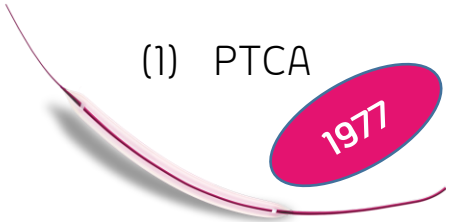
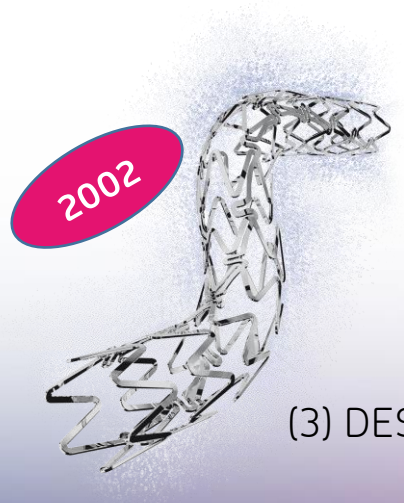
DES polymers

Evolution of Interventional cardiology

(1) PTCA

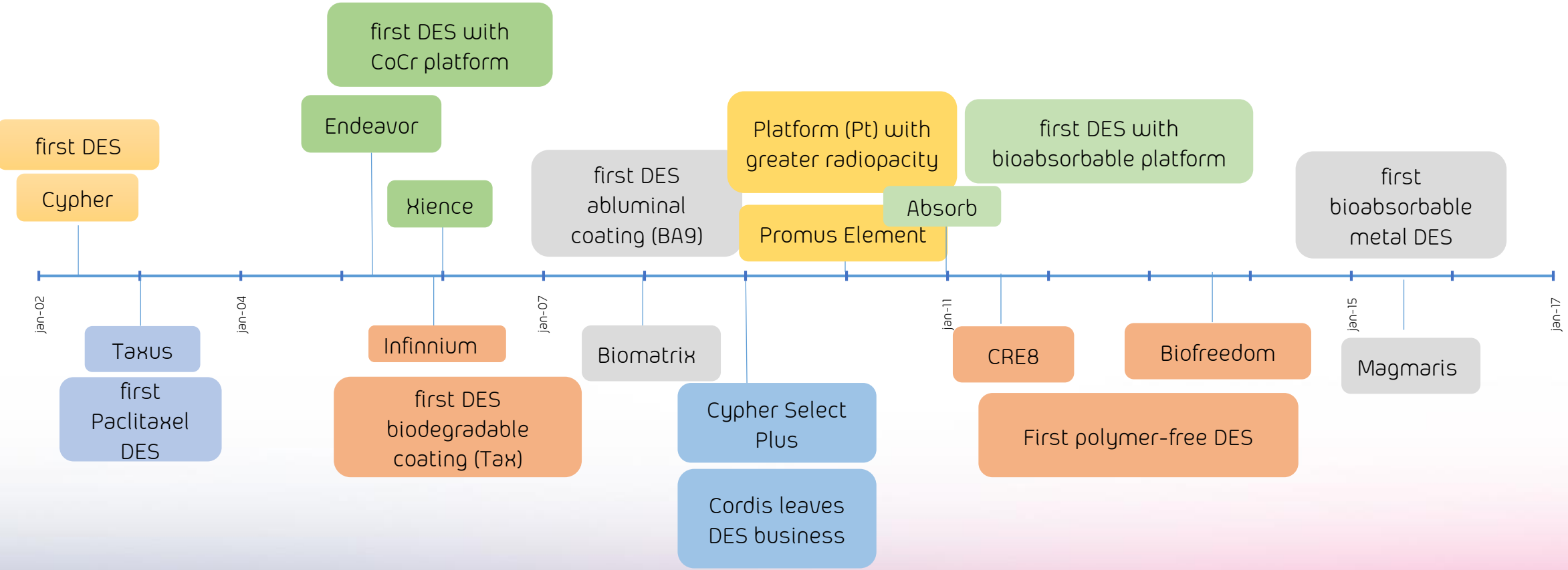


(2) Stent



(3) DES

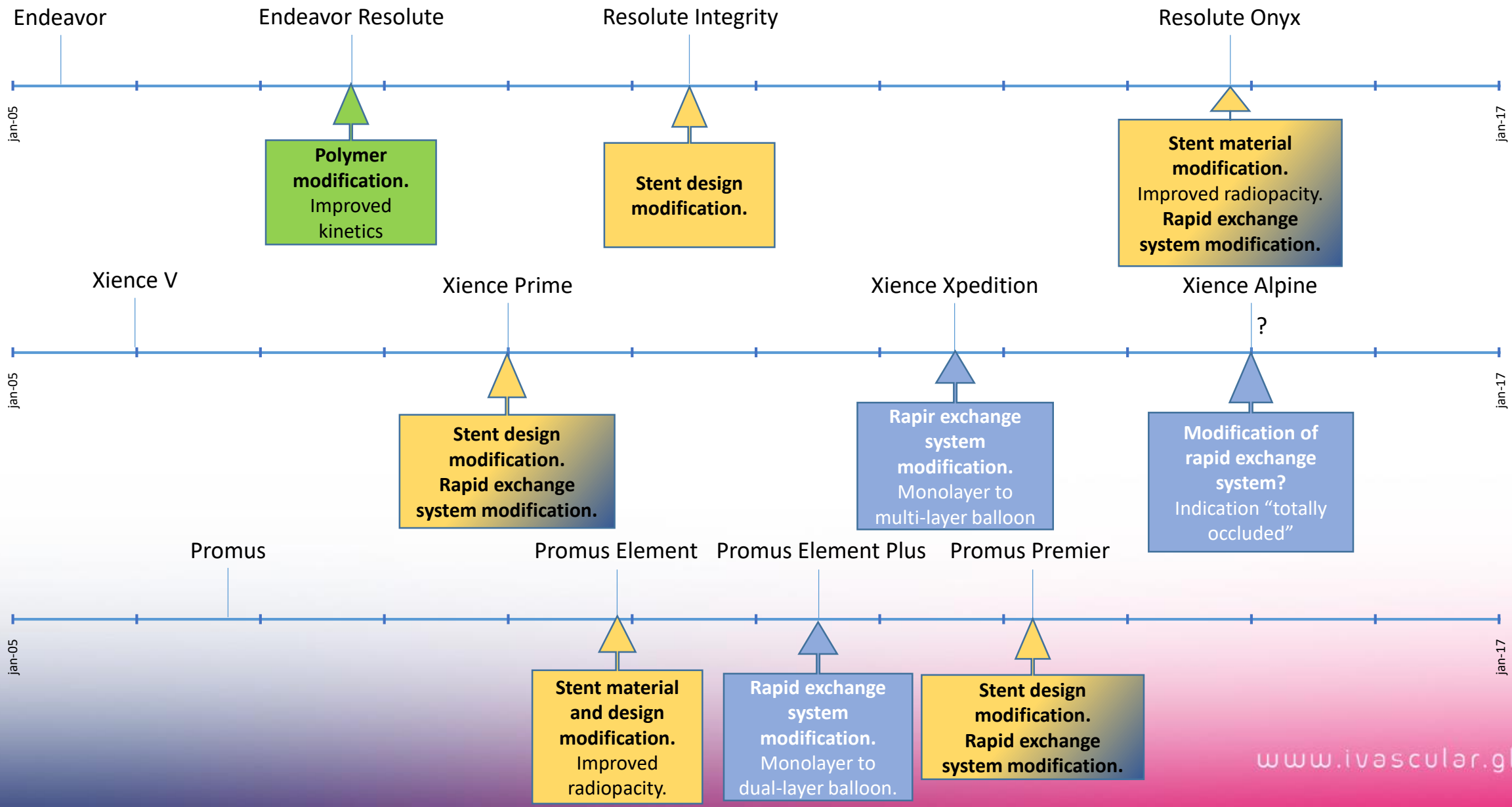
Historical evolution of DES

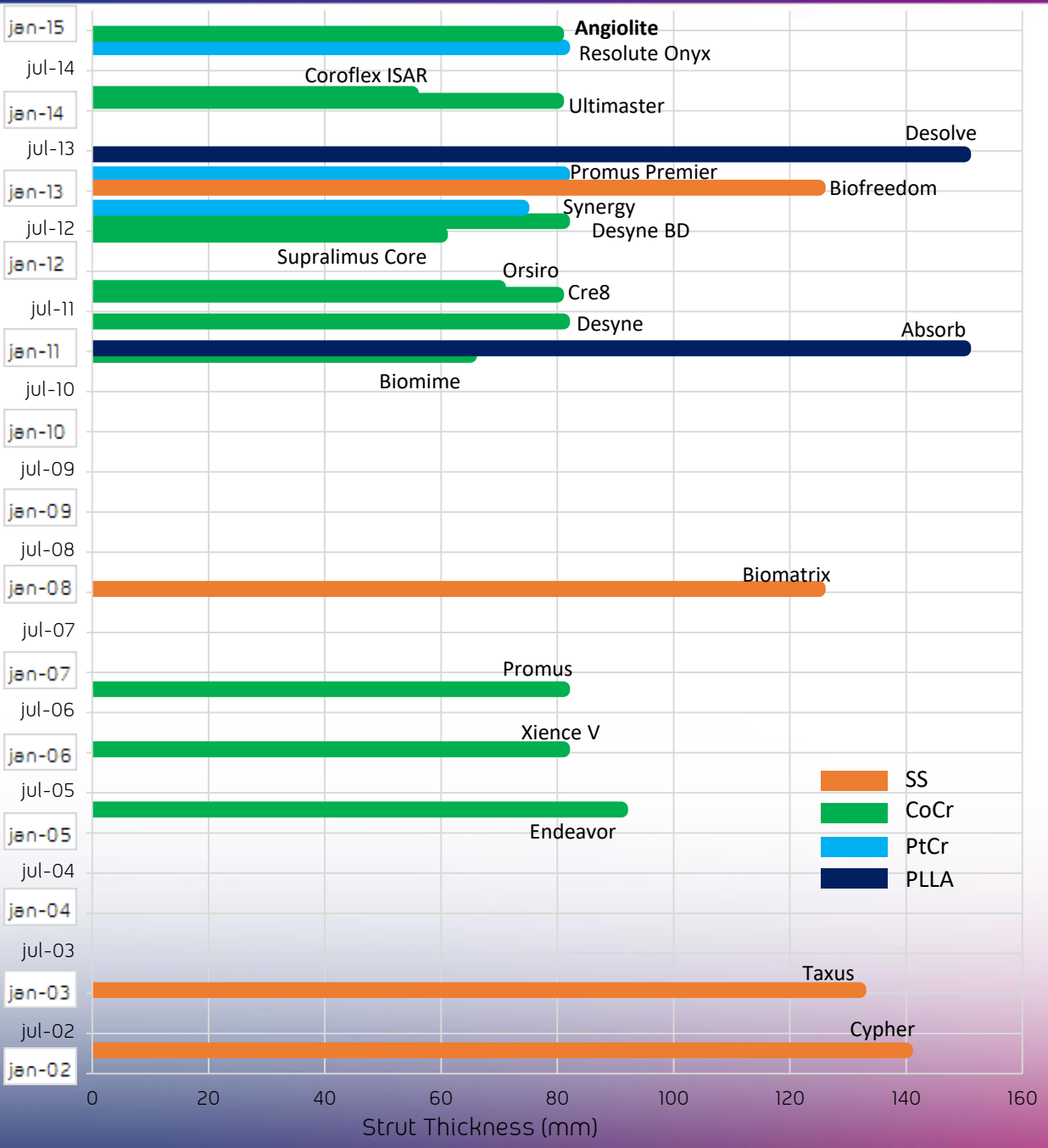


DES market representatives

	DES	Company	Platform	material platform	drug
biostable coating	Xience Xpedition	Abbott	Multilink 8	CoCr L605	Everolimus
	Promus Premier	Boston Scientific	Premier	PtCr	Everolimus
	Resolute Onyx	Medtronic		MP35N + Pt/Ir	Zotarolimus
	Angiolite	**iVascular**	**Architect**	**CoCr L605**	**Sirolimus**
Biodegradable coating	Orsiro	Biotronik	ProKinetic	CoCr L605	Sirolimus
	Ultimaster	Terumo	Kaname	CoCr L605	Sirolimus
	Synergy	Boston Scientific		PtCr	Everolimus
	MiStent	Stentys	Eurocor's Genius Magic	CoCr	Sirolimus
	Biomatrix Neoflex	Biosensors	Juno	SS	Biolimus BA9
	Biomime	Meril Life	Nexgen	CoCr	Sirolimus
	Desyne BD	Elixir Medical	Core	CoCr	Novolimus
	Coracto	AlviMedica	Constant	SS	Sirolimus
	Supralimus Core	Sahajanand Medical Tech	Coronnium	CoCr	Sirolimus
	Alex	Balton		CoCr	Sirolimus
Biodegradable stent	Absorb	Abbott	BVS	PLLA	Everolimus
	Desolve	Elixir Medical		PLLA	Novolimus
Polymer-free stent	Biofreedom	Biosensors	Juno	SS	Biolimus BA9
	CRE8	AlviMedica	Chrono	CoCr	Sirolimus
	Coroflex ISAR	Bbraun	Coroflex Blue	CoCr	Sirolimus

