



Université Lille Nord de France



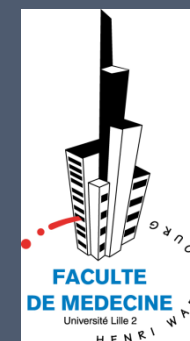
Centre Hospitalier Régional
Universitaire de Lille



Inserm

Institut national
de la santé et de la recherche médicale

STENTING, LE POINT SUR LA BIOCOMPATIBILITÉ



N. Blanchemain, F. Chai, M. Gargouri, J. Sobocinski, S. Haulon

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Les maladies cardiovasculaires

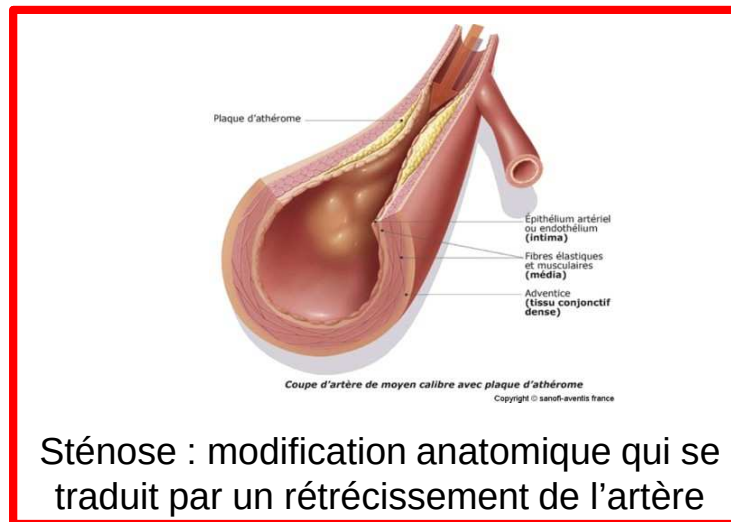
Première cause de mortalité dans les pays occidentaux

2



- Facteurs non modifiables : âge, sexe, antécédents médicaux personnels et familiaux
- Facteurs de risques modifiables : Cholestérol, diabète, hypertension, consommation de tabac, surpoids et sédentarité

Conséquences cliniques



Sténose : modification anatomique qui se traduit par un rétrécissement de l'artère



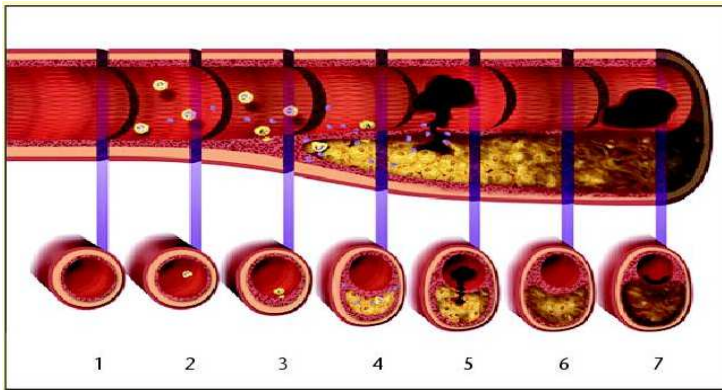
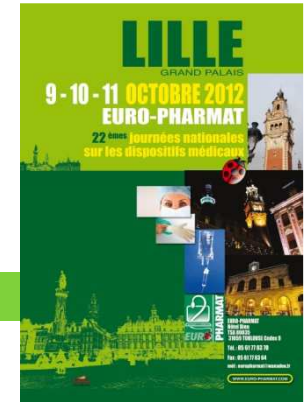
Anévrisme : Dilatation localisée de la paroi d'une artère aboutissant à la formation d'une poche.



L'athérosclérose

Prise en charge médicamenteuse

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Plaque d'athérome d'une coupe de la carotide

■ Statines

- Inhibition de l'HMG-Coenzyme A réductase
- Anti-inflammatoires
- Stabilisation de la plaque par une inhibition de la minéralisation

■ AAP : Clopidogrel

- Effet vasodilatateur
- Diminution de la réactivité des CML

■ Cilostazol

- Vasodilatateurs
- inhibe la prolifération des CMLs
- Rôle antiangiogénique

■ Héparines

- Action anticoagulantes: facteurs IIa et Xa
- Limite la migration et prolifération des CMLs

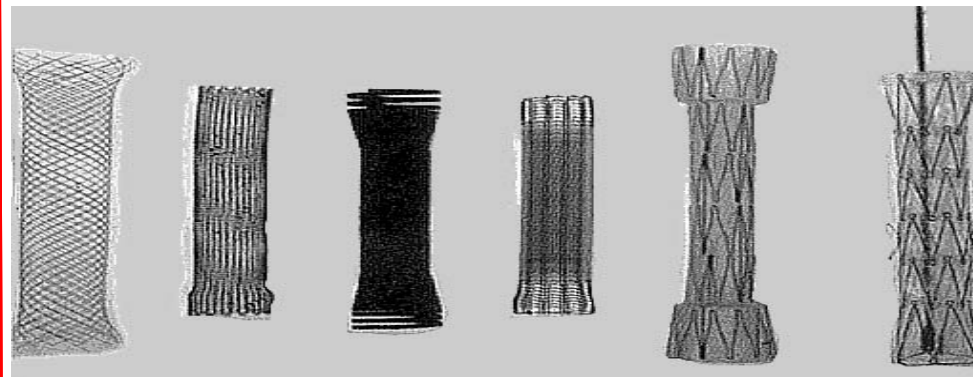
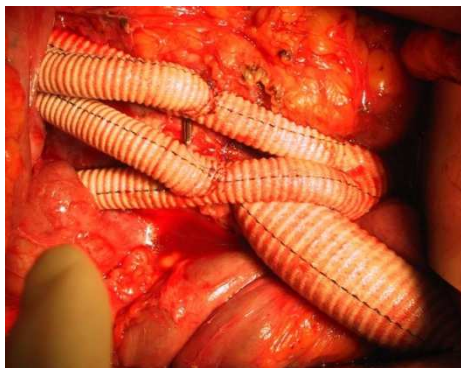
Quelles solutions?

Prise en charge chirurgicale

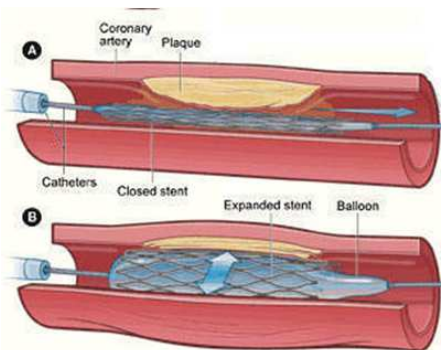
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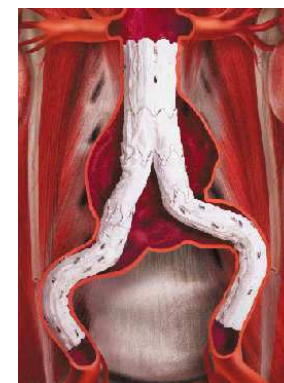
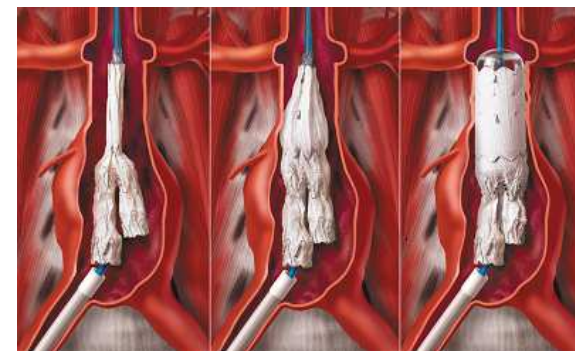
Prothèse vasculaire en PET tissé/ tricoté (Dacron®) ou en PTFE (Teflon®) pour le pontage



