All-comers LEADERS trial:
Biolimus eluting stent reduces mortality in patients with high SYNTAX scores in the "all-comers" LEADERS trial

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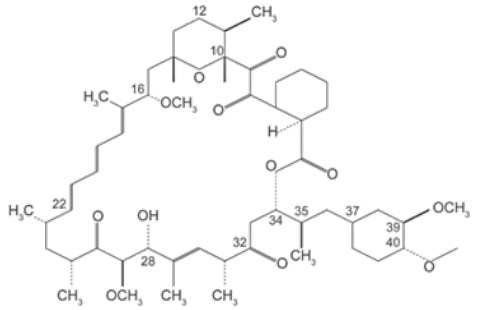
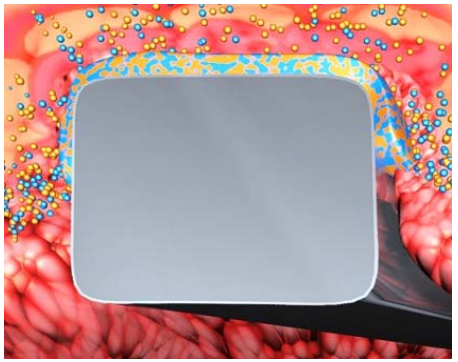
EuroPCR, Tuesday, May 25th , 2010
Rm 252B 13:30-14:45

BioMatrix Flex™ (BES)

- Biolimus is a sirolimus analogue with 10x higher lipophilicity and similar potency
- Biolimus (at a concentration of 15.6 μg/mm) is eluted abluminally from a biodegradable polylactic acid polymer
- Polylactic acid is co-released with biolimus and completely disolves into carbon dioxide and water after a 6-9 months period
- The stainless steel stent platform has a strut thickness of 120 μm





Background and Objectives

Background:

- The SYNTAX score (SXscore) has been shown to be an effective predictor of clinical outcomes in patients with multivessel disease undergoing percutaneous coronary intervention (PCI).
- LEADERS trial is the first “all-comers” trial that collected SYNTAX score prospectively.

Objective:

- assessment of the predictive value of the SXscore for major adverse cardiac events in the “all-comers” population of the LEADERS trial
- assessment of the effect of stent treatment (BES versus SES) in the three SYNTAX score tertiles

Methods

- The SXscore was prospectively collected in 1,397 of the 1,707 patients enrolled in the LEADERS trial (patients post-surgical revascularization were excluded) based on baseline diagnostic angiogram assessed by independent analysts at the CRO.

- Post-hoc analysis was performed by stratifying clinical outcomes at 1 and 2 year follow-up, according to one of three SYNTAX score tertiles.

Trial Design

Stable and ACS Patients Undergoing PCI

Assessor-blind
1:1 Randomisation

N=1700 Patients

BES
BioMatrix Flex N=850

SES
Cypher Select N=850

1:3 Randomisation

BES		SES	
Clinical F/U N=640	Angio F/U N=210	Clinical F/U N=640	Angio F/U N=210

1º endpoint: CV death, MI, clinically-indicated TVR (9 month)
2º endpoints: Death, CV death, MI, TLR, TVR
Stent thrombosis according to ARC

Angiographic study: In-stent % diameter stenosis
Late loss, binary restenosis

DAPT recommended for 12 month

Clinical Trial Organization

- **Event Adjudication Committee**
  - C. Hanet, E. McFadden, P.W. Radke, B.J.W.M. Rensing, E. Ronner, W. Rutsch, H.H. Tilsted, J. Vos, P. Vranckx
- **Data and Safety Monitoring Board**
  - J.G.P. Tijssen, M.E. Bertrand, P. Urban
- **Data Management and Coordination Center**
  - Cardialysis, Rotterdam, the Netherlands
    G.A. van Es, Y. Teunissen, J. de Groot, T. de Vries
- **Angiographic Core Laboratory**
  - Cardialysis, Rotterdam, the Netherlands
- **Data Monitoring**
  - Premier Research Group, Ulrike Gross, Witten, Germany
- **Independent Statistical Analysis**
  - CTU Bern and Institute for Social and Preventive Medicine University of Bern, Switzerland: S. Wandel, P. Jüni

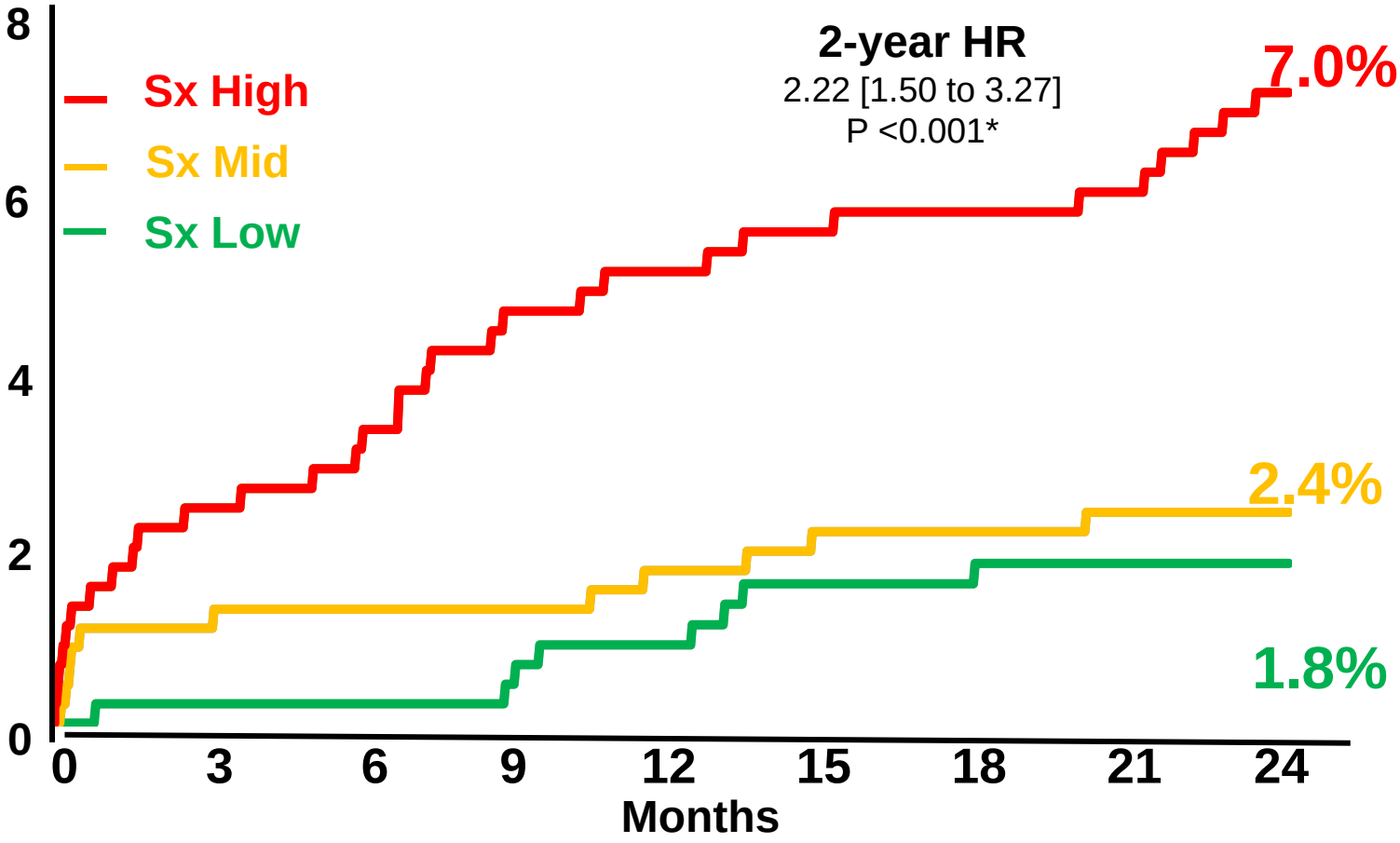
Baseline clinical characteristics based on Syntax tertiles

