Antiplatelet Therapy and Stent Thrombosis
Lessons from j-Cypher and RESTART

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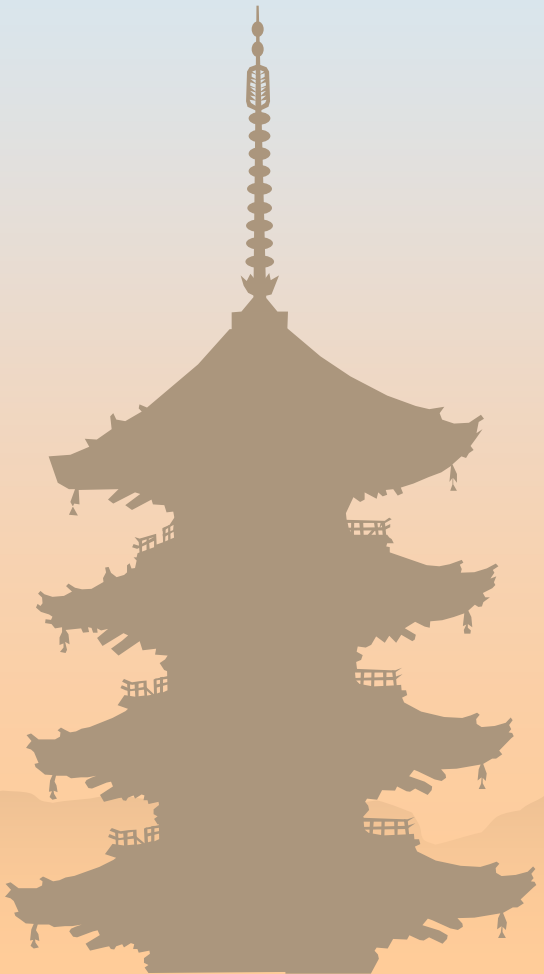

JCR 2010, Korea, Busan.

The j-Cypher Registry

Antiplatelet Therapy and Stent Thrombosis After Sirolimus-Eluting Stent Implantation

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Background—The influences of antiplatelet therapy discontinuation on the risk of stent thrombosis and long-term clinical outcomes after drug-eluting stent implantation have not yet been addressed adequately.

Methods and Results—In an observational study in Japan, 2-year outcomes were assessed in 10 778 patients undergoing sirolimus-eluting stent implantation. Data on status of antiplatelet therapy during follow-up were collected prospectively. Incidences of definite stent thrombosis were 0.34% at 30 days, 0.54% at 1 year, and 0.77% at 2 years. Thienopyridine use was maintained in 97%, 62%, and 50% of patients at 30 days, 1 year, and 2 years, respectively. Patients who discontinued both thienopyridine and aspirin had a significantly higher rate of stent thrombosis than those who continued both in the intervals of 31 to 180 days, 181 to 365 days, and 366 to 548 days after stent implantation (1.76% versus 0.1%, $P<0.001$; 0.72% versus 0.07%, $P=0.02$; and 2.1% versus 0.14%, $P=0.004$, respectively). When discontinuation of aspirin was taken into account, patients who discontinued thienopyridine only did not have an excess of stent thrombosis in any of the time intervals studied. Adjusted rates of death or myocardial infarction at 24 months were 4.1% for patients taking thienopyridine and 4.1% for patients not taking thienopyridine ($P=0.99$) in the 6-month landmark analysis.

