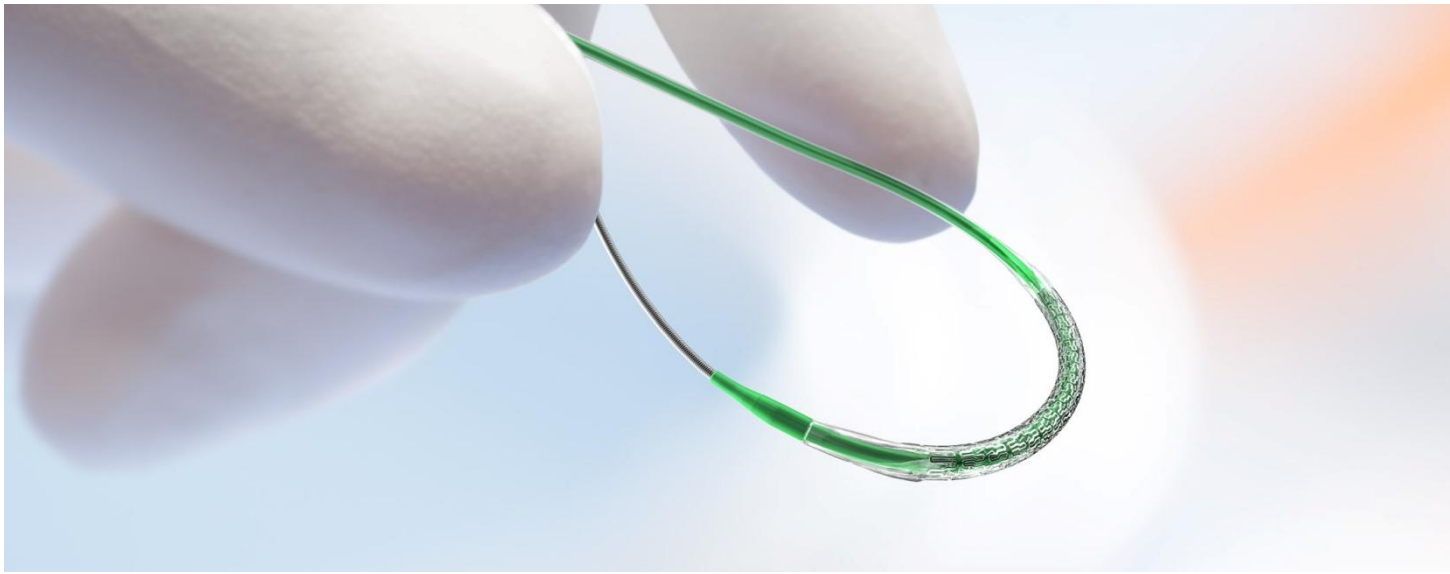


Polymer-Free Stent

CX - ISAR

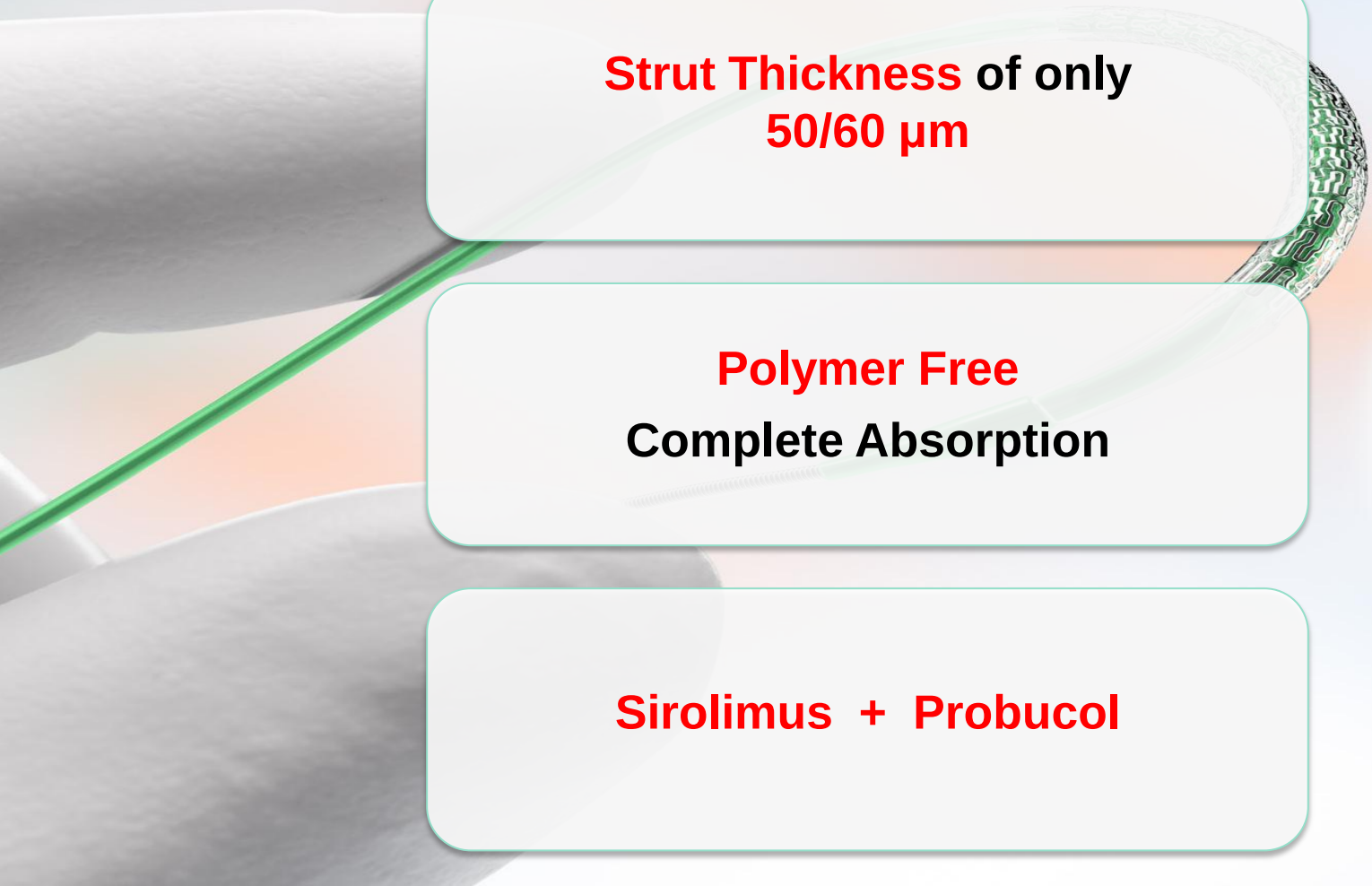
Moo Hyun Kim, MD, FACC

on behalf of

Dr. Florian Krackhardt, Germany

CX – ISAR Stent : Features

Intracoronary Stenting and Angiographic Results



Strut Thickness of only
50/60 µm

Polymer Free

Complete Absorption

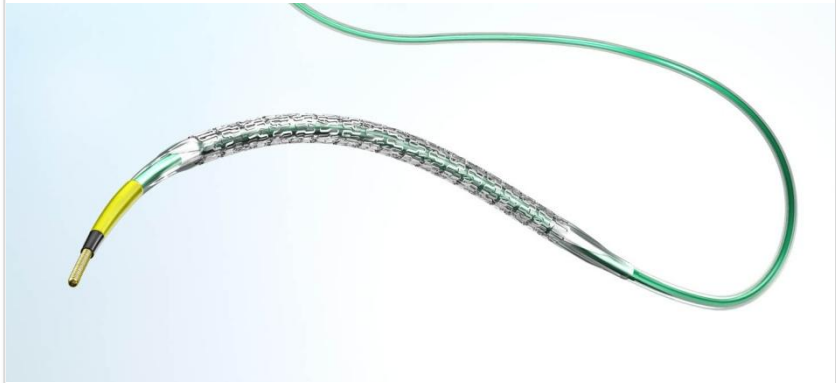
Sirolimus + Probucol

Stent Platform

Best Stent Performance through ultra-low strut thickness with **Cobalt Chromium**

