# **Current status of DES :** Clinical evidences of Ultimaster

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## **Evolution of Coronary Stent Innovation**



- in-stent restenosis (ISR)
- Late stent thrombosis (LST)

### In stent restenosis

- Higher degree of vessel injury with stent increased the extent of NIH
  - Dominant cause of restenosis after stent implantation.
- Inflammatory response to vessel wall injury
  - fibroblast growth and smooth muscle cell hyperplasia.
- Mechanistically contributing factors to ISR
  - Acute or subacute prolapse of the disrupted plaque
  - Elastic recoil of the vessel wall
  - Constrictive remodeling
  - Neointimal hyperplasia (due to ECM deposition and SMC hyperplasia)
  - De novo in-stent atherosclerosis (neoatherosclerosis)
- Angiographic restenosis
  - re-narrowing of > 50% of the vessel diameter as determined by coronary angiography
- Clinical restenosis
  - restenosis accompanied by requirement for re-treatment (Sx or sign of ischaemia)

## From DP-ZES vs BP-BES (SORT OUT VI) trial...

	Durable- polymer zotarolimus- eluting stent (n=1502)	Biodegradable- polymer biolimus- eluting stent (n=1497)	Risk difference (95% CI)	p value
Events at 12 months				
Composite primary endpoint*	79 (5·3%)	75 (5·0%)	0·3% (-1·3 to 1·9)	0.72
All-cause mortality	50 (3·3%)	40 (2·7%)	0·7% (-0·5 to 1·9)	0.28
Cardiac mortality	22 (1·5%)	26 (1·7%)	-0·3% (-1·2 to 0·6)	0.58
Composite secondary endpoint†	206 (13.8%)	215 (14·3%)	-0.6% (-0.3 to 1.9)	0.67
Myocardial infarction	31 (2·1%)	<u>30 (2·0%)</u>	0·1% (-0·9 to 1·1)	0.89
Target-vessel revascularisation	67 (4·5%)	71 (4.7%)	-0·3% (-1·8 to 1·2)	0.75
Target-lesion revascularisation	52 (3.5%)	47 (3.1%)	0·3% (-0·9 to 1·6)	0.60
Stent thrombosis‡				
Definite	9 (0.6%)	6 (0·4%)	0·2% (-0·3 to 0·7)	0.44
Acute (<24 h)	1 (0.1%)	0 (0·0%)	0·1% (-0·1 to 0·2)	0.32
Subacute (24 h to 30 days)	4 (0.3%)	1 (0.1%)	0·2% (-0·1 to 0·6)	0.10
Late (31 days to 12 months)	4 (0.3%)	5 (0·3%)	-0·1% (-0·5 to 0·3)	0.74
Probable	3 (0.2%)	1 (0.1%)	0·1% (-0·1 to 0·4)	0.32
Definite or probable	12 (0.8%)	7 (0.5%)	0·3% (-0·2 to 0·9)	0.25
Possible	7 (0.5%)	14 (0.9%)	–0·5% (–1·1 to 0·1)	0.13

Clinical restenosis

## **Stent thrombosis**

- Characterized by angiographic or postmortem evidence of recently formed thrombus in a previously stented segment
- Mix of thrombotic and inflammatory components including platelet-rich thrombus, fibrin fragments, and leukocytes of both neutrophil and eosinophil lineage.



## **Incidence of ST**

• 18,334 patients undergoing PCI from 1998 to 2011 at 2 centers in Germany



## **Risk factors of stent failure**



#### Neoatherosclerosis as a common pathway in stent failure !!

### IVUS findings in stent thrombosis - RI & malapposition

	ST (n = 18)	Control Subjects (n = 36)	p Value
Reference segment			
Mean EEM CSA, mm <sup>2</sup>	13.6 ± 3.9	13.7 ± 3.5	0.50
Mean lumen CSA, mm <sup>2</sup>	6.9 ± 1.7	6.9 ± 1.8	0.96
Stent segment			
Mean EEM, mm <sup>2</sup>	19.4 ± 5.8	15.1 ± 4.6	0.003
Remodeling index	1.24 (1.06–1.43)	0.99 (0.90–1.11)	< 0.001
Mean stent CSA, mm <sup>2</sup>	7.8 ± 1.6	7.6 ± 1.4	0.42
Minimal stent CSA, mm <sup>2</sup>	5.7 ± 1.4	5.9 ± 1.4	0.99
Minimal stent $CSA < 4 \text{ mm}^2$	3 (16.7)	3 (8.3)	0.38
Stent expansion index	$0.87 \pm 0.3$	0.91 ± 0.3	0.69
ISA	14 (77.8)	15 (41.7)	0.01
Maximal ISA CSA, mm <sup>2</sup>	4.11 ± 2.3	1.16 ± 1.5	0.001

### OCT findings in stent thrombosis - Strut coverage & malapposition

		ST (n = 18 Lesions; 4,407 Struts)	Control Subjects (n = 36 Lesions; 9,064 Struts)	p Value
C	ross-section level analysis			
	Analyzed cross-sections/patient, n	27 ± 12	30 ± 13	0.47
	Struts analyzed/cross-section, n	6.78 ± 1.22	6.74 ± 1.41	0.93
	Frequency of cross-sections with uncovered struts, %	33.30 (11.82–53.00)	0.00 (0.00–7.80)	0.003
	Frequency of cross-sections with $>$ 30% uncovered struts, %	21.59 (0.00–43.70)	0.00 (0.00-6.09)	0.002
	Maximum length of segments with uncovered struts, mm	3.30 (1.35–4.13)	0.90 (0.00–1.55)	<0.001
	Maximum length of segments with malapposed struts, mm	1.40 (0.68–1.93)	0.00 (0.00-0.00)	0.001
	Maximum malapposition distance, mm	0.35 (0.00–0.75)	0.00 (0.00-0.62)	0.002
	Area of malapposition, mm <sup>2</sup>	1.02 (0.00–1.92)	0.00 (0.00-0.32)	0.002
	Minimum stent area, mm <sup>2</sup>	5.04 ± 1.23	5.50 ± 1.27	0.26
	Mean stent area, mm <sup>2</sup>	7.24 ± 0.97	7.69 ± 1.61	0.20
	Mean neointimal area, mm <sup>2</sup>	1.57 ± 0.68	1.68 ± 0.71	0.41
S	trut-level analysis			
	Number of struts analyzed/patient	244 ± 131	251 ± 86	0.81
	Number of uncovered struts/patient	25.00 (8.25–52.25)	9.00 (4.25–14.00)	0.006
	Frequency of uncovered struts/patient, %	12.27 (5.50–23.33)	4.14 (3.00–6.22)	0.001
	Number of malapposed struts/patient	10.00 (2.25–21.75)	4.00 (0.00-7.00)	0.02
	Frequency of malapposed struts/patient, %	4.60 (1.85–7.19)	1.81 (0.00–2.99)	0.001
	Neointimal thickness of covered struts, mm	0.23 ± 0.15	0.17 ± 0.09	0.28

### Key mechanisms of DES failure

- Stent underexpansion
- Malapposition
- Incomplete lesion/stent coverage
- In-stent neoatherosclerosis

### Stent Thrombosis of 1<sup>st</sup> G. DES : Hypersensitivity reaction to polymer

.... concerns about the potential for late stent thrombosis with DES related to hypersensitivity reaction to polymer and delayed vessel healing ....



Extensive inflammation with a focal giant cell reaction around stent strut (\*) and surrounding polymer



giant cells (arrowheads) around a polymer remnant that has separated from stent strut and numerous eosinophils within arterial wall. Virmani et at. *Circulation* 2004

## **Evolution of Coronary Stent Innovation**



- Late stent failures
  - in-stent restenosis (ISR)
  - Late stent thrombosis (LST)

## **HATTRICK-OCT Trial**

- Early neointimal coverage (OCT) and vasodilator response (invasive thermodilution-derived CFR at 3M)
- BP-SES vs. DP-ZES in 44 ACS pts.

Primary endpoints :	Variable	BP-SES group (n=22)	DP-ZES group (n=22)	P-value
% uncovered struts & CFR	Cross-sectional analysis	(	· · ·	
	No. cross-sections analyzed	425	425	1.0
	Struts per cross-section	11.5±0.66	12.9±1.2	<0.001
	Stent area (mm²)	6.8±1.6	7.5±1.7	0.09
	Lumen area (mm²)	6.5 [2.2]	7.1 [2.6]	0.06
	NIH area (μm²)	380 [410]	460 [550]	0.11
	% NIH area	5.7 [5.9]	5.7 [7.6]	0.69
	Strut-level analysis			
	Total no. struts analyzed	4,897	5,467	0.13
	NIH thickness (µm)	69.1±58.2	76.5±82.9	0.15
	Uncovered struts	189 (3.9)	495 (8.9)	<0.001
	Malapposed struts	101 (2.1)	292 (5.3)	<0.001
	Stent-level analysis			
	% Uncovered struts	3.9±3.2	8.9±6.9	0.019
	Stents with >5% uncovered struts	7 (31.8)	14 (63.6)	0.069
	% Malapposed struts	2.2±3.7	4.3±9.5	0.33
	Intra-stent thrombus	2 (9.1)	1 (4.5)	1.0
Variable	BP-SES group (n=18)	DP-ZES group (n=16)	P-value	
Fractional flow reserve	0.87±0.07	0.87±0.06	0.93	
Coronary flow reserve	3.0±1.3	3.2±1.0	0.56	
Coronary flow reserve <2.5	8 (44.4)	2 (12.5)	0.06	
Index of microcirculatory resistance	19.2±8.1	22.7±13.0	0.32	Circ J 2015; 79: 360

