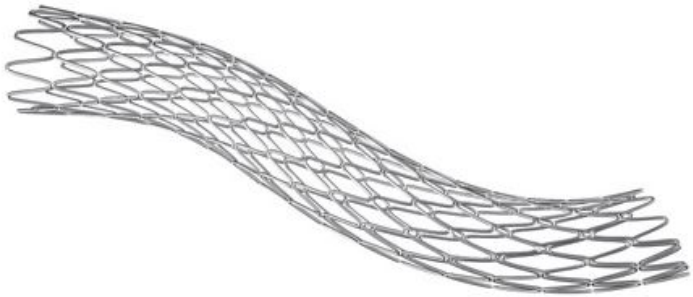
Medtronic

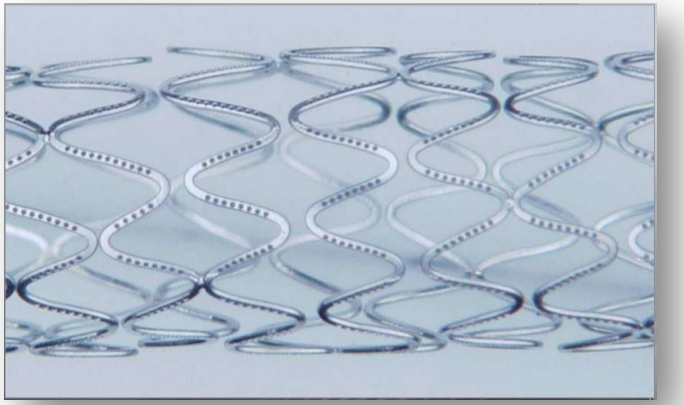
Cardiac and Vascular

Interventional Pipeline

STENTS ACTIFS: état des lieux

De Resolute Integrity aux nouvelles générations





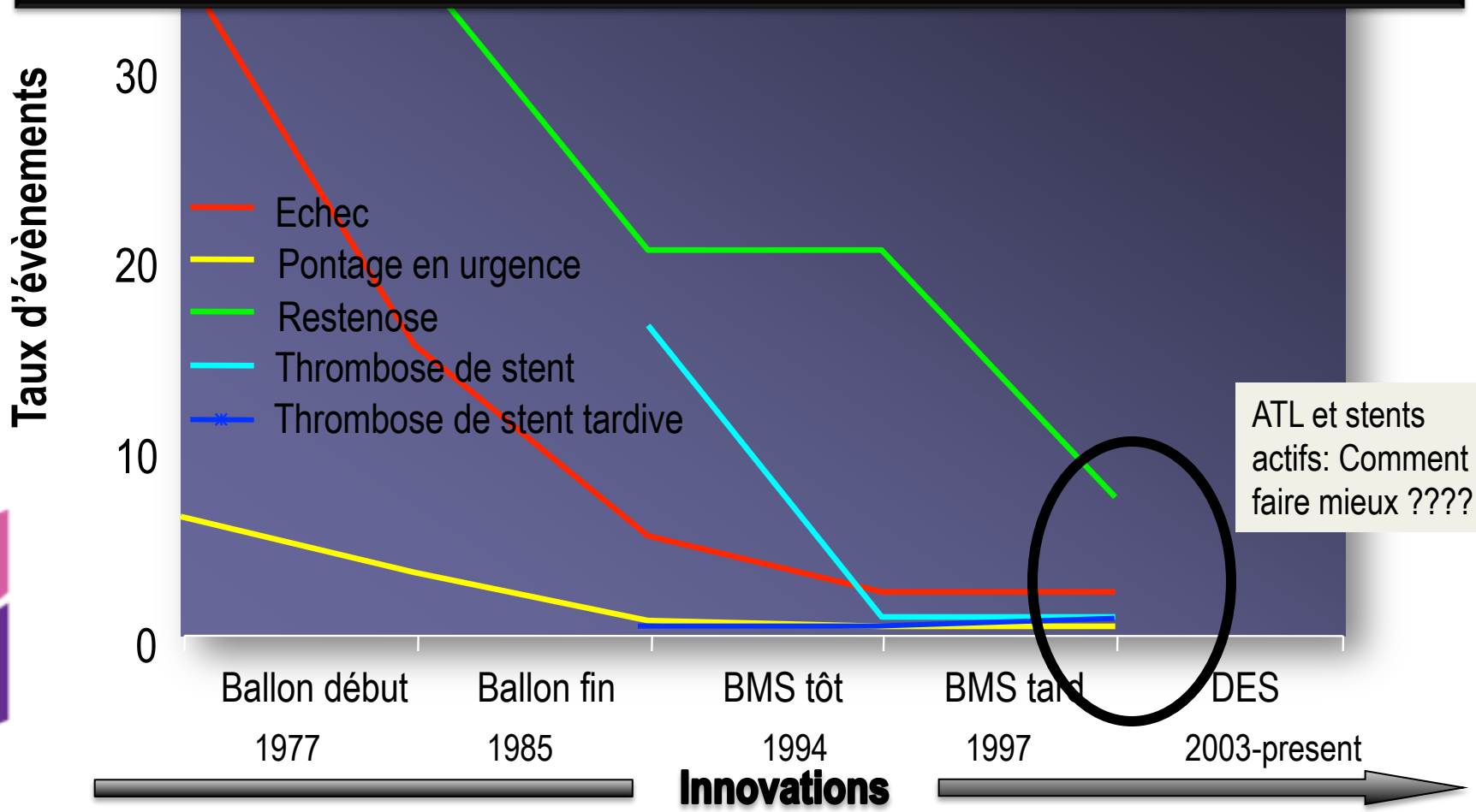
Dr Jean-Christophe MACIA

Département de cardiologie

MONTPELLIER

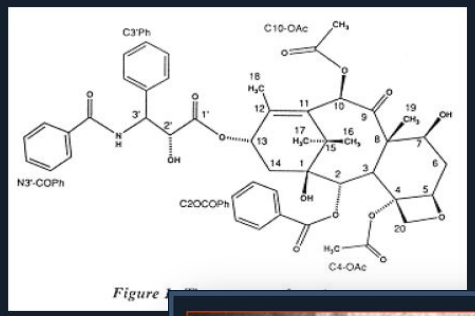
Evolution de l'angioplastie

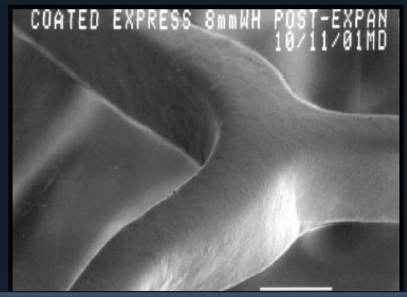
Depuis 30 ans: progrès remarquables,
meilleur savoir faire et avancées technologiques
Innovations = solutions à des problèmes majeurs
mais résultats encore imparfaits

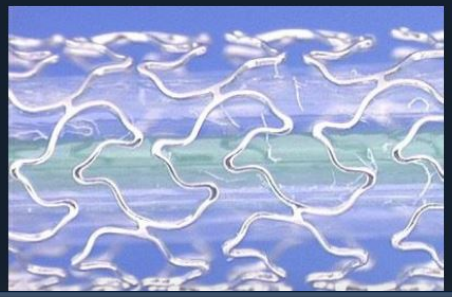


DES 1ère G

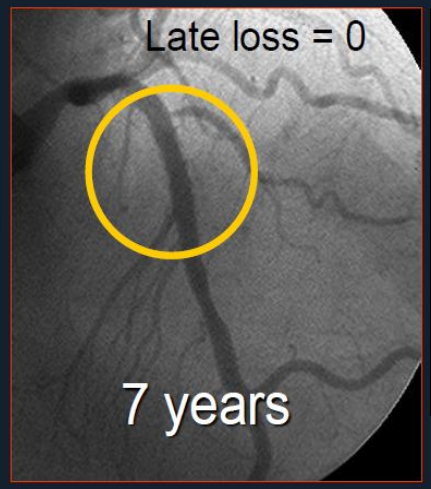
TAXUS

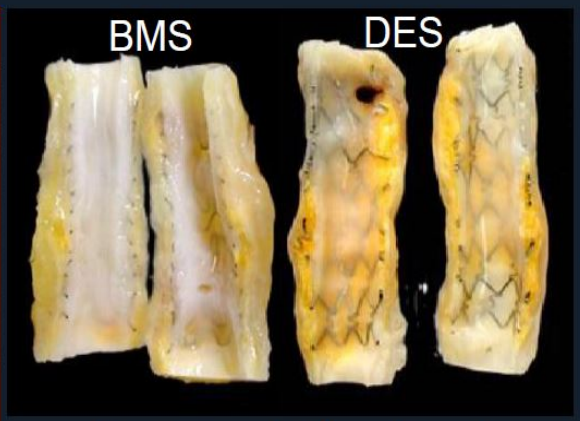






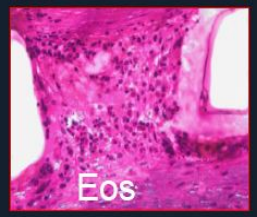
Cypher



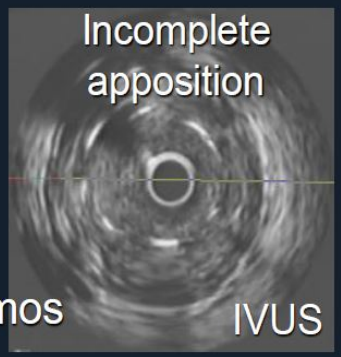


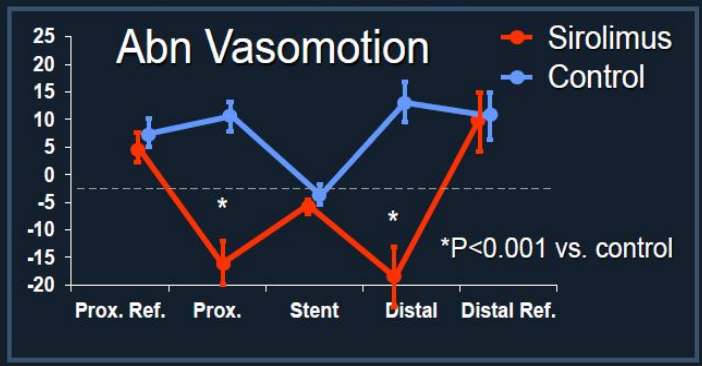
Delayed Healing!