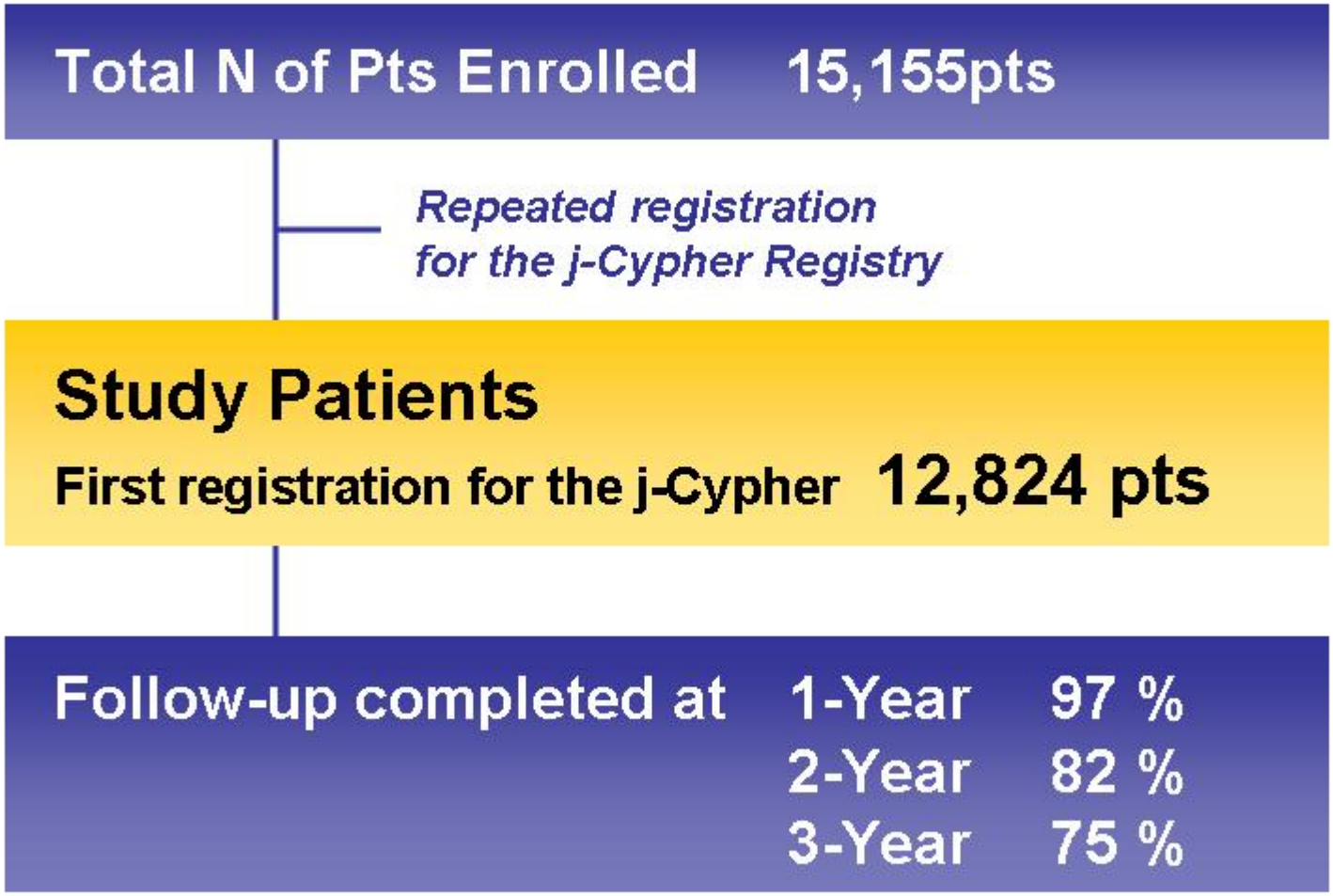
Conclusions—Discontinuation of both thienopyridine and aspirin, but not discontinuation of thienopyridine therapy only, was associated with an increased risk of stent thrombosis. Landmark analysis did not suggest an apparent clinical benefit of thienopyridine use beyond 6 months after sirolimus-eluting stent implantation. **(*Circulation*. 2009;119:987-995.)**

Key Words: aspirin ■ follow-up studies ■ stents ■ coronary disease ■ thrombosis

Circulation. 2009;119:987-995

Study Patients for the Current Analysis

J-CYPHER Registry



- Design of this registry was multi-center prospective enrollment of consecutive patients for real world clinical entity.

Pattern of Stent Use

Study Lesions 19,675 lesions

- *GW/Balloon Failure* — *139 lesions*
- *Non-stent PCI Alone* — *650 lesions*

Attempt of Deploying Stents 18,886 lesions

- *BMS and/or Other DES* — *1300 lesions*
- *Delivery failure* — *2 lesions*

Attempt of Deploying SES 17,584 lesions

- *BMS and/or Other DES* — *9 lesions*
- *Delivery failure* — *20 lesions*

Successful Deployment of SES 17,545 lesions (99.8%)

