

# **Is Diabetes Influence Different According to the Ethnics?**

**Kyoto University Hospital**

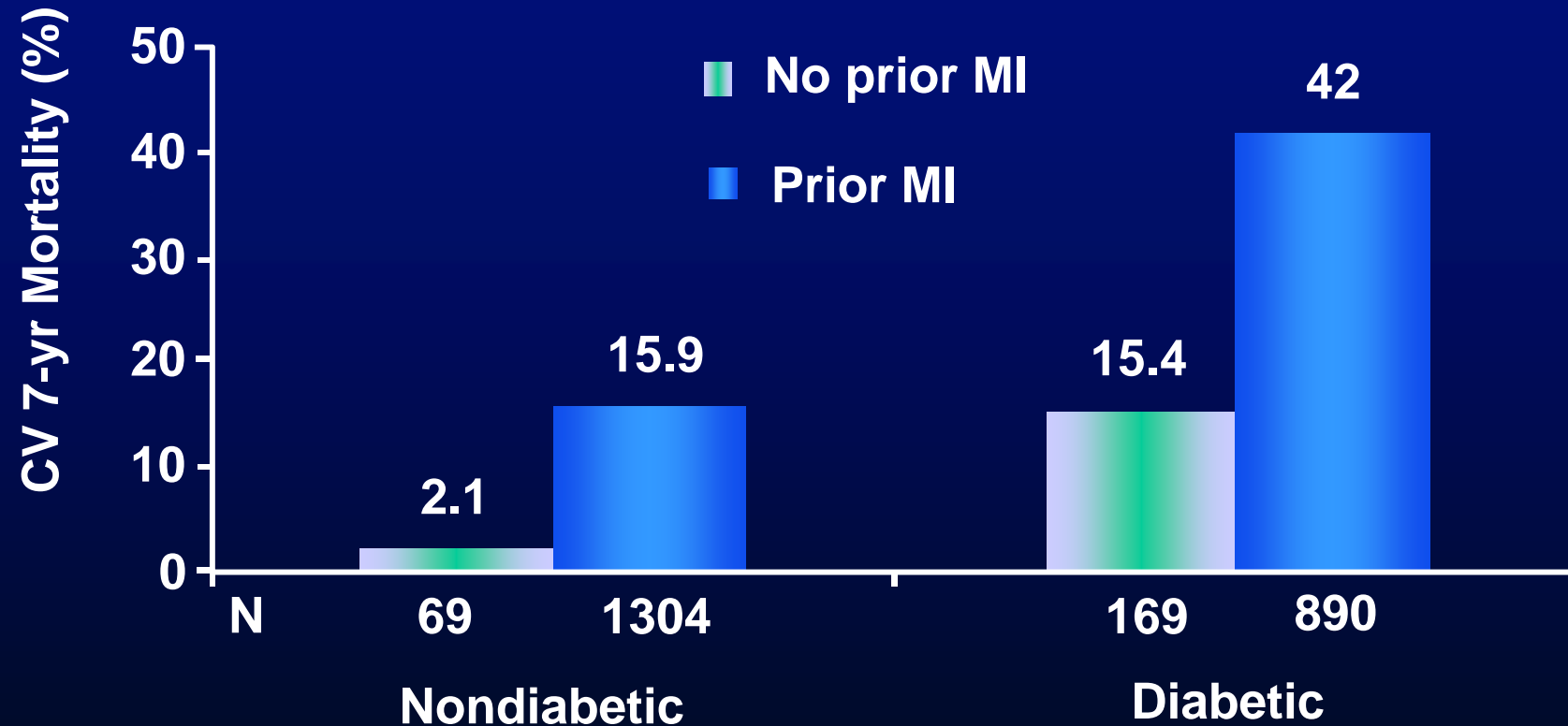
**Takeshi Kimura**



*Kyoto University Hospital Cardiovascular Medicine*

# Diabetes and Cardiovascular Disease

Diabetes Is a CAD Equivalent and Prognosis of Diabetic CAD Is Worse Than That of Non-diabetic CAD.



Although this notion has been widely reported in the Western literature, is it really applicable to Japanese patients?

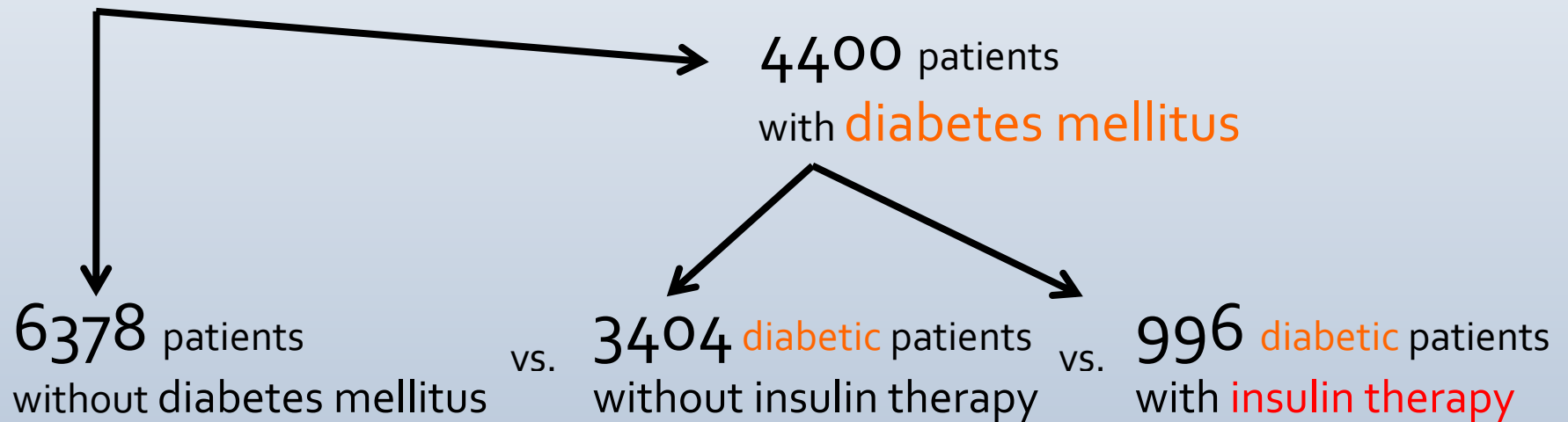
# j-Cypher registry (August 2004-November 2006)

