… un viaje desde el Polímero Permanente al Stent Sin Polímero

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JORNADAS CIENTÍFICAS Y GREMIALES CACI 2021
4 Y 5 DE DICIEMBRE 2021 . HOTEL HILTON - PRESENCIAL

1ra Generacion DES

Droga: Sirolimus, Paclitaxel

Plataforma: Acero Inoxidable

Polimero: Durable

2da Generacion DES

Droga: Everolimus, Zoarolimus

Plataforma: Cr Co, Strut Fino

Polimero: Biodegradable

Nueva Generacion DES

Droga: Sirolimus

Plataforma: Cr Co, Strut Fino, Sup Microporosa, Recubrimiento Abluminal

Polimero: Sin Polimero

DESAFIOS DE LOS POLIMEROS EN DES

Los polímeros (duraderos o biocompatibles) son una parte integral de la matriz de liberación de fármacos en los DES de generación actual, ya que garantizan la cinética de liberación del fármaco activo, el determinante clínico de la eficacia antirestenótica.

Sin embargo, se sabe que las propiedades mecánicas de la jaula metálica y las reacciones inflamatorias agresivas durante la erosión del polímero causan

- Deposición persistente de fibrina
- Endotelialización retardada
- Inflamación crónica
- Activación plaquetaria persistente
- Protrombogenicidad (potencial para causar trombosis del stent)

Polímeros: un mal esencial en los stents liberadores de fármacos

Obtención de polímeros en stents liberadores de fármacos como excipiente:

- Hubo muchas empresas que se embarcaron en stents liberadores de fármacos que no utilizaban ningún polímero o formador de matrices y los fármacos simplemente se rociaban sobre la superficie metálica de los stents. Tales DES como

- - Conor (Conor Medsystem EE. UU.) Med

- - Stent Janus (Sorin Biomedico Cardio, Italia)

- - Axxion (fabricado por Biosensosrs, Europa)

- no lograron controlar la reestenosis y fueron retirados del mercado después de que los datos clínicos mostraran una eficacia inferior. La razón atribuida fue una liberación de fármaco más rápida en comparación con las bases de polímero DES, que fue ineficaz para controlar la reestenosis. Hubo una búsqueda continua de un excipiente que pueda ser una alternativa a los polímeros para retardar la liberación del fármaco y crear una cinética de liberación ideal.

Delta
SANATORIO

VIVO ISAR

PRIMER STENT FARMACOLOGICO CON DOBLE DROGA Y SIN POLIMERO

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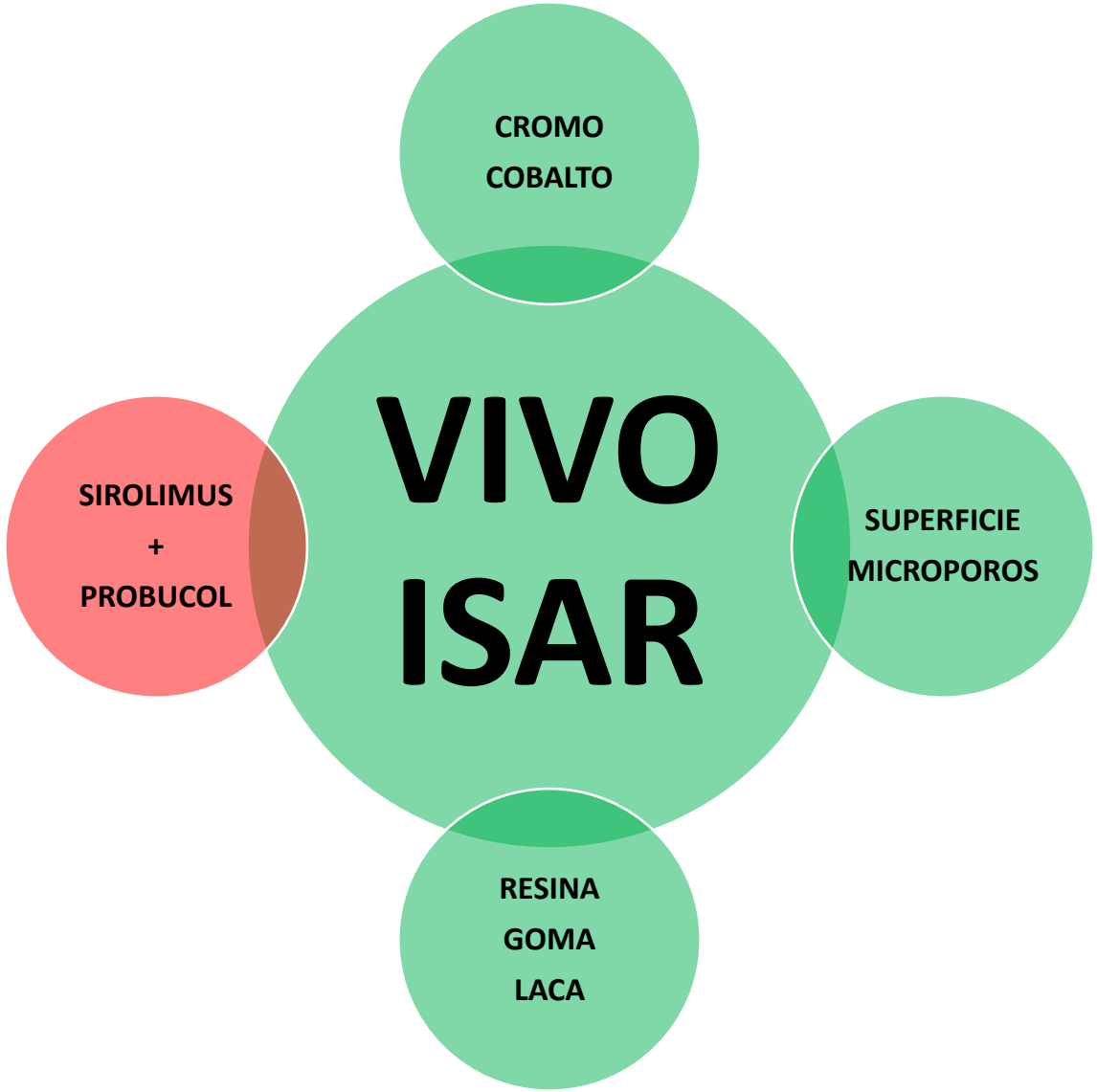
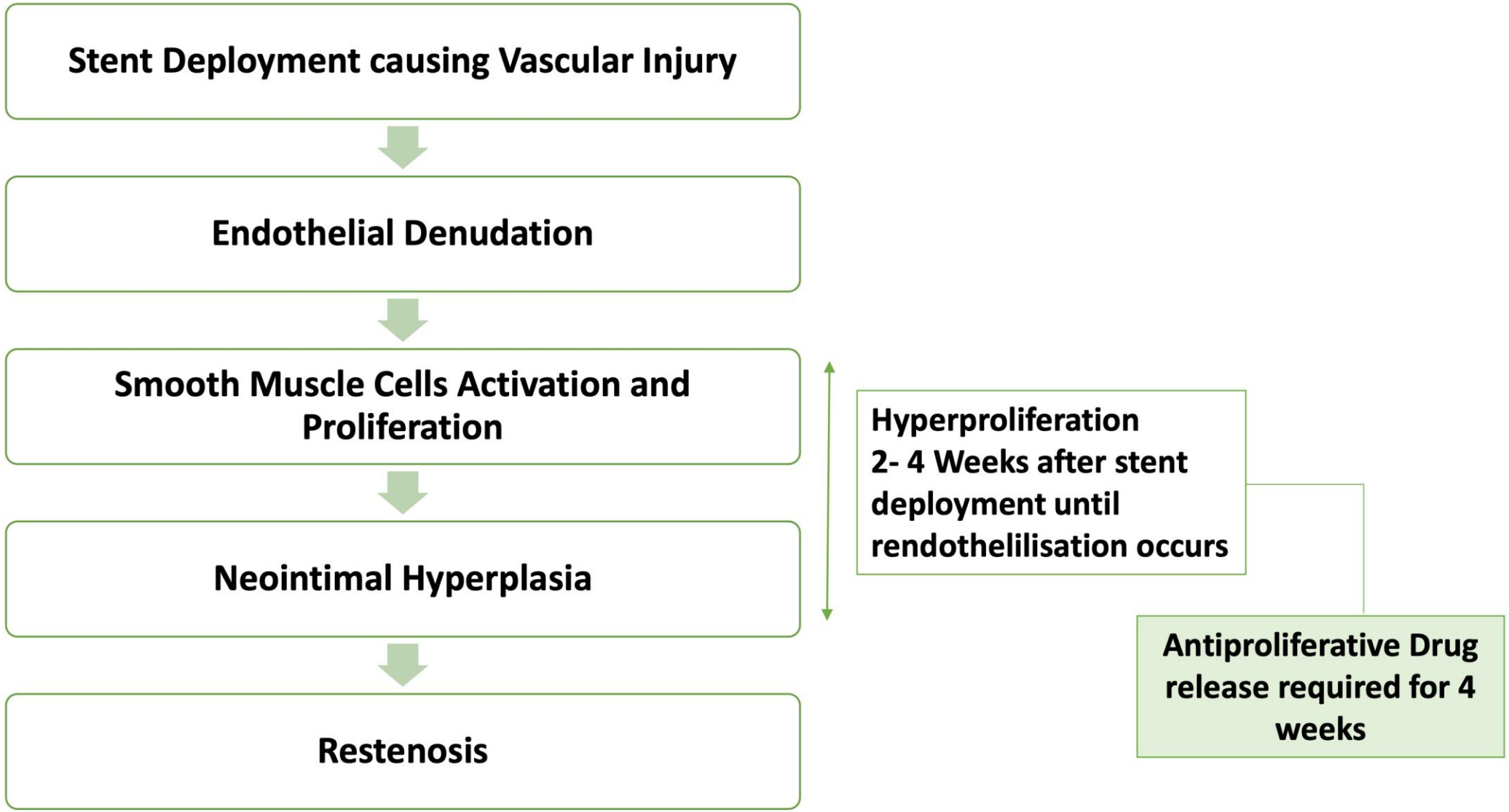


TECNOLOGIA DE DOBLE DROGA

Sirolimus

- Un inmunosupresor bien estudiado y clínicamente probado
- Sirolimus inhibe la activación de células T y células B al reducir su sensibilidad a la interleucina-2 (IL-2) a través del objetivo de inhibición de la rapamicina en mamíferos (mTOR). El mecanismo de acción de Sirolimus es unirse a la proteína citosólica FKbinding protein 12 (FKBP12)
- El efecto antiproliferativo e inmunosupresor de Sirolimus se utiliza junto con los stents coronarios para prevenir la reestenosis en las arterias coronarias.
- La dosis de fármaco nominal para el dispositivo es de 12,5 µg de fármaco sirolimus por milímetro de longitud del stent. Por lo tanto, la dosis máxima nominal del fármaco sirolimus para un stent de 48 mm es de 600 microgramos.

Why Sirolimus Optimal Release is required



TECNOLOGIA DE DOBLE DROGA

Probucol

- La historia del probucol es peculiar. Persuadidas por la evidencia que respalda la hipótesis de los lípidos, varias empresas intensificaron su búsqueda de medicamentos no tóxicos para reducir el colesterol durante las décadas de 1960 y 1970. Dow Chemical Company fue uno de ellos. Como resultado de una pantalla aleatoria de su biblioteca química, encontraron Probucol (4,4 ’ - (isopropilidenoditio) bis (2, 6-di-t-butilfenol)

- El compuesto fue eficaz para reducir los niveles de colesterol en ratones, ratas y monos y no tuvo efectos tóxicos aparentes incluso en dosis muy altas (hasta 5.280 mg / kg en roedores). Las pruebas preliminares mostraron rápidamente que el compuesto también es muy eficaz para reducir los niveles de colesterol en humanos. Los niveles de colesterol en plasma se redujeron entre un 10 y un 20 por ciento. No hubo reducción en los niveles de triglicéridos. Los primeros estudios de probucol se han revisado extensamente. El uso de Probucol depende de la dosis que fue de 1 gramo por día como dosis estándar. En dosis de 500 mg dos veces al día, el probucol redujo los niveles de colesterol total entre un 10 y un 20 por ciento sin toxicidad grave por el fármaco.

The New England Journal of Medicine

VOLUME 337 AUGUST 7, 1997 NUMBER 6

PROBUCOL AND MULTIVITAMINS IN THE PREVENTION OF RESTENOSIS AFTER CORONARY ANGIOPLASTY

JEAN-CLAUDE TARDIF, M.D., GILLES CÔTÉ, M.D., JACQUES LESPÉRANCE, M.D., MARTIAL BOURASSA, M.D., JEAN LAMBERT, PH.D., SERGE DOUCET, M.D., LUC BILODEAU, M.D., STANLEY NATTEL, M.D., AND PIERRE DE GUISE, M.D., FOR THE MULTIVITAMINS AND PROBUCOL STUDY GROUP*

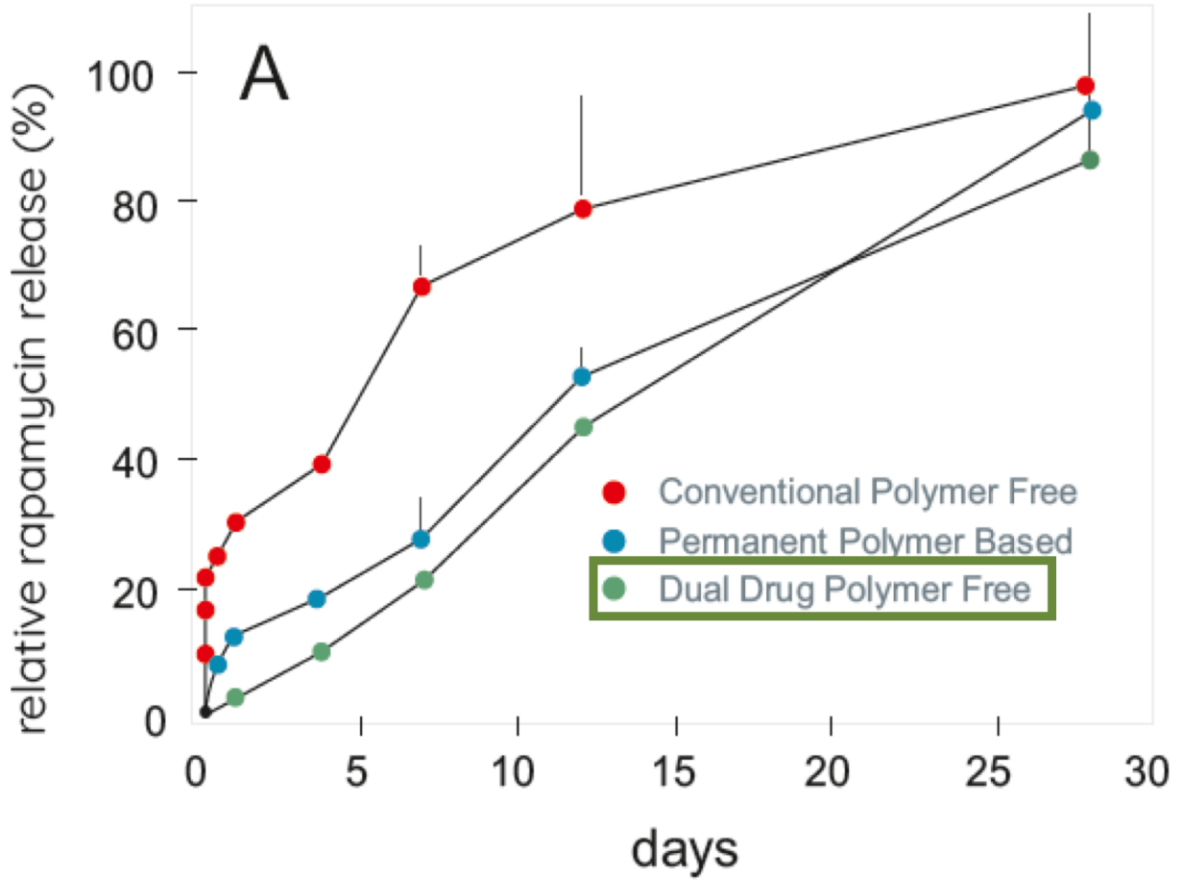
TECNOLOGIA DE DOBLE DROGA

Probucol

- El probucol se utiliza como componente de la matriz de recubrimiento del stent como alternativa al polímero.
- Debido a su alta lipofilicidad, asegura una cinética de liberación óptima de Sirolimus
- Impone un efecto antioxidante con mayor eficacia anti-reestenótica que ha demostrado ser beneficioso no solo para la prevención de la reestenosis sino también para la desaceleración de la progresión de la aterosclerosis.
- Probucol facilita la endotelización del stent, lo que reduce la magnitud de la hiperplasia de la neoíntima y la aparición de trombosis del stent.