Baseline clinical variables, (%)	SX score <8 N=464	SX score 8-16 N=472	SX score >16 N=461	p-value on Trend (2-sided)
Age >65	45	48	52	0.048
Male	75	73	74	0.79
Diabetes	20	25	24	0.15
Current smoking	29	26	27	0.61
Hypertension	76	75	70	0.048
Hypercholesterolemia	68	67	62	0.06
Family history	43	40	36	0.034
Renal insufficiency	4	5	6	0.09
Previous MI	29	31	30	0.69
Previous PCI	39	35	32	0.036
Clinical presentation:				
Stable	32	33	23	0.008
Unstable	27	33	19	0.002
STEMI	10	19	28	<0.0001

Baseline angiographic characteristics by Syntax tertiles

Angiographic variable	SX score <8	SX score 8-16	SX score >16	p-value
No. of diseased lesions per patient (based on SYNTAX application)	1.5	2.4	3.5	<0.001
No. of treated lesions per patient (as defined by Corelab)	1.2	1.5	1.7	<0.001
Coronary artery treated				
LAD	35%	51%	64%	<0.001
LCX	30%	31%	36%	0.079
RCA	47%	44%	38%	0.007
2-vessel disease	11%	22%	30%	<0.001
3-vessel disease	1%	3 %	5%	<0.001
Stent type				
Biolimus	49%	50%	52%	NS
Sirolimus	51%	50%	48%	NS
Number of implanted stents	1.5	1.9	2.3	<0.001
Total stent length/patient (mm)	26	34	43	<0.001
Chronic total occlusion	1%	2%	4%	0.006
Moderate to severe calcification	5%	20%	40%	<0.001
Bifurcation lesion	12%	34%	40%	<0.001
Use of 2b3a	17%	24%	33%	<0.001

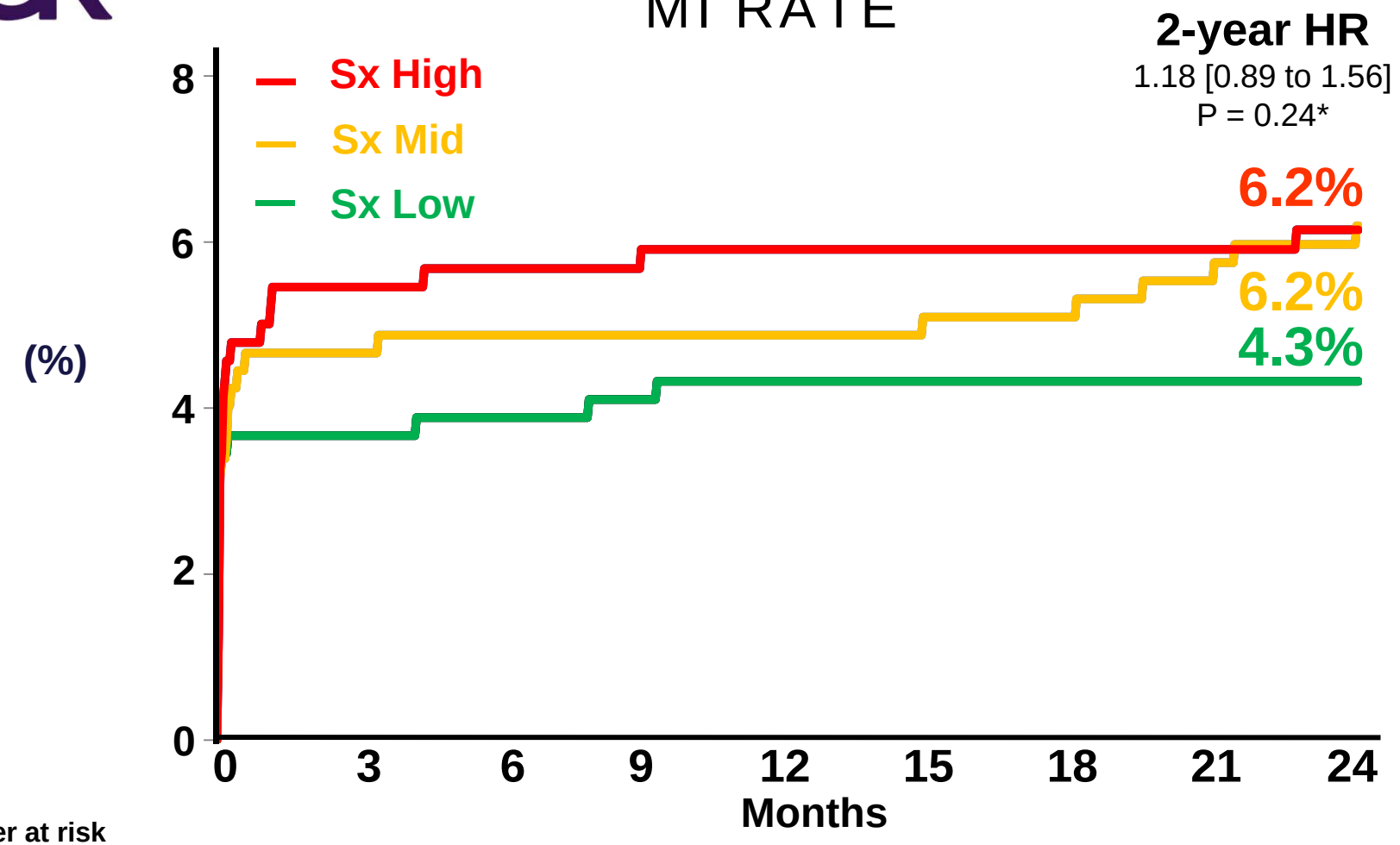
SYNTAX SCORE IN LEADERS: CARDIAC DEATH RATE



Number at risk									
Sx Low	464	461	459	457	449	439	431	429	425
Sx Mid	472	465	463	461	460	456	451	450	445
Sx High	461	450	446	440	433	430	426	425	421

