Le Rêve Eveillé du Stent Bio Actif de 3ème Génération !

APPAC 6/7/8 JUIN 2018 Palais des Congrès BIARRITZ 20e édition

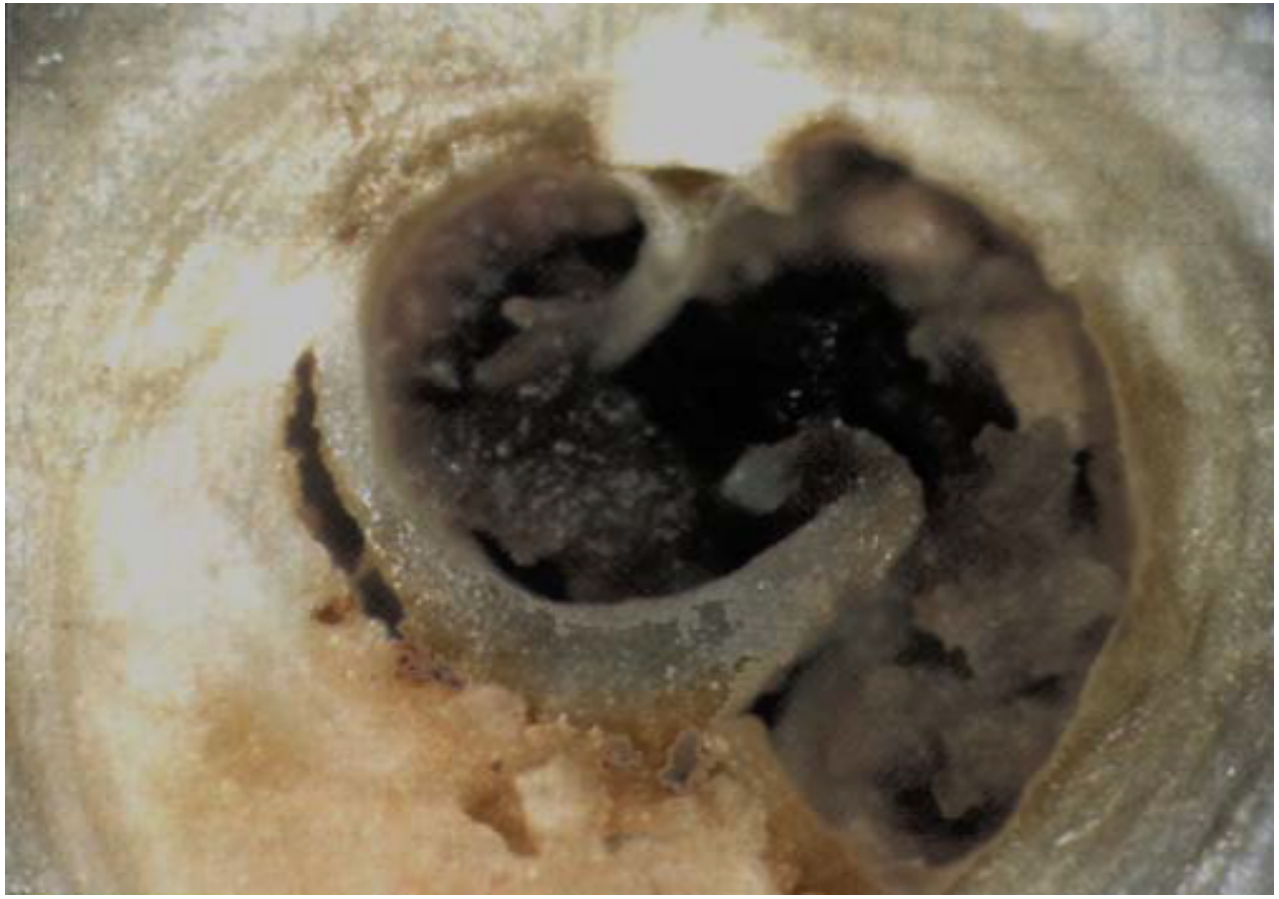
5 6 7 JUIN 2019

A propos de l'étude TIDES-ACS

APPAC Ensemble, imaginons la cardiologie de demain

Dr P. LEFEBVRE

CHU Charleroi



Conflits d’intérêts

Aucun dans le cadre de cette présentation

Je suis Belge (désolé)


JE SERAI BREF

Paclitaxel-Coated Balloon Angioplasty Versus Drug-Eluting Stent in Acute Myocardial Infarction.

The REVELATION Randomized Trial. JACC 2019.

- 120 pts STEMI, FFR à 9 mois.
- At 9 months after enrolment, the mean fractional flow reserve value was 0.92 +/- 0.05 in the DCB group (n:35) and 0.91 +/- 0.06 in the DES group (n : 38) (p = 0.27).
- One abrupt vessel closure requiring treatment occurred after treatment with DCB.
- Up to 9-months follow-up, 2 patients required non urgent target lesion revascularization (1 in each group).

TiTAN / OPTIMAX: Stent Biologiquement-Actif (BAS)

Etudes in Vitro

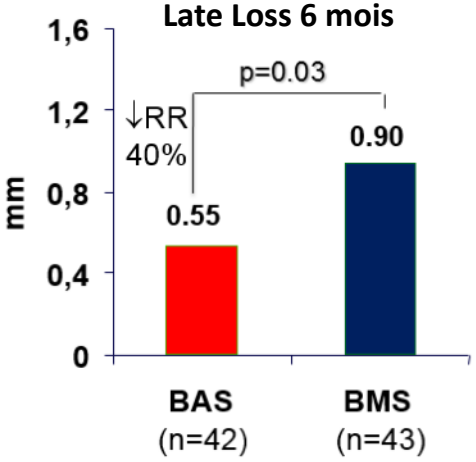
- Réduction du phénomène inflammatoire [1]
- Amélioration de la biocompatibilité [1]
- Réduction de l'agrégation plaquettaire et de la croissance fibrineuse [2]
- Accélération du phénomène de réendothélialisation [3]
- Réduction du processus thrombotique [4]
- Présence de NO de surface [5]

1-Steinemann ; Injury 1996 ; Vol.27 Supl.3 : SC16-22 Institut de physique expérimentale Université Lausanne
1-Williams; Journal of Med.Engineering and Technologies; 1997 Jul; 1(4) : 195-198
2-Zhang et col. Journal of Biomaterial Medical Research 1998; 42:, 128-133
2-Gotman. Journal of Endourology 1997; Vol.11 n°6 : 383-389
2-Tsyganov et col. Nuclear Instruments and methods in physics research 2007; -B257: 122-127
3-Yeh et col., Journal of Biomedical Material research, 2006; RES 76 A: 835-841
4-Zhang et col. ; Surface and Coatings Technology 84 (1996) 476-479
5-Windecker et col. ; Eurointervention 2006, 2: 146-148

Etudes cliniques - TiNOX

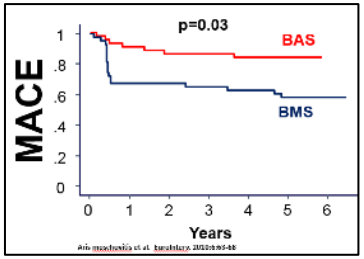
Efficacité du BAS (p=0.03) vs. le stent nu
sur la réduction du Late Loss (Perte lumière tardive)

Late Loss 6 mois



Windecker Circulation 2005

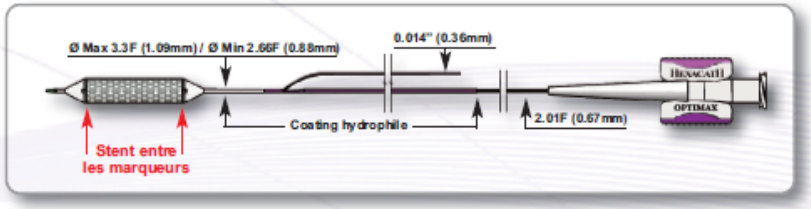
MACE 60 mois

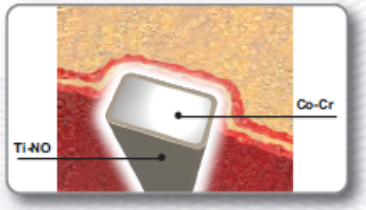


EuroIntervention 2010

TITAN OPTIMAX

STENT BIOACTIF COATÉ Ti-NO





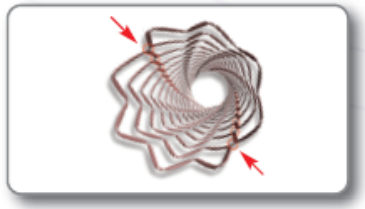
Maille du Stent Bioactif Optimax

TABLEAU DE COMPLIANCE

	Bars	Ø mm							XL	
		2.0	2.25	2.50	2.75	3.00	3.50	4.00	4.50	5.00
PN	8	2.00	2.25	2.50	2.75	3.00	3.50	4.00	4.50	5.00
	9	2.03	2.28	2.53	2.78	3.03	3.53	4.03	4.53	5.03
	10	2.06	2.31	2.56	2.81	3.06	3.56	4.06	4.56	5.06
	11	2.09	2.34	2.59	2.84	3.09	3.59	4.09	4.59	5.09
	12	2.12	2.37	2.62	2.87	3.12	3.62	4.12	4.62	5.12
	13	2.15	2.40	2.65	2.90	3.15	3.65	4.15	4.65	5.15
	14	2.18	2.43	2.68	2.93	3.18	3.68	4.18	4.68	5.18
	15	2.21	2.47	2.71	2.96	3.21	3.71	4.21	4.71	5.21
RBP	16	2.24	2.50	2.74	2.99	3.24	3.74	4.24	4.74	5.24
	17	2.30	2.53	2.77	3.02	3.27	3.77	4.27	4.77	5.27
	18	2.33	2.56	2.80	3.05	3.30	3.80	4.30	4.80	5.30
	19	2.36	2.59	2.83	3.08	3.33	3.83	4.33	4.83	5.33
	20	2.39	2.62	2.86	3.12	3.36	3.86	4.36	4.86	5.36
Ø Max. Expansion		2.75 mm		4.5 mm					5.5 mm	
Epaisseur mailles		60 µ		75 µ					120 µ	

