

De nieuwste stents met de nieuwste eigenschappen

Lieuwe H. Piers

Cardioloog in opleiding

Onze Lieve Vrouwe Gasthuis

Amsterdam





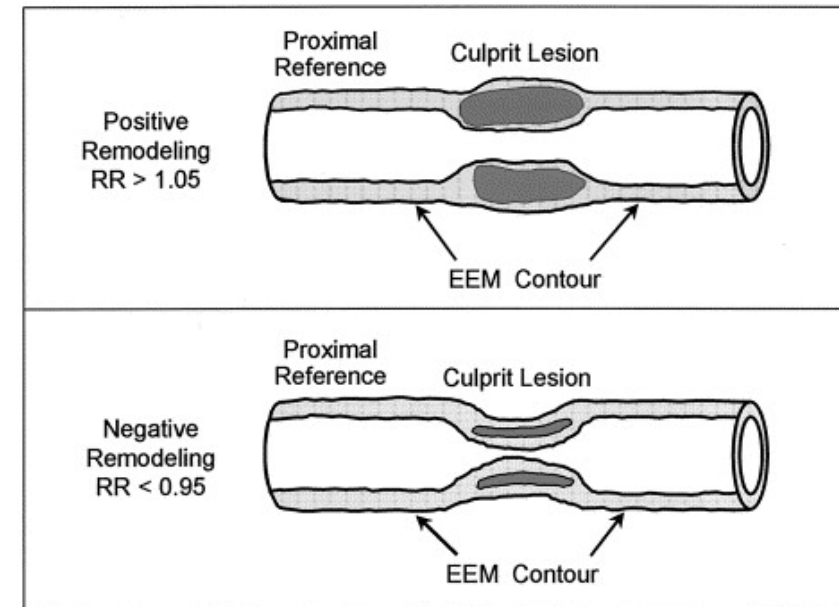
Overzicht

- Terminologie
- Key points
- Van toen tot nu
- Problemen met de huidige stents
- Wat zijn de oplossingen
- Wat zijn de nieuwste stents
 - Drug eluting balloon
 - Bioresorbable scaffold
 - Dual therapy stent
- Casus
- Wrap up
- Discussie



Terminologie

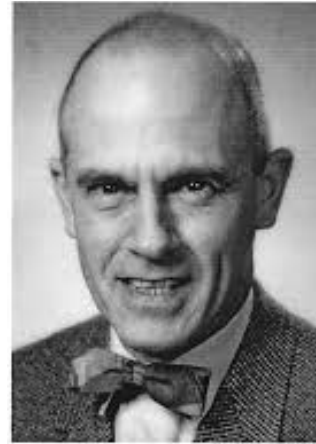
- PCI = percutane coronair interventie
- BMS = bare metal stent
- DES = drug eluting stent
- DEB = drug eluting balloon
- BVS = bioresorbable of bioabsorbable vascular scaffold
- DTS = dual therapy stent, of ECS = endothelium capturing stent
- DAPT = dubbele antiplaatjes therapie
- Recoil = terugveren van de vernauwing
- Remodelling = verandering in diameter



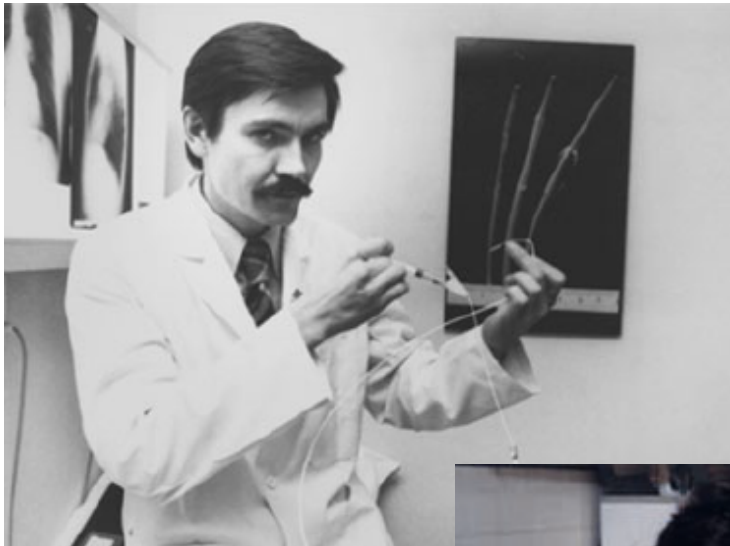
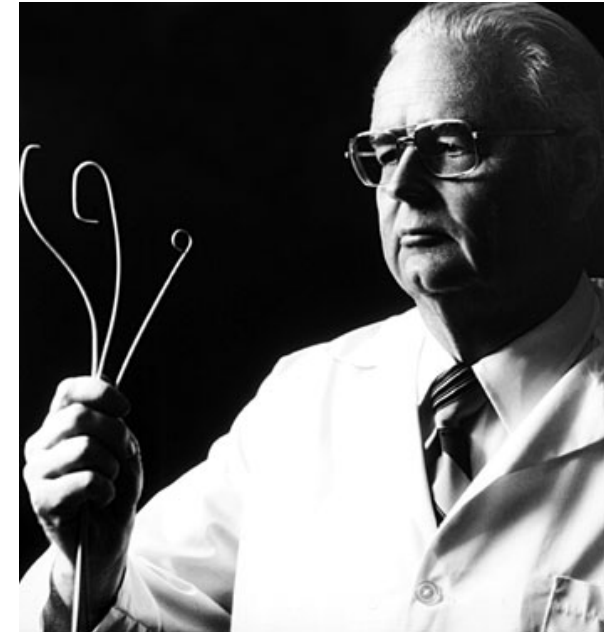
Key points

- Stent gaat snelle recoil tegen en bedekt dissectie en plaque
- Probleem is restenose en thrombose
- Neointima proliferatie en onvolledige endothelialisatie
- Stent blijft achter, lastig in de toekomst (en onnodig?)
- Met DEB lokale behandeling tegen negatieve remodelling
- BVS resorbeert in 2-5 jaren
- Echter mogelijk groter risico op in-stent trombose
- DTS bevordert endothelialisatie
- Mogelijk kortere behandeling met DAPT

Van toen tot nu



1964



1977



Dotter & Judkins, *Circulation* 1964
Grüntzig, *Lancet*, 1978

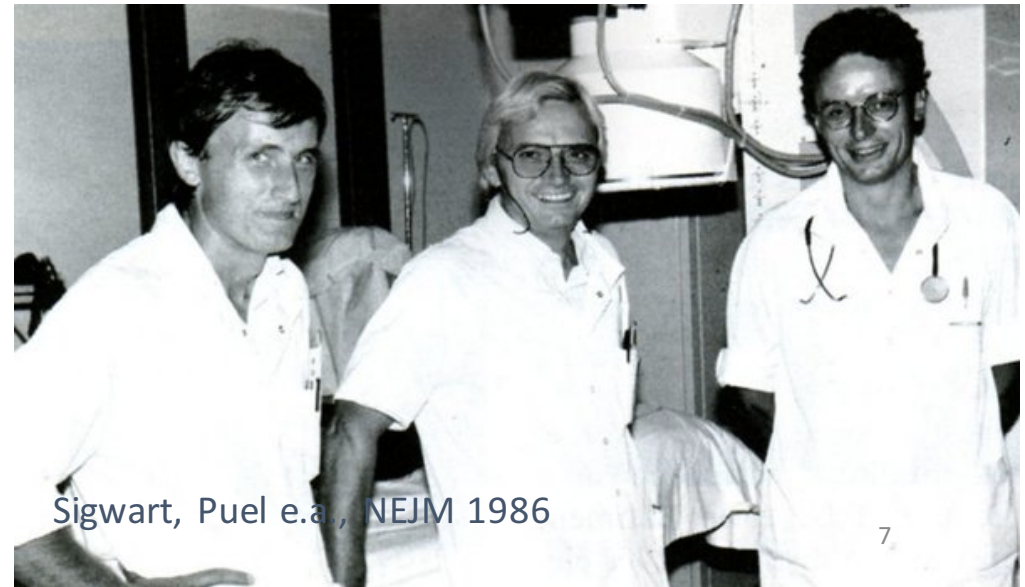


Van toen tot nu (2)

- POBA – plain old balloon angioplasty
- Onvoorspelbaar resultaat zowel
 - acuut → directe occlusie
 - later → negatieve remodelling

