Dipartimento di Scienze Cardiovascolari Respiratorie Nefrologiche Anestesiologiche e Geriatriche
Umberto I Policlinico di Roma
Sapienza Università di Roma

Advancing PCI outcome in diabetics with the innovative Cre8™ EVO DES

Cre8™ EVO: paving the way for DES efficacy in diabetics

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Alvimedica

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Disclosure statement

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
Grant/Research Support *Consulting Fees/Honoraria* *Major Stock Shareholder/Equity* *Royalty Income* *Ownership/Founder* *Intellectual Property Rights* *Other Financial Benefit*	• *Biosensors, Abbott, Boston Scientific, Alvimedica, Terumo, Medtronic, Shockwave,Orbus Neich*

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Direct resistance of VSMCs to “-limus” drugs

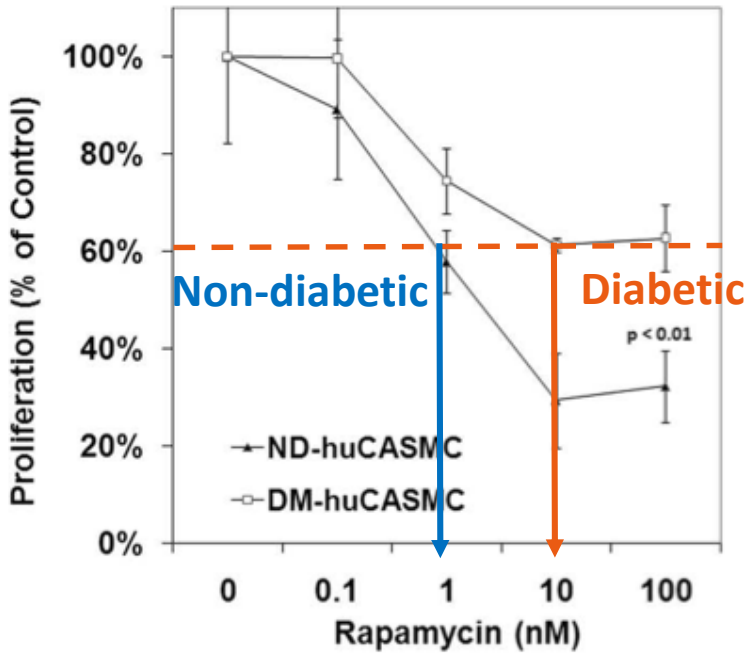


Figure 1. Rapamycin dose-response curves for proliferation of human coronary artery smooth muscle cells (huCASMCs) from nondiabetic (ND-huCASMC) and diabetic (DM-huCASMC) patients.

10 times higher “-limus” concentration is needed in the diabetic cell to achieve similar inhibition seen in non-diabetic one

Relative Resistance to Mammalian Target of Rapamycin Inhibition in Vascular Smooth Muscle Cells of Diabetic Donors

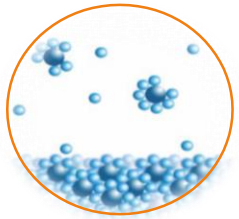
Daniel J. Lightell, Jr., BS,* T. Cooper Woods, PhD*†

*Institute for Translational Research, Molecular Cardiology Laboratory, Ochsner Clinic Foundation, New Orleans, LA
†Department of Pharmacology and Experimental Therapeutics, Louisiana State University Health Sciences Center, New Orleans, LA

Cre8™ EVO: Polymer-free Amphilimus™ eluting stent

Abluminal Reservoir Technology

The only polymer-free technology able to precisely control abluminal drug elution

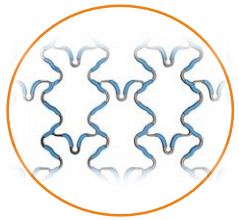


Amphilimus™ formulation: Sirolimus + Fatty Acid

Fatty Acids enhance drug distribution and maximize drug bioavailability increasing device efficacy, particularly in diabetic patients

Bio Inducer Surface

Proven hemo-/bio-compatibility versus vessel wall and blood flow



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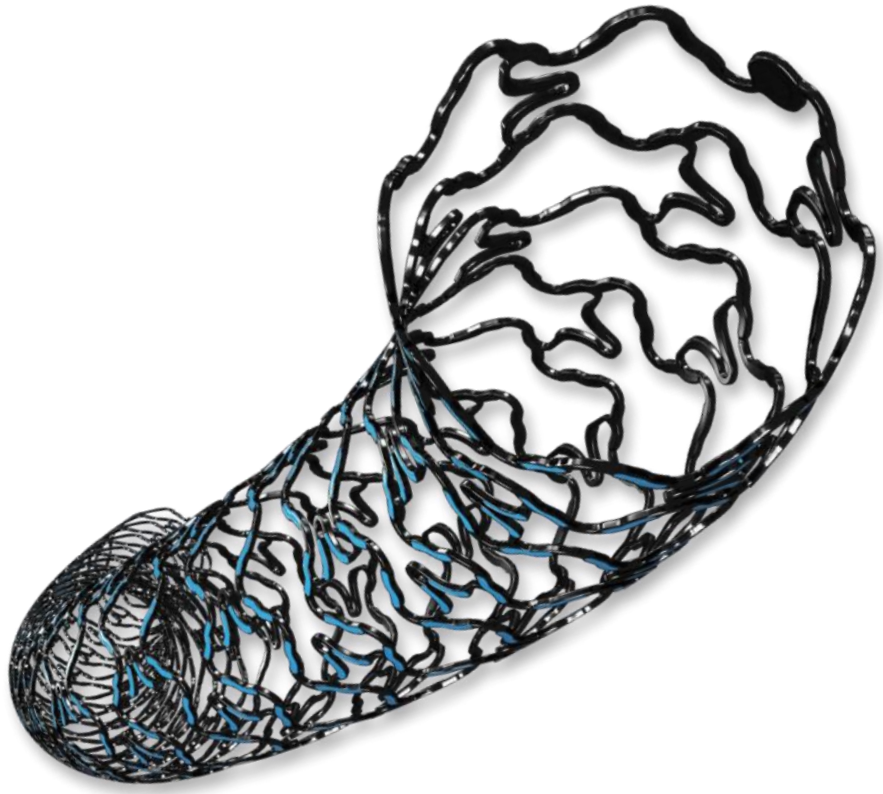

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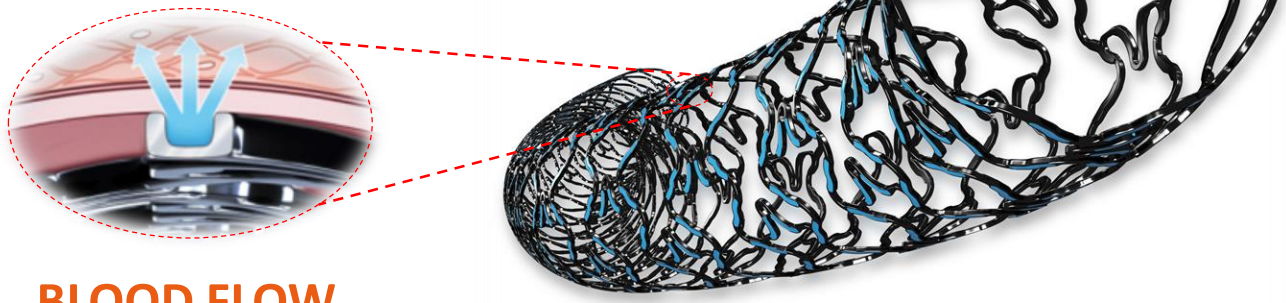
Abluminal Reservoir Technology

Alvimedica utilizes a proprietary polymer-free drug release system **constituted by reservoirs on the stent's outer surface**