#### **BP- vs DP-DES for late loss**

#### Meta-analysis including 20 studies w/ 20,005 pts (median clinical fup of 1 year)

							BPDES	DPDES		DPDES
Author	Study	Year	Journal	Data reported	Pts number	Randomization	TYPE	TYPE	BPDES TYPE	TYPE
Windecker	BIOFLOW II	2013	EuroPCR	9 months clinical + angiographic follow-up	452	yes (2:1)	SES	EES	Orsiro <sup>TM</sup>	Xience V <sup>TM</sup>
Smits	COMPARE II	2013	Lancet	1 year clinical follow-up	2,707	yes (2:1)	BES	EES	Nobori <sup>TM</sup>	Xience V <sup>TM</sup>
Kruckoff	COSTAR II	2008	JACC	1 year clinical follow-up	1,675	yes (3:2)	PES	PES	CoStar <sup>TM</sup>	Taxus Espress <sup>TM</sup>
Wijns	DESSOLVE II	2012	JACC	1 year clinical + angiographic follow-up	181	yes (2:1)	SES	ZES	Elixir DESyne <sup>TM</sup>	Endeavor <sup>TM</sup>
Ge	<b>EVOLUTION</b>	2012	EuroPCR	1 year clinical follow-up	1,909	yes (2:1)	SES	SES	Excel <sup>TM</sup>	Cypher Select <sup>TM</sup>
Meredith	EVOLVE	2012	JACC	<ol> <li>year clinical + angiographic follow-up</li> </ol>	190	yes (1:1)	EES	EES	Promus Element <sup>TM</sup>	Synergy <sup>TM</sup>
Abizaid	EXCELLA BD	2012	JACC	1 year clinical + angiographic follow-up	146	yes (3:1)	NES	ZES	Elixir DESyne <sup>TM</sup>	Endeavor <sup>TM</sup>
Verheye	EXCELLA II	2012	JACC	<ol> <li>year clinical + angiographic follow-up</li> </ol>	210	yes (2:1)	NES	ZES	Elixir DESyne <sup>TM</sup>	Endeavor <sup>TM</sup>
Mehilli	ISAR TEST3	2008	Eur Heart J	1 year clinical + angiographic follow-up	404	yes (1:1)	SES	SES	BP 0.4% rapamycin stent	Cypher Select <sup>TM</sup>
Byrne I	ISAR TEST3	2009	Heart	2 year clinical + angiographic follow-up	404	yes (1:1)	SES	SES	BP 0.4% rapamycin stent	Cypher Select <sup>TM</sup>
Kufner	ISAR TEST4	2011	CCI	6 months angiographic follow-up	2,016	yes (2:1:1)	SES	SES/EES	BP 0.4% rapamycin stent	Cypher Select <sup>TM</sup> , Xience <sup>TM</sup>
Byrne III	ISAR TEST4	2011	JACC	3 years clinical follow-up	2,603	yes (2:1:1)	SES	SES/EES	BP 0.4% rapamycin stent	Cypher Select <sup>TM</sup> , Xience <sup>TM</sup>
Windecker	LEADERS	2008	Lancet	9 months clinical + angiographic follow-up	1,707	yes (1:1)	BES	SES	BioMatrix Flex <sup>TM</sup>	Cypher Select <sup>TM</sup>
Stefanini	LEADERS	2011	Lancet	4 year clinical follow-up	1,707	yes (1:1)	BES	SES	BioMatrix Flex <sup>TM</sup>	Cypher Select <sup>TM</sup>
Xu	na	2011	Chinese Med J	<ol> <li>year clinical + angiographic follow-up</li> </ol>	324	no	SES	ZES	Tivoli <sup>TM</sup>	Endeavor <sup>TM</sup>
Lee	na	2012	JACC	1 year clinical follow-up	604	no	BES	ZES/EES	Nobori <sup>TM</sup>	Resolute <sup>TM</sup> , Xience <sup>TM</sup>
Ormiston	NEVO RES-1	2010	Circ Cardiovasc Int	1 year clinical + angiographic follow-up	394	yes (1:1)	SES	PES	Nevo <sup>TM</sup>	Cypher Select <sup>TM</sup>
Abizaid II	NEVO RES-1	2013	Eurointervention	2 year clinical + angiographic follow-up	394	yes (1:1)	SES	PES	Nevo <sup>TM</sup>	Cypher Select <sup>TM</sup>
Natsuaki	NEXT	2013	ACC	1 year clinical + angiographic follow-up	3,235	yes (1:1)	BES	EES	Nobori <sup>TM</sup>	Xience V <sup>TM</sup> or Promus <sup>TM</sup>
Ostojic	NOBORI CORE	2008	Eurointervention	1 year clinical + angiographic follow-up	107	no	BES	SES	Nobori <sup>TM</sup>	Cypher Select <sup>TM</sup>
Kadota	NOBORI JAPAN	2011	CCI	1 year clinical + angiographic follow-up	326	yes (3:2)	BES	SES	Nobori <sup>TM</sup>	Cypher Select <sup>TM</sup>
Kimura	NOBORI JAPAN	2012	JACC	3 years clinical follow-up	326	yes (3:2)	BES	SES	Nobori <sup>TM</sup>	Cypher Select <sup>TM</sup>
Chevalier I	NOBORI1	2007	Eurointervention	1 year clinical + angiographic follow-up	120	yes (2:1)	BES	PES	Nobori <sup>TM</sup>	Taxus Liberté <sup>TM</sup>
Chevalier II	NOBORI1 Phase1	2009	Circ Cardiovasc Int	1 year clinical + angiographic follow-up	243	yes (2:1)	BES	PES	Nobori <sup>TM</sup>	Taxus Liberté <sup>TM</sup>
Christiansen	SORT-OUT V	2013	Lancet	1 year clinical follow-up	2,468	yes (1:1)	BES	SES	Nobori <sup>TM</sup>	Cypher Select <sup>TM</sup>

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#### **BP-vs DP-DES** for late loss

	Expe	erimen	tal	C	ontrol			Std. Mean Difference	Std. Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI		
2.2.1 1st generation DP-DES											
Chevalier, NOBORI1	0.09	0.26	84	0.15	0.29	31	3.9%	-0.22 [-0.64, 0.19]			
Chevalier, NOBORI1 phase1	0.1	0.35	143	0.18	0.44	76	7.1%	-0.21 [-0.49, 0.07]			
Kadota, NOBORI Japan	0.05	0.37	207	0.07	0.41	138	9.7%	-0.05 [-0.27, 0.16]			
Mehilli, ISAR-TEST3	0.18	0.48	199	0.23	0.52	195	10.6%	-0.10 [-0.30, 0.10]			
Ormiston, NEVO-RES1	0.05	0.32	186	0.2	0.42	166	9.9%	-0.40 [-0.62, -0.19]			
Ostoijc, NOBORI Core	0.13	0.35	60	0.2	0.41	50	4.6%	-0.18 [-0.56, 0.19]			
Windecker, LEADERS	0.08	0.45	248	0.15	0.46	229	11.6%	-0.15 [-0.33, 0.03]			
Subtotal (95% CI)			1127			885	57.3%	-0.18 [-0.27, -0.09]	•		
Heterogeneity: Tau <sup>2</sup> = 0.00; Ch	i"= 6.47	df = 6	(P = 0.	37); 12 =	7%						
Test for overall effect: Z = 3.79	(P = 0.00	001)									
2.2.2 2nd generation DP-DES											
Kufner, ISAR-TEST4	0.21	0.5	1323	0.22	0.5	1314	18.6%	-0.02 [-0.10, 0.06]	-		
Natsuaki, NEXT	0.03	0.39	295	0.06	0.45	293	12.7%	-0.07 [-0.23, 0.09]			
Windecker, BIOFLOW II	0.09	0.35	278	0.09	0.33	14	2.5%	0.00 [-0.54, 0.54]			
Xu, TIVOLI	0.25	0.33	175	0.42	0.55	128	9.0%	-0.39 [-0.62, -0.16]			
Subtotal (95% CI)			2071			1749	42.7%	-0.12 [-0.28, 0.04]	-		
Heterogeneity: Tau <sup>a</sup> = 0.02; Ch	i" = 8.95	df = 3	(P = 0.	03); 1==	66%						
Test for overall effect: Z = 1.44	(P = 0.15	5)									
Total (95% CI)			3198			2634	100.0%	-0.15 [-0.24, -0.06]	•		
Heterogeneity: Tau <sup>2</sup> = 0.01; Ch	i" = 20.0	9, df =	10 (P =	0.03); 1	= 509	%			1. 1. 1. 1. 1		
Test for overall effect: Z = 3.30	(P = 0.00)	10)							-1 -0.5 0 0.5 1		
Test for subgroup differences:	Chi# = 0	42. df	= 1 (P =	= 0.52).	1= 0%	6			Favours BP-DES Favours DP-DES		

#### In-stent late lumen loss

	в	P-DES		D	P-DES			Std. Mean Difference	Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% CI
2.1.1 1st generation DP-DES		1.0							
Chevalier, NOBORI1	0.15	0.27	84	0.32	0.33	31	5.8%	-0.59 [-1.01, -0.17]	•
Chevalier, NOBORI1 phase1	0.11	0.3	143	0.32	0.5	76	6.6%	-0.55 [-0.83, -0.27]	
Kadota, NOBORI Japan	0.12	0.3	207	0.14	0.34	138	6.9%	-0.06 [-0.28, 0.15]	
Mehilli, ISAR-TEST3	0.17	0.45	199	0.23	0.46	195	7.0%	-0.13 [-0.33, 0.07]	
Ormiston, NEVO-RES1	0.13	0.31	186	0.36	0.48	166	7.0%	-0.57 [-0.79, -0.36]	
Ostolic, NOBORI Core	0.1	0.26	60	0.13	0.44	50	6.1%	-0.08 [-0.46, 0.29]	
Windecker, LEADERS	0.13	0.46	248	0.19	0.5	229	7.1%	-0.12 [-0.30, 0.05]	
Subtotal (95% CI)			1127			885	46.5%	-0.29 [-0.47, -0.11]	•
Heterogeneity: Tau <sup>2</sup> = 0.04; Ch	i" = 22.5	4, df =	6 (P = 1	0.0010)	P= 7	3%			
Test for overall effect: Z = 3.10	(P = 0.00	)2)							
2.1.2 2nd generation DP-DES									
Abizaid, EXCELLA BD	0.12	0.15	119	0.67	0.47	38	5.7%	-2.07 [-2.50, -1.64]	•
Kufner, ISAR-TEST4	0.24	0.6	1323	0.26	0.5	1314	7.4%	-0.04 [-0.11, 0.04]	-+
Meredith, EVOLVE	0.1	0.25	94	0.15	0.34	98	6.6%	-0.17 [-0.45, 0.12]	
Natsuaki, NEXT	0.17	0.35	295	0.14	0.36	293	7.2%	0.08 [-0.08, 0.25]	+
Verheye, EXCELLA II	0.11	0.32	140	0.63	0.42	70	6.4%	-1.45 [-1.77, -1.13]	•
Wijns, DESSOLVE II	0.27	0.46	108	0.58	0.43	52	6.3%	-0.68 [-1.02, -0.35]	← − − −
Windecker, BIOFLOW II	0.1	0.32	278	0.1	0.29	149	7.0%	0.00 [-0.20, 0.20]	
Xu, TIVOLI	0.25	0.33	175	0.57	0.55	128	6.9%	-0.73 [-0.97, -0.50]	
Subtotal (95% CI)			2532			2142	53.5%	-0.60 [-0.97, -0.23]	
Heterogeneity: Tau <sup>a</sup> = 0.27; Ch	i* = 191.	02, df:	= 7 (P <	0.0000	)1); P=	96%			
Test for overall effect: Z = 3.17	(P = 0.00	)2)							
Total (95% CI)			3659			3027	100.0%	-0.45 [-0.66, -0.24]	•
Heterogeneity: Tau <sup>2</sup> = 0.16; Ch	i" = 215.	95, df:	= 14 (P	< 0.000	01); P	= 94%			1. de 1. de
Test for overall effect: Z = 4.13	(P < 0.00	001)							-1 -U.5 0 0.5
Test for subgroup differences:	Chi <sup>2</sup> = 2	22. df	= 1 (P =	= 0.14).	1 = 55	.0%			Favours BP-DES Favours DP-D

#### In-segment late lumen loss

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### **BP- vs DP-DES** for harder endpoints