12824 patients with first registration

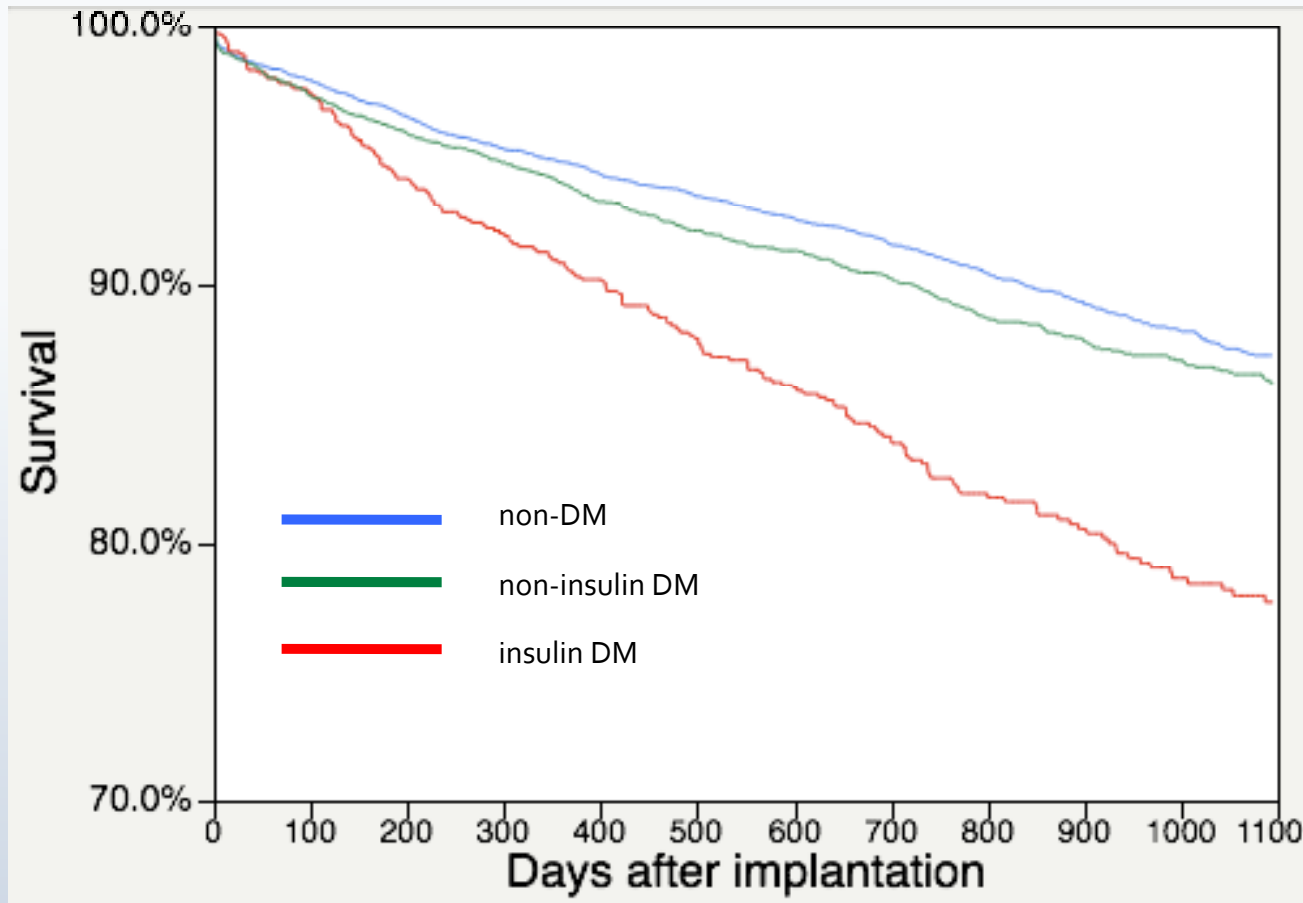


Patients excluded:  
10 patients with non-SES treatment  
(non-stent, BMS, other type of DES)  
Patients excluded:  
2034 patients with hybrid treatment  
(SES and BMS or other type of DES or devices)  
Patients excluded:  
2 patients with unsuccessful procedure

10778 patients  
treated exclusively with SES



# MACE (Death+QMI+Stroke) Free Survival



Log-rank

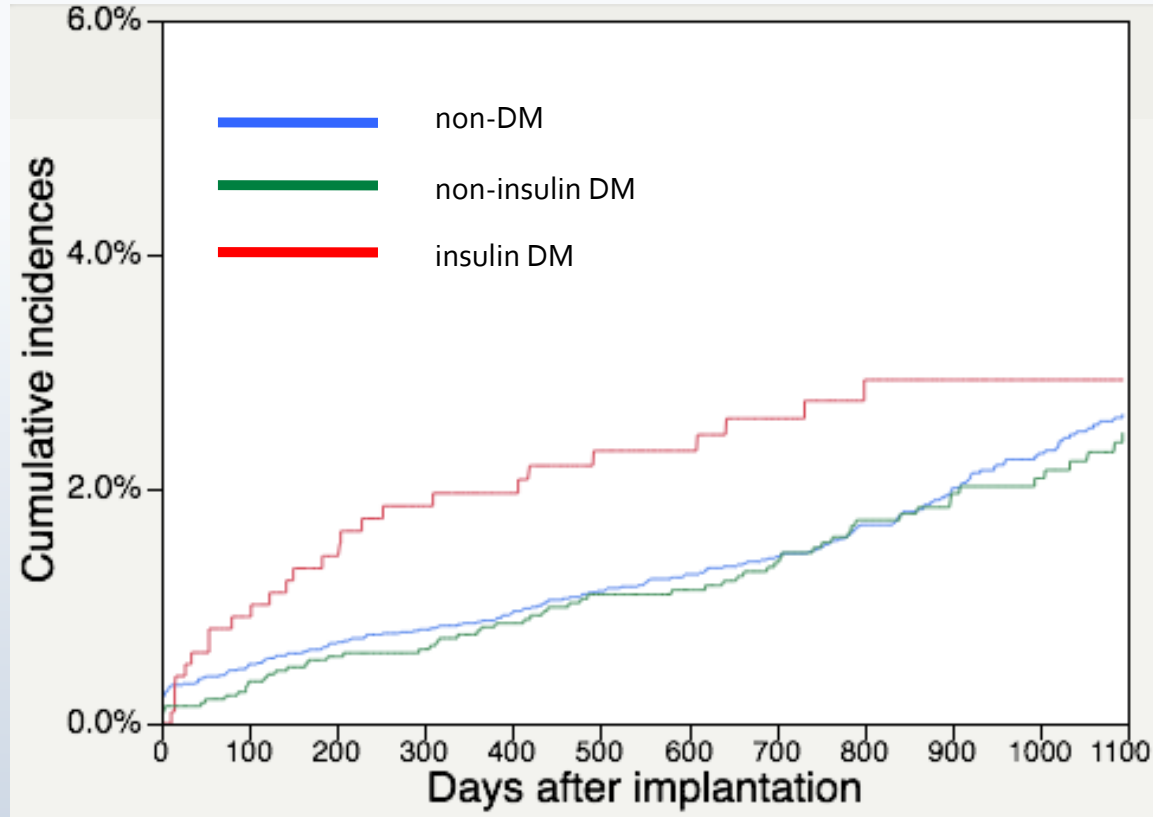
\* p value: vs. non-DM patients

] p=0.06

] p<0.001

		0 Days	30 Days	365 Days	730 Days	1095 Days
non-DM	at risk	6378	6271	5863	4442	1977
	cumulative incidence n, %	0 %	1.3 %	5.3 %	8.7 %	649, 13 %
non-insulin DM	at risk	3404	3348	3088	2361	1135
	cumulative incidence n, %	0 %	1.3 %	6.1 %	10 %	392, 14 %
insulin-DM	at risk	996	984	873	636	312
	cumulative incidence n, %	0 %	1.1 %	9.4 %	17 %	185, 22 %

# QMI



Log-rank

\* p value: vs. non-DM patients

$p=0.57$ 
 $p=0.14$

		0 Days	30 Days	365 Days	730 Days	1095 Days
non-DM	at risk	6378	6271	5863	4442	1977
	cumulative incidence n, %	0 %	0.4 %	0.9 %	1.5 %	2.7 %
non-insulin DM	at risk	3404	3348	3088	2361	1135
	cumulative incidence n, %	0 %	0.2 %	0.8 %	1.5 %	2.5 %
insulin-DM	at risk	996	984	873	636	312
	cumulative incidence n, %	0 %	0.5 %	2.0 %	2.6 %	2.9 %