Stent nu métallique en alliage de titane, acier inoxydable ou CoCr pour rouvrir la lumière artérielle (sténose)



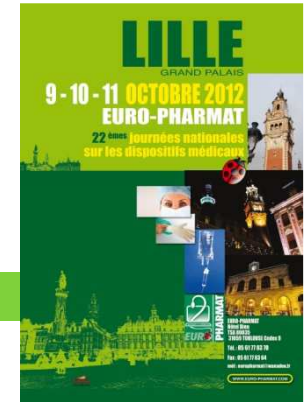
Stent couvert ou endoprothèse pour la dilatation d'artère (anévrisme)



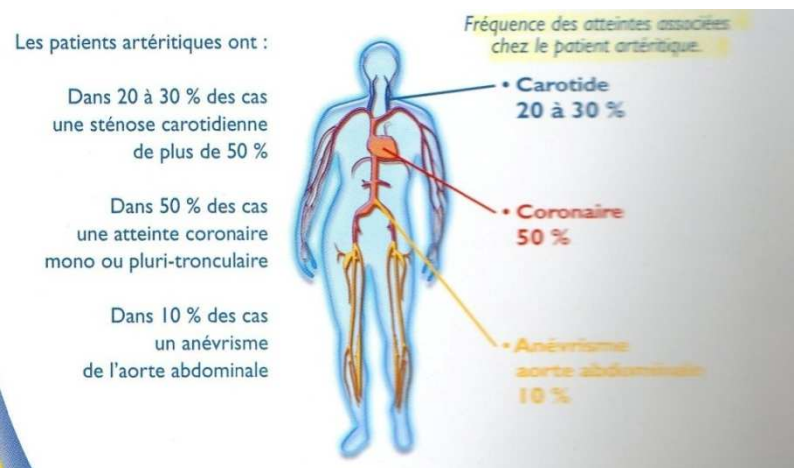
Quelles solutions?

Les stents métalliques

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Localisation préférentielle

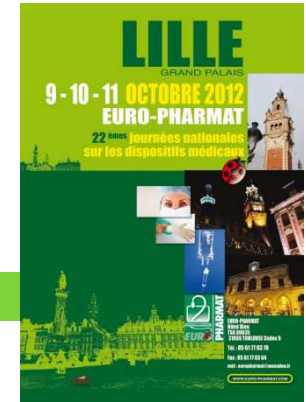


Différents matériaux

- Acier 316L
 - Ballon expansible
 - Auto expansible
- CoCr
 - Ballon expansible
- NiTiNOL
 - Auto-expansible

Quelles sont les complications?

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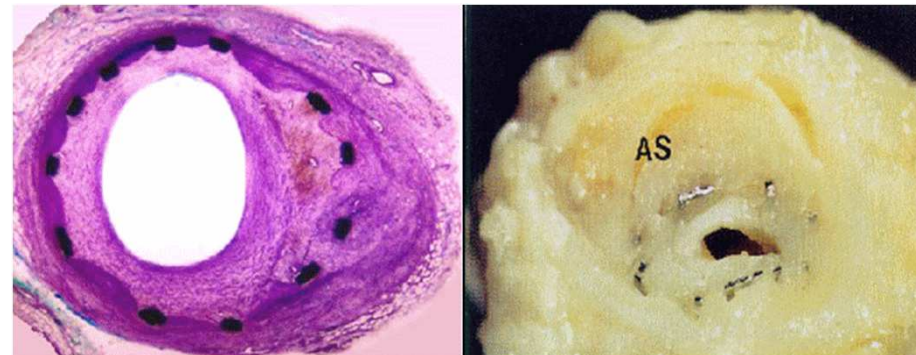
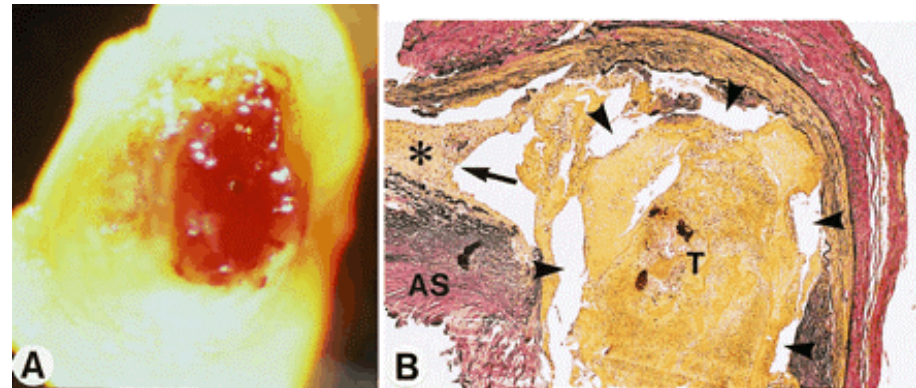


Thrombose

- Précoce et aiguë, 5 % des cas avec une inflammation importante

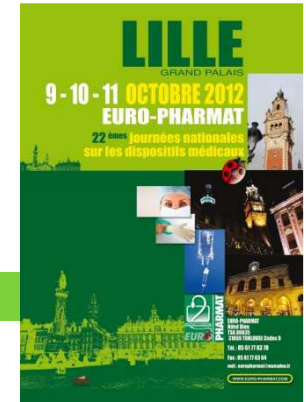
Resténose intra-stent

- Tardive et progressive, 30% à 6 mois vs 45% pour l'angioplastie
→ Hyperplasie néointimale
- Cellules musculaires lisses
- Réaction inflammatoire (cellules géantes et macrophages)
- Néo-angiogénèse