CX-Blue Ultra

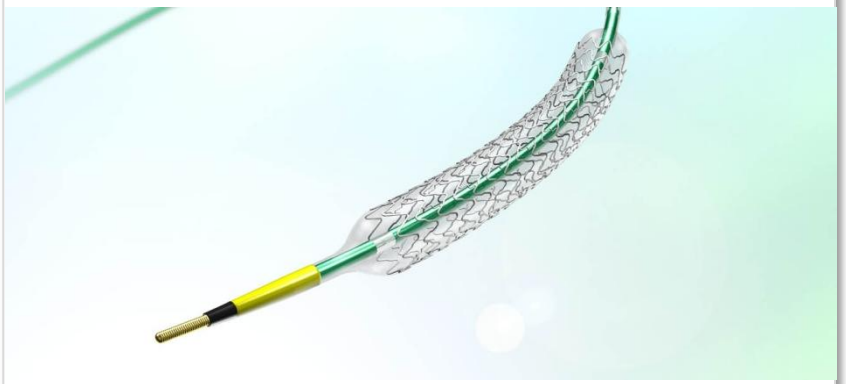
For 2.0 - 2.5 mm diameter



- **50 µm stent**
- **less metal, less foreign response**
- **less injury**

CX-Blue Neo

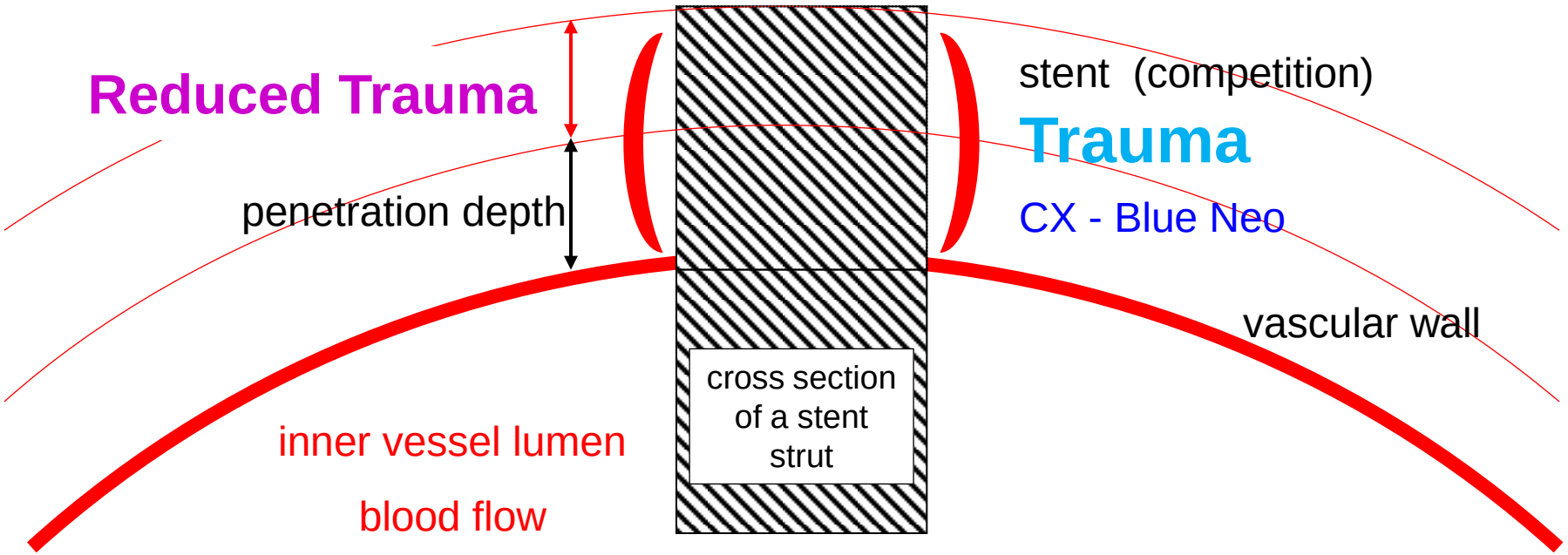
For 2.75 - 4.0 mm diameter



- **60 µm stent**
- **best crimp-profile**
- **high flexibility**

Stent Platform

Traumatization of the vascular wall



Clinical Evaluation with Stent Platform

Intracoronary Stenting and Angiographic Results

Strut Thickness Effect on Restenosis Outcome (ISAR-STEREO) Trial

Adnan Kastrati, MD; Julinda Mehilli, MD; Josef Dirschinger, MD; Franz Dotzer, MD; Helmut Schühlen, MD; Franz-Josef Neumann, MD; Martin Fleckenstein, MD; Conrad Pfafferott, MD; Melchior Seyfarth, MD; Albert Schömig, MD

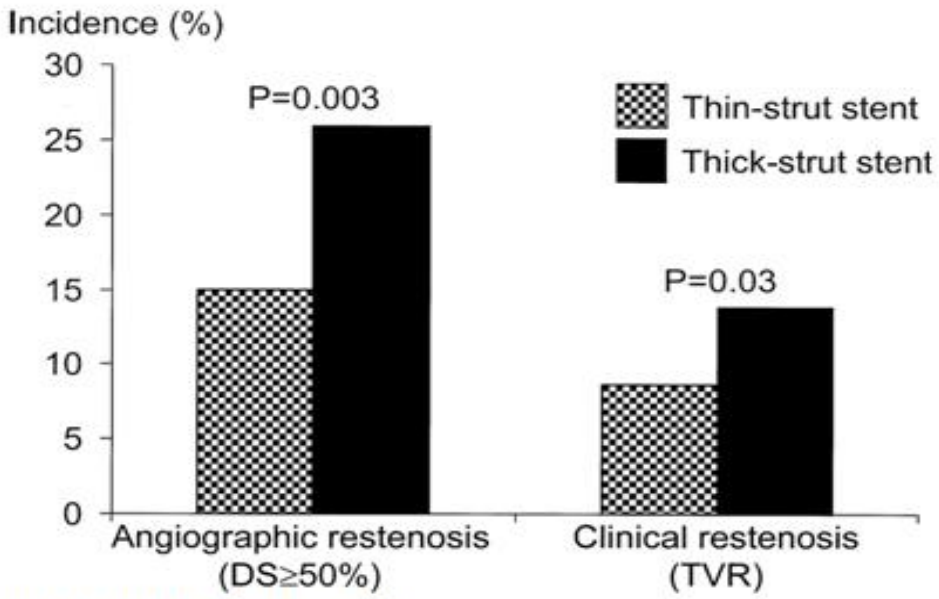
From the Deutsches Herzzentrum, Munich, Germany.

Correspondence to Dr Adnan Kastrati, Deutsches Herzzentrum, Lazarettstraße 36, 80636 München, Germany. E-mail kastrati@dhm.mhn.de

Clinical Evaluation with Stent Platform

Clinical superiority of Thin Strut Stents

Study	Restenosis with 50 µm strut thickness	Restenosis with common strut thickness	p-value	Number of patients
ISAR Stereo I*	**15 %**	**26 %**	**0.01**	**651**
ISAR Stereo II**	**18 %**	**31 %**	**0.001**	**611**