ARTERIAL WALL

Drug elution is controlled and directed exclusively towards the vessel wall



BLOOD FLOW

No polymer

No drug

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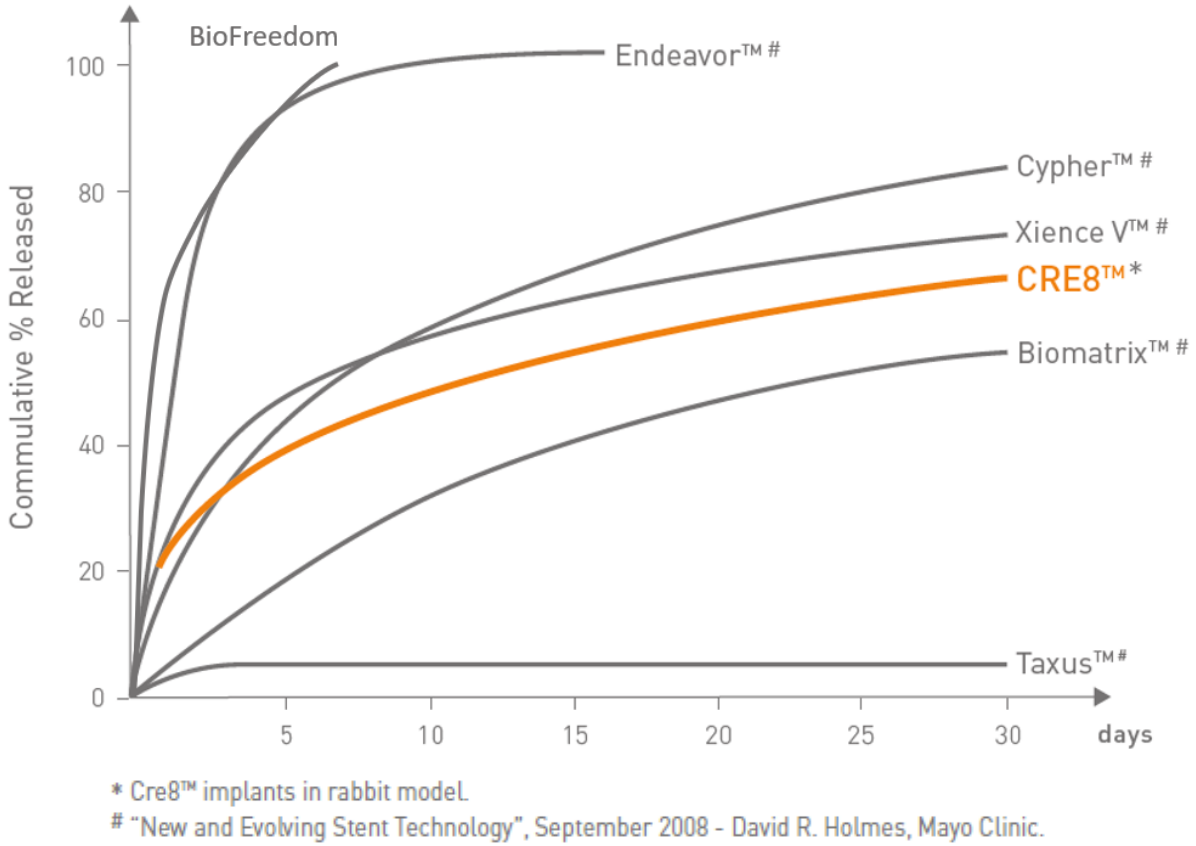
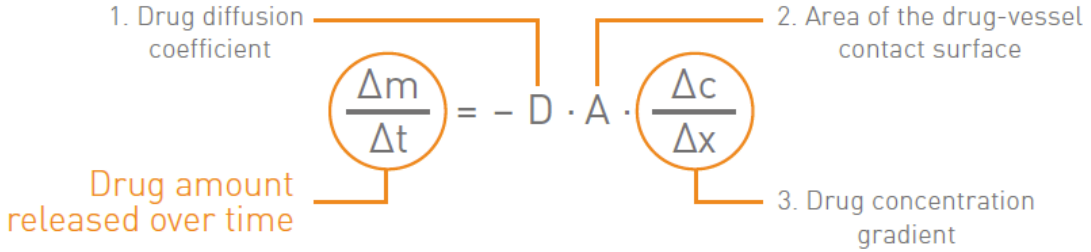
Cre8™ EVO kinetic release



* Cre8™ implants in rabbit model.
# "New and Evolving Stent Technology", September 2008 - David R. Holmes, Mayo Clinic.

- **Peak drug tissue concentration during the first days**
- **50% drug elution in approximately 18 days**
- **65%-70% drug elution within 30 days**
- **Complete drug elution within 90 days**

FICK LAW (diffusion)



The amount of drug released overtime is proportional to the area of contact and to the drug concentration gradient

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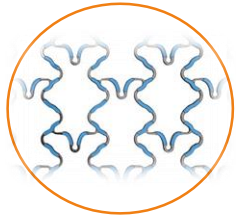
Cre8™ EVO - the ONLY DES in the world releasing a FORMULATION

BioInducer Surface

Proven hemo-/bio-compatibility versus vessel wall and blood flow



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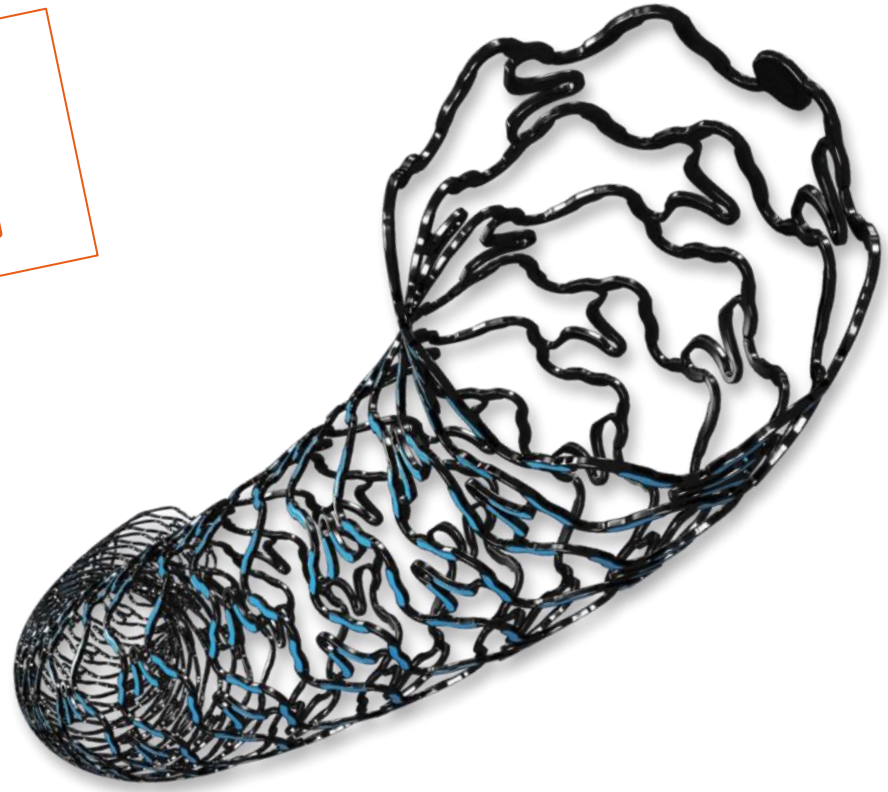

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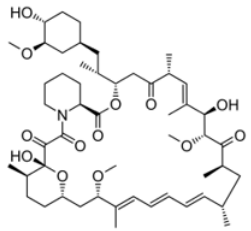
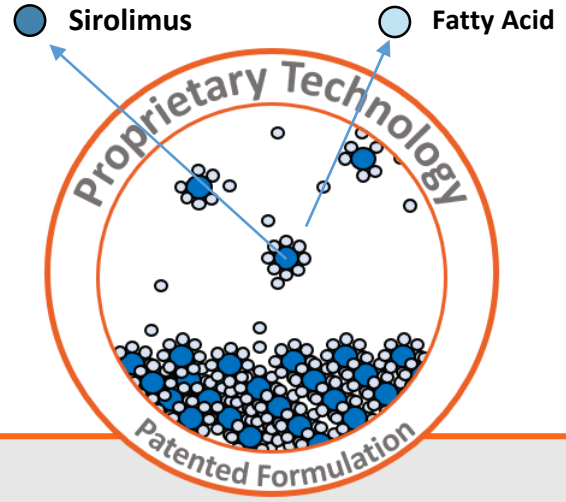
Amphilimus™ Formulation

Sirolimus



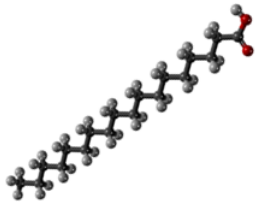
- Immunosuppressant
- Anti-proliferative action
- Anti-microbial
- Inhibitor of inflammatory cell activities
- High potency



Sirolimus and Fatty Acid are eluted together

Combined effect!