IN VITRO DATA (Ø): +/- 0.1mm

Design à cellules ouvertes



Design à 2 hélicoïdes de lien

Profils du Stent Bioactif Optimax

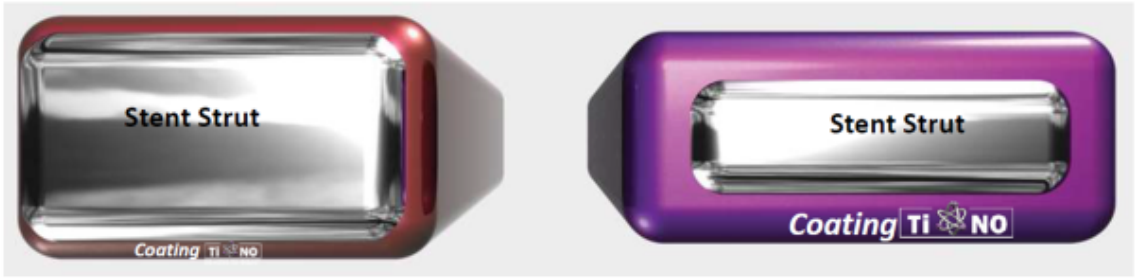
Le stent TiTAN OPTIMAX dispose d'une plateforme en cobalt-chrome. Son revêtement bioactif en oxynitrure de titane (Ti-NO) se caractérise par la présence de particules de NO à la surface du stent, permettant une cicatrisation rapide dès 2 semaines mis en évidence par OCT ce qui a fait l'objet d'une publication. Plusieurs autres mécanismes sous-tendent l'action biologique du Ti-NO : inhibition de l'agrégation plaquettaire, moindre croissance de la fibrine, diminution de la formation de thrombus et réduction de l'inflammation. Chez les patients instables en Syndrome Coronarien Aigu (STEMI/NSTEMI), 3 études randomisées TIDES-ACS (Optimax vs. DES 3rd Generation), BASE-ACS (TiTAN2 vs. DES 2nd Generation) et TITAX-AMI (TiTAN vs. DES 1st Generation) ont documenté les performances de la technologie de coating Bio-Actif Ti-NO sur 2743 patients.

HEXACATH

Fabricant français depuis 24 ans

Coating renforcé

- Plus forte concentration d'Oxynitrure de Titane
- Moins thrombogène
- Ré-endothélialisation plus rapide



PREUVES

TiTAN OPTIMAX est biologiquement actif => PREUVE SUR L'HOMME

10 ans de médecine basée sur des preuves

TiNOX (vs BMS - 2005)
TITAX-AMI (vs TAXUS - 2007)
BASE-ACS (vs Xience V - 2011)
TIDES-ACS (vs Synergy - 2018)

Causes of DES Thrombosis

- *The polymer* (hypersensibility reactions, inflammatory and thrombogenic) !
- *The drug* (delayed healing and incomplete late stent apposition)
- *The procedure* (suboptimal stent deployment and in/ outflow problems)
- *The patient* (anti-platelet resistance, intrinsic thrombogenicity and more complex lesions)

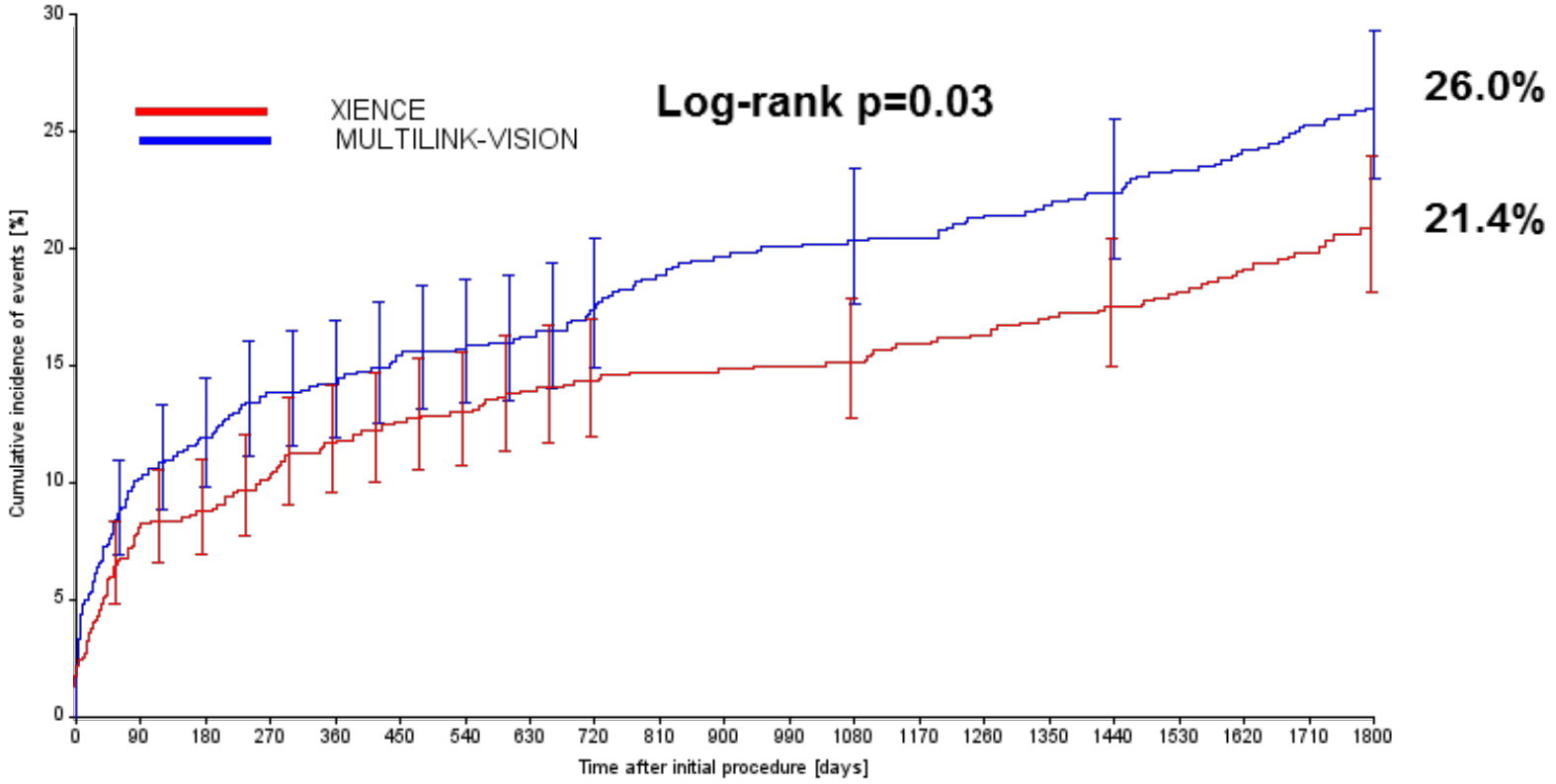
Increased sensitivity to obligatory prolonged dual antiplatelet regimens

Everolimus-eluting stents versus bare-metal stents in ST-segment elevation myocardial infarction. Five-year results of the EXAMINATION Trial

Manel Sabaté
on behalf of the EXAMINATION investigators

Lancet 2015

Patient-oriented endpoint
(all-cause death, any myocardial infarction or any revascularization)



Lancet 2016

“There were six prespecified secondary outcomes, of which five were reported in the article and one was not. Additionally, the Article reports the prespecified primary composite outcome at four additional non-prespecified timepoints; and ten new outcomes that were not prespecified, reporting eight of these at five timepoints each. None of these novel outcomes is adequately declared as non-prespecified…”

Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial *Lancet* 2012; 380: 1482–90

Table 3 presents outcomes at 30-day and 1-year follow-up. The patient-oriented primary endpoint occurred in 89 (11·9%) patients of the EES group and 106 (14·2%) patients of the BMS group (figure 2A and table 3). Hence, the superiority hypothesis was not met for this global primary endpoint. The rates for the individual components of the primary endpoint were similar to those for the composite endpoint between the two groups (table 3). The findings for the primary endpoint were consistent across prespecified stratified analyses (appendix).

