Drug Eluting Stents: Where Are We Going?

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President St. Joseph's Heart and Vascular Institute
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EMORY
UNIVERSITY

TCTAP 2013,
18th ANGIOPLASTY SUMMIT, Seoul, S. Korea
Main Arena, Level 3,
April 25, 4:00 - 4:15 pm

Elizabeth G. Nabel, M.D., and Eugene Braunwald, M.D.

N Engl J Med 2012;366:54-63.

1958 Coronary arteriography developed (Sones)

1962 First beta-blocker developed (Black)

1976 First HMG CoA reductase inhibitor described (Endo)

2009 Left-ventricular assist device as destination therapy in advanced heart failure shown to be effective

1961 Risk factors defined

1969 First description of CABG (Favaloro)

1980 First implantable cardioverter–defibrillator developed (Mirowski)

2007 Benefit of cardiac resynchronization therapy in heart failure demonstrated

2009 Genomewide association in early-onset MI described

1954 First open-heart procedure (Gibbon)

1961 Coronary care unit developed (Julian)

1972 NHBPEP

1985 TIMI 1

2002 Efficacy of drug-eluting vs. bare-metal stents determined

2009 Deep gene sequencing for responsiveness to cardiovascular drugs performed

1979 Coronary angioplasty developed (Grüntzig)

1992 SAVE

1986 GISSI and ISIS-2

1993 Superiority of primary PCI vs. fibrinolysis in acute MI noted

1985 NCEP

2002 ALLHAT

Deaths per 100,000 Population

600
500
400
300
200
100
0

1950
1960
1970
1980
1990
2000
2010
2020

Year

Circulation

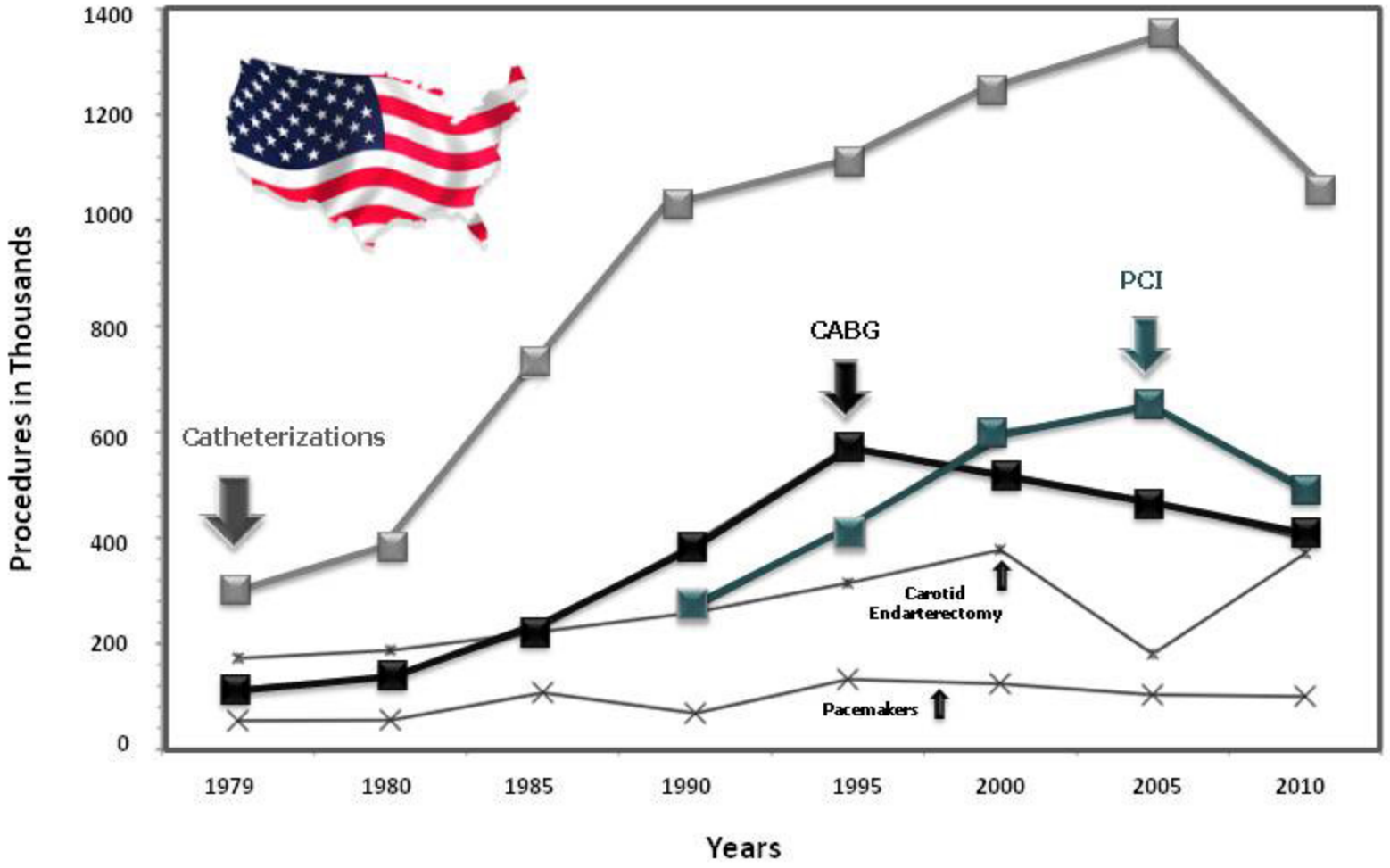
Heart Disease and Stroke Statistics—2013 Update

A Report From the American Heart Association

American Heart Association
Learn and Live

Trends in Cardiovascular Procedures, United States of America: 1979 to 2010

Go AS et al. Circulation 2013;127:e6-e245



What are the major problems with DES?

- **Stent Thrombosis,**

  although reduced with newer generation DES,
  still remains an issue

- **Stent Restenosis,**

  although dramatically reduced with
  newer generation DES still remains an issue,
  especially in complex lesions and specific clinical subsets

Where are we going with-

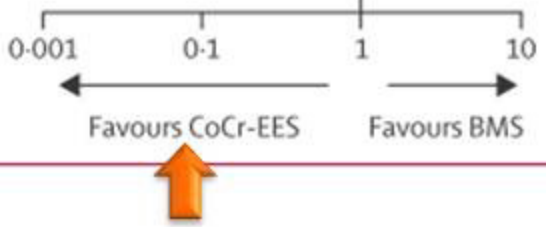
- **Technology**
- **Clinical Application**
- **Industry**

Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis

Lancet 2012; 379: 1393–402

- 49 RCT with > 50.000 pt
- 2nd generation **CoCr EES** emerged as the device with the **lowest rate of ST** compared with BMS or other DES

	log (odds ratio)	SE	Weight	Odds ratio IV, random, 95% CI
(A) Definite thrombosis				
Direct estimate	−1·427	0·519	32·4%	0·24 (0·09–0·66)
Indirect estimate	−1·421	0·359	67·6%	0·24 (0·12–0·49)
Total (95% CI)			**100·00%**	**0·24 (0·14–0·43)**
Test for overall effect Z=4·82 (p<0·00001)				
(B) Definite or probable thrombosis				
Direct estimate	−0·968	0·377	39·4%	0·38 (0·18–0·80)
Indirect estimate	−1·122	0·304	60·6%	0·33 (0·18–0·59)
Total (95% CI)			**100·00%**	**0·35 (0·22–0·55)**
Test for overall effect Z=4·48 (p<0·00001)				



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The risk of ST (ARC criteria) has been reduced but not eliminated…

Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR)

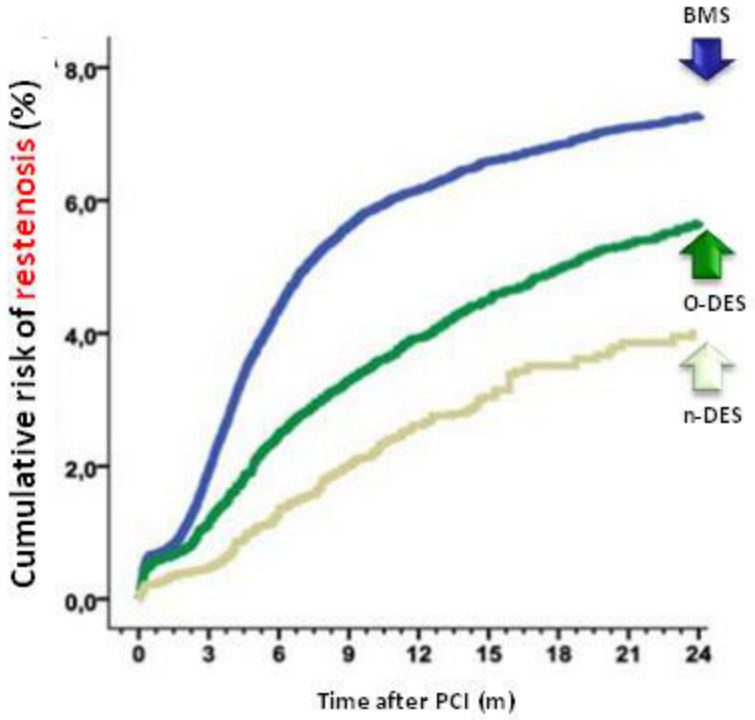
Sarno G. et al. Eur Heart J. 2013;127:e6-e245

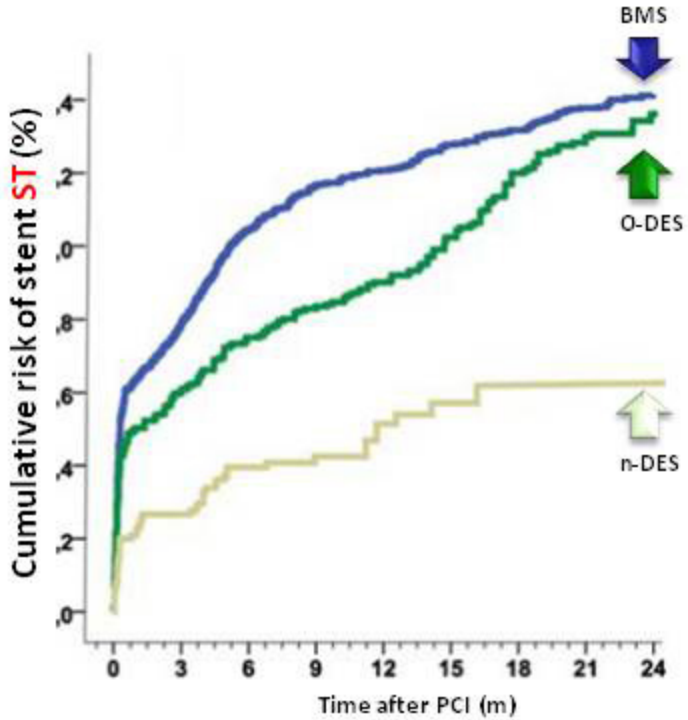
EUROPEAN SOCIETY OF CARDIOLOGY

94.384 stent implantations
BMS: 64.631, **o-DES:** 19.2012, **n-DES:** 10.551

Older generation DES (o-DES):
Cypher and Cypher Select (Cordis Corporation, Miami, FL, USA),
Taxus Express and Taxus Liberte´ (Boston Scientific Corporation)
Endeavor (Medtronic Inc.)

Newer generation DES (n-DES):
Endeavor Resolute (Medtronic Inc.),
XienceV, Xience Prime (Abbott Laboratories)
Promus, Promus Element (Boston Scientific Corporation).





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Endeavor Resolute (Medtronic Inc.),
XienceV, Xience Prime (Abbott Laboratories)
Promus, Promus Element (Boston Scientific Corporation).

PCI with n-DES was associated with:

38% lower risk of clinically meaningful restenosis,

43% lower risk of definite ST,

in this observational study from a large real-world population.