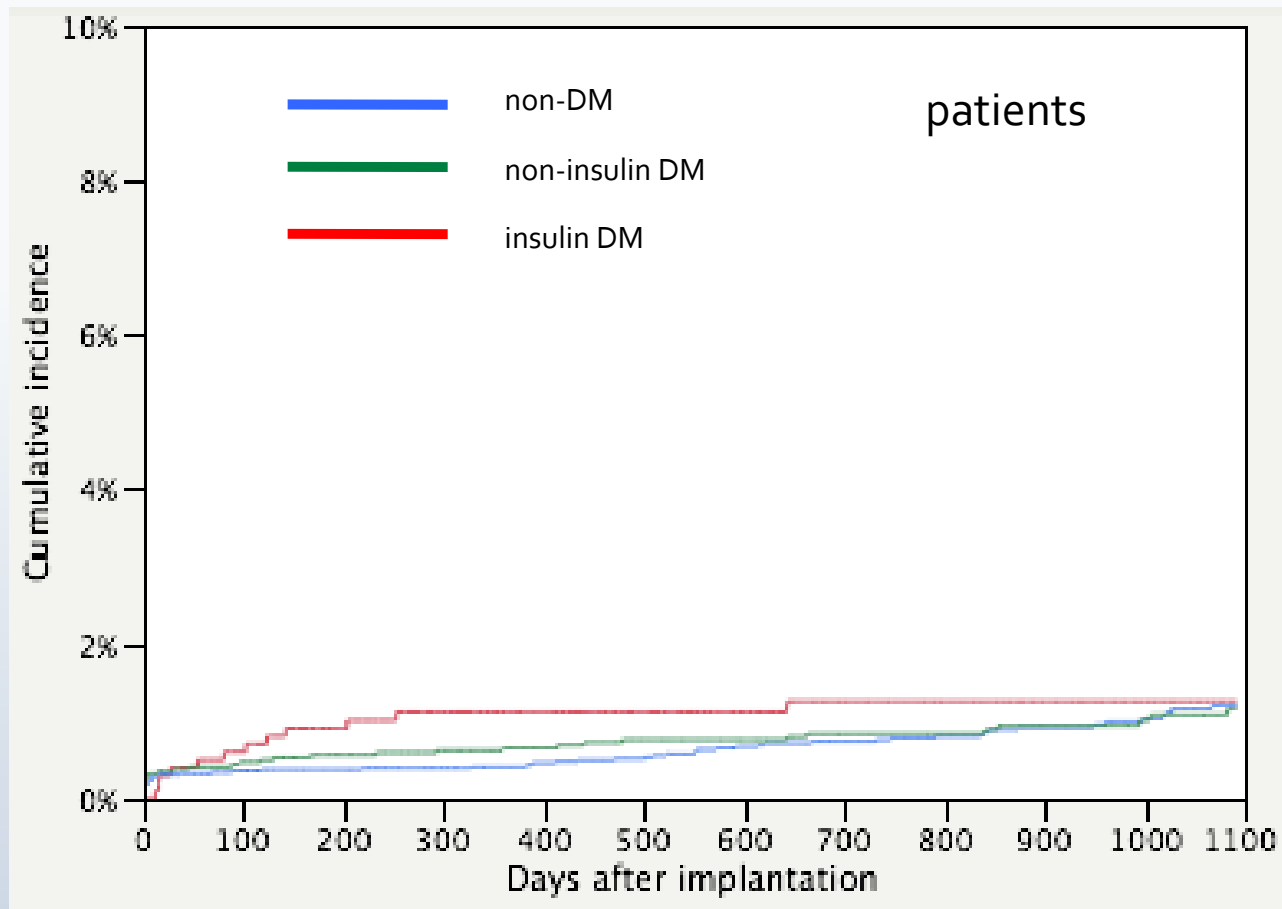
# Death QMI Stroke

Multivariable analysis  
with dummy variables

	Hazard ratio	95% CI	* p value
Diabetes - non-insulin	<b>1.02</b>	<b>0.96 – 1.09</b>	<b>0.47</b>
Diabetes - insulin	<b>1.12</b>	<b>1.03 – 1.23</b>	<b>0.01</b>

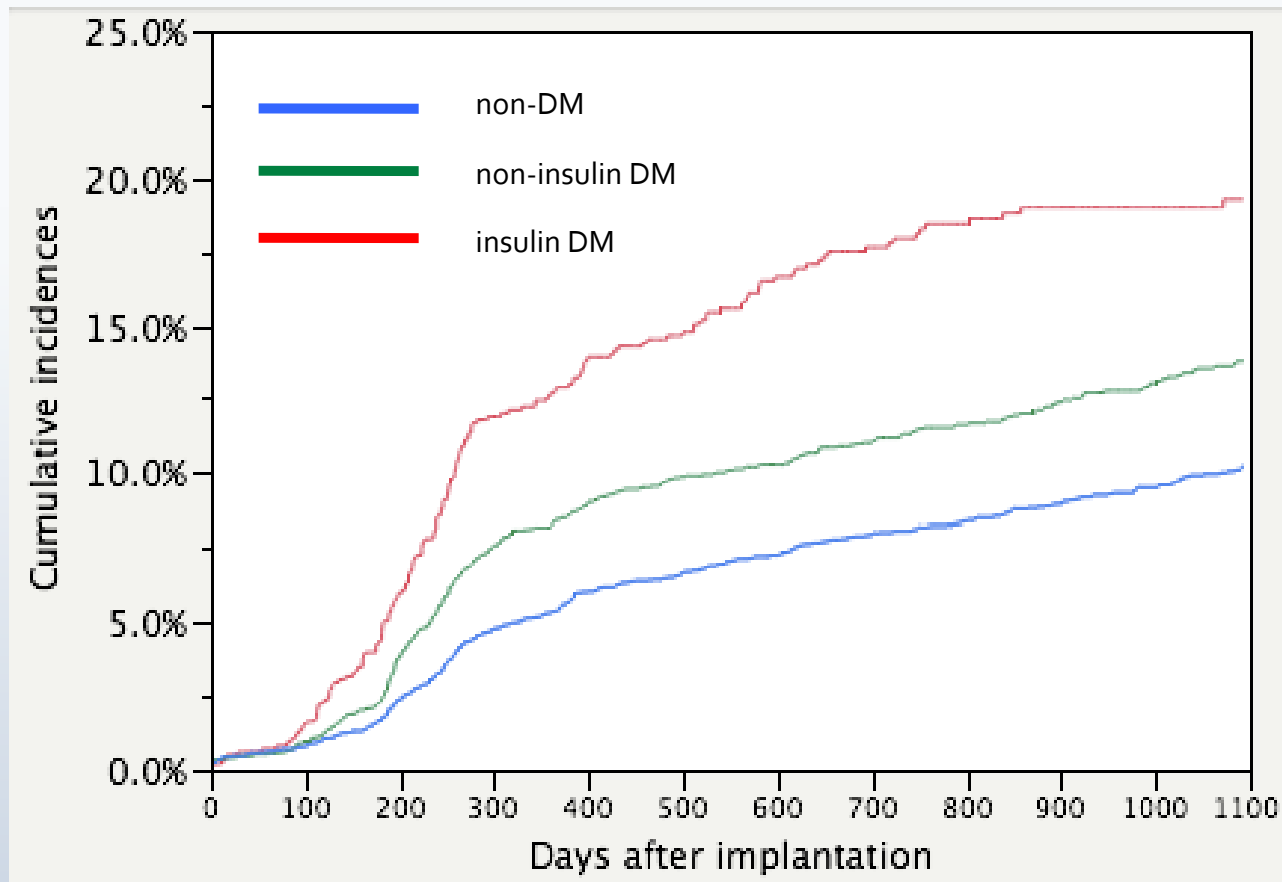
\* p value: vs. non-DM patients

# ARC definite Stent Thrombosis



		0 Days	30 Days	365 Days	730 Days	1095 Days
non-DM	at risk	6378	6299	5960	4559	2050
	cumulative incidence	0 %	0.3 %	0.4 %	0.7 %	57, 1.2 %
non-insulin DM	at risk	3404	3347	3130	2423	1179
	cumulative incidence	0 %	0.4 %	0.7 %	0.8 %	32, 1.2 %
insulin-DM	at risk	996	988	898	667	334
	cumulative incidence	0 %	0.4 %	1.1 %	1.3 %	12, 1.3 %

# TLR



## Log-rank

\* p value: vs. non-DM patients

$p < 0.001$   
 $p < 0.001$

		0 Days	30 Days	365 Days	730 Days	1095 Days
non-DM	at risk	6378	6271	5863	4442	1977
	cumulative incidence n, %	0 %	0.5 %	5.4 %	8.1 %	535, 10 %
non-insulin DM	at risk	3404	3348	3088	2361	1135
	cumulative incidence n, %	0 %	16, 0.5%	,8.4 %	11 %	394, 14 %
insulin-DM	at risk	996	984	873	636	312
	cumulative incidence n, %	0 %	6, 0.6 %	,13 %	,17 %	168, 19 %



# TLR

## Multivariable analysis

logistic regression model  
with dummy variables

	Odds ratio	95% CI	* p value
Diabetes - non-insulin	<b>1.24</b>	<b>1.05 – 1.45</b>	<b>0.009</b>
Diabetes - insulin	<b>1.52</b>	<b>1.19 – 1.92</b>	<b>0.0006</b>

\* p value: vs. non-DM patients

Comparison of Baseline Characteristics and Clinical Outcome  
In Patients Undergoing Coronary Revascularization  
Japan versus United States

