LEADERS

A Prospective, Randomised, Non-Inferiority Trial Comparing Biolimus-Eluting Stent With Biodegradable Polymer Versus Sirolimus-Eluting Stent With Durable Polymer

3-Year Clinical Follow-Up

Patrick W. Serruys

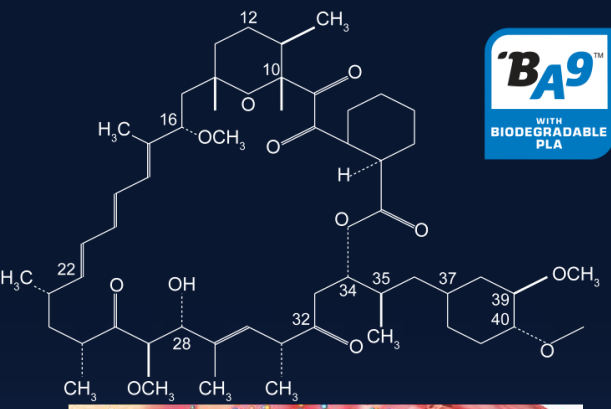
Pawel Buszman, Axel Linke, Thomas Ischinger, Franz Eberli, Roberto Corti, Volker Klauss, William Wijns, Marie-Claude Morice, Carlo di Mario, Robert-Jan van Geuns, Pedro Eerdmans, Gerrit-Anne van Es, Peter Jüni, Stephan Windecker

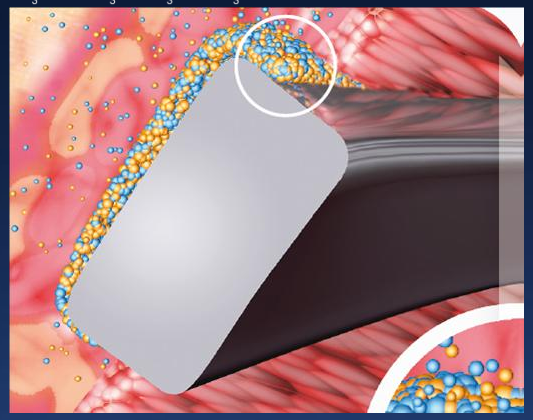
Background: LEADERS out to 2-Years

- **Comparison of BES with biodegradable polymer to SES with durable polymer resulted in:**
  - Non-inferior MACE rate at 9 months* (primary endpoint met):
    9.2% BES vs. 10.5% SES, $P_{non\text{-}inf}$ =0.003
  - Non-inferiority in MACE confirmed at:
    12 months** (10.7% BES vs. 12.2% SES, $P_{non\text{-}inf}$ <0.001)
    24 months (13.0% BES vs. 15.4% SES, $P_{non\text{-}inf}$ <0.001)
- **Three year clinical outcomes have not yet been reported before the TCT 2010 conference**

*Windecker S et al. *THE LANCET* 2008; 372 No 9644: 1163-1173
**Garg S et al. EuroIntervention 2010;

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.

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

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 months)
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

Data Management & Angio Core Lab: Cardialysis

Independent Statistical Analysis: CTU Bern

Patient Eligibility

Inclusion Criteria

Coronary artery disease

- Stable angina
- Silent ischemia
- Acute coronary syndrome including UA, NSTEMI and STEMI

At least one lesion with

- Diameter stenosis >50%
- RVD: 2.25-3.5 mm
- Number of lesions: no limitation
- Number of vessels: no limitation
- Lesion length: no limitation

Written informed consent

Exclusion Criteria

Known allergy to

- Aspirin, clopidogrel, heparin, stainless steel, sirolimus, biolimus, contrast material

Planned, elective surgery within 6 months of PCI unless dual APT could be maintained

Pregnancy

Participation in another trial

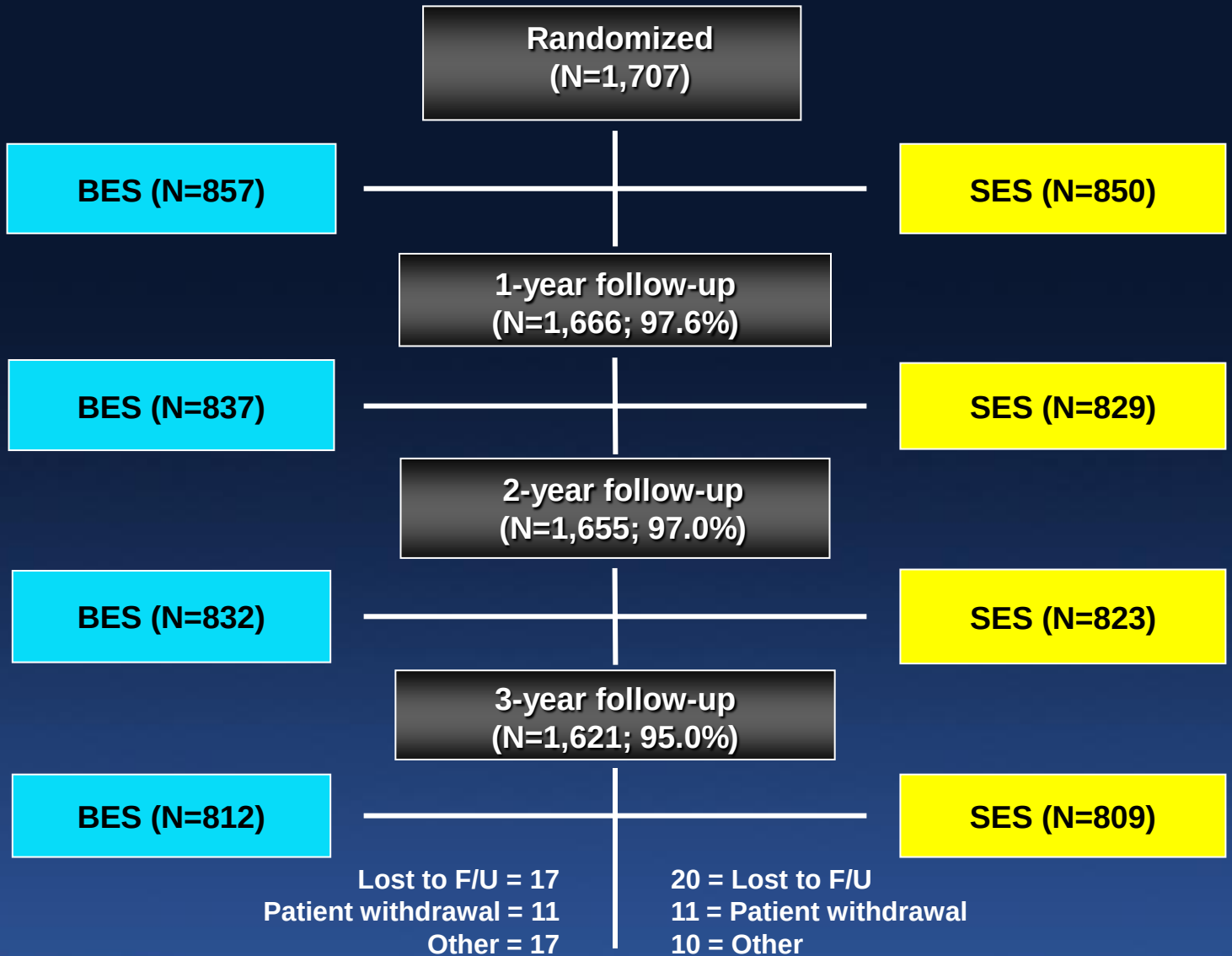
Patient Demographics

	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	40%	44%
Smoking	24%	25%
Previous MI	32%	33%
Previous PCI	36%	37%
- with drug-eluting stent	12%	14%
Previous CABG	11%	13%
Chronic stable angina	45%	44%