VIVO ISAR
Polymer-Free Sirolimus Eluting Stent

Drug Release Kinetics



- Faster Drug Release compromises the DES ability to prevent smooth cell proliferation for complete 4 weeks, hence increased chances of restenosis

VIVO ISAR besides not having polymer, demonstrated optimal Drug Release Kinetics with prolonged release of Sirolimus which is 80% in 28 days

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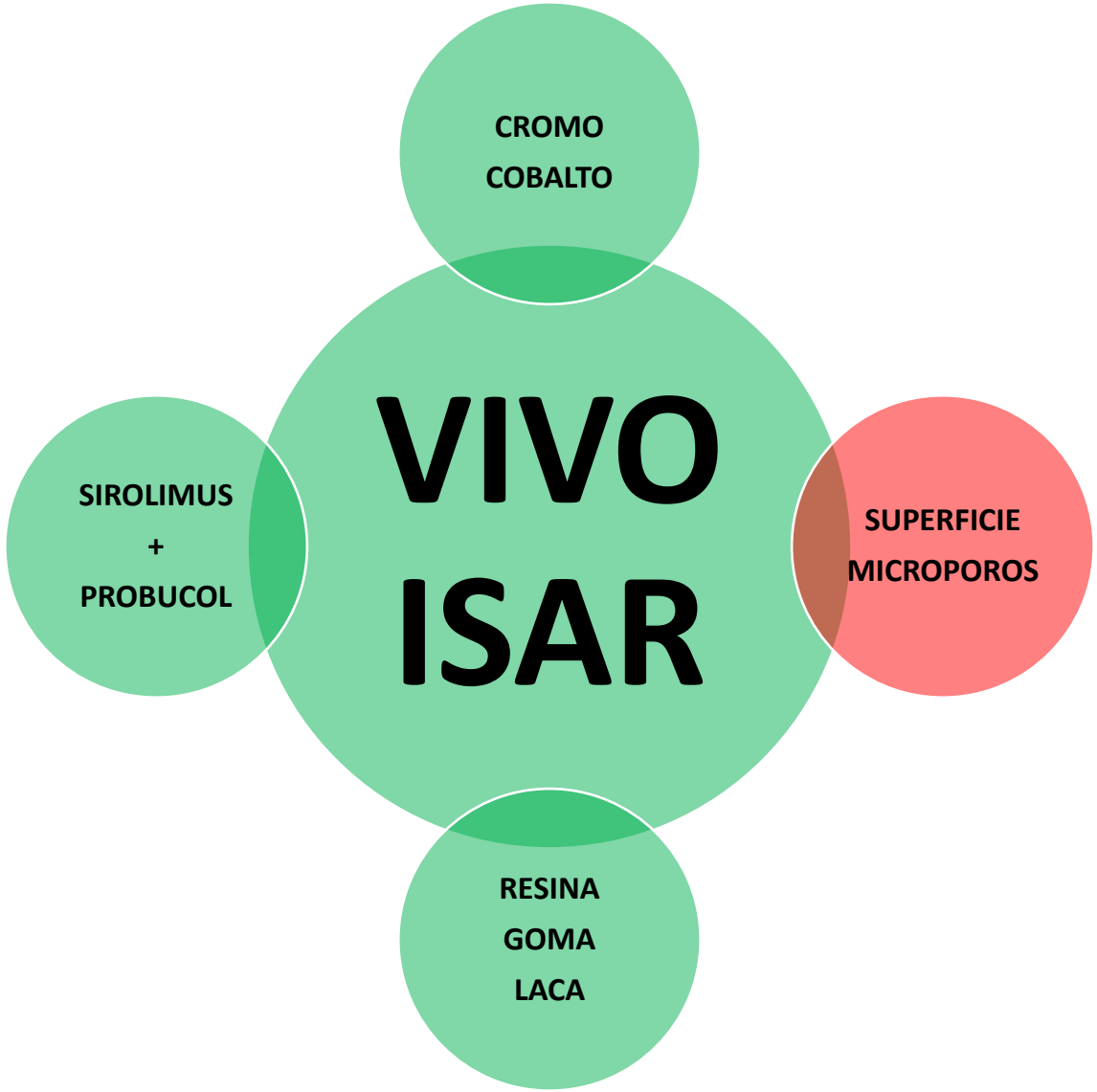
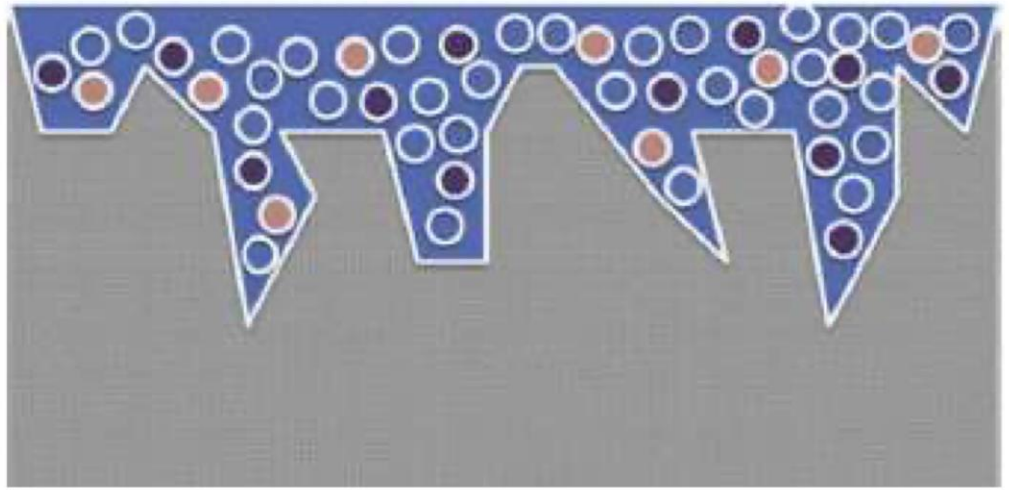


VIVOISAR
Polymer-Free Sirolimus Eluting Stent

Micro-Porous Surface

- **The micro-pores on its surface act like reservoirs for delivering the drug to the targeted site using van-der-walas forces to control the release-kinetics of the drug**

- **Micro-pores also reduce the carrier load by 1/4th as compared to other DES**

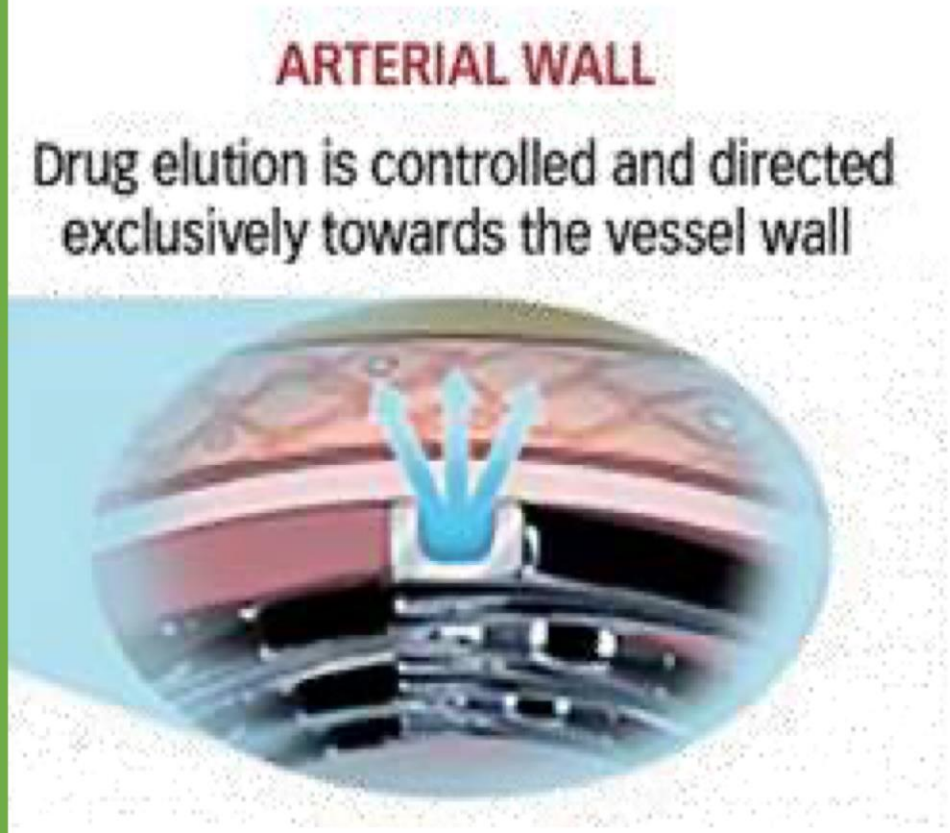


R-proS stent platform that consists of a blend of sirolimus (open circles), probucol (purple filled circles) and shellac (pink filled circles)

vivoISAR

Polymer-Free Sirolimus Eluting Stent

Abluminal Coating



Abluminal Coating leads to Directional drug release only to target tissue and less systemic exposure of drug which leads to faster healing

Abluminal coating ensures-

- **Better Endothelialisation**
- **Reduces the incidence of stent thrombosis**

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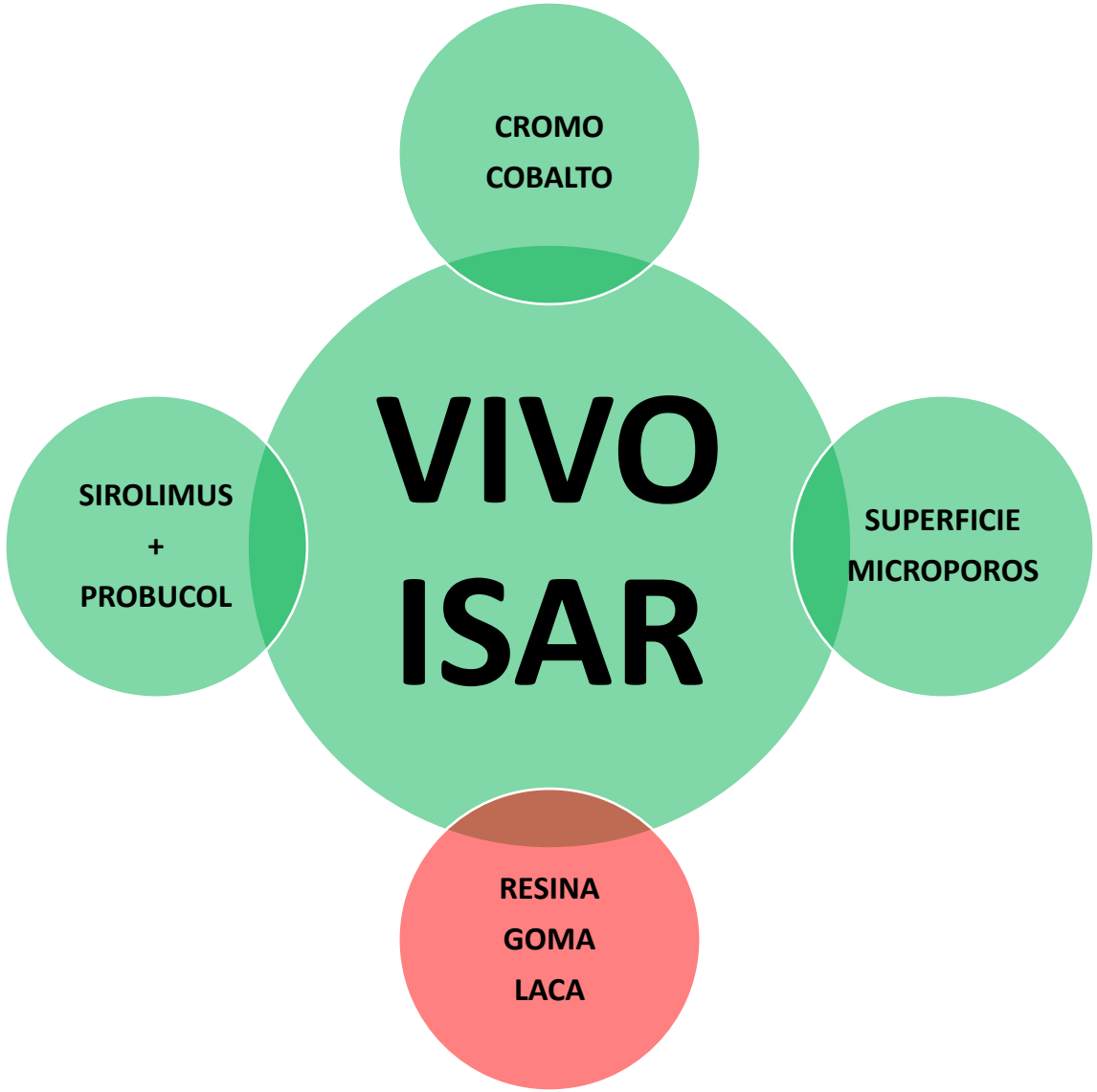
SANATORIO



RESINA DE GOMA LACA

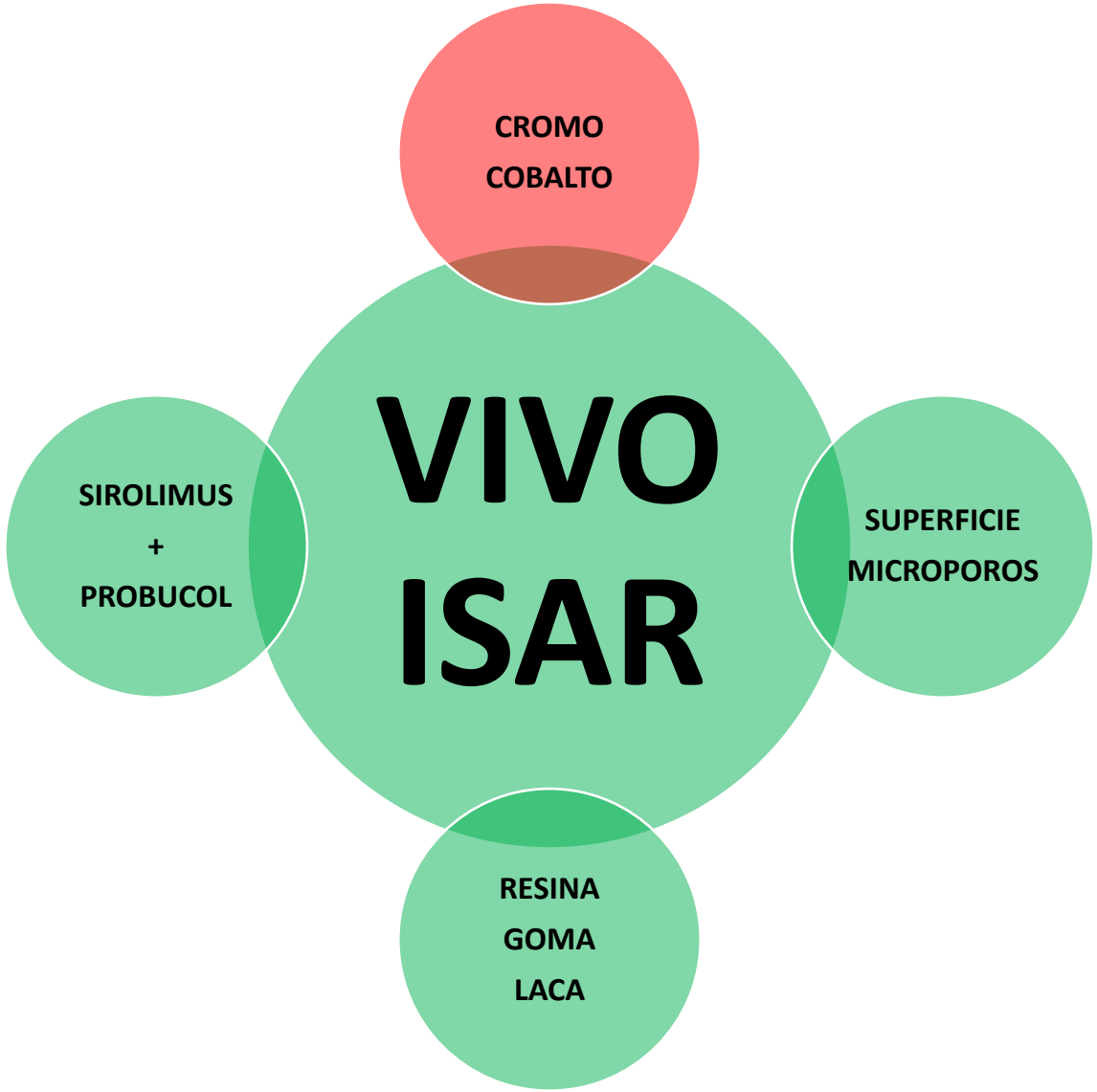
Resina de Goma Laca

- La resina de Goma Laca ayuda a la capa superior suave del stent

- Previene la ruptura de la matriz de doble fármaco durante la expansión del stent

- La resina de goma laca también previene la formación de escamas y la formación de telarañas en la mezcla de fármacos.

