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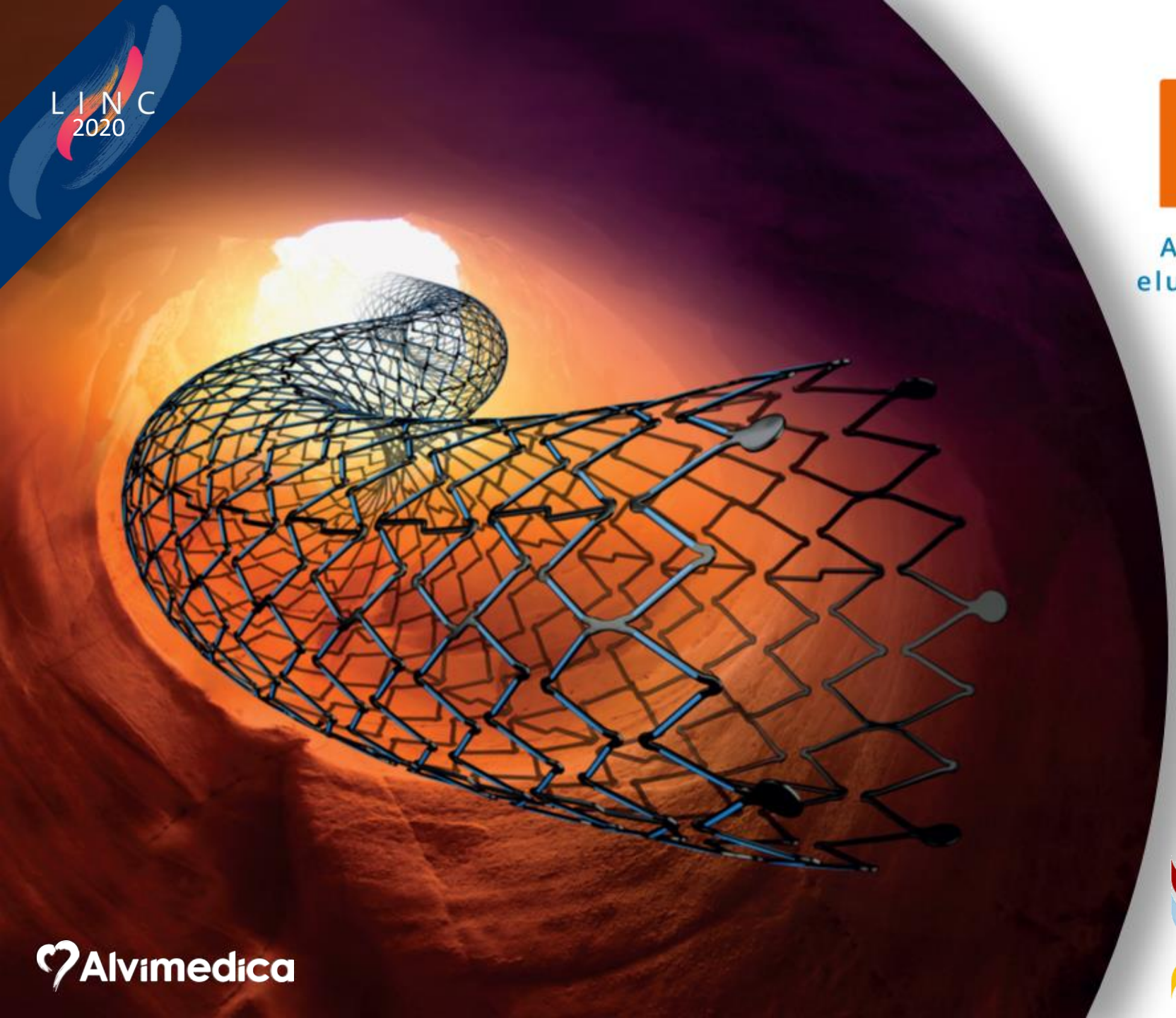

NiTiDES

Amphilimus™(Sirolimus + Fatty Acid) eluting Peripheral Self-Expanding stent

# NiTiDES: the innovative approach of SFA lesions


Dr. A. Kahlberg

Associate Professor of Vascular Surgery
Vita-Salute University, San Raffaele Hospital, Milan - *Italy*


Alvimedica

OSPEDALE SAN RAFFAELE

UNIVERSITÀ VITA-SALUTE SAN RAFFAELE UniSR QUID EST HOMO?

# Disclosure

**Speaker: ANDREA KAHLBERG**

Investigator for trials sponsored by Abbott, Alvimedica, Boston Scientific, Cook Medical, Medtronic, Cordis, W.L. Gore

Lecturer at courses/symposia hosted by Abbott, Biovascular, Alvimedica, Boston Scientific, Cook Medical, Medtronic, W.L. Gore, Terumo

Proctorship for W.L. Gore

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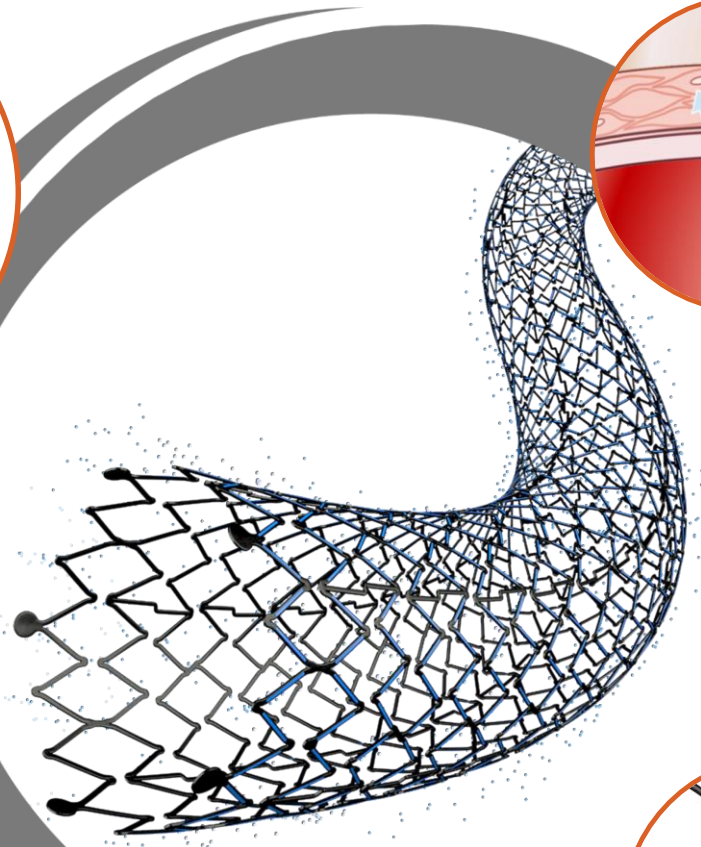
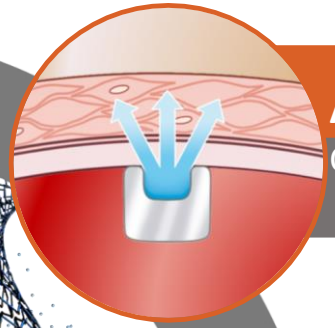
NiTiDES

# NiTiDES: platform characteristics

**Polymer-Free self-expanding DES**

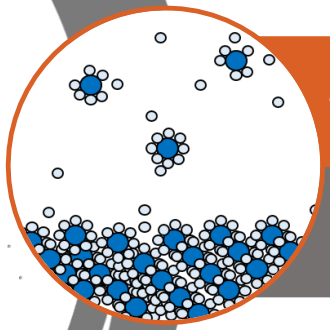
Avoids all the well known drawbacks due to the presence of a polymer interface with blood flow or vessel wall





**Abluminal Reservoir Technology**

Controlled and directed elution to the vessel wall



**Amphilimus™ Formulation**

(Sirolimus + Fatty Acid)

Enhanced drug bioavailability, permeability and maximized product overall safety and efficacy