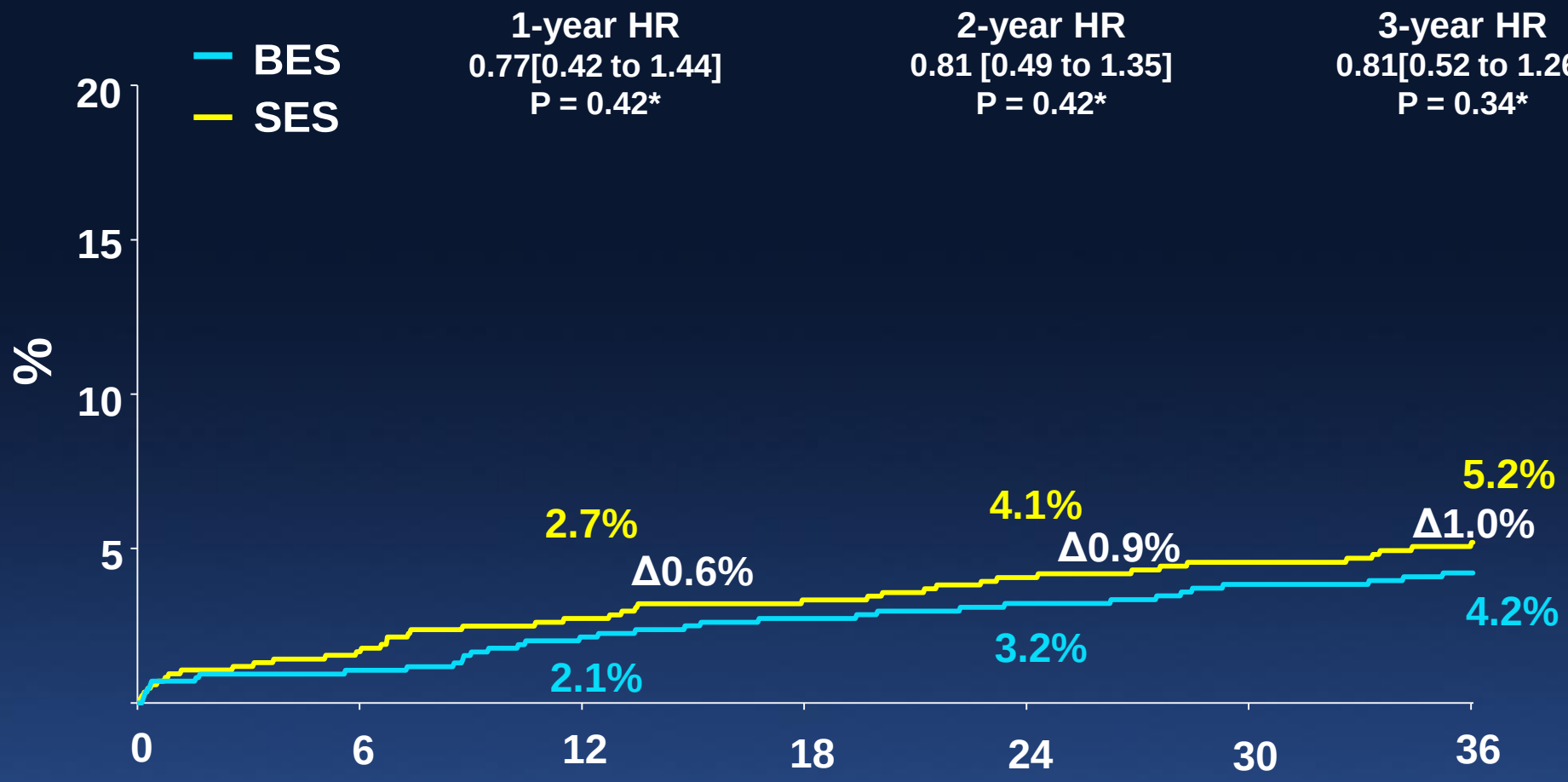
Patient Characteristics

	BES 857 Patients	SES 850 Patients
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



