



RESTART
Registry of Stent Thrombosis for
review And Re-evaluation

Time Dependent Differences

**in the Demographics and Clinical Outcome of
Stent Thrombosis of Sirolimus-eluting Stent**

: Final result from the RESTART

(REgistry of Stent Thrombosis for review And Re-evaluaTion)

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Background



Although stent thrombosis (ST) is a dreaded complication of PCI using DES, ST has not been adequately characterized yet mainly due to its low prevalence. Previous studies reporting risk factors of ST were hampered by the small number of events analyzed in each study. Furthermore, no previous study evaluated the differences between late ST and very late ST in terms of baseline characteristics, clinical presentation and long-term outcome.

The current study was undertaken to characterize ST further according to the timing of ST in a large number of patients with ST after sirolimus-eluting stent (SES) implantation in the real world clinical practice in Japan.



Study Outline



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REgistry of ST-elevation Thrombolysis for
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- ▶ Retrospective large-scale observational study

- ▶ Study population
 - Patients with ARC Definite ST of SES

 - Cases reported to J&J before starting the current research
(May, 2004 - June, 2008)

 - Additional cases reported for the current research

- ▶ Participating centers:
 - 543 centers among 1335 Japanese PCI centers

 - representing 41% of all PCI centers and 56% of PCI cases in Japan

- ▶ Study period : Aug. - Dec. 2008



Study Population



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N of ST cases analyzed		611 cases
Angiographic confirmation		610 cases
Pathologic confirmation		5 cases
Early ST	(~30 days)	322 cases
Acute ST	(~24 hours)	52 cases
Subacute ST	(1~30 days)	270 cases
Late ST	(31~365 days)	105 cases
Very late ST	(366 days~)	184 cases



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Clinical Presentation of ST

	Early ST	Late ST	Very late ST	p value		
	N=322	N=105	N=184	EST vs. LST	EST vs. VLST	LST vs. VLST
Clinical presentation				0.1	0.18	0.4
STE-ACS	68%	64%	72%			
NSTE-ACS	21%	30%	23%			
Cardiac arrest	11%	6.0%	5.8%			
Multivessel ST	4.4%	1.0%	3.3%	0.06	0.55	0.19
ST related to surgery	2.8%	7.6%	6.0%	0.04	0.08	0.59
ST within 30 days after surgery	1.6%	7.6%	3.8%	0.004	0.12	0.17



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Initial TIMI Flow Grade at Time of ST

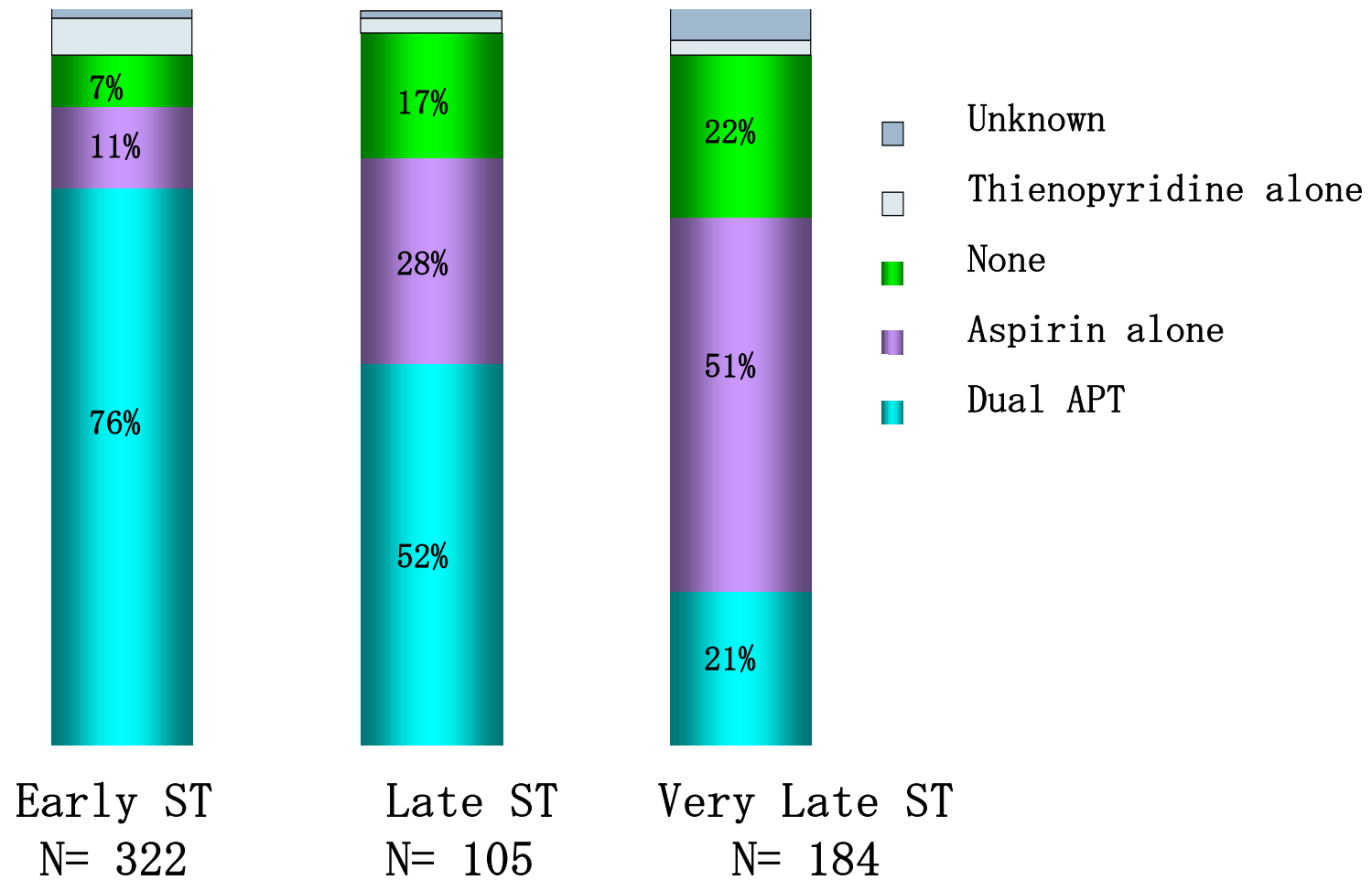
	Early ST	Late ST	Very late ST	p value		
	N=322	N=105	N=184	EST vs. LST	EST vs. VLST	LST vs. VLST
Initial TIMI flow				0.0001	0.5	0.0001
TIMI 0	84%	52%	79%			
TIMI 1	3.3%	12%	4.1%			
TIMI 2	3.3%	8.1%	5.8%			
TIMI 3	9.7%	28%	11%			



