Thrombose de stent:
gestion de l'anti-aggrégation plaquettaire et place du coating

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Conflits d'interêt

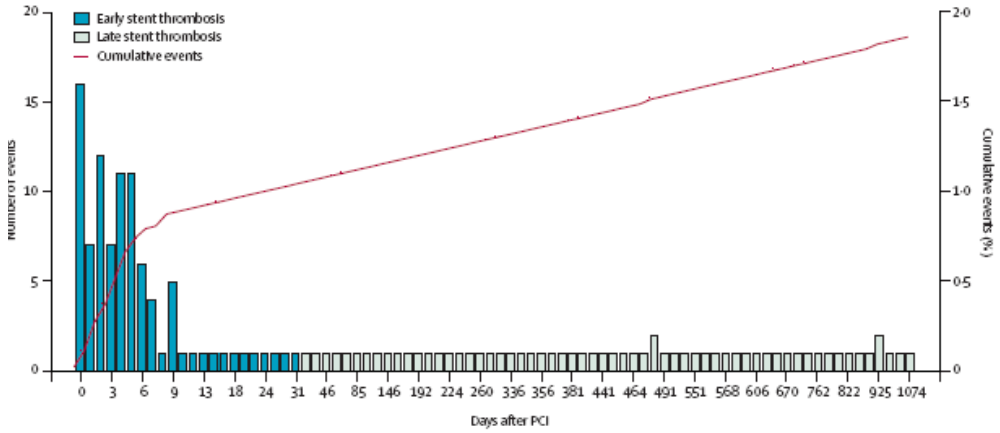
BONELLO Laurent

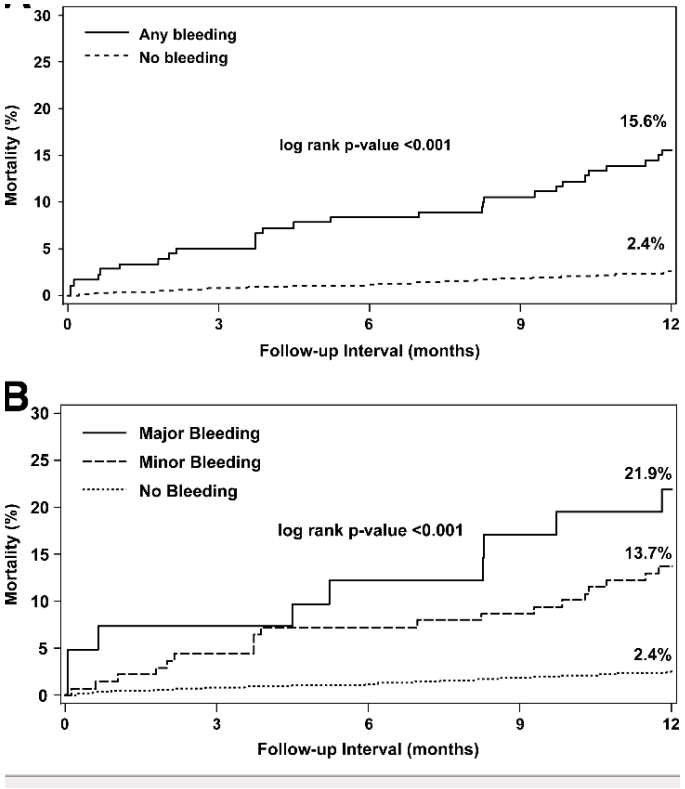
I have the following potential conflicts of interest to report:

- ***x*** **Research grants: Astrazeneca**

- ***x*** **Lecteure fees: Astrazeneca, Sanofi, Eli lilly, Medtronic, Cordis, Boston, Abbot**

TROMBOSES DE STENT SAIGNEMENTS





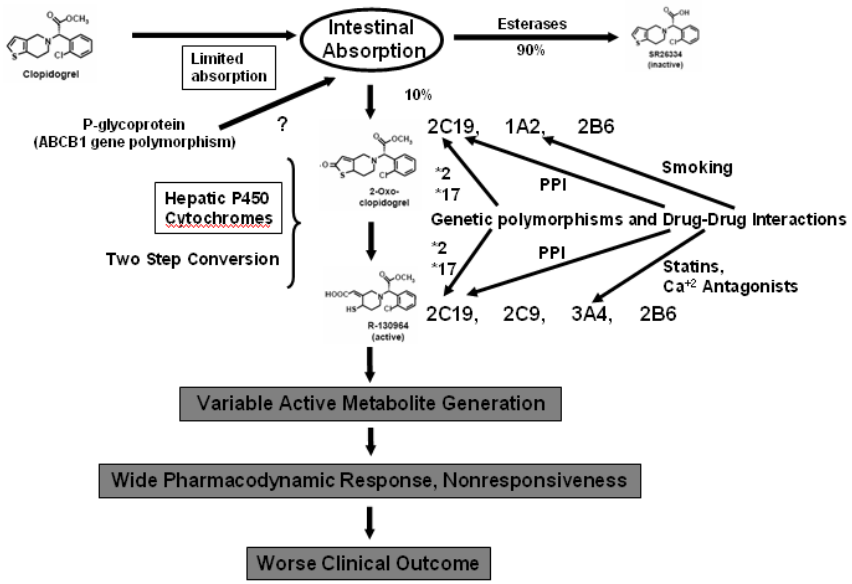
Thromboses de stent = événements précoces

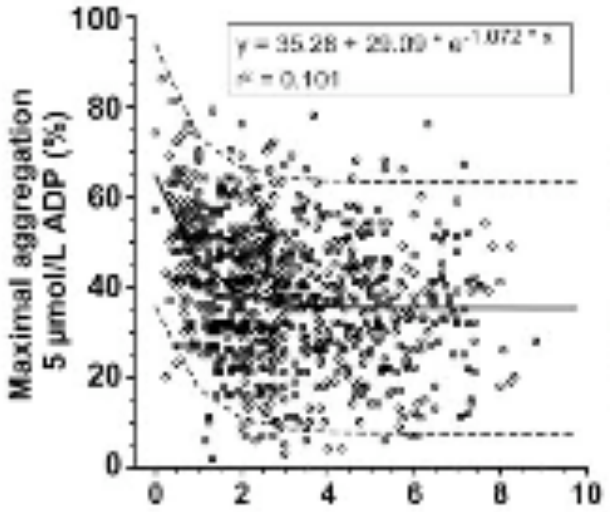
Wiviott SD et al. Lancet 2008

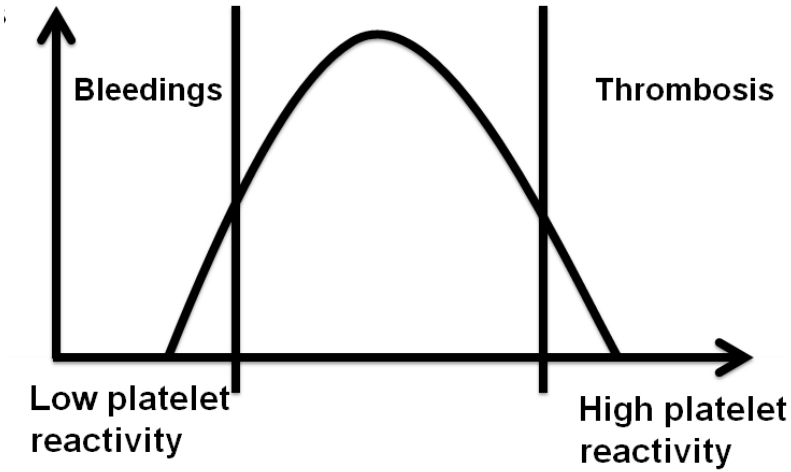
Saignements associés à la mortalité

Lindsey JB, JACC Cardiovasc Interv. 2009

Clopidogrel: Gold-standard ?







