Late Catch-up after SES Implantation

Late Restenosis & Clinical Event Catch-up in the Long-term Follow-up

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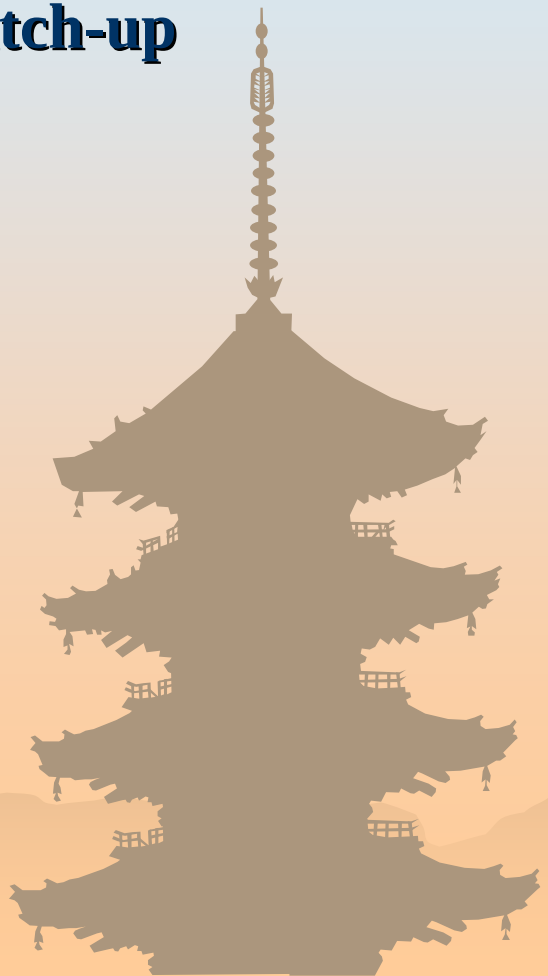


JCR 2010, Korea, Busan.

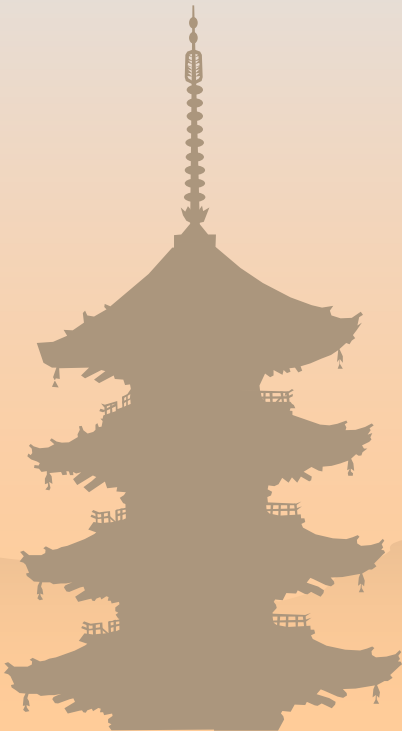
Introduction

- It yet has not been clarified whether there is a late catch-up phenomenon in terms of TLR after SES relative to BMS implantation.

- There is not a large scale study demonstrating the existence of “a late catch-up phenomenon” after SES as compared with BMS.

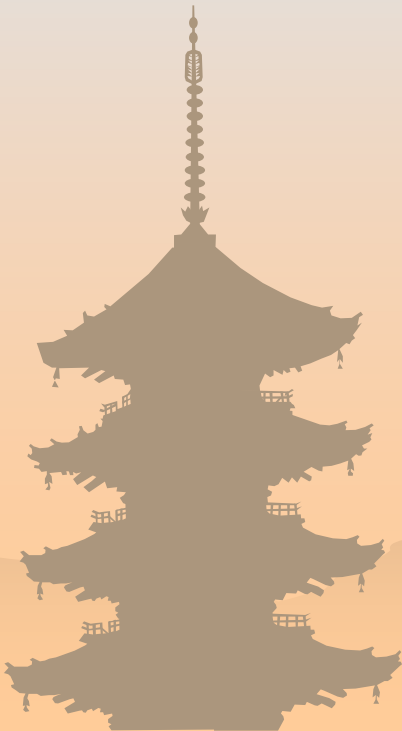
Methods

- **To evaluate the incidence and the risk factors of late TLR after SES in comparison with BMS, 3-year data of the j-Cypher Registry were examined.**



Study Population

- Design of this registry was multi-center prospective enrollment of consecutive patients for real world clinical entity.
- Between August 2004 and November 2006, 12,824 patients with 19,675 lesions were enrolled in the registry.
- These 2 groups constituted the study population.
  - SES group
    - 17,050 lesions treated exclusively with SES
  - BMS group
    - 1,259 lesions treated exclusively with BMS.