The risk has been reduced but not eliminated…

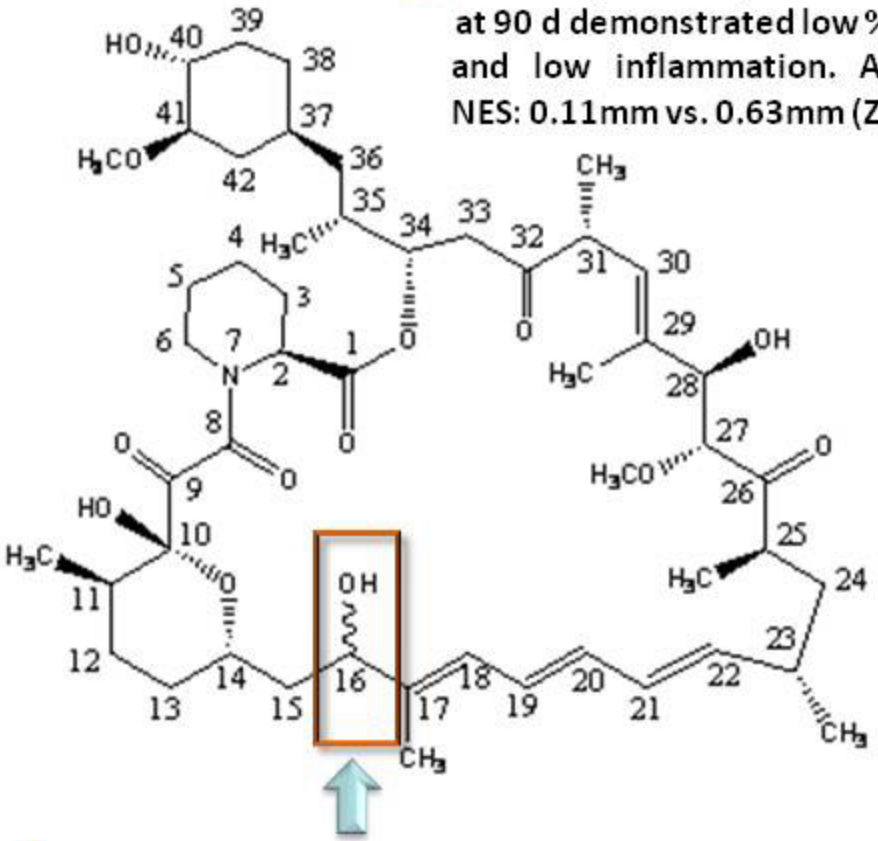
Where are we going with Technology?

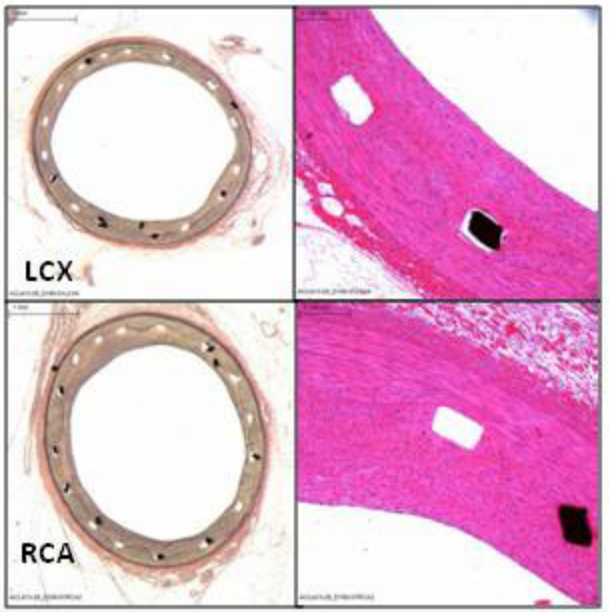
- **Drug**
  - Novel Antiproliferative Drugs
- **Polymer**
  - Bioresorbable polymer
  - Polymer composition
  - No polymer
- **Selective Drug Delivery**
  - Abluminal Coating
- **Alloy**
  - Metallic, Durable
  - Metallic, Bioresorbable
  - Polymeric, Bioresorbable
- **Alloy Design**
  - Longitudinal Integrity
  - Strut Cross Linkage
- **Strut Design and Thickness**
  - Open/Closed cells
  - Hybrid cells
  - Thinner struts
  - Mesh covered struts
- **Dedicated Stents**
  - Bifurcation stenting

A randomised comparison of novolimus-eluting and zotarolimus-eluting coronary stents: 9-month follow-up results of the EXCELLA II study

Serruys PW. et al. EuroIntervention. 2010; 6; 195-205

2. Histomorphometry and histopathology at 90 d demonstrated low % area stenosis and low inflammation. Angiographic LLL NES: 0.11mm vs. 0.63mm (ZES) ($p<0.0001$)





DESyne Novolimus Eluting Stent (Elixir), crimped CoCr platform, strut thickness: 80µm

1. **Modification that aims to create a drug with similar efficacy to current agents with a lower dose and polymer load.**

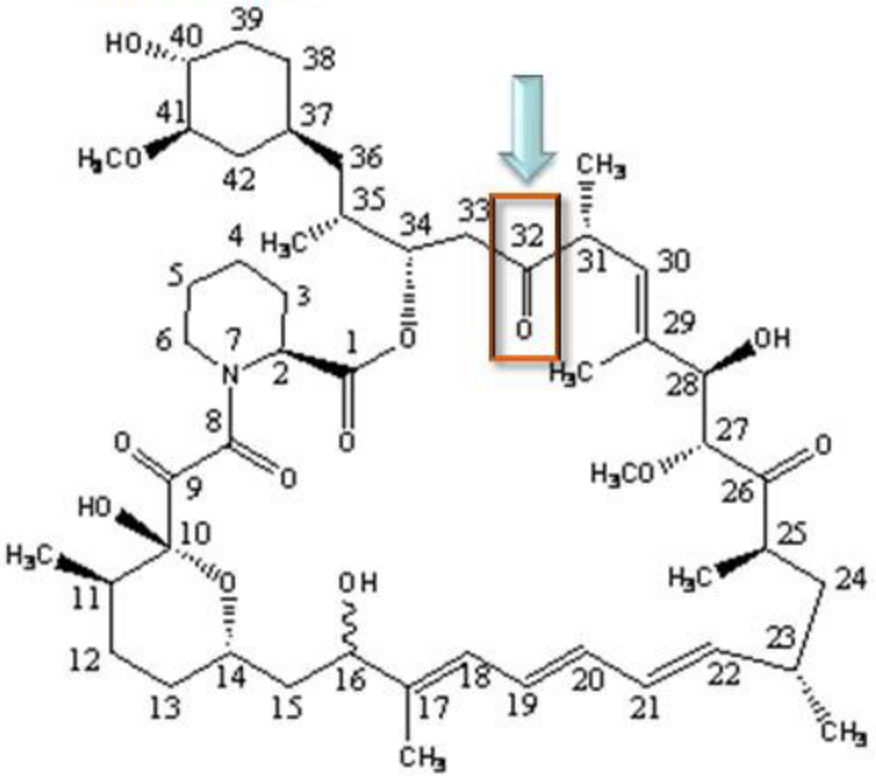
The purified durable methacrylate polymer controls the elution of Novolimus (a sirolimus analogue), which is produced via removal of a methyl-group from C16, as opposed to modification of C40 on the macrocyclic ring.

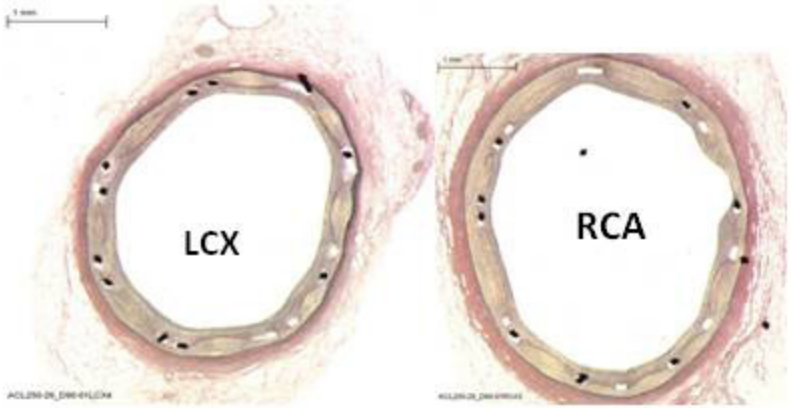
Novel Antiprolif. Drugs

Multi-center first-in-man study with the lowest known limus dose on the Elixir medical Myolimus™ eluting coronary stent system with a durable polymer: 12-month clinical and six month angiographic and IVUS follow-up

Rutsch W. et al. EuroPCR , abstract, 2010

1. **Modification that aims to create a drug with similar efficacy to current agents but requires a lower dose and polymer load.**
   The polylactide polymer coating controls the elution of Myolimus which is produced via removal of an oxygen from C32, as opposed to modification of C40 on the macrocyclic ring.





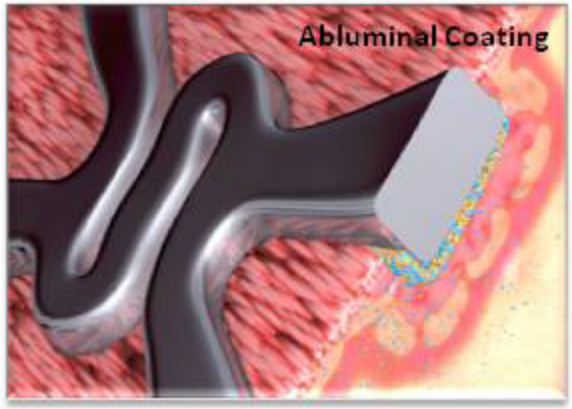
2. Histomorphometry and histopathology at 90 days demonstrated safety: Low % area stenosis & Low inflammation

3. LLL by quantitative coronary angiography (QCA) at 6m was 0.15±0.11mm; IVUS % neointimal volume was 1.4±1.2mm^3
   (Comparable to conventional DES)

Novel Antiprolif. Drugs

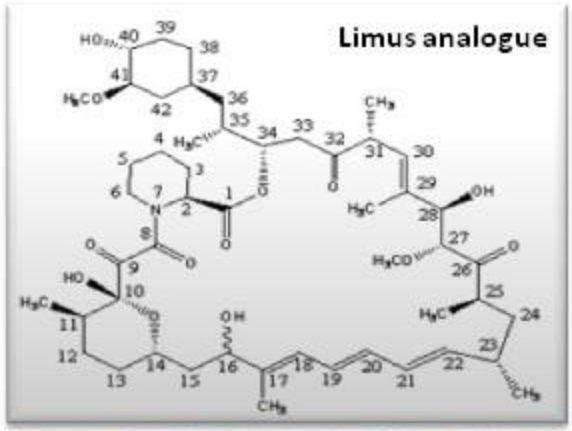
Biodegradable Polymer DES

BioMatrix® stent (Biosensor)



Biodegradable Coating

- Abluminal Coating
- Controlled Biodegradability
- Precise Drug Release Kinetics
- Simultaneous Polymer Degradation and Drug Release



Biolimus A9™ (rapamycin derivative)

- A Potent New "Limus" Designed for Stent Applications
- Powerful anti-proliferative and anti-inflammatory properties
- Prevents Smooth Muscle Cell Proliferation
- Highly Lipophilic with Optimal Local Tissue Uptake

Bio degradable Polymer

Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial

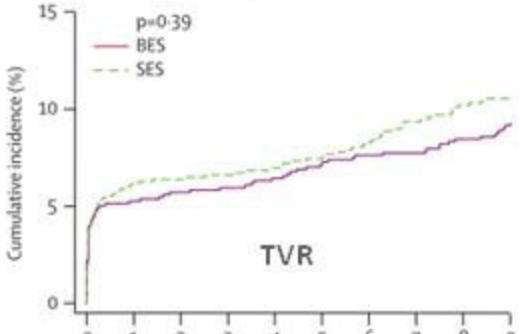
Windecker S. et al. Lancet 2008; 372:1163–73

ELSEVIER

Interpretation Our results suggest that a stent eluting biolimus from a biodegradable polymer represents a safe and effective alternative to a stent eluting sirolimus from a durable polymer in patients with chronic stable coronary artery disease or acute coronary syndromes.