Dans l'angor stable

Patients à haut risque de thrombose de stent: monitoring du clopidogrel: VerifyNow, VASP, multiplate

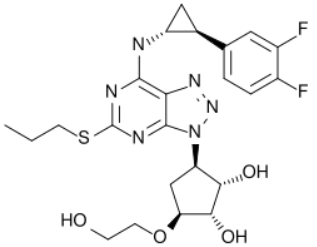
-Bifurcation

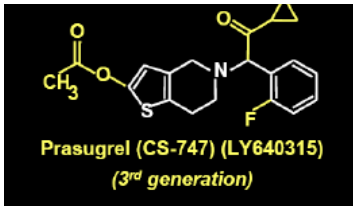
-TCG

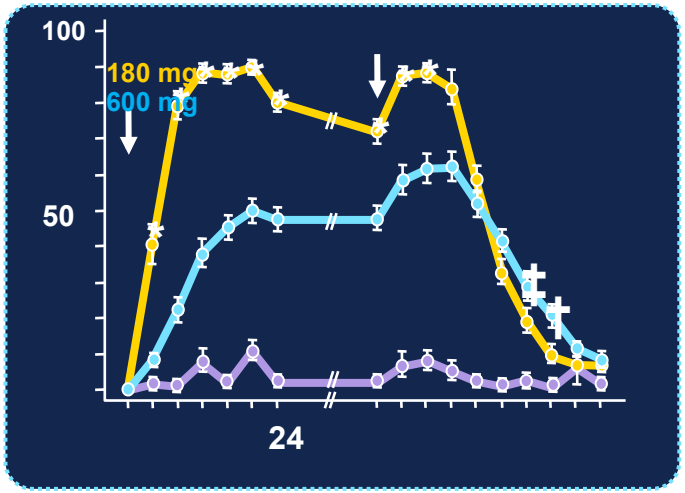
-Lésion longue (>30 mm)

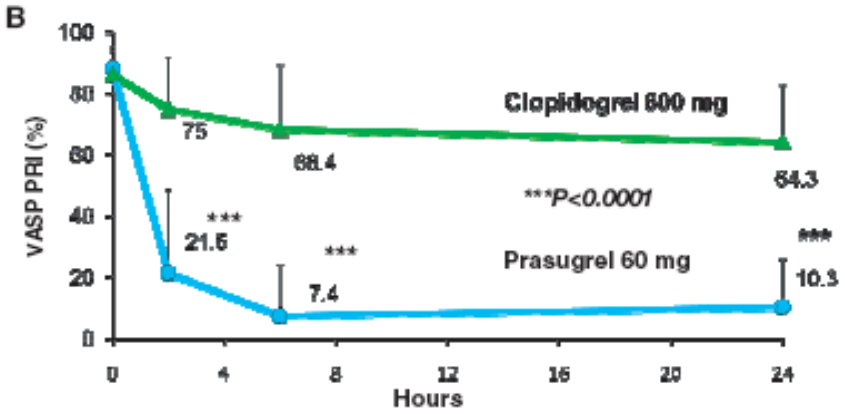
Assay	Cut-Off Value	Endpoint
VerifyNow P2Y12 Assay	>235 PRU	6 months Post-PCI CVD + MI + stent thrombosis
LTA	>46% 5μM ADP >59% 20μM ADP	2 years post-PCI MACE
VASP-PRI	>48% PRI	6 months Stent thrombosis
LTA VASP-PRI	>70% 10μM ADP >53% PRI	1 month Post-PCI MACE + stroke
VASP-PRI	>50% PRI	6 months Post-PCI MACE
VerifyNow P2Y12 Assay	≥240	1 year CV death and non-fatal MI
Multiplate analyzer-ADP	>468 AU*min 6.4μM ADP	30 day stent thrombosis
LTA	>67% 10μM ADP	1 month Stent thrombosis
LTA VerifyNow P2Y12 assay Plateletworks	>42.9% 5μM ADP >64.5% 20μM ADP >236 PRU >80.5% 20μM ADP	1 year death, MI, stent thrombosis, and stroke

Nouveaux antagonistes du P2Y12 dans les SCA



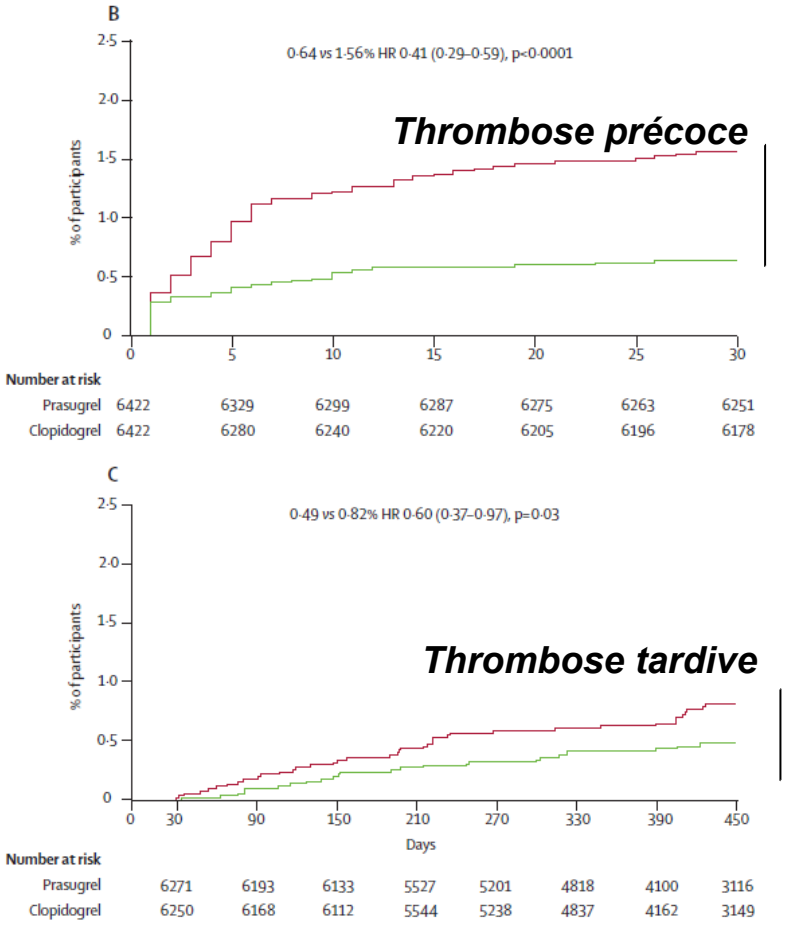






Molécule	Classe	Administration	Métabolisme	Pic d'effet	Réversibilité	½ vie
Ticolpidine	Thiénopyridine	Orale	Conversion prodrogue médiée par le	4jours	Irréversible	NP
Clopidogrel		Orale		2-6heures		
Prasugrel		Orale		1 heure		
Cangrelor	ATP analogue	Intraveineuse	N'est pas une prodrogue	30minutes	Réversible	3 – 5mn
Ticagrelor	CPTP*	Orale		2 heures		12heures

Prasugrel et thrombose de stent dans le SCA traitée par angioplastie



	Prasugrel	Clopidogrel	Hazard ratio (95% CI)	p
Any stent (n=12 844)				
Definite ST	0·88%	2·03%	0·42 (0·31–0·59)	<0·0001
Definite/probable ST	1·13%	2·35%	0·48 (0·36–0·64)	<0·0001
Definite/probable/possible ST	1·54%	2·75%	0·56 (0·43–0·73)	<0·0001
Bare-metal stent only (n=6461)				
Definite ST	0·96%	2·13%	0·44 (0·29–0·69)	0·0002
Definite/probable ST	1·27%	2·41%	0·52 (0·35–0·77)	0·0009
Definite/probable/possible ST	1·77%	2·84%	0·63 (0·45–0·89)	0·007
Drug-eluting stent only (n=5743)				
Definite ST	0·70%	1·92%	0·35 (0·21–0·61)	0·0001
Definite/probable ST	0·84%	2·31%	0·36 (0·22–0·58)	<0·0001
Definite/probable/possible ST	1·13%	2·68%	0·41 (0·27–0·63)	<0·0001
Sirolimus-eluting stent only (n=2454)				
Definite ST	0·42%	1·69%	0·26 (0·10–0·69)	0·004
Definite/probable ST	0·68%	2·10%	0·33 (0·15–0·73)	0·004
Definite/probable/possible ST	0·95%	2·57%	0·38 (0·19–0·76)	0·004
Paclitaxel-eluting stent only (n=2766)				
Definite ST	0·82%	1·95%	0·40 (0·19–0·84)	0·012
Definite/probable ST	0·82%	2·32%	0·33 (0·16–0·68)	0·002
Definite/probable/possible ST	1·16%	2·67%	0·41 (0·22–0·76)	0·004

-60%

Wiviott Lancet 2008

PLATO Trial « invasif »