The j-Cypher Registry Investigators

Shin Koga Hospital
Shinbeppu Hospital
Sendai Kousei Hospital
Akane Foundation Tsuchiya General Hospital
Teikyo University Hospital
Tokushima Red Cross Hospital
Tominaga Hospital
National Toyohashi Higashi Hospital
Nanpuh Hospital
University Hospital of Fukuoka
Fukuyama Cardiovascular Hospital
Fujita Health University The 2nd Hospital
Hokuto Cardiovascular Hospital
Hokkko Memorial Hospital
Maizuru Kyosai Hospital
Matsue Red Cross Hospital
Mie Heart Center
Miyazaki Medical Association Hospital
Japanese Red Cross Society Wakayama Medical Center
Yamaguchi University Hospital
Ehime pref. Central Hospital
Ogaki Municipal Hospital
Osaka City General Hospital
Osaka Red Cross Hospital
Osaka Saiseikai Noe Hospital
Kanazawa Cardiovascular Hospital
Syonan Kamakura General Hospital
Kawasaki Social Insurance Hospital
Kishiwada Tokusyukai Hospital
Kyusyu Cardiovascular Center
Kyoto University Hospital
Kyoto Second Red Cross Hospital
Kurashiki Central Hospital
Gunma Cardiovascular Center
Noto General Hospital
Kokura Memorial Hospital
National Cardiovascular Center
Saiseikai Kumamoto Hospital
Saitama Cardiovascular And Respiratory Center
Shizuoka General Hospital

Baseline Patient Characteristics Compared Between SES-treated and BMS-treated Lesions

Variables	SES	BMS	p value
Number of lesions	17050	1259	
Patient factor			
Age ≥ 80	2294 (13%)	215 (17%)	0.0005
Male gender	12797 (75%)	948 (75%)	0.85
Multivessel disease	10703 (63%)	1121 (89%)	<0.0001
Ejection fraction ≤ 40%	1773 (12%)	129 (13%)	0.2
ESRD (eGFR < 30 and/or HD)	1837 (11%)	114 (9%)	0.051
Hemodialysis	922 (5.4%)	47 (3.7%)	0.072
Diabetes	7259 (43%)	540 (43%)	0.83

Baseline Lesion Characteristics Compared Between SES-treated and BMS-treated Lesions

Variables	SES	BMS	p value
Number of lesions	17050	1259	
Emergent procedure	1633 (9.6%)	619 (49%)	<0.0001
STEMI culprit lesion	817 (4.8%)	438 (35%)	<0.0001
Unprotected LMCA	480 (2.8%)	47 (3.7%)	0.071
Chronic total occlusion	1469 (8.6%)	53 (4.2%)	<0.0001
In-stent restenosis	2036 (12%)	16 (1.3%)	<0.0001
Severe calcification	1499 (8.8%)	91 (7.2%)	0.051
Vessel size < 2.5mm	4841 (29%)	290 (25%)	0.0099
Lesion length ≥ 30mm	2643 (15%)	93 (8.3%)	<0.0001
AHA/ACC B2/C	11150 (68%)	878 (73%)	<0.0001
Bifurcation	3289 (19%)	129 (10%)	<0.0001
Two stents for bifurcation	578 (3.4%)	22 (1.8%)	0.0006

The reason why we did not make any statistical adjustment.

- This j-Cypher registry was basically designed to enroll SES implantation.
- A profound selection bias for use of BMS in this cohort.
- The number of the BMS-treated lesions was small.

