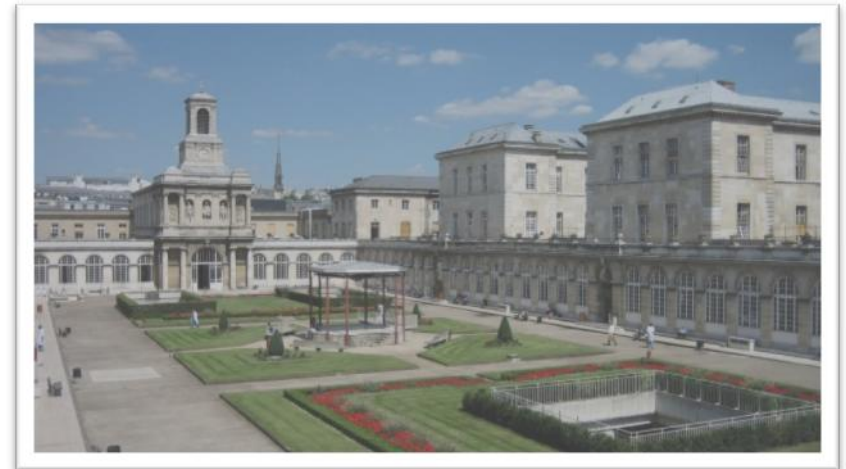


# Vers la fin des stents actifs avec polymère??

Georgios Sideris  
Hôpital Lariboisière Paris



# Vers la fin des stents actifs avec polymère??

- Pas de conflit d'intérêt majeur.....
  - Invité par B Braun
  - Investigateur étude SENIOR, e-Biomatrix.

Un polymère sinon rien...



## Merci B Braun...

- *Ainsi, nous sommes quasi obligés d'être malhonnête lors de controverse, ou tout du moins légèrement tentés de l'être. De cette façon, **la faiblesse de notre intelligence et la perversité de notre volonté se soutiennent mutuellement.***

# Un polymère sinon rien...

Thromboses de stent  
TVR ?  
Durée du tt AAP  
Angor stable?  
RIS  
Lésion longue?  
Diabète?  
SCA ?  
TLR ?

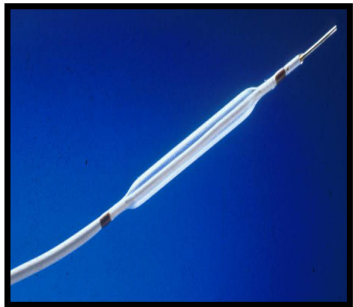
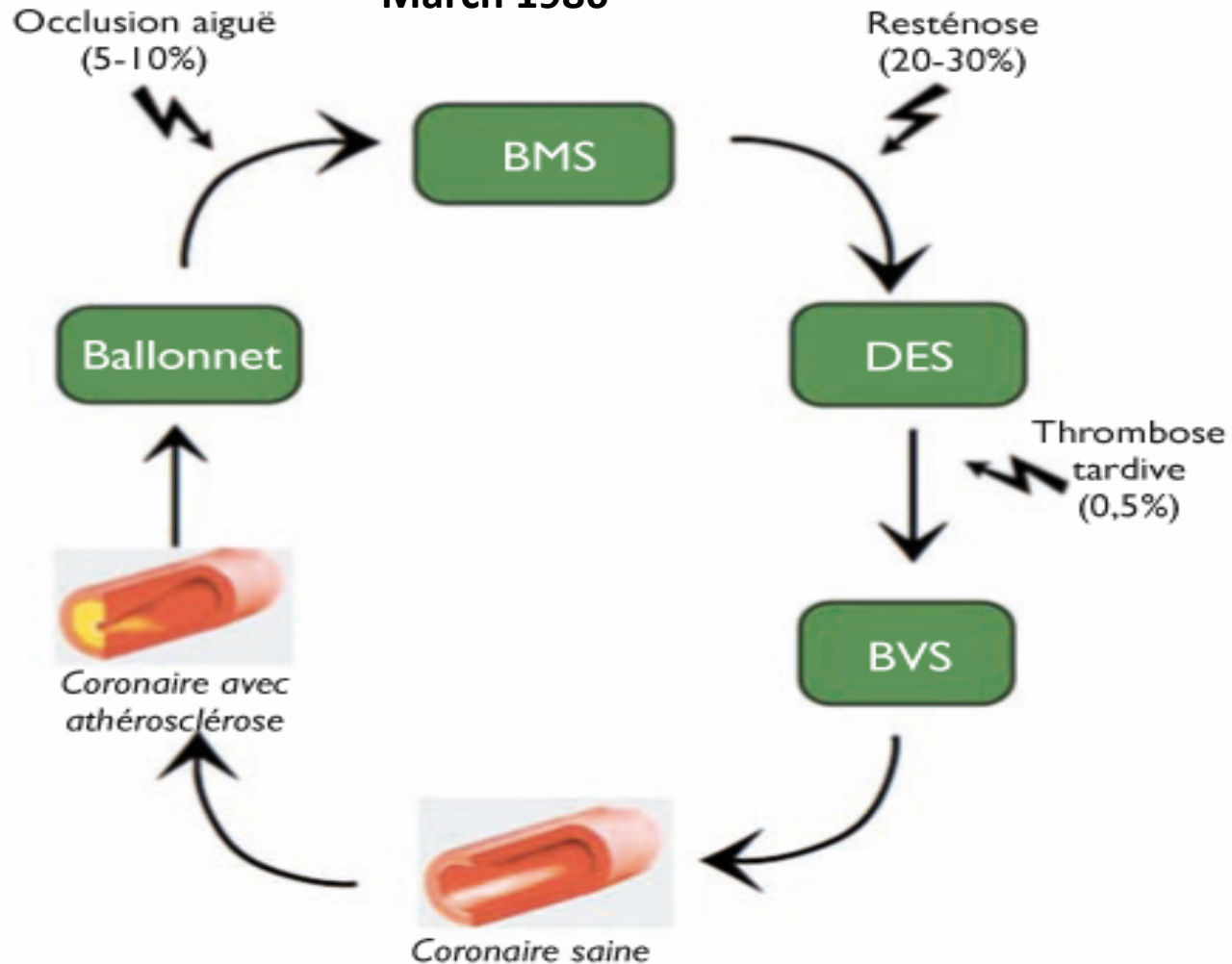


