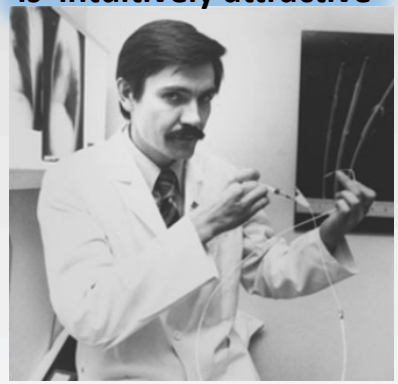
Existing Drug Coated Balloon Technology

Đeiti Prvulović, MD PhD
Croatia

„leaving nothing behind” approach

is intuitively attractive



First PCI:
Andreas Grüntzig, 16 September 1977.

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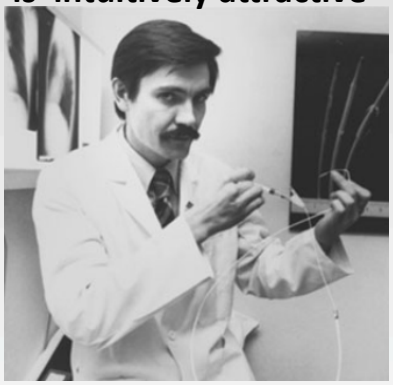

First PCI:
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Do we need stenting?

Editorial

The Bailout Stent

Is a Friend in Need Always a Friend Indeed?

Patrick W. Serruys, MD, PhD; David Keane, MB, MRCPI

When invited to write an editorial on bailout stenting, many titles came to mind—"The Double-Edged Sword," "Friend or Foe," and "Jekyll and Hyde"—to convey the current balance of the efficacy and the risk associated with bailout stent therapy. Rather than consolidating the role of stenting

Circulation 1993;88(5 Pt 1):2455–2457.

The ideal delivery device:

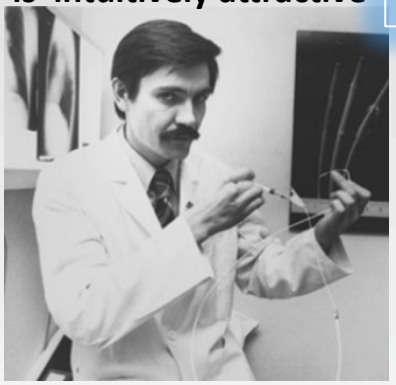
would deliver and retain adequate amounts of drug to the vessel wall

for sufficient periods of time to ensure a therapeutic effect,

without injury or compromising blood flow and the delivery device.

„leaving nothing behind" approach

is intuitively attractive



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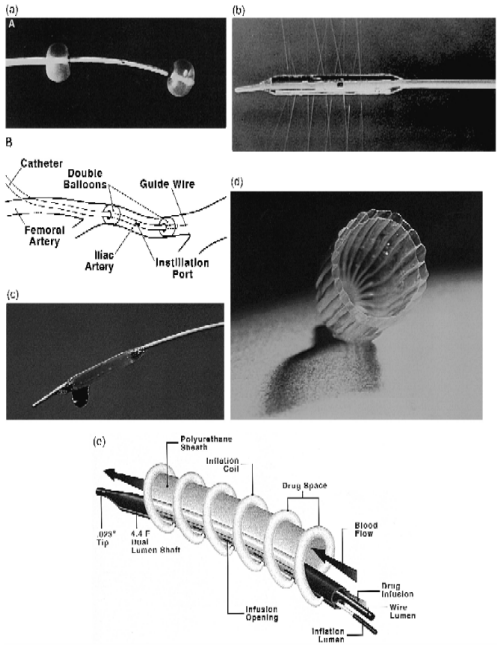
Circulation 1993;88(5 Pt 1):2455–2457.

Review

Local drug delivery systems and prevention of restenosis

David Brieger, Eric Topol *



Cardiovascular Research 35 (1997) 405–413

„leaving nothing behind”
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is intuitively attractive

First PCI:
Andreas Grüntzig, 16 September 1977.

Do we need stenting?

European Heart Journal (2012) 33, 16–25
doi:10.1093/eurheartj/ehr364

CURRENT OPINION

From metallic cages to transient bioresorbable scaffolds: change in paradigm of coronary revascularization in the upcoming decade?