**First Elective Isolated Coronary Revascularization Procedures**

**CREDO-Kyoto  
PCI/CABG Registry  
Cohort-1**

**Year 2000-2002**

**8871 Patients**

**PCI 6510 patients**

**CABG 2361 patients**

***Texus Heart Institute  
Research Database***

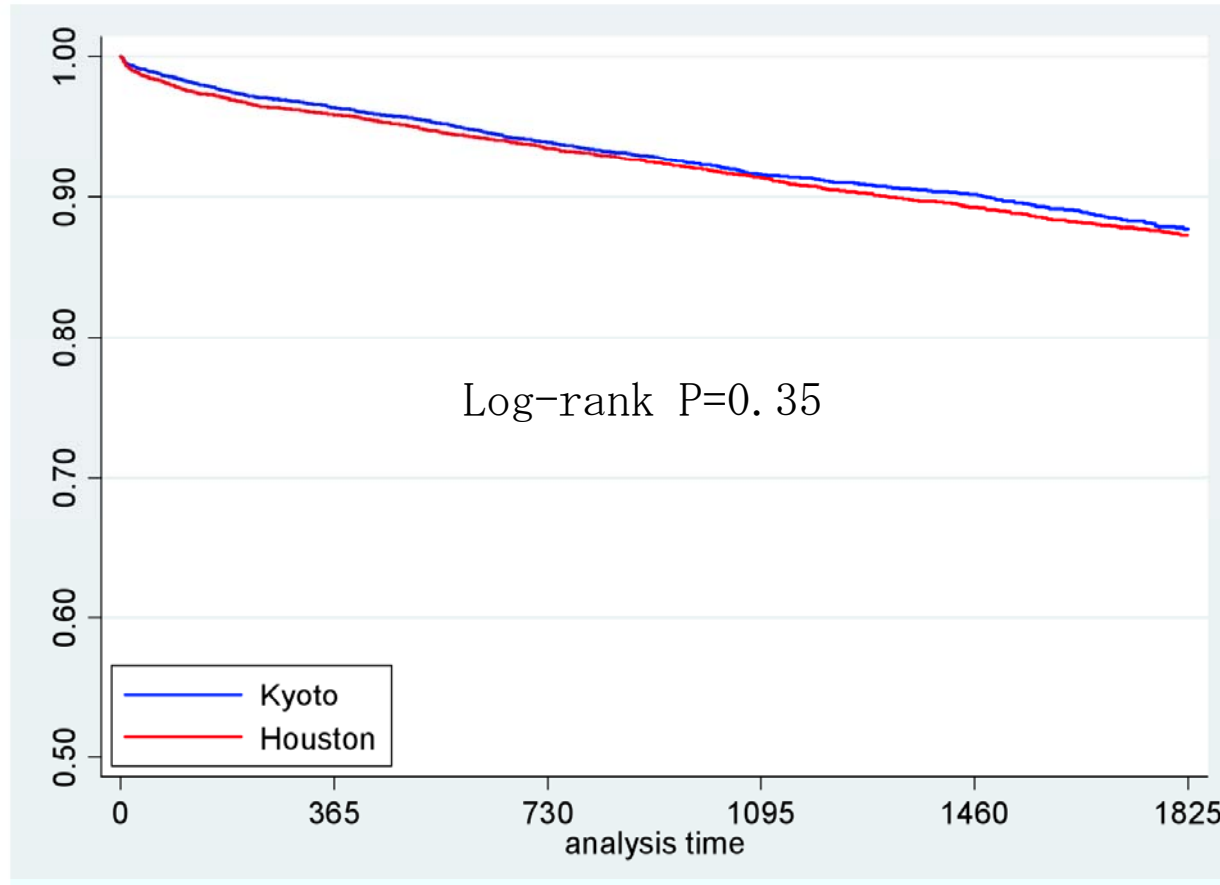
**Year 1999-2003**

**7229 Patients**

**PCI 4076 patients**

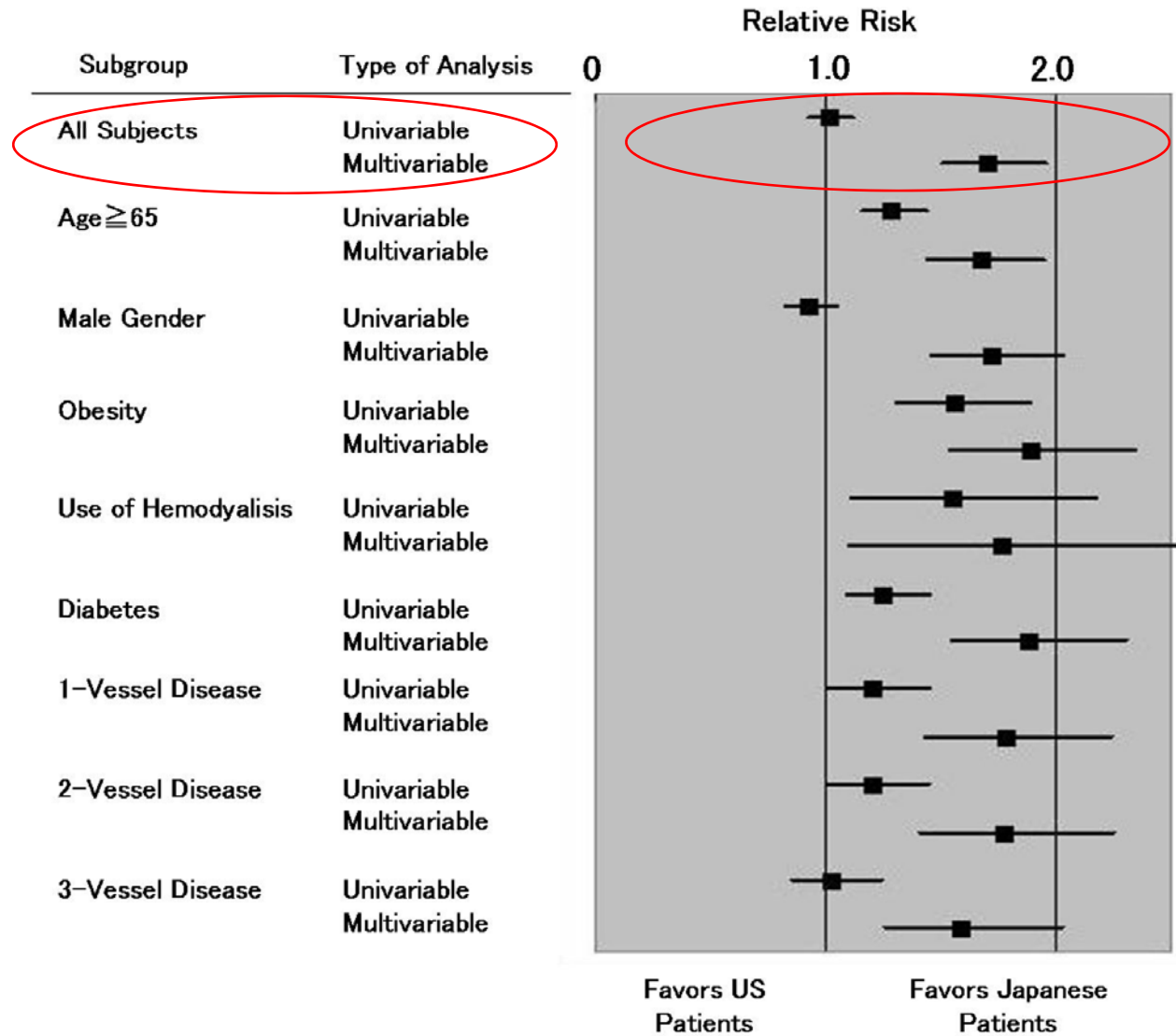
**CABG 3153 patients**

# Unadjusted Kaplan-Meier Survival Curve



		30 days	1 year	2 years	3 years	4 years	5 years
Kyoto		0.992	0.964	0.939	0.916	0.901	0.877
n	8,871	8,734	8,389	7,971	5,855	3,080	1,135
Houston		0.988	0.959	0.935	0.913	0.893	0.873
n	7,229	7,143	6,928	6,756	6,599	5,243	3,940

# Unadjusted and Adjusted Risk for Long-term Mortality



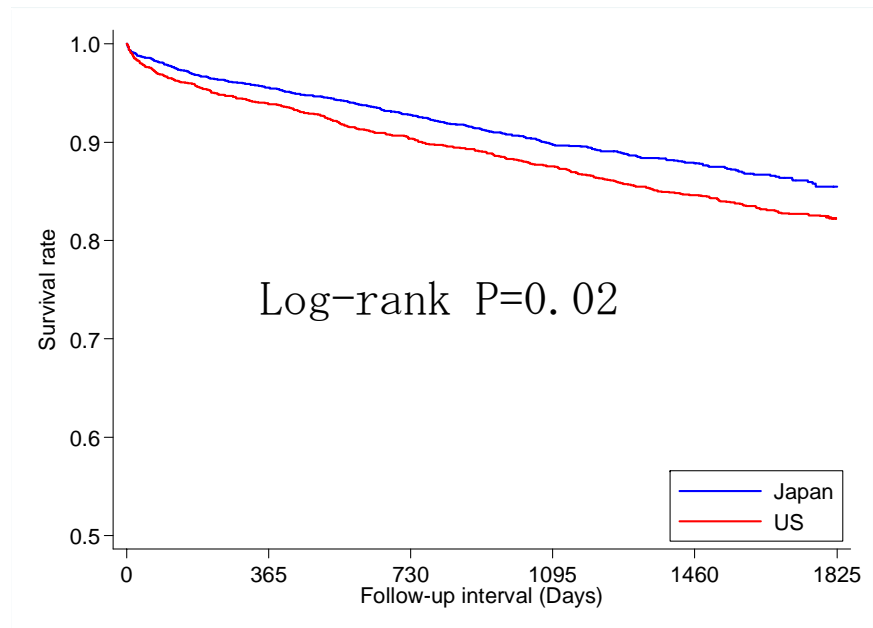
## CREDO-Kyoto PCI/CABG Registry Cohort-1 versus Texas Heart Institute Research Database