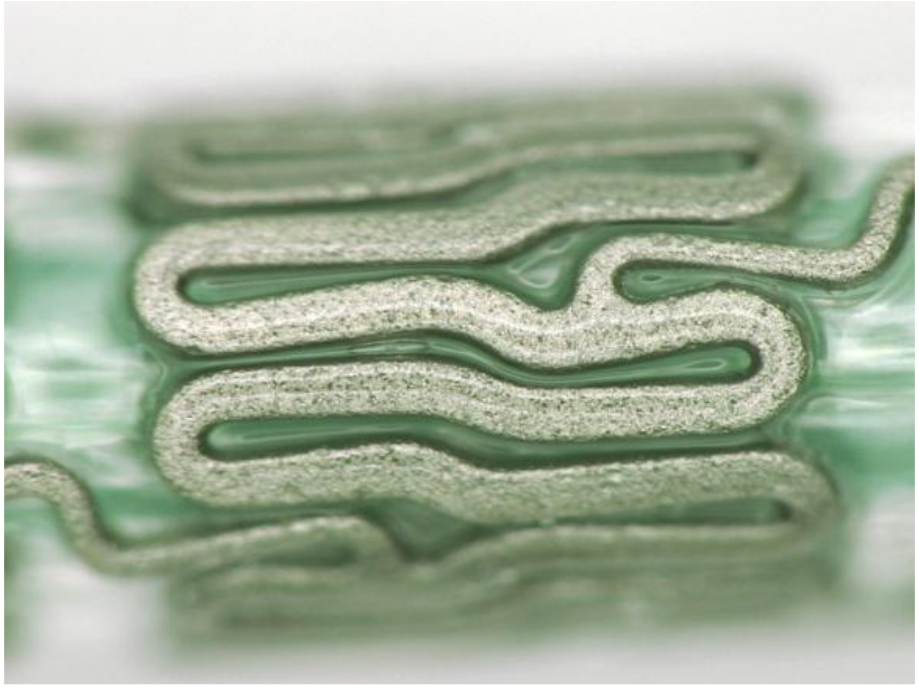


Kastrati A et al. Circulation 2001;103:2816-2821

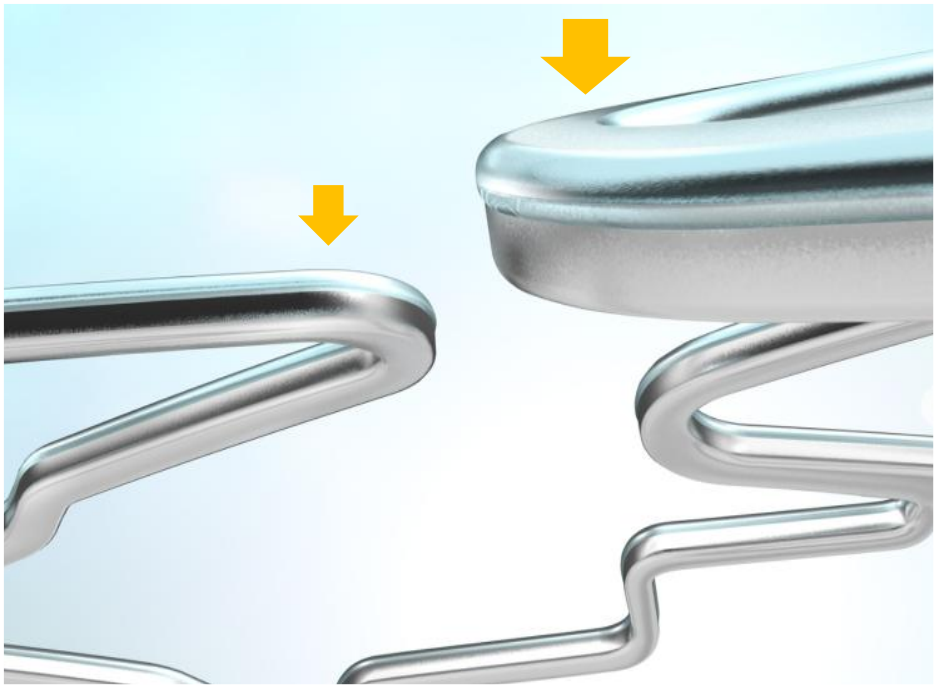
American Heart Association
Learn and Live

Polymer-Free Matrix

Microporous
Stent Surface Modification

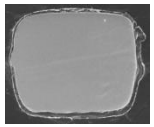
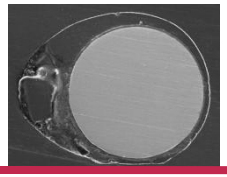
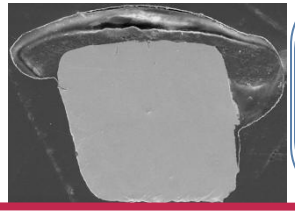
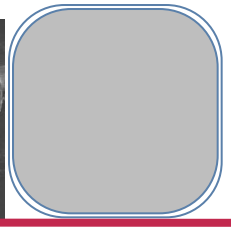


Abluminal Coating
on Surface



Improved healing, More targeted tissue release, Less systemic exposure

Stent Platform By Products

Durable Polymer Coated Stents				Bioabsorbable Polymer Coated Stents		Bio-absorbable Scaffold	Polymer-Free Coated Stent
Xience Prime™	Xience Xpedition™	Resolute Integrity™	PROMUS Element™	Orsiro™	BioMatrix Flex™	Absorb BVS	**ISAR**
							
Strut Thickness (nominal and measured)							
81 µm (0.0032”)	81 µm (0.0032”)	89 µm (0.0035”)	81 µm (0.0032”)	60/80 µm (0.0024/ 0.0031”)	120 µm (0.0047”)	150 µm (0.0059”)	**50/60 µm** (0.0020”/ 0.0024”)
Coating Thickness (nominal and measured)							
Conformal 8µm / side 4 - 10 µm	Conformal 7.8µm/ side 4 - 10 µm	Conformal 6µm / side 5 - 38 µm	Conformal 8µm	Asymetr. 7µm 7 - 9 µm	Abluminal 10µm 10 - 25µm	Conformal 3µm	**Abluminal** 4 µm
Content (nominal)							
Everolimus 100 µg/cm²	Everolimus 88 µg/cm²	Zotarolimus 160 µg/cm²	Everolimus 100 µg/cm²	Sirolimus 140 µg/cm²	Biolimus A9 15.6 µg/mm²	Everolimus 98 µg/cm²	Sirolimus 120 µg/cm²

Source: R&D, internal tests

Trackability (track length passed by 3.0 x 18/19 mm)

30% b
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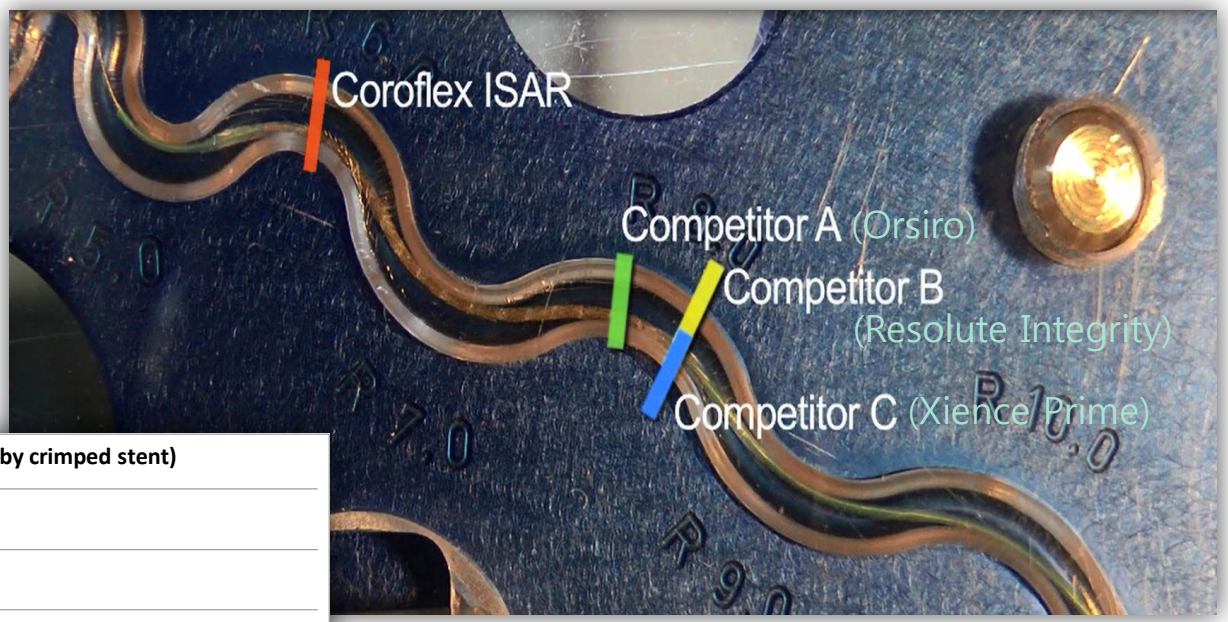
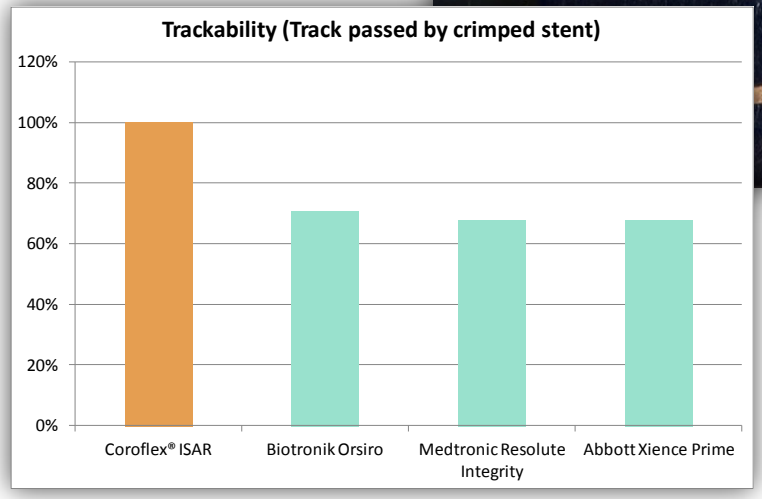
acking





- Coroflex ISAR shows the best trackability and continues the superior performance of all Coroflex stent delivery systems.

