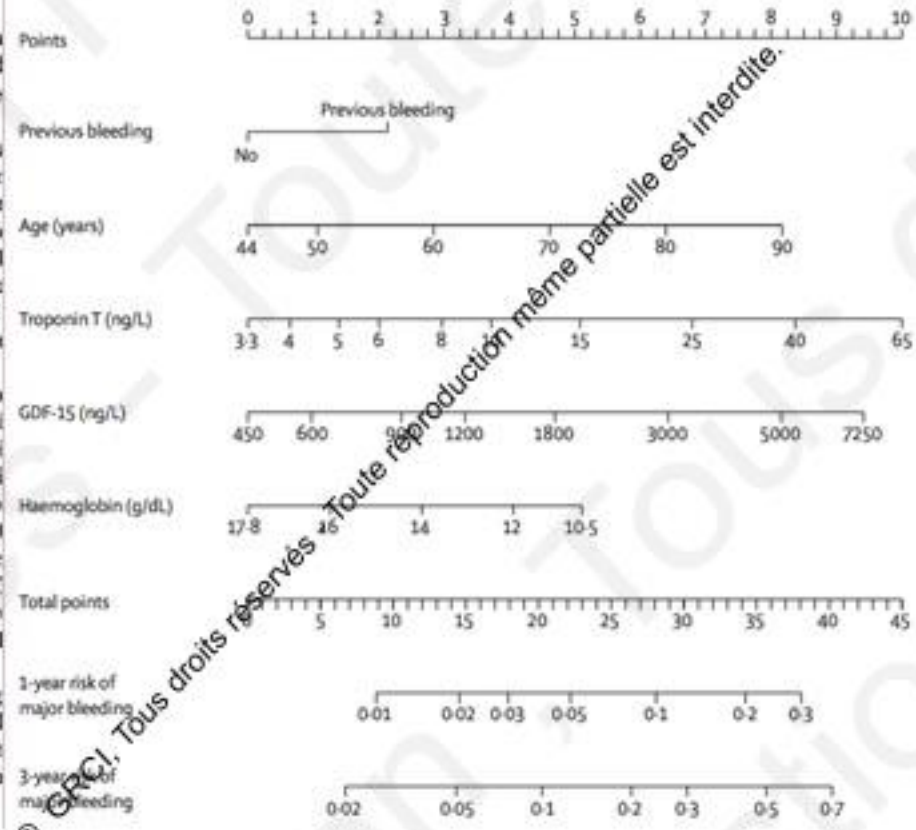
- **HASBLED**
  - Age>65 1
  - HTA 1
  - Renal failure 1
  - Hepatic failure 1
  - Labile INR 1
  - Alcool or drug abuse 1

- **Overlap entre les scores**
- **Facteurs réversibles dans HASBLED; réévaluations**

The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study

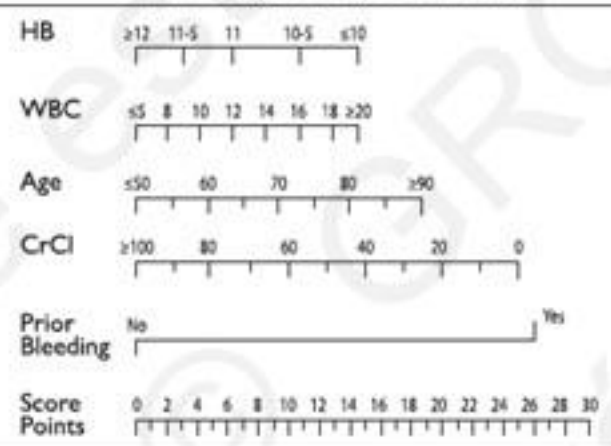
ABC score : plus performant que le score HASBLED ?





Hijazi *Lancet* 2016 p 2302

Risque hémorragique et SCA
PRECISE DAPT-Score, inadapté en cas de trithérapie

	PRECISE-DAPT score[18]	DAPT score[15]
Time of use	At the time of coronary stenting	After 12 months of uneventful DAPT
DAPT duration strategies assessed	Short DAPT (3–6 months) vs. Standard/long DAPT (12–24 months)	
Score calculation[a]		
Score range	0 to 100 points	
Decision making cut-off suggested	Score ≥25 → Short DAPT Score <25 → Standard/long DAPT	Score ≥2 → Long DAPT Score <2 → Standard DAPT
Calculator	www.precisedaptscore.com	www.daptstudy.org

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Methods

Study design and population

The PRECISE-DAPT collaborative study included a total of 14 963 patients with coronary artery disease who underwent elective, urgent, or emergent PCI with coronary stent implantation and subsequent DAPT (appendix p 24). DAPT consisted of an association of aspirin plus a $P2Y_{12}$ inhibitor, most commonly clopidogrel (88%), whereas patients with an indication for long-term oral anticoagulation were excluded. Patients were pooled at an individual level from eight contemporary multicentre randomised clinical trials[16–18]. The patients were enrolled in 139 different clinical sites from 12 countries worldwide (appendix p 25). Extensive details regarding the pooled

Risque hémorragique élevé si PRECISE-DAPT score > 25

Recommandations ESC 2017
Facteurs de risque de thrombose de stent

- 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.

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Recommandations ESC 2017
Durée de la bithérapie APP
en cas de traitement anticoagulant

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.	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, which outweigh the bleeding risk.	IIa	B
Dual therapy with clopidogrel 75 mg/day and OAC should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk.	IIa	A

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Recommandations ESC 2017
Durée de la bithérapie APP
en cas de traitement anticoagulant

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 *q.d.* may be used instead of rivaroxaban 20 mg *q.d.*	IIb	B
The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC.	III	C

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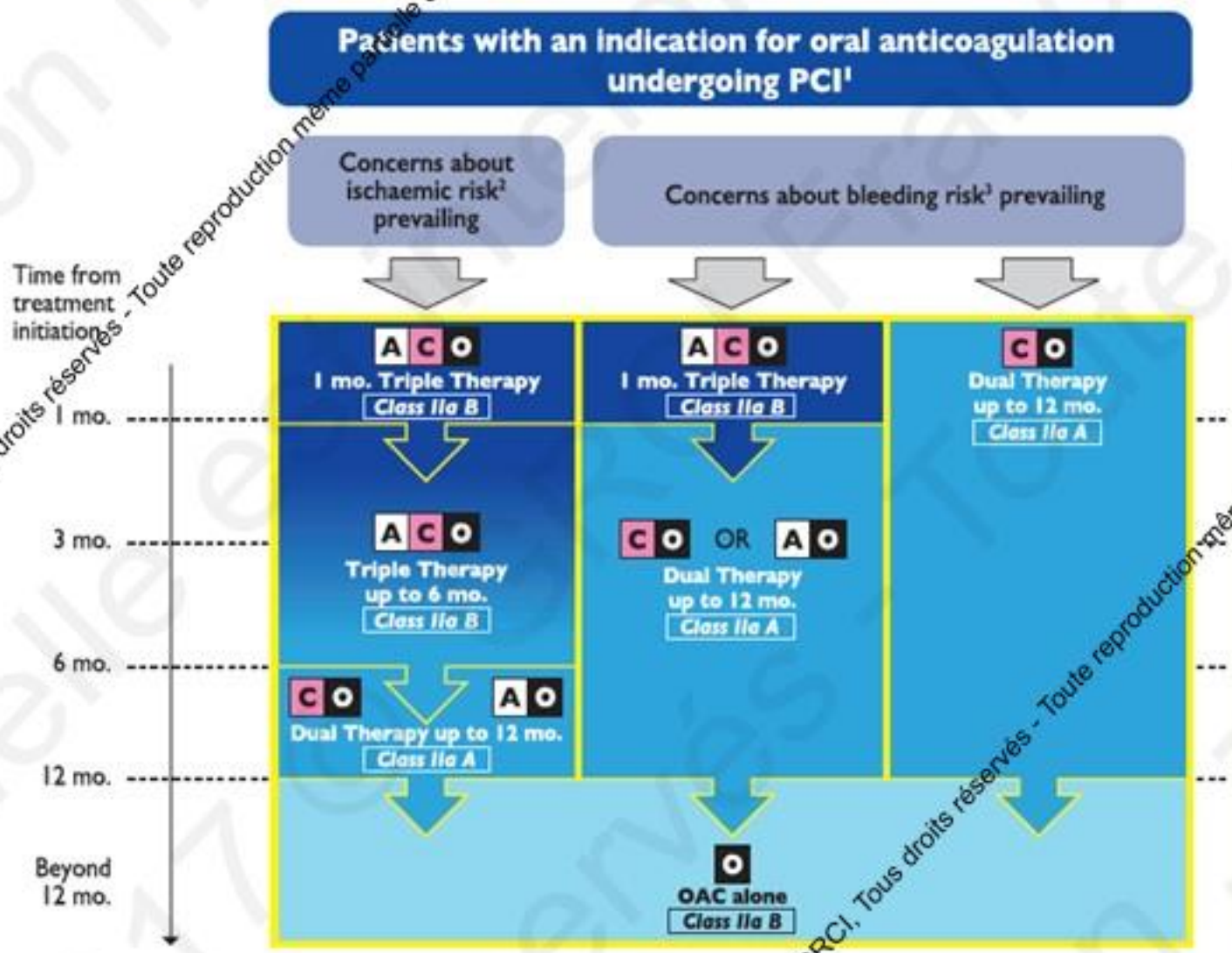

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Alternative à la tri-thérapie AC+2APP

Bitherapie AC+1APP

Etude WOEST

WOEST

Study Design-2

1:1 Randomisation:

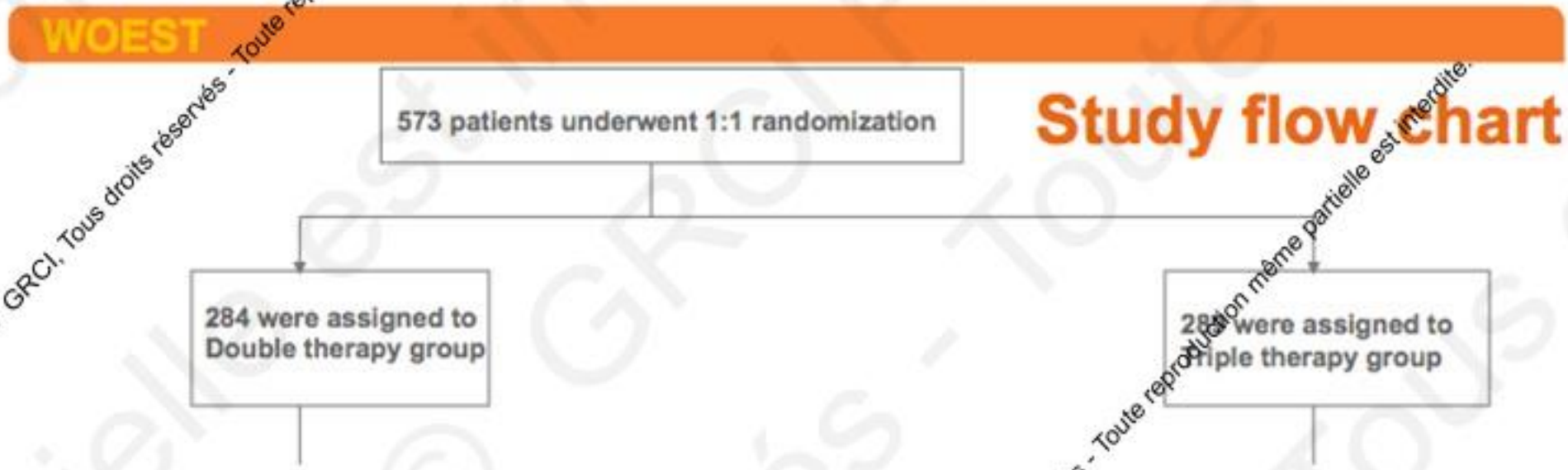
Double therapy group:	Triple therapy group
OAC + 75mg Clopidogrel qd	OAC + 75mg Clopidogrel qd + 80mg Aspirin qd
1 month minimum after BMS 1 year after DES	1 month minimum after BMS 1 year after DES

Follow up: 1 year

Primary Endpoint: The occurence of all bleedings events (TIMI criteria)

Dewilde JM Lancet 2012 p1107

Etude WOEST



Open label

Dewilde JM Lancet 2012 p1107

Etude WOEST

WOEST

Baseline Characteristics

	Double therapy n=279 (%)	Triple therapy n=284 (%)
Age	70.3 (±7.3)	69.5(±8.0)
Male gender	214 (76.7%)	234 (82.4%)
BMI (kg/m2)	27.5 (±4.3)	27.9 (±4.2)
Current Smoker	60 (21.5%)	42 (14.8%)
Diabetes	68 (24.4%)	72 (25.4%)
Hypertension	193 (69.2%)	193 (68.0%)
Hypercholesterolemia	191 (68.5%)	205 (72.2%)
History of MI	96 (34.4%)	100 (35.2%)
History of Heart Failure	71 (25.4%)	70 (24.6%)
History of Stroke	49 (17.6%)	50 (17.6%)
History of PCI	86 (30.8%)	101 (35.6%)
History of CABG	56 (20.1%)	74 (26.1%)
History of GI bleeding	14 (5.0%)	14 (4.9%)
Indication for OAC		
AF/Aflutter	164 (69.5%)	162 ([illegible]%)
Mechanical valve	24 (10.2%)	[illegible] (10.7%)
Other (pulmonary embolus,	48 (20.3%)	47 (20.1%)
EF<30%, Apical thrombus...)		
ACS at baseline	69 (25.0%)	86 (30.6%)