Delta
SANATORIO

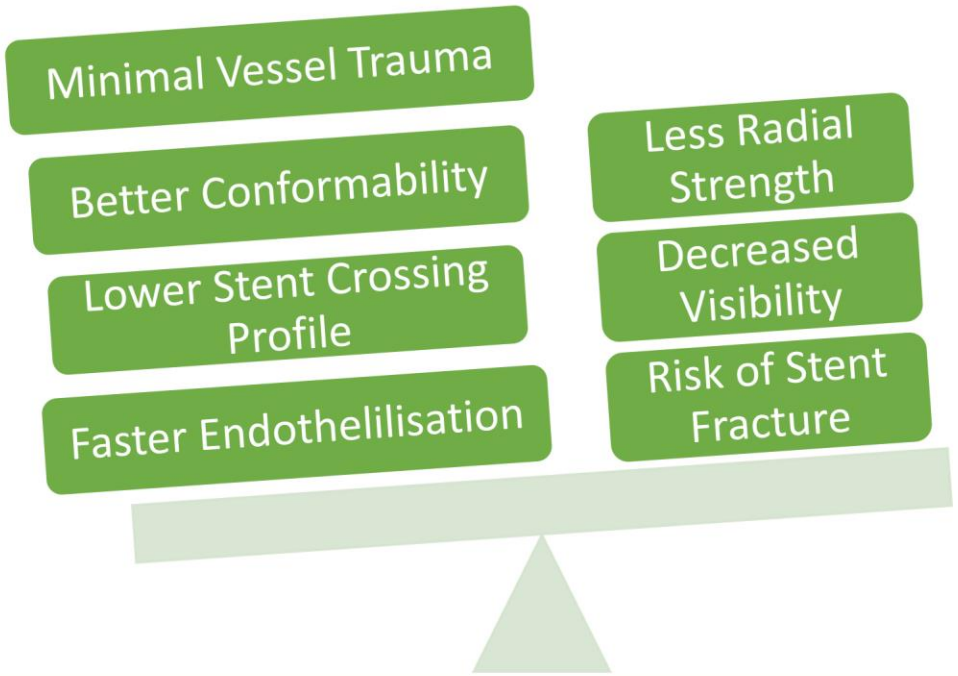


VIVO ISAR

Polymer-Free Sirolimus Eluting Stent

Advantages of Low Strut Thickness

Disadvantages of Low Strut Thickness



VIVO ISAR

Polymer-Free Sirolimus Eluting Stent

Maintain the balance

VIVO ISAR offers optimal strut thickness of 78µm maintaining its radial strength

Ultrathin	Thin	Intermediate	Thick
Less than 75 µm	75- 100 µm	100- 120 µm	More than 120 µm


ESTUDIOS CLINICOS

AÑOS
DATOS CLINICOS DE EFICACIA & SEGURIDAD

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LIMITLESS POSSIBILITIES

2004 Catheterization & Cardiovascular Interventions

A los 2 años, se encontró que la superficie microporosa era igualmente segura en comparación con la superficie electropulida.

2008 Biomaterials

En un estudio preclínico, VIVO ISAR demostró una cinética de liberación de fármaco ideal y una mejor endotelización en comparación con el stent CON polímero convencional

2010 JACC

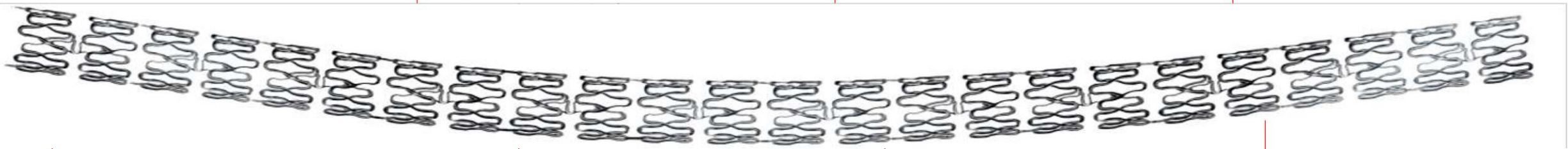
2016 JACC

2016 Cardiovascular Diabetology

2017 SCAI Society for Cardiovascular Angiography & Interventions

2020 JACC

2021 Clinical Research in Cardiology



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LIMITLESS POSSIBILITIES

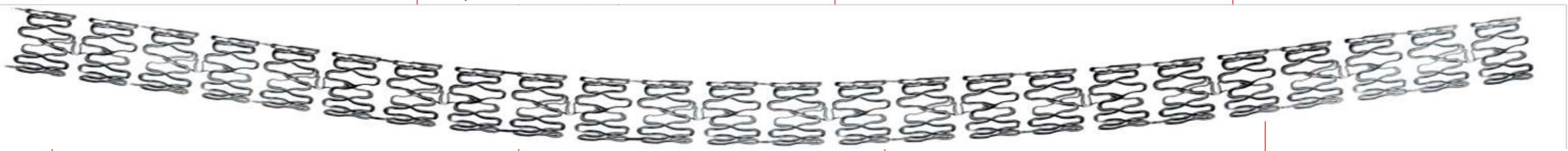
REESTENOSIS

2004 Catheterization & Cardiovascular Interventions

2008 Biomaterials

2010 JACC

A los 2 años, VIVO ISAR demostró una reducción del 43% en la reestenosis binaria en comparación con Endeavour



2016 JACC

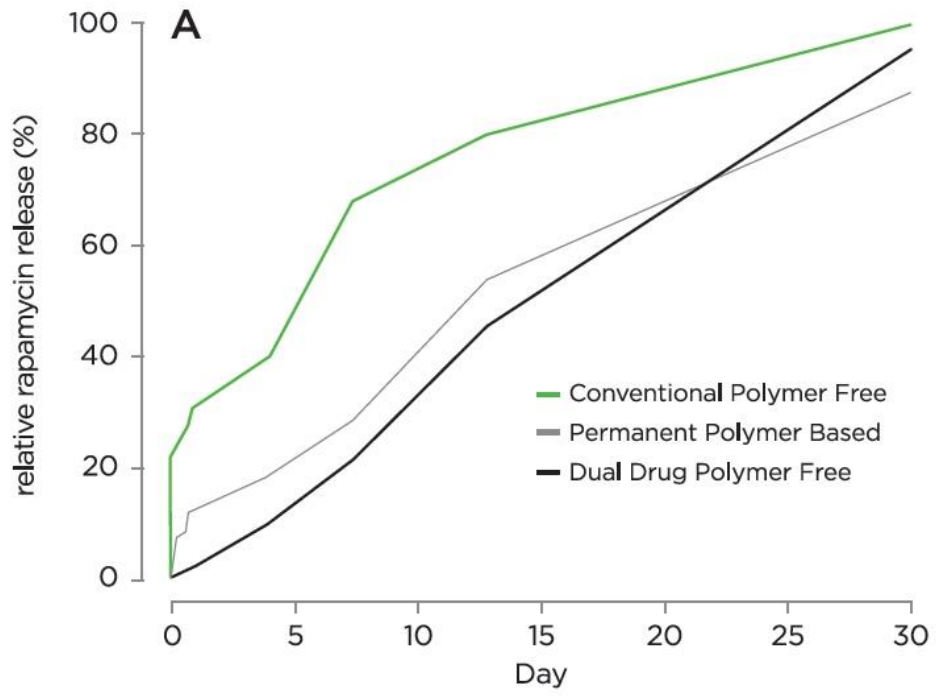
2016 Cardiovascular Diabetology

2017 SCAI Society for Cardiovascular Angiography & Interventions

2020 JACC

2021 Clinical Research in Cardiology

-> 2008 Biomaterials



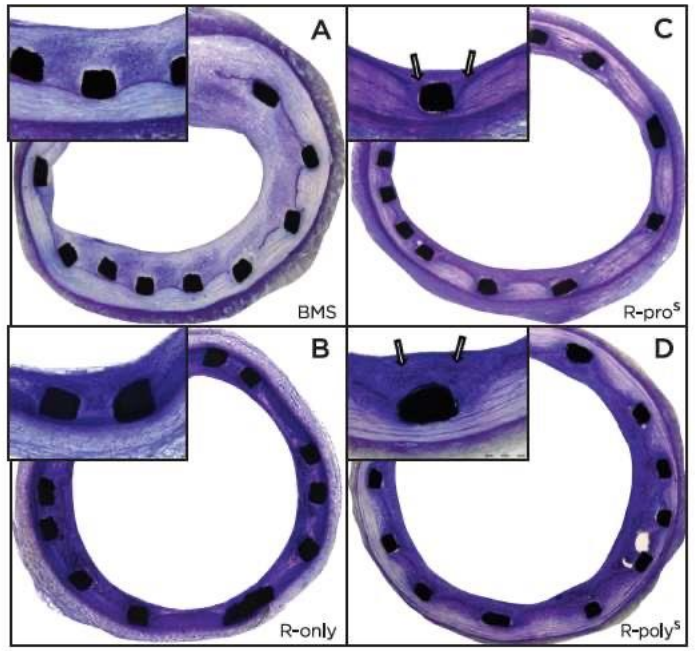
Objetivo:

Estudiar la evaluación preclínica de dos nuevas tecnologías de revestimiento de DES que se abstienen del uso de un polímero duradero.

- VIVO ISAR demostró una cinética de liberación de fármacos ideal para una mejor eficacia anti-reestenótica en comparación con el stent convencional libre de polímero basado en polímeros

- Liberación prolongada del fármaco, que es del 80% en 28 días

-> 2008 Biomaterials



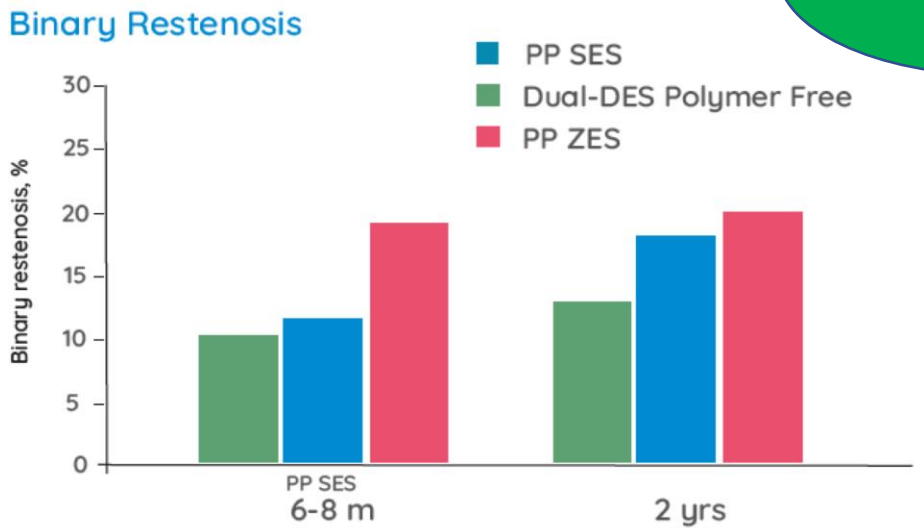
VIVO ISAR demostró:

- Inflamación baja
- Menos deposición de fibrina
- Mejor endotelialización

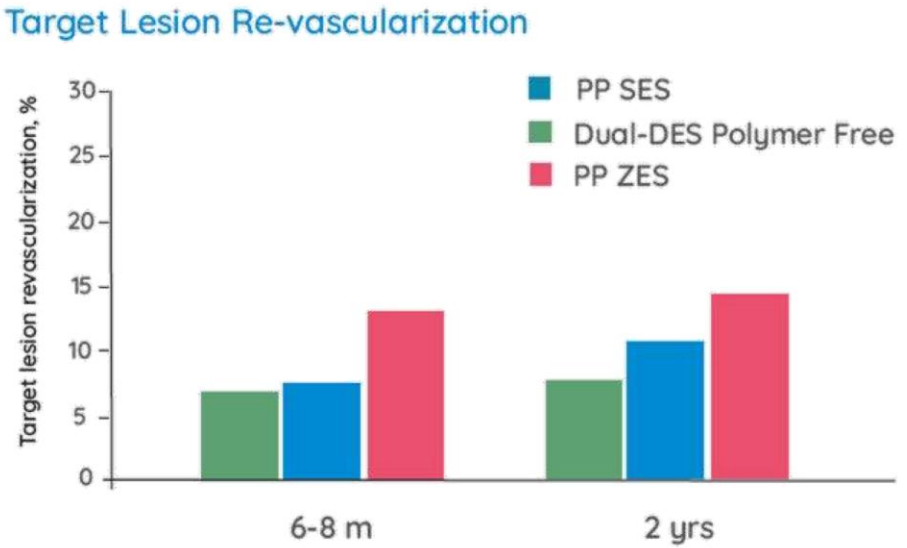
VIVO ISAR | 2 years Clinical Data-

Primary End Points: Binary angiographic restenosis

REESTENOSIS



Secondary Endpoints: Angiographic in-stent late loss/ target lesion revascularization (TLR), death/myocardial infarction and stent thrombosis



Results: At 2 years, VIVO ISAR demonstrated 43% reduction in binary restenosis in comparison to ZES (Endeavor Sprint) and 23% reduction in comparison to SES (Cypher).

Results: VIVO ISAR showed lower rates of TLR in comparison to permanent polymer DES.

AÑOS
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2004 Catheterization & Cardiovascular Interventions

2010 JACC

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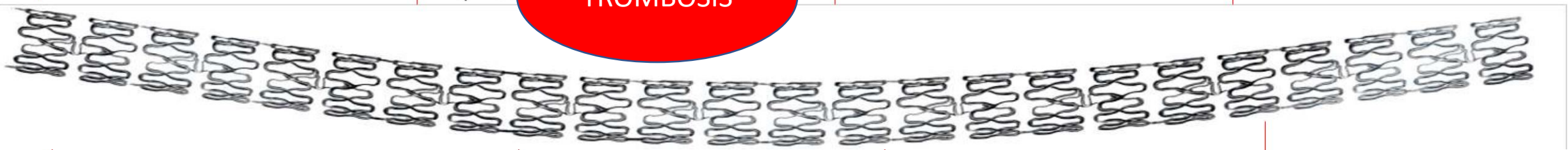
TROMBOSIS



2008 Biomaterials

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A los 5 años, VIVO ISAR sin polímero muestra tasas similares de trombosis del stent definitiva o probable que PP-ZES

VIVO ISAR | 5 years Clinical Data- JACC

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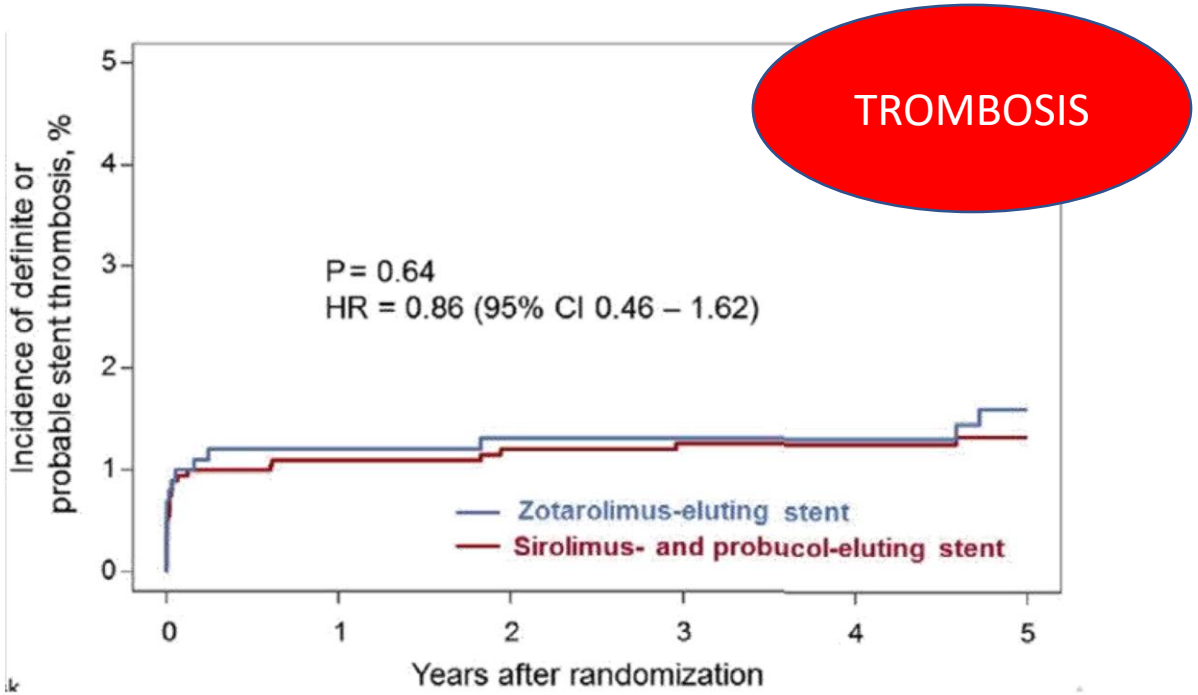
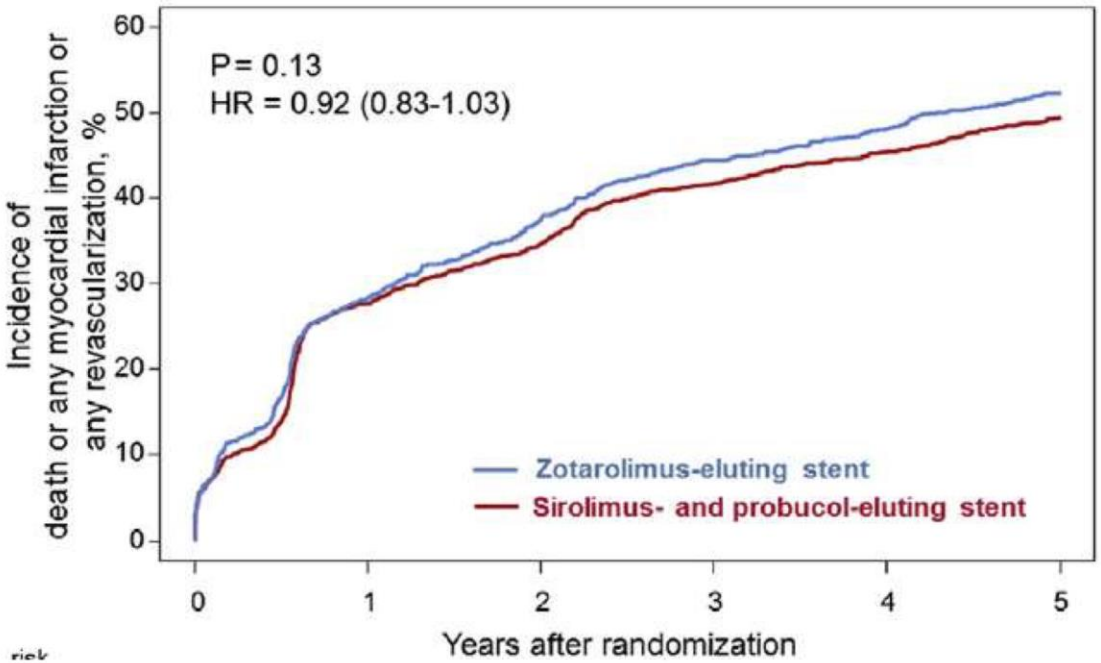
LIMITLESS POSSIBILITIES