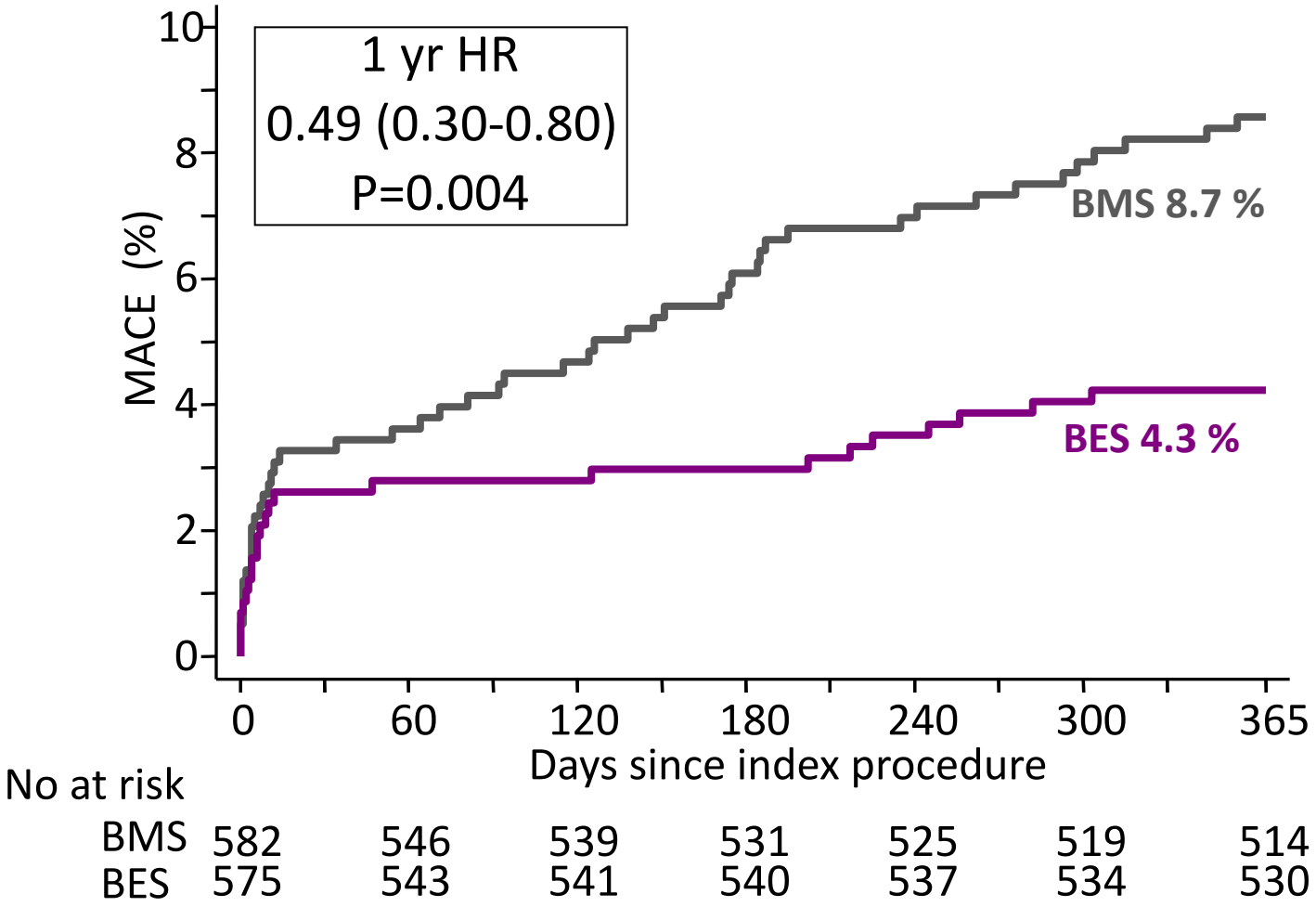
L'objectif de SUPERIORITE n'a pas été atteint.

Biolimus-Eluting Stents With Biodegradable Polymer Versus Bare Metal Stents in Acute Myocardial Infarction: the COMFORTABLE AMI Trial

Lorenz Räber, Henning Kelbæk, Miodrag Ostojic, Andreas Baumbach, David Tüller, Clemens v. Birgelen, Dik Heg, Marco Roffi, Aris Moschovitis, Ahmed A. Khattab, Peter Wenaweser, Robert Bonvini, Giovanni Pedrazzini, Ran Kornowski, Klaus Weber, Thomas F. Lüscher, Masanori Taniwaki, Bernhard Meier, Peter Jüni, Stephan Windecker

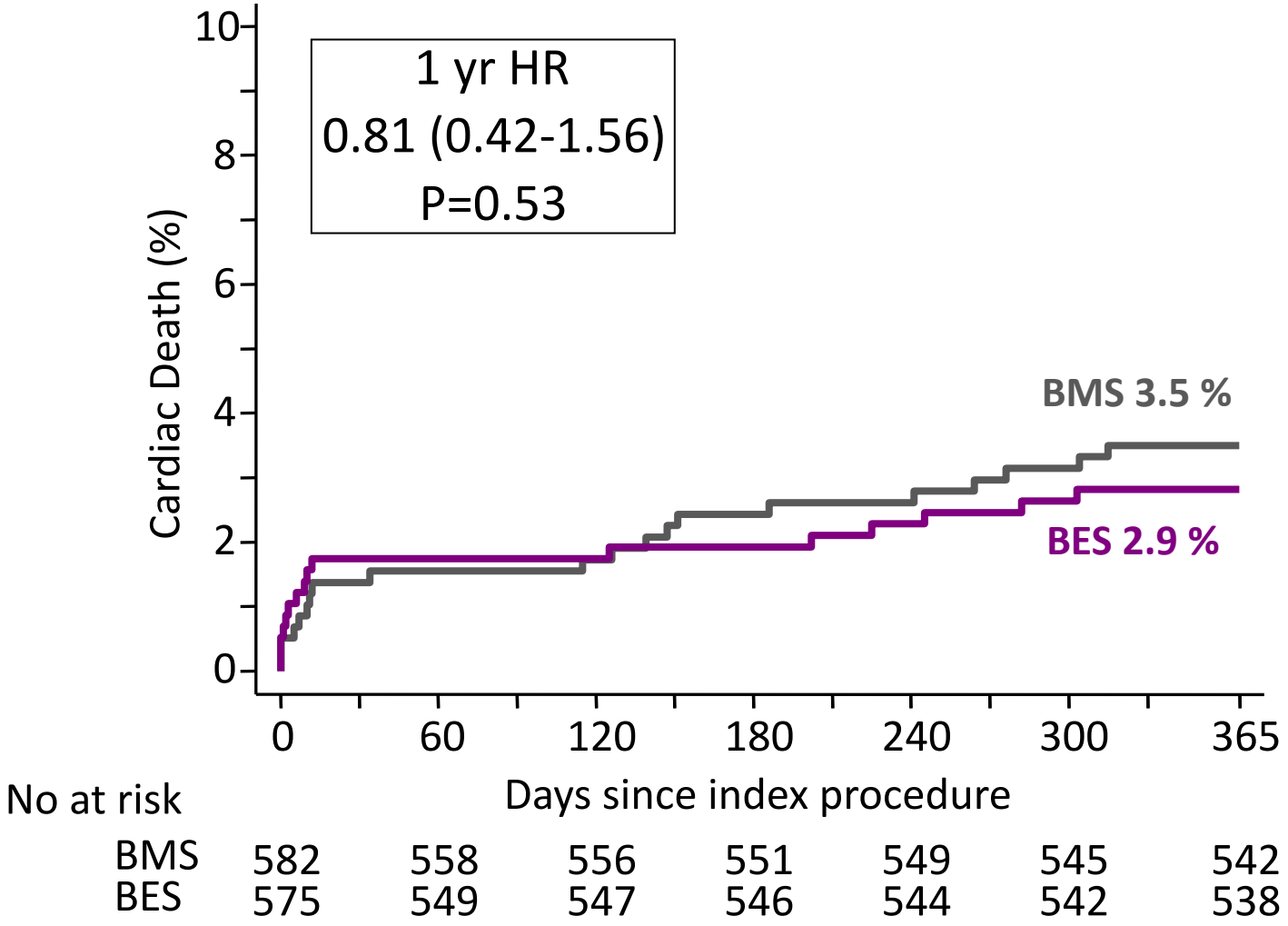
NTC00962416

Primary Endpoint – MACE @ 1 Year



Clinical outcomes were adjudicated by an independent and blinded CEC

2nd Endpoint – Cardiac Death



Clinical outcomes were adjudicated by an independent and blinded CEC

COMFORTABLE AMI

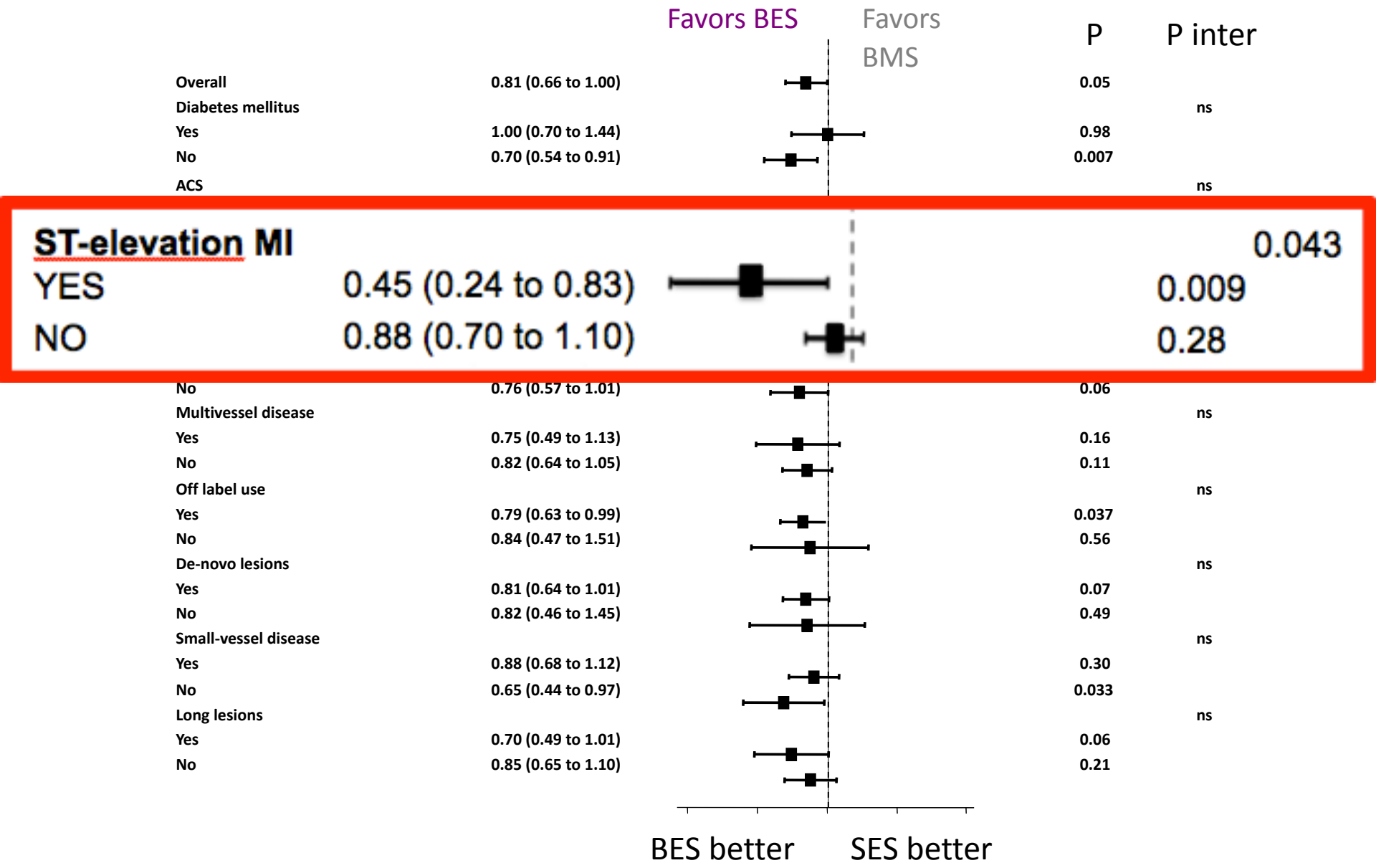
* Control device

The Gazelle is a BMS consisting of a similar stainless steel platform to that of the BioFreedom stent, but without the texturing of the abluminal surface. It is laser-cut from a stainless steel tube. Each corrugated ring has a total of six serially connected segments. The stent rings are connected by two short flexible links with successive pairs of these oriented in a 90° quadrature around the circumference of successive rings. The strut thickness is 120 μ. The stent has been shown to be associated with good angiographic and clinical results, comparable with other BMS, and had a late angiographic in-stent loss of 0.86 ± 0.56 mm at 6 months.[28] In addition, it served as the BMS control in the recently published COMFORTABLE trial.[29] Its use in the present trial will allow for the intended double-blind design, thus avoiding any potential imbalance for the duration of DAPT during follow-up.