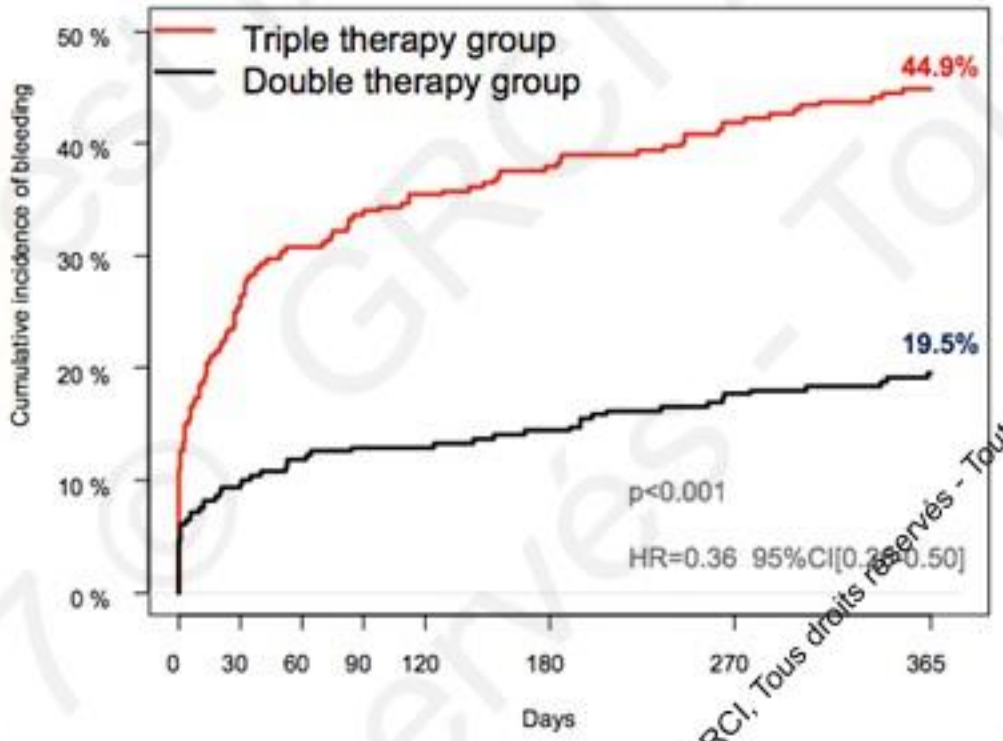
ST ANTONIUS

Dewilde JM Lancet 2012 p1107

Etude WOEST

WOEST

Primary Endpoint: Total number of TIMI bleeding events

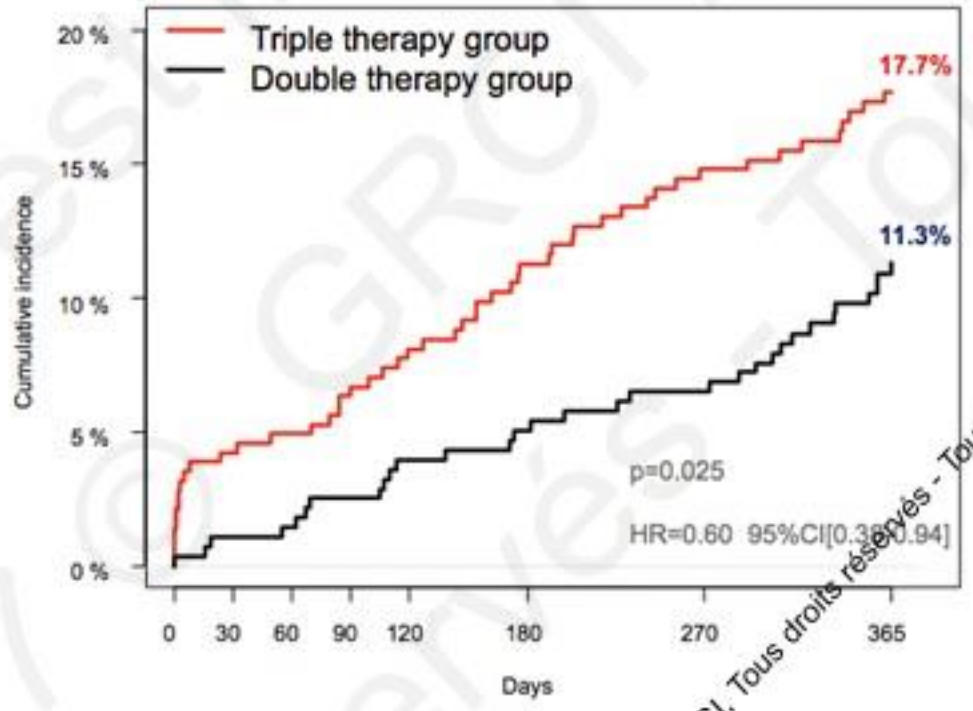


Dewilde JM Lancet 2012 p1107

Etude WOEST

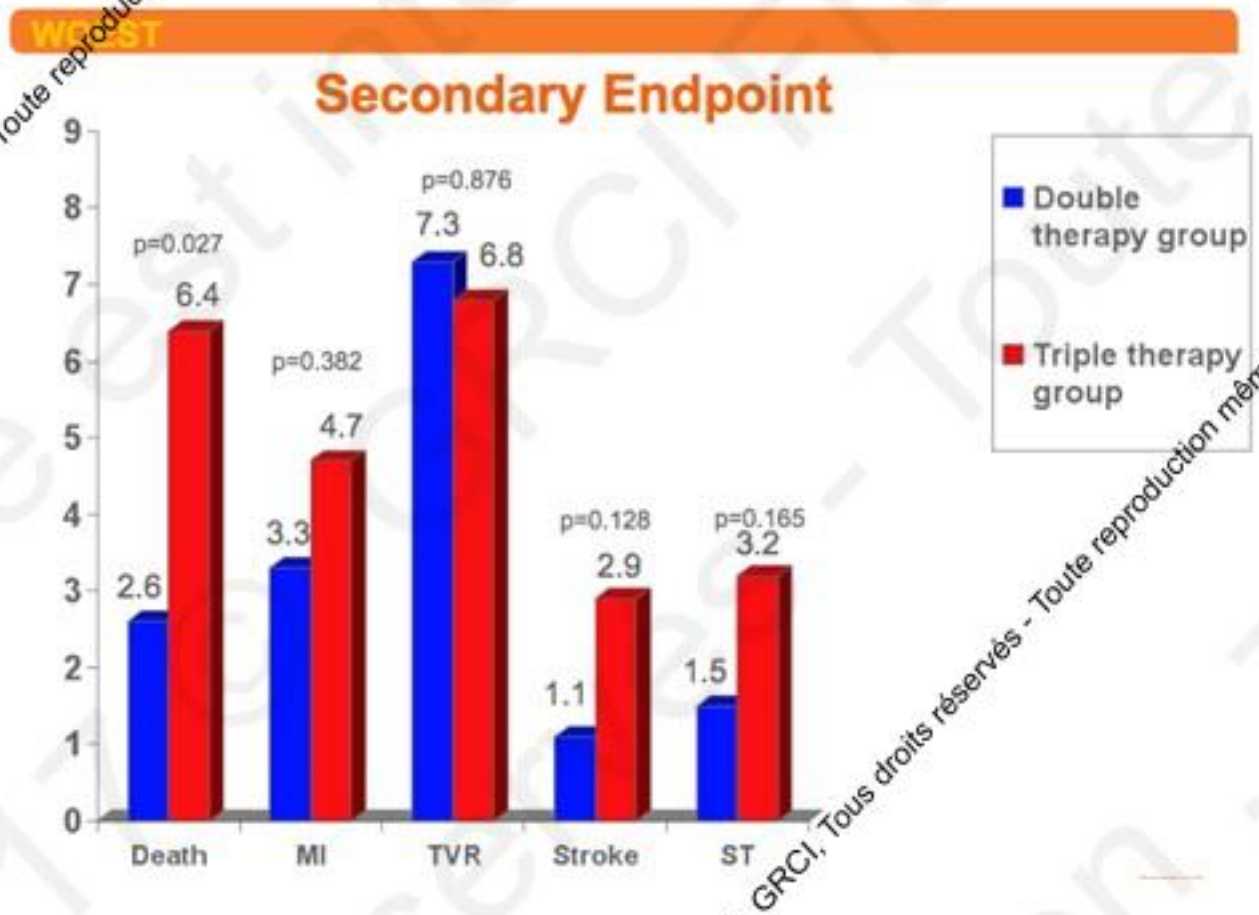
WOEST

Secondary Endpoint (Death, MI,TVR, Stroke, ST)



Dewilde JM Lancet 2012 p1107

Etude WOEST

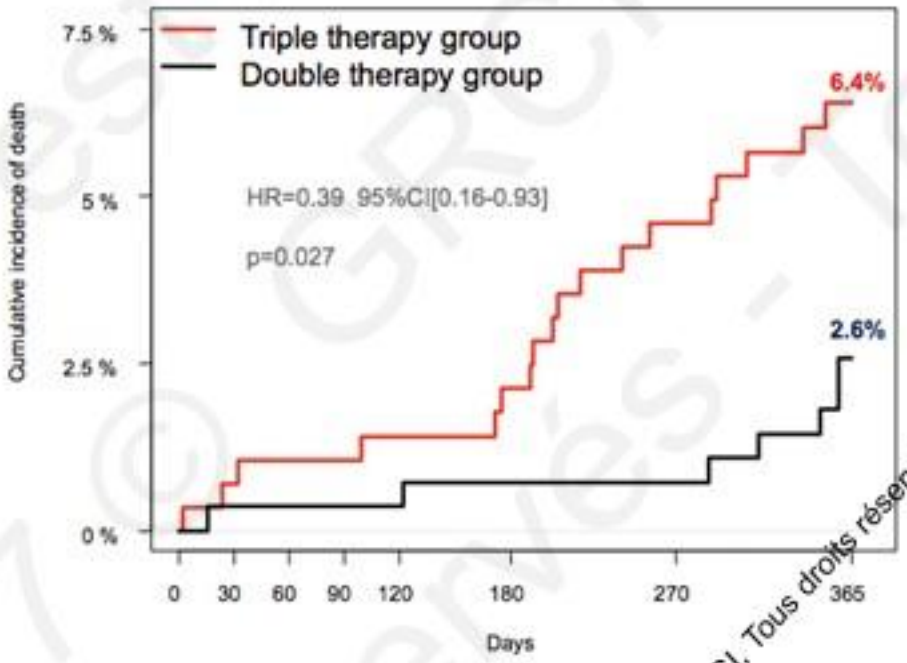


Dewilde JM Lancet 2012 p1107

Etude WOEST

WOEST

All-Cause Mortality



Dewilde JM Lancet 2012 p1107

Etude WOEST

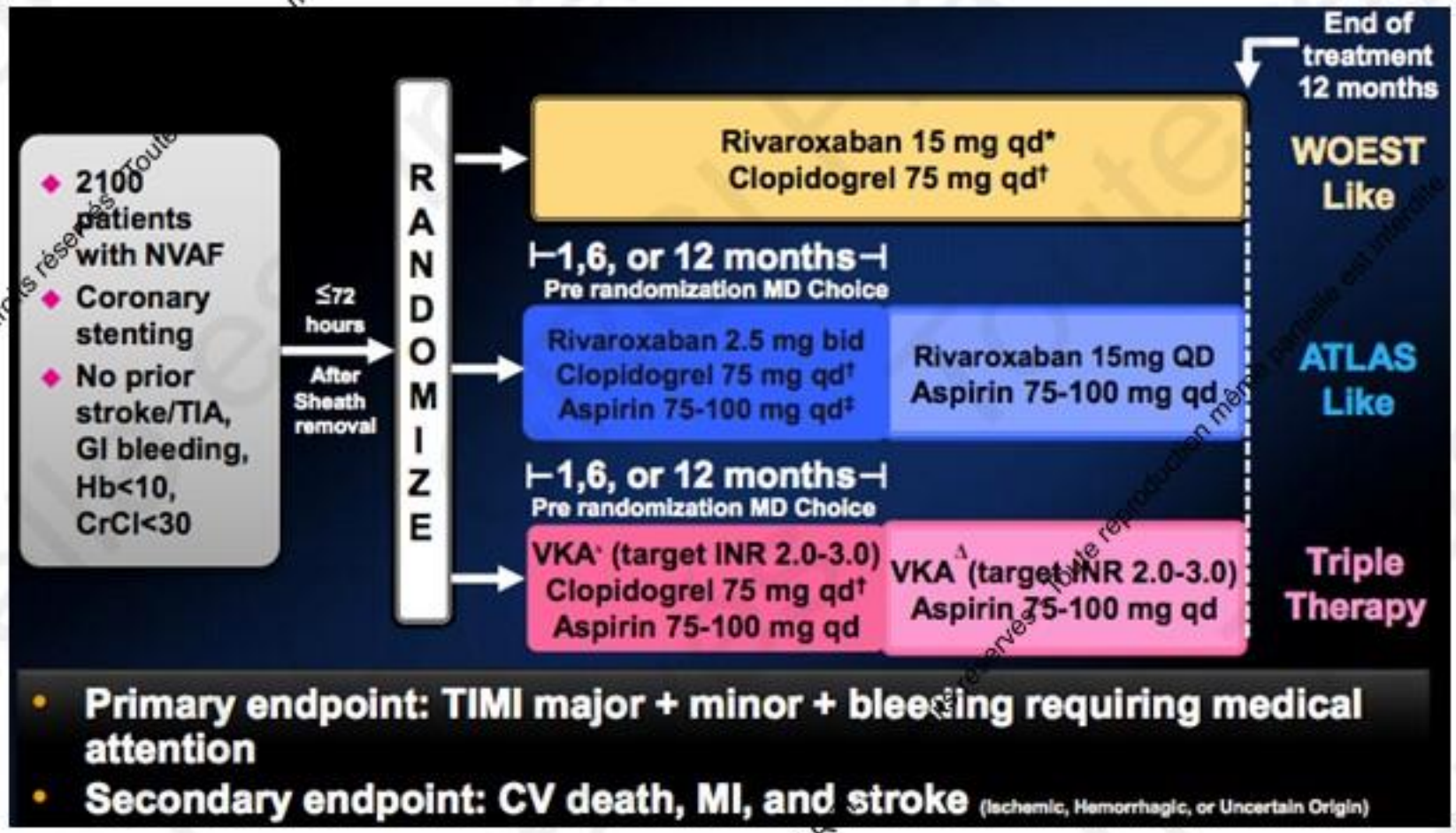
WOEST

Limitations

- The study was powered to show superiority on the primary bleeding endpoint, but not to show non-inferiority on the secondary endpoint
- Open label trial design with its inherent bias
- Classification of smaller bleeding, although well defined and blindly adjudicated, may be subjective

