

LEADERS: 5-Year Follow-up

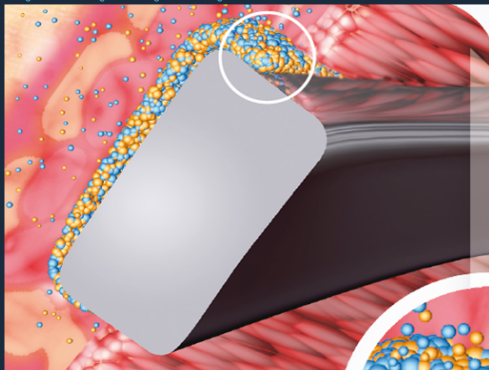
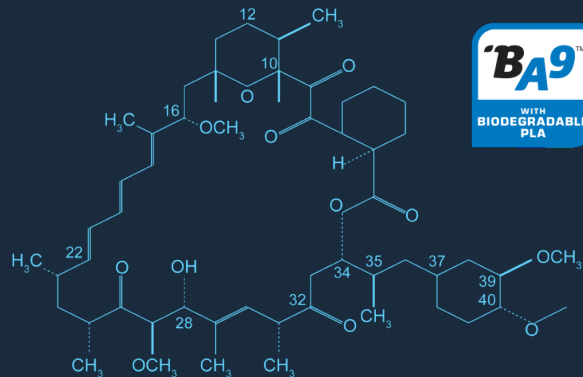
**from a Prospective, Randomized Trial of Biolimus
A9-eluting Stents with a Biodegradable Polymer vs.
Sirolimus-eluting Stents with a Durable Polymer :**

Final Report of the LEADERS study

Antoine Py
Clinique de l'Europe
Amiens

11139-000-EN

Biolimus-A9™ Eluting Stent



- Biolimus is a semi-synthetic sirolimus analogue with **10x higher lipophilicity** and similar potency as sirolimus.
- Biolimus is immersed at a concentration of 15.6 µg/mm into a biodegradable polymer, polylactic acid, and applied solely to **the abluminal stent surface** by a fully automated process.
- Biolimus is co-released with polylactic acid and completely desolves into carbon dioxide and water after **a 6-9 months period**.
- The stainless steel stent platform has a strut thickness of 120 µm with a quadrature link design.

Circulation

Cardiovascular Interventions

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Polymer-Free Biolimus A9-Coated Stent Demonstrates More Sustained Intimal Inhibition, Improved Healing, and Reduced Inflammation Compared With a Polymer-Coated Sirolimus-Eluting Cypher Stent in a Porcine Model

Norio Tada, Renu Virmani, Gordon Grant, Lauren Bartlett, Alexander Black, Claudia Clavijo, Uwe Christians, Ron Betts, Doug Savage, Shih-Horng Su, John Shulze and Saibal Kar

Circ Cardiovasc Interv 2010;3;174-183

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Polymer-Free Biolimus A9–Coated Stent Demonstrates More Sustained Intimal Inhibition, Improved Healing, and Reduced Inflammation Compared With a Polymer-Coated Sirolimus-Eluting Cypher Stent in a Porcine Model

Norio Tada, MD; Renu Virmani, MD; Gordon Grant; Lauren Bartlett, BS; Alexander Black, MB, BS; Claudia Clavijo, MD; Uwe Christians, MD, PhD; Ron Betts, PhD; Doug Savage, PhD; Shih-Horng Su, PhD; John Shulze; Saibal Kar, MD

Background—Drug-eluting stents effectively reduce restenosis but may increase late thrombosis and delayed restenosis. Persistent polymer, the drug, or a combination of both could be responsible. Local delivery of Biolimus A9, a rapamycin derivative, from a polymer-free BioFreedom stent (Biosensors International) may prevent these complications.

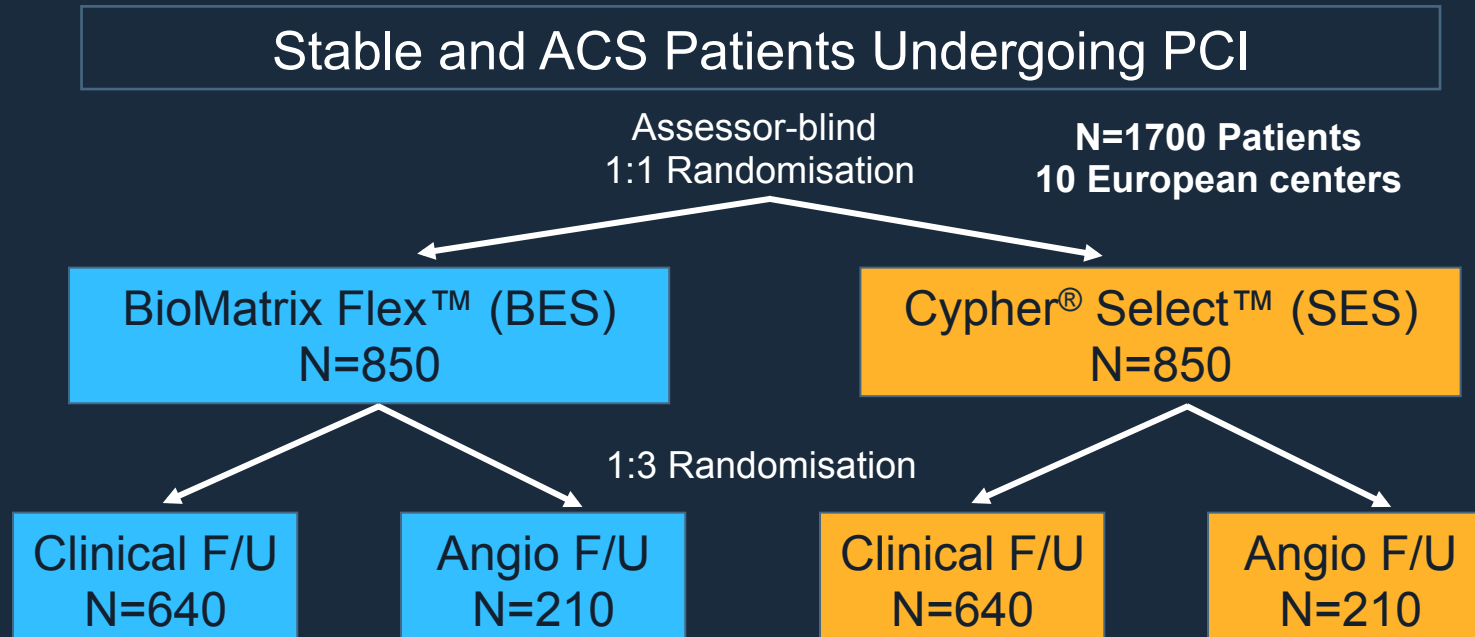
Methods and Results—We compared high-dose (HD) (225 $\mu\text{g}/14$ mm Biolimus A9) and low-dose (LD) (112 $\mu\text{g}/14$ mm Biolimus A9) BioFreedom stents with a polymer-coated sirolimus-eluting Cypher stent (SES) and a bare-metal stent (BMS) at 28 days and 180 days in an overstretch coronary mini-swine model with histomorphometric and histological analysis. At 28 days, there was a reduction in neointimal proliferation by HD, LD, and SES compared with BMS (neointimal thickness: HD, 0.080 ± 0.032 ; LD, 0.085 ± 0.038 ; SES, 0.064 ± 0.037 ; BMS, 0.19 ± 0.111 mm; $P < 0.001$; BMS > HD/LD/SES). At 180 days, both BioFreedom stents were associated with reduced neointimal proliferation, whereas SES exhibited increased neointima (neointimal thickness: HD, 0.12 ± 0.034 ; LD, 0.10 ± 0.040 ; SES, 0.20 ± 0.111 ; BMS, 0.17 ± 0.099 mm; $P < 0.001$; SES > HD/LD; BMS > LD). At 180 days, BioFreedom stents showed decreased fibrin and inflammation, including granuloma and giant cells, compared with SES.

Conclusions—The polymer-free Biolimus A9–coated stent demonstrates equivalent early and superior late reduction of intimal proliferation compared with SES in a porcine model. After implantation of BioFreedom stent, delayed arterial healing was minimal, and there was no increased inflammation at 180 days compared with SES implantation. The use of polymer-free stents may have a potential long-term benefit over traditional polymeric-coated drug-eluting stents.

(*Circ Cardiovasc Interv.* 2010;3:174-183.)

Key Words: restenosis ■ inflammation ■ polymer-free drug-coated stents ■ Biolimus A9 ■ sirolimus

LEADERS 'all-comers' Trial Design



1° endpoint:

2° endpoints:

Angiographic study:

DAPT recommended for 12 months

MACE: Cardiac death, MI, clinically-indicated TVR (9 mo)

Death, CV death, MI, TLR, TVR

Stent thrombosis according to ARC

In-stent % diameter stenosis (9 mo)

Late loss, binary restenosis

Patient Demographics

	BES 857 Patients	SES 850 Patients
Age in years	65 ± 11	65 ± 11
Male gender	75%	75%
Arterial hypertension	74%	73%
Diabetes mellitus	26%	23%
- insulin-dependent	10%	9%
Hypercholesterolemia	65%	68%
Family history of CAD	40%	44%
Smoking	24%	25%
Previous MI	32%	33%
Previous PCI	36%	37%
- with drug-eluting stent	12%	14%
Previous CABG	11%	13%