Anti-platelet Therapy at Time of ST



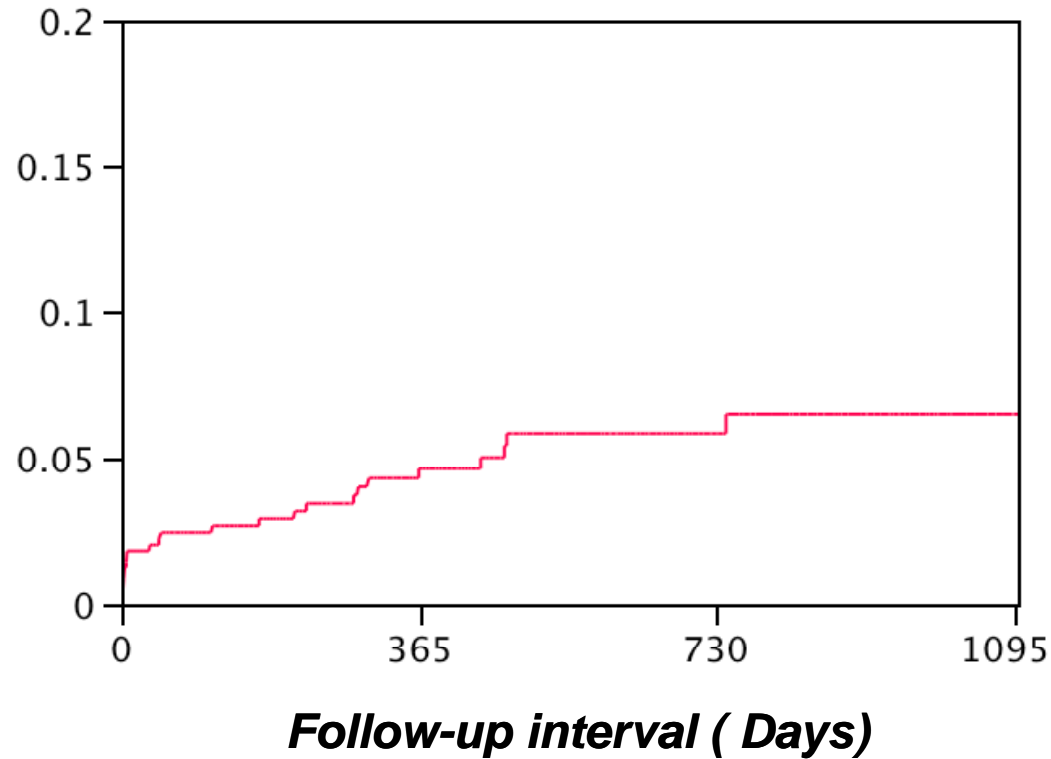
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Cumulative Incidence of Recurrent ST