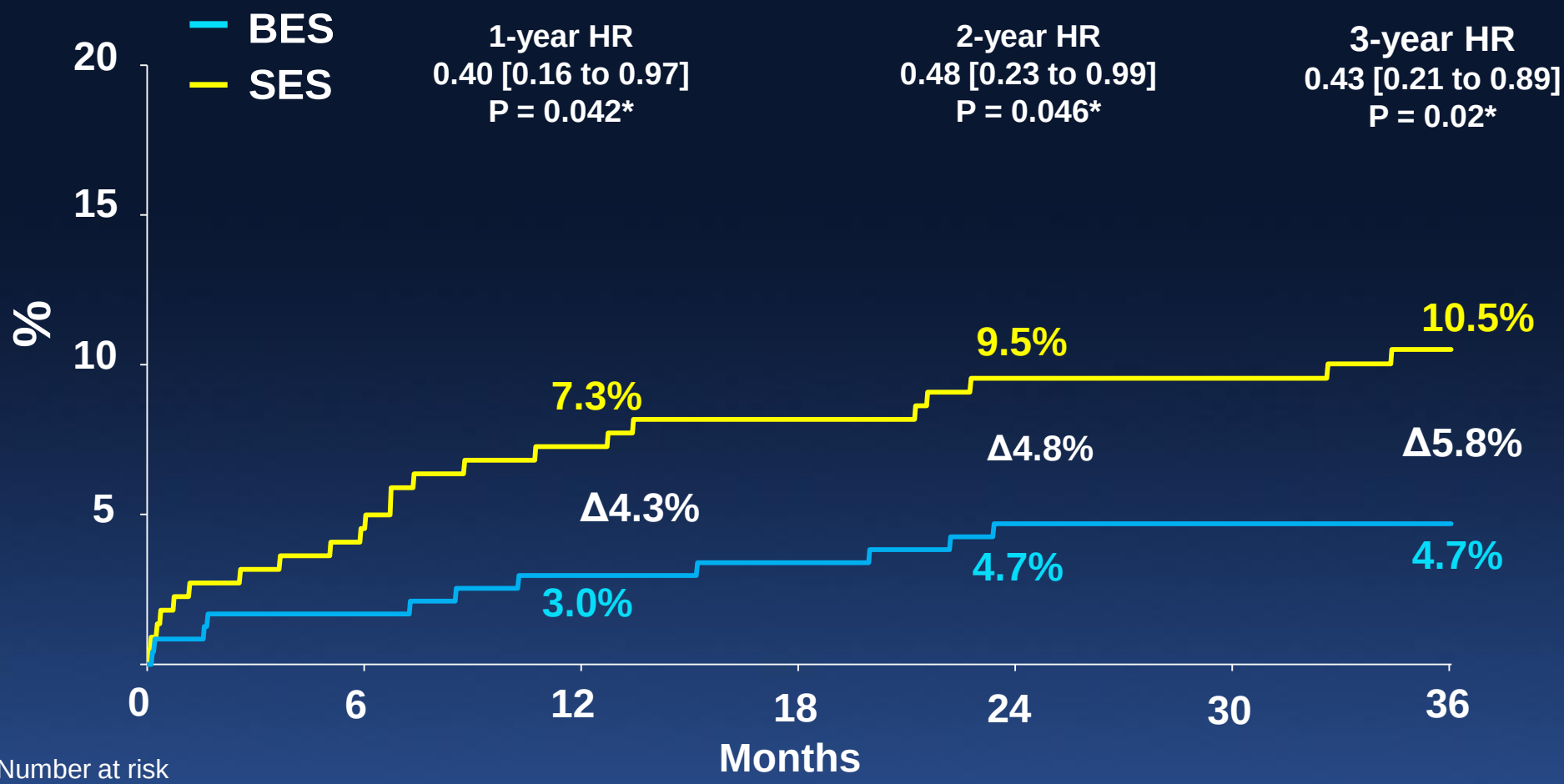
Cardiac Death



Number at risk							
BES	857	849	822	812	803	790	747
SES	850	846	815	807	797	777	733

*P values for superiority

Cardiac Death
in High Syntax Score (>16)