### Demographics of Diabetic Patients: Japan versus United States

Variable	Japanese Patients (N=3,473)	US Patients (N=2,224)	P value
Age (years)	66.7 (9.3)	62.5 (10.3)	<0.001
Women	31.8	35.8	0.002
BMI (kg/m <sup>2</sup> )	23.8 (3.3)	30.7 (6.3)	<0.001
CABG	31.7	50.1	<0.001
Myocardial Infarction	29.1	35.6	<0.001
Heart Failure	19.7	21.8	0.061
NYHA class IV	2.2	11.6	<0.001
PVD	14.4	18.5	<0.001
Stroke	18.8	7.3	<0.001
Hemodialysis	5.6	2.7	<0.001
Hypertension	70.9	84.8	<0.001
Smoking	50.1	41.6	<0.001
Insulin using DM	21.6	22	0.7

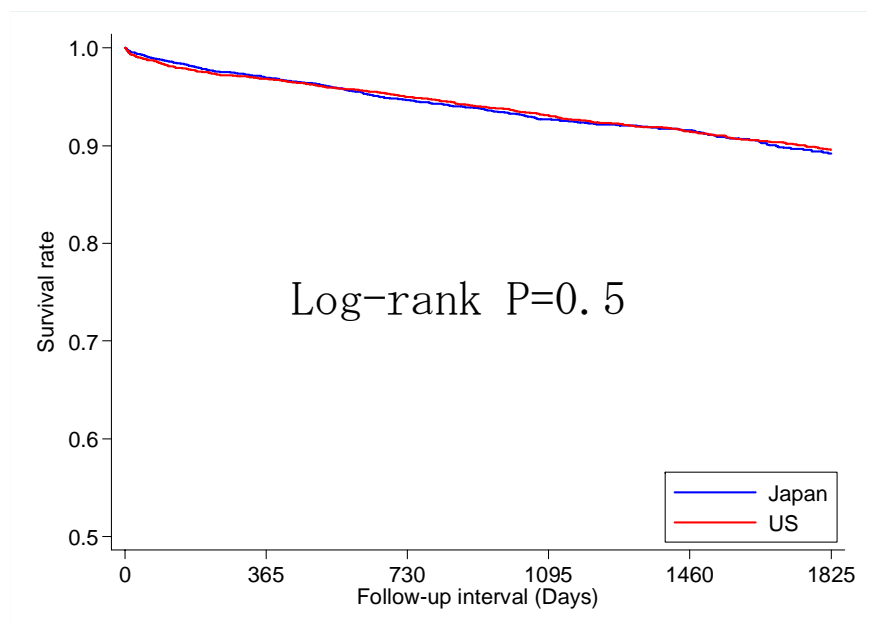
# Unadjusted Kaplan-Meier Survival Curve

## Diabetes Subgroup



		30d	1y	2y	3y	4y	5y
Japan	population at risk	3407	3250	3069	2245	1200	472
n=3473	survival rate	0.9882	0.9555	0.9274	0.8977	0.8786	0.8547
United States	population at risk	2186	2087	2009	1948	1487	1095
n=2224	survival rate	0.9825	0.9384	0.9033	0.8754	0.8461	0.8227

## Non-Diabetes Subgroup

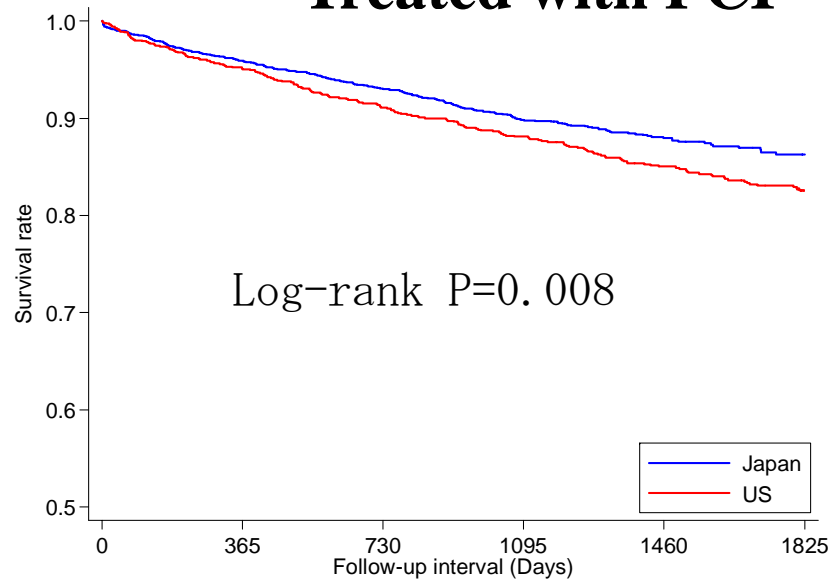


		30d	1y	2y	3y	4y	5y
Japan	population at risk	5317	5128	4891	3604	1880	663
n=5387	survival rate	0.9942	0.9696	0.9466	0.927	0.9155	0.8916
United States	population at risk	4893	4780	4689	4595	3704	2797
n=4940	survival rate	0.9909	0.9682	0.9498	0.9307	0.9144	0.8958

# Unadjusted Kaplan-Meier Survival Curve

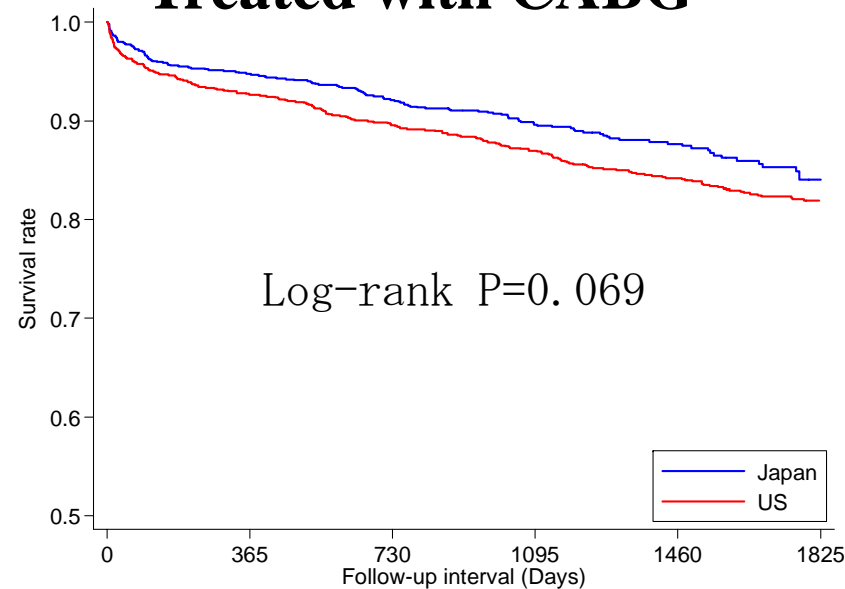
## Diabetic Patients

### Treated with PCI



		30d	1y	2y	3y	4y	5y
Japan	population at risk	2340	2233	2102	1533	775	301
n=2373	survival rate	0.992	0.9591	0.9303	0.8983	0.8794	0.8627
US	population at risk	1105	1056	1012	979	709	509
n=1110	survival rate	0.9946	0.9505	0.9108	0.8811	0.8502	0.8258

### Treated with CABG



		30d	1y	2y	3y	4y	5y
Japan	population at risk	1068	1018	968	714	425	171
n=1100	survival rate	0.98	0.9476	0.9212	0.8964	0.8767	0.8403
United States	population at risk	1082	1032	998	970	780	587
n=1114	survival rate	0.9704	0.9263	0.8958	0.8697	0.8418	0.8192

## **Is Diabetes Influence Different According to the Ethnic?**

1. In a large, real world study in Japanese patients with SES implantation, there was diabetes-associated excess risk of TLR regardless of insulin use.

However, regarding serious cardiovascular events such as death/MI/stroke, an excess risk was seen only in the insulin-treated diabetic patients. The risk for serious cardiovascular events was similar between non-insulin-treated diabetic patients and non-diabetic patients.

2. In comparing long-term outcome after coronary revascularization between CREDO-Kyoto registry and Texus Heart Institute database, survival outcome seemed to be more favorable in Japanese patients as compared with US patients. Better survival outcome was particularly prominent in diabetic patients.