dreamstime



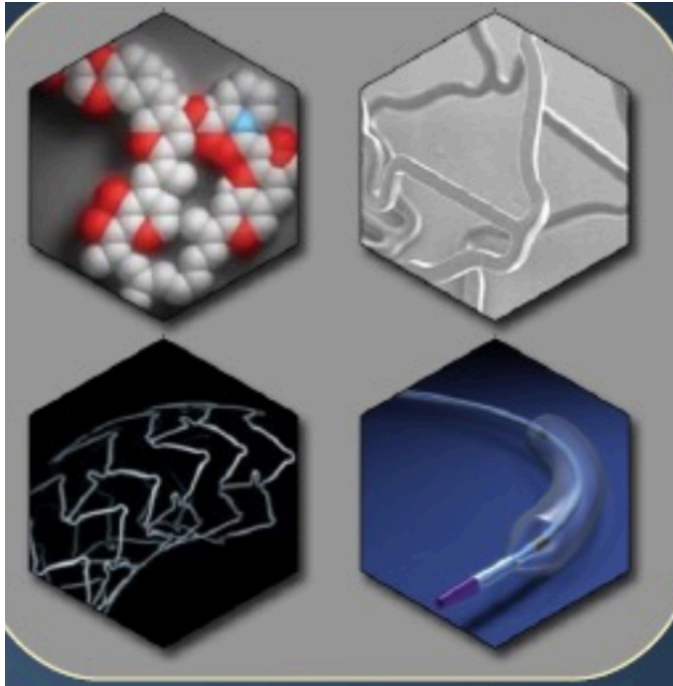
# ATL au ballon-Restauration artérielle

Jacques Puel  
March 1986



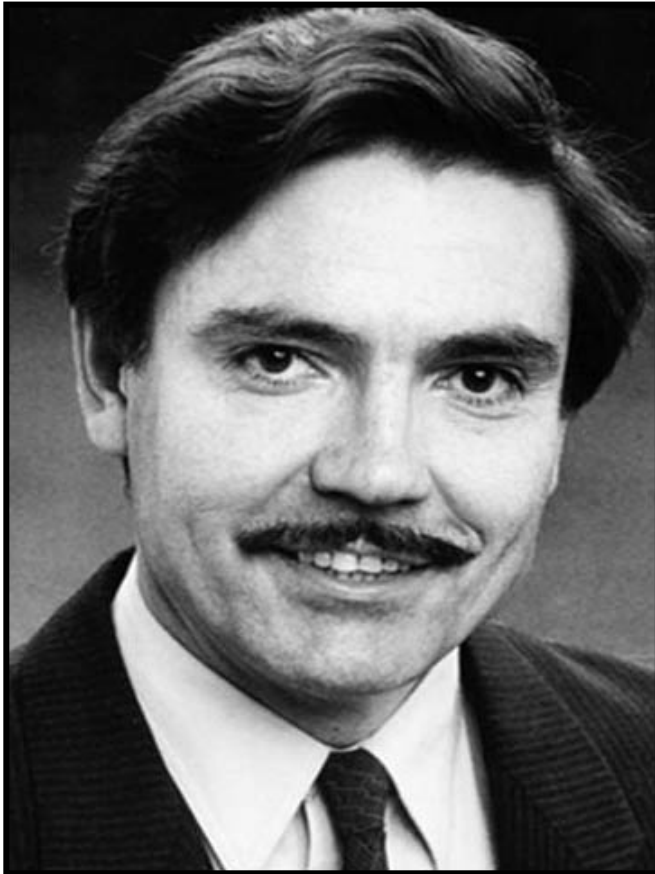
Zurich  
1977

## Un polymère sinon rien...



*Les grands hommes marchent sur leur ombre : Ils anticipent l'avenir.*

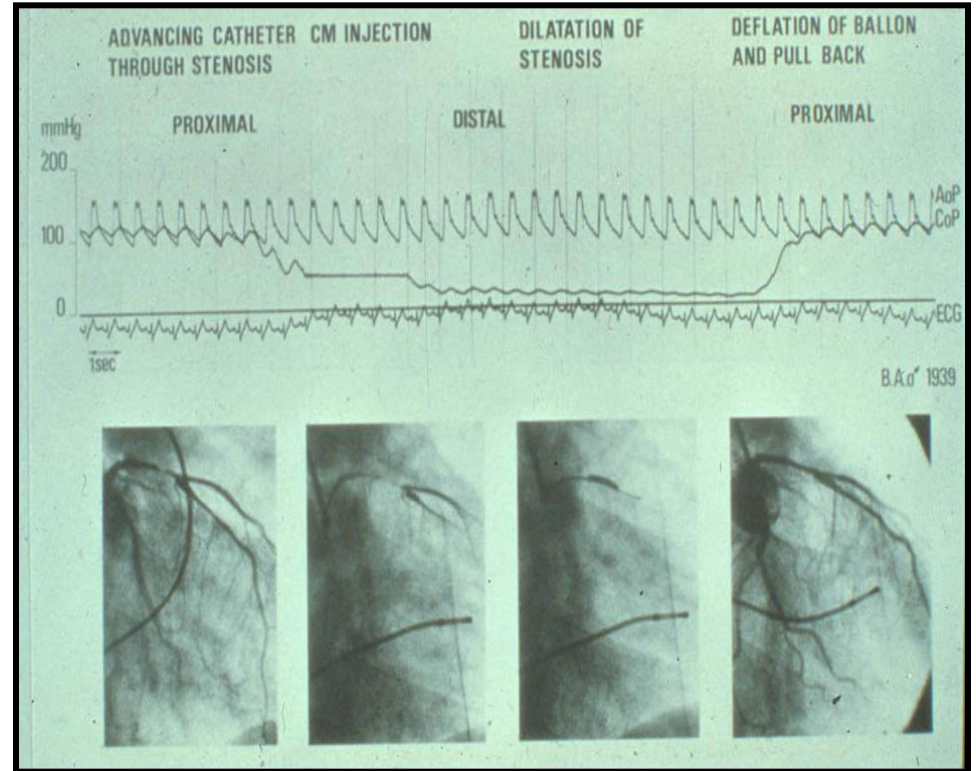
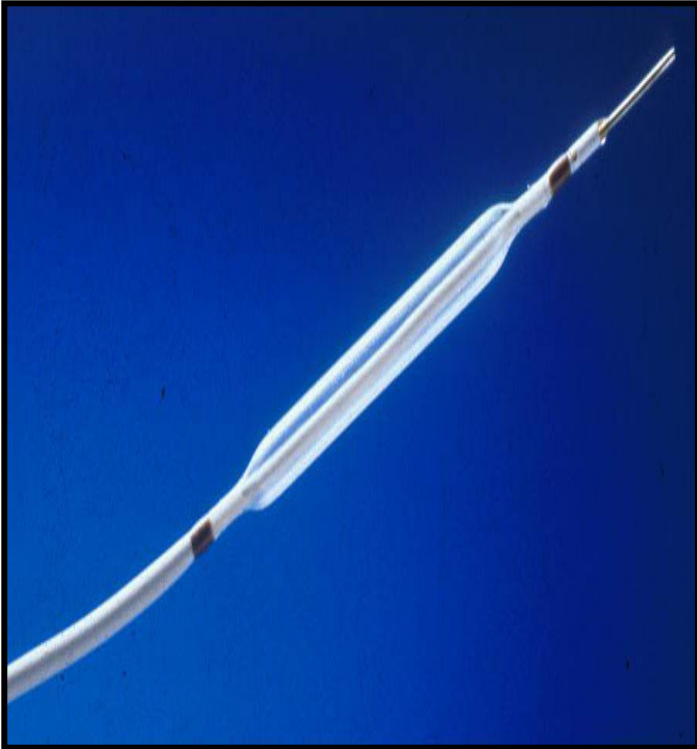
# ATL au ballon-Restauration artérielle



Andreas Roland Gruentzig  
(1939–1985)



# The first coronary angioplasty in Zurich 1977



First coronary balloon catheter as used in the initial series of patients

## ATL au ballon : limites..

### Influence of Balloon Size on Initial Success, Acute Complications, and Restenosis After Percutaneous Transluminal Coronary Angioplasty

#### A Prospective Randomized Study

Gary S. Roubin, MB, PhD, John S. Douglas Jr., MD,  
Spencer B. King III, MD, Sufen Lin, MS, Nancy Hutchison, BSN,  
Ronald G. Thomas, PhD, and Andreas R. Gruentzig, MD

*Circulation* Vol 78, No 3, September 1988

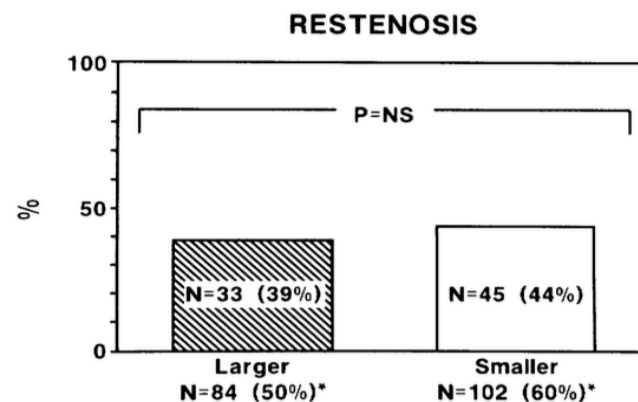


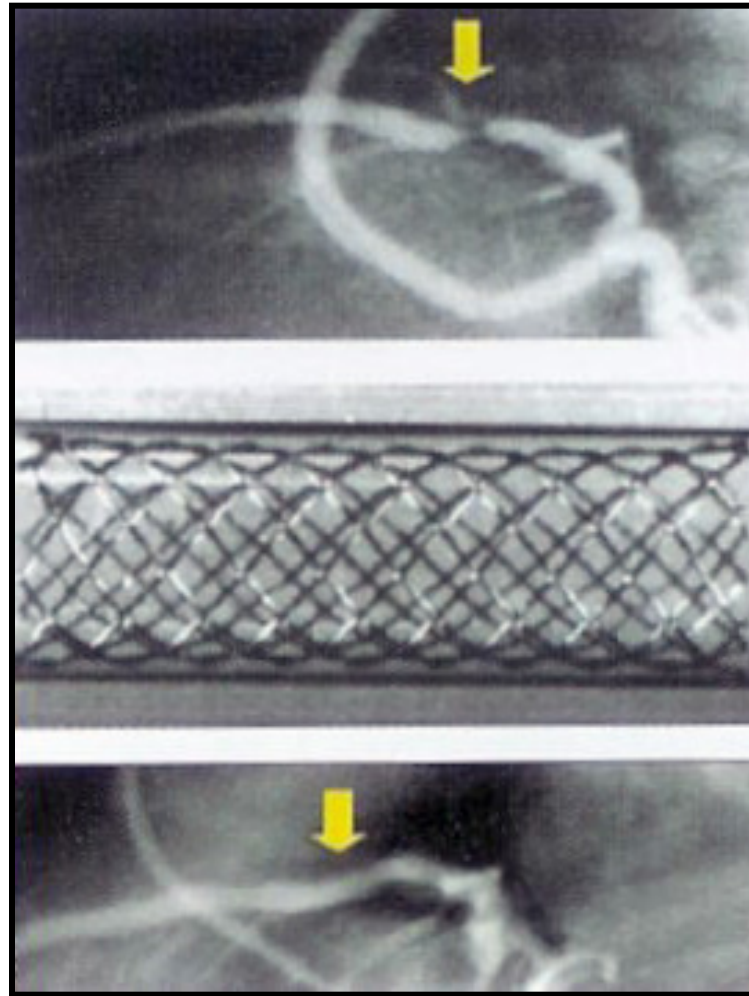
FIGURE 3. Incidence of restenosis in the two treatment groups. (%)\*Represents the angiographic restudy rates in the two groups (p=NS).

TABLE 3. Acute Complications

	Total (n = 336)	Larger balloon (n = 169)	Smaller balloon (n = 167)	p
Total MI	18 (5.4%)	13 (7.7%)	5 (3%)	0.056
Q wave MI	4 (1.2%)	3 (1.8%)	1 (0.6%)	
Non-Q wave MI	14 (4.2%)	10 (5.9%)	4 (2.4%)	
CABG				
Total	19 (5.7%)	13 (7.7%)	6 (3.6%)	
Emergency	18 (5.4%)	12 (7.1%)	6 (3.6%)	0.15
Elective	1 (0.3%)	1 (0.6%)	0	
Death	0	0	0	

MI, myocardial infarction; CABG, coronary artery bypass graft surgery.

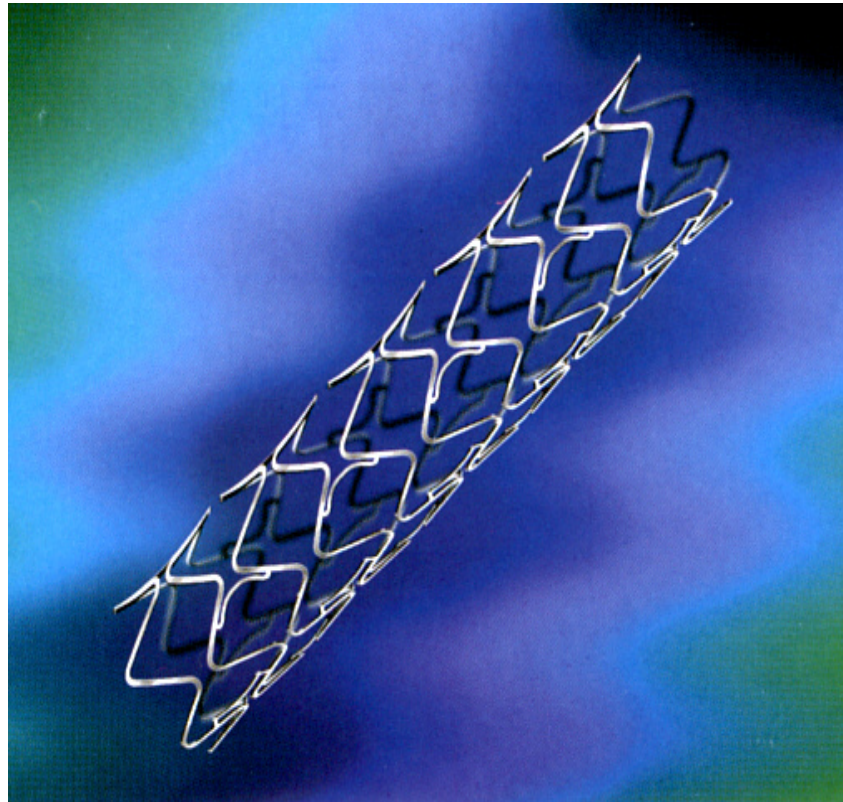
# The first stent implantation in man



First stent implantation in man (Jacques Puel, March 1986)