Main market DES development

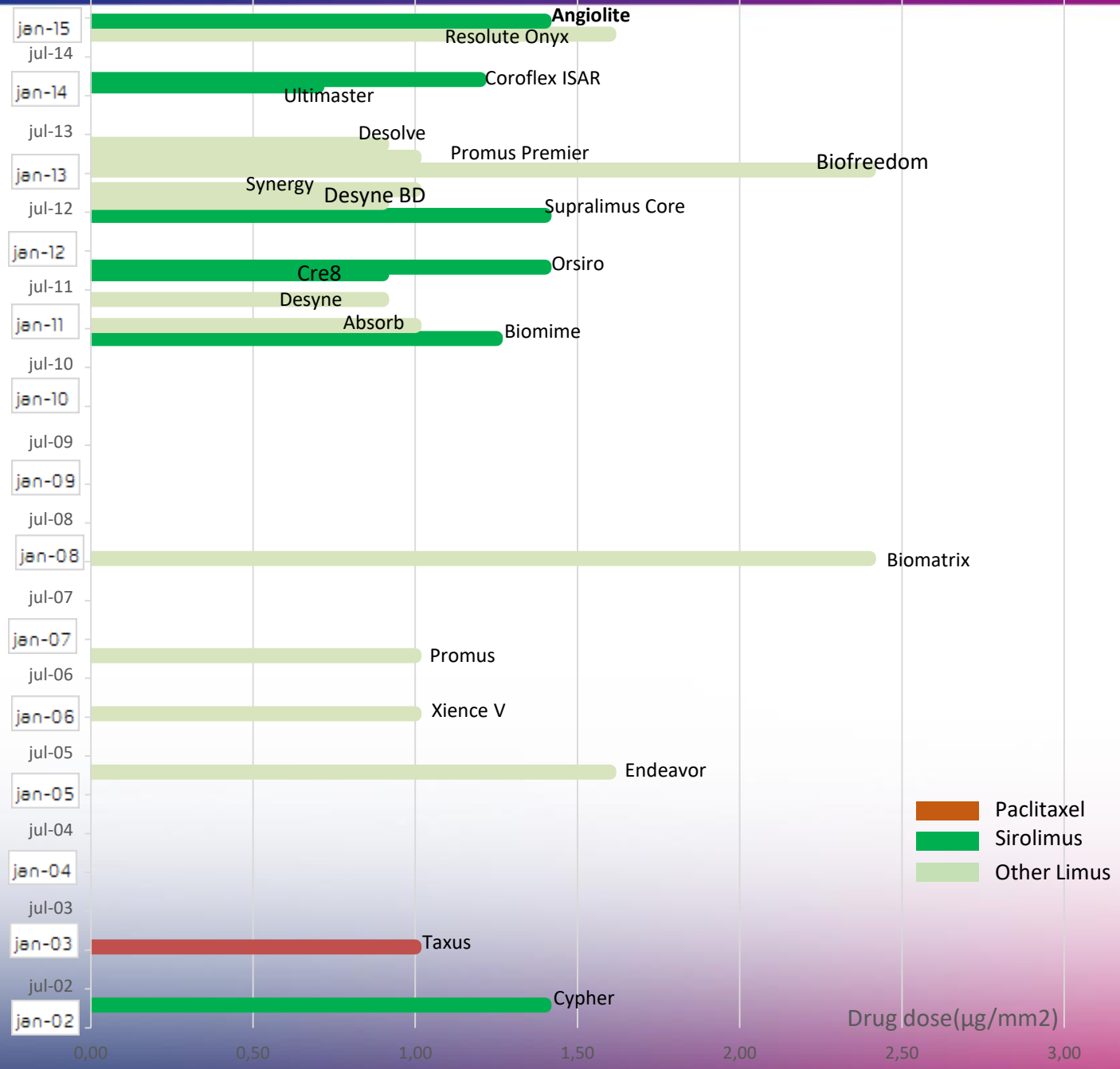




Historical evolution of DES: Platform strut thickness

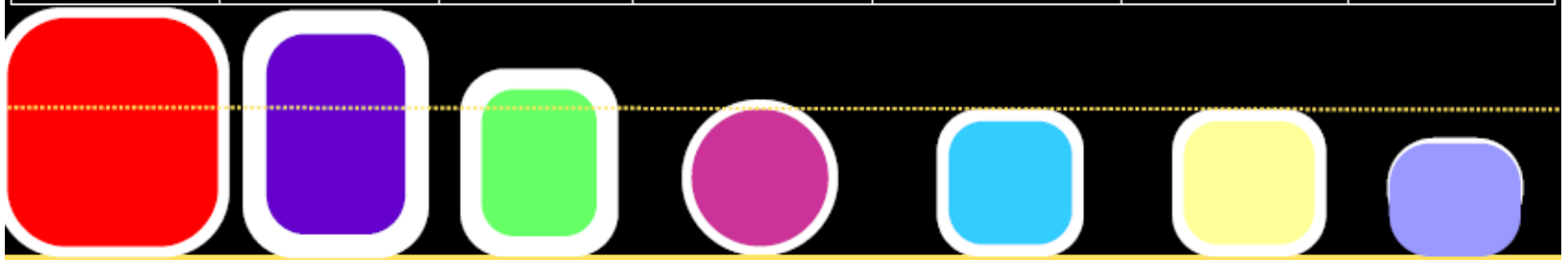
- SS disappearance
- CoCr predominates
- Appearance of the alloys with greater radiopacity (Pt)
- Bioabsorbables have not been imposed
- Strut thickness tends to decrease (60-80 μm)

Historical evolution of DES: Drug Dosage



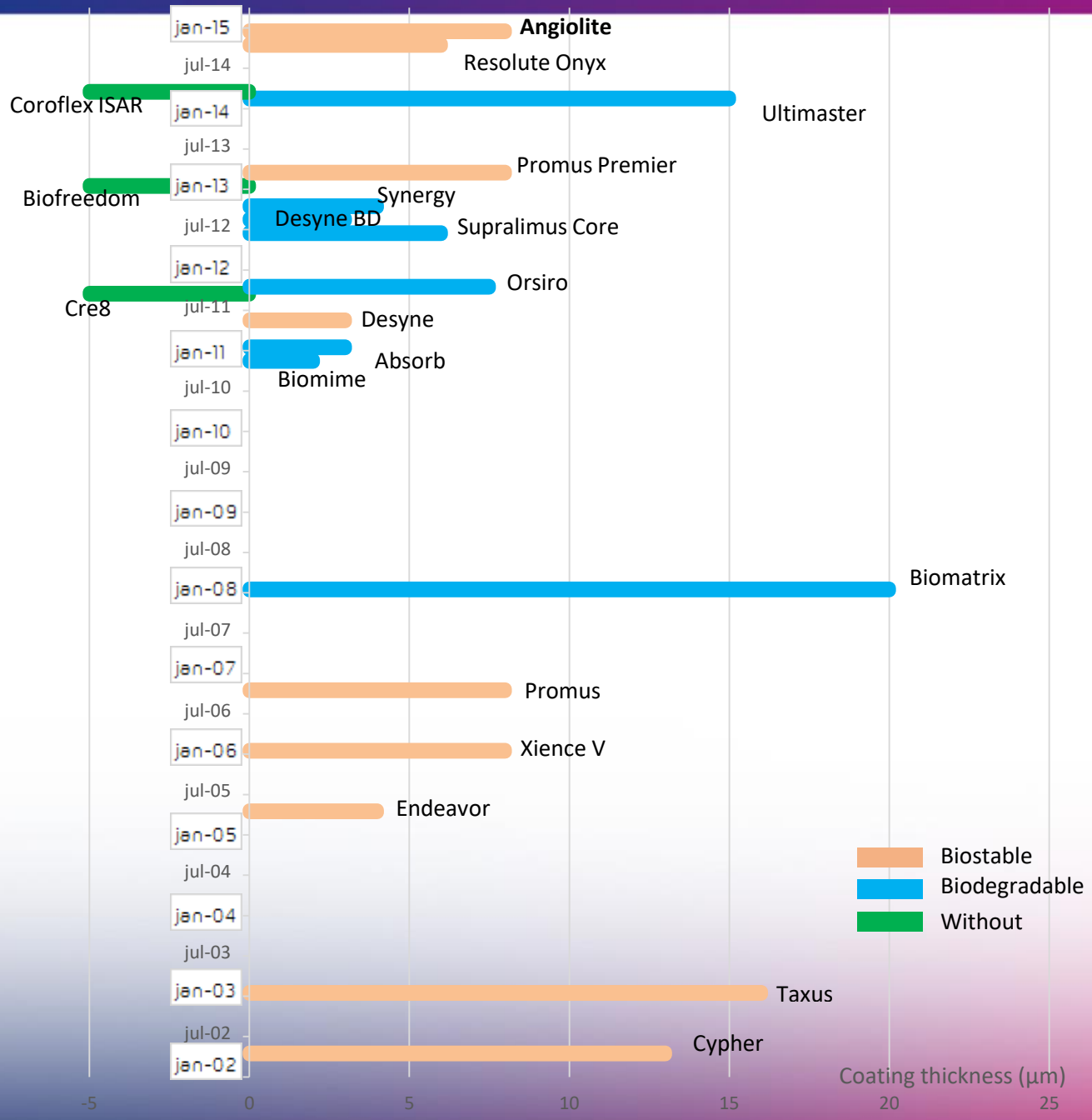
- Taxol disappearance
- No limus superior to Sirolimus.
- Tendency in dose reduction:
  - Before 2010, dose ≥ 1,0 µg/mm^2
  - After 2010, 30-40% DES dose < 1,0.