Drug Coating

Sirolimus - Established anti-inflammatory and anti-proliferative agent

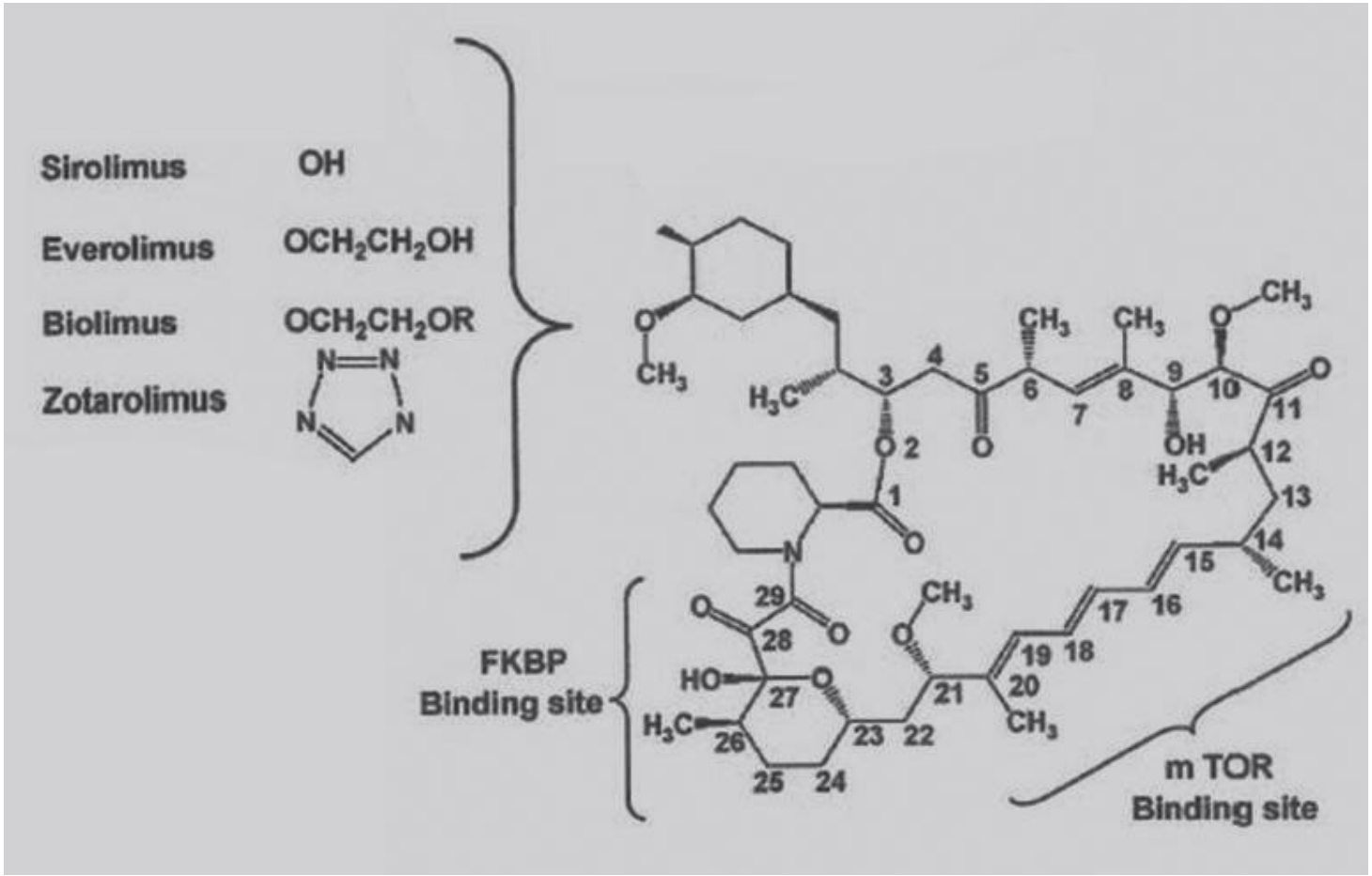
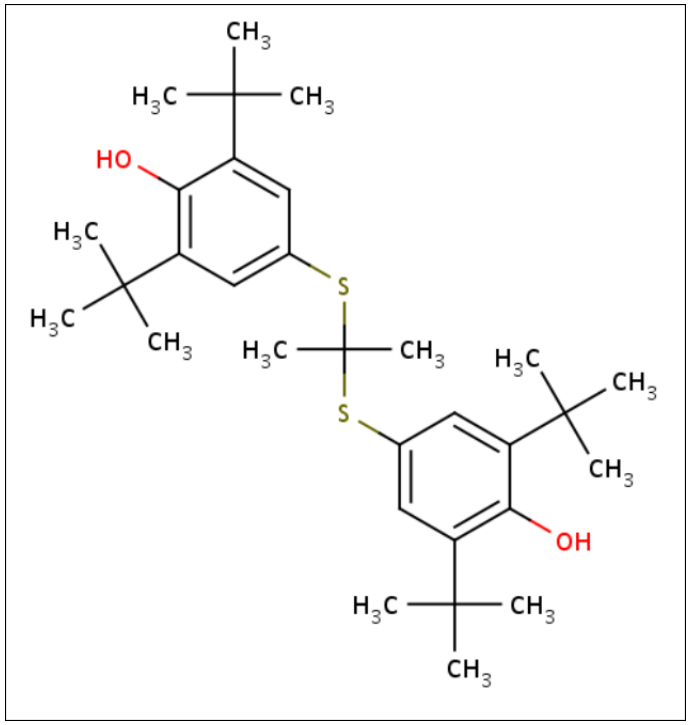


Figure: Chemical structure of Limus derivates

Matrix Coating Technology



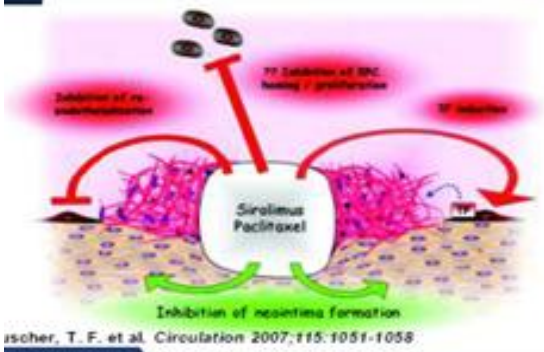
Probucol is a potent

1. **Antioxidant**
2. Highly **Lipophilic**
3. **Release kinetics** of sirolimus

Kim W et al., Effect of Anti-Oxidant (Carvedilol and Probucol) Loaded Stents in a Porcine Coronary Restenosis Model. Circ J 2005; 69: 101– 106

Limitations of Polymer

Limitations of polymer use and metallic backbones in current DES



ischer, T. F. et al. Circulation 2007;115:1051-1058

- Stent thrombosis (late, very late) / Forced prolonged DAT duration / Bleeding / Resistance
- Delayed endothelialization
- Inflammation / Hypersensitivity
- Aneurysms
- Late catch-up
- Polymer disruption
- Remodeling (constrictive / expansive)
- Functional integrity