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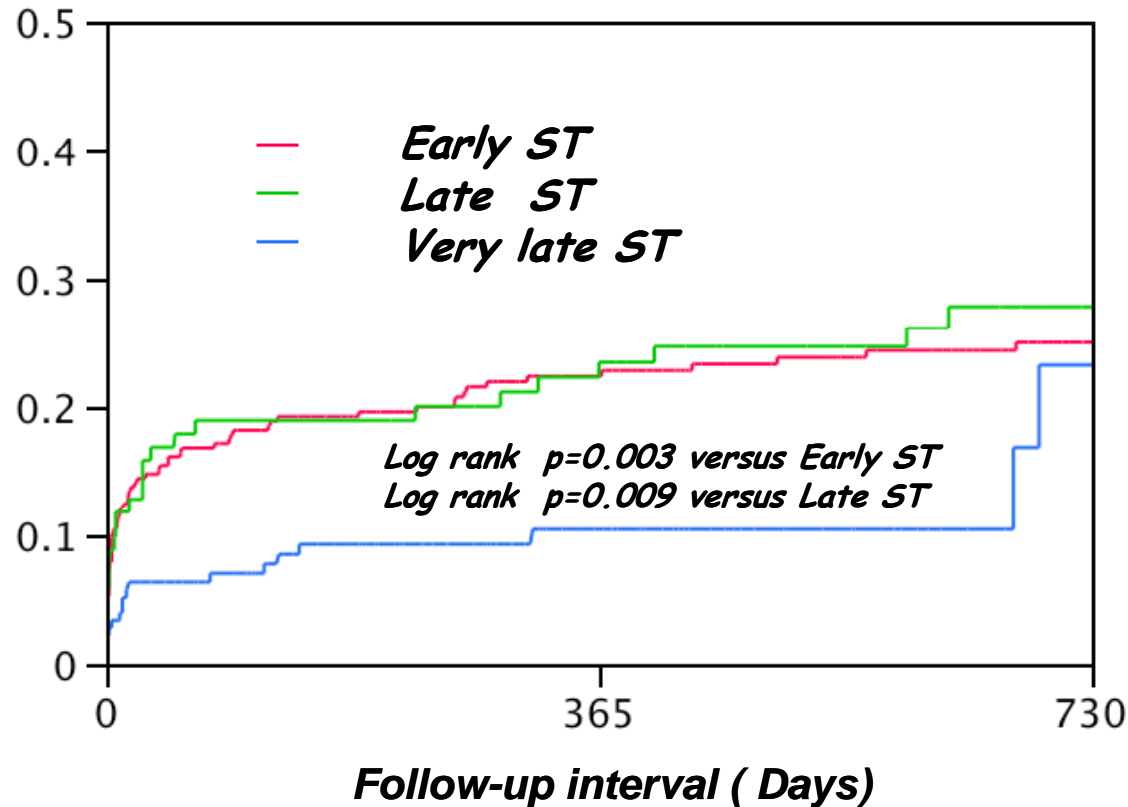


	<i>7 Days</i>	<i>30 Days</i>	<i>1 Yr</i>	<i>2 Yrs</i>
<i>Incidence</i>	1.8%	1.8%	4.6%	5.9%
<i>N of events</i>	10	10	21	24
<i>N of pts at risk</i>	611	525	479	290

Cumulative Mortality After ST



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Cox proportional
Hazard Model

P = 0.06 versus *Early ST*
P = 0.85 versus *Late ST*

		30 Days	1 Yr	2 Yrs
<i>Early ST</i>		14.8%	22.4%	25.0%
<i>n of pts at risk</i>	322	253	175	108
<i>Late ST</i>		15.9%	23.5%	27.8%
<i>n of pts at risk</i>	105	83	65	37
<i>Very late ST</i>		6.3%	10.5%	23.3%
<i>n of pts at risk</i>	184	153	63	12

Characteristics of Early ST



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 Registry of ST-elevation Myocardial Infarction for
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	Early ST	Late ST	Very late ST	p value		
	N=322	N=105	N=184	EST vs. LST	EST vs. VLST	LST vs. VLST
Prior PCI	42%	50%	54%	0.16	0.009	0.48
Acute MI	30%	24%	22%	0.19	0.03	0.69
Emergency procedure	37%	32%	26%	0.43	0.01	0.26
Diabetes	43%	54%	32%	0.04	0.02	0.0002
Insulin use	11%	22%	5.1%	0.005	0.03	0.0001