- *Combined with Other Stent Types* — *495 lesions*

Treated Exclusively by SES 17,050 lesions

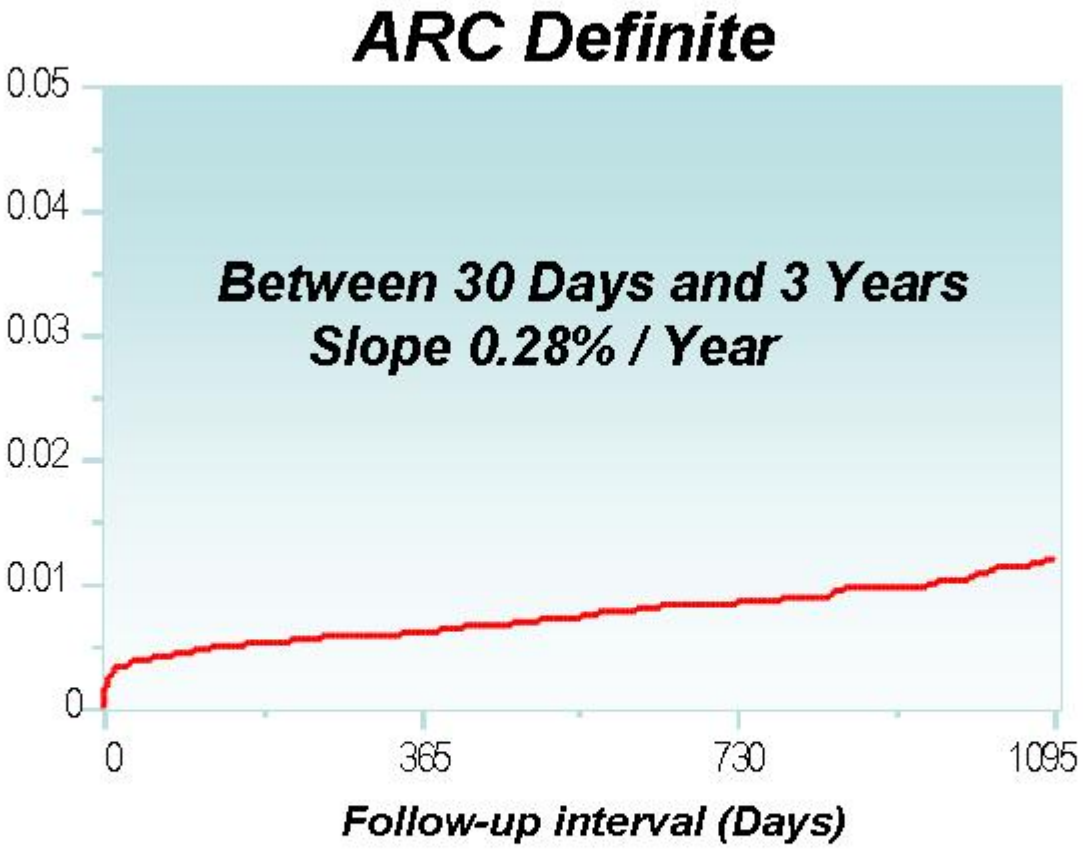
Baseline Characteristics

	N=12,824
Age (years)	68.4 ± 10.3
≥ 80 y.o.	13 %
Male	75 %
Diabetes	41 %
Insulin use	9 %
Renal failure (e-GFR< 30ml/min, Non-HD)	5 %
Hemodialysis	5 %
Stroke	9 %
Peripheral vascular disease	12 %

Lesion Characteristics

	N= 19,675	
STEMI culprit lesion	1,321 lesions	(7%)
In-stent restenosis	2,198 lesions	(11%)
CTO	1,796 lesions	(9%)
Vessel size < 2.5mm	5,748 lesions	(30%)
Lesion length $\geq$ 30mm	2,833 lesions	(15%)
Heavily calcified lesion	1,789 lesions	(9%)
Bifurcation	3,716 lesions	(19%)
Final 2 stent approach	757 lesions	(4%)

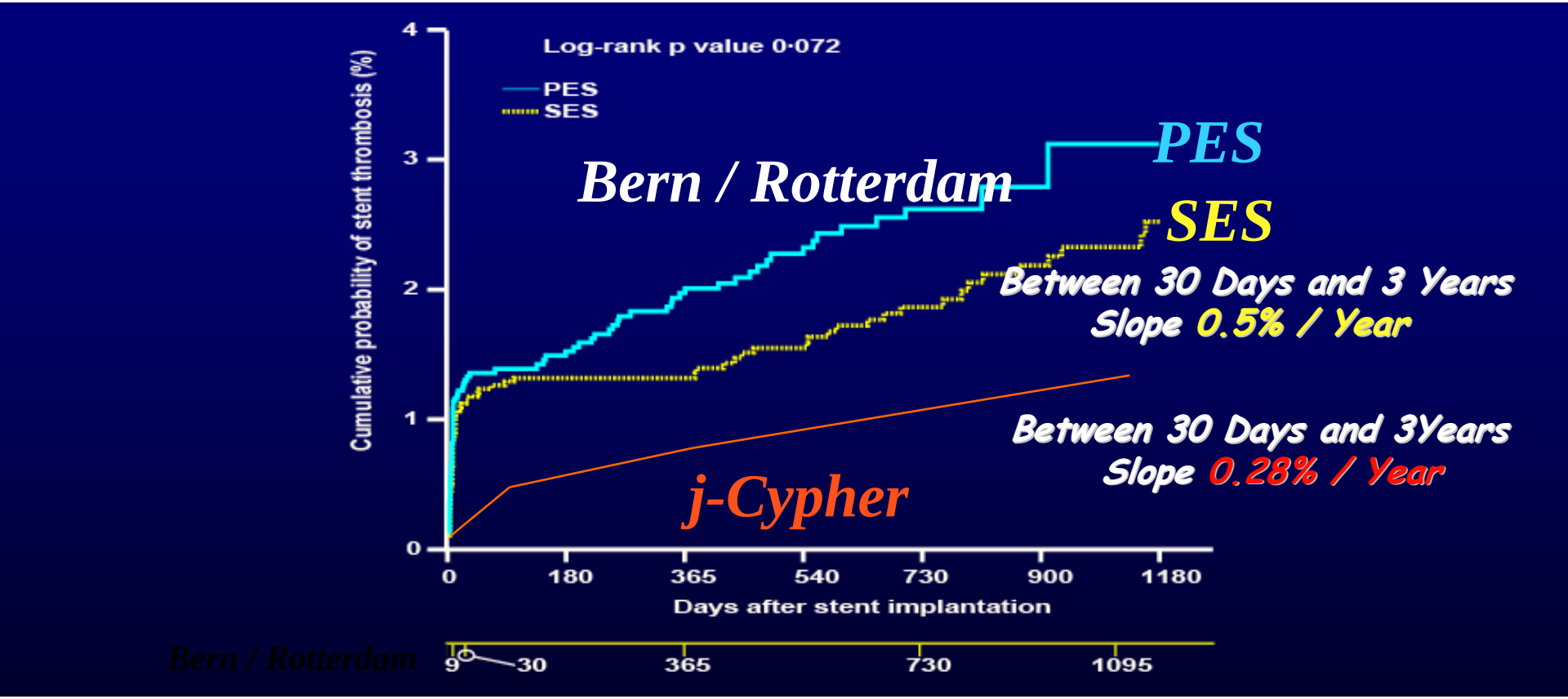
Stent Thrombosis



		30 Days	1 Yr.	2 Yrs.	3 Yrs.
Cumulative incidences		0.36%	0.61%	0.84%	1.18%
n of pts at risk	12,824	12,625	11,843	9,036	4,191

Events: Not yet fully adjudicated

Definite Stent Thrombosis: Bern/Rotterdam vs j-Cypher



Incidence, PES (%)	1.2	1.3	2.0	2.7	3.2
Patients at risk (n)	3626	3493	2667	1131	68