Stent Strut Profiles or New Stent Platforms

1st Generation			2nd Generation			3rd Gen
Cypher™	TAXUS Express™	TAXUS Liberte™	Resolute Integrity™	Xience V™ Xience Prime™	PROMUS Element™	SYNERGY™
						
Drug Type						
Sirolimus	Paclitaxel	Paclitaxel	Zotarolimus	Everolimus	Everolimus	Everolimus
Drug Concentration						
1.4 µg/mm²	1 µg/mm²	1 µg/mm²	1.6 µg/mm²	1 µg/mm²	1 µg/mm²	~1 µg/mm²
Avg. Coating Thickness						
7µm / side	16µm/side	14µm/side	6µm / side	8µm / side	8µm / side	4µm
Strut Thickness						
140 µm (0.0055")	132 µm (0.0052")	96 µm (0.0038")	89 µm (0.0035")	81 µm (0.0032")	81 µm (0.0032")	74 µm (0.0029")
BMS Platform						
Bx Velocity™	Express™	Liberte™	Integrity™	Vision™ and Multi Link 8™	Element™	SYNERGY™
Material						
Stainless Steel	Stainless Steel	Stainless Steel	Cobalt Nickel	Cobalt Chromium	Platinum Chromium	Platinum Chromium

Angiolite

Drug Type
Sirolimus
Drug concetration
1,4 µg/mm²
Avr. Coating Thickness
8 µm
Strut thicknees
75 µm
BMS Paltform
Specific
Material
Cobalt Chromiun



Historical Evolution of DES: Type of Coating

- New DES with non-biostable coating
- DES biostable coating are still the reference
- DES without polymer coating does not exceed DES with polymer coating
- Tendency to decrease thickness, there are thickness›5 µm.
- Trend toward non-coated part (abluminal / total).

Evolution DES: companies strategy

	BS	BD	PF	BA
Abbott				
AlviMedica				
Balton				
Bbraun				
Biosensors				
Biotronik				
Boston Scientific				
Elixir Medical				
iVascular				
Medtronic				
Sahajanand Medical Tech				
Terumo				

There is no clear strategy, as an alternative future to DES with biostable polymer coating

iVascular

Angiolite vs…

Xience Xpedition (Abbott)

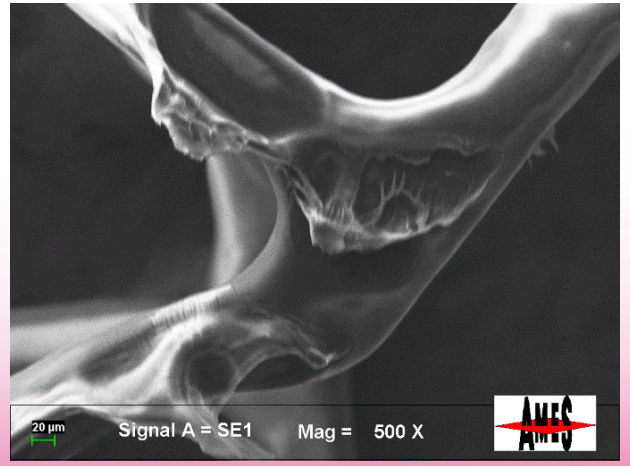
1. Sirolimus is the best drug for this application, the other –limus drugs have been developed to be out of the patent*
2. Angiolite has better mechanical properties (radial force) than Xience
3. The design of the stent Multilink (Xience) is not specific for DES
4. Higher strut coverage at 3-month 86.3% vs 81,5% Xience. (ANCHOR study)

*Transp. Proced. 30, 2192-2194 (1998), Expert Opin. Invest. Drugs 11, (2002), Eur Heart J. 27, 988-993 (2006)

