# LEADERS: 4-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.

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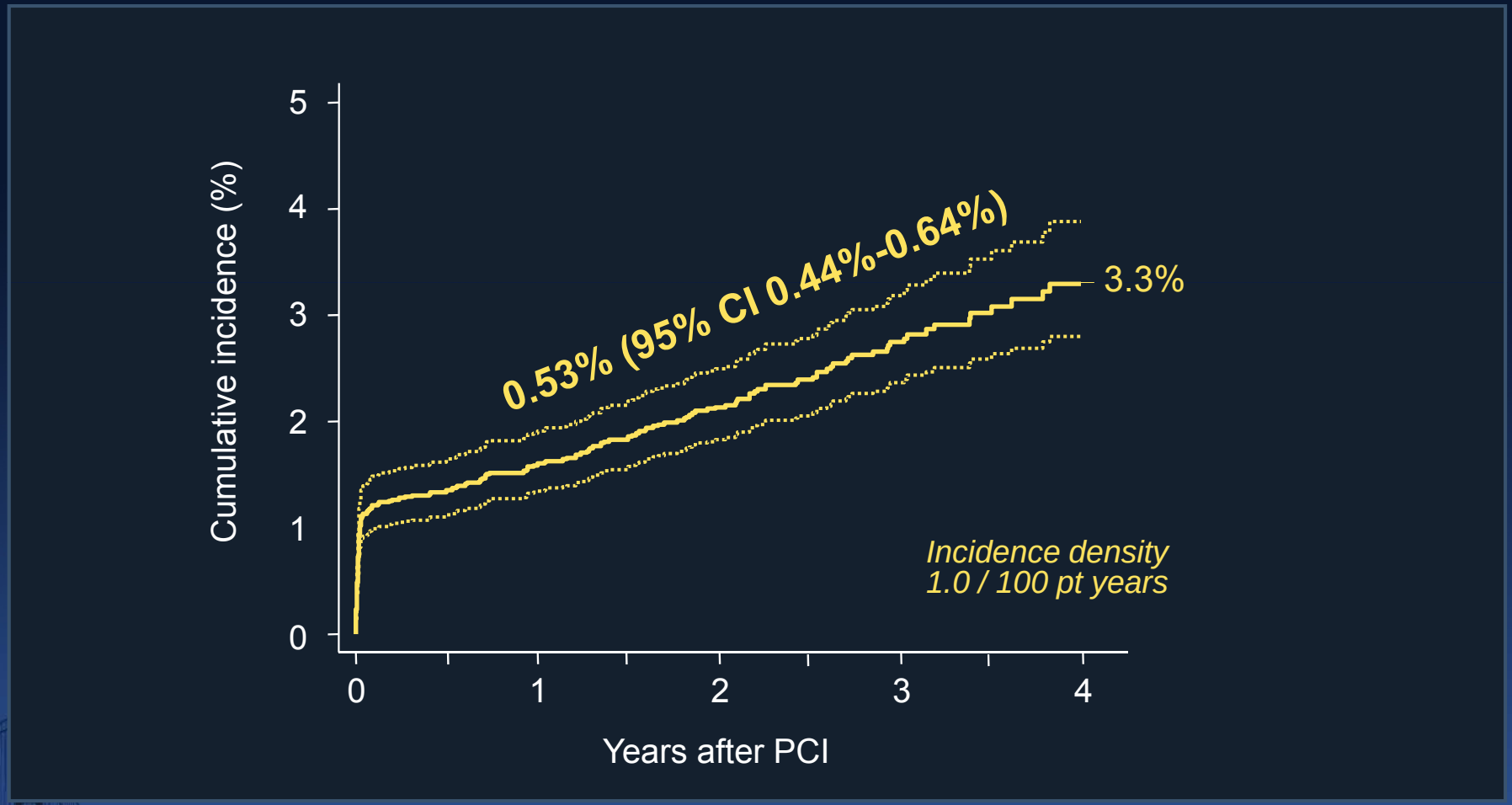
# Disclosure Statement of Financial Interest

**I, Thomas Ischinger, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.**

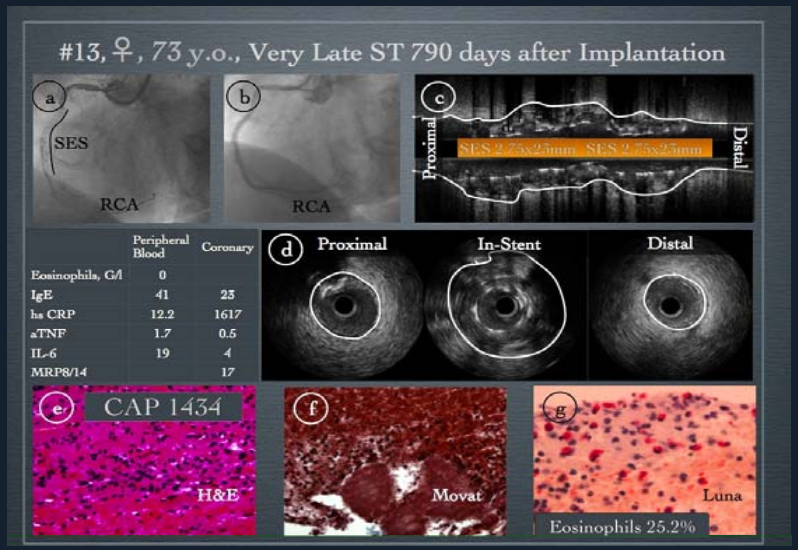
# Definite Stent Thrombosis with Early Generation Drug-Eluting Stents




Daemen J, et al. *Lancet* 2007; 369:667-78.