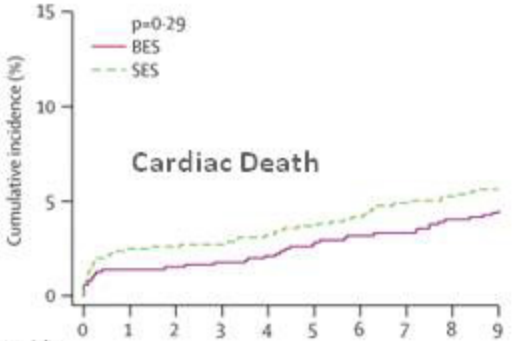
All p-values for superiority

A



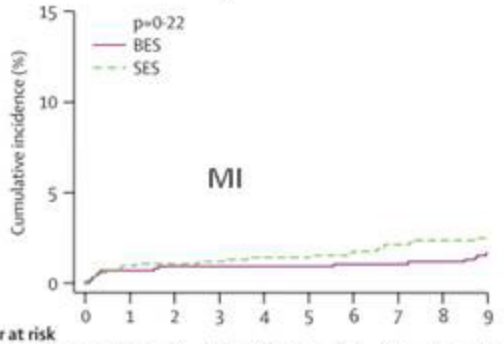
Number at risk

BES	857	806	798	796	792	784	779	777	771	761
SES	850	791	786	784	781	777	771	758	751	746



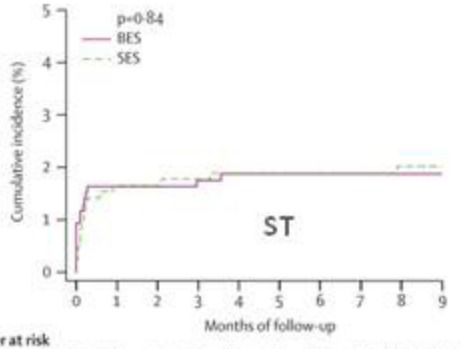
Number at risk

BES	857	835	827	825	822	814	808	806	800	791
SES	850	815	810	808	804	800	794	781	776	770



Number at risk

BES	857	845	838	838	838	835	831	830	829	821
SES	850	835	831	830	828	828	826	819	817	813



Number at risk

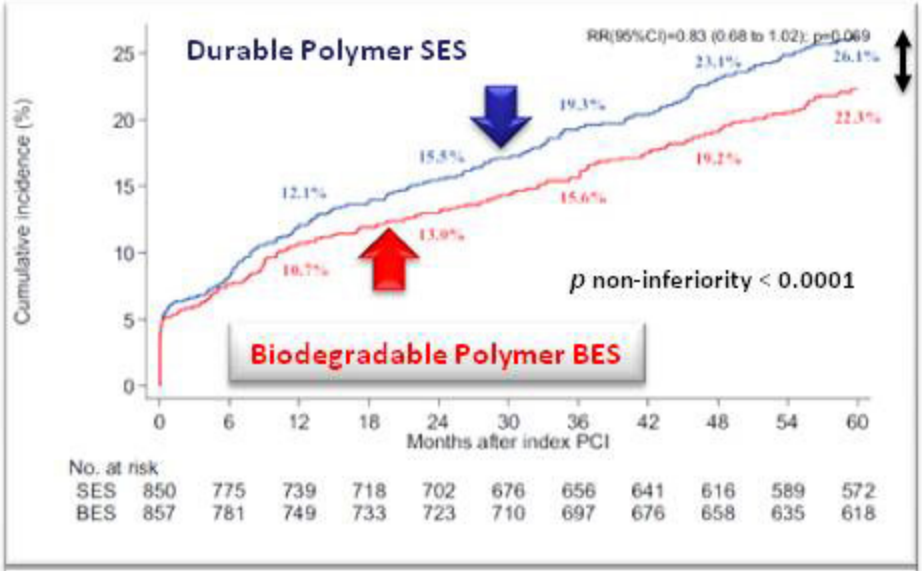
BES	857	833	826	825	824	821	818	817	816	808
SES	850	822	818	816	815	815	813	806	803	799

	Biolimus-eluting stent	Sirolimus-eluting stent	Difference	
			Estimate (95% CI)	p value
Late loss (mm)‡				
In-stent	0·13 (0·46)	0·19 (0·50)	−0·05 (−0·14 to 0·05)	0·34
In-segment	0·08 (0·45)	0·15 (0·46)	−0·07 (−0·16 to 0·02)	0·12
Binary restenosis				
In-stent	14/253 (5·5%)	20/231 (8·7%)	3·2 (−1·7 to 7·9)	0·20
In-segment	17/253 (6·7%)	25/231 (10·8%)	4·1 (−1·5 to 9·7)	0·15

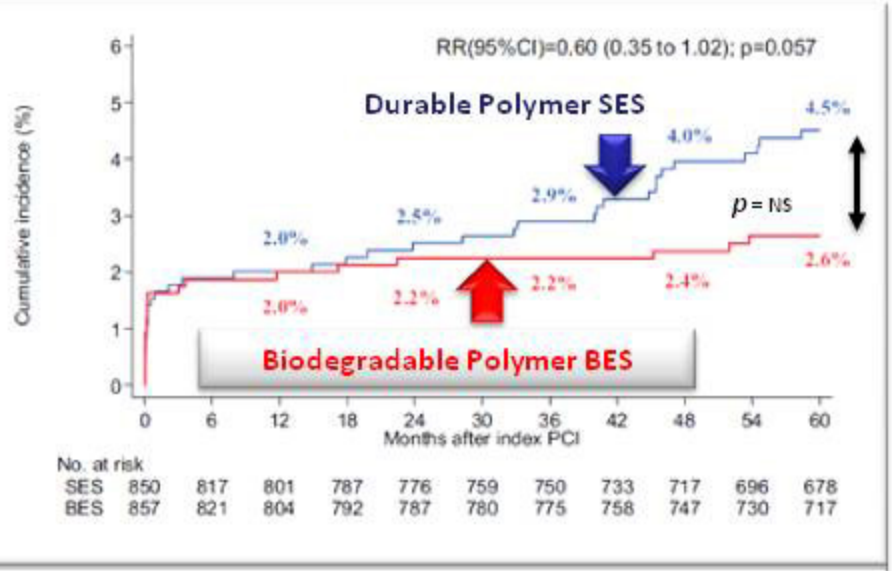
Final 5-year report of the Limus Eluted From A Durable Versus ERodabale Stent Coating (LEADERS) randomised, non-inferiority trial

Serruys PW. et al. JACC Cardiovasc. Interv. 2013, in press

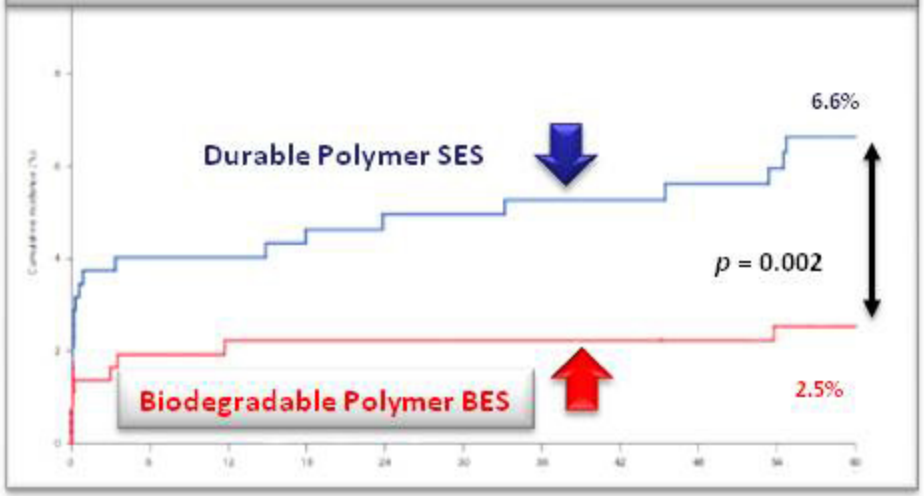
All cause Death, any MI, all cause revascularisation



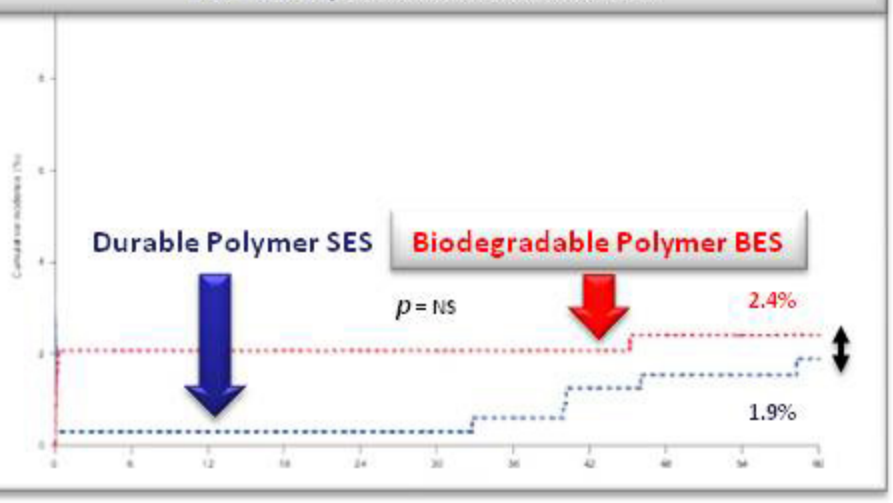
Definite Stent Thrombosis (ST) (ARC criteria)