Dewilde JM Lancet 2012 p1107

PIONNEER-AF-PCI



Gibson N Engl J Med 2016 p 375

PIONNEER-AF-PCI

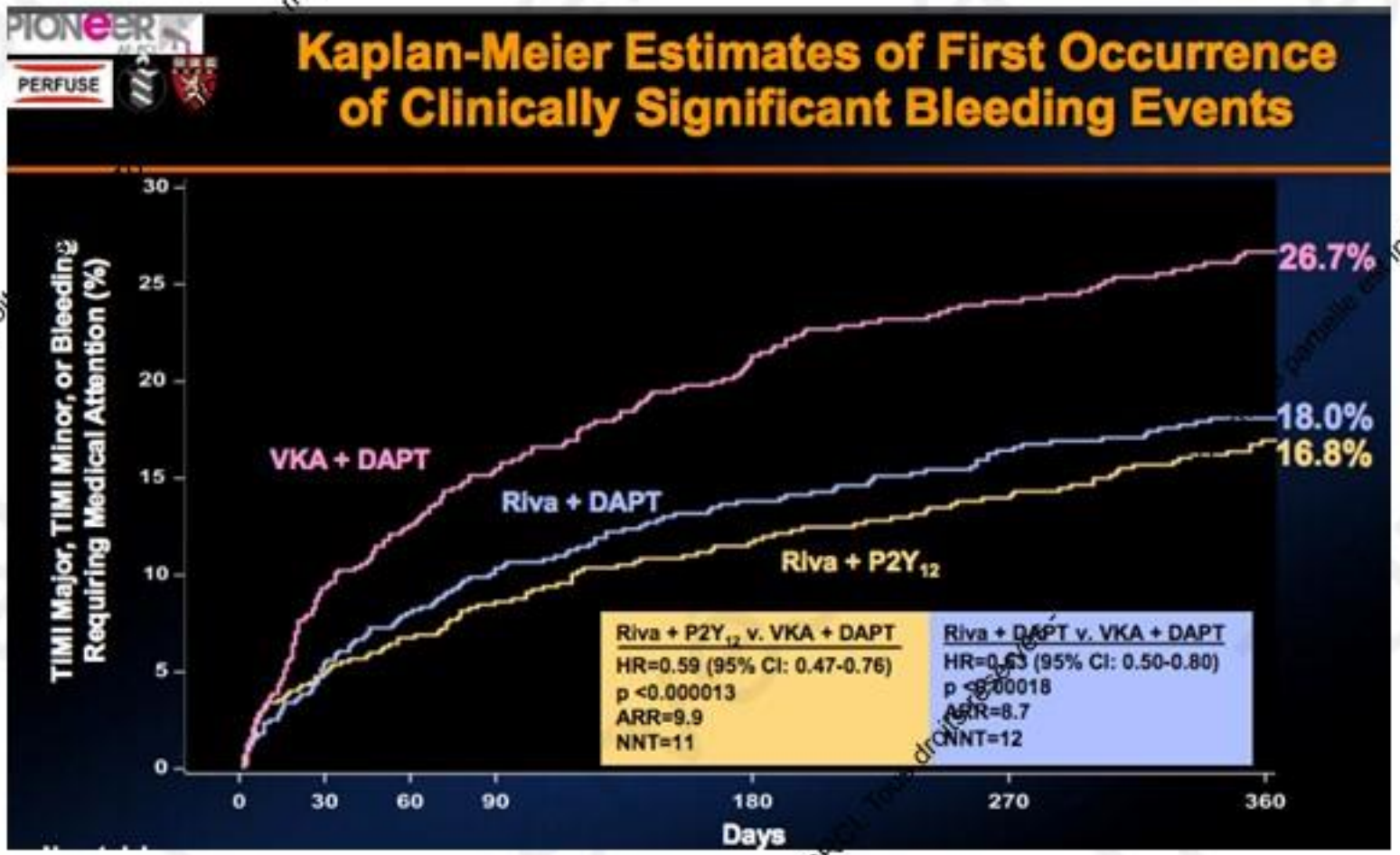
PERFUSE

Baseline Characteristics

	Riva + P2Y$_{12}$ (N=709)	Riva + DAPT (N=709)	VKA + DAPT (N=706)
Age, mean ± SD	70.4 ± 9.1	70.0 ± 9.1	69.9 ± 8.7
Sex, female, n (%)	181 (25.5%)	174 (24.5%)	188 (26.6%)
Diabetes Mellitus, n (%)	204 (28.8%)	199 (28.1%)	221 (31.1%)
Type of Index Event, n (%)			
NSTEMI	130 (18.5%)	129 (18.4%)	123 (17.8%)
STEMI	86 (12.3%)	97 (13.8%)	74 (10.7%)
Unstable Angina	145 (20.7%)	148 (21.1%)	164 (23.7%)
Stable Angina	340 (48.5%)	329 (46.8%)	330 (47.8%)
Drug-eluting stent, n (%)	464 (65.4%)	471 (66.8%)	468 (66.5%)
Type of Atrial Fibrillation, n (%)			
Persistent	146 (20.6%)	146 (20.6%)	149 (21.1%)
Permanent	262 (37.0%)	238 (33.6%)	243 (34.5%)
Paroxysmal	300 (42.4%)	325 (45.8%)	313 (44.4%)