Stent Thrombosis Rates with VIVO ISAR At 5 Years



Results: VIVO ISAR with No Polymer demonstrates similar rates definite or probable stent thrombosis as PP-ZES

Death/ MI/ Revascularization at 5 years



Results: VIVO ISAR with NO Polymer demonstrates non-inferiority PP–ZES

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LIMITLESS POSSIBILITIES

2004 Catheterization & Cardiovascular Interventions

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2016 Cardiovascular Diabetology

A los 5 años, los resultados de los pacientes tratados con VIVO ISAR en comparación con los ZES basados en polímeros duraderos fueron similares en el subgrupo de Diabetes.

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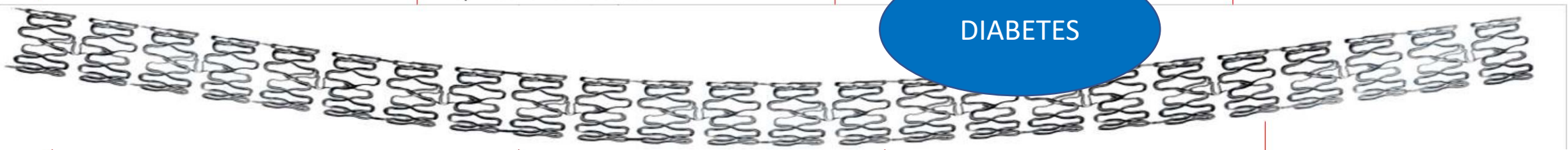

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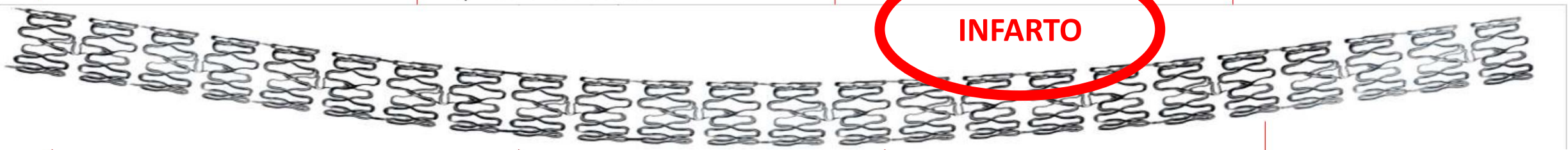
2020 JACC



2008 Biomaterials

2016 JACC

2017 SCAI Society for Cardiovascular Angiography & Interventions

2021 Clinical Research in Cardiology

A los 5 años, los resultados de los pacientes tratados con VIVO ISAR en comparación con los ZES basados en polímeros duraderos fueron similares en el subgrupo de STEMI.

AÑOS
DATOS CLINICOS DE EFICACIA & SEGURIDAD

SEGURIDAD Y EFICACIA

2004 Catheterization & Cardiovascular Interventions

2008 Biomaterials

2010 JACC

2016 JACC

2016 Cardiovascular Diabetology

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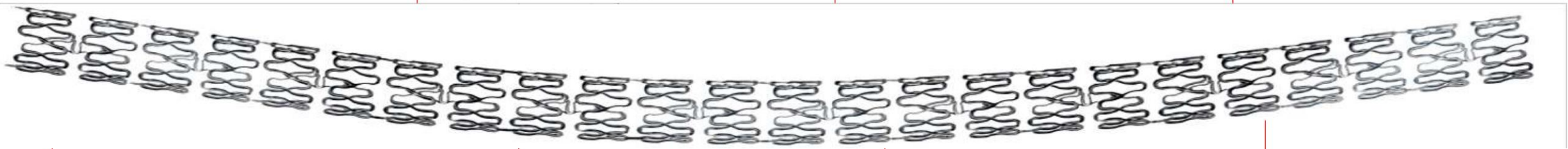
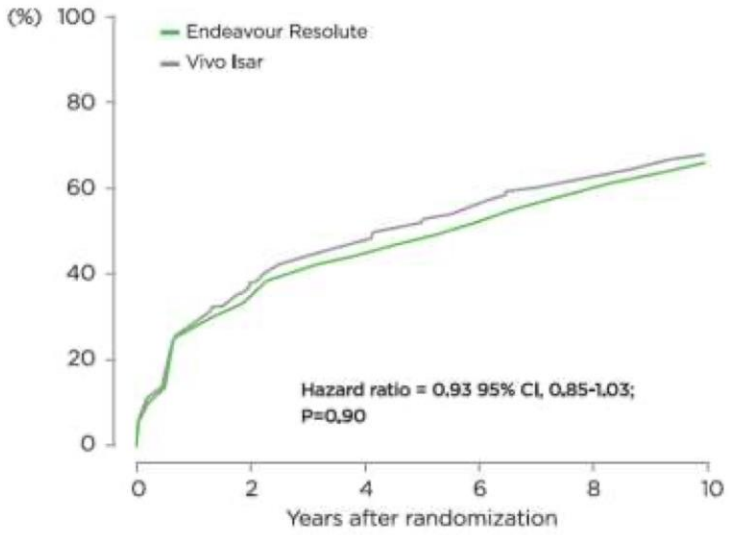
En este análisis a largo plazo a los 10 años, VIVO ISAR sin polímero mostró un perfil de eficacia y seguridad similar al de Resolute Integrity



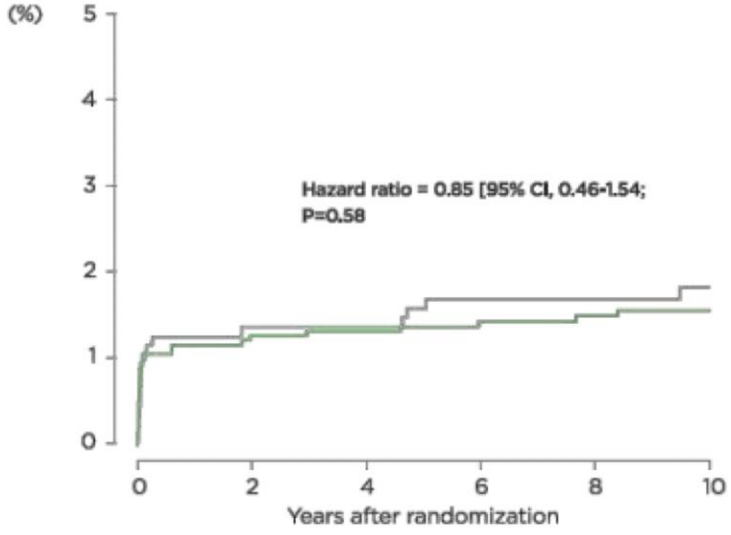
2021 Clinical Research in Cardiology

SEGURIDAD Y EFICACIA

In this unique long-term analysis at 10 years,
Polymer free VIVO ISAR showed similar efficacy and safety profile as Resolute Integrity



Cumulative Incidence of
Definite/Probable Stent Thrombosis



Cumulative Incidence of POCE
All cause death, any MI or any revascularization

Comparison of Clinical outcomes at 10 years in patients treated with VIVO ISAR versus Resolute Integrity

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DATOS CLINICOS DE EFICACIA & SEGURIDAD

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LIMITLESS POSSIBILITIES

2004 Catheterization & Cardiovascular Interventions

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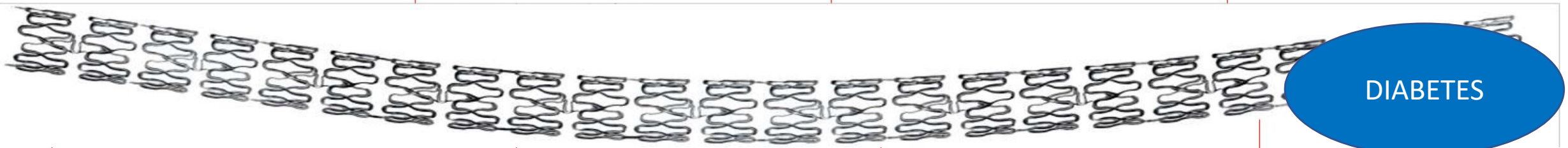

DIABETES

2008 Biomaterials

2016 JACC

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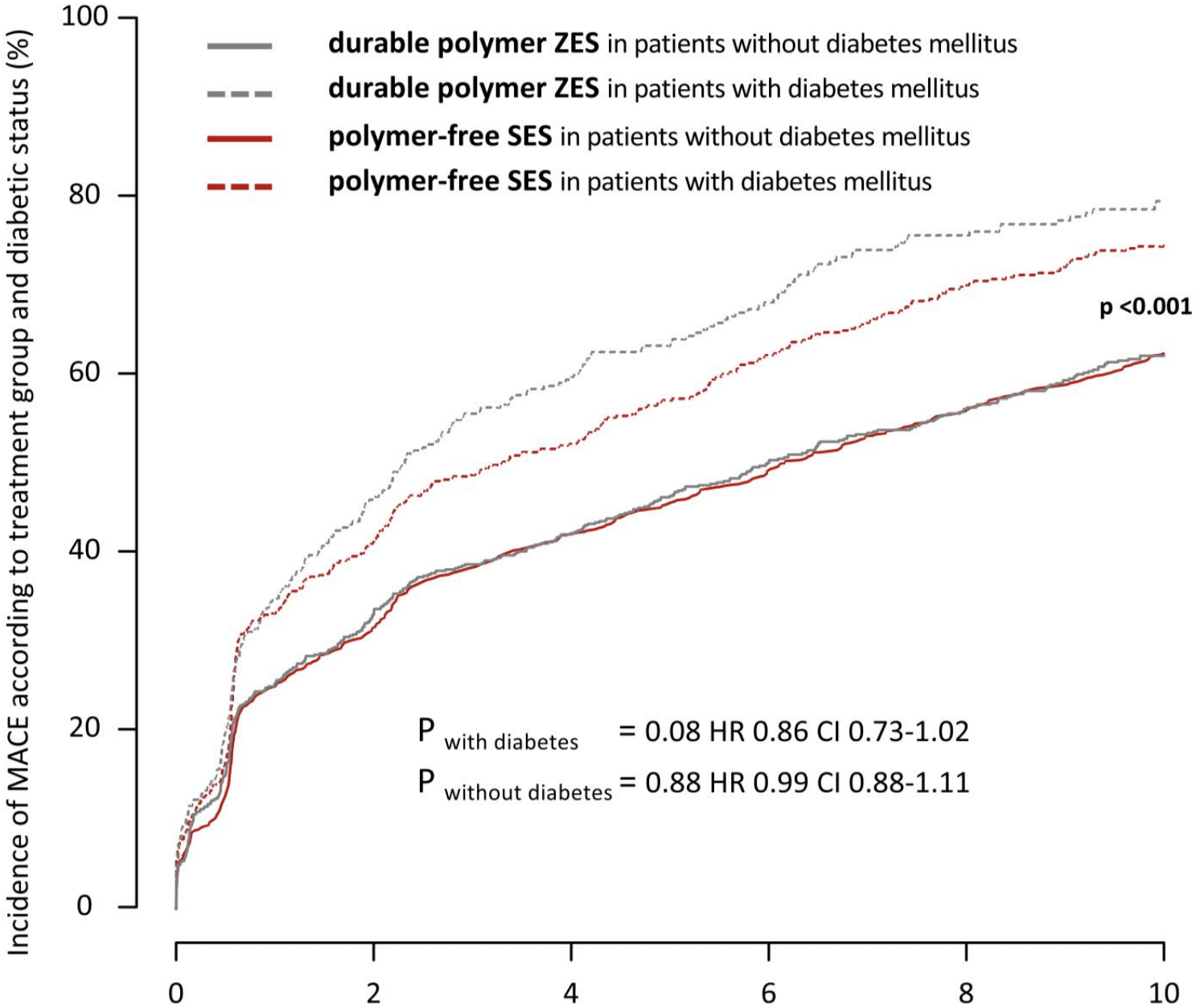
2021 Clinical Research in Cardiology

A los 10 años, los resultados de los pacientes tratados con VIVO ISAR en comparación con los ZES basados en polímeros duraderos fueron similares en el subgrupo de Diabetes.


durable polymer ZES in patients without diabetes mellitus
durable polymer ZES in patients with diabetes mellitus
polymer-free SES in patients without diabetes mellitus
polymer-free SES in patients with diabetes mellitus
p <0.001
P with diabetes = 0.08 HR 0.86 CI 0.73-1.02
P without diabetes = 0.88 HR 0.99 CI 0.88-1.11
Incidence of MACE according to treatment group and diabetic status (%)
100
80
60
40
20
0
0
2
4
6
8
10
Years after randomization
No. of patients at risk

DIABETES

Future beyond Polymers

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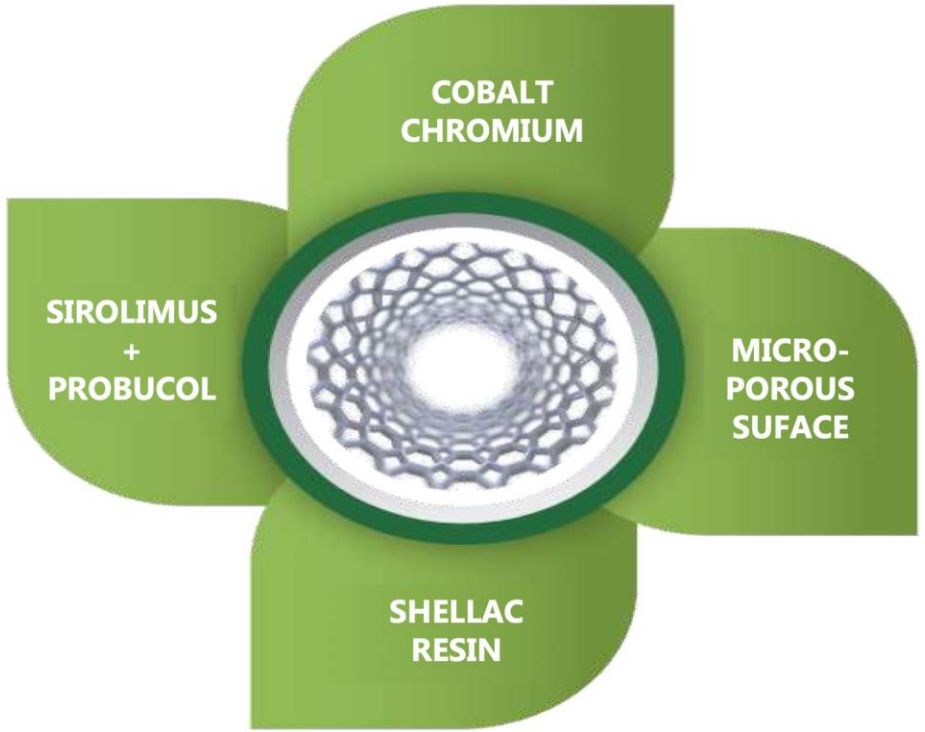
LIMITLESS POSSIBILITIES

vivoISAR
Polymer-Free Sirolimus Eluting Stent

World's 1st Dual Drug Polymer-free Drug Eluting Stent



Using Probucol as an alternative to polymer for stent coating matrix ensuring optimal release kinetics of Sirolimus