Definite ST/ High SYNTAX Score > 12



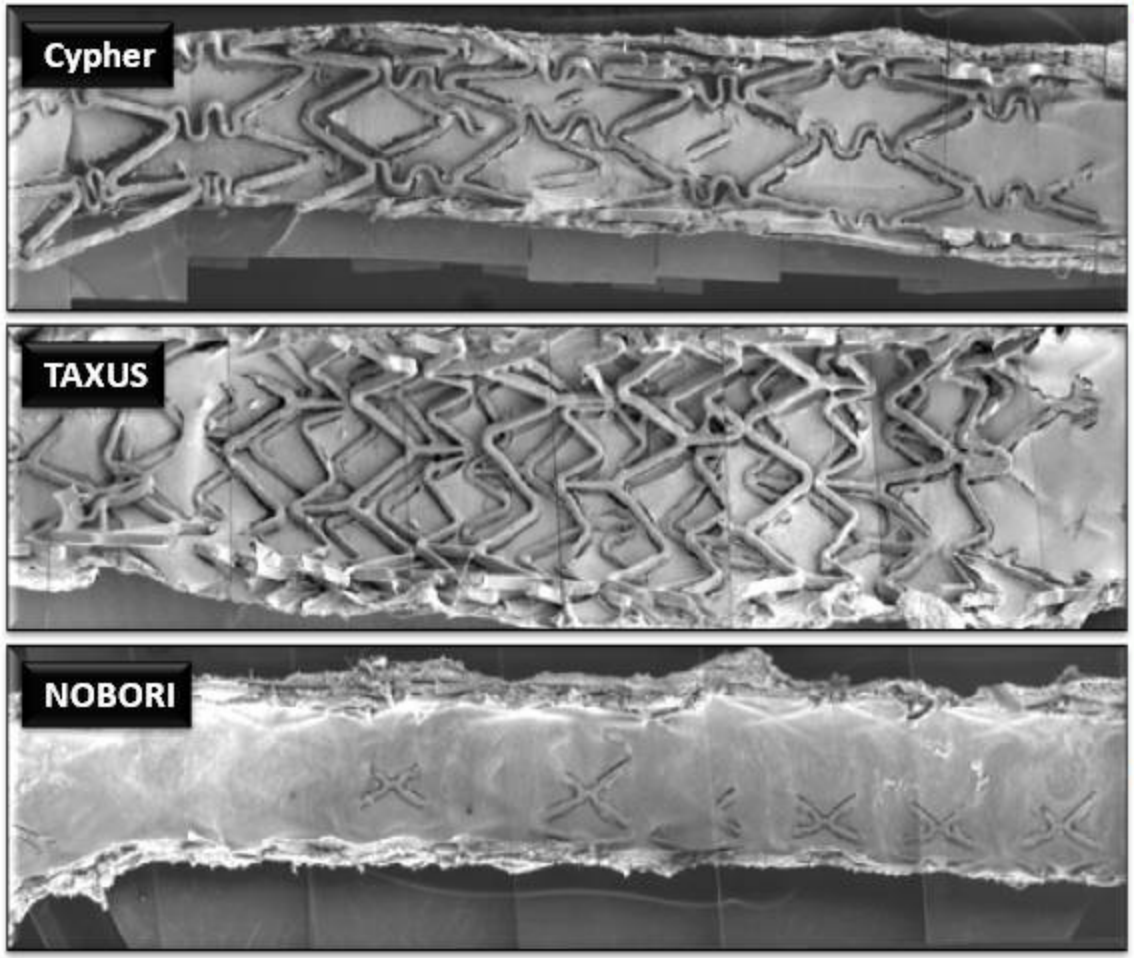
Definite ST/ Low SYNTAX Score <12

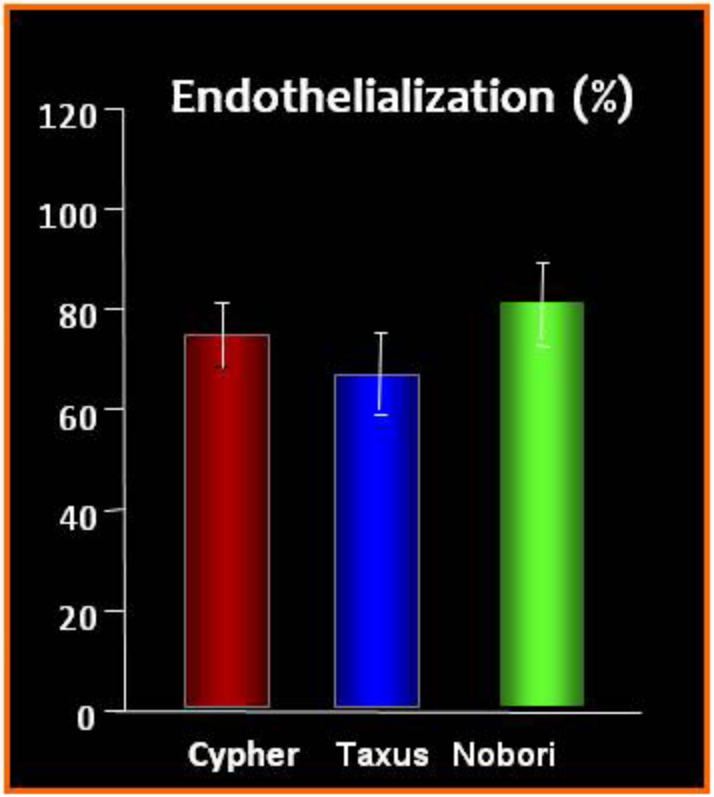


Biodegradable Polymer DES

Nobori® stent (TERUMO)

Comparison of Various overlapped DES in Rabbit Iliac Arteries at 28-days





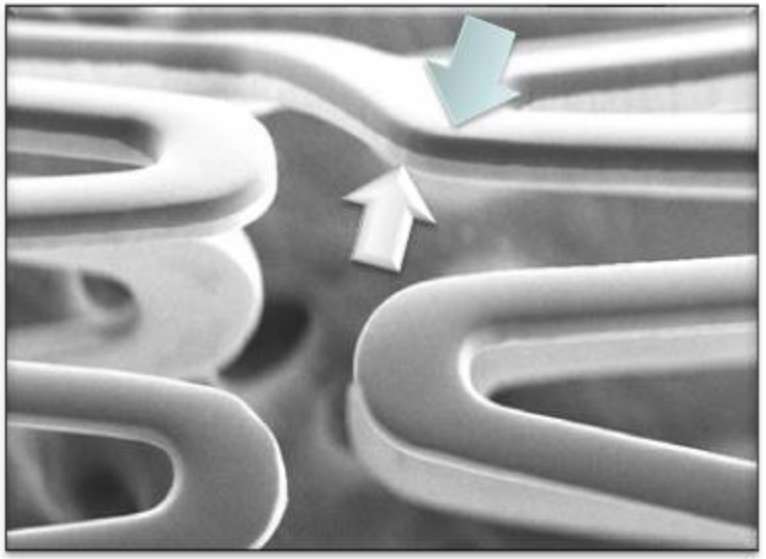
Finn A, et al. Circulation 2005

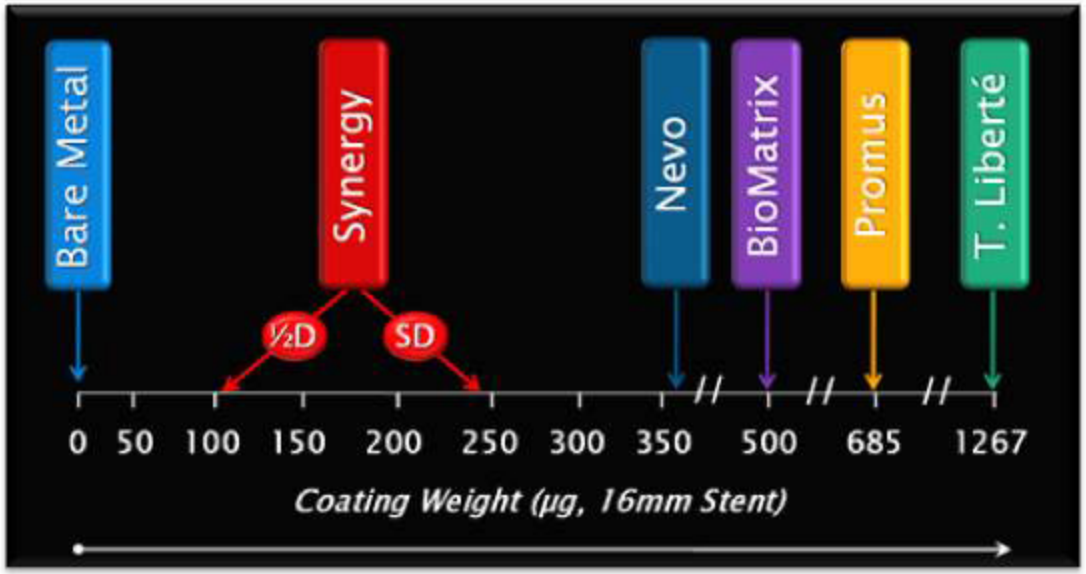
Biodegradable Ultrathin Polymer DES

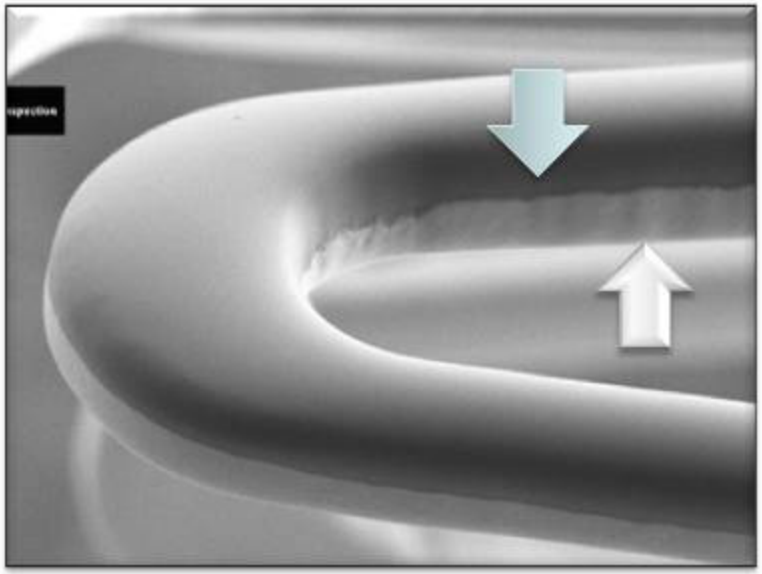
Synergy® stent (Boston Scientific)

- Bioerodable polymer is only applied at the abluminal surface of the stent
- Maximum coating thickness 3µm (low dose) and 4µm (high dose)

(Ultrathin coating)





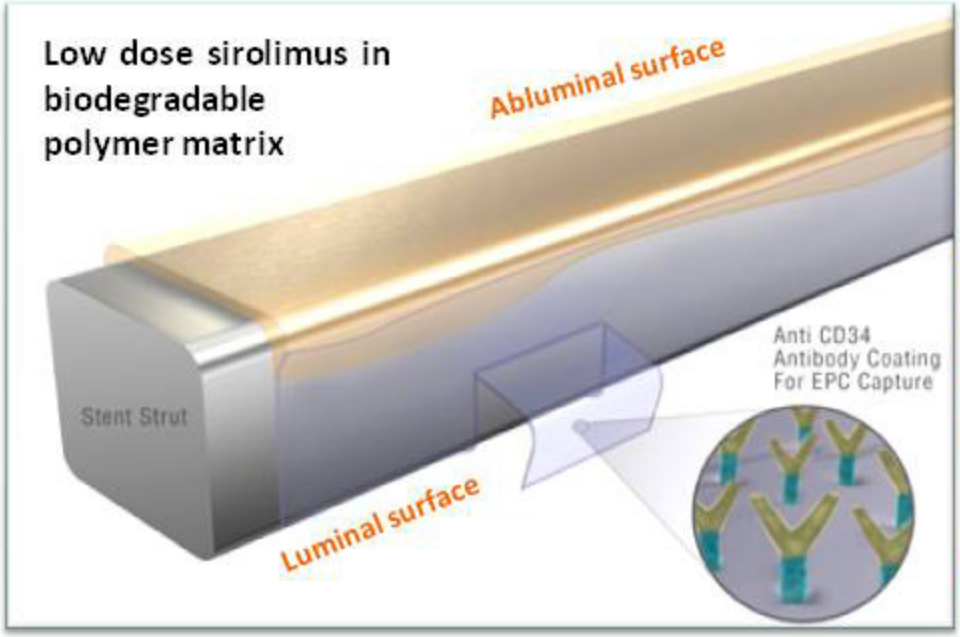


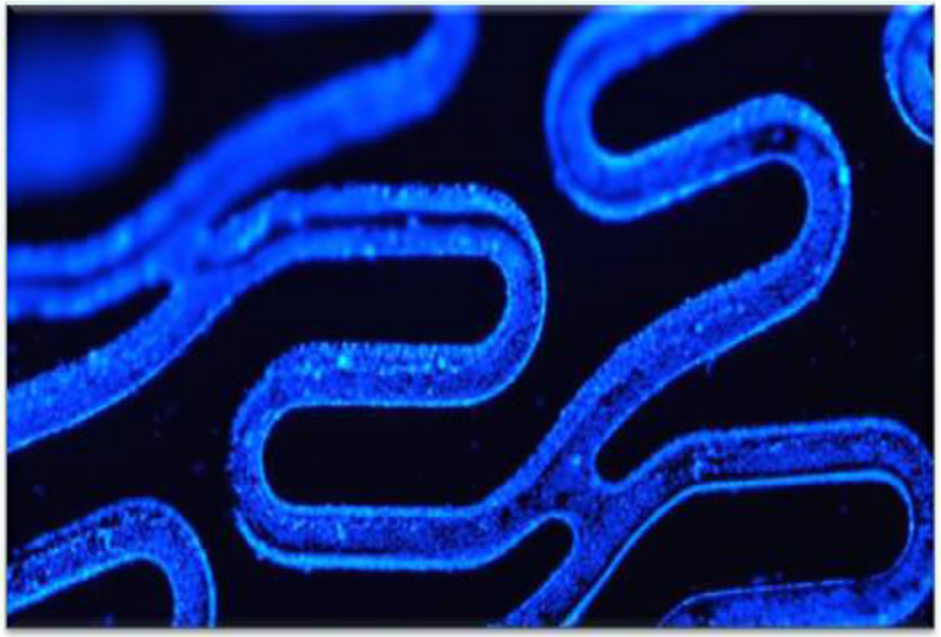
Selective Drug Delivery

Combo ® stent (Orbus Neich)

Rapamycin (5 µg/mm) applied in biodegradable SynBiosys polymer on the abluminal side

Anti-CD34 surface to promote healing through rapid stent endothelialization.