#### Weighted Mean Differences & Odds Ratios for Various Endpoints

	Study number	BP-DES pt/ lesion number	DP-DES pt/ lesion number	WMD or OR	95% CI	<i>P</i> level for overall effect
In stent LLL	15	3,659	3,027	-0.45	-0.66 to $-0.24$	< 0.0001
In segment LLL	11	3,198	2,796	-0.15	-0.24 to $-0.06$	0.001
Overall death	17	9,323	8,113	0.94	0.80 to 1.11	0.48
Cardiac death	16	8,052	6,431	0.90	0.71 to 1.14	0.39
MI	18	10,806	8,884	01:08	0.92 to 1.28	0.34
TLR	17	8,718	7,598	0.82	0.65 to 1.04	0.10
TVR	15	10,138	8,372	1.04	0.84 to 1.27	0.74
Acute/subacute ST	16	9,238	7,371	1.23	0.80 to 1.90	0.34
Late/very late ST	17	9,359	7,431	0.51	0.30 to 0.86	0.01

## **BP-DES vs 2<sup>nd</sup> G. DP-DES**

#### Meta-analysis including 16 RCTs w/ 19,886 pts (mean duration 26 months).

	Number of	Patients (N)	DAPT Duration	Follow-Up		<b>BP-DES Characteristics</b>			
Study/First Author (Ref. #)	BP-DES	DP-DES	(Months)	(Months)	Stent	Strut Thickness (µm)	Drug		
BASKET-PROVE II (20)	765	765	12	24	Nobori	120	Biolimus		
BIOFLOW II (21)	298	154	>6	12	Orsiro	60	Sirolimus		
BIOSCIENCE (22)	1063	1056	12	24	Orsiro	60	Sirolimus		
CENTURY II (23)	551	550	>6	9	Ultimaster	80	Sirolimus		
COMPARE II (24)	1,795	912	12	36	Nobori	120	Biolimus		
DESSOLVE II (25)	123	61	6 to 12	9	MiStent	64	Sirolimus		
EVERBIO II (26)	80	80	>6	9	<b>BioMatrix Flex</b>	112	Biolimus		
EVOLVE FHU (27)	193	98	>6	24	Synergy	74	Everolimus		
EVOLVE II (28)	846	838	>6	12	Synergy	74	Everolimus		
ISAR-TEST 4 (29)	1,299	1,304	>6	60	Yukon choice PC	87	Sirolimus		
LONG-DES V (30)	245	255	>12	12	Nobori	120	Biolimus		
NEXT (31)	1,617	1,618	>3	36	Nobori	120	Biolimus		
Separham et al. (32)	100	100	>12	12	BioMatrix	112	Biolimus		
SORT OUT VI (33)	1,497	1,502	>12	12	BioMatrix Flex	112	Biolimus		
TARGET I (34)	227	231	>12	12	Firehawk	86	Sirolimus		
Xu et al. (35)	168	156	6	24	Tivoli	80	Sirolimus		

#### **TABLE 1** Continued

		BP-DES Chara	acteristics	DP-DES Characteristics					
Study/First Author (Ref. #)	Scaffold Material	Drug Release (Months)	Polymer Biodegradation (Months)	Stent	Strut Thickness (µm)	Drug	Scaffold Material		
BASKET-PROVE II (20)	SS	6-9	12	Xience Prime	81	Everolimus	Co-Cr		
BIOFLOW II (21)	Co-Cr	12	14	Xience Prime	81	Everolimus	Co-Cr		
BIOSCIENCE (22)	Co-Cr	12	14	Xience Prime	81	Everolimus	Co-Cr		
CENTURY II (23)	Co-Cr	4	4	Xience V	81	Everolimus	Co-Cr		
COMPARE II (24)	SS	6-9	12	Xience V/ Prime	81	Everolimus	Co-Cr		
DESSOLVE II (25)	Co-Cr	9	3	Endeavor	91	Zotarolimus	Co-Cr		
EVERBIO II (26)	SS	6-9	6-9	Promus Element	81	Everolimus	Pl-Cr		
EVOLVE FHU (27)	Pl-Cr	3	4	Promus Element	81	Everolimus	Pl-Cr		
EVOLVE II (28)	Pl-Cr	3	4	Promus Element	81	Everolimus	Pl-Cr		
ISAR-TEST 4 (29)	SS	1	2-3	Xience V	81	Everolimus	Co-Cr		
LONG-DES V (30)	SS	6-9	12	Promus Element	81	Everolimus	Pl-Cr		
NEXT (31)	SS	6-9	12	Xience/Promus	81	Everolimus	Co-Cr/Pl-Cr		
Separham et al. (32)	SS	6-9	12	Xience V	81	Everolimus	Co-Cr		
SORT OUT VI (33)	SS	6-9	6-9	Resolute Integrity	91	Zotarolimus	Co-Cr		
TARGET I (34)	Co-Cr	1	6-9	Xience V	81	Everolimus	Co-Cr		
Xu et al. (35)	Co-Cr	1	6	Endeavor	91	Zotarolimus	Co-Cr		

### **BP-DES vs 2<sup>nd</sup> G. DP-DES**

	BP-D	ES	DP-D	ES		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
BASKET-PROVE II	10	765	7	765	3.6%	1.43 [0.55, 3.73]	
BIOFLOW-II	2	298	1	154	0.7%	1.03 [0.09, 11.31]	
BIOSCIENCE	33	1063	33	1056	17.2%	0.99 [0.62, 1.60]	-+-
CENTURY II	5	551	6	550	3.1%	0.83 [0.26, 2.71]	
COMPARE II	52	1795	23	912	15.8%	1.15 [0.71, 1.86]	-
DESSOLVE II	1	117	1	60	0.7%	0.51 [0.03, 8.06]	
EVERBIO	0	80	0	80		Not estimable	
EVOLVE FHU	2	191	0	98	0.3%	2.58 [0.12, 53.18]	
EVOLVE II	4	846	7	838	3.6%	0.57 [0.17, 1.93]	
ISAR-TEST 4	64	1299	33	652	22.8%	0.97 [0.65, 1.47]	-
LONG-DES V	2	245	1	255	0.5%	2.08 [0.19, 22.81]	2. <u></u> 2
NEXT	43	1617	38	1618	19.7%	1.13 [0.74, 1.74]	-
SEPARHAM et al	0	100	0	100		Not estimable	
SORT OUT VI	26	1497	22	1502	11.4%	1.19 [0.68, 2.08]	
TARGET I	1	227	0	231	0.3%	3.05 [0.13, 74.54]	
XU et al	1	168	0	156	0.3%	2.79 [0.11, 67.91]	
Total (95% CI)		10859		9027	100.0%	1.08 [0.89, 1.31]	•
	***		172				
Risk Ratio		13 (P =	0.99); l <sup>z</sup> :	= 0%			
M-H, Fixed, 95% Cl		P = 0.48	5)				
-							Tavois BF-DES Tavois DF-DES
+							Cardiac death
+							

#### **TVR**

								172
	BP-D	ES	DP-D	ES		Risk Ratio	Risk Ratio	13 (P = 0.99); I <sup>≥</sup> = 0%
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl	P = 0.46)
BASKET-PROVE II	38	765	36	765	5.7%	1.06 [0.68, 1.65]		
BIOFLOW-II	22	298	13	154	2.7%	0.87 [0.45, 1.69]		
BIOSCIENCE	81	1063	75	1056	11.9%	1.07 [0.79, 1.45]	+	
CENTURY II	21	551	17	550	2.7%	1.23 [0.66, 2.31]		
COMPARE II	137	1795	59	912	12.4%	1.18 [0.88, 1.58]	+	
DESSOLVE II	1	117	2	60	0.4%	0.26 [0.02, 2.77]		
EVERBIO	8	80	14	80	2.2%	0.57 [0.25, 1.29]		
EVOLVE FHU	7	191	10	98	2.1%	0.36 [0.14, 0.91]		
EVOLVE II	32	846	29	838	4.6%	1.09 [0.67, 1.79]	+	
ISAR-TEST 4	170	1299	77	652	16.3%	1.11 [0.86, 1.43]	+	
LONG-DES V	9	245	5	255	0.8%	1.87 [0.64, 5.51]		
NEXT	177	1617	155	1618	24.6%	1.14 [0.93, 1.40]	+	
SEPARHAM et al	0	100	0	100		Not estimable		
SORT OUT VI	71	1497	67	1502	10.6%	1.06 [0.77, 1.47]	+	
TARGET I	1	227	3	231	0.5%	0.34 [0.04, 3.24]		
XU et al	7	168	15	156	2.5%	0.43 [0.18, 1.03]		
Total (95% CI)		10859		9027	100.0%	1.06 [0.96, 1.18]	•	
Total events	782		577					
Heterogeneity: Chi <sup>2</sup> =	16.56, df	= 14 (P	= 0.28); P	= 15%	io			
Test for overall effect:	Z=1.17 (	P = 0.24	4)				Eavors BP-DES Eavors DP-DES	

### **BP-DES vs 2<sup>nd</sup> G. DP-DES**

	BP-D	ES	DP-DI	S		<b>Risk Ratio</b>	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
BASKET-PROVE II	3	765	5	765	4.4%	0.60 [0.14, 2.50]	
BIOFLOW-II	0	298	0	154		Not estimable	
BIOSCIENCE	40	1063	50	1056	44.5%	0.79 [0.53, 1.19]	
CENTURY II	5	551	5	550	4.4%	1.00 [0.29, 3.43]	
COMPARE II	23	1795	13	912	15.3%	0.90 [0.46, 1.77]	-
DESSOLVE II	1	117	1	60	1.2%	0.51 [0.03, 8.06]	
EVERBIO	0	80	0	80		Not estimable	
EVOLVE FHU	0	191	0	98		Not estimable	
EVOLVE II	3	846	5	838	4.5%	0.59 [0.14, 2.48]	
SAR-TEST 4	15	1299	9	652	10.6%	0.84 [0.37, 1.90]	
LONG-DES V	3	245	0	255	0.4%	7.28 [0.38, 140.30]	
NEXT	5	1617	4	1618	3.5%	1.25 [0.34, 4.65]	
SEPARHAM et al	0	100	0	100		Not estimable	
SORT OUT VI	7	1497	12	1502	10.6%	0.59 [0.23, 1.48]	
FARGET I	0	227	0	231		Not estimable	
(U et al	1	168	0	156	0.5%	2.79 [0.11, 67.91]	
fotal (95% CI)		10859		9027	100.0%	0.83 [0.64, 1.09]	•
Fotal events	106		104				
Heterogeneity: Chi <sup>2</sup> =	4.26, df =	10 (P =	0.93);  *=	:0%			
Fest for overall effect:	Z=1.32 (	P = 0.19	))				Favors BP-DES Favors DP-DES

MI 

Study or Subgroup

BP-DES

DP-DES

Ris **Risk Ratio** M-H, Fixed, 95% Cl Events Total Events Total Weight M-H, Fixed, 95% Cl ----5 3% 0.86 [0.46, 1.60]