Angiolite vs…

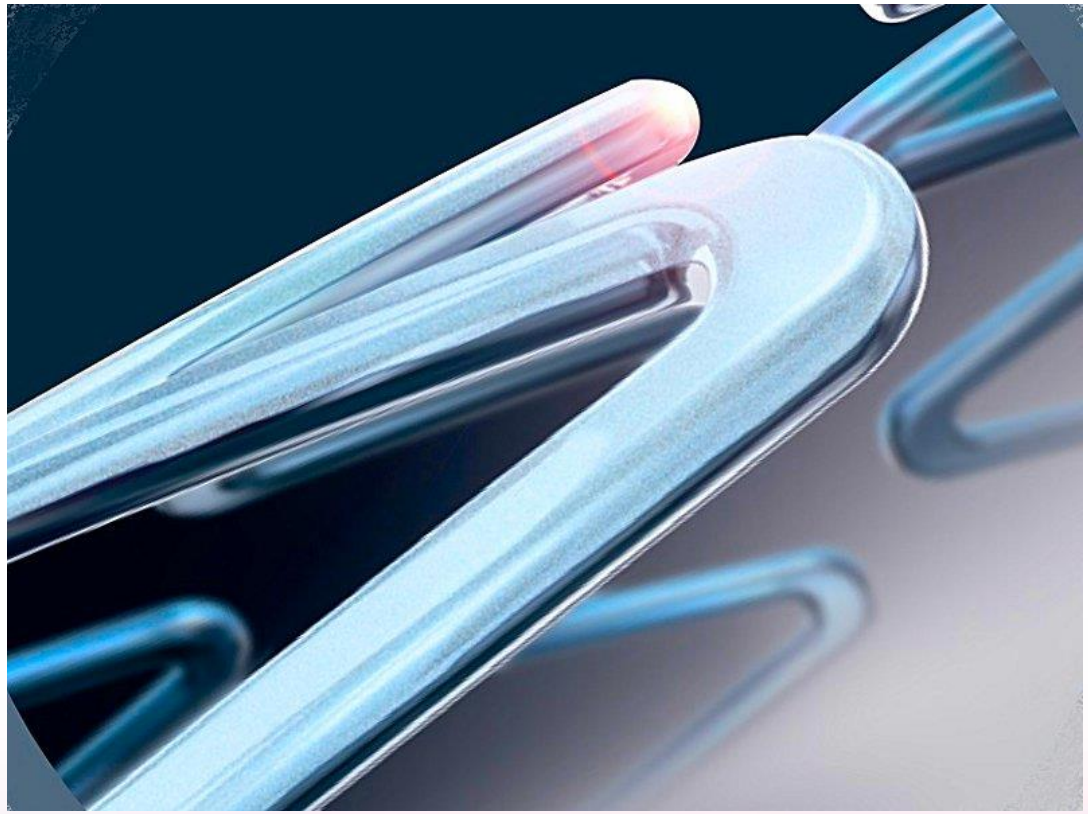
Promus Premier (Boston Scientific)

1. Sirolimus is the best drug for this application, the other–limus drugs have been developed to be out of the patent.
2. Angiolite has better mechanical properties (radial force) than Promus Premier

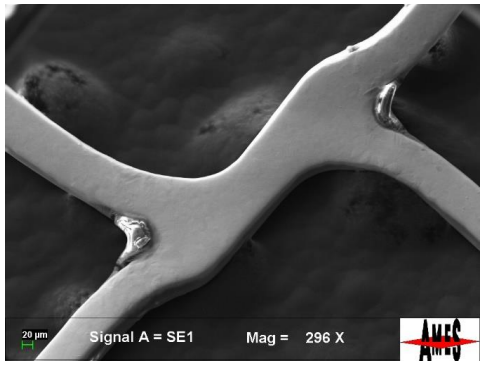


Concept: Biodegradable

- Although drug-eluting stents are effective, they appear to invoke a thrombogenic response.
- Polymers have the potential to become thrombogenic. Thick, durable and permanent polymers were the cause of some of the thromboses observed with first-generation devices.
- Bioabsorbable polymers disappear within 9 months.
- Biodegradable stents are a promising alternative to permanent stents and may eventually be used to solve the lingering problem of in-stent restenosis.



Angiolite vs…



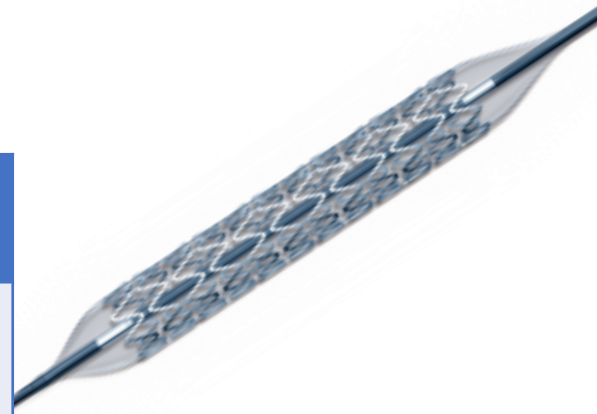
Synergy (Boston Scientific)

1. Bad appearance of the coating, accumulation in corners
2. Insufficient mechanical properties, great number of delamination on the expansion.
3. Angiolite has better mechanical properties (radial force) than Synergy

Angiolite vs…

Biomatrix (Biosensors) / Nobori (Terumo)

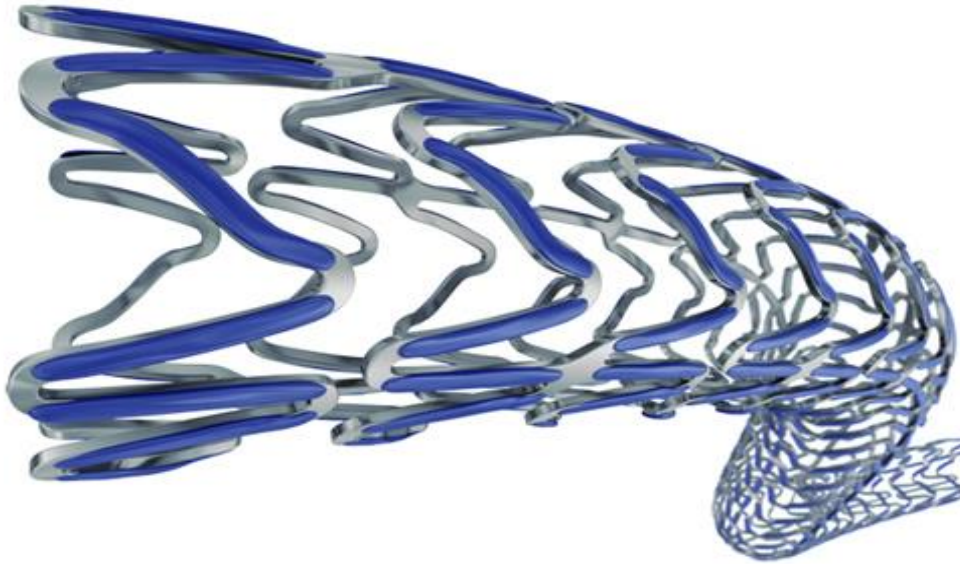
1. Improved safety endpoints (reduced rates of MI and definite stent thrombosis, respectively) with 2nd BS compared to the 1st BD
2. SS platform provoke more damage to the artery
3. The design of the stents Juno (Biomatrix) and S-stent (Nobori) is not specific for DES



Angiolite vs…

Ultimaster (Terumo)

1. Century trial - small number of patients (21), does not allow drawing any firm conclusions concerning clinical outcomes.
2. High coating thickness with a low drug dosage.



ABSORB, Abbott

Abbott Laboratories: *"Absorb GT1 BVS will only be available for use in clinical registry setting at select sites/institutions."*

ABSORB III trial 2-year results:

- significant increase in target lesion failure.

ABSORB II trial 3-year results:

- significantly higher rate of target vessel MI

AIDA trial (Absorb vs Xience)

- Increased stent thrombosis, including late stent thrombosis.