*P values for superiority

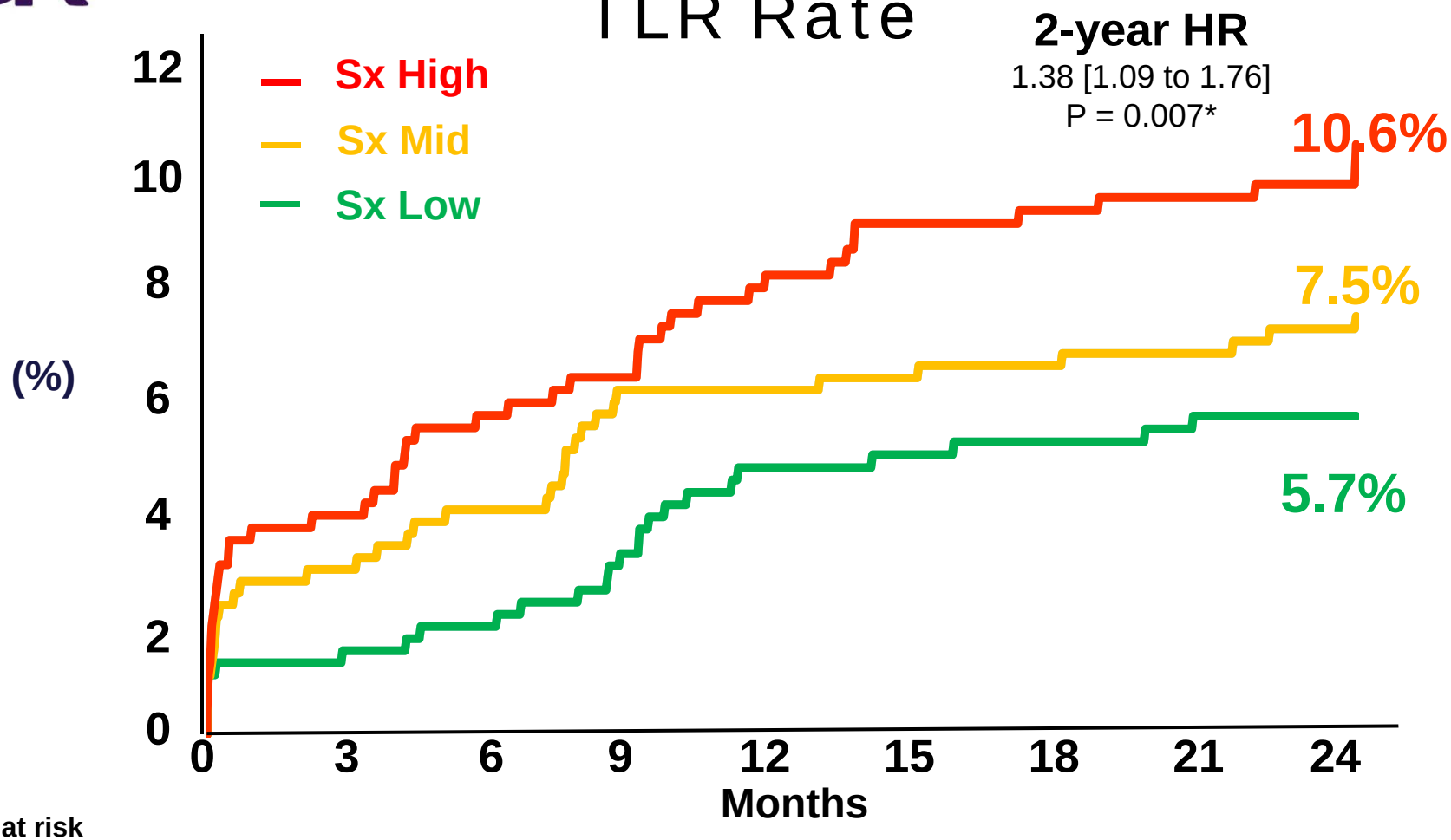
SYNTAX SCORE IN LEADERS: MI RATE



Number at risk									
Sx Low	464	444	442	440	433	422	416	414	410
Sx Mid	472	447	446	444	443	439	435	434	426
Sx High	461	426	421	414	409	406	403	402	397

*P values for superiority

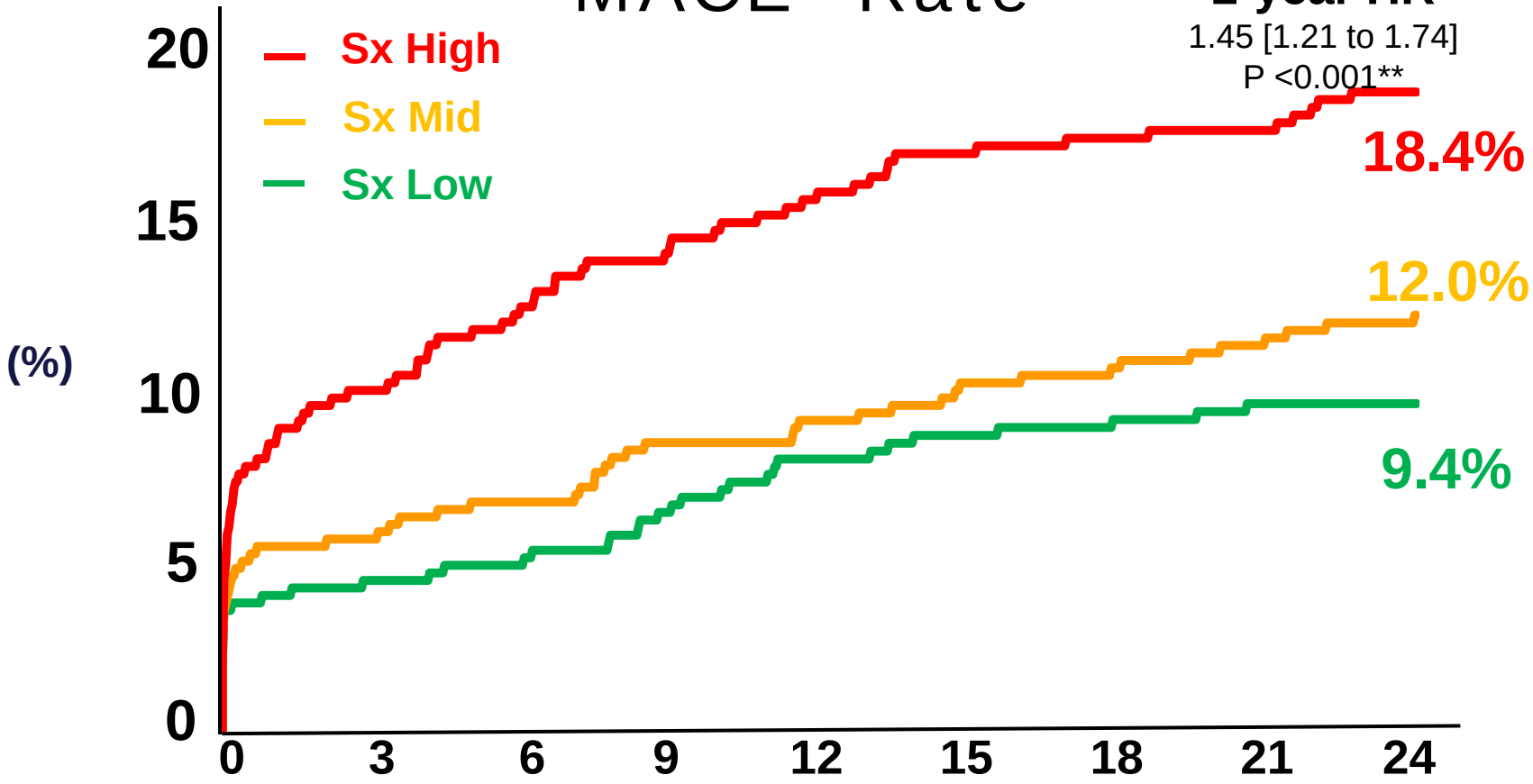
SYNTAX Score in LEADERS: TLR Rate



Number at risk									
Sx Low	464	455	452	448	436	419	411	408	402
Sx Mid	472	455	452	446	434	430	425	423	418
Sx High	461	431	427	414	406	397	390	388	382

*P values for superiority

SYNTAX Score in LEADERS: MACE* Rate



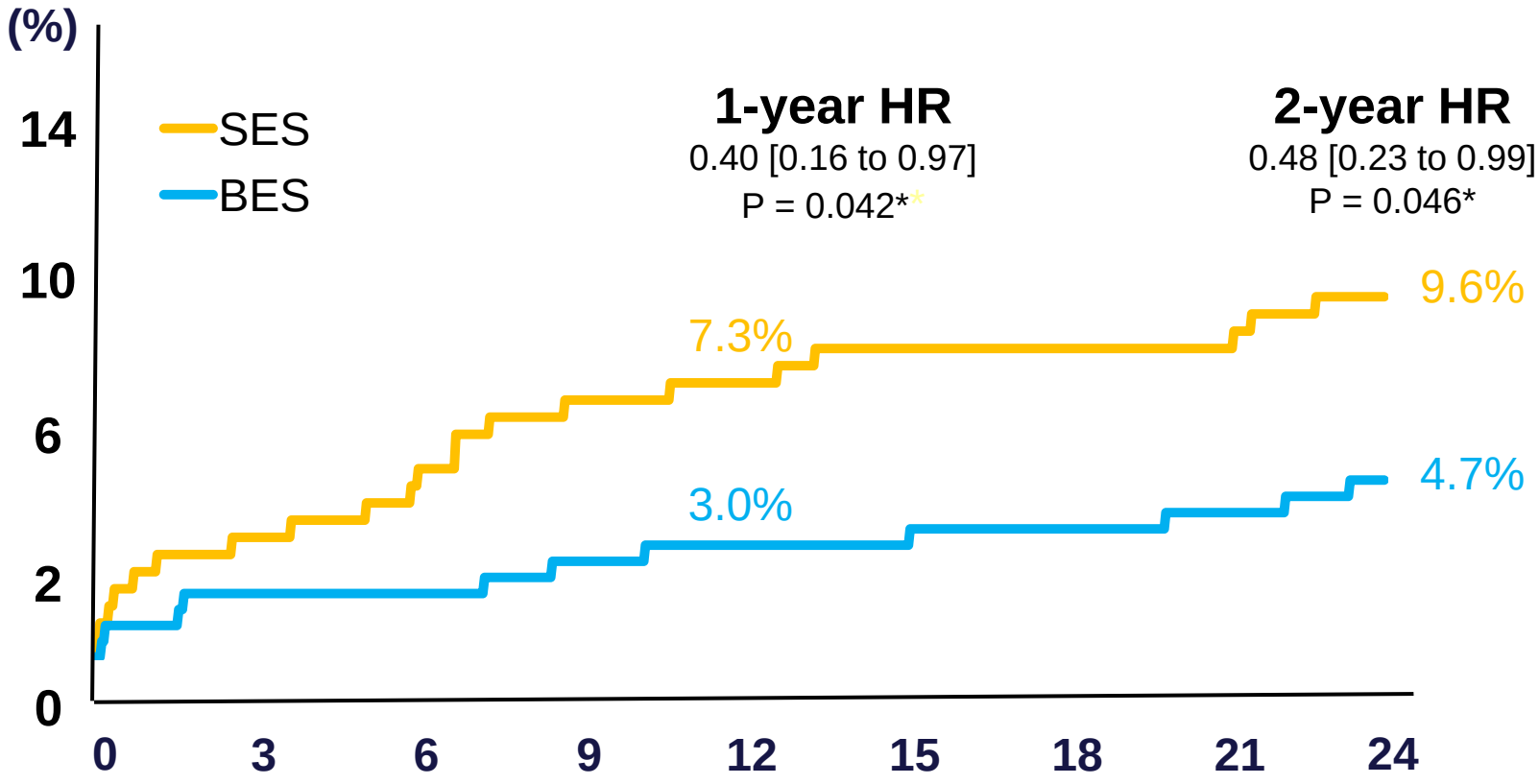
Number at risk									
Sx Low	464	444	440	437	425	409	402	399	393
Sx Mid	472	445	443	437	428	424	417	414	406
Sx High	461	419	412	399	390	382	375	373	369