Angioscopy

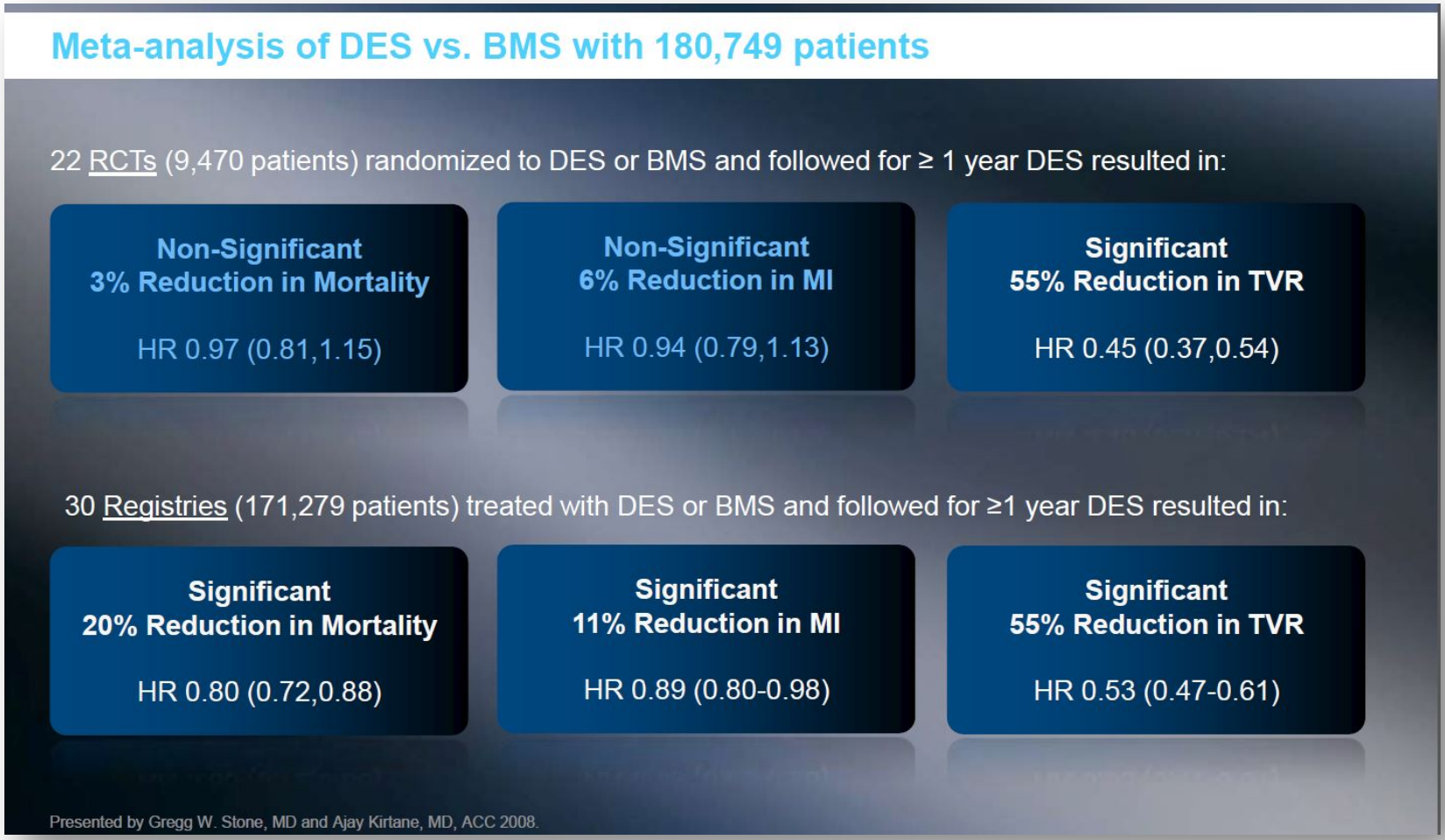


Inflammation





DES 1ère G:



0.6% de thrombose de stent/an

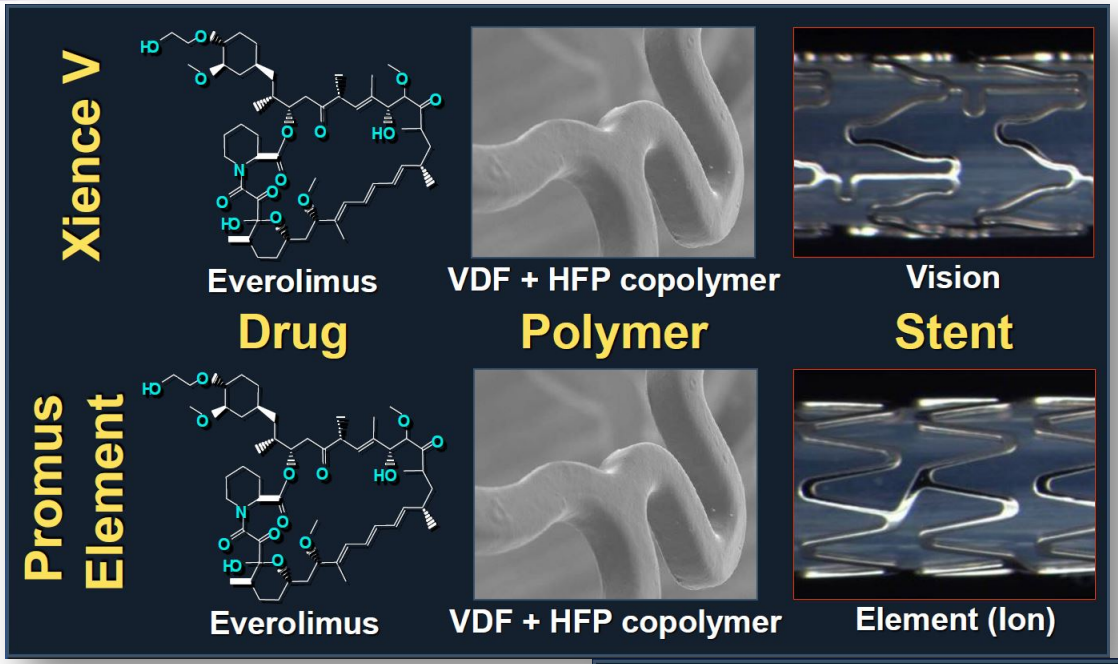
Bern-Rotterdam Registry
Daemon J Lancet 2007;369:667-78

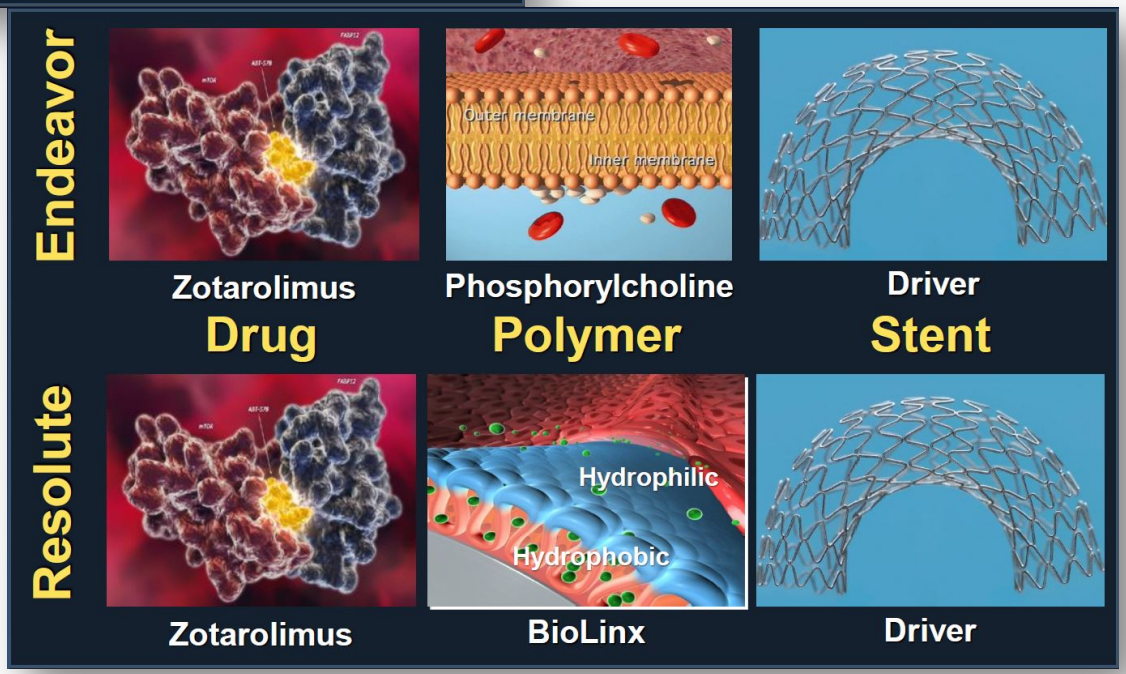
Evolution de l'angioplastie

- Par rapport aux BMS, les DES de 1ère G ont diminué le risque de resténose et de réintervention

- Leur risque de thrombose >1 an est plus élevé que celui des BMS

DES 2ème G

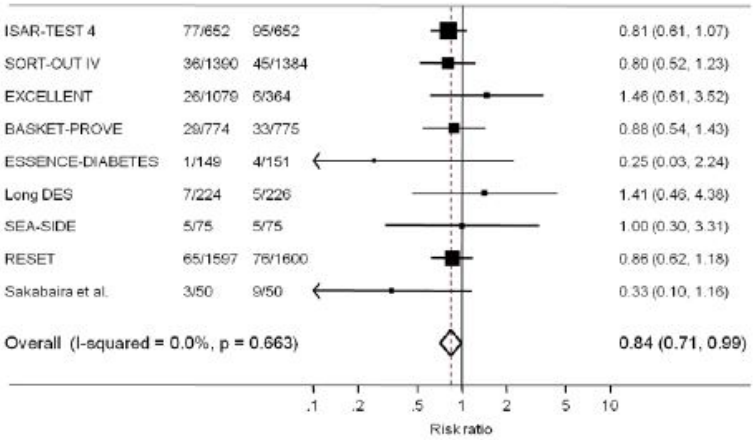

Xience V
Everolimus
Drug
VDF + HFP copolymer
Polymer
Vision
Stent
Promus Element
Everolimus
VDF + HFP copolymer
Element (Ion)


Endeavor
Zotarolimus
Drug
Outer membrane
Inner membrane
Phosphorylcholine
Polymer
Driver
Stent
Resolute
Zotarolimus
Hydrophilic
Hydrophobic
BioLinx
Driver

euro PCR 2013

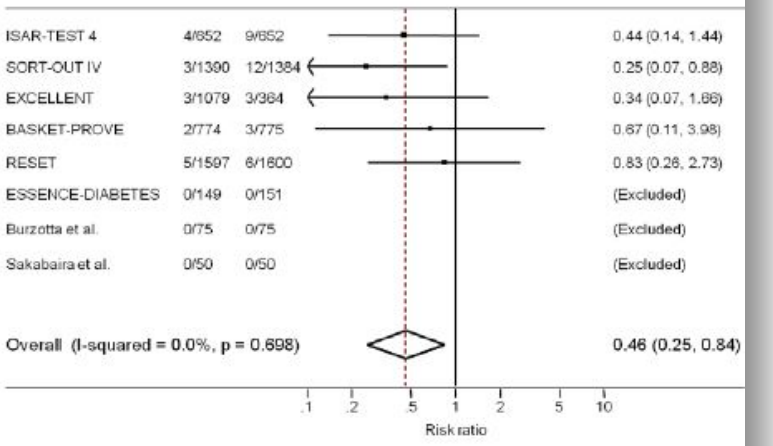
Everolimus-Eluting Versus Sirolimus-Eluting Durable Polymer Stents