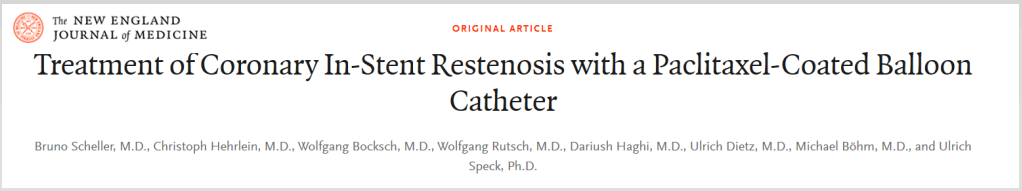
Patrick W. Serruys*, Hector M. Garcia-Garcia, and Yoshinobu Onuma

Circulation 1993;88(5 Pt 1):2455–2457.

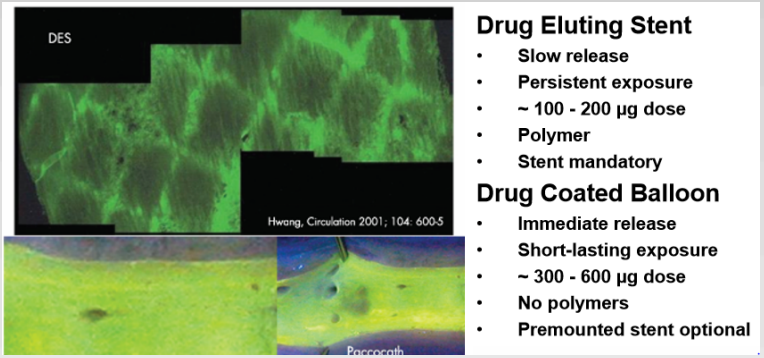
Review

ention of restenosis

Cardiovascular Research 35 (1997) 405–413



November 16, 2006.



Where are we now ?

skeptic

I use DCB when I feel that stent is not the best choice. DCB is on the shelves of my cath lab as a adjunctive and complementary tool, not to replace stents.

enthusiastic adopter

strategy of optimized angioplasty, with intension to finish procedure with DCB, with only provisional stent implantation

	population (x1000)	PCI total, n	Total PCI with DCB,n
Belgium	11299	26985	186 - **0,69 %**
Denmark	5669	10386	363 - **3,5 %**
Egypt	86814	104000	n.a.
France	64395	128000	n.a.
Israel	8463	21690	n.a.
Italy	59797	146420	n.a.
Kazakhstan	17557	14217	12
Macedonia	2071	3637	n.a.
Poland	38611	124876	3307 - **2,65 %**
Serbia	7095	12941	174 - **1,34 %**
Spain	46449	67671	2357 - **3,48 %**
Sweden	9382	20744	1296 – **6,25 %**
Switzerland	8327	24158	n.a.
Turkey	78741	105000	n.a.
United Kingdom	64715	97376	n.a. (PCI without stent – 8,2%)

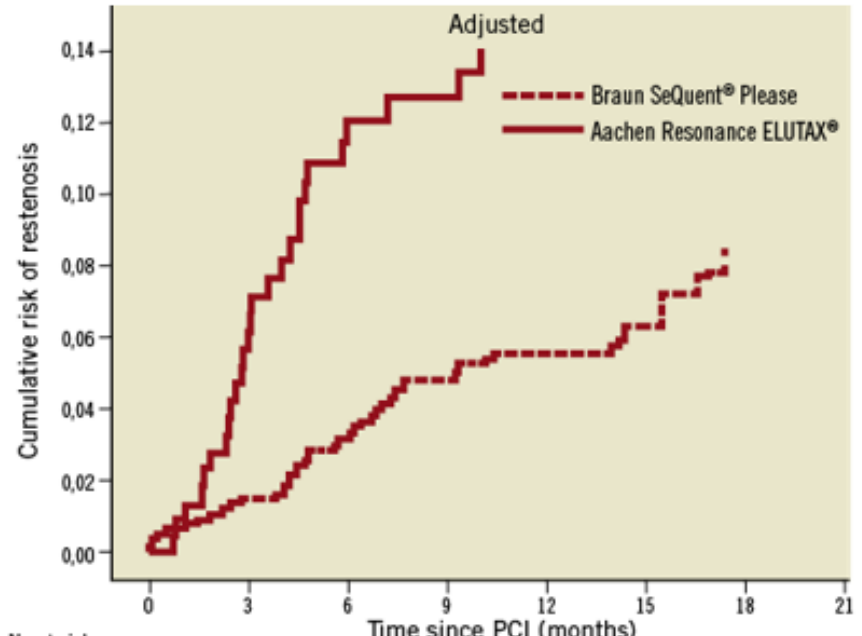
Current trends in coronary interventions: an overview from the EAPCI registries EuroIntervention 2017;13:Z8-Z10