"*Given the lack of putative benefit in the ABSORB Japan and ABSORB II trials, the advantage of bioresorbable technology over metallic stents remains to be established." ©*

Polymer-free

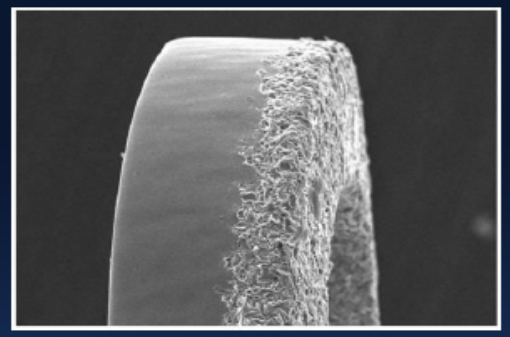
BioFreedom Stent (Biosensors)

Hypothesis: Polymer-free drug release via porous-eluting stents may reduce late events caused by polymer stent coatings.

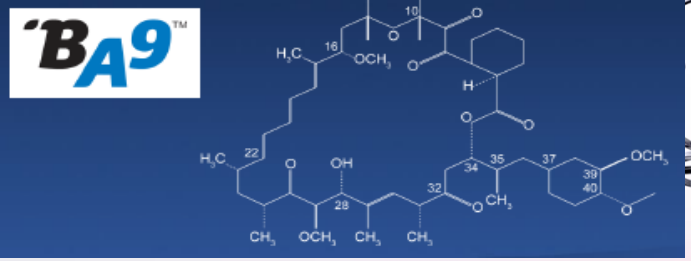
Potential advantages

- Avoid long term late adverse effects that might be attributable to the polymer
- Improved surface integrity since there is no polymer to be sheared or pealed away from the stent struts
- Possible shorter need of dual antiplatelet therapy

Selectively micro-structured surface holds drug in abluminal surface structures



Biolimus A9 - lipophilic



Angiolite vs…

Biofreedom (Biosensors)

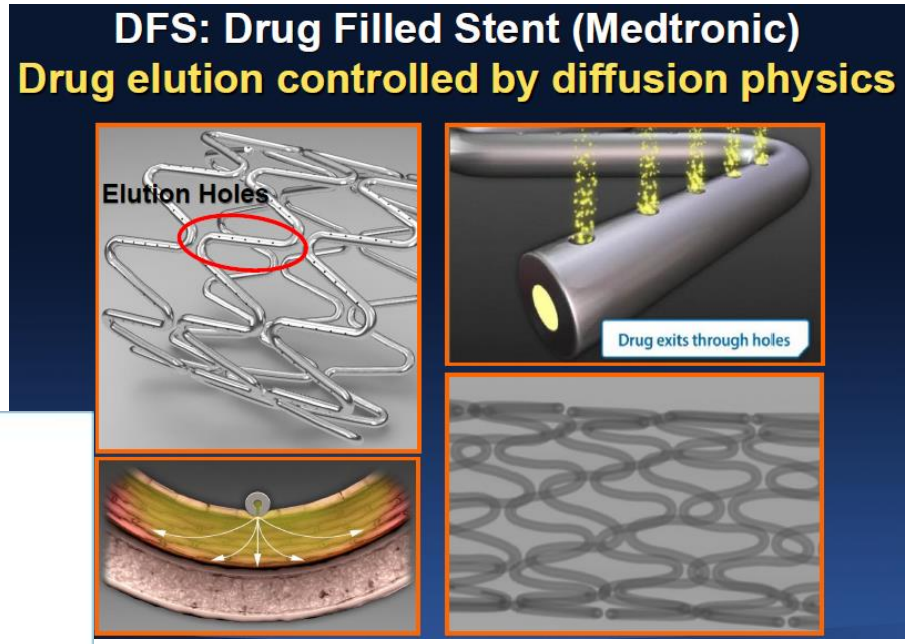
1. SS platform provoke more damage to the artery
2. Drug without polymer elute too fast
3. Without polymer is difficult to assure coating integrity, especially in calcified lesions
4. The design of the stent Gazelle* (Biofreedom) is not specific for DES

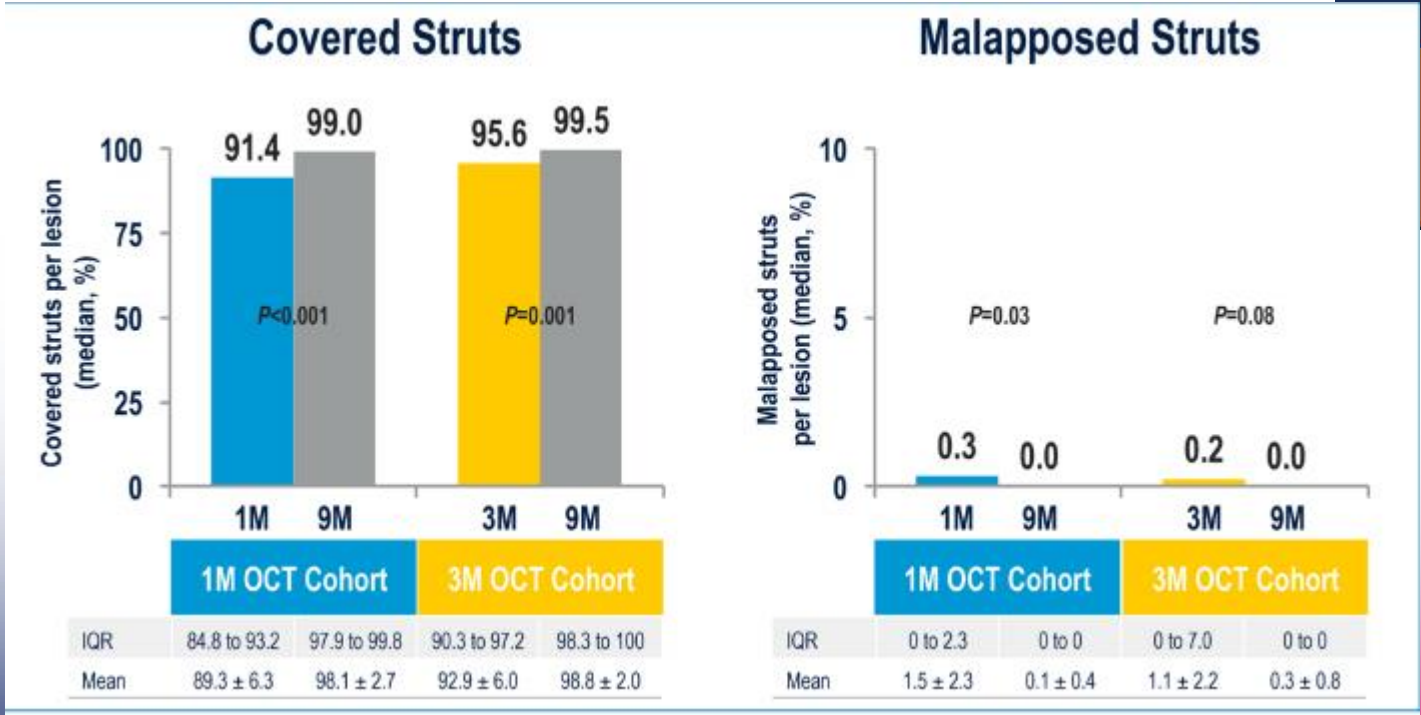
Drug-filled stent (DFS)

Same stent design as Resolute.