ST 

BASKET-PROVE II	18	765	21	765	5.3%	0.86 [0.46, 1.60]	
BIOFLOW-II	9	298	4	154	1.3%	1.16 [0.36, 3.72]	
BIOSCIENCE	62	1063	73	1056	18.5%	0.84 [0.61, 1.17]	
CENTURY II	11	551	15	550	3.8%	0.73 [0.34, 1.58]	
COMPARE II	93	1795	42	912	14.1%	1.13 [0.79, 1.61]	+
DESSOLVE II	3	117	2	60	0.7%	0.77 [0.13, 4.48]	
EVERBIO	0	80	1	80	0.4%	0.33 [0.01, 8.06]	
EVOLVE FHU	6	191	0	98	0.2%	6.70 [0.38, 117.77]	
EVOLVE II	45	846	40	838	10.2%	1.11 [0.74, 1.69]	+
ISAR-TEST 4	70	1299	32	652	10.8%	1.10 [0.73, 1.65]	+
LONG-DES V	34	245	40	255	9.9%	0.88 [0.58, 1.35]	
NEXT	64	1617	60	1618	15.2%	1.07 [0.76, 1.51]	+
SEPARHAM et al	2	100	0	100	0.1%	5.00 [0.24, 102.85]	
SORT OUT VI	30	1497	31	1502	7.8%	0.97 [0.59, 1.60]	-
TARGET I	3	227	5	231	1.3%	0.61 [0.15, 2.52]	
XU et al	4	168	2	156	0.5%	1.86 [0.34, 10.00]	
Total (95% CI)		10859		9027	100.0%	1.00 [0.87, 1.15]	+
Total events	454		368				
Heterogeneity: Chi <sup>2</sup> = 7	.64, df=	15 (P = 0	.94); I <sup>z</sup> =	= 0%			
Test for overall effect: Z	.= 0.03 (	P = 0.98)					Eavore RP_DES_Eavore DP_DES
							FAVOIS DE-DES FAVOIS DE-DES

### BP-DES vs 2<sup>nd</sup> G. DP-DES - beyond 1 year

#### Landmark analysis for cardiac outcomes

Analysis (No. of Trials Included)	TVR RR (95% CI)	Cardiac Death RR (95% CI)	MI RR (95% CI)	Definite/Probable ST RR (95% CI)
Outcomes at 1 yr (12)	1.08 (0.94-1.23)	1.05 (0.82-1.36)	1.02 (0.87-1.20)	0.82 (0.59-1.12)
Outcomes at the longest follow-up (16)	1.06 (0.96-1.18)	1.08 (0.89-1.31)	1.00 (0.87-1.15)	0.83 (0.64-1.09)
Landmark analysis beyond 1 yr (6)	1.12 (0.93-1.35)	1.13 (0.82-1.56)	0.95 (0.71-1.29)	0.87 (0.49-1.53)

#### VLST

	BP-DI	S	DP-DI	ES .		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
BASKET-PROVE II	1	765	1	765	3.9%	1.00 [0.06, 15.96]	
BIOSCIENCE	11	1063	15	1056	58.9%	0.73 [0.34, 1.58]	
COMPARE II	9	1795	4	912	20.8%	1.14 [0.35, 3.70]	<b>_</b>
ISAR-TEST 4	2	1299	0	652	2.6%	2.51 [0.12, 52.24]	
NEXT	1	1617	3	1618	11.7%	0.33 [0.03, 3.20]	
XU et al	1	168	0	156	2.0%	2.79 [0.11, 67.91]	
Total (95% CI)		6707		5159	100.0%	0.87 [0.49, 1.53]	•
Total events	25		23				
Heterogeneity: Chi <sup>2</sup> =	2.09, df=	5 (P =	0.84); l <sup>z</sup> =	= 0%			
Test for overall effect:	Z=0.49 (	(P = 0.6	52)				Favors BP-DES Favors DP-DES

## BP-DES vs 2<sup>nd</sup> G. DP-DES - subgroup analysis

An alteria (Marcal Tailata ta alteria)				Definite (Deckels of DD (050) (C)
Analysis (No. of Trials Included)	IVR RR (95% CI)	Cardiac Death RR (95% CI)	MI RR (95% CI)	Definite/Probable ST RR (95% CI)
BP eluting drug				
Biolimus (7)	1.11 (0.97-1.28)	1.18 (0.90-1.54)	1.02 (0.84-1.23)	0.88 (0.56-1.39)
Sirolimus (7)	1.02 (0.86-1.22)	0.99 (0.74-1.32)	0.92 (0.73-1.16)	0.83 (0.59-1.17)
BP-DES strut thickness				
Thin struts (9)	1.00 (0.85-1.17)	0.97 (0.73-1.28)	0.98 (0.81-1.20)	0.81 (0.58-1.13)
Thick struts (7)	1.11 (0.97-1.28)	1.18 (0.90-1.54)	1.02 (0.84-1.23)	0.88 (0.56-1.39)
BP-DES scaffold				
Alloy (8)	0.94 (0.76-1.15)	0.96 (0.65-1.42)	0.95 (0.76-1.20)	0.81 (0.56-1.16)
Stainless steel (8)	1.11 (0.99-1.26)	1.12 (0.89-1.40)	1.03 (0.87-1.22)	0.87 (0.58-1.30)
BP-DES drug release				
<6 months	0.99 (0.81-1.21)	0.96 (0.67-1.38)	1.08 (0.83-1.40)	0.86 (0.47-1.57)
>6 months	1.09 (0.97-1.24)	1.13 (0.89-1.42)	0.97 (0.83-1.14)	0.83 (0.61-1.12)
Polymer degradation				
<6 months	0.99 (0.81-1.21)	0.93 (0.65-1.34)	1.09 (0.84-1.42)	0.84 (0.47-1.51)
>6 months	1.09 (0.97-1.24)	1.14 (0.90-1.43)	0.97 (0.83-1.14)	0.83 (0.61-1.13)
DP eluting drug				
Everolimus (13)	1.09 (0.97-1.21)	1.06 (0.86-1.31)	1.00 (0.87-1.15)	0.86 (0.65-1.14)
Zotarolimus (3)	0.92 (0.68-1.24)	1.18 (0.69-2.03)	1.01 (0.64-1.59)	0.66 (0.29-1.52)
DAPT duration				
$\geq$ 6 months (8)	0.95 (0.79-1.15)	0.94 (0.66-1.33)	1.09 (0.84-1.42)	0.84 (0.47-1.51)
≥12 months (7)	1.13 (0.99-1.28)	1.14 (0.87-1.50)	0.94 (0.77-1.14)	0.81 (0.59-1.11)

BIOFLOW-II	0	298	0	154		Not estimable	
BIOSCIENCE	40	1063	50	1056	44.5%	0.79 [0.53, 1.19]	-
CENTURY II	5	551	5	550	4.4%	1.00 [0.29, 3.43]	
DESSOLVE II	1	117	1	60	1.2%	0.51 [0.03, 8.06]	
EVOLVE FHU	0	191	0	98		Not estimable	
EVOLVE II	3	846	5	838	4.5%	0.59 [0.14, 2.48]	
ISAR-TEST 4	15	1299	9	652	10.6%	0.84 [0.37, 1.90]	
TARGET I	0	227	0	231		Not estimable	
XU et al	1	168	0	156	0.5%	2.79 [0.11, 67.91]	
Subtotal (95% CI)		4760		3795	65.7%	0.81 [0.58, 1.13]	•
Total events	65		70				
Heterogeneity: Chi <sup>2</sup> = 0.1	99, df=	5 (P = 0.	96); I <sup>a</sup> =	0%			
Test for overall effect Z:	= 1.23 (	P = 0.22)	)				
4.1.2 THICK STRUTS							
BASKET-PROVE II	3	765	5	765	4.4%	0.60 [0.14, 2.50]	
COMPARE II	23	1795	13	912	15.3%	0.90 [0.46, 1.77]	-
EVERBIO	0	80	0	80		Not estimable	
LONG-DES V	3	245	0	255	0.4%	7.28 [0.38, 140.30]	
NEXT	5	1617	4	1618	3.5%	1.25 [0.34, 4.65]	
SEPARHAM et al	0	100	0	100		Not estimable	
SORT OUT VI	7	1497	12	1502	10.6%	0.59 [0.23, 1.48]	
Subtotal (95% CI)		6099		5232	34.3%	0.88 [0.56, 1.39]	•
Total events	41		34				
Heterogeneity: Chi <sup>2</sup> = 3.	26, df=	4 (P = 0.	52); I <sup>2</sup> =	0%			
Test for overall effect Z:	= 0.55 (	P = 0.58)	)				
Total (95% CI)		10859		9027	100.0%	0.83 [0.64, 1.09]	•
Total events	106		104				
Heterogeneity: Chi <sup>2</sup> = 4	26. df=	10 (P = I	0.93); 17=	= 0%			have also the second
Test for overall effect Z	= 1.32 (	P = 0.19	)				0.01 0.1 1 10 100
Test for subgroup differ	ences: (	Chi# = 0.1	, 08. df = 1	(P = 0	.77). P= 0	3%	Favors BP-DES Favors DP-DES

BP-DES

Study or Subgroup 4.1.1 THIN STRUTS DP-DES

Events Total Events Total Weight M-H, Fixed, 95% Cl

**Risk Ratio** 

**Risk Ratio** 

M-H, Fixed, 95% CI

	At least 6 m	onths	At least 12 n	nonths		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% Cl
10.2.1 At Least 6 mor	ths of DAPT						
BIOFLOW-II	0	298	0	154		Not estimable	
CENTURY II	5	551	5	550	4.6%	1.00 [0.29, 3.43]	
DESSOLVE II	1	117	1	60	1.2%	0.51 [0.03, 8.06]	
EVERBIO	0	80	0	80		Not estimable	
EVOLVE FHU	0	191	0	98		Not estimable	
EVOLVE II	3	846	5	838	4.6%	0.59 [0.14, 2.48]	
SAR-TEST 4	15	1299	9	652	11.0%	0.84 [0.37, 1.90]	
<u al<="" et="" td=""><td>1</td><td>168</td><td>0</td><td>156</td><td>0.5%</td><td>2.79 [0.11, 67.91]</td><td></td></u>	1	168	0	156	0.5%	2.79 [0.11, 67.91]	
Subtotal (95% CI)		3550		2588	21.9%	0.84 [0.47, 1.51]	<b>+</b>
Total events	25		20				
Heterogeneity: Chi#=	0.97, df = 4 (F	e = 0.91);	I <sup>#</sup> = 0%				
Test for overall effect	Z = 0.57 (P =	0.57)					
10.2.2 At least 12 mo	nths of DAPT						
BASKET-PROVE II	3	765	5	765	4.6%	0.60 [0.14, 2.50]	
BIOSCIENCE	40	1063	50	1056	46.1%	0.79 [0.53, 1.19]	-
COMPARE II	23	1795	13	912	15.9%	0.90 [0.46, 1.77]	
LONG-DES V	3	245	0	255	0.5%	7.28 [0.38, 140.30]	
SEPARHAM et al	0	100	0	100		Not estimable	
SORT OUT VI	7	1497	12	1502	11.0%	0.59 [0.23, 1.48]	
TARGET I	0	227	0	231		Not estimable	
Subtotal (95% CI)		5692		4821	78.1%	0.81 [0.59, 1.11]	•
Total events	76		80				
Heterogeneity: Chi <sup>2</sup> =	2.86, df = 4 (F	e = 0.58);	I <sup>2</sup> = 0%				
Test for overall effect	Z=1.30 (P=	0.19)					
Fotal (95% CI)		9242		7409	100.0%	0.82 [0.62, 1.08]	•
Total events	101		100				
Heterogeneity: Chi# =	3.85, df = 9 (F	e = 0.92);	I#= 0%				
Test for overall effect	Z = 1.42 (P =	0.16)					0.01 0.1 1 10 100 Eavors PP.DES Eavors DP.DES
Tool for outparoup diff.	arenees Chiz	- 0.01 -	K - 1 /D - 0.0	1 17 - 006			ravuis pr-beo Favois DP-DES

### **BMS vs DP-DES vs BP-BES for clinical outcomes**

- Network meta-analysis using 89 trials w/ 85,490 pts (BMS, DP-DES, & BP-BES)
- Principal endpoint : definite or probable ST within 1 year.