Fatty Acid



- Sustained drug elution timing
- Modulated drug bioavailability
- Raised homogeneous drug distribution
- Enhanced drug stability

Sirolimus molecule is 4 times bigger than the Fatty Acid molecule

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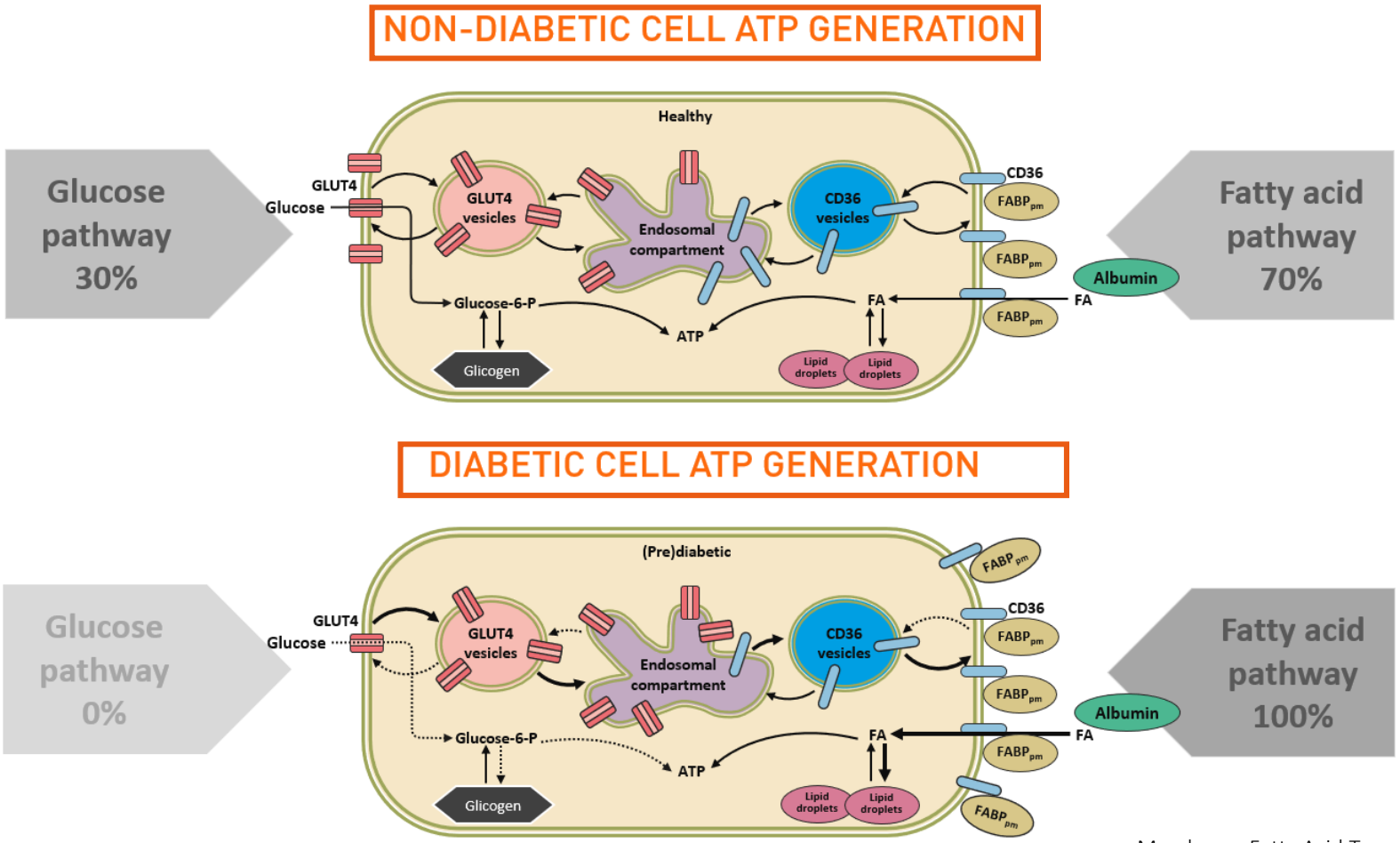
In diabetic cells:

The key role of Fatty Acids for ATP generation



Two pathways for ATP generation:

1. Glucose pathway (30%)
2. Fatty acid pathway (70%)

Membrane protein overexpression leads to higher fatty acids bindings/ traslocation.
(Glucose pathway not active)

Membrane Fatty Acid Transporters as Regulators of Lipid Metabolism: Implications for Metabolic Disease – Glatz J; 2010 Physiol Rev 90: 367–417

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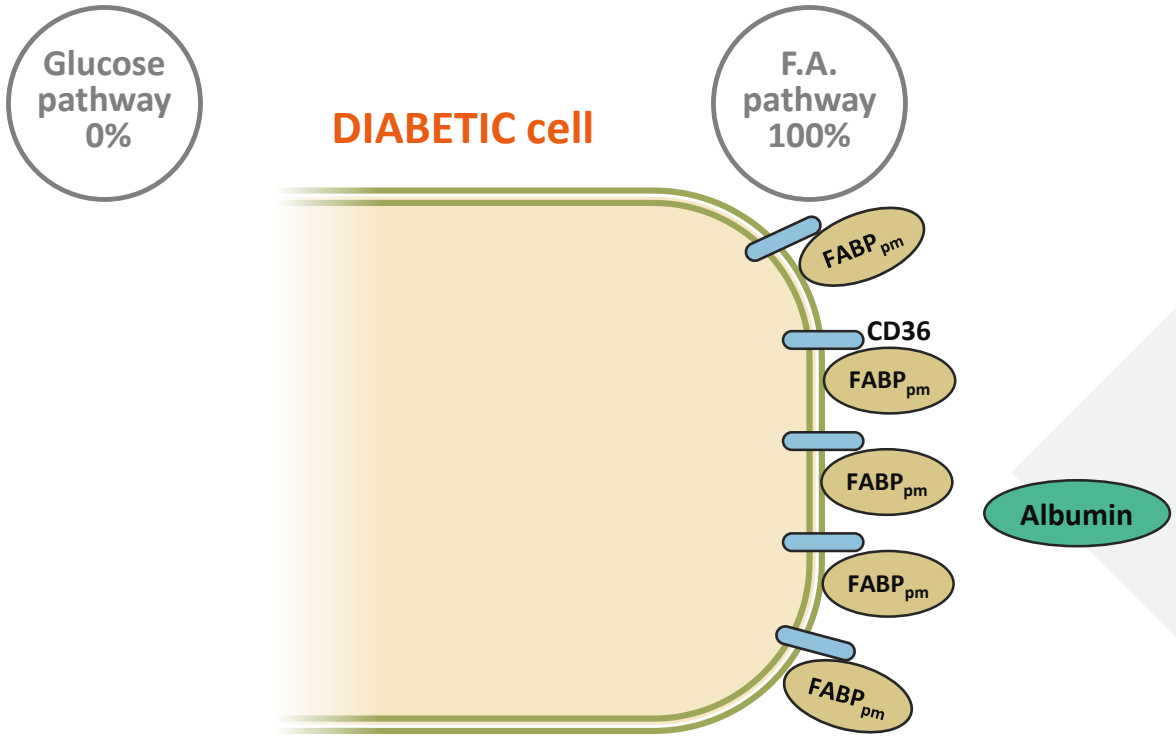
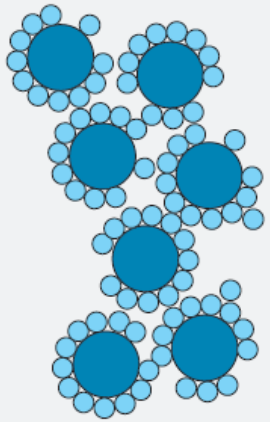
For Diabetics:

Higher Sirolimus concentration inside the cell





Limus drug
+ Fatty acid

The higher Fatty Acid intake favors higher Sirolimus presence inside the diabetic cells (bioavailability).