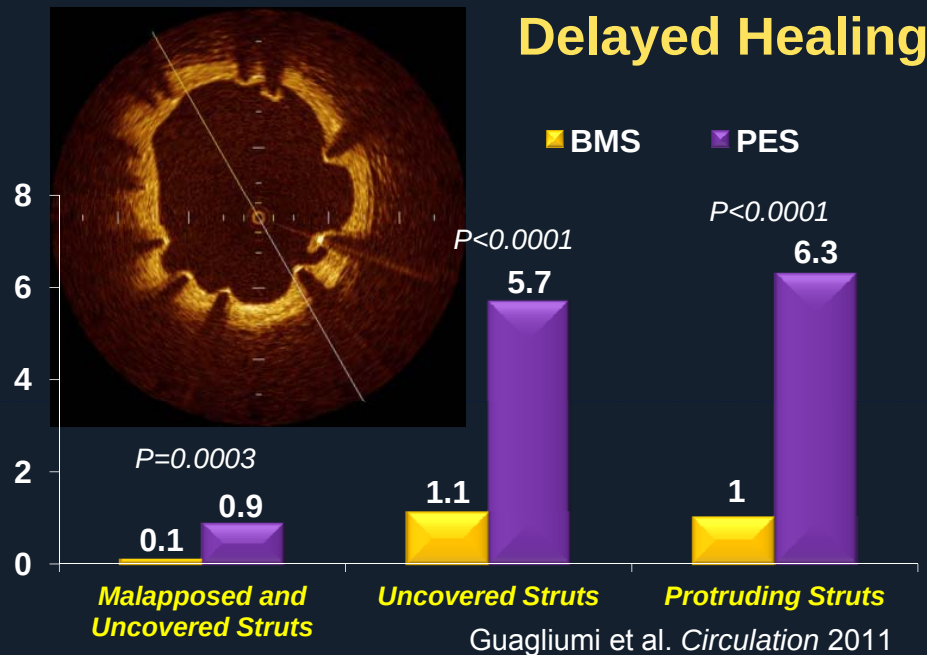
# Pathophysiology of Very Late ST

## Eosinophilic Infiltrates



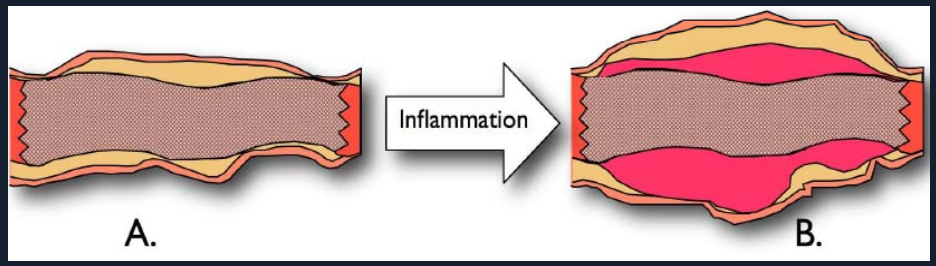

Cook et al. *Circulation* 2009

## Delayed Healing



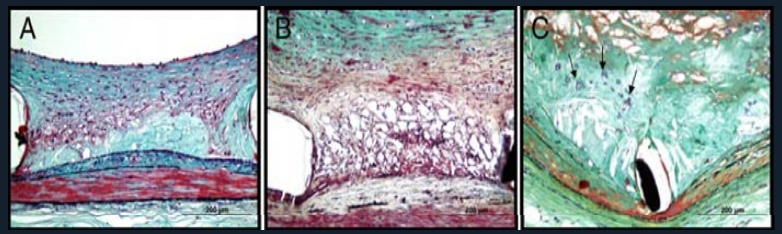

Guagliumi et al. *Circulation* 2011

## Vessel Remodeling



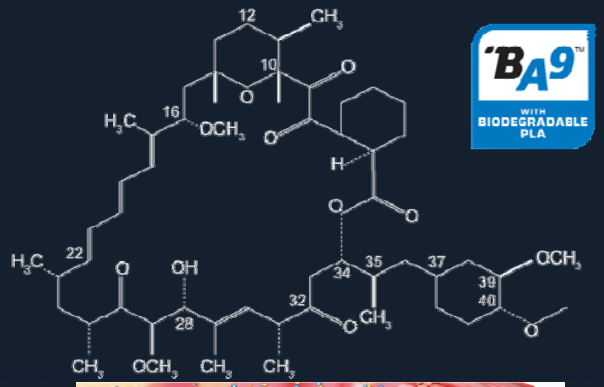

Cook et al. *Circulation* 2007

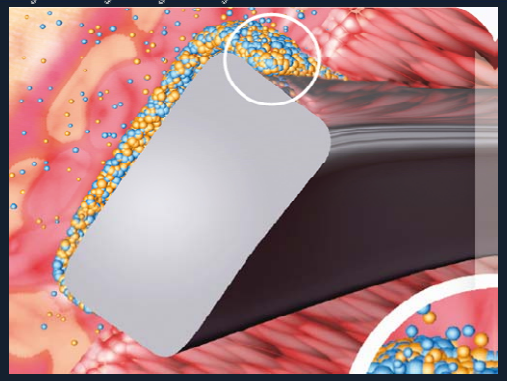
## Neoatherosclerosis




Nakazawa *JACC* 2011

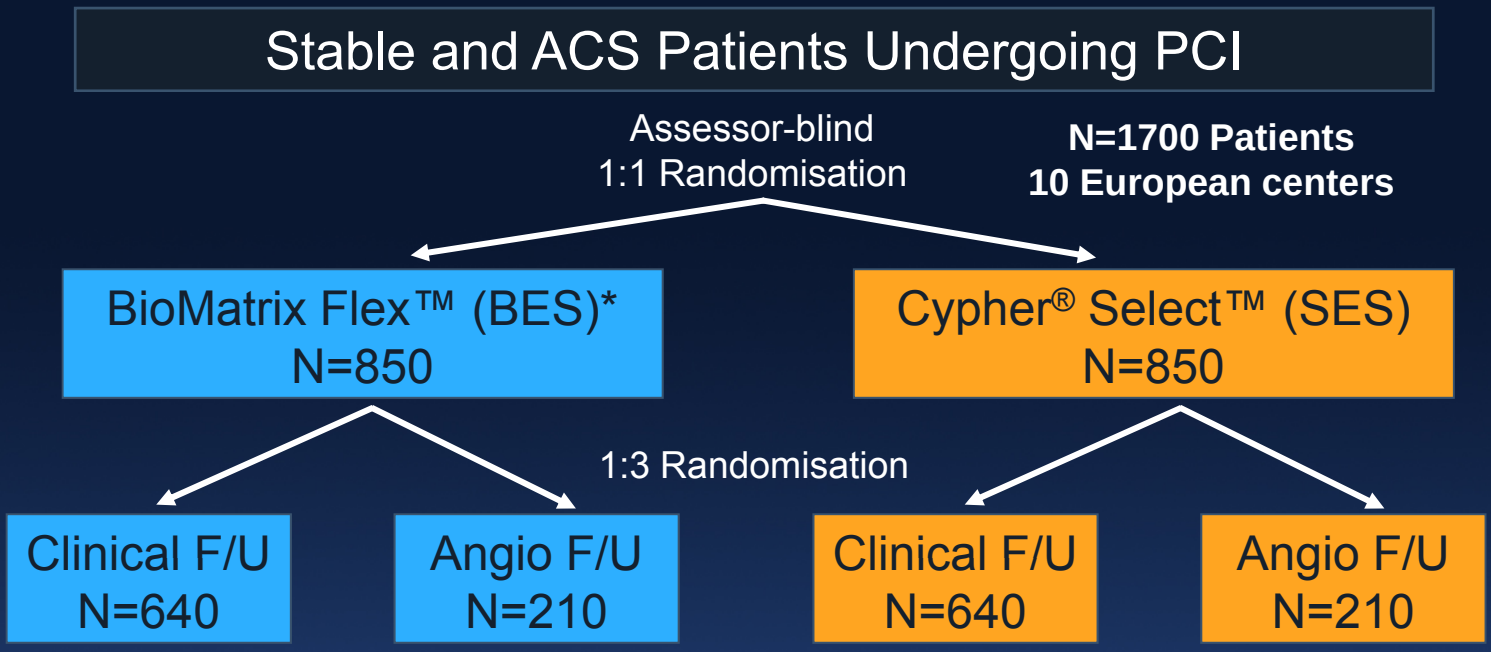
# Biolimus-A9™ Eluting Stent



- 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.

# LEADERS 'all-comers' Trial Design




**1º endpoint:** **MACE: Cardiac death, MI, clinically-indicated TVR (9 mo)**

2º endpoints: Death, CV death, MI, TLR, TVR
Stent thrombosis according to ARC

**Angiographic study:** **In-stent % diameter stenosis (9 mo)**
Late loss, binary restenosis

DAPT recommended for 12 months

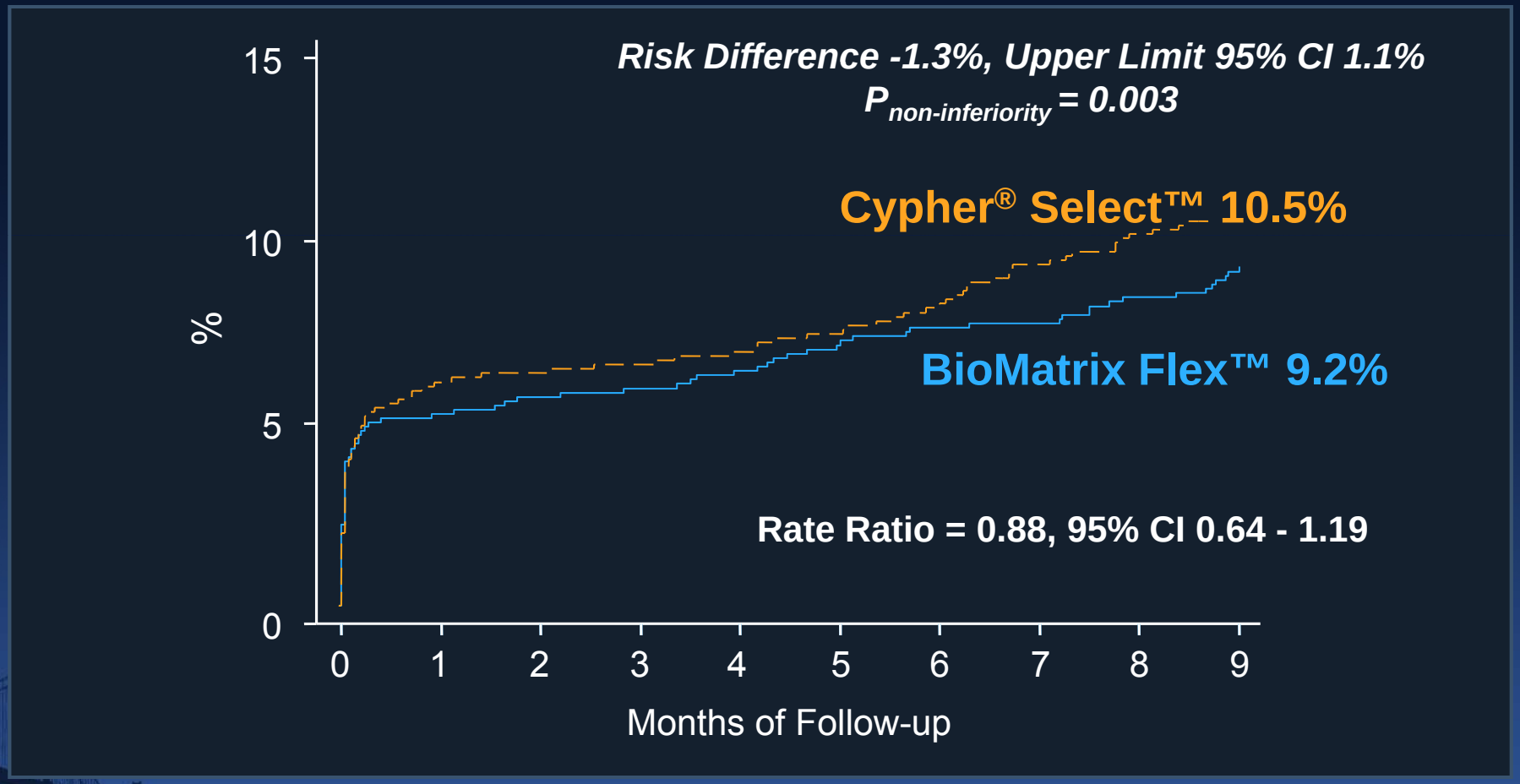
# Patient Demographics

| | BES<br>857 Patients | SES<br>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% |