Characteristics of Late ST



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	Early ST	Late ST	Very late ST	p value		
	N=322	N=105	N=184	EST vs. LST	EST vs. VLST	LST vs. VLST
Body mass index	23.8±3.4	22.3±3.4	24.2±3.4	0.0002	0.23	0.0001
Heart failure	19%	33%	13%	0.003	0.11	0.0001
Diabetes	43%	54%	32%	0.04	0.02	0.0002
Insulin use	11%	22%	5.1%	0.005	0.03	0.0001
Hypertension	72%	84%	69%	0.01	0.54	0.006
Hemodialysis	4.4%	29%	4.9%	0.0001	0.78	0.0001



Characteristics of Very Late ST



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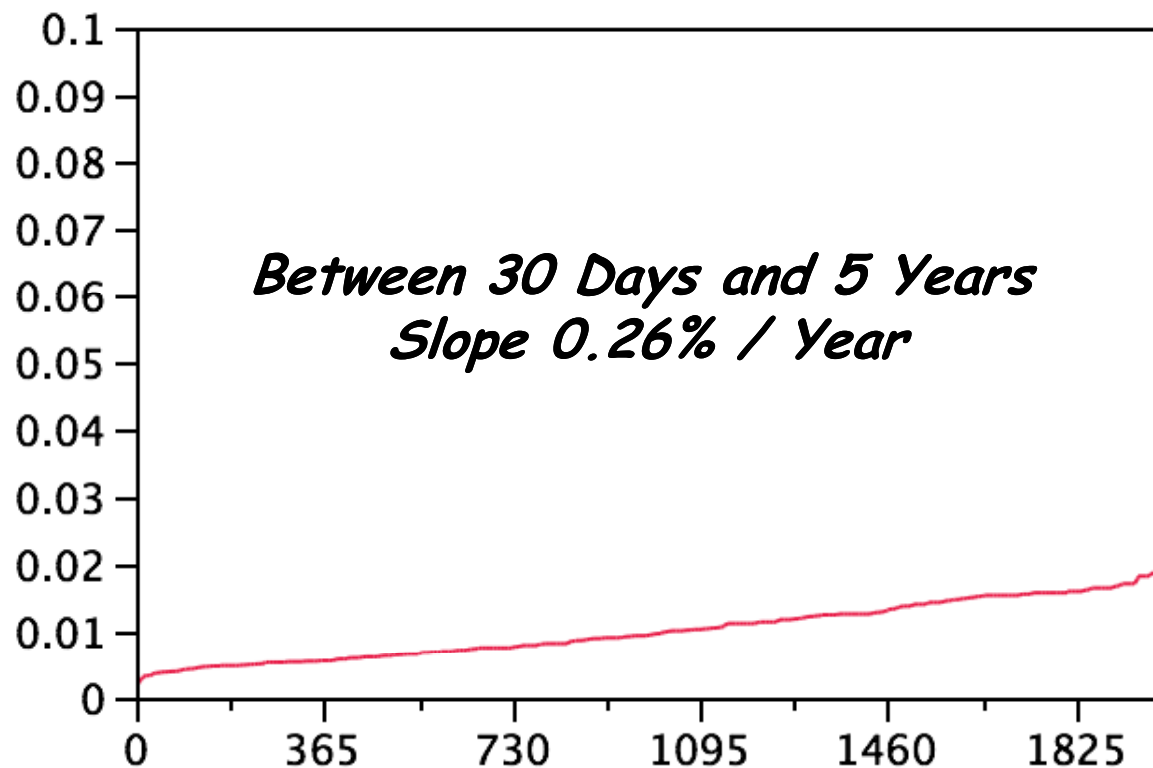
	Early ST N=322	Late ST N=105	Very late ST N=184	p value		
				EST vs. LST	EST vs. VLST	LST vs. VLST
Age (years)	67.1 ± 10.7	68.0 ± 10.8	62.9 ± 12.3	0.46	0.0001	0.0003
Diabetes	43%	54%	32%	0.04	0.02	0.0002
Insulin use	11%	22%	5.1%	0.005	0.03	0.0001
Current smoker	31%	27%	42%	0.38	0.01	0.0007
Statin use	46%	43%	57%	0.67	0.02	0.03
Average stent diameter (mm)	2.88 ± 0.36	2.88 ± 0.34	2.96 ± 0.35	0.99	0.01	0.06
Single vessel disease	37%	33%	45%	0.52	0.08	0.06



Stent Thrombosis of SES

J-CYPHER Registry

ARC Definite



Follow-up interval (Days)