*MACE as a composite of cardiac death, MI, or clinically indicated TVR
**P values for superiority

Cox regression analysis showing HR for treatment with BES versus SES in the overall population at 1 year. There is a trend to 26% reduction in event rate when BES is used.

	HR	CI	p-value
SYNTAX score (high vs. mid)	**1.47**	**1.19-1.84**	**<0.001**
Diabetes	**1.54**	**1.08-2.19**	**0.016**
BES vs SES	**0.74**	**0.54-1.03**	**0.07**
beta-blocker use	**0.96**	**0.68-1.36**	**0.83**
STEMI	**1.01**	**0.66-1.55**	**0.96**

Cardiac Death in High Syntax Score (>16)

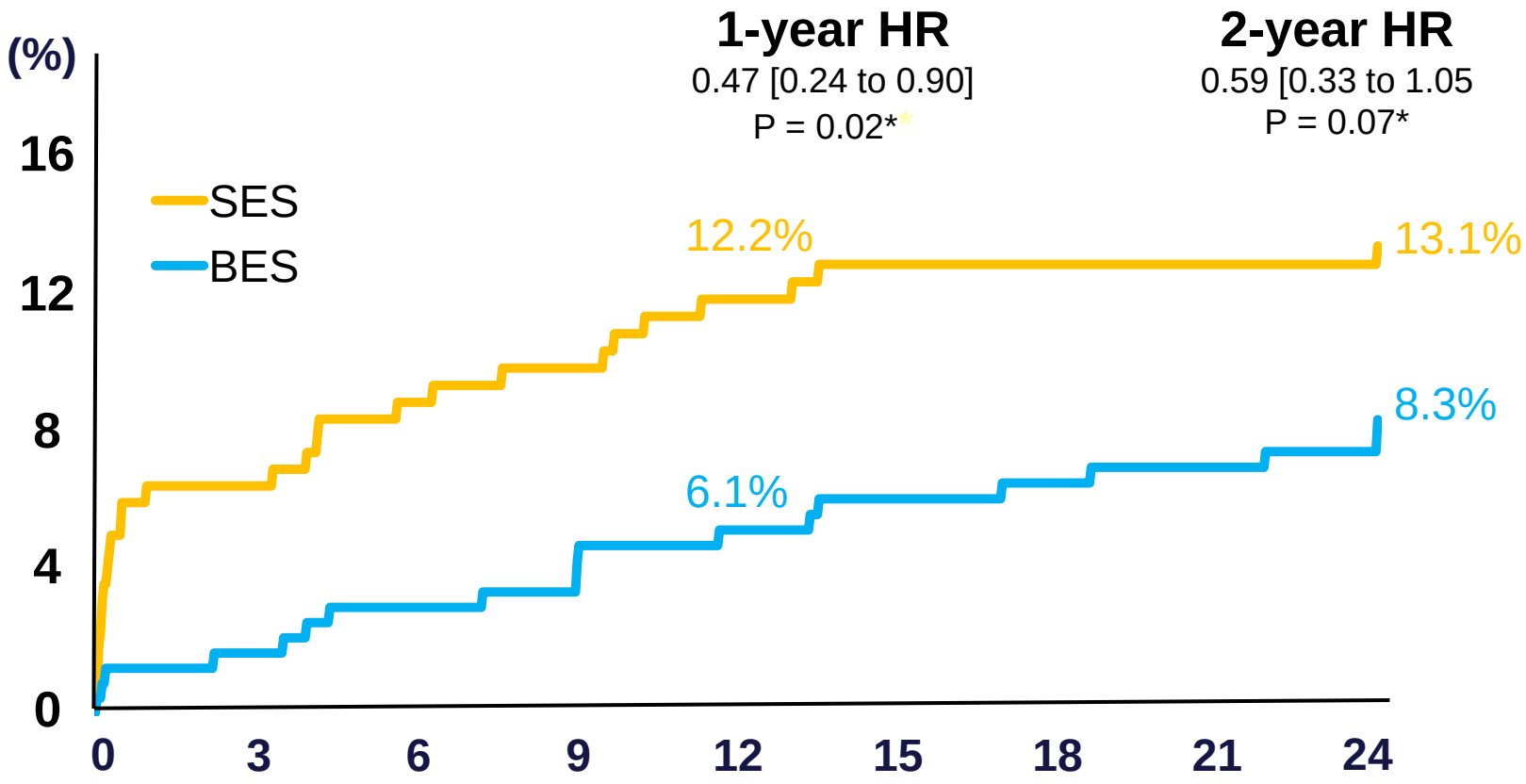


Number at risk

BES	239	235	233	231	228	226	225	224	222
SES	222	215	213	209	205	204	201	201	199

*P values for superiority

TLR in High Syntax Score (>16)