Currently available coronary paclitaxel DCB

Manufacturer	Balloon	Excipient	Balloon type	Dosage (µg/mm²)	CE mark
B.Braun	SeQuent Please	iopromide	SC	3.0	2009
Boston scientific	Agent™	ATBC	SC	2.2	2014
Medtronic	IN.PACT™ Falcon	urea	SC	3.0	2009
EuroCor	DIOR II	Schellac	SC	3.0	2009
CR bard	Lutonix DCB (Moxy)	Polysorbate and sorbitol	SC	2.0	2011
Biotronic	Pantera Lux	BTHC	SC	3,0	2010
Aachen resonance	Elutax SV	-	SC	2,2	2008
iVascular	Essential	-	SC	3.0	2014
Acrostac	Genie	-	SC	NA	2007
Minvasys	Danubio	BTHC	SC	2,5	2011
Cardionovum	Primus	Shellac	SC	3.0	2012
Blue medical devices	Protégé	unknown	NC	3,0	2012

None of the devices is currently approved by the FDA for clinical use.

No class effect exists among the different paclitaxel DCBs



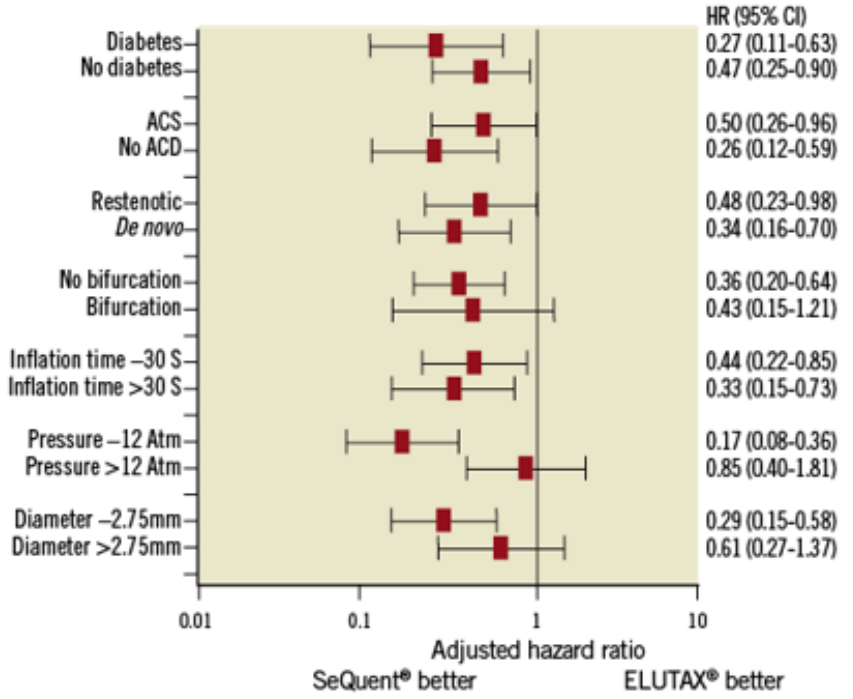


Table 2. Background characteristics of lesion type segment, treatment.

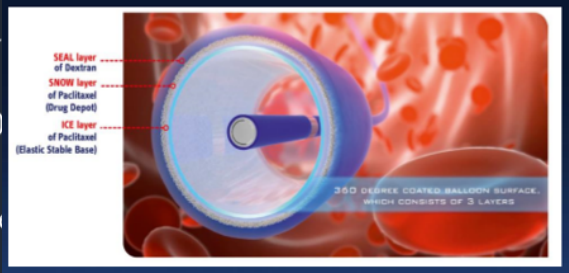
% (n=)	BSP (n=919)	ARE (n=217)
Lesion type:		
De novo	41.2	63.1
Restenosis (after POBA)	3.2	1.4
In-stent restenosis	55.6	35.5
Bifurcation	14.3	22.6

Bondesson, P. et al. Comparison of two drug-eluting balloons: a report from the SCAAR registry EuroIntervention 2012;8:444-449

Comparison of various LLL in DCB studies (SVD setting)

Dior I (first generation) - paclitaxel sprayed onto the surface - the drug was lost during transit and manipulation