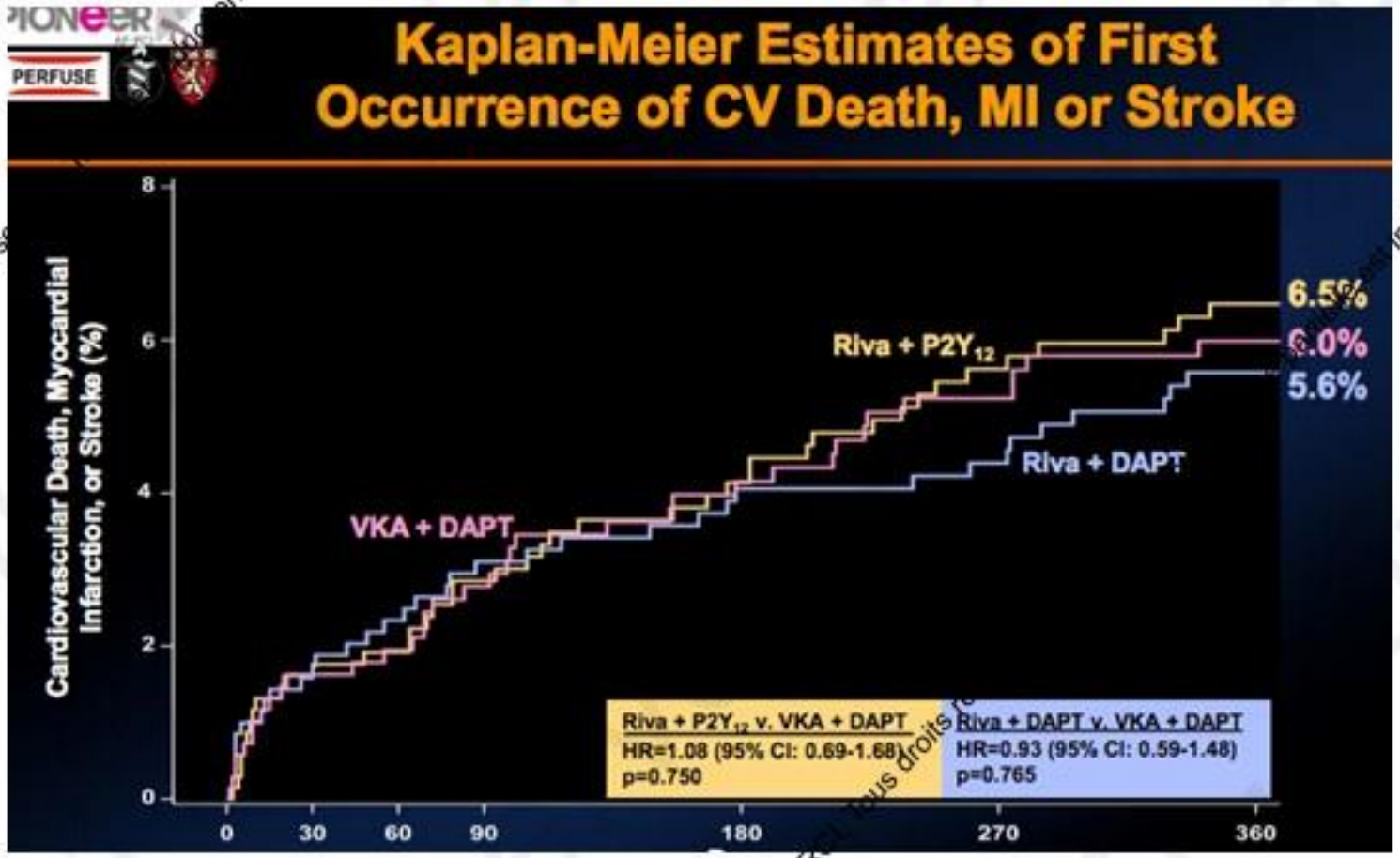
Gibson N Engl J Med 2016 p 375

PIONNEER-AF-PCI



Gibson N Engl J Med 2016 p 375

PIONNEER-AF-PCI



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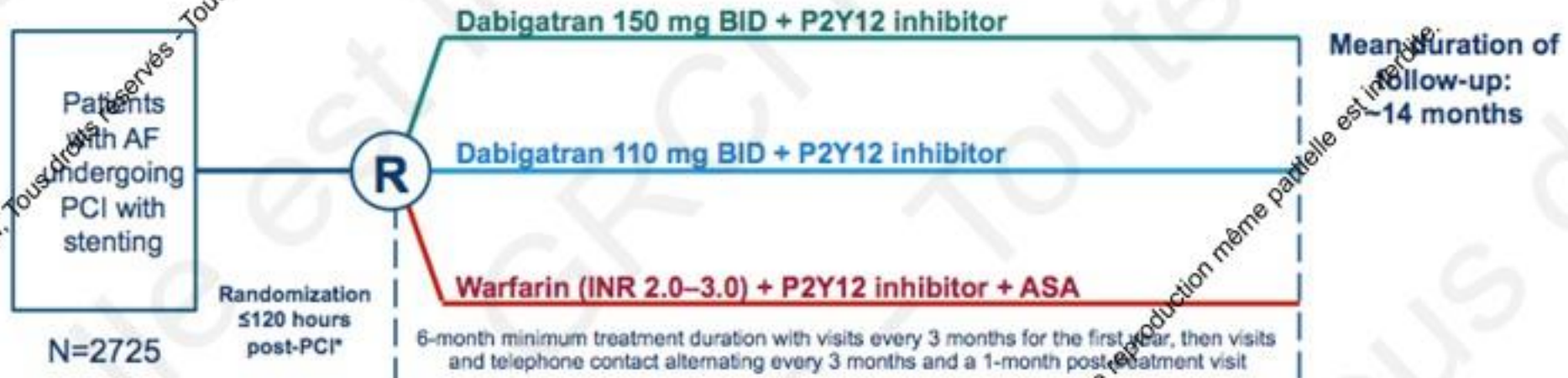
Etude RE-DUAL PCI



In the group that received triple therapy with warfarin, the duration of aspirin therapy was just 1 to 3 months; we adopted this approach in accordance with evolutions in practice and guidelines.[27,28] In effect, triple therapy shifted to dual therapy for most of the trial period; despite this factor, we found that the risk of bleeding was approximately one half and one quarter lower in the 110-mg and 150-mg dual-therapy groups, respectively, than in the triple-therapy group. The results of the PIONEER AF-PCI trial (Open-Label,

Canon N Engl J Med 2017 p 377

Etude RE-DUAL PCI

RE-DUAL PCI
Study in NVAF patients undergoing PCI

Baseline characteristics

	Dabigatran 110 mg dual therapy (n=981)	Warfarin triple therapy (n=981)	Dabigatran 150 mg dual therapy (n=763)	Corresponding Warfarin triple therapy (n=764)
Age, years, mean	71.5	71.7	68.6	68.8
≥80 (US, ROW), ≥70 (Japan), %	22.9	22.9	1.0	1.0
<80 (US, ROW), <70 (Japan), %	77.1	77.1	99.0	99.0
Male, %	74.2	76.5	77.6	77.7
Baseline CrCl, mL/min, mean	76.3	75.4	83	81.3
Diabetes mellitus, %	36.9	37.8	34.1	39.7
CHA_2DS_2–VASc score (mean)	3.7	3.8	3.3	3.6
Modified HAS-BLED score at baseline (mean)	2.7	2.8	2.6	2.7
ACS indication for PCI, %	51.9	48.4	51.2	48.3
DES only, %	82.0	84.2	81.4	83.5

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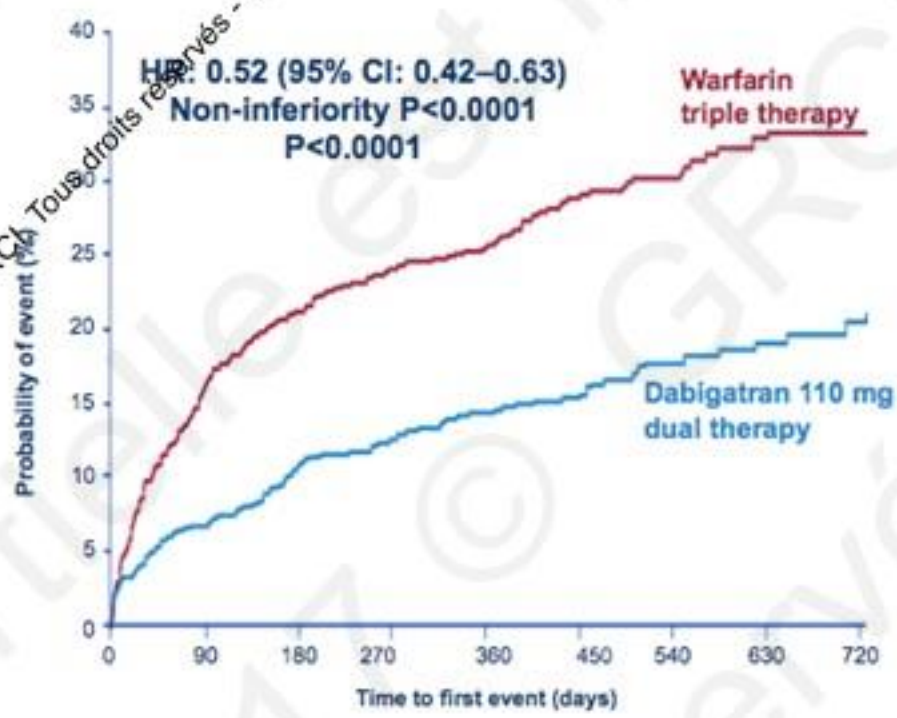
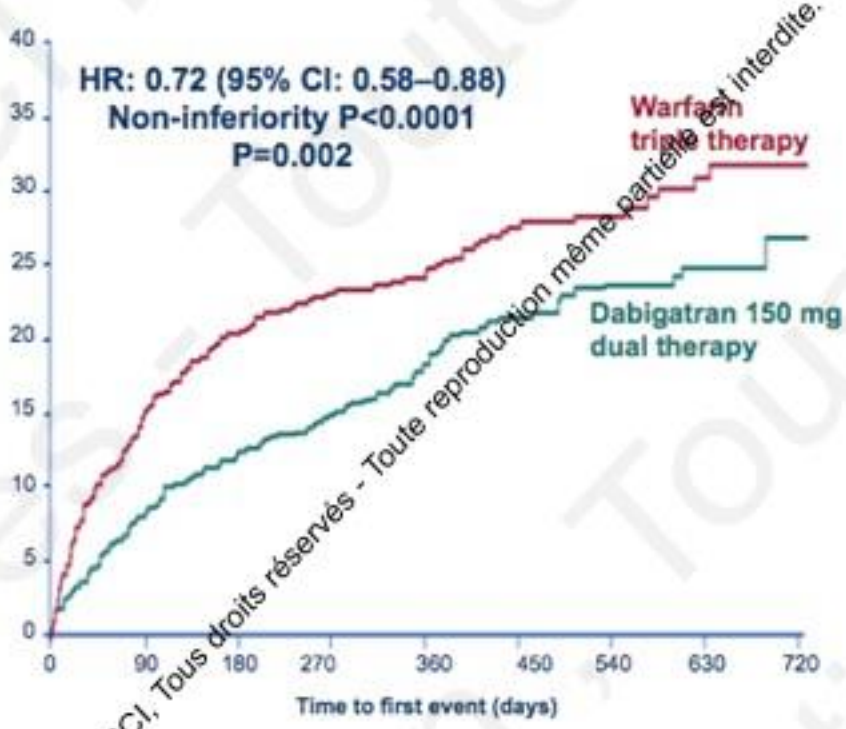
Etude RE-DUAL PCI

Primary Endpoint: Time to first ISTH major or clinically relevant non-major bleeding event

RE-DUAL PCI
Study in NVAF patients undergoing PCI





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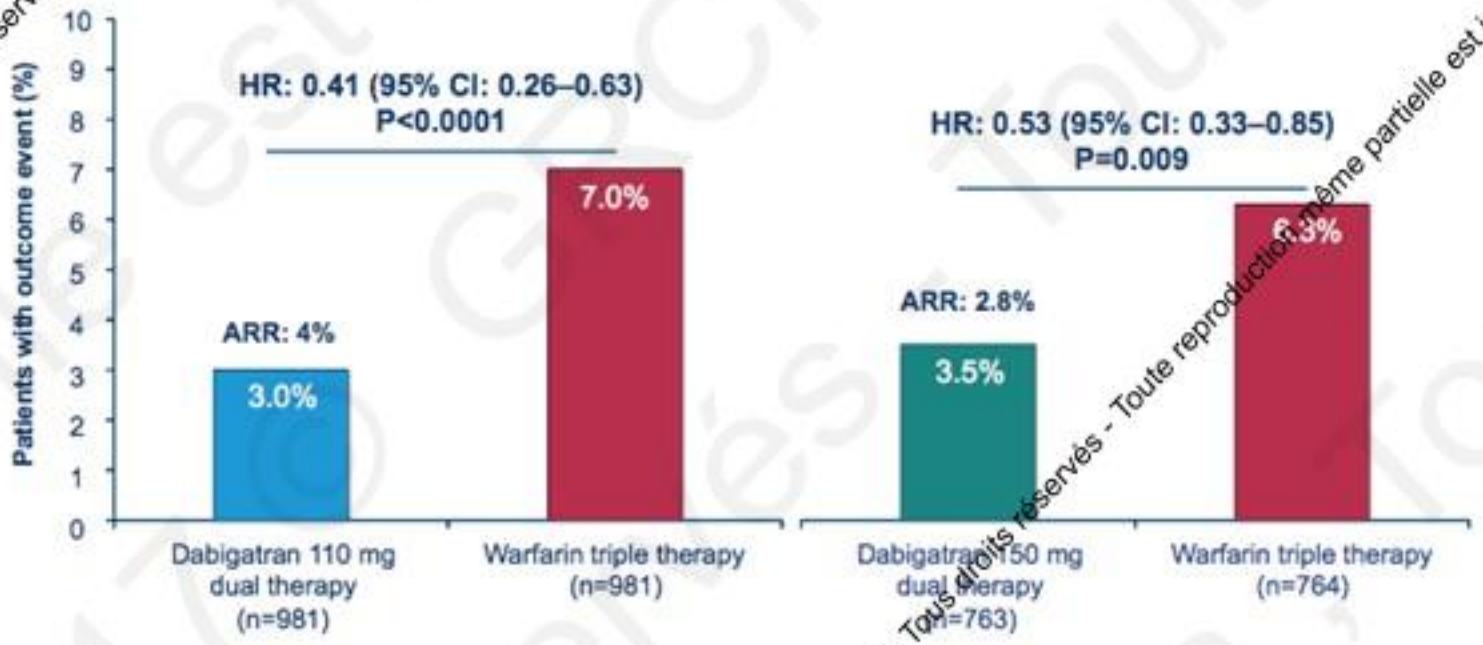
Etude RE-DUAL PCI