# Patient Characteristics

| | BES<br>857 Patients | SES<br>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% |

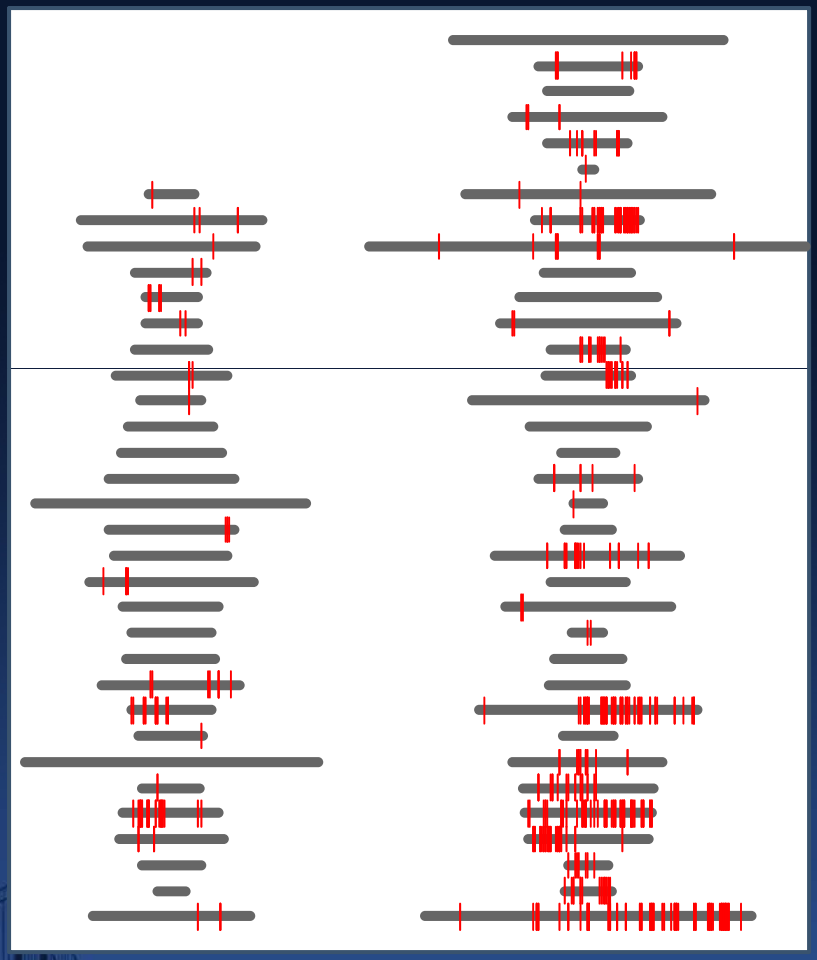
# LEADERS Primary Endpoint
# MACE (Cardiac Death, MI and ci-TVR)
# @ 9 Months