STU					
PICCOLETO	Dior I	RCT	PTX	0.78	0.48
PEPCAD SVD	Paccocath tech.	Reg.	PTX	0.28 ± 0.53	-
BELLO	In.Pa				
Dissections after DCB	Elutax SV 70				
RESTORE SVD	R				
FASICO NATIVES	Mag				
PICCOLETO II	Elutax SV	RCT	PTX	0.04 ± 0.28	0.17 ± 0.39



- SEAL layer made of DEXTRAN, an hydrogel with hydrophilic features, to obtain a longer drug absorption in time
- drug deployed on inflated balloon
- lower dose PTX (2.2 micrg/mm2)
- higher PTX persistance at 30 days (5-8% of the drug)

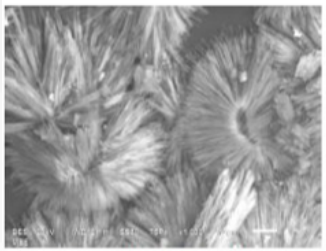
Components influencing DCB performance

Excipients -essential role -directly impact paclitaxel tissue pharmacokinetics

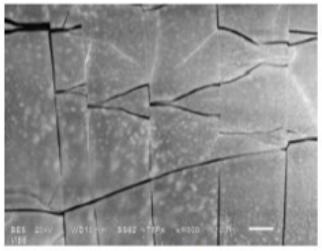
- iopromide
- shellac
- urea
- acetiyl tributyl citrate
- polisorbat + sorbitol
- butyryl-trihexyl citrate (BTHC)
- poliethylenglycol

Differences in coating integrity, adhesion, vessel wall transfer and particulate matter.

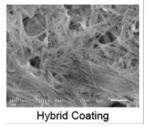
Drug morfology

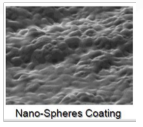

Crystalline Coating

- more insoluble forms
- more brittle coating
- prolonged retention of the drug into the vessel wall
- higher downstream particle loss
- much higher presence of the drug on the surface at 24 h and 7 and 28 days


Amorphous Coating

- highly soluble forms
- more homogeneous and reproducible coating
- shorter drug retention profiles following paclitaxel delivery


Hybrid Coating


Nano-Spheres Coating

Components influencing DCB performance

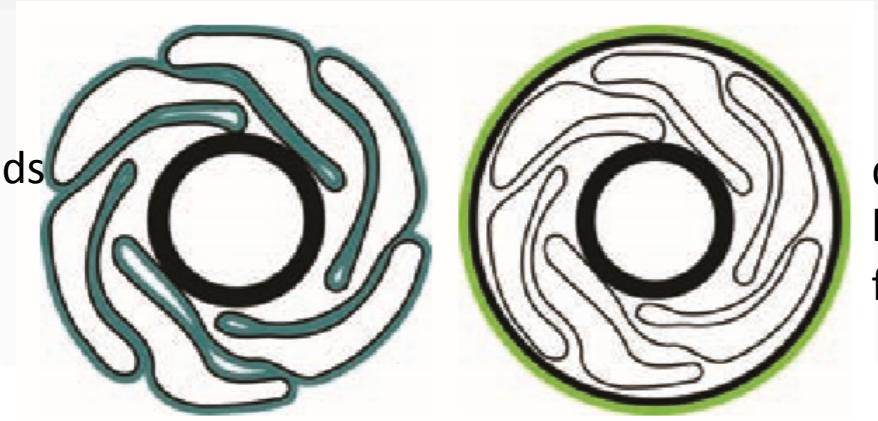
Coating methodology

dip coating
micropipette coating
spray coating

Surface properties, physical drug release and tissue uptake and particulate matter.

Coating geometry

high concentrations within the balloon folds and lower concentrations at the outer balloon



drug-coated wrapped balloon highly elastic wrap around the folded balloon

What is ideal DCB ? What do we expect from industry?

Balloon:

lesion crossing issue – no bulky device
deliverability – trackability – crossability - pushability

Drug:

limus vs paclitaxel

Drug carrier:

most critical, key to design of device

- uniform coating surface, robuste integrity
- no fragmentation, no fragile coating
- minimal handling damage – shelf life stability
- low in transit loss, no wash off
- particulate generation (size, solubility)
- no local toxic effects acutely and later
- faster uptake of drug and longer retention in tissue
- increased bio-availability and bio-compatibility
- low systemic doze - does not produce off-target adverse events

What is ideal DCB ? What do we expect from industy?