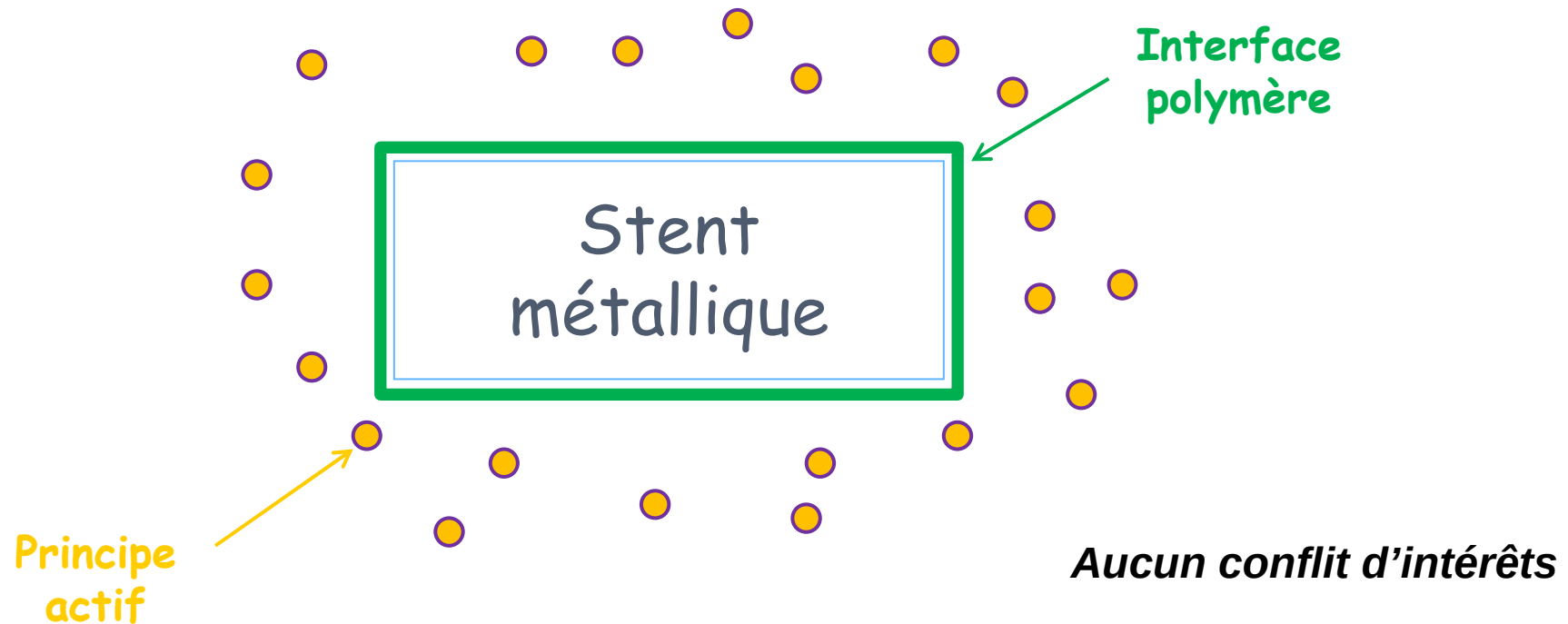


Drug eluting stent: Une solution?

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La cible : les cellules musculaires lisses
La protection : les cellules endothéliales



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Drug eluting stent: Une solution?

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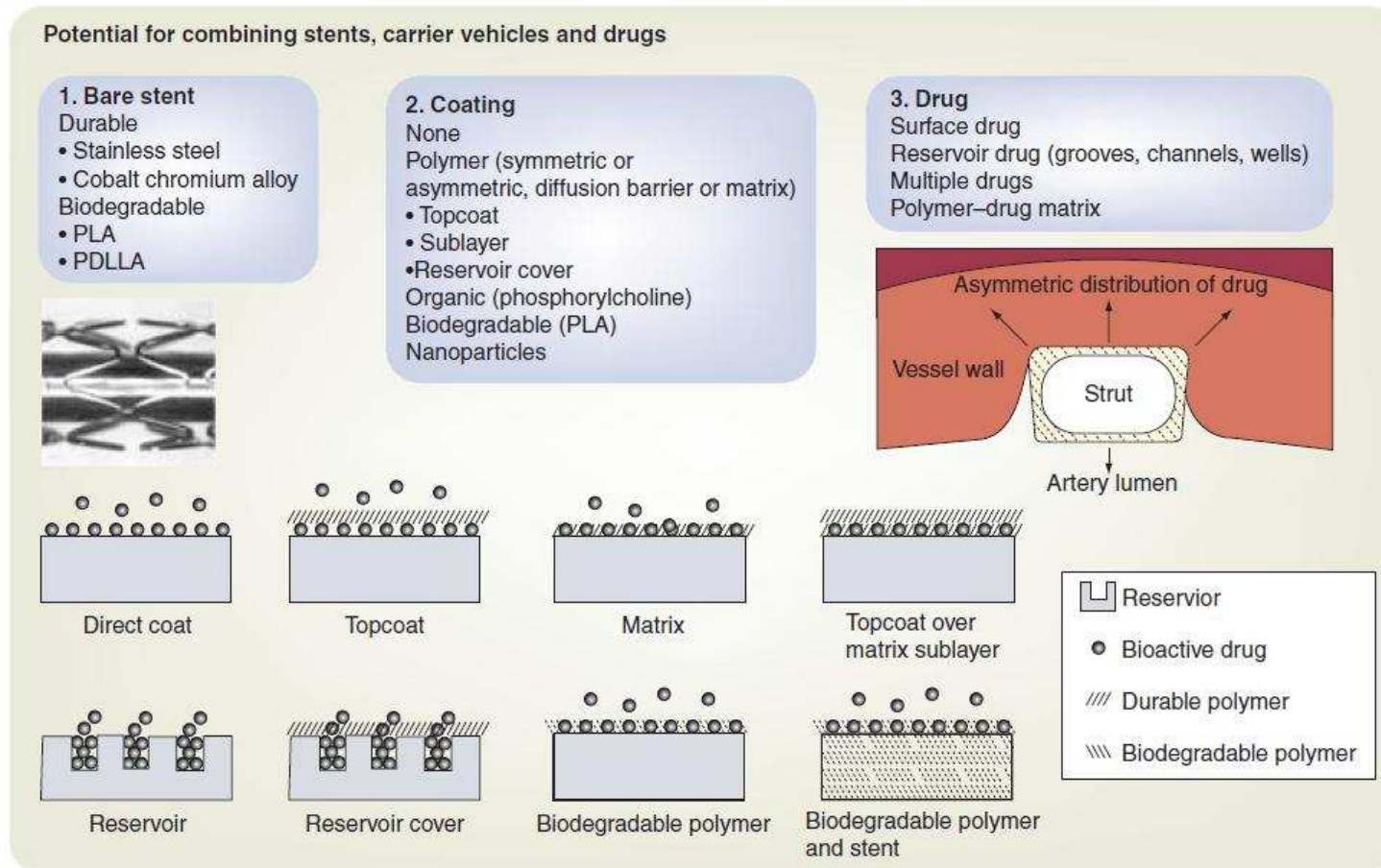


Figure 2. Components of drug-eluting stents.
PLA: Polylactic acid.

Grube et al., Expert Rev Med Device, 2006

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Drug eluting stent: Une solution?

Sans matrice polymère

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Zilver PTX Stent, Cook Médical

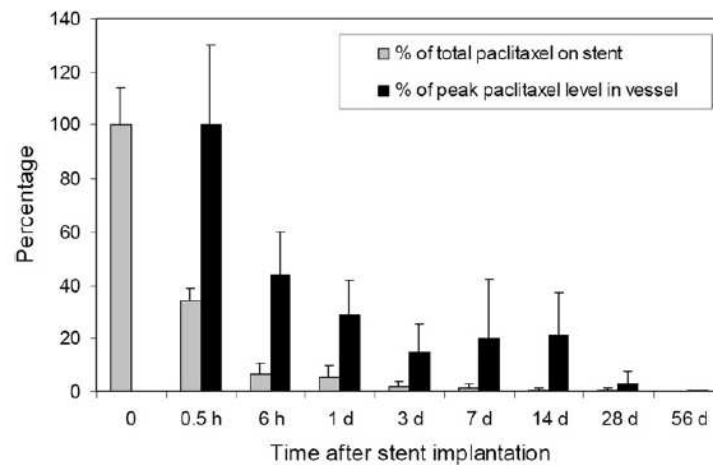


Figure 2. Relative paclitaxel levels remaining on the stent and in the artery with stent implanted over time (h = hours, d = days). Gray bars show the amount of paclitaxel remaining on stent ($n = 8$ each) expressed as a percentage of the total paclitaxel carried by an unimplanted stent (100% gray bar shown at 0 h). Black bars show the amount of paclitaxel in artery with stent implanted ($n = 8$ each) expressed as a percentage of the peak arterial level (100% black bar shown at 0.5 h). Error bars represent standard deviations.