3 layers:

- Outer cobalt chromium
- Middle tantalum layer
- inner lumen coated with sirolimus





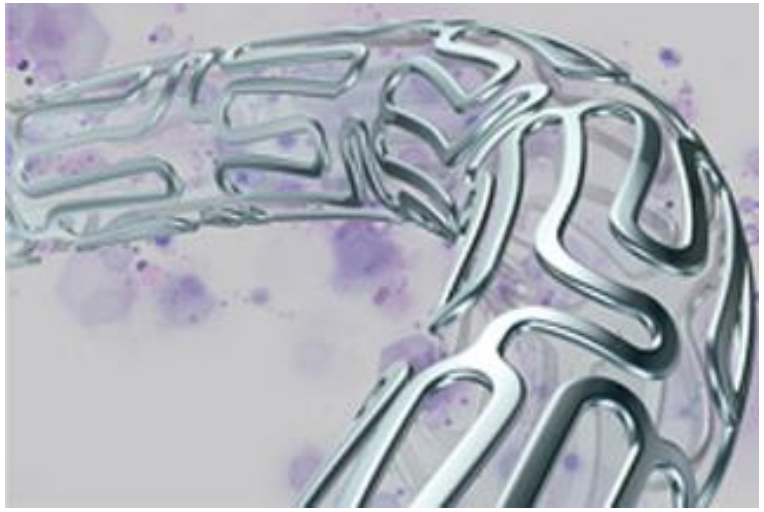
Clinical Update

PRISON IV investigation

Osiro (Biotronik)
Sirolimus-eluting stent (SES)
with a **biodegradable polymer**

VS

Xience (Abbott)
Everolimus-eluting stent (EES)
with a **durable polymer**



Primary endpoint
in-segment late lumen loss **0.12±0.59**
in-stent/in-segment **binary restenosis 8.0 %**
Rate of reocclusion 2.2 %

.

Primary endpoint
In-segment late lumen loss: **0.07±0.46 mm**
in-stent/in-segment **binary restenosis 2.1 %**
Rate of reocclusion 1.4 %

At 12-month follow-up, clinically indicated target lesion and vessel revascularization, **target vessel failure and major adverse cardiac events** were comparable between both groups

Competitors

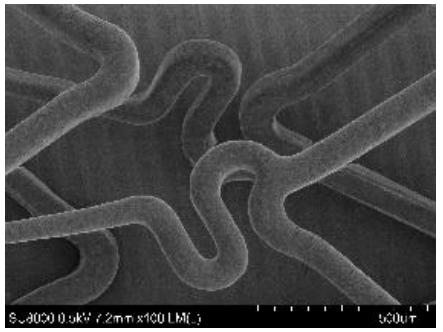
Portfolio of DES

ANCHOR Trial - Angiolite
TRANSFORM-OCT Synergy (Boston Scientific) vs Resolute (Medtronic)
COMPARATIVE TRIAL: Xience (Abbott) Zotarolimus vs Endeavor (Medtronic) Everolimus
CENTURY TRIAL Ultimaster (Terumo)

Competition

Portfolio of DES,

ANGIOLITE



	Boston Scientific Synergy	Terumo Ultimaster	Medtronic Resolute	Abbott Xience	Medtronic Endeavor*	iVascular Angiolite[3]
Sirolimus		+				+
Everolmus	+			+		
Zotalimus			+		+	
Biolimus						

OCT results at 3-month follow-up

	Medtronic Resolute	Abbott Xience	Medtronic Endeavor*	iVascular Angiolite[3]
# patients	45	36	24	**25**
Covered struts rate, %	78,4	81,5	81,5	**86,3**
Incomplete struts apposition, %	no data	2,3	1,4	**1,3**
Uncovered struts, %	no data	29,8	27,8	**7,5**
Neointimal thickness, µm	no data	59	126	**74**

QCA results

	Terumo Ultimaster	Medtronic Resolute	Abbott Xience	iVascular Angiolite
# patients	21	22	19	**56**
LLL (late lumen loss), mm	0,04	0,46	0,11	**0,07**
Binary restenosis, %	0,9	18,8	4,6	**0**

The **Ultimaster** OCT study from Terumo also has very low LLL and restenosis rate (0,9%). However, its **small number of patients (21),** does **not allow drawing any firm conclusions concerning clinical outcomes.**

ANCHOR

Post-Intervention, 3- and 6-Month Follow-Up QCA

	3-month	6-month
Pre-PCI	**n=28**	**n=70**
RVD, mm	3.01 ± 0.50	3.08 ± 0.67
MLD, mm	0.77 ± 0.32	0.90 ± 0.37
DS, %	73.6 ± 11.6	70.2 ± 12.0
Lesion length, mm	14.3 ± 5.8	13.0 ± 5.3
Post-PCI	**n=28**	**n=70**
RVD	2.99 ± 0.44	2.90 ± 0.58
MLD, mm	2.73 ± 0.44	2.66 ± 0.48
DS, %	7.4 ± 11.0	6.3 ± 12.7
Follow-up	**n=21**	**n=56**
In-stent MDL, mm	2.67 ± 0.42	2.56 ± 0.53
In-segment MLD, mm	2.07 ± 0.46	2.28 ± 0.59
In-stent DS, %	4.1 ± 15.1	8.8 ± 9.1
In-stent late loss, mm	0.03 ± 0.24	0.07 ± 0.37
In-stent binary restenosis, n (%)	0	0

The ANCHOR study results confirm the safety and efficacy of the Angiolite SES from iVascular (LVD Biotech) for the treatment of patients with de novo lesions.

High Efficacy

Proven and mainly supported by a **binary restenosis of 0%**, **low in-stent late lumen loss 0,07mm.**

High Safety

Supported by a very **Low target lesion failure rate 1%**, caused by **1% of target lesion revascularization.**

ANGIOLITE Trial

Non-inferiority Randomized Clinical Trial comparing the efficacy of Angiolite vs Xience in patients with PCI indication

LESION TYPE	Ischemic de novo >70% lesions in arteries with diameters between 2mm and 4mm
DEVICE	ANGIOLITE DES
PI	Dr. José Moreu Burgos (H Virgen de la Salud, Toledo, Spain)
DESIGN	Randomized, prospective and multicenter phase IV trial with CE-marked medical device, to be used according to the instructions for use and in the approved indications.

PATIENTS	200	INCLUSION	5 months	FOLLOW UP	1m | 6m | 12m

Results

Table 1. **Baseline characteristics**

	Angiolite N=110	Xience N=113	p
Age (years)	62.40 ±10.5	63.58 ±9.5	0.3797
Sex (male)	87 (79.1)	88 (77.9)	0.8253
Never Smoking	38 (35.8)	45 (41.7)	0.5840
Diabetes	27 (25.5)	32 (29.6)	0.4962
Hyperglycemia	60 (56.6)	55 (50.9)	0.4049
Hypertension	61 (57.5)	70 (64.8)	0.2753
Previous PCI	10 (9.4)	21 (19.3)	0.0402
History of MI prior to current episode of care	7 (6.6)	17 (15.6)	0.0363

The safety population consisted of **223 patients** with a mean age of 63.0 (± 10.0) years and a gender distribution of 78.5 / 21.5% men / women.