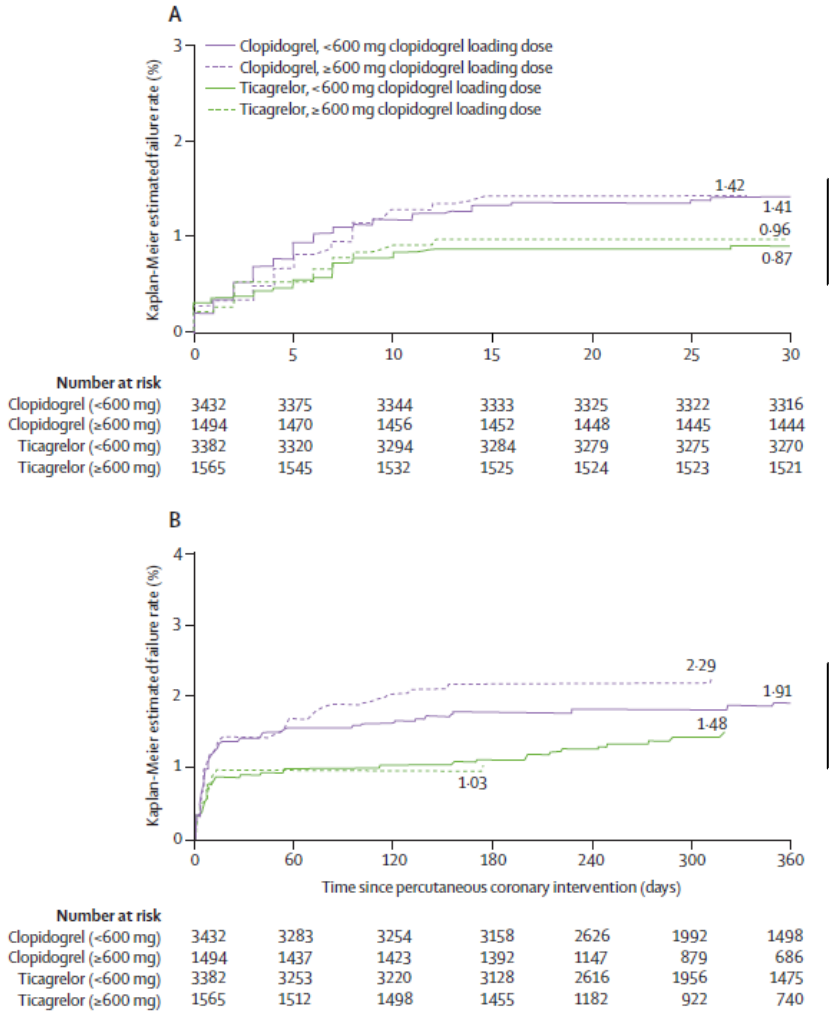


Figure 6: **Kaplan-Meier estimates of definite (angiographically documented) stent thrombosis during 30 days (A) and 360 days (B) in patients given ticagrelor versus clopidogrel**

Stent thrombosis (n)	4949	4928	..	..
Definite	62 (1·3%)	97 (2·0%)	0·64 (0·46–0·88)	0·0054
Patients with a drug-eluting stent	17 (1·3%)	25 (1·8%)	0·69 (0·37–1·27)	0·2304
Patients with a bare-metal stent	45 (1·4%)	72 (2·1%)	0·62 (0·43–0·90)	0·0115
Definite or probable	104 (2·2%)	142 (3·0%)	0·73 (0·57–0·94)	0·0142
Patients with a drug-eluting stent	32 (2·3%)	36 (2·5%)	0·90 (0·56–1·45)	0·6581
Patients with a bare-metal stent	72 (2·2%)	106 (3·1%)	0·67 (0·50–0·91)	0·0092
Total (definite, probable, or possible)	132 (2·8%)	179 (3·8%)	0·73 (0·59–0·92)	0·0068
Patients with a drug-eluting stent	41 (3·1%)	53 (3·8%)	0·78 (0·52–1·17)	0·2349
Patients with a bare-metal stent	91 (2·7%)	126 (3·8%)	0·71 (0·55–0·94)	0·0142

Data are number (Kaplan-Meier estimated % at 360 days), unless otherwise indicated. p values calculated by use of univariate Cox model, unless otherwise indicated. *Excludes silent myocardial infarction. †Data are number (%), and p values calculated with Fisher's exact test.

- 40%

Cannon Lancet 2010

RECOMMANDATIONS anti-agrégants pour SCA

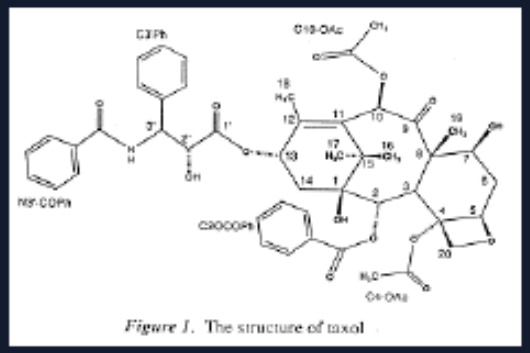
STEMI			
Antiplatelet therapy			
	ASA	I	B
	Clopidogrel[f] (with 600 mg loading dose as soon as possible)	I	C
	Prasugrel[d]	I	B
	Ticagrelor[d]	I	B

NSTE-ACS			
Antiplatelet therapy			
	ASA	I	C
	Clopidogrel (with 600 mg loading dose as soon as possible)	I	C
	Clopidogrel (for 9–12 months after PCI)	I	B
	Prasugrel[d]	IIa	B
	Ticagrelor[d]	I	B

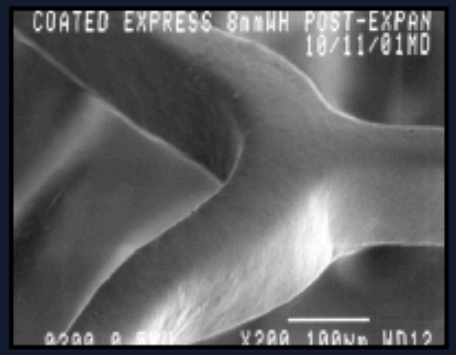
PR testing is a 2b recommendation to prevent thrombotic events and proposed to stratify patients requiring surgery while on therapy