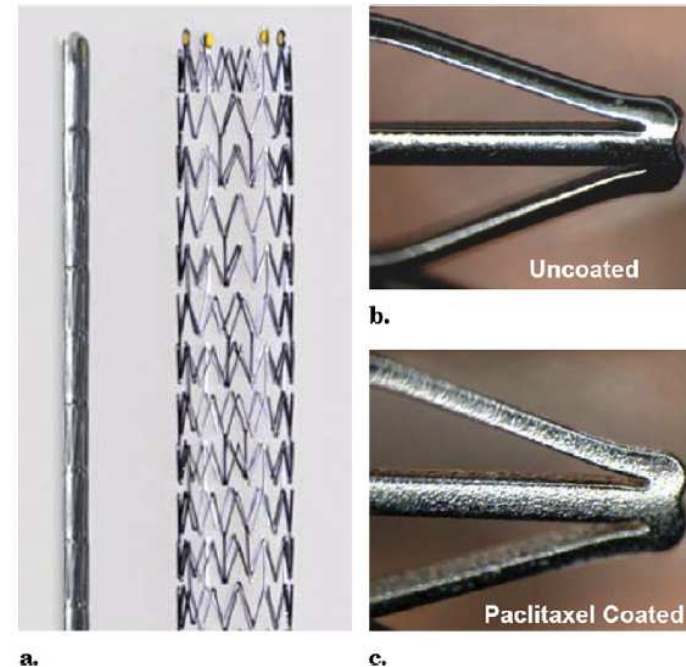
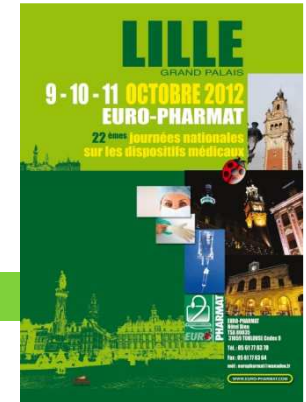


Figure 1. Zilver PTX drug-eluting stent (Cook Medical, Inc, Bloomington, Indiana). (a) Compressed (left) and fully expanded (right) stent. (b,c) Close-up views of bare stent struts and stent struts with the polymer-free paclitaxel coating. (Available in color online at www.jvir.org.)

Dake et al., J Vasc Interv Radio, 2011

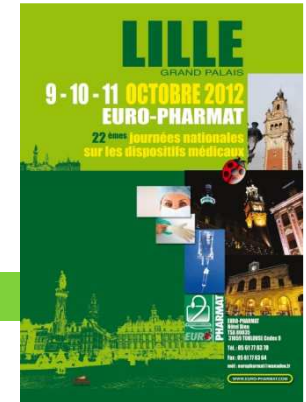
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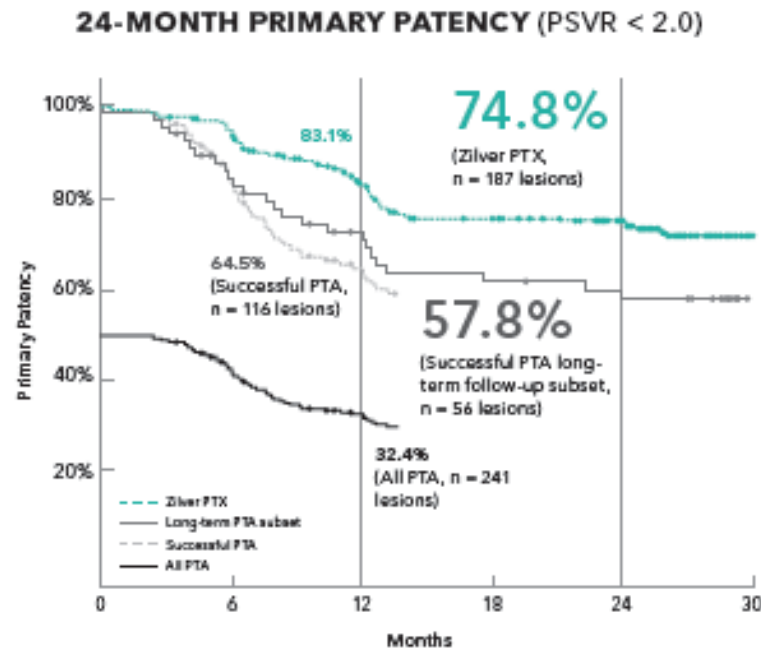
Drug eluting stent: Une solution?

Sans matrice polymère

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COOK[®] MEDICAL **Zilver[®] PTX[®]**
DRUG-ELUTING PERIPHERAL STENT

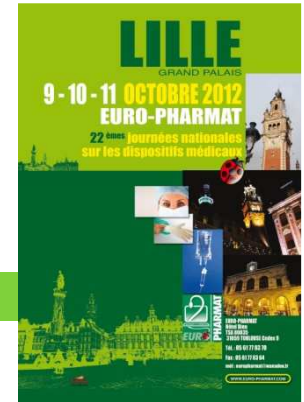


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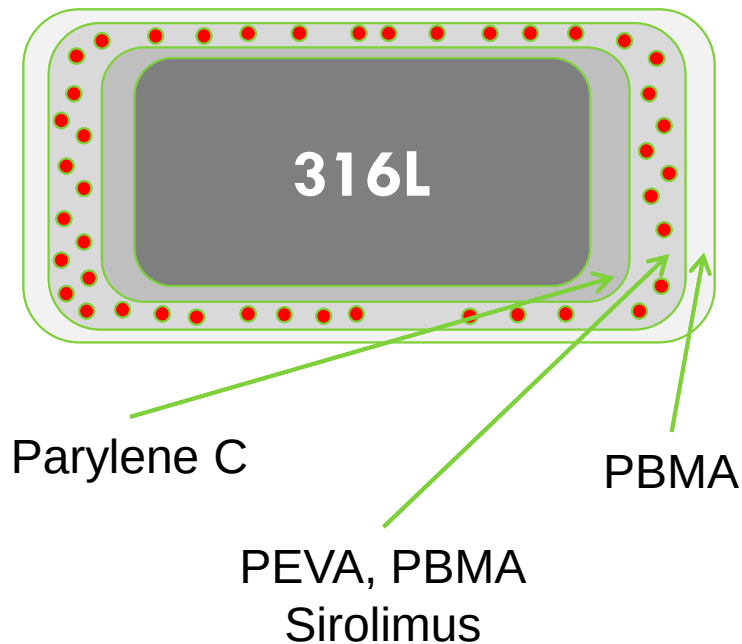
Drug eluting stent: Une solution?

Polymère non résorbable

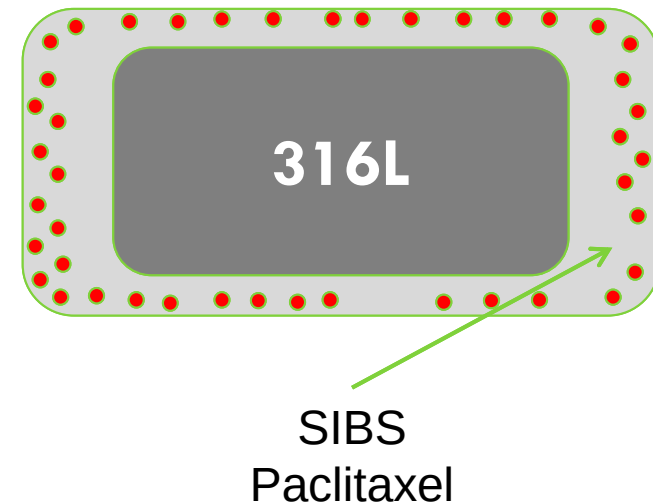
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Cypher, Johnson & Johnson, Cordis



Taxus, Boston Scientific



PEVA : Poly Ethylène-co-vinyl acétate
PBMA : Poly-n-butyl méthacrylate

SIBS : Poly Styrène isobutylène styrène

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Drug eluting stent: Une solution?

