TNT session

2018 euro PCR

"Amphilimus™ Eluting Stent: leveraging on innovative technology to go beyond current PCI clinical boundaries in diabetic and HBR patients"

Rethinking DES technology to advance device efficacy and safety

Robert A. Byrne MB BCh PhD FESC

Deutsches Herzzentrum München

EAPCI European Society of Cardiology PCR

Potential conflicts of interest

Speaker's name: **Robert Byrne**

☑ Lecture fees:

B. Braun Melsungen, Biotronik, Boston Scientific, Micell Technologies

☑ Research grants to institution:

Boston Scientific, Celonova Biosciences

Amphilimus™ Eluting Stent

Rethinking DES technology to advance device efficacy and safety

Introduction & unmet needs	1
Limitations of DES in patients with diabetes mellitus	2
Amphilimus™ formulation	3
Abluminal reservoir drug technology	4
Cre8™ EVO: new stent architecture	5
Take home message	6

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DES with "comparable features" provide "comparable clinical results"

The latest DES technologies have led to generally comparable results in "standard" patients

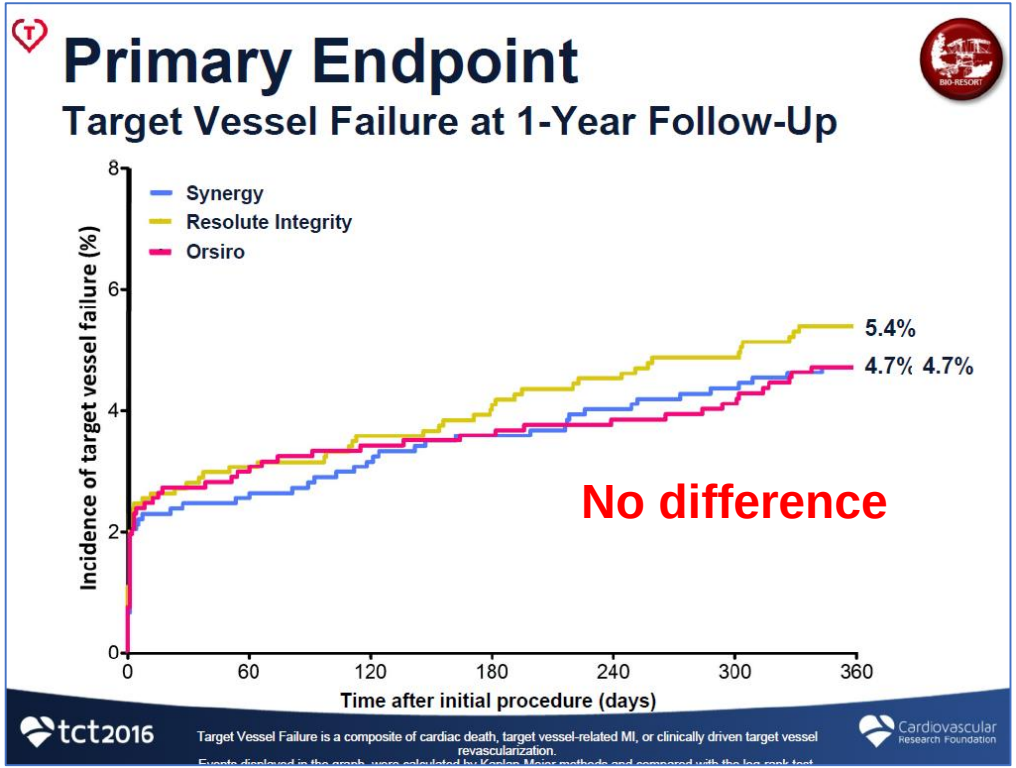
BIO-RESORT (TWENTE III)

Randomized comparison among

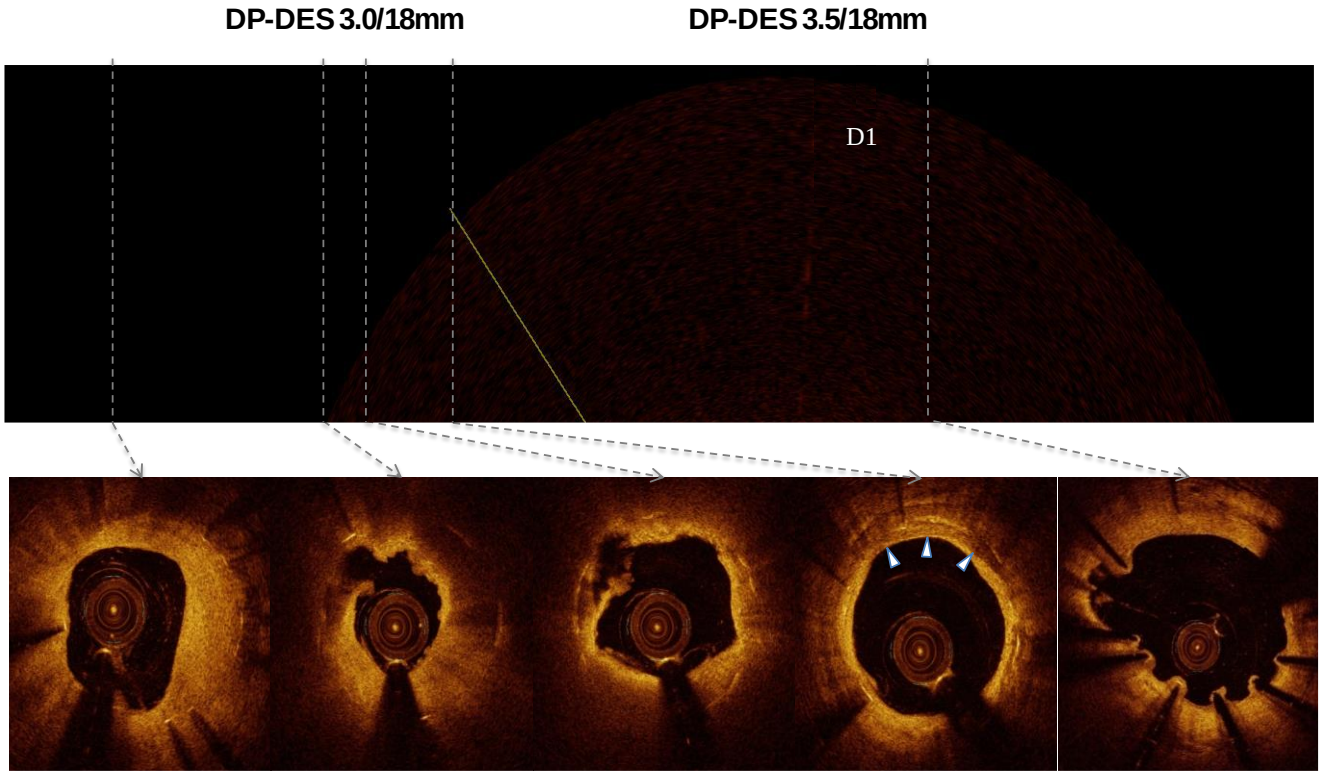
- "Resolute Integrity" (Durable Polymer)
- "Synergy" (BP – Fast degradation)
- "Orsiro" (BP – Slow degradation)