Incidence, SES (%)	1.0	1.1	1.3	1.9	2.5
Patients at Risk (n)	3535	3508	2671	1710	903

j-Cypher

Cumulative Incidence (%)	0.3	0.4	0.6	0.8
Patients at Risk (n)	12447	12355	10889	3923

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

Predictors of Early ST

Univariate analysis

Early ST in 43 lesions among 17050 lesions treated exclusively by Cypher

Variables	Present		Absent		P Value
	N	Incidence	N	Incidence	
Hemodialysis	922	0.45%	16,128	0.24%	0.25
Two stents for bifurcation	578	0.52%	16,463	0.24%	0.19
Ostial RCA	397	0.25%	16,623	0.25%	1.0
Diabetes (Insulin)	1,710	0.35%	15,340	0.24%	0.39
Lesion length $\geq$ 30mm	2,463	0.24%	14,375	0.25%	0.95
In-stent restenosis	2,036	0.2%	15,009	0.26%	0.59
Diabetes	7,259	0.28%	9,791	0.24%	0.6
Bifurcation	3,289	0.24%	13,755	0.26%	0.91
Multivessel CAD	10,703	0.23%	6,347	0.3%	0.34
CTO	1,469	0.14%	15,546	0.26%	0.35
Unprotected LMCA	483	0.21%	16,567	0.25%	0.84
Ostial CX	120	0.83%	16,900	0.25%	0.2
LVEF $\leq$ 40%	1,773	0.46%	13,002	0.22%	0.07

Predictors of Early ST

Univariate analysis

Early ST in 43 lesions among 17,050 lesions treated exclusively by Cypher

Variables	Present		Absent		P Value
	N	Incidence	N	Incidence	
Age ≥ 80	2,294	0.13%	14,756	0.27%	0.22
Male gender	12,797	0.29%	4,253	0.14%	0.1
Vessel size < 2.5mm	4,841	0.25%	12,012	0.25%	0.99
ESRD (e-GFR < 30/Non-HD)	915	0 %	16,132	0.27%	0.12
STEMI	817	0.99%	16,233	0.22%	0.0001
Ostial LAD	482	0 %	16,538	0.26%	0.26
Emergency procedure (ACS)	1,633	0.87%	15,417	0.19%	0.0001
IVUS use	7,569	0.29%	9,428	0.22%	0.38

Predictors of Early ST

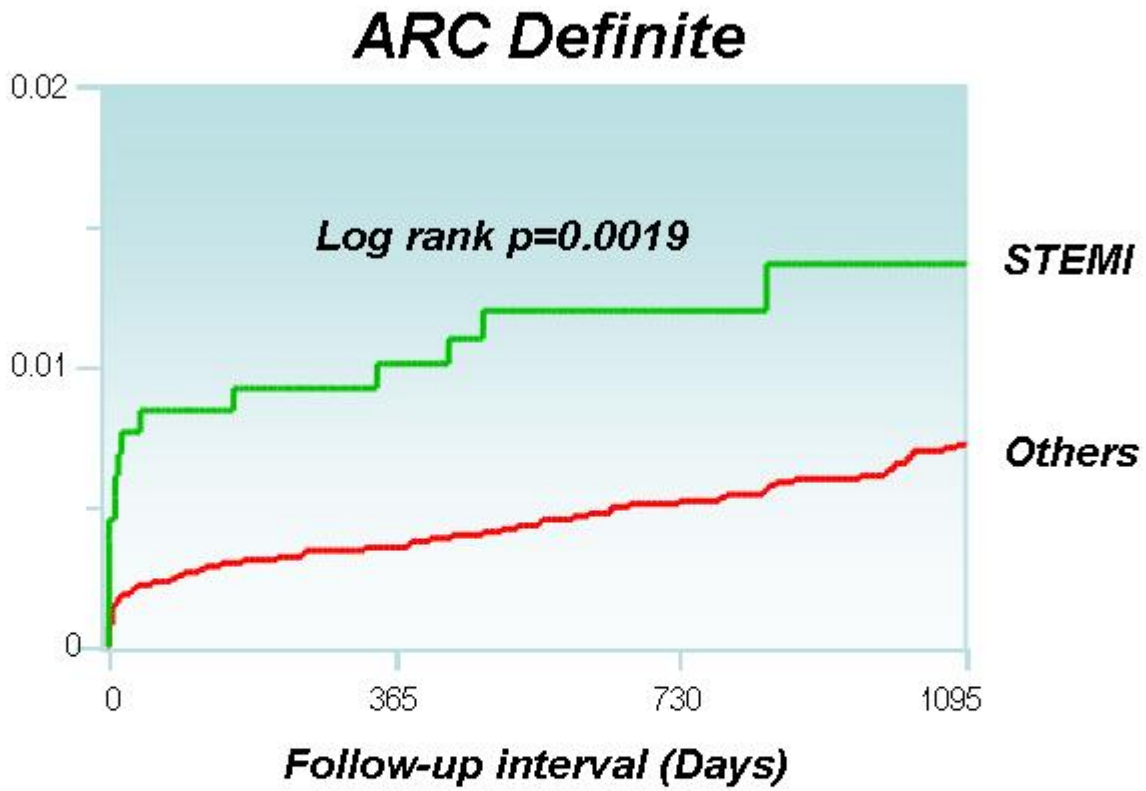
Multivariable analysis

Early ST in 43 lesions among 17,050 lesions treated exclusively by Cypher

Factors	R.R.	95%C.I.	P Value
Emergency procedure (ACS)	1.88	(1.13 - 2.9)	0.02
Male gender	1.45	(0.95 - 2.49)	0.09
LVEF $\leq$ 40%	1.29	(0.84 - 1.87)	0.23

Those variables with p value <0.1 in the univariable analysis were incorporated into the multivariable model. STEMI was excided from the final model.