Target Lesion Revasc



Favors EES *Favors SES*

Definite ST



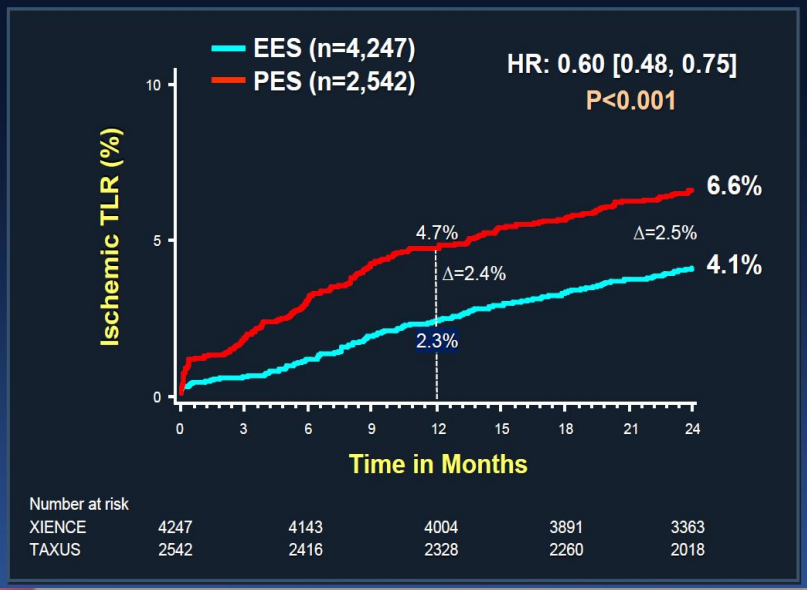
Favors EES *Favors SES*

Meta-Analysis N = 11,167

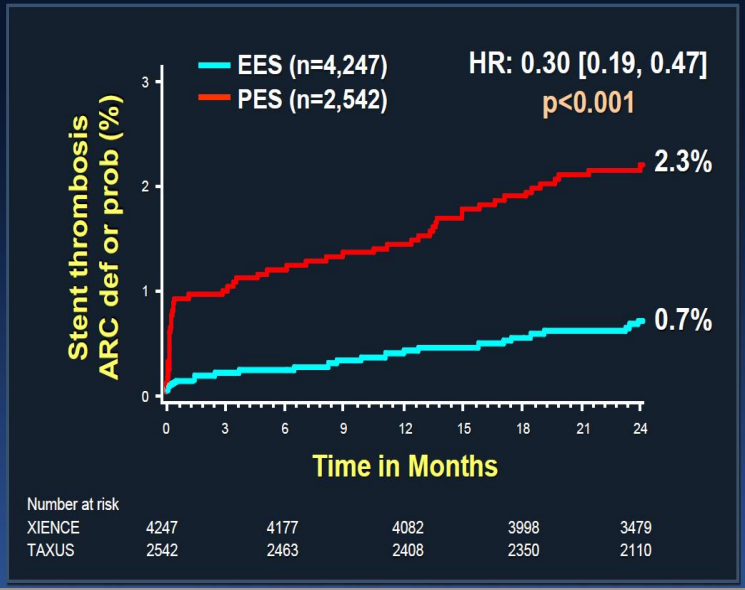
Stephan Windecker

DES 2ème G

SPIRIT II, III, IV and COMPARE trials
Pooled database analysis (n=6,789)
Ischemic TLR



SPIRIT II, III, IV and COMPARE trials
Pooled database analysis (n=6,789)
Stent thrombosis (ARC definite/probable)



Kereiakes DJ et al. EuroIntervention 2011:7:74-83

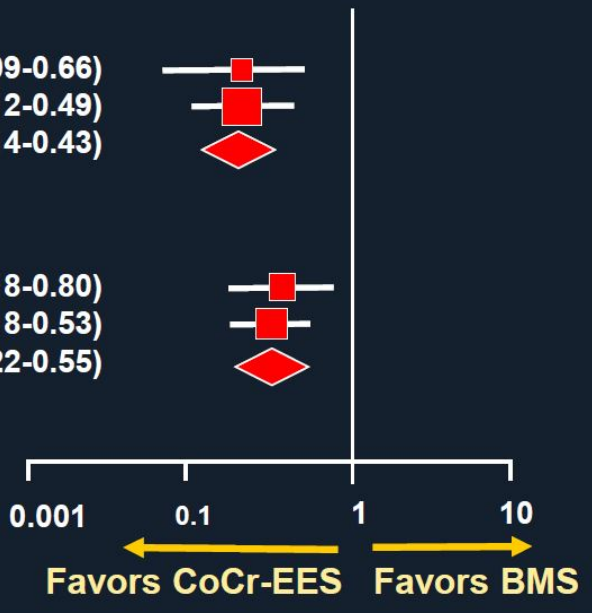
DES 2ème G

Stent Thrombosis Network Meta-analysis

49 RCTs, 50,844 pts

Consistency between direct and indirect estimates of 1-year stent thrombosis for CoCr-EES vs. BMS

	Log (odds ratio)	SE	Weight	Odds Ratio IV Random, 95% CI
Definite stent thrombosis				
Direct estimate	-1.427	0.519	32.4%	0.24 (0.09-0.66)
Indirect estimate	-1.421	0.359	67.6%	0.24 (0.12-0.49)
Total (95% CI)			100.00%	0.24 (0.14-0.43)
Test for overall effect Z=4.82 (*p*<0.00001)				
Definite or probable thrombosis				
Direct estimate	-0.968	0.377	39.4%	0.38 (0.18-0.80)
Indirect estimate	-1.122	0.304	60.6%	0.33 (0.18-0.53)
Total (95% CI)			100.00%	0.35 (0.22-0.55)
Test for overall effect Z=4.48 (*p*<0.00001)				



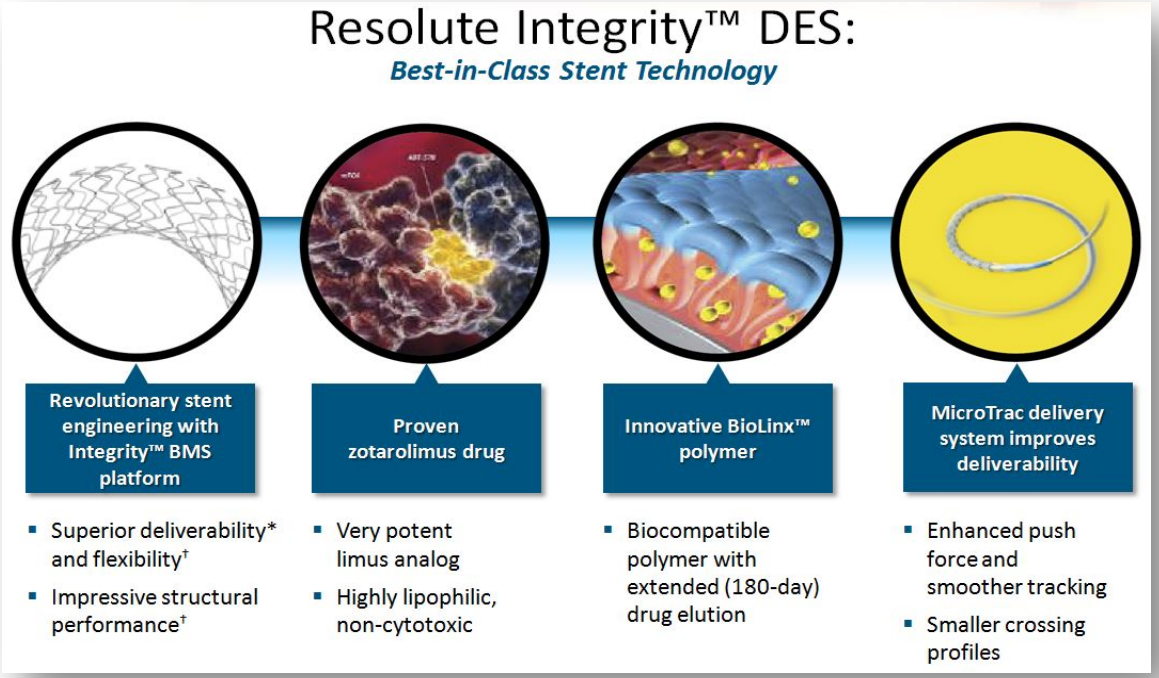
IV = inverse variance
SE = standard error

Palmerini T et al. *Lancet* 2012

- En comparaison des 1ère G les DES de 2ème G sont au moins aussi efficaces et plus sûrs, avec un taux de thrombose très bas

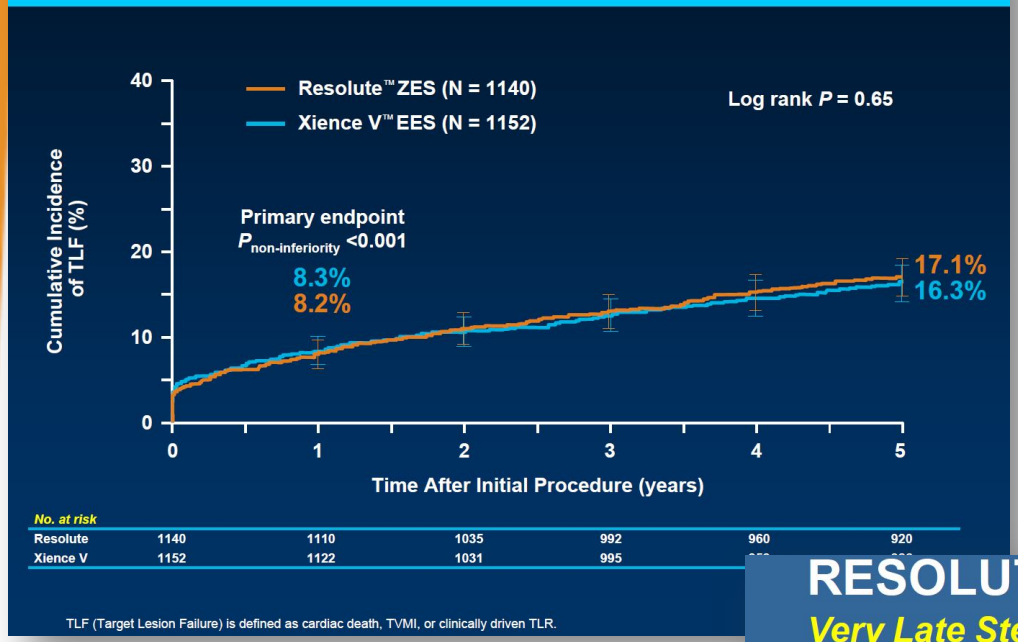
- Ils sont à la fois plus efficaces et plus sûrs que les BMS

Comment ces avancées ont-elles été possibles ?