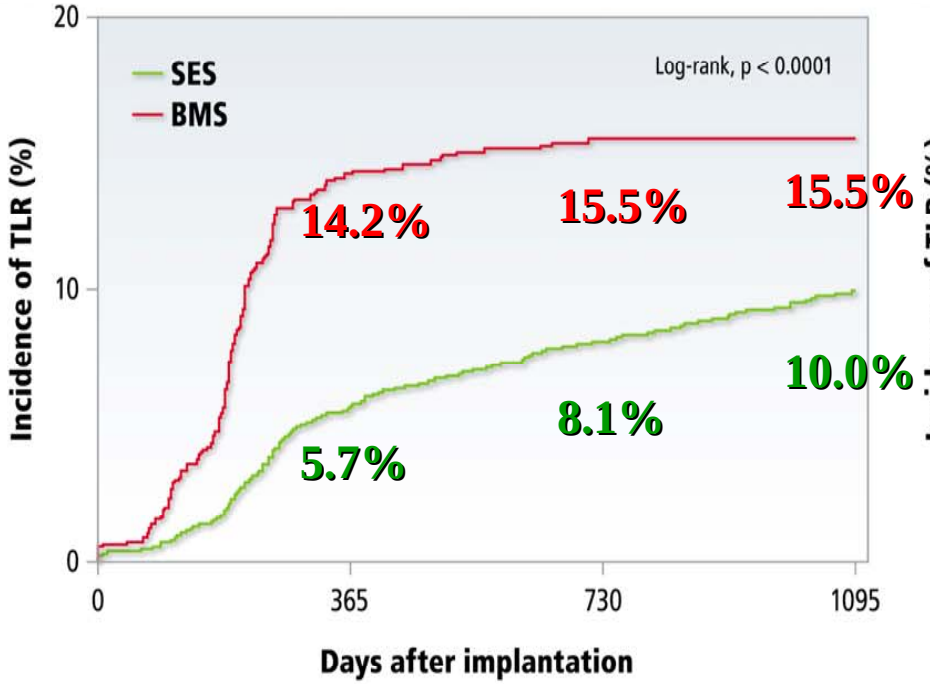
- We considered that application of the standard statistical methods to adjust the differences in baseline characteristics is flawed in this situation.

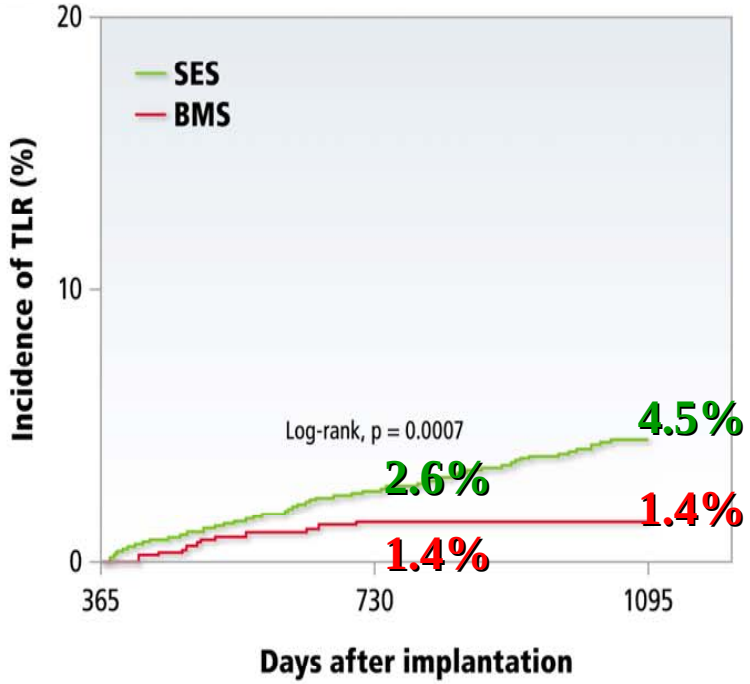
Definitions for TLR

- **TLR was defined as re-treatment (either PCI or CABG).**

- **TLR procedures were divided into**
  - **early TLR within the first year**
  - **late TLR beyond 1 year after the index procedure**

Overall incidence of TLR and incidence of late TLR compared between SES-treated and BMS-treated lesions.