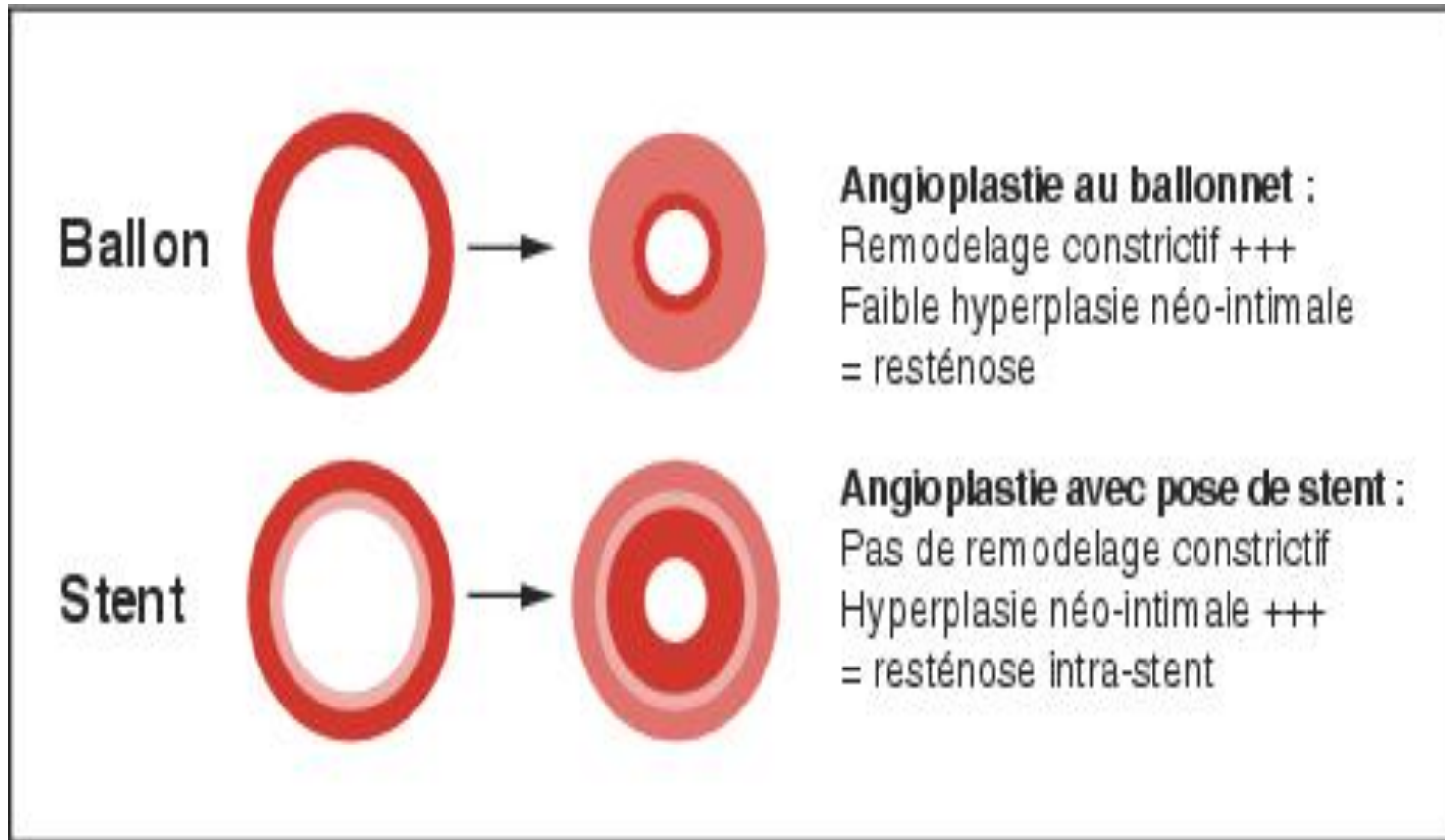
# BMS

**316 L**  
**Co-Cr**  
**Pt-Cr**

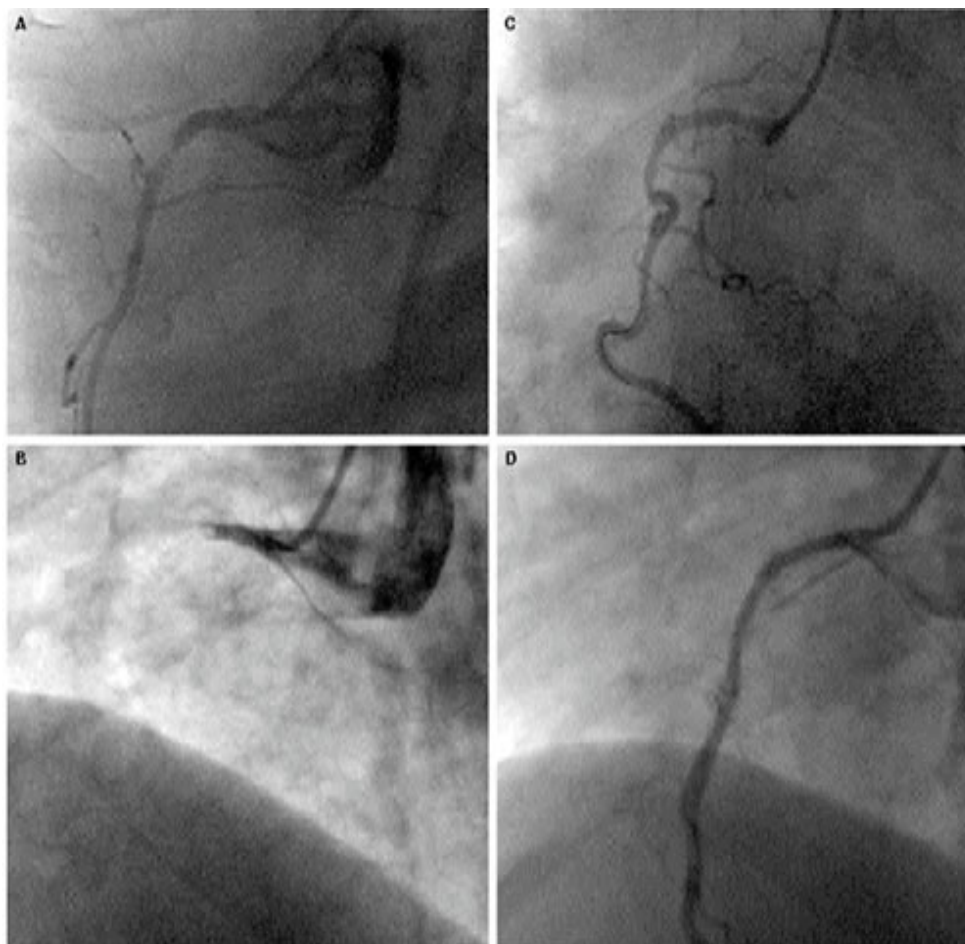


**Force radiale**  
**Flexibilité**  
**Conformabilité**

# ATL au ballon-Restauration artérielle



# Thrombose de stent.....



**Figure 1.** (A) Stenosis in the right coronary artery (RCA) on first presentation. (B) Total in-stent thrombosis in the proximal right coronary artery (RCA). (C) Thrombotic occlusion of the RCA was recanalized with simple balloon angioplasty. (D) TIMI II-III flow in the RCA after balloon angioplasty.

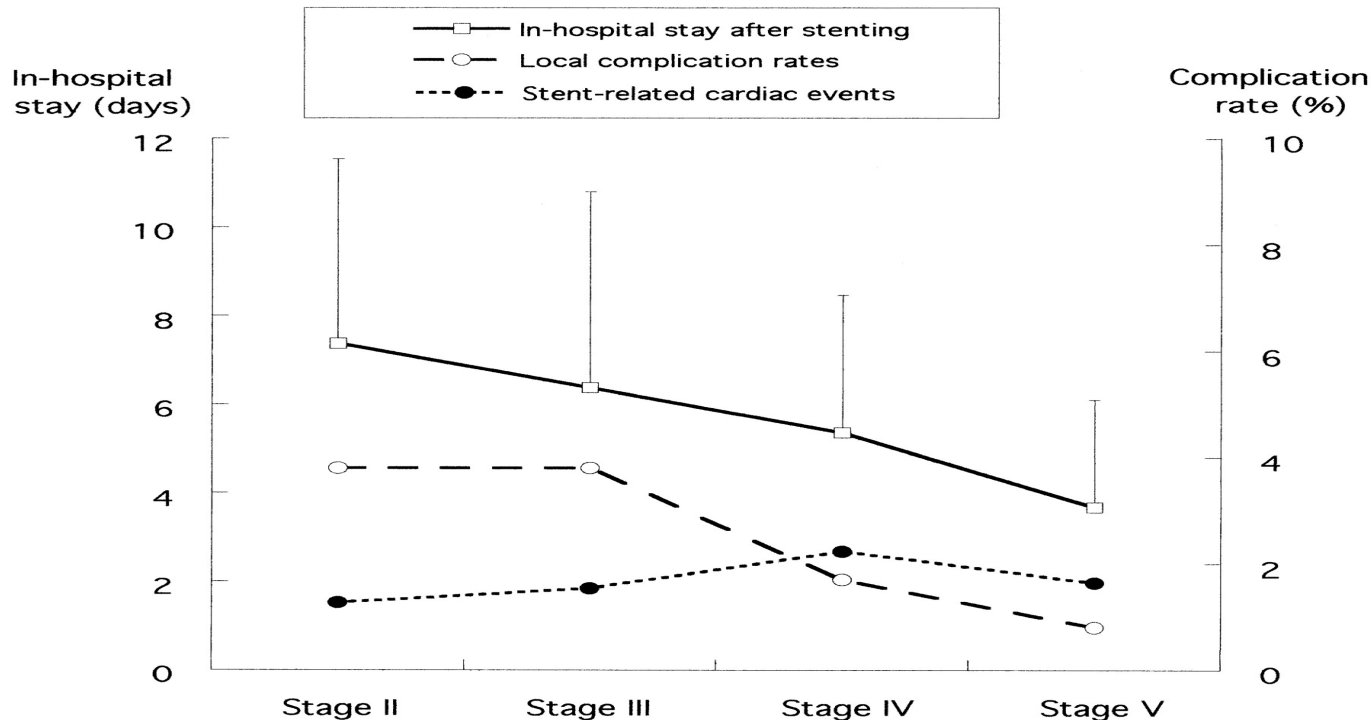
# La solution.....