Drug:
limus

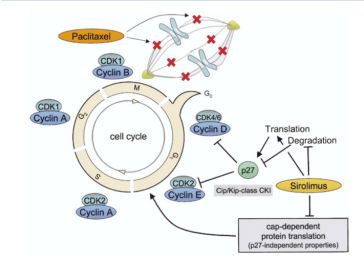
(Siro)limus is drug of choice for coronary DES supported by solid clinical based evidence

Baber U, Mehran R, Sharma SK, et al. Impact of the everolimus eluting stent on stent thrombosis: a meta-analysis of 13 randomized trials. J Am Coll Cardiol 2011;58:1569–77

Palmerini T, Kirtane AJ, Serruys PW, et al. Stent thrombosis with everolimus-eluting stents: meta-analysis of comparative randomized controlled trials. Circ Cardiovasc Interv 2012;5:357–64

Garg S, Serruys PW. Coronary stents: current status.J Am Coll Cardiol. 2010 Aug 31;56(10 Suppl):S1-42.

Schomig A, Dibra A, Windecker S, et al. A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. J Am Coll Cardiol 2007;50:1373– 80.

	Paclitaxel	Sirolimus
Mode of action 	in mitosis (M) phase – at a stage at which cells divide – apoptotic cell death likely to occur **cytotoxic**	Inhibit cell in the G1 phase – initial phase **cytostatic**
inhibition of SMC proliferation	**++**	**++**
inhibition of SMC migration	**++**	**+**
inhibition of EC proliferation	**++**	**++**
immunosuppressive properties	**++**	**(+)/-**
therapeutic range	**narrow** apoptosis even in therapeutic range, necrosis at higher doses	**wide**
tissue absorbtion	**fast**	**slow**
tissue retention	**short**	**long**
distribution in vascular wall	**adventitia** (inferior role in pathophysiology of ISR)	**equal**
impact on LLL	++	+

What is ideal DCB ? What do we expect from industy?

Attribute	Limus	Paclitaxel
Nature of drug	Less lipophilic	Higly lipophilic
Ease of coating	Very hard	Easy
Tissue absorbtion and elution	More difficult	easier

What is ideal DCB ? What do we expect from industy?

Comprehensive animal and human data are warranted.

Preclinical work:

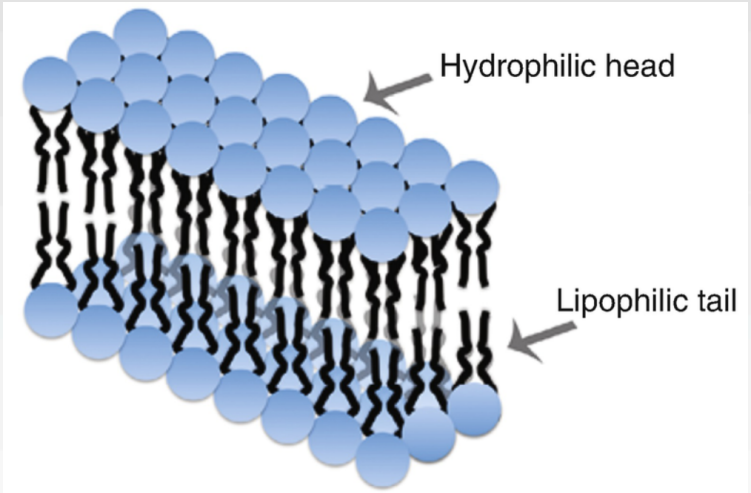
- data from in vivo and in vitro testing
- dose finding studies
- PK and histology studies
- effect of surface texture and balloon folding on drug bioavailability
- drug lost/retained during balloon transit and inflation
- drug retention in artery wall
- excipient dose studies
- local tissue dose/response to establish the lowest effective dose

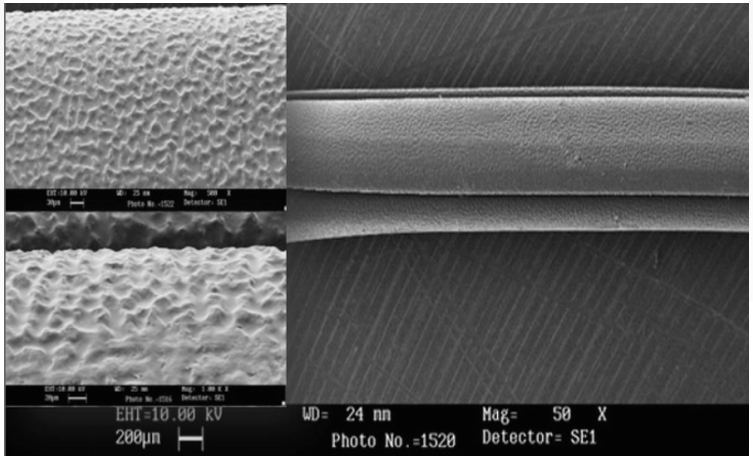
Clinical studies:

- initial assessment of device handling & performance, proof of concept, and safety
- acceptable results to justify a larger pivotal trial (RCT recommended)
- worldwide clinical experience : supportive data of DCB safety and effectiveness

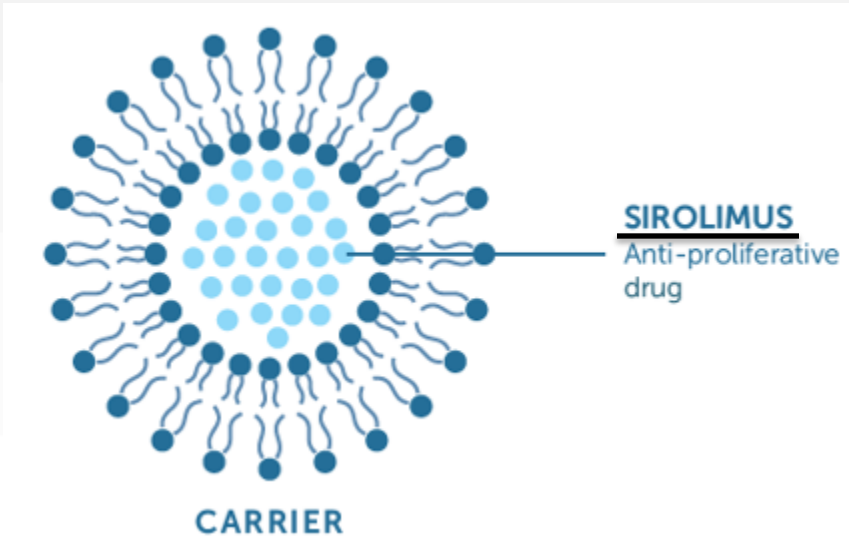
Magic Touch Sirolimus-Eluting Balloon

Excipient - lipid-based component with a hydrophilic head and two lipophilic tails - membrane that encapsulates the particle and ensures needed lipophilicity





Carrier fully encapsulates the drug particles
Nano-particles are 0.35 µm – allows drug entry to intima and up to adventitia