Number at risk

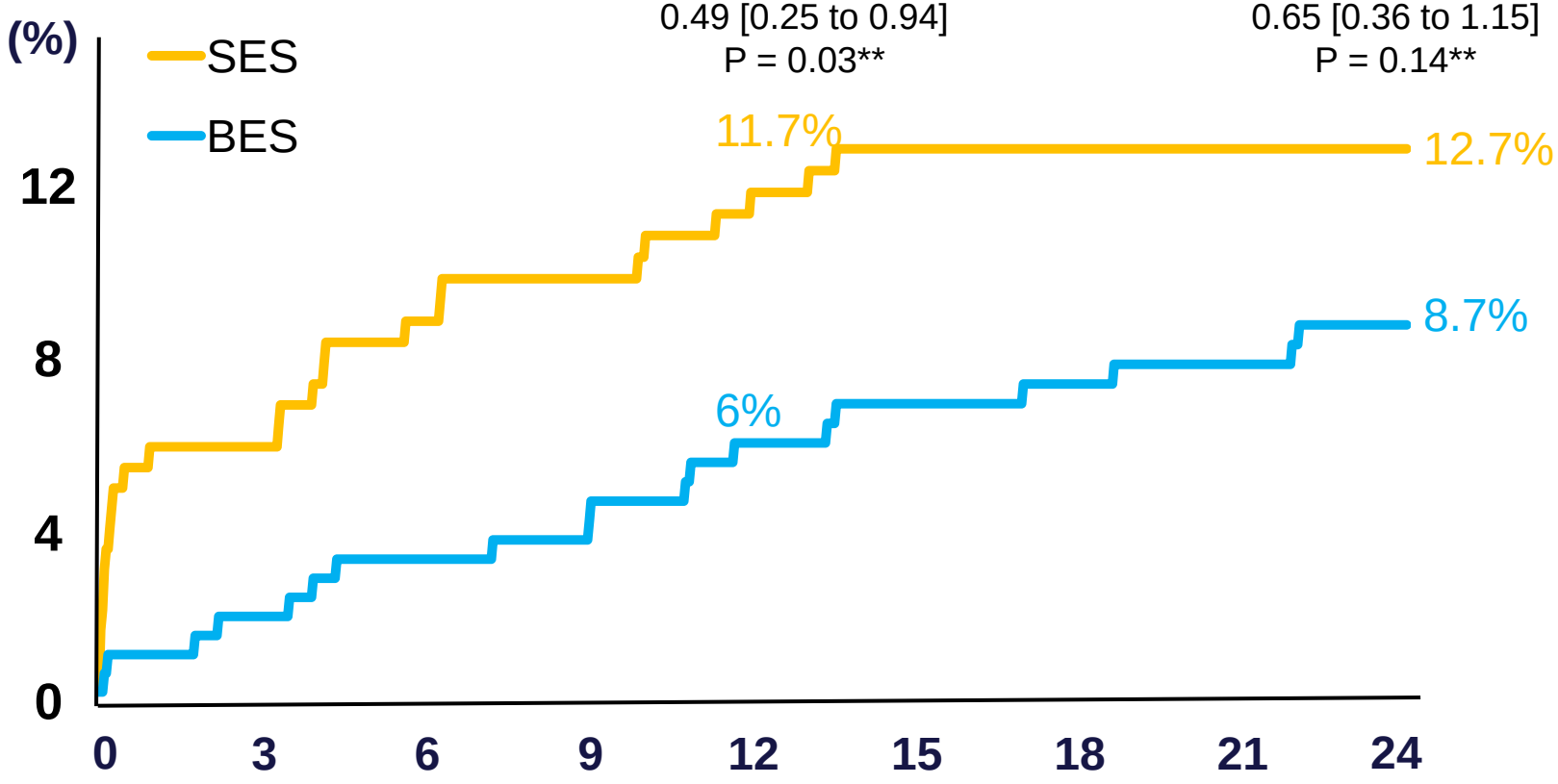
BES	239	231	229	224	220	216	213	211	209
SES	222	200	198	190	186	181	177	177	173

*P values for superiority

TVR* in High Syntax Score (>16)

1-year HR
0.49 [0.25 to 0.94]
P = 0.03**

2-year HR
0.65 [0.36 to 1.15]
P = 0.14**



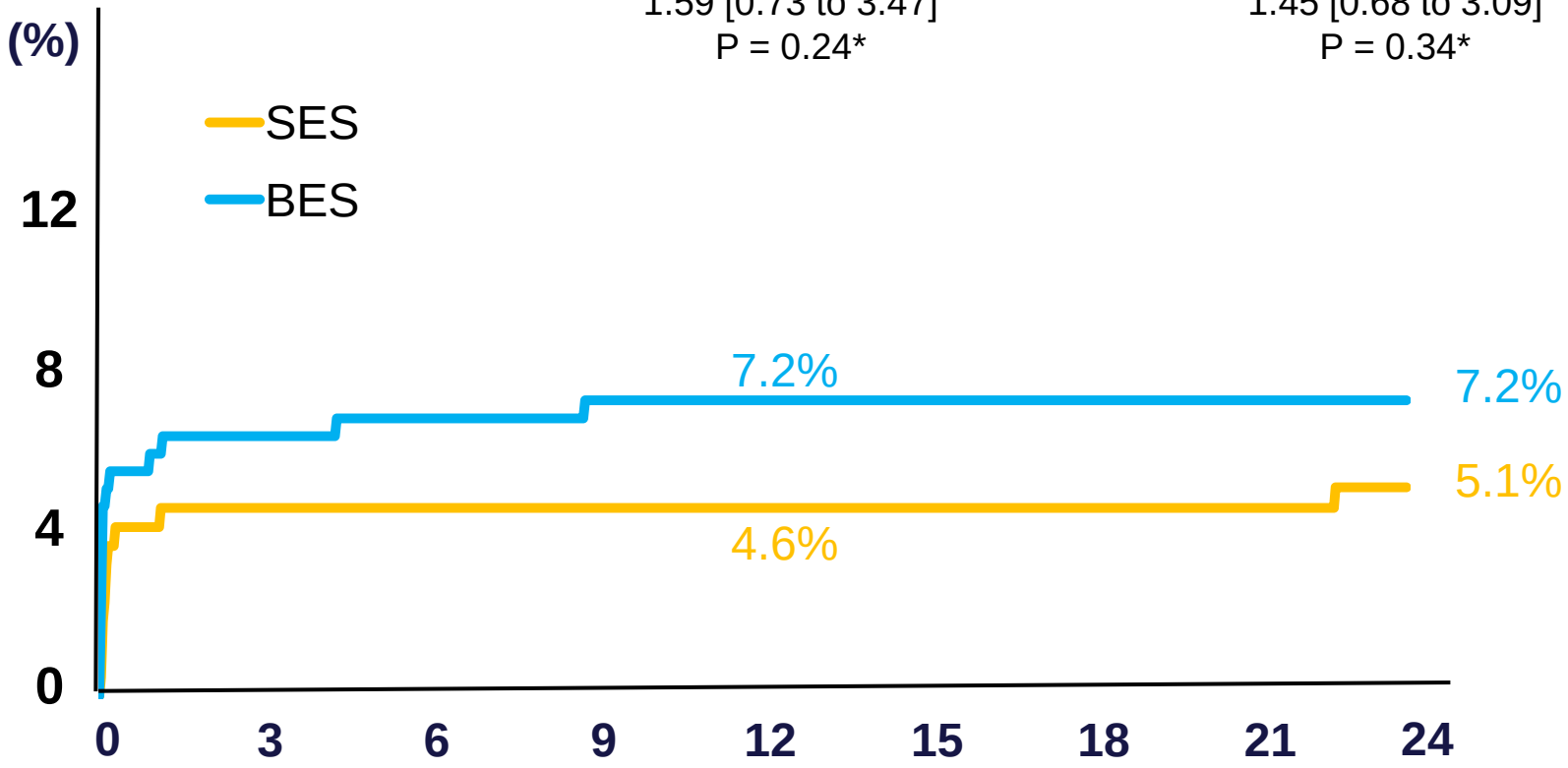
Number at risk									
BES	239	231	228	223	220	214	211	209	207
SES	222	201	199	190	186	181	177	177	173

*Clinically indicated TVR **P values for superiority

MI in High Syntax Score (>16)