RE-DUAL PCI
Study in NVAF patients undergoing PCI

Rates of TIMI major or minor bleeding



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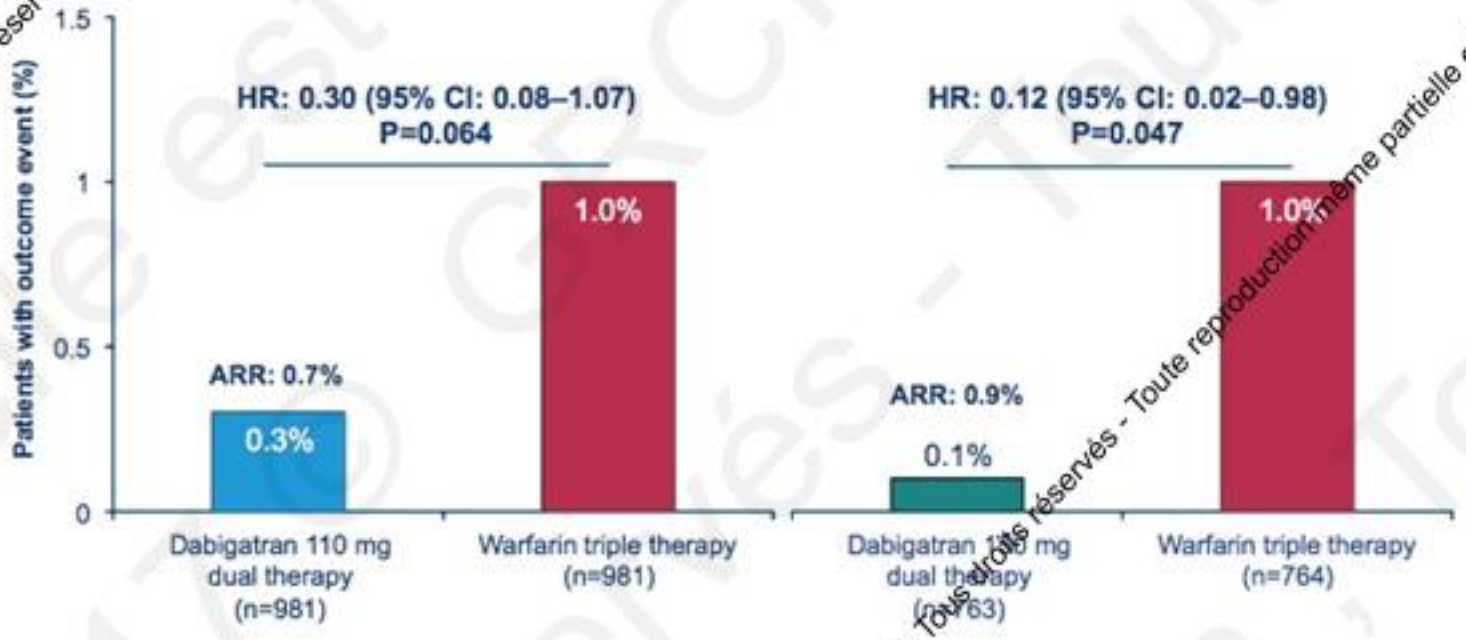
Etude RE-DUAL PCI

RE-DUAL PCI
Study in NVAF patients undergoing PCI

Rate of intracranial haemorrhage



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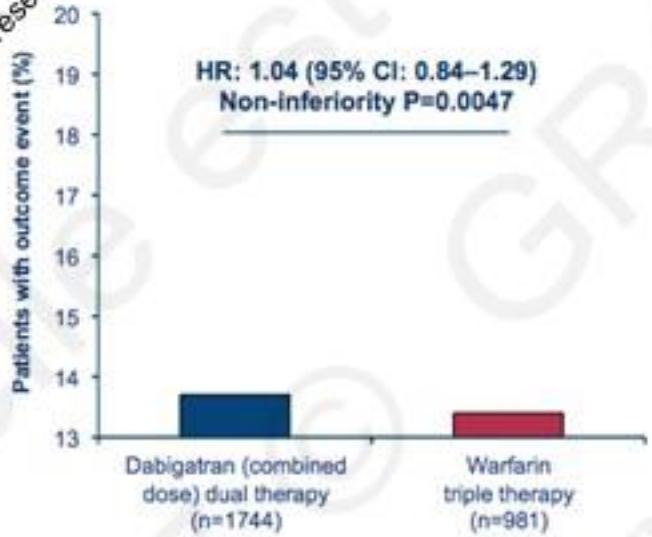
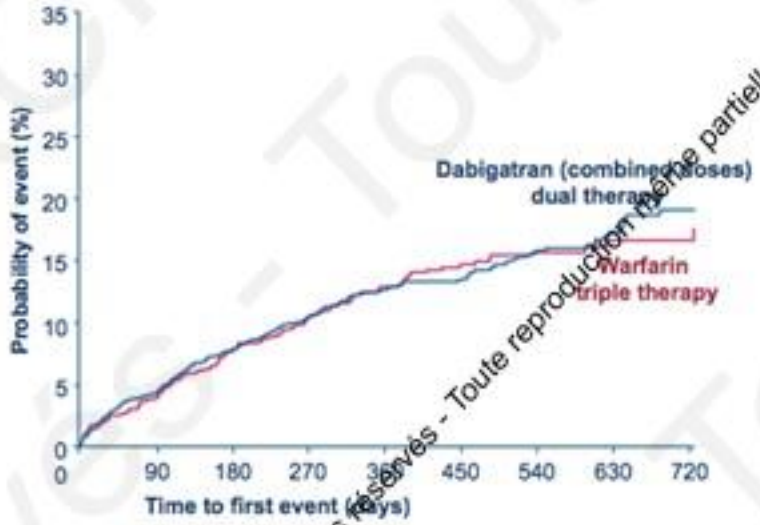
Etude RE-DUAL PCI

Time to death or thromboembolic event, or unplanned revascularization

RE-DUAL PCI
Study in NVAF patients undergoing PCI





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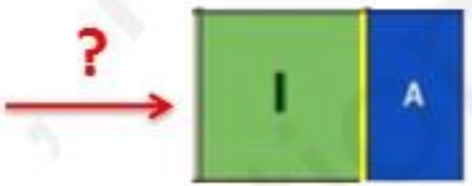
Recommandations ESC 2017
Durée de la bithérapie APP
en cas de traitement anticoagulant

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.	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, which outweigh the bleeding risk.	IIa	B
Dual therapy with clopidogrel 75 mg/day and OAC should be considered as an alternative to 1-month triple antithrombotic therapy in patients in whom the bleeding risk outweighs the ischaemic risk.	IIa	A



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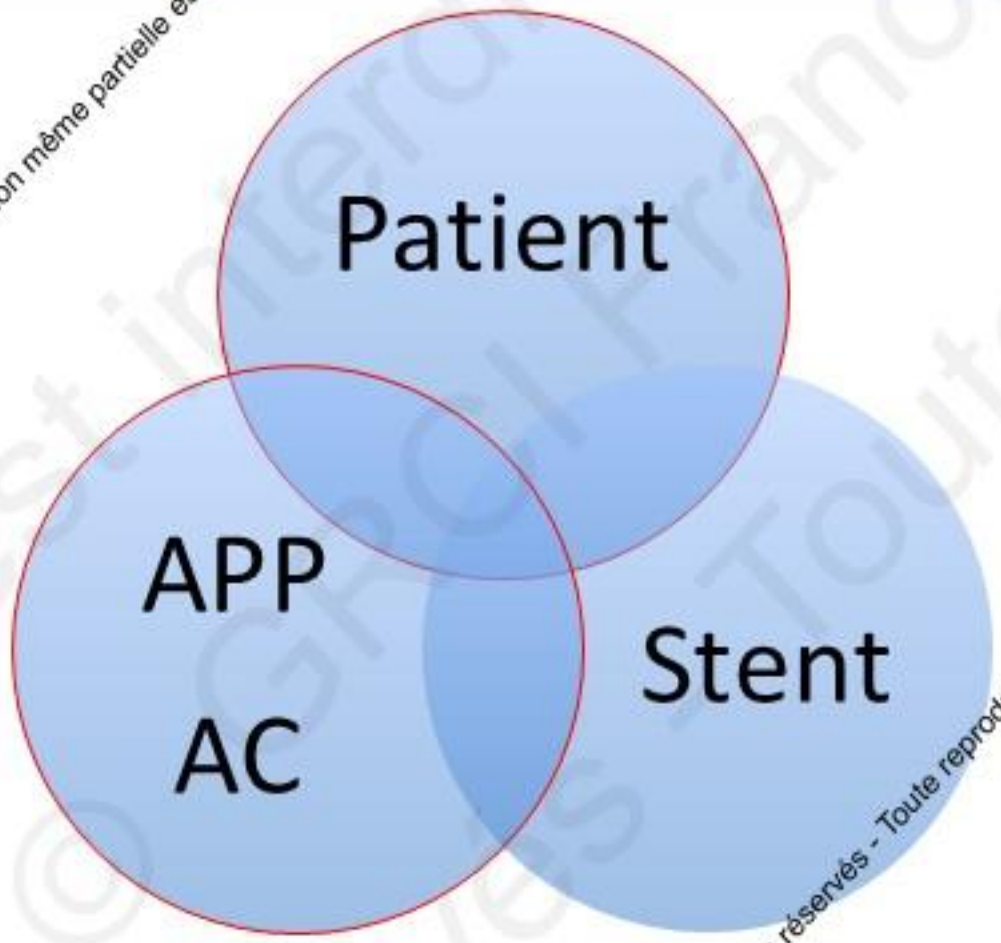