Limitations

The use of the Gazelle BMS in the control arm is critical to ensure a double-blinded design. Although data on direct comparisons with other BMS are not available, it is possible that other BMS with thinner struts could be associated with a lower incidence of TLR.[34]

COMFORTABLE AMI – BACKGROUND II



Ce qu'on veut ns faire croire…
Ce que l'on ne dit pas…

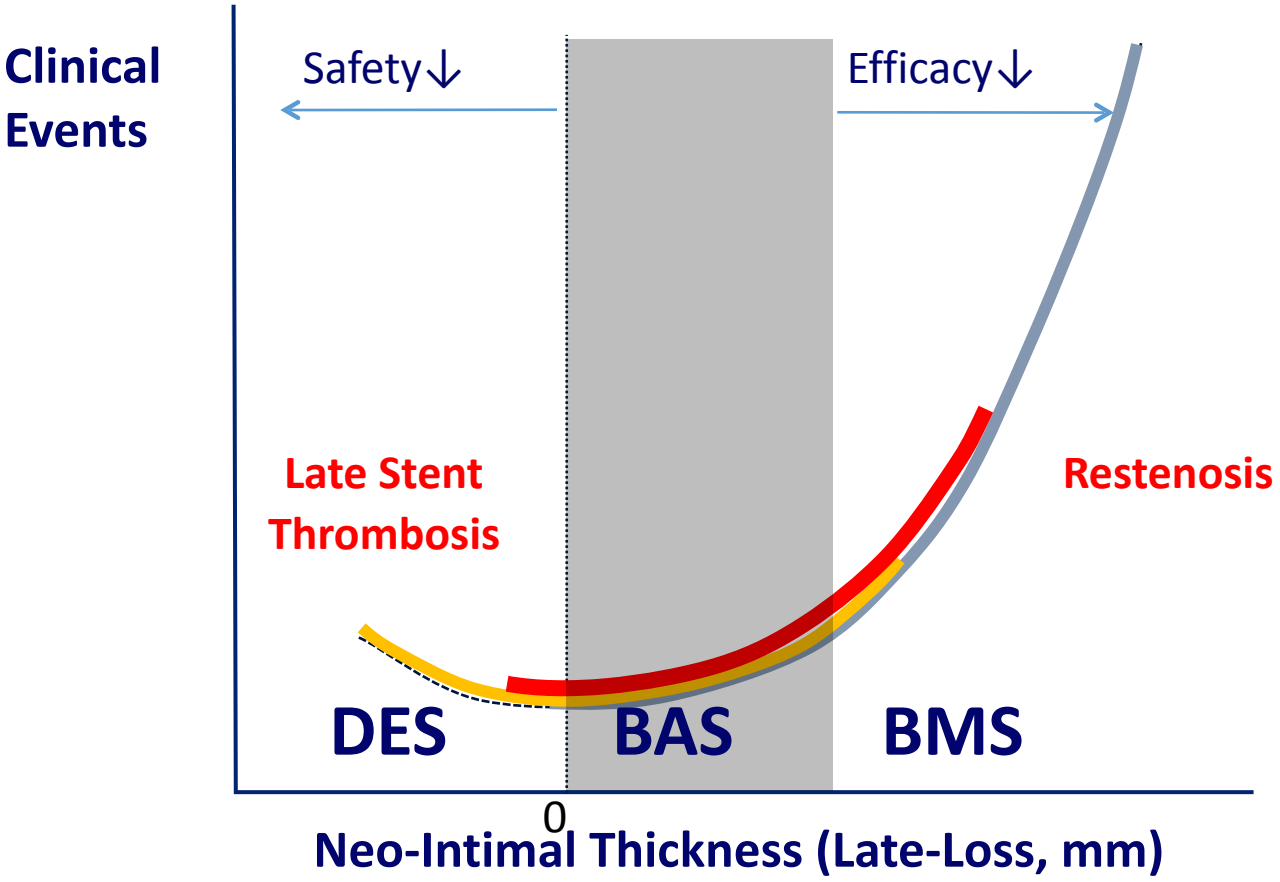
- Aujourd'hui, les Guidelines recommandent un virage à 180 degrés dans l'infarctus (STEMI/NSTEMI) en faisant la promotion du TOUT DES.
- Sur quelles preuves ?
- Peu/pas d' étude dans le NSTEMI…
- 2 gdes études dans le STEMI (EXAMINATION=> endpoint primaire non atteint, problèmes méthodologiques et COMFORTABLE AMI=> stent nu comparateur de 120 microns)
- IVUS à 5 ans ds COMFORTABLE AMI (2.1% vs 0.15%)

2014 ESC/EACTS Guidelines on myocardial revascularization

NSTEMI

The safety and efficacy of DES have not been prospectively tested in a specific population of patients with NSTE-ACS, but this subset comprises up to 50% of patients included in most stent trials particularly those with an all-comer design. There is no particular safety concern in NSTE-ACS as new-generation DES have shown superior safety and efficacy in both SCAD and STEMI patients. Accordingly, new-generation DES are preferred over BMS as the default option.[196] Dual antiplatelet therapy (DAPT) should be maintained for 12 months, irrespective of stent type.

Trading-Off Safety and Efficacy



2018 euroPCR

OPTIMAX OCT
Faster and more complete healing by TiNOX coated stents in ACS patients

Bernard De Bruyne

Cardiovascular Center Aalst, Belgium

Methods

OPTIMAX-OCT

- Patients with STEMI or Non-STEMI
- Native arteries
- Length <24 mm

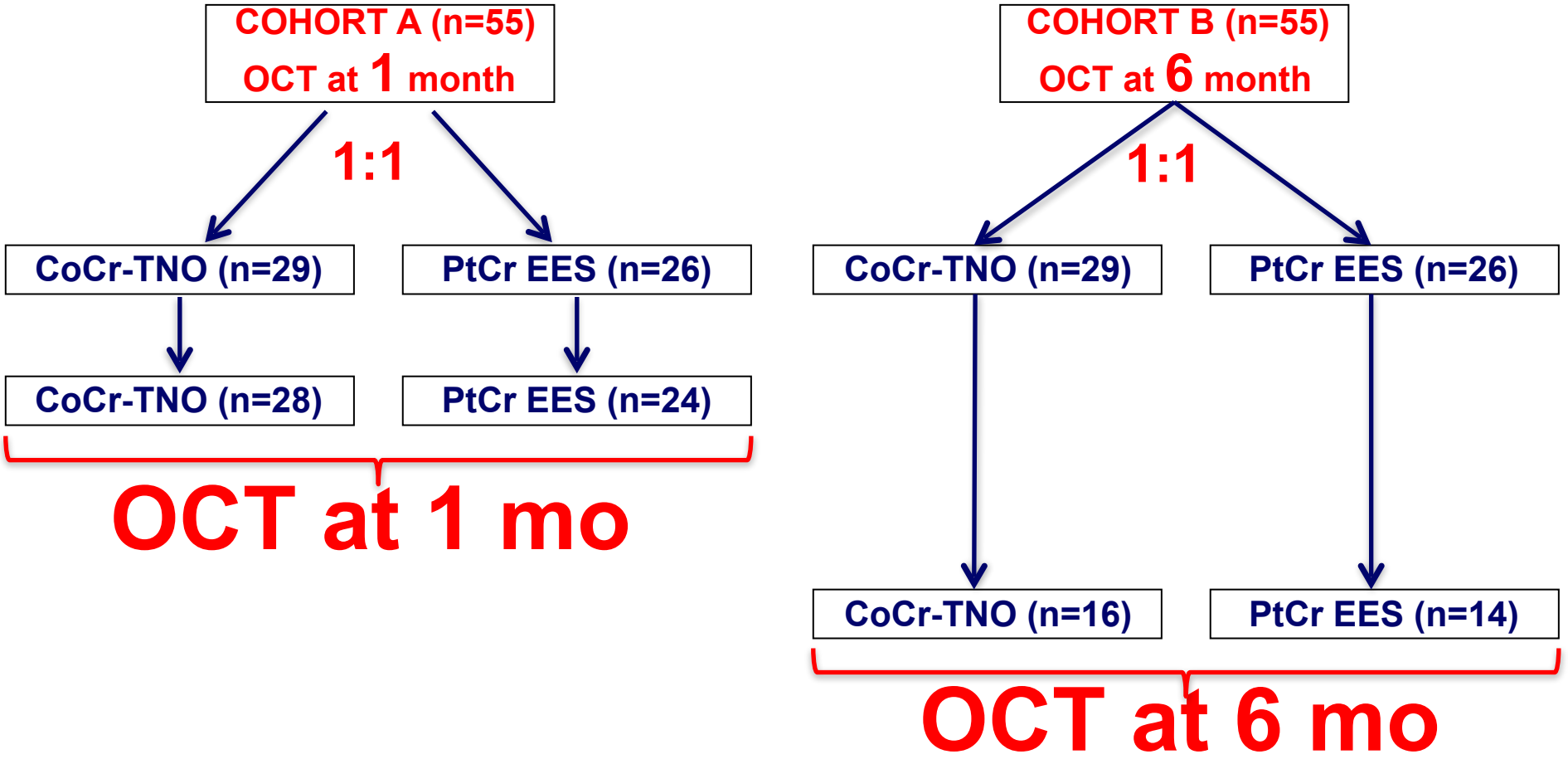
- Cohort A: OCT at 1 month
- Cohort B: OCT at 6 months