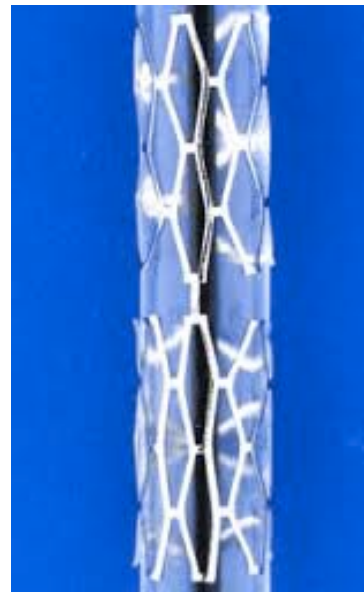
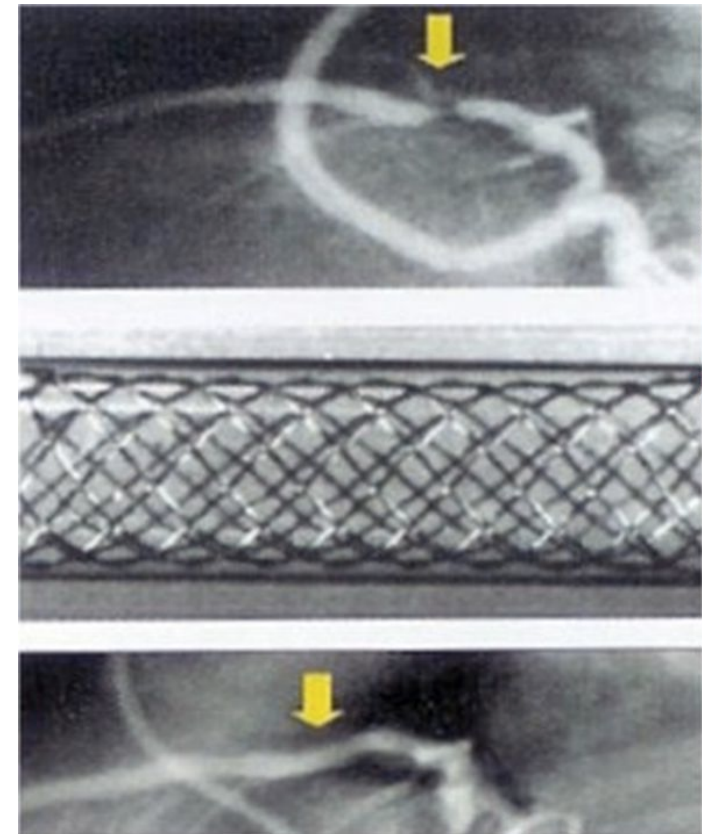


1986



Van toen tot nu (3)

- Stent
 - Afdekken van een dissectie
 - Afdekken beschadigde plaque
 - Betere dilatatie
 - Tegengaan van recoil
 - Tegengaan negatieve remodelling



1986

Palmaz-Schatz stent, Johnson & Johnson

olvg 



Van toen tot nu (4)

Table 1 Historical milestones in coronary artery stenting

Time	Person(s)	Landmark events
1964	Dotter and Judkins	Conceptual description of coronary angioplasty using an implantable prosthetic device
May 1977	Gruntzig and Myler	First coronary angioplasty during coronary artery bypass graft surgery
September 1977	Andreas Gruntzig	First coronary angioplasty in an awake patient; a revolution in interventional cardiology
1979	Geoffrey Hartzler	First balloon angioplasty to treat AMI
1986	Sigwart and Puel	The first implantation of a stent in human coronary arteries; second revolution in interventional cardiology
1991	Cannon and Roubin	First coronary stenting to treat AMI
1994	Serruys <i>et al.</i> and Fischman <i>et al.</i>	Publication of first two landmark (Benestent and STRESS) trials
1994	FDA	FDA-approved use of stents to treat acute and threatened vessel closure after failed balloon angioplasty
1999	Eduardo Sousa	The first drug (sirolimus) eluting stent implanted in human coronary artery; third revolution in interventional cardiology
2002–04	EME and FDA	Approvals of Cypher and Taxus stents in Europe and USA
2011	EME	Approval of Absorb BVS (bioresorbable vascular scaffold) in Europe; fourth revolution in interventional cardiology

FDA, Food and Drug Administration USA; EME, European Medicines Agency.

Iqbal, BMD, 2013



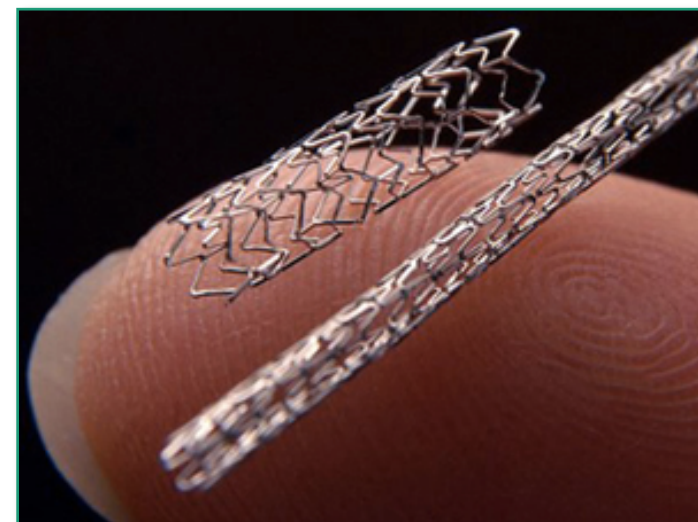
Van toen tot nu (4)

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Iqbal, BMD, 2013



Xience, Abbott

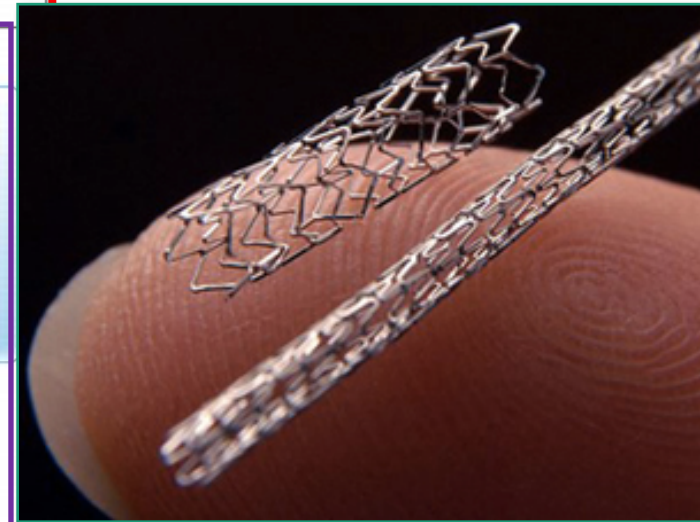
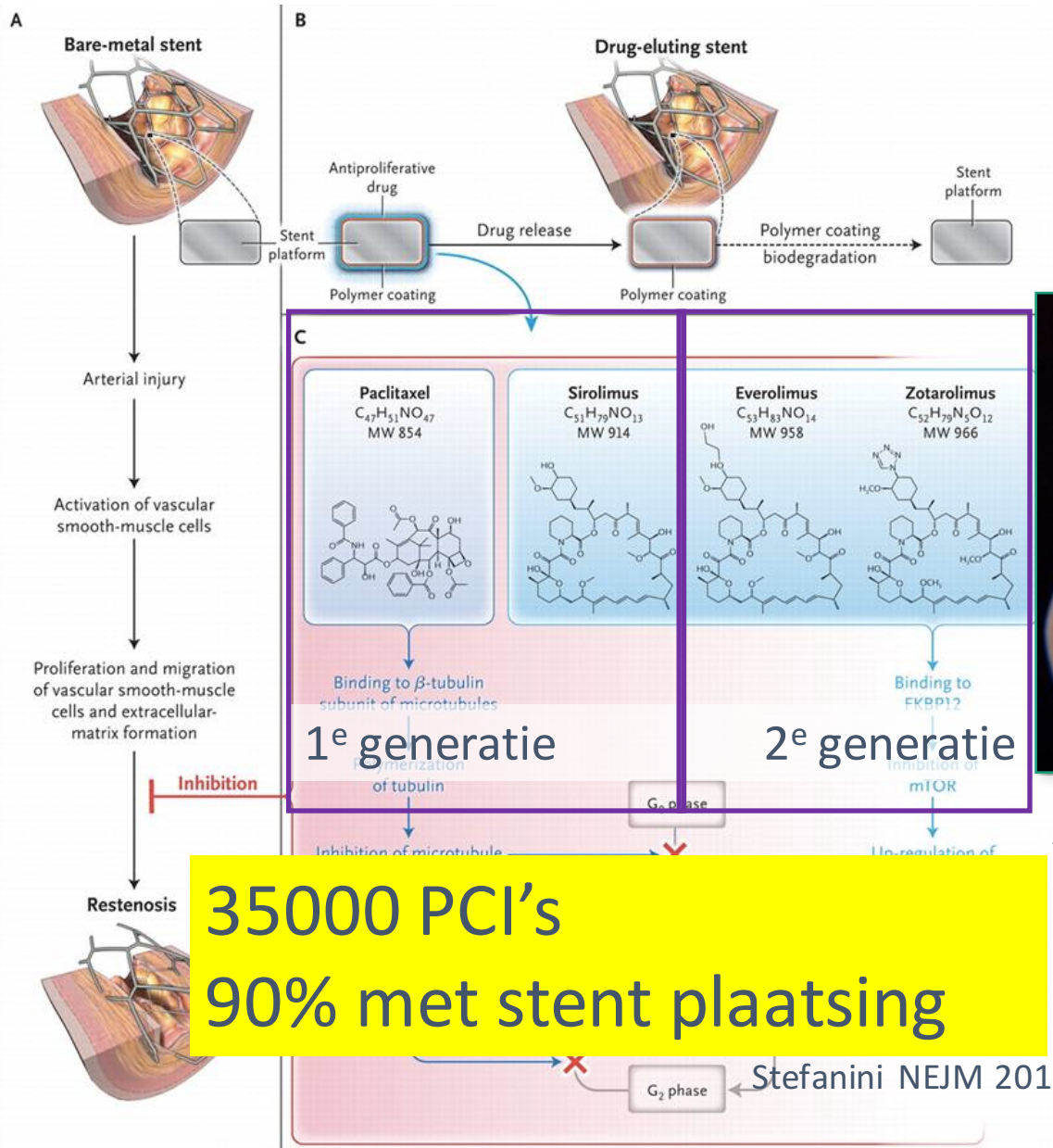