PREMIERE GENERATION DE DES

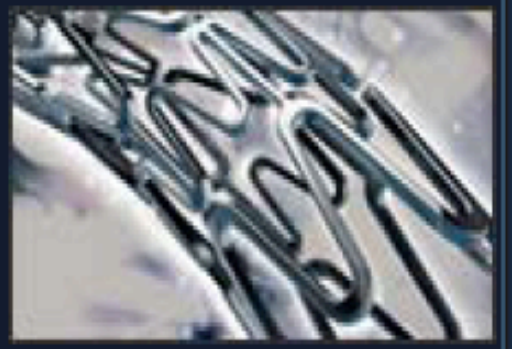
TAXUS



Paclitaxel



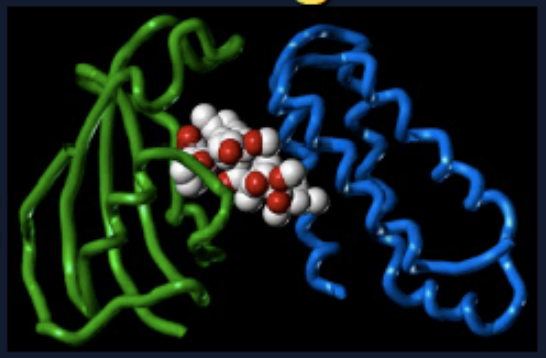
Polyolefin derivative



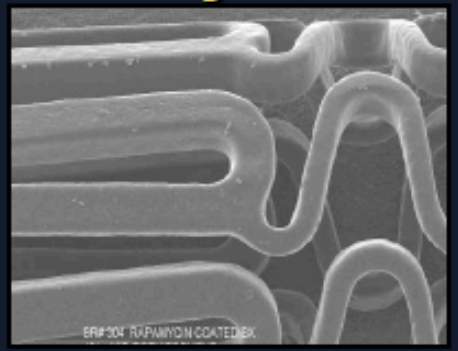
Express²

Drug | Polymer | Stent

Cypher



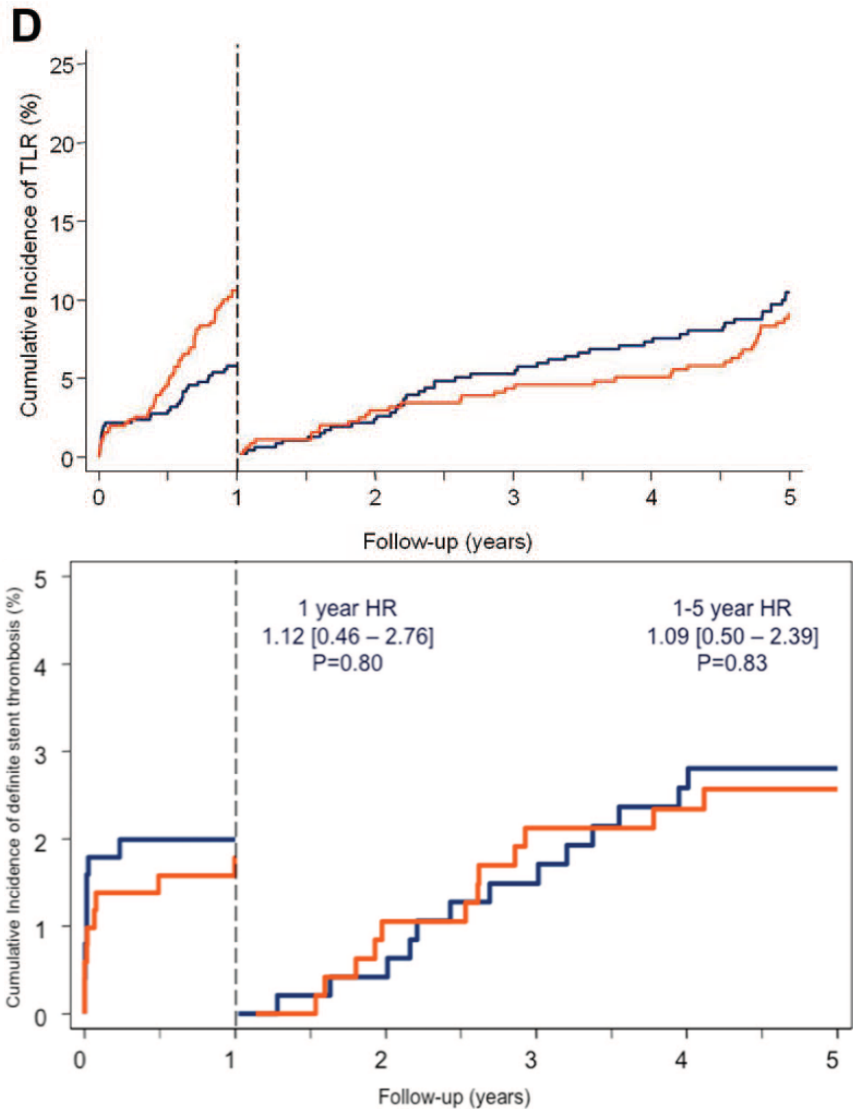
Sirolimus

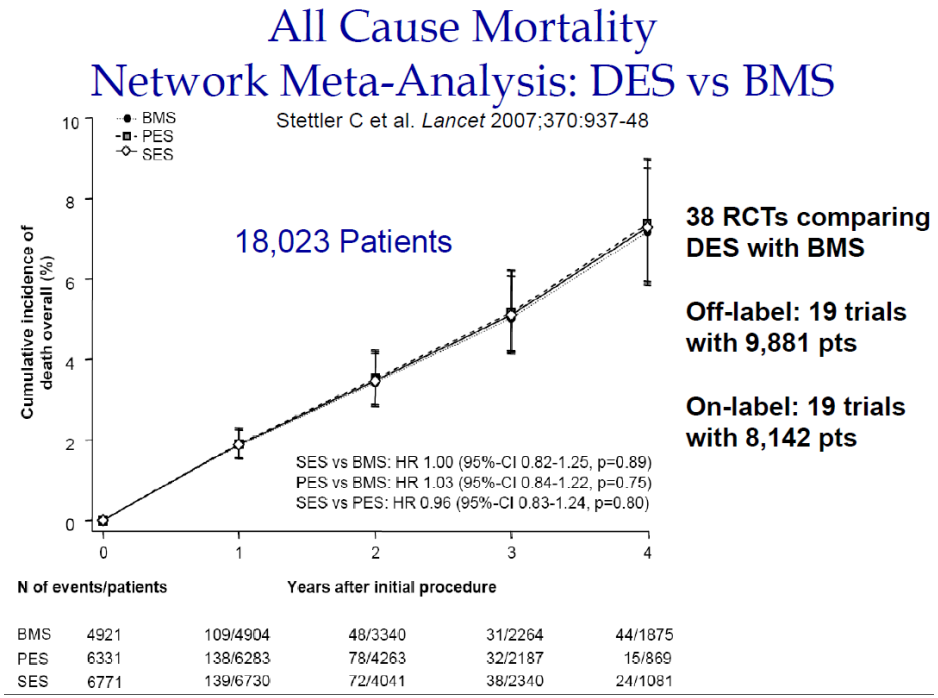


PEVA + PBMA blend

BX Velocity

LIMITES DE LA PREMIERE GENERATION DE STENTS ACTIFS





38 RCTs comparing DES with BMS

Off-label: 19 trials with 9,881 pts

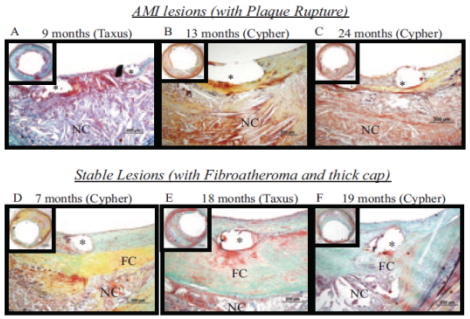
On-label: 19 trials with 8,142 pts

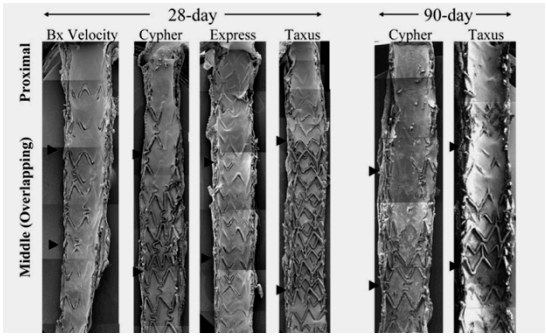
Thromboses tardives, late catch-up.

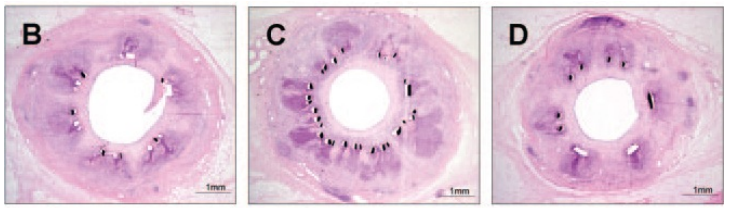
Late. trial Circ 2011

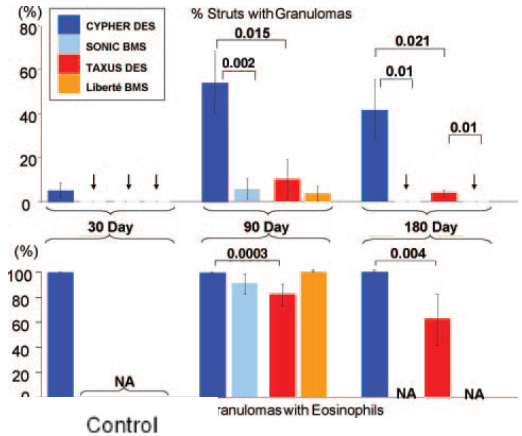
Mécanismes thromboses tardives

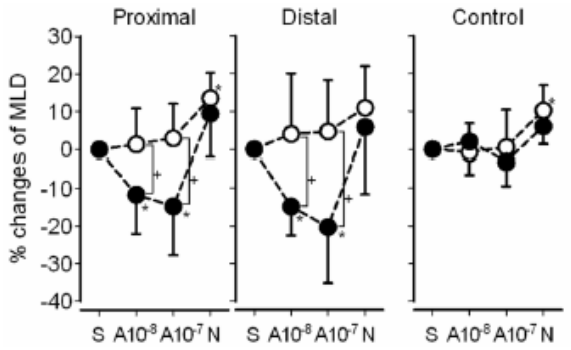
- **Retard de ré-endothélialisation**
- **Inflammation**
- **Dysfonction endothéliale**





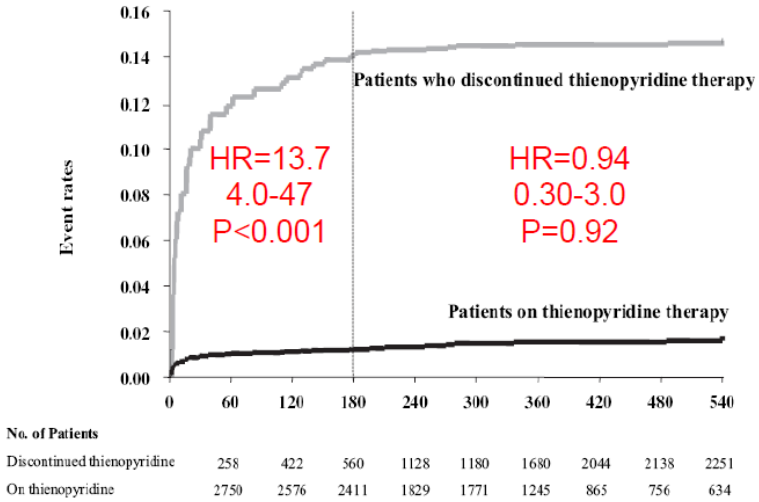






Indication à une anti-agrégation prolongée (>6 mois)

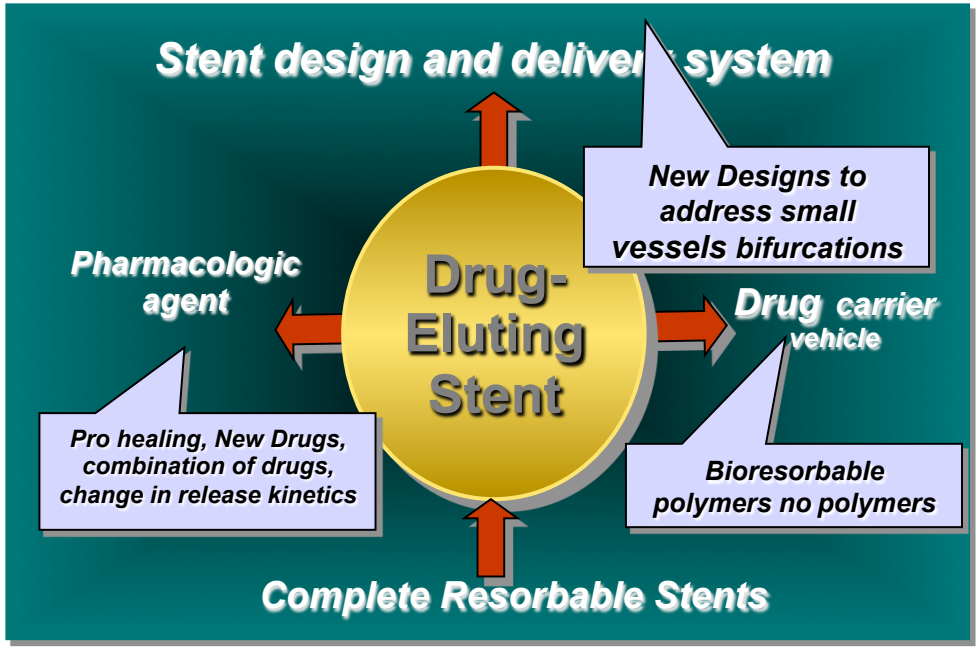
	Hazard Ratio (95% Confidence Interval)	*P* Value
Cumulative stent thrombosis		
Premature antiplatelet therapy discontinuation	89.78 (29.90-269.60)	<.001
Renal failure	6.49 (2.60-16.15)	<.001
Bifurcation lesion	6.42 (2.93-14.07)	<.001
Diabetes	3.71 (1.74-7.89)	.001
Left ventricular ejection fraction per 10% decrease	1.09 (1.05-1.13)	<.001