Stent Thrombosis in STEMI



		30 Days	1 Yr.	2 Yrs.	3 Yrs
STEMI		0.76%	1.01%	1.21%	1.37%
	1,321	1,269	1,149	831	342
Others		0.2%	0.36%	0.51%	0.73%
	18,354	18,108	17,013	13,013	6,001

Predictors of LST / VLST

Univariate analysis

LST / VLST in 67 lesions among 16,801 lesions treated exclusively by Cypher

Variables	Present		Absent		P Value
	N	Incidence	N	Incidence	
Hemodialysis	884	1.15%	15,917	0.53%	0.0003
Two stents for bifurcation	564	1.37%	16,228	0.54%	0.002
Ostial RCA	391	0.84%	16,381	0.56%	0.26
Diabetes (Insulin)	1,690	0.57%	15,111	0.57%	0.32
Lesion length $\geq$ 30mm	2,426	0.79%	14,166	0.54%	0.25
In-stent restenosis	2,017	0.69%	14,779	0.55%	0.39
Diabetes	7,144	0.54%	9,657	0.59%	0.71
Bifurcation	3,238	0.46%	13,557	0.6%	0.74
Multivessel CAD	10,527	0.58%	6,274	0.55%	0.76
CTO	1,452	0.83%	15,315	0.54%	0.17
Unprotected LMCA	469	0.67%	16,332	0.57%	0.39
Ostial CX	117	0.88%	16,655	0.57%	0.43
LVEF $\leq$ 40%	1,711	0.19%	12,861	0.58%	0.15

Study population: Those patients who were free from stent thrombosis at 30 days

Predictors of LST / VLST

Univariate analysis

LST / VLST in 67 lesions among 16801 lesions treated exclusively by Cypher

Variables	Present		Absent		P Value
	N	Incidence	N	Incidence	
Age ≥ 80	2,230	0.33%	14,571	0.6%	0.13
Male gender	12,627	0.63%	4,174	0.36%	0.2
Vessel size < 2.5mm	758	0.58%	11850	0.57%	0.4
ESRD (e-GFR < 30/Non-HD)	861	1.44%	15,937	0.53%	0.004
STEMI	779	0.44%	16,022	0.57%	0.62
Ostial LAD	469	0.28 %	16,303	0.58%	0.49
Emergency procedure (ACS)	1,559	0.29%	15,242	0.59%	0.23
IVUS use	7,461	0.55%	9,288	0.58%	0.75

Predictors of LST / VLST

Multivariable analysis

LST / VLST in 67 lesions among 16,801 lesions treated exclusively by Cypher

Factors	*R.R.*	*95%C.I.*	*P Value*
Hemodialysis	*1.91*	*(1.29 - 2.65)*	*0.002*
ESRD (e-GFR < 30/Non-HD)	*1.81*	*(1.2 - 2.65)*	*0.007*
Two stents for bifurcation	*1.81*	*(1.17 - 2.59)*	*0.01*

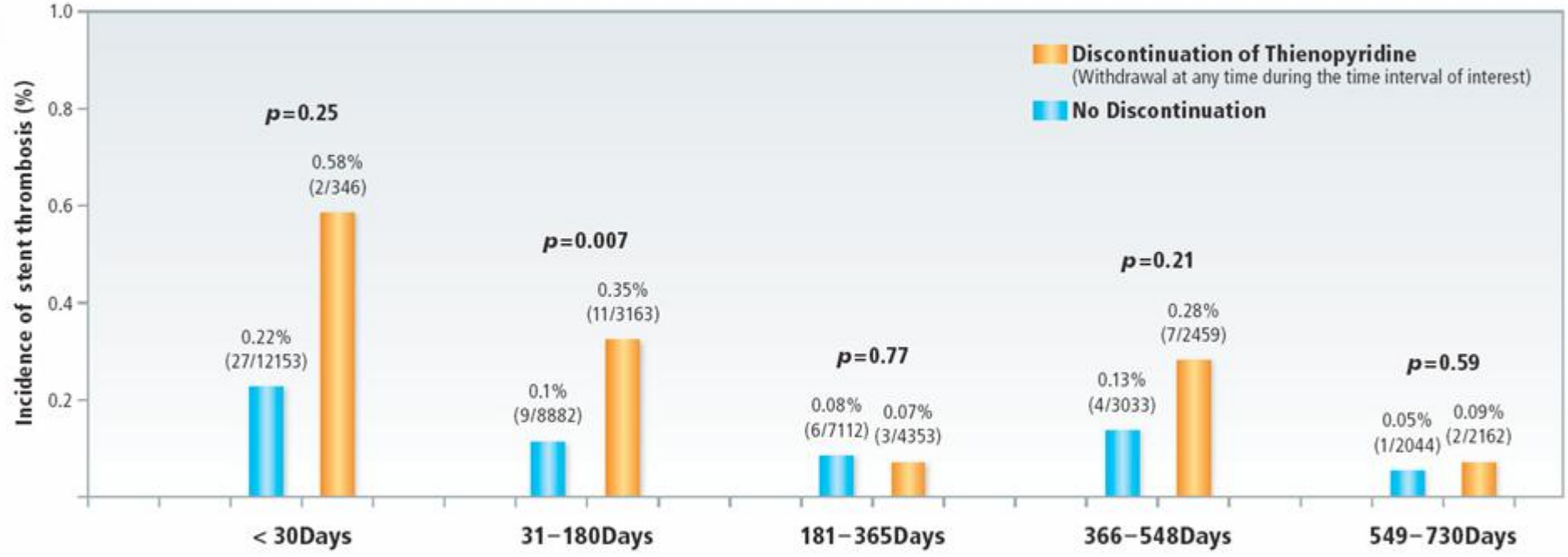
Those variables with p value < 0.1 in the univariable analysis were incorporated into the multivariable model.