Polymère non résorbable

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Cypher, Johnson & Johnson, Cordis

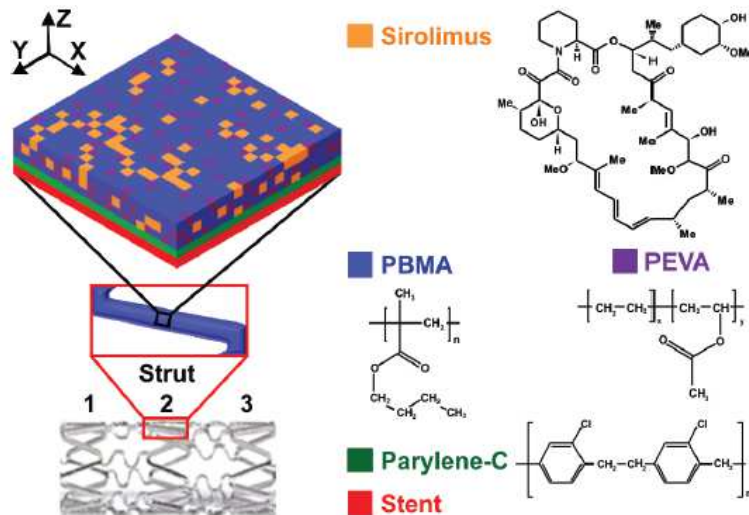


Figure 1. Side-view schematic of the CYPHER stent (bottom left) with strut locations 1–3 separated by purple dashed lines. A location on strut 2 is magnified (red box), with an ROI outlined (black box) and remagnified. A 3D schematic of the ROI (upper left) shows sirolimus, PBMA, PEVA, parylene-C, and the stent represented by color-coded orange, blue, purple, green, and red blocks, respectively. The chemical structures of all coating components are shown.

- Polymère PEVA (Poly Ethylène-co-vinyl acétate) / PBMA (Poly-n-butyl méthacrylate) non résorbable avec un ratio de 67/33.

- Polymères biocompatibles

- Epaisseur totale des couches de polymères 12,6 μm

- 2 μm de parylène-C

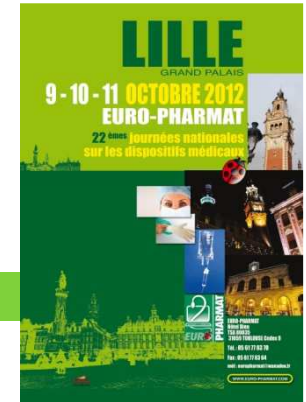
- 10 μm de PEVA/PBMA/sirolimus

- 0,6 μm de PBMA

- Sirolimus 1 $\mu\text{g}/\text{mm}^2$

Biggs et al., Langmuir, 2012

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Drug eluting stent: Une solution?

Polymère non résorbable

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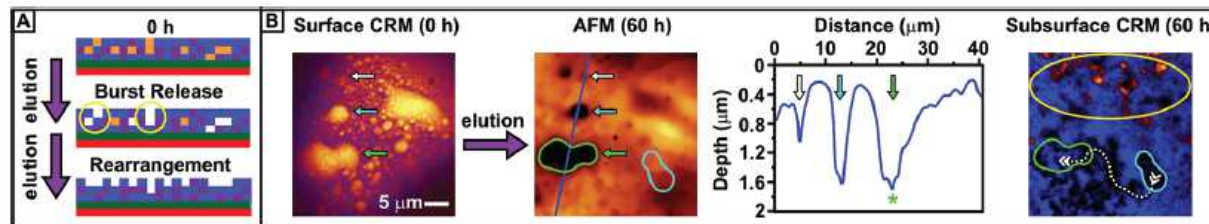
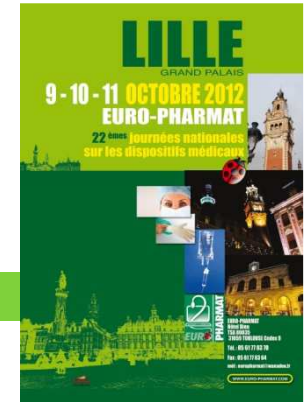
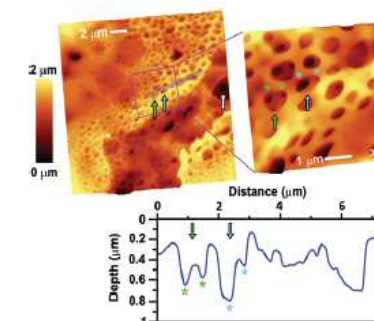


Figure 5. (A) Schematic representation of the elution process. The regions outlined in yellow mark locations where pore throat structures would be expected. (B) Locations of three drug-rich regions marked by white, light-blue, and green arrows in the surface CRM image at $t = 0$ h corresponding to three pores in the AFM image at 60 h of elution. An AFM line scan profile (blue line) of the three pores reveals a pore throat (green asterisk) at the base of the surface pore outlined in green. The phantom pore location (light-blue outline) is highlighted in both the AFM and subsurface CRM images (far right) at 60 h of elution. A dashed pathway in the subsurface CRM image navigates the vacated subsurface drug micronetwork from the phantom pore location to the location of the pore throat. A yellow oval marks isolated drug-rich pockets still present beneath the surface.

- Diffusion du Sirolimus, pas d'élimination du polymère
- 50% de libération en 10 jours, 90% en 60 jours, 100% après 90 jours



Raval et al., *Mechanism of Controlled release Kinetics from Medicam devices*, 2010

Biggs et al., *Langmuir*, 2012

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Drug eluting stent: Une solution?