RESOLUTE All Comers

Target Lesion Failure to 5 Years

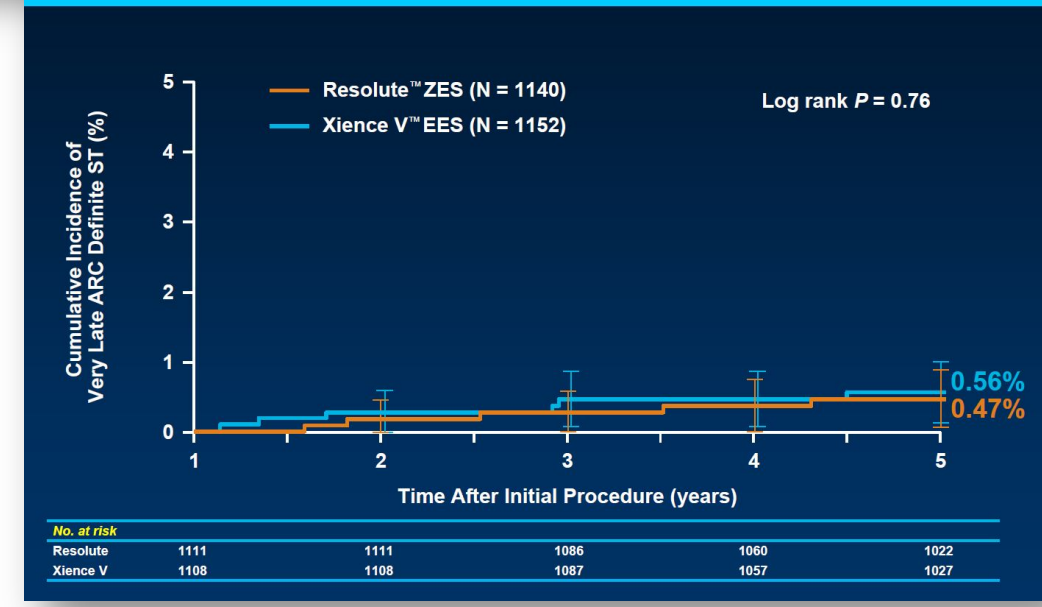


TLF (Target Lesion Failure) is defined as cardiac death, TVMI, or clinically driven TLR.

DES 2ème G

RESOLUTE All Comers

Very Late Stent Thrombosis: Definite



Stephan Windecker

euro PCR PCR2014

Plateforme : Les critères de choix

Struts et matériau

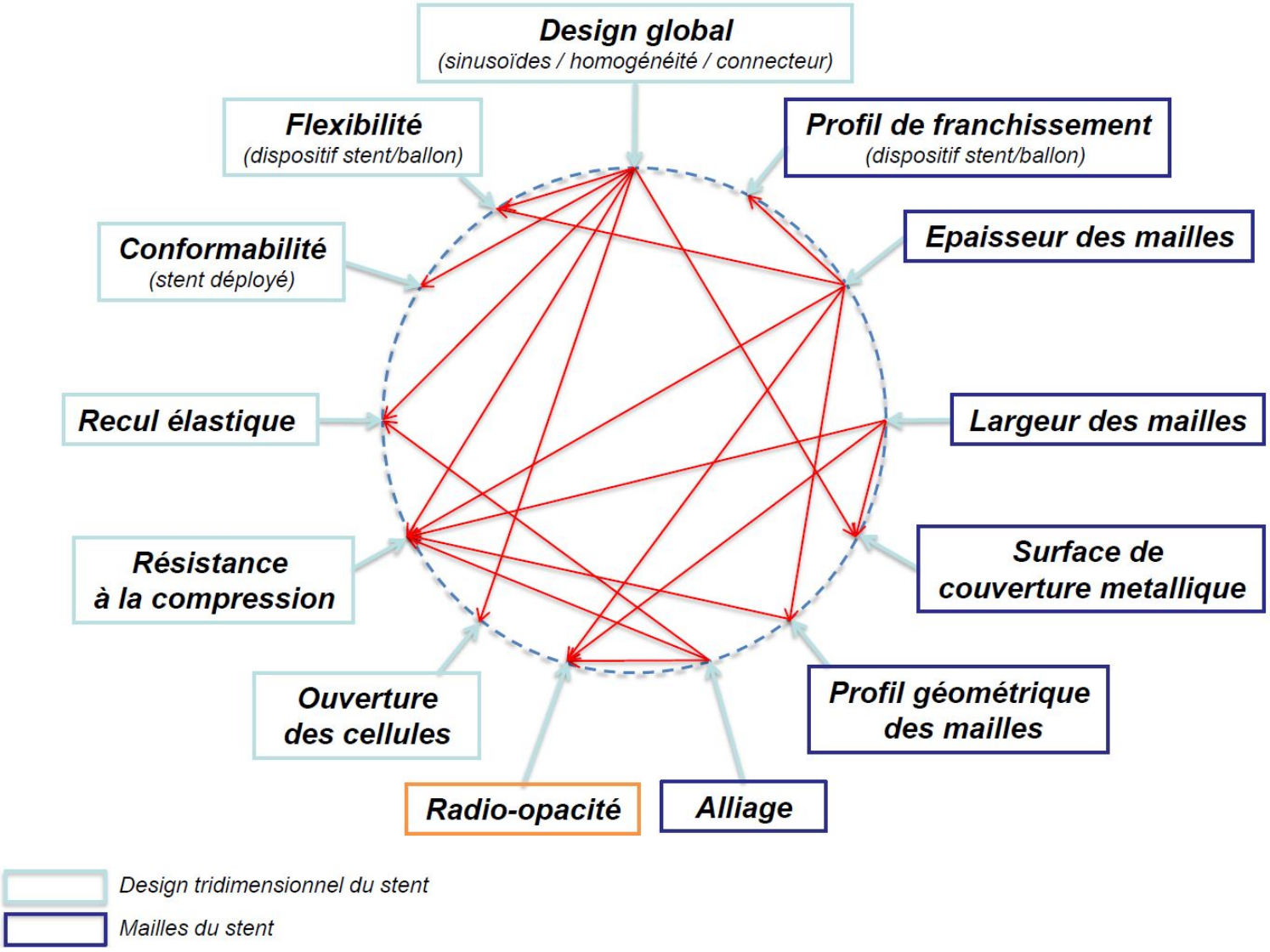
- Matériau de l'endoprothèse
- Epaisseur de maille

Design

- Modulaire / tubulaire
- 2 liens vs 3 liens
- Contention
- Force radiale / Recoil
- Raccourcissement
- Capacité d'expansion / tailles disponibles
- Comportement dans les bifurcations

Le design a un impact sur les résultats cliniques et le comportement mécanique du stent