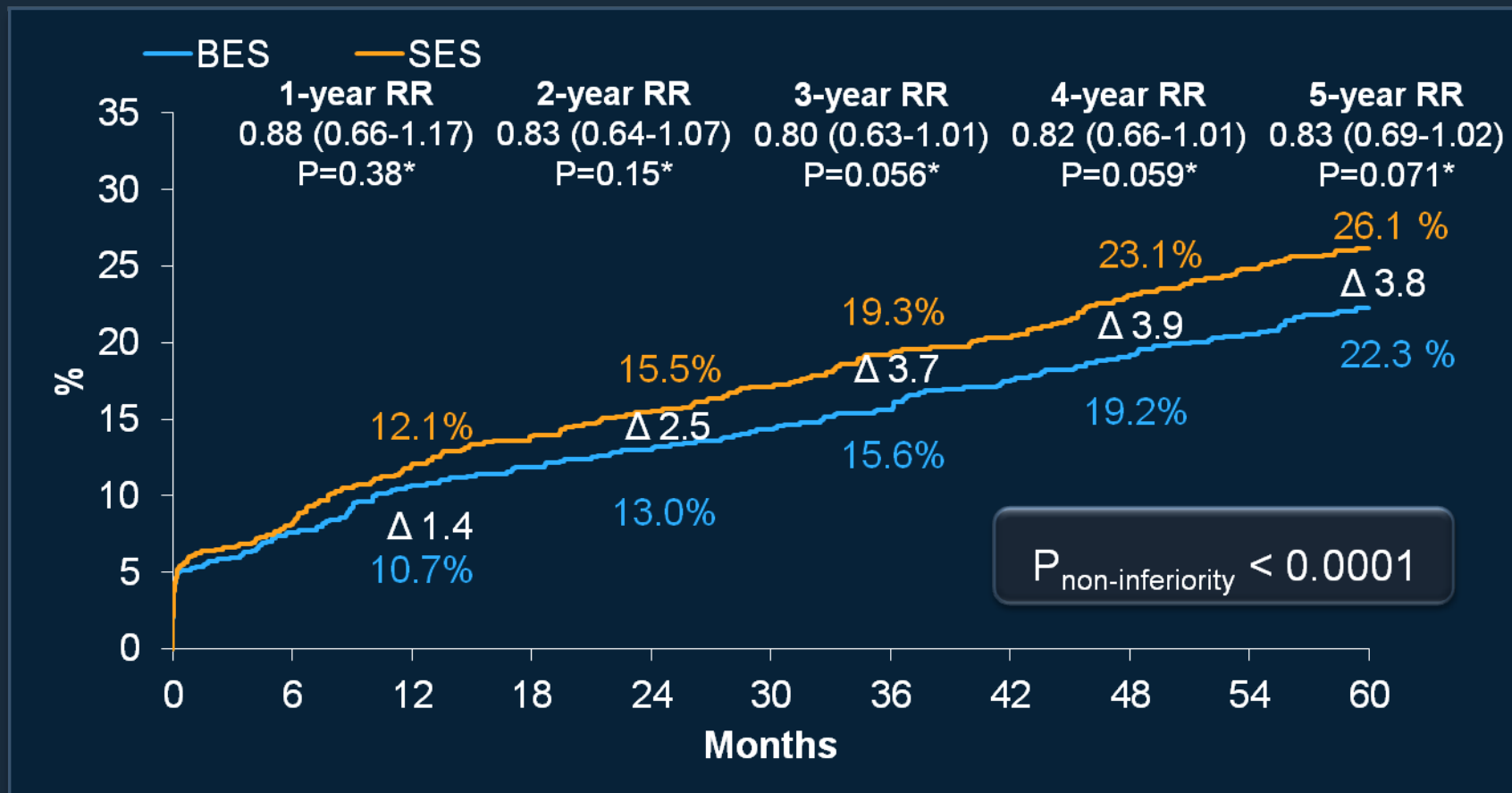
Patient Characteristics

	BES 857 Patients	SES 850 Patients
Chronic stable angina	45%	44%
Acute coronary syndrome	55%	56%
• Unstable angina	22%	21%
• Non-ST-elevation MI	17%	18%
• ST-elevation MI	16%	17%
Left ventricular ejection fraction	56 ± 11%	55 ± 12%
Number of lesions per patient	1.5 ± 0.7	1.4 ± 0.7
Lesions per patient		
• 1 lesion	63%	69%
• 2 lesions	29%	22%
• 3 lesions	7%	8%
• > 4 lesions	1%	2%
De novo lesions	92%	91%
Long lesions (>20 mm)	31%	27%
Small vessels (RVD ≤2.75 mm)	68%	67%
Off label use	81%	78%

Patient Flow - Clinical



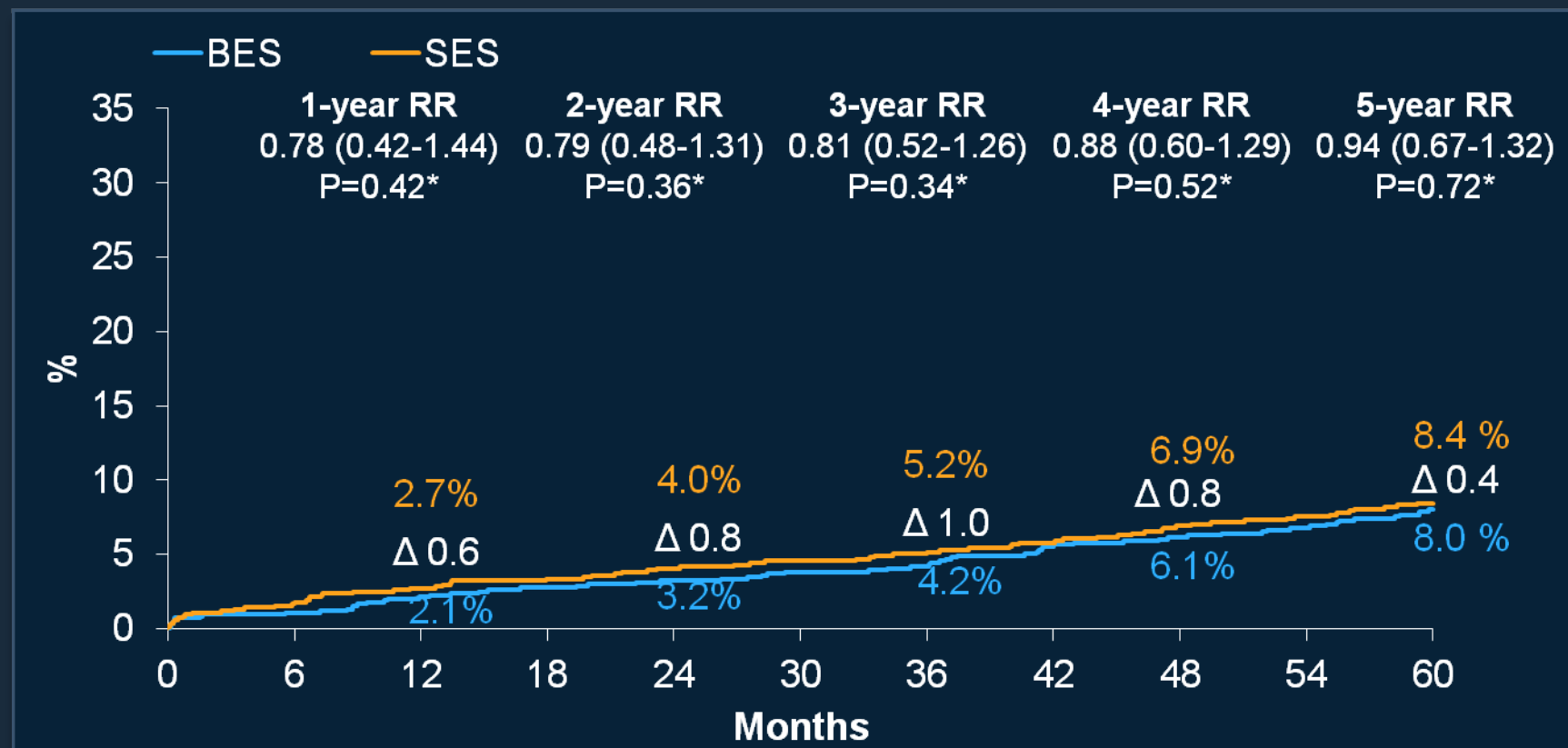
MACE (Cardiac Death, MI and ci-TVR)