Polymère non résorbable

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Taxus, Boston Scientific

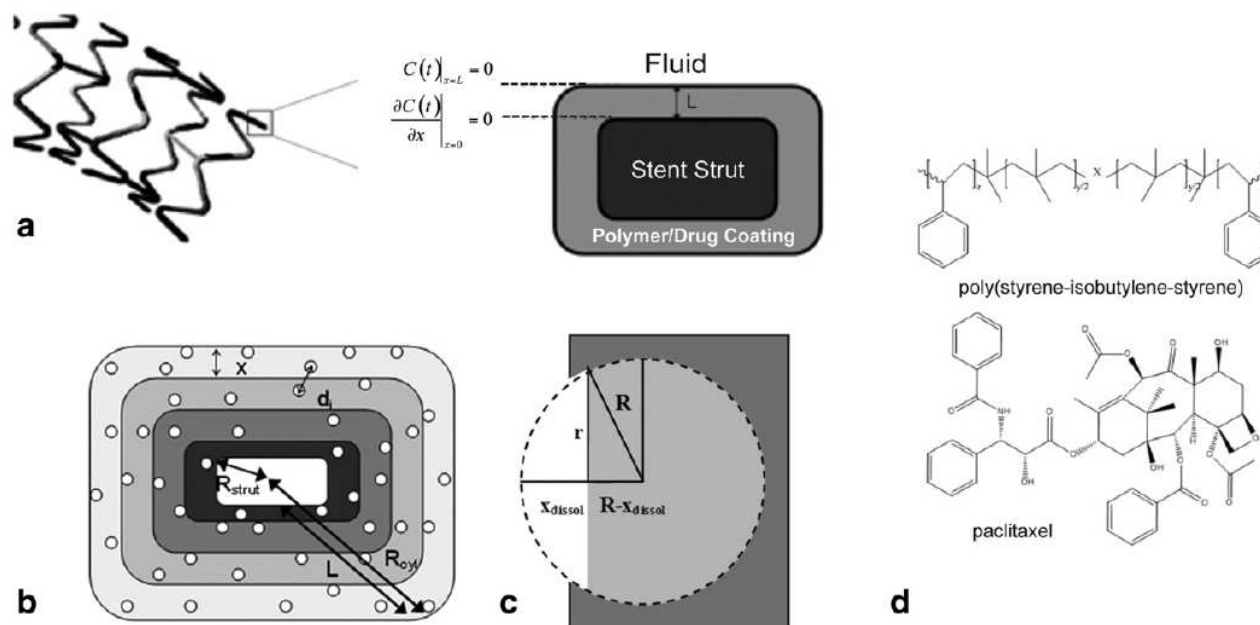


Fig. 1. Schematic of drug release from the polymer coating on the TAXUS[®] Express[®] stent. (a) In the diffusion and diffusion with bulk dissolution models, drug diffuses from the polymer phase to the fluid phase. The flux is zero at the stent-strut interface, such that $\partial C/\partial x|_{x=0} = 0$, and sink conditions are maintained at the polymer-fluid interface, such that $C(x=L) = 0$. (b) In the osmotic gradient model, a metal strut of radius R_{strut} is coated with polymer containing drug. The polymer coating is of thickness L , yielding a total cylinder radius of $R_{cyl} = R_{strut} + L$. Individual drug particle centers are separated by d_p . The cross section of the cylinder is divided into concentric annuli of width x , the average distance between particle centers, which is a function of loading percent and average particle radius. (c) In the surface dissolution model, a moving front of fluid dissolves particles of drug with convective transfer coefficient, h . The exposed particle surface area (m^2) is a function of dissolution depth (x_{dissol}) and time (t). (d) Chemical structures of poly(styrene-isobutylene-styrene) (SIBS) and paclitaxel (PTX).

Sirianni et al., J. Controlled Release, 2012

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Drug eluting stent: Une solution?

Polymère non résorbable

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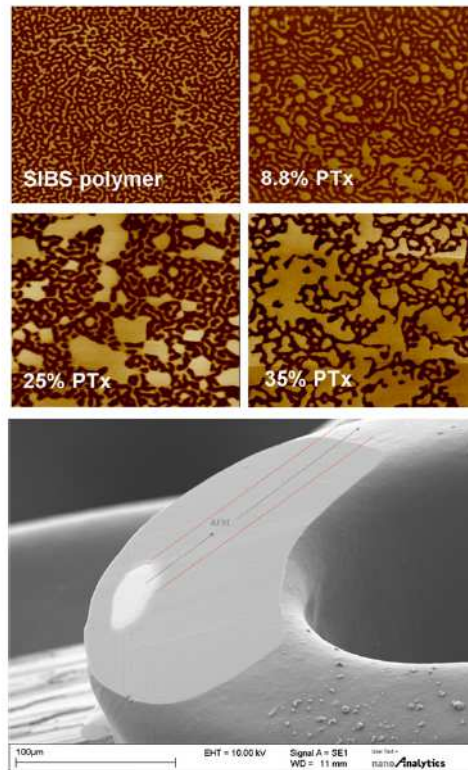


Fig. 4. AFM phase images ($2\mu\text{m} \times 2\mu\text{m}$) of subsurface stent coatings showing morphology of SIBS polymer without drug and with paclitaxel incorporated at 8.8, 25 or 35% loading of drug in polymer [2]. Images highlight the two-phase morphology of the polymer as well as the distribution and increasing size of drug depots (large light colored spaces) as percent drug loading increases. The SEM (lower panel) shows a typical coated stent after cryomicrotomy preparation of subsurface samples for AFM.

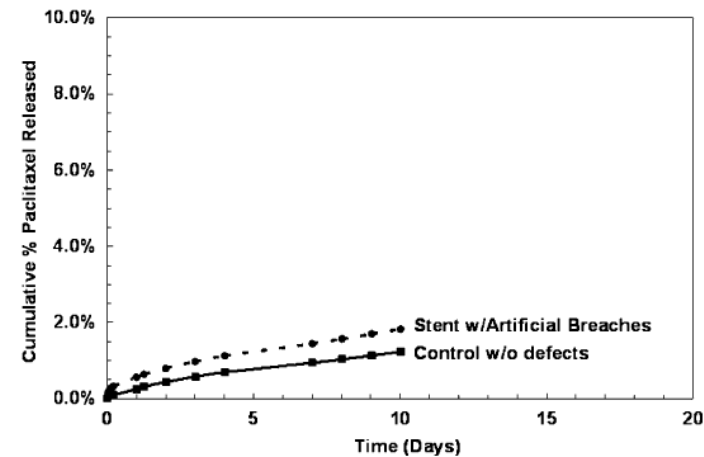
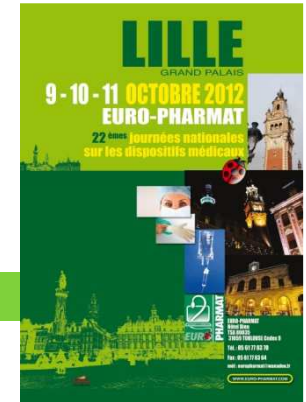


Fig. 6 Percent cumulative paclitaxel release from TAXUS[®] Express[®] Paclitaxel-Eluting Coronary Stents with simulated coating breaches

- Elution du Paclitaxel avec un profil bi-phasique
- 10% de libération après 10 jours, 90% du Paclitaxel reste piégé dans le polymère

Sirianni et al., *J. Controlled Release*, 2012
Boden et al., *J. Mater Sci: Mat Med*, 2009

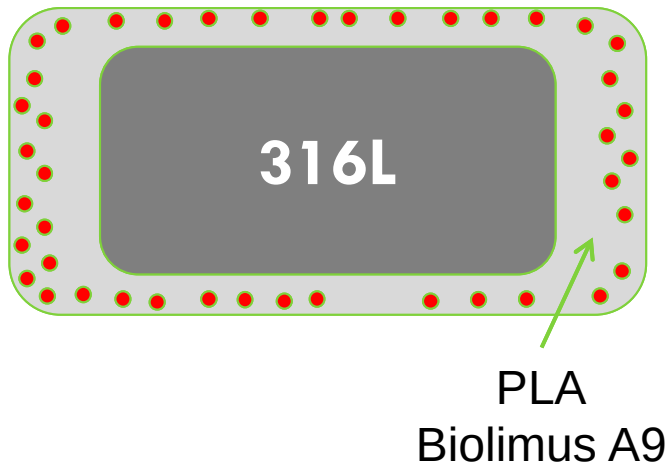


Drug eluting stent: Une solution?

Polymère résorbable

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Biomatrix, Biosensors Interventional Technologies



- PLA bio-résorbable (6-9 mois), épaisseur 15 μm
- Chargement 50/50 en PLA/Biolimus A9
- 15.6 μg de Biolimus par mm de stent
- Libération pendant 4 semaines

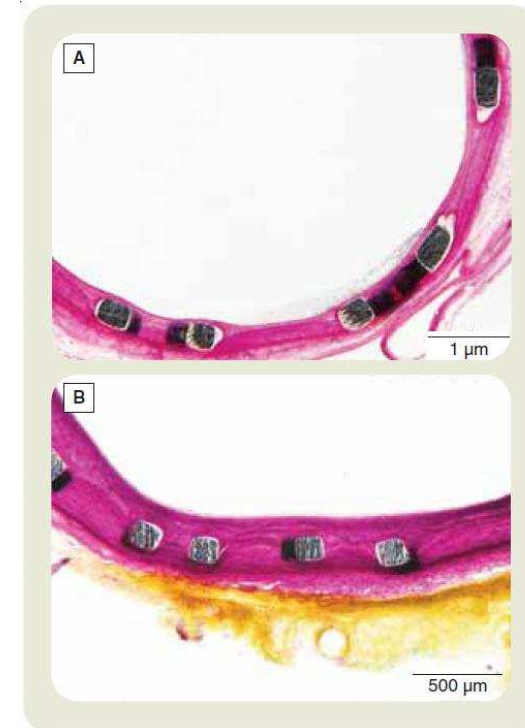
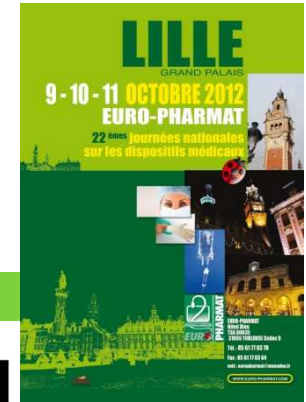


Figure 8. BioMatrix 28-day histology in the porcine overstretch model.