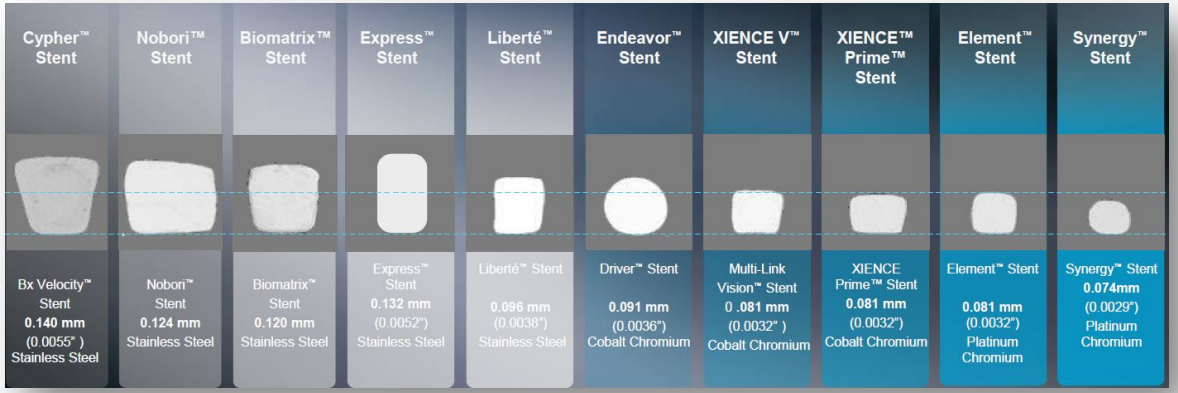
Plateforme : Les critères de choix

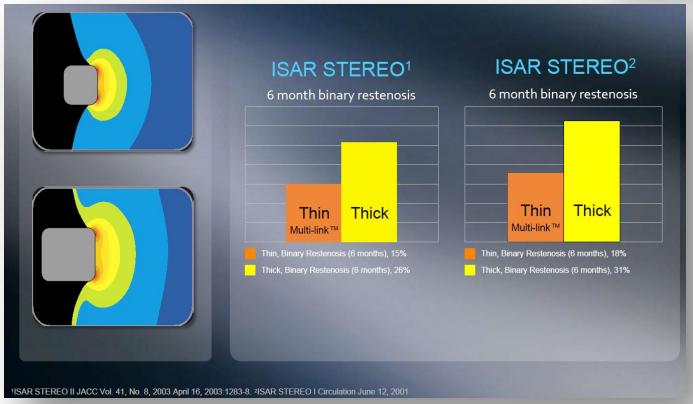


D'après Finet

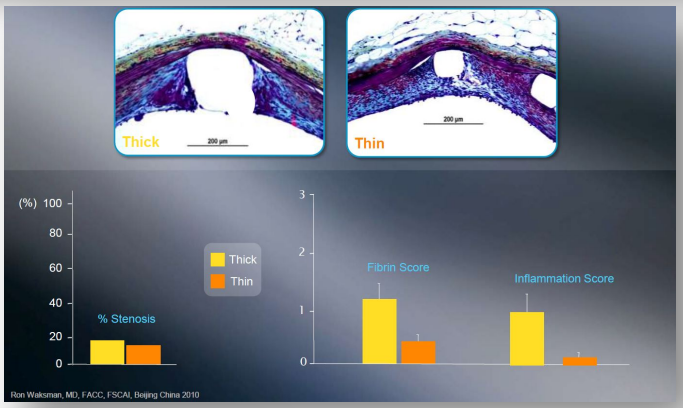
Plateforme : Les critères de choix

↓ L'épaisseur des struts

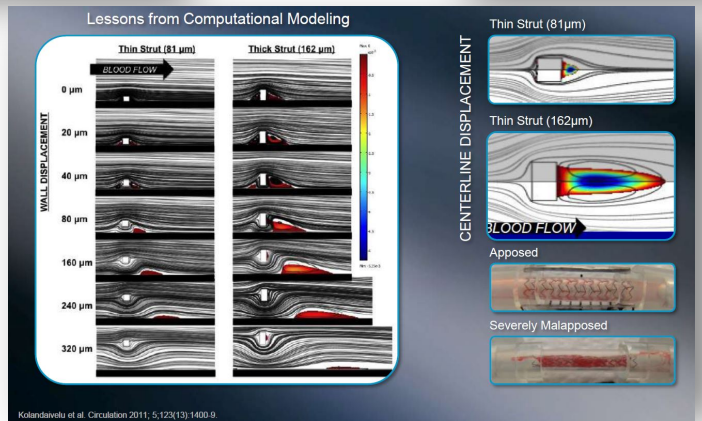




↓ La resténose



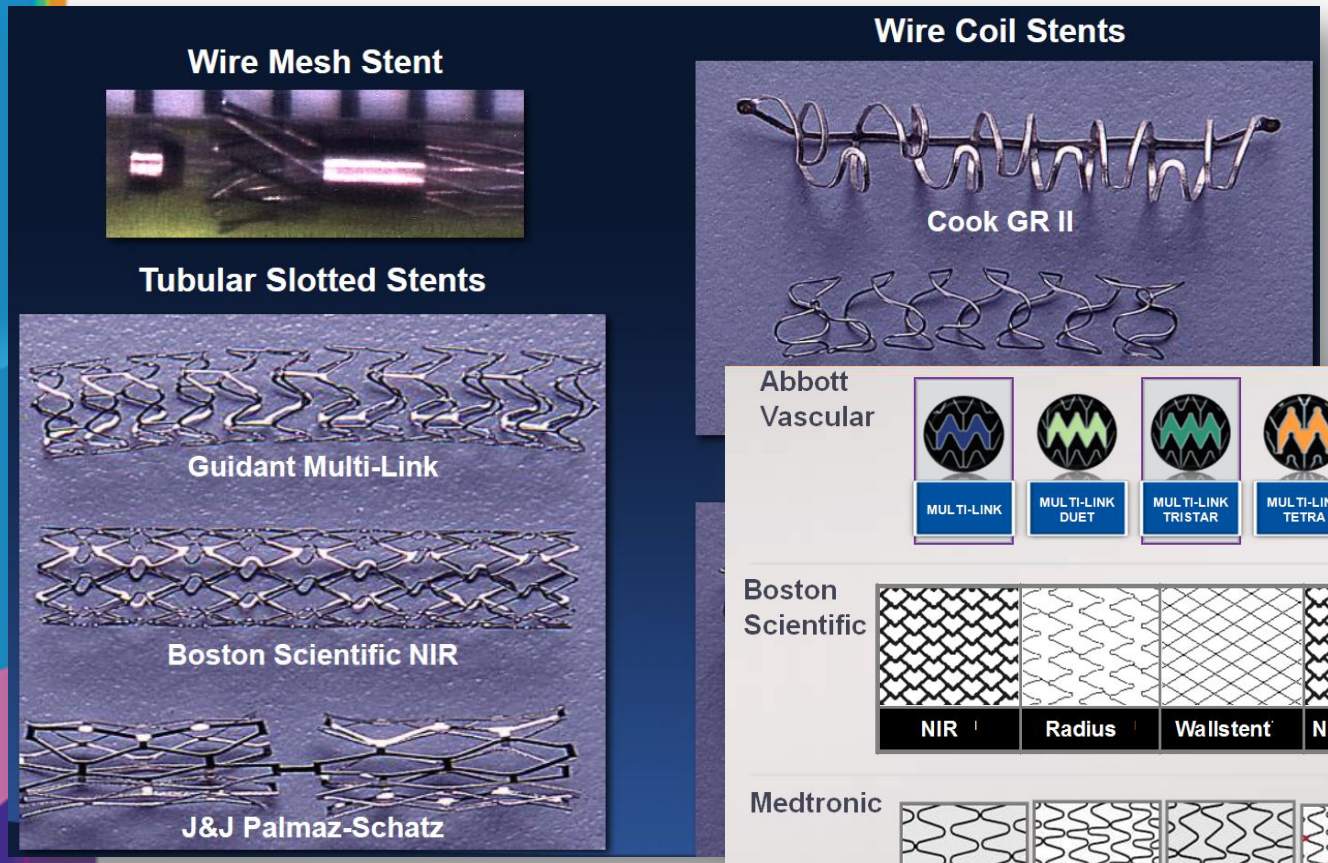
↓ L'inflammation

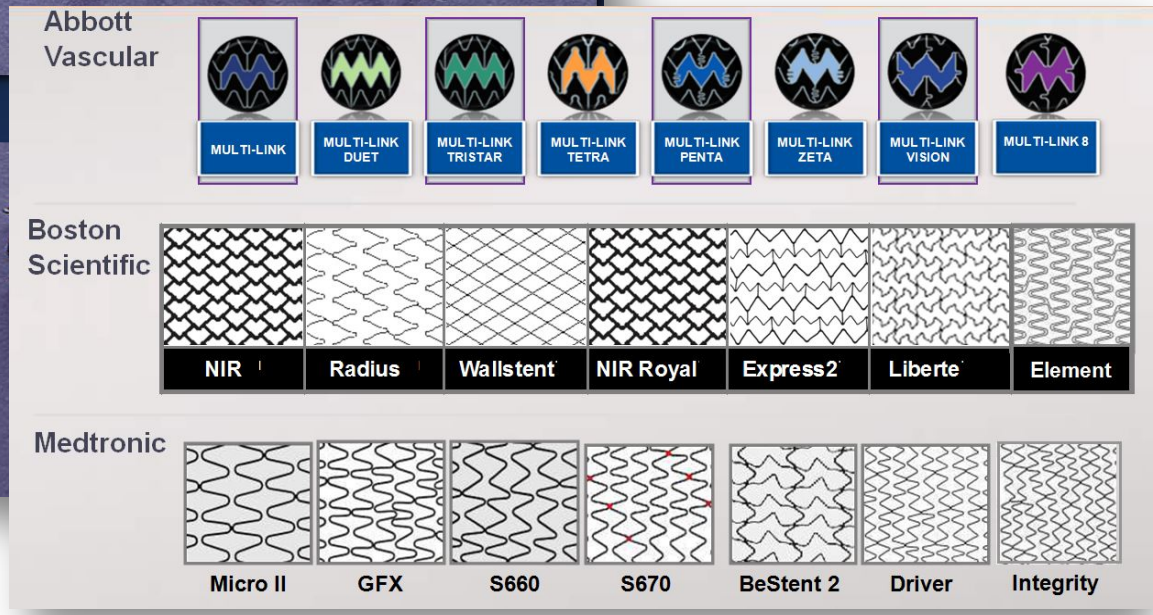


↓ La thrombogénicité

Plateforme : Les critères de choix

Le design du stent





Plateforme : Les critères de choix

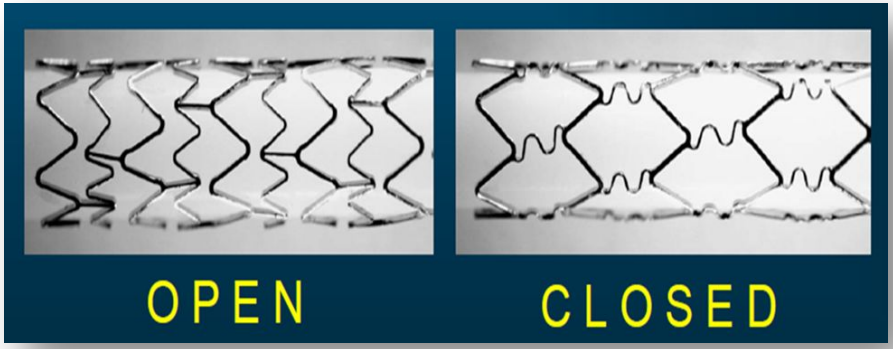
Le design du stent

- Les connecteurs
  - Flexibilité – déliverabilité
  - Conformabilité – apposition dans le vaisseau
  - Résistance à la fracture (↑ MACE)
  - Comportement dans les bifurcations

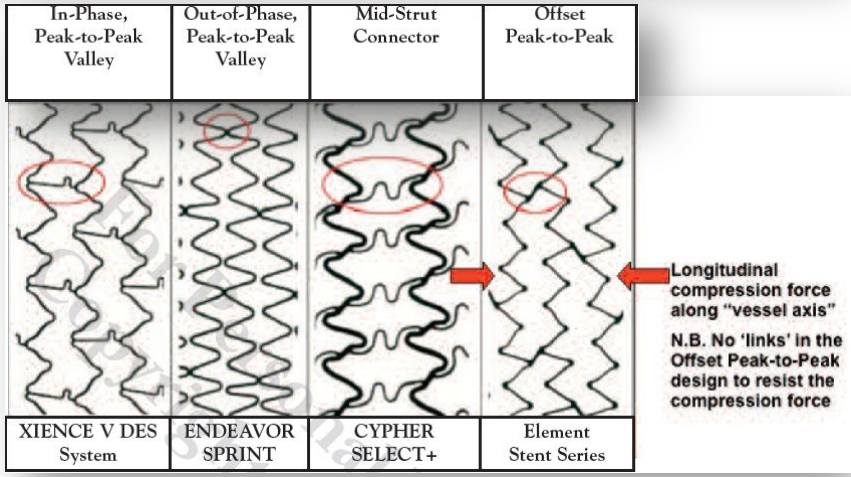
Connectors	P Element	Xience Prime	Xience V	Biomatrix	Resolute Integrity
	2	3	3	3	2

- Les cellules:

OPEN Cell
  - ↓ Ratio métal-artère
  - ↑ Conformabilité
  - ↑ accès aux branches collatérales
  - ↓ Homogénéité de la délivrance de drogue
  - ↓ Force radiale
  - ↑ Prolapsus de plaque

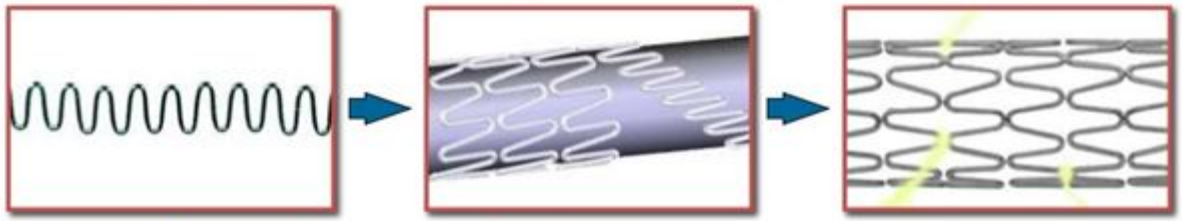


- La géométrie des liens et le risque de compression longitudinale

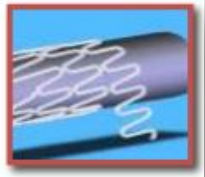


Plateforme : integrity et évolutions

Medtronic's Continuous Sinusoid Technology



Sinusoidal Formed Wire | Helical Wrap | Laser Fused



The stent platform for new BMS and future generation DES

Bare Metal Stents **Drug-Eluting Stents**

Integrity BMS

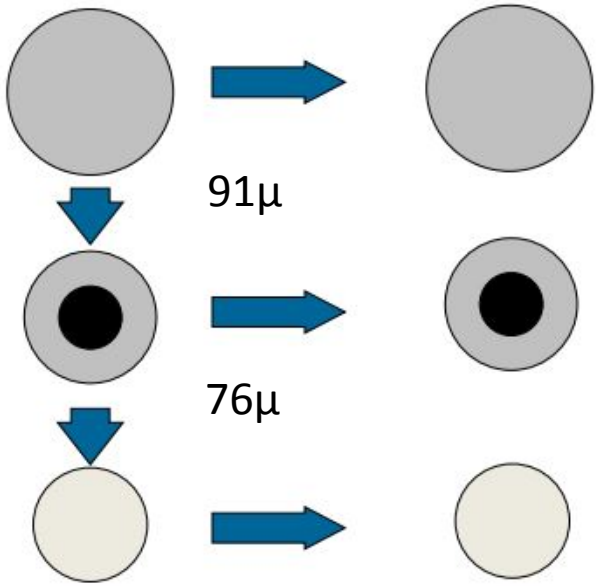
- First-generation continuous sinusoid platform stent
- Thin Round Struts ~0.0036" (91 microns)

Core wire

- Different materials for inner and outer portion of strut
- Can impact characteristics like radiopacity, radial strength, etc.

New alloys

- Different materials never before used due to manufacturing/ engineering limitations.