	30 Days	1 Yr.	2 Yrs.	3 Yrs.	4 Yrs.	5 Yrs.
<i>Cumulative incidences</i>	0.34%	0.55%	0.76%	1.03%	1.33%	1.6%
<i>N of pts at risk</i>	12812	12627	11967	10813	9244	7640

Risk Factors for Early ST of SES

J-CYPHER Registry

Variables	Present	Absent	Univariate	p value	Multivariable	p Value
	N of events /N of patients	N of events /N of patients	H.R. (95%C.I.)		H.R. (95%C.I.)	
Acute coronary syndrome	19/3178 (0.6%)	25/9634 (0.3%)	2.32 (1.26-4.19)	0.008	2.16 (1.17-3.92)	0.01
Proximal LAD target	30/6590 (0.5%)	14/6222 (0.2%)	2.03 (1.1-3.94)	0.02	1.87 (1.01-3.64)	0.048
Prior heart failure	11/1791 (0.6%)	33/11021 (0.3%)	2.07 (0.997-3.96)	0.051		
Male gender	38/9643 (0.4%)	6/3169 (0.2%)	2.08 (0.95-5.47)	0.07		
Body mass index < 25.0	23/8332 (0.3%)	21/4476 (0.5%)	0.59 (0.33-1.07)	0.08		
IVUS-use	26/6063 (0.4%)	18/6698 (0.3%)	1.6 (0.88-2.96)	0.12		
Side-branch stenting	5/730 (0.7%)	39/12072 (0.3%)	2.13 (0.73-4.92)	0.15		
Age≥80 years	3/1664 (0.2%)	41/11148 (0.4%)	0.49 (0.12-1.35)	0.19		

Risk Factors for Late ST of SES

J-CYPHER Registry

Variables	Present	Absent	Univariate	p value	Multivariable	p Value
	N of events /N of patients	N of events /N of patients	H.R. (95%C.I.)		H.R. (95%C.I.)	
	(1-Year Incidence)	(1-Year Incidence)				
Diabetes mellitus	20/5312 (0.4%)	6/7500 (0.1%)	4.75 (2.03-13.0)	0.0002	1.51 (1.3-1.76)	<.0001
Hemodialysis	7/680 (1.2%)	19/12132 (0.2%)	7.19 (2.81-16.4)	0.0002	5.61 (2.1-13.62)	0.001
Side-branch stenting	7/730 (1.0%)	19/12072 (0.2%)	6.21 (2.43-14.14)	0.0005	5.1 (1.83-12.5)	<.0001
Body mass index < 25.0	22/8332 (0.3%)	4/4476 (0.1%)	3.0 (1.15-10.27)	0.02	2.75 (1.04-9.45)	0.04
ESRD without hemodialysis	4/628 (0.7%)	22/12184 (0.2%)	3.86 (1.13-10.1)	0.03	4.21 (1.19-11.73)	0.03
Unprotected LMCA target	4/582 (0.7%)	22/12230 (0.2%)	3.93 (1.15-10.3)	0.03	1.72 (0.47-5.09)	0.38

Risk Factors for Very Late ST of SES

J-CYPHER Registry

Variables	Present	Absent	Univariate	p value	Multivariable	p Value
	N of events /N of patients (5-Year Incidence)	N of events /N of patients (5-Year Incidence)	H.R. (95%C.I.)		H.R. (95%C.I.)	
Current smoking	37/2604 (2.0%)	65/10208 (0.8%)	2.32 (1.53-3.45)	0.0001	2.02 (1.33-3.04)	0.001
Multi-vessel stenting	36/3568 (1.3%)	66/9244 (0.9%)	1.55 (1.02-2.31)	0.04	1.54 (1.02-2.3)	0.04
Male gender	88/9643 (1.2%)	14/3169 (0.6%)	2.0 (1.18-3.66)	0.009	1.61 (0.93-2.99)	0.09
Age \geq 80 years	4/1664 (0.3%)	98/11050 (1.1%)	0.36 (0.11-0.87)	0.02	0.44 (0.14-1.07)	0.07
Acute coronary syndrome	32/3178 (1.5%)	70/9634 (0.9%)	1.52 (0.99-2.29)	0.06		
Prior heart failure	6/1791 (0.3%)	96/11021 (1.1%)	0.51 (0.2-1.07)	0.08		
Lesion length \geq 30 mm	27/2574 (1.5%)	74/9954 (1.0%)	1.48 (0.93-2.26)	0.09		
Peripheral vascular disease	7/1523 (0.7%)	95/11289 (1.1%)	0.62 (0.26-1.24)	0.19		