**Influence of diabetes appeared to be different according to the ethnics.**

**Recognition of this notion might have had influence on selection of coronary revascularization strategies (PCI/CABG) in Japanese clinical practices.**



ARC  
definite **ST**

**Multivariable analysis**  
logistic regression model  
with dummy variables

	Hazard ratio	95% CI	* p value
<b>Diabetes - non-insulin</b>	<b>0.89</b>	<b>0.56 – 1.40</b>	<b>0.63</b>
<b>Diabetes - insulin</b>	<b>0.99</b>	<b>0.47 – 1.89</b>	<b>0.97</b>

\* p value: vs. non-DM patients

*Living in Japan was an Independent Predictor of Lower Rates of Cardiovascular Events in the REACH Registry*

**Table 4** Three-year event rates by geographic region

	North America	Latin America	Western Europe	Eastern Europe	Middle East	Asia	Australia	Japan	Total	P-value
n	11 604	1206	12 218	4326	392	3144	2551	4234	39 675	
All-cause mortality	9.80	11.51	9.25	11.68	7.87	9.85	6.86	5.21	9.06	<0.0001
95% CI	8.97–10.61	9.47–13.47	8.53–9.96	10.36–12.97	5.08–10.53	8.51–11.16	5.80–7.90	4.47–5.94	8.54–9.57	
Vascular death	6.02	7.61	5.79	9.03	5.61	6.64	2.70	2.42	5.57	<0.0001
95% CI	5.35–6.68	5.90–9.27	5.20–6.36	7.81–10.22	3.24–7.90	5.51–7.75	2.06–3.34	1.91–2.92	5.15–5.99	
MI/stroke/vascular death	11.99	13.65	11.85	17.99	13.25	13.13	7.57	8.63	11.96	<0.0001
95% CI	11.08–12.90	11.46–15.77	11.06–12.64	16.47–19.47	9.70–16.64	11.68–14.56	6.44–8.69	7.67–9.58	11.37–12.54	
MI/stroke/vascular death/rehospitalization	29.27	25.83	30.69	39.58	30.45	23.03	23.51	17.34	28.39	<0.0001
95% CI	28.09–30.43	23.24–28.32	29.62–31.75	37.90–41.21	25.85–34.77	21.38–24.64	21.68–25.29	16.10–18.56	27.62–29.16	

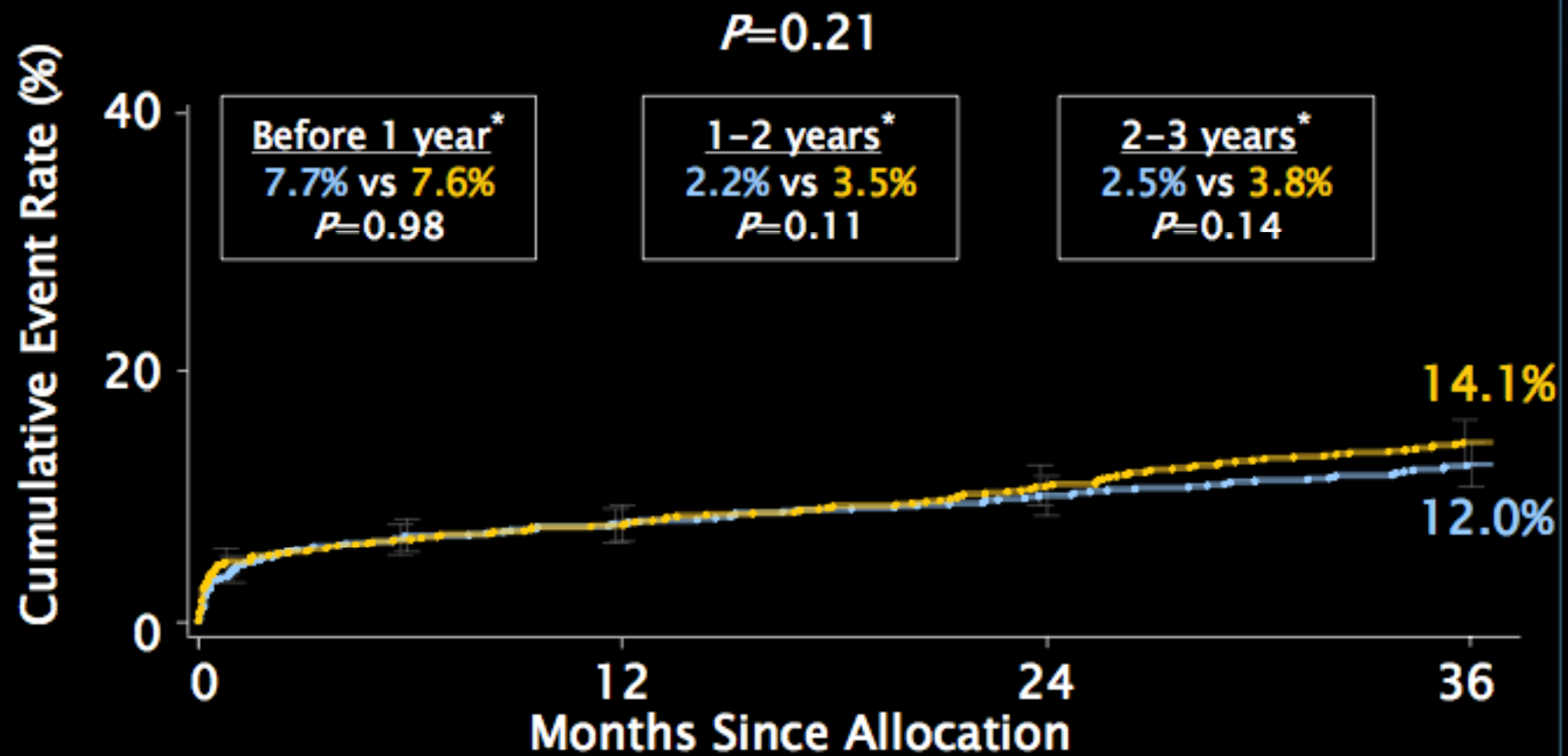
CI, confidence interval; MI, myocardial infarction.

Major 3-year vascular outcome events and all-cause mortality for symptomatic patients in the REACH Registry. Some regions had higher than average rates of outcome events such as Eastern Europe and the Middle East; other regions such as Asia, Australia, and Japan had event rates that were lower than average. Event rates are age- and sex-adjusted. P-values indicate a statistically significant difference between at least one region and another.

# All-Cause Death/CVA/MI to 3 Years SYNTAX

■ CABG (N=897)

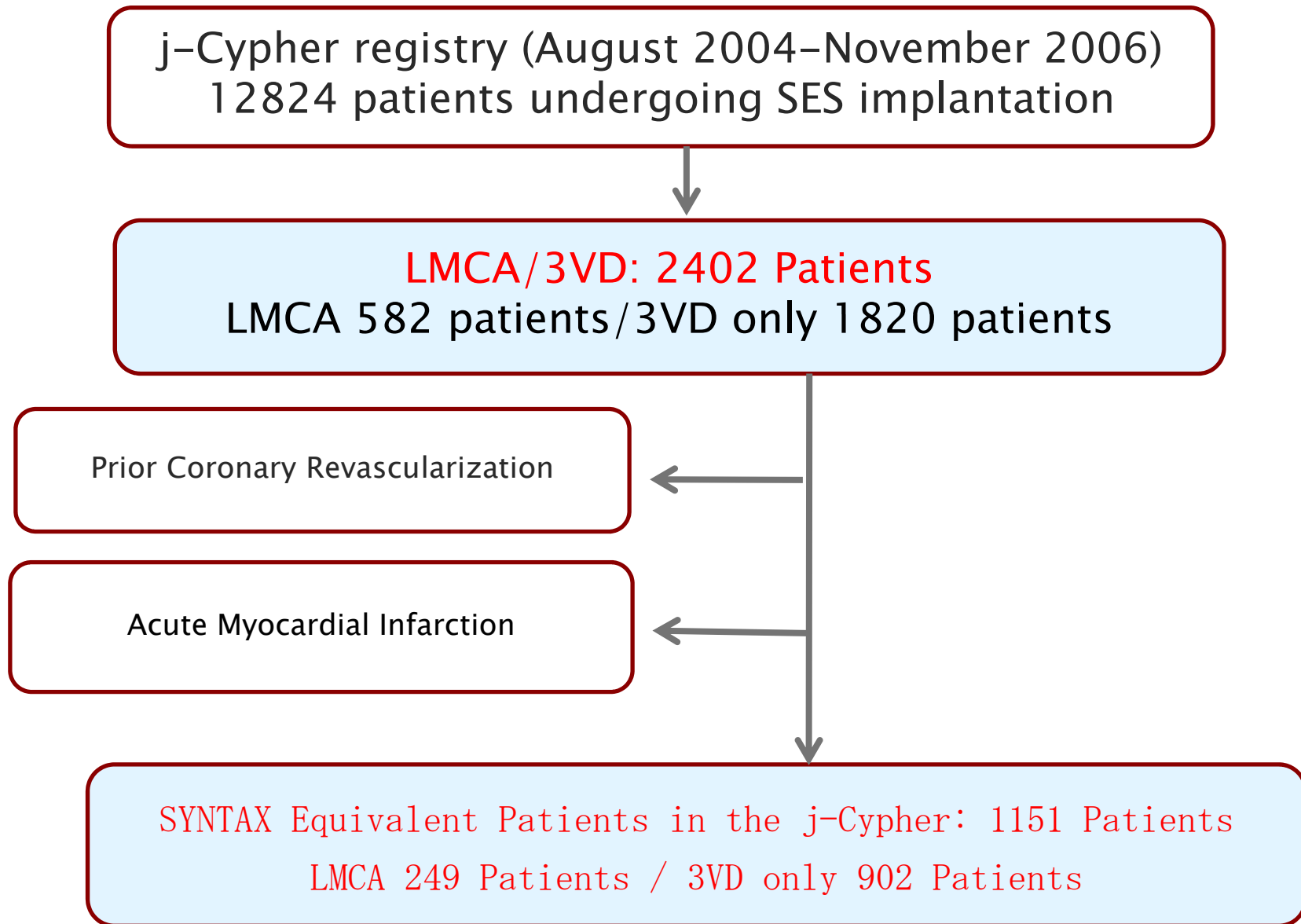
■ TAXUS (N=903)