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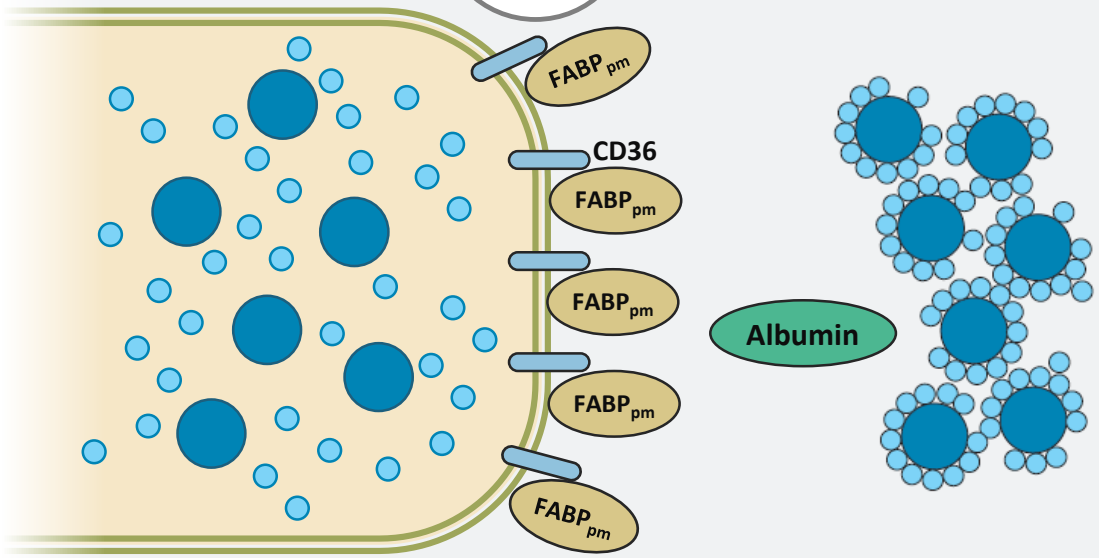
For Diabetics:

Higher Sirolimus concentration inside the cell

Glucose pathway 0%

F.A. pathway 100%

DIABETIC cell



Limus drug
+ Fatty acid

"Trojan horse -like" effect!

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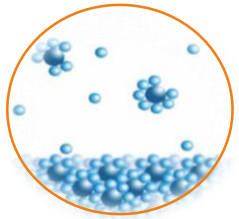

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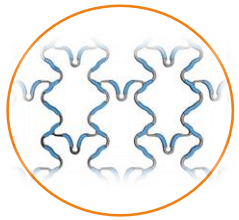

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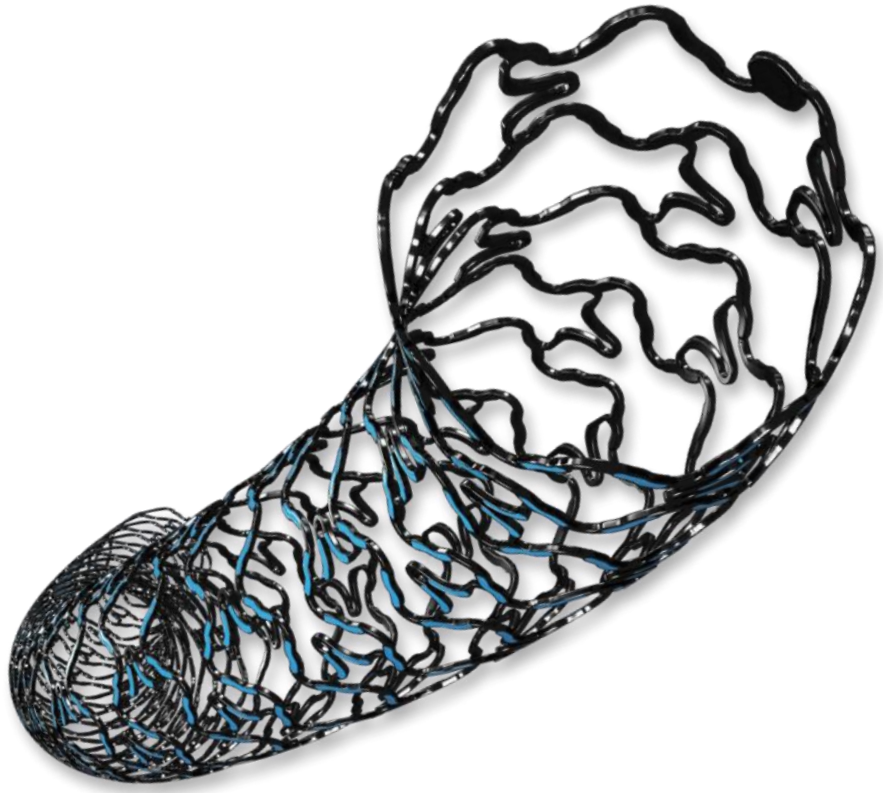

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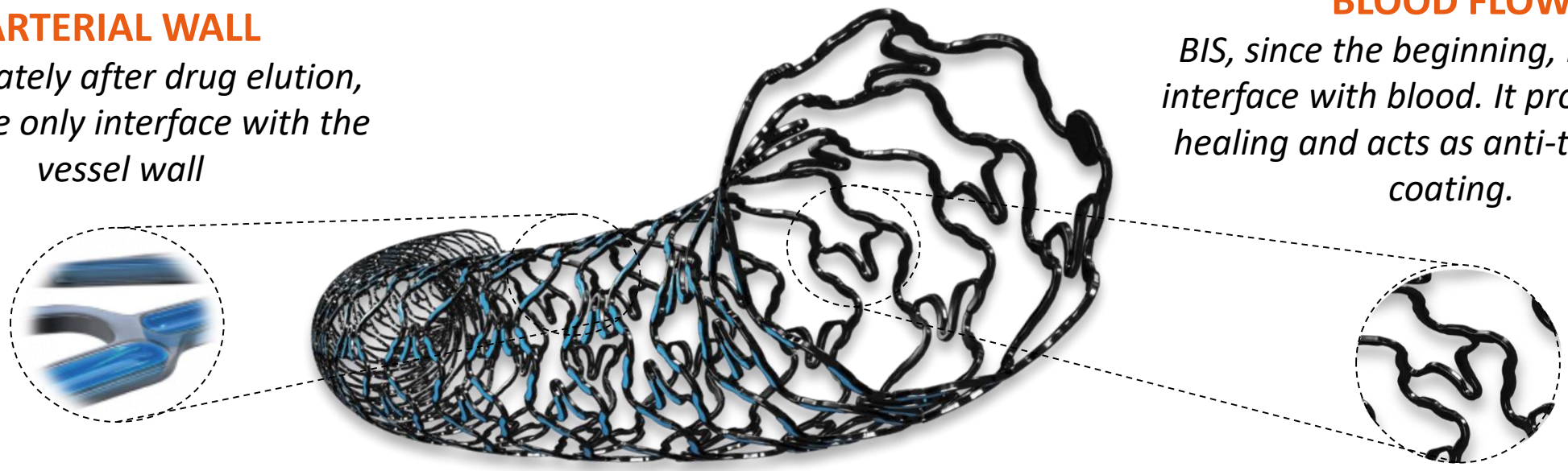
Bio Inducer Surface (BIS)

The Bio Inducer Surface, **ultra thin (<0.3µm) pure carbon coating**, is INTEGRALLY applied to the Cre8™ EVO very thin platform (70-80µm) before the drug loading.