Independent Risk Factors for ST of SES

J-CYPHER Registry

Early ST

Acute Coronary Syndrome, Proximal LAD Target

Late ST

Diabetes, Hemodialysis, Side-branch Stenting,
Small BMI, ESRD pre HD

Very Late ST

Current Smoking, Multi-vessel Stenting

Mechanisms of Stent Thrombosis

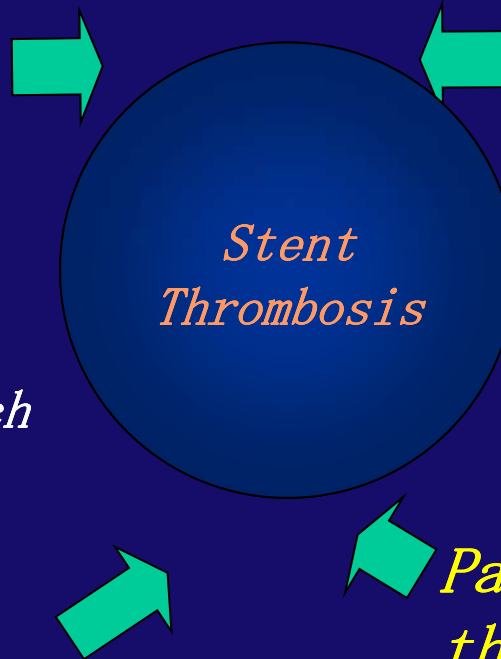
Multi-factorial and Different According to the Timing of ST

Procedural Factors

- *Inadequate stent expansion*
- *Residual dissection*
- *Bifucation stenting using 2-stents approach*
- *Multiple stenting in diffuse disease*

Pro-thrombotic Milieu

- *Acute coronary syndrome*
- *Diabetes*
- *Renal failure*



Platelet Activation

- *Discontinuation of anti-platelet Tx.*
- *Resistance to anti-platelet Tx.*
- *Activation of platelets (e.g. surgery)*

Pathology of the Vessel Wall

- *Delayed healing*
- *Inflammation*
- *Hypersensitivity*
- *Vulnerable neointima*
- *De novo atherosclerosis*

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Summary

1. RESTART is the largest ever reported registry of DES thrombosis enrolling 611 patients with ST (early ST 322, late ST 105 and very late ST 184).
2. Clinical presentations of ST were ST elevation ACS in 60-70%, non-ST elevation ACS in 20-30% and cardiac arrest in 5-10% irrespective of the timing of ST.
3. Multivessel ST was observed in 1-4% of all ST.
4. ST related to surgical procedures accounted for 3% of early ST and 6-7% of late / very late ST
5. TIMI 2/3 flow at the time of ST was more frequently observed in patients with late ST than those with early ST or very late ST.
6. The rate of recurrent ST at 1 year after the index ST event was 4.6%.
7. The mortality rate at 1 year after the index ST event was 10-20%. Although the crude mortality rate was significantly lower in patients with very late ST than those with early ST or late ST, there was no significant mortality differences among the 3 groups after adjusting baseline characteristics.



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Summary

8. Patients with early ST as compared with those with very late ST were more often treated in the setting of acute myocardial infarction and less often had history of PCI.
9. Patients with late ST as compared with those with both early ST and very late ST had more often end-stage renal disease on hemodialysis, history of heart failure, diabetes, hypertension and small body mass index.
10. Patients with VLST as compared with those with both EST and LST were younger, more often current smokers, more often on statins at the time of discharge from the index hospitalization and had less often diabetes.
11. Time dependent differences in the demographic features and clinical outcome of patients with ST suggest the possible differences in the predominant pathophysiologic mechanisms of ST according to the timing after SES implantation.



Methods



1. Evaluate the differences in baseline characteristics and clinical presentation of ST according to the timing of occurrence
 1. Evaluate the relation between discontinuation of antiplatelet therapy (APT) and ST
 1. Evaluate treatment strategies of ST and long-term event rates after ST including rate of recurrent ST
 1. Investigate angiographic and IVUS characteristics of ST
-