Grube et al., *Expert Rev Med Device*, 2006

Drug eluting stent: Une solution?

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BMS, 24 mois



DES, 24 mois

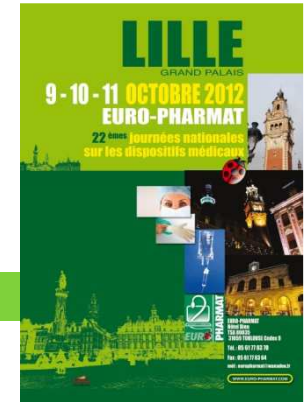


**En coronaire, aucun n'a montré sa
supériorité par rapport à l'autre**

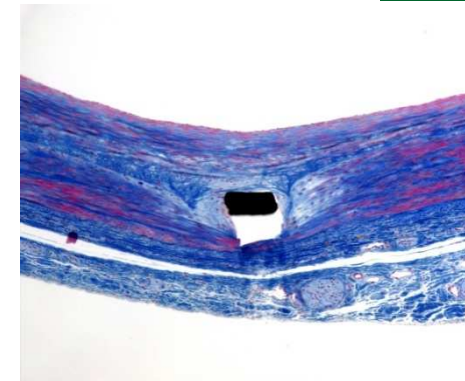
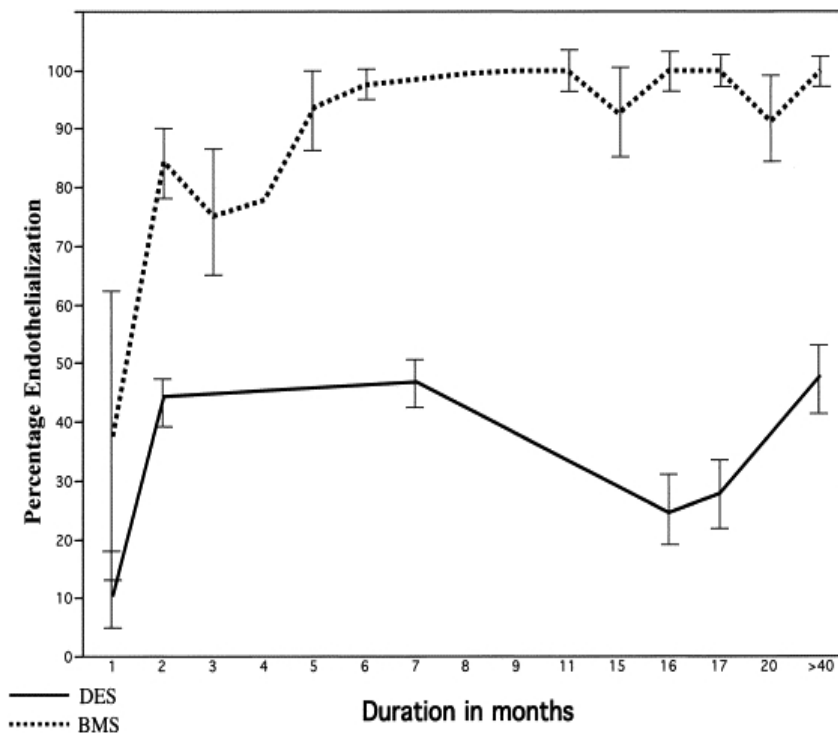
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Drug eluting stent: Une solution?

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On réduit prolifération des CML...



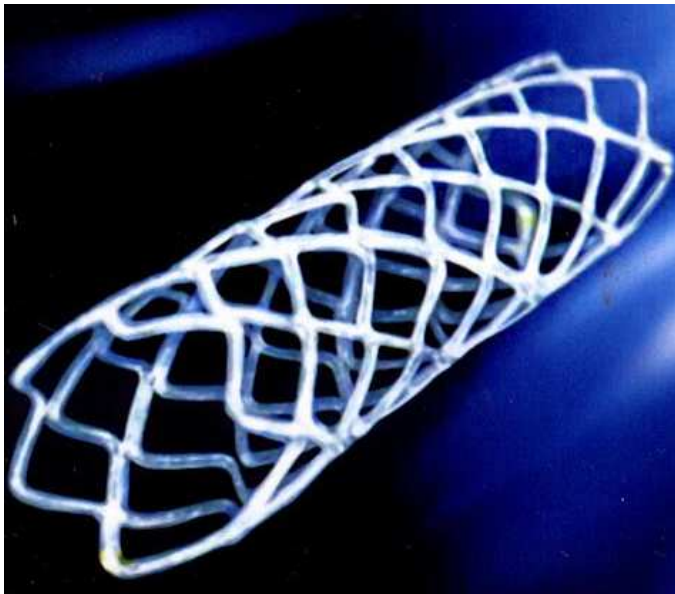
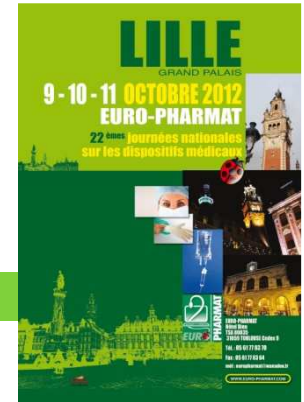
... Mais on réduit la prolifération des cellules endothéliales ...

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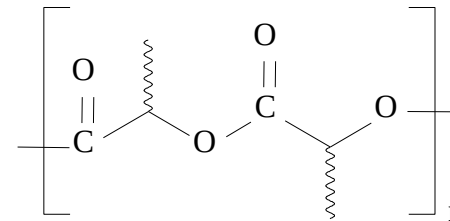
Drug eluting stent: nouvelles pistes?

Polymère adsorbable

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- Structure PLLA (acide poly-L-lactique) biocompatible et bioresorbable



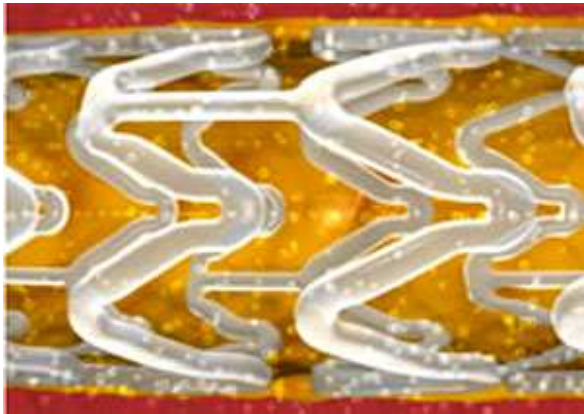
- Etude à long terme → application coronaire
- Marque CE et FDA dans 2 ans (prévision)

Drug eluting stent: nouvelles pistes?