**Bio Inducer Surface (BIS)**

2nd generation pure carbon coating

Optimal haemo-compatibility vs. lumen blood flow

Alvimedica

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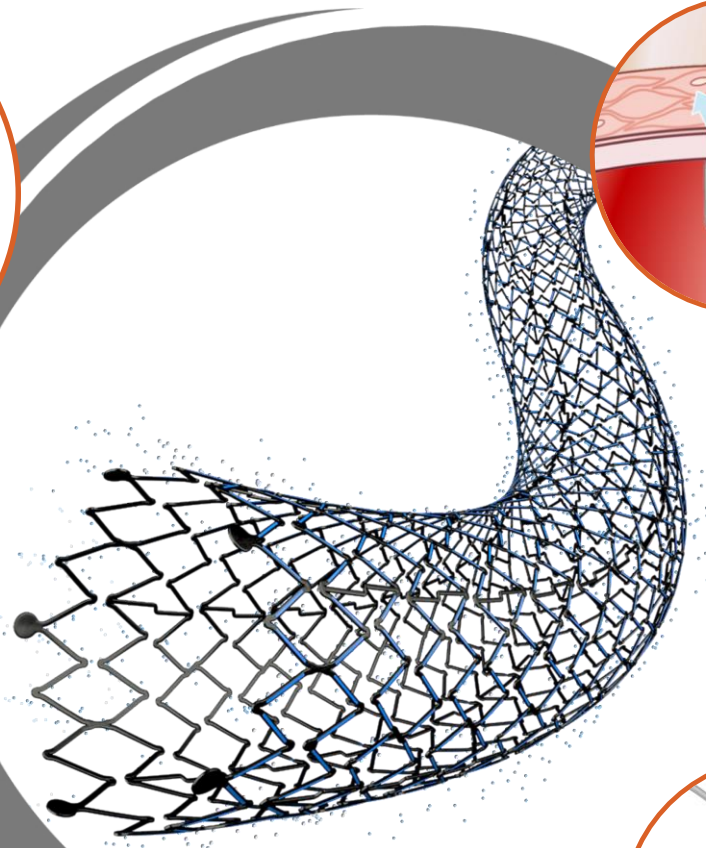

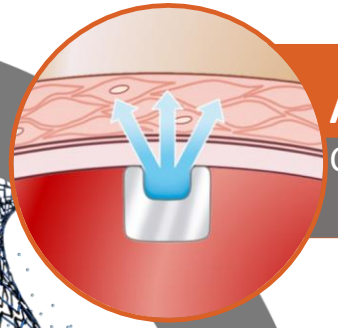

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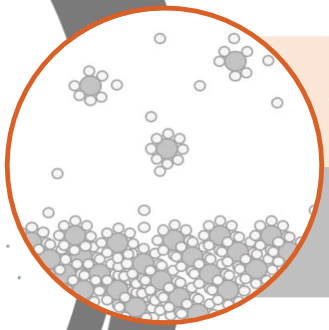

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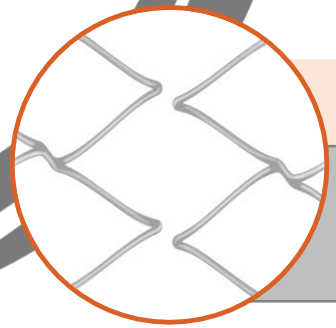

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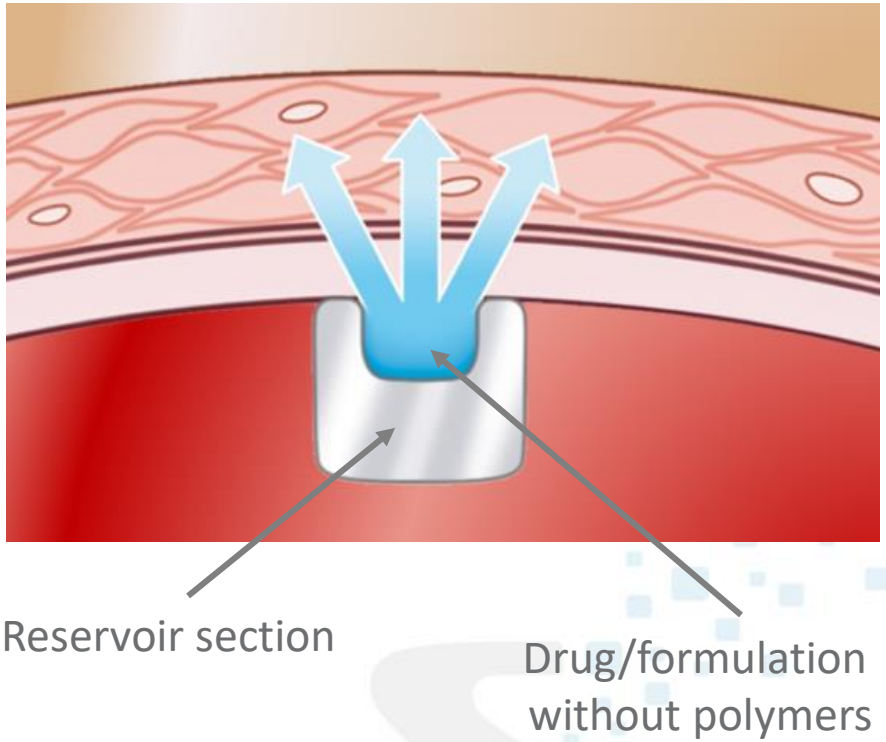
Alvimedica

# NiTiDES: Abluminal Reservoir Technology

In the **Abluminal Reservoir Technology** the drug is loaded into reservoirs without the need of any kind (durable or degradable) polymer.

The reservoirs are uniformly distributed on the stent struts.

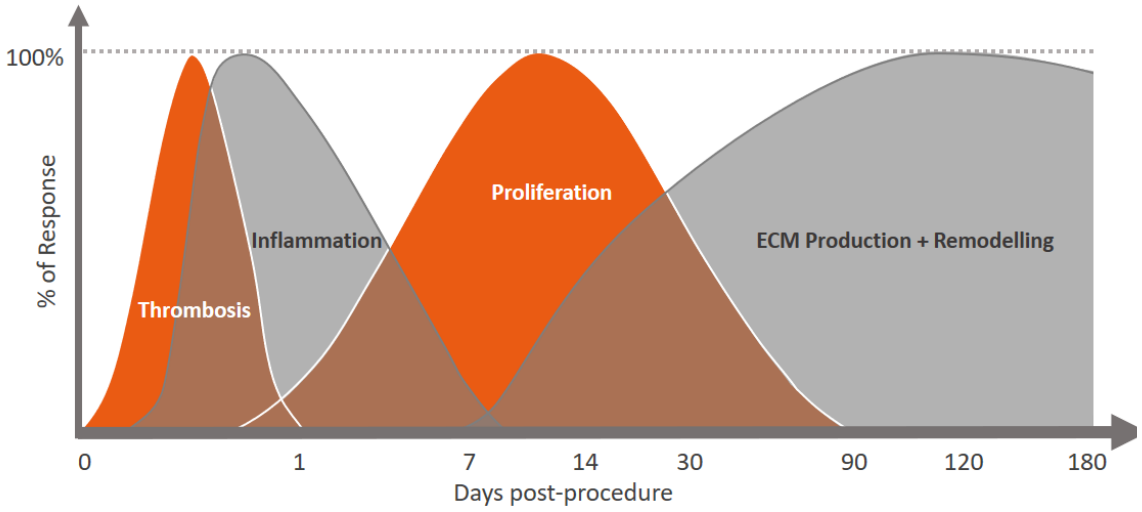


# NiTiDES: Abluminal Reservoir Technology

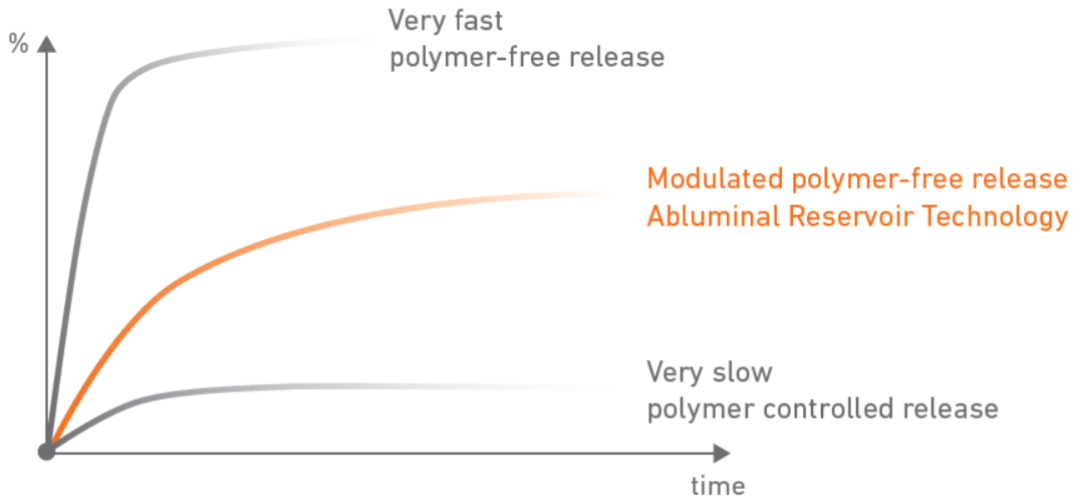
Thanks to the **Abluminal Reservoir Technology** it's possible to optimize and modulate a specific release kinetic curve without the use of any polymer.

This it fundamental to control the restenosis cascade, triggering factors and proliferation activities.