Anti-platelet Therapy Discontinuation

J-CYPHER Registry

Stent Thrombosis and Discontinuation of Thienopyridine

Incidence of Definite Stent Thrombosis

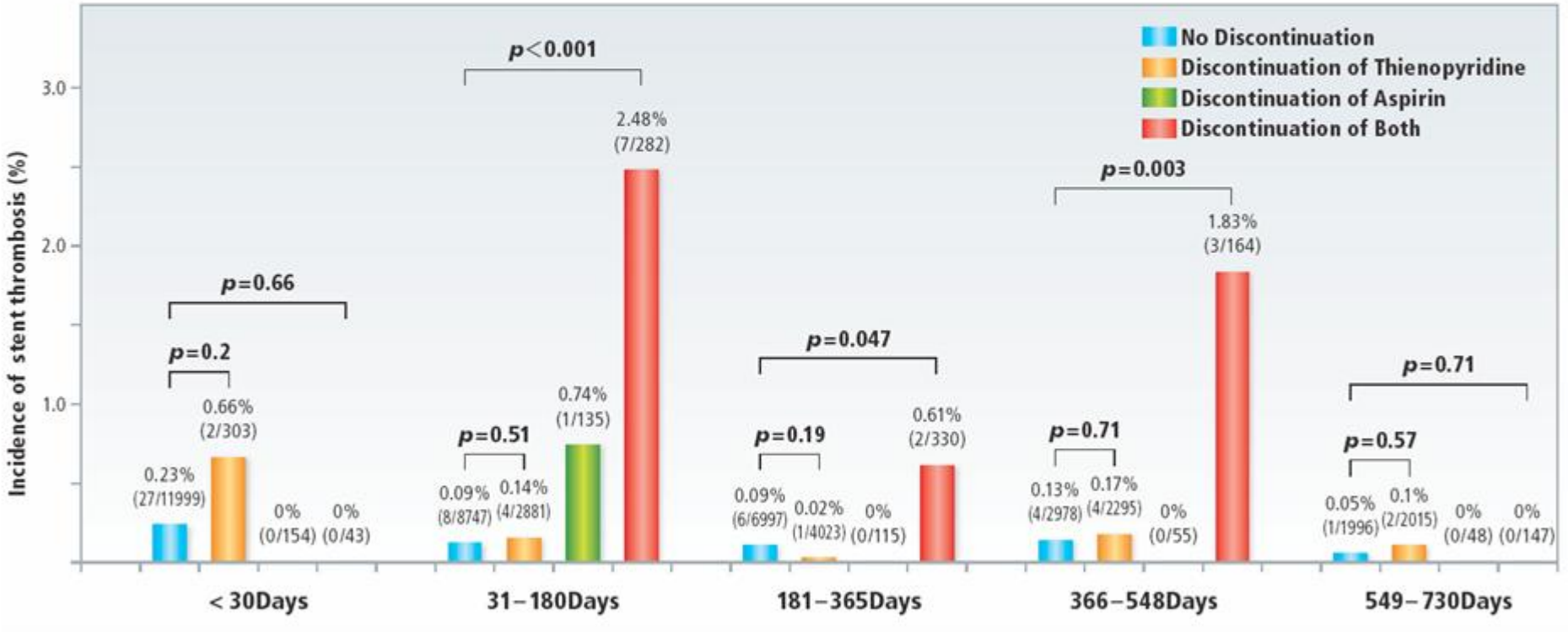


Anti-platelet Therapy Discontinuation

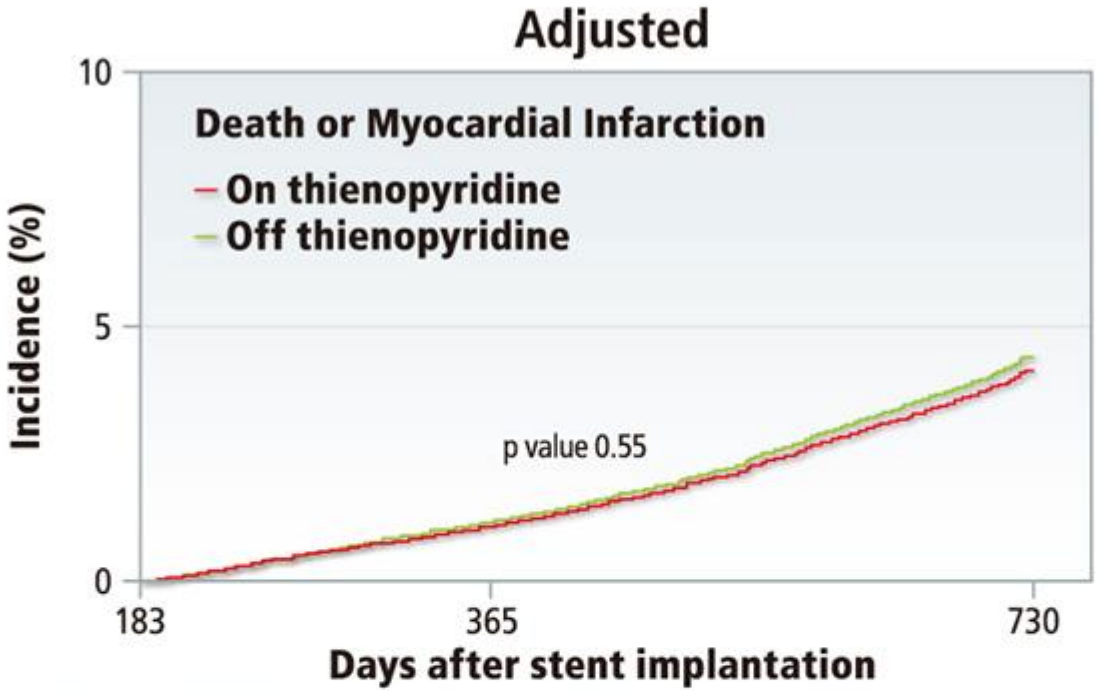
J-CYPHER Registry

Stent Thrombosis and Discontinuation of Aspirin and/or Thienopyridine

Incidence of Definite Stent Thrombosis



6-Month Landmark Analysis



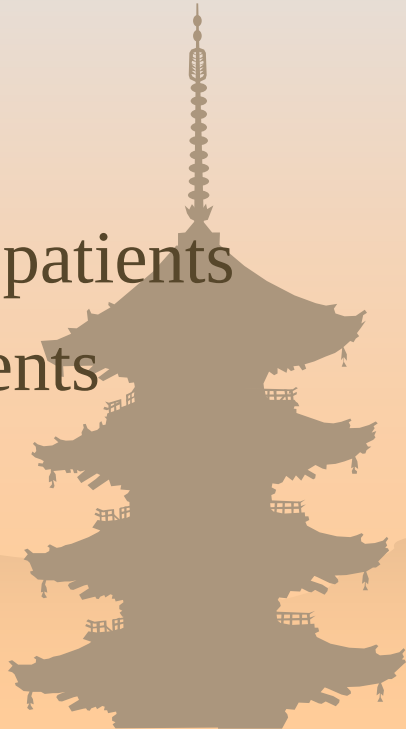
Days after stent implantation	183	365	730
Cumulative incidence, On thienopyridine		1.1%	4.2%
Cumulative incidence, Off thienopyridine		1.2%	4.5%

Inclusion criteria : Patients free from cardiovascular events (death/MI/Stroke/ST) and on aspirin at 6 months landmark

RESTART

- REgistry of Stent Thrombosis for review And Re-evaluaTion

- 611 patients with ARC-definite ST
