Late Complication: Stent Fractures and Restenosis

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Thin Stent Strut Profiles on New Stent Platforms

	1 st Generation			Future 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/mm ²	l μg/mm²	lµg/mm²	1.6 µg/mm²	1 μg/mm²	l 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		

The SYNERGY™ stent is an investigational device in the US and Japan and not for sale.

Representative Images of 2nd- vs. 1st-generation DES in Human Coronary Arteries

1st-generation DES

2nd-generation DES

SES 13 months PES 11 months

E-ZES 3 months **CoCr-EES 6 months**





Otsuka F, MD. AHA2011

Late Stent Thrombosis in CoCr-EES vs. 1st-generation DES



Otsuka F, MD. TCT2011

55M, CoCr-EES implanted within PES in RCA 6 months antemortem, died suddenly.



CoCr-EES strutsPES struts



Morphometric Analysis

CoCr-EES vs. 1st-generation DES



Values are expressed as medians (interquartile range). Bar graph shows median values.



Morphometric Analysis

CoCr-EES vs. 1st-generation DES



Values are expressed as medians (interquartile range) or means \pm SD. Bar graph shows median or mean values.

Otsuka F, MD. TCT2011

Maximum Neointimal Thickness and Prevalence of Unhealed Struts Stratified by Duration of Implant

Maximum neointimal thickness

Prevalence of unhealed struts*



Maximum neointimal thickness are expressed as median values.



* An unhealed strut was defined as >30% ratio of uncovered-to-total stent struts per cross section. (Finn AV, et al. Circulation 2007;115:2435-41.)



Classification of Stent Fractures

Fracture



I=single strut fracture, II=2 or more struts fracture without deformation, III=2 or more struts fracture with deformation, IV=multiple fractures with acquired transection without gap, V=multiple fractures with acquired transections with gap

Among 200 DES lesions in the CVPath registry, stent fracture was documented in 51 (SES 32, PES 19) lesions (29%). Grade V fracture was identified in 9 (SES 6, PES 3) lesions.



Nakazawa G, et al. JACC 2009;54:1924-31

Grade V Stent Fracture





65 yrs old F stent duration 172 days. Presented with AMI - LST





- Among 177 DES lesions in the CVPath registry, stent fracture was documented in 51 (SES 32, PES 19) lesions (29%).
- Grade V fracture was identified in 9 (SES 6, PES 3) lesions.

Nakazawa G, et al. JACC 2009 🖁



Potential Contribution of Neointimal Coverage to the Flexibility of the Stents

BMS







Greater neointimal coverage Less flexibility

Less neointimal coverage Greater flexibility

Data on File at CVPath

CoCr-EES Fracture in Human Autopsy Cases

Case	Age	Sex	Vessel	Stent type	Duration of implant (days)	Cause of death	Stent outcome	Fracture grade
1	55	М	RCA (prox)	Taxus x1 + Xience V x2	180	SRD (LST)	LST at non-FS	Ш
2	56	М	LAD (prox)	ML Vision x1 + Xience V x1 + ML Vision x1	80	NCD (ARDS, vasculitis)	Restenosis at non-FS	L
3	51	М	LOM (dist)	Xience V x1	101	SRD (restenosis with diffuse CAD)	Restenosis at FS	V
4	82	М	SVG (prox)	Xience V x1	360	NSRCD (diffuse CAD)	Patent	L
5	70	F	LM-LCX (prox)	Xience V x2	167	SRD (restenosis)	Restenosis at FS	III
	70	F	RCA (dist)	Xience V x1	167	SRD (restenosis)	Restenosis at FS	Ш

ARDS=acute respiratory distress syndrome, CAD=coronary artery disease, FS=fracture site, LST=late stent thrombosis, NCD=non-cardiac death, NSRCD=non-stent related cardiac death, SRD=stent related death

CoCr-EES fracture was identified in 6 lesions (from 5 patients) among 46 lesions (13%).