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FDA, Food and Drug Administration

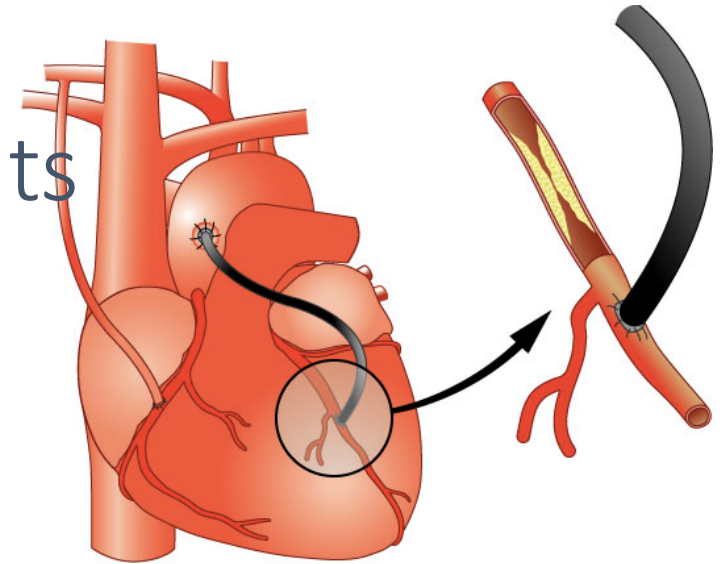


Xience, Abbott



Problemen met de huidige stents

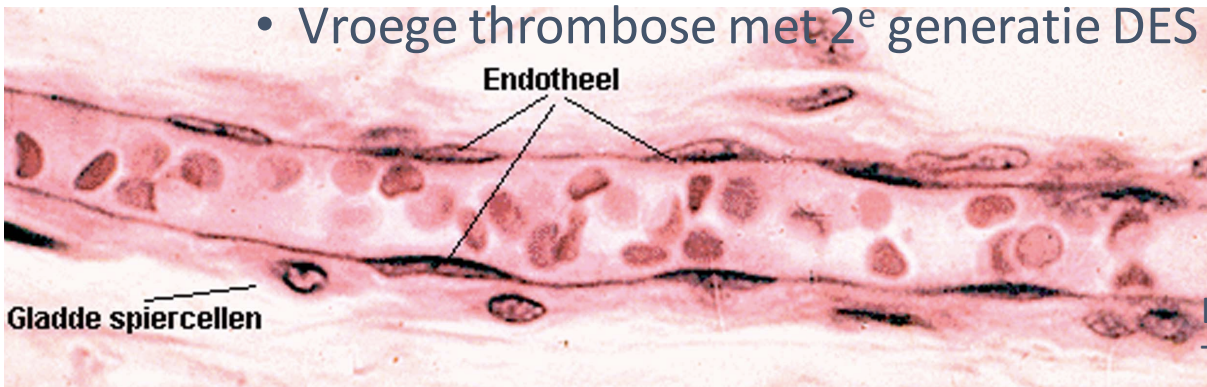
- Stent fixeert de diameter, geen vasoactieve respons mogelijk
- Jailing van zijtakken
- Op plaats van stent kan geen graft gezet worden
- Geen in-stent evaluatie met CT coronairangiografie
- Afwijkingen op MRI
- Thrombose van de stent
- In-stent restenose



Problemen met de huidige stents (2)

- Thrombose van de stent

- Stentstruts zorgt voor sterke activatie stollingscascade, derhalve plaatjesremming
- Beschermend endotheel wordt kapot gemaakt
- Endothelialisatie verloopt traag
- Vroeg, < 30 dagen = 50-70%
- Laat, > 30 dagen
- Mortaliteit 20%
- Vroege thrombose met 2^e generatie DES is < 1%, laat tot 3 jaar ~1.5%



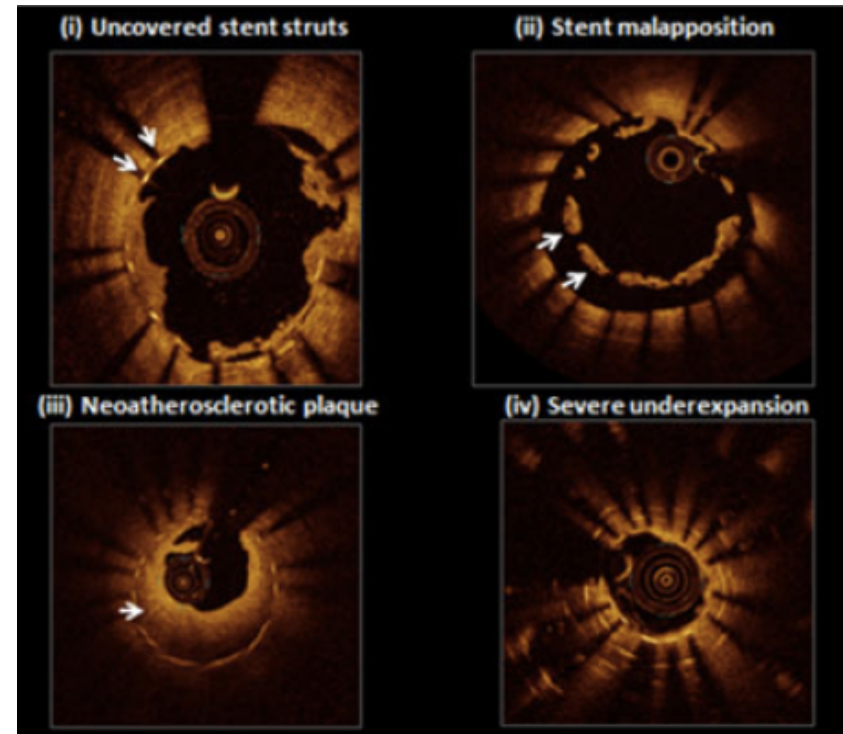
Byrne, Eur Heart J, 2013

Tada, JACC Cardiovasc Interv, 2013

Problemen met de huidige stents (3)

- Thrombose van de stent
 - Patiëntafhankelijk
 - DM, antiplaatjes medicatie
 - Procedure gerelateerd
 - Stentontplooiing, te kleine stent
 - **Stent gerelateerd**
 - Onvolledige endothelialisatie
 - Neoatherosclerose en vervolgens plaqueruptuur

DAPT



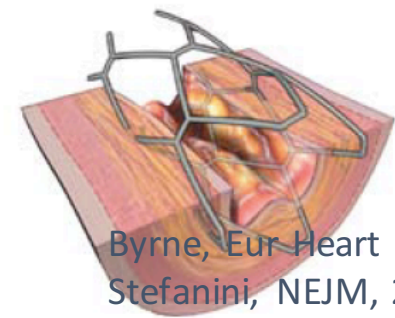
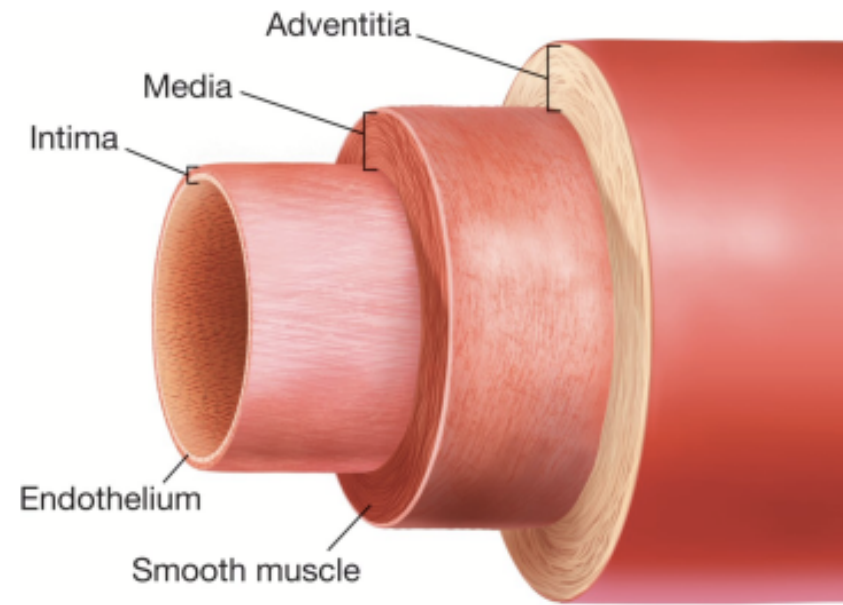
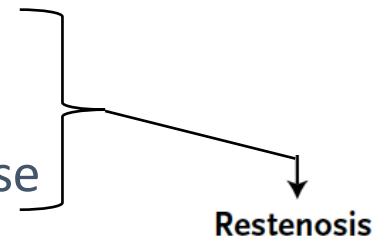
Byrne, Eur Heart J, 2013