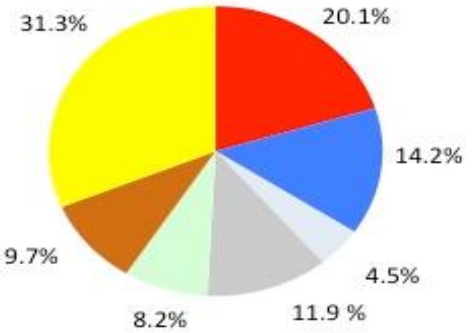
1200 patients per arm

3600 patients in total



Late stent failure after new generation DES



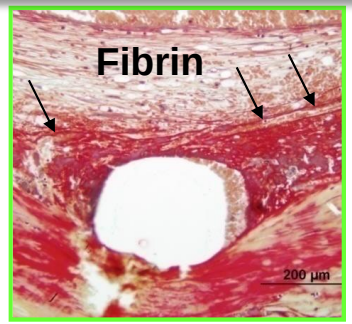


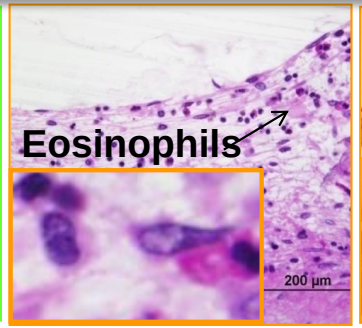
Uncovered struts
Malapposed struts
Underexpansion
Restenosis
Other
No dominant cause identifiable
Neoatherosclerosis

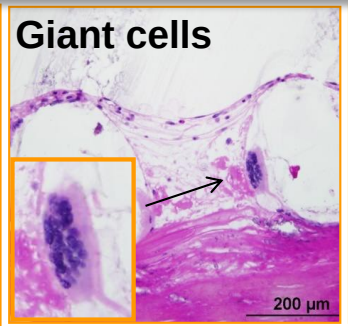
Adriaenssens, Joner et al. | Circulation 2017

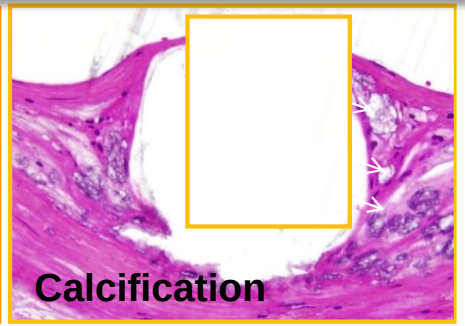
Polymer presence & inflammation

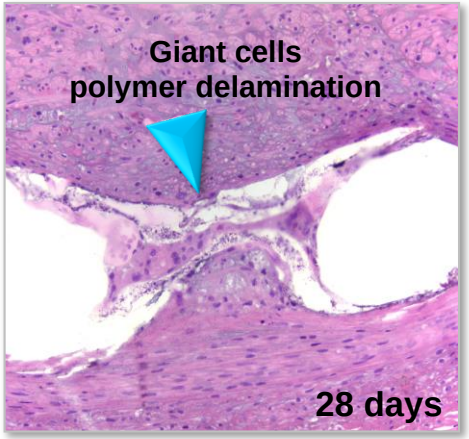
Inflammatory response to polymer coatings plays a central role in DAH