Windecker S. et al., The Lancet 2008; 372 No. 9644: 1163-1173

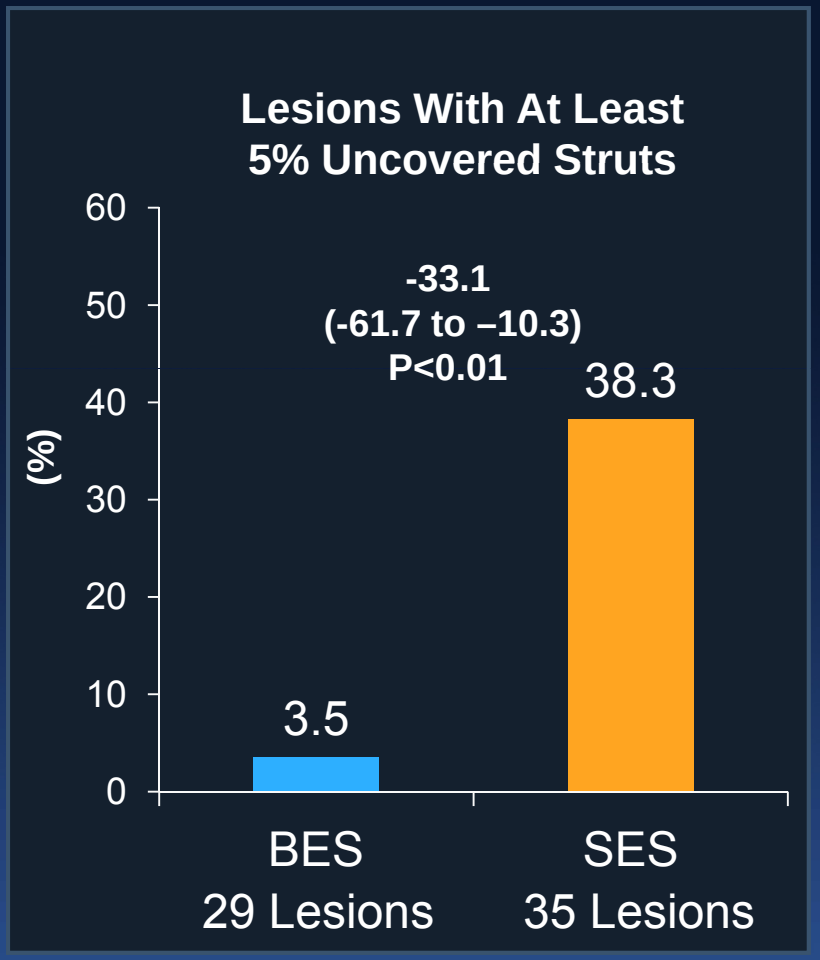
# LEADERS - OCT Substudy @ 9 Months

**Barlis P et al. Eur Heart J 2010**

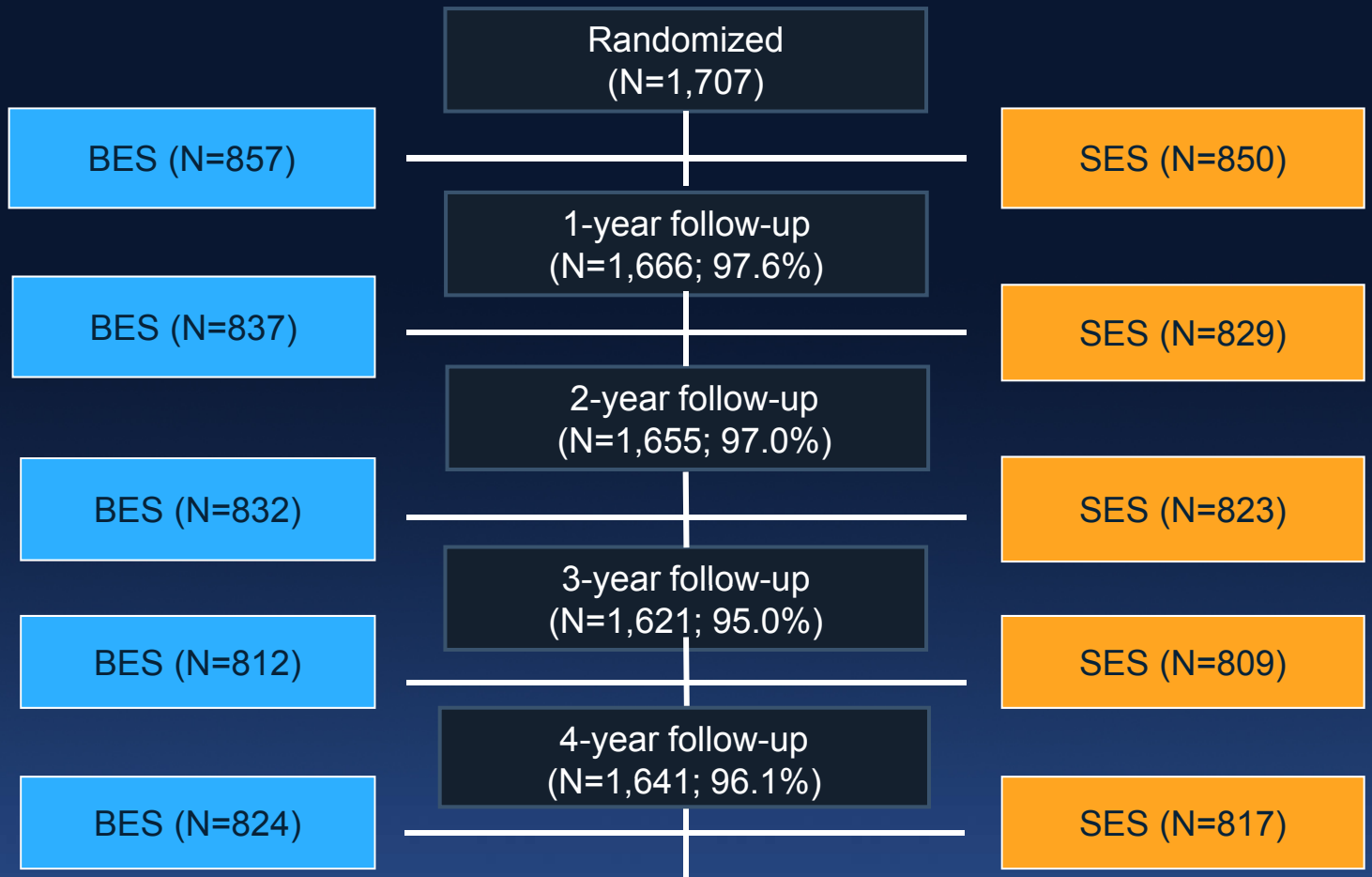


BES
29 Lesions

SES
35 Lesions



# Patient Flow - Clinical



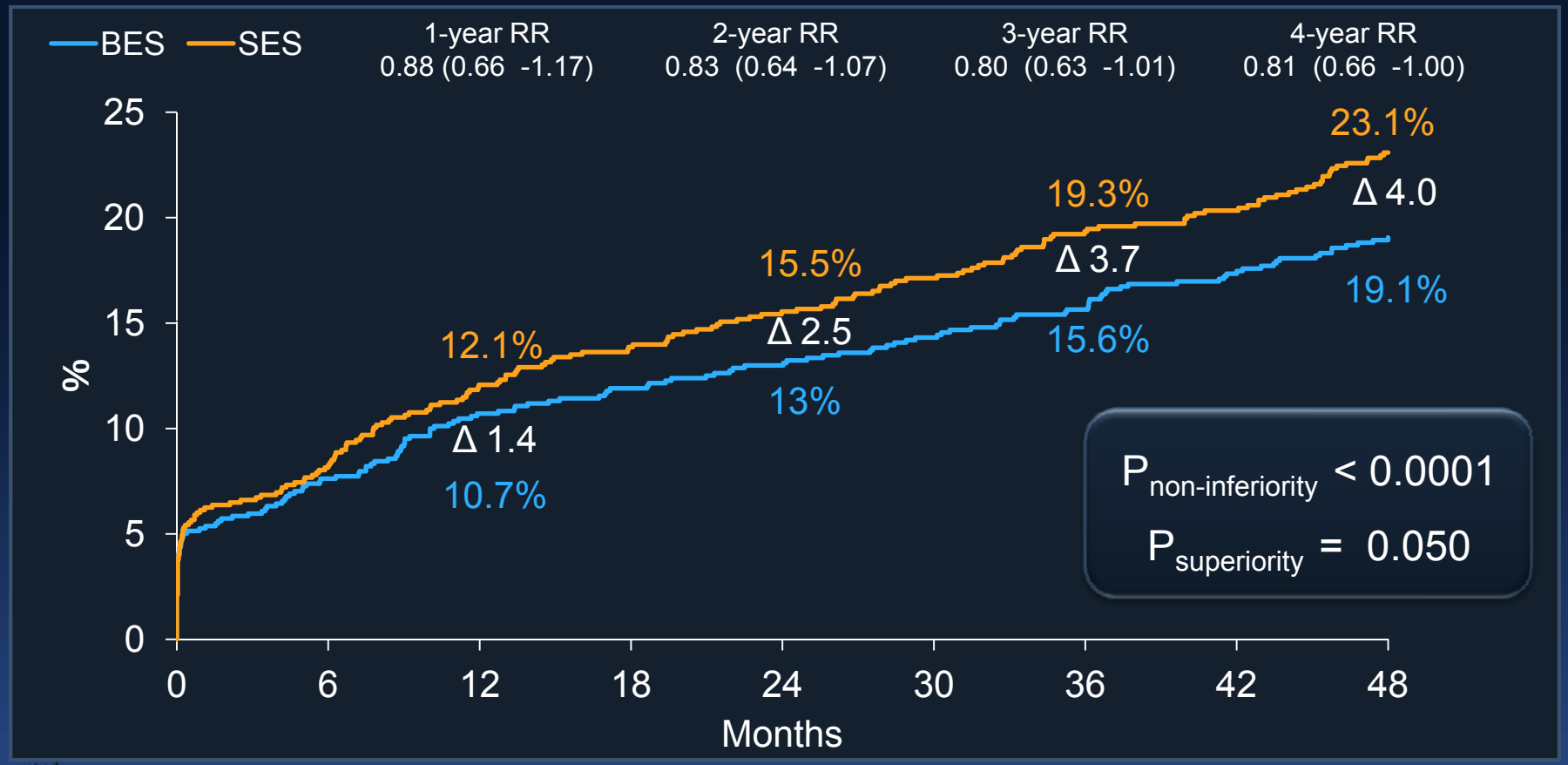

21 Lost to FU
- 14 lost to FU and alive
- 7 lost to FU and vital status unknown

12 withdrew

18 Lost to FU
- 10 lost to FU and alive
- 8 lost to FU and vital status unknown

15 withdrew

# MACE

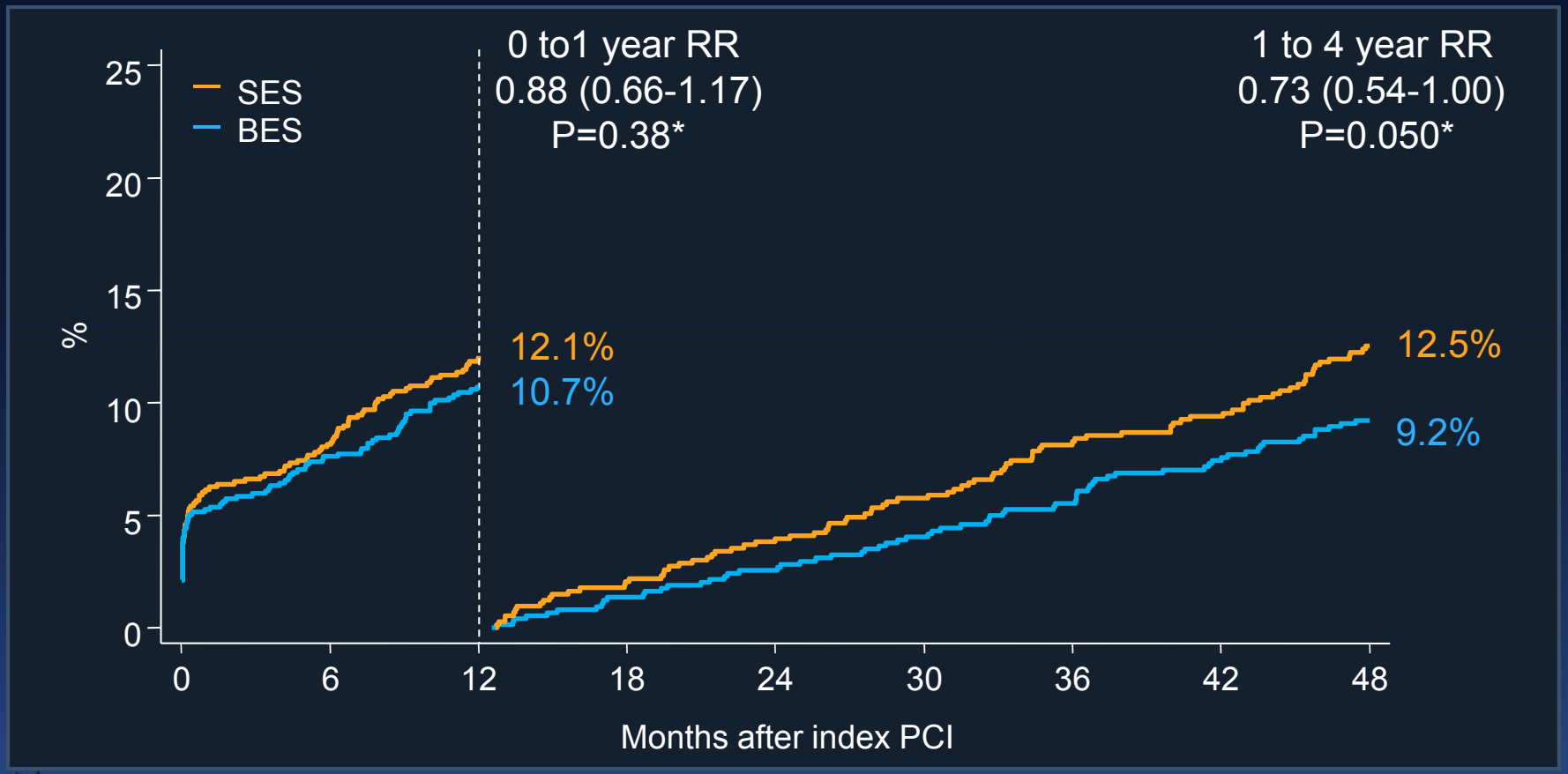



Numbers at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SES | 850 | 775 | 738 | 718 | 702 | 676 | 656 | 639 | 614 |
| BES | 857 | 781 | 749 | 733 | 723 | 710 | 697 | 677 | 659 |