THE EASTBOURNE REGISTRY

THE ALL-COMERS SIROLIMUS-COATED BALLOON EUROPEAN REGISTRY

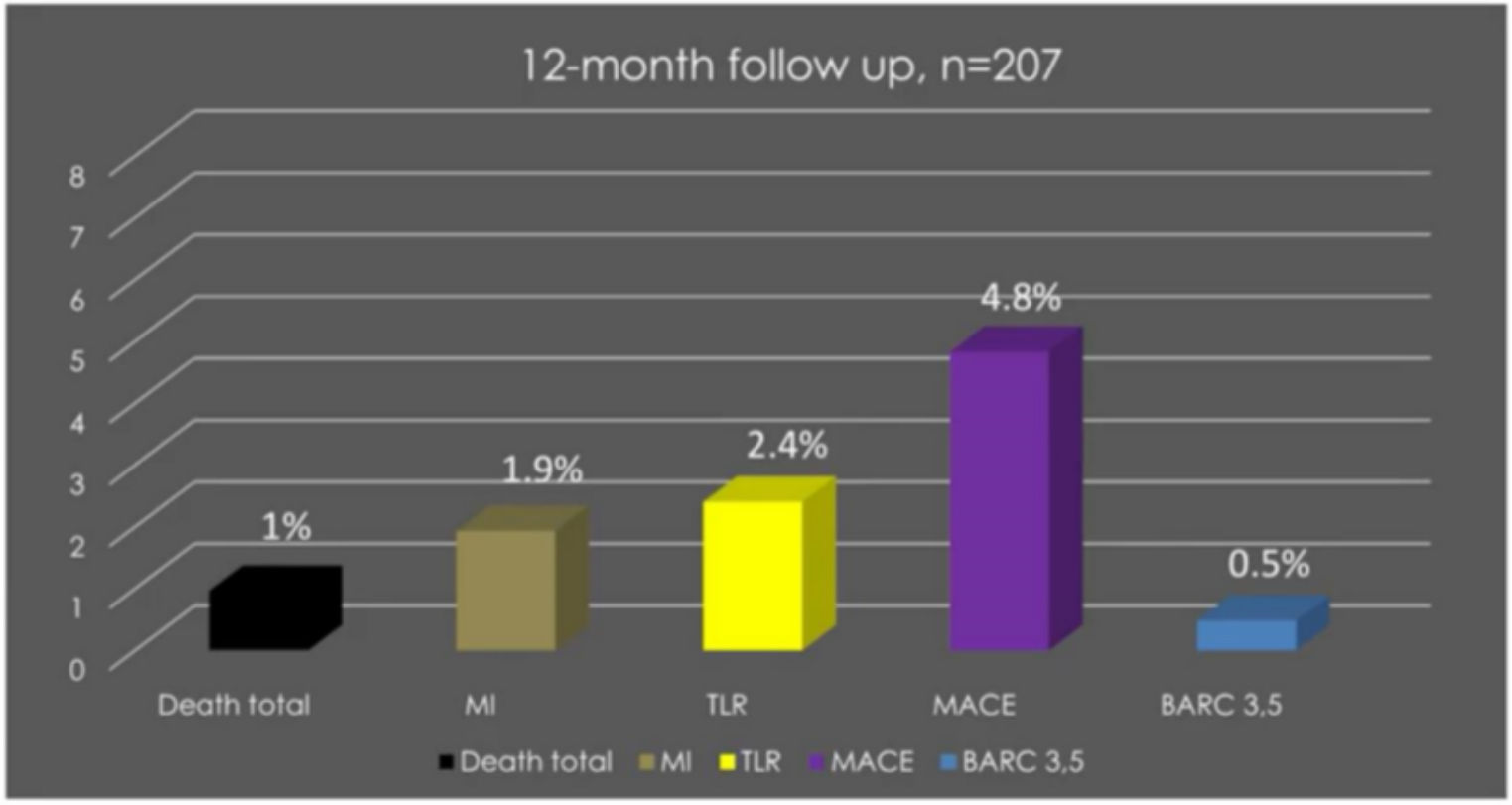
To observe and evaluate the performance of a Sirolimus-eluting Drug-Coated Balloon (SCB) for the treatment of *any type of coronary lesions*, including native vessel disease and in-stent restenosis.

- Prospective, multicenter, spontaneous clinical registry
- External validation of quality of data input
- Centralised clinical event assessment
- 2,000 real world, all comers patients, consecutive enrollment at 35 european/asiatic sites
- Clinical follow up to 36 months
- Primary Investigator B. Cortese, Chairman A. Colombo
- Prespecified interim analysis (1,000 patients enrolled)

January 2019: EASTBOURNE interim analysis

THE EASTBOURNE REGISTRY

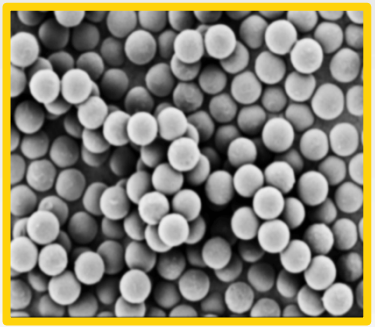
THE ALL-COMERS SIROLIMUS-COATED BALLOON EUROPEAN REGISTRY



Med Alliance
SELUTION™ Sirolimus DCB

Micro-reservoirs made out of biodegradable polymer intermixed with Sirolimus:

- Controlled and sustained drug release mechanism
- Maintains therapeutic effect in tissue over long period of time



Novel Cell Adherent Technology – CAT™:

- CAT™ transfer membrane houses and protects micro-reservoirs during balloon insertion, lesion crossing and expansion
- CAT™ transfer membrane with embedded micro-reservoirs releases from balloon delivery system and adheres to vessel lumen with short balloon inflations

SELUTION DSR

Prospective, open label, multi-center RCT with angiographic endpoints
Patients with CAD with ISR **or** Bifurcation with side-branch lesion **or** distal lesions in small vessels

Large centres in countries where Paclitaxel DCB are approved and reimbursed

SELUTION™ DCB

145 Patients
1:1 randomization

Paclitaxel DCB

Clinical FU

1 mo | 3 mo | 9 mo | 1 yr | 2 yrs

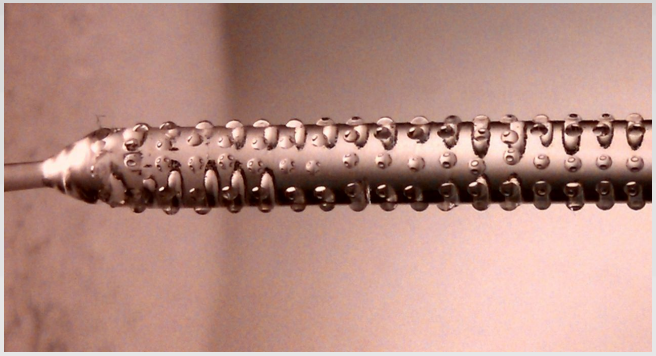
Angio FU
Optional IVUS FU

Primary endpoint: S-DCB superiority for % diameter restenosis vs P-DCB at 9 months