Number at risk

SES	850	774	738	718	701	676	655	640	616	589	572
BES	857	780	749	733	723	710	697	675	657	635	618

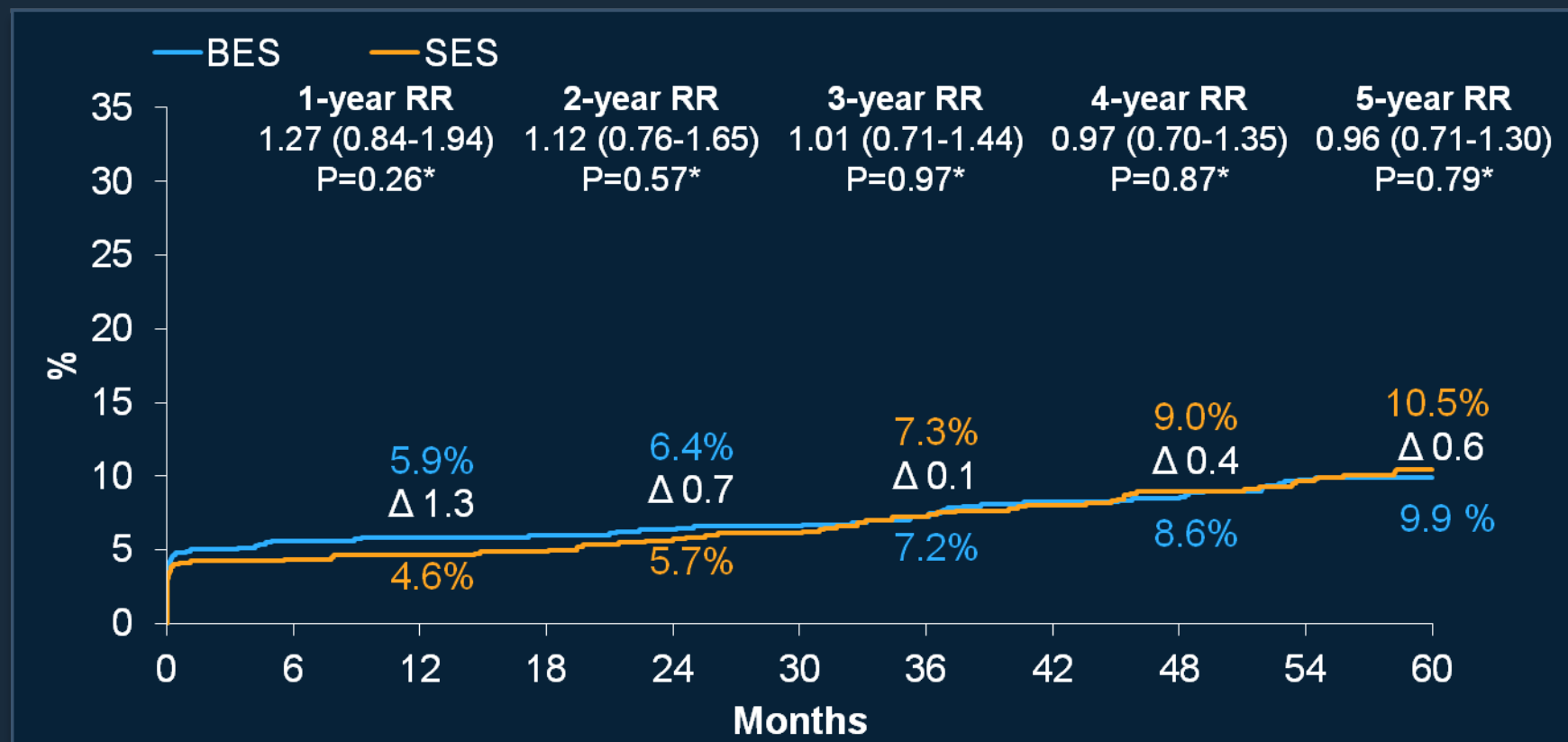
Cardiac Death



Number at risk

SES	850	829	814	802	793	776	767	753	742	721	704
BES	857	832	817	806	801	794	788	770	760	744	731

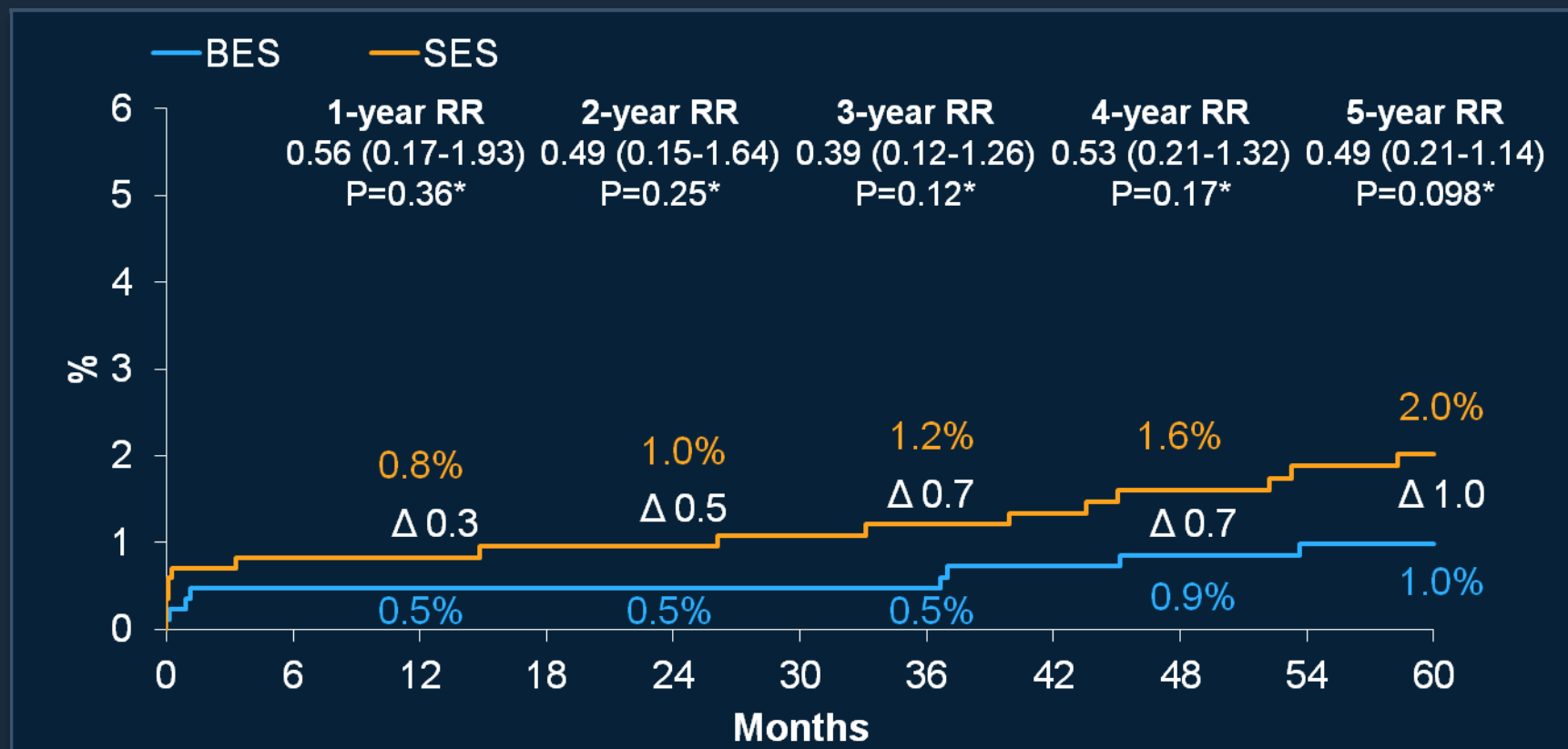
MI



Number at risk

SES	850	796	781	767	752	733	717	700	684	661	644
BES	857	791	779	768	761	752	744	721	710	687	675

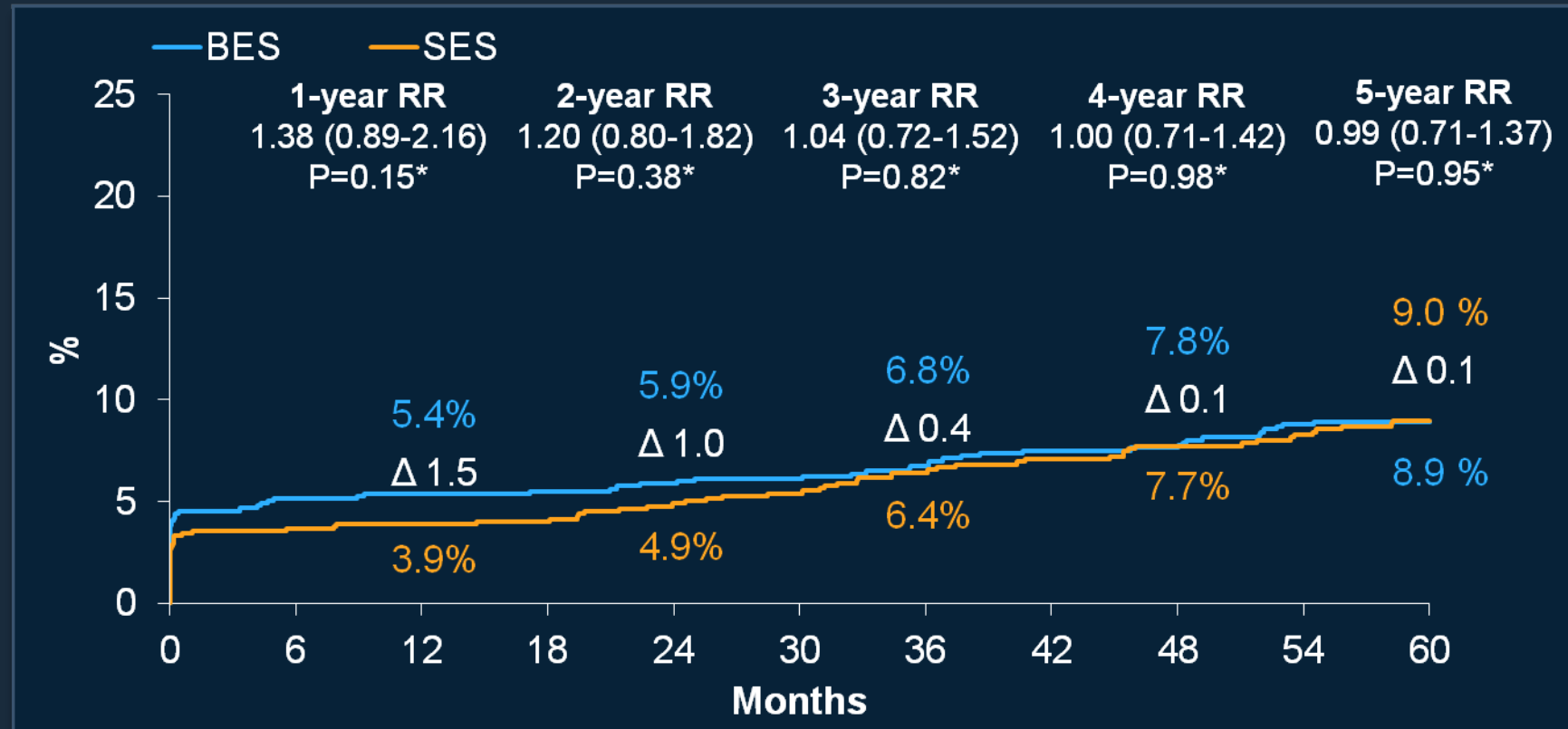
QW-MI



Number at risk

SES	850	823	808	795	786	768	759	745	733	710	694
BES	857	828	813	802	798	791	786	767	756	739	726

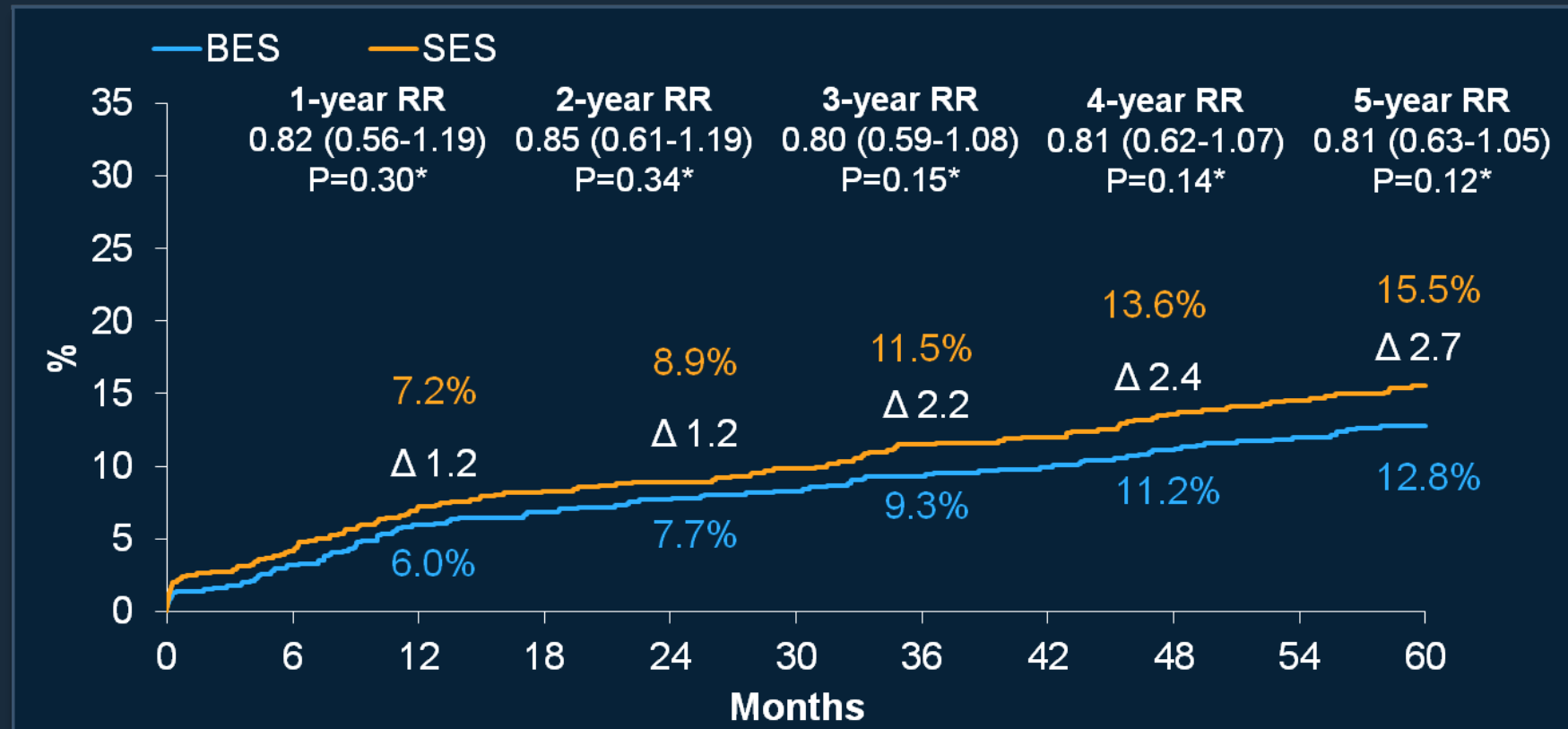
Non QW-MI



Number at risk

SES	850	802	787	774	759	739	724	707	692	670	653