Matrix Coating Technology

Polymer-Free Matrix Coating Technology

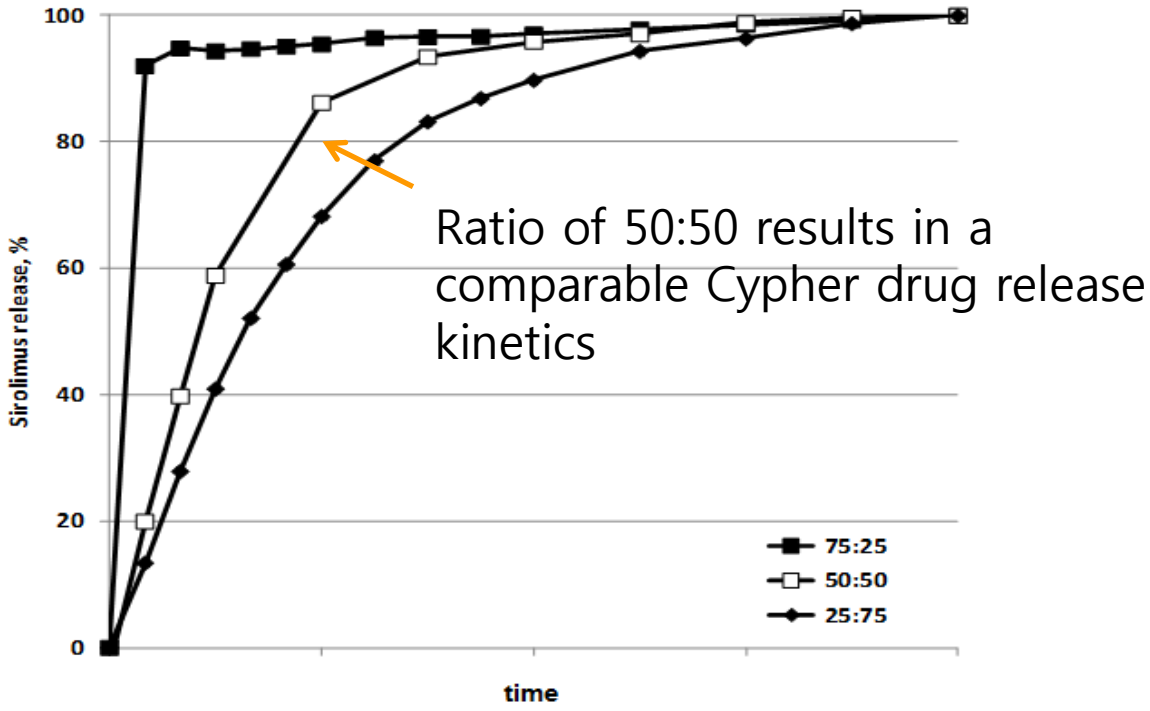
- The Coroflex ISAR stent is covered with a Sirolimus containing matrix, which consists in equal shares (1:1) of the drug Sirolimus (active agent) and Probucol (excipient - matrix builder)
- Probucol is used as an hydrophobic, antioxidantic excipient. The release of Sirolimus is controlled by the Probucol. Probucol is needed to bind the drug on the stent and to facilitate a controlled & continuous drug release.
- Probucol mimics the function of a polymer by retarding the release of Sirolimus over a time period of several weeks
- The drug load is 1.2µg/mm² Sirolimus
- The Matrix Coating is applied only on the abluminal Coroflex ISAR stent surface for improved endothelial healing

Coroflex® ISAR
Abluminal, Polymer-Free Drug Delivery

Matrix Coating Technology

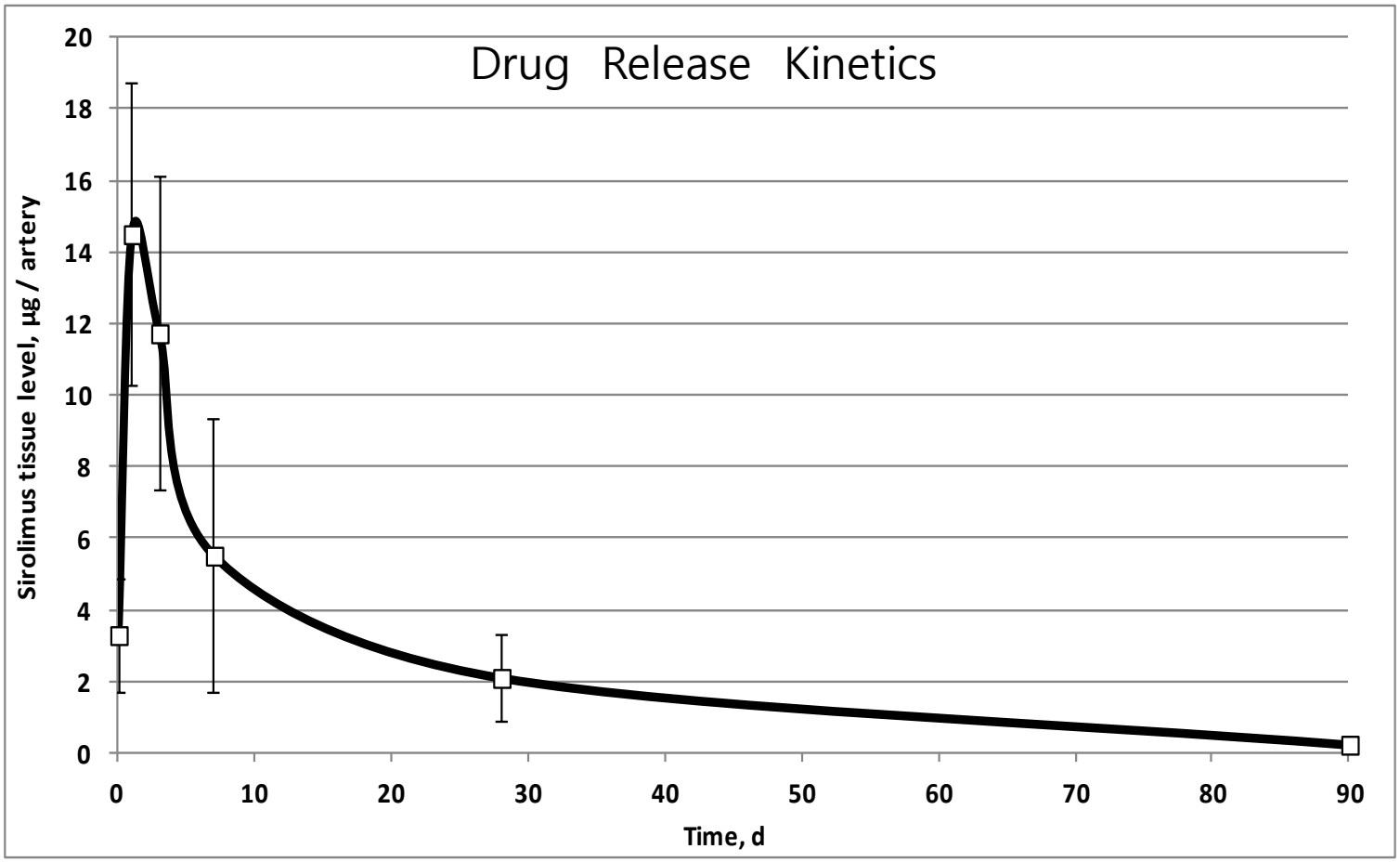
Drug Release Kinetics

depends on the 'sirolimus:probucol ratio' in the coating of CX ISAR



The 50:50 ratio corresponds to the drug release of the Cypher stent without using a non-degradable polymer!

Matrix Coating Technology



CX-ISAR Drug Matrix is >80% released & bio-resorbed after 30 days

The release has been completed at 90 days.