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## BMS vs DP-DES vs BP-BES for late (> 1 year) outcomes



#### В

Long-term myocardial infarction



#### С

Long-term target vessel revascularization





#### Ε

Long term definite/probable stent thrombosis







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### **BMS vs DP-DES vs BP-BES**

- mixed treatment comparison meta-analysis

- 126 randomized trials & 258,544 pt years of fup
- Long term efficacy (TVR, TLR) & safety (death, MI, ST)
- Landmark analysis



Outo	ome: TVR							
	Treatment	Control	Treatment	Control	Rate	Ratio	95%	Crl
	eee	Ve DMC	<b></b>	1		0.45	0.40	0.40
	DEC	Vs. DMS	× 🛧			0.45	0.40	0.49
	PES	Vs. BMS	<u> </u>			0.62	0.55	0.68
	COUPEES	VS. BMS				0.40	0.34	0.45
	PTCr EES	Vs. BMS				0.37	0.26	0.52
	ZES-E	Vs. BMS	· · ·			0.59	0.51	0.70
	ZES-R	Vs. BMS				0.38	0.28	0.49
	BP-DES	Vs. BMS				0.41	0.35	0.48
	PES	Vs. SES		•		1.38	1.25	1.53
	CoCr EES	Vs. SES	◆	1		0.89	0.78	1.01
	PtCr EES	Vs. SES		-		0.82	0.57	1.15
	ZES-E	Vs. SES				1.32	1.16	1.54
	7ES.P	Ve SES		+ ·		0.85	0.65	1.09
	PD DEC	Va. SES		-		0.00	0.79	1.05
	BP-DE5	VS. 3E5				0.52	0.79	1.05
	CoCr EES	Vs. PES				0.64	0.56	0.74
	PtCr EES	Vs. PES				0.59	0.41	0.84
	ZES-E	Vs. PES		≻		0.96	0.83	1.13
	ZES.R	Ve PES	- <b></b>			0.62	0.46	0.79
	PP.DES	Ve DES	- <b>-</b> -			0.66	0.57	0.78
	BF+DE3	VS. FEO				0.00	0.57	0.70
	PtCr EES	Vs. CoCr EES				0.92	0.66	1.28
	ZES-E	Vs. CoCr EES				1.48	1.26	1.81
	ZES-R	Vs. CoCr EES	_			0.96	0.75	1.21
	BP-DES	Vs. CoCr EES	-			1.03	0.89	1.21
	7FS-F	Vs. PtCr FFS				1.61	1.13	2.37
	ZES-R	Vs. PtCr EES	_	<b>→</b>		1.04	0.71	1.52
	BP-DES	Vs. PtCr EES	_	<b>`</b>		1.11	0.79	1.63
	0. 010			·				
	ZES-R	Vs. ZES-E	<u> </u>			0.65	0.47	0.85
	BP-DES	Vs. ZES-E	- <b>-</b>			0.69	0.56	0.84
	BP-DES	Vs. ZES-R	<del>_</del>	┝──		1.07	0.83	1.44
		0.10	1.	00	10.00			
			RR (9	5% Crl)				