BES	857	795	783	772	764	755	746	724	714	692	680

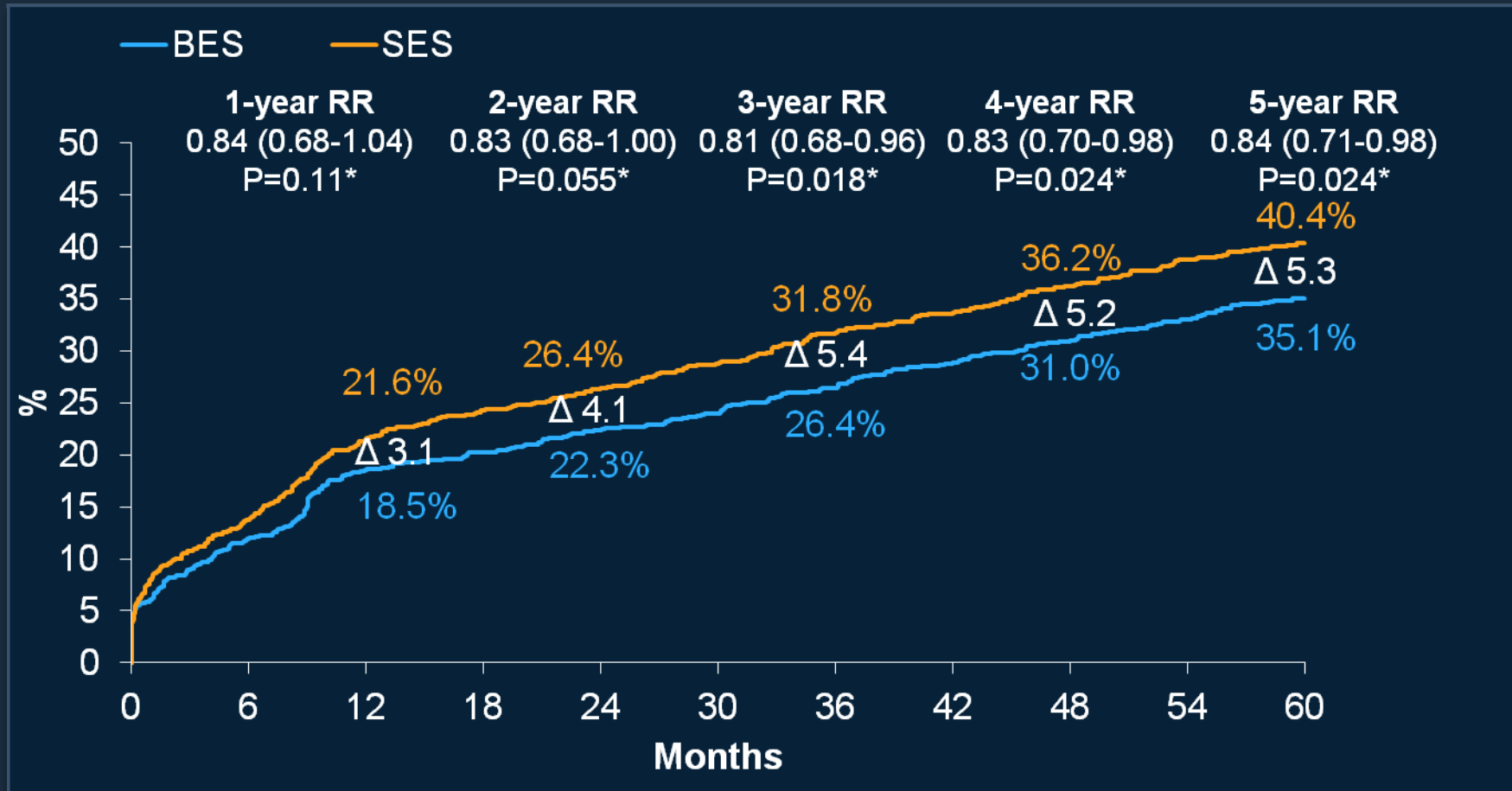
Clinically-Indicated TVR



Number at risk

SES	850	797	760	741	727	704	685	668	646	620	600
BES	857	809	776	758	748	736	725	706	687	668	650

Patient Oriented Composite Endpoint (All-cause Death, Any MI, All Revascularization)



Number at risk

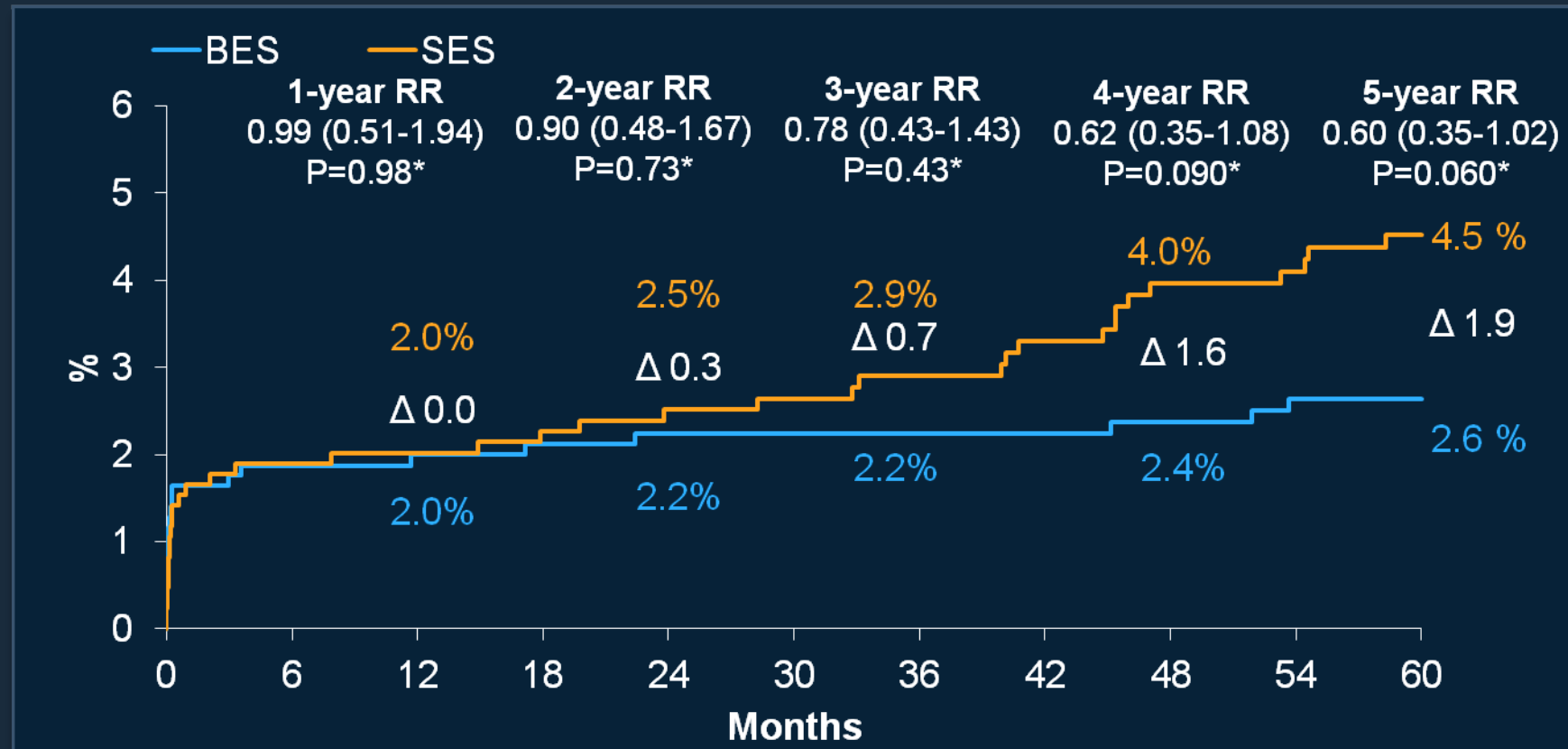
SES	850	729	661	637	618	594	569	551	530	504	491
BES	857	749	689	672	654	639	619	597	579	557	540

POCE = all death, MI, any revascularization (includes adjudicated and non-adjudicated events)

* p-value for superiority

Serruys et al., oral abstract presentation, TCT 2012

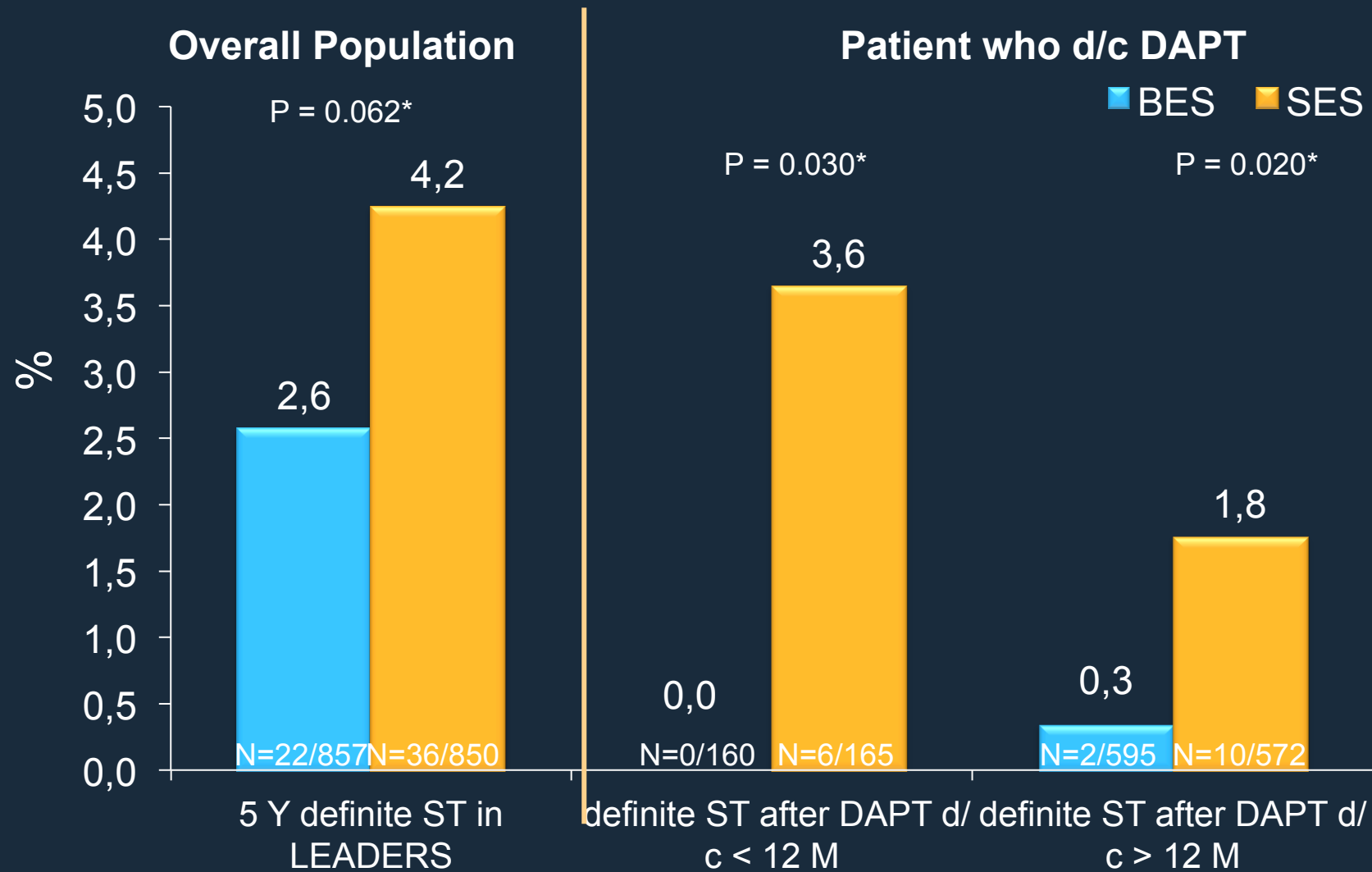
Definite Stent Thrombosis (ARC)