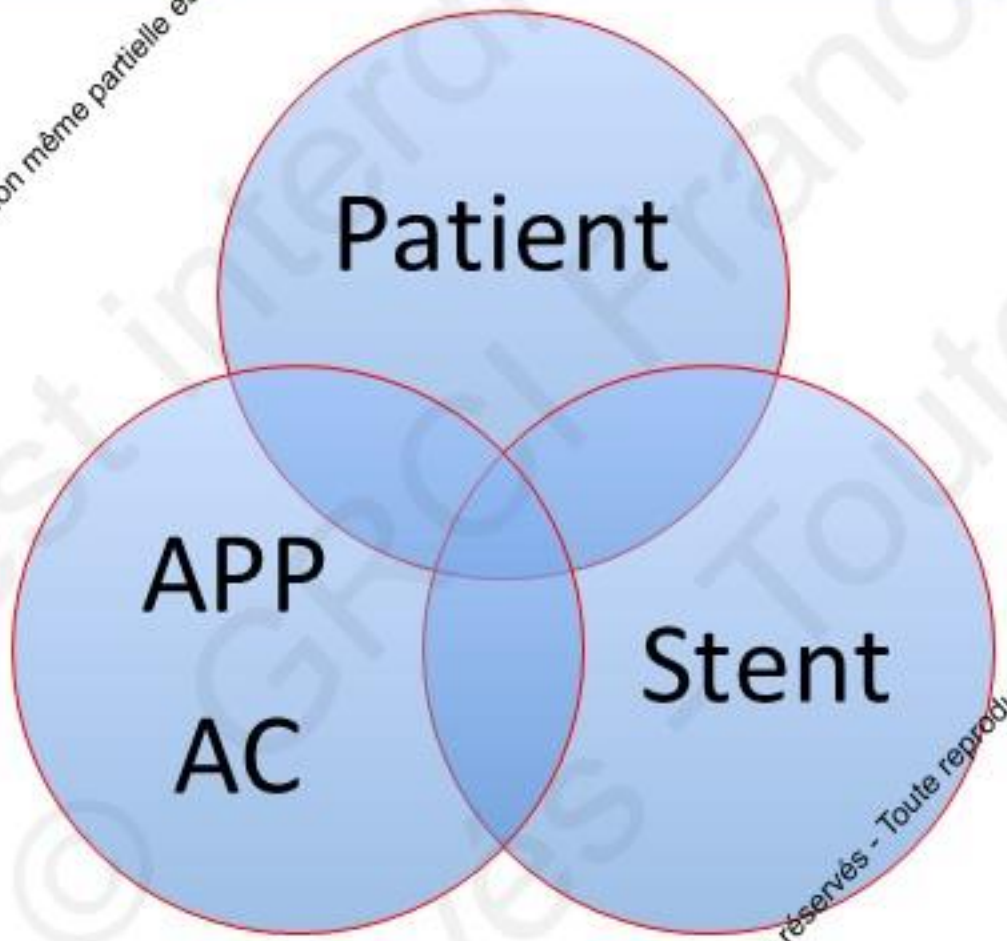

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Étude LEADERS FREE

BMS vs. DES, DAPT 1 mois

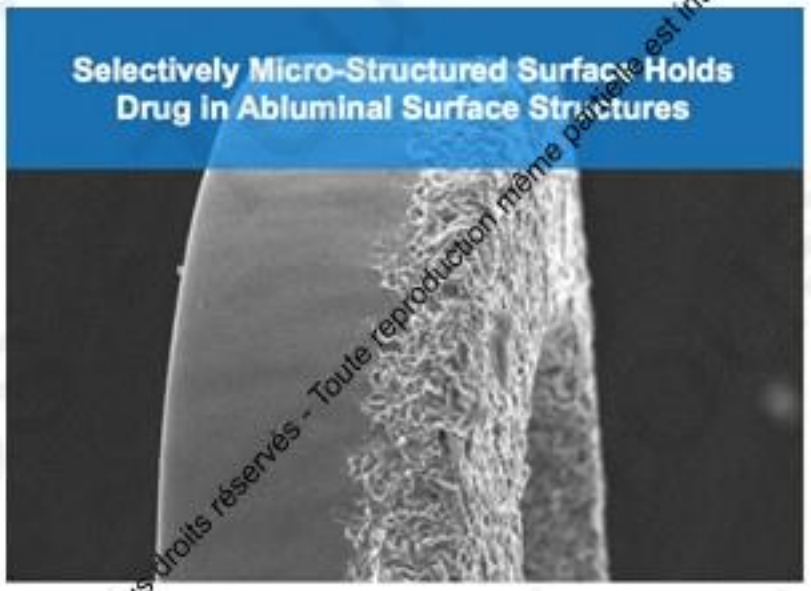
LEADERS FREE Trial Design

Prospective, double-blind randomized (1:1) trial
2466 High bleeding risk (HBR) PCI patients

BioFreedom™ DCS **vs.** Gazelle™ BMS

DAPT mandated for 1 month only, followed by long-term SAPT

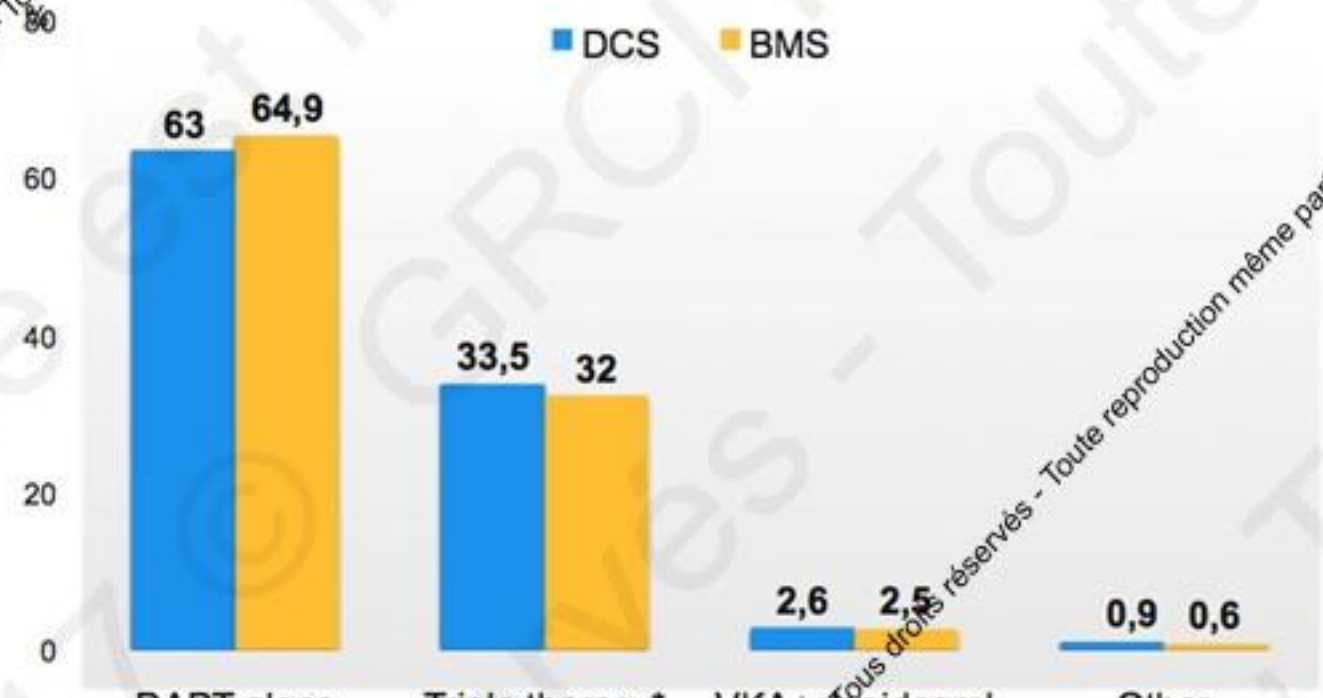
- **Primary safety endpoint:**
  Composite of cardiac death, MI, definite / probable stent thrombosis at 1 year (non-inferiority then superiority)
- **Primary efficacy endpoint:**
  Clinically-driven TLR at 1 year (superiority)