MACE = Cardiac death, MI, or Clinically-indicated TVR

# MACE
# Landmark Analysis @ 1 Year

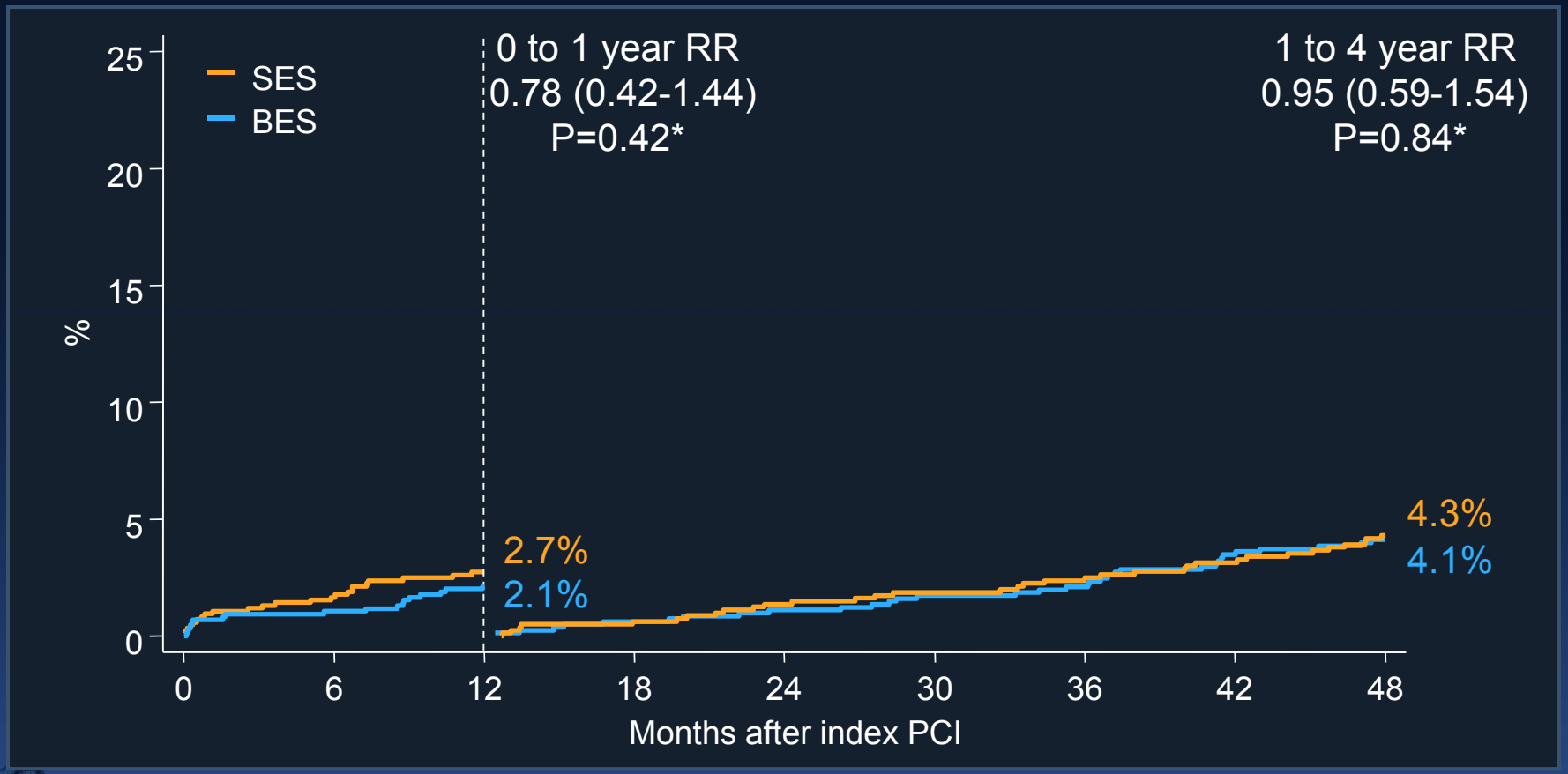



No. at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SES | 850 | 775 | 738 | 718 | 702 | 676 | 656 | 639 | 614 |
| BES | 857 | 781 | 749 | 733 | 723 | 710 | 697 | 677 | 659 |

P for interaction=0.39
* P values for superiority

# Cardiac Death
# Landmark Analysis @ 1 Year




No. at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SES | 850 | 830 | 814 | 802 | 793 | 776 | 768 | 751 | 739 |
| BES | 857 | 834 | 817 | 806 | 801 | 794 | 787 | 770 | 759 |

P for interaction=0.61
* P values for superiority

TCT2011

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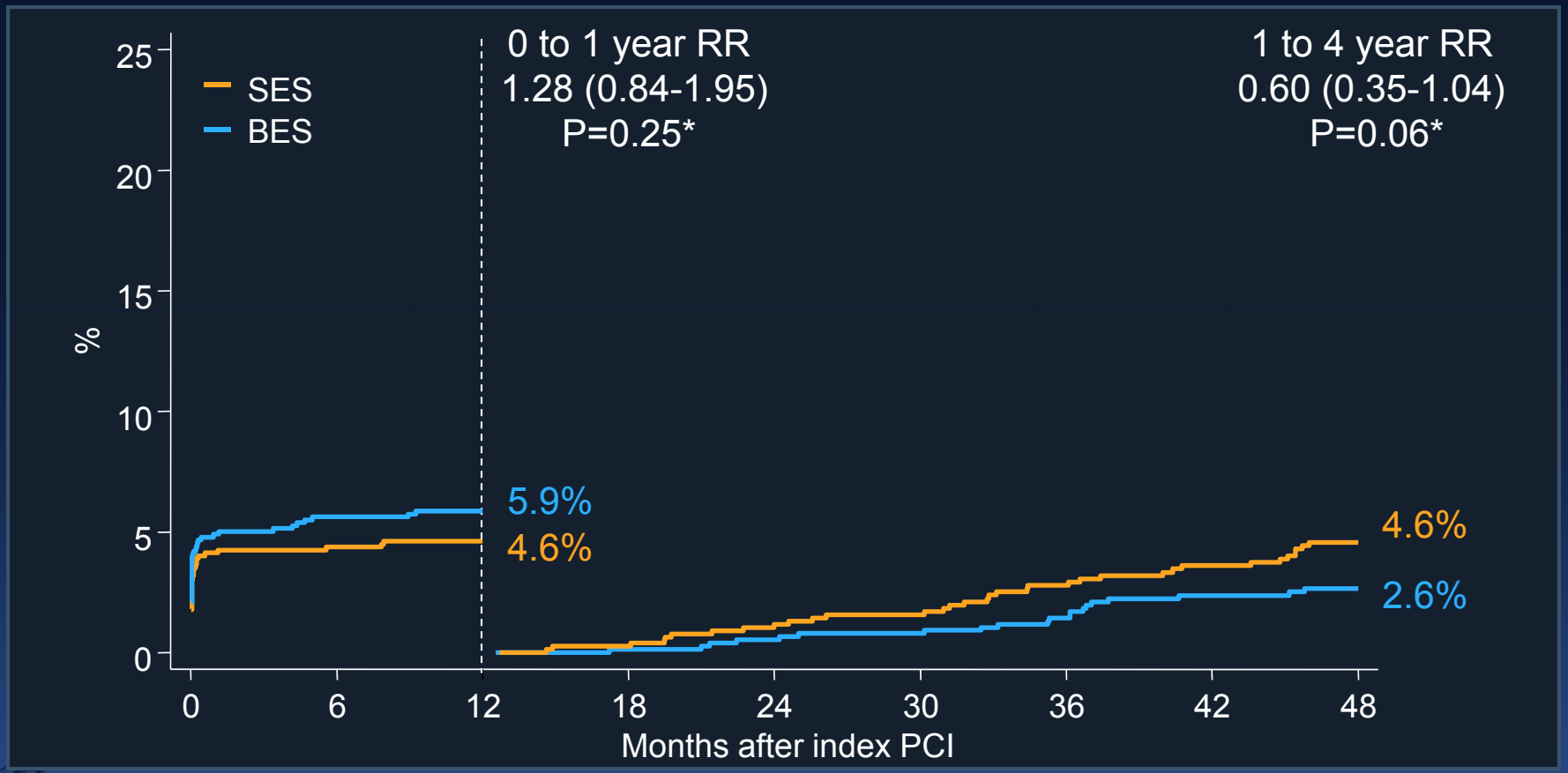
# Myocardial Infarction
## Landmark Analysis @ 1 Year