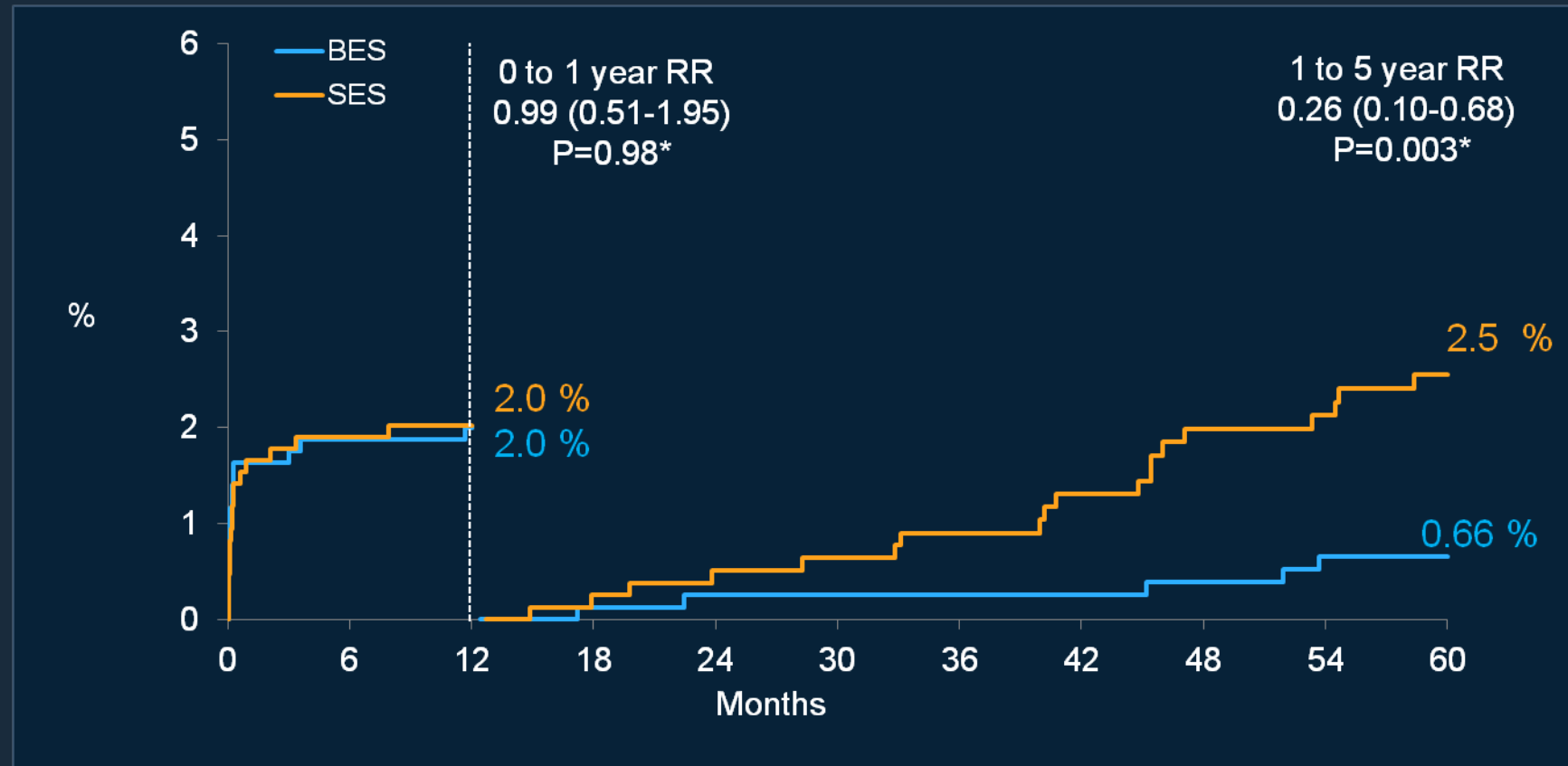
Number at risk

SES	850	816	801	787	776	759	749	732	717	696	678
BES	857	819	804	792	787	780	775	757	747	730	717

Effect of DAPT Discontinuation



Definite ST (ARC) Landmark Analysis @ 1 Year



Durable/Biodegradable Polymer DES

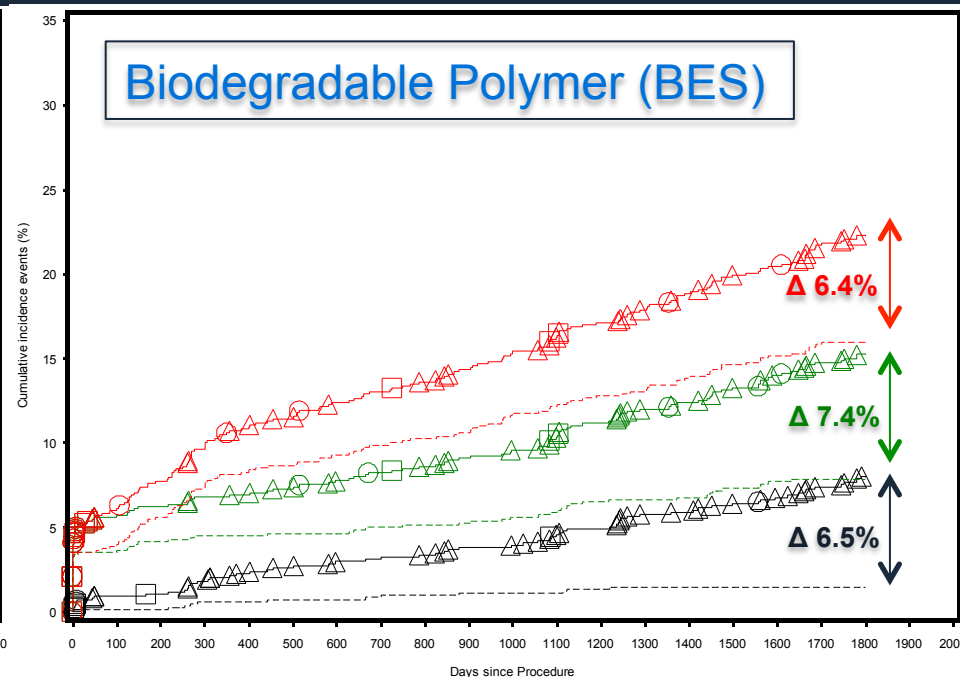
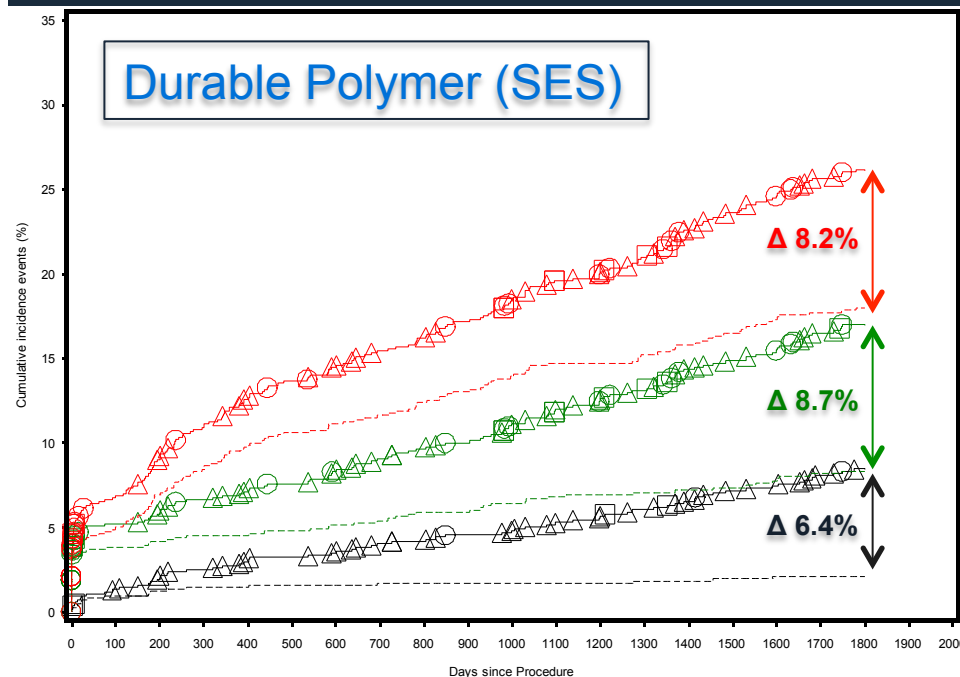
Clinical Events (Corrected KM Estimates) Linked to to ARC Definition ST