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LIMITLESS POSSIBILITIES

Endomedical S.R.L.
INSUMOS MÉDICOS

GRACIAS

Delta
SANATORIO

VIVO ISAR | Clinical Trials

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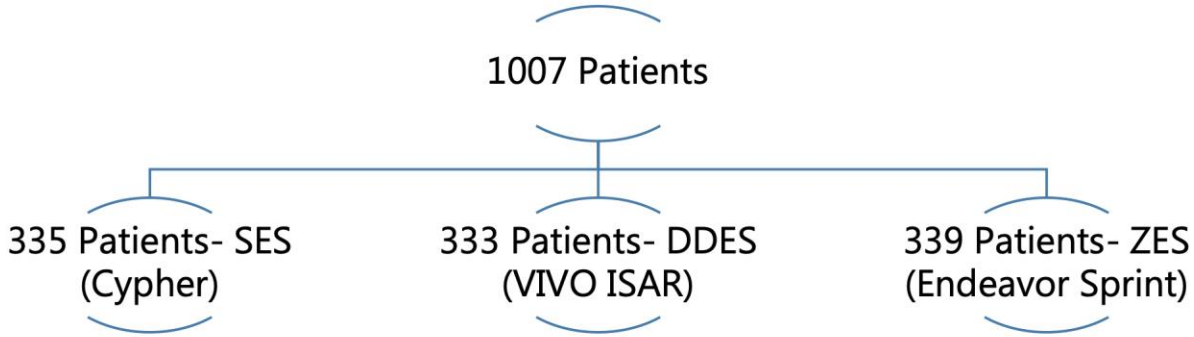
LIMITLESS POSSIBILITIES

Objective	Number of Patients	Duration (in years)	Conclusion
To study the pre-clinical assessment of two novel DES coating technologies that abstain from use of a durable polymer	In- Vitro	NA	VIVO ISAR demonstrated ideal Drug Release Kinetics and low inflammation, less fibrin deposition and better endothelialization as compared to polymer based and conventional polymer free stent
2-Year Clinical and Angiographic Outcomes From a Randomized Trial of Polymer-Free Dual Drug-Eluting Stents Versus Polymer-Based Cypher and Endeavor, Drug-Eluting Stents.	1007	2	VIVO ISAR demonstrated 43% reduction in binary restenosis in comparison to ZES (Endeavor Sprint) and 23% reduction in comparison to SES (Cypher). It also showed lower rates of TLR in comparison to permanent polymer DES.
The aim of this study was to evaluate the late clinical performance of a polymer free DDES compared with a new-generation durable polymer-based Zotralimus-eluting stent in 3002 patients at 5 years.	3002	5	VIVO ISAR with No Polymer demonstrates similar rates of definite or probable stent thrombosis as PP-ZES
To Assess the long-term efficacy and safety of novel polymer-free Sirolimus and Probucol-eluting stent in diabetic patients at 5 yr follow up in patients with STEMI.	311	5	Long-term outcomes of patients treated with VIVO ISAR compared with durable polymer based Zotarolimus-eluting stent were similar in subgroup of STEMI.
To assess the long-term efficacy and safety of novel polymer-free Sirolimus and Probucol-eluting stent in diabetic patients at 5 years follow up in patients with Diabetes	875	5	Long-term outcomes of patients treated with VIVO ISAR compared with durable polymer based Zotarolimus-eluting stent were similar in sub group of Diabetes.
Ten-year Clinical Outcomes From A Randomized Trial of Polymer-free Sirolimus- And Probucol-eluting Stents versus Permanent Polymer Zotarolimus-Eluting Stents in patients with Coronary Artery Disease	3002	10	In this long-term analysis at 10 years, Polymer free VIVO ISAR showed similar efficacy and safety profile as Resolute Integrity
To assess the long-term efficacy and safety of novel polymer-free Sirolimus and Probucol-eluting stent in diabetic patients at 10 years follow up in patients with Diabetes	3002	10	Long-term outcomes of patients treated with VIVO ISAR compared with durable polymer based Zotarolimus-eluting stent were similar in sub group of Diabetes.

VIVO ISAR | 2 years Clinical Data-

Objective: 2-Year Clinical and Angiographic Outcomes From a Randomized Trial of Polymer-Free Dual Drug-Eluting Stents Versus Polymer-Based Cypher and Endeavor, Drug-Eluting Stents.

Methodology: 1007 Patients were enrolled and randomized. The patients were followed up at 2 years.



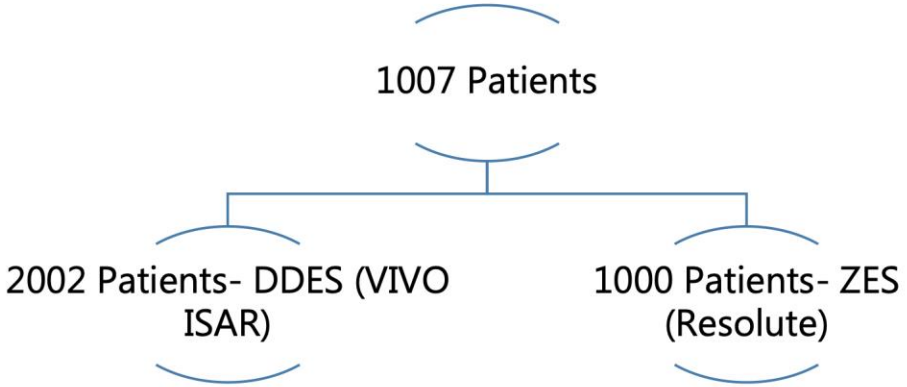
Primary End Points: Binary angiographic restenosis

Secondary Endpoints: Angiographic in-stent late loss /target lesion revascularization (TLR), death/myocardial infarction and stent thrombosis

5 years Clinical Data-

Objective: The aim of this study was to evaluate the late clinical performance of a polymer free DDES compared with a new-generation durable polymer-based Zotarolimus-eluting stent in 3002 patients at 5 years.

Methodology: 3002 patients were enrolled and randomized. The patients were followed up at 5 years.



Studies in Patients With Co-Morbidities

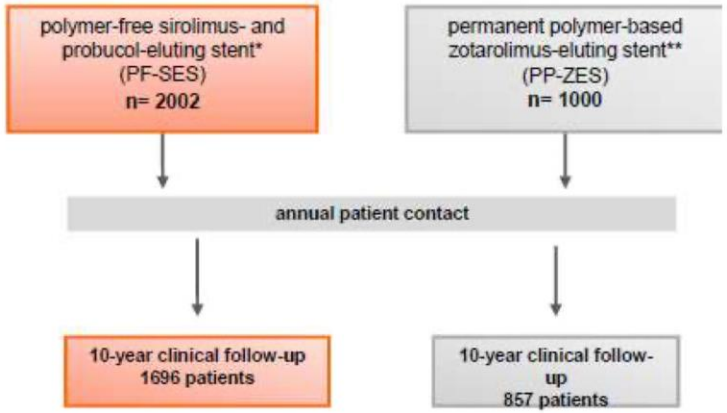
VIVO ISAR is also studied in patients with co-morbidities like:

- STEMI- 311 patients
- Diabetes- 875 patients

The patients were followed for 5 years.

Objective: Ten-year Clinical Outcomes From A Randomized Trial of Polymer-free Sirolimus- And Probucol-eluting Stents versus Permanent Polymer Zotarolimus-Eluting Stents in patients with Coronary Artery Disease

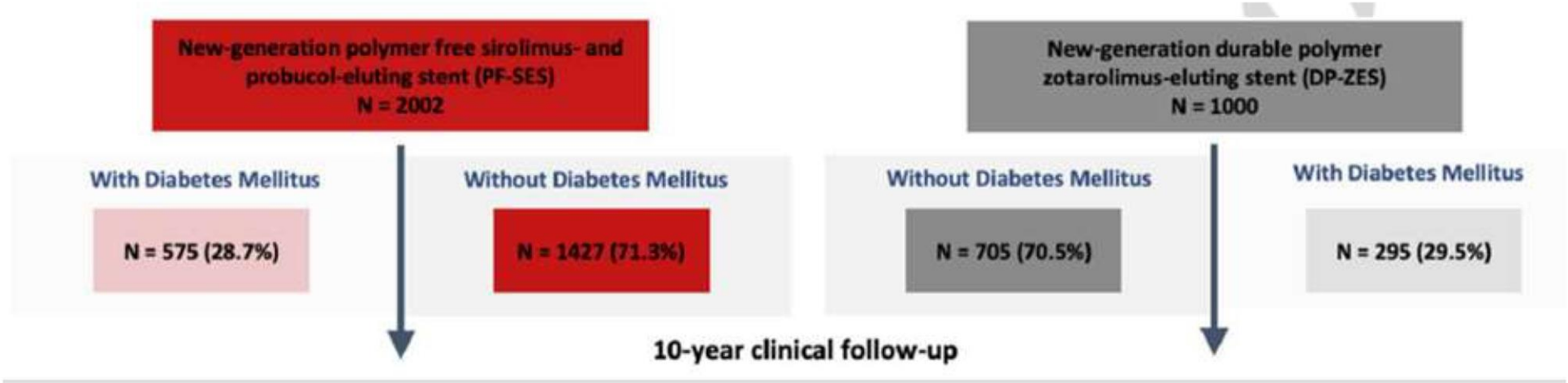
Methodology: 3002 Patients were enrolled and randomized. The patients were followed up at 10 years.



Primary End Points: DOCE (Device oriented composite endpoint) of cardiac death, target vessel-related myocardial infarction or target lesion revascularization

Secondary Endpoints: POCE (Patient-oriented composite endpoint) of all-cause death, any myocardial infarction or any revascularization and definite/probable stent thrombosis

Very long-term outcomes in diabetic patients with coronary artery disease (CAD) undergoing percutaneous coronary intervention (PCI) with the durable polymer Zotarolimus-eluting stent (DP-ZES) and the polymer-free Sirolimus- and Probucol-eluting stent (PF-SES),

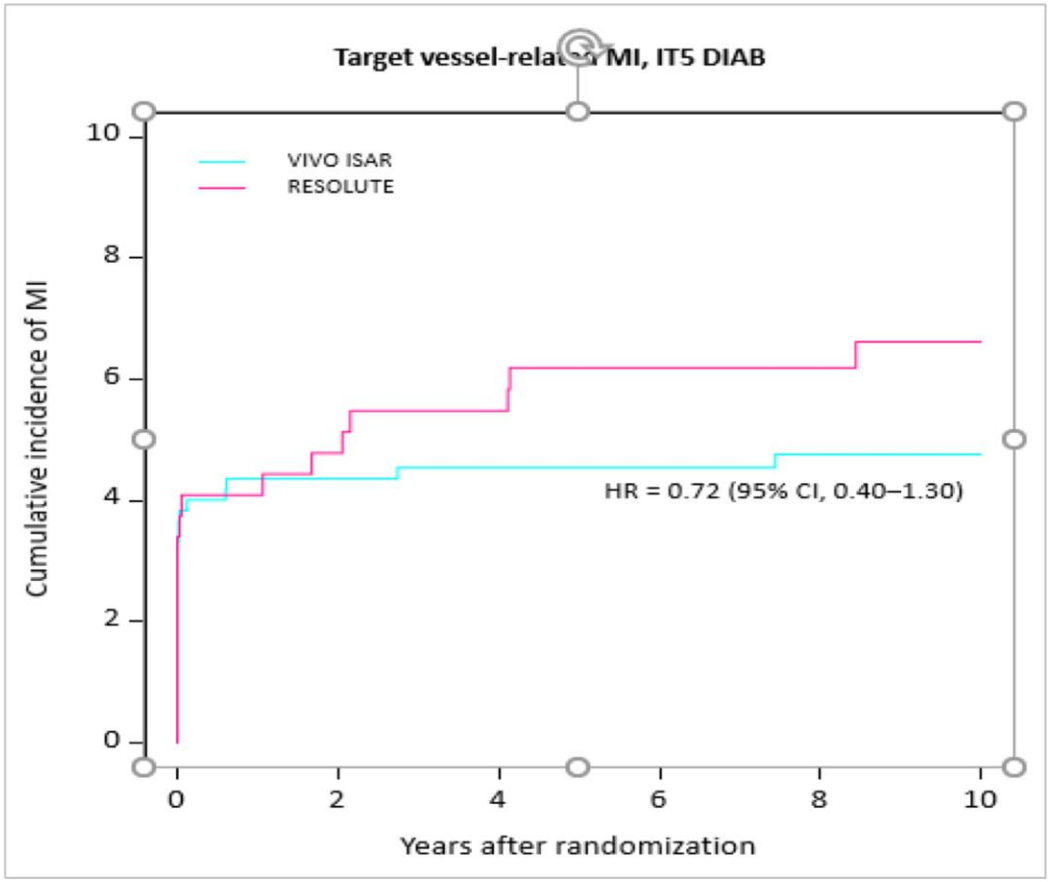


Primary endpoints:

- Major Adverse Cardiac Events (MACE)
- Myocardial Infarction (MI)
- Revascularization

Secondary endpoints:

- Cardiac Death
- Target Lesion Revascularization (TLR)
- Target Vessel Revascularization (TVR)
- Definite /Probable Stent Thrombosis



Notably low rates of Target vessel Related Myocardial Infarction **– 33%**

translumina
LIMITLESS POSSIBILITIES

Competitor Analysis

Communication Point for Xience Expedition(Abbott)	Counter Point for VIVO ISAR
Legacy	Translumina's new image with Technology Advanced Products
USFDA	USFDA is only required to market the product in US- **Business Call not to enter the market yet** **USFDA doesn't mean safety-** USFDA approved stents Cypher (J&J), Taxus (Boston Scientific), Absorb (Abbott) were called back because of increased risk of patient's safety
Vast clinical data	VIVO ISAR has robust clinical data at 2,5 and 10 years published in indexed journals including Diabetes and STEMI patient subset.
STOP DAPT : DAPT for 3 months followed up till 1 year	In Pre-Clinical trials, it has been observed that Sirolimus and Probucol are released in 4-6 weeks leaving BMS. DAPT can be given for 1 month followed by single anti-platelet therapy SECURE Registry aims that VIVO ISAR offers required safety for shortening the duration of dual antiplatelet therapy to 1 month in CAD patients and high anti-restenotic efficacy of 2nd generation DES.
1.01 mm Crossing Profile	Lower crossing profile of 0.89mm ensures easier cross, better push and deliverability of the stent Higher crossing profile increases the chances of vessel trauma.
Permanent Polymer (fluoro-polymer)	Polymer Degradation usually takes 4-6 months, with Probucol it only takes 4-6 weeks Presence of a polymer permanently in the body is unnecessary when it's proven through studies that durable polymer DES & polymer free DES have comparable clinical outcomes. Polymer function in optimum drug release kinetics is rendered useless once the entire drug is eluted besides inducing the chances of late adverse events in the vessel

Communication Point for Xience Skypoint(Abbott)	Counter Point for VIVO ISAR
Legacy	Translumina's new image with Technology Advanced Products
USFDA, CE	USFDA is only required to market the product in US- **Business Call not to enter the market yet** **USFDA doesn't mean safety-** USFDA approved stents Cypher (J&J), Taxus (Boston Scientific), Absorb (Abbott) were called back because of increased risk of patient's safety VIVO ISAR has CE mark
Vast clinical data	VIVO ISAR has robust clinical data at 2,5 and 10 years published in indexed journals including Diabetes and STEMI patient subset.
Now approved for use in HBR patients with one-month DAPT labeling – as short as 28 days	In Pre-Clinical trials, it has been observed that Sirolimus and Probucol are released in 4-6 weeks leaving BMS. DAPT can be given for 1 month followed by single anti-platelet therapy SECURE Registry aims that VIVO ISAR offers required safety for shortening the duration of dual antiplatelet therapy to 1 month in CAD patients and high anti-restenotic efficacy of 2nd generation DES.
1.01 mm Crossing Profile	Lower crossing profile of 0.89mm ensures easier cross, better push and deliverability of the stent Higher crossing profile increases the chances of vessel trauma.
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Improved maximum stent expansion and better longitudinal strength	Only minor iterations are made across various generations of Xience but no significant evolutionary change has happened

Communication Point for BioFreedom (Biosensors)	Counter Point for VIVO ISAR
Large Strut Thickness of 120 µm	Large strut thickness of BioFreedom (120µm) causes higher chance of vessel trauma, lower trackability and stent thrombosis. VIVO ISAR offers optimal strut thickness of 78µm maintaining its radial strength & minimizing the chances of vessel trauma
Polymer-free	BioFreedom has no replacement for polymer to ensure optimal release kinetics of Biolimus, while VIVO ISAR contains well studied drug Probucol as a replacement for polymer. Polymer Degradation usually takes 4-6 months, with Probucol it only takes 4-6 weeks
Clinical Studies: 3 years of safety & efficacy data- LEADERS FREE I LEADERS FREE II LEADERS FREE III	VIVO ISAR has robust clinical data at 2,5 and 10 years published in indexed journals including Diabetes and STEMI patient subset.
Selectively Micro-Structured Surface (SMS) Only the abluminal surface of the stent receives SMS treatment, allowing BA9™ to be contained within the micro-structured surface and delivered with high specificity to the vessel wall of the coronary lesions.	VIVO ISAR has a microporous surface (patented technology) that combines the synergistic effect of surface modification and biodegradable polymer to create optimum release. Stent surface is coated abluminally with no drug or polymer on the luminal side of the stent for enhanced safety & faster endothelialization. VIVO ISAR has hybrid design for maximum side branch access.