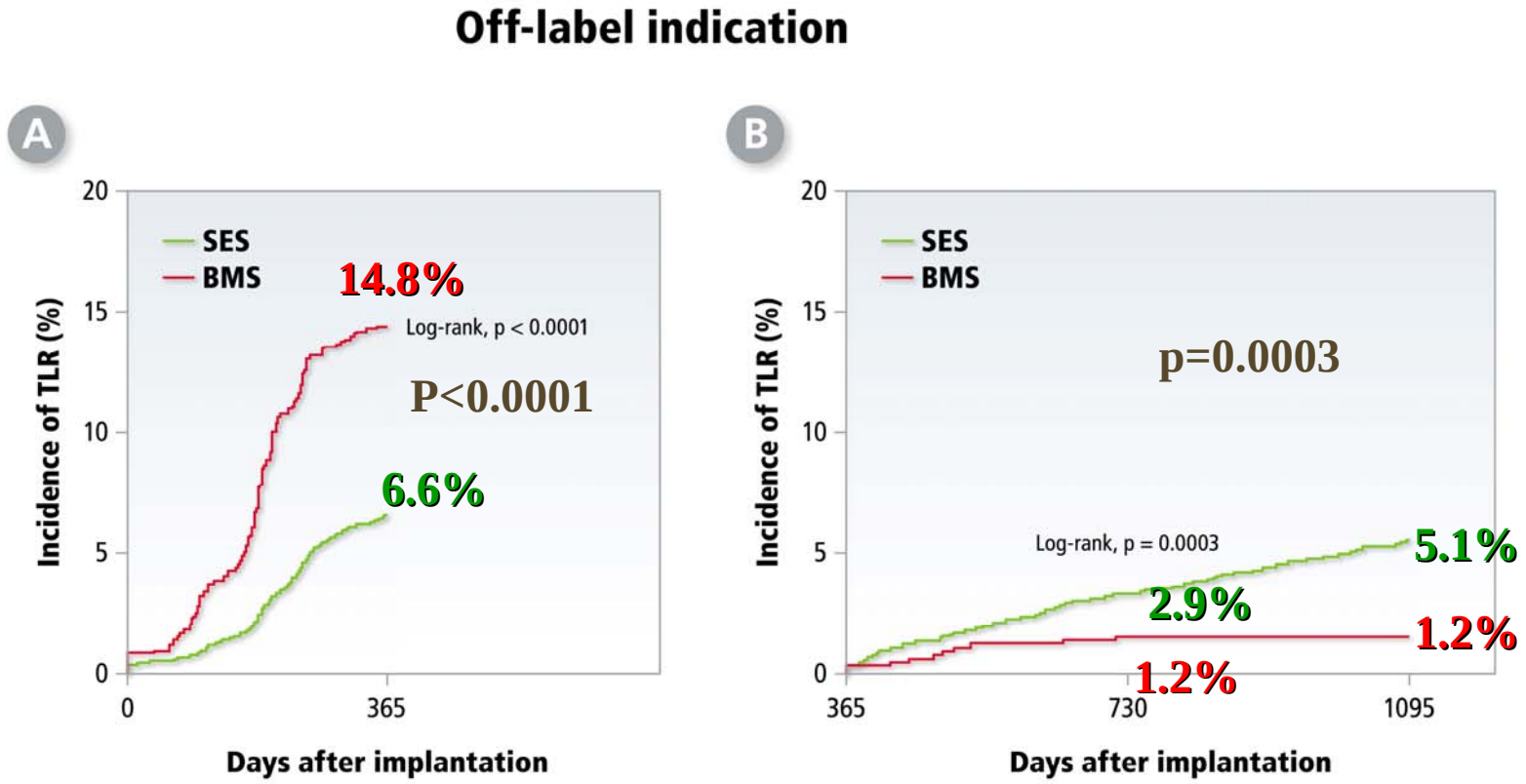
Days after implantation	0	365	730	1095	365	730	1095
Incidence of TLR							
SES	0%	5.7%	8.1%	10.0%	0%	2.6%	4.5%
BMS	0%	14.2%	15.5%	15.5%	0%	1.4%	1.4%

Nakagawa Y, et al. Am J Cardiol in Press, available online 21 June 2010

Definitions for On-label and Off-label

- On-label use was defined according to the entry criteria of SIRIUS trial.
- Lesions with on-label indication were defined as
  - *de-novo* lesions
  - < 30 mm in length
  - 2.5 to 3.5 mm in diameter
  - culprit lesions of recent myocardial infarction
  - ostial lesion
  - bifurcation lesion
  - thrombus containing lesion
  - severely calcified lesion
- The latter excluded lesions and all other lesions were classified as lesions with off-label indication.

Incidence of early and late TLR in the off-label lesions.