Klugherz BD, Llanos G, Lieuallen W, et al; Twenty-eight-day efficacy and phamacokinetics of the sirolimus-eluting stent. Coron Artery Dis. 2002 May;13(3):183-8

Technical Data

Technical Data	
Coating technology	Abluminal, polymer-free coating
Proximal shaft	1.9 F
Distal shaft	2.5 F
Usable length	145 cm
Stent strut thickness	Ø 2.00 – 2.5 mm 50 µm 'Ultra' stent architecture Ø 2.75 – 4.0 mm 60 µm 'Neo' stent architecture
Stent length	Ø 2.00 – 2.5 mm: 9/14/16 – 32 mm 'Ultra' stent architecture Ø 2.75 – 4.0 mm: 8/13/16 – 32 mm 'Neo' stent architecture
Guiding catheter compatibility	5 F / "kissing balloon": 6 F
Guide wire compatibility	0.014" (0.36 mm)
Nominal Pressure (NP) Rated Burst Pressure (RBP)	10 atm 18 atm (Ø 4.0 mm 15 atm)
Crossing profile	0.031" – 0.037" (0.79 mm – 0.93 mm)
Lesion entry profile	0.016" (0.41 mm)

Polymer-Free Sirolimus- and Probucol-Eluting Versus New Generation Zotarolimus-Eluting Stents in Coronary Artery Disease : Test Efficacy of Sirolimus- and Probucol-Eluting Versus Zotarolimus-Eluting Stents (ISAR-TEST 5) Trial

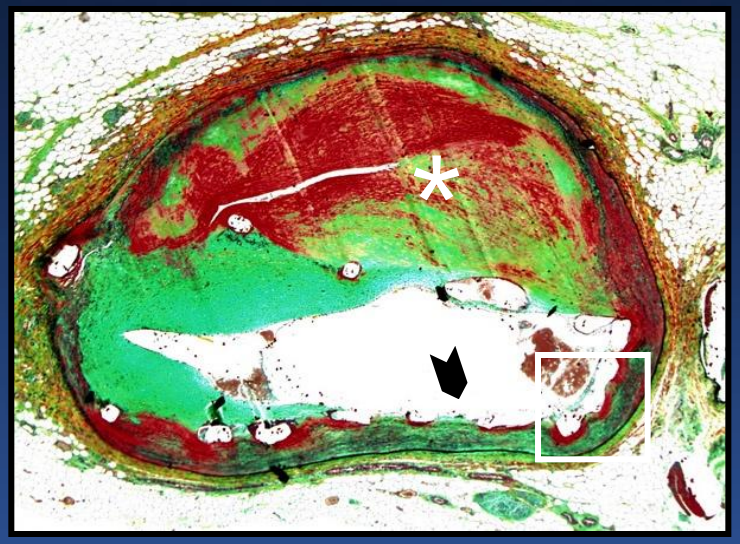
J. Mehilli, MD

A. Kastrati, R.A. Byrne, S. Massberg, K. Tiroch, S. Schulz, J. Pache, M. Fusaro, K-L. Laugwitz, A. Schömig

Deutsches Herzzentrum & 1. Med. Klinik rechts der Isar
Technische Universität Munich Germany

Background

In comparison with BMS, DES are associated with a small excess of late events occurring more than one year after intervention



The pathological substrate underlying these events is delayed arterial healing and inflammatory response to DES permanent polymer coatings

Inclusion & Exclusion Criteria

Inclusion criteria

Patients with ischemic symptoms or evidence of myocardial ischemia in the presence of ≥50 % *de novo* stenosis located in native coronary arteries

Informed, written consent

Exclusion criteria

Age < 18 years

Cardiogenic shock

Target lesion located in the left main stem

Target lesion located in the bypass graft

Malignancies with life expectancy <1 year

Allergies to study medication

Primary Endpoint

Composite of

cardiac death,

target vessel-related myocardial infarction

target lesion revascularization

at 1-year post index PCI

Secondary Endpoints

- All cause mortality
- Incidence of definite/probable stent thrombosis at 1-year post index PCI

- In-segment binary restenosis
- In-stent late luminal loss at follow-up angiography

Sample Size Calculation

Hypothesis:

Rapamycin/Probucol-eluting stent (Dual-DES) is not inferior to zotarolimus-eluting stent (Endeavor Resolute) in terms of device-oriented major adverse cardiac events

Assumptions:

Incidence of primary endpoint in both groups 10%
Margin of non-inferiority 3%
Power of 80%
One-sided α-level of 0.05
Random sequence 2:1
Needed total # of patients: **3000**

(accounting for possible losses at follow-up)

ISAR-TEST-5

***I**ntracoronary **S**tenting and **A**ngiographic **R**esults:*
***T**est **E**fficacy of Rapamycis/Probucol- and Zotarolimus-Eluting **ST**ents - 5*

3002 patients with *de novo* lesions

Rapamycin/Probucol-Eluting DES
(Dual-DES)
n=2002

Zotarolimus-Eluting DES
(ZES)
n=1000

6 to 8-month repeat angiogram

12-month clinical follow-up

Follow-Up Protocol

600 mg Clopidogrel

PCI

ASS 500 mg

0	30 d	6-8 mo.	12 mo.
serial CK + CKMB measurements	clinical follow-up (100%)	repeat angiography (76%)	clinical follow-up (98%)

Clopidogrel	2x75 mg/day until discharge 75 mg at least 6 months after index PCI
Aspirin	200 mg/d indefinitely

Baseline clinical characteristics

	Dual-DES n=2002	ZES n=1000
Age, years	67.7±11.2	68.1±10.8
Female, %	24	24
Art. hypertension, %	67	67
Diabetes, %	29	30
Current smoker, %	18	17
Prior bypass surgery, %	9	10
Prior MI, %	29	30
Hyperlipidemia, %	63	65

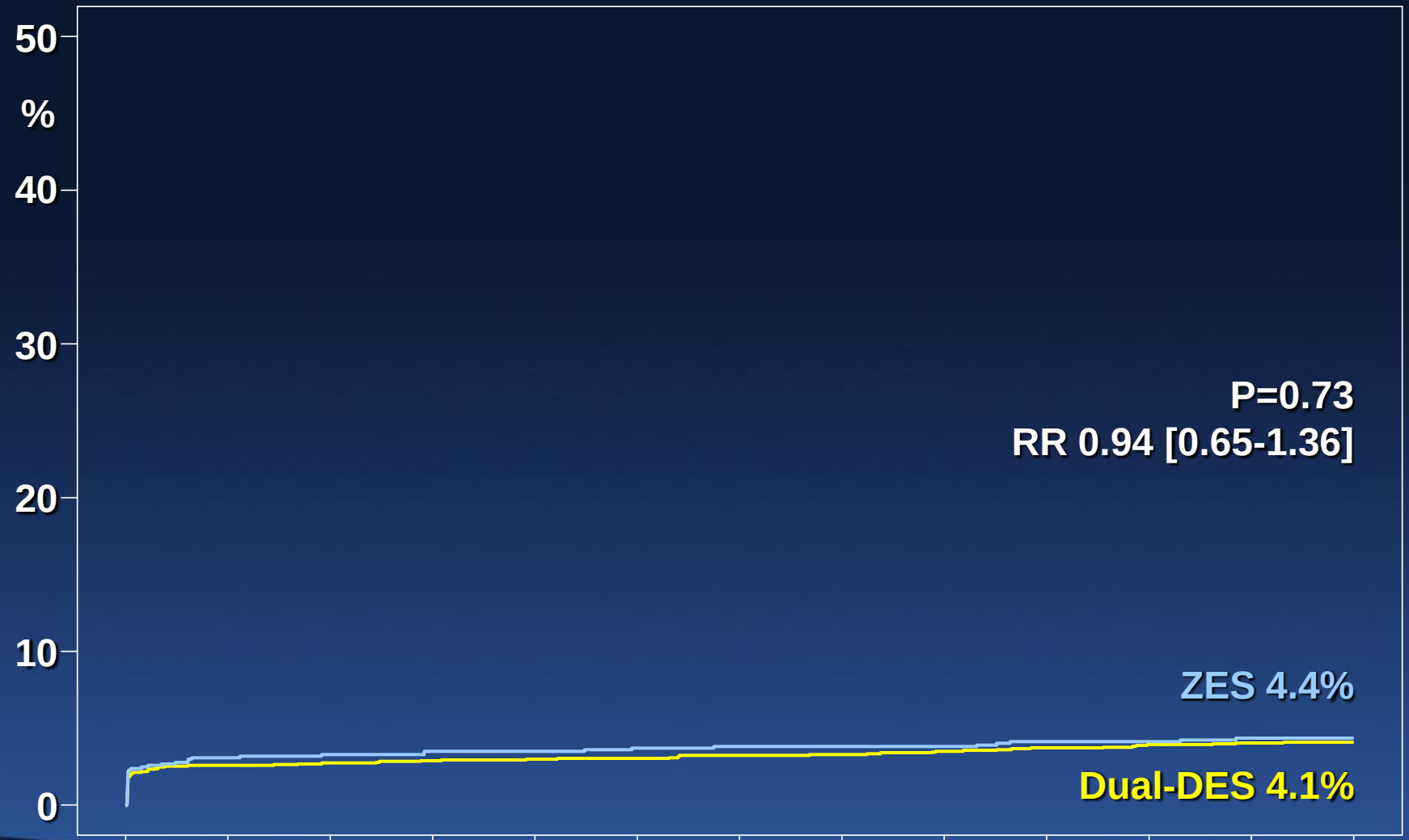
Baseline clinical characteristics

	Dual-DES n=2002	ZES n=1000
Clinical presentation, %		
acute MI	11	10
unstable angina	30	33
stable angina	59	57
Multivessel disease, %	82	86
Multilesion PCI, %	36	38
LV ejection fraction, %	52.6±11.9	52.4±11.4