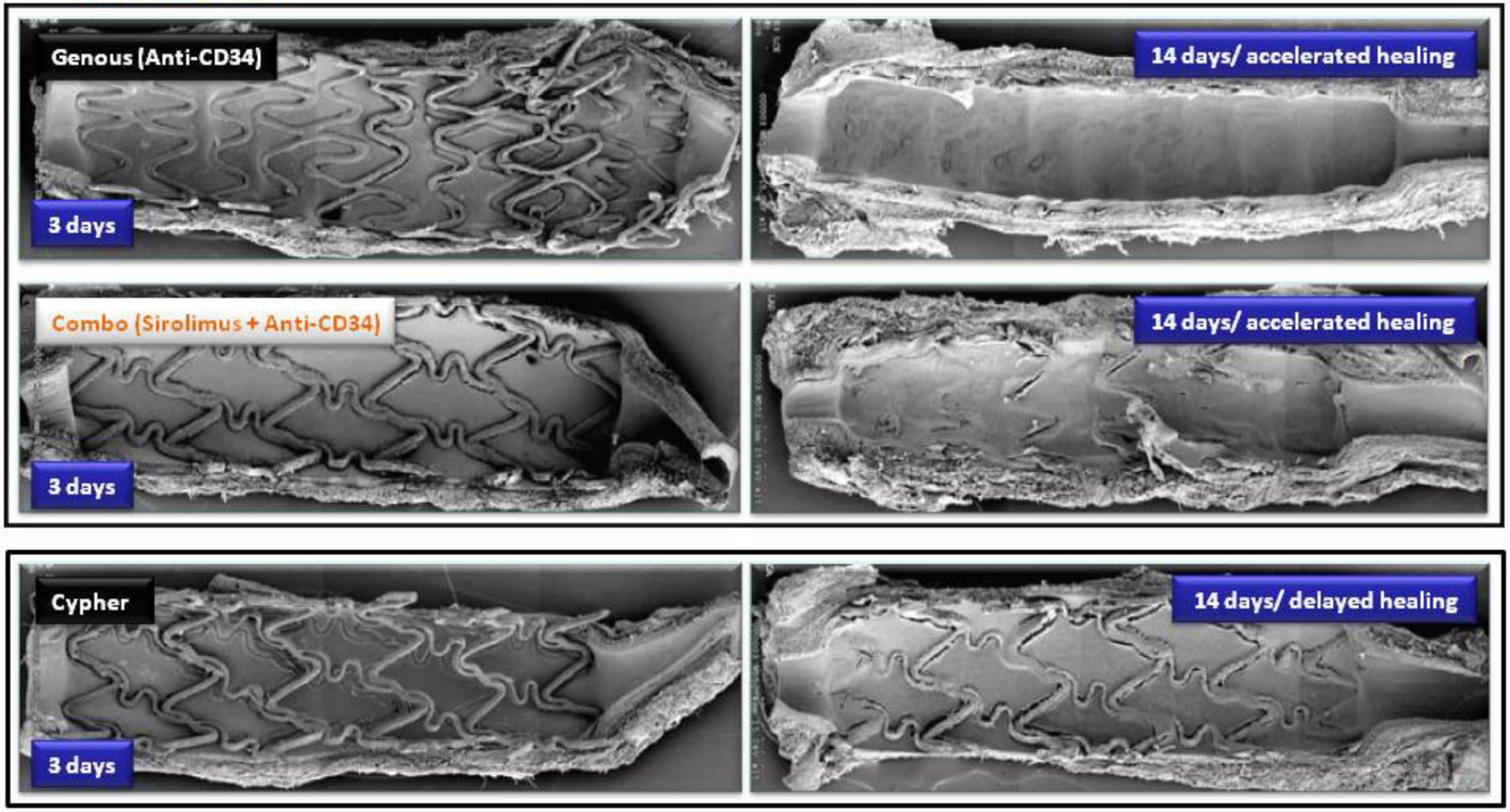




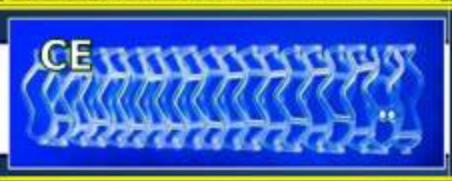
Development of a Novel Prohealing Stent Designed to Deliver Sirolimus From a Biodegradable Abluminal Matrix

American Heart Association
Learn and Live

Both optical coherence tomography and histology demonstrate that **Combo stents (anti-CD34 sirolimus-eluting stents)** promote endothelialization while reducing neointimal formation and inflammation.



Bioresorbable Metallic DES & Bioresorbable Polymeric Scaffolds

Company / Device	Design of the biorsorbable device	Strut thickness, (μ m)	Polymer / Drug	Absorption time	Late loss, (mm)
Kyoto Medical/ Igaki-Tamai		170	PLLA	2 years (y)	0.48 (6 m)
Biotronik / DREAMS		125	Mg alloy (AMS-4) / sirolimus	4 to 6 months (m)	0.68 (6 m)
Abbott / ABSORB BVS*		150	PLLA/ everolimus	2 y	0.19 (6 m)
Reva Medical / ReSolve		200	Tyrosine poly carbonate with iodine / sirolimus abluminal	2 y	1.81 (6 m)
-/ BTI		200	Salicylic acid into polymer (PLA or adipic acid)/ sirolimus	6 m	NA
Elixir / DESolve		150	PLLA/ novolimus	1 to 2 y	0.19 (6m)

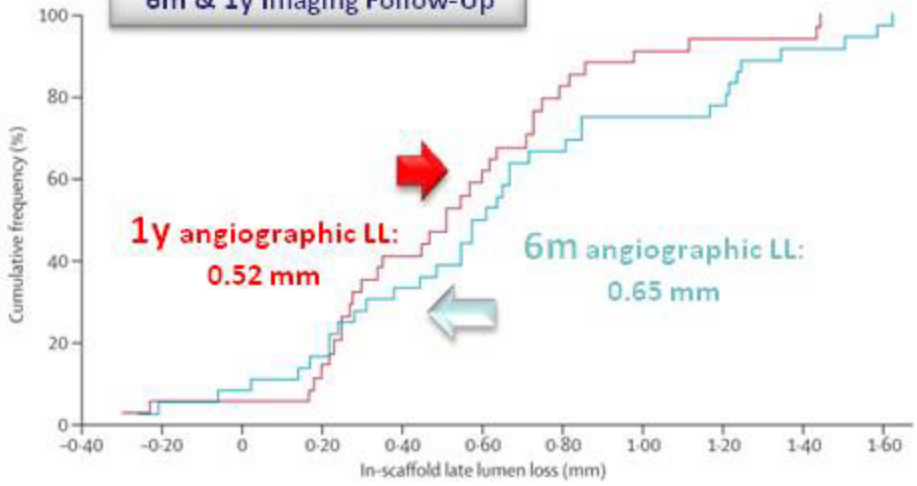
Gogas BD. et al. HJC 2012

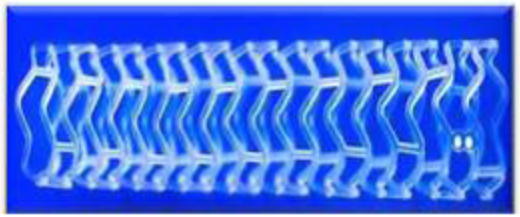
Bioresorbable Metallic DES & Bioresorbable Polymeric Scaffolds

Safety and performance of the drug-eluting absorbable metal scaffold (DREAMS) in patients with de-novo coronary lesions: 12 month results of the prospective, multicentre, first-in-man BIOSOLVE-I trial

Haude M. et al. Lancet. 2013, Jan 14 [Epub ahead of print]

6m & 1y Imaging Follow-Up





First Serial Assessment at 6 Months and 2 Years of the Second Generation of Absorb Everolimus-Eluting Bioresorbable Vascular Scaffold

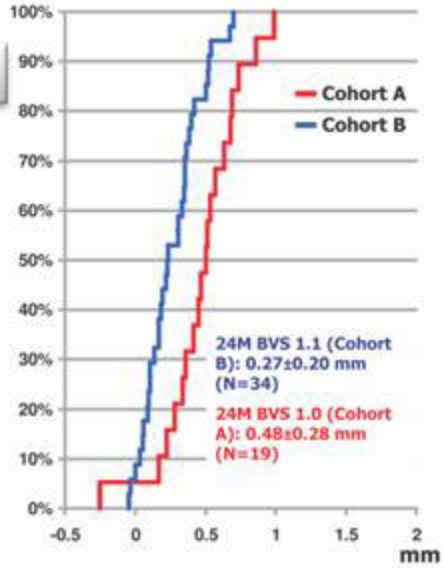
A Multi-Imaging Modality Study

Ormiston J. et al. Circ Cardiovasc Interv. 2012; 5: 620-632

2y Imaging Follow-Up

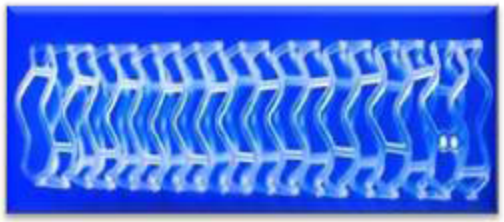
2y angiographic LL:
0.27 mm

(with the 2nd generation BVS, BVS 1.1)



Interpretation Our results show feasibility, a good safety profile, and promising clinical and angiographic performance results up to 12 months for DREAMS. Our promising clinical results show that absorbable metal scaffolds might be an alternative to polymeric absorbable scaffolds.

Bioresorbable Metallic DES & Bioresorbable Polymeric Scaffolds



Will bioresorbable scaffolds be as good as metal for scaffolding complex and calcified lesions ?

Will they be suitable for bifurcation lesions ?

Will thick struts present problems ?

Will preemptive stenting of "vulnerable" but non obstructive plaques occur ?

Will improvements in medical therapy trump invasive prevention in trials ?

Can bioresorbable technology become cost competitive with low cost DES ?

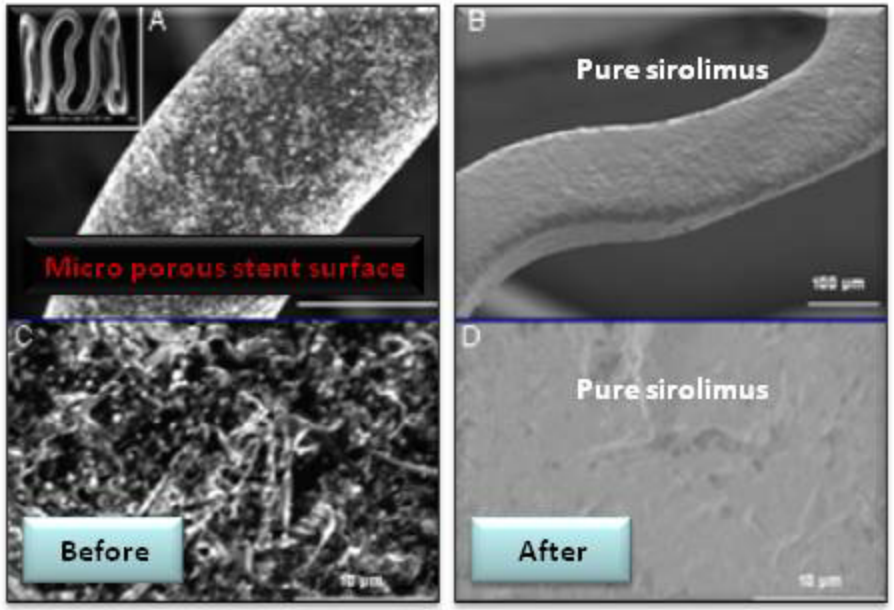
CATHETERIZATION & CARDIOVASCULAR INTERVENTIONS

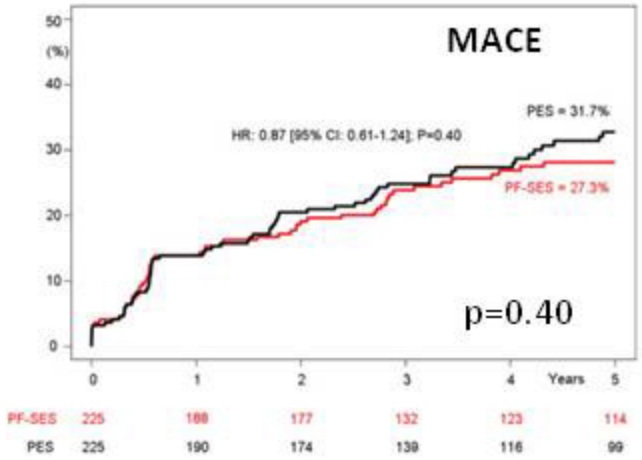
Polymer free (PF) DES
YUKON CHOICE® stent (Translumina)