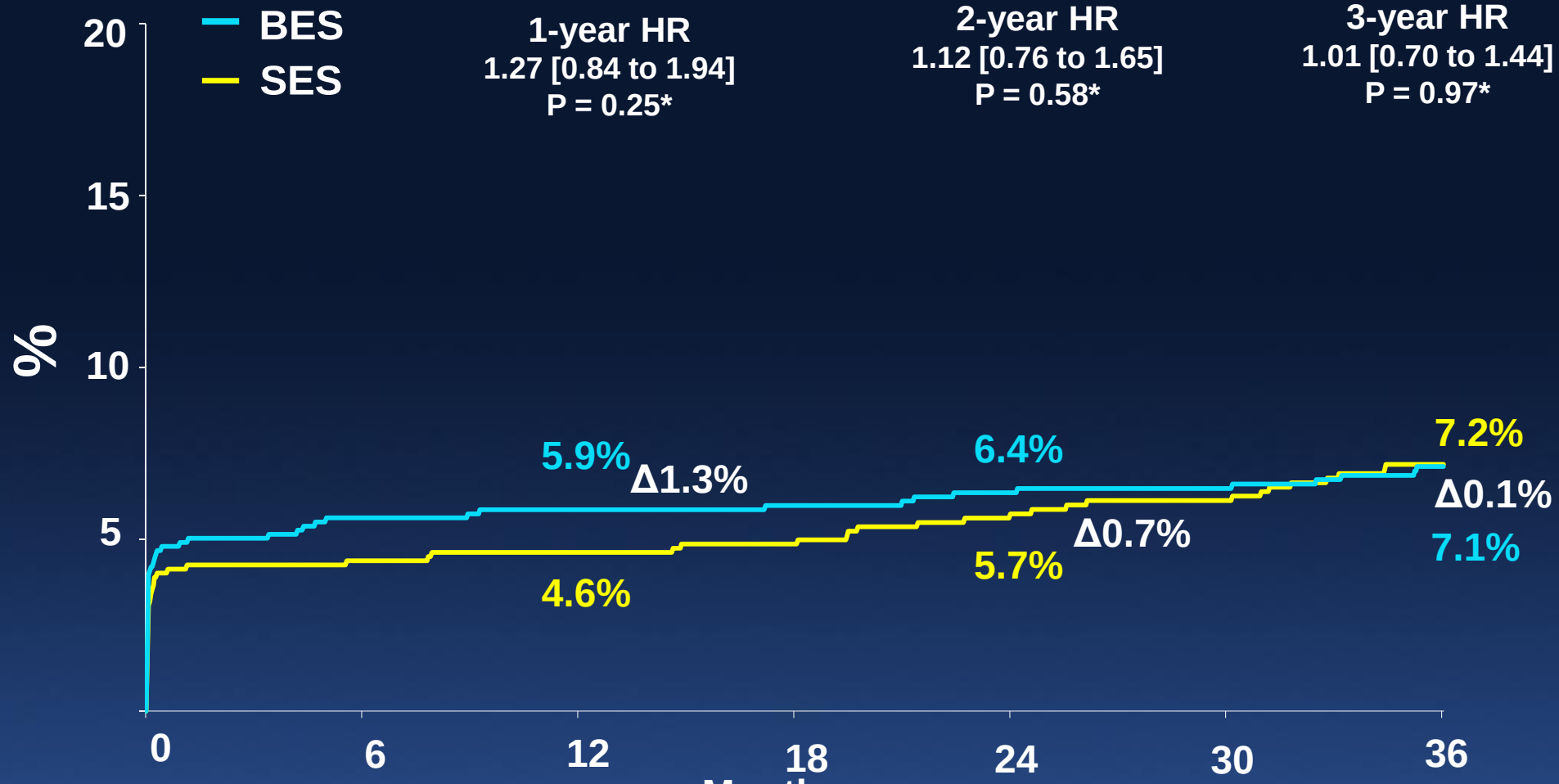


Number at risk

BES	239	238	228	226	224	220	213
SES	222	221	205	204	201	193	180

*P values for superiority

All MI

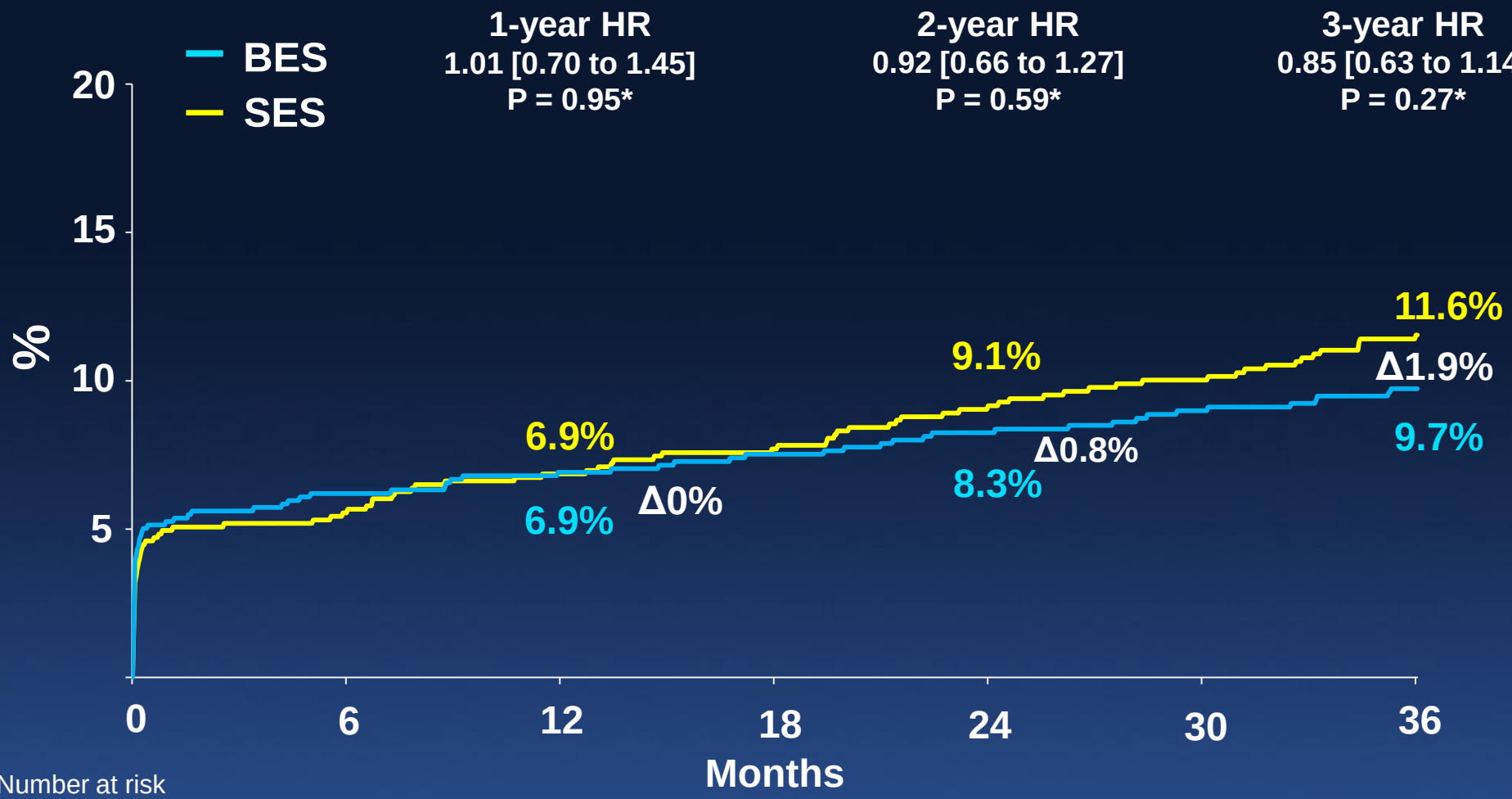


Number at risk

BES	857	848	781	771	762	747	709
SES	850	841	781	772	759	734	689

*P values for superiority

Cardiac Death or MI