### The restenosis cascade




### The DES landscape



# NiTiDES: Abluminal Reservoir Technology

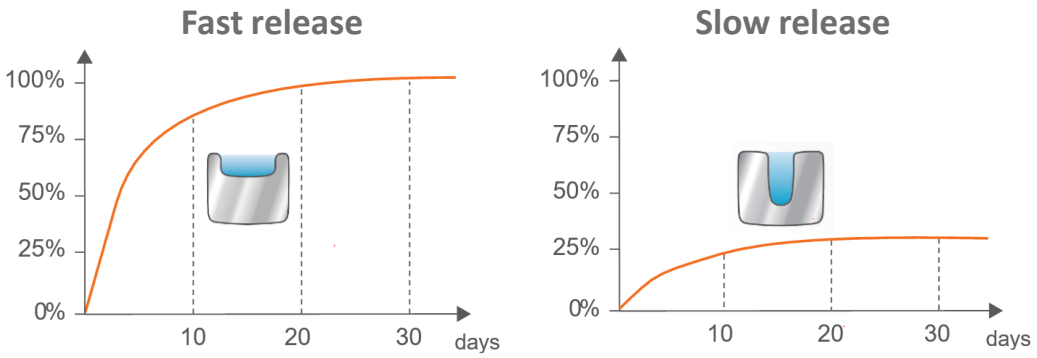
The reservoir's design fixes the drug amount and elution kinetic to the vessel wall without the use of any polymer

FICK LAW:

$$\frac{\Delta m}{\Delta t} = -D \cdot A \cdot \frac{\Delta c}{\Delta x}$$

- $\frac{\Delta m}{\Delta t}$: Drug amount over the time
- $A$: Area of the drug-vessel contact surface
- $\frac{\Delta c}{\Delta x}$: Drug concentration gradient
- $D$: Drug diffusion coefficient

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




The reservoir's design directly impacts on drug amount and release kinetic

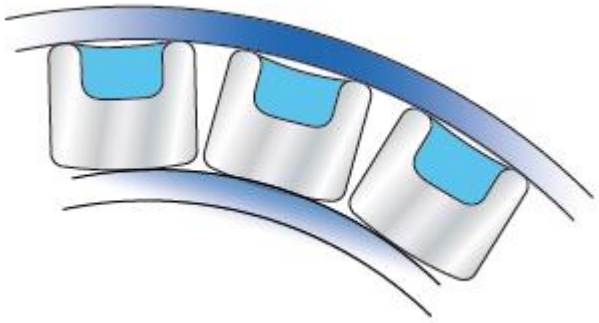
# NiTiDES: Abluminal Reservoir Technology

The **Abluminal Reservoir Technology** is the only solution able to protect the drug / formulation:

- During the crimping.
- During the shelf-life.
- During the stent implantation.

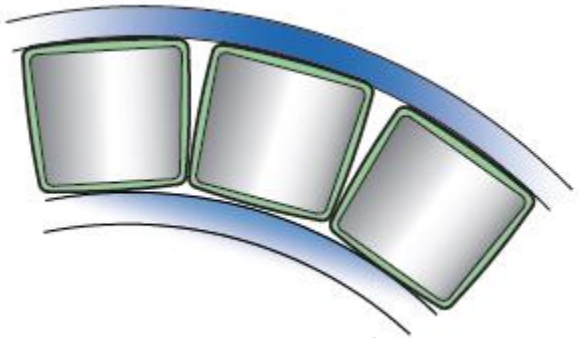
Stent struts sections inside the catheter sheath.

**NiTiDES**



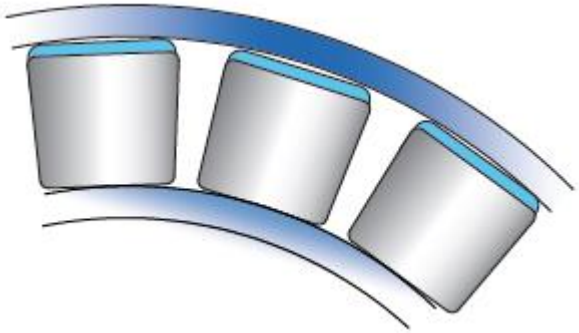
**Abluminal Reservoir Technology**

**Solution B**



**Permanent polymer conformal coating**

**Solution C**



**Abluminal polymer-free coating**

The active substance is not in contact with the external jacket, which means that there are no interactions / frictions potentially dangerous for the drug release.

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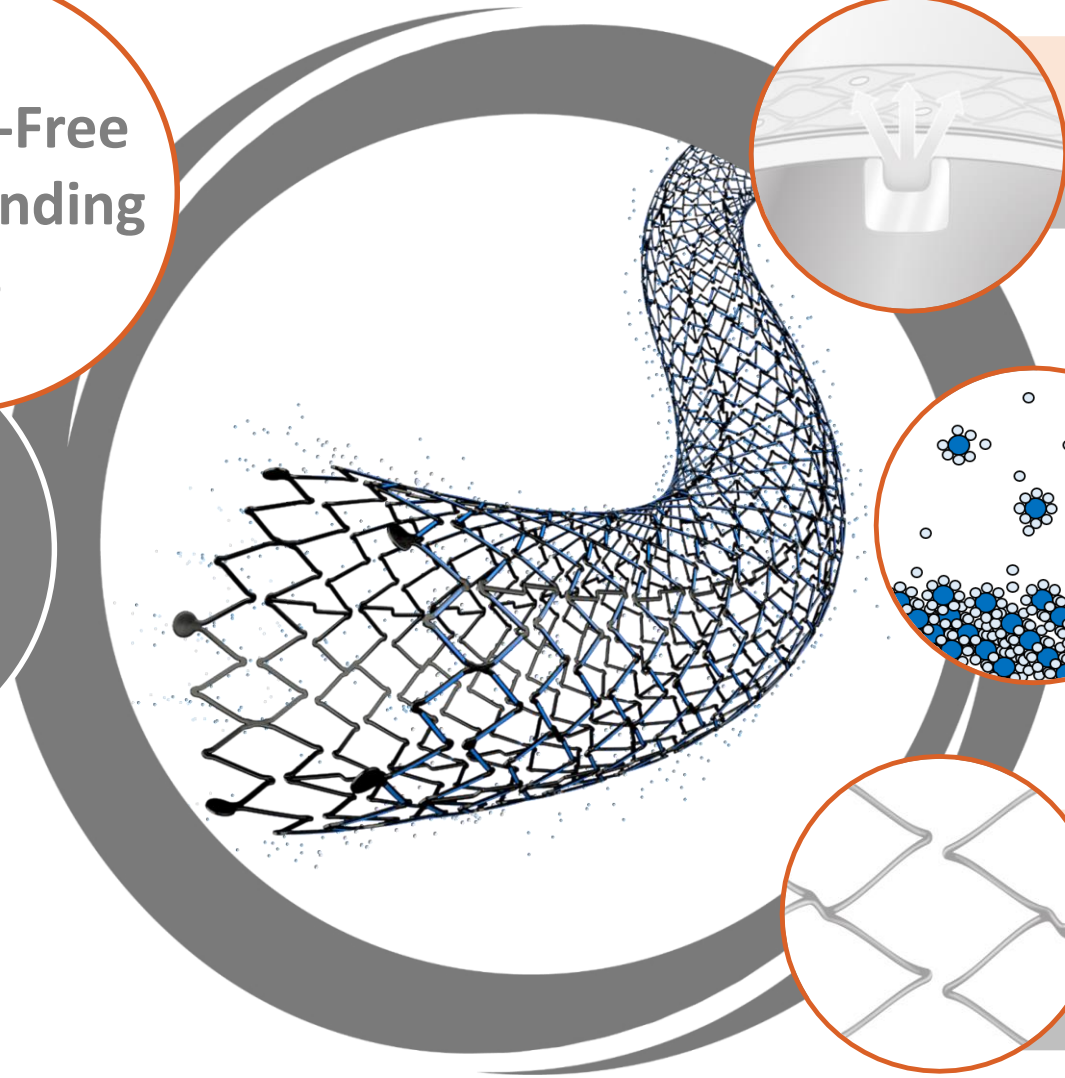
# NiTiDES: platform characteristics

**Polymer-Free self-expanding DES**

Avoids all the well known drawbacks due to the presence of a polymer interface with blood flow or vessel wall