## Intracoronary Stent Implantation Without Ultrasound Guidance and With **Replacement of Conventional Anticoagulation by Antiplatelet Therapy**

30-Day Clinical Outcome of the French Multicenter Registry

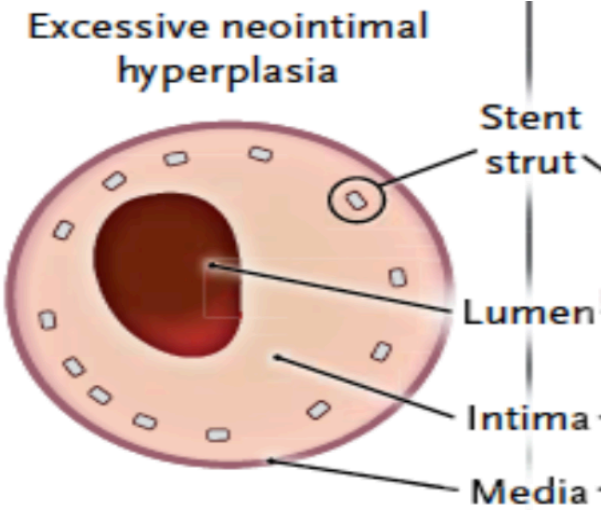
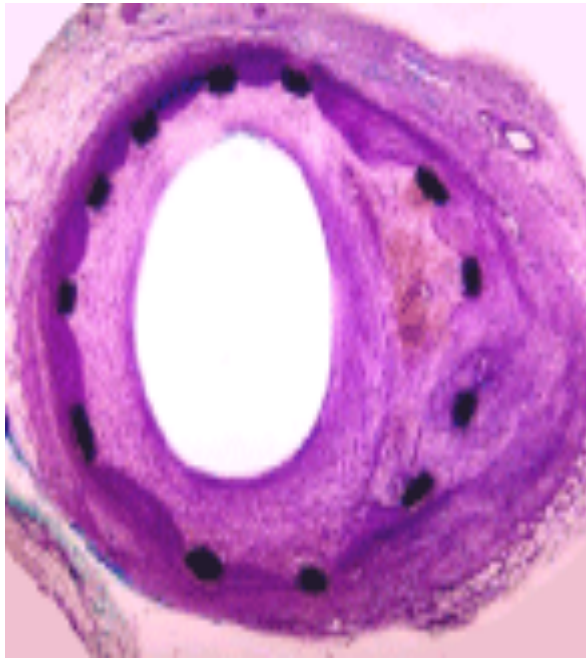
Gaetan J. Karrillon et al

**In-hospital stay after stenting procedure, stent-related cardiac events, and local bleeding complication rates during the different phases of the study.**



# Resténose intra-stent

BMS

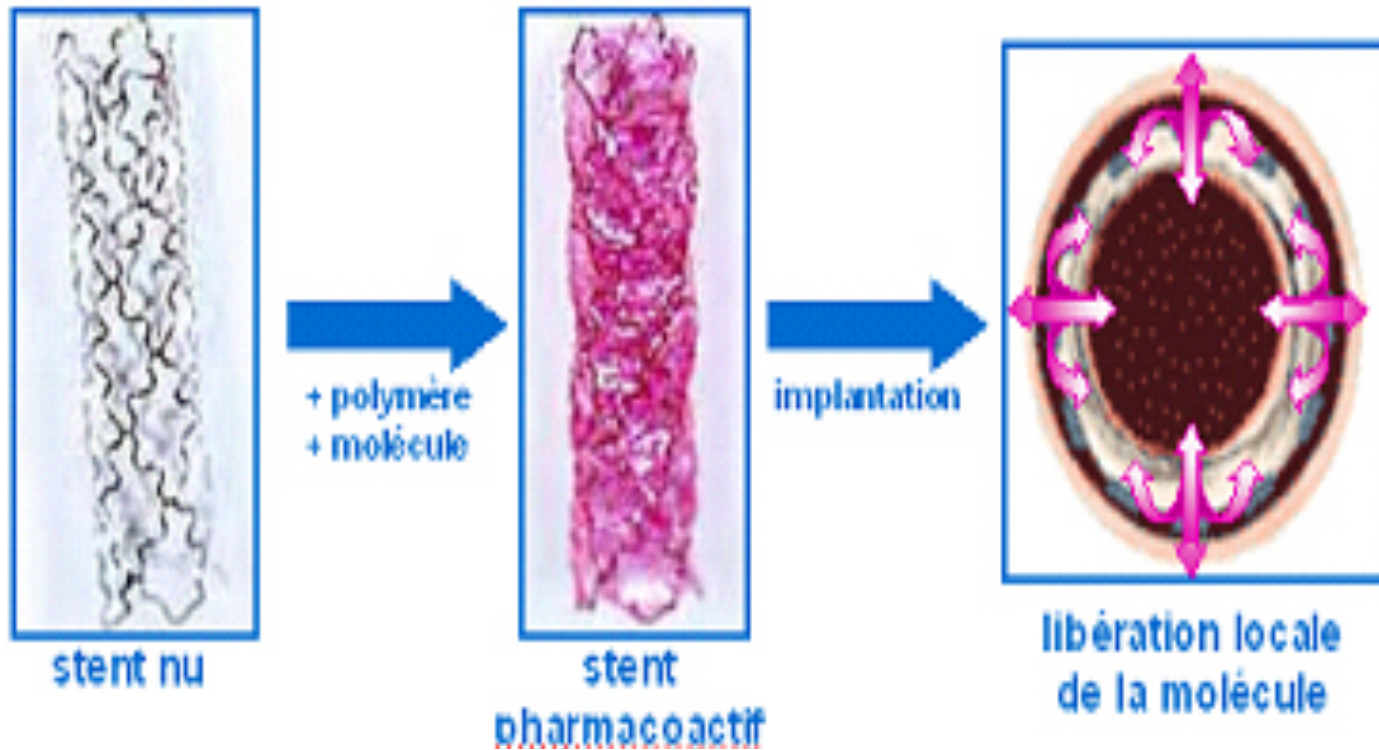


Stefanini GG, N Engl J Med 2013;368:254-65

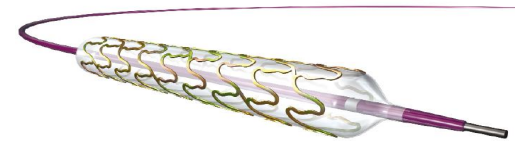
BMS



# La solution.....



# Endoprothèses coronaires actives: l'idéal....



## The New England Journal of Medicine

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VOLUME 346

JUNE 6, 2002

NUMBER 23



### A RANDOMIZED COMPARISON OF A SIROLIMUS-ELUTING STENT WITH A STANDARD STENT FOR CORONARY REVASCULARIZATION

MARIE-CLAUDE MORICE, M.D., PATRICK W. SERRUYS, M.D., PH.D., J. EDUARDO SOUSA, M.D., JEAN FAJADET, M.D.,  
ERNESTO BAN HAYASHI, M.D., MARCO PERIN, M.D., ANTONIO COLOMBO, M.D., G. SCHULER, M.D., PAUL BARRAGAN, M.D.,  
GIULIO GUAGLIUMI, M.D., FERENC MOLNÁR, M.D., AND ROBERT FALOTICO, PH.D., FOR THE RAVEL STUDY GROUP\*

# The New England Journal of Medicine

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VOLUME 346

JUNE 6, 2002

NUMBER 23



## A RANDOMIZED COMPARISON OF A SIROLIMUS-ELUTING STENT WITH A STANDARD STENT FOR CORONARY REVASCULARIZATION

REVASCULARIZATION AT 1, 6, AND 12 MONTHS.

**Results** At six months, the degree of neointimal proliferation, manifested as the mean ( $\pm$ SD) late luminal loss, was significantly lower in the sirolimus-stent group ( $-0.01 \pm 0.33$  mm) than in the standard-stent group ( $0.80 \pm 0.53$  mm,  $P < 0.001$ ). None of the patients in the sirolimus-stent group, as compared with 26.6 percent of those in the standard-stent group, had restenosis of 50 percent or more of the luminal diameter ( $P < 0.001$ ). There were no episodes of stent thrombosis. During a follow-up period of up to one year, the overall rate of major cardiac events was 5.8 percent in the sirolimus-stent group and 28.8 percent in the standard-stent group ( $P < 0.001$ ). The difference was due entirely to a higher rate of revascularization of the target vessel in the standard-stent group.

**Conclusions** As compared with a standard coronary stent, a sirolimus-eluting stent shows considerable promise for the prevention of neointimal proliferation, restenosis, and associated clinical events. (N Engl J Med 2002;346:1773-80.)

Copyright © 2002 Massachusetts Medical Society.

# Le doute.....

Monday, March 5, 2007 Last Update: 8:12 AM ET

## **Reconsidering Heart Bypass Surgery**

After more than a decade-long decline, is bypass surgery poised for a comeback?



# Thromboses tardives avec stent actifs??....

Lancet 2004;364:1519

## Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy

Eugène P McFadden, Eugenio Stabile, Evelyn Regar, Edouard Cheneau, Andrew T L Ong, Timothy Kinnaird, William O Suddath, Neil J Weissman, Rebecca Torguson, Kenneth M Kent, August D Pichard, Lowell F Satler, Ron Waksman, Patrick W Serruys

Although the safety profiles of coronary stents eluting sirolimus or paclitaxel do not seem to differ from those of bare metal stents in the short-to-medium term, concern has arisen about the potential for late stent thromboses related to delayed endothelialisation of the stent struts. We report **four cases of angiographically-confirmed stent thrombosis that occurred late after elective implantation of polymer-based paclitaxel-eluting (343 and 442 days) or sirolimus-eluting (335 and 375 days) stents, and resulted in myocardial infarction. All cases arose soon after antiplatelet therapy was interrupted.** If confirmed in systematic long-term follow-up studies, our findings have potentially serious clinical implications.

Metallic coronary stents are implanted in more than 1.5 million patients per year. Polymer-based coronary stents eluting sirolimus or paclitaxel substantially reduce the need for repeat percutaneous intervention compared with bare-metal stents, and drug-eluting stents are rapidly replacing bare-metal stents. A meta-analysis<sup>1</sup> of 11 randomised trials (5013 patients) showed no evidence that the short-to-medium-term safety profiles of sirolimus-eluting or paclitaxel-eluting stents differed from those of bare-metal stents. However, these trials were not powered to detect or exclude an effect of drug-eluting stents on rare events such as stent thrombosis.