httol	Treatment	Control	0.83 0.86 0.85 0.81 0.80 1.17 0.70 0.71 0.74 0.74 0.63 0.63 0.63 0.63 0.63 0.63 0.63 0.63	95% 0.72 0.86 0.55 0.44 0.67 0.66 1.05 0.66 1.05 0.65 0.67 0.79 0.57 0.70 0.57 0.70 0.57 0.70 0.58 0.67 1.02 0.88 1.06 0.88 0.87 0.72 0.86 0.85 0.85 0.85 0.85 0.85 0.85 0.85 0.85	Cri 0.93 1.10 0.75 0.87 0.92 0.92 0.92 0.92 0.95 1.33 0.91 1.05 1.12 1.14 1.43 0.99 0.99 0.93 0.93 0.93 1.57 1.14 1.43 1.44 1.42 1.42 1.42 1.42
. BMS . BMS . BMS . BMS . BMS . BMS . BMS . SES . PES . PES . PES . CocrEES . CocrEES . CocrEES . CocrES . CocrES . ZES-E . ZES-E . ZES-E . ZES-R			0.83 0.83 0.85 0.65 0.61 0.80 0.71 0.80 1.17 0.79 0.80 0.74 0.88 0.97 0.67 0.63 0.83 0.83 0.83 0.83 0.83 0.83 0.83 0.8	0.72 0.86 0.55 0.55 0.66 1.05 0.86 0.55 0.86 0.55 0.86 0.55 0.86 0.57 0.79 0.67 1.02 0.67 1.02 0.88 1.06 0.83 0.84 0.67 0.55 0.44 0.67 0.55 0.86 0.86 0.86 0.86 0.86 0.86 0.86 0.86	0.93 1.10 0.75 0.95 0.95 0.92 1.33 0.91 1.05 1.12 1.14 1.13 0.77 0.88 0.99 0.98 0.99 1.33 0.99 1.57 1.41 1.49 1.52 1.76 1.72 1.72 1.72 1.72
. BMS . BMS . BMS . BMS . BMS . BMS . BMS . BMS . SES . ZES . SES . ZES			0.83 0.88 0.85 0.81 0.80 1.17 0.79 0.74 0.79 0.74 0.88 0.86 0.86 0.86 0.85 0.63 0.63 0.63 0.63 0.63 0.63 0.63 0.63	0.72 0.86 0.86 0.55 0.44 0.67 0.55 0.66 0.68 0.65 0.66 0.65 0.66 0.67 0.77 0.68 0.67 0.68 0.67 0.68 0.67 0.68 0.67 0.68 0.67 0.68 0.67 0.68 0.66 0.57 0.66 0.56 0.66 0.56 0.66 0.56 0.66 0.56 0.66 0.56 0.66 0.56 0.66 0.56 0.66 0.56 0.66 0.56 0.5	0.33 1.10 0.75 0.87 0.92 0.92 0.96 1.33 0.91 1.33 0.91 1.12 1.14 1.13 0.77 0.88 0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.82 1.76 1.82
. BMS . BMS . BMS . BMS . BMS . BMS . BMS . SES . SES . SES . SES . SES . SES . SES . SES . PES . PES . PES . PES . CocrEES . CocrEES . CocrEES . CocrEES . CocrEES . CocrEES . CocrEES . PES . CocrEES . CocrEES . CocrEES . PES . CocrEES . CocrEES . CocrEES . PES . CocrEES . CocrEES			0.88 0.65 0.61 0.80 0.71 0.80 1.17 0.74 0.86 0.86 0.97 0.67 0.67 0.63 0.83 0.83 0.83 0.83 0.83 0.83 0.83 1.10 1.23 1.10 1.23 1.10 1.23 1.10 1.22	0.86 0.55 0.44 0.55 0.55 0.66 1.05 0.68 0.55 0.66 0.67 0.79 0.57 0.46 0.70 0.68 0.67 1.02 0.68 0.67 1.02 0.87 0.68 0.67 1.06 0.83 0.78 0.78	1.10 0.75 0.87 0.92 0.96 1.33 0.91 1.05 1.12 1.12 1.14 1.13 0.77 1.41 1.49 1.85 1.57 1.41 1.49 1.82
. BMS . BMS . BMS . BMS . BMS . SES . ZES-E . ZES-E . ZES-E			0.65 0.61 0.61 0.71 0.79 0.79 0.79 0.74 0.88 0.86 0.97 0.63 0.83 0.83 0.83 0.83 0.83 0.83 0.83 0.8	0.55 0.44 0.67 0.55 0.66 0.55 0.86 0.85 0.85 0.85 0.67 0.79 0.57 0.46 0.77 0.68 0.67 1.02 0.88 1.06 0.88 1.06 0.87 0.87	0.75 0.87 0.92 0.95 0.92 0.96 1.33 0.91 1.05 1.12 1.14 1.13 0.77 0.88 0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.82 1.76 1.82
BMS           BMS           BMS           BMS           BMS           SES           SES           SES           SES           SES           SES           SES           SES           PES           PPS           PPS           CocrEES           CocrEES           CocrEES           CocrEES           PCYEES           PCYEES           PCYES           ZES-E           ZES-E           ZES-R           0.10			0.61 0.60 0.71 0.80 0.74 0.74 0.74 0.74 0.74 0.85 0.86 0.97 0.67 0.63 0.63 0.63 0.63 0.63 0.63 0.63 0.63	0.44 0.67 0.55 0.66 1.05 0.68 0.55 0.86 0.67 0.79 0.57 0.68 0.67 0.57 0.68 0.67 0.57 0.68 1.06 0.57 0.88 1.06 0.88 1.06	0.87 0.87 0.92 0.96 1.33 0.91 1.05 1.12 1.14 1.14 1.13 0.77 0.88 0.99 0.97 1.33 1.57 1.41 1.85 1.76 1.82 1.19 1.21
E BMS E BMS E BMS E BMS SES SES SES SES SES SES SES SES SES S			0.81 0.80 0.71 0.80 1.17 0.79 0.74 0.98 0.86 0.97 0.67 0.63 0.83 0.83 0.83 0.83 0.83 0.83 0.83 0.8	0.44 0.67 0.55 0.66 1.05 0.68 0.55 0.86 0.57 0.79 0.57 0.57 0.68 0.70 0.57 0.68 1.06 0.93 0.78 0.87 0.87 0.66	0.85 0.92 0.95 0.92 0.96 1.33 0.91 1.05 1.12 1.14 1.13 0.88 0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. BMS . BMS . BMS . SMS . SES . SES . SES . SES . SES . SES . SES . PES . PES . Cocr EES . Cocr EES . Cocr EES . Cocr EES . Cocr EES . Cocr EES . Rocr EES . Rocr EES . ZES-E . ZES-E . ZES-R			0.80 0.71 0.79 0.74 0.79 0.74 0.86 0.86 0.86 0.86 0.87 0.63 0.63 0.63 0.63 0.63 0.63 0.63 0.63	0.67 0.55 0.66 1.05 0.68 0.55 0.86 0.67 0.79 0.57 0.57 0.57 0.57 0.68 0.67 0.57 0.68 1.06 0.93 0.73 0.73 0.73 0.73 0.73 0.66	0.95 0.92 0.96 1.33 0.91 1.05 1.12 1.14 1.14 1.13 0.77 0.88 0.99 0.97 1.33 1.57 1.41 1.49 1.25 1.76 1.82
. BMS . BMS . SES . SES . SES . SES . SES . SES . SES . SES . PES . PES . PES . PES . PES . CocrEES . CocrEES . CocrEES . CocrEES . CocrEES . PCrEES . PCrEES . PCrEES . PCrEES . ZES-E . ZES-E . ZES-E			0.71 0.80 1.17 0.74 0.84 0.86 0.97 0.67 0.63 0.83 0.83 0.83 0.83 0.83 0.83 1.33 1.23 1.10 1.22 1.32 1.31 0.88 1.31	0.55 0.66 1.05 0.68 0.55 0.67 0.79 0.57 0.67 0.70 0.57 0.68 0.67 0.68 1.06 0.93 0.78 0.87 0.66 0.77	0.92 0.96 1.33 0.91 1.12 1.14 1.13 0.77 0.88 0.99 0.98 0.99 0.98 0.99 0.99 0.99
. BMS . SES . PES . PES . PES . CoCrEES . CoCrEES . CoCrEES . CoCrEES . CoCrEES . CoCrEES . COCRES . PCS . COCRES . COCRES . PCS . PCS . COCRES . PCS . COCRES . PCS . PCS . COCRES . PCS . P			0.80 1.17 0.79 0.74 0.38 0.85 0.97 0.67 0.63 0.97 0.82 0.95 1.23 1.10 1.22 1.22 1.22 1.16 1.31 0.88 1.01 1.17	0.66 1.05 0.68 0.57 0.79 0.57 0.46 0.70 0.57 0.68 1.02 0.88 1.06 0.93 0.78 0.87 0.66 0.78	0.96 1.33 0.91 1.05 1.12 1.14 1.14 1.33 0.77 0.88 0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.9 1.21
. SES . SES . SES . SES . SES . SES . SES . PES . PES . PES . PES . CocrEES . CocrEES . CocrEES . CocrEES . CocrEES . PCY EES . PCY EES . PCY EES . PCY EES . PCY EES . ZES-E . ZES-E . ZES-R			1.17 0.79 0.74 0.86 0.97 0.67 0.63 0.83 0.83 0.83 0.83 0.83 0.83 0.83 1.33 1.23 1.23 1.10 1.22 1.32 1.31 0.88 1.31	1.05 0.68 0.55 0.67 0.79 0.57 0.46 0.77 0.57 0.68 0.67 1.02 0.88 1.06 0.93 0.78 0.87 0.66 0.78	1.33 0.91 1.05 1.12 1.14 1.13 0.77 0.88 0.99 0.98 0.98 0.98 0.97 1.33 1.57 1.41 1.57 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. SES SES SES SES SES SES SES PES PES PES			1.17 0.79 0.74 0.38 0.86 0.97 0.67 0.63 0.73 0.82 0.95 1.23 1.10 1.22 1.22 1.22 1.22 1.16 1.31 0.88 1.01	1.05 0.68 0.55 0.86 0.67 0.79 0.57 0.46 0.70 0.68 1.06 1.02 0.88 1.06 0.33 0.78 0.87 0.66 0.78	1.33 0.91 1.05 1.12 1.14 1.13 0.77 0.88 0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. SES . SES . SES . SES . SES . SES . PES . PES . PES . PES . PES . CocrEES . CocrEES . CocrEES . CocrEES . CocrEES . PCY ES . PCY ES . PCY ES . PCY ES . PCY ES . PCY ES . ZES-E . ZES-E			0.79 0.74 0.86 0.97 0.67 0.63 0.83 0.83 0.83 0.83 1.23 1.23 1.23 1.10 1.22 1.32 1.31 0.88 1.01	0.68 0.55 0.86 0.67 0.79 0.57 0.57 0.57 0.57 0.68 0.67 1.02 0.88 1.06 0.93 0.78 0.87 0.66 0.78	0.91 1.05 1.12 1.14 1.13 0.77 0.88 0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
3ES         3ES           3ES         3ES           3ES         3ES           PES         PES           PES         PES           CoCrEES         CoCrEES           COCRES         COCRES           PRCYEES         PRCYEES           PRCYES         ZES-E           ZES-R         0.10			0.74 0.88 0.86 0.97 0.67 0.83 0.73 0.82 0.95 1.23 1.10 1.22 1.22 1.22 1.22 1.31 0.88 1.01	0.55 0.86 0.67 0.79 0.57 0.46 0.70 0.57 0.68 0.67 0.68 1.06 0.93 0.78 0.87 0.66 0.87	1.05 1.12 1.14 1.13 0.77 0.88 0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. 265 . 265 . 368 . 368 . 965 . 965			0.38 0.36 0.57 0.67 0.63 0.53 0.53 0.53 0.53 1.23 1.23 1.23 1.22 1.31 0.82 1.31 1.31 0.83 1.31	0.35 0.86 0.67 0.79 0.57 0.57 0.57 0.57 0.57 0.58 0.70 0.57 0.68 1.06 0.93 0.78 0.87 0.87 0.66 0.78	1.12 1.14 1.13 0.77 0.88 0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. SES . SES . SES . PES . PES . PES . PES . PES . PES . CoCrEES . CoCrEES . CoCrEES . CoCrEES . CoCrEES . CoCrEES . PC: EES . PC: EES . PC: EES . PC: EES . PC: EES . ZES-E . ZES-E . ZES-R			0.98 0.86 0.97 0.67 0.63 0.83 0.83 0.95 1.23 1.10 1.23 1.10 1.22 1.32 1.16 1.31 1.31 0.88 1.31	0.86 0.67 0.79 0.57 0.46 0.70 0.57 0.68 0.68 0.68 1.06 0.93 0.78 0.87 0.87 0.66	1.12 1.14 1.13 0.77 0.88 0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. SES . SES . SES . PES . PES . PES . CoCr EES . PCr EES . PCr EES . ZES-E . ZES-E . ZES-R			0.86 0.97 0.67 0.83 0.73 0.82 0.95 1.23 1.10 1.10 1.22 1.12 1.16 1.31 0.88 1.01	0.67 0.79 0.57 0.46 0.70 0.57 0.68 0.67 1.02 0.88 1.06 0.93 0.78 0.87 0.66 0.78	1.14 1.13 0.77 0.88 0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. SES . PES . PES . PES . PES . PES . CoCr EES . CoCr EES . CoCr EES . CoCr EES . CoCr EES . PCr EES . PCr EES . PCr EES . ZES-E . ZES-E . ZES-R			0.97 0.67 0.63 0.83 0.93 0.95 1.23 1.10 1.22 1.31 1.31 1.31 0.88 1.01	0.79 0.57 0.46 0.70 0.57 0.68 0.67 1.02 0.88 1.06 0.93 0.78 0.87 0.66 0.78	1.13 0.77 0.88 0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. PES . PES . PES . PES . CoCr EES . PCr EES . PCr EES . PCr EES . ZES-E . ZES-E . ZES-R			0.67 0.63 0.83 0.73 0.82 0.95 1.23 1.10 1.22 1.12 1.16 1.31 0.88 1.01	0.57 0.46 0.70 0.57 0.68 0.67 1.02 0.88 1.06 0.93 0.78 0.87 0.66 0.78	0.77 0.88 0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. PES PES PES PES PES PES PES PES Coor EES Coor EES Coor EES Coor EES Coor EES Picr EES Picr EES Picr EES Picr EES ZES-E ZES-E ZES-R 2 2 2 2 2 2 2			0.67 0.63 0.63 0.73 0.82 0.95 1.23 1.10 1.22 1.32 1.31 0.88 1.01	0.57 0.46 0.70 0.57 0.68 0.67 1.02 0.88 1.06 0.93 0.78 0.87 0.66 0.78	0.77 0.88 0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. PES PES PES			0.63 0.83 0.73 0.82 0.95 1.23 1.10 1.22 1.12 1.16 1.31 0.88 1.01 1.11 1.12	0.46 0.70 0.57 0.68 0.67 1.02 0.88 1.06 0.93 0.78 0.87 0.66 0.78	0.88 0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
PES PES PES CocrEES CocrEES CocrEES PCCRES PCCRES PCCRES PCCRES ZES-E ZES-E ZES-E			0.83 0.73 0.82 0.95 1.23 1.10 1.22 1.32 1.32 1.34 1.16 1.31 0.88 1.01	0.70 0.57 0.68 0.67 1.02 0.88 1.06 0.93 0.78 0.87 0.66 0.78	0.99 0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
, PES , PES , CoCrEES , CoCrEES , CoCrEES , CoCrEES , CoCrEES , CoCrEES , CoCrEES , PCrEES , PCrEES , PCrEES , ZES-E , ZES-E , ZES-R 0.10			0,73 0,82 0,95 1,23 1,10 1,22 1,32 1,12 1,12 1,12 1,16 1,13 0,88 1,01 1,13	0.57 0.68 0.67 1.02 0.88 1.06 0.93 0.78 0.87 0.66 0.78	0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
PES . Cocr EES . Cocr EES . Cocr EES . Cocr EES . Cocr EES . Picr EES . Picr EES . Picr EES . ZES-E . ZES-E . ZES-R 0.10	1.00		0.73 0.82 0.95 1.23 1.10 1.22 1.32 1.32 1.33 1.16 1.31 0.88 1.01	0.57 0.68 0.67 1.02 0.88 1.06 0.93 0.78 0.87 0.66 0.78	0.98 0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. CoCr EES . PCr EES . PCr EES . ZES-E . ZES-E . ZES-R 0.10	1.00		0.82 0.95 1.23 1.10 1.22 1.32 1.16 1.31 0.88 1.01	0.68 0.67 1.02 0.88 1.06 0.93 0.78 0.87 0.66 0.78	0.97 1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. Coor EES . Coor EES . Coor EES . Coor EES . Coor EES . Pror EES . Pror EES . Pror EES . ZES-E . ZES-E . ZES-R	1.00		0.95 1.23 1.10 1.22 1.32 1.16 1.31 0.88 1.01	0.67 1.02 0.88 1.06 0.93 0.78 0.87 0.66 0.78	1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. cocr EES . cocr EES . cocr EES . cocr EES . cocr EES . PCr EES . PCr EES . ZES-E . ZES-E . ZES-R 0.10	1.00		0.95 1.23 1.10 1.22 1.32 1.16 1.31 0.88 1.01	0.67 1.02 0.88 1.06 0.93 0.78 0.87 0.87 0.66 0.78	1.33 1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. Coor EES . Coor EES . Coor EES . Pror EES . Pror EES . Pror EES . ZES-E . ZES-E . ZES-R 0.10	1.00		1.23 1.10 1.22 1.32 1.16 1.31 0.88 1.01	1.02 0.88 1.06 0.93 0.78 0.87 0.66 0.78	1.57 1.41 1.49 1.85 1.76 1.82 1.19 1.21
. Cocr EES . Cocr EES . Picr EES . Picr EES . ZES-E . ZES-E . ZES-R 0.10	1.00		1.10 1.22 1.32 1.16 1.31 0.88 1.01	0.88 1.06 0.93 0.78 0.87 0.66 0.78	1.41 1.49 1.85 1.76 1.82 1.19 1.21
. COCY EES . PCY EES . PCY EES . PCY EES . ZES-E . ZES-E . ZES-R 0.10	1.00		1.22 1.32 1.16 1.31 0.88 1.01	1.06 0.93 0.78 0.87 0.66 0.78	1.49 1.85 1.76 1.82 1.19 1.21
. PICF EES . PICF EES . ZES-E . ZES-E . ZES-R 0.10	1.00	-	1.32 1.16 1.31 0.88 1.01	0.93 0.78 0.87 0.66 0.78	1.85 1.76 1.82 1.19 1.21
. PICF EES . PICF EES . PICF EES . ZES-E . ZES-E . ZES-R 0.10	1.00		1.32 1.16 1.31 0.88 1.01	0.93 0.78 0.87 0.66 0.78	1.85 1.76 1.82 1.19 1.21
. PICT EES . PICT EES . ZES-E . ZES-E . ZES-R 0.10	1.00		1.16 1.31 0.88 1.01	0.78 0.87 0.66 0.78	1.76 1.82 1.19 1.21
. PICr EES . ZES-E . ZES-R . ZES-R 0.10	1.00	• 	1.31 0.88 1.01	0.87 0.66 0.78	1.82 1.19 1.21
. zes-e . zes-e . zes-r 0.10	1.00		0.88 1.01	0.66 0.78	1.19 1.21
. zes-e . zes-e . zes-r 0.10	1.00		0.88 1.01	0.66 0.78	1.19 1.21
. zes-e . zes-r 0.10	1.00		1.01	0.78	1.21
. zes-r 0.10	1.00		1.13		
0.10	1.00		1.13		
0.10	1.00			0.84	1.49
0.10	1.00				
ontrol	Treatment	Control	Rate Ratio	95%	Cri
BMS		_	1.01	0.76	1 33
DMC	-	<u>~</u>	1 17	0.91	1.50
BMS			0.35	0.21	0.53
DMS		-	0.50	0.21	1 12
. Dino	-		0.30	0.21	1.15
. BMS			0.79	0.51	1.32
. BMS			0.88	0.37	1.91
BMS			0.71	0.48	1.05
070		<b>~</b>		0.00	4.00
. 323	T		1.17	0.88	1.59
. 525		_	0.34	0.22	0.55
. SES			0.50	0.20	1.18
. SES		25	0.78	0.55	1.22
SES			0.84	0.36	2.15
. SES			0.71	0.49	1.01
. PES			0.30	0.18	0.45
. PES			0.42	0.17	0.98
PES			0.66	0.43	1.05
PES			0.73	0.30	1.70
PES			0.61	0.37	0.89
and the second second					
. CoCr EES	-+	~	1.40	0.65	3.17
. CoCr EES	1		2.23	1.33	4.15
CoCr EES			2.47	1.24	4.96
			2.04	1.27	3.35
. CoCr EES					0,00000
. CoCr EES		A	1.60	0.60	4.29
. CoCr EES			4 70	0.67	4.35
. CoCr EES . PtCr EES . PtCr EES	=		1.70	0.58	3.52
. CoCrEES . PtCrEES . PtCrEES . PtCrEES	=		1.42		
. PtCr EES . PtCr EES . PtCr EES . PtCr EES	=		1.42	0.40	2.78
. CoCrEES . PtCrEES . PtCrEES . PtCrEES . ZES-E			1.42	0.42	1.47
. CoCrEES . PtCrEES . PtCrEES . PtCrEES . PtCrEES . ZES-E . ZES-E			1.70 1.42 1.08 0.91	0.42	
Cocr EES Ptcr EES Ptcr EES Ptcr EES ZES-E ZES-E ZES-E			1.70 1.42 1.08 0.91	0.42	1.96
Cocrees Ptcrees Ptcrees Ptcrees . Zes-e . Zes-e . Zes-R			1.70 1.42 1.08 0.91 0.80	0.42 0.50 0.39	1.96
CocrEES PICrEES PICrEES PICrEES PICrEES ZES-E ZES-E ZES-R 0.10		•	1.70 1.42 1.08 0.91 0.80	0.42 0.50 0.39	1.96
	PES PES CoCr EES CoCr EES CoCr EES CoCr EES	PES  PES Co-C+ EES CO-C+ E	PES COCT EES	PES         0.66           PES         0.73           PES         0.61           Occr.EES         2.40           Occr.EES         2.04           Vicr.EES         1.60           Vicr.EES         1.70           Vicr.EES         1.60           Vicr.EES         1.60	PES 0.66 0.43 PES 0.73 0.30 Cocr EES 0.71 0.30 Cocr EES 2.23 1.33 Cocr EES 2.247 1.24 PCC EES 1.50 0.60 NCT EES 1.50 0.50 0.50 0.50 0.50 0.50 0.50 0.50