  - Early within 30 days, EST: 322 patients
  - Late between 31 and 365 days, LST: 105 patients
  - Very late beyond 1 year, VLST: 184 patients



RESTART

Comparisons of Baseline Demographics, Clinical Presentation, and Long-Term Outcome Among Patients With Early, Late, and Very Late Stent Thrombosis of Sirolimus-Eluting Stents

Observations From the Registry of Stent Thrombosis for Review and Reevaluation (RESTART)

Takeshi Kimura, MD; Takeshi Morimoto, MD; Ken Kozuma, MD; Yasuhiro Honda, MD; Teruyoshi Kume, MD; Tadanori Aizawa, MD; Kazuaki Mitsudo, MD; Shunichi Miyazaki, MD; Tetsu Yamaguchi, MD; Emi Hiyoshi; Eizo Nishimura; Takaaki Isshiki, MD; for the RESTART Investigators

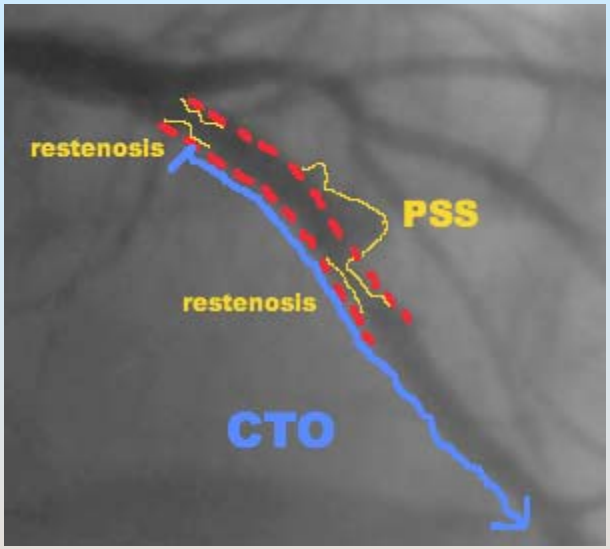
Background—Stent thrombosis (ST) after sirolimus-eluting stent implantation has not yet been adequately characterized, mainly because of its low incidence.