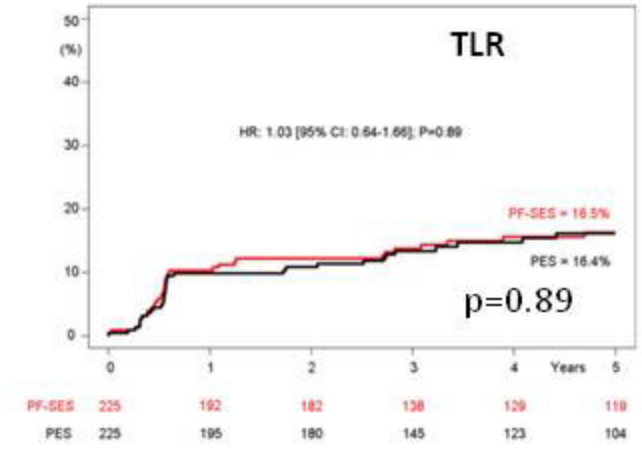
SCAI

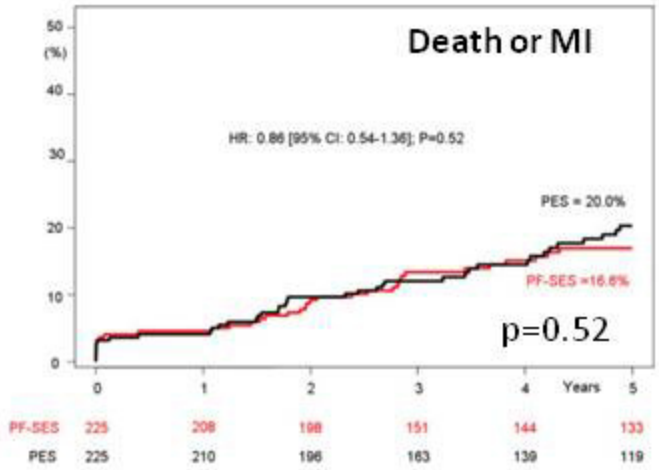
Five-Year Clinical Outcomes of a Polymer-Free Sirolimus-Eluting Stent Versus a Permanent Polymer Paclitaxel-Eluting Stent: Final Results of the Intracoronary Stenting and Angiographic Restenosis – Test Equivalence Between Two Drug-Eluting Stents (ISAR-TEST) Trial

King L. et al. Cath Card Interv. 2013, E 23-28









Overall there was no signif. difference in clinical outcomes between PF SES and PES at 5 years.

This supports the durability and efficacy of PF DES.

Reducing strut thickness… What have we achieved?

2013 → 2000

Mitsu	BioMime	XIENCE PRIME	ENDEAVOR RESOLUTE	TAXUS Liberte	CYPHER
					
Strut Thickness:	Strut Thickness:	Strut Thickness:	Strut Thickness:	Strut Thickness:	Strut Thickness:
40 µm	65 µm	81 µm	91 µm	97 µm	**140 µm**
Alloy:	Alloy:	Alloy:	Alloy:	Alloy:	Alloy:
Cobalt Chromium	Cobalt Chromium	Cobalt Chromium	Cobalt Nickel	316L Stainless Steel	316L Stainless Steel
Polymer Thickness:	Polymer Thickness:	Polymer Thickness:	Polymer Thickness:	Polymer Thickness:	Polymer Thickness:
< 2 µm	2 µm	7.8 µm	6.2 µm	17.8 µm	12.6 µm

MERIL LIFE SCIENCES

MERIL LIFE SCIENCES | Abbott A Promise for Life | Medtronic When Life Depends on Medical Technology | Boston Scientific Delivering what's next. | Johnson & Johnson

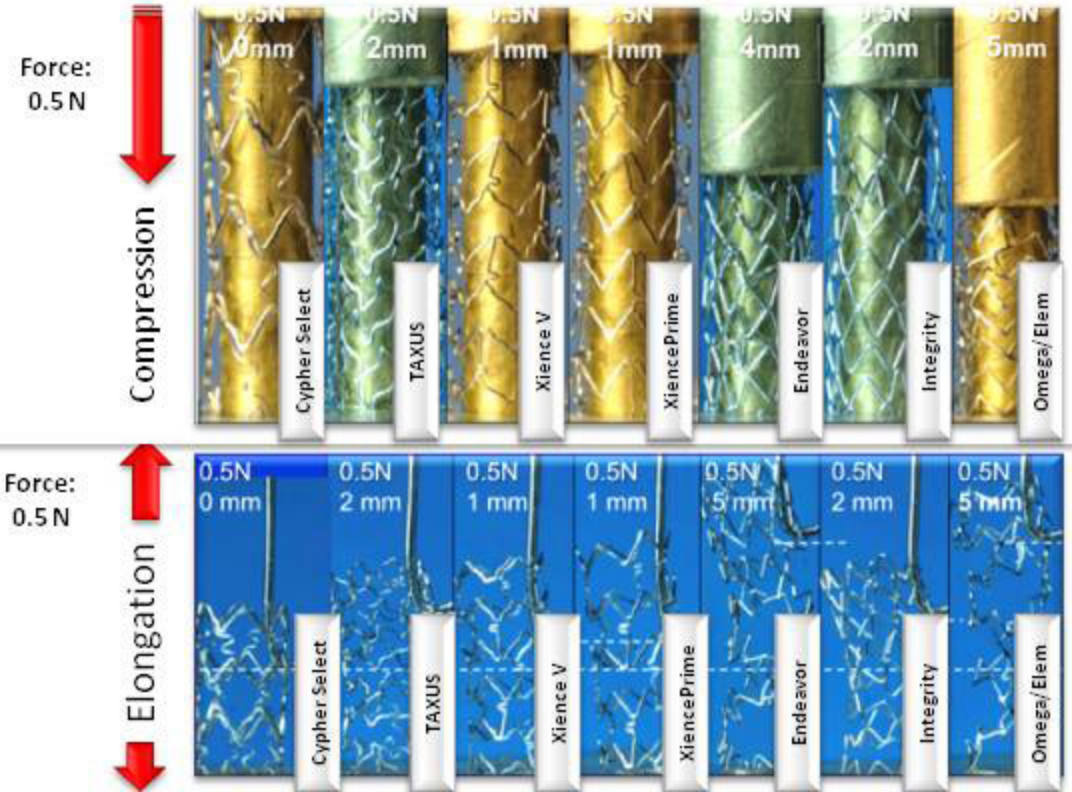
Alloy Design,
Importance of Strut Cross Linkage

Stent Longitudinal Integrity

Ormiston J. et al. JACC Cardiovasc Interv. 2011; 4(12):1310-7

Stents with **2 connectors** between hoops have **less longitudinal strength** when exposed to **compressing or elongating forces** than those with more connectors

Cypher Select was not compressed and appeared to have the greatest longitudinal stability



Alloy Design,
Thinner Struts

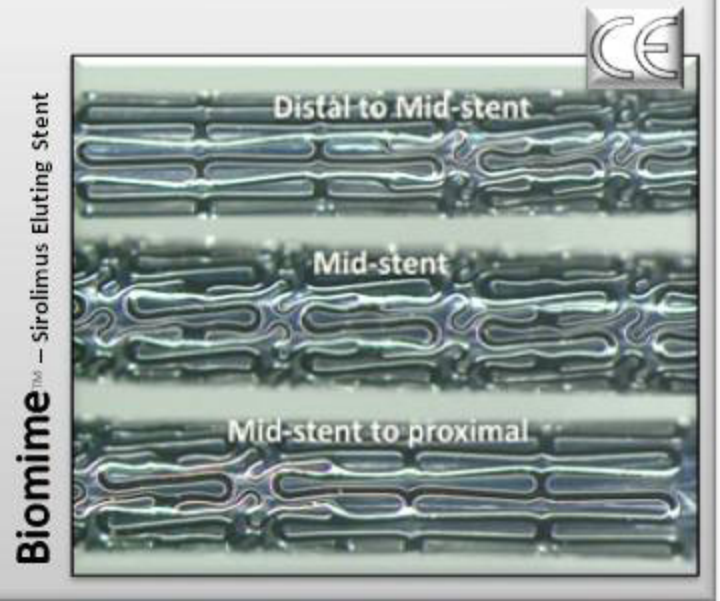
Not commercially available yet

Closed cells at the edges

Open cells in the middle parts of the stent

MERIL Life Sciences

Hybrid Design



Where are we going with Clinical Application?

Stent Utilization in stable CAD

- Influence of guidelines recommending OMT, FAME I suggesting that stents be limited
- Influence of FAME II suggesting that stenting improves outcomes

Stenting or CABG?

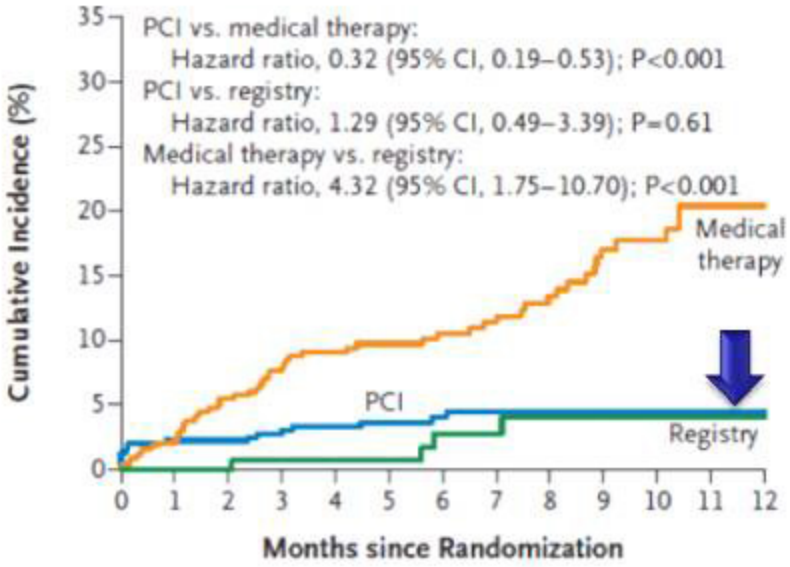
- Influence of SYNTAX Score in treating LM or MV disease
- Influence of FREEDOM trial in treating DM + Multivessel (Better with CABG, but is it for all?)

Fractional Flow Reserve–Guided PCI versus Medical Therapy in Stable Coronary Disease

Bernard De Bruyne, N Engl J Med 2012;367:991-1001.

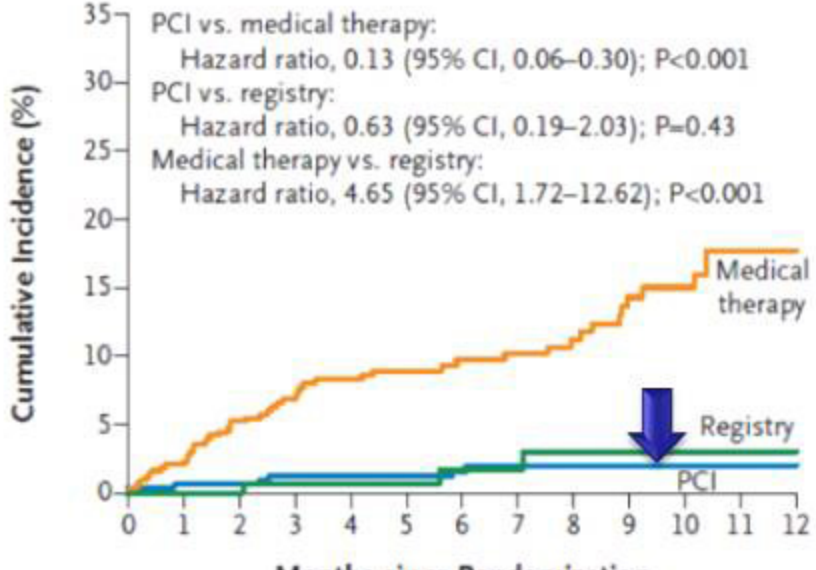
In patients with stable CAD and functionally significant stenoses, FFR guided PCI + OMT as compared with OMT alone decreased the need for urgent revascularization

Primary Endpoint: Death, MI or Urgent Revascularization



No. at Risk													
Medical therapy	441	414	370	322	283	253	220	192	162	127	100	70	37
PCI	447	414	388	351	308	277	243	212	175	155	117	92	53
Registry	166	156	145	133	117	106	93	74	64	52	41	25	13