93.5% of the patients presented at least one risk factor, the most frequent risk factor being hypertension (61.2%) followed by dyslipidemia (53.7%).

Results

Table 2. Procedure outcomes

	Angiolite N=110	Xience N=113
Lesion classification		
A	23 (16.1)	33 (22.1)
B1	77 (53.8)	65 (43.6)
B2	30 (21.0)	46 (30.9)
C	13 (9.1)	5 (3.4)
Calcification	20 (14.0)	16 (10.7)
Lesion length	17.40 (6.74)	17.58 (8.05)
Number of lesions treated	1.31 (0.62)	1.38 (0.61)
Balloon pre-dilatation	87 (60.8)	88 (59.1)
Angiographic success	28 (84.8)	18 (78.3)

A total of **292 procedures** were performed in **223 patients** (1.3 procedure / patient). 91.0% of the procedures had radial access, in 13.4% OCT was performed and IVUS was used in 1.4%. Mean LVEF was 58.3 (± 8.8)%.

Direct stenting was attempted in 39.4% of the procedures, of which 94.0% were successful. Pre-dilatation with the balloon was necessary in 59.9% of the procedures and a post-dilation in 22.3%. An additional stent was required in 10.6% of the procedures.

99.7% of the procedures were successful and there was a complication with the Xience stent during the procedure. 99.7% of the patients had a TIMI 3 and 61.6% had residual stenosis.

Table 3. In-Hospital Outcomes

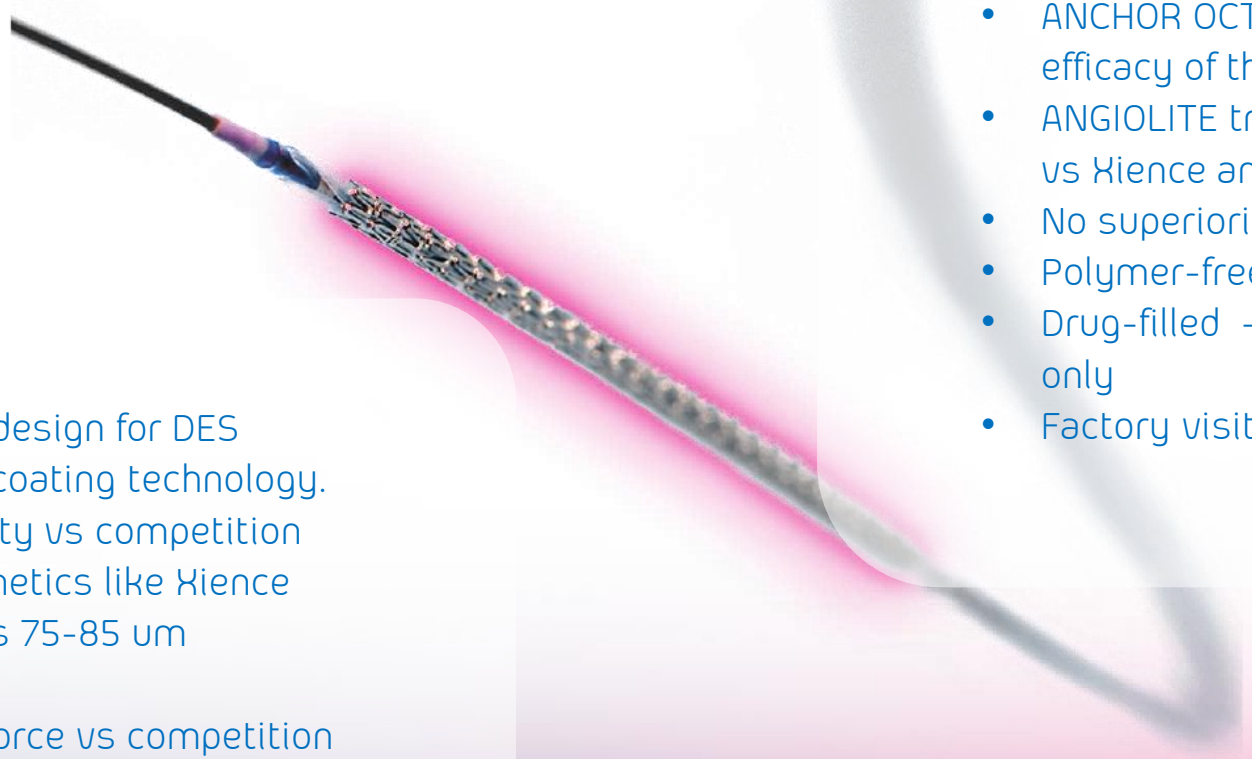
Outcomes (n)	Angiolite	Xience
Death	0	0
Myocardial infarction	0	0
Major vascular complications	0	0
Stroke	0	0
Coronary revascularization	0	0

Table 4. Post-Intervention, 6-Month Follow-Up QCA

	Angiolite	Xience	p
Pre-PCI	**n=110**	**n=113**	
MLD (mm) mean (SD)	0.90 (0.4)	1.04 (0.5)	0.0249
RVD (mm), mean (SD)	2.88 (0.8)	2.88 (0.8)	0.9909
DS (%), mean (SD)	69.33 (11.5)	64.16 (12.6)	0.0038
Post-PCI	**n=110**	**n=113**	
MLD (mm) mean (SD)	2.48 (0.5)	2.50 (0.5)	0.7837
RVD (mm), mean (SD)	2.83 (0.6)	2.81 (0.5)	0.8805
DS (%), mean (SD)	12.52 (5.7)	11.18 (5.7)	0.1106
Follow-up, n (%)	**n=33 (29.2)**	**n=23 (20.9)**	
In-stent			
MLD (mm) mean (SD)	2.39 (0.4)	2.45 (0.5)	0.5531
RVD (mm), mean (SD)	2.81 (0.5)	2.79 (0.5)	0.9104
DS (%), mean (SD)	14.84 (8.7)	12.04 (7.2)	0.1911
Acute gain (mm), mean (SD)	1.58 (0.6)	1.45 (0.6)	0.1320
In-stent late lost (mm), mean (SD)	**0.07 (0.4)**	**0.09 (0.4)**	0.7931
In-stent binary restenosis (%)	**0**	**0**	

In this preliminary **QCA data Angiolite shows non-inferiority vs Xience**.
Even though not all the patients data was analyzed yet**, Angiolite** already **shows similar safety as Xience**.

Key selling points of Angiolite



- Specific stent design for DES
- TransferWise coating technology. Coating integrity vs competition
- Sirolimus & kinetics like Xience
- Strut thickness 75-85 um
- A+ trackability
- Double radial force vs competition
- Minimum recoil vs competition

- ANCHOR OCT study confirms the safety and efficacy of the Angiolite DES.
- ANGIOLITE trial Angiolite shows non-inferiority vs Xience and similar safety as Xience.
- No superiority of 2nd BD vs 2nd BS
- Polymer-free only clinical data vs BMS
- Drug-filled - available for investigational use only
- Factory visit to show integral manufacture