Guagliumi, JACC Cardiovasc interv, 2012

Problemen met de huidige stents (4)

- In-stent restenose

- Beschadiging vaatwand door stent leidt tot ontstekingsreactie
- Ontwikkeling neointima vanuit gladde spiercellen
- Verdikking van de neointima
 - Zgn. neointima proliferatie
- Ontwikkeling neoatherosclerose



Byrne, Eur Heart J, 2013
Stefanini, NEJM, 2013

Problemen met de huidige stents (5)

- In-stent restenose
 - Patiëntafhankelijk
 - DM, nierinsufficiëntie
 - Procedure gerelateerd
 - Langere stents, kleinere vaten (< 2.5mm), reststenose
 - **Stent gerelateerd**
 - Grootte van de struts
 - Polymeer waar drug aan zit
 - BMS ~30%, DES ~12%

Byrne, Eur Heart J, 2013
Schiele, Z Kardiol 2005

Wat zijn de oplossingen

- Doorontwikkelen DES
 - Nieuwe antiproliferatieve stoffen
 - Plaatsing van de drug
 - Biodegradable polymeren
 - Polymeer-vrije DES
 - Dunnere stentstruts

Byrne, Eur H J 2015
Iqbal, BMD 2013



Durable polymer-coated stent	Biodegradable polymer-coated stent					
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Abbott/ Boston	Medtronic	Biosensors	Terumo	Translumina	Boston	Biotronik
Xience/ Promus	Resolute	BioMatrix	Ultimaster	Yukon Choice PC	Synergy	Orsiro
CoCr/PtCr-EES	CoNi-ZES	316L-BES	CoCr-SES	316L-SES	PtCr-EES	CoCr-SES



Strut thickness

81 μm	91 μm	120 μm	80 μm	87 μm	74 μm	60 μm
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Polymer coating

Circumferential	Abluminal	Circumferential
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Wat zijn de oplossingen (2)

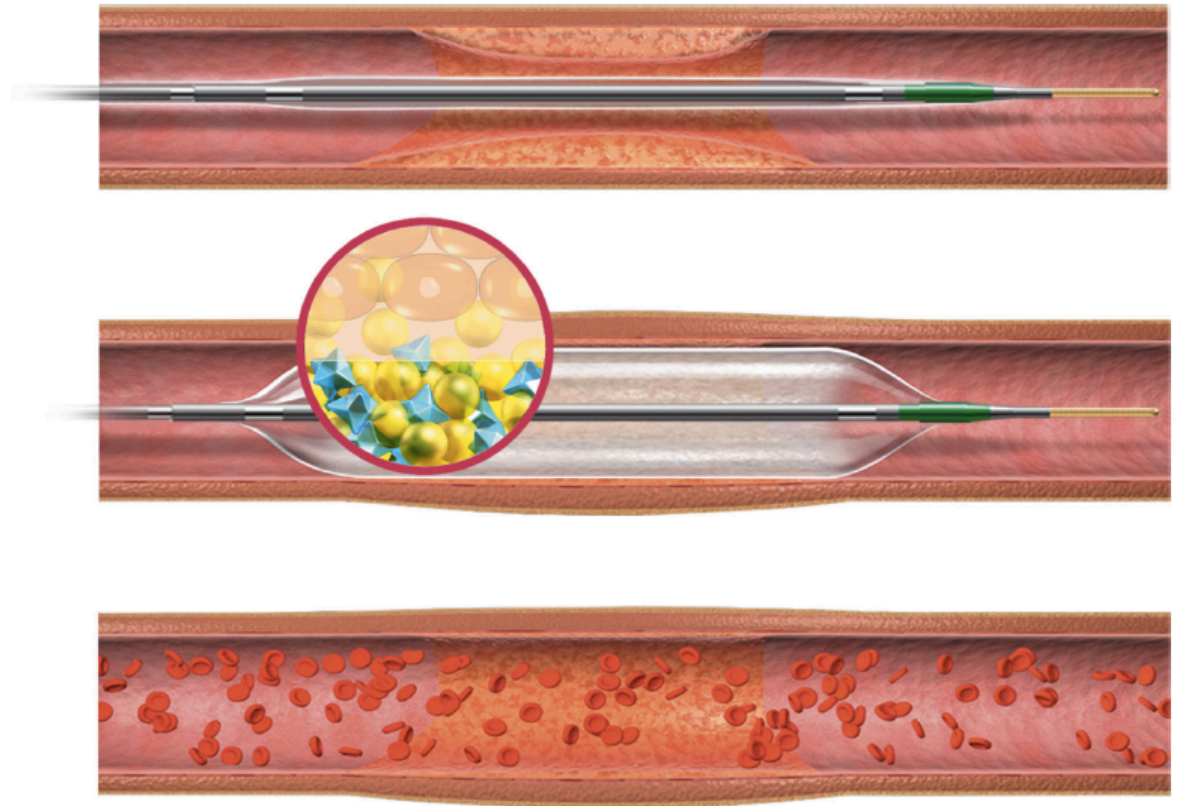
- Doorontwikkelen DES
 - Nieuwe antiproliferatieve stoffen
 - Plaatsing van de drug
 - Biodegradable polymeren
 - Polymeer-vrije DES
 - Kleinere stentstruts
- “Leave nothing behind”
 - Drug eluting balloon
 - Bioresorbable vascular scaffold
- Endothelialisatie bevorderen
 - Dual therapy stent

Byrne, Eur H J 2015
Iqbal, BMD 2013



Drug eluting balloon

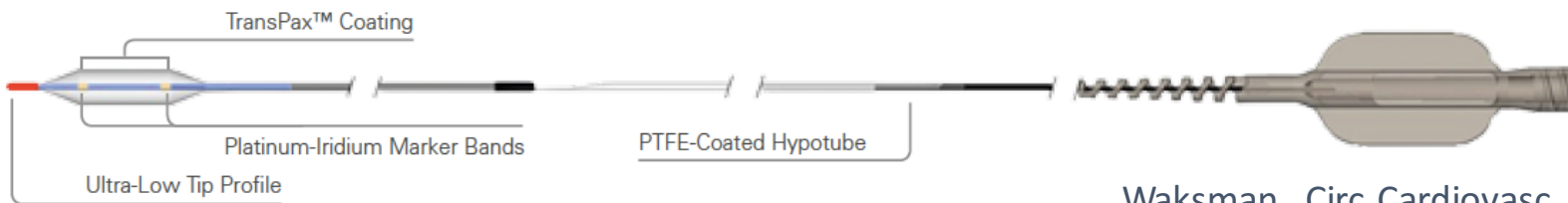
- POBA met Paclitaxel
- Drug gaat eraf binnen 1 minuut
- Geen hoge druk nodig
- Risico blijft acute recoil en dissectie wordt niet afgedekt