Characteristics of Acute ST and Subacute ST



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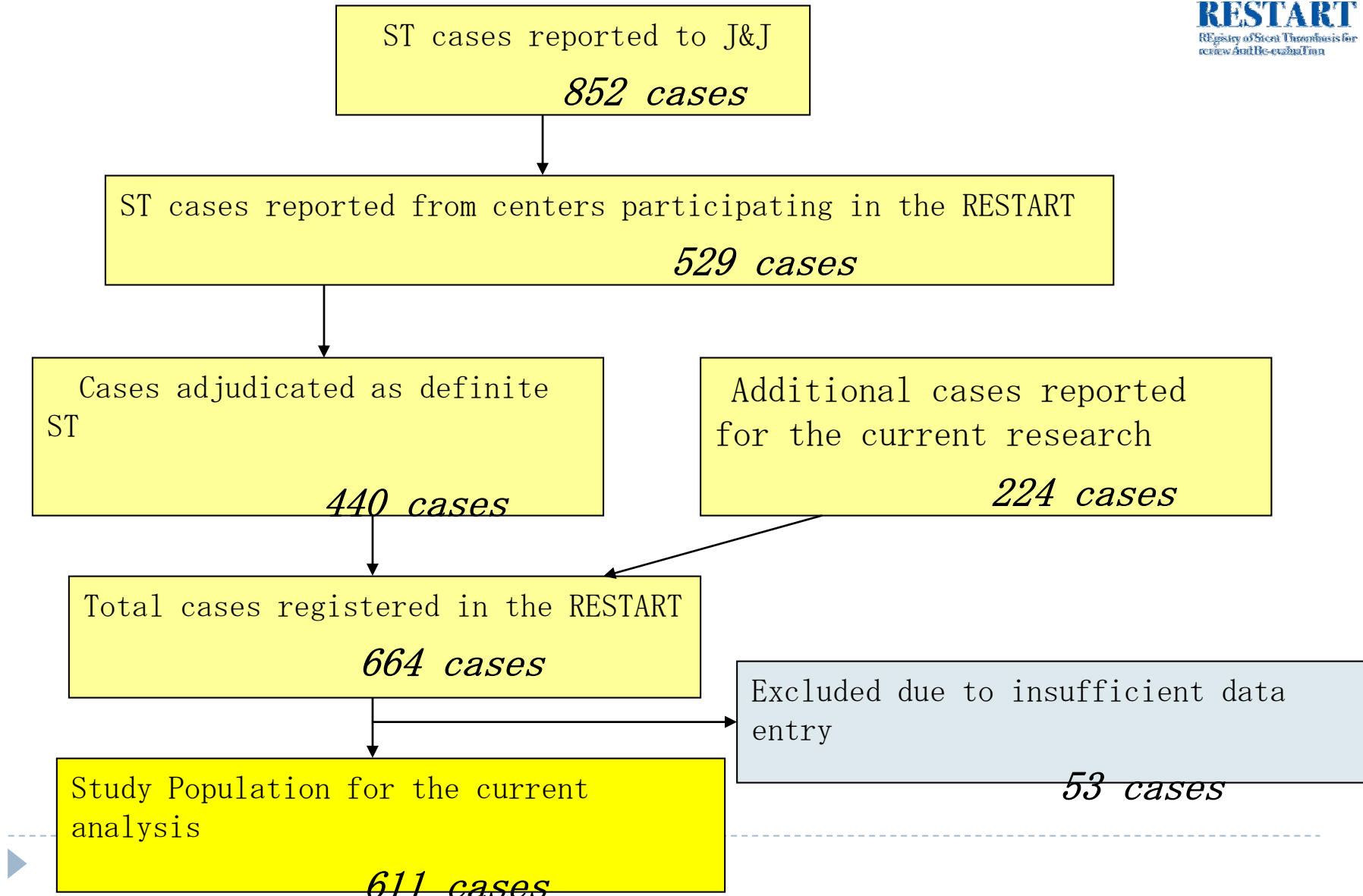
	Acute ST	Subacute ST	p value
	N=52	N=270	
Age (years)	63.6 ± 10.4	67.8 ± 10.6	0.009
Prior PCI	27%	44%	0.02
Acute MI	42%	28%	0.047
Emergency procedure	50%	34%	0.03
N of stents / patient	1.75 ± 0.97	2.11 ± 1.25	0.02