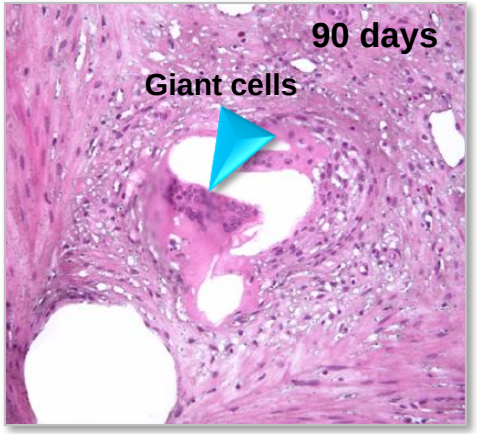


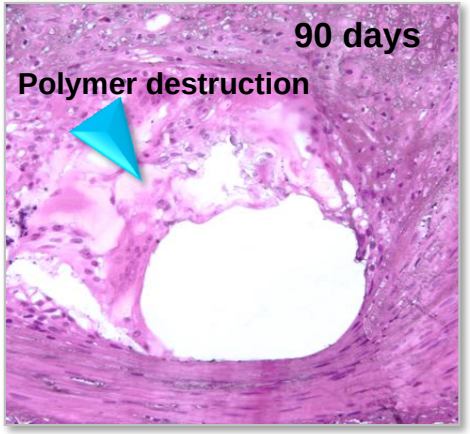






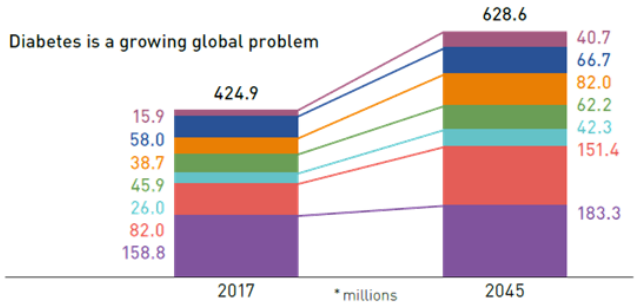




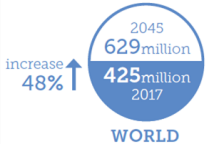


Diabetes Mellitus & PCI

The number of DM pts is quickly growing

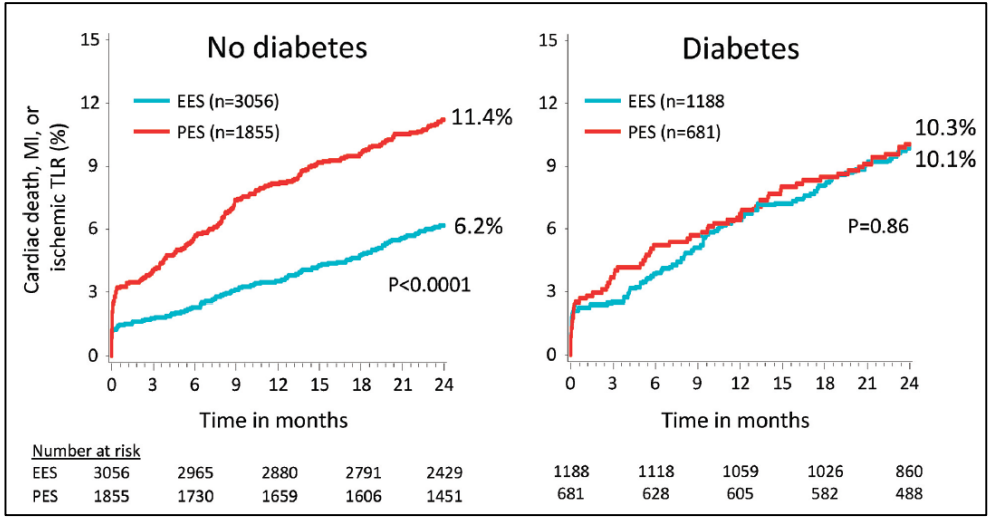


IDF DIABETES ATLAS
Eighth edition 2017



DES performance in DM pts is still unsatisfactory

SPIRIT/ COMPARE pooled patient level analysis
(Spirit II, Spirit III, Spirit IV, Compare - 6789 pts)



Circulation. 2011;124:893-900.

To advance DES performance we probably should:

1. **SAFETY = avoid inflammatory triggers (polymers?) while keeping a controlled & slow abluminal release from a "thin but visible platform"**

2. **EFFICACY = find a way to overcome "-limus drug resistance" which reduces DES efficacy when present**

Amphilimus™ Eluting Stent

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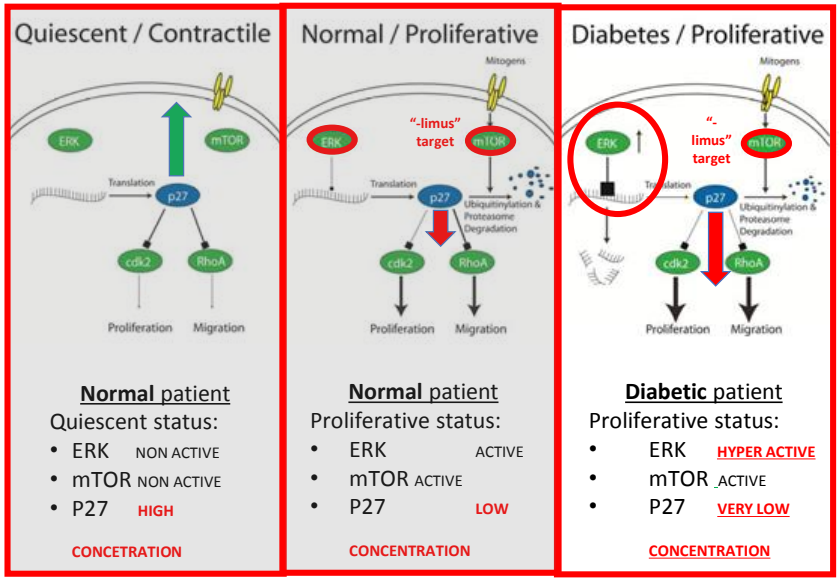
Why -limus drugs are less effective in diabetics

FACT #1:

Direct Resistance of diabetic cells to –limus drugs

Direct resistance of VSMCs to –limus drugs

Dysregulation of the Mammalian Target of Rapamycin and p27^{Kip1} Promotes Intimal Hyperplasia in Diabetes Mellitus



Pharmaceuticals **2013**, *6*, 716-727

10 times higher "-limus" concentration is needed in the diabetic cell to achieve similar inhibition seen in non-diabetic cell!