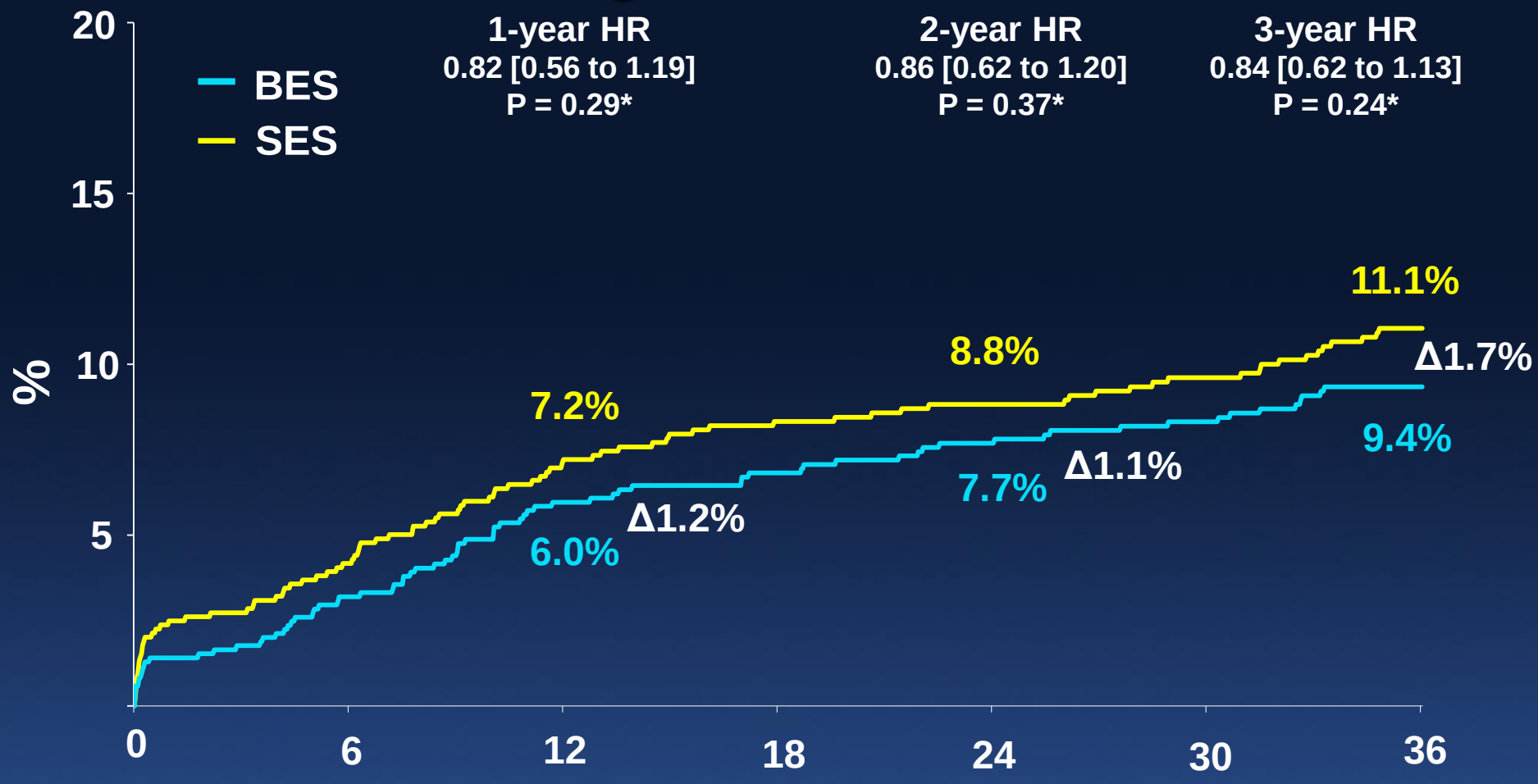


Number at risk

BES	857	850	781	773	764	749	709
SES	850	846	782	774	762	736	691

*P values for superiority

Clinically-Indicated TVR

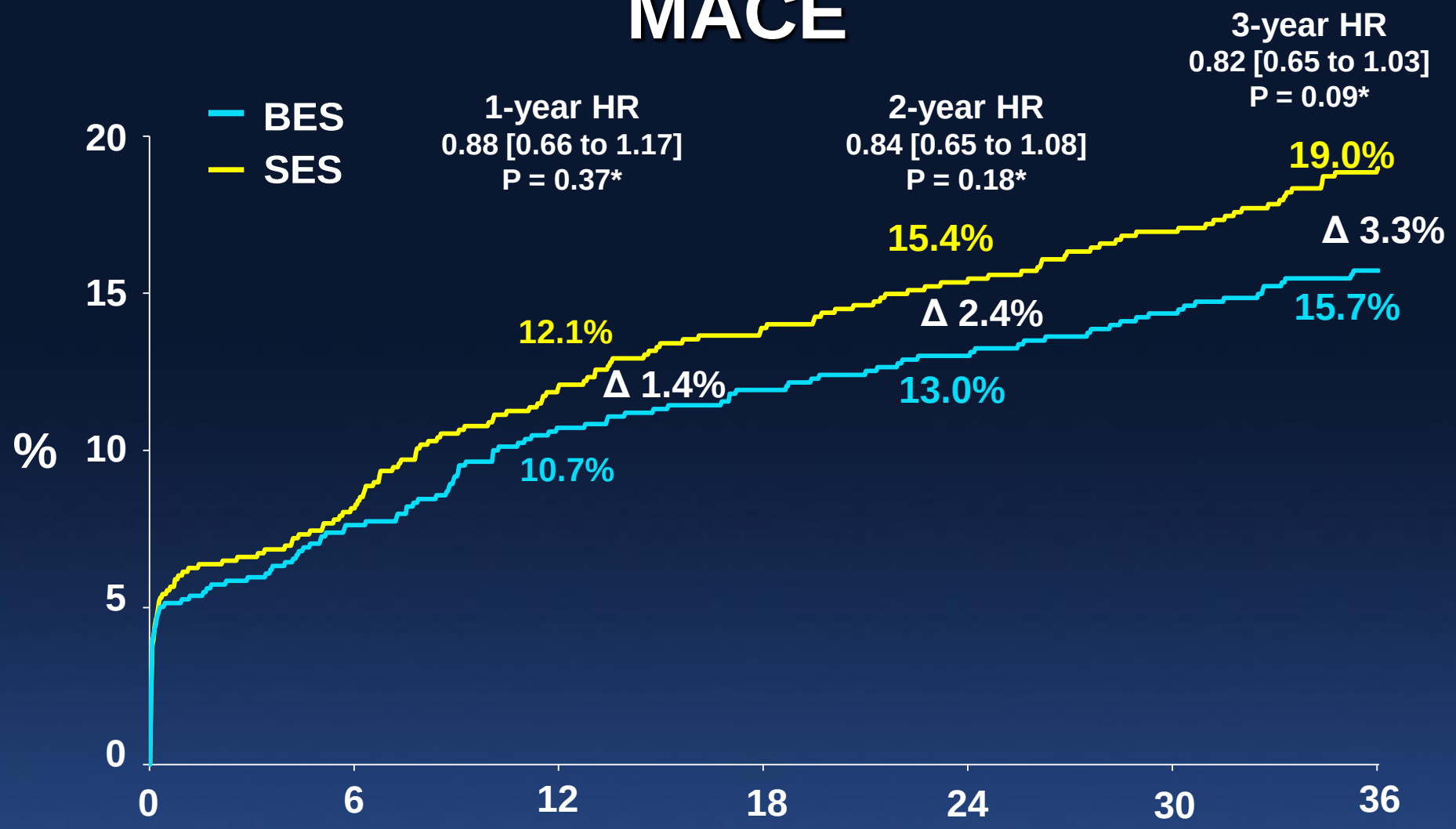


Number at risk

BES	857	847	790	769	754	735	692
SES	850	841	772	752	733	710	665

*P values for superiority