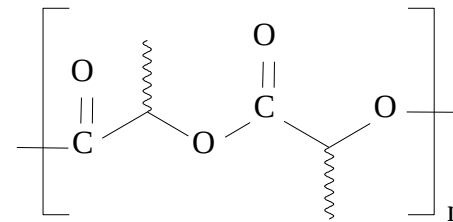
Polymère adsorbable

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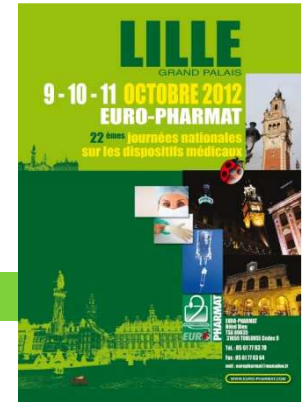
Adsorb, Abbot Vascular



- Structure PLLA (acide poly L-lactique) et PDLLA (acide poly D-L-lactique) biocompatible et bio résorbable (2 ans)

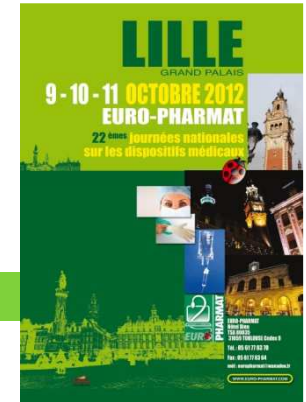


- La matrice polymère est chargée d'évérolimus
- Stent en test aux USA, pas de marquage
- Pas de thrombose et pas d'AAP



Drug eluting stent: nouvelles drogues?

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Molécules antiprolifératives immunosuppressives:

- Analogues de la Rapamycine (Everolimus ou Tacrolimus)
- Sirolimus
- Paclitaxel
- Biolimus
- Zotarolimus



Circulation Journal
Official Journal of the Japanese Circulation Society
<http://www.j-circ.or.jp>

ORIGINAL ARTICLE
Cardiovascular Intervention

First-in-Man Study of Simvastatin-Eluting Stent in De Novo Coronary Lesions – The SIMVASTENT Study –

Alexandre C. Zago, MD, PhD; Bruno S. Matte, MD; Luciana Reginato;
Germán Iturry-Yamamoto, MD, PhD; Ana Krepsky, MD;
Luiz Carlos C. Bergoli, MD; Julise Balvedi; José C. Raudales, MD, PhD;
Eduardo K. Saadi, MD, PhD; Alcides J. Zago, MD, PhD

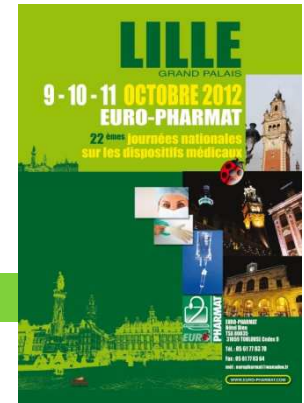
- Stent 316L chargé à 0,4 $\mu\text{g}/\text{mm}^2$ de simvastatine
- Polymère bio-résorbable
- 30% de simvastatine libérée en 14 jours et 40% en 30 jours
- Patients traités ensuite avec clopidogrel
 - pas assez de patients (28)
 - Augmenter la quantité de simvastatine

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Drug eluting stent: l'avenir?

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Université Lille 2
Droit et Santé



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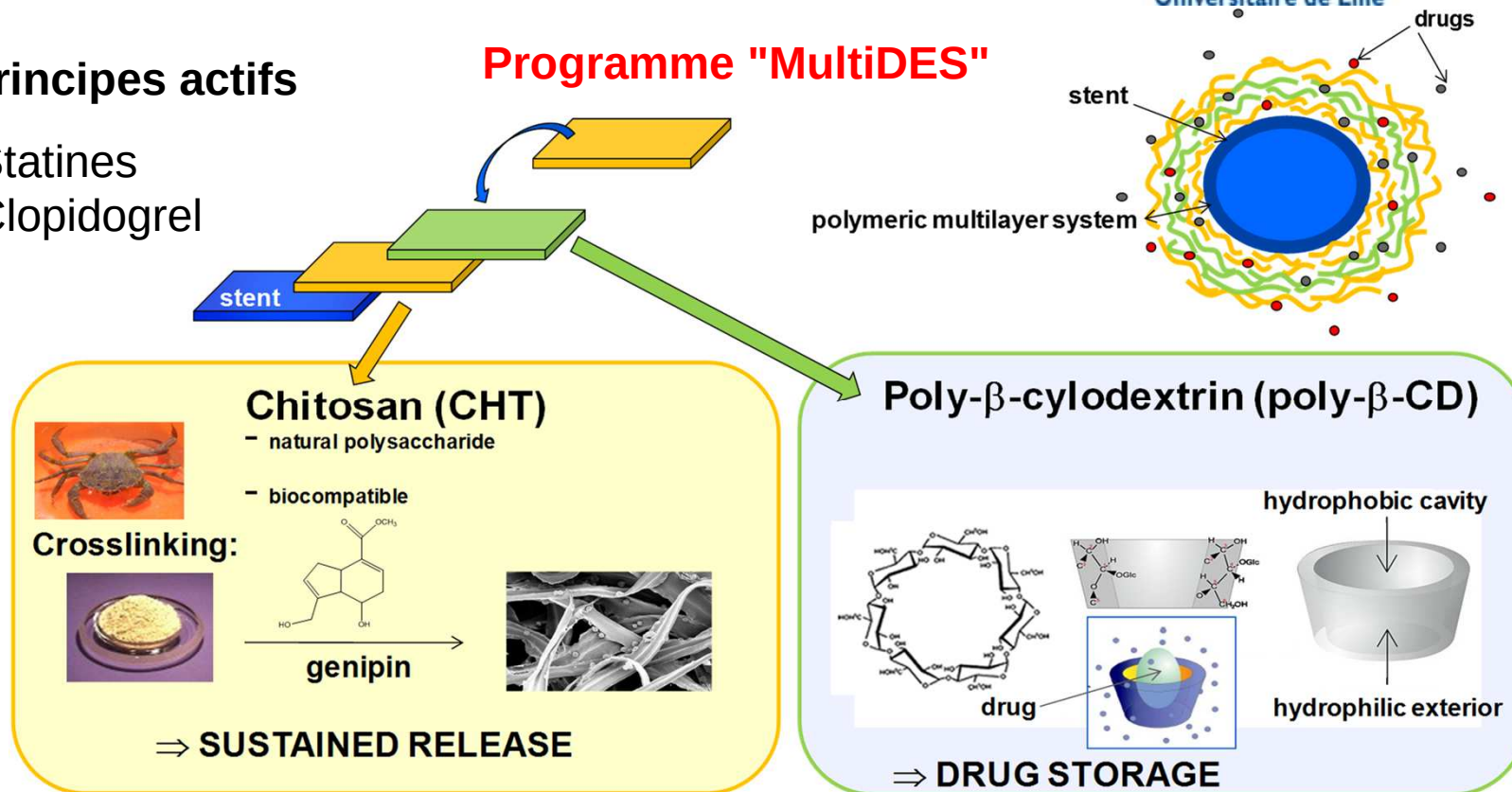


Centre Hospitalier Régional
Universitaire de Lille

Principes actifs

- Statines
- Clopidogrel

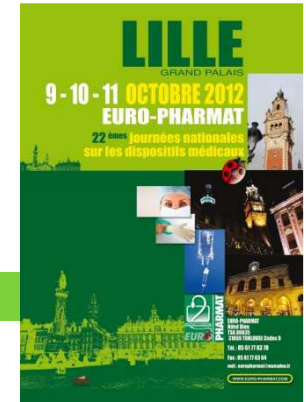
Programme "MultiDES"



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Conclusion

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▪ Evolution des matériaux de choix pour les DES

- Base Métallique (CoCr, 316L, NiTiNOL)
 - Polymères non résorbables
 - Polymères résorbables
- Base polymère
 - Polymères à base d'acide lactique

▪ Evolution des principes actifs pour les DES

- Paclitaxel et sirolimus
- Dérivés de sirolimus , biolimus, everolimus, Zotarolimus

▪ Vers de nouvelles perspectives

- Seuls quelques stents ont été présentés dans ce document (Xience, Abbott; Endeavour, Medtronic, etc...)
- Perspectives vers de nouvelles drogues plus sélectives?

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