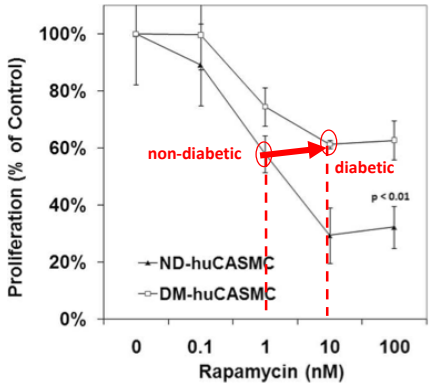


Figure 1. Rapamycin dose-response curves for proliferation of human coronary artery smooth muscle cells (huCASMCs) from nondiabetic (ND-huCASMC) and diabetic (DM-hu-CASMC) patients.

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

David 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

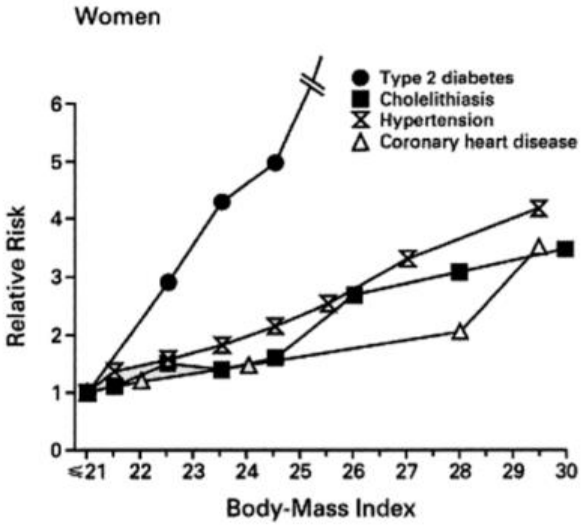
Why -limus drugs are less effective in diabetics

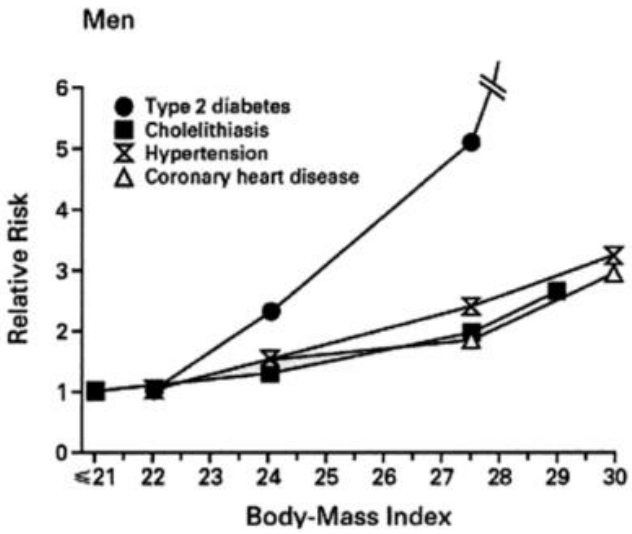
FACT #2:

Effect of other hormones

Diabetes and Overweight

Overweight is a risk factor for diabetes and for CVD.





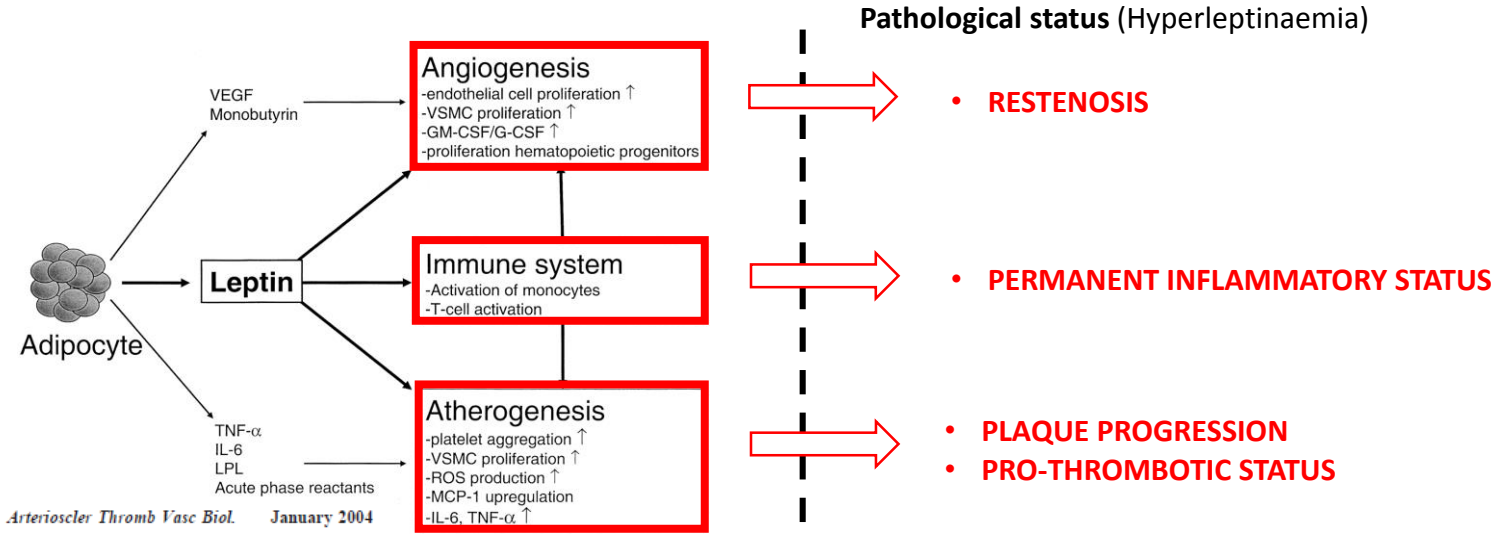
Dietz W H, et al. *NEJM*. 1999; 341:427.