ARTERIAL WALL

Immediately after drug elution, BIS is the only interface with the vessel wall



BLOOD FLOW

BIS, since the beginning, is the only interface with blood. It promotes fast healing and acts as anti-thrombotic coating.

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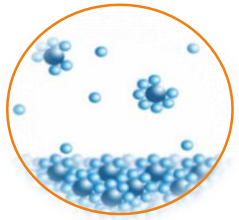

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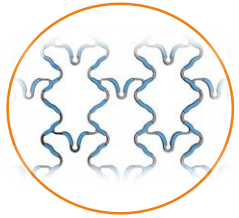

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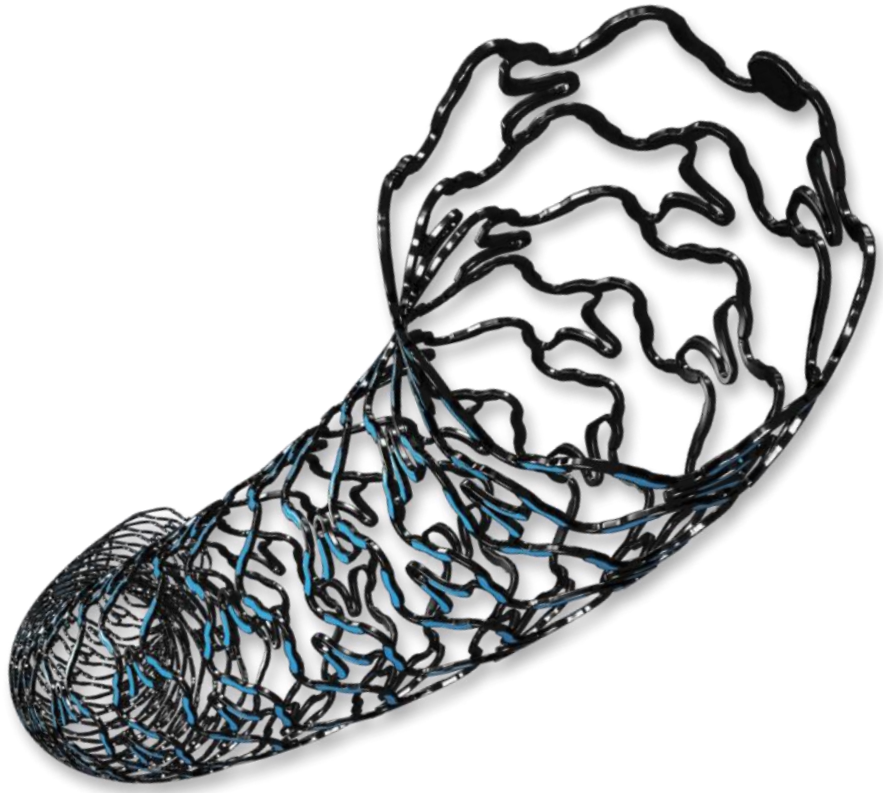

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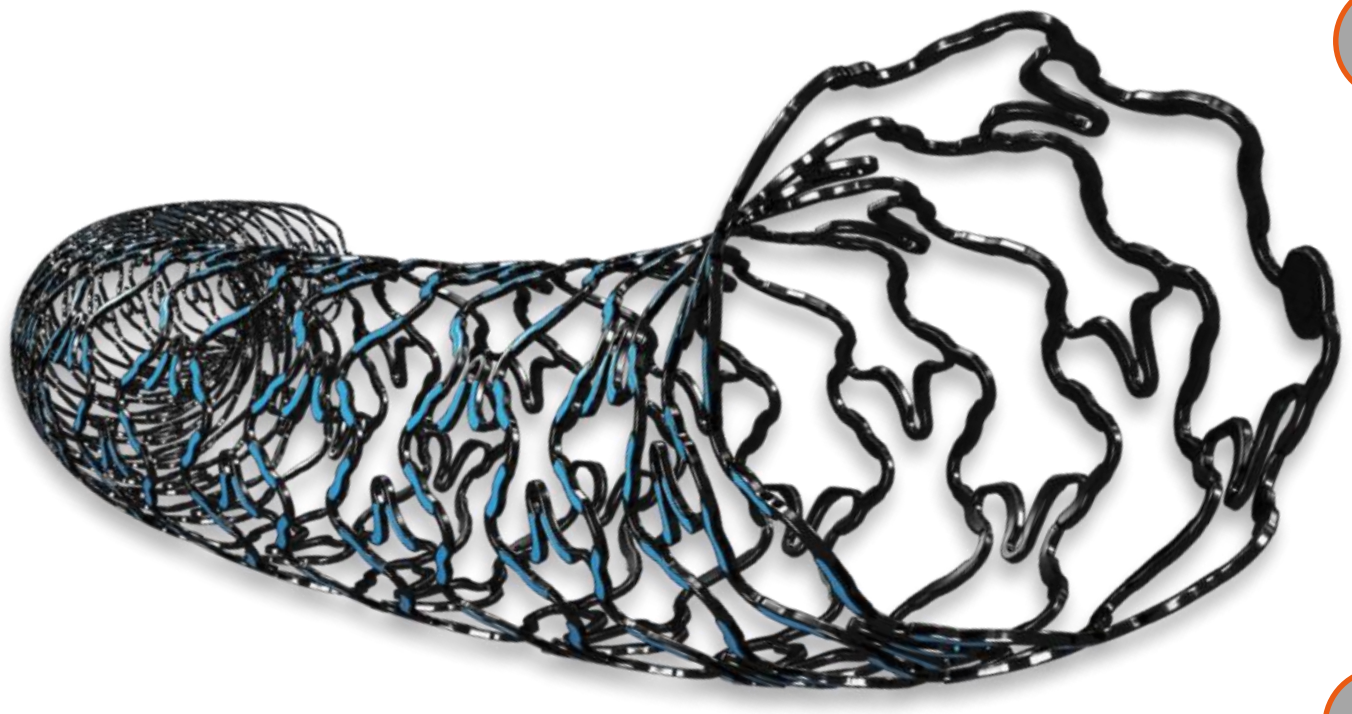
Cre8™ EVO

L605 CoCr stent



- New Cell Architecture
- Thin CoCr stent struts (70/80µm)
- Homogeneous scaffolding & Sidebranch-ability
- Low recoil
- No foreshortening
- Radiopaque Markers
- Longitudinal Integrity