○ ○ ○ Definite ST
□ □ □ Probable ST
△ △ △ Possible ST

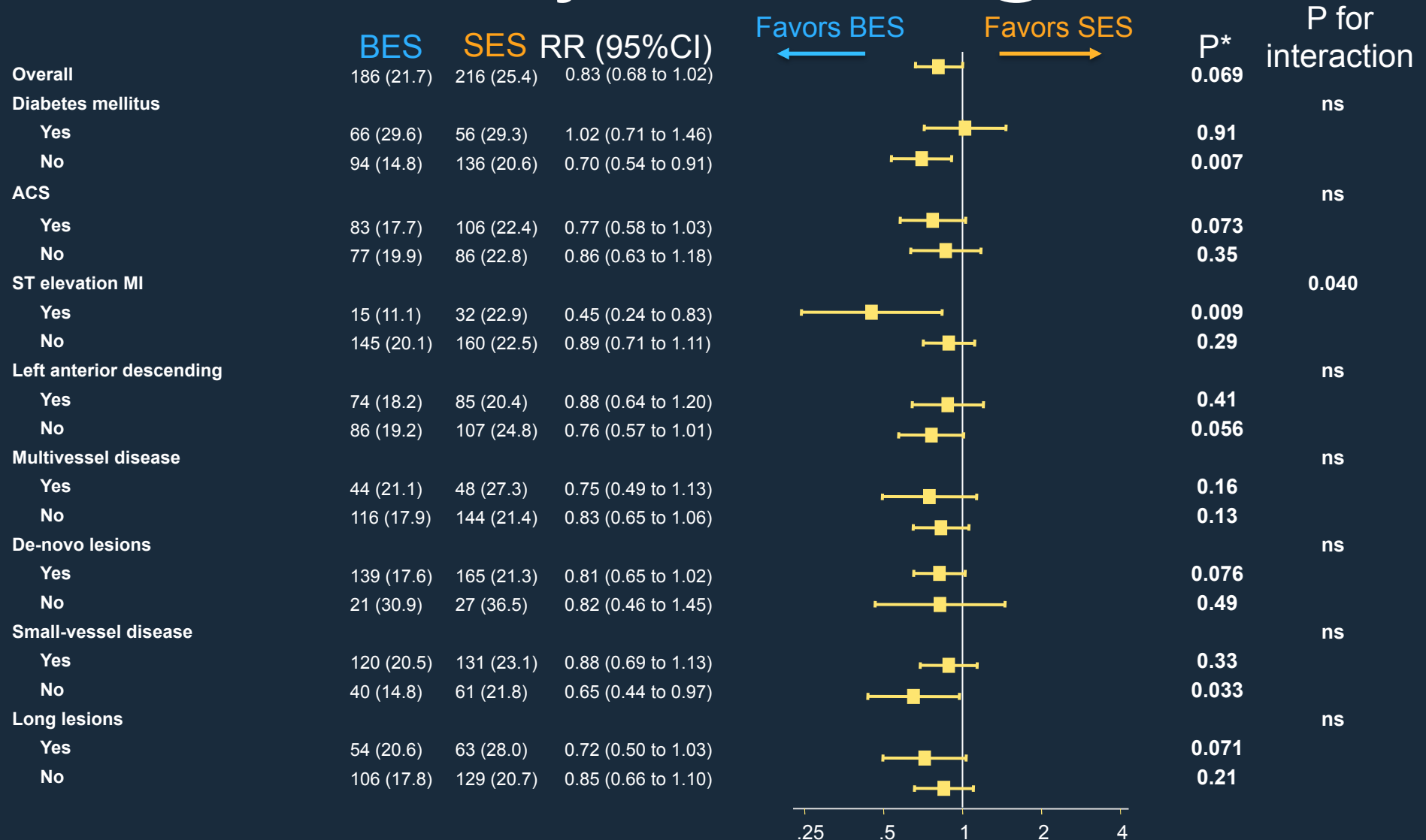
Cardiac Death/MI/Ci TVR

Cardiac Death/MI

Cardiac Death



Stratified Analysis of MACE @ 5 Years





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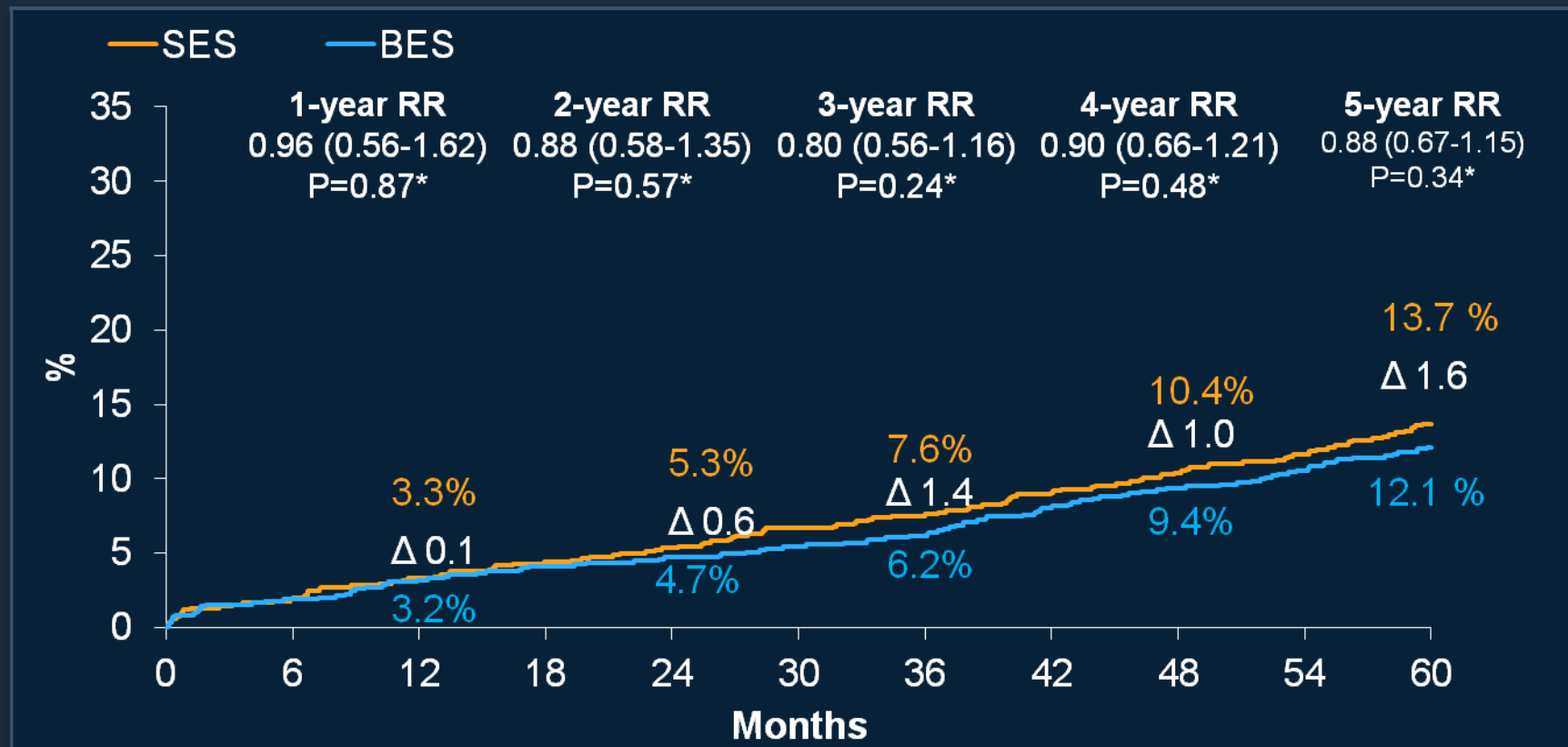
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Conclusions

- Biodegradable polymer BES maintained non-inferiority and improved long-term clinical outcomes compared to SES through 5 years ($P_{\text{sup}} = 0.071$)
- Biodegradable polymer BES demonstrated a 74% relative risk reduction in very late definite stent thrombosis (VLST)
- The benefit of biodegradable polymer BES emerged in the very late phase and was mainly driven by a lower risk of MACE associated with definite VLST