- Blinded OCT analysis
  - ✓ Luminal area
  - ✓ NIH area
  - ✓ Percentage uncovered struts
  - ✓ Malapposed struts
  - ✓ NIH tickness
  - ✓ Malapposition distance

Flow Chart

OPTIMAX-OCT

110 patients with ACS (STEMI or NSTEMI)

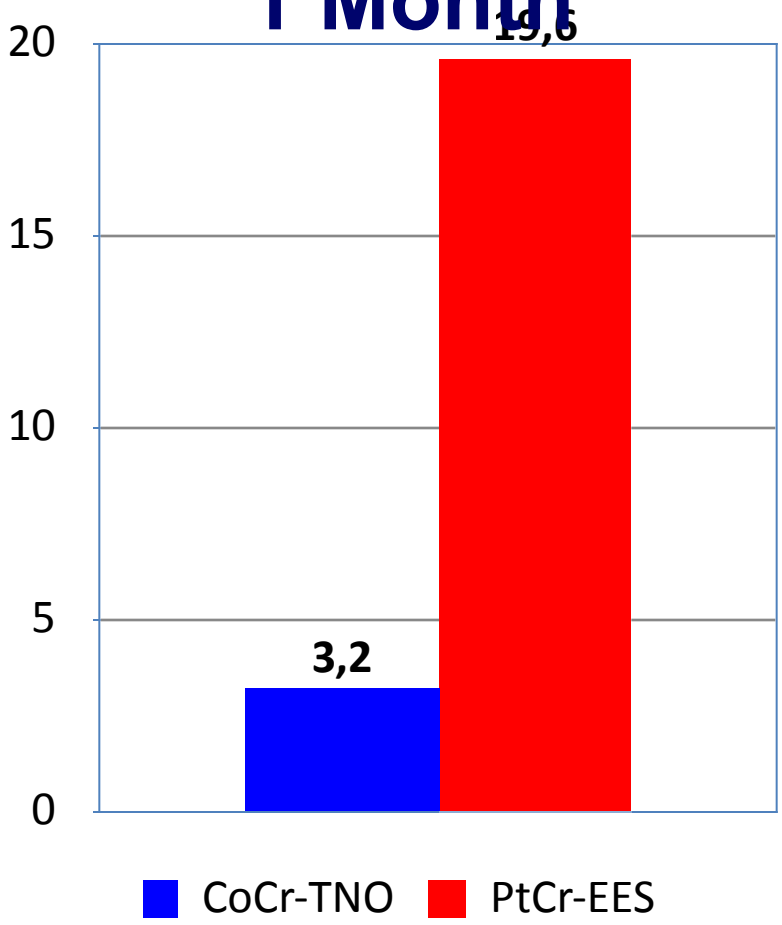


Results

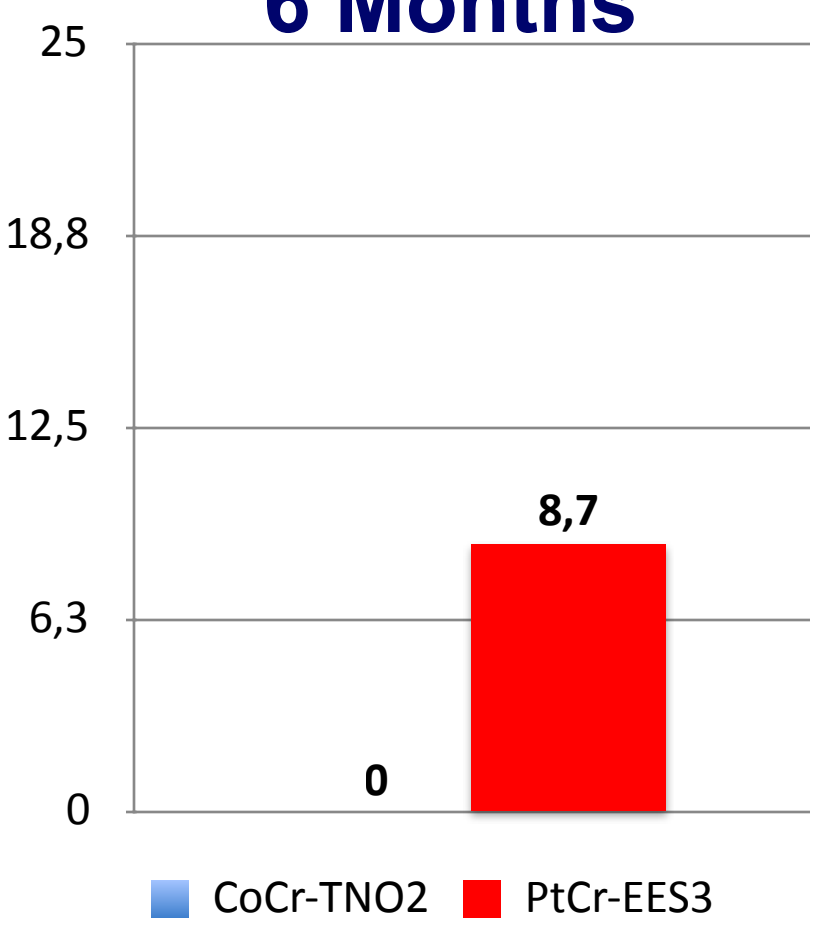
OPTIMAX-OCT

Uncovered Struts (% of pts)

1 Month



6 Months

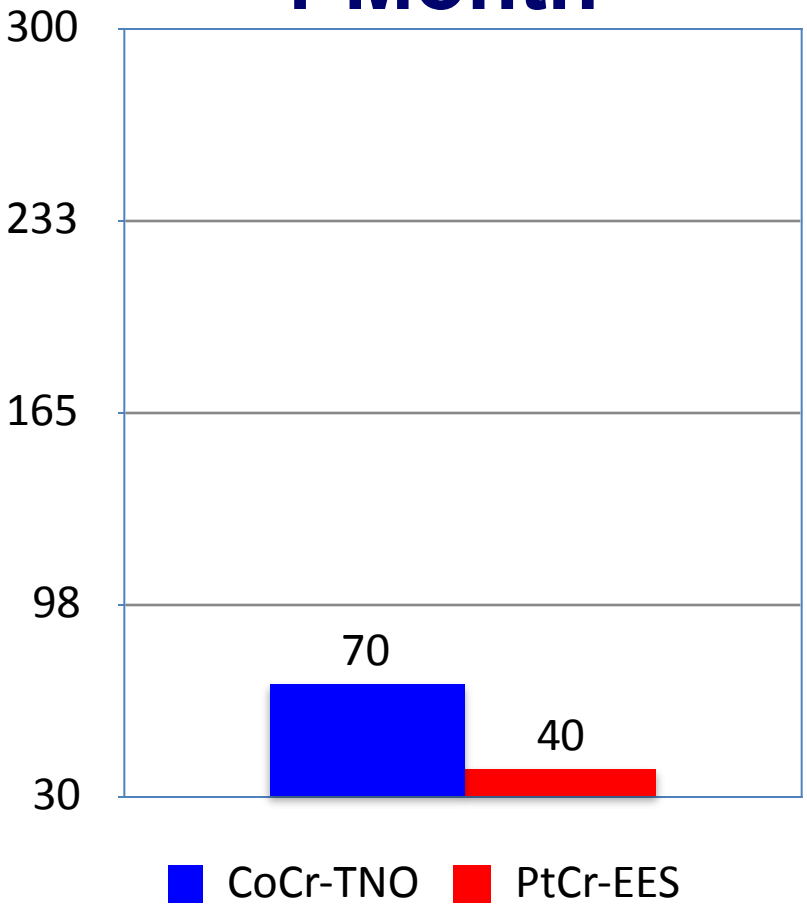


Results

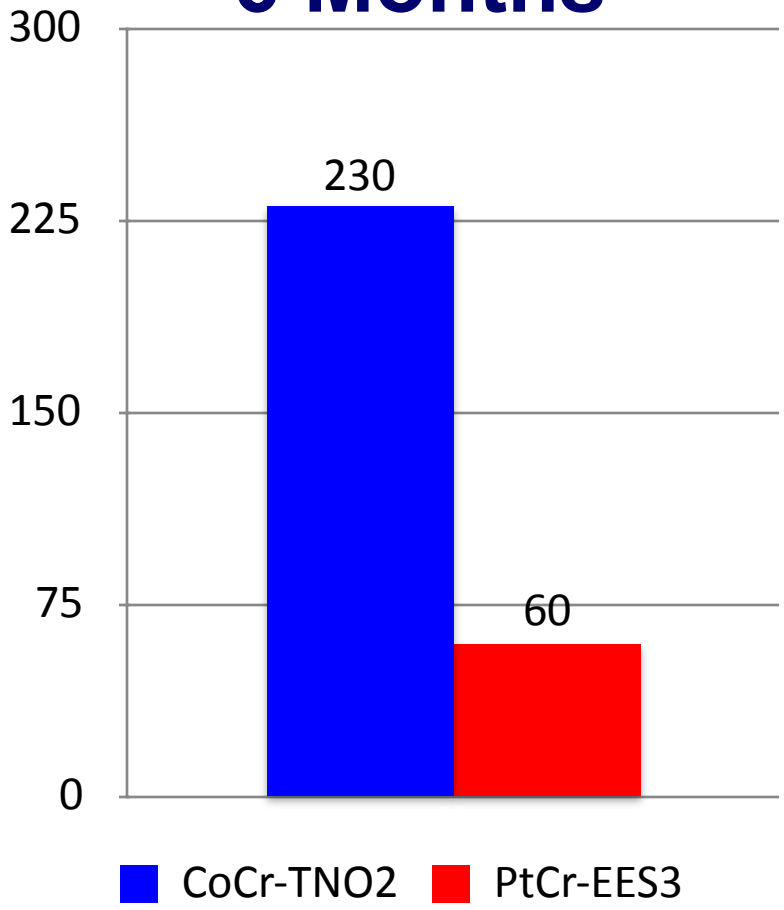
OPTIMAX-OCT

NIH Tickness (micrometer)