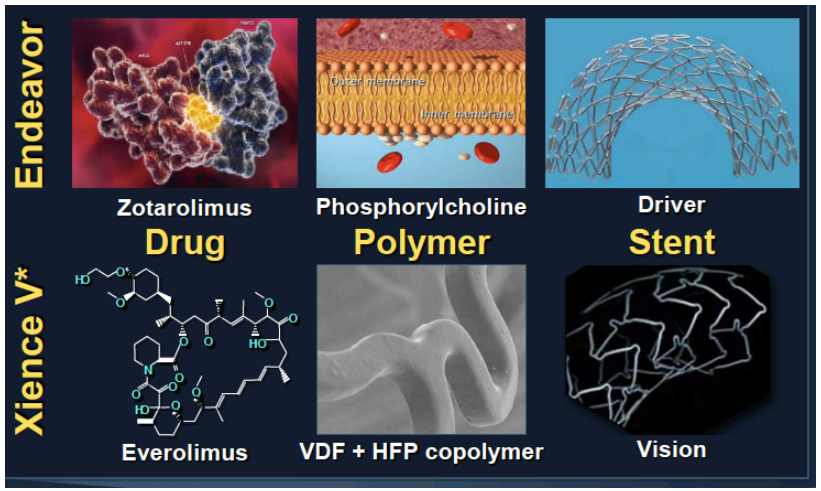


Iakovou JAMA 2005

Airodi et al. circulation 2007

2 ème génération de DES



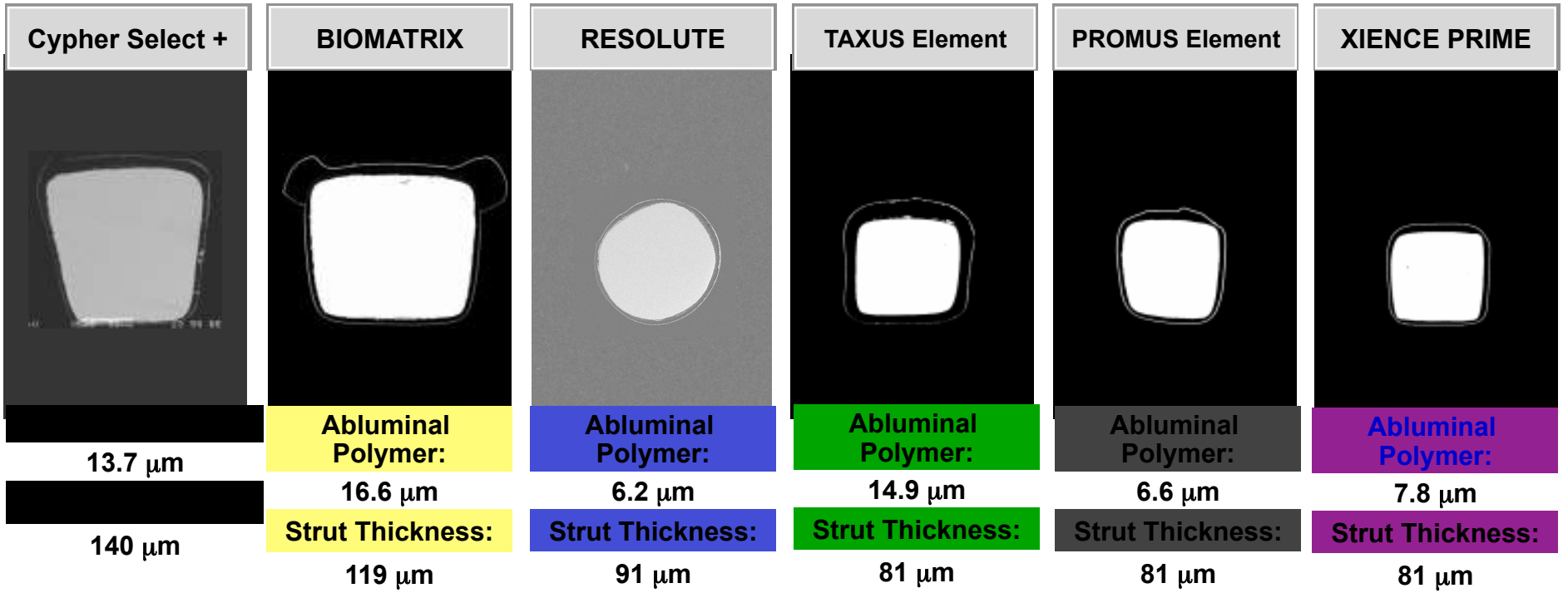


-Nouvelles prothèses

-Nouveaux polymères

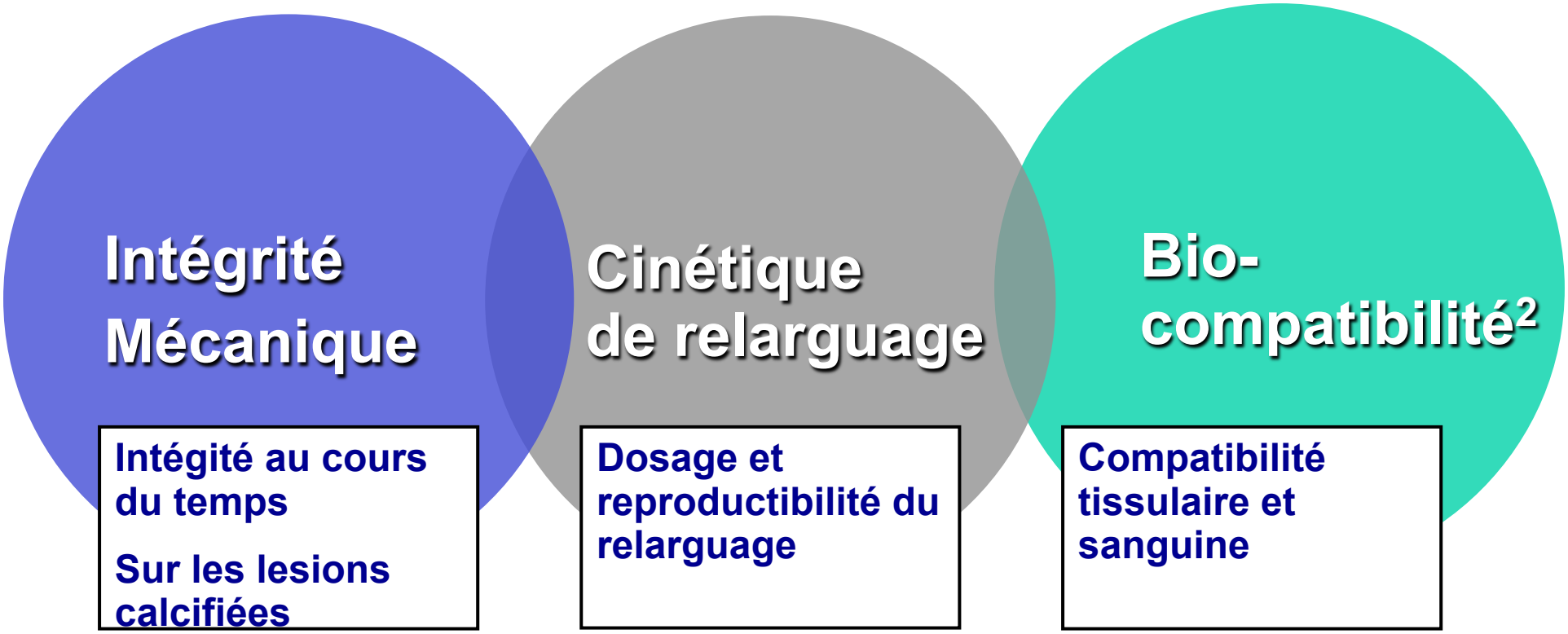
-Nouvelles drogues

L'AMELIORATION DES PROTHESES

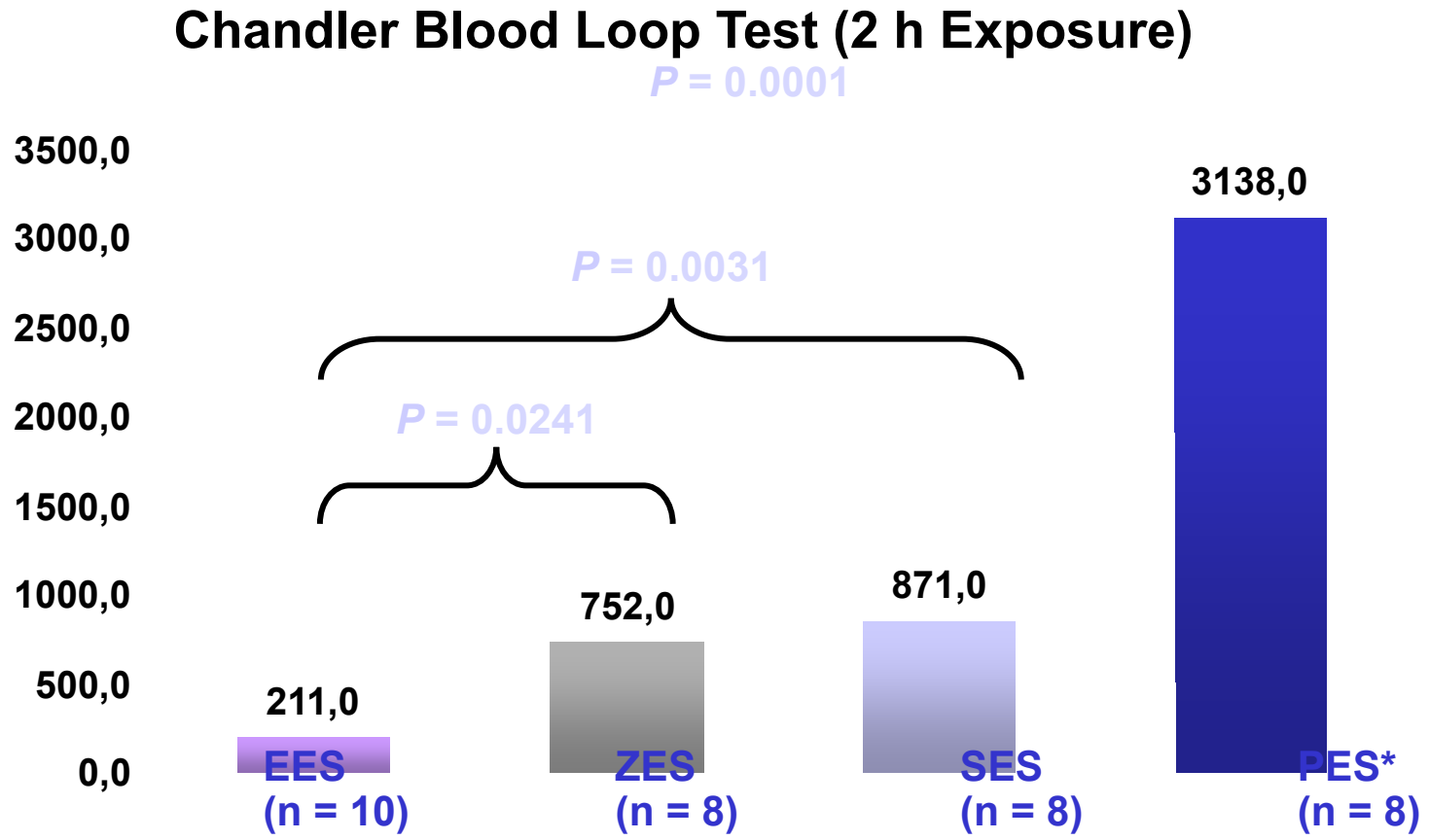