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NiTiDES

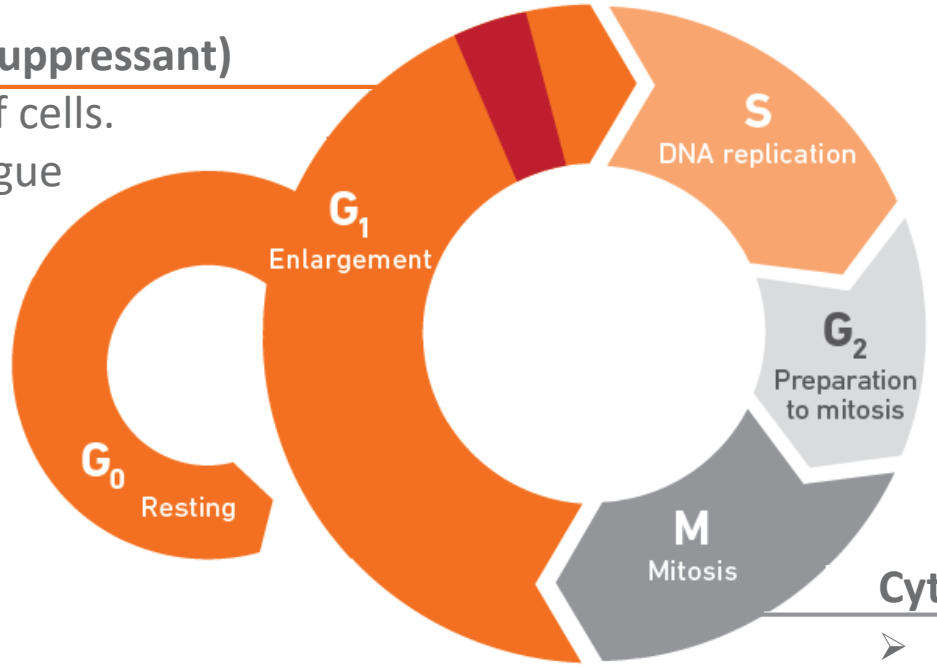
Alvimedica

# Which drug a SFA DES should release?

At today we can have different anti-proliferative drugs which act in different moments of the cell cycle:

**Cytostatic Drug (immunosuppressant)**

- Prevent proliferation of cells.
- Sirolimus and its analogue




**Cytotoxic Drug (chemotherapyc)**

- Induce the cellular apoptosis (death)
- Paclitaxel

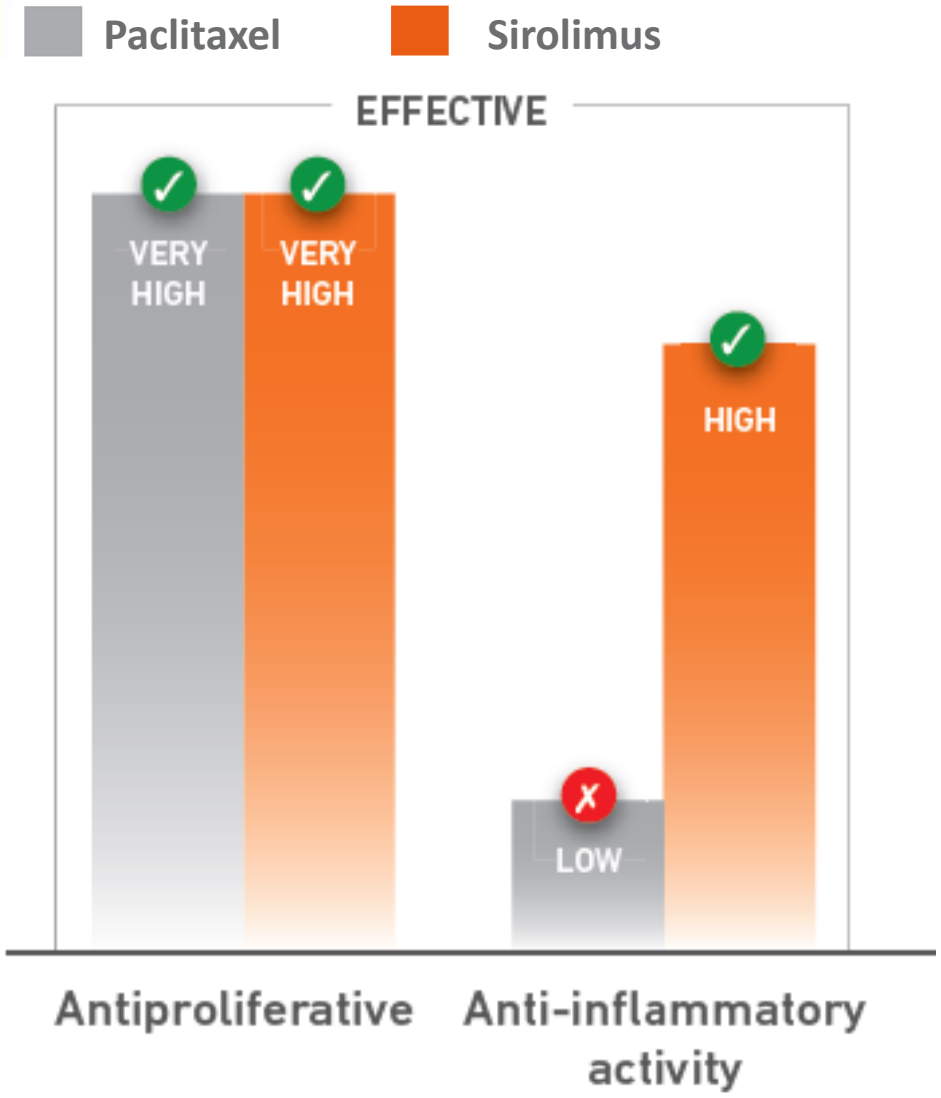
It has been verified that coronary and femoro-popliteal arteries have similar cell biology and they respond with a close antiproliferative mechanism after the delivery of the drug.

# Which drug a SFA DES should release?

**Ideal Drug**

- **Effective**
  - Anti-inflammatory activity
  - Antiproliferative
- **Long tissue residence**
  - Uniform drug tissue distribution
  - Lipophilicity
  - Tissue drug retention
- **Low toxicity**

# Sirolimus vs Paclitaxel: effectiveness

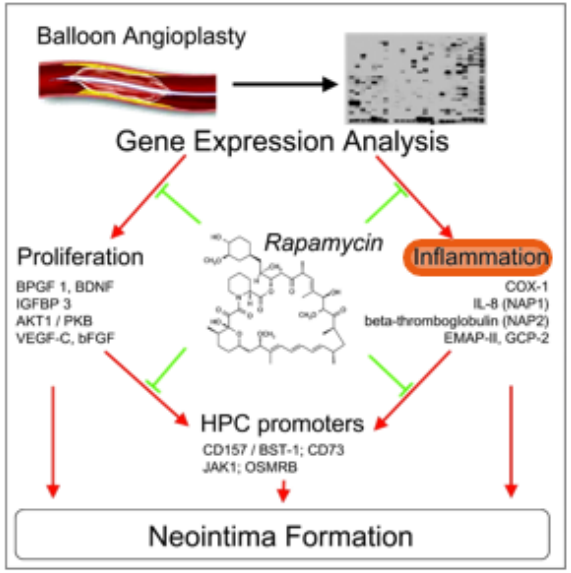



Parry et al. Eur J Pharmacol 2005

## Reducing the tissue inflammation

«Rapamycin (Sirolimus) attenuates vascular wall inflammation and progenitor cell promoters after angioplasty.»

T.G. Nührenberg et al. *The FASEB Journal* **2005,** 19, 246-248.