No. at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SES | 850 | 797 | 781 | 767 | 753 | 733 | 718 | 699 | 682 |
| BES | 857 | 793 | 779 | 768 | 761 | 752 | 744 | 723 | 712 |

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P for interaction=0.031
* P values for superiority

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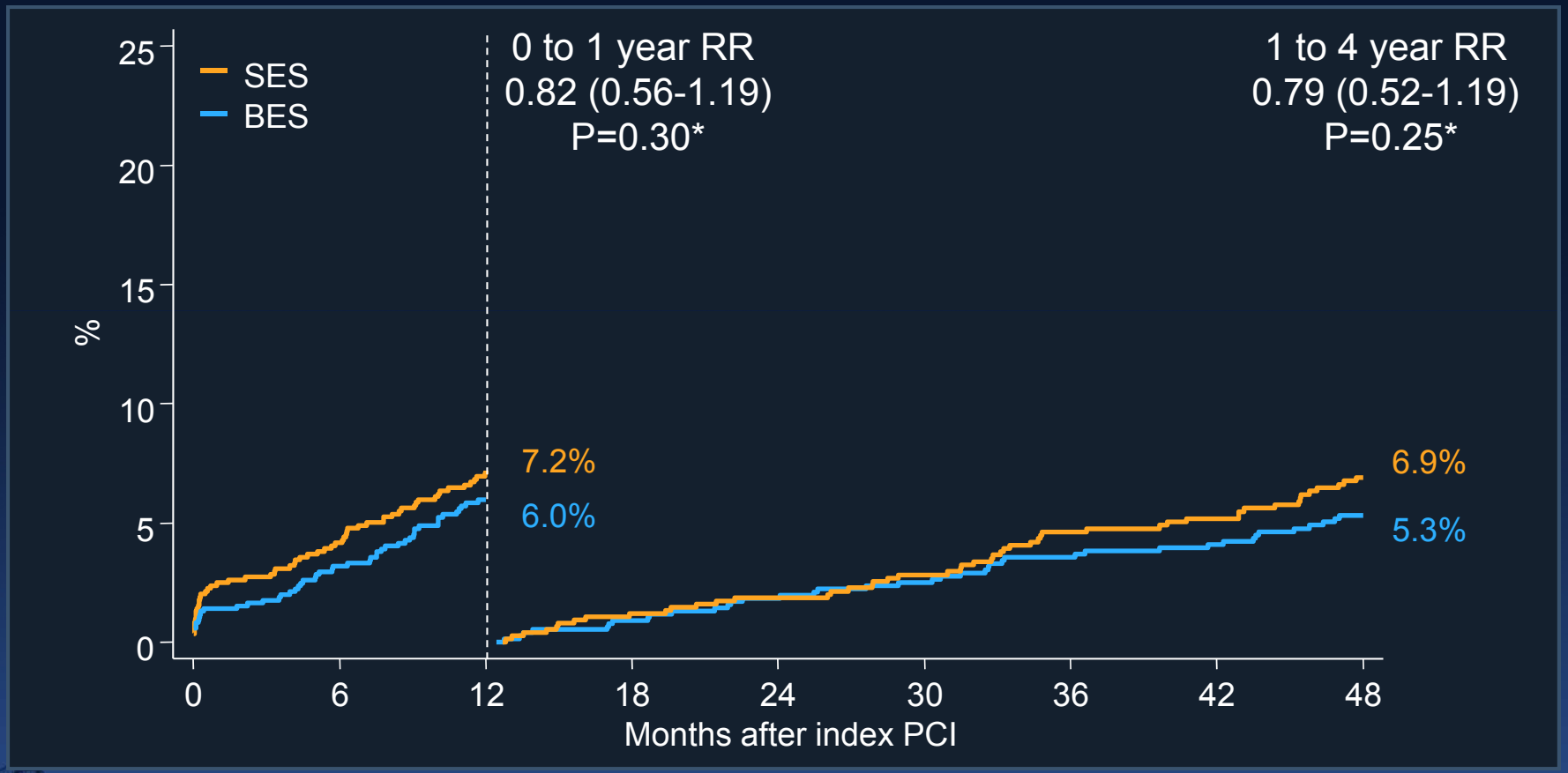
# Clinically-indicated TVR
## Landmark Analysis @ 1 Year

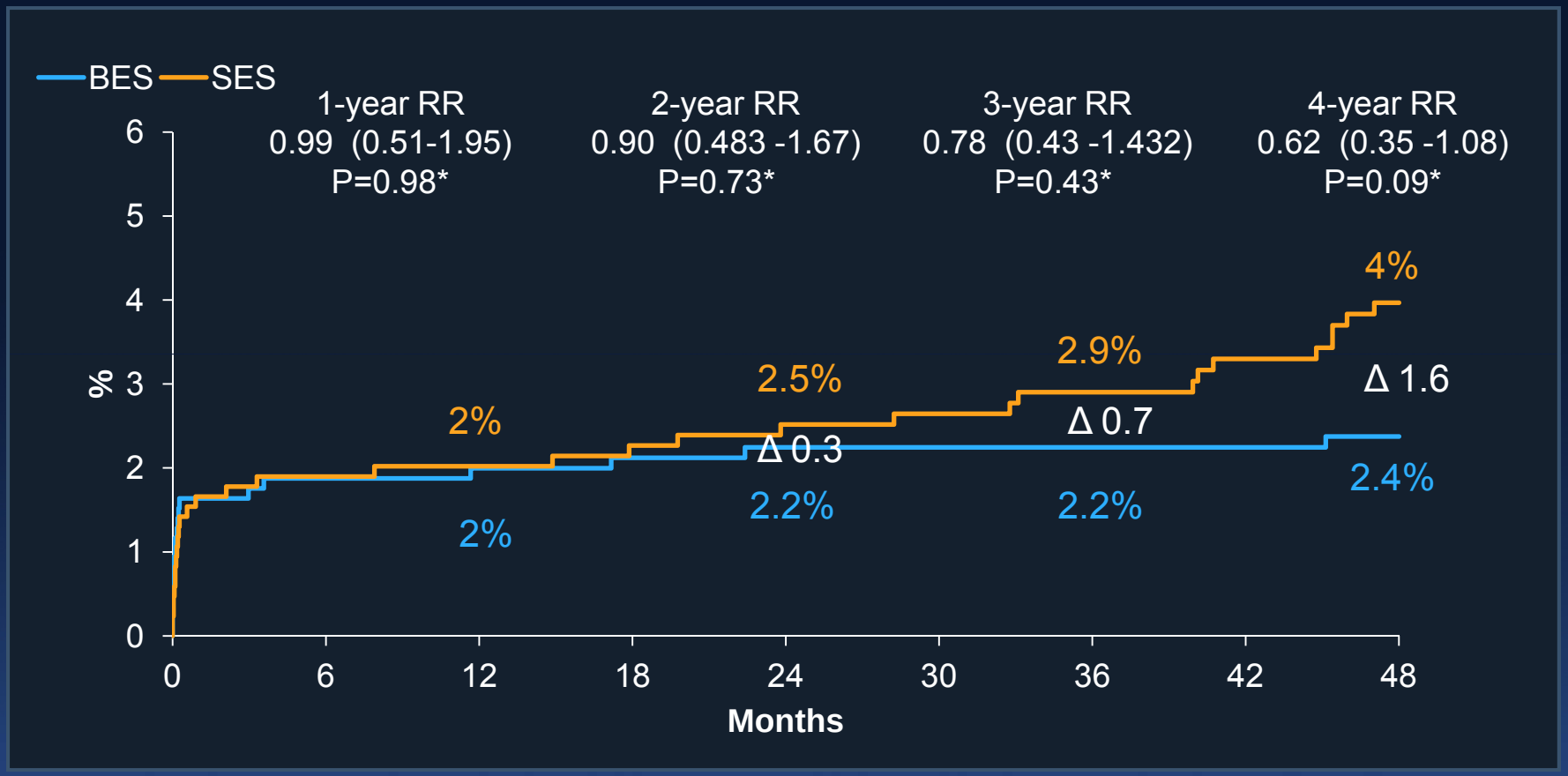



No. at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SES | 850 | 798 | 761 | 741 | 727 | 704 | 686 | 667 | 644 |
| BES | 857 | 810 | 776 | 758 | 748 | 736 | 725 | 708 | 689 |