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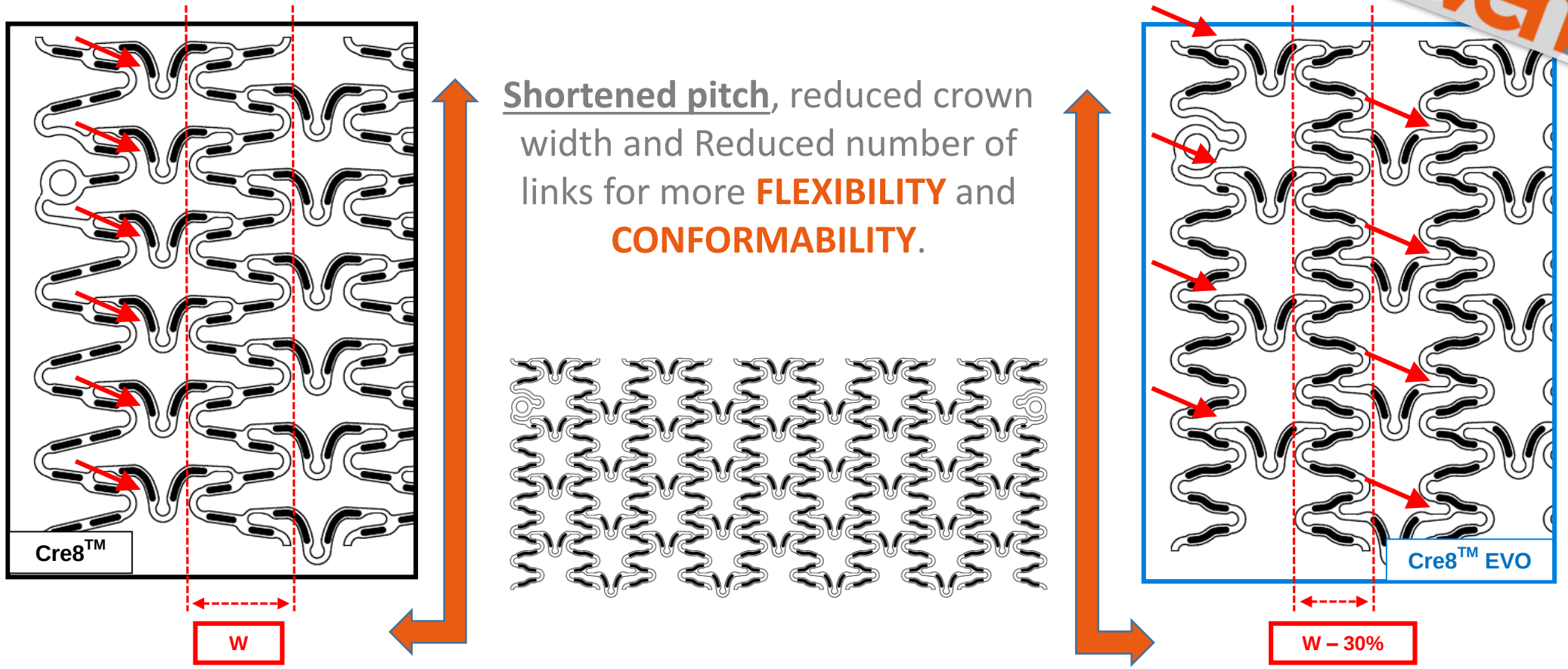
EvenArt: Cre8™ EVO vs. Cre8™

New DES architecture benefits



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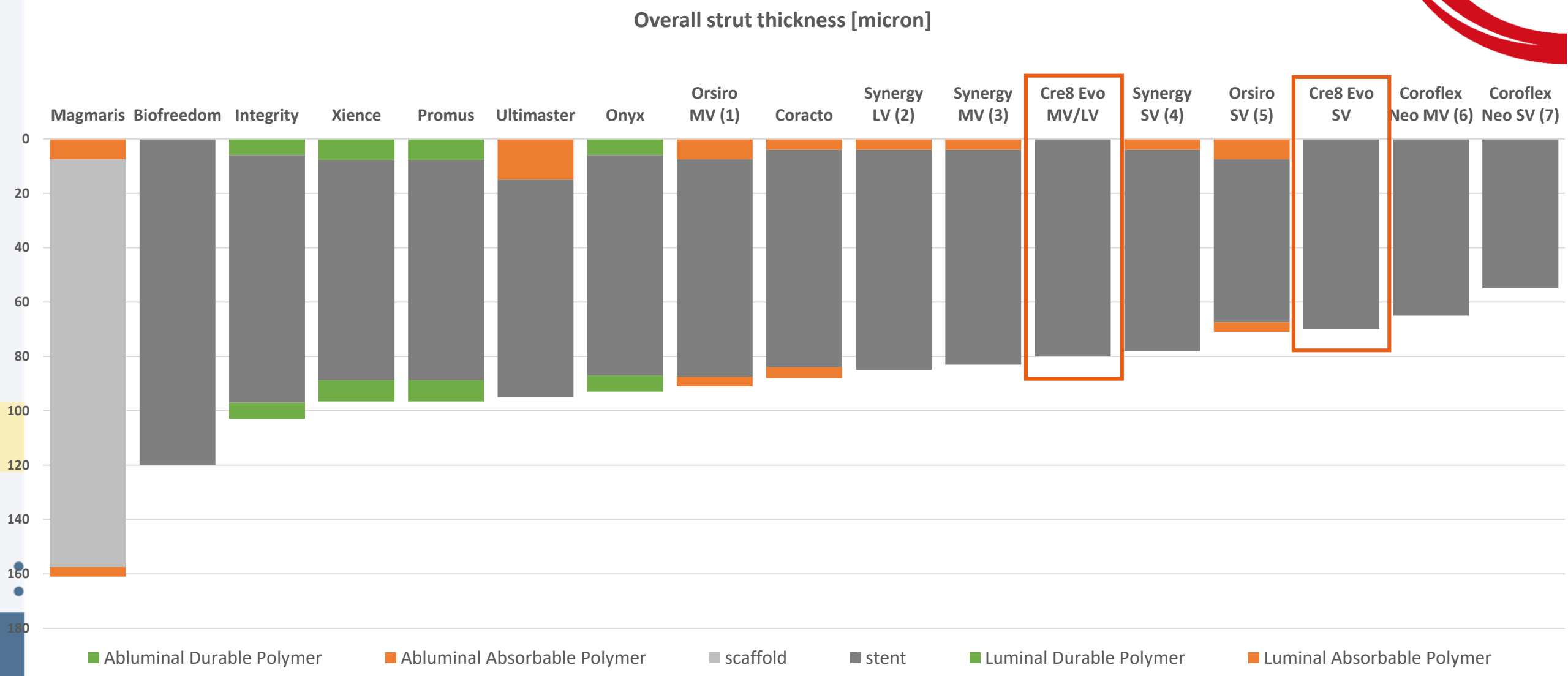
Strut thickness comparison