All Death

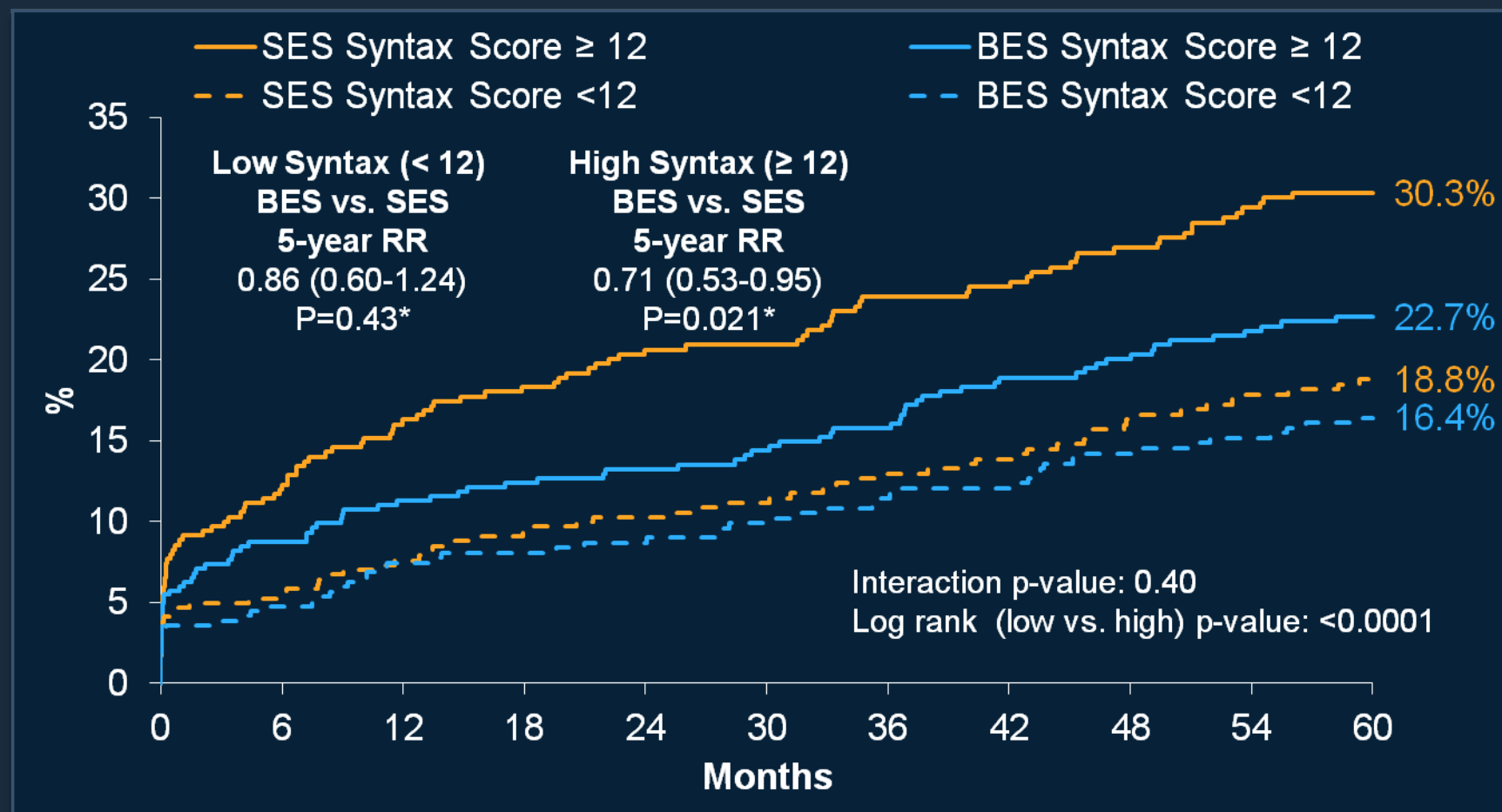


Number at risk

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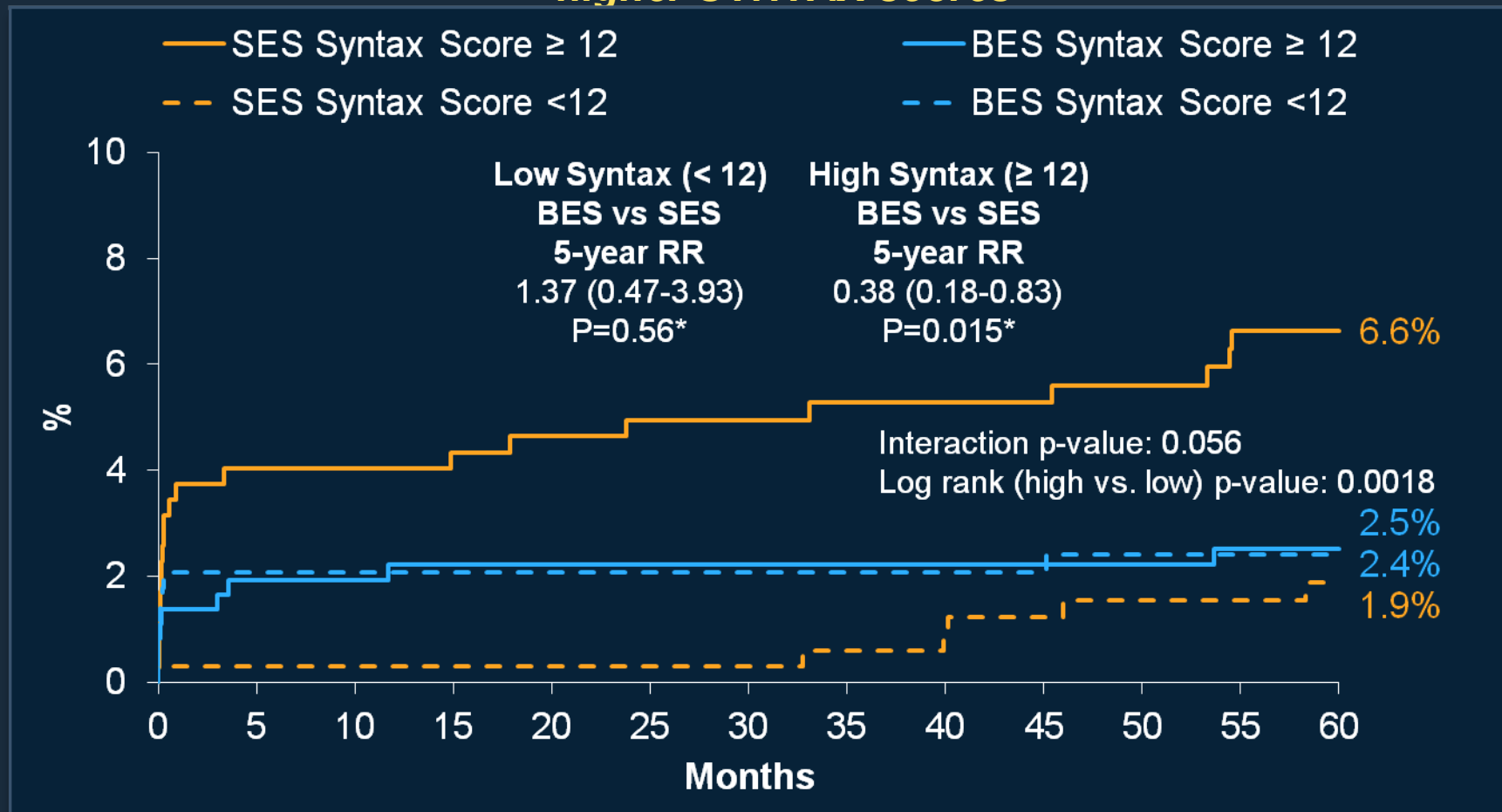
MACE @ 5 Years Separated by Median SYNTAX Score (12)

The SYNTAX score has no significant effect on the primary endpoint between BES and SES

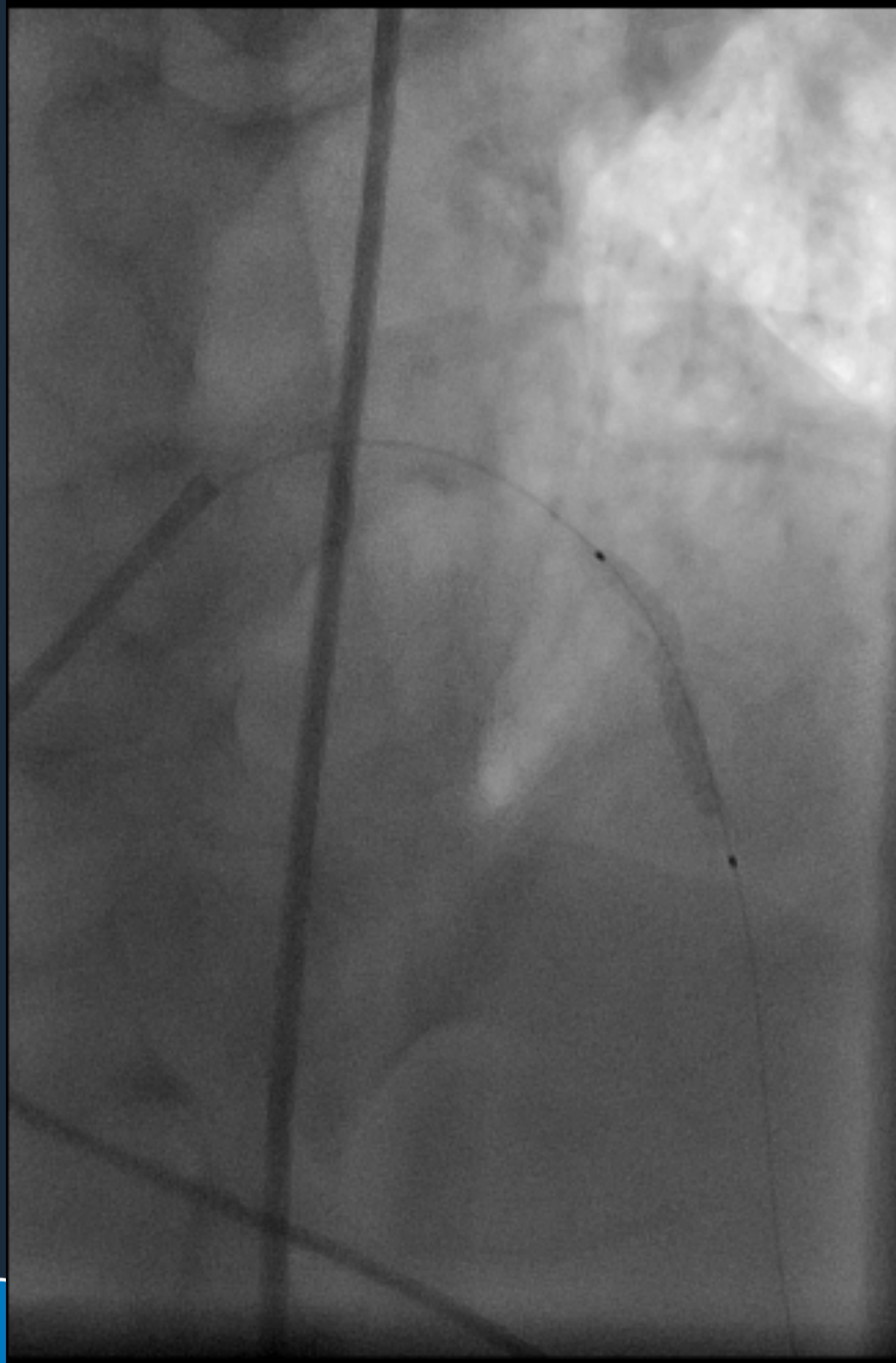


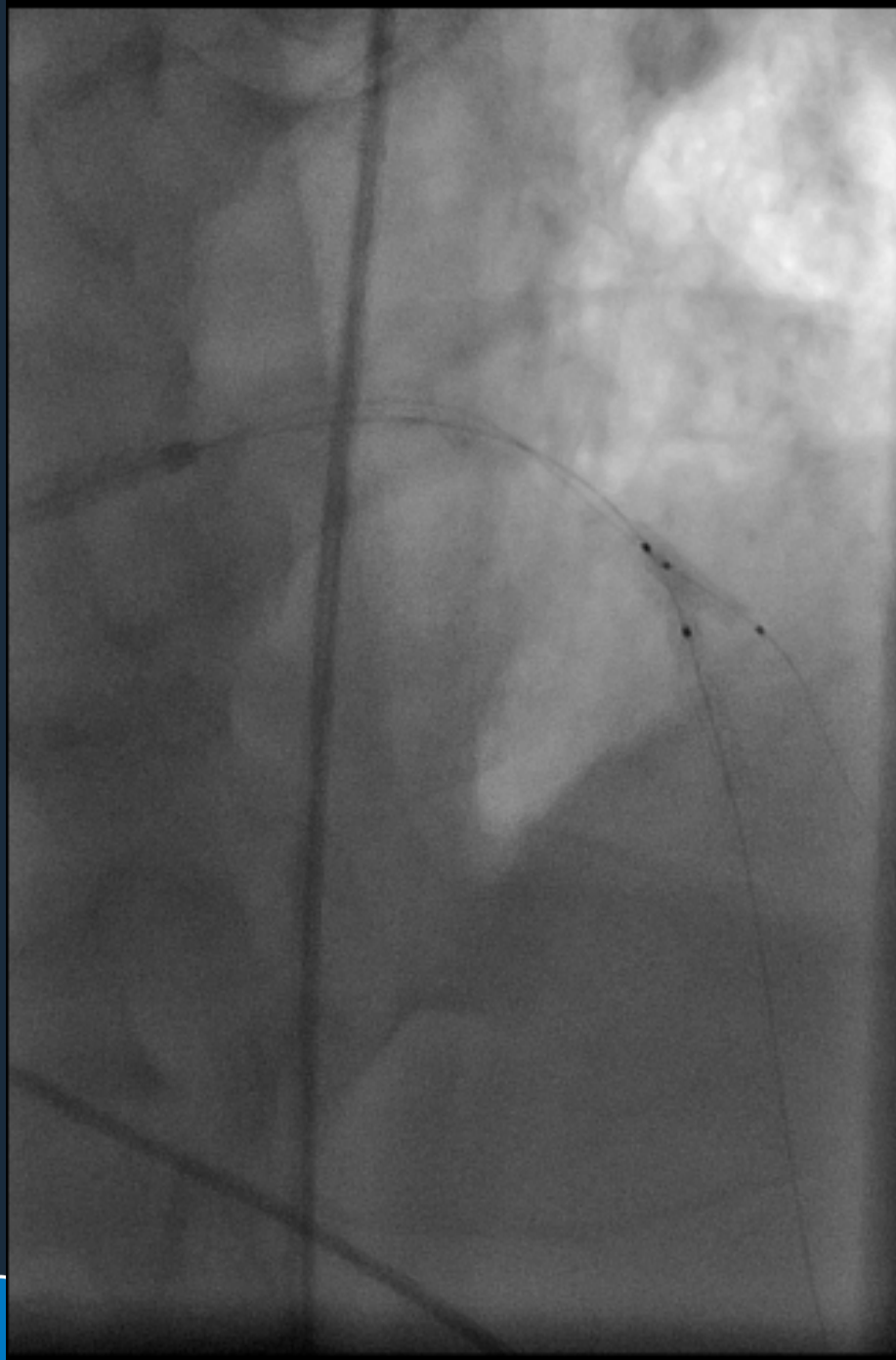
Definite ST @ 5 Years Separated by Median SYNTAX Score (12)

BES is associated with a significant reduction in definite ST in the higher SYNTAX scores