P for interaction=0.89
* P values for superiority

# Definite Stent Thrombosis (ARC)

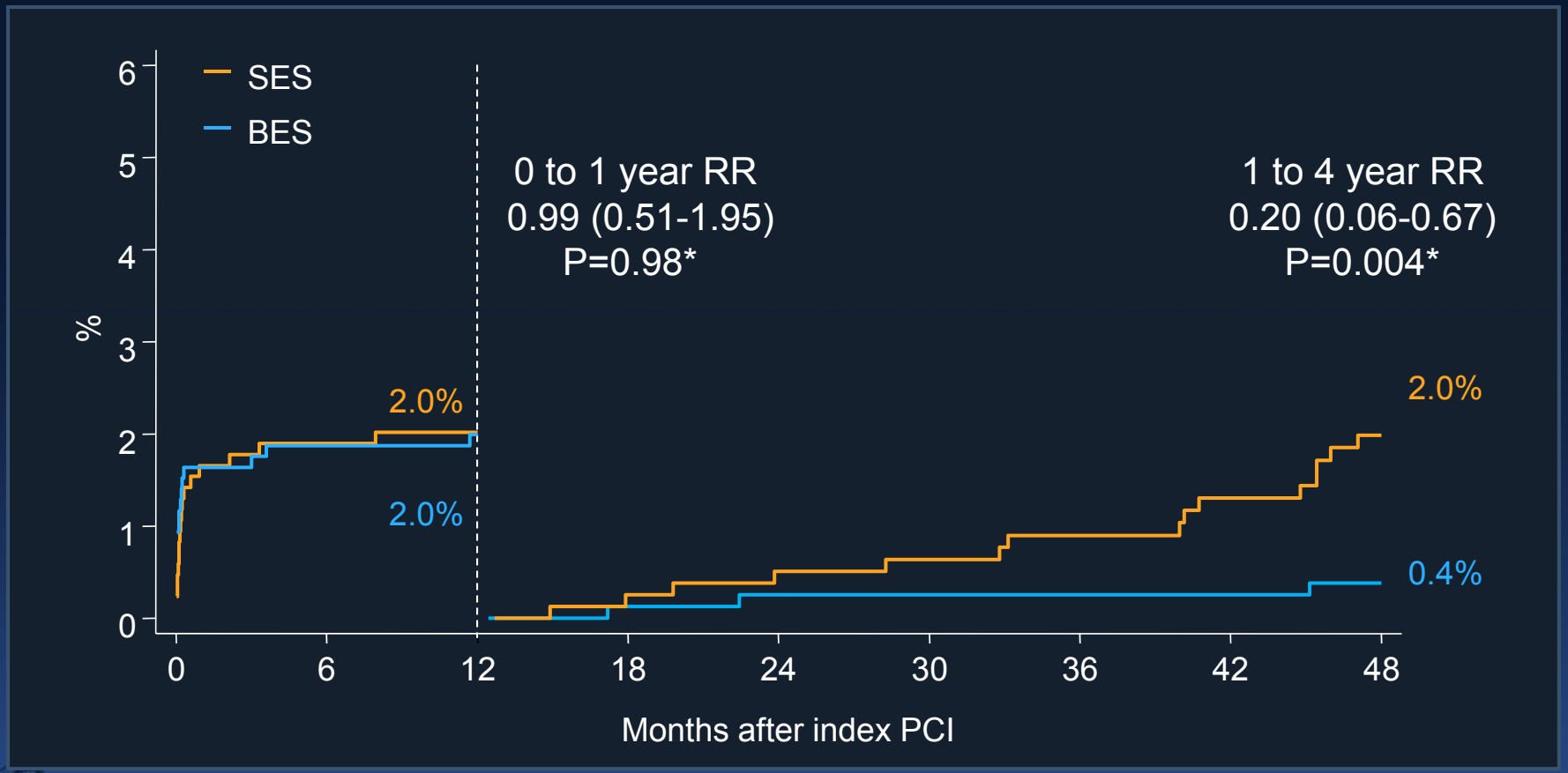



Number s at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SES | 850 | 817 | 801 | 787 | 776 | 759 | 750 | 730 | 714 |
| BES | 857 | 821 | 804 | 792 | 787 | 780 | 774 | 757 | 746 |

* P values for superiority

# Definite ST
# Landmark Analysis @ 1 Year




No. at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| SES | 850 | 817 | 801 | 787 | 776 | 759 | 750 | 730 | 714 |
| BES | 857 | 821 | 804 | 792 | 787 | 780 | 774 | 757 | 746 |

P for interaction=0.017
* P values for superiority

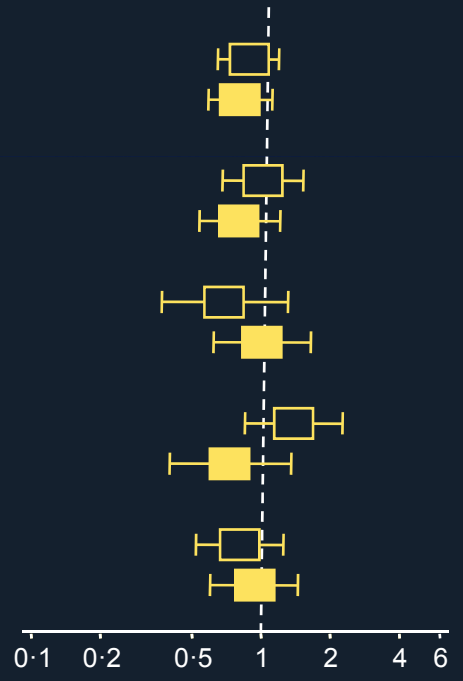
# Antiplatelet Agent Utilization

| | BES | SES | P value* |
|---|---|---|---|
| Aspirin | | | |
| At 1 year | 786/810 (97%) | 770/801 (96%) | 0.32 |
| At 2 years | 749/789 (95%) | 733/777 (94%) | 0.60 |
| At 3 years | 714/757 (94%) | 709/748 (95%) | 0.69 |
| At 4 years | 694/745 (93%) | 681/730 (93%) | 0.93 |
| Clopidrogel or ticlopidine | | | |
| At 1 year | 552/810 (68%) | 534/801 (67%) | 0.53 |
| At 2 years | 185/789 (23%) | 189/774 (24%) | 0.68 |
| At 3 years | 148/757 (20%) | 153/749 (20%) | 0.67 |
| At 4 years | 119/745 (16%) | 135/730 (18%) | 0.21 |
| Dual antiplatelet therapy | | | |
| At 1 year | 536/810 (66%) | 513/801 (64%) | 0.37 |
| At 2 years | 171/789 (22%) | 168/777 (22%) | 0.98 |
| At 3 years | 126/757 (17%) | 133/749 (18%) | 0.57 |
| At 4 years | 96/745 (13%) | 111/730 (15%) | 0.21 |

* P values for superiority

# Cardiac Events NOT ASSOCIATED with Definite Stent Thrombosis through 4 Years

| | BES | SES | Risk ratio (95% CI) | P Value* | P for interaction |
|---|---|---|---|---|---|
| **Cardiac death, MI, or ci-TVR** | | | | | 0.70 |
| ≤1 year | 78/857 | 87/850 | 0.89 (0.65-1.20) | 0.44 | |
| 1 to 4 years | 67/749 | 79/738 | 0.81 (0.59-1.12) | 0.21 | |
| **Cardiac death or MI** | | | | | 0.43 |
| ≤1 year | 48/857 | 47/850 | 1.02 (0.68-1.53) | 0.94 | |
| 1 to 4 years | 43/779 | 52/781 | 0.80 (0.54-1.21) | 0.30 | |
| **Cardiac death** | | | | | 0.35 |
| ≤1 year | 16/857 | 23/850 | 0.69 (0.37-1.31) | 0.25 | |
| 1 to 4 years | 33/817 | 32/814 | 1.01 (0.62-1.65) | 0.96 | |
| **MI** | | | | | 0.11 |
| ≤1 year | 39/857 | 28/850 | 1.39 (0.85-2.27) | 0.19 | |
| 1 to 4 years | 18/779 | 24/781 | 0.73 (0.40-1.35) | 0.31 | |
| **Clinically-indicated TVR** | | | | | 0.64 |
| ≤1 year | 37/857 | 45/850 | 0.81 (0.52-1.25) | 0.33 | |
| 1 to 4 years | 39/776 | 40/760 | 0.94 (0.60-1.45) | 0.77 | |