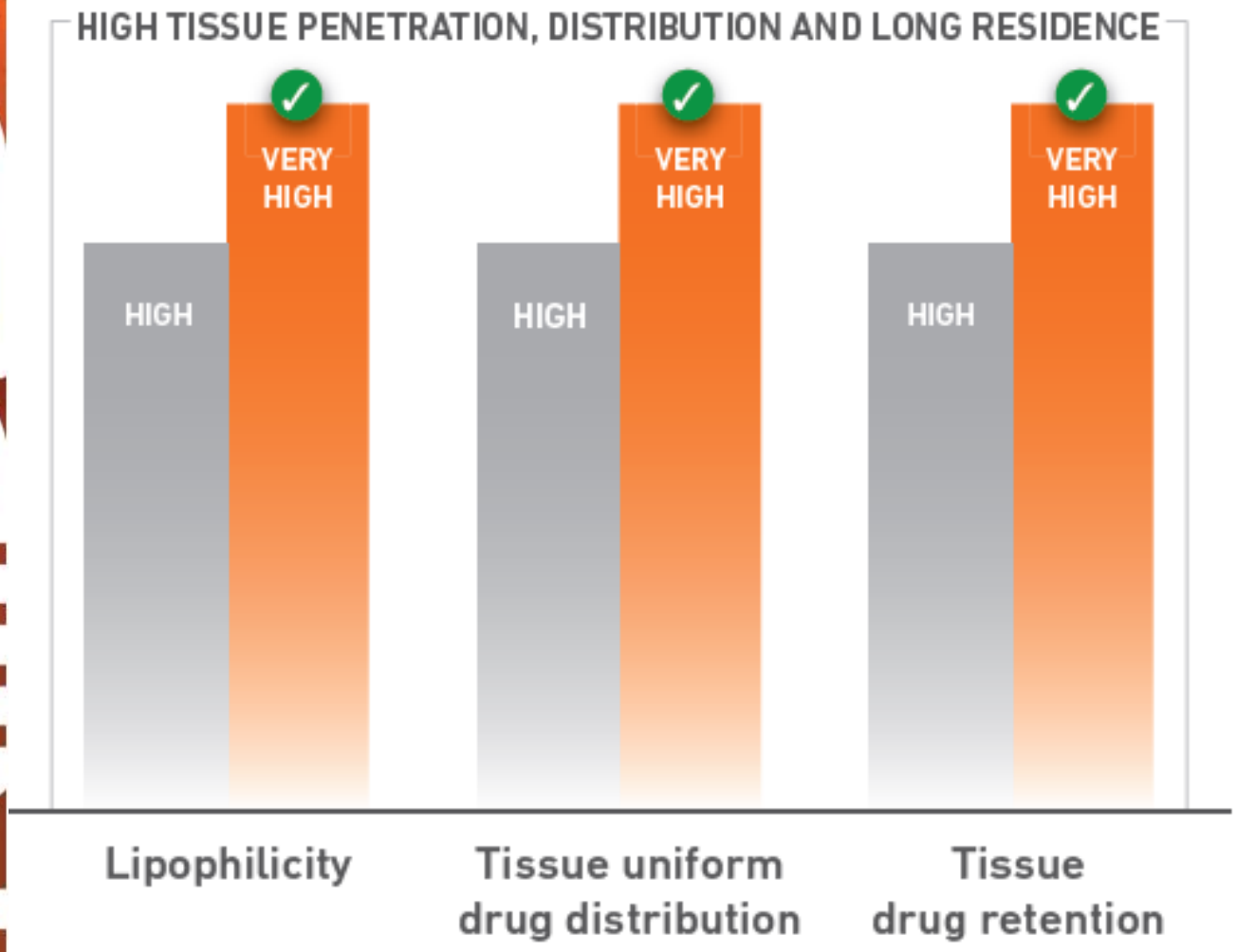



Paclitaxel has no recognized anti inflammatory action.

Nührenberg et al. The FASEB Journal 2005

# Sirolimus vs Paclitaxel: tissue behavior

Paclitaxel  Sirolimus



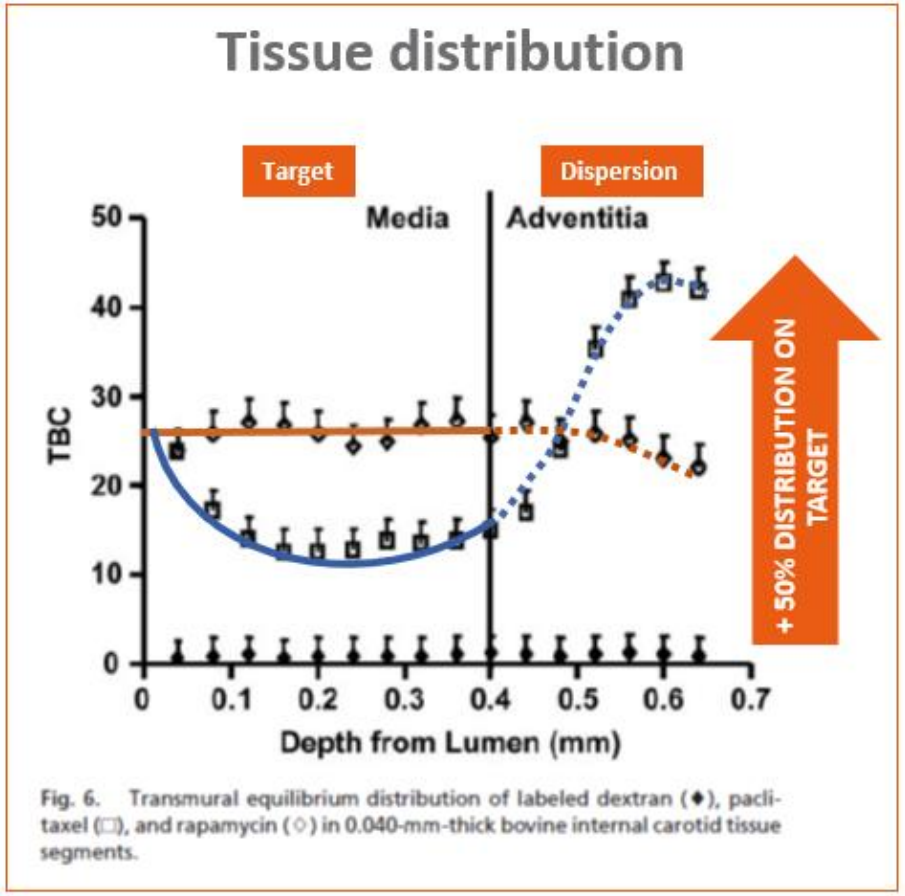



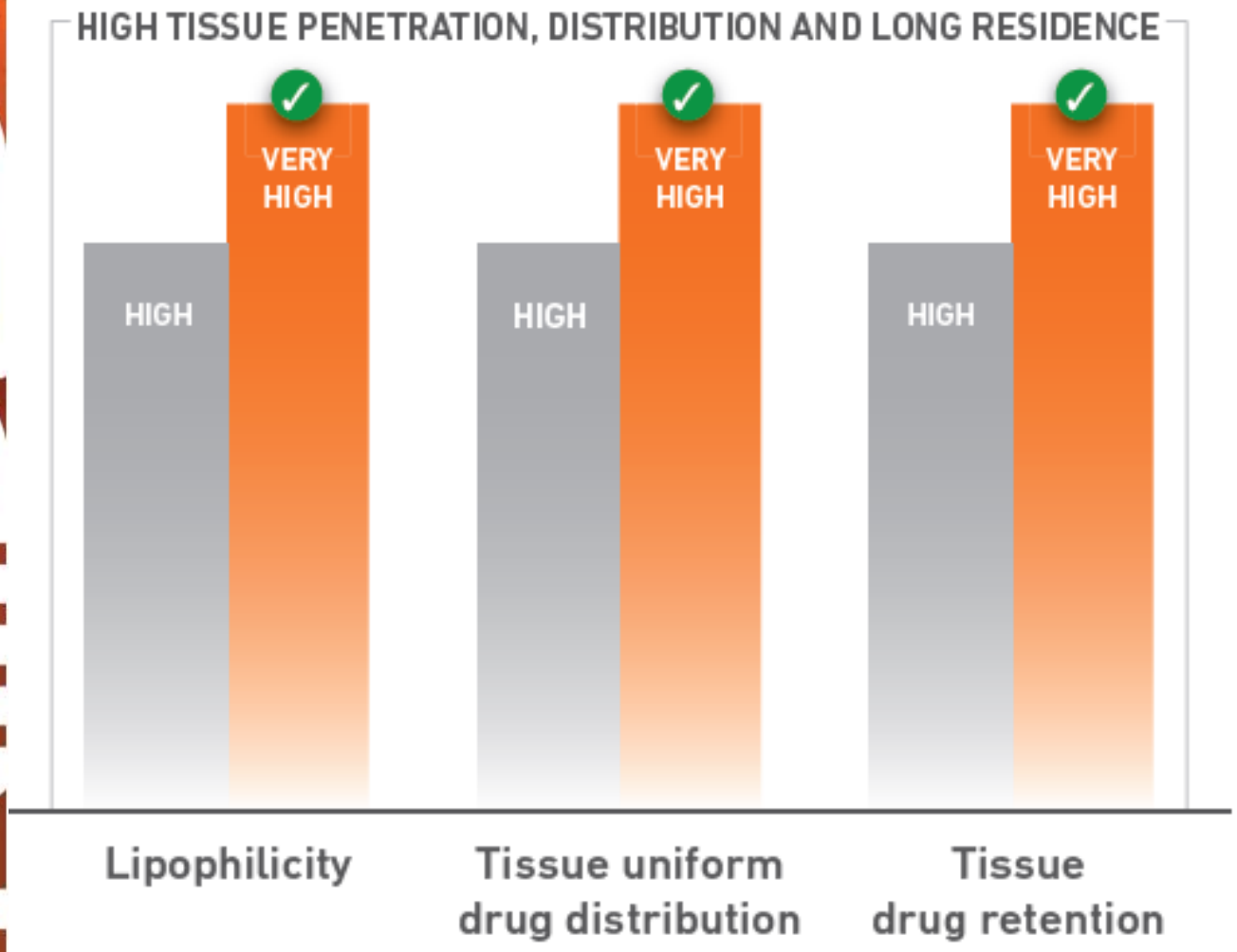

Fig. 6. Transmural equilibrium distribution of labeled dextran (♦), paclitaxel (□), and rapamycin (○) in 0.040-mm-thick bovine internal carotid tissue segments.