Days after implantation	0	365	365	730	1095
Incidence of TLR					
SES	0%	6.6%	0%	2.9%	5.1%
BMS	0%	14.8%	0%	1.2%	1.2%

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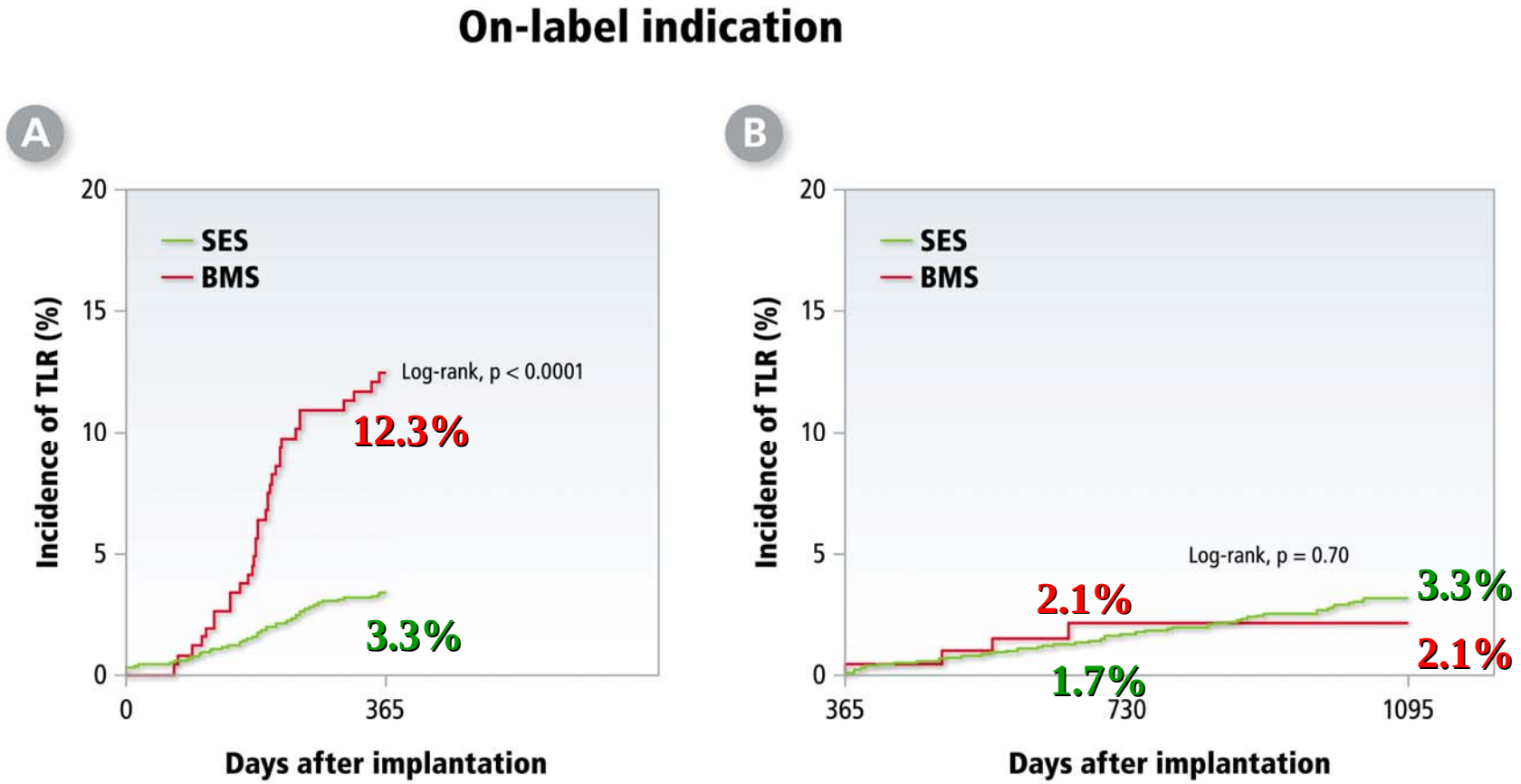
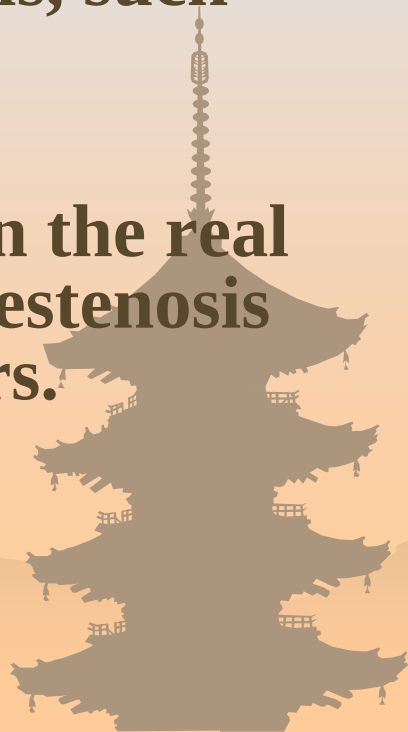
Incidence of early and late TLR in the on-label lesions.