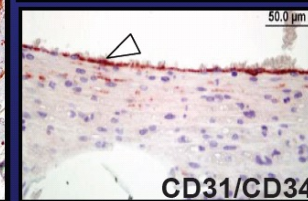
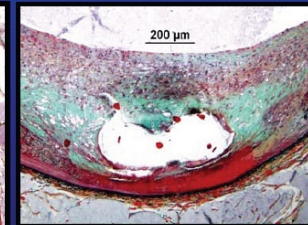
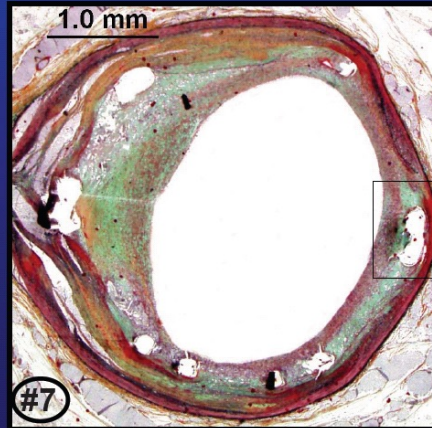
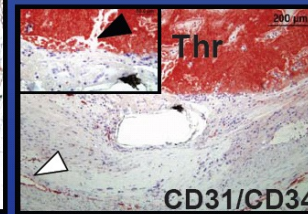
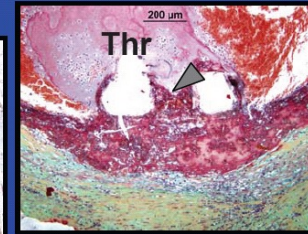
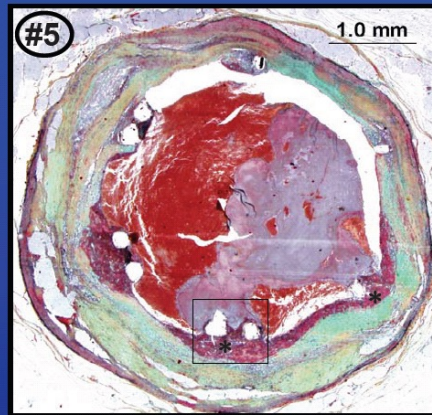
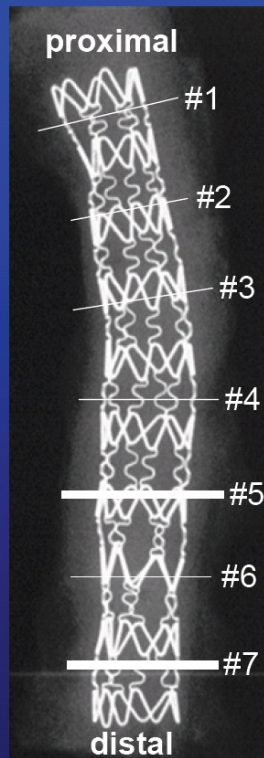
Stent thrombosis usually results in ST-segment elevation myocardial infarction or death. Angiographically documented late (>6 months) stent thrombosis is extremely rare with bare-metal stents, recent

angiography showed an isolated proximal lesion of the left anterior descending artery (figure 1A). Electrophysiological investigations were negative. The patient underwent percutaneous intervention with one paclitaxel-eluting stent (3.5 mm diameter, 16 mm long; Taxus Express 2), in April, 2003 (figure 1B and 1C) and was subsequently asymptomatic. In June, 2004, aspirin was discontinued before resection of a newly diagnosed colon carcinoma. 1 week later, on the evening of surgery, 442 days after stenting, the patient developed anterior myocardial infarction. Angiography showed stent occlusion (figure 1D) and extensive thrombus after guidewire passage (figure 1E). Percutaneous intervention restored vessel patency; peak concentration of creatine kinase was 3500 IU/L.

A 42-year-old man admitted to hospital with chest pain

# Scénario catastrophe.....

## Lack of Re-Endothelialization at Sites of Thrombosis in DES



Du calme.....

*The* NEW ENGLAND  
JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

MARCH 8, 2007

VOL. 356 NO. 10

A Pooled Analysis of Data Comparing Sirolimus-Eluting Stents  
with Bare-Metal Stents

Christian Spaulding, M.D., Joost Daemen, M.D., Eric Boersma, Ph.D., Donald E. Cutlip, M.D.,  
and Patrick W. Serruys, M.D., Ph.D.

**CONCLUSIONS**

In a pooled analysis of data from four trials comparing sirolimus-eluting stents and bare-metal stents, no significant differences were found between the two treatments in rates of death, myocardial infarction, or stent thrombosis. (ClinicalTrials.gov numbers, NCT00233805, NCT00381420, NCT00232765, and NCT00235144.)

# Thrombose de stent.....

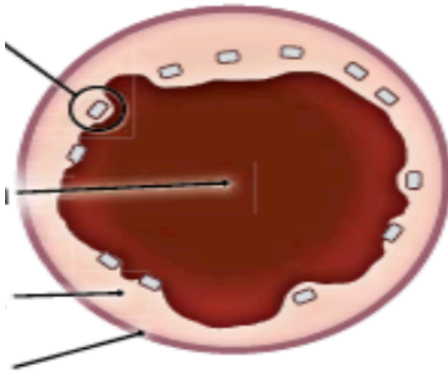
**Table 2.** Incidences of Death, Myocardial Infarction, and Stent Thrombosis after 440 Days of Follow-up.\*

End Point	Sirolimus-Stent Group (N= 878)	Bare-Metal-Stent Group (N= 870)	Adjusted Hazard Ratio (95% CI)	P Value
	<i>number (percent)</i>			
Death	57 (6.7)	46 (5.4)	1.24 (0.84–1.83)	0.28
Cardiovascular cause	29 (3.5)	23 (2.7)	1.26 (0.73–2.18)	0.40
Noncardiovascular cause	28 (3.3)	23 (2.8)	1.22 (0.70–2.11)	0.49
MI	55 (6.4)	53 (6.2)	1.03 (0.71–1.51)	0.86
Q-wave	18 (2.1)	11 (1.3)	1.64 (0.78–3.47)	0.20
Non-Q-wave	37 (4.3)	43 (5.0)	0.85 (0.55–1.33)	0.48
Death or Q-wave MI	70 (8.2)	55 (6.5)	1.28 (0.90–1.82)	0.17
Death or any MI	100 (11.6)	90 (10.5)	1.11 (0.83–1.47)	0.48
Stent thrombosis as defined in protocols†				
Acute	0	0	—	
Subacute	4 (0.5)	1 (0.1)	4.02 (0.45–35.98)	0.21
Late	6 (0.7)	4 (0.5)	1.50 (0.42–5.30)	0.53
Stent thrombosis as defined by the ARC‡				
Acute	0	0	—	
Subacute	4 (0.5)	3 (0.5)	1.34 (0.30–5.93)	0.70
Late	3 (0.3)	11 (1.3)	0.18 (0.04–0.81)	0.03
Very late	23 (2.8)	14 (1.7)	1.65 (0.85–3.20)	0.14
Definite	10 (1.2)	7 (0.8)	1.43 (0.54–3.76)	0.47
Definite or probable	13 (1.5)	15 (1.8)	0.87 (0.41–1.82)	0.70
Any	30 (3.6)	28 (3.3)	1.07 (0.64–1.79)	0.80



# Thrombose de stent.....

Delayed arterial  
healing



## Les DES de 1ère génération

- Retard d'endothélialisation des mailles
- Remodelage artériel
- Dépôt persistant de plaquettes et de fibrine
- Néoathérosclérose précoce



DES Sirolimus

*The* NEW ENGLAND JOURNAL of MEDICINE

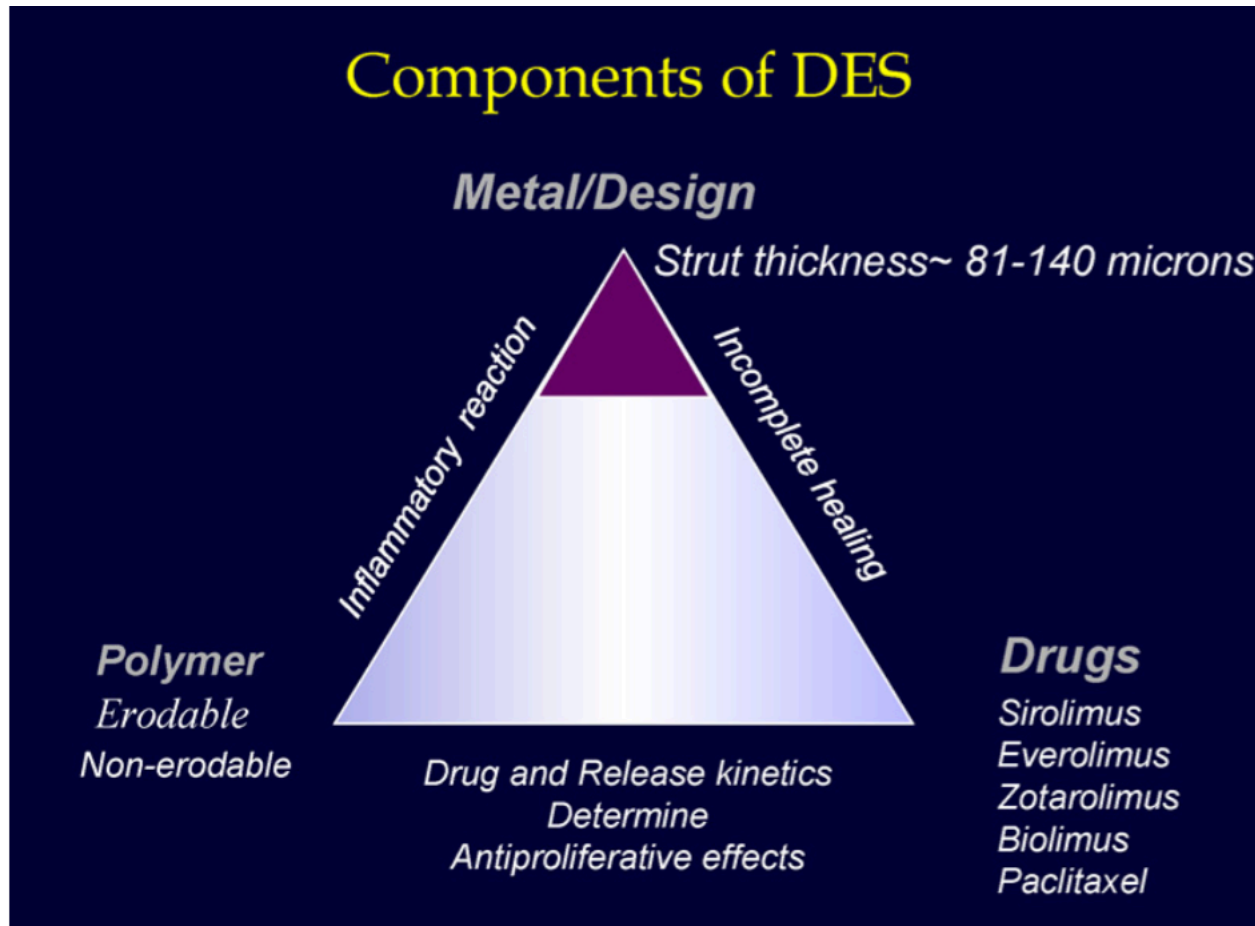
REVIEW ARTICLE

DRUG THERAPY

Drug-Eluting Coronary-Artery Stents








Giulio G. Stefanini, M.D., and David R. Holmes, Jr., M.D.