Drug Bank data

Levin et al. PNAS 2004

# Sirolimus vs Paclitaxel: tissue behavior

Paclitaxel  Sirolimus

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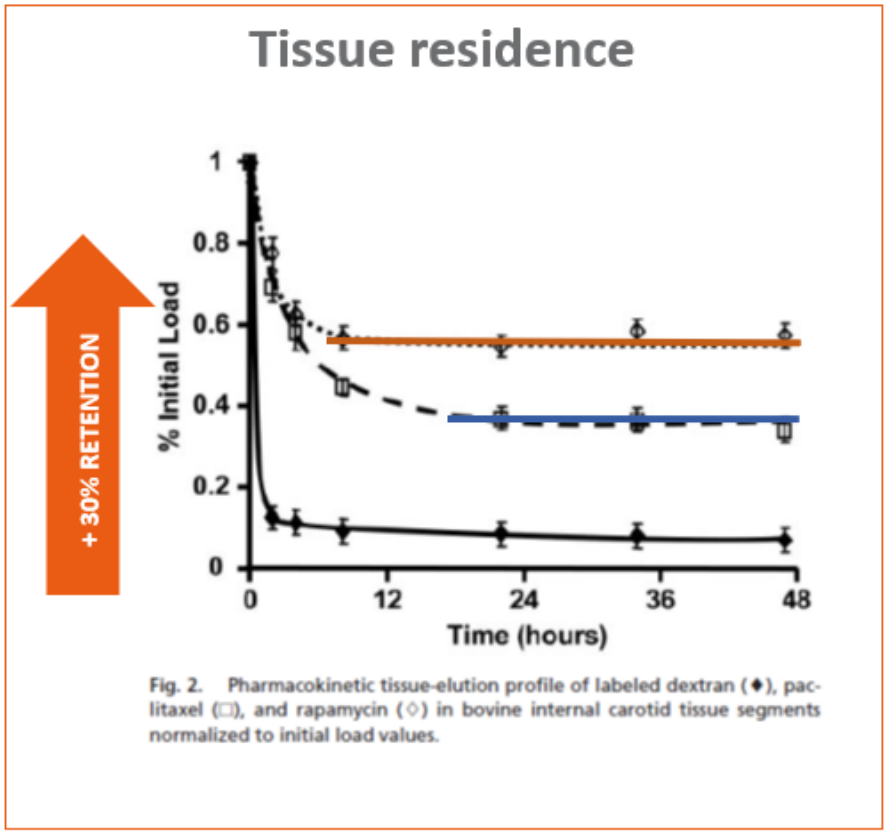


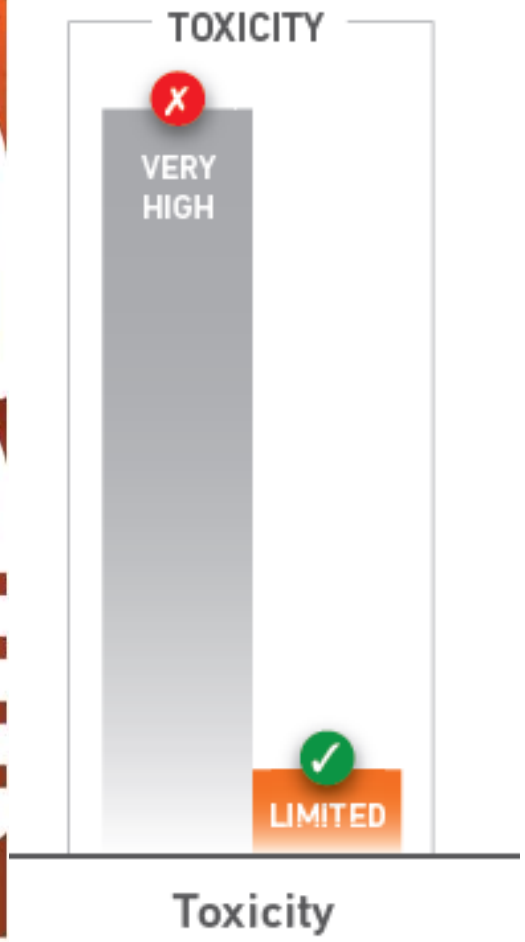

Fig. 2. Pharmacokinetic tissue-elution profile of labeled dextran (♦), paclitaxel (□), and rapamycin (◇) in bovine internal carotid tissue segments normalized to initial load values.