Epaisseur de maille, meilleur franchissement
Réduction de la réaction inflammatoire et ré-endothélialisation précoce

AMELIORATION DES POLYMÉRES

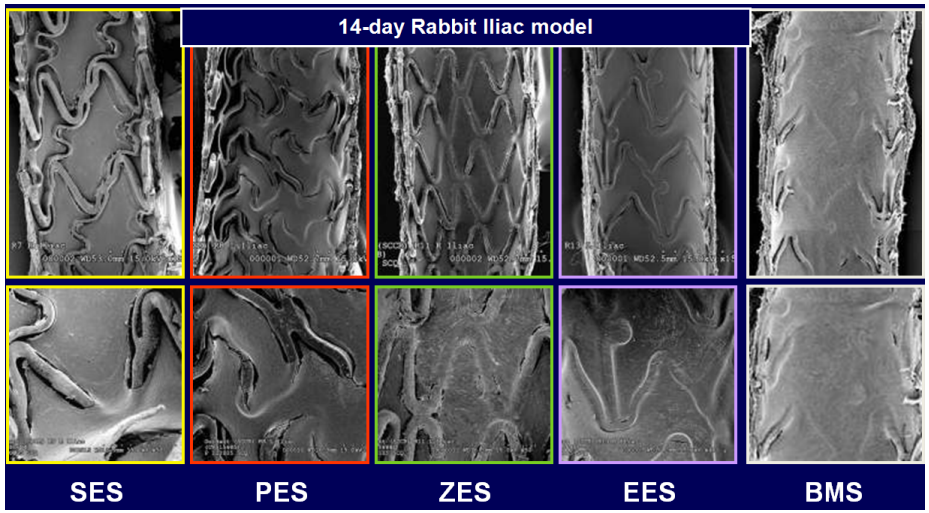


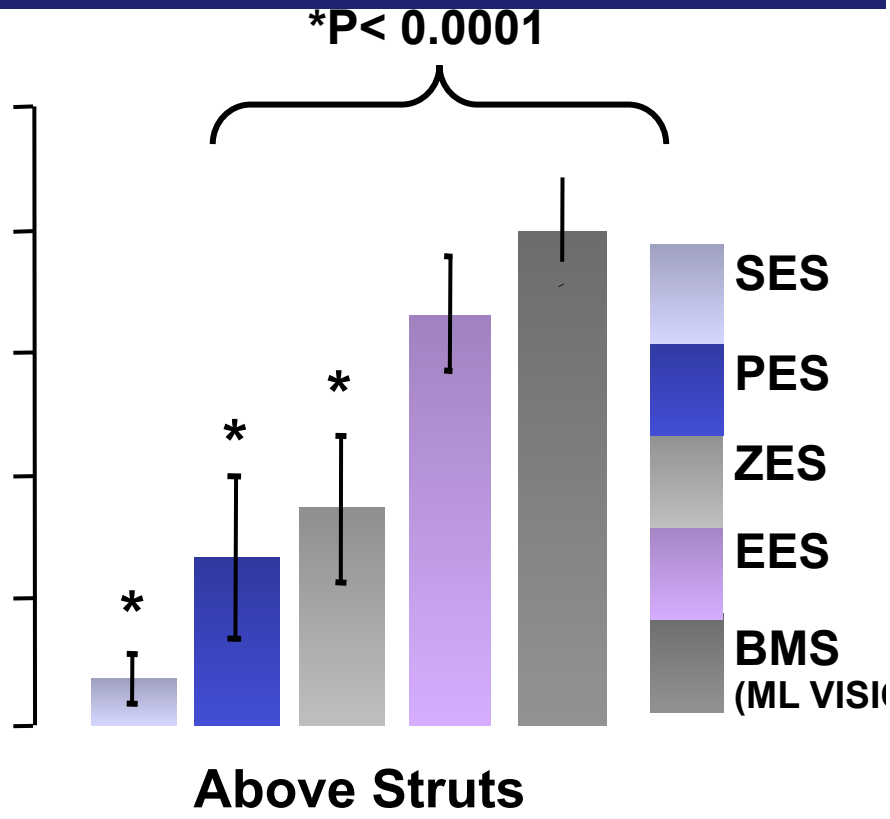
COPOLYMERES FLUORÉS RÉDUISENT LA FORMATION DE THROMBUS



*Taxus Liberté
Paton et al. US Patent 5,356,668. 1994
Data on file at Abbott Vascular.