Cumulative KM Event Rate  $\pm$  1.5 SE; log-rank  $P$  value; \*Binary rates

ITT population

*Analysis of SYNTAX Equivalent Patients in the j-Cypher Registry*



# Baseline Clinical and Procedural Characteristics

## SYNTAX Equivalent Patients in the j-Cypher vs. SYNTAX

	j-Cypher	SYNTAX PCI RCT	SYNTAX PCI Registry
Variables	N=1151	N=903	N=192
Age (years)	69.4±10.7	65.2±9.7	71.2±10.4
Male	71.0%	76.4%	70.3%
BMI	23.7±3.4	28.1±4.8	28.0±5.5
Medically-treated diabetes	38.3%	25.6%	30.2%
Insulin-requiring diabetes	12.6%	9.9%	15.1%
Current smoker	22.5%	18.5%	11.3%
Prior MI	12.7%	31.9%	40.4%
Prior stroke	14.1%	3.9%	7.8%
Congestive heart failure	17.8%	4.0%	9.7%
Unstable angina	21.6%	28.9%	38.0%
Ejection fraction <30%	4.8%	1.3%	5.7%
EuroSCORE	4.9±3.0	3.8±2.6	5.8±3.1
Attempted CTO (per patient)	19.9%	not reported	not reported
Number of stents implanted	2.9±1.6	4.6±2.3	3.1±1.8
Total stent length (mm)	64.0±38.6	86.1±47.9	58.5±41.2
Long stenting (>100mm)	15.6%	33.2%	12.2%

# One-Year Clinical Outcome

SYNTAX Equivalent Patients in the j-Cypher vs. SYNTAX

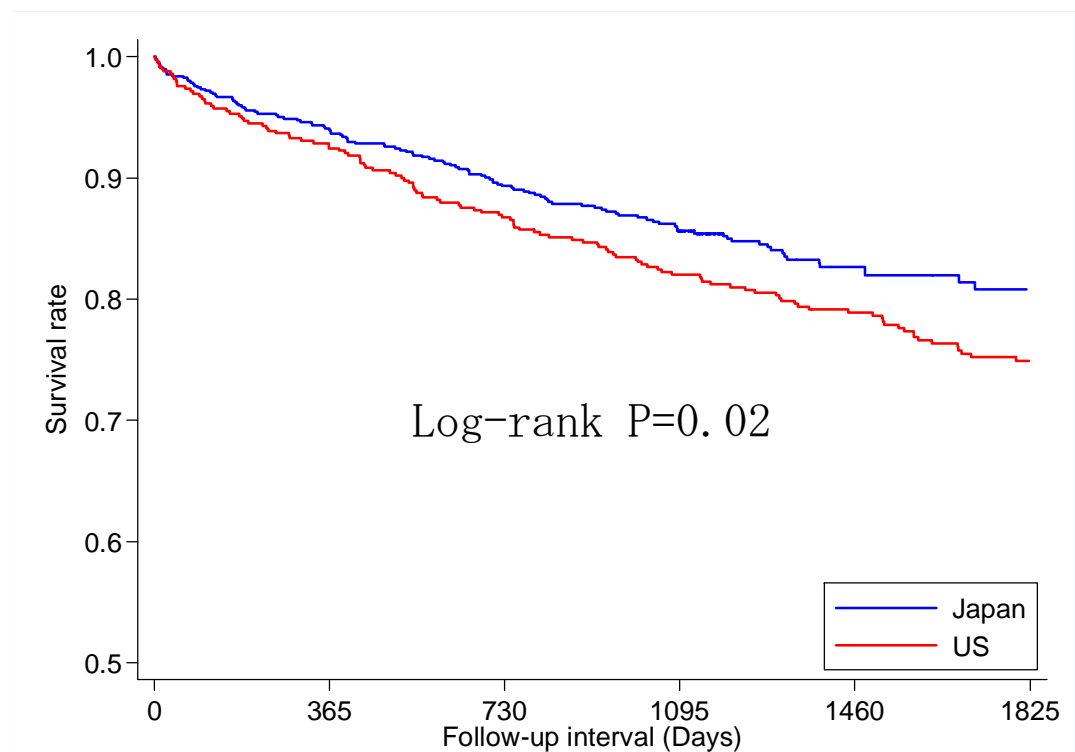
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	j-Cypher	SYNTAX PCI RCT	SYNTAX PCI Registry
Outcome measures	N=1151	N=903	N=192
Death	6.1%	4.4%	7.3%
Cardiac death	3.9%	3.7%	4.7%
Myocardial infarction	1.3%	4.8%	4.2%
ST (Protocol)	0.7%	3.3%	1.7%
Stroke	2.7%	0.6%	0.0%
Repeat revascularization	32.9%	13.5%	12.0%
Death/MI/Stroke/Revascularization	39.4%	17.8%	20.4%

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## *Unadjusted Kaplan-Meier Survival Curve*