MACE



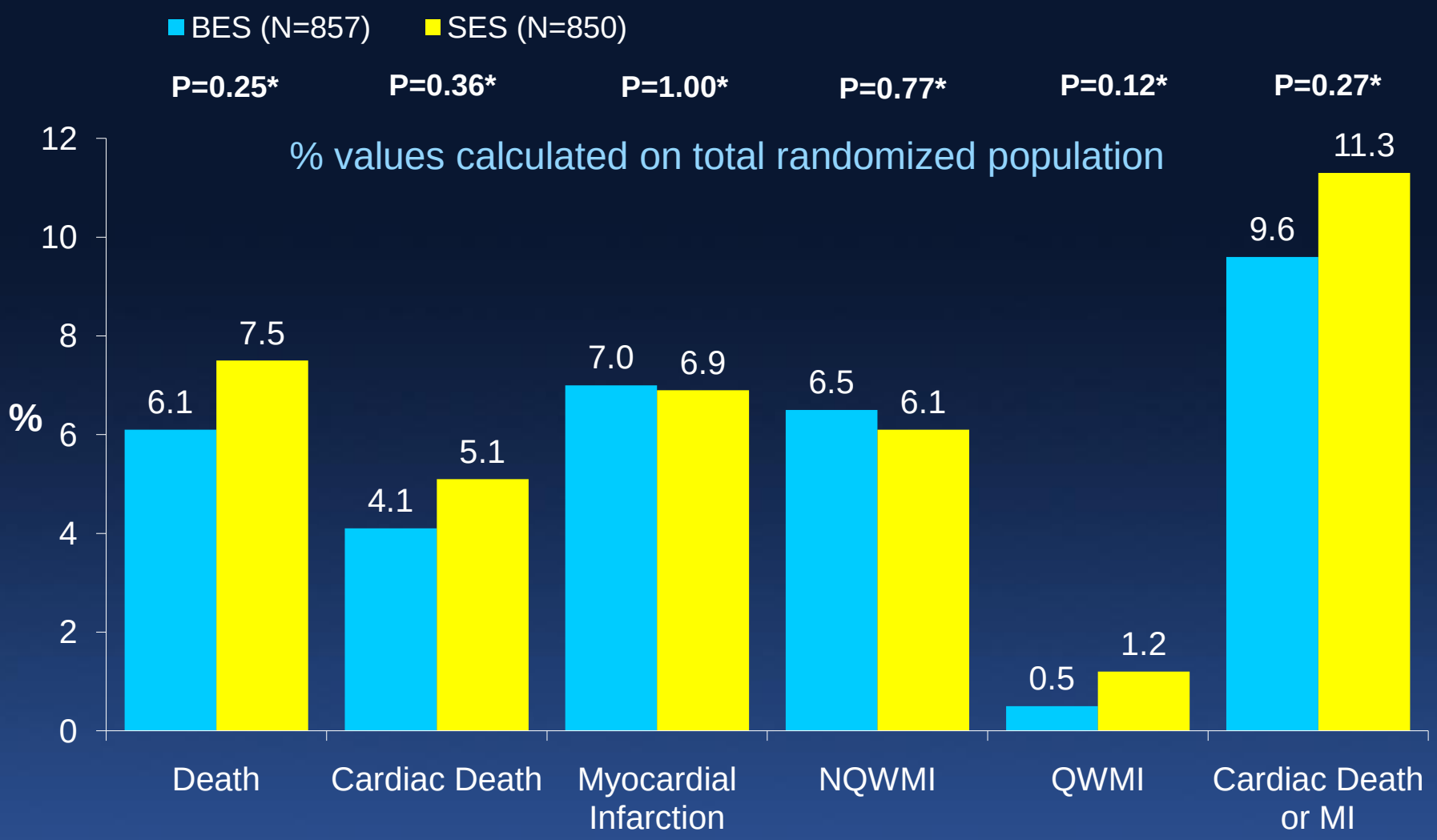
Number at risk

BES	857	851	761	743	729	712	668
SES	850	846	749	732	713	686	639

MACE = Cardiac Death, MI, or Clinically-Indicated TVR

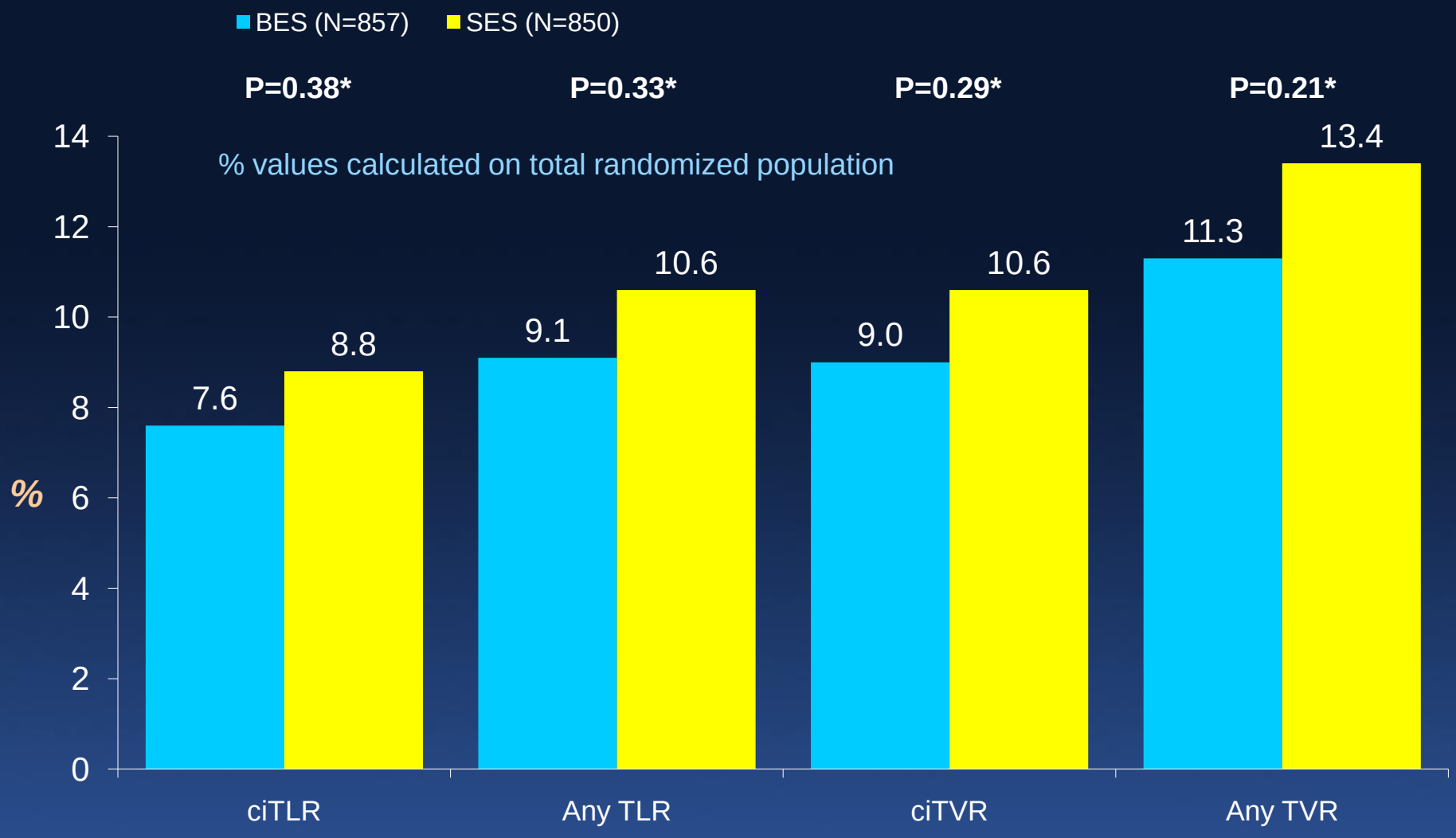
* P values for superiority

3-Year Safety Endpoints



*P values for superiority (Fisher Exact Test)