Xience V[™] Restenosis Associated with Stent Fracture

70-year-old woman, CoCr-EES implanted in RCA for 6 months



Proximal

Foerst JR, et al. J Am Coll Cardiol Intv 2012;5:239-42.

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Foerst JR, et al. J Am Coll Cardiol Intv 2012;5:239-42.



Xience V[™] Grade V Fracture with In-stent Restenosis





PROMUS Element™ Stent

Conformable platform allows artery to retain natural curvature



Results from case studies are not predictive of results in other cases.

Edge Effects, Shear Stress, and Restenosis Shear stress changes may affect restenosis



Stent implantation changes 3D vessel geometry

Changes in shear stress occur near stent edges and may result in restenosis



Hikita et al. Scandinav Cardiovasc Jour 2009;43:298-303

Vessel Angulation and Straightening

Pronounced straightening of stented artery associated with MACE



Pre-stent vessel angulation \geq 33.5° and change in vessel angulation post-stent \geq 9.1° found to be significant predictors of MACE

MACE includes death,nonfatal MI, and revascularization Gyongyosi et al, JACC 2000;35:1580-9

Increased Fracture Resistance with Flexibility Bend Fatigue Bench Test



Data on file at Boston Scientific. 3.0mm diameter stents, 5mm test length. Bench test results not necessarily indicative of clinical performance.

General criteria for selecting a polymer for use as biomaterial

- Does not evoke an inflammatory/toxic response, disproportionate to its beneficial effect
- Is metabolized in the body after fulfilling its purpose, leave no trace
- Is easily processed into the final product form
- Has acceptable shelf life
- Is easily sterilized

Why bioabsorbable polymer coatings make more sense than durable polymer metallic stent

Drawbacks of durable polymer DES

- DES result in delayed healing especially in AMI and/or bifurcation lesions, and DAPT is required for at least 1year and may be longer because of poor endothelialization
- Permanent non-erodable polymer may induce inflammation and hypersensitivity vasculitis
- Polymer coating is left permanently even when not needed
- Constant irritant may lead to long term restenosis

Induce neoatherosclerosis within the stented segments

Virmani R, MD. LDDR2012

Durable Polymer May Induce Inflammation

Hypersensitivity Reaction to SES 40F, died suddenly 4 days after surgical removal of melanoma.

40F, died suddenly 4 days after surgical removal of melanoma. DAPT was discontinued 5 days before surgery.

Focal Inflammation in CoCr-EES



Nakazawa G, et al. JACC 2011;57:390-8





Otsuka F, MD. TCT2011

Neoatherosclerosis Following PES, SES, and BMS Implantation



BMS



JACC 2011;57:1314-22 Otsuka F, et al. G, Nakazawa

Impact of Strut Thickness on Vascular Healing and Neointimal Formation in BMS





Virmani R, MD. TCT2011

Impact of Strut Thickness on Vascular Healing and Neointimal Formation in BMS



Liberté Express Element

Soucy N, Feygin J et al, EuroIntervention. 2010 Nov;6(5):630-7

Future Generation DES: Bioabsorbable Polymer Technologies

SYNERGY[™] Stent Platform in Perspective

Durable Polymer-Coated Stents			Bioabsorbabl	e Polymer Coated Stents	Bioabsorbable Stent				
Xience V™ & Prime™	PROMUS Element™	Resolute Integrity™	SYNERGY™	BioMatrix Flex™	BVS				
			Drug Type						
Everolimus	Everolimus	Zotarolimus	Everolimus	Biolimus A9	Everolimus				
Drug Concentration									
1 µg/mm²	l μg/mm²	1.6 µg/mm ²	~1 µg/mm²	15.6 μg/mm**	1 µg/mm²				
		Av	g. Coating Thick	kness					
8µm / side	8µm / side	6µm / side	4µm	10µm	3µm / side				
Strut Thickness									
81 μm (0.0032")	81 μm (0.0032")	89 μm (0.0035")	74 μm (0.0029")	120 μm (0.0047")	150 μm (0.0059")				
Material									
Cobalt Chromium	Platinum Chromium	Cobalt Nickel	Platinum Chromium	Stainless Steel	Polylactic Acid (PLLA)				

**Data reported as drug load / length. The SYNERGY™ stent is an investigational device in the US and Japan and not for sale.