Urgent Revascularization



No. at Risk													
Medical therapy	441	414	371	325	286	256	223	195	164	129	101	71	38
PCI	447	421	395	356	315	285	248	217	180	160	119	93	53
Registry	166	156	145	133	117	106	94	75	65	53	42	26	13

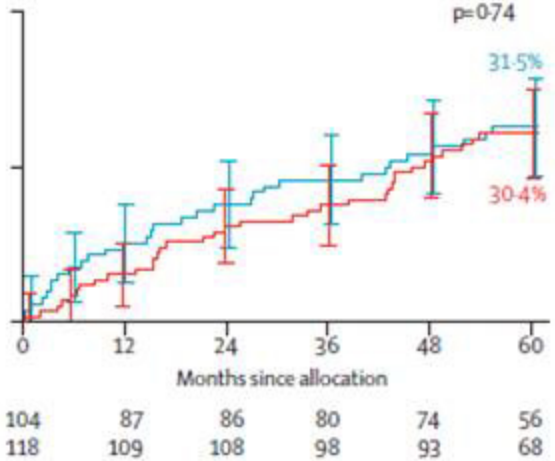
1. The % of patients who had a primary endpoint event was: 4.3% (PCI) vs. 12.7% (OMT), (p<0.001)
2. This difference was driven by a lower rate of urgent revascularization in the PCI (1.6%) vs. the OMT (11.1%), (p<0.001)

Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial

Friedrich W Mohr, Lancet 2013; 381: 629–38

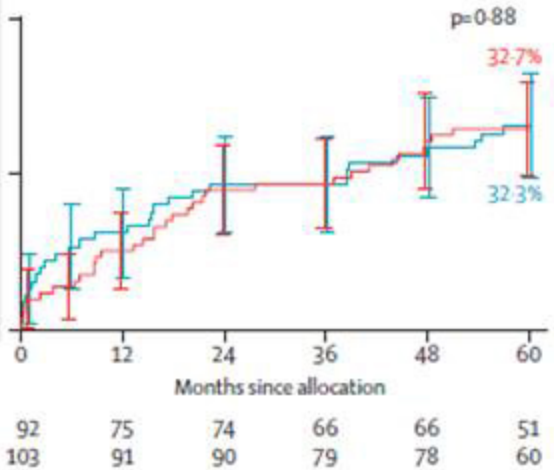
Left Main subgroup

Low SX: 0-22

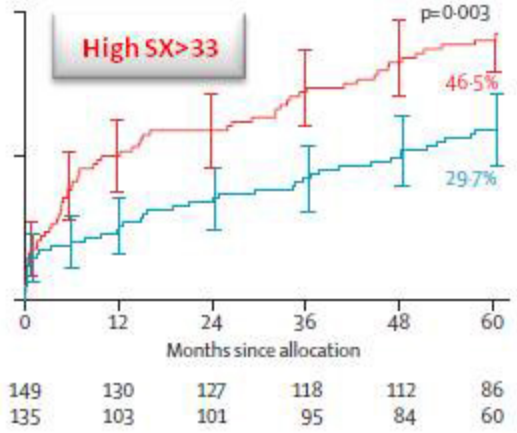


PCI acceptable alternative to CABG in patients with Low or Intermediate SX scores.

Intermediate SX: 23-32



High SX>33



CABG remains the standard of care for patients with High SX scores.

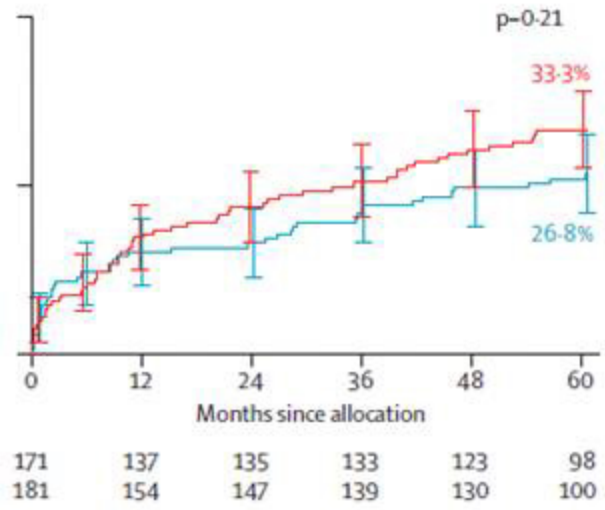
Left Main Coronary Stenting Crossing the Rubicon?

Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial

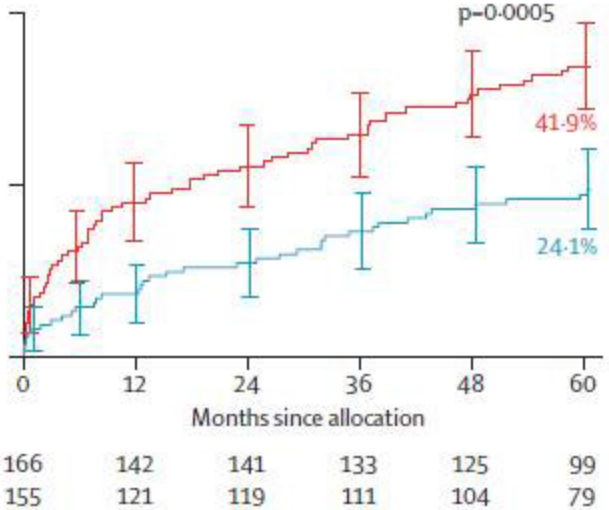
Friedrich W Mohr, *Lancet* 2013; 381: 629–38

MV subgroup

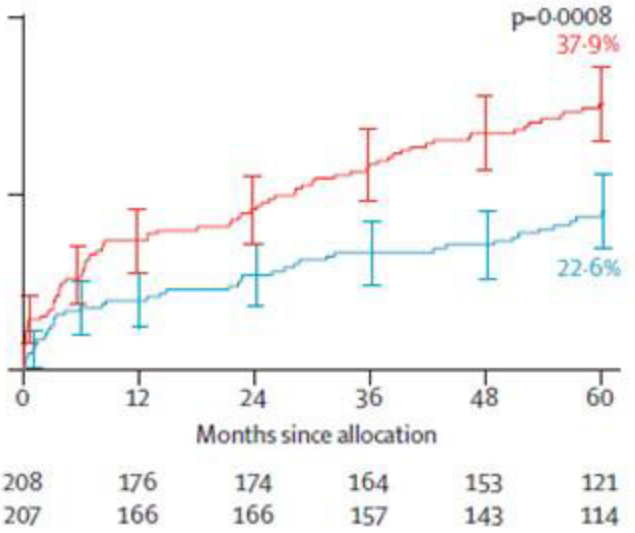
Low SX: 0-22



Intermediate SX: 23-32



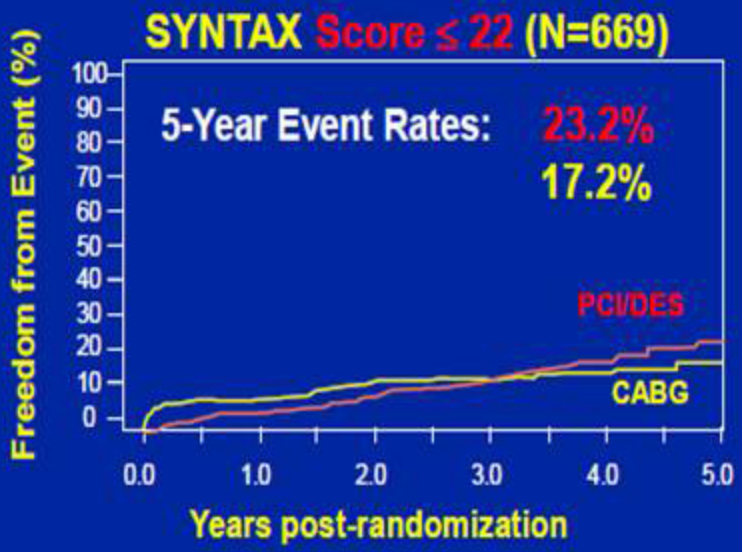
High SX: > 33

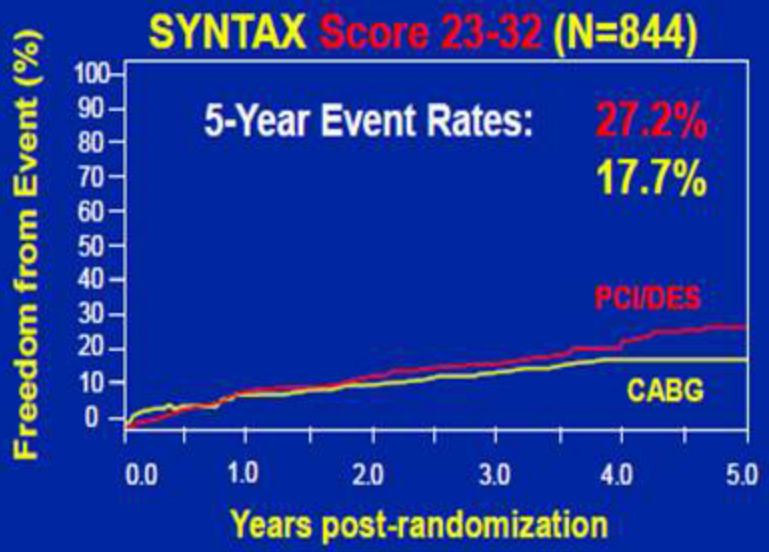


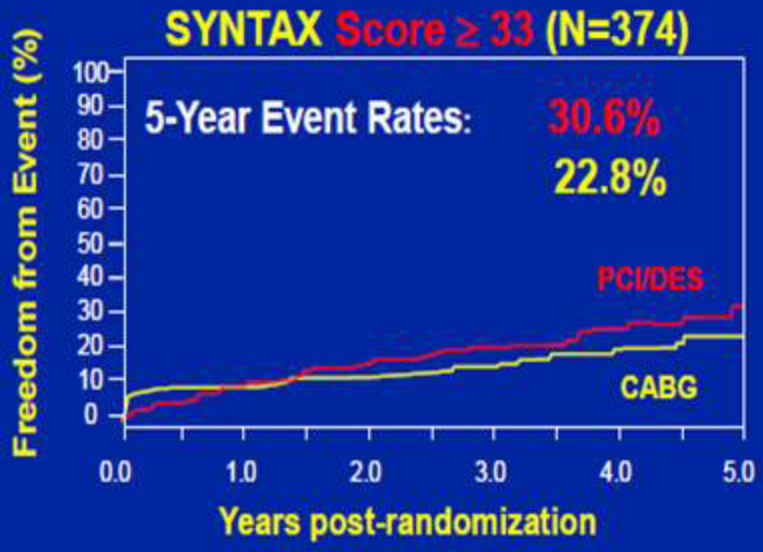
PCI comparable to CABG

CABG

PRIMARY ENDPOINT – DEATH / STROKE / MI
TREATMENT / SYNTAX INTERACTION - p=0.58





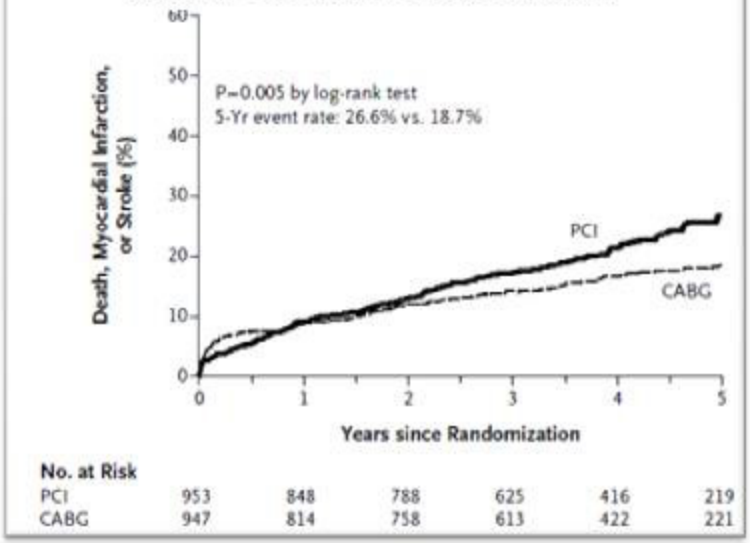


Strategies for Multivessel Revascularization in Patients with Diabetes

Michael E. Farkouh, N Engl J Med 2012;367:2375-84.