# Thrombosis de stent.....



# DES 2<sup>e</sup> génération

## Epaisseur des mailles et des revêtements

Stent à polymère permanent		Stent à polymère bioabsorbable				Bioabsorbable Scaffold
Abbott/Boston Xience/Promus <sup>1</sup> CoCr/PtCr-EES	Medtronic Resolute <sup>1</sup> CoNi-ZES	BIOSENSORS BioMatrix <sup>1</sup> 316L-BES	Terumo Ultimaster <sup>1</sup> CoCr-SES	Boston Synergy <sup>1</sup> PtCr-EES	BIOTRONIK Orsiro <sup>1</sup> CoCr-SES	Abbott Absorb <sup>2</sup> PLLA-EES
						
81 µm	91 µm	120 µm	80 µm	74 µm	60 µm	150 µm
Type de revêtement						
Circonférentiel 7-8 µm/side	Circonférentiel 6 µm/side	Abluminale 10 µm	Abluminale 15 µm	Abluminale 4 µm	Circonférentiel 4-7 µm/side	Circonférentiel 3 µm/side

Source 1: GG Stefanini, M Taniwaki, S Yoneda, Coronary stents: novel development, Heart doi:10.1136/heartjnl-2012-303522; 2: IT Meredith, Scientific symposium, TCT 2013

## Intérêt DES 2<sup>e</sup> génération.

	<b>New DES</b>	<b>Early DES</b>	<b>BMS</b>	<b>p</b>
Death or MI	9.2%	10.9%	12.8%	0.001
Stent thrombosis	1.1%	2.1%	1.3%	0.01
TLR	6.3%	7.8%	18.6%	0.001 / 0.005

- ↑ Délivrabilité (finesse et structure du stent)
- ↑ Compatibilité (polymère et drogue)
- ↓ Inflammation locale
- ↓ Resténose
- ↓ Risque de thrombose
- ↓ Bithérapie AAP

The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

DRUG THERAPY

Drug-Eluting Coronary-Artery Stents

Giulio G. Stefanini, M.D., and David R. Holmes, Jr., M.D.

# Intérêt DES 2<sup>e</sup> génération.

**Table 3.** Efficacy and Safety of Drug-Eluting Stents, Bare-Metal Stents, and Coronary-Artery Bypass Grafting (CABG), According to Clinical Indication.\*

Outcome and Intervention	Stable Coronary Artery Disease	Acute Myocardial Infarction	Diabetes	Multivessel Disease	Left Main Coronary Artery Disease
<b>Restenosis</b>					
Implantation of bare-metal stent	+	+	+	+	+
Implantation of drug-eluting stent					
Early-generation	++	++	++	++	++
New-generation	+++	+++	++	++ [+]	++ [+]
CABG	+++	–	+++	+++	+++
<b>Cardiac death, myocardial infarction, or stent thrombosis</b>					
Implantation of bare-metal stent	+	+	+	+	+
Implantation of drug-eluting stent					
Early-generation	+	+/-	+	+	+
New-generation	+ [+]	+ [+]	+	+ [+]	++ [+]
CABG	+	–	++	++	++

*The NEW ENGLAND JOURNAL of MEDICINE*

REVIEW ARTICLE

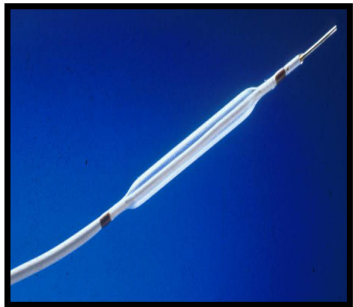
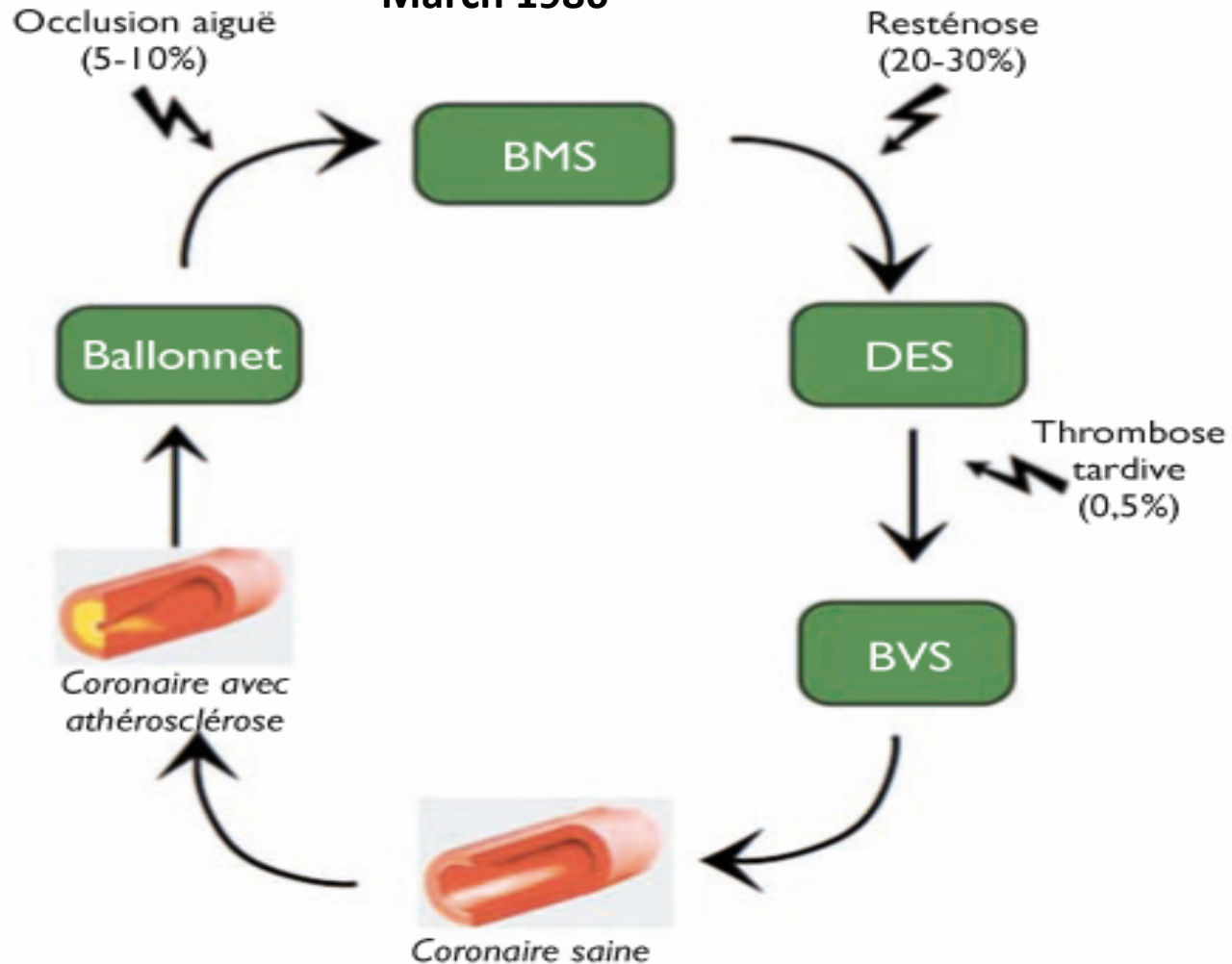
DRUG THERAPY

Drug-Eluting Coronary-Artery Stents

Giulio G. Stefanini, M.D., and David R. Holmes, Jr., M.D.


# ATL au ballon-Restauration artérielle

Jacques Puel  
March 1986



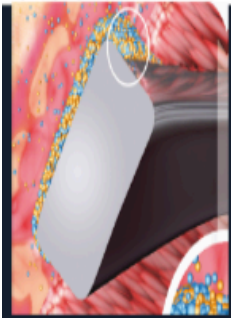
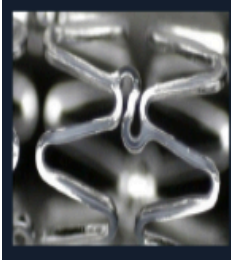
Zurich  
1977

# ATL au ballon-Restauration artérielle

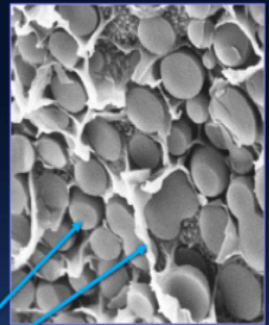



**Biolimus A9**  
10x higher lipophilicity

- Biolimus is a semi-synthetic sirolimus analogue with **10x higher lipophilicity** and similar potency as sirolimus.
- Biolimus is immersed at a concentration of 15.6 µg/mm into a biodegradable polymer, polylactic acid, and applied solely to **the abluminal stent surface** by a fully automated process.
- Biolimus is co-released with polylactic acid and completely desolves into carbon dioxide and water after **a 6-9 months period**.
- The stainless steel stent platform has a strut thickness of 120 µm with a **quadrature link design**.