Fröhlig, BMC 2013

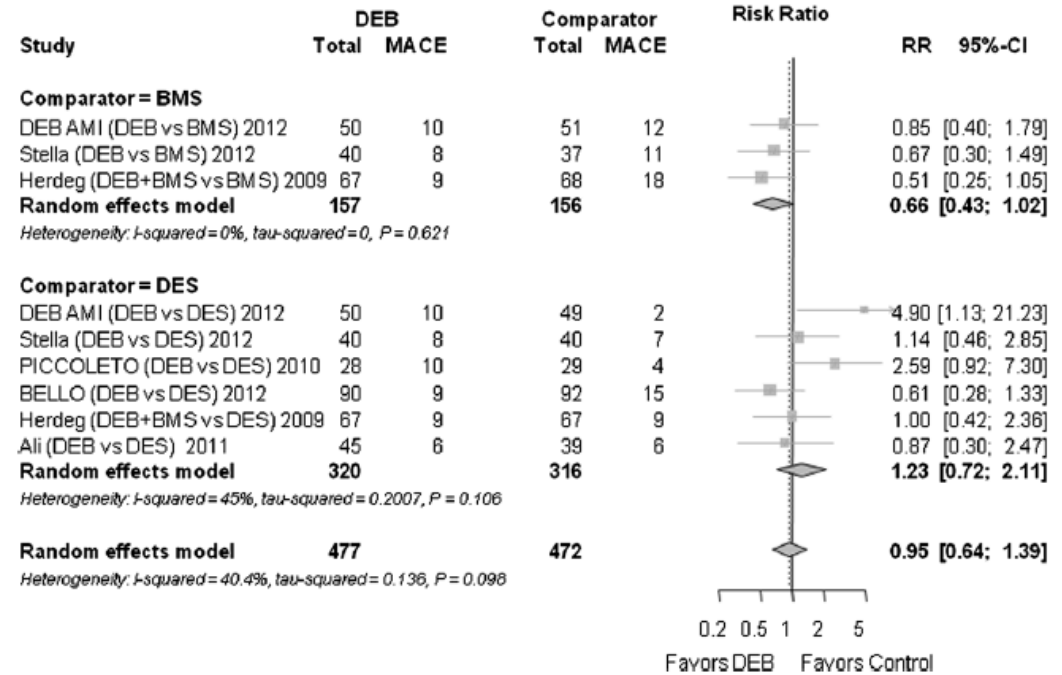
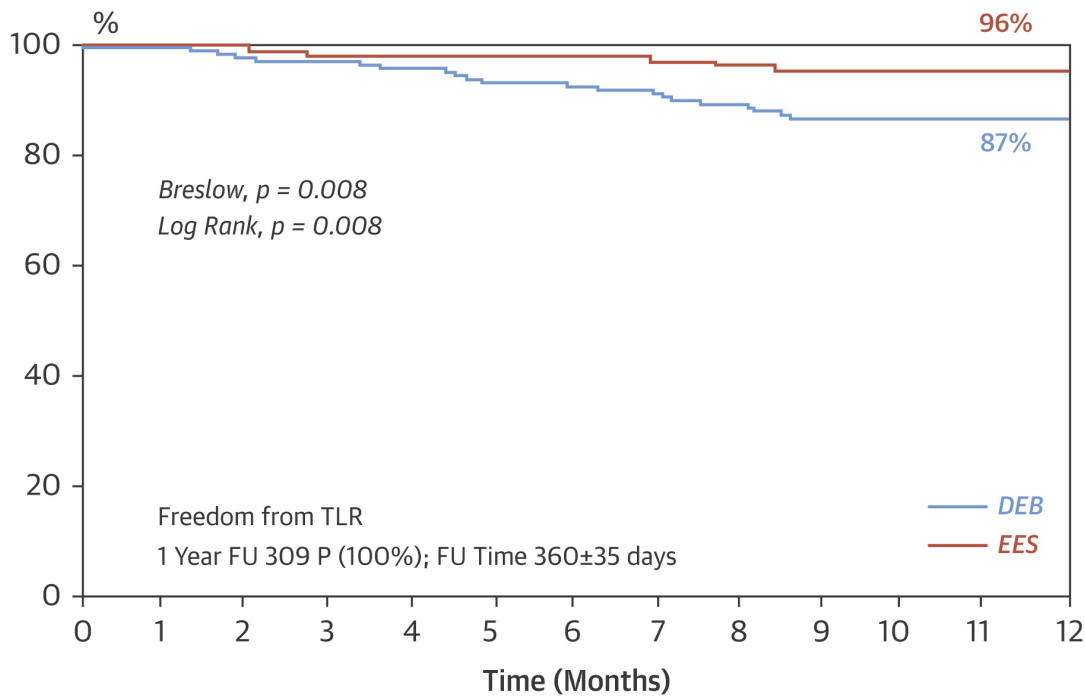
Drug eluting balloon (2)

- Paclitaxel gaat negatieve remodeling tegen
- Er blijft geen stent achter
- In stent restenose
- Kleine vaten (<2.5mm)
- Tortueuze vaten, waar een stent niet passeert



Waksman, Circ Cardiovasc Interv 2009

Drug eluting balloon (3)



Fröhlig, BMC 2013
Alfonso JACC 2015

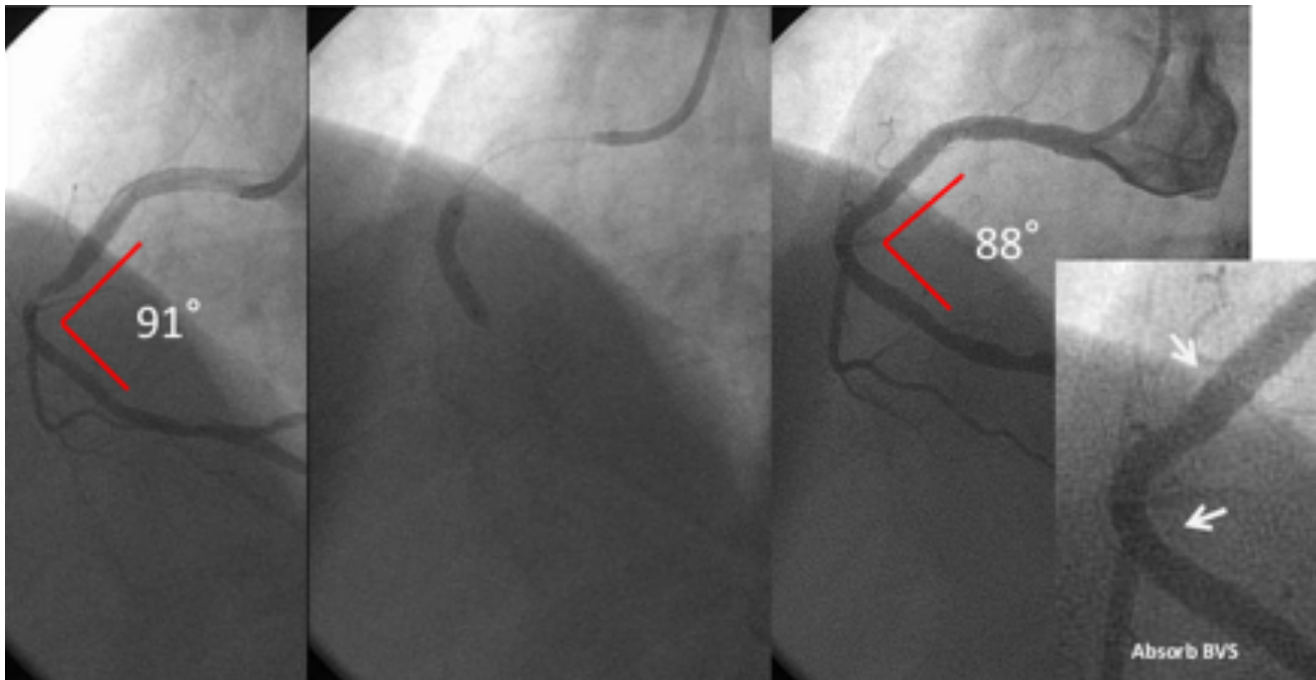
Bioresorbable vascular scaffold

- Scaffold:
 - Metaal
 - Bioabsorbable
 - Melkzuur
 - Bioresorbable
- Polymeer
- Drug

Table 3 Summary of biodegradable stents used in clinical studies

Stent	Manufacturer	Material	Coating	Drug	Thickness of struts (μm)	Resorption time (months)
Metallic						
AMS 1.0	Biotronik	Mg	None	None	165	<4
AMS 3.0	Biotronik	Mg	None	Paclitaxel	125	>4
AMS 4.0	Biotronik	Mg	PLLA	Sirolimus	120	>4
Polymeric						
Igaki-Tamai	Kyto Medical	PLLA	None	None	170	24
BVS 1.0	Abbott Vascular	PLLA	PDLLA	Everolimus	150	24
BVS 1.1	Abbott Vascular	PLLA	PDLLA	Everolimus	150	24
DESolve	Elixir	PLLA	None	Myolimus	150	12–24
Ideal BioStent	Xenogenics	SA/AA	Salicylate	Sirolimus	175	>12
REVA	REVA Medical	PTD-PC	None	None	200	24
ReZolve	REVA Medical	PTD-PC	None	Sirolimus	115–230	4–6
ART 18AZ	ART	PDLLA	None	None	170	3–6
Amaranth	Amaranth	PLLA	None	None	150–200	3–6