1 Month



6 Months



Results

Restenosis Rate at 6 Months

Synergy: 0%

OPTIMAX: 0%

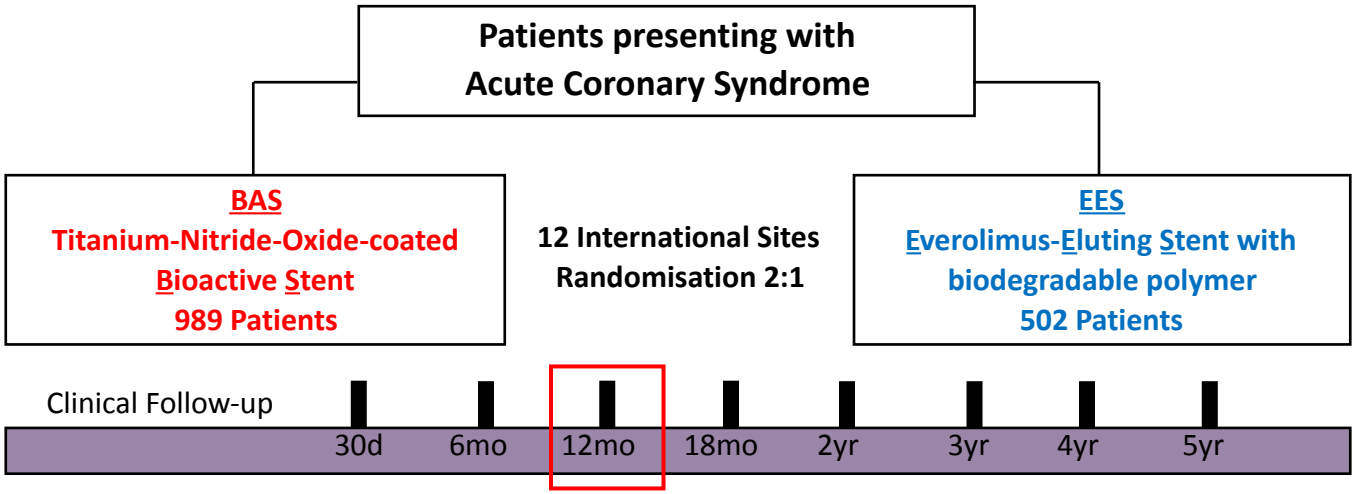
Summary

In patients with ACS, CoCr-TNO-stent (OPTIMAX) implantation was associated with lower rates of uncovered and malapposed struts, as compared to PtCr-BP EES (SYNERGY)

Neo-intimal thickness was larger and luminal aere was smaller with the CoCr-TNO-stent (OPTIMAX) as compared to PtCr-BP EES (SYNERGY)

The restenosis rate after 6 months rate is 0% after both stents

TIDES-ACS



Primary Endpoint: MACE (Cardiac death, MI, and TLR) at 12 months

Co-Primary Endpoint: Cardiac death, MI, major bleeding at 18 months

PI *P Karjalainen (FIN)*

Co-PI *K Kervinen (FIN), J van Der Heyden (NED), H Romppanen (FIN), P Tonino (NED)*

CEC *J Marco (FRA), A de Belder (UK), R Wiseth (NOR), J Gomez-Hospital (SPA), D Formigli (ITA)*

ClinicalTrials.gov: NCT02049229
Minerva Cardioangiol. 2015;63:21-9.

TIDES-ACS Clinical Characteristics

	BAS (n=989)	EES (n=502)	P value
Age (years)	62.7 ± 11.0	62.6 ± 10.5	0.85
Male (%)	75.3	76.3	0.70
Diabetes (%)	14.2	12.5	0.43
- Insulin treated (%)	2.3	3.8	0.14
Hyperlipidemia (%)	41.5	40.2	0.66
Hypertension (%)	46.8	43.6	0.25
Current smoker (%)	31.2	35.9	0.08
Prior myocardial infarction (%)	7.6	9.0	0.37
Prior PCI (%)	7.0	6.6	0.83
Prior CABG (%)	0.6	1.2	0.23
NSTEMI (%)	46.3	45.0	0.66
STEMI (%)	44.9	47.6	0.32

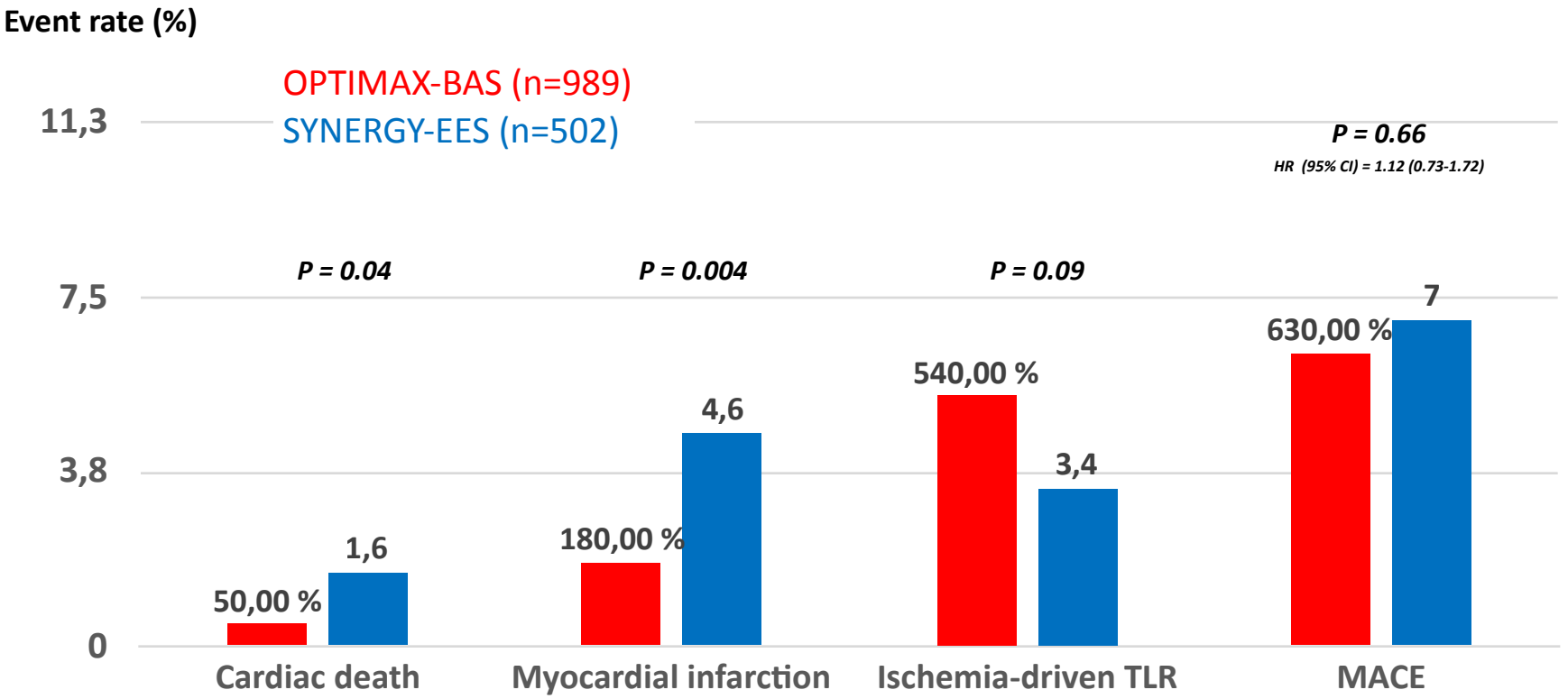
TIDES-ACS Devices

	Cobalt-chromium-based BAS (OPTIMAX™)	Platinum-chromium-based biodegradable-polymer EES (SYNERGY™)
Stent Platform	Cobalt-chromium platform Helicoidal Design Strut thickness 75 µm	Platinum-chromium platform Slotted Tube Strut thickness (74-81) µm
Drug	---	Everolimus
Drug Density	---	100 µg/cm^2
Coating	Titanium-Nitride-Oxide	---
Polymer	---	Abluminal poly (D,L-lactide-co-glycolide) (4 µm)
Manufacturer	Hexacath, Paris, France	Boston Scientific Corp. MA. USA

TIDES-ACS Clinical Sites

Investigators	Hospital	n
J Lalmand	C.H.U. de Charleroi, Charleroi, Belgium	50
P Tonino	Heartcenter Catharina Hospital, Eindhoven, Netherlands	391
M Laine, M Pentikäinen	Helsinki University Hospital, Helsinki, Finland	27
J Sia, T Pinola	Kokkola Central Hospital, Kokkola, Finland	82
H Romppanen, A Perälä	Kuopio University Hospital, Kuopio, Finland	220
P Frambach	INCCI Luxembourg Hospital, Luxembourg	86
J van der Heyden	St Antonius Hospital, Nieuwegein, Netherlands	236
K Kervinen, M Niemelä	Oulu University Hospital, Oulu, Finland	128
P Karjalainen, W Nammas, J Mikkelsson	Satakunta Central Hospital, Pori, Finland	174
A Serra	Hospital Sant Pau, Barcelona, Spain	30
Dr. Vaquerino, M Fuertes	Hospital del Mar, Barcelona, Spain	17
M Pietilä, J Airaksinen	Turku University Hospital,Turku, Finland	50