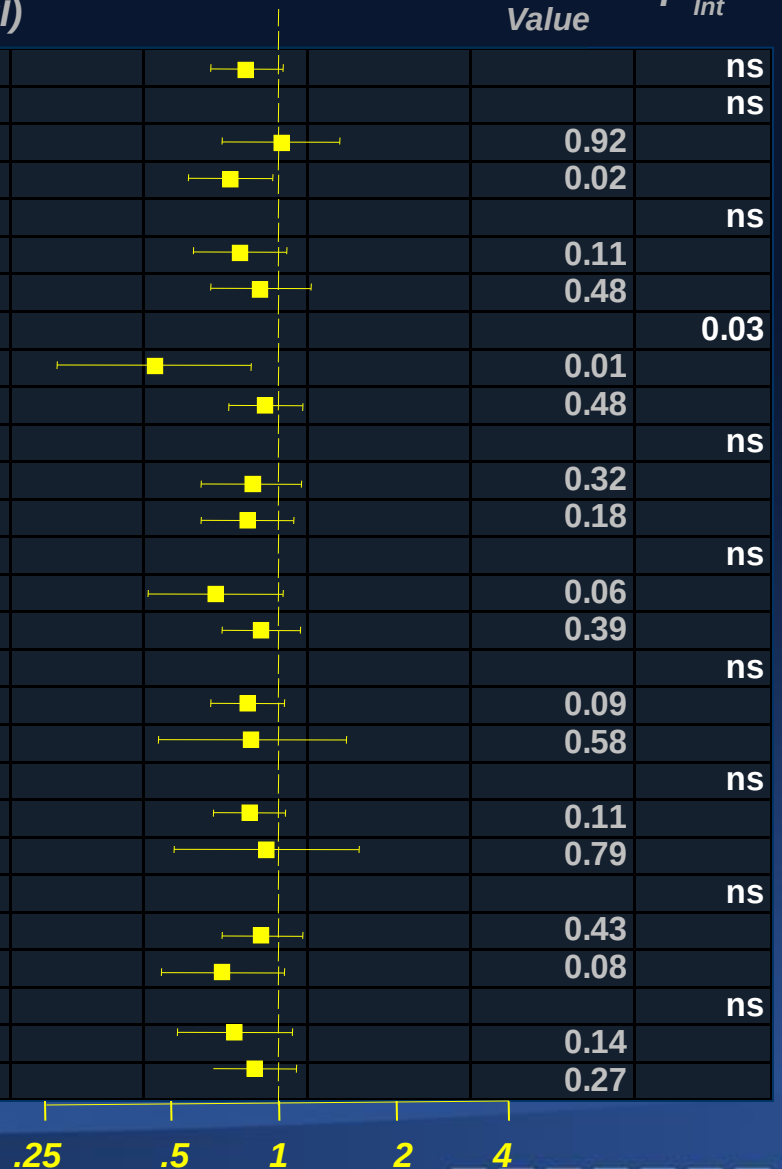
3-Year Efficacy Endpoints



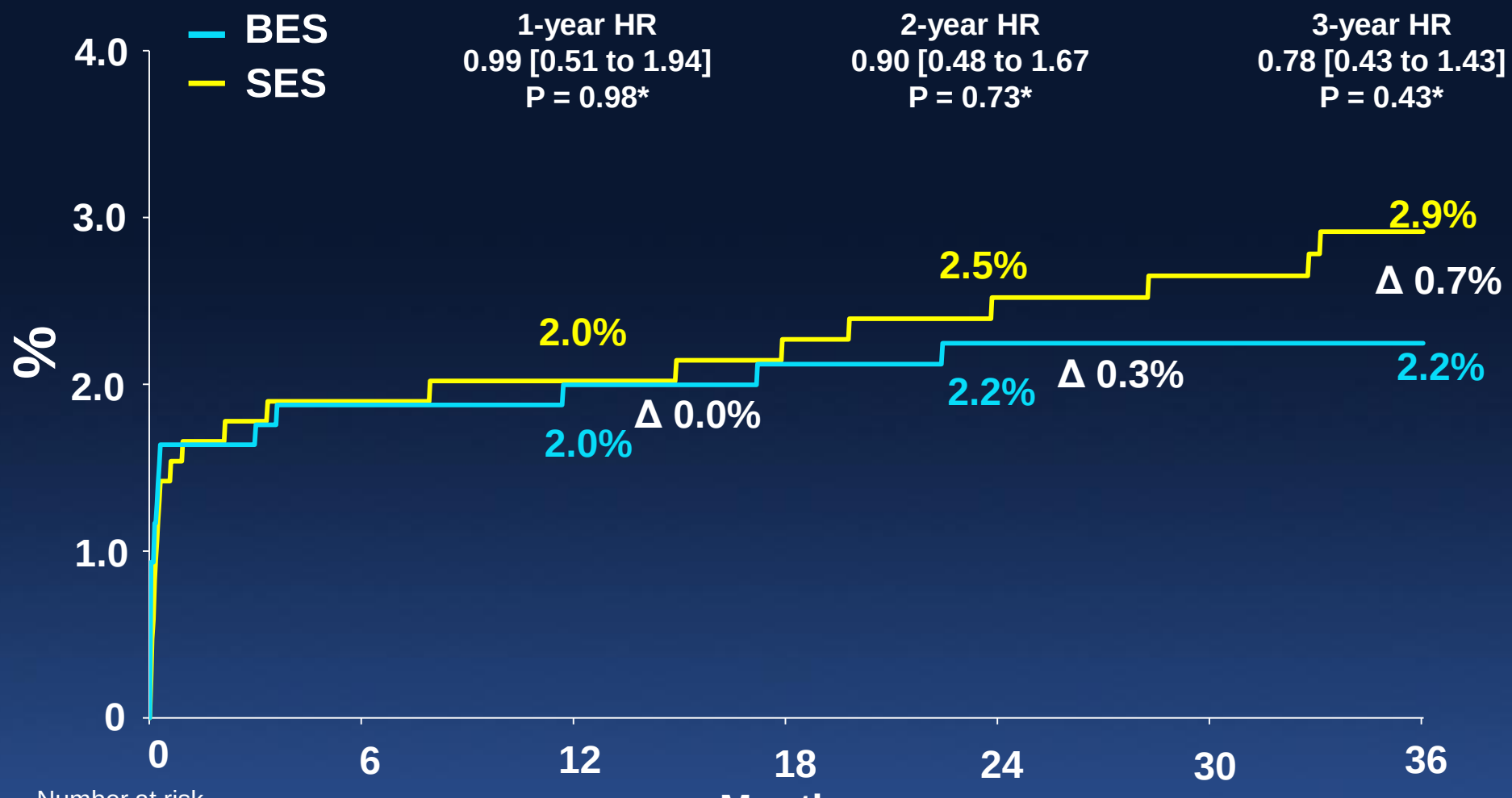
*P values for superiority (Fisher Exact Test)

Stratified Analysis of MACE @ 3 Years

	BES	SES	Risk Ratio (95% CI)	P Value	P Int
Overall	132/857	157/850	0.80 (0.63 to 1.03)		ns
Diabetes mellitus					ns
Yes	53/223	45/191	1.02 (0.68 to 1.52)	0.92	
No	79/634	112/659	0.72 (0.54 to 0.96)	0.02	
Acute coronary					ns
Yes	68/470	87/473	0.77 (0.56 to 1.06)	0.11	
No	64/387	70/377	0.88 (0.63 to 1.25)	0.48	
ST-elevation MI					0.03
Yes	13/135	29/140	0.43 (0.22 to 0.83)	0.01	
No	119/722	128/710	0.91 (0.71 to 1.18)	0.48	
Left anterior					ns
Yes	59/407	71/417	0.84 (0.59 to 1.17)	0.32	
No	73/449	86/431	0.81 (0.59 to 1.11)	0.18	
Multivessel disease					ns
Yes	33/209	42/176	0.65 (0.41 to 1.03)	0.06	
No	99/648	115/674	0.89 (0.68 to 1.16)	0.39	
Off-label use					ns
Yes	116/696	135/665	0.81 (0.63 to 1.04)	0.09	
No	16/160	22/183	0.83 (0.44 to 1.59)	0.58	
De-novo lesions					ns
Yes	114/788	136/774	0.82 (0.64 to 1.05)	0.11	
No	18/68	21/74	0.92 (0.49 to 1.73)	0.79	
Small-vessel disease					ns
Yes	96/585	104/568	0.89 (0.68 to 1.18)	0.43	
No	36/271	53/280	0.68 (0.45 to 1.04)	0.08	
Long lesions					ns
Yes	46/262	52/225	0.74 (0.50 to 1.10)	0.14	
No	86/594	105/623	0.85 (0.64 to 1.13)	0.27	