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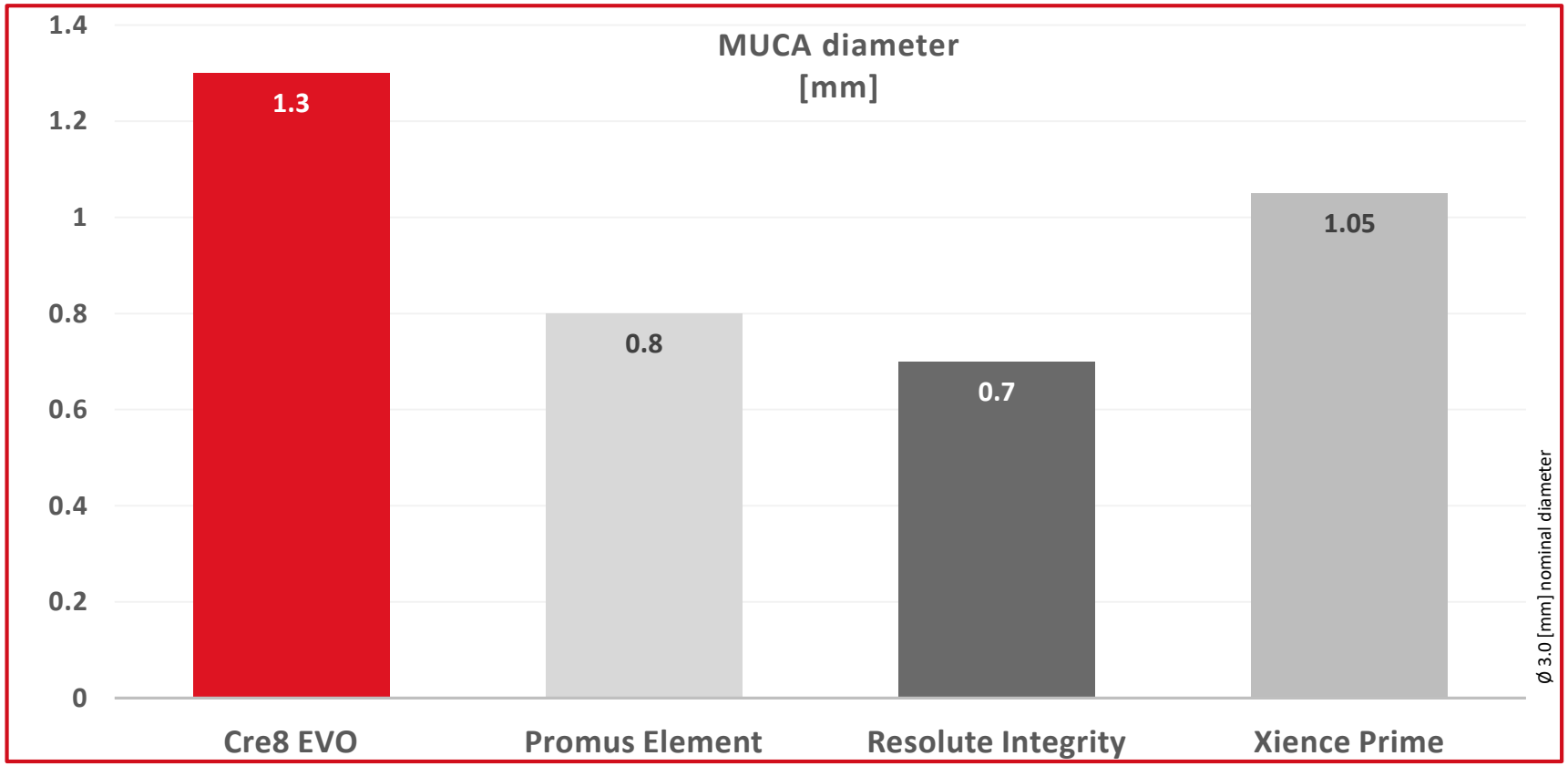
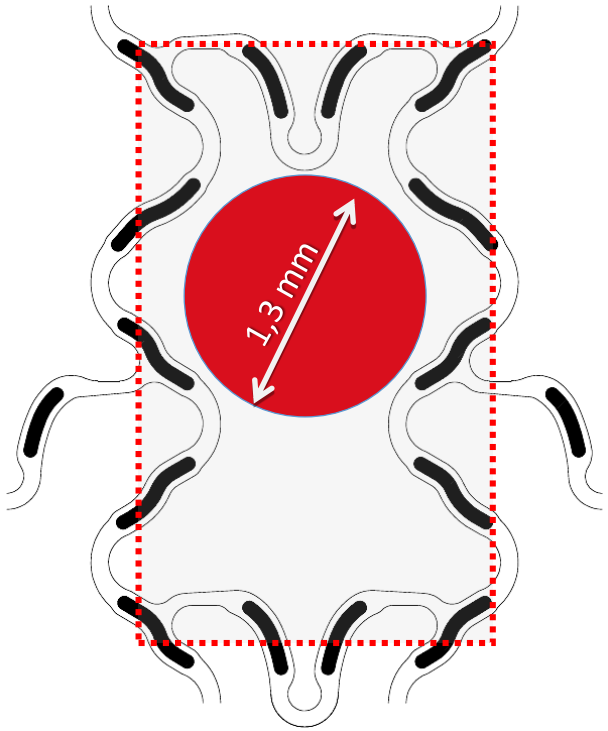
Cre8™ EVO: side branch access

Cre8™ EVO EvenArt stent design allows a MUCA (Maximum Unprotected Circular Area) diameter of 1,3mm (like Cre8™) which provides homogeneous scaffolding as well as optimal side branch access.





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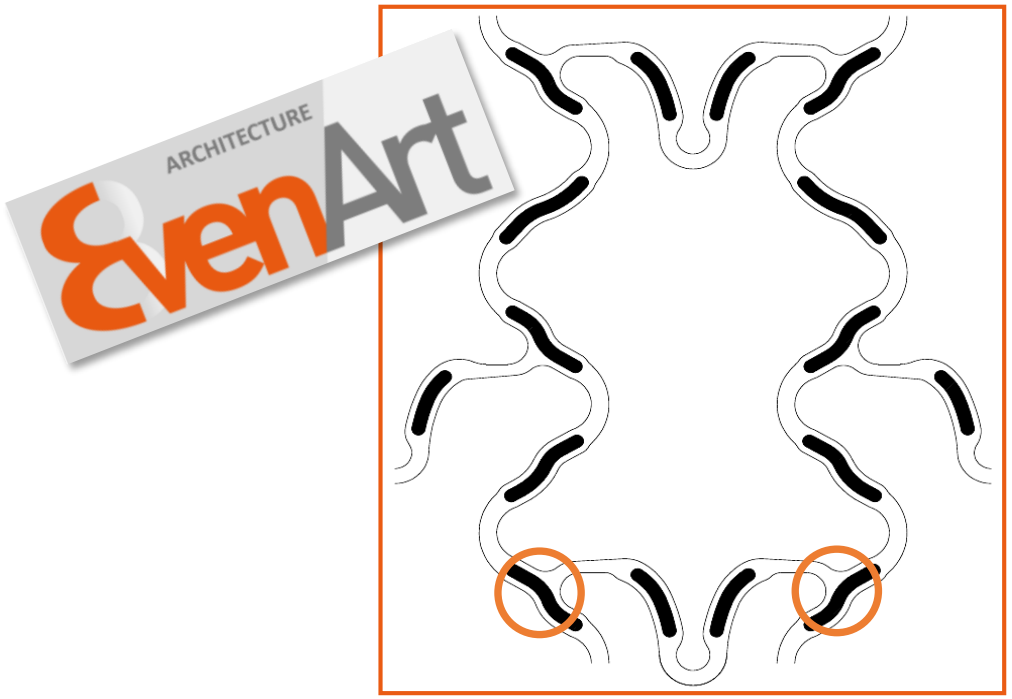
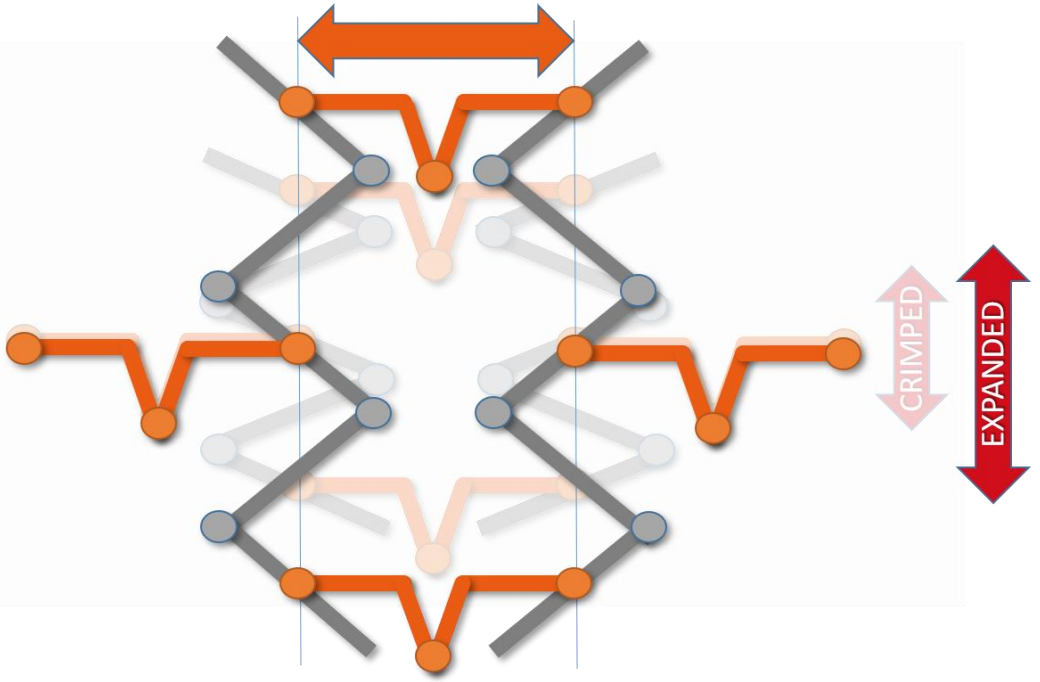
Cre8™ EVO: No foreshortening