1-year HR
1.59 [0.73 to 3.47]
P = 0.24*

2-year HR
1.45 [0.68 to 3.09]
P = 0.34*

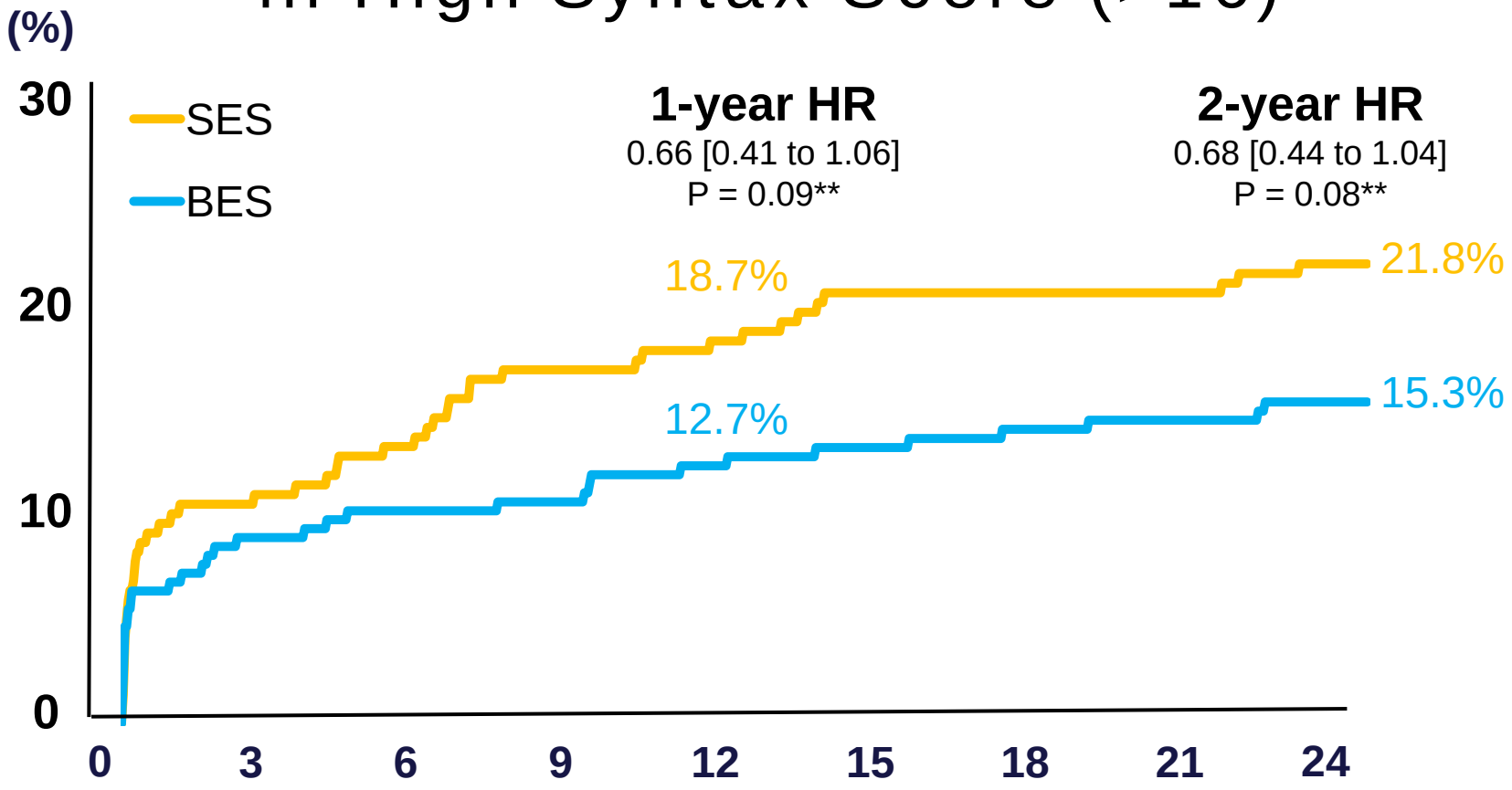


Number at risk

BES	239	220	218	215	212	211	210	209	207
SES	222	206	203	200	197	195	193	193	190

*P values for superiority

MACE* Rate in High Syntax Score (>16)



Number at risk									
BES	239	221	216	211	207	203	201	199	197
SES	222	198	196	188	183	179	174	174	172

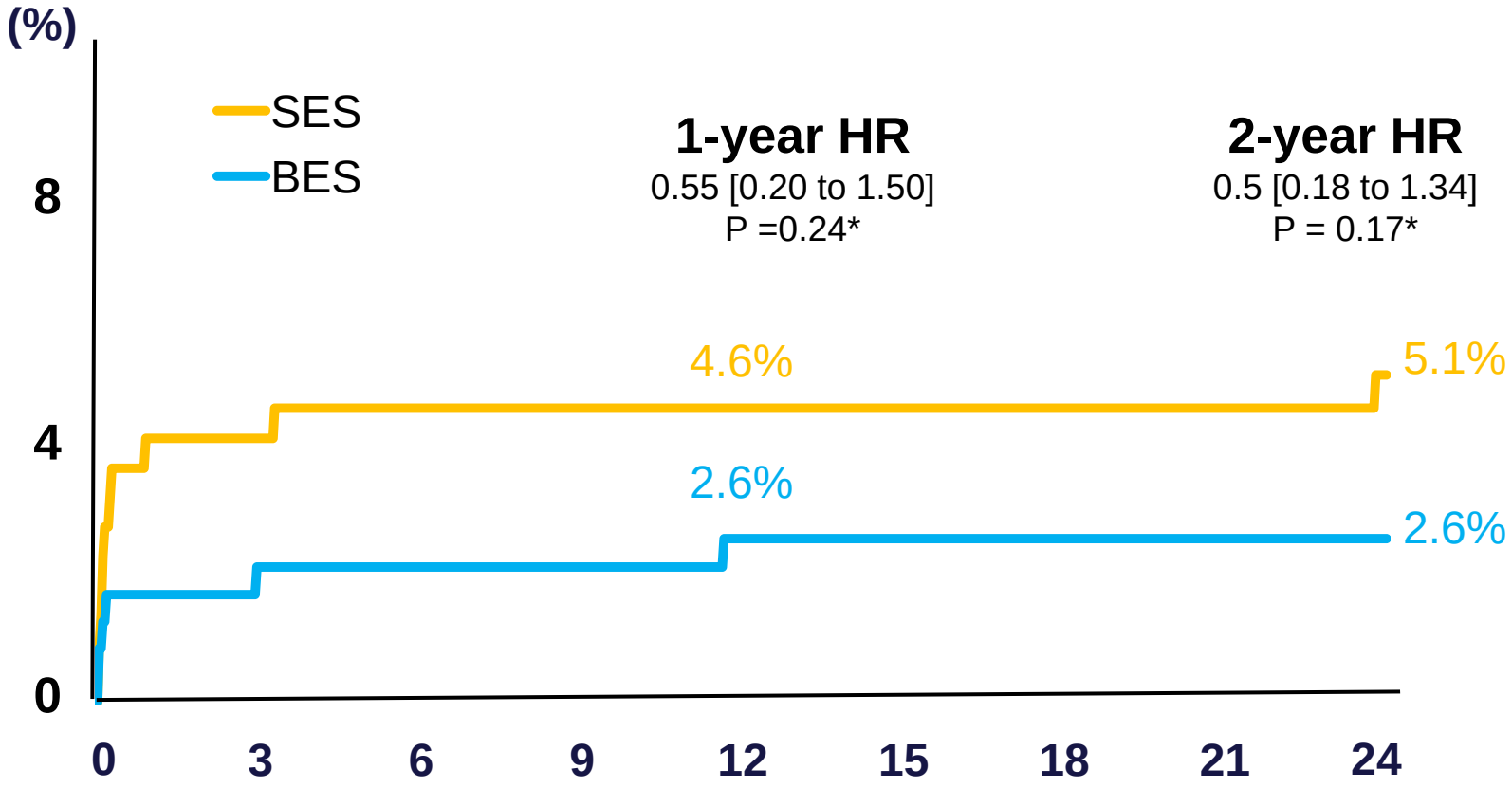
*MACE as a composite of cardiac death, MI, or clinically indicated TVR

**P values for superiority

What are the potential mechanisms?