Impact of PVDF on Strut Coverage and EC Function



Expression of VE-Cadherin



Jeff Garanich, PhD. TCT 2011

SYNERGYTM Stent Preclinical Data

Quiescent Vascular Response Throughout PLGA Bioabsorption



SYNERGY Stent

PLGA Only Control Stent

Bare PtCr Stent

Wilson et al. EuroIntervention, 2012;8:250-257

The SYNERGY[™] stent is an investigational device in the US and Japan and not for sale.

Long Term Vascular Healing of Fourth Generation Drug Eluting Stents



Short term healing effect due to the anti-proliferative effect of Everolimus on cell proliferation

Long term healing effect following the inhibitory effect based on a BMS platform

Greg Wilson, MD. ACC 2011 The SYNERGY Stent is an investigational device in the US and Japan and not for sale

SYNERGY Stent Efficacy (Bioequivalence) Study in the FHS Coronary Model

Histological Morphometric Data at 28-Days

SYNERGY ½ Dose		Lumen (mm²)	Stent (mm²)	EEL (mm²)	Percent Stenosis (%)	Thickness (mm)
	SYNERGY	5.5 ± 1.4	9.6 ± 0.9	9.6 ± 0.9	43.0 ± 9.8	0.43 ± 0.1
PROMUS Element	SYNERGY ½ Dose	6.4 ± 2.4	11.4 ± 1.2	11.2 ± 1.2	45.1 ± 18.4	0.51 ± 0.3
	PROMUS Element	6.9 ± 1.5	10.9 ± 1.2	10.9 ± 1.2	36.7 ± 9.5	0.38 ± 0.1
Bare Element	Bare Element	2.5 ± 1.2	10.0 ± 1.4	9.8 ± 1.4	75.6 ± 9.2	0.91 ± 0.1
	p value	<0.001	0.07	0.30	<0.001	<0.001

Barbara A. Huibregtse. TCT 2010

SYNERGY

The SYNERGY Stent is an investigational device in the US and Japan and not for sale

Everolimus Effect on Inflammation Following DES Implantation (28 Days)



Juan Granada, MD. EuroPCR 2012

Score

The SYNERGY Stent is an investigational device in the US and Japan and not for sale

Summary

Late Complication: Stent Fractures and Restenosis

- 2nd-generation CoCr-EES shows a significantly lower prevalence of LST/VLST with less uncovered struts, less inflammation, and less fibrin deposition as compared to 1st-generation SES and PES.
- The overall frequency of stent fracture in CoCr-EES was lower than that in SES and PES; however, fracture-related restenosis or thrombosis was comparable among the groups. Therefore, stent fracture remains an important issue even in CoCr-EES, where further modification(s) of stent design and procedural strategy may be required.
- Permanent durable polymers may induce inflammation (including hypersensitivity reaction) and neoatherosclerosis within the stented segment.
- Bioabsorbable polymers are more likely to be less toxic to the vessel wall especially when they are only on the abluminal surface, absorb in 120 days leaving no trace, and the stent is flexible.



Acknowledgments

<u>Funding</u>

CVPath Institute Inc.

CVPath Institute

Fumiyuki Otsuka, MD, PhD Kenichi Sakakura, MD Kazuyuki Yahagi, MD Elena Ladich, MD Robert Kutz, MS Ed Acampado, DVM Youhui Liang, MD Abebe Atiso, HT Jinky Beyer **Giselle Magsalin** Hedwig Avallone, HT Lila Adams, HT Hengying Ouyang, MD Frank D Kolodgie, PhD