Secondary endpoints:
LLL at 9 months
Primary angiographic EP for each of the 3 groups
Device success (in cath lab)
Procedure success (at discharge)
Freedom from TVF at 360 and 720 days
Components of TVF at 360 and 720 days
Freedom from angina at 360 and 720 days
QOL & Cost-effectiveness at 360 days
IVUS determined minimal DSA at 9 months (optional)

DAPT: 30 days in both arms (if no stent in main branch for S group)

The Virtue angioplasty balloon (Caliber Therapeutics, New Hope, Pennsylvania)



porous balloon, delivers sirolimus in a nanoencapsulated liquid formulation

SABRE trial: single-arm feasibility study, 50 ISR patient

- 100% procedural success rate

- primary safety endpoint of 30-day target lesion failure, including cardiac death, target vessel MI and clinically driven target lesion revascularization, occurred in no patients
- The primary performance endpoint was 6-month in-segment late lumen loss, which was 0.31 ± 0.52 mm
- At 6 months, binary restenosis occurred in 19.1% of patients, MACE occurred in 10.2% and diameter stenosis was a mean of 30.3 ± 19.9%.

Verheye S et al. The SABRE Trial (Sirolimus Angioplasty Balloon for Coronary In-Stent Restenosis): Angiographic Results and 1-Year Clinical Outcomes. JACC Cardiovasc Interv. 2017 Oct 23;10(20):2029-2037

Novel Sirolimus–Coated Balloon Catheter: In Vivo Evaluation in a Porcine Coronary Model

Yvonne Patricia Clever, Daniel Peters, Jorge Calisse, Stephanie Bettink, Madeleine-Caroline Berg, Christian Sperling, Michael Stoever, Bodo Cremers, Bettina Kelsch, Michael Böhm, Ulrich Speck and Bruno Scheller

Circ Cardiovasc Interv. 2016;9:

Table 1. Sirolimus Coatings Studied in the Different Experiments

Coating	Dose Density, µg/mm²	Crystal Modification	Additive
AS 1	0.9	Amorphous	Probucol
AS 7	7	Amorphous	Probucol
IIIb	7	Mixture of amorphous and crystalline form	Butylated hydroxy toluene
Vb 4	4	Crystalline	Butylated hydroxy toluene
Vb 7	7	Crystalline	Butylated hydroxy toluene

IIIb indicates less amorphous sirolimus coating; AS, amorphous sirolimus coating; and Vb, crystalline sirolimus coating.

Loss of the selected coating in the valve, guiding catheter, and blood was low (2±14% of dose).

Acute drug transfer to the vessel wall was 14.4±4.6% with the crystalline coating, whereas the amorphous coatings were less effective in this respect.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 12, NO. 6, 2019
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PUBLISHED BY ELSEVIER

Treatment of Coronary Drug-Eluting Stent Restenosis by a Sirolimus- or Paclitaxel-Coated Balloon

Rosli Mohd Ali, MD,[a] Muhamad Ali S.K. Abdul Kader, MD,[b] Wan Azman Wan Ahmad, MD,[c] Tiong Kiam Ong, MD,[d] Houng Bang Liew, MD,[e] Al-Fazir Omar, MD,[f] Ahmad Syadi Mahmood Zuhdi, MD,[c] Amin Ariff Nuruddin, MD,[f] Beatrix Schnorr, PhD,[g] Bruno Scheller, MD[h]

50 patients

Novel SCB (SeQuent SCB, 4 mg/mm2) vs PCB (SeQuent Please Neo, 3 mg/mm2)

After 6months, in-segment **LLL** was

0.21 ± 0.54 mm in the PCB group versus **0.17 ± 0,55** mm in the SCB group

(p=NS; per-protocol analysis)

Clinical events up to 12 months also did not differ between the groups.

Conclusions

- DCB technology evolve toward the development of new delivery methods and new drugs

- for the broader adoption of these technologies DCB must be tested in RCT with sufficient statistical power to detect at least noninferiority against new generation DES with hard clinical endpoints