Communication Point for Coroflex ISAR Neo(B Braun)	Counter Point for VIVO ISAR
Ultra Low Strut Thickness of 55/65 µm	Ultra Low strut thickness compromises on the Radial strength and visibility of stents. VIVO ISAR offers optimal strut thickness of 78µm maintaining its radial strength even in tortuous vessels
Clinical Studies: ISAR Test (6-8 months follow up)	VIVO ISAR has robust clinical data at 2,5 and 10 years published in indexed journals including Diabetes and STEMI patient subset.
Stent lengths availability	Unlike Coroflex ISAR NEO, VIVO ISAR offers stent lengths of 40,44,48µm also as longer lengths are desired for longer vessels

Communication Point for Resolute Onyx(Medtronic)	Counter Point for VIVO ISAR
Zotarolimus, 85% released in 60 days; 100% released by 180 days	Hyperproliferation 2- 4 Weeks after stent deployment until rendothelilisation occurs, VIVO ISAR besides not having polymer, demonstrated optimal Drug Release Kinetics with prolonged release of Sirolimus which is 80% in 28 days
Clinical Studies: Resolute Clinical Program (5 years follow-up) 1 month DAPT in HBR patients	VIVO ISAR has robust clinical data at 2,5 and 10 years published in indexed journals including Diabetes and STEMI patient subset.
Permanent Polymer	Drug and Polymer in VIVO ISAR are co-released in 30-45 days while Biodegradable polymer degrades in 90 days. Presence of a polymer permanently in the body is unnecessary when it's proven through studies that durable polymer DES & polymer free DES have comparable clinical outcomes at 5 years. **Published in EuroIntervention (2014)** Polymer function in optimum drug release kinetics is rendered useless once the entire drug is eluted besides inducing the chances of late adverse events in the vessel
DAPT 28 : 1 month DAPT in HBR patients	In Pre-Clinical trials, it has been observed that Sirolimus and Probucol are released in 4-6 weeks leaving BMS. DAPT can be given for 1 month followed by single anti-platelet therapy SECURE Registry aims that VIVO ISAR offers required safety for shortening the duration of dual antiplatelet therapy to 1 month in CAD patients and high anti-restenotic efficacy of 2nd generation DES.
0.91 mm Crossing Profile	Lower crossing profile of 0.89mm ensures easier cross, better push and deliverability of the stent Higher crossing profile increases the chances of vessel trauma.

Communication Point for Cre8 (AlviMedica)	Counter Point for VIVO ISAR
Abluminous Reservoir Technology precisely controls abluminal drug elution	Microporous surface: The micro-pores on its surface act like reservoirs for delivering the drug to the targeted site using van-der-walas forces to control the release-kinetics of the drug Micro-pores also reduce the carrier load by 1/4th as compared to other DES Abluminal Coating leads to Directional drug release only to target tissue and less systemic exposure of drug which leads to faster healing. Abluminal coating ensures- -Better Endothelialisation -Reduces the incidence of stent thrombosis
Amphilimus formulation: Sirolimus + Fatty Acid	Cre8 has no replacement for polymer to ensure optimal release kinetics of Sirolimus, while VIVO ISAR contains well studied drug Probucol as a replacement for polymer. Polymer Degradation usually takes 4-6 months, with Probucol it only takes 4-6 weeks
Clinical Studies: 5 year follow up in patients (registry)	VIVO ISAR has robust clinical data at 2,5 and 10 years published in indexed journals including Diabetes and STEMI patient subset. In Pre-Clinical trials, it has been observed that Sirolimus and Probucol are released in 4-6 weeks leaving BMS. DAPT can be given for 1 month followed by single anti-platelet therapy SECURE Registry aims that VIVO ISAR offers required safety for shortening the duration of dual antiplatelet therapy to 1 month in CAD patients and high anti-restenotic efficacy of 2nd generation DES.

Communication Point for Synergy (Boston Scientific)	Counter Point for VIVO ISAR
Pt- Cr platform for improved visibility & deliverability	Pt-Cr platform in Synergy leads to foreshortening of stents that may affect stent performance and the rate of restenosis
1.01 mm Crossing Profile	Lower crossing profile of 0.89mm that ensures easier cross, better push and deliverability
Biodegradable polymer	Polymer Degradation usually takes 4-6 months, with Probucol it only takes 4-6 weeks
Clinical Studies: Short DAPT (1 month/3 months follow up) EVOLVE (6 months follow up) EVOLVE II (12 months follow up) SYNTAX II (3 years follow up)	VIVO ISAR has robust clinical data at 2,5 and 10 years published in indexed journals including Diabetes and STEMI patient subset. In Pre-Clinical trials, it has been observed that Sirolimus and Probucol are released in 4-6 weeks leaving BMS. DAPT can be given for 1 month followed by single anti-platelet therapy SECURE Registry aims that VIVO ISAR offers required safety for shortening the duration of dual antiplatelet therapy to 1 month in CAD patients and high anti-restenotic efficacy of 2nd generation DES.

Communication Point for Supraflex Cruz(SMT)	Counter Point for VIVO ISAR
Ultra Low Strut Thickness of 60 µm	Ultra Low strut thickness compromises on the Radial strength and visibility of stents. VIVO ISAR offers optimal strut thickness of 78µm maintaining its radial strength
Biodegradable polymer	Polymer Degradation usually takes 4-6 months, with Probucol it only takes 4-6 weeks
Clinical Studies: SiBi (4-6 weeks follow up) TAXCO (6 months follow up)	VIVO ISAR has robust clinical data at 2,5 and 10 years published in indexed journals including Diabetes and STEMI patient subset.

Communication Point for Ultimaster(Terumo)	Counter Point for VIVO ISAR
No drug coating on the stent platform at which high stress is concentrated when stent is over-expanded. Ultimaster keeps polymer integrity even when the stent is expanded to the maximum diameter.	There is Restenosis risk around the area in proximity with stent with no drug coating; also this infers that polymer coating can break with physical stress at other parts as well.
Durable flexible tip minimizes the clearance gap between the tip and guide wire	Lower crossing profile of 0.89mm ensures easier cross, better push and deliverability of the stent
Pioneer of biodegradable DES	Pioneer of polymer free DES
Biodegradable polymer	Polymer Degradation usually takes 4-6 months, with Probucol it only takes 4-6 weeks
Clinical Studies: 5 year follow up in bifurcation sub study	VIVO ISAR has robust clinical data at 2,5 and 10 years published in indexed journals including Diabetes and STEMI patient subset.

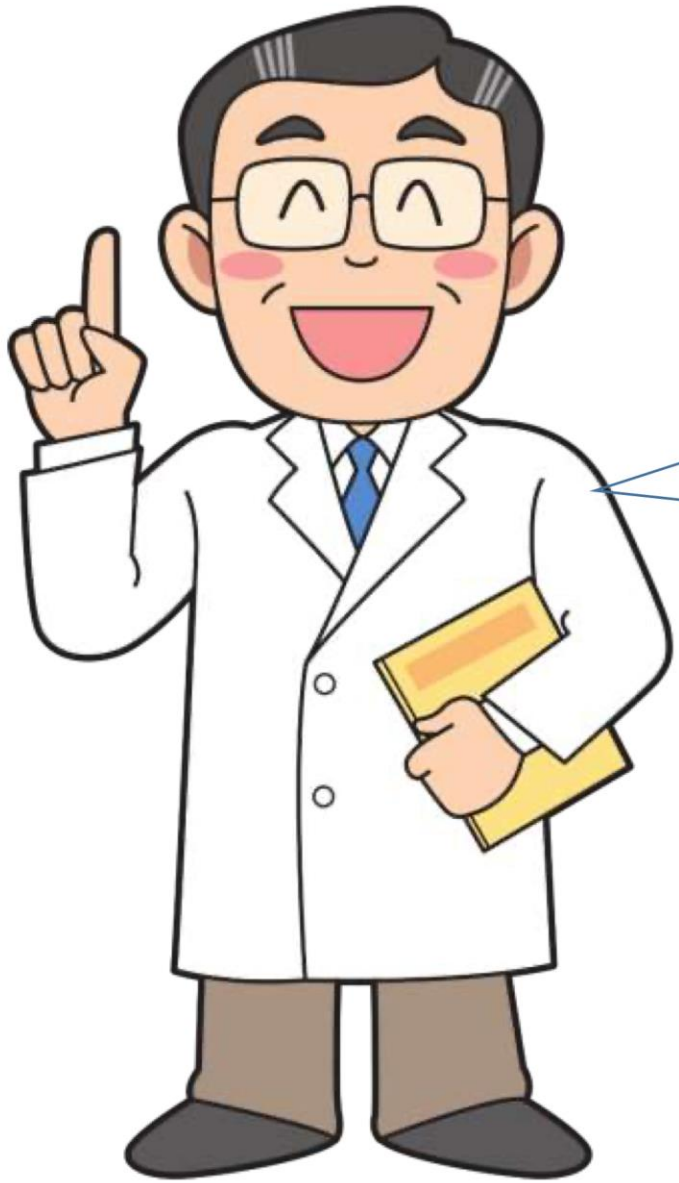
Communication Point for Orsiro(Biotronik)	Counter Point for VIVO ISAR
Clinical Studies: BIOFLOW I,II (12 months follow up) BIOSCIENCE (12 months follow up) BIORESORT (12 months follow up) SORT OUT VII (12 months follow up)	VIVO ISAR has robust clinical data at 2,5 and 10 years published in indexed journals including Diabetes and STEMI patient subset.
Biodegradable polymer	Polymer Degradation usually takes 4-6 months, with Probucol it only takes 4-6 weeks
Ultra Low Strut Thickness of 60 µm	Ultra Low strut thickness compromises on the Radial strength and visibility of stents. VIVO ISAR offers optimal strut thickness of 78µm maintaining its radial strength

Communication Point for Abluminus (Concept Medical)	Counter Point for VIVO ISAR
Clinical Studies: en-ABL1 Study (1 month follow up) Ability Diabetes Global (1 year follow up)-On going Ability RCT (1 year follow up)-On going	VIVO ISAR has robust clinical data at 2,5 and 10 years published in indexed journals including Diabetes and STEMI patient subset.
Biodegradable polymer	Polymer Degradation usually takes 4-6 months, with Probucol it only takes 4-6 weeks
On-label indication for Diabetes Mellitus	VIVO ISAR offers 4 years data-**Published in International Journal of Cardiology (2013)** and 10 years of Safety & Efficacy Clinical data in Diabetes patient subset-**Published in Journal of the American Heart Association (2021)**
0.97mm Crossing Profile	Lower crossing profile of 0.89mm that ensures easier cross, better push and deliverability

FREQUENTLY ASKED QUESTIONS

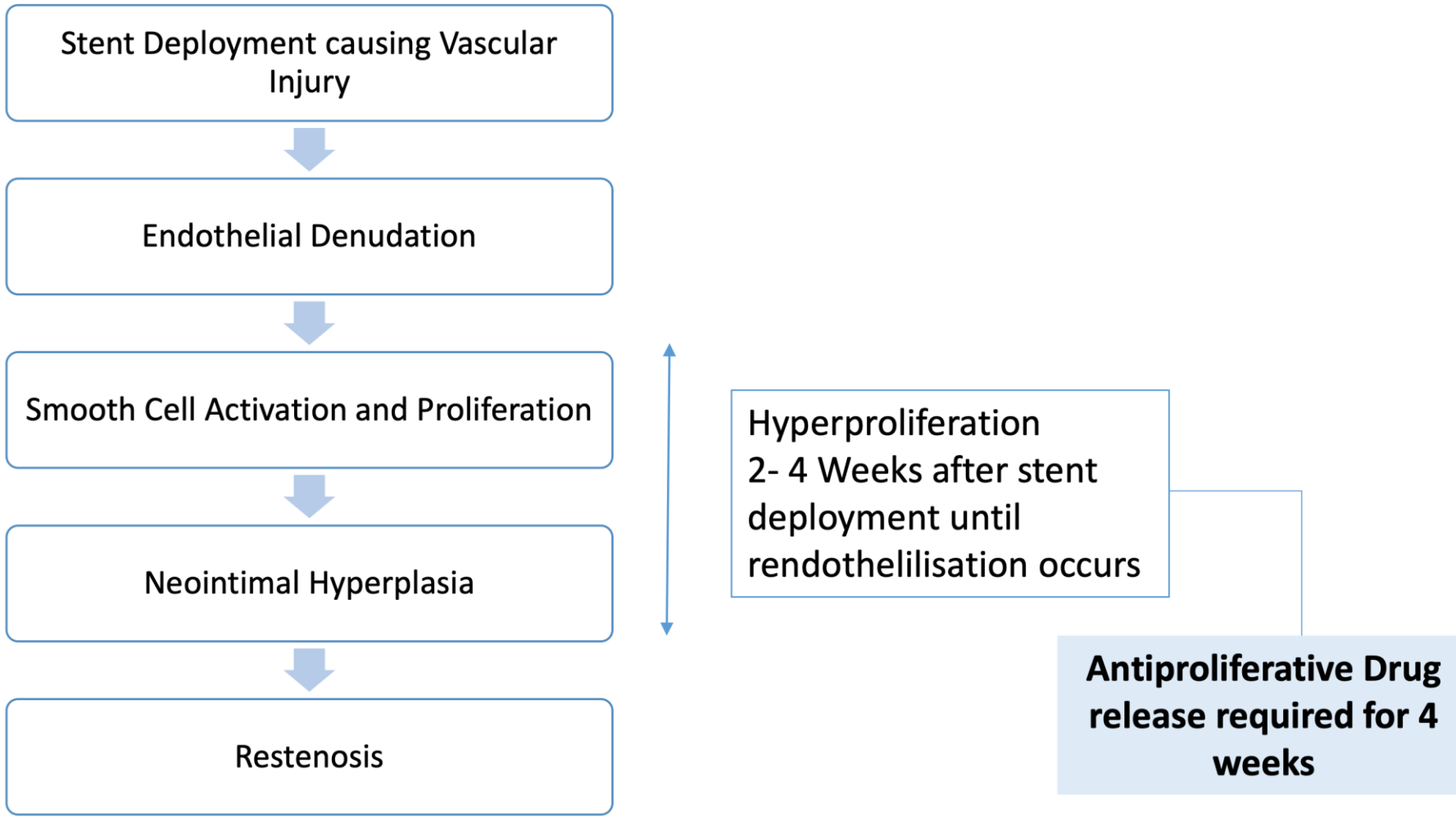
What is marketing positioning of VIVO ISAR within the Translumina pipeline

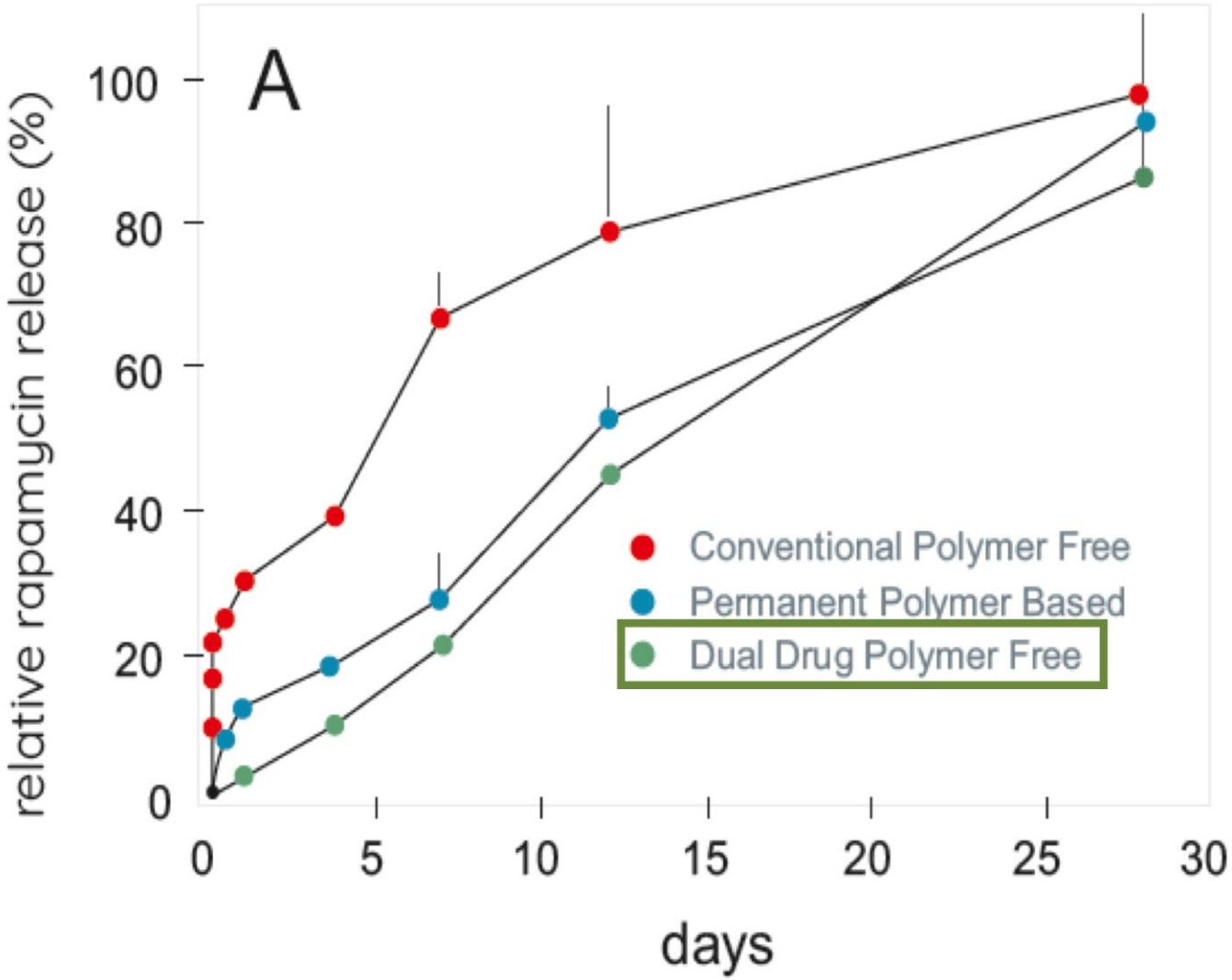
- Premium stent
- Next Generation DES: Future Beyond Polymer with enhanced Safety & Efficacy at 10Yrs