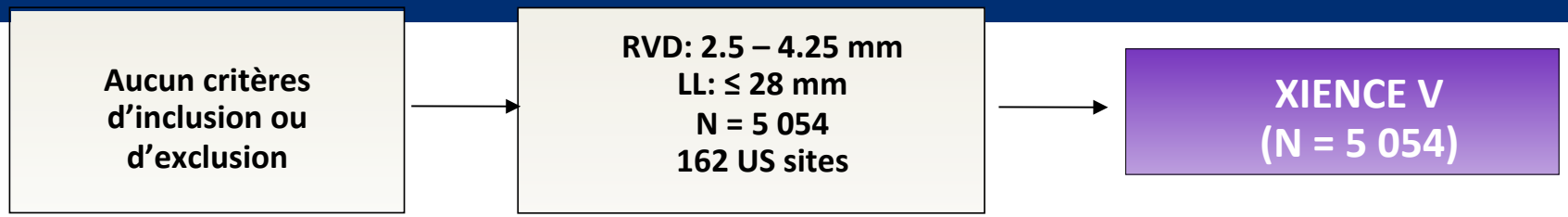
Modification du polymére et de l’élution





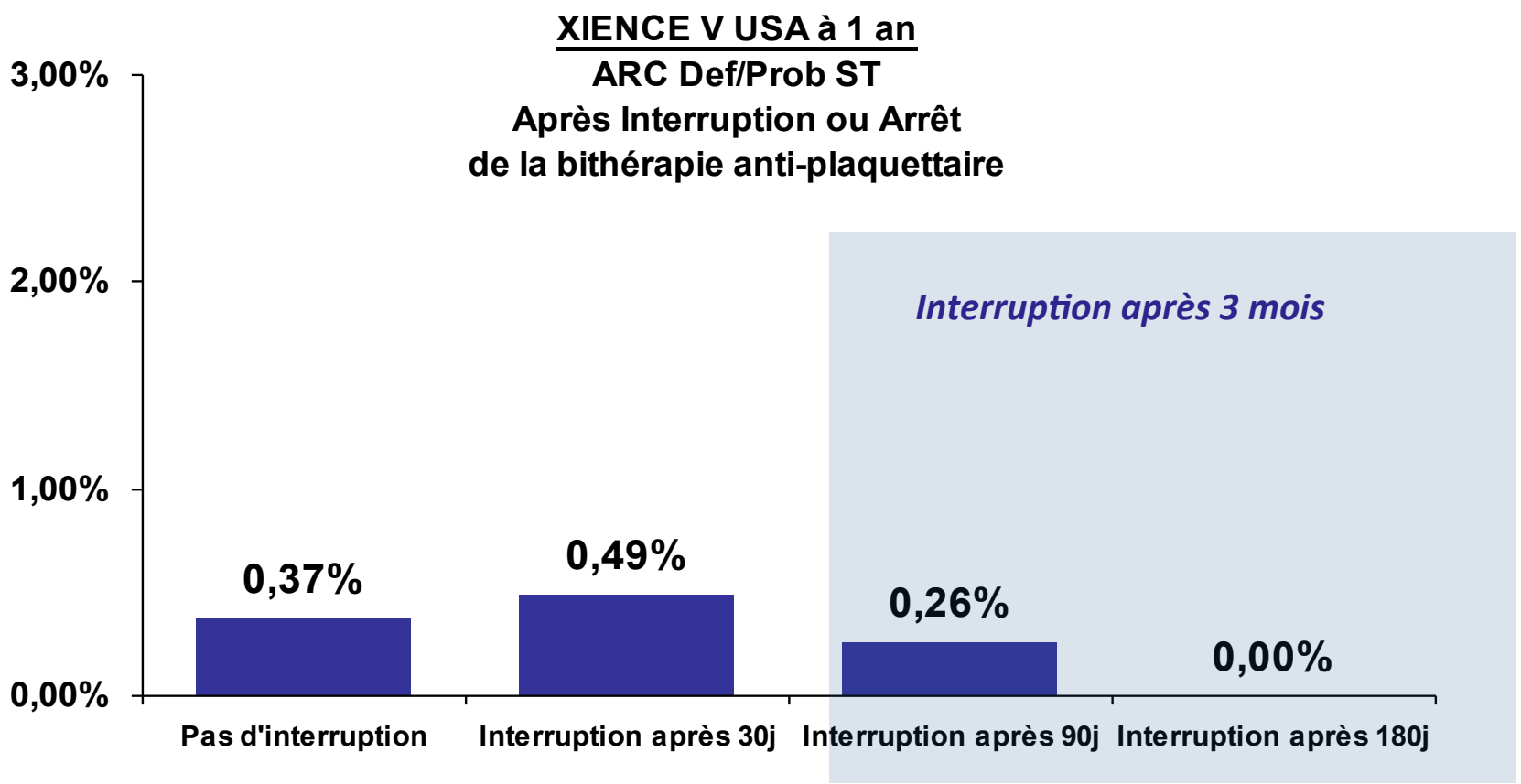
Ré-endothélialisation plus rapide 2eme generation (EES)

• XIENCE V USA : Registre prospectif multi-centrique dans 162 centres US sur 5054 patients « vraie vie »



Interruption temporaires % (N)	**5.6% (N = 243)**
Durée de l'Interruption (jours)	20.3 ± 46.9 (N = 243)
Top 3 Raisons de l'Interruption	Chirurgie = 35.4% Effets secondaires* = 30.5% Non Compliance du patient = 9.5%
Arrêts Permanents % (N)	**8.5% (N = 366)**
Jour de l'arrêt (jours)	239.2 ± 140.4 (N = 366)
Top 3 Raisons de l'arrêt	Effets secondaires* = 21.9% Chirurgie = 10.7% Risques de saignements accrus = 9.6%

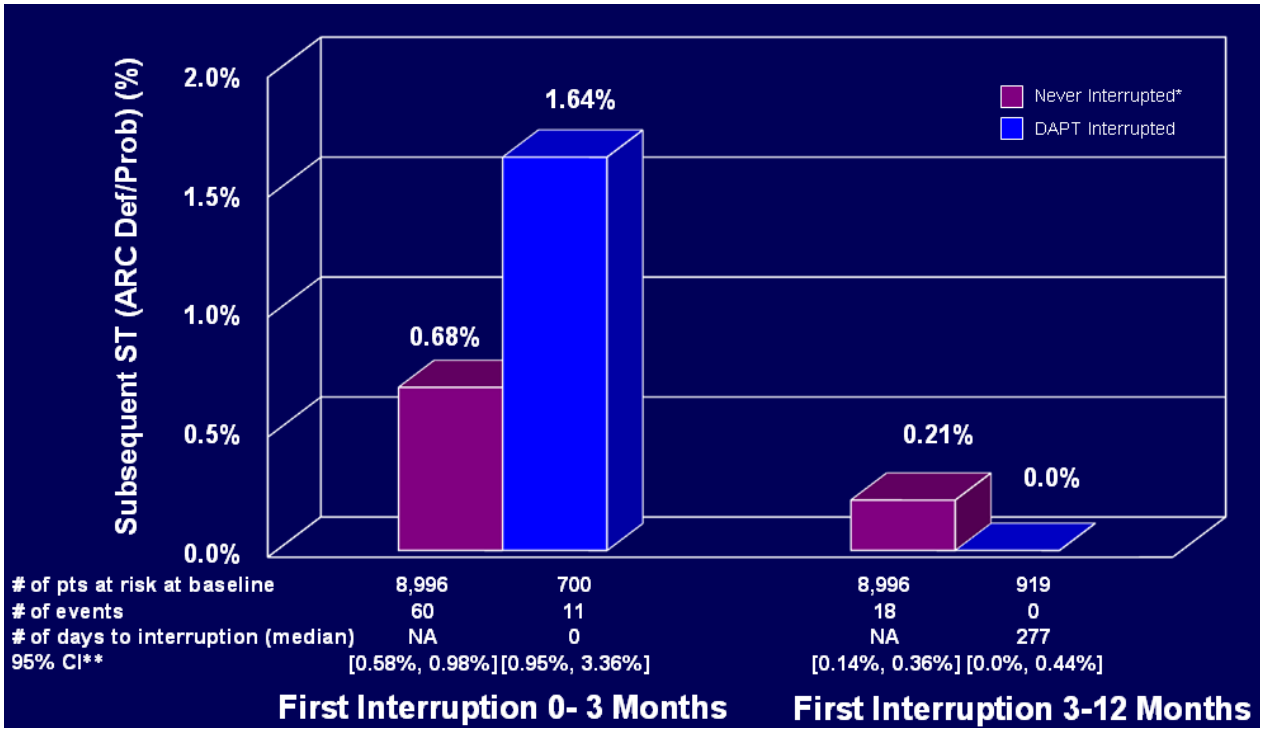
XIENCE V USA: Taux de thrombose à 1 an chez les patients « *vraie vie* » ayant arrêté ou interrompu la bithérapie après 3 mois



Ces résultats ne représentent en aucun cas des recommandations de gestion de la bithérapie anti-agrégante plaquettaire
Source: James Hermiller, XIENCE V USA Registry, 1-Year Results, PCR 2010. Les données d'arrêt ou d'interruption de la bithérapie anti-plaquettaire sont basées sur une analyse post-hoc
Patients à risque standard: Sous-groupe de la population générale de l'étude se rapprochant des populations des études SPIRIT III & IV. (Défini comme patients avec lésions ≤ 28 mm, 2.5 mm ≤RVD≤4.25 mm, exclus les lésions de CTO, pontages, bifurcation avec une branche fille> 2 mm, ostiales, tronc commun, ISR, >2 lésions stentées dans le même vaisseau, > 2 vaisseaux traités, AMI, insuffisance rénale, FE<30%, procédures en plusieurs étapes).

Peut-on réduire la durée de la bithérapie <6 mois ?