PNAS | June 22, 2004 | vol. 101 | no. 25 | 9463–9467

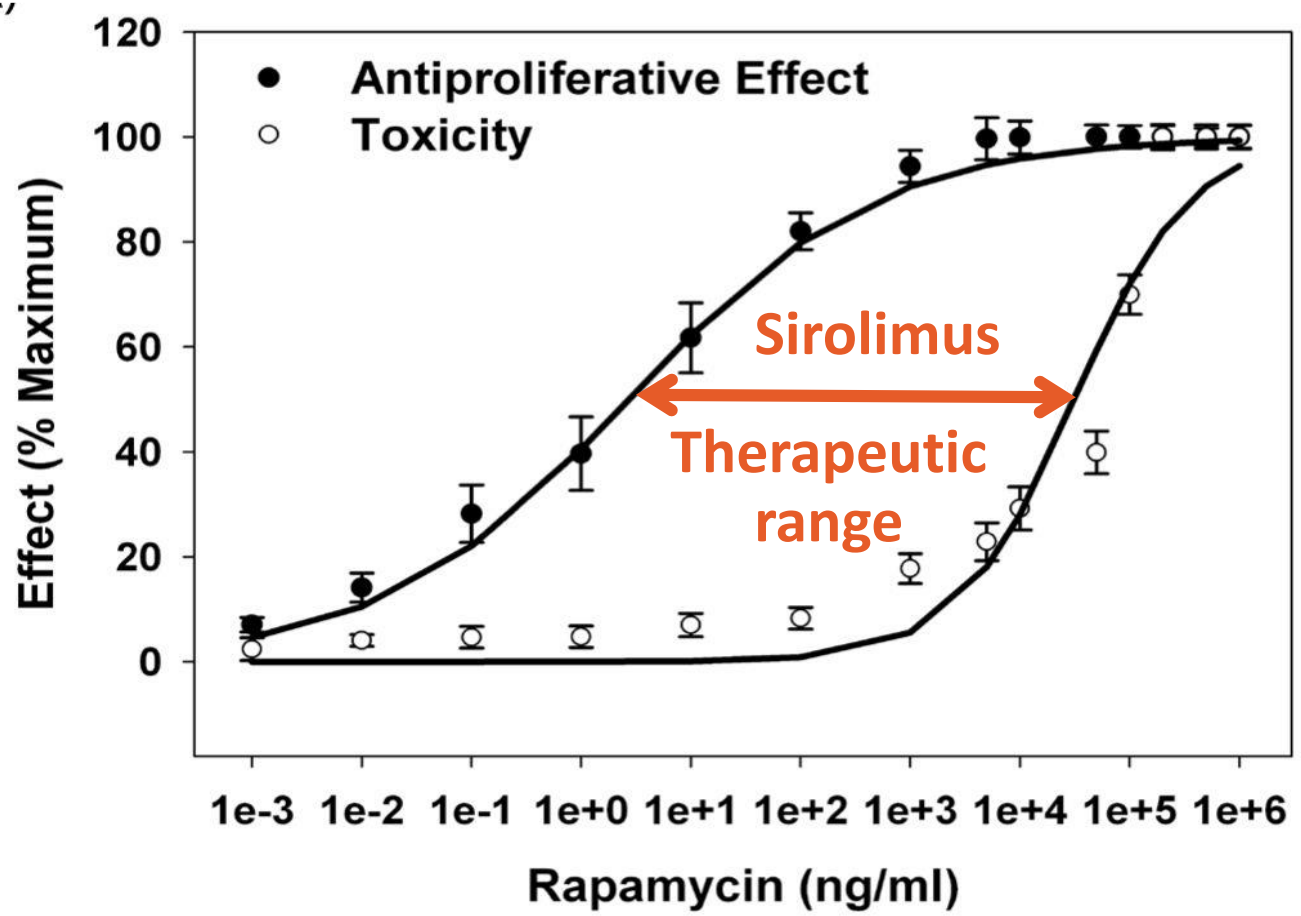
Levin et al. PNAS 2004

# Sirolimus vs Paclitaxel: toxicity

Paclitaxel  Sirolimus




## Toxicity related to Therapeutic range




Wessely et al. JACC 2006

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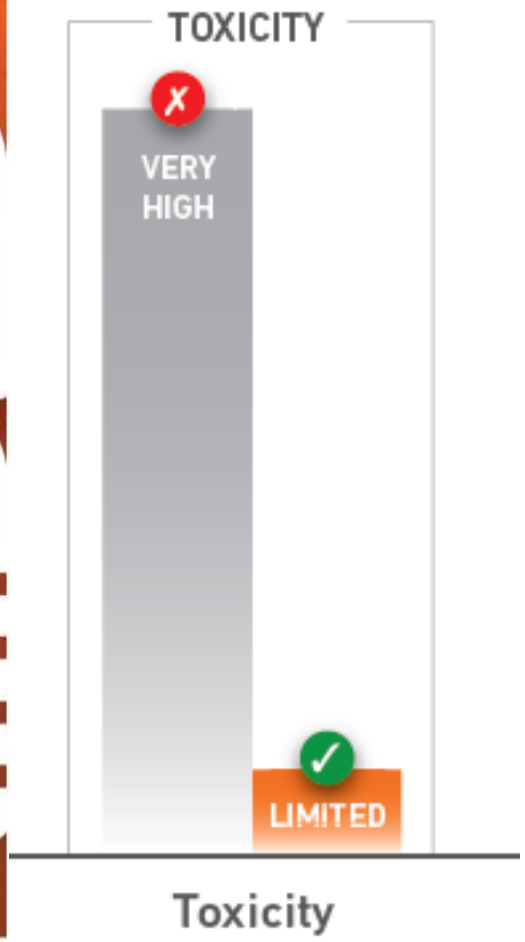
Paclitaxel  Sirolimus

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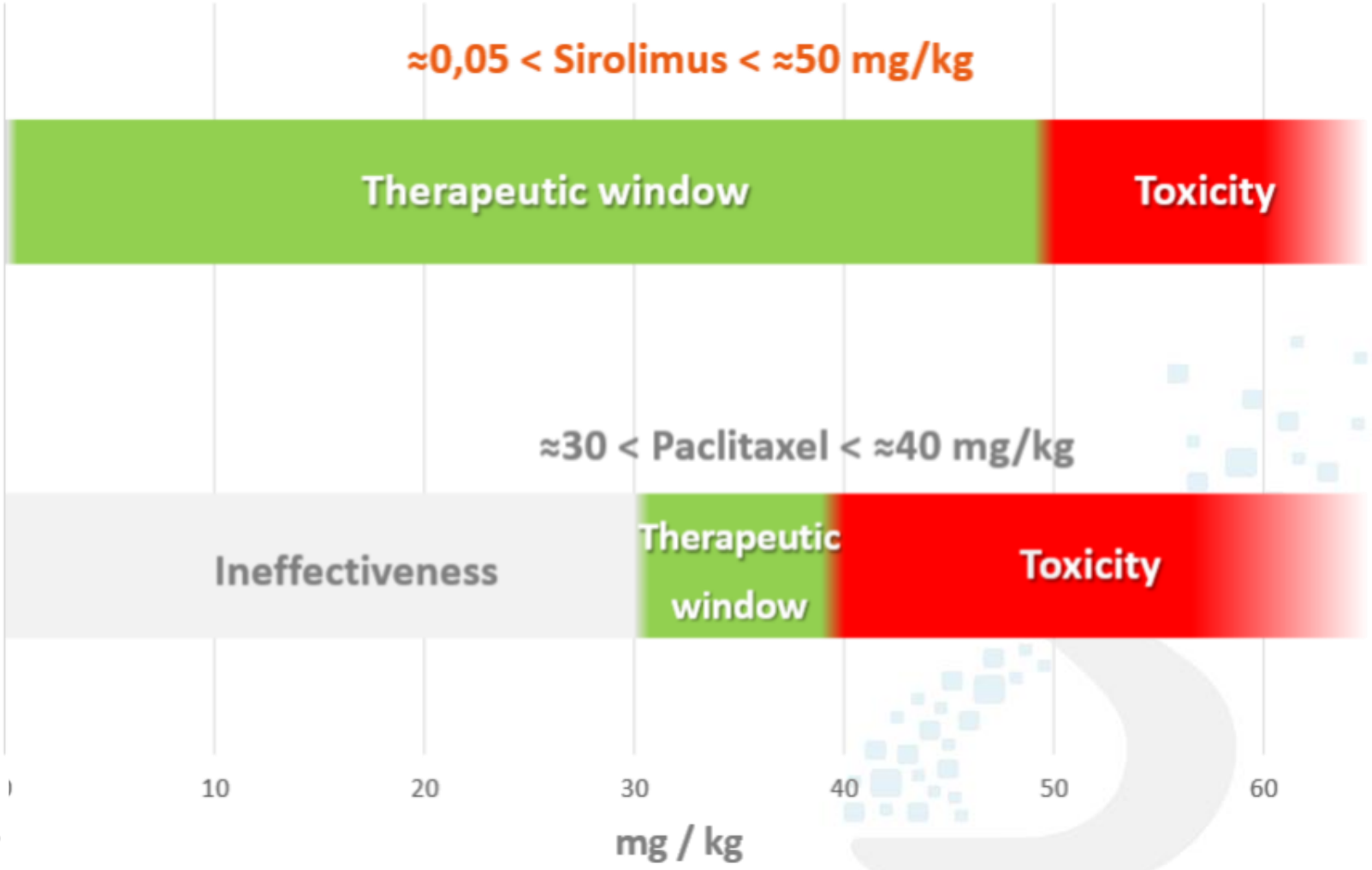
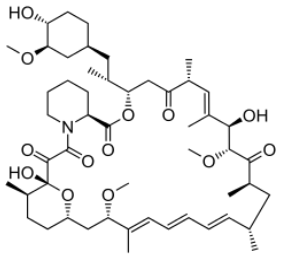


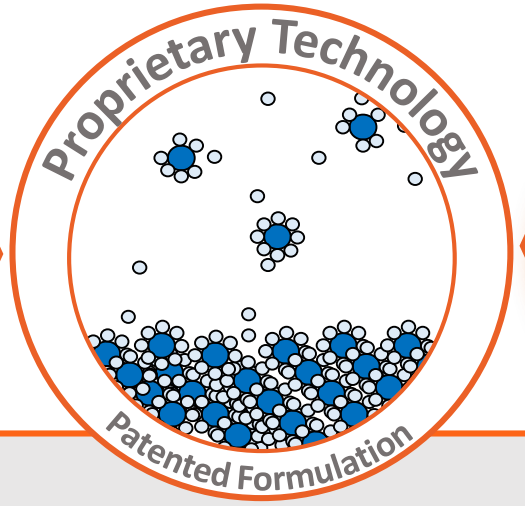

Wessely et al. JACC 2006

# NiTiDES: Amphilimus™ formulation

## Sirolimus



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




## Fatty Acid

- ↑ drug elution timing
- Modulate bioavailability
- Homogeneous distribution
- Enhance drug stability

- Homogeneous distribution
- Enhanced drug stability

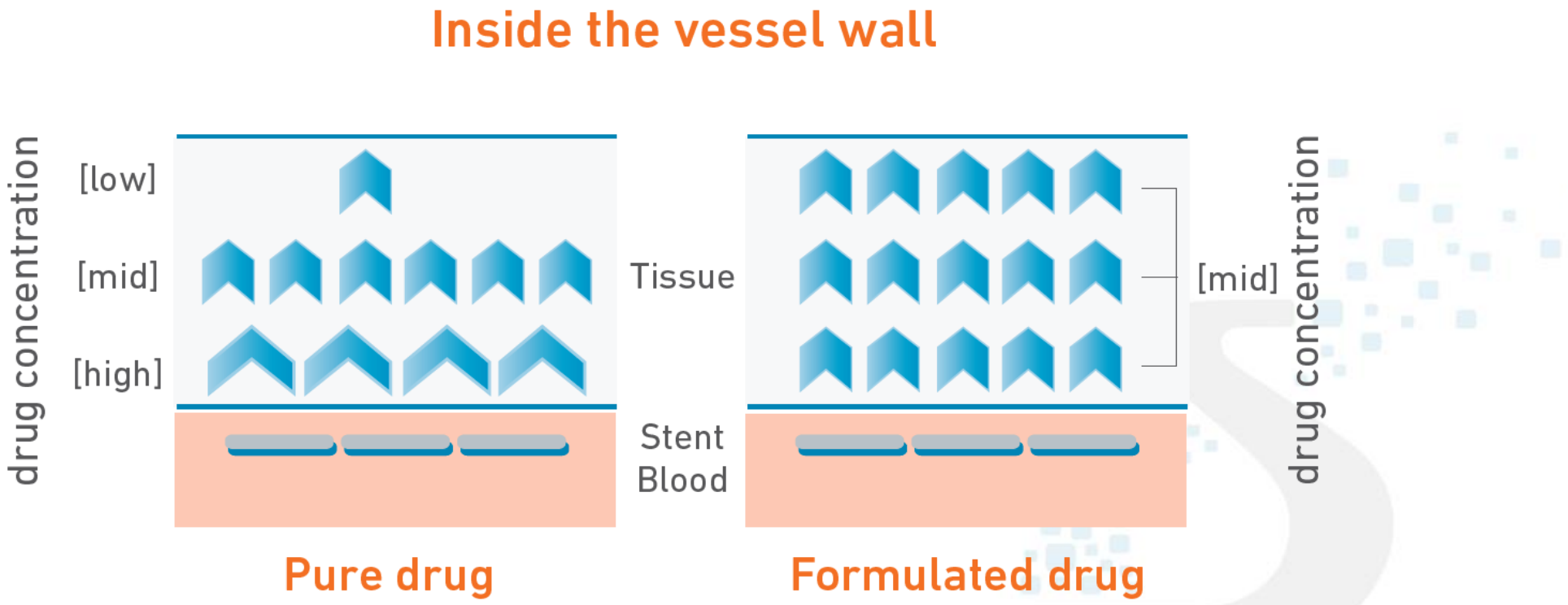
**Sirolimus and Fatty Acid are eluted together**