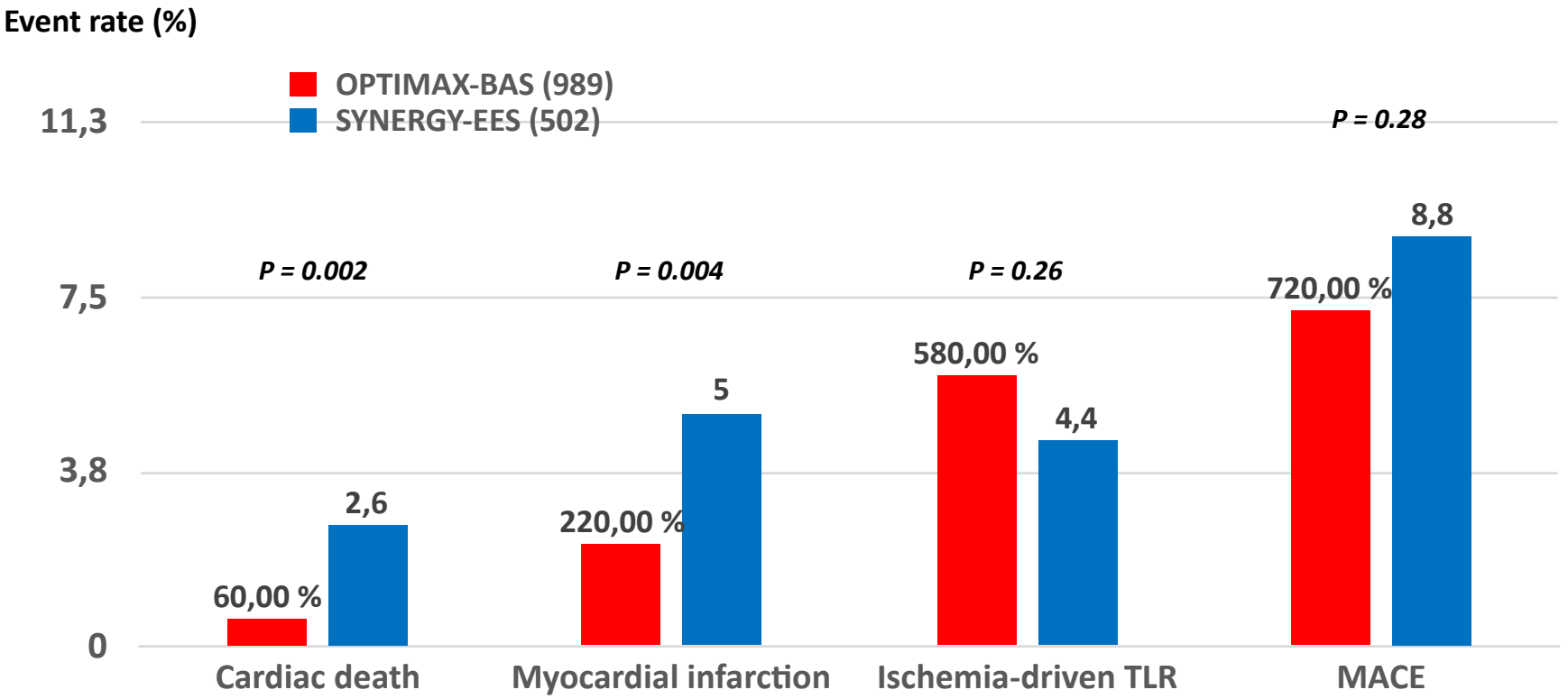
TIDES-ACS MACE at 12 months



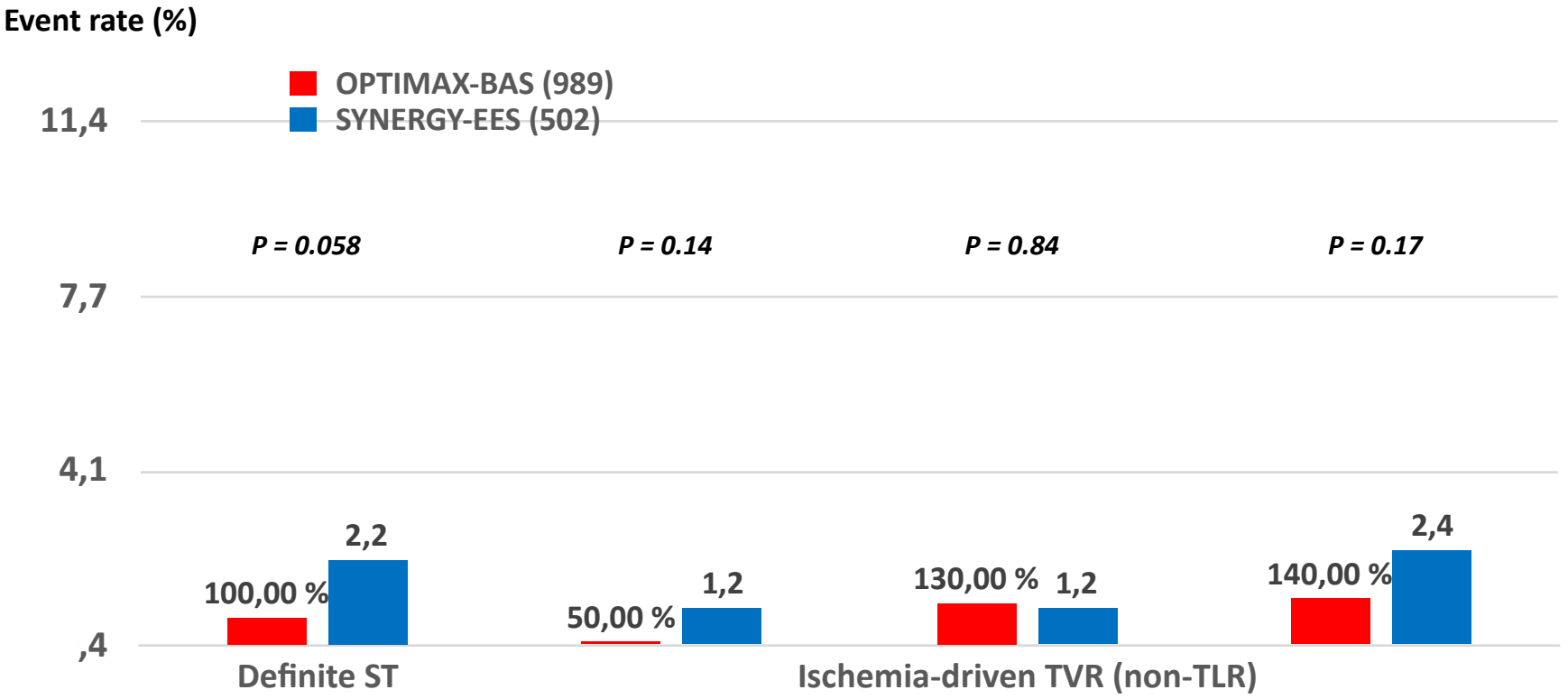
Definite stent thrombosis: 1.0% for BAS and 2.0% for EES (p=0.15)

ESC Meeting Barcelona 2017

TIDES-ACS MACE at 18 months

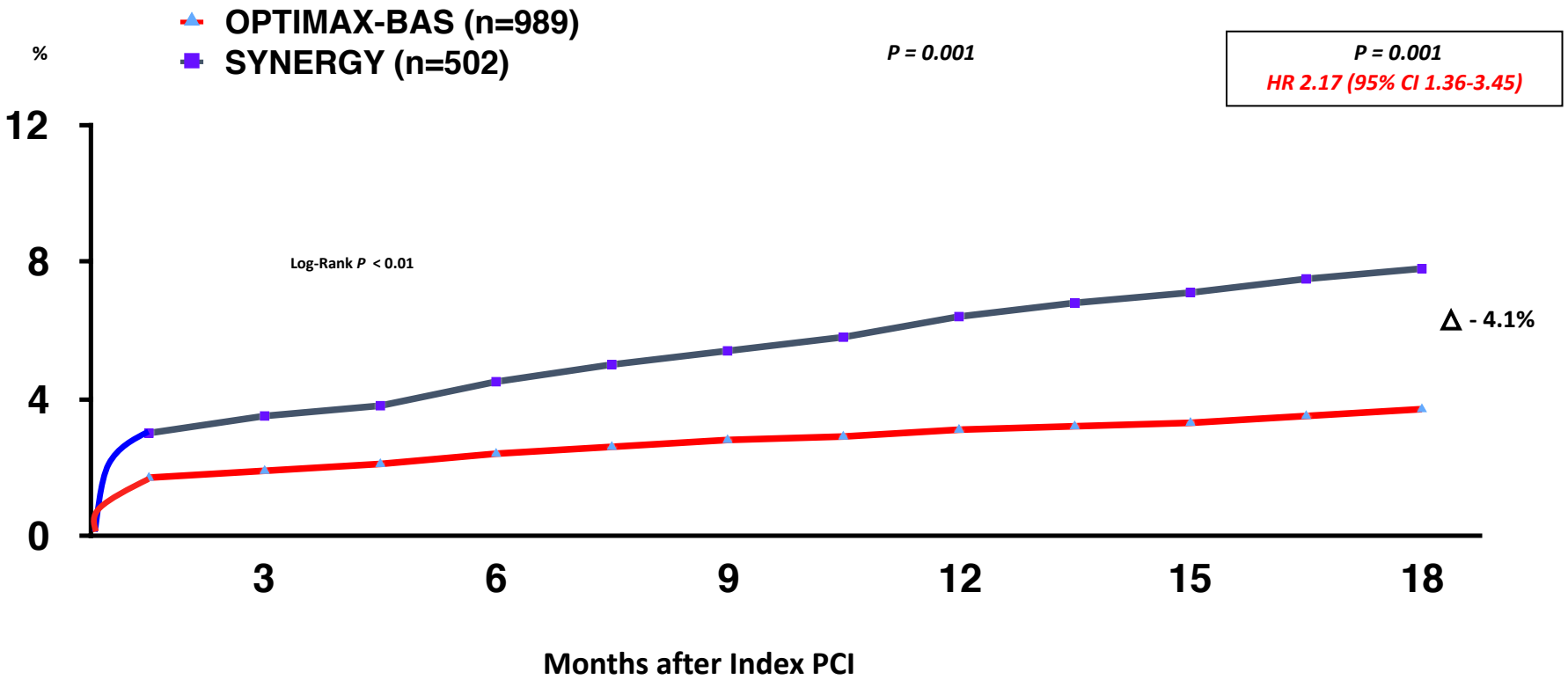


TIDES-ACS other events at 18 months



TIDES-ACS

Co-primary endpoint at 18 months



* Co-primary endpoint = myocardial infarction (MI), cardiac death and major bleeding

Conclusions

Le stent bioactif OPTIMAX n'est pas inférieur au stent délivrant de l'Evérolimus (SYNERGY) pour le 1er critère composite (mortalité cardiaque, infarctus, TLR).