In patients with DM and MV CAD, CABG was superior to PCI by reducing rates of death and myocardial infarction with a higher rate of stroke

Primary Outcome: Death, Stroke, MI



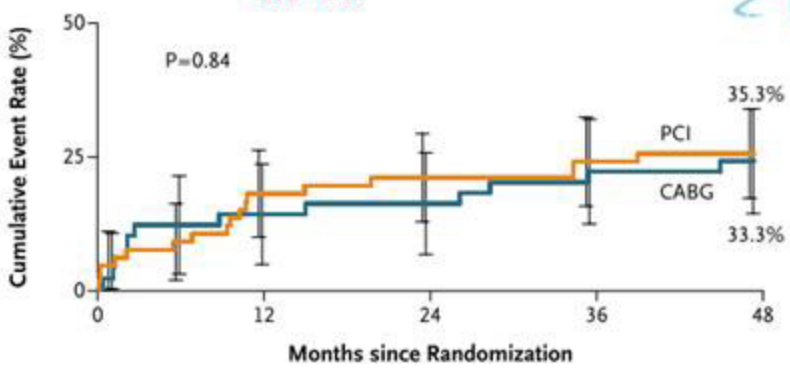
The Trial was Heavily Criticized…because not all 3VDs are similar…

CORRESPONDENCE

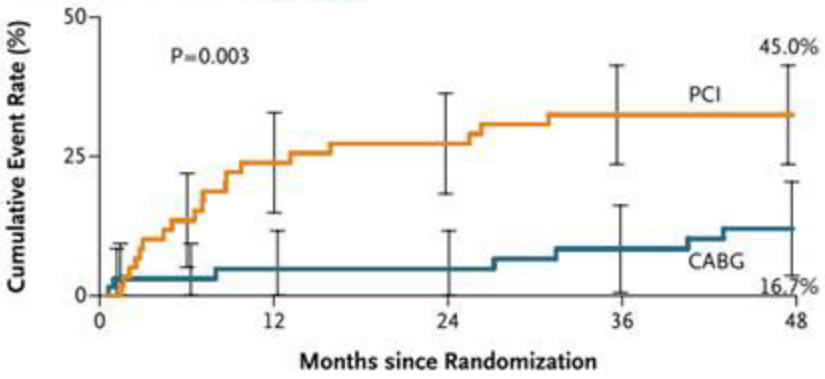
Patrick W. Serruys, M.D., Ph.D.

Erasmus MC

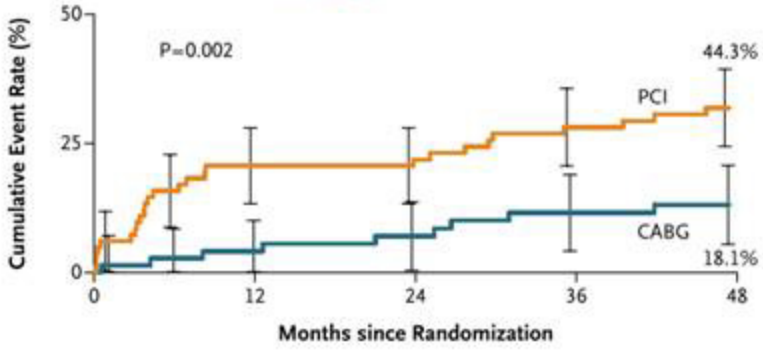
SYNTAX Score 0–22 3VD + DM



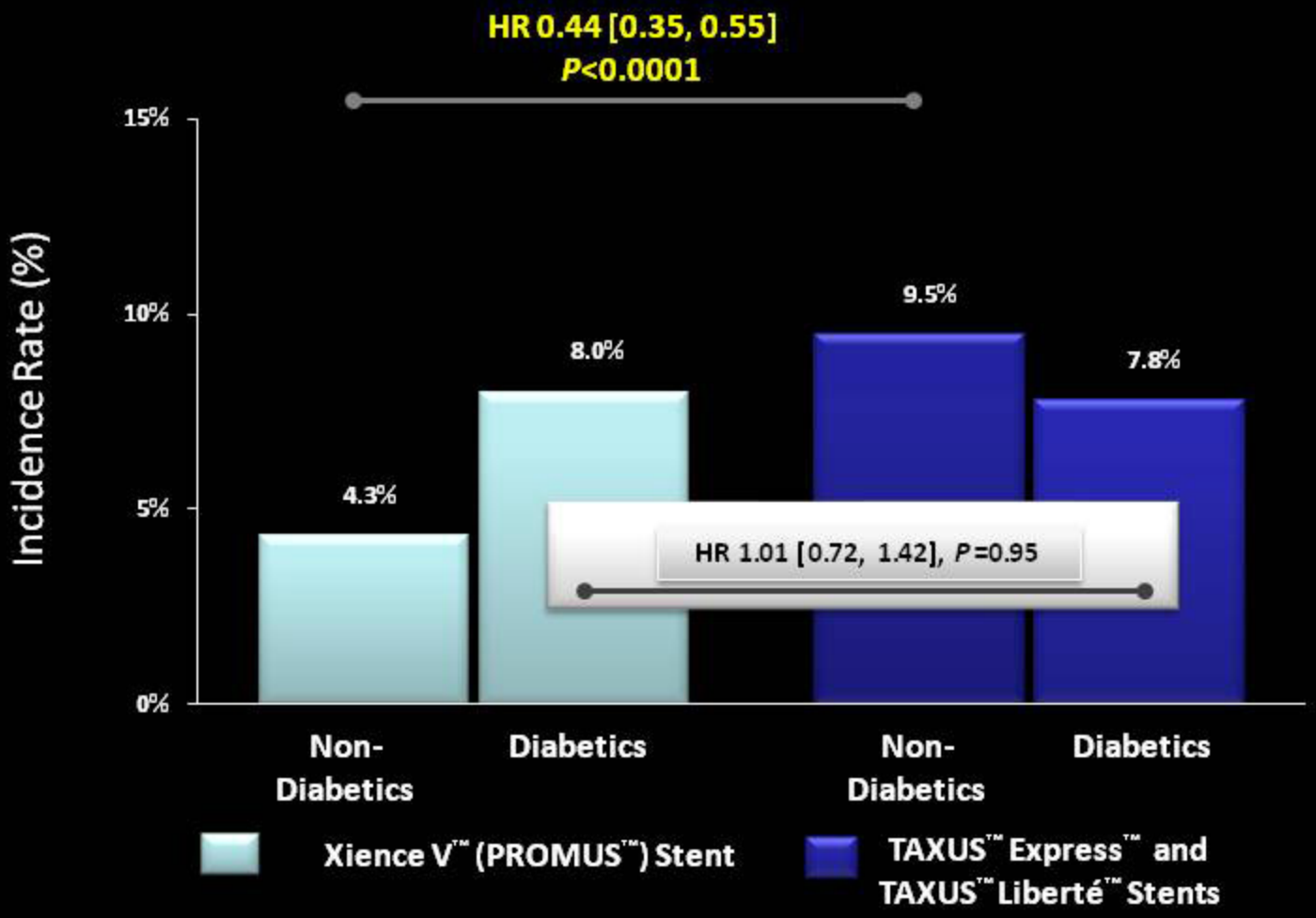
SYNTAX Score ≥33 3VD + DM



SYNTAX Score 23–32 3VD + DM



SPIRIT II, III, IV, and COMPARE Meta 12-Month MACE Results by Diabetic Status



Stone, G. TCT 2010

MACE = Cardiac Death, Target Vessel MI, Ischemia Driven TLR.
Overall non-diabetic n=3911 and diabetic n=1869. N by diabetic status and stent type not reported.

Clinical Outcome of Patients With and Without Diabetes Mellitus After Percutaneous Coronary Intervention With the Resolute Zotarolimus-Eluting Stent

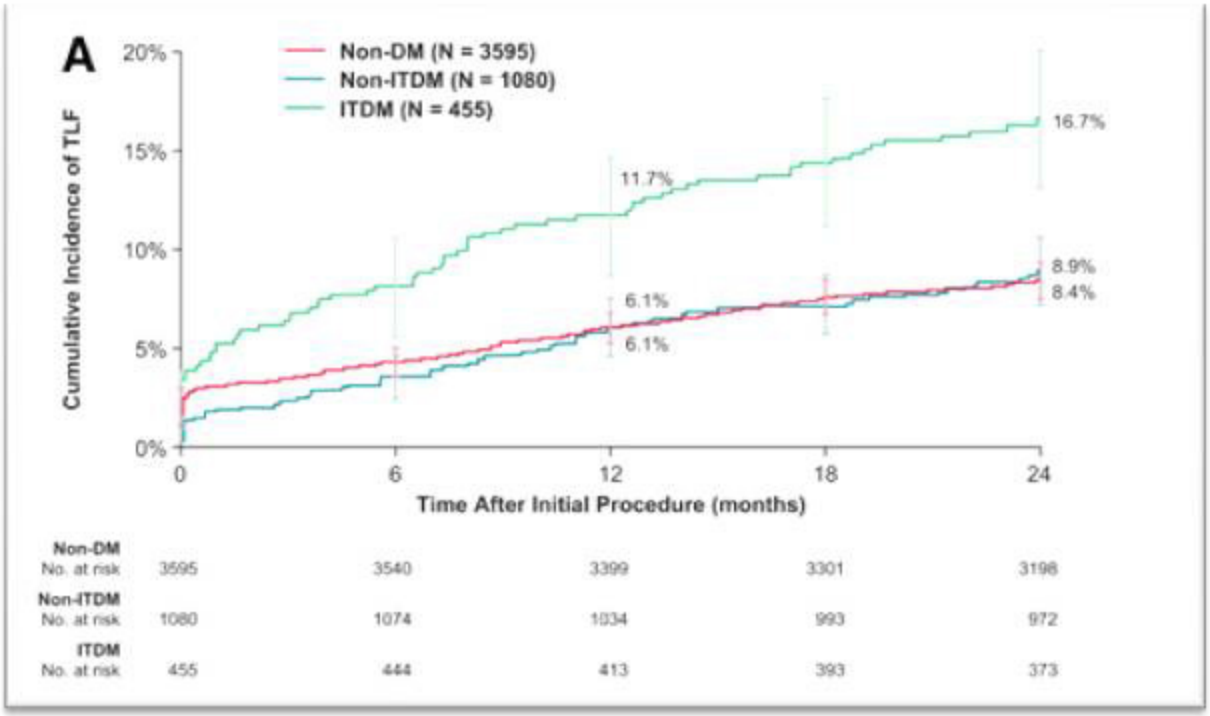
2-Year Results From the Prospectively Pooled Analysis of the International Global RESOLUTE Program

Silber S. et al. JACC Cardiovasc Interv. 2013; 4(12):1310-7

The R-ZES is safe and effective in patients with DM

Long-term clinical data of patients with noninsulin-treated DM are equivalent to patients without DM

Patients with insulin-treated DM remain a higher risk subset.



Where are we going with Industry?

1. *Through a more relaxed pathway to innovation, some of the technology advances of the future will clearly come from other countries.*
2. *With Health Costs out of control in many Western countries (the United States being the poster child) the ability to deliver care at a fraction of the costs in Western countries will gain increased attention.*

FACTS:

1. The global market for coronary stent devices reached $7.1 billion in 2011
2. By 2016 it is expected that total market value will reach $10.6 billion
3. American Revenue: 40% share and is expected to grow by 8.9% (2016)
4. European Revenue: 37% share and is expected to grow by 5.2% (2016)

Data provided by BCC Research, 2013

Future Progress for DES :

Deliverable, Visible, Trackable, Conformable device

No stent thrombosis, BMS like

Shortened DAPT requirement

Low TLR, Low clinical symptom recurrence

Reduced Polymer Load

- Abluminal polymer
- Bioerodable polymer
- No polymer

Reduced Drug Load

Stent Delivery System

- Stent material
- Thinner struts
- Stent geometry
- Surface coating

...and there is still room for Future progress & Innovation