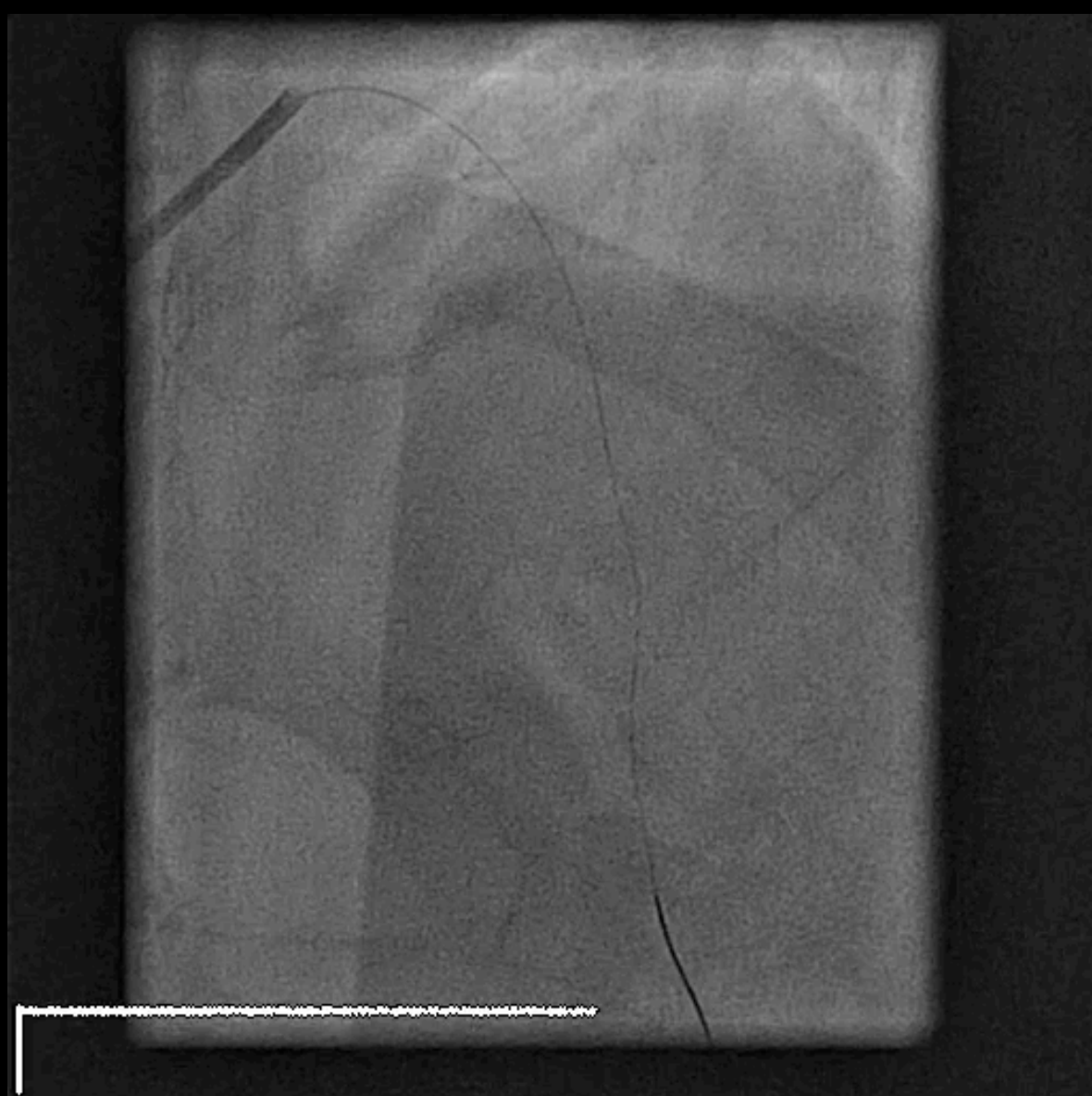
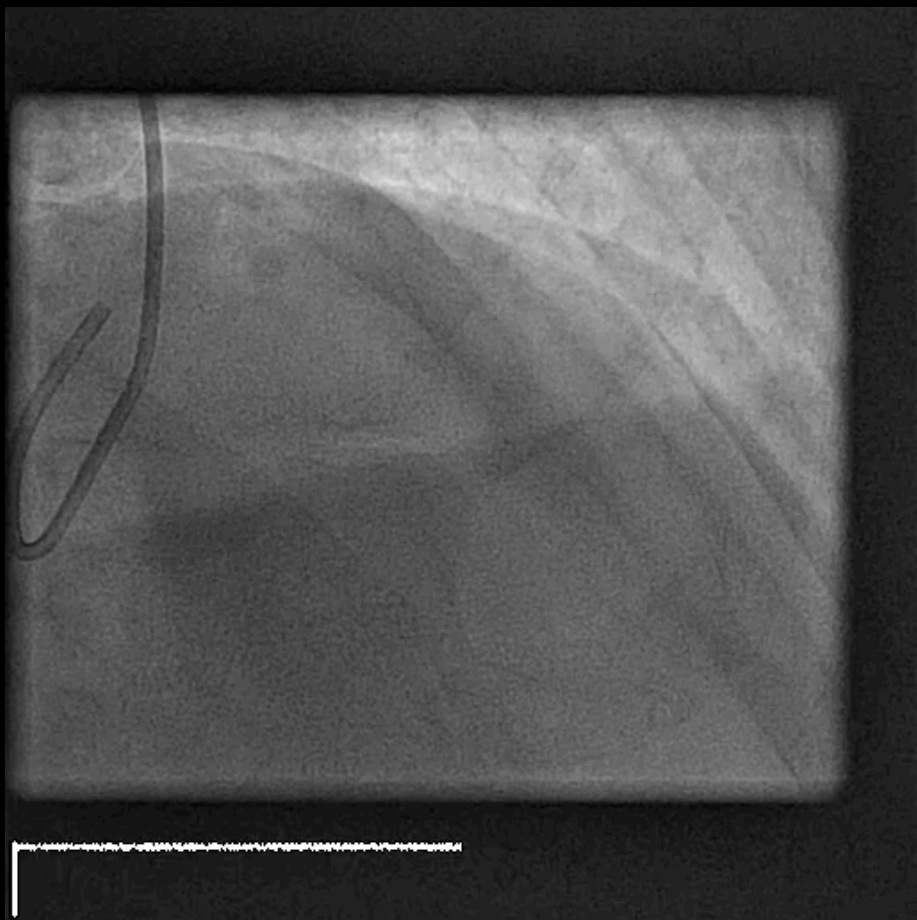
Bioresorbable vascular scaffold (2)



Serruys PCR 2010

An endoscopic view of the colon, showing a large, polypoid lesion (polyp) protruding from the mucosal surface. The lesion is dark and has a lobulated, irregular shape. The surrounding mucosa is reddish and appears normal. A white horizontal line with small tick marks is visible at the bottom of the image, likely a scale or measurement tool.

ABSORB Cohort B - Courtesy of RJ van Geuns, Erasmus Medical Center, Rotterdam



Bioresorbable vascular scaffold (6)

- Herstel van vasomotore functie
 - Diermodellen
 - Beperkte data in mensen
- Even veilig als 2^e generatie DES (Xience) wat betreft
 - Significante restenose
 - Myocardinfarct en dood
- Herstel curvatuur van het vat
- Graft na 24 maanden mogelijk

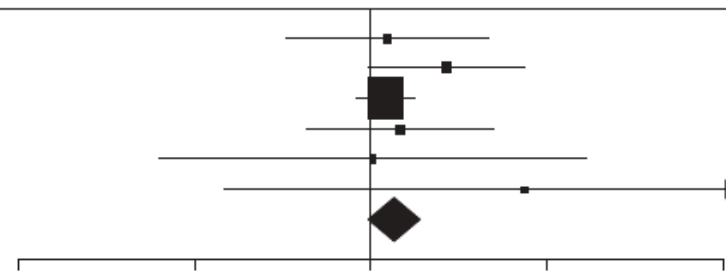
Sarno, Int J Cardiovasc Imaging 2012
Stone, Lancet 2016



Bioresorbable vascular scaffold (7)

B Myocardial infarction

	BVS		EES		Weight (%)	Fixed-effects odds ratio (95% CI)
	Events	Total	Events	Total		
ABSORB China	5	238	4	237	6.1	1.25 (0.33-4.66)
ABSORB II	15	335	2	166	10.1	2.71 (0.97-7.56)
ABSORB III	90	1313	38	677	74.5	1.23 (0.84-1.79)
ABSORB Japan	9	265	3	133	7.2	1.48 (0.44-4.98)
EVERBIO II	1	78	1	80	1.4	1.03 (0.06-16.55)
TROFI II	1	95	0	96	0.7	7.47 (0.15-376.35)
Overall	121	2324	48	1389	100	1.36 (0.98-1.89)