**Combined effect!**

Sirolimus molecule is 4 times bigger than the Fatty Acid molecule

# NiTiDES: Amphilimus™ formulation

Fatty Acid (small molecules) are characterized by an excellent permeability through cell membrane that allows a homogeneous Sirolimus distribution and action on the whole vessel tissue.



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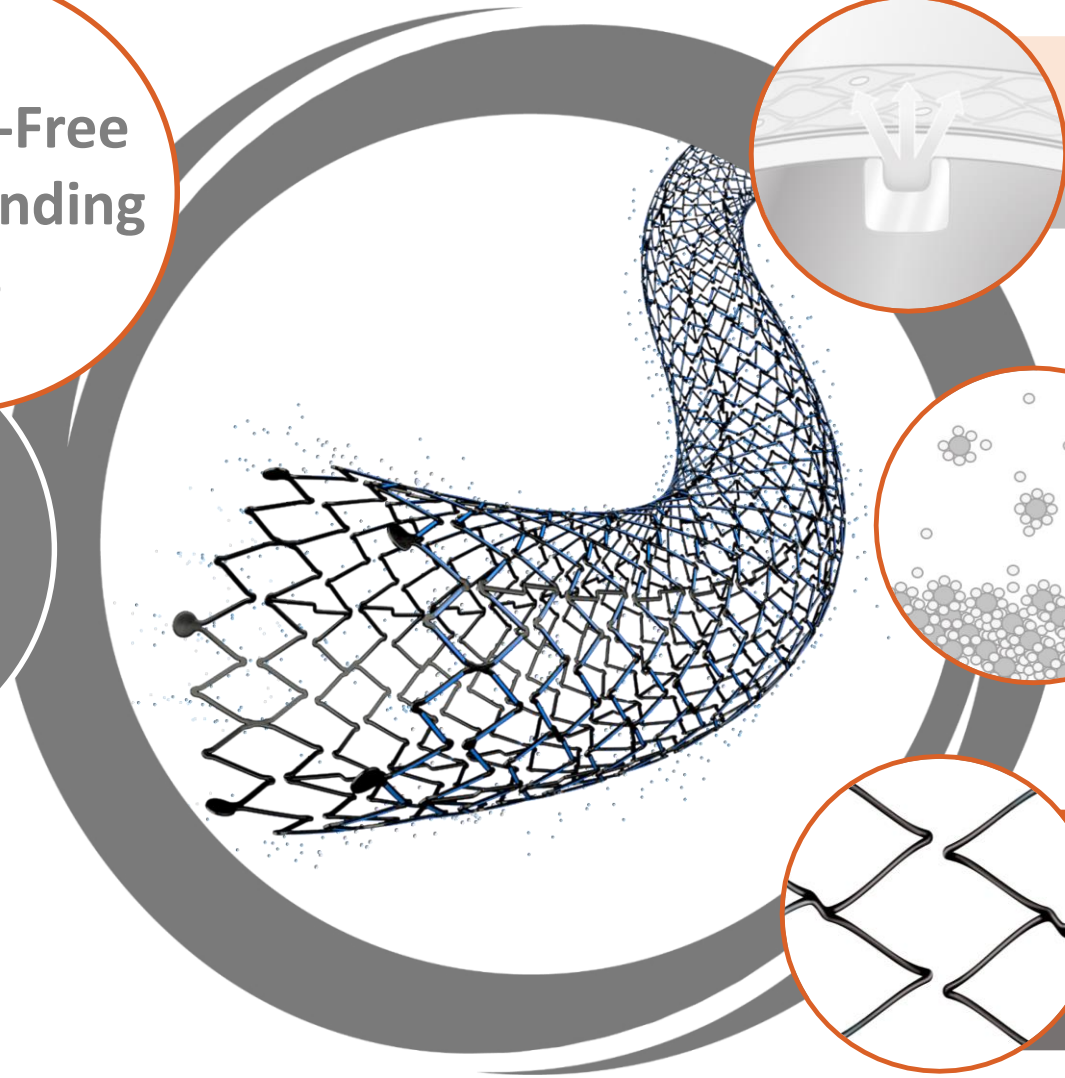



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**Bio Inducer Surface (BIS)**

2nd generation pure carbon coating

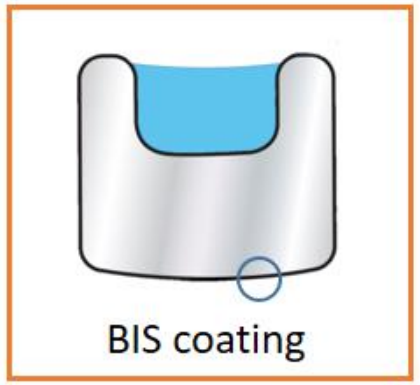
Optimal haemo-compatibility vs. lumen blood flow

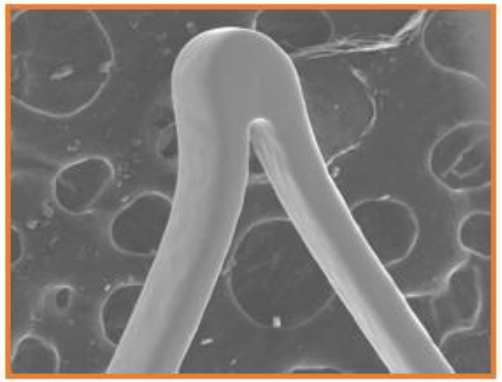
NiTiDES

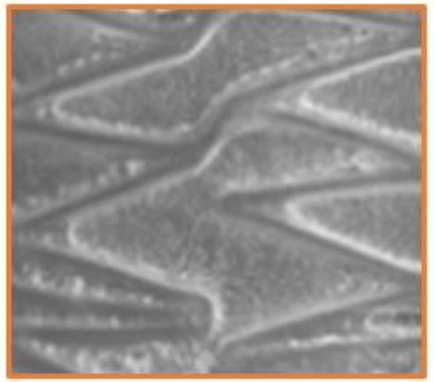
Alvimedica

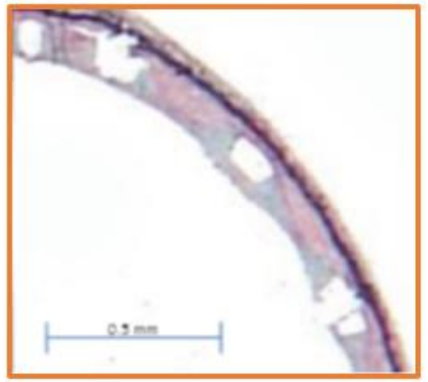
# NiTiDES: Bio Inducer Surface

The Bio Inducer Surface (BIS), an ultra thin film (<0.3µm) of pure carbon coating, is INTEGRALLY applied to the Alvimedica stent platform.







The features of the Bio Inducer Surface are:

- **Surface able to accelerate endothelialization and to establish a functional layer:** Reduced thrombogenicity & reduced inflammatory trigger.
- **Effective barrier versus heavy metal ions release:** Reduced inflammatory process.
- **Inert physical/chemical surface:** Reduced foreign body reaction.

# Conclusions

**NiTiDES** owns unique engineering and technological features

**possible *game changer* in the current SFA DES landscape**

- the **Sirolimus** drug that optimizes the efficacy and safety DES profile
- the **Fatty Acid** formulated with Sirolimus (Amphilimus™ formulation) that increases the penetration and availability of the effective drug
- the **Abluminal Reservoir Technology** that protects the drug formulation during the implant and modulates the drug release without any polymer
- the **Bio Inducer Surface (BIS)** that improves Nitinol bio/haemo-compatibility

# Thank you!

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San Raffaele University & Hospital
Milano, *Italy*