## Abluminal Bioabsorbable Polymer SYNERGY Stent (BSC)

Drug & Polymer Coating

Abluminal (4µm)

Everolimus Drug  
PLGA Polymer

SEM of coating (x5000)

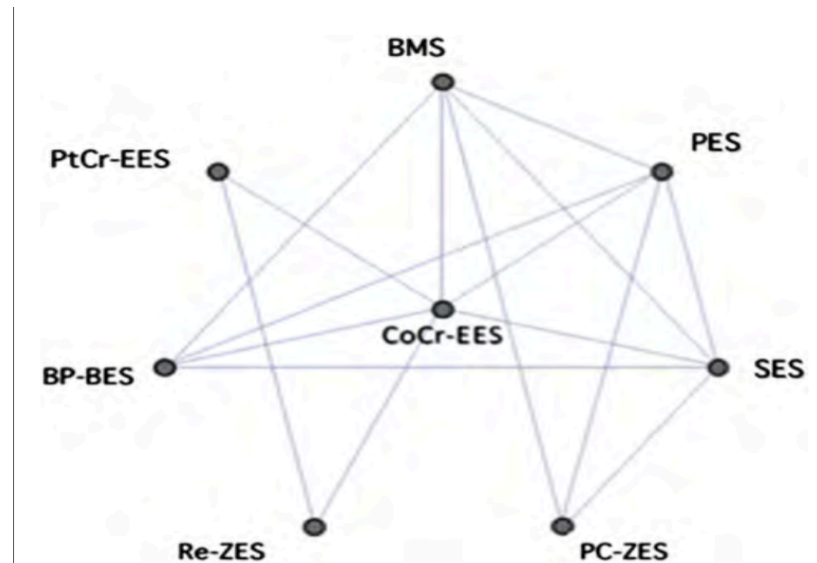
Luminal

Platform	Polymer Coating	Drug
Platinum chromium • 74 µg (0.0029in)	PLGA • Abluminal • 4 µm thick • Undetectable in 4 mo	Everolimus • 100 µg/cm <sup>2</sup> • Elutes in 3 months

PHARMACEUTICAL RESEARCH  
A Division of Novartis

NEW YORK-PRESBYTERIAN  
MEDICAL CENTER  
NewYork-Presbyterian

# Polymère permanent vs Biodégradable



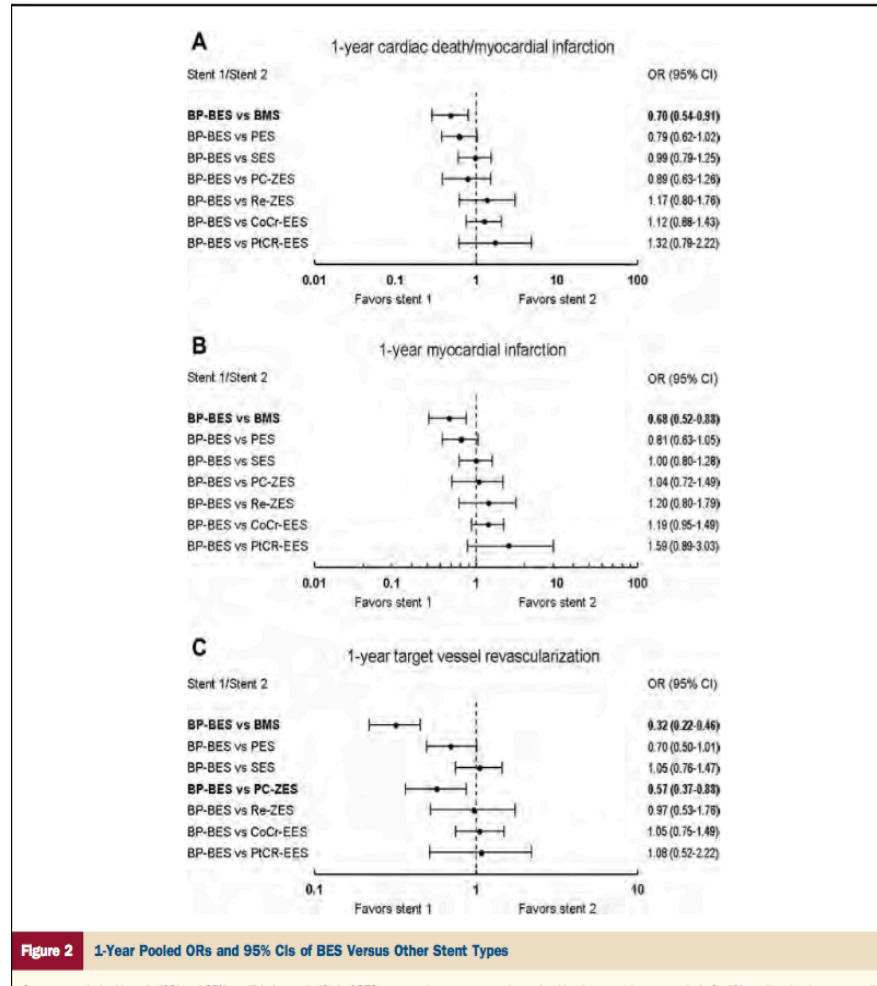
**Figure 1**

## Evidence Network Between Stents Included in the Meta-Analysis

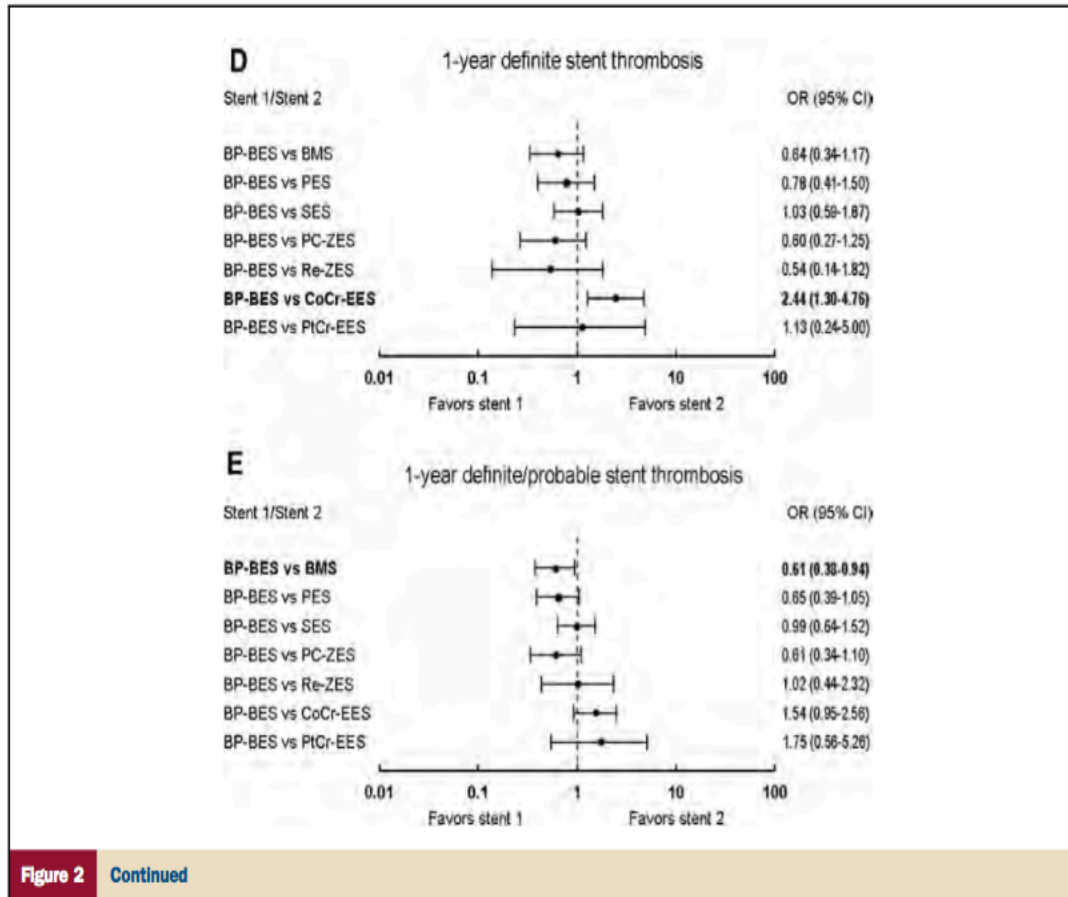
BMS = bare-metal stent(s); BP-BES = bioabsorbable polymer biolimus-eluting stent(s); CoCr-EES = cobalt-chromium everolimus-eluting stent(s); PC-ZES = phosphorylcholine polymer-based zotarolimus-eluting stent(s); PES = paclitaxel-eluting stent(s); PtCr-EES = platinum-chromium everolimus-eluting stent(s); Re-ZES = Resolute zotarolimus eluting stent(s); SES = sirolimus-eluting stent(s).