Study	XIENCE V (N=10,615)
SPIRIT V	1,662
SPIRIT Women	1,506
XIENCE V USA	6,516
XIENCE V India	931



Méta-analysis comparant la thrombose de stent DES et BMS

Network meta-analysis, randomised controlled trials comparing different drug-eluting stents or drug-eluting with bare-metal stents were identified

49 trials including 50 844 patients randomly assigned to treatment groups were analysed.

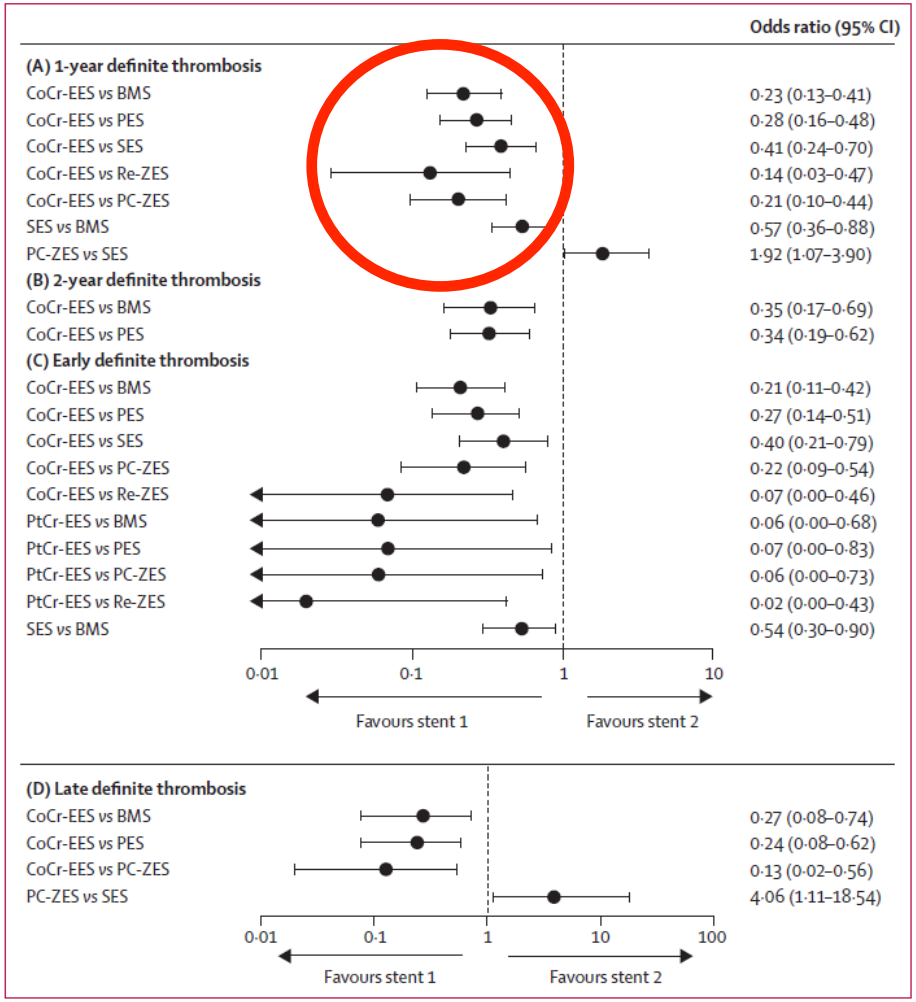


Figure 3: Pooled odds ratios and 95% CIs determined by network meta-analysis for 1-year (A), 2-year (B), early (C), and late (D) definite stent thrombosis

Palmierini lancet 2012

DES > BMS ?

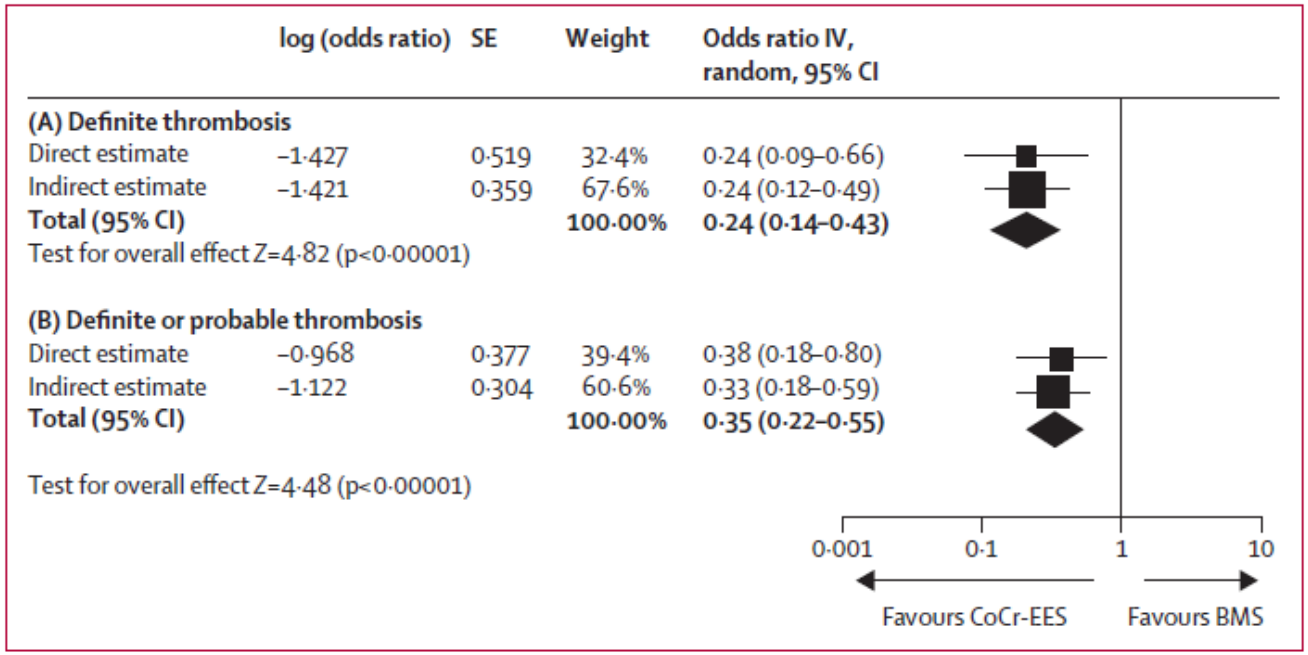


Figure 5: Consistency between direct and indirect estimates of definite (A) and definite or probable (B) stent thrombosis at 1 year between CoCr-EES and BMS

Risque de thrombose de stent réduit avec le CoCr-EES par rapport au BMS à 1 et 2 ans.

CONCLUSION

- Réduction du risque de thrombose de stent avec la deuxième génération
- Taux de complications hémorragiques non négligeable
- Recommandation si DES: 6 à 12 mois
- Arrêt possible à 3 mois pour éverolimus

Study	Patients (n)	Randomization	Primary Outcome Measure	Secondary Endpoint
ISAR-SAFE NCT00661206	PCI-DES (6000)	6 mo vs. 12 mo	15 months Death/MI/stroke/ TIMI major bleed	Individual component endpoints
ISAR-CAUTION NCT00640679	PCI-DES (3000)	12 mo vs. tapered within 4 weeks after 12 months	3 months CV death, non-fatal MI or ST, stroke, major bleeding or rehospitalization due to acute coronary syndrome	The individual components of the primary endpoint. All cause mortality
ARCTIC NCT00827411	Elective PCI –DES (2466)	12 mo vs. 18-24 mo	12 months Composite end point of death, MI, stroke, Urgent revascularization, ST	Individual component endpoints
OPTIDUAL NCT00822536	DES –PCI (n=1966)	12 mo vs. 36-48 mo	3 years death, non fatal myocardial infarction, non fatal stroke and severe bleeding	Individual component endpoints Stent thrombosis (ARC), Target vessel revascularization
DAPT Study NCT00977938	DES/BMS –PCI (n=20645)	12 mo vs. 30 mo	30 months 1.Death/MI/stroke at 33 mo 2.Def/prob ST at 33 mo	GUSTO Bleeding
ITALIC NCT00780156	PCI-DES (n=3200)	6 mo vs. 36 mo in deem aspirin good responder	12 months death, MI repeat urgent revasc, stroke requiring a new hospitalisation and major bleedings	Individual component endpoints At 24 and 36 months and bleeding complications
REAL-LATE NCT00484926	PCI DES (n=1625)	12-month vs 24	2-year cardiac death/MI	ARC ST, bleeding
ZEST-LATE NCT00590174	PCI with SES, PES, ZES (n=1357) 12-month EF	12 vs 24 mo	2-year death/MI	ARC ST, bleeding
SEASIDE NCT00963781	PCI ZES 900 non-ACS	6 months	1-year death/MI/stroke	GUSTO bleeding CYP2C19
DATE registry NCT00418860	823 non-ACS	3 months	1-year cardiac death/MI/ST	Individual component endpoints, TLR
OPTIMIZE NCT01113372	PCI-ZES N=3120 non-STEMI	3 vs 12	1-year death/MI/stroke/ TIMI major bleed	ARC stent thrombosis

Une nouvelle et encore meilleure génération chasse la précédente ….

MERCI