Methods and Results—The Registry of Stent Thrombosis for Review and Reevaluation (RESTART) is a Japanese nationwide registry of sirolimus-eluting stent–associated ST comprising 611 patients with definite ST (early [within 30 days; EST], 322 patients; late [between 31 and 365 days; LST], 105 patients; and very late [>1 year; VLST], 184 patients). Baseline demographics, clinical presentation, and long-term outcome of sirolimus-eluting stent–associated ST were compared among patients with EST, LST, and VLST. Baseline demographics were significantly different according to the timing of ST. Characteristic demographic factors for LST/VLST versus EST identified by multivariable model were hemodialysis, end-stage renal disease not on hemodialysis, absence of circumflex target, target of chronic total occlusion, prior percutaneous coronary intervention, and age <65 years. For LST versus VLST, they were hemodialysis, heart failure, insulin-dependent diabetes mellitus, and low body mass index. Patients with LST had a significantly higher rate of Thrombolysis in Myocardial Infarction grade 2/3 flow (36%) at the time of ST than those with EST (13%) ($P<0.0001$) and VLST (17%; $P<0.0001$). Mortality rate at 1 year after ST was significantly lower in patients with VLST (10.5%) compared with those with EST (22.4%; $P=0.003$) or LST (23.5%; $P=0.009$).

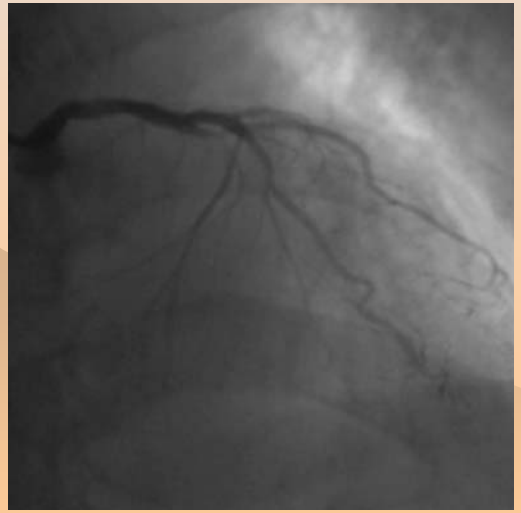
Conclusion—ST timing–dependent differences in baseline demographic features, Thrombolysis in Myocardial Infarction flow grade, and mortality rate suggest possible differences in the predominant pathophysiological mechanisms of ST according to timing after sirolimus-eluting stent implantation. (*Circulation*. **2010;122:52-61.**)

Circulation 2010;122:52-61

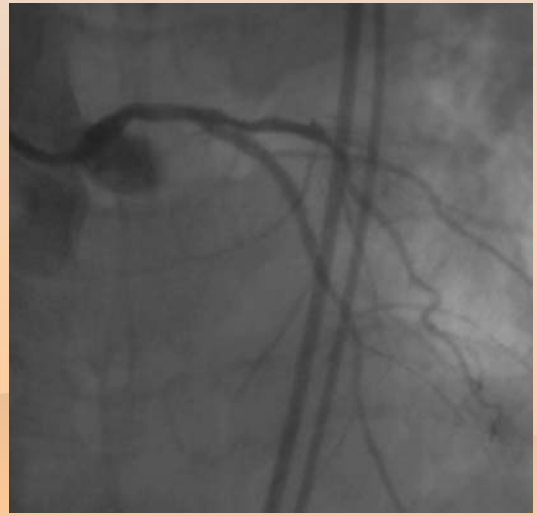
Peri-Stent contrast Staining(PSS)



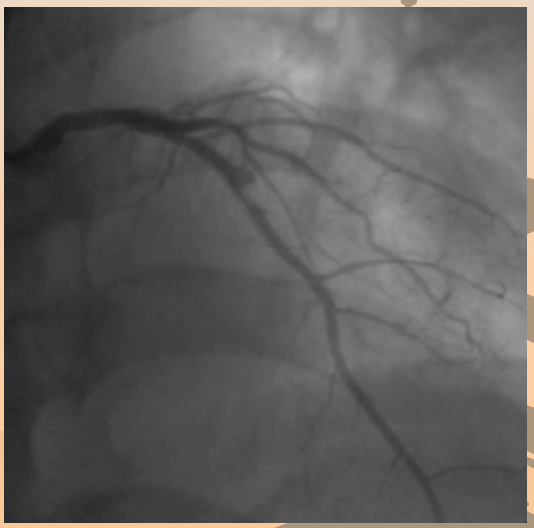
CTO



Immediately after PCI



2.5 years after



Late Aquired PSS at the timing of ST

According to the definition (>20% of the stent diameter at the site of PSS)

Summary

Three - year result from the j-Cypher registry suggests

1. *Stent thrombosis rate of SES at 1 year in the real world clinical practice in Japan was confirmed to be very low (0.6%) in a large scale multi-center registry with acceptable follow-up rate.*

2. *Very late stent thrombosis was confirmed to be a continuous hazard up to 3 years after SES implantation. However, the rate of late stent thrombosis up to 3 years seemed to be acceptably low (0.28% / year).*

Summary

Three - year result from the j-Cypher registry suggests

3. ***Regarding the predictors for stent thrombosis, only emergency procedure for ACS emerged as the independent predictor for early stent thrombosis.***
   Hemodialysis, pre-dialysis end-stage renal disease, and side branch stenting for bifurcation were identified to be the independent predictors for late or very late stent thrombosis.

Summary

Three - year result from the j-Cypher registry suggests

4. ***Analysis of the relation between discontinuation of anti-platelet therapy and ST in various time intervals after SES implantation suggested that discontinuation of both thienopyridine and aspirin, but not discontinuation of thienopyridine therapy only, was associated with an increased stent thrombosis risk.***

5. ***Landmark analysis did not suggest apparent clinical benefit of thieopyridine use beyond 6 months after sirolimus-eluting stent implantation.***