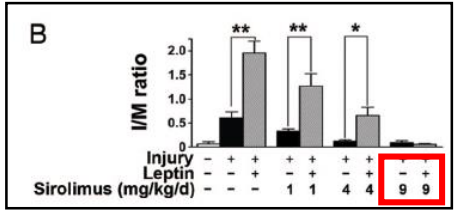
90% of diabetic patients (Type 2) are overweight or obese

(Obesity Society Feb. 2015)

Leptin: Effects at vascular level

Leptin is an hormone secreted by adipocytes (cells distributed ubiquitously throughout the body, also **perivascularly**, particularly in overweight patients) with specific vascular effects.





9 times higher "-olimus" concentration is needed to block leptin-induced hyperplasia.

19006–19011 | PNAS | December 2, 2008 | vol. 105 | no. 48

Why -limus drugs are less effective in diabetics

To improve PCI efficacy in diabetic patients we need to increase the «limus» drug concentration inside the diabetic cells!

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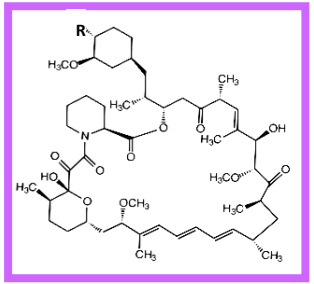
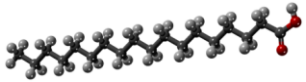
Amphilimus™ Formulation

Sirolimus



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

Fatty Acid



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

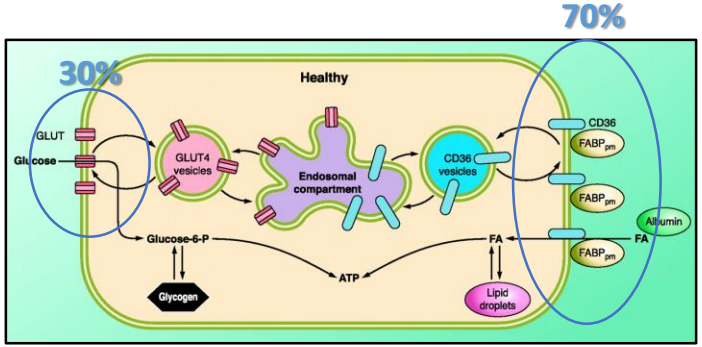
Proprietary technology

Sirolimus and Fatty Acid are eluted together

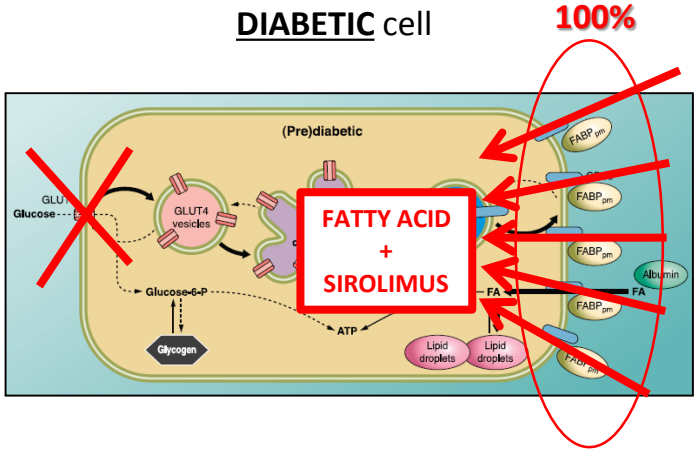
Combined effect

The key role of Fatty Acids in diabetes for ATP generation

NON-Diabetic cell



DIABETIC cell



Two pathways for ATP generation:

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

- **Membrane protein overexpression leads to higher fatty acids bindings/ translocation.**