How do you ensure optimal drug release kinetics in VIVO ISAR

Why Sirolimus Optimal Release is required





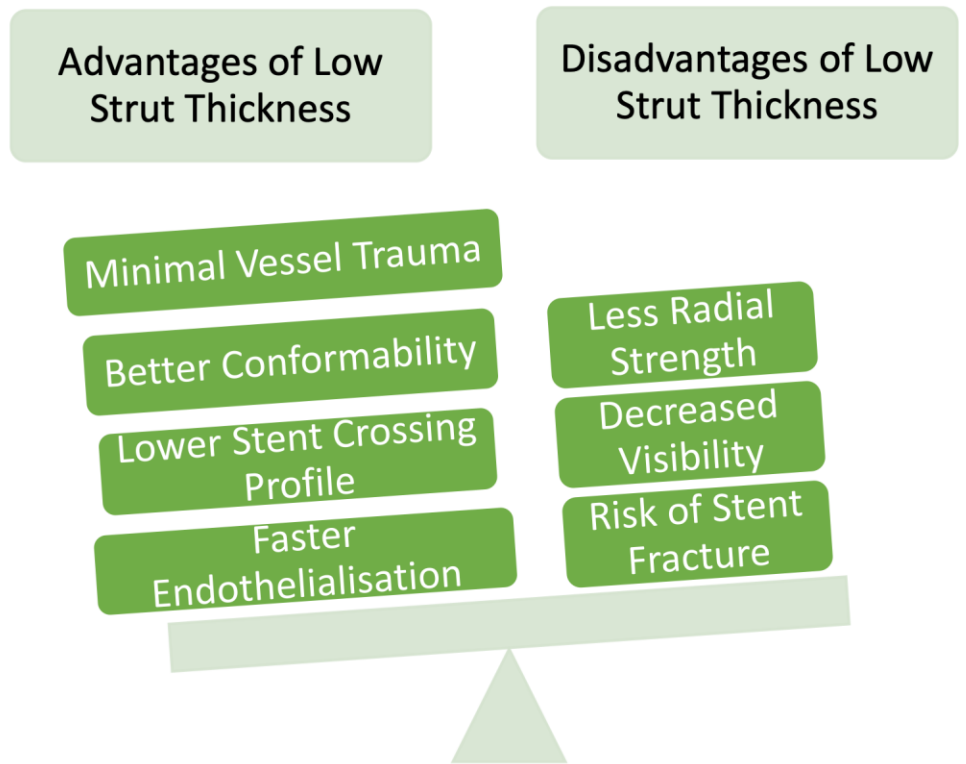
- Faster Drug Release compromises the DES ability to prevent smooth cell proliferation for complete 4 weeks, hence increased chances of restenosis

VIVO ISAR besides not having polymer, demonstrated optimal Drug Release Kinetics with prolonged release of Sirolimus which is 80% in 28 days

Why strut thickness is important?

Strut Thickness

Ultrathin	Thin	Intermediate	Thick
Less than 75 µm	75- 100 µm	100- 120 µm	More than 120 µm



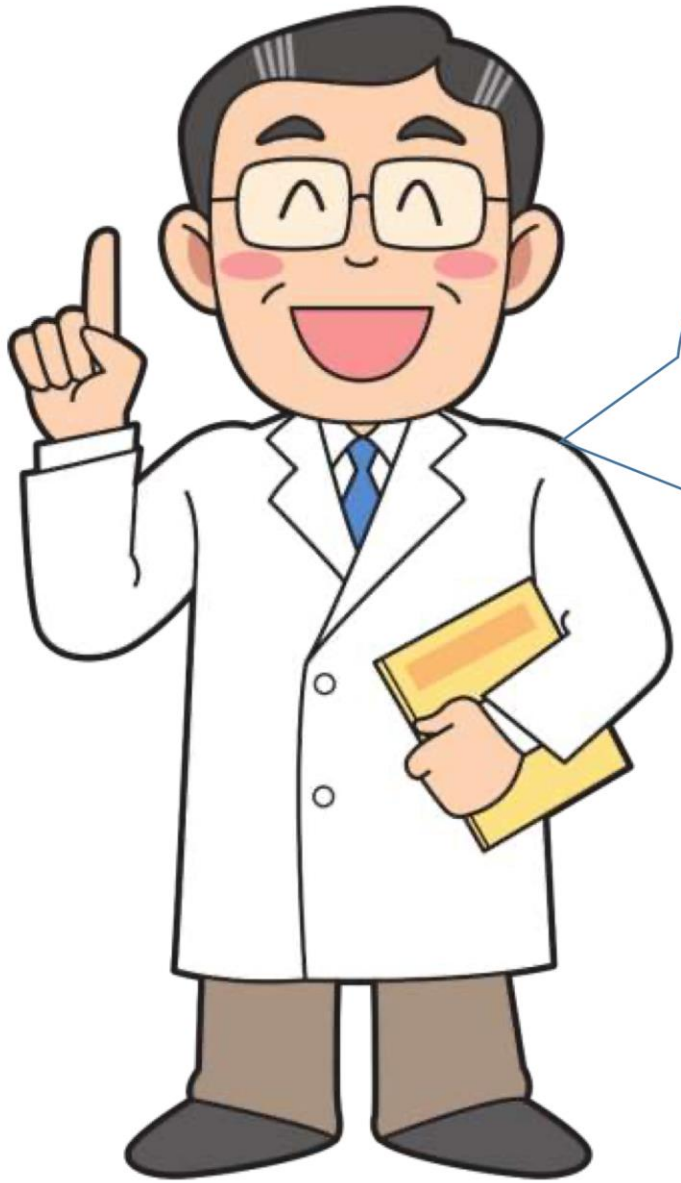
Thin Stents-Maintain the balance

What are the advantages of microporous surface?

- Micropores act like reservoirs for delivering drug to the targeted site
- One million pores per cm2 with average depth of 2µm
- Ensures optimal drug release (Van der Waals forces)
- Increases surface area hence allows minimal use of polymer thereby reducing the polymeric load to 1/4th

What are the benefits of Abluminal coating?

- Faster endothelization as drug is targeted to abluminal side
- Reduced chances of stent thrombosis.



What is the scientific evidence to support this statement "Shellac resin promotes a smooth stent top layer and prevents the two-drug matrix from collapsing during stent expansion" ?

Shellac Resin

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Biomaterials xxx (2008) 1–6

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

The pre-clinical assessment of rapamycin-eluting, durable polymer-free stent coating concepts

Kristin Steigerwald [a,1], Sabine Merl [a,1], Adnan Kastrati [a], Anna Wieczorek [a], Marc Vorpahl [a], Raimund Mannhold [b], Michael Vogeser [c], Jörg Hausleiter [a], Michael Joner [a], Albert Schömig [a], Rainer Wessely [a,*]

[a] Deutsches Herzzentrum and 1 Medizinische Klinik, Klinikum rechts der Isar, Technische Universität, Munich, Germany
[b] Molecular Drug Research Group, Universität Düsseldorf, Düsseldorf, Germany
[c] Institut für Klinische Chemie, Ludwig-Maximilians-Universität München, Germany

"Findings suggest that top coating of a biodegradable polymer with a resin like shellac may inhibit inflammatory processes that can be associated with adverse outcomes, albeit there is an increase in fibrin deposition compared to uncoated or rapamycin only coated stents"

https://translumina.com/wp-content/uploads/2020/12/2008-Biomaterials.pdf

Shellac Resin

European Heart Journal (2009) **30**, 923–931
doi:10.1093/eurheartj/ehp044

CLINICAL RESEARCH
Interventional cardiology and angiology

A polymer-free dual drug-eluting stent in patients with coronary artery disease: a randomized trial vs. polymer-based drug-eluting stents

Robert A. Byrne[1]*, Julinda Mehilli[1], Raisuke Iijima[1], Stefanie Schulz[1], Jürgen Pache[1], Melchior Seyfarth[1], Albert Schömig[1,2], and Adnan Kastrati[1] for the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting STents (ISAR-TEST-2)

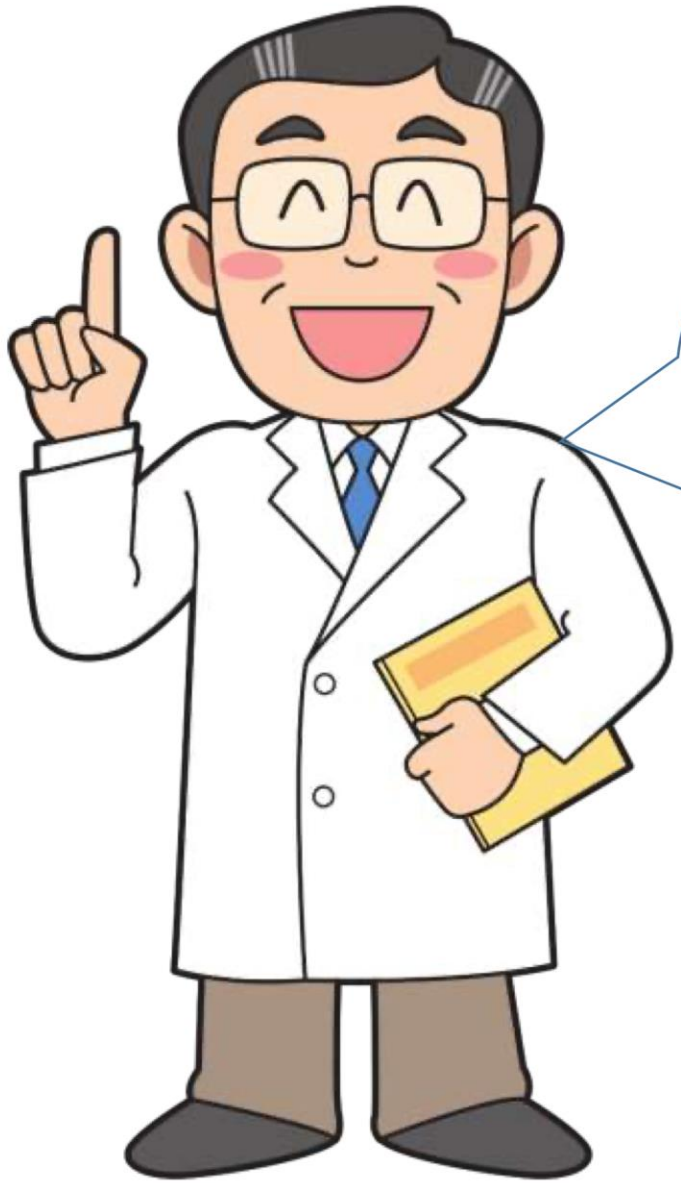
[1]ISAR Centre, Deutsches Herzzentrum, Technische Universität, Lazarettstrasse 36, 80636 Munich, Germany; and [2]1. Medizinische Klinik rechts der Isar, Munich, Germany

Received 27 October 2008; revised 5 December 2008; accepted 19 December 2008; online publish-ahead-of-print 24 February 2009

Aims Long-term polymer residue in the coronary milieu is a consequence of current drug-eluting stent (DES) therapy and has been implicated in late adverse events. We developed a novel polymer-free rapamycin- and probucol-eluting stent (Dual-DES) and compared its efficacy against commercially available permanent polymer-based sirolimus-eluting (SES; Cypher) and zotarolimus-eluting (ZES; Endeavor) stents.

- Shellac resin is a biocompatible resin widely used in the coating of medical tablets; its release kinetics are similar to those of both active drugs.
- The inclusion of resin allows for improved adherence of the drug mixture to the stent surface and enhances the structural integrity of the coating.
- No traces of rapamycin, probucol, or resin are observable beyond 6–8 weeks

https://academic.oup.com/eurheartj/article/30/8/923/433917



VIVO ISAR data is followed up in which patient subsets?

- Diabetes
- STEMI

Why was Probucol added in VIVO ISAR?

- Probucol: It is historically proven to impose anti-restenosis effects through anti-oxidative and direct anti-proliferative effects.
- Though in VIVO ISAR, it is not used as an Active Pharmaceutical Ingredient.
- Probucol here mimics the role of a Polymer thus functioning as a drug carrier.
- Probucol is used as a Matrix-Builder for the controlled release of Sirolimus.
- Probucol binds the drug on the stent and its properties of being hydrophobic and anti-oxidative, facilitates a controlled and continuous drug release.
- Probucol has added safety of also being used as an oral drug and proven its safety even at much higher doses in human body upto 500mg. The excipients which are used in other DES have no safety data at any concentrations

What is the crossing profile of VIVO ISAR?

VIVO ISAR has lowest crossing profile of 0.89 mm

What were the outcomes of 10 year follow up data?

- Numerically low event rates of all-cause mortality,
- Notably low rates of target vessel related MI i.e. 1.2%,
- Low rates of definite stent thrombosis.

How much drug is released in VIVO ISAR?

80% of Drug is released in 28 Days.

What are precise dosages of Sirolimus and Probucol in VIVO ISAR? Why were these dosages chosen (why not more or less)?

- Probucol matrix builder used in the formulation is at a ratio of 1:1 with Sirolimus drug.
- The Nominal Drug dose for the device is 12.5 µg of Sirolimus drug per millimeter of Stent length. Hence, the maximum Nominal Sirolimus Drug dose for a 48 mm of Stent is 600 micrograms.
- Dosages are in accordance with the drug Therapeutic window-The dose range of a drug that provides safe and effective therapy with minimal adverse effects.

How to justify premium pricing for VIVO ISAR?

- Technological advancement: VIVO ISAR is not an iteration but an evolution
- Next Generation DES: Future Beyond Polymer with enhanced Safety & Efficacy at 10Yrs.
- Longest studied DES: 10 years of clinical follow-up data in complex patient subsets of Diabetes and STEMI

What is the metal-to-artery ratio for VIVO ISAR?