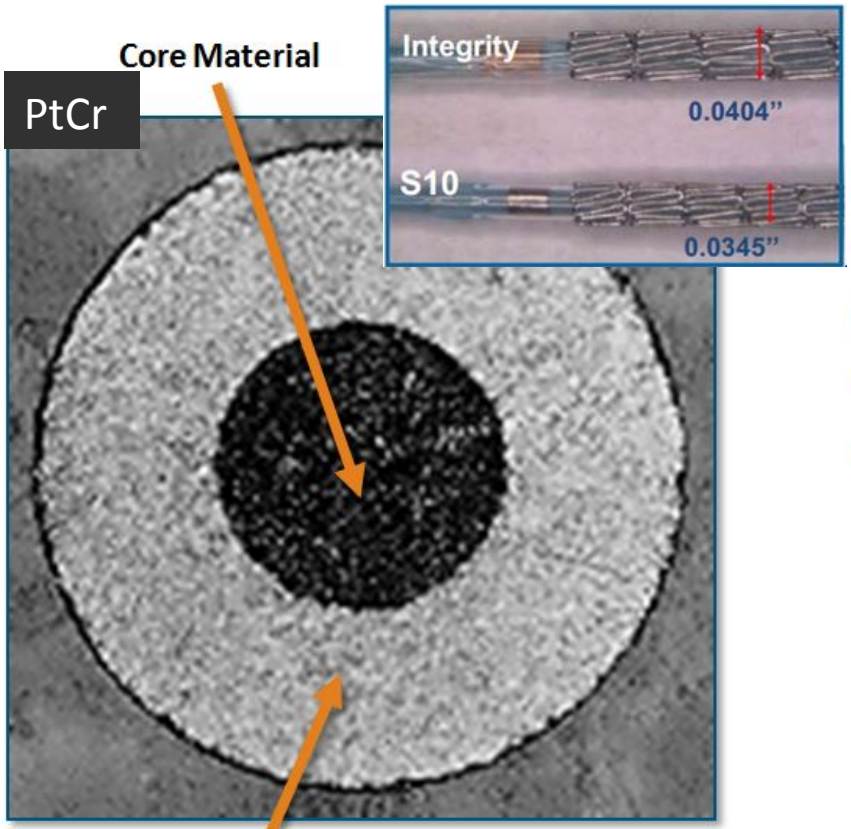


Platforms for next gen DES coatings

- PC Polymer
- BioLinx Polymer
- Bioabsorbable polymer

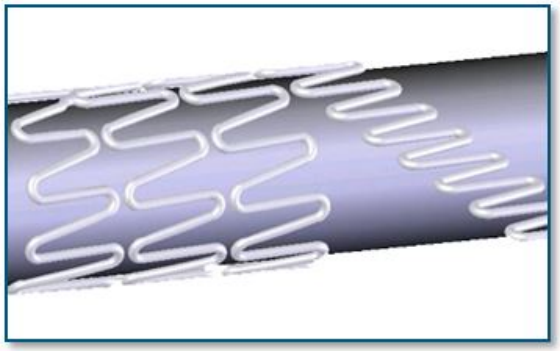
Plateforme : integrity et évolutions

Medtronic "S10 Core Wire" DES Technology



Goal: Best-in-class performance vs. future competitive stents

- Continuous Sinusoid Technology (CST)
- Thin strut, low crossing profile
- High radiopacity
- Proven BioLinx™ polymer/Zotarolimus coating



DES 2ème G

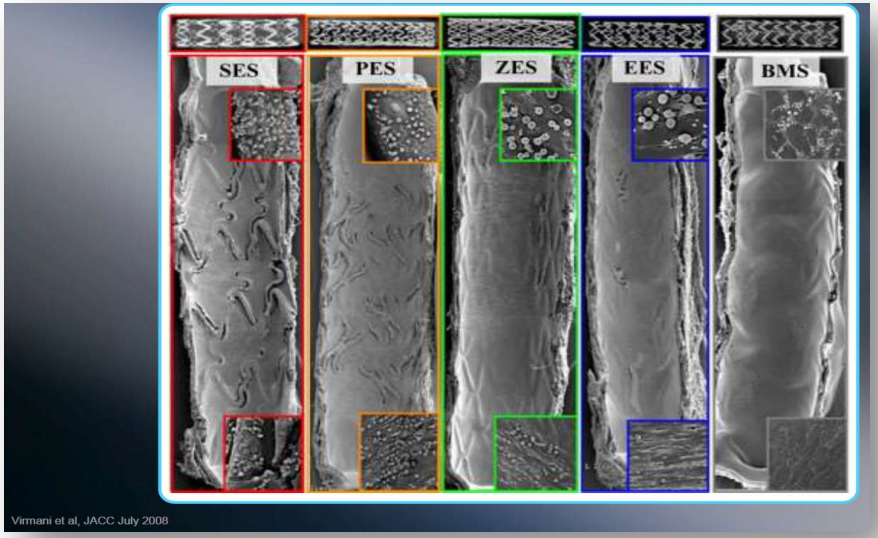
SES>PES (LLL , TLR)
-> Limus (macrocyclic lactone agent)

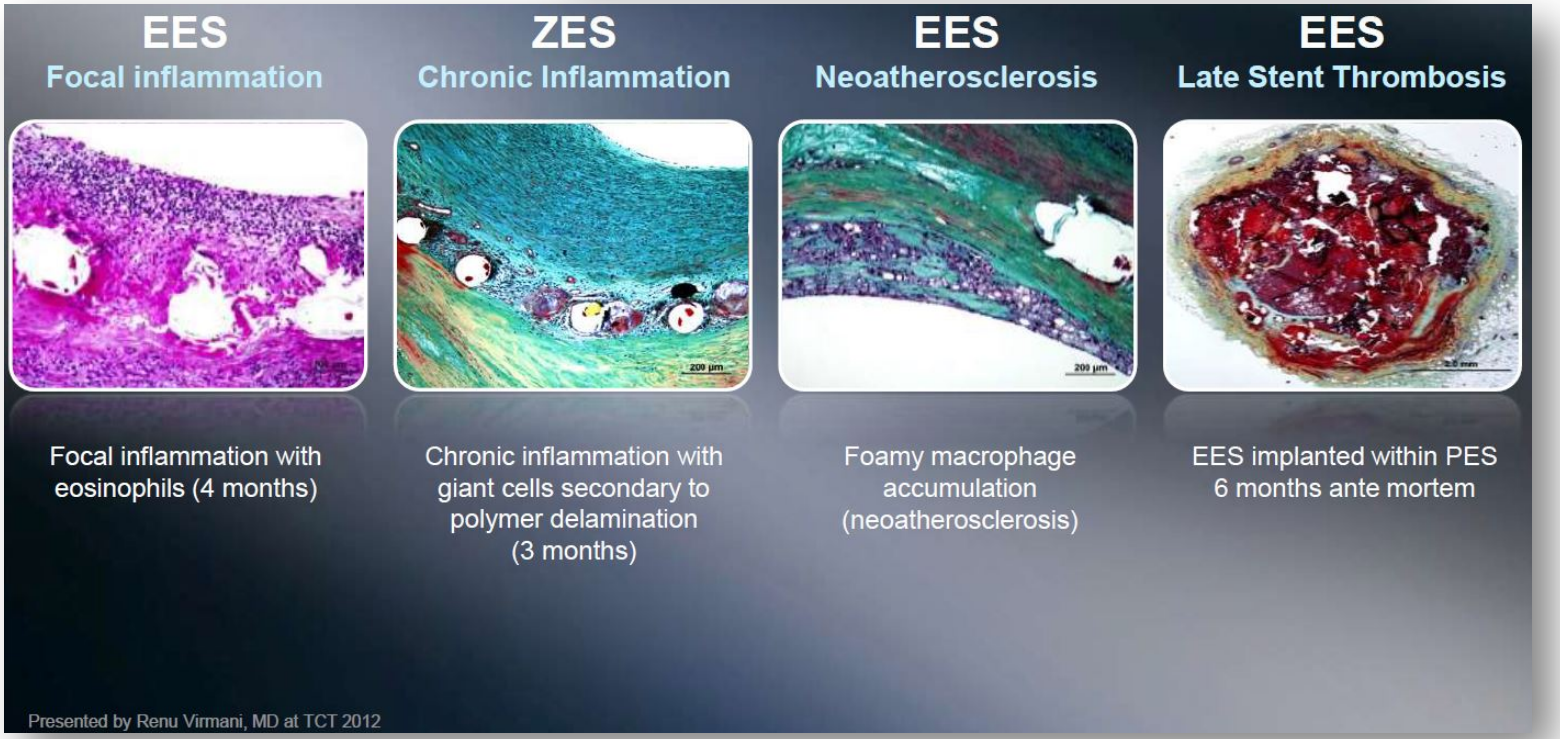
Quantité, composition, biocompatibilité, temps de dégradation, réponse inflammatoire et immunologique

Stent	Drug (concentration)	Polymer	Maximum polymer thickness (μm)	Release kinetics (days)	Metal	Strut thickness (μm)
First generation						
Cypher® (Cordis Corporation, Miami Lakes, FL, USA)	Sirolimus (140 μg/cm²)	Poly(ethylene co-vinyl acetate) and poly(n-butyl methacrylate)	12.6	80% (28)	SS	140
TAXUS® Express (Boston Scientific Scimed, Inc. Corporation, Maple Grove, MN, USA)	Paclitaxel (100 μg/cm²)	Poly(styrene-b-isobutylene-b-styrene)	16.0	<10% (28)	SS	132
TAXUS Liberté® (Boston Scientific Scimed, Inc. Corporation)	Paclitaxel (100 μg/cm²)	Poly(styrene-b-isobutylene-b-styrene)	16.0	<10% (28)	SS	97
Second generation						
Endeavor® (Medtronic Vascular, Inc., Santa Rosa, CA, USA)	Zotarolimus (100 μg/cm²)	Phosphorylcholine	4.1	95% (14)	CoCr	91
Resolute® (Medtronic Vascular, Inc.)	Zotarolimus (100 μg/cm²)	BioLinx® (Medtronic Vascular, Inc.)	4.1	85% (60)	CoCr	91
Xience V® (Abbott Cardiovascular Systems, Inc., Santa Clara, CA, USA)	Everolimus (100 μg/cm²)	Poly(vinylidene fluoride-hexafluoropropylene)	7.6	80% (28)	CoCr	81
TAXUS Element® (Boston Scientific Scimed, Inc. Corporation)	Paclitaxel (100 μg/cm²)	Poly(styrene-b-isobutylene-b-styrene)	15.0	<10% (90)	PtCr	81
PROMUS Element® (Boston Scientific Scimed, Inc. Corporation)	Everolimus (100 μg/cm²)	Poly(vinylidene fluoride-hexafluoropropylene)	6.0	87% (90)	PtCr	81