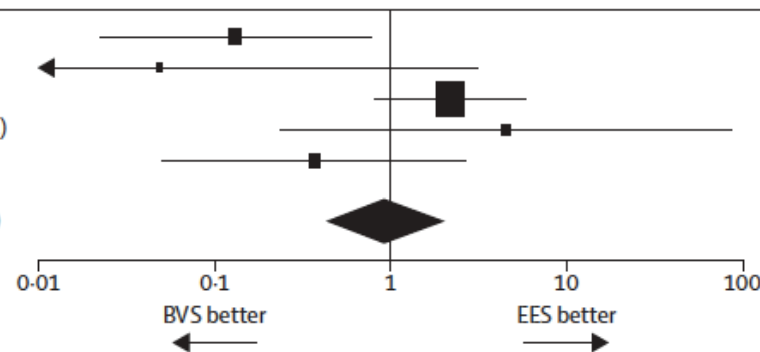


Heterogeneity: $\chi^2=2.80$, $df=5$; $p=0.73$; $I^2=0\%$
 Test for overall effect: $Z=1.86$; $p=0.06$

Random-effects odds ratio 1.36 (95% CI 0.98-1.89)

C Death

	BVS		EES		Weight (%)	Fixed-effects odds ratio (95% CI)
	Events	Total	Events	Total		
ABSORB China	0	238	5	237	18.0	0.13 (0.02-0.77)
ABSORB II	0	335	1	166	3.2	0.05 (0.00-3.15)
ABSORB III	15	1313	3	677	58.1	2.18 (0.82-5.81)
ABSORB Japan	2	265	0	133	6.4	4.51 (0.24-85.41)
EVERBIO II	1	78	3	80	14.2	0.37 (0.05-2.68)
TROFI II	0	95	0	96		Not estimable
Overall	18	2324	12	1389	100	0.95 (0.45-2.00)



Heterogeneity: $\chi^2=11.47$, $df=4$; $p=0.02$; $I^2=65\%$
 Test for overall effect: $Z=0.14$; $p=0.89$

Random-effects odds ratio 0.95 (95% CI 0.45-2.00)

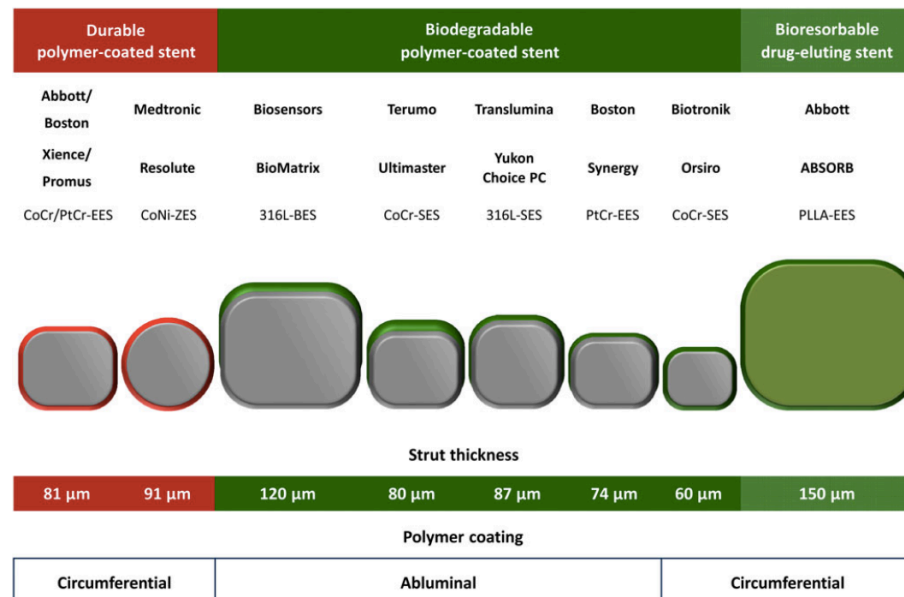
Cassese, Lancet 2016

Bioresorbable vascular scaffold (8)

	BVS (n=2164)	CoCr-EES (n=1225)	Fixed-effects RR (95% CI)	p value
Patient-oriented composite endpoint (mortality, myocardial infarction, or revascularisation)	255/2147 (11.9%)	129/1212 (10.6%)	1.09 (0.89–1.34)	0.38
Device-oriented composite endpoint (target lesion failure)	141/2147 (6.6%)	63/1212 (5.2%)	1.22 (0.91–1.64)	0.17
Early (0–30 days)	89/2154 (4.1%)	32/1222 (2.6%)	1.49 (1.00–2.22)	0.051
Late (30 days–1 year; landmark)	53/2140 (2.5%)	31/1211 (2.6%)	0.97 (0.62–1.51)	0.90
All-cause mortality	17/2147 (0.8%)	9/1212 (0.7%)	1.12 (0.47–2.69)	0.80
Cardiac	8/2147 (0.4%)	4/1212 (0.3%)	1.26 (0.33–4.82)	0.74
Non-cardiac	9/2147 (0.4%)	5/1212 (0.4%)	1.02 (0.32–3.25)	0.97
All myocardial infarction	123/2147 (5.7%)	49/1212 (4.0%)	1.34 (0.97–1.85)	0.08
Peri-procedural (Absorb III definition)	62/2126 (2.9%)	26/1196 (2.2%)	1.29 (0.82–2.03)	0.27
Peri-procedural (SCAI definition)	16/2126 (0.8%)	9/1196 (0.8%)	0.97 (0.44–2.14)	0.94
Non-peri-procedural (Absorb III definition)	61/2144 (2.8%)	22/1211 (1.8%)	1.48 (0.91–2.40)	0.11
Target vessel-related myocardial infarction	110/2147 (5.1%)	40/1212 (3.3%)	1.45 (1.02–2.07)	0.04
Non-target vessel-related myocardial infarction	15/2147 (0.7%)	11/1212 (0.9%)	0.75 (0.34–1.66)	0.48
All revascularisation	169/2147 (7.9%)	93/1212 (7.7%)	1.02 (0.80–1.30)	0.89
Ischaemia-driven target lesion revascularisation	57/2147 (2.7%)	28/1212 (2.3%)	1.14 (0.73–1.79)	0.56
Ischaemia-driven target vessel revascularisation	92/2147 (4.3%)	45/1212 (3.7%)	1.14 (0.80–1.62)	0.47
Device thrombosis (definite or probable)	28/2130 (1.3%)	7/1204 (0.6%)	2.09 (0.92–4.75)	0.08
Definite	24/2130 (1.1%)	6/1204 (0.5%)	2.06 (0.85–5.03)	0.11
Probable	4/2130 (0.2%)	1/1204 (0.1%)	2.28 (0.28–18.51)	0.44
Early (0–30 days)	20/2152 (0.9%)	6/1221 (0.5%)	1.76 (0.72–4.34)	0.22
Late (30 days–1 year; landmark)	8/2128 (0.4%)	1/1204 (0.1%)	4.10 (0.52–32.56)	0.18

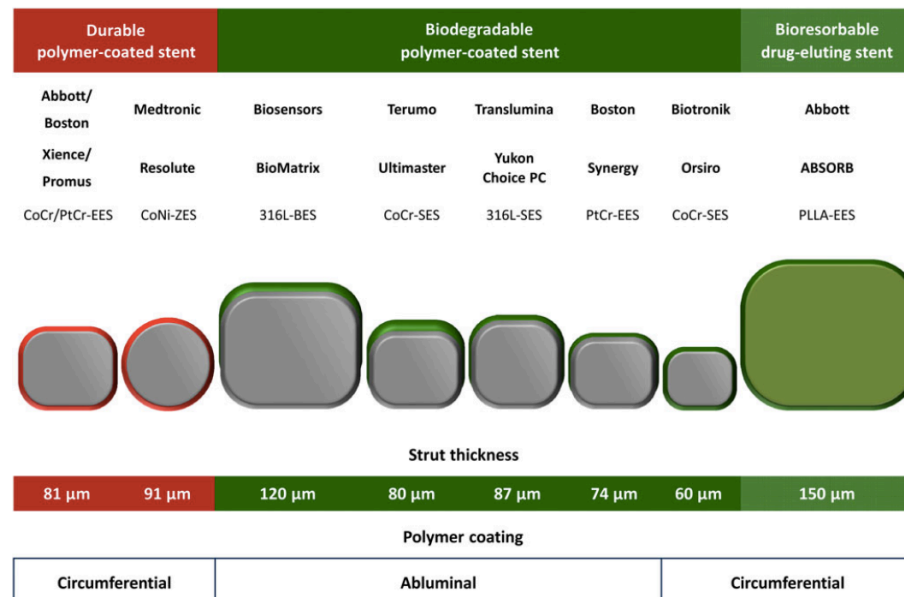
Bioresorbable vascular scaffold (9)

- Scaffold minder sterk dan stent, mogelijk breuk van struts
- Dikke stentstruts
 - Echter de zorg bestaat dat dunnere struts breekbaarder zijn
 - Bioabsorbable struts met Magnesium-basis sterker?
- Leercurve



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Bioresorbable vascular scaffold (9)

5 Ps for optimal implantation of Absorb

1. Prepare the Lesion
2. Properly Size the Vessel
3. Post-Dilate with a Non-Compliant Balloon
4. Pay Attention to Expansion Limits
5. Prescribe Dual Anti-Platelet Therapy

van struts

der zijn

Bioresorbable
drug-eluting stent

Abbott

ABSORB

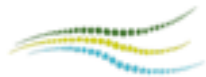
PLLA-EES



150 µm

Circumferential

olvg 
32



Absorb is authorized for sale in CE Mark and certain independently regulated countries outside the United States. Please check the regulatory status of the device in your geographical location before distribution. For presentation outside the U.S. and Japan only.