- This can only be speculative…. At this time, however…

Definite Stent Thrombosis in High Syntax Score (>16)

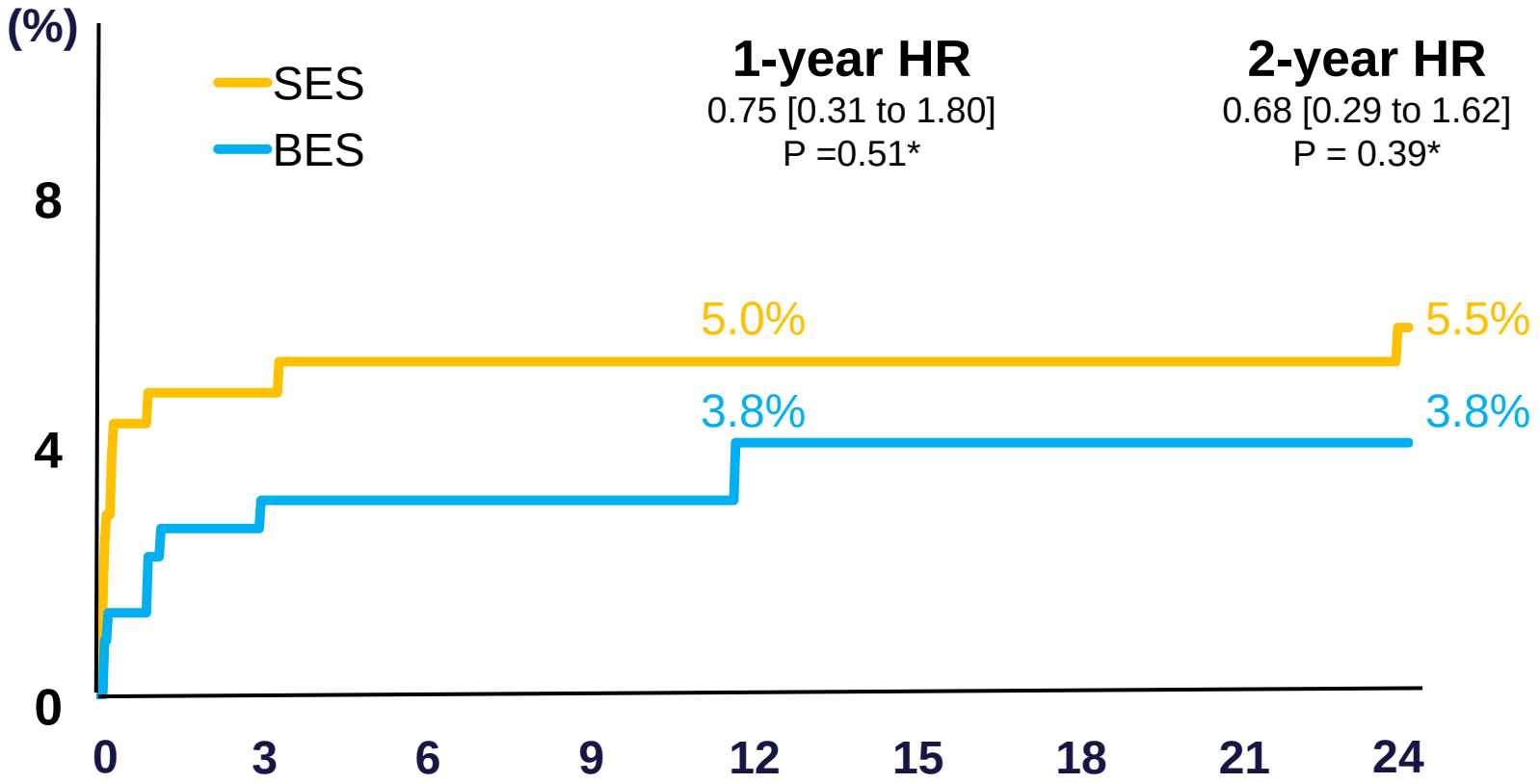


Number at risk

BES	239	230	228	225	223	220	219	218	216
SES	222	205	203	199	196	194	192	192	188

*P values for superiority

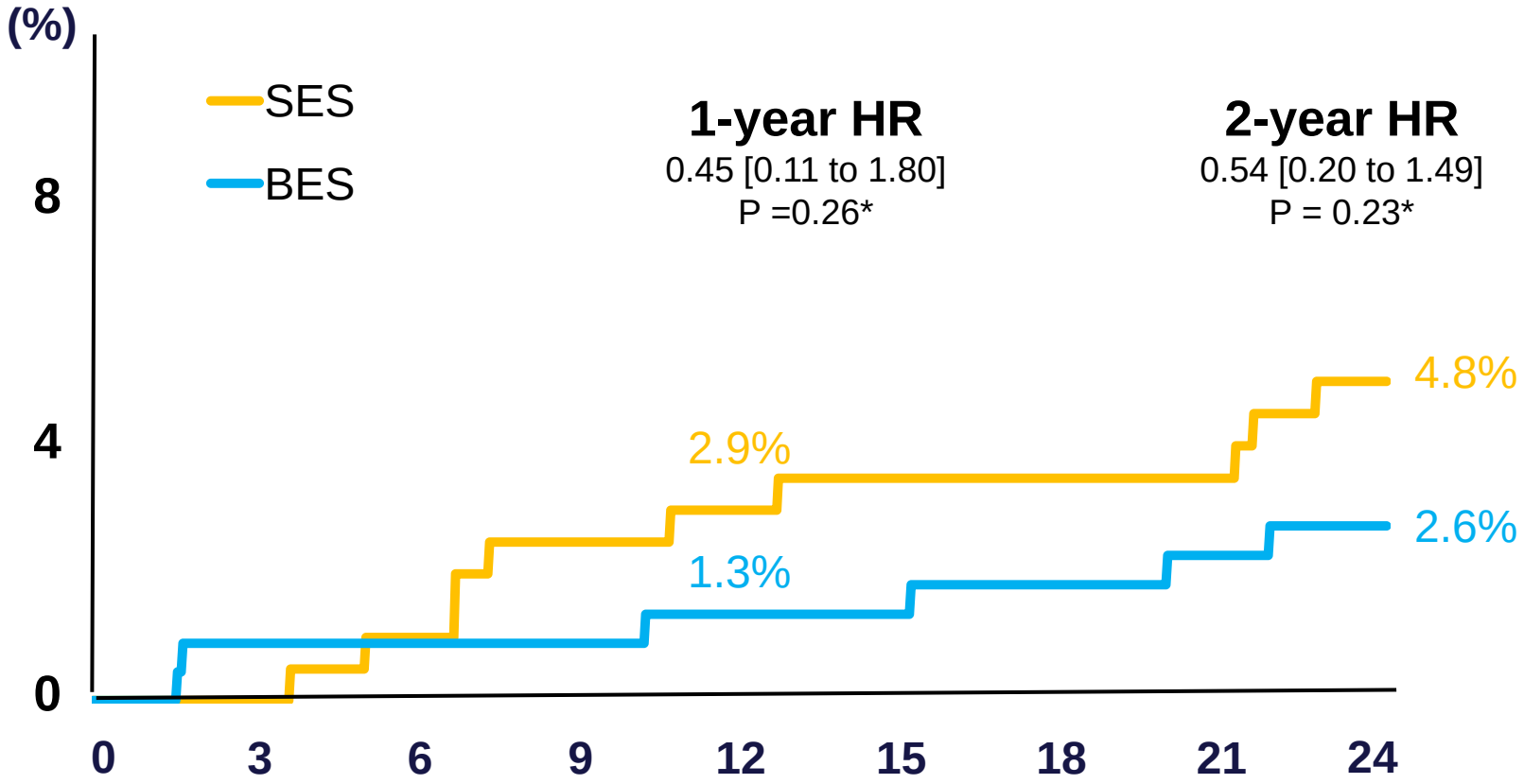
Definite and Probable Stent Thrombosis in High Syntax Score (>16)



Number at risk									
BES	239	229	226	223	221	218	217	216	214
SES	222	205	203	199	196	194	192	192	188

*P values for superiority

Possible Stent Thrombosis in High Syntax Score (>16)