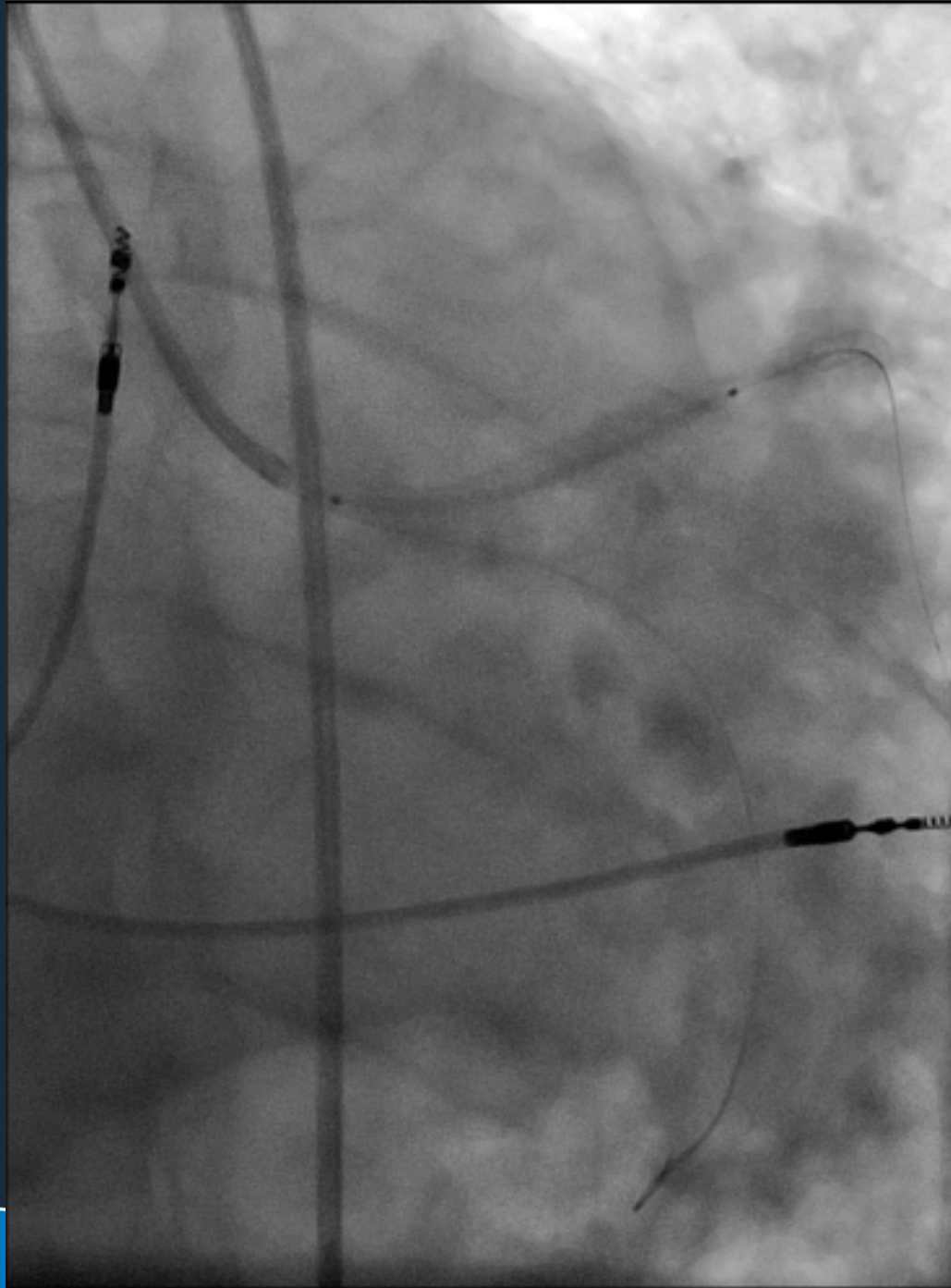


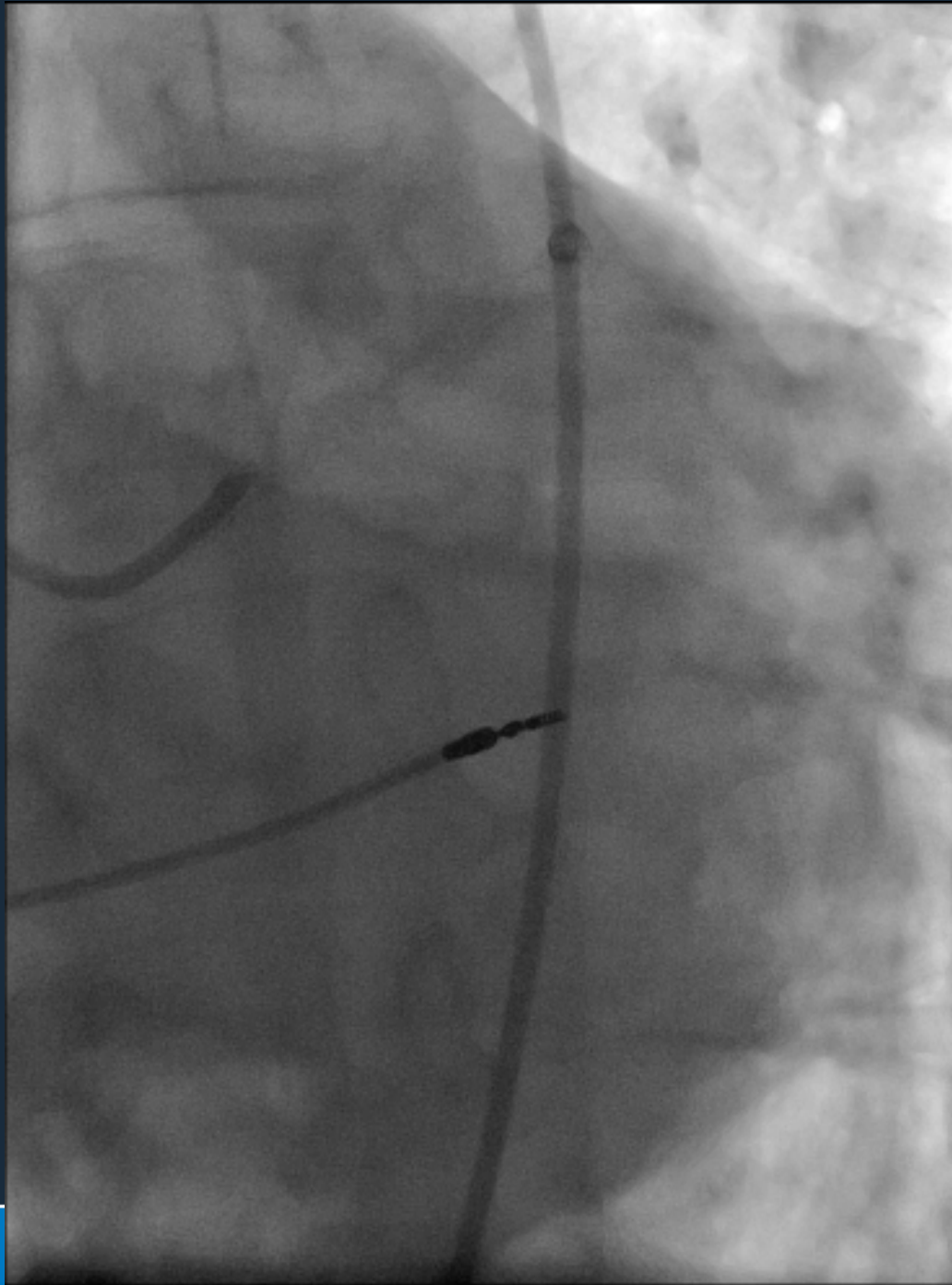








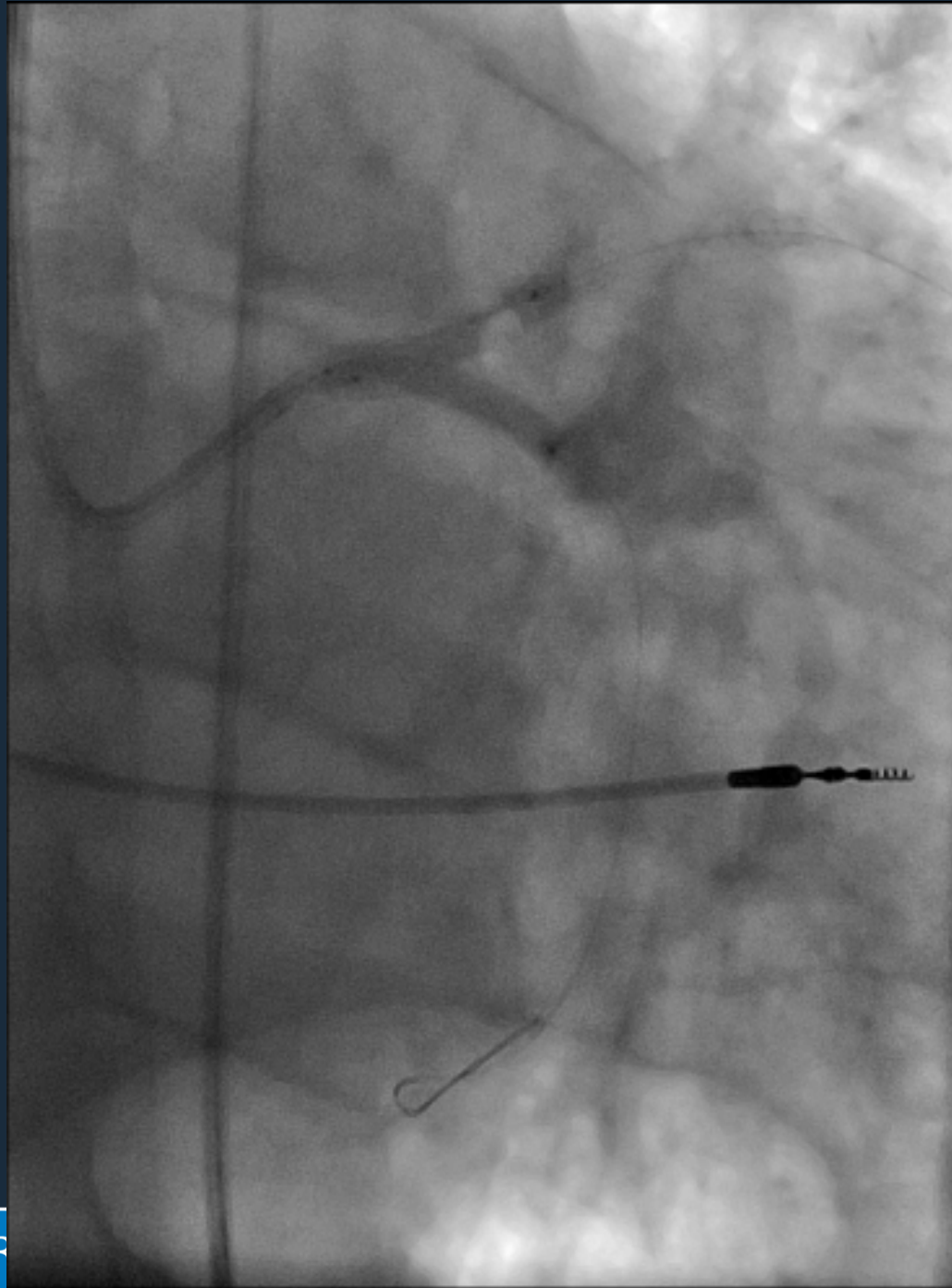






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LEADERS



Ouverture maximale des cellules

- - BioMatrix Flex™ (3,0mm): 3,34 mm
- - BioMatrix Flex™ (3,5mm): 4,19 mm
- Surdilatation maximale du stent (stents de 3.0 – 3.5 – 4.0 mm de diamètre) pour gestion de bifurcations avec POT (proximal optimisation technique) ou kissing-balloons