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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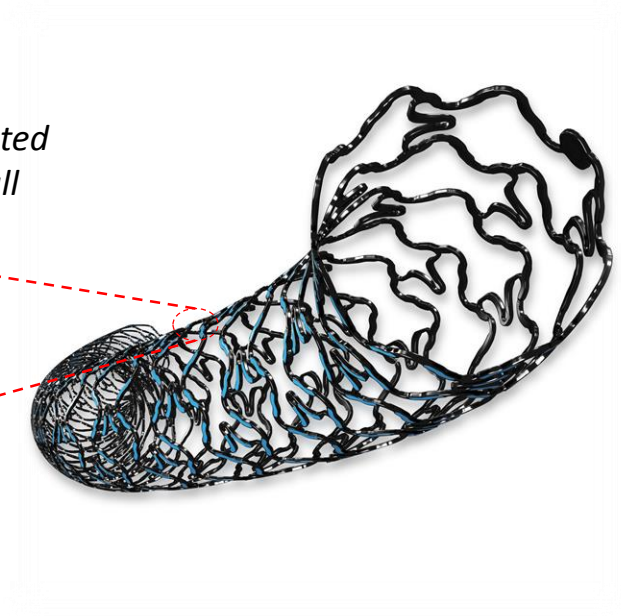
Abluminal Reservoir Technology

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

ARTERIAL WALL

Drug elution is controlled and directed exclusively towards the vessel wall



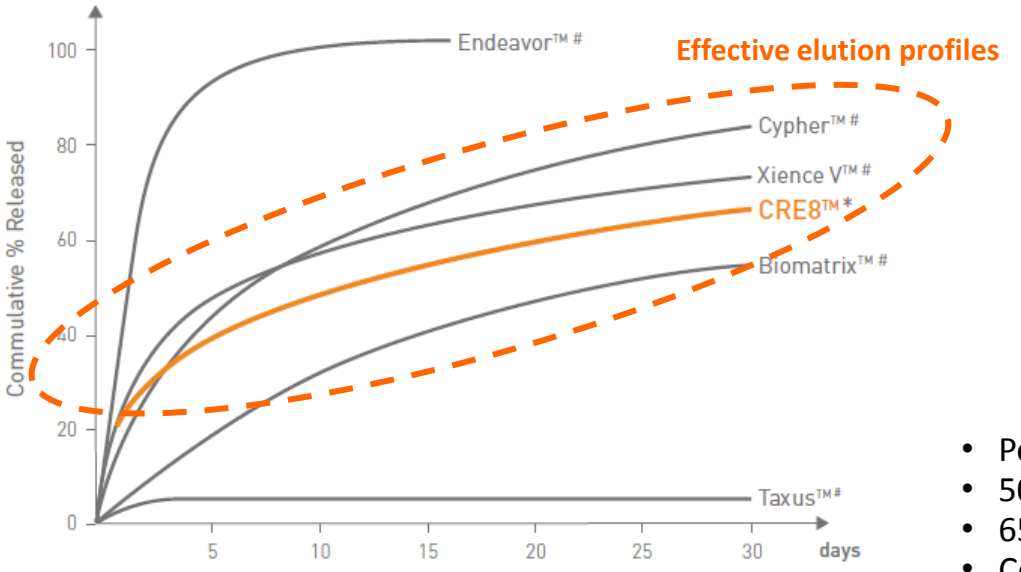
BLOOD FLOW

No polymer

No drug

Abluminal Reservoir Technology

Abluminal Reservoir is the ONLY polymer-free technology able to provide the same elution kinetic obtained by the most effective polymeric DES.



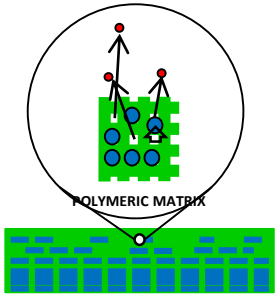
* Cre8™ implants in rabbit model.
\# "New and Evolving Stent Technology", September 2008 - David R. Holmes, Mayo Clinic.

The Reservoir shape defines drug release kinetic (Fick law)

- 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

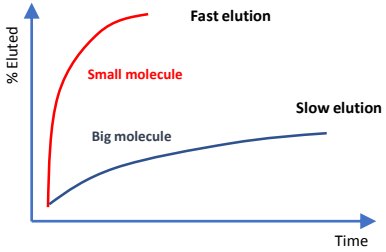
Abluminal Reservoir Technology

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



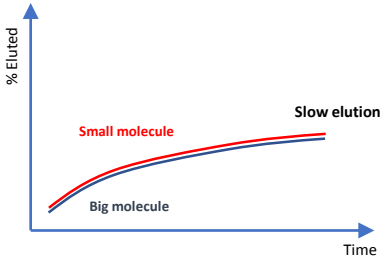
Polymers

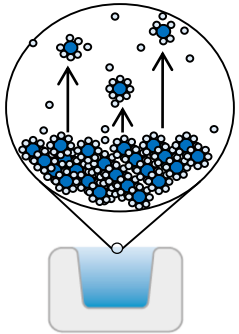
Polymers act as a "filter" (porosity) determining which molecules are very fast released (small ones) and those slowly released (big ones)



Abluminal Reservoir

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





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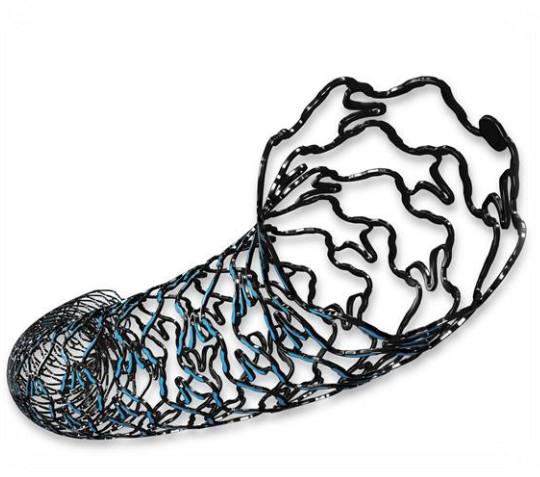
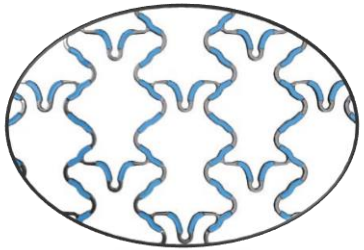
New Stent Architecture (EvenArt)