Days after implantation	0	365	365	730	1095
Incidence of TLR					
SES	0%	3.3%	0%	1.7%	3.3%
BMS	0%	12.3%	0%	2.1%	2.1%

Nakagawa Y, et al. Am J Cardiol in Press, available online 21 June 2010

- **In lesions with on-label indications, the late catch-up phenomenon was not evident.**
- **This result could explain that the late catch-up phenomenon was not apparent in the long-term follow-up data of pivotal randomized trials, such as RAVEL and SIRIUS.**
- **In the whole spectrum of lesions treated in the real world, the efficacy of SES in preventing restenosis was considered to be maintained at 3 years.**



Risk Factors of Early TLR by Univariate and Multivariate Analysis

Variables	Uni				Multi	
	Incidence of TLR (%)					
	Yes	No	0dds ratio	p value	0dds ratio	p value
Male gender	6.1	5.1	1.22	0.012	1.25	0.019
Body mass index < 25	6.3	5.2	1.20	0.0081	1.20	0.029
Hemodialysis	20.1	5.2	3.89	<0.0001	3.01	<0.0001
Diabetes	7.6	4.6	1.64	<0.0001	1.41	<0.0001
Ostial RCA	17.9	5.6	3.20	<0.0001	2.82	<0.0001
In-stent restenosis	9.1	5.4	1.67	<0.0001	1.75	<0.0001
Severe calcification	12.7	5.2	2.43	<0.0001	1.73	<0.0001
Lesion length ≥ 30mm	11.0	5.0	2.18	<0.0001	2.01	<0.0001
AHA/ACC B2/C	7.2	3.3	2.20	<0.0001	1.51	<0.0001
Two stents for bifurcation	16.5	5.5	3.00	<0.0001	3.30	<0.0001

Risk Factors of Late TLR by Univariate and Multivariate Analysis

	Uni				Multi	
	Incidence of TLR (%)					
Variables	Yes	No	0dds ratio	p value	0dds ratio	p value
ESRD (eGFR < 30 and/or HD)	18.4	7.9	2.32	<0.0001	1.55	0.0336
Hemodialysis	25.7	8.1	3.16	<0.0001	3.75	<0.0001
Ostial RCA	15.9	8.5	1.87	0.003	1.85	0.0137
Vessel size < 2.5mm	10.0	8.2	1.22	0.0384	1.35	0.0049
Lesion length ≥ 30mm	14.5	7.8	1.86	<0.0001	1.79	<0.0001
AHA/ACC B2/C	10.2	5.6	1.82	<0.0001	1.56	0.0002
Two stents for bifurcation	14.2	8.5	1.67	0.0073	1.64	0.0262

Risk Factors of Late TLR by Univariate and Multivariate Analysis

Variables	Uni				Multi	
	Incidence of TLR (%)					
	Yes	No	0dds ratio	p value	0dds ratio	p value
ESRD (eGFR < 30 and/or HD)	18.4	7.9	2.32	<0.0001	1.55	0.0336
Hemodialysis	25.7	8.1	3.16	<0.0001	3.75	<0.0001
Ostial RCA	15.9	8.5	1.87	0.003	1.85	0.0137
Vessel size < 2.5mm	10.0	8.2	1.22	0.0384	1.35	0.0049
Lesion length ≥ 30mm	14.5	7.8	1.86	<0.0001	1.79	<0.0001
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Two stents for bifurcation	14.2	8.5	1.67	0.0073	1.64	0.0262

Study Limitation

- **Although patients and lesion characteristics were significantly different between lesions treated with SES and BMS, we did not correct the background factors.**
- **However, because the cumulative incidence curves of TLR after SES and BMS implantation separated in opposite directions before and after 1 year, existence of the late catch-up phenomenon seemed to be robust even without statistical adjustment.**

Late Progression After Sirolimus-Eluting Stent Implantation for de Novo Lesions

– Comparison With Bare Metal Stent Implantation –

Nobuo Shiode, MD; Kinya Shirota, MD; Fumiyo Tsunoda, MD;
Yasuko Kato, MD; Mai Fujiwara, MD; Asao Mimura, MD