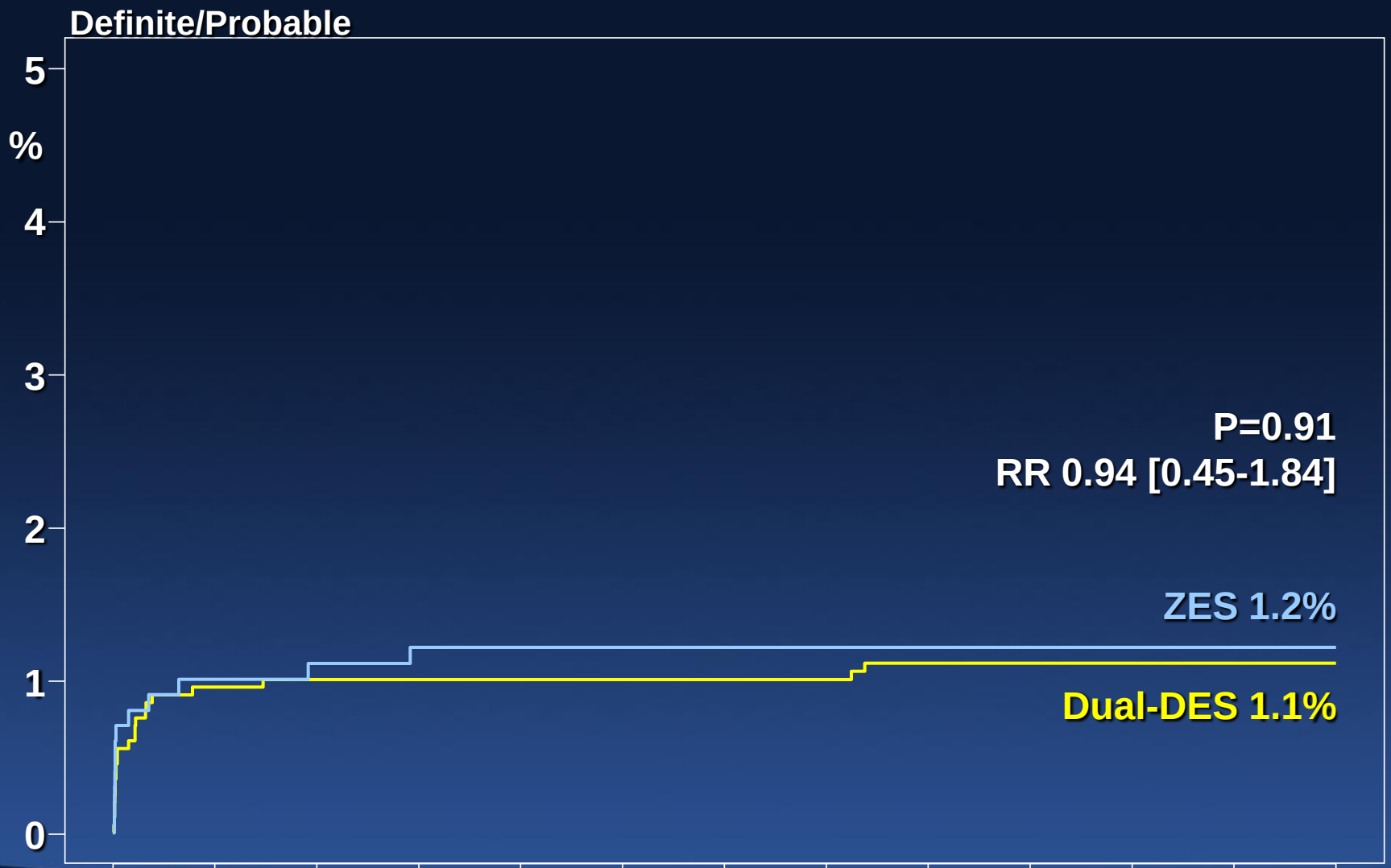
Angiographic characteristics

	Dual-DES n=2912	ZES n=1479
Target vessel, %		
left anterior descending	45	45
left circumflex	24	26
right coronary artery	31	29
Bifurcation, %	27	29
Complex morphology, %	74	74
Lesion length, mm	16.4±9.6	16.9±10.0
Vessel size, mm	2.78±0.50	2.80±0.50