# Polymère permanent vs Biodégradable



# Polymère permanent vs Biodégradable



# Polymère permanent vs Biodégradable

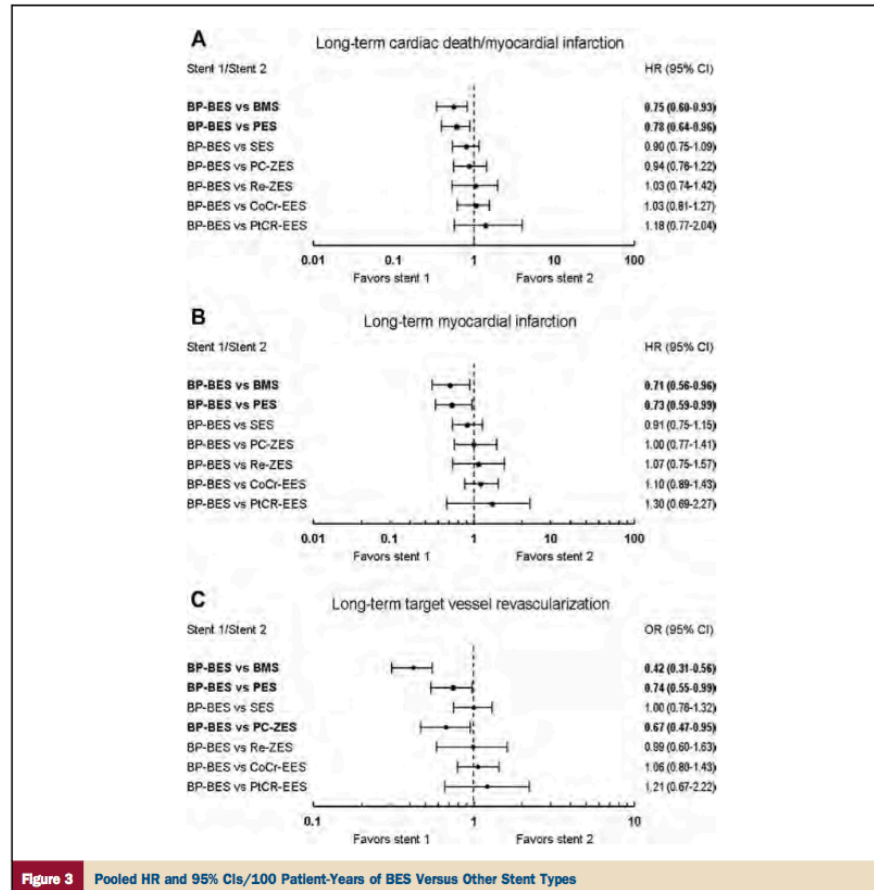


Figure 3 Pooled HR and 95% CIs/100 Patient-Years of BES Versus Other Stent Types

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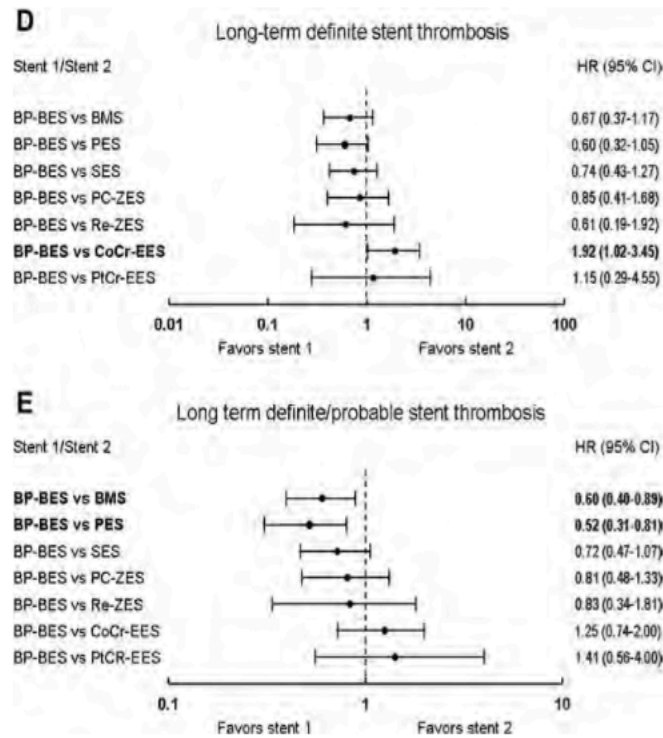
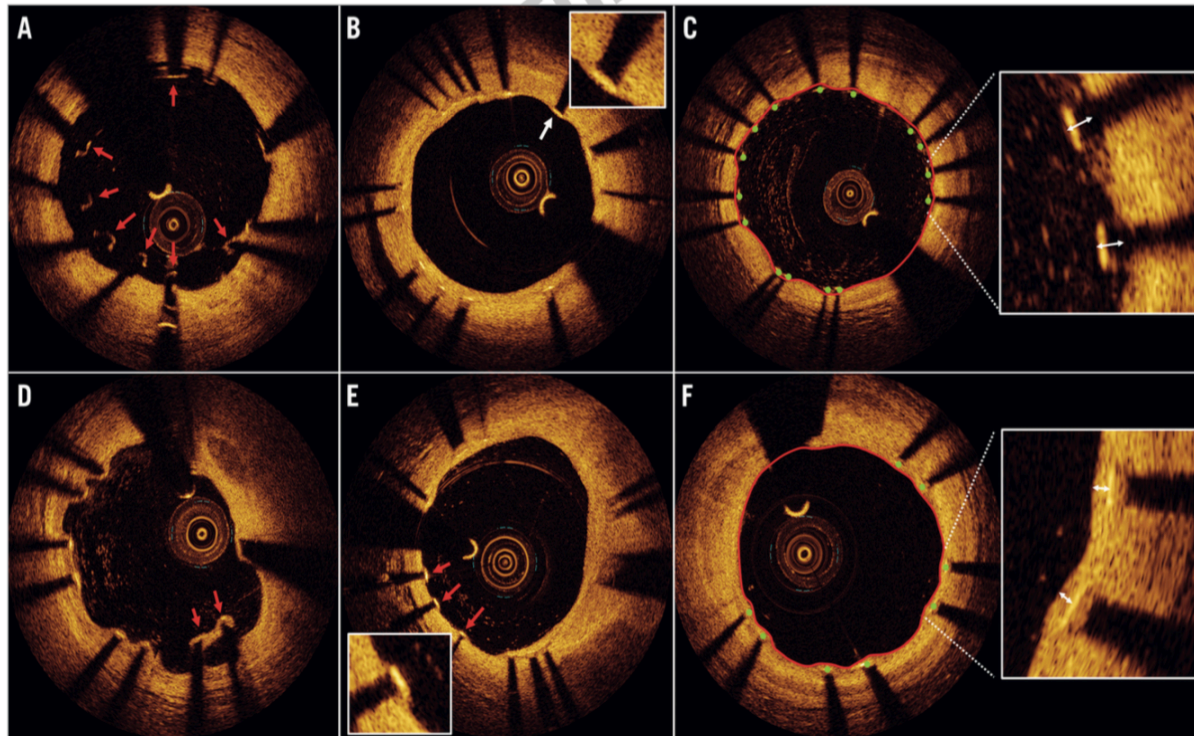


Figure 3 Continued

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**Figure 1.** OCT analysis of stent apposition and coverage. A) OCT immediately after implantation. Red arrows indicate malapposed struts. B) OCT at nine months after DES implantation. All struts are well apposed and covered with a thin layer of neointima. C) Illustration of the ODIERNA software programme for the automated analysis of stent strut apposition. After delineation of the lumen contour (red line), automatic stent strut detection is achieved (green dots at the top of the stent struts) and malapposition distance can be calculated. D) Red arrows indicate malapposed struts in a DES at nine-month follow-up. E) Heterogeneous healing of stent struts at nine-month follow-up, with red arrows indicating uncovered struts, while the other struts in this frame are covered with a healthy layer of neointima. F) Automated analysis of neointimal coverage of stent struts. OCT: optical coherence tomography.

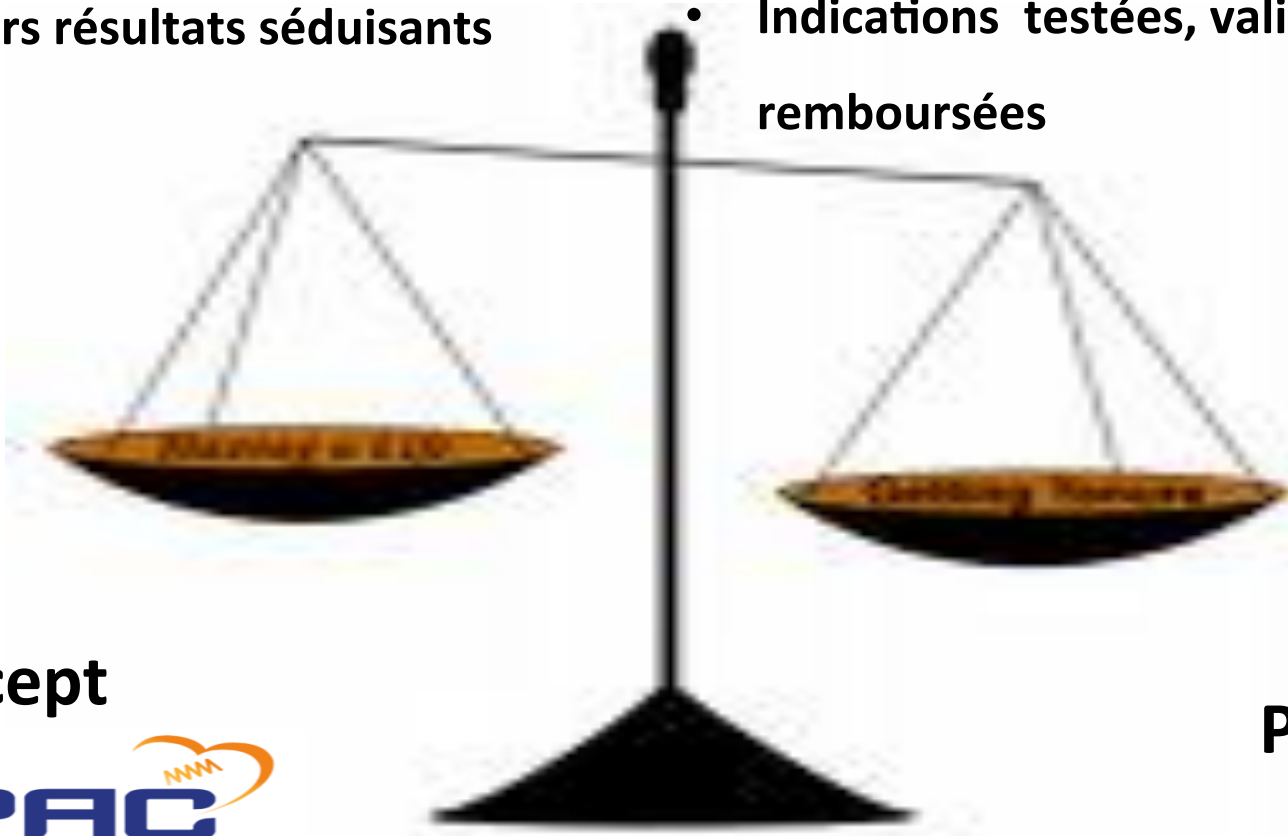
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## Conclusions

In conclusion, a significantly higher percentage of uncovered struts was detected with OCT in the biodegradable polymer-coated BES compared with the durable fluoropolymer-coated EES at nine-month follow-up in the setting of STEMI, non-STEMI and stable/unstable angina. Our findings do not support improved midterm healing characteristics of stents with biodegradable polymer-based biolimus elution as compared to current second-generation permanent polymer DES.

# Polymère ?

- Concept séduisant
- Approche innovante
- Premiers résultats séduisants
- Concept validé
- Recul (temps et nombre de lésions)
- Indications testées, validées et remboursées



**Concept**

**Preuves**

# Polymère ?

- *Est beau ce qui est connu sans concept comme objet d'une satisfaction nécessaire.*
- *Idéalement nous sommes ce que nous pensons. Dans la réalité, nous sommes ce que nous accomplissons.*





- *dans une controverse, c'est celui qui est convaincu par l'autre qui gagne, car il a appris quelque chose tandis que son contradicteur repart comme il est venu avec pour seule consolation le plaisir - non négligeable - d'avoir partagé quelque chose avec un semblable.*

**merci**

# Stents en pratique clinique

*« Aimons la vérité qui nous reprend,  
et défions-nous de celle qui nous flatte ».*

merci