An innovative stent architecture has been developed to improve even more the homogeneous drug distribution within the vessel wall, in particular in case of complex coronary anatomies and pathologies like those of diabetic patients

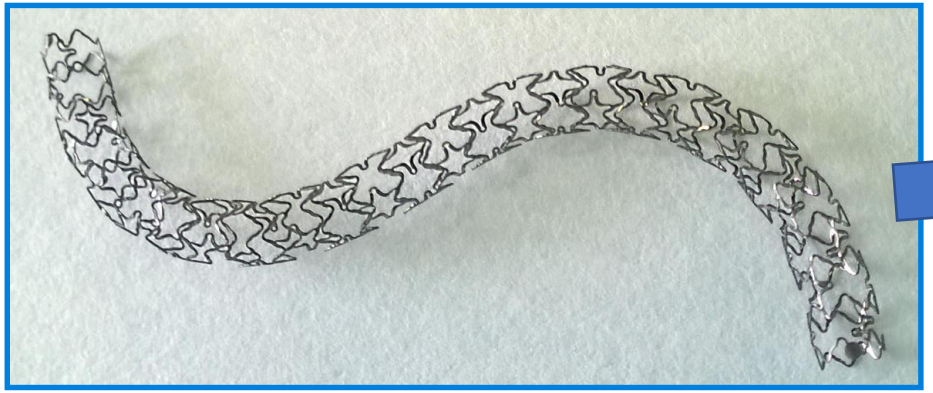


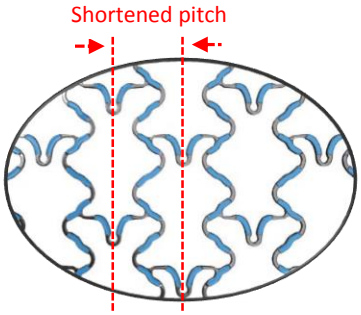


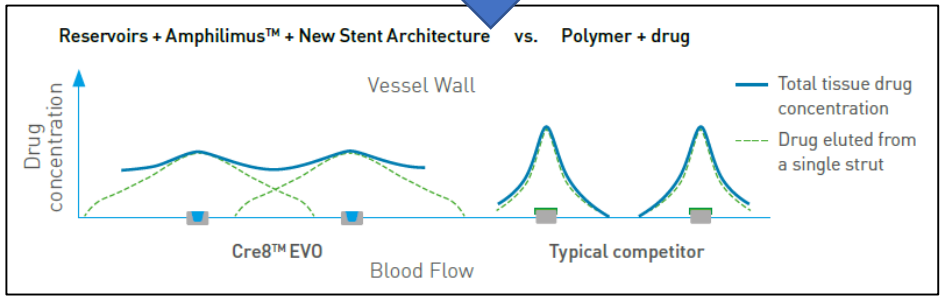
New stent architecture

#1 - New Stent Architecture (EvenArt) for maximized efficacy

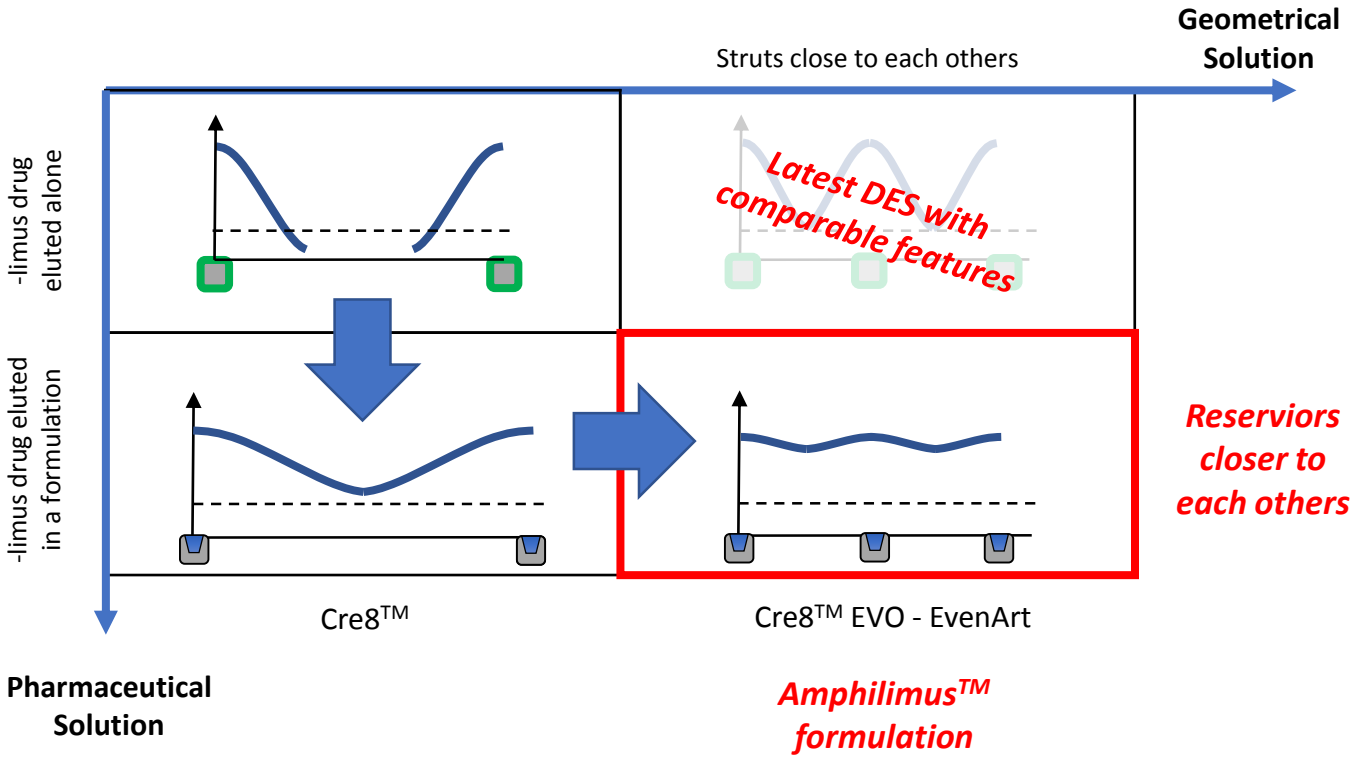
Shortened pitch with reduced crown width and different link number/ pattern **enhance Elution Profile** in challenging anatomies/ conditions