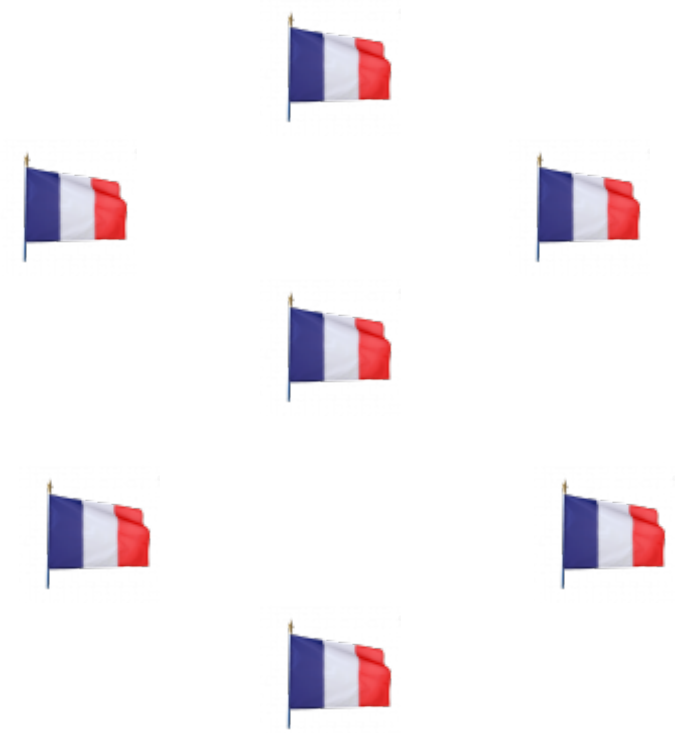
Le stent bioactif OPTIMAX apparait supérieur au stent délivrant de l'Evérolimus (SYNERGY) pour le 2ème critère composite (mortalité cardiaque, infarctus, hémorragie majeure).

Le stent bioactif semble une excellente alternative au DES ds la prise en charge des ACS…; pensez aux avantages de la ré-endothélialisation rapide et homogène…

- **L'étude TIDES ACS se heurte à une opposition de l'industrie (US ?? et autres) et n'est toujours pas publiée par… mépris… ?**
- **En l'état une métanalyse réalisée par F. Daoud (Pessac), présentée à l'AHA 2018 (montrant – de thrombose de stent à 1 an et 5 ans), est dans le même état que TIDES ACS…**
- **Il faudrait peut-être réagir en justifiant que les équipes qui font confiance à la France doivent soutenir son industrie dans des indications bien précises…**
- **J'ai connu des français plus chauvins…**

Prenez-soin aussi de votre patrimoine industriel…

Qui n’est pas (encore) le mien…



ne pose pas de questions
on va finir en retard !!


SE SOUVENIR DU NOM DE CINQ FRUITS ET LÉGUMES PAR JOUR
EST UN EXCELLENT EXERCICE CONTRE LA MALADIE D'ALZHEIMER

Back up slides

TIDES-ACS
ARC Stent Thrombosis at 12 months

	OPTIMAX BAS (n=989) n (%)	SYNERGY EES (n=502) n (%)	*P Value*
Definite ST	10 (1.0)	10 (2.0)	0.15
Probable ST	1 (0.1)	4 (0.8)	0.047
Definite or Probable ST	11 (1.1)	14 (2.8)	0.01

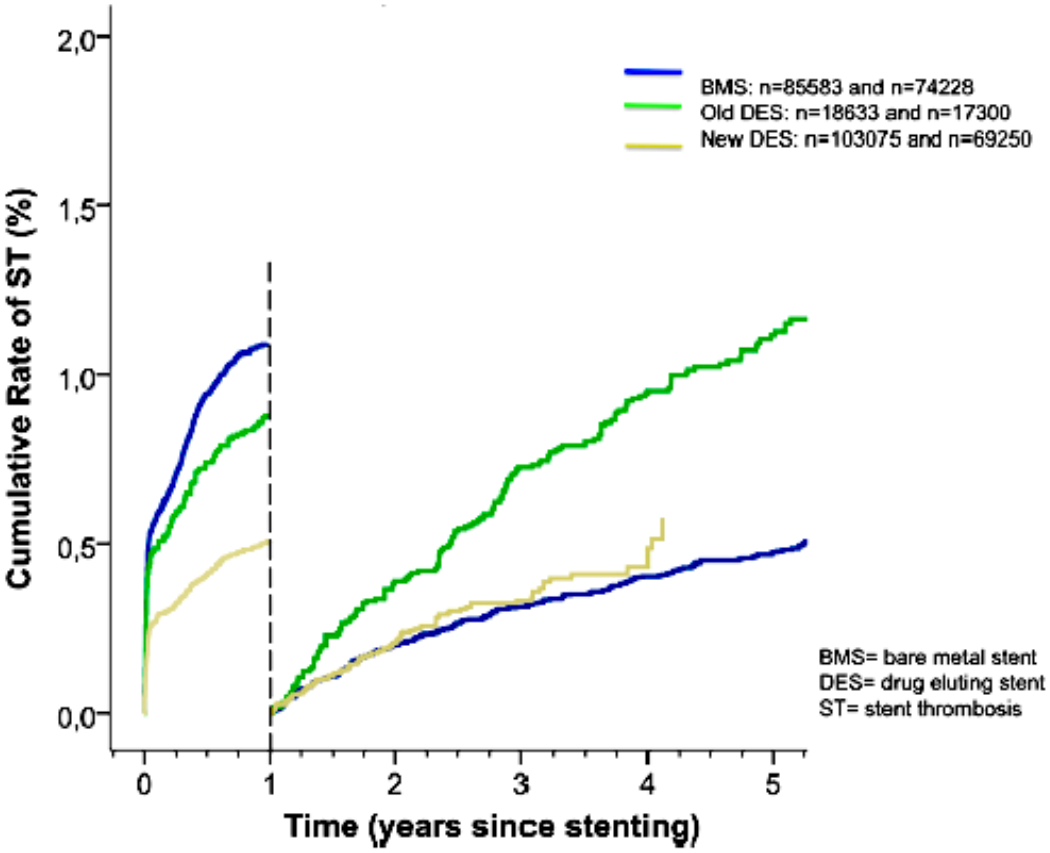
TIDES-ACS Lesion Characteristics

	BAS (n=989)	EES (n=502)	*P value*
No. of lesions treated/patient	1.17 ± 0.44	1.18 ± 0.49	0.83
2 or 3 vessels treated	36.0%	36.7%	0.75
RVD[a] (mm)	3.20 ± 0.45	3.21 ± 0.45	0.67
Lesion length (mm)	14.9 ± 6.5	14.8 ± 5.9	0.81
Culprit lesion location			
- LAD	45.7%	45.8%	0.86
- Cx	21.2%	20.0%	0.65
- RCA	33.0%	34.1%	0.56
B2/C type complex lesion	22.5%	21.7%	0.67
Thrombus in culprit lesion	33.1%	36.7%	0.18

[a] Reference vessel diameter

Stent thrombosis rates the first year and beyond with new- and old-generation drug-eluting stents compared to bare metal stents

Christoph Varenhorst[1,2] · Martin Lindholm[3] · Giovanna Sarno[1,2] · Göran Olivecrona[4] · Ulf Jensen[5] · Johan Nilsson[6] · Jörg Carlsson[7] · Stefan James[1,2] · Bo Lagerqvist[1,2]



Clinical Res Cardiol 2018

2007 – 2017
Stent BAS vs. Stents actif pour le SCA

2007

TiTAN vs TAXUS

(1st generation DES)

N=425

	1 an*	P	5 ans**	P
~~MACE~~	~~10.3 vs 12.8~~	~~NI~~	16.4 vs 25.1	0.03
Décès C.	0.5 vs 1.9	0.2	1.9 vs 5.7	0.04
IDM	4.2 vs 8.1	0.1	8.4 vs 18	0.004
Def. ST	0.4 vs 3.3	0.031	0.9 vs 7.1	0.001
TLR	9.3 vs 7.1	0.5	**11.2 vs 10.9**	0.92

*EuroIntervention 2008;4:234-241

**Int J Cardiol 2013 Sep 30; 168(2) 1214-9 doi

2011

TiTAN2 vs XIENCE V

(2nd generation DES)

N=827

1 an*	P	5 ans**	P
9.6 vs 9.0	NI	14.4 vs 17.8	0.26
1.9 vs 1.0	0.39	2.8 vs 3.8	0.76
2.2 vs 5.9	0.007	5.9 vs 9.7	0.028
0.7 vs 2.2	0.07	1.1 vs 3.8	0.015
6.5 vs 4.9	0.37	**8.3 vs 9.9**	0.58

*EuroIntervention 2012;8:306-315

**Int J Cardiol 222 (2016) 275-280

2017

TiTAN

OPTIMAX vs SYNERGY

(3rd generation DES)

N=1491

1 an*	P
6.3 vs 9.0	NI
0.5 vs 1.6	0.04
1.8 vs 4.6	0.004
0.7 vs 2.2	0.07
5.4 vs 3.4	0.09

*Late Breaking Science Session Congrès ESC Barcelone 2017