BMJ. 2013 Nov 8;347:f6625

#### **BMS vs DP-DES vs BP-BES**

#### - Landmark analysis beyond 1 year

Outcome: TV Treatment	Control	Treatment	Control	Rate Ratio	95%	Crl			
BP-DES	Vs. BMS	-		0.67	0.45	0.95			
BP-DES	Vs. SES	-	-	0.79	0.54	1.08			
BP-DES	Vs. PES	-	-	0.79	0.53	1.13			
BP-DES	Vs. CoCr EES	_	▶-	1.15	0.74	1.72			
BP-DES	Vs. PtCr EES		<b>~</b>	1.50	0.62	3.54			
BP-DES	Vs. ZES-E	-	-	0.97	0.60	1.46			
BP-DES	Vs. ZES-R	-	<u> </u>	1.02	0.53	2.04			
0.10 1.00 10.00 RR (95% Cri)									
Outcome: MI Treatment	Control	Treatment	Control	Rate Ratio	95%	Crl			
Outcome: MI Treatment BP-DES	Control Vs. BMS	Treatment	Control	Rate Ratio 0.80	95% 0.53	Crl 1.37			
Outcome: MI Treatment BP-DES BP-DES	Control Vs. BMS Vs. SES	Treatment	Control	Rate Ratio 0.80 0.69	95% 0.53 0.49	Crl 1.37 1.09			
Outcome: MI Treatment BP-DES BP-DES BP-DES	Control Vs. BMS Vs. SES Vs. PES	Treatment	Control	Rate Ratio 0.80 0.69 0.63	95% 0.53 0.49 0.39	Crl 1.37 1.09 1.13			
Outcome: MI Treatment BP-DES BP-DES BP-DES BP-DES	Control Vs. BMS Vs. SES Vs. PES Vs. CoCr EES	Treatment	Control	Rate Ratio 0.80 0.69 0.63 1.03	95% 0.53 0.49 0.39 0.67	Crl 1.37 1.09 1.13 1.95			
Outcome: MI Treatment BP-DES BP-DES BP-DES BP-DES BP-DES	Control Vs. BMS Vs. SES Vs. PES Vs. CoCr EES Vs. PtCr EES	Treatment	Control	Rate Ratio 0.80 0.69 0.63 1.03 0.74	95% 0.53 0.49 0.39 0.67 0.20	Crl 1.37 1.09 1.13 1.95 2.51			
Outcome: MI Treatment BP-DES BP-DES BP-DES BP-DES BP-DES BP-DES	Control Vs. BMS Vs. SES Vs. PES Vs. CoCr EES Vs. PtCr EES Vs. ZES-E	Treatment	Control	Rate Ratio 0.80 0.69 0.63 1.03 0.74 0.87	95% 0.53 0.49 0.39 0.67 0.20 0.50	Crl 1.37 1.09 1.13 1.95 2.51 1.59			
BP-DES BP-DES BP-DES BP-DES BP-DES BP-DES BP-DES BP-DES BP-DES	Control Vs. BMS Vs. SES Vs. PES Vs. CoCr EES Vs. PtCr EES Vs. ZES-E Vs. ZES-R	Treatment	Control	Rate Ratio 0.80 0.69 0.63 1.03 0.74 0.87 0.92	95% 0.53 0.49 0.39 0.67 0.20 0.50 0.42	Crl 1.37 1.09 1.13 1.95 2.51 1.59 3.08			

Outcome: De Treatment	Control	Treatment	Control	Rate Ratio	95% Crl
BP-DES	Vs. BMS	-		0.85	0.61 1.19
BP-DES	Vs. SES	*		0.89	0.69 1.17
BP-DES	Vs. PES	-	-	0.99	0.68 1.36
BP-DES	Vs. CoCr EES	-	<b>~</b>	1.52	1.02 2.22
BP-DES	Vs. PtCr EES	-	-	2.03	0.95 4.08
BP-DES	Vs. ZES-E	-	-	1.02	0.73 1.46
BP-DES	Vs. ZES-R		◆—	1.28	0.71 2.48
	0.1	0 1.0 RR (9	0 5% Crl)	10.00	
Outcome: De Treatment	efinite ST Control	Treatment	Control	Rate Ratio	95% Crl
BP-DES	Vs. BMS			1.02	0.33 3.42
BP-DES	Vs. SES			0.29	0.10 0.82
BP-DES	Vs. PES			0.51	0.16 1.69
BP-DES	Vs. CoCr EES		<b></b>	1.81	0.44 7.09
BP-DES	Vs. PtCr EES		•	1.11	0.12 7.79
BP-DES	Vs. ZES-E		<b></b>	- 1.39	0.44 5.62
BP-DES	Vs. ZES-R		<b></b>	1.68	0.20 15.70
	0.	.10 1. RR (	.00 95% Crl)	10.00	MJ. 2013

BMJ. 2013 Nov 8;347:f6625

### **Porcine coronary model**

#### **3M** histomorphometric analysis

Measurements	EES n=6	BES n=5	SES n=6	<i>p</i> -value
EEL area (mm²)	7.50±0.66	8.21±0.89	8.47±2.09	0.46
Stent area (mm²)	6.19±0.50	6.83±0.77	6.74±1.50	0.52
Lumen area (mm²)	3.31±0.88	3.07±1.34	1.67±0.73*	0.03
Neointimal area (mm²)	2.88±0.47	3.76±0.91	5.07±1.54**	0.01
Area stenosis (%)	47.23±10.77	56.00±16.87	75.91±9.80*	0.0047
Neointimal thickness (mm)	0.39±0.09	0.50±0.22	0.80±0.24*	0.0083
Injury score	0.45±0.22	0.78±0.59	1.64±0.57*	0.0022
Fibrin score	0.33±0.35	0.75±0.79	0.31±0.29	0.29
Struts with granuloma (%)	2.32±3.49	5.05±7.31	45.47±34.06*	0.0033
Inflammatory score	0.50±0.42	0.80±0.88	2.92±1.42*	0.0014
Giant cells (%)	1.98±2.08	2.08±0.85	43.65±22.67*	0.0001
*Significantly different from FF	S and RES **Sid	nificantly differe	ant from EES_EEI	• external

\*Significantly different from EES and BES. \*\*Significantly different from EES. EEL: external elastic lamina





#### Biodegrada ble polymer

EuroIntervention. 2014;10:717
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#### 6M histomorphometric analysis

Measurements	EES n=6	BES n=6	SES n=6	<i>p</i> -value	
EEL area (mm²)	7.02±0.93	8.01±1.07	7.30±1.87	0.44	
Stent area (mm²)	5.93±0.74	6.79±0.85	5.86±1.23	0.21	
Lumen area (mm²)	2.40±1.47	2.91±1.40	1.83±0.68	0.34	
Neointimal area (mm²)	3.53±1.00	3.88±0.70	4.04±0.66	0.54	
Area stenosis (%)	60.99±20.52	58.62±14.73	69.44±6.29	0.44	
Neointimal thickness (mm)	0.53±0.23	0.48±0.14	0.58±0.05	0.56	
Injury score	0.87±0.65	0.97±0.34	1.71±0.71*	0.05	
Fibrin score	0.03±0.7	0	0	0.39	
Struts with granuloma (%)	1.57±2.49	0.25±0.61	27.09±36.94	0.08	
Inflammatory score	0.39±0.60	0.28±0.29	1.63±1.53*	0.049	
Giant cells (%)	3.56±7.22	0.25±0.62	27.73±37.86	0.09	
*Significantly different from EES and BES. EEL: external elastic lamina					