DRUG/ EFFICACY matrix



#2 - Cre8™ EVO - New Stent Architecture (EvenArt) and delivery system for better Deliverability/ Conformability

Vessel features in diabetic patients

VESSEL CALIBRE - smaller sized vessels

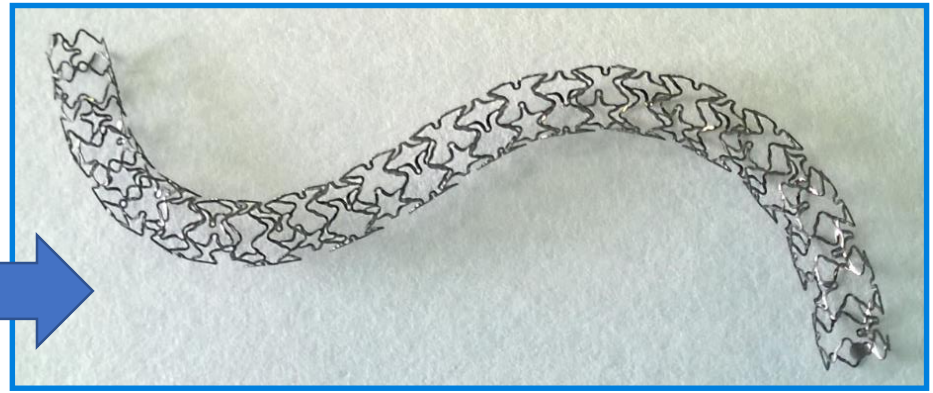
VESSEL INVOLVEMENT - higher incidence of multivessel disease

LOCATION OF LESIONS - proximal segments, LM

TYPE OF LESIONS - CTO and bifurcation lesions

COLLATERAL CIRCULATION - impaired circulation

CORONARY ARTERY CALCIFICATION - increased coronary artery calcifications



Cre8™ EVO new stent architecture, coupled with enhanced delivery system, allows for excellent device **Deliverability** and **Conformability** in any anatomy; even in the most challenging patients/ settings (diabetics)

Cre8™ EVO - Features summary

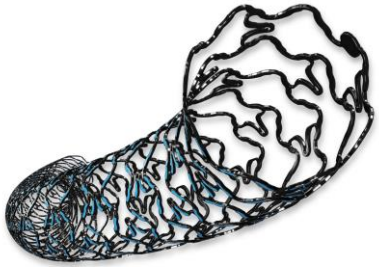
DES features

- Polymer-free DES
- Reservoir Technology
- Amphilimus™ Formulation (Sirolimus 0,9 $\frac{\mu g}{mm^2}$ + Fatty Acid)
- EvenArt stent architecture
- Bio Inducer Surface (pure Carbon surface)
- Zero stent shortening upon expansion
- 2 Platinum markers @ stent ends
- Co-Cr thin stent strut: 70/80 µm

Delivery System features

- Balanced and hydrophilic coated shaft
- Short balloon tapers
- RBP = 18atm for the entire product catalogue (from 2.25 to 4.5mm)

		NOMINAL LENGTHS [mm]							
		9	13	16	20	26	33	40	46
DIAMETERS [mm]	2,25	x	x	x	x	x	x	x	
	2,50	x	x	x	x	x	x	x	x
	2,75	x	x	x	x	x	x	x	x
	3,00	x	x	x	x	x	x	x	x
	3,50	x	x	x	x	x	x	x	x
	4,00	x	x	x	x	x	x		
	4,50		x	x	x	x	x		



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Conclusions

1. *Despite overall good outcomes with DES, opportunities exist to improve DES SAFETY and EFFICACY, particularly in patients with diabetes*
2. *Patients with diabetes are probe to lower DES EFFICACY due to:*
   - *Reduced responsive to –limus drugs*
   - *High blood levels of the hormone leptin*
3. *Prolonged elution of the Amphilimus™ formulation from abluminal reservoirs allows for higher –limus drug concentration to re-establish VSMCs inhibition and prevent in-stent restenosis*
4. *Cre8™ EVO, with its new stent architecture and delivery system, can:*
   - *Further advance DES efficacy specifically in complex anatomies/patients*
   - *Provide excellent device deliverability and conformability*