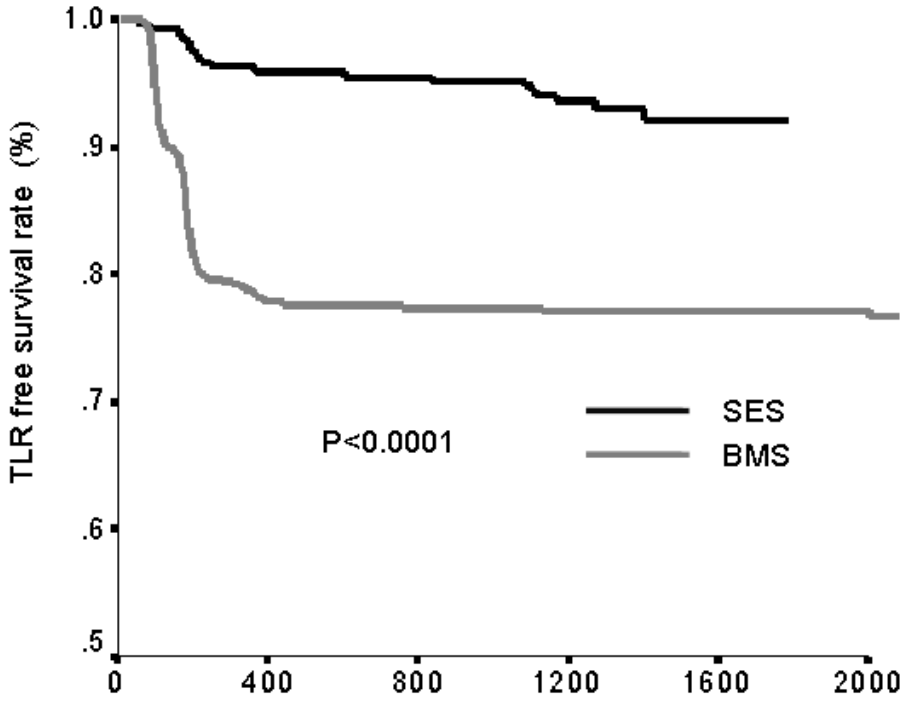
Background: In previous studies, the minimal luminal diameter (MLD) of lesions treated with a bare metal stent (BMS) was shown to improve from 6 months to 3 years. However, the long-term response to a sirolimus-eluting stent (SES) implantation remains unclear.

Methods and Results: To evaluate 6-month, 12-month and 3-year outcomes, clinical and angiographic follow-up data were analyzed for 367 consecutive patients (506 de novo lesions) who underwent successful SES implantation compared to follow-up data for 617 consecutive patients (802 de novo lesions) who underwent BMS implantation. Clinical follow-up information was obtained for 363 SES-treated patients (98.9%) and 581 BMS-treated patients (94.2%) at 1 year, and 334 SES-treated patients (91.0%) and 566 BMS-treated patients (91.7%) at 3 years. At 3 years, there were no significant differences in the cumulative cardiac death and myocardial infarction. Target lesion revascularization (TLR) rates were significantly higher in BMS-treated patients than in SES-treated patients. In BMS-treated patients, most TLR was performed within 450 days, however, after 450 days, the TLR rate was significantly lower than that for the SES-treated patients. In quantitative coronary angiographic data, among lesions that required no revascularization at the initial 12-month follow up, MLD increased significantly from the 12-month to the 3-year follow-up angiography in BMS-treated lesions. However, MLD decreased significantly in SES-treated lesions.

Conclusions: From a 12-month follow-up to a 3-year follow-up, stenosis in BMS-treated lesions regressed, but stenosis in SES-treated lesions progressed. And late TLR was more frequently required in the SES-treated patients.
(*Circ J* 2010; **74:** 1104 – 1110)

Shiode N, et al. Circ J 2010, 74: 1104-1110.

TLR-free survival curves in comparison SES and BMS.