9~14% depending on size

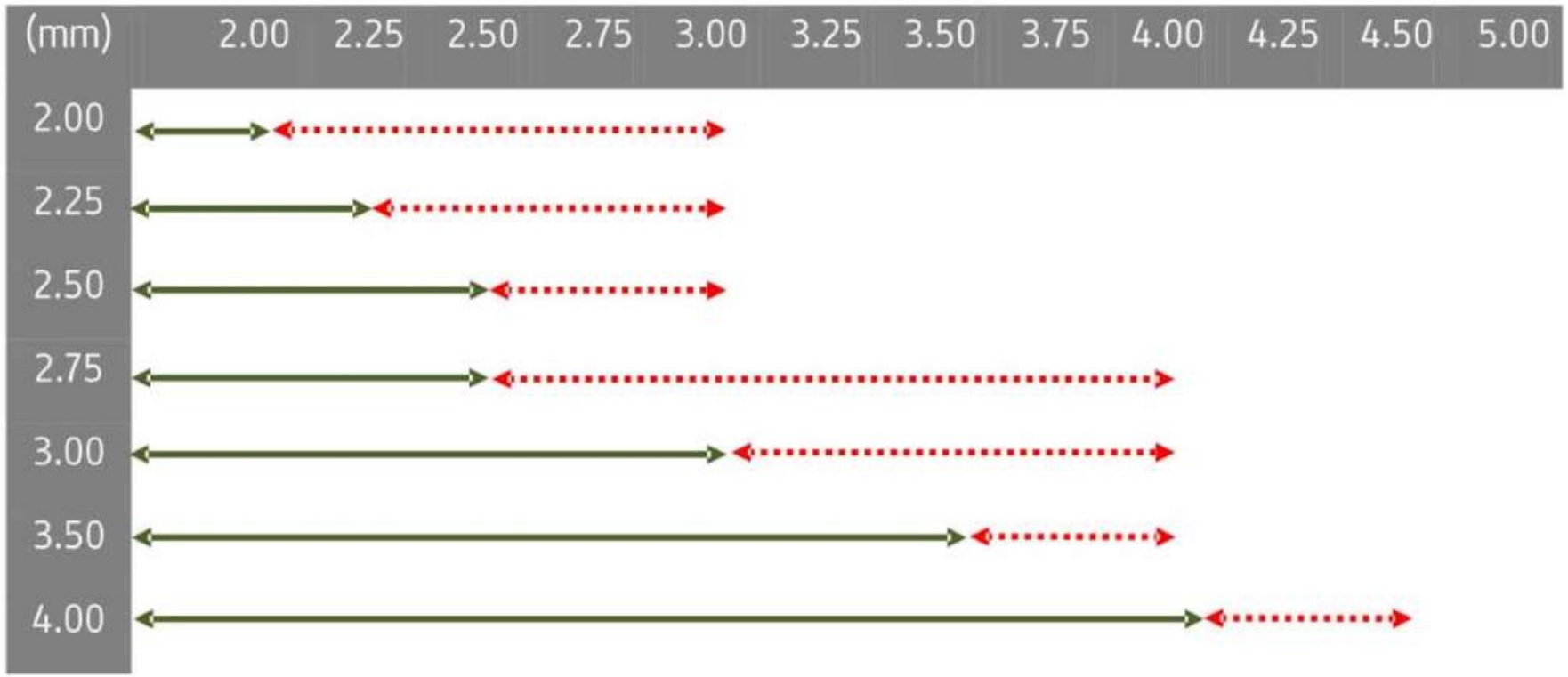
Does VIVO ISAR expand beyond its given diameter?

Why Stent Expansion is required?

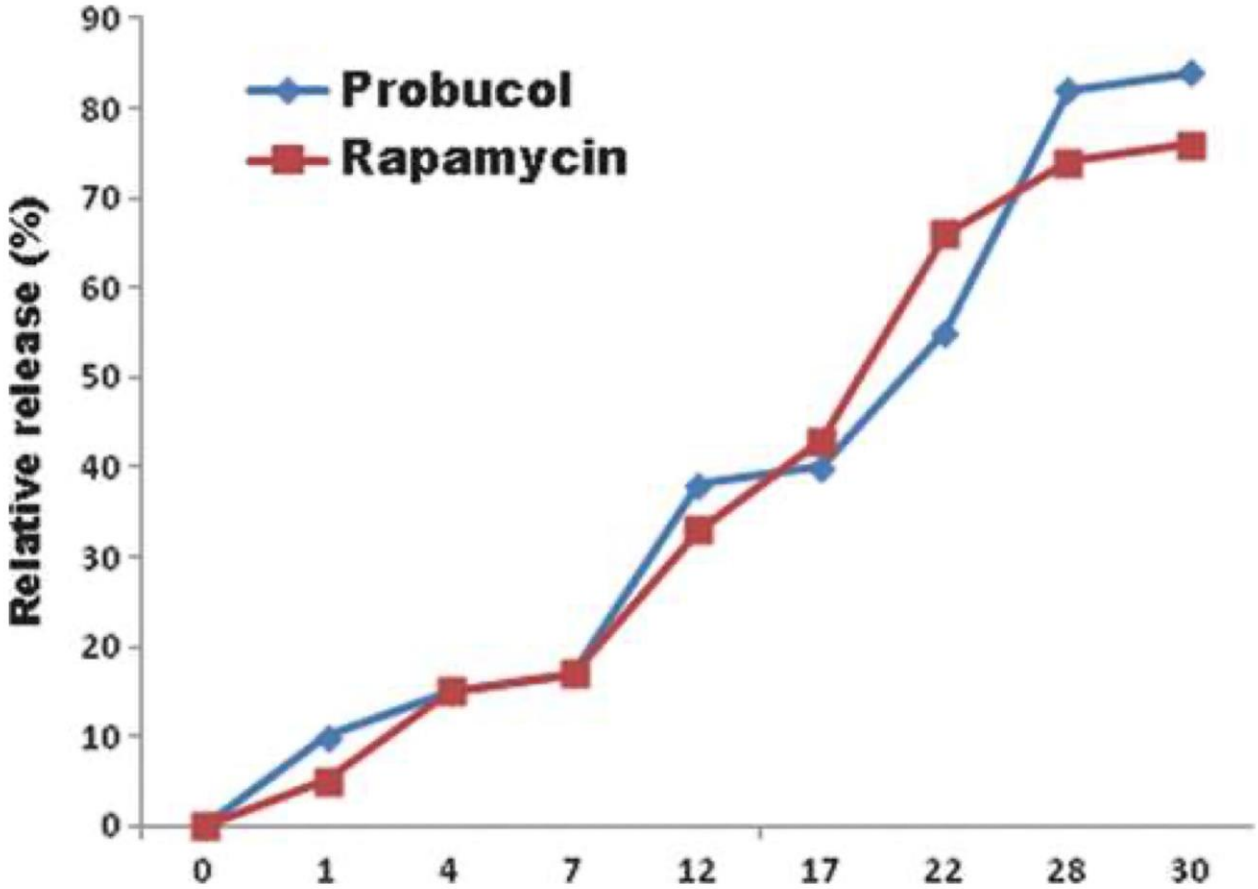
Selecting a smaller stent for a given vessel diameter due to technical reasons leads to Malapposition.

Malapposed stents leads to Stent Thrombosis

VIVO ISAR engineered to expand



For how long DAPT has to be continued?



- In Pre-Clinical trials, it has been observed that Sirolimus and Probucol are released in 4-6 weeks leaving BMS

- DAPT can be given for 1 month followed by single anti-platelet therapy

Competitor's Information

Company Name	Premium	Major Communication Point
Abbott	Expedition Alpine	STOPDAPT 90 study - APT is given till 90 days and then stopped and taken a follow-up for 2 years
Medtronic	Onyx	DAPT 28 - DAPT is given upto 28 days and then stopped and taken a follow-up for the same
Boston	Synergy	EVOLVE DAPT - DAPT is given for 90 days and then stopped and taken a follow up for 2 years

Are there any studies planned to confirm the feasibility of using a short DAPT for VIVO ISAR?

SECURE Global Registry aims that VIVO ISAR offers required safety for shortening the duration of dual antiplatelet therapy to 1 month in CAD patients and high anti-restenotic efficacy of 2nd generation DES.

Why do I believe VIVO ISAR is safe

VIVO ISAR- World's Longest Studied DES

In Pre- Clinical Assessment

- VIVO ISAR demonstrated ideal Drug Release Kinetics for better anti-restenotic efficacy compared to polymer based and conventional polymer free stent
- Prolonged Drug Release which is 80% in 28 days

2 Years Data-JACC

At 2 years, VIVO ISAR demonstrated 43% reduction in binary restenosis in comparison to ZES and 23% reduction in comparison to SES.

5 Years Data-JACC

VIVO ISAR with No Polymer demonstrates similar rates definite or probable stent thrombosis as PP-ZES

Established Safety and Efficacy in Complex Patient Subsets- Diabetes and STEMI

Followed upto 5 years

Established Safety and Efficacy with 10 years clinical data

3002 patients were followed up

Established Safety and Efficacy with 10 years clinical data in Diabetes patient subset

3002 patients were followed up

Current Challenges with Polymer based DES

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LIMITLESS POSSIBILITIES

Polymers (Durable or Biocompatible) are an integral part of Drug Release Matrix in current generation DES as they ensure the release kinetics of the active drug, the clinical determinant of antirestenotic efficacy.

However, the mechanical properties of the metallic cage and aggressive inflammatory reactions during polymer erosion are known to cause

- Persistent Fibrin Deposition
- Delayed Endothelialisation
- Chronic Inflammation
- Persistent Platelet Activation
- Prothrombogenecity (potential to cause Stent thrombosis)

Current Polymer DES are also associated with Flaking, Peeling and Webbing which leads to impaired action of drug.

Polymers-An essential evil in Drug Eluting Stents

*For Internal Purpose Only

VIVOISAR

Polymer-Free Sirolimus Eluting Stent

Ensured Safety
with Probucol maintaining
optimum drug release kinetic

Enhanced Deliverability
with Lowest Crossing Profile

Faster Endothelialization
with Thin Strut maintaining
Optimum Radial Strength

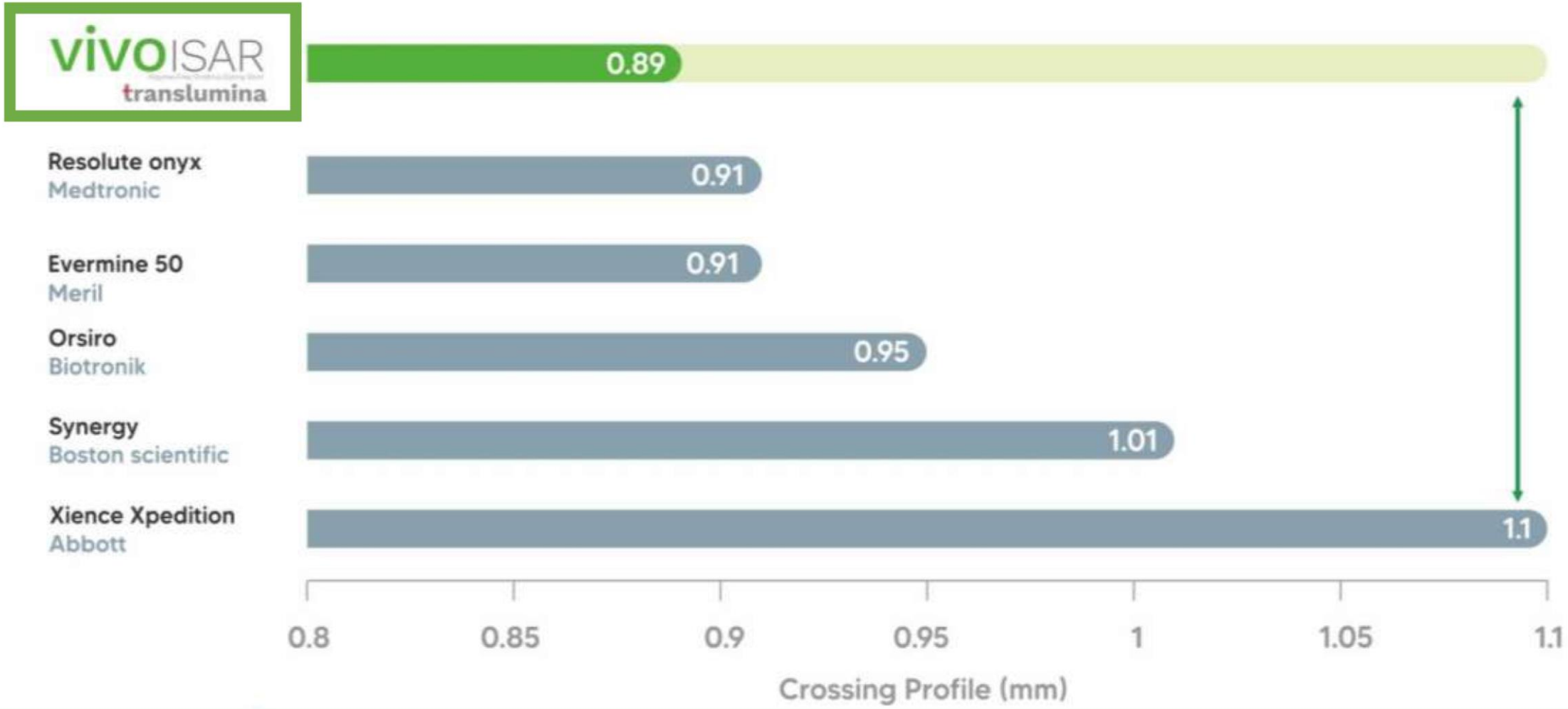
Enhanced Visibility
with Co-Cr

*For Internal Purpose Only

VIVOISAR

Polymer-Free Sirolimus Eluting Stent

Enhanced Deliverability with Lowest Crossing Profile



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VIVO ISAR
Polymer-Free Sirolimus Eluting Stent

World's Longest Studied DES

In Pre- Clinical Assessment

- VIVO ISAR demonstrated Ideal Drug Release Kinetics for better anti-restenotic efficacy compared to polymer based and conventional polymer free stent
- Prolonged Drug Release which is 80% in 28 days

2 Years Data-JACC

At 2 years, VIVO ISAR demonstrated 43% reduction in binary restenosis in comparison to PP-ZES and 23% reduction in comparison to PP-SES.

5 Years Data-JACC

VIVO ISAR with No Polymer demonstrates similar rates definite or probable stent thrombosis as PP-ZES

Established Safety and Efficacy in Complex Patient Subsets- Diabetes and STEMI

Followed upto 5 years

Established Safety and Efficacy with 10 years clinical data

3002 patients were followed up

vivo ISAR

Polymer-Free Sirolimus Eluting Stent

Ordering Information

Length Ø [mm]	VIVO ISAR Reference No.						
	Diameter (mm)						
	2.00 mm	2.25 mm	2.50 mm	2.75 mm	3.00 mm	3.50 mm	4.00 mm
8.00	VISR2008	VISR2208	VISR2508	VISR2708	VISR3008	VISR3508	VISR4008
12.00	VISR2012	VISR2212	VISR2512	VISR2712	VISR3012	VISR3512	VISR4012
16.00	VISR2016	VISR2216	VISR2516	VISR2716	VISR3016	VISR3516	VISR4016
18.00	VISR2018	VISR2218	VISR2518	VISR2718	VISR3018	VISR3518	VISR4018
21.00	VISR2021	VISR2221	VISR2521	VISR2721	VISR3021	VISR3521	VISR4021
24.00	VISR2024	VISR2224	VISR2524	VISR2724	VISR3024	VISR3524	VISR4024
28.00	VISR2028	VISR2228	VISR2528	VISR2728	VISR3028	VISR3528	VISR4028
32.00	VISR2032	VISR2232	VISR2532	VISR2732	VISR3032	VISR3532	VISR4032
36.00				VISR2736	VISR3036	VISR3536	VISR4036
40.00				VISR2740	VISR3040	VISR3540	VISR4040
44.00				VISR2744	VISR3044	VISR3544	VISR4044
48.00				VISR2748	VISR3048	VISR3548	VISR4048

* Please contact our Customer Care for available sizes

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LIMITLESS POSSIBILITIES

Technical Specifications

Device	Polymer-Free Sirolimus-Eluting Coronary Stent System
Description	Polymer Free Sirolimus Eluting Cobalt Chromium stent (Hybrid Cell Design) mounted on a rapid exchange PTCA Balloon Catheter. The Device is coated with a proprietary formulation of Sirolimus Drug in a Polymer Free Drug delivery matrix of Probucol (Matrix Builder) with Shellac Resin.
STENT SYSTEM	
Stent Material	Cobalt Chromium Alloy L605
Stent Design	Modular Multicellular Design
	Small Vessel and Medium Vessel as per diameter
Stent Lengths (mm)	8,12, 16, 18, 21, 24, 28, 32, 36, 40, 44 & 48 mm
Stent Diameters (mm)	2.00, 2.25, 2.50, 2.75, 3.00, 3.50, 4.00 mm
Stent Surface Modification	Sandblasted Microporous Surface
Strut Thickness (µm)	Small Vessel – 68 µm, Medium Vessel – 79 µm
Strut Width (µm)	Small Vessel – 78 µm, Medium Vessel – 88 µm
Metal to Artery Ratio	9~14% depending on size
Radial Force (Strength)	High
Crimped Stent Profile	0.85~1.10 mm
Radiopacity	Good Visibility
Foreshortening	Average NMT 7. 5%
Degree of elastic recoil	Average less than 7%
Flexibility	Highly flexible design with link

STENT DELIVERY SYSTEM	
Stent Delivery System (SDS)	Semi-compliant Balloon based delivery with two radiopaque markers. Balloon is about 1 mm longer than the stent length.
Delivery Method	Rapid Exchange Method (25 cm Exchange shaft)
Balloon Material	Modified Polyamide material (Semi-Compliant)
Balloon Marker and Material	2 Nos of Platinum / Iridium marker for stent length
Tip Entry Profile	0.016” ± 0.001” (0.41 mm)
SDS Length	143 cm ± 5 cm
Guide Wire compatibility	0.014” recommended
Guiding Catheter compatibility	Minimum 5 French
Crossing Profile	0.89 mm
Nominal Pressure (NP)	11 atm
Rated Burst Pressure	16 atm
Post dilatation	SV-805mN (25%) MV-997mN (25%)
ACTIVE INGREDIENTS	
Active Pharma Ingredient	Sirolimus Drug (also known as Rapamycin)
Drug Dose	2.60 µg/mm^2
DRUG DELIVERY MATRIX	
Drug Matrix builder	Probucol, which acts as retardant to Sirolimus Drug release
Excipient	Shellac Resin (Wax Free)