Urban N Engl J Med 2015 p 2038

Etude LEADERS FREE

Antithrombotic Medication at Discharge



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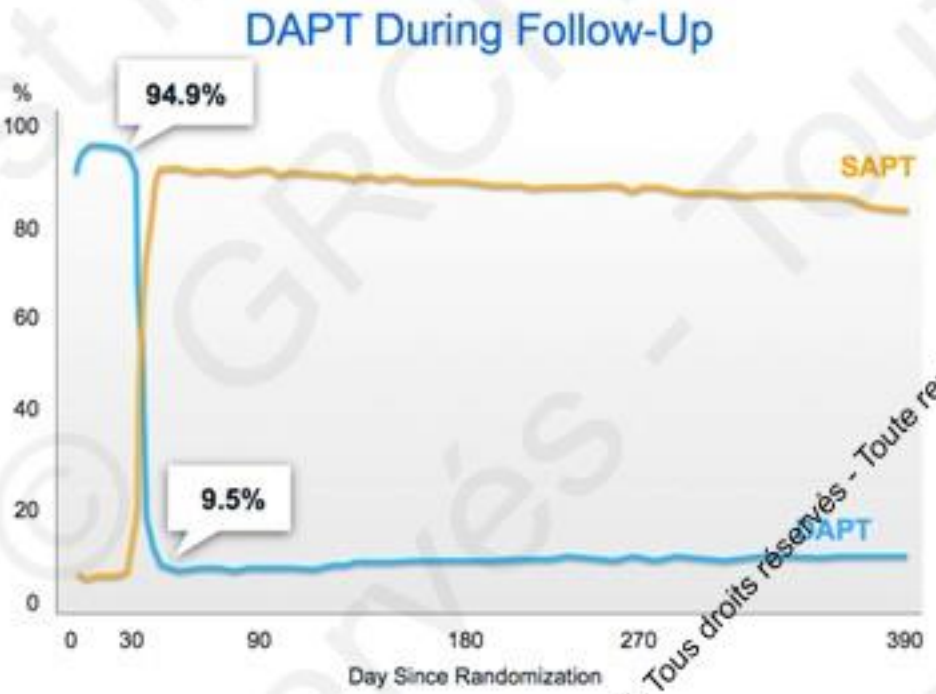
Etude LEADERS FREE



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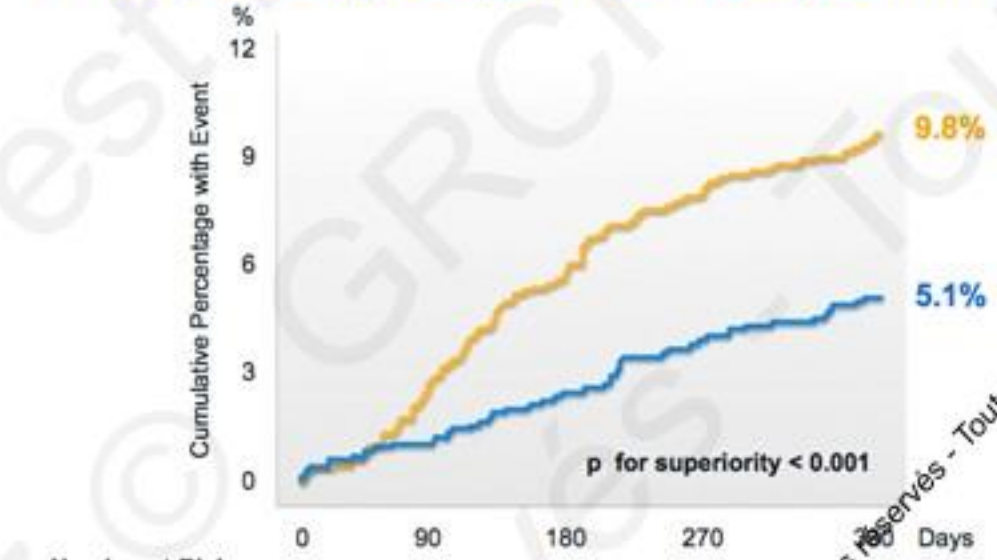
Etude LEADERS FREE

Primary Efficacy Endpoint (Clinically-Driven TLR)



Number at Risk					
DCS	1221	1167	1130	1098	1053
BMS	1211	1131	1072	1034	984

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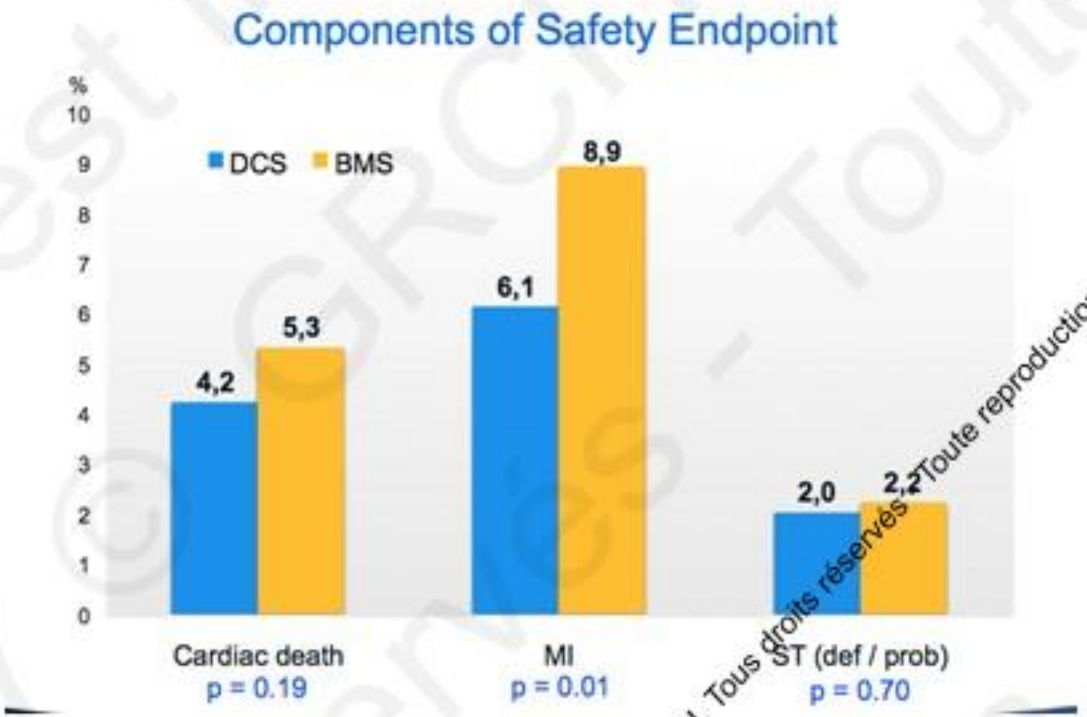

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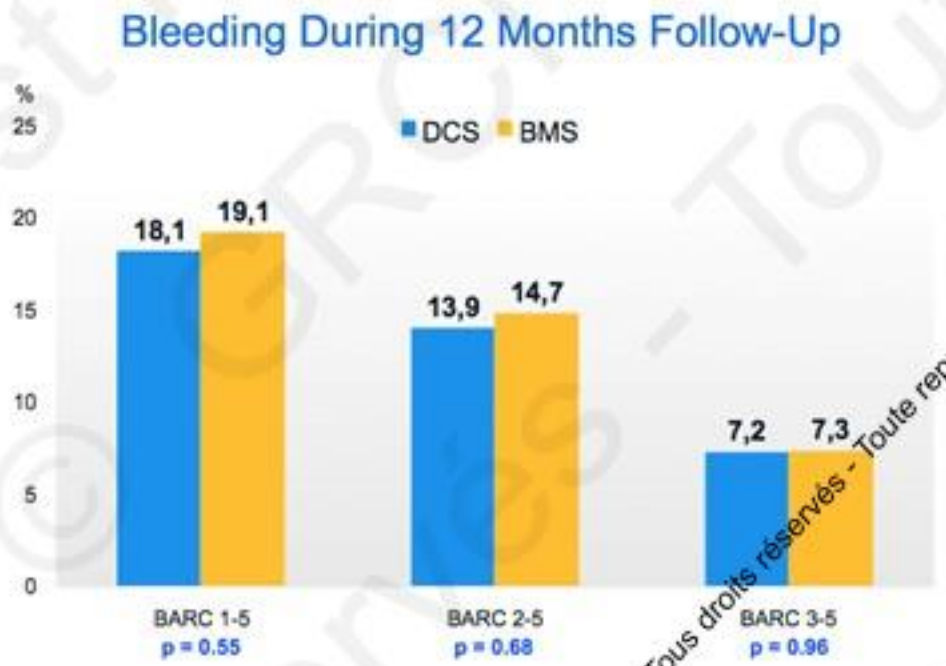
Etude LEADERS FREE



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- Efficacité et sécurité d'emploi d'un stent actif sans polymère
- Bithérapie APP 1 mois vs. 12 mois
- Absence de surrisque de thrombose de stent

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Conclusion

- FA et stenting = situation fréquente
- Risque hémorragique important
- Tendance: bithérapie avec AOD à dose réduite + clopidogrel
- Risque thrombotique élevé: trithérapie
  - La plus courte possible (1 mois)
  - avec AOD à dose réduite
- Thérapeutique au cas par cas
- Stents actifs de dernière génération (2ieme ou 3ieme génération, Biofreedom®)
- Autres mesures préventives du risque hémorragique
  - Voie radiale
  - IPP