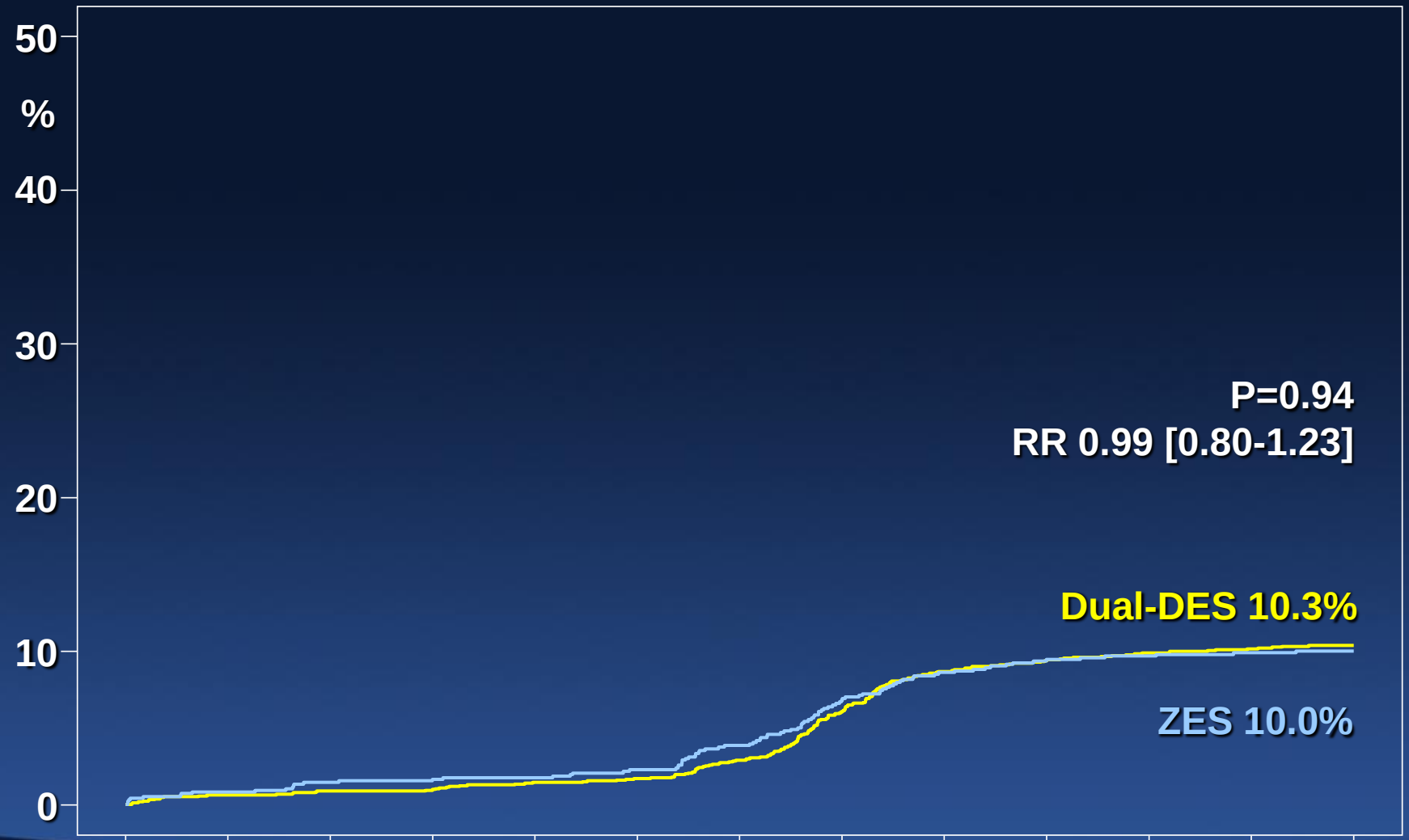
Cardiac Death or MI at 1 Year



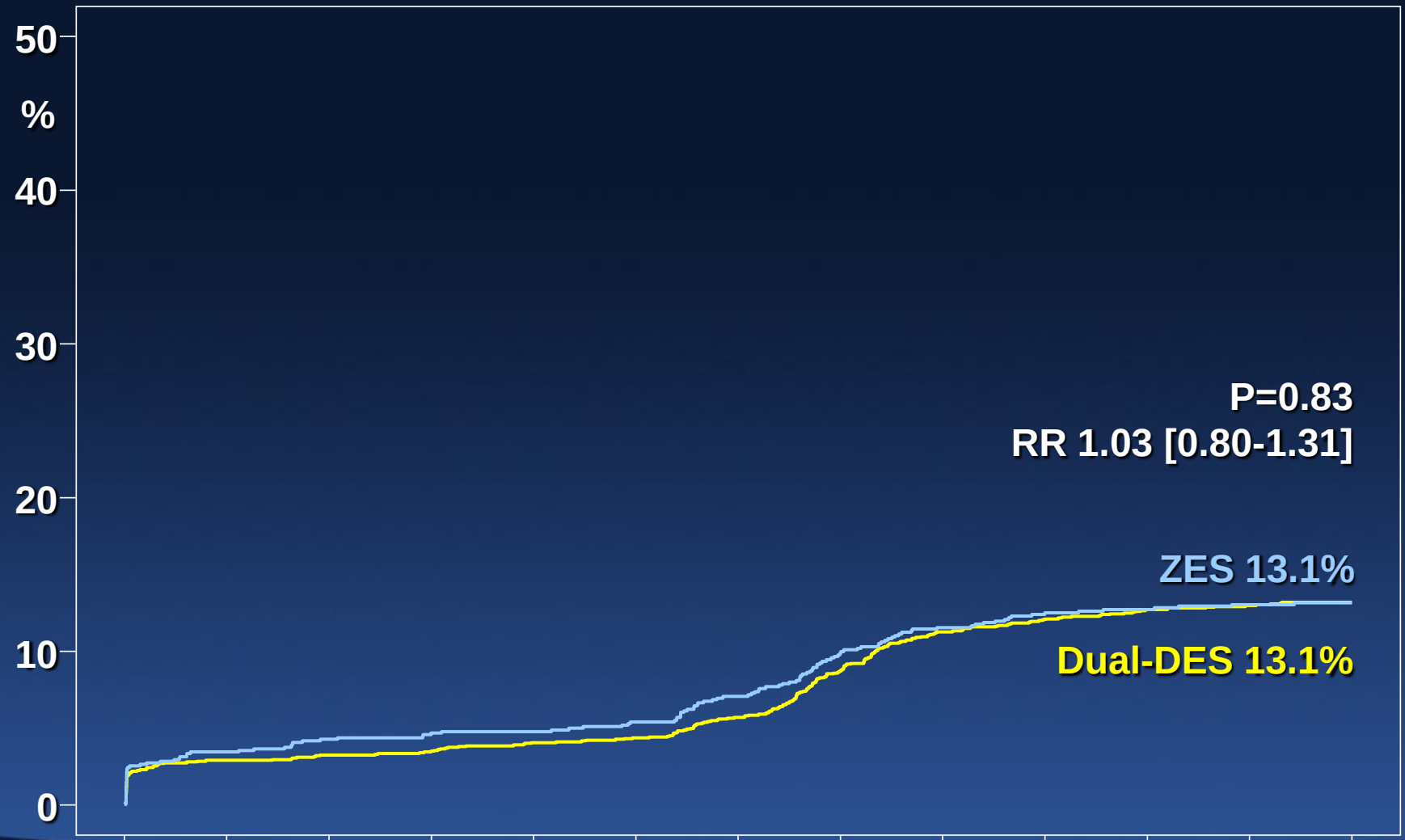
Stent Thrombosis at 1 Year



Target Lesion Revascularization

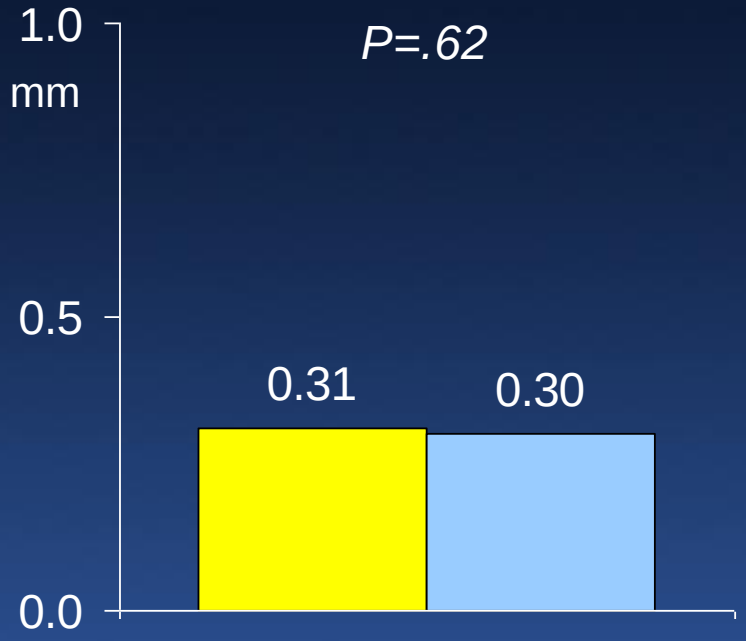


Cardiac Death/TV-related MI/TLR

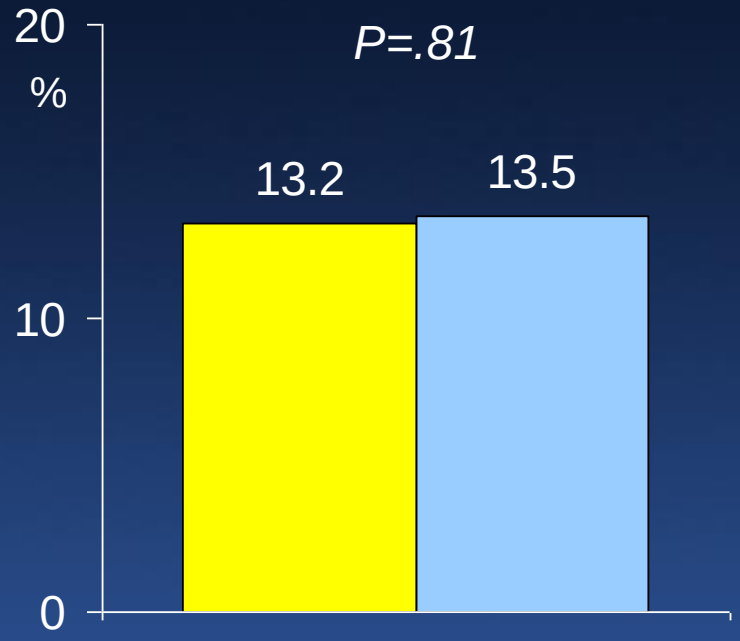


Angiographic Restenosis

In-stent late lumen loss



In-segment binary restenosis



Dual-DES ZES

Summary

Out to 12 months Sirolimus and Probucol-Eluting stent is **non-inferior** to the permanent polymer-based zotarolimus-eluting stent in a large-scale study powered for clinical endpoints.

Their performance was comparable with regard to hard clinical endpoints – stent thrombosis, death or MI – as well as clinical and angiographic parameters of restenosis.