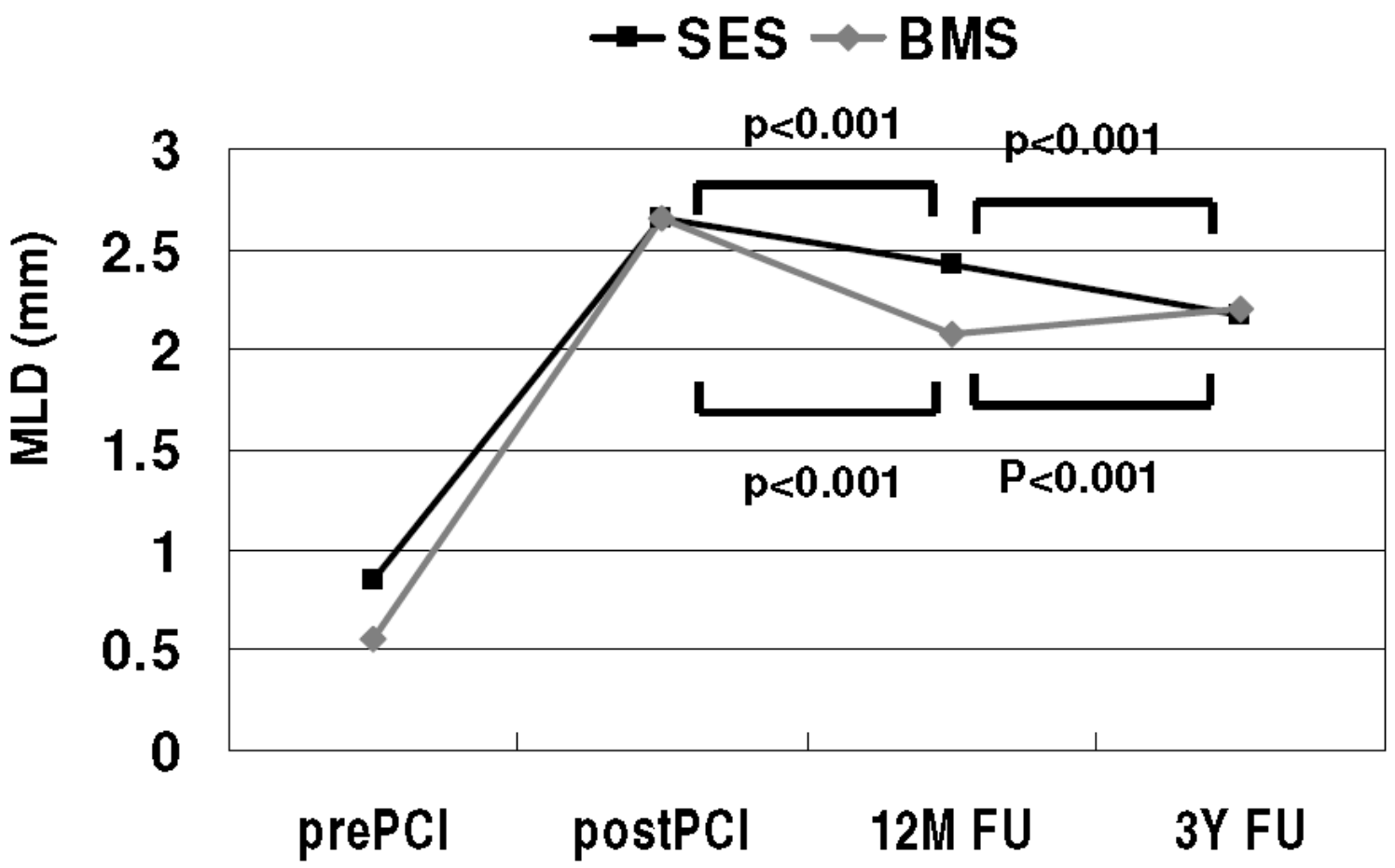


patients at risk					
SES	366	325	296	189	38
BMS	615	400	360	323	276

Shiode N, et al. Circ J 2010, 74: 1104-1110.

Change of MLD at 12-month and 3-year F/U in comparison SES and BMS

Change of MLD 1-3 years, among lesions that required no TLR



Shiode N, et al. Circ J 2010, 74: 1104-1110.

Speculative Mechanisms of the Late Catch-up Phenomenon

- Some smooth muscle cells at stent-implanted sites are not entirely exposed to the drug.

  The cells which fail to stay in contact with the drug may not be inhibited, thus inducing their proliferation.

  A larger period of time is required for such a lesion to advance and become apparent as restenosis requiring TLR.
- Another possible cause
  - Long-term inflammation
  - New atheroma formation within the stent
  - Progressive atherosclerosis at margins
  - Tissue growth at the site of stent fracture
  - Very late stent thrombosis

Conclusion

1. A late catch-up phenomenon was observed as indicated by the increasing incidence of late TLR after SES implantation, but not after BMS implantation.
2. The independent predictors for late TLR were generally common to those for early TLR.
3. Longer-term follow-up studies are necessary to evaluate the real clinical significance of this phenomenon.
4. Investigation on the mechanisms of the late catch-up phenomenon might lead to future development of an improved DES.