Study Population



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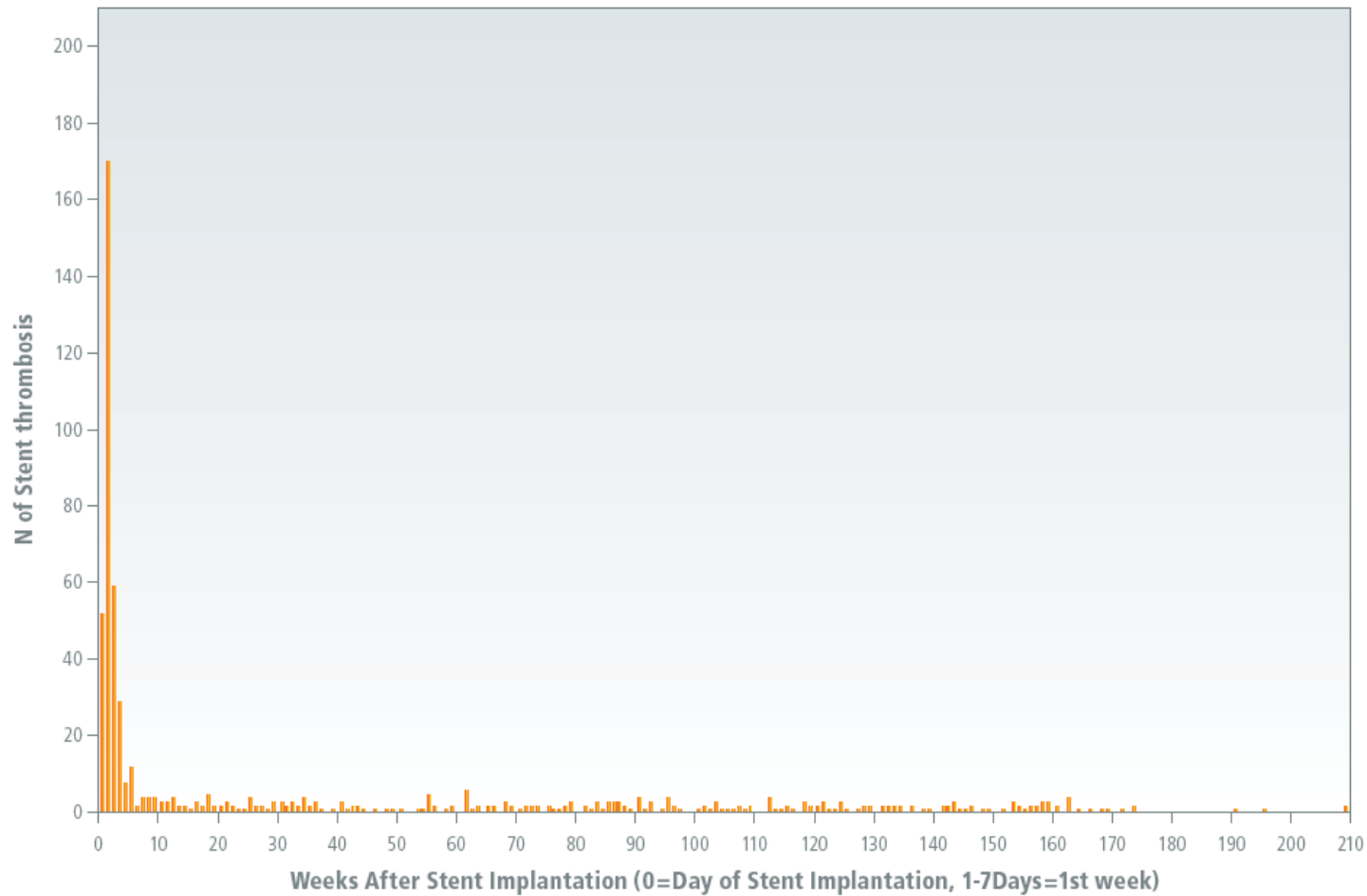


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Number of Cases with Stent Thrombosis (Weekly)





Treatment of ST

	Early ST N=322	Late ST N=105	Very late ST N=184	p value		
				EST vs. LST	EST vs. VLST	LST vs. VLST
Treatment of ST						
Any PCI	97%	96%	98%	0.61	0.67	0.43
Thrombus aspiration	78%	69%	81%	0.04	0.51	0.03
Balloon dilatation	94%	92%	92%	0.47	0.26	0.84
Additional stent placement	32%	35%	43%	0.67	0.02	0.16
DES	18%	12%	19%			
BMS	14%	23%	24%			
IABP	41%	30%	27%	0.053	0.001	0.51
PCPS	8.3%	5.0%	4.5%	0.25	0.11	0.87
Emergency CABG	1.6%	0%	1.1%	0.09	0.68	0.18





Outcome of ST

	Early ST N=322	Late ST N=105	Very late ST N=184	p value		
				EST vs. LST	EST vs. VLST	LST vs. VLST
Final TIMI flow				0.8	0.38	0.68
TIMI 0	6.2%	6.1%	3.5%			
TIMI 1	2.3%	4.0%	4.1%			
TIMI 2	7.5%	6.1%	8.8%			
TIMI 3	84%	84%	84%			
Final diagnosis of MI	90%	85%	90%	0.17	0.89	0.17
Q-wave MI	65%	57%	71%	0.12	0.24	0.02
Non-Q wave	24%	28%	20%	0.5	0.23	0.12



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Number of Cases with Stent Thrombosis (Daily)