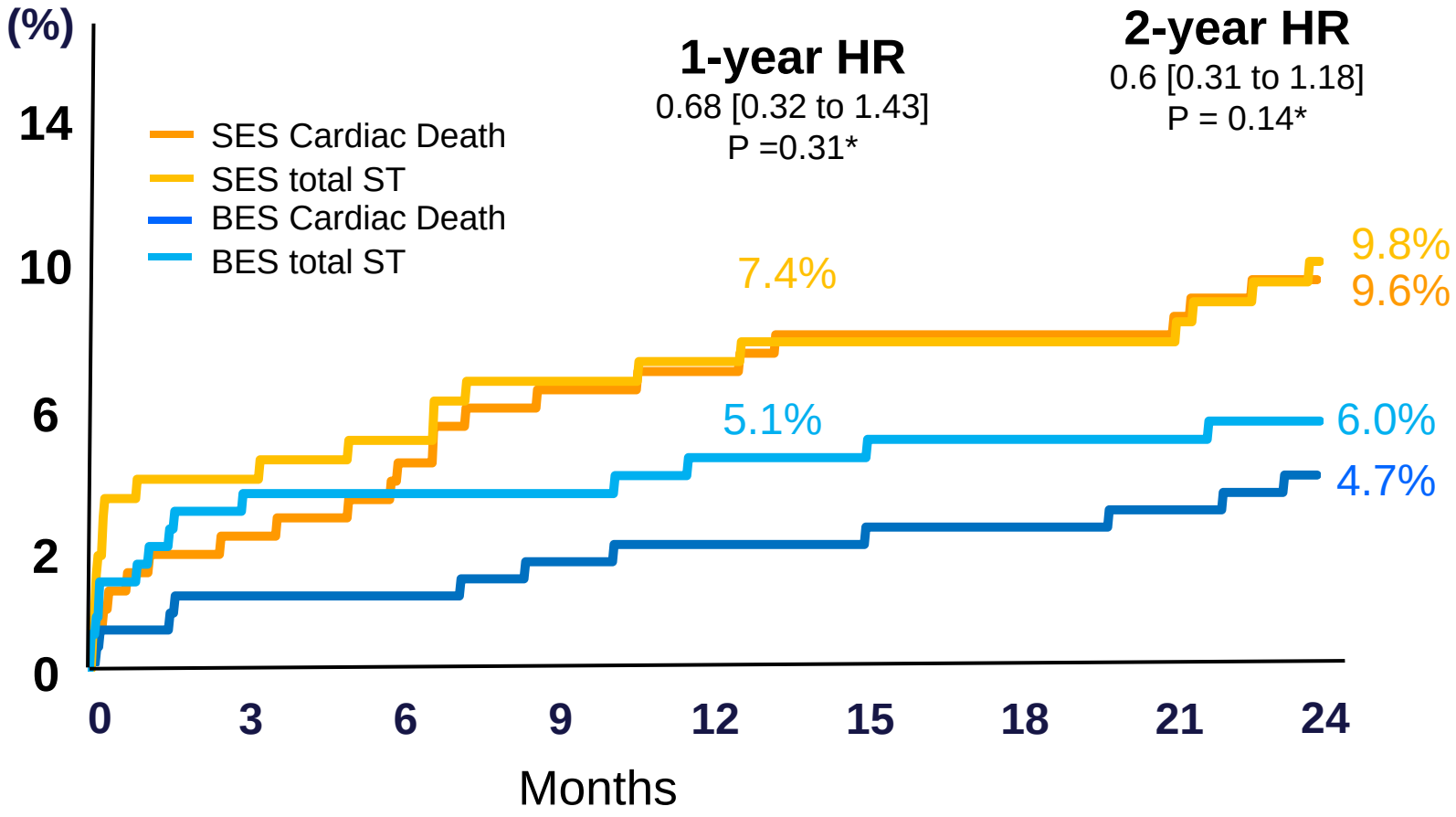


Number at risk

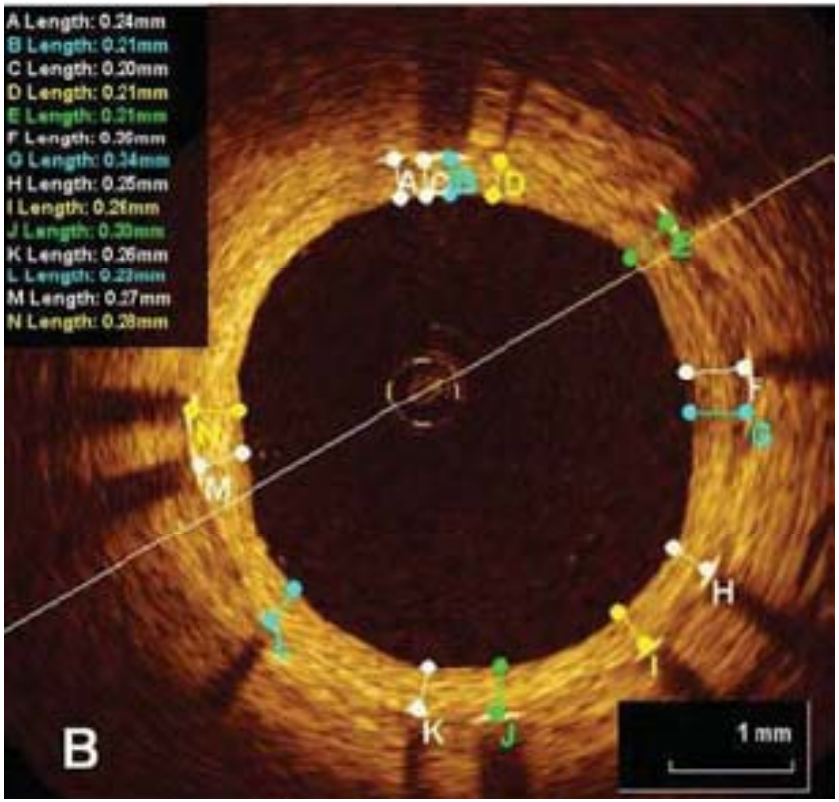
BES	239	235	233	230	228	226	225	224	222
SES	222	214	213	209	205	203	201	201	199

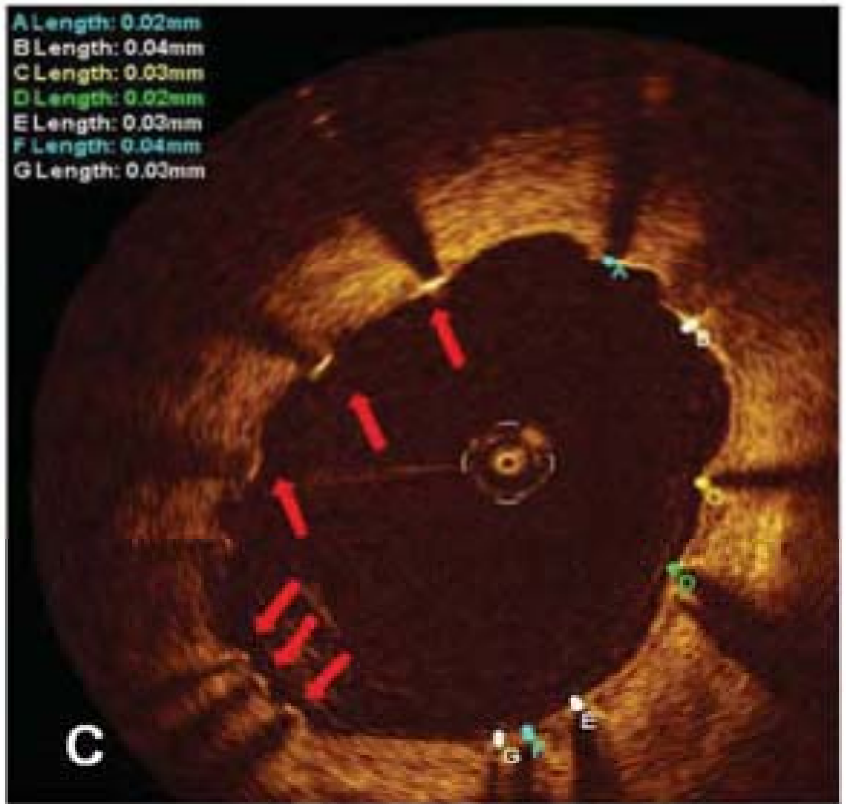
*P values for superiority

Stent Thrombosis/ Cardiac Death in High Syntax Score (>16)



OCT images of strut coverage





BES

SES

Peter Barlis, et al., European Heart Journal (2010) 31, 165–176

Conclusions

- These are hypothesis-generating subgroup analyses which are underpowered and suffer from limitations
- Biolimus eluting stent appears to offer an advantage in treating patients with complex disease and high Syntax score over sirolimus eluting stent
- Larger cohort of prospectively collected data as well as mechanistic insights are needed to confirm these findings.