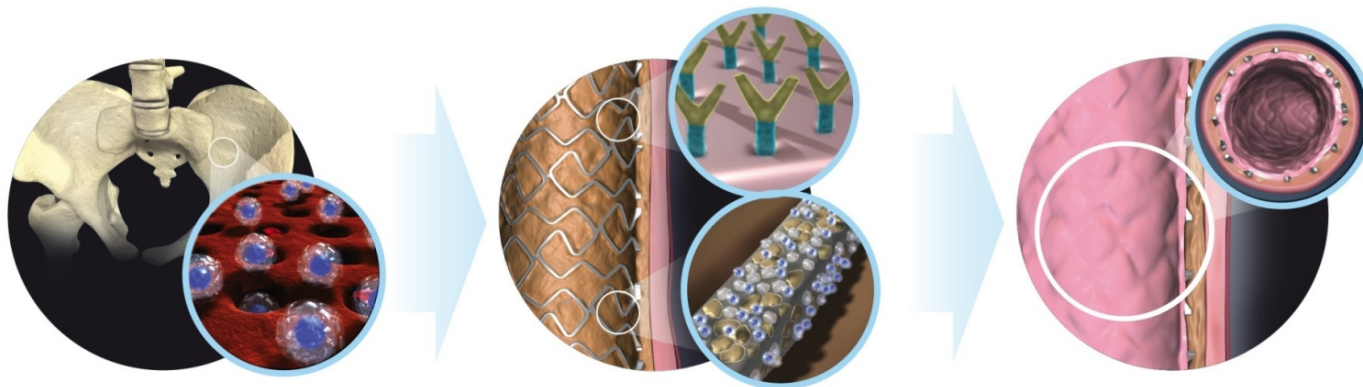
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AP2937171-0US Rev. H



Dual therapy stent, COMBO-stent

- Stainless steel stent
- Buitenzijde sirolimus met afbreekbaar polymeer
- Binnenzijde CD34+-endotheelvoorlopercel antilichamen



Bone marrow derived EPCs circulate in the blood stream.

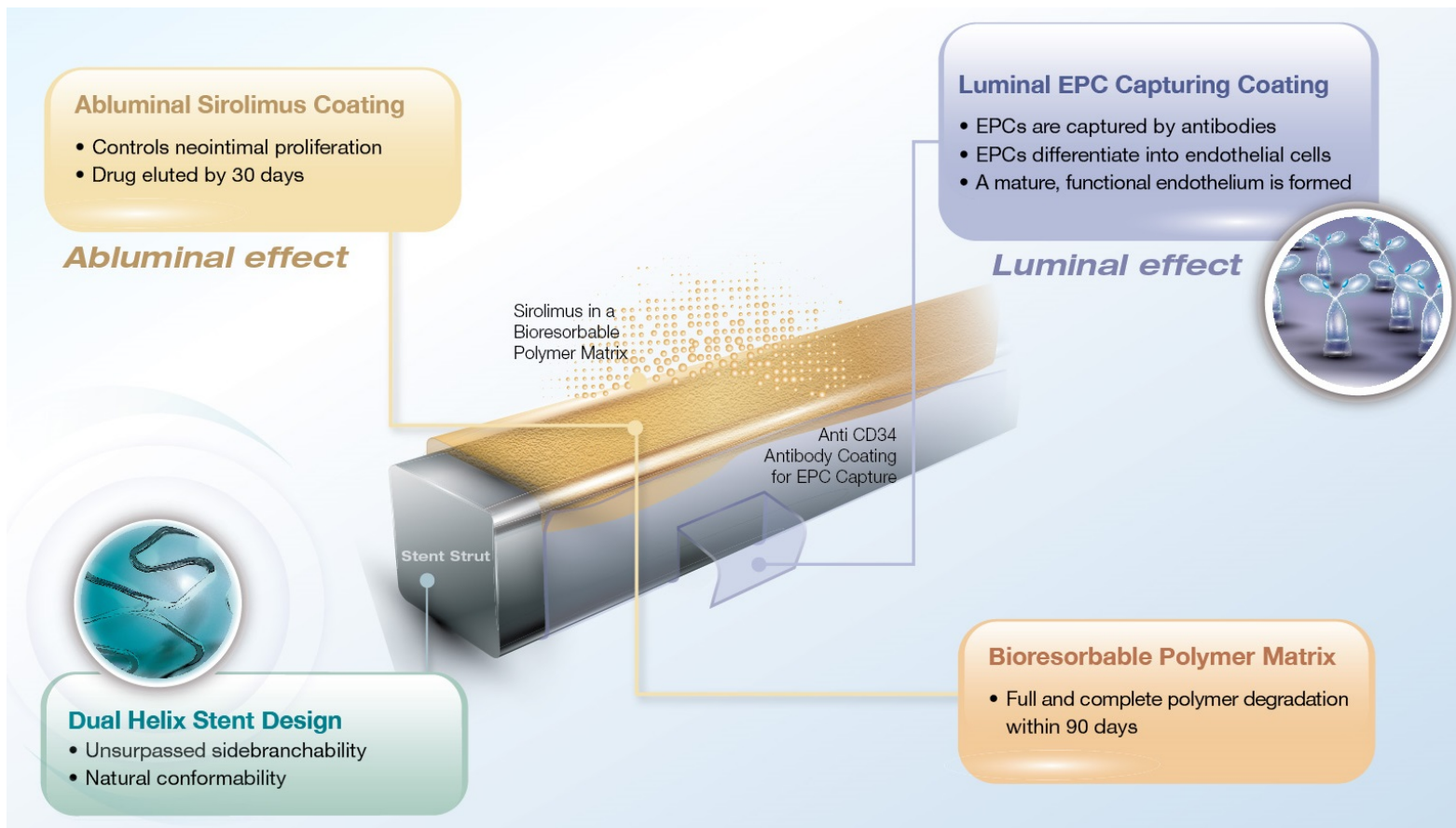
Genous with anti-hCD34 antibody on the stent surface captures EPCs.

EPCs mature into endothelial cells, healing the artery with restored endothelium.

Dual therapy stent (2)

- <https://www.orbusneich.com/en/media/images-videos>

Dual therapy stent (3)



Dual stent therapy (4)

- Belangrijke eigenschap is de “genezende” werking door actieve endothelialisatie
- Immers: incomplete endothelialisatie leidt tot trombose en endotheel beschermt tegen neointima proliferatie
- Preklinische studies tonen dat <2 weken 99% van de struts is bedekt met endotheel (t.o.v. 55% met DES)
- Niet slechter dan een DES wat betreft dood, infarct of re-interventie op 1 jaar
- 1 maand DAPT is voldoende



Casus

- Man 35 jaar
- familiale hypercholesterolemie, gebruikt statine
- angina pectoris
- CAG: uitgebreid coronairlijden, significante laesie mid-LAD en MO



Casus

- Man 65 jaar
- PCI 2014 RCx DES Xience, overigens wandonregelmatigheden
- Angina pectoris
- CAG: in-stent restenose RCx



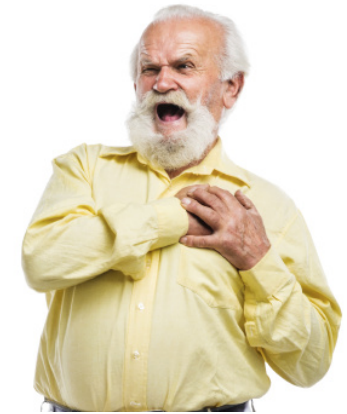
Casus (2)

- Vrouw 30 jaar
- blanco
- STEMI anterior
- CAG: geen tekenen atherosclerose, dissectie proximale LAD



Casus (3)

- Man 75 jaar
- Uretersteen, waarvoor vergruizing gepland
- NSTEMI
- CAG: diffuse atherosclerose, significante laesie distale RCA



Wrap up

- Stent gaat snelle recoil tegen en bedekt dissectie en plaque
- Probleem is restenose en thrombose
- Neointima proliferatie en onvolledige endothelialisatie
- Stent blijft achter, lastig in de toekomst (en onnodig?)
- DES met afbreekbare polymeren
- Met DEB lokale behandeling tegen negatieve remodelling
- BVS resorbeert in 2-5 jaren
- Echter mogelijk groter risico op in-stent trombose
- DTS bevordert endothelialisatie
- Mogelijk kortere behandeling met DAPT

Discussie



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