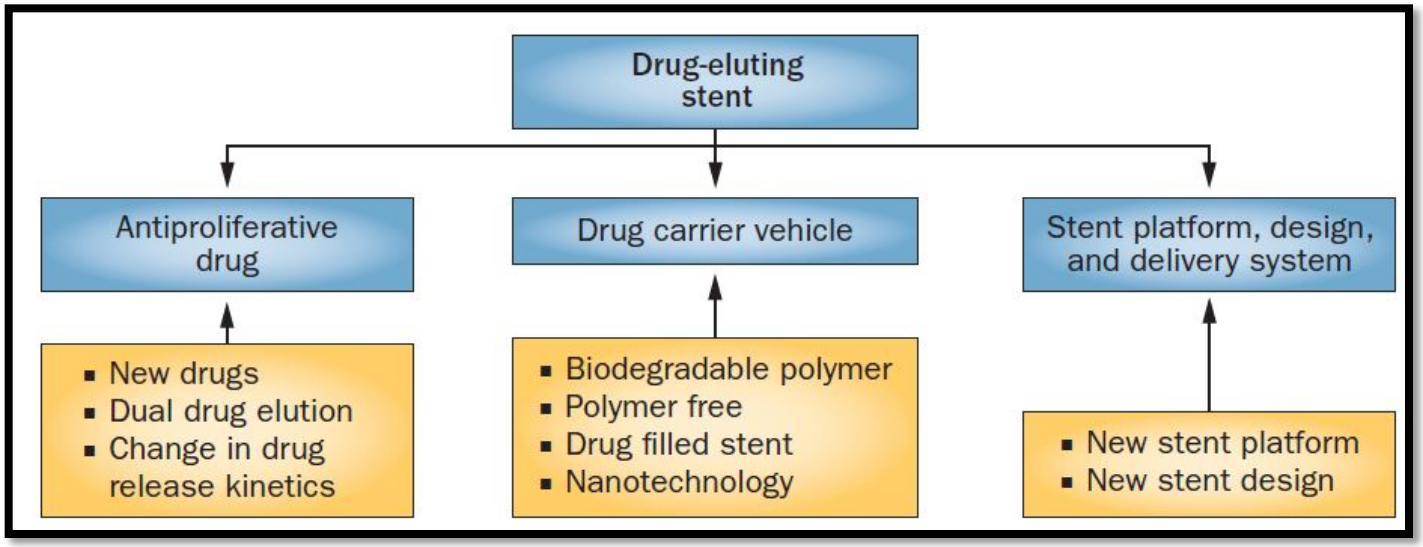
Garg, S. *et al. Nat. Rev. Cardiol.* **10**, 248–260 (2013)

Malgré ces avancées …





DES: comment améliorer encore sécurité et efficacité ?



Garg, S. *et al. Nat. Rev. Cardiol.* **10**, 248–260 (2013)

- Trois approches pour réduire les évènements tardifs:
  - DES métallique et **polymère résorbable**
  - DES métallique **sans polymère**
  - **BioResorbable Scaffolds**

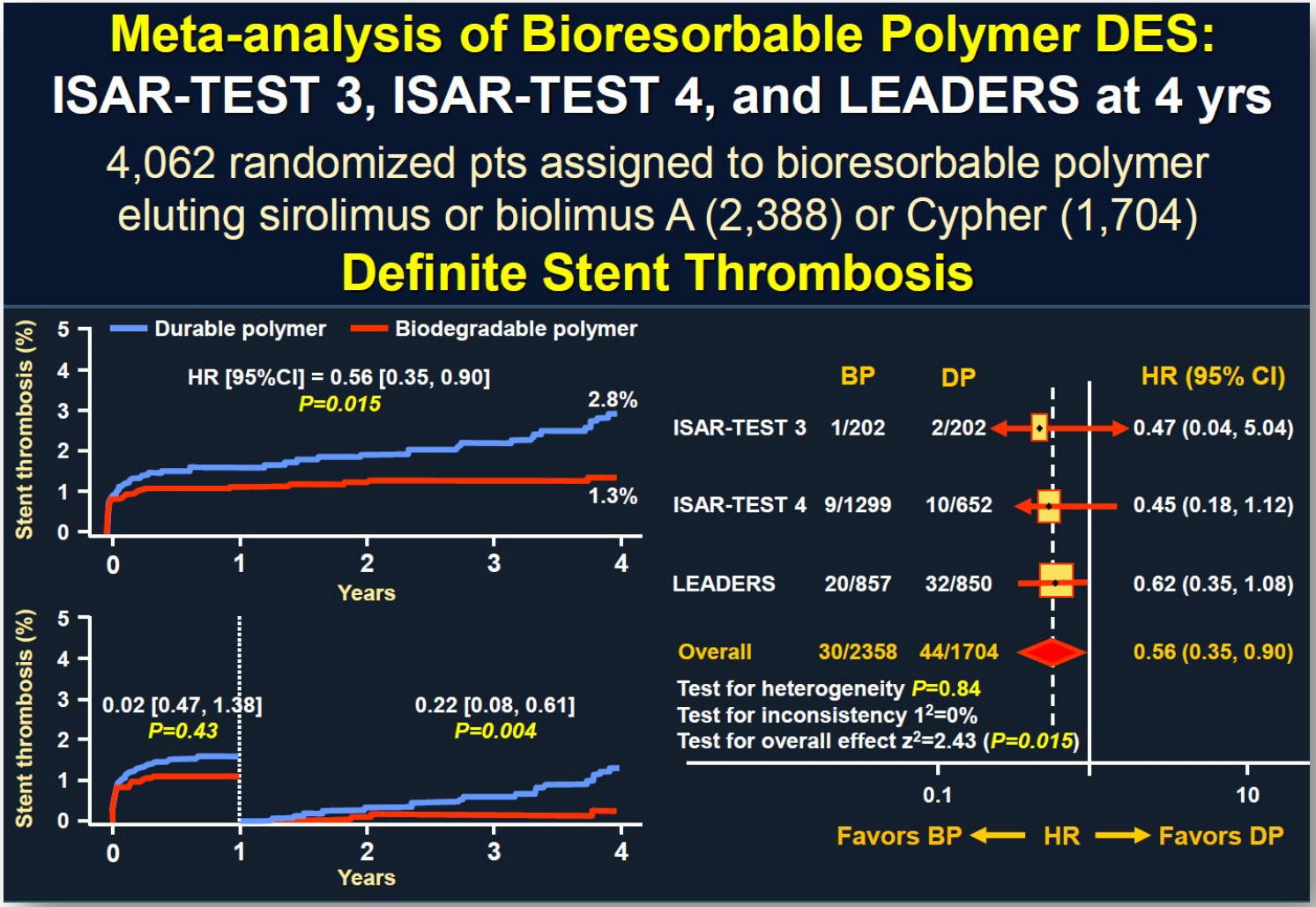
DES à polymère résorbable

Stent	Drug (concentration)	Polymer	Maximum polymer thickness (μm)	Duration of biodegradation (months)	Release kinetics (days)	Metal	Strut thickness (μm)
Axxess® (Biosensors Europe S.A. Corporation, Morges, Switzerland)	Biolimus A9 (22 μg/mm)	PLA*	15*	6–9	45% (30)	Nitinol	152
BioMatrix® (Biosensors Europe S.A. Corporation)	Biolimus A9 (15.6 μg/mm)	PLA*	10*	6–9	45% (30)	SS	112
Combo® (OrbusNeich Medical, Inc., Ft Lauderdale, FL, USA)	EPC + Sirolimus (5 μg/mm)	PLA, PLGA, CAP*	3–5*	<3	95% (35)	SS	100
DESyne® BD (Elixir Medical Corporation, Sunnyvale, CA, USA)	Novolimus (5 μg/mm)	PLA	<3	6–9	90% (90)	CoCr	81
Elixir Myolimus™ (Elixir Medical)	Myolimus (3 μg/mm)	PLA	<3	6–9	90% (90)	CoCr	80
Infinnium™ (Sahajanand Medical Technologies Ltd, Surat, India)	Paclitaxel (122 μg/19 mm)	PLLA, PLGA, PLC, PVP	4–5	7	50% (9–11)	SS	80
MiStent® (Micell Technologies, Inc., Durham, NC, USA)	Crystalline sirolimus (NA)	PLGA	NA	3	100% (60)	CoCr	64
Nobori® (Terumo Corporation, Tokyo, Japan)	Biolimus A9 (15.6 μg/mm)	PLA*	10*	6–9	45% (30)	SS	112
Supralimus™ (Sahajanand Medical Technologies Ltd)	Sirolimus (125 μg/19 mm)	PLLA, PLGA, PLC, PVP	4–5	7	50% (9–11)	SS	80
SYNERGY® (Boston Scientific Scimed, Inc. Corporation, Maple Grove, MN, USA)	Everolimus (LD: 56 μg/20 mm) (SD: 113 μg/20 mm)	PLGA rollcoat*	LD: 3; SD: 4	3	50% (60)	PtCr	71

*Abluminal polymer. Abbreviations: CAP, κ- caprolactone; CoCr, cobalt chromium; EPC, endothelial progenitor capture; LD, low dose; NA, not available; PLA, polylactic acid; PLC, 75/25 poly-L-lactide; PLGA, poly(lactide-co-glycolide); PLLA, poly-L-lactic acid; PtCr, platinum chromium; PVP, polyvinyl pyrrolidone; SD, standard dose; SS, stainless steel.

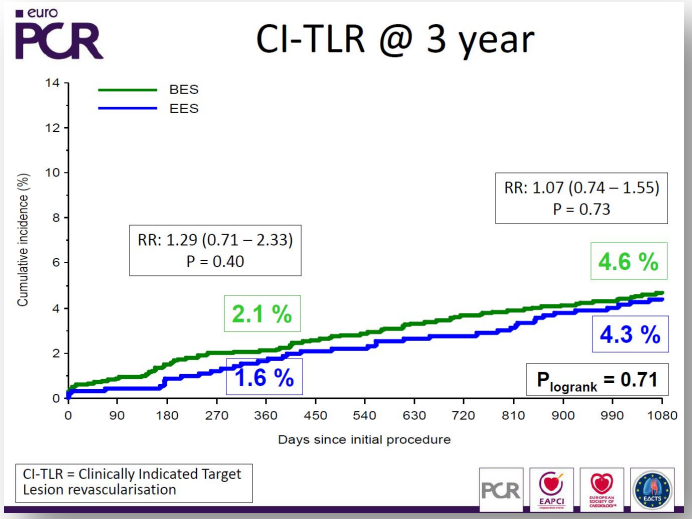
Garg, S. *et al. Nat. Rev. Cardiol.* **10**, 248–260 (2013)