No foreshortening:

The specific design guarantees 0% foreshortening during the expansion of the stent



Midpoint connections avoid any FORESHORTENING upon stent expansion



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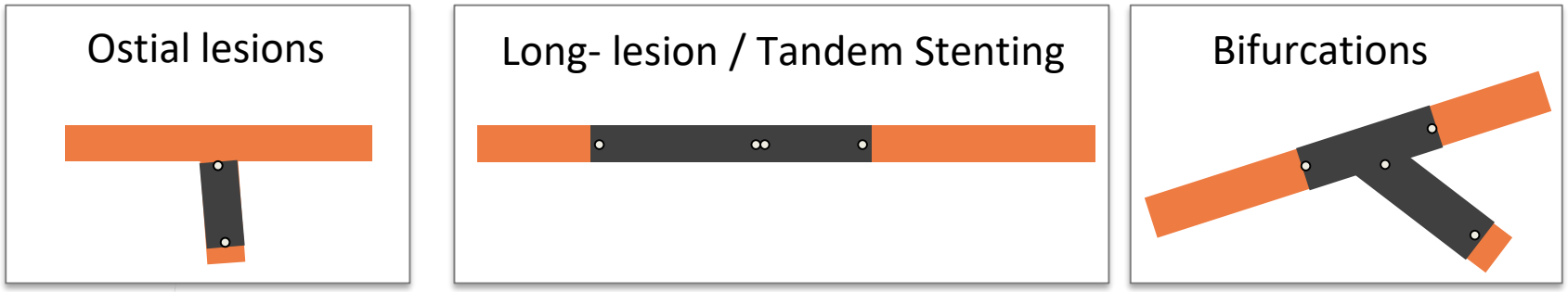
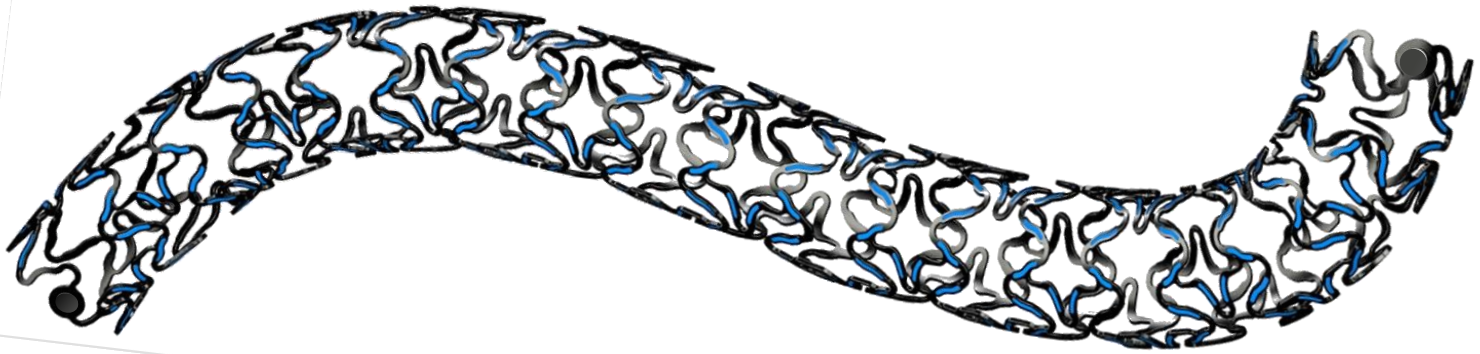
Cre8™ EVO

No foreshortening + Radiopaque Markers = Precise implant

A precise positioning, thanks to the stent markers and no stent foreshortening, reduces the risk of thrombosis and persistent restenosis





Conclusions

- The **Abluminal Reservoir Technology** is the only one on the market able to combine a precisely controlled drug elution (2/3months) into a thin strut (70/80µm) polymer-free platform

- The **lack of polymer** avoids inflammatory triggers provided by the polymeric presence and **Bio Inducer Surface** minimizes pro-thrombotic stimuli and promotes a fast stent struts coverage.

- The innovative **Amphilimus™ formulation** (Sirolimus + organic acid) enhances drug bioavailability & tissue permeability especially into diabetic cells.

- The new **CR8Evo architecture** better perfomances in challenging lesions showing a superior crossability and an excellent trackability

- **In diabetics** RCT's and Registry showed the superiority of this formulation compared with other DES of second generation

- The **SUGAR Trial** with more than **1000 pts** will definitely give us an answer on the best DES treatment in this challenge subset of patients

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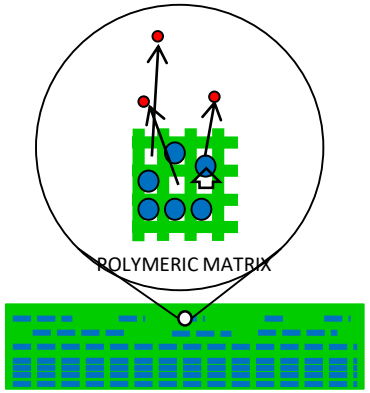
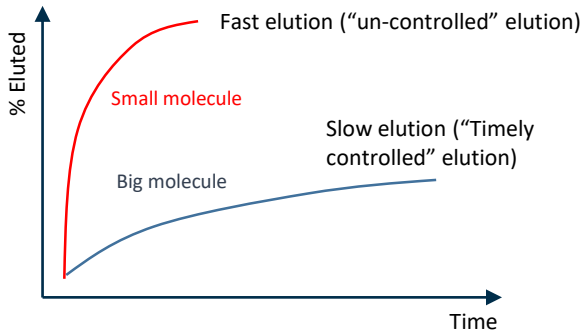
Abluminal Reservoir Technology

Polymer-free Abluminal Reservoirs, contrary to polymers, allow a mix of substances to be simultaneously eluted for a maximized synergetic effect



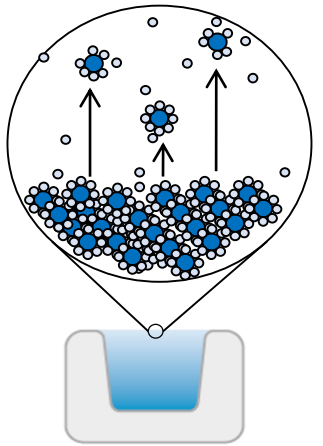
Polymers

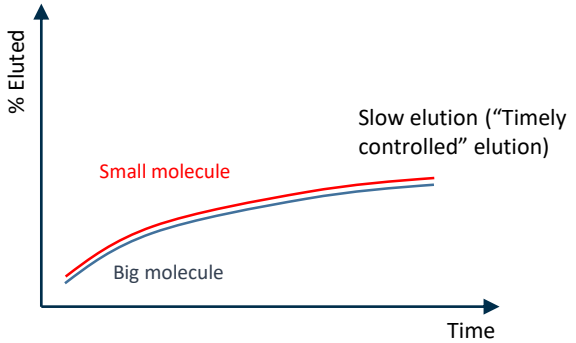
Polymers act as a "filter" (porosity) determining which molecules are very fast released (small ones) and those slowly released (big ones)



Abluminal Reservoir

Abluminal Reservoir allows different substances to be simultaneously eluted - the kinetic release is fixed by the reservoir shape.





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