Definite ST through 3 years

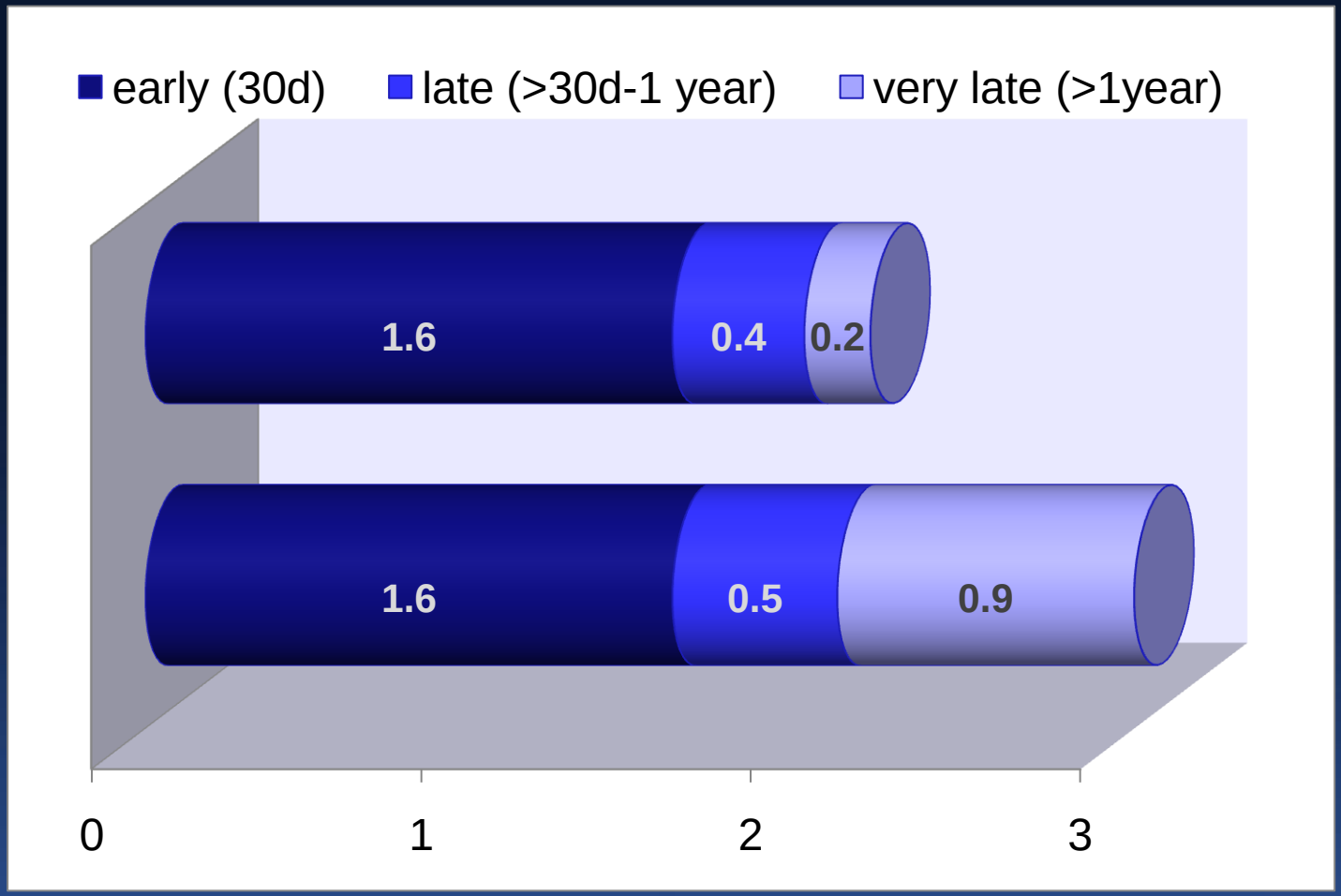


Number at risk

BES	857	846	808	797	787	774	732
SES	850	841	801	792	779	758	715

*P values for superiority

Definite Stent Thrombosis



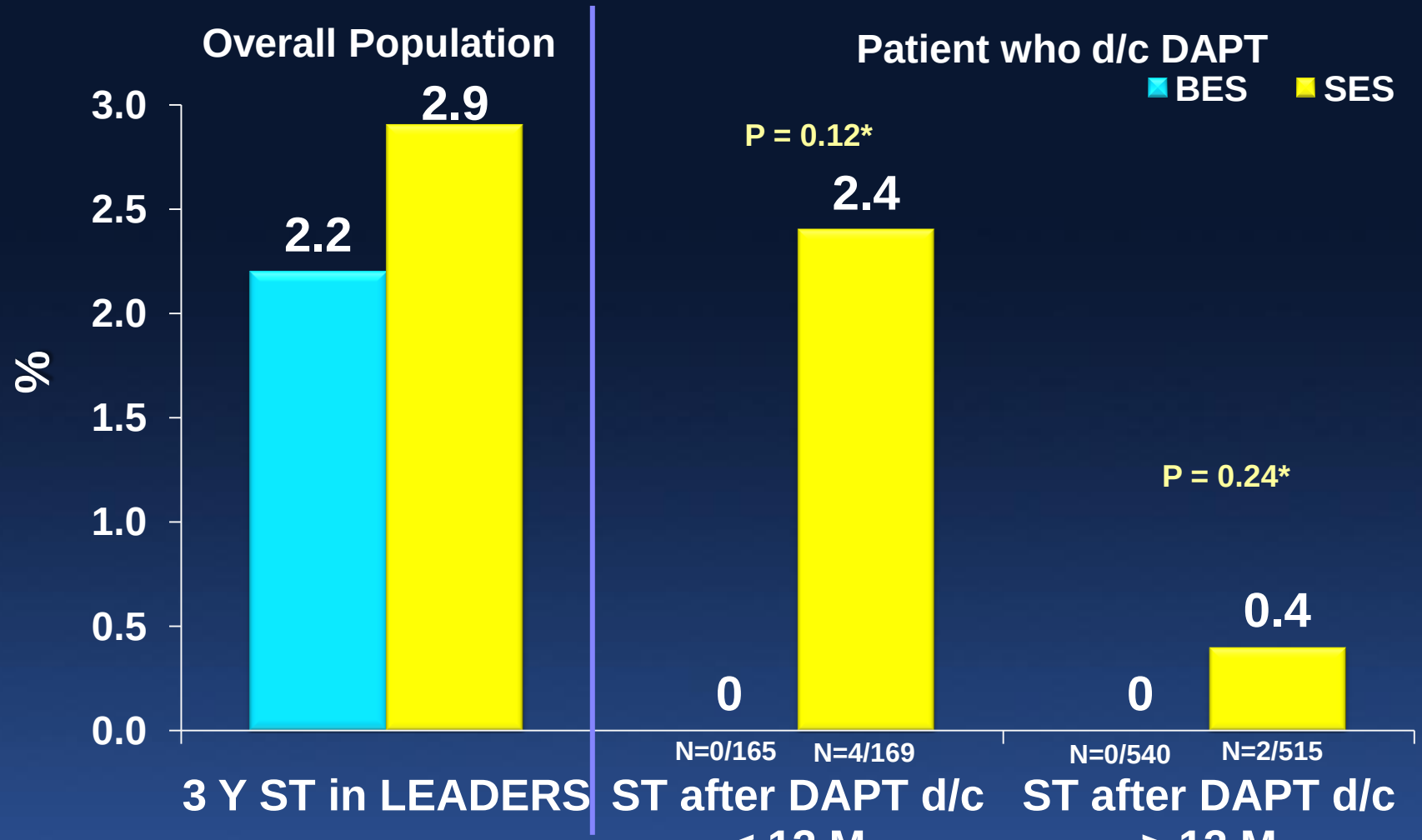
Definite Stent Thrombosis %

According to ARC Definition

Antiplatelet Agent Utilization

	BES	SES	P value
Aspirin			
- At 9 months	96.6% (n=818)	97.4% (n=798)	**0.39**
- At 12 months	97.0% (n=810)	96.1% (n=801)	**0.34**
- At 24 months	94.9% (n=789)	94.2% (n=778)	**0.58**
- At 36 months	94.3% (n=757)	94.8% (n=746)	**0.73**
Clopidrogel/Thienopyridine			
- At 9 months	95.6% (n=818)	95.2% (n=798)	**0.81**
- At 12 months	68.1% (n=810)	66.5% (n=801)	**0.52**
- At 24 months	23.4% (n=789)	24.3% (n=778)	**0.72**
- At 36 months	19.6% (n=757)	20.4% (n=747)	**0.75**

Effect of DAPT Discontinuation



*P values for superiority (Fisher Exact Test)

Summary Conclusions

1. Overall population

- Non-inferiority of BES vs SES in an all-comers population was sustained up to 3 years

- In the overall LEADERS population there were similar outcomes for BES and SES with respect to MACE, Cardiac Death, MI and clinically-indicated TVR

- The Kaplan-Meier curves for MACE continue to diverge showing lower event rates for BES

Summary Conclusions

2. Subgroup analysis

- STEMI patients
  - Significant reduction of MACE with BES compared to SES
    - (9.6% vs 20.7% P_{sup} = 0.01)

3. Very Late Stent Thrombosis

- Although this was an all-comers study, definite very late stent thrombosis events were rare (BES 0.2% vs SES 0.9% P_{Sup}= 0.43)
- There were no VLST events in BES patients between 2 and 3 year clinical FU
- No VLST events in patients where a BES was implanted in native coronary arteries