### OCT substudy of NEXT trial

- 91 pts (55 EES-treated lesions in 48 patients and 51 BES-treated lesions in 43 patients)
- 8–12 months follow-up OCT imaging

	EES	BES	P-value
Stent struts			
No. struts	8,996	8,745	
Well-apposed and covered struts	8,762 (97.4)	7,920 (90.6)	<0.001
Well-apposed and uncovered struts	217 (2.4)	712 (8.1)	<0.001
Malapposed and covered struts	2 (0.02)	25 (0.3)	< 0.001
Malapposed and uncovered struts	15 (0.2)	88 (1.0)	<0.001
Stent-treated lesions			
No. stent-treated lesions	55	51	
Neointimal coverage over stent struts			
Uncovered struts (%)	3±7	9±10	<0.001
Lesions with any uncovered struts	28 (51)	42 (82)	<0.001
Frames with >30% uncovered struts (%)	4±10	6±11	0.375
Maximum length of segments with uncovered struts (mm)	1.0±1.4	3.1±3.2	<0.001
Stent malapposition			
Malapposed struts (%)	0.2±0.8	1.3±2.8	0.006
Lesions with any malapposed struts	6 (11)	14 (27)	0.028
Maximum length of segments with stent malapposition (mm)	0.1±0.3	0.3±0.5	0.030
Intra-stent thrombus	2 (4)	5 (10)	0.258
Morphometry			
Minimum lumen area (mm²)	5.20±2.19	5.69±2.05	0.242
Minimum stent area (mm <sup>2</sup> )	6.13±2.24	6.41±2.20	0.515
Maximum neointima area (mm²)	1.56±0.66	1.31±0.75	0.069
Maximum stent malapposition area (mm <sup>2</sup> )	0.16±0.60	0.30±0.69	0.275
Lumen volume (mm <sup>3</sup> )	108.07±53.74	115.96±40.50	0.398
Stent volume (mm <sup>3</sup> )	123.54±61.05	128.47±46.44	0.643
Neointima volume (mm <sup>3</sup> )	15.79±11.54	13.09±12.58	0.253
Stent malapposition volume (mm <sup>3</sup> )	0.31±1.28	0.58±1.57	0.336

## Ultimaster



- Thin strut CoCr stent
- Abluminal gradient coating with bioresorbable and elastic polymer
- Bioabsorbtion in 3-4 months
- Sirolimus 3.9 µg/mm stent
- ULTIMASTER® is a new reduced dose sirolimus-eluting stent using an abluminal bioabsorbable coating (Ultimaster; Terumo, Tokyo, Japan), which has a potential to obtain a different arterial healing than early generation of permanent polymer-based DES.
- However, the time course of early vascular healing has not been fully elucidated in STEMI and SAP, which hampers an understanding of "mechanisms" of the risk reduction for stent thrombosis.

## Various clinical programs covered by Ultimaster®

Approximately 45,000pts worldwide planned in studies with Ultimaster DES

#### Worldwide

#### Japan

TCD-10023 PK	CENTURY	CENTURY II	MASTER	MODEL U-SES	CENTURY JSV
20 pts	105 pts	1,123 pts	500 pts	1,500pts	70pts
Single arm	Single arm	Randomised 1:1vsPP-EES	Randomised 3:1vsBMS	Single arm	Single arm
Pharmaco-kinetics	Selected patients (CE mark approved)	Real world global study	STEMI	3 months DAPT	Stents <b>Φ</b> 2.25mm
Published	Published	Published	PCR2016	On-going	PCR2016
DISCOVERY 1TO3	e-Ultimaster	MASTER DAPT		MECHANISM- Ultimaster AMI	MECHANISM- Ultimaster Elective
60 pts	Approximately 37,000pts	4,300pts		100pts	100pts
Single arm	Single arm	Randomised 1:1		Single arm	Single arm
Multivessel disease OFDI strut coverage	All-comers	1 month DAPT for High Bleeding Risk patients		Early OFDI strut coverage for AMI patients	Early OFDI strut coverage for Elective patients
PCR2016	On-going	On-going		On-going	On-going

Barbato E et al. EuroIntervention. 2015;11:541–8; Saito S et al. Eur Heart J 2014;35:2021–31; Stojkovic S et al. Fundam Clin Pharmacol 2015;29:95–105; Barbato E Presented at EuroPCR 2015, abstract OP047; Stankovic G. Presented at EuroPCR 2015; Smits P. Presented at EuroPCR 2015; Data on file at Terumo Corporation

## **CENTURY II series**



A large, prospective, multicentre, intercontinental study has directly studied Ultimaster vs Xience



**Primary endpoint : Freedom from TLF at 9 months** 

\*1123 enrolled, 1119 in intention-to-treat population; <sup>†</sup>2-year data reported for key subgroups; TLF, target lesion failure

Saito S et al. Eur Heart J 2014;35:2021–31; Lesiak M. Presented at EuroPCR 2015, abstract OP016; Merkely B. Presented at EuroPCR 2015, abstract OP 135; Iniguez R. Presented at EuroPCR 2015, abstract OP071; Valdés M. Presented at EuroPCR 2015, abstract OP043.

#### Favourable outcomes in a randomized study vs Xience

Primary endpoint was met. Ultimaster showed similar freedom from TLF to Xience in first 9 months.



#### TLF rate remained similar for Ultimaster and Xience for up to 2 years



#### There are no VLST reported between 12 and 24 months for Ultimaster,

#### which further demonstrated good safety profile for this stent.

	Ultimaster Npt=551	Xience Npt=550	P-value
Stent thrombosis, Def+prob	6 (1.1)	6 (1.1)	0.99
early, n (%)	3 (0.54)	3 (0.55)	
late, n (%)	3 (0.54)	3 (0.54)	
very late, n (%)	0 (0.0)	0 (0.0)	
DAPT,			
12 months, %	66.1	64.9	0.68
24 months, %	31.1	29.2	0.50
Any bleeding, %			
12 months, %	8.0	10.7	0.12
24 months, %	9.8	11.5	0.37
Any angina			
12 months, %	5.8	5.3	0.74
24 months, %	5.5	7.4	0.23

Saito S presented at TCT2015.

## Safety & efficacy confirmed in high-risk patients

#### Death and MI at 2 years remained low and comparable to Xience:<sup>1,2</sup>

roportion of patients (%)



1. Based on ST rates from CENTURY and CENTURY II trials, Ultimaster IFU and data on file at Terumo Corporation; 2. Saito S et al. Eur Heart J 2014;35:2021–31; 3. Orvin K et al. Catheterization cardiovascular interventions. DOI: 10.1002/ccd.26150; 4. Merkely B. Presented at EuroPCR 2015, abstract OP135; 5. Valdés M. Presented at EuroPCR 2015, abstract OP043; 6. Wöhrle J et al. Presented at EuroPCR 2015, abstract OP066; 7. Iniguez R. Presented at EuroPCR 2015, abstract OP071; 8. Fabbiocchi F et al. Presented a t EuroPCR 2015, abstract OP016.

## Safety & efficacy confirmed in high-risk patients

#### **Proven clinical efficacy**

Clinically driven TLR at 2 years remained low and comparable to Xience:<sup>1</sup>



1. Saito S et al. Eur Heart J 2014;35:2021–31; 2. Orvin K et al. Catheterization cardiovascular interventions. DOI: 10.1002/ccd.26150; 3. Merkely B. Presented at Euro PCR 2015, abstract OP135; 4. Valdés M. Presented at EuroPCR 2015, abstract OP043; 5. Wöhrle J et al. Presented at EuroPCR 2015, abstract OP066; 6. Iniguez R. Presented at EuroPCR 2015, abstract OP071; 7. Fabbiocchi F et al. Presented at EuroPCR 2015, abstract POS155; 8. Lesiak M. Presented at EuroPCR 2015, abstract OP016.

#### - Bifurcation lesions



Log-rank p=0.3571

#### **CENTURY II** - Multivessel disease

#### **TLF Kaplan-Meier curves – 4 years**



#### - MVD & DM



#### - Small vessel disease



#### - NSTEMI subgroup/MASTER



#### - Long lesion

#### Long lesion treated with overlapping stents (n=110)



EuroPCR 2017

## Safety and efficacy of Ultimaster in STEMI patients

#### **MASTER: 500 STEMI patients, randomised 3:1 vs Kaname BMS**

Generate further evidence for benefits of primary PCI with BP- DES in patients with STEMI



Triple primary endpoint at 1 (safety), 6 (efficacy) and 12 months (safety/efficacy)

M. VALDES-CHAVARRI. Presented at EuroPCR 2016

## Safety and efficacy of Ultimaster in STEMI patients

#### Primary safety endpoint at 1 month was met.



Primary safety endpoint:

Composite of all-cause death, recurrent MI, unplanned infarct-related artery (IRA) revascularization, stroke, definite stent thrombosis or major bleeding at 1 month

## Safety and efficacy of Ultimaster in STEMI patients

#### Ultimaster showed significant difference with BMS in TVF at 12 month



Primary endpoint: TVF at 12 M.

TVF : Target Vessel Failure (composite endpoint of cardiac death and MI not clearly attributable to a non-target vessel , and clinically driven TVR)

\* Definite or probable ST according to ARC definitions

M. VALDES-CHAVARRI. Presented at EuroPCR 2016

## **DISCOVERY 1TO3**

#### - Assess endothelial coverage at 1, 2 and 3 months by OFDI

#### **DISCOVERY 1TO3**

Investigate possibility for shorter DAPT by generating relevant clinical scientific data 60 MVD patients with OFDI, single arm, primary endpoint TLF @ 12M.



### 85% strut coverage as early as 1 month



Presented at EuroPCR 2016

## **MECHANISM-ULTIMASTER trial**

#### Objective:

 To assess the early and late vascular healing to ULTIMASTER DES for treatment of patients with STEMI and SAP.

#### Design:

 Prospective multicenter registry, Investigators initiated study with 21 investigators conducted in Japan

#### Primary Endpoint:

 Percentage of stent strut coverage by OFDI at 1 month (STEMI) and 3 month (Elective) evaluated by independent imaging core laboratories

## **MECHANISM-ULTIMASTER trial**



### **MECHANISM-ULTIMASTER trial**

**PEP : % uncovered struts** 



### Conclusion

- ✓ Advantage of BP-DES
- ✓ Superiority of BP-DES to BMS and 1<sup>st</sup> G. DP-DES
- ✓ Similar efficacy and safety of BP-DES to 2<sup>nd</sup> G. DP-DES
  - ✓ Limited data on the superiority of EES to BP-DES
- ✓ Higher rates of inflammation during active bioresorption of polymer
- ✓ Ultimaster put up a good fight against EES.
- Biodegradability of polymer & the optimal combination of stent alloy, design,
  - strut thickness, polymer, and drug all combined determine the safety of DES.

# Thank you for your attention^^.