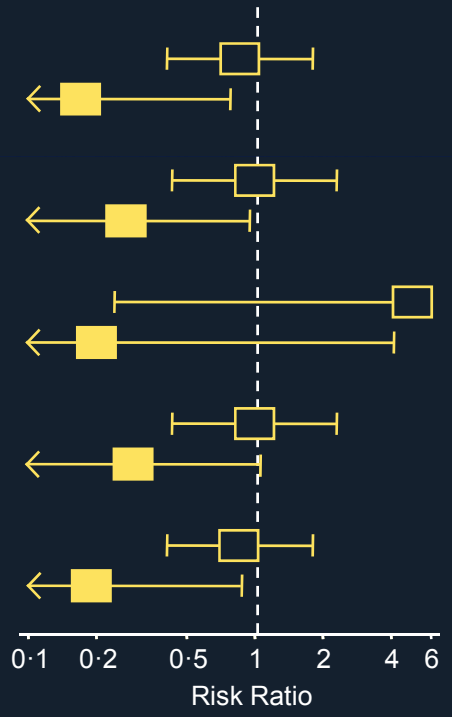

≤1 year

1 to 4 year

* P values for superiority

# Cardiac Events ASSOCIATED with Definite Stent Thrombosis through 4 Years

| | BES | SES | Risk ratio (95% CI) | P Value* | P for interaction |
|---|---|---|---|---|---|
| **Cardiac death, MI, or ci-TVR** | | | | | 0.049 |
| ≤1 year | 13/857 | 15/850 | 0.86 (0.41-1.80) | 0.68 | |
| 1 to 4 years | 2/749 | 11/738 | 0.17 (0.04-0.78) | 0.009 | |
| **Cardiac death or MI** | | | | | 0.08 |
| ≤1 year | 11/857 | 11/850 | 1.00 (0.43-2.30) | 0.99 | |
| 1 to 4 years | 3/779 | 11/781 | 0.27 (0.08-0.95) | 0.029 | |
| **Cardiac death** | | | | | 0.14 |
| ≤1 year | 2/857 | 0/850 | 4.97 (0.24-103.4) | 0.50 | |
| 1 to 4 years | 0/817 | 2/814 | 0.20 (0.01-4.12) | 0.25 | |
| **MI** | | | | | 0.11 |
| ≤1 year | 11/857 | 11/850 | 1.00 (0.43-2.30) | 0.99 | |
| 1 to 4 years | 3/779 | 10/781 | 0.29 (0.08-1.06) | 0.06 | |
| **Clinically-indicated TVR** | | | | | 0.07 |
| ≤1 year | 13/857 | 15/850 | 0.85 (0.41-1.80) | 0.68 | |
| 1 to 4 years | 2/776 | 10/760 | 0.19 (0.04-0.87) | 0.017 | |



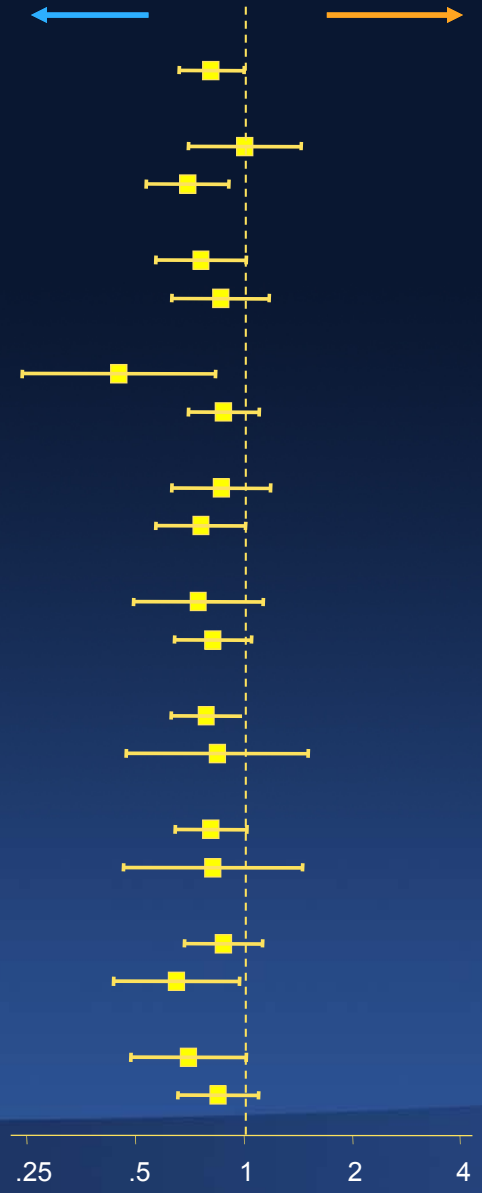

≤1 year

1 to 4 year

* P values for superiority

# Stratified Analysis of MACE @ 4 Years

| | BES | SES | RR (95%CI) | P* | P for interaction |
|---|---|---|---|---|---|
| Overall | 160/857 | 192/850 | 0.81 (0.66 to 1.00) | 0.05 | |
| Diabetes mellitus | | | | | ns |
| Yes | 65/223 | 56/191 | 1.00 (0.70 to 1.44) | 0.98 | |
| No | 94 /634 | 136/659 | 0.70 (0.54 to 0.91) | 0.007 | |
| ACS | | | | | ns |
| Yes | 82/470 | 106/473 | 0.76 (0.57 to 1.01) | 0.06 | |
| No | 77/387 | 86/377 | 0.86 (0.63 to 1.17) | 0.34 | |
| ST elevation MI | | | | | 0.043 |
| Yes | 15/135 | 32/140 | 0.45 (0.24 to 0.83) | 0.009 | |
| No | 144/722 | 160/710 | 0.88 (0.70 to 1.10) | 0.26 | |
| Left anterior descending | | | | | ns |
| Yes | 73/407 | 85/417 | 0.86 (0.63 to 1.18) | 0.36 | |
| No | 86/449 | 107/431 | 0.76 (0.57 to 1.01) | 0.06 | |
| Multivessel disease | | | | | ns |
| Yes | 44/209 | 48/176 | 0.75 (0.49 to 1.13) | 0.16 | |
| No | 115/648 | 144/674 | 0.82 (0.64 to 1.05) | 0.11 | |
| Off label use | | | | | ns |
| Yes | 139/696 | 165/665 | 0.79 (0.63 to 0.99) | 0.037 | |
| No | 20/160 | 27/183 | 0.84 (0.47 to 1.51) | 0.56 | |
| De-novo lesions | | | | | ns |
| Yes | 138/788 | 165/774 | 0.81 (0.64 to 1.01) | 0.07 | |
| No | 21/68 | 27/74 | 0.82 (0.46 to 1.45) | 0.49 | |
| Small-vessel disease | | | | | ns |
| Yes | 119/585 | 131/568 | 0.88 (0.68 to 1.12) | 0.30 | |
| No | 40/271 | 61/280 | 0.65 (0.44 to 0.97) | 0.033 | |
| Long lesions | | | | | ns |
| Yes | 53/262 | 63/225 | 0.70 (0.49 to 1.01) | 0.06 | |
| No | 106/594 | 129/623 | 0.85 (0.65 to 1.10) | 0.21 | |




* P values for superiority

# Conclusions

- Biodegradable polymer BES maintained non-inferiority and improved long-term clinical outcomes compared to SES through 4 years ($P_{sup}$ = 0.050)
- Biodegradable polymer BES demonstrated a 80% 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
- The LEADERS trial provides the 1st evidence of improved clinical outcomes versus the gold standard 1st generation SES
- These findings provide the basis for the proof of concept of biodegradable polymer DES

Embargo: Nov 9, 2011—**02.00** (GMT)

THE LANCET

# Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised non-inferiority trial

*Giulio G Stefanini*, Bindu Kalesan*, Patrick W Serruys, Dik Heg, Pawel Buszman, Axel Linke, Thomas Ischinger, Volker Klauss, Franz Eberli, William Wijns, Marie-Claude Morice, Carlo Di Mario, Roberto Corti, Diethmar Antoni, Hae Y Sohn, Pedro Eerdmans, Gerrit-Anne van Es, Bernhard Meier, Stephan Windecker, Peter Jüni*

## Summary

**Background** The effectiveness of durable polymer drug-eluting stents comes at the expense of delayed arterial healing and subsequent late adverse events such as stent thrombosis (ST). We report the 4 year follow-up of an assessment of biodegradable polymer-based drug-eluting stents, which aim to improve safety by avoiding the persistent inflammatory stimulus of durable polymers.

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See Online/Comment