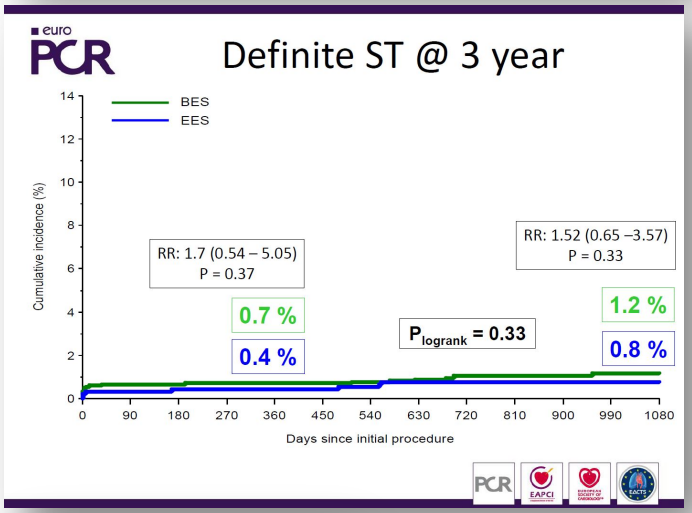
DES à polymère résorbable



Stefanini GG et al. *EHJ* 2012;33:1214–22

DES à polymère résorbable

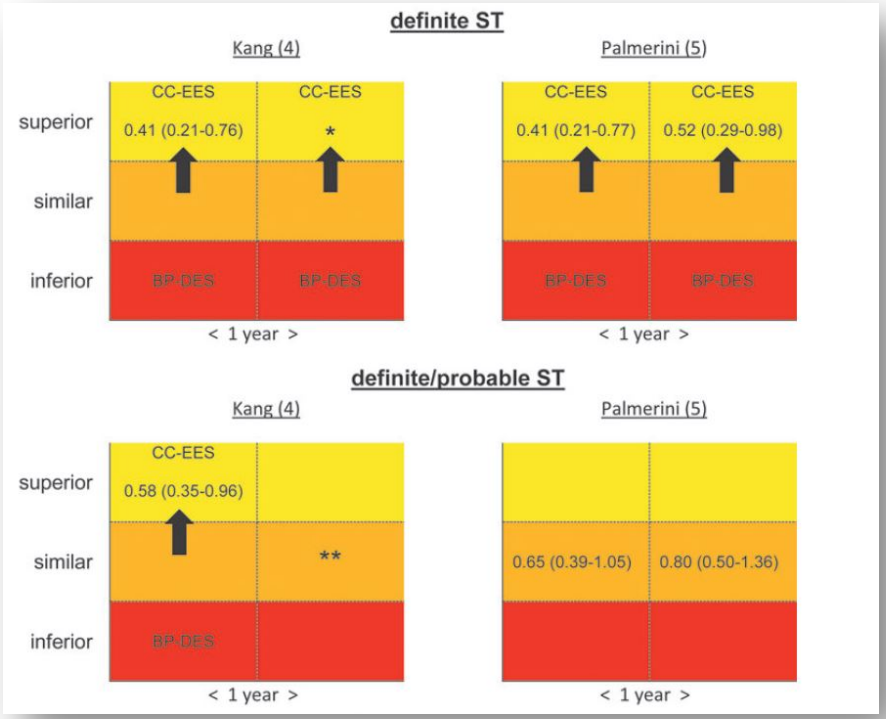




COMPARE II trial
3 year follow-up data

Pieter Smits

PCR2014



D'après Pfisterer EHJ 2014

Métaanalyses de
Palmerini n=85490
Kang n=90584

DES sans polymère

BioFreedom Stent (Biosensors)

Hypothesis: Polymer-free drug release via poro… stents may reduc… caused by poly… coating

Selectively micro-structured surface holds drug in abluminal surface structures

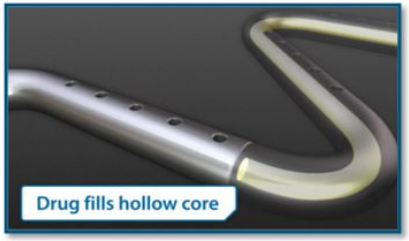
Potential ad…

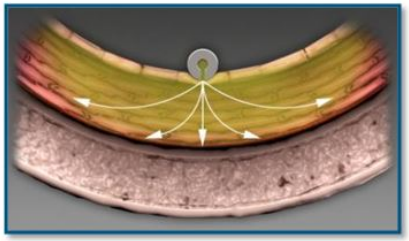
- Avoid long term la… effects that might … the polymer
- Improved surface … there is no polyme… or pealed away fr… struts
- Possible shorter r… antiplatelet therap…

Medtronic

Drug-Filled Stent (DFS) Technology

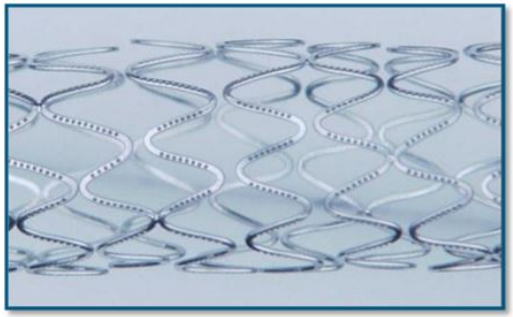
Polymer Free Drug Delivery





Design Goals:

- Bare Metal Surface
- Design to improve drug carrier issues such as:
  - Polymer biocompatibility
  - Inflammation upon polymer degradation
  - Surface coating durability
- Allow for controlled, prolonged, and tailored elution profiles



BioResorbable Scaffolds

Novel devices

Bioresorbable scaffolds: rationale, current status, challenges, and future

Javaid Iqbal[1], Yoshinobu Onuma[1], John Ormiston[2], Alexandre Abizaid[3], Ron Waksman[4], and Patrick Serruys[1]*

European Heart Journal (2014) **35**, 765–776

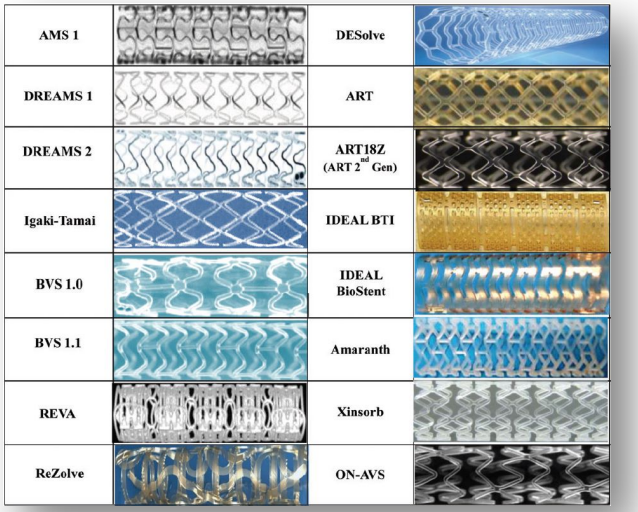


Table 4 Summary of clinical trials with bioresorbable scaffolds

Scaffold	Clinical study	Number of patients	Major endpoints	Late loss (mm)	TLR	MACE
Metallic						
AMS-1	PROGRESS-AMS	63	MACE at 4 months	1.08 at 4 months	24% at 4 months	24% at 4 months
DREAMS-1	BIOSOLVE-I	46	Target lesion failure at 6 and 12 months	0.64 at 6 months 0.52 at 12 months	4.3% at 6 months 6.5% at 12 months	4.3% at 6 months 6.5% at 12 months
Polymeric						
Igaki-Tamai	Igaki-Tamai study	15	Acute recoil, late loss, and MACE at 6 months	0.48 at 6 months	6.7% at 6 months	6.7% at 6 months
BVS 1.0	ABSORB Cohort A	30	Acute success, MACE up to 5 years	0.44 at 6 months	0% at 6 months, 0% at 5 years	3.3% at 6 months, 3.4% at 5 years
BVS 1.1	ABSORB Cohort B	101	LLL, TLR, and MACE at 6 months, 1, 2, and 3 years	0.19 at 6 months 0.27 at 12 months	3.6% at 12 months	9% at 2 years 10% at 3 years
DESolve	DESolve 1	15	LLL at 6 months	0.19 at 6 months	6.7% at 12 months	20% at 12 months
	DESolve NX	120	Procedural success, LLL at 6 months, and MACE up to 5 years	0.21 at months	1.6% at 6 months	3.25% at 6 months
REVA	RESORB	27	MACE	1.81 at 6 months	66.7% at 6 months	
ReZolve	RESTORE	50	TLR at 6 months, LLL at 12 months	0.20 at 12 months for $n = 8$	2 of 12 at 6 months	2 of 12 at 6 months

LLL, late lumen loss; MACE, major adverse cardiac events; TLR, target lesion revascularization.

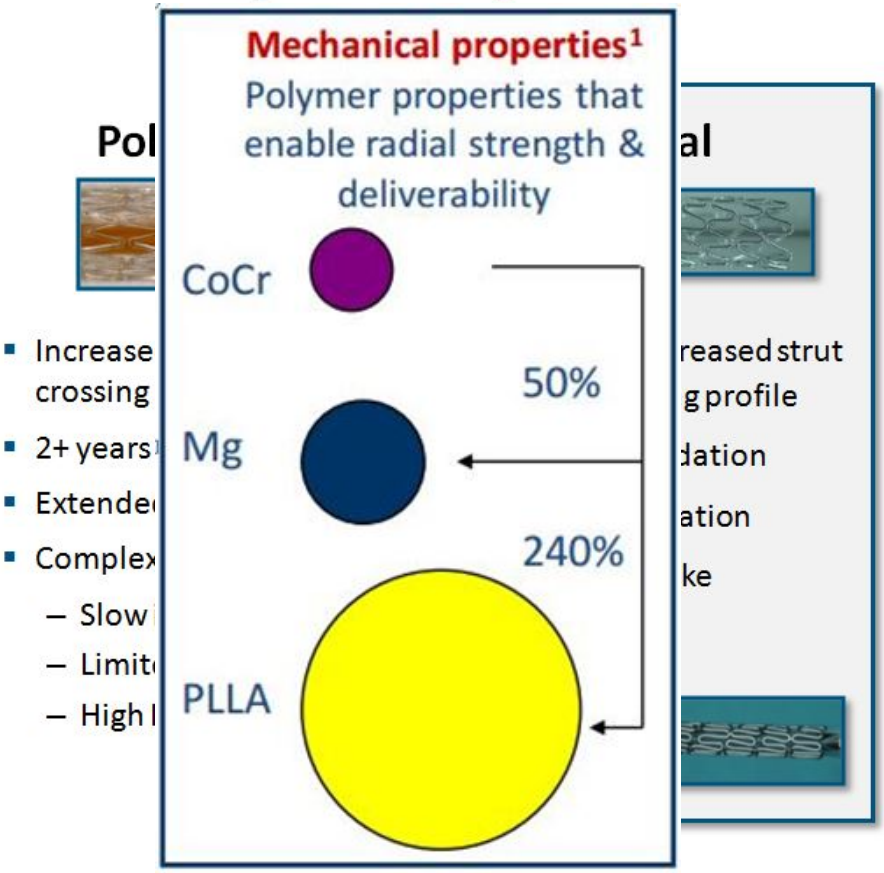
BioResorbable Scaffolds

Medtronic

Bioabsorbable Stent Technology

Objective: DES-like performance with clinically relevant degradation time

Design Targets	Medtronic Goal
Efficacy equivalent to DES	In all lesions treated by DES
Adequate radial strength	3-6 months
Appropriate degradation time	6-12 months
Anticipated DAPT duration	Equal or better than current DES
Adequate deliverability & conformability	Similar to current DES
Minimal change to implant procedure	Similar to current DES



Conclusions

- Problèmes de Sécurité à long terme des DES de 1ère G
  - → modifications des plateformes, polymères, drogues
- DES 2ème G plus sûrs et au moins aussi efficaces que les 1ère G mais évènements très tardifs persistants (thrombose, resténos)
  - → DES 3ème G = à polymère biodégradable ↓ DAPT
    - Alternative efficace et sûre au polymères durables
    - Autres pistes: sans polymères, totalement résorbables
      - Quid des évènements à long terme ?
- Si essais DES biorésorbables montrent:
  - ↓évènements tardifs 1-5 ans
  - Effet favorable sur les plaques → DES 4ème G