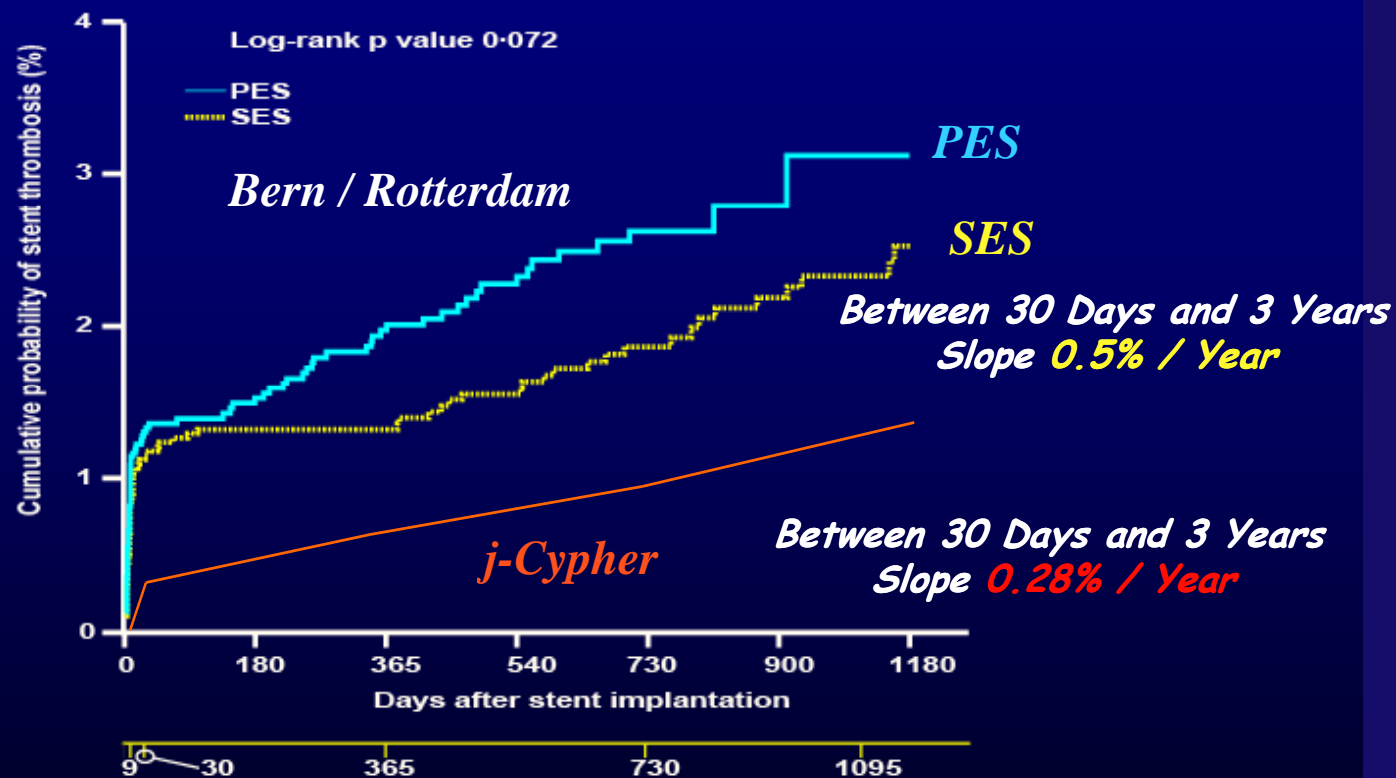
### *Insulin-treated Diabetic Patients*



		30d	1y	2y	3y	4y	5y
Japan	population at risk	736	688	630	448	241	112
n=750	survival rate	0.9853	0.9394	0.8932	0.8562	0.8266	0.8081
United States	population at risk	485	455	426	403	319	242
n=490	survival rate	0.9878	0.9245	0.8673	0.8204	0.7889	0.7492

# Definite Stent Thrombosis

## Bern/Rotterdam vs j-Cypher



### Bern / Rotterdam

Incidence, PES (%)	1.2	1.3	2.0	2.7	3.2
Patients at risk (n)	3626	3493	2667	1131	68
<b>Incidence, SES (%)</b>	<b>1.0</b>	<b>1.1</b>	<b>1.3</b>	<b>1.9</b>	<b>2.5</b>
<b>Patients at Risk (n)</b>	<b>3535</b>	<b>3508</b>	<b>2671</b>	<b>1710</b>	<b>903</b>

### j-Cypher

Cumulative Incidence (%)	0.3	0.4	0.6	0.8	1.2
Patients at Risk (n)	12682	12625	11843	9036	4191



# Baseline Characteristics

J-CYPHER Registry

## *j-Cypher Registry*

*Bern/Rotterdam*

*N=12824*

*N=8146*

*Age (years)*

*68.4 ± 10.3*

*62.6 ± 11.6*

*Male*

*75 %*

*75 %*

*Diabetes*

*41 %*

*16 %*

*Hypertension*

*75 %*

*46 %*

*Current smoking*

*20 %*

*37 %*

*Acute coronary syndrome*

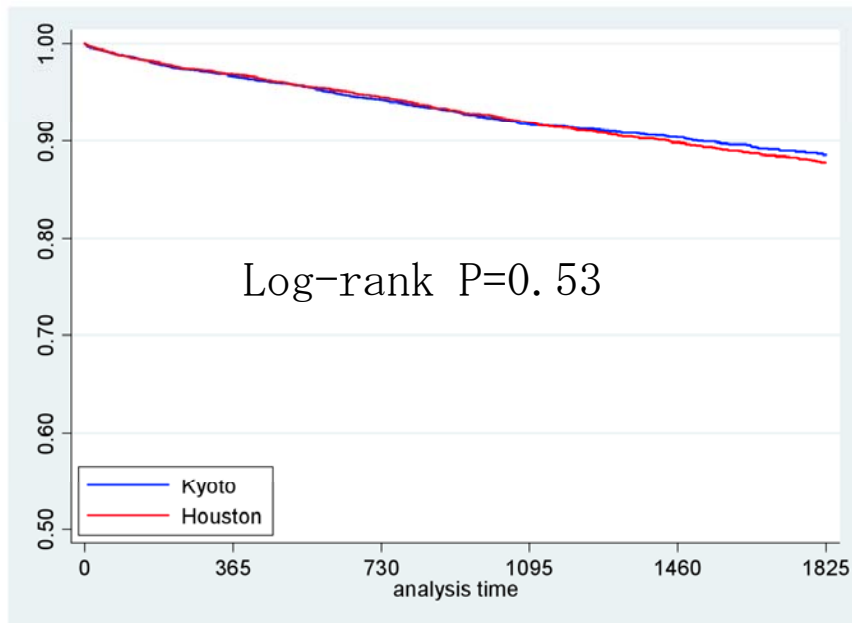
*25 %*

## *Risk Factors for Long-term Mortality*

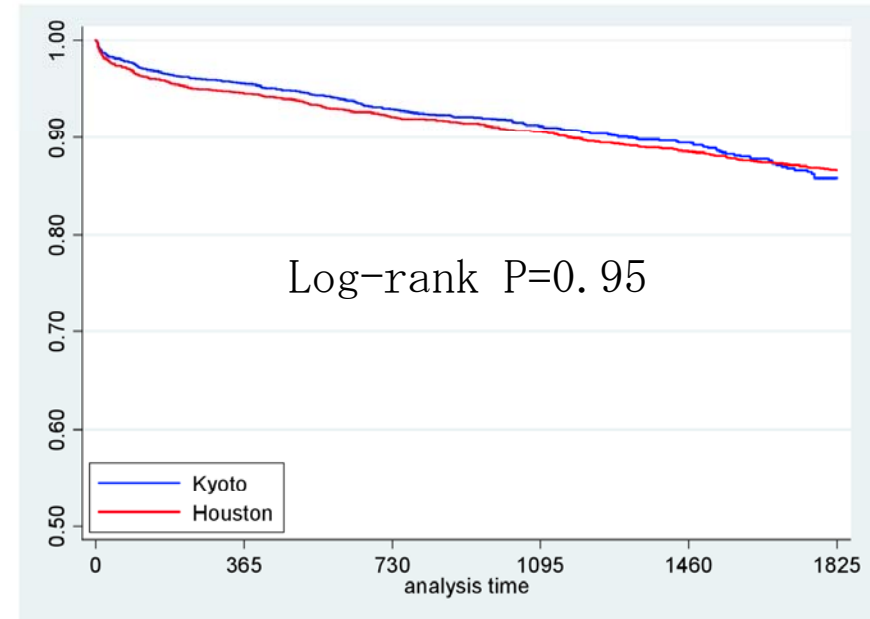
Variable	Japan		United States	
	HR	95% CI	HR	95% CI
Age $\geq 65$ years	2.74	2.29–3.27	3.01	2.65–3.43
Women	1.04	0.90–1.20	1.43	1.26–1.63
Hypertension	1.09	0.94–1.27	1.77	1.51–2.08
Diabetes mellitus	1.39	1.22–1.59	1.78	1.57–2.02
Hyperlipidemia	0.59	0.51–0.67	0.61	0.54–0.69
Family history of coronary artery disease	0.66	0.53–0.82	0.65	0.56–0.74
Smoking	0.91	0.80–1.05	1.08	0.96–1.22
Body mass index $\geq 25$ kg/m <sup>2</sup>	0.46	0.38–0.55	0.56	0.49–0.64
Previous myocardial infarction	1.45	1.26–1.67	1.36	1.21–1.54
History of heart failure	3.13	2.71–3.62	3.56	3.12–4.07
New York Heart Association class IV	3.17	2.25–4.46	2.96	2.50–3.50
Peripheral vascular disease	2.20	1.86–2.60	2.60	2.27–2.98
Cerebrovascular disease	1.78	1.52–2.07	2.42	1.98–2.97
Renal function				
Serum creatinine level $\leq 179$ $\mu\text{mol/L}$	1.00	—	1.00	—
Serum creatinine level $> 179$ $\mu\text{mol/L}$	6.98	5.54–8.78	2.68	2.30–3.13
Hemodialysis	6.12	5.07–7.40	8.83	6.68–11.7
No. of diseased vessels:				
1 Vessel	1.00	—	1.00	—
2 Vessels	1.48	1.23–1.78	1.22	1.04–1.43
3 Vessels	2.09	1.74–2.52	1.59	1.31–1.93
Left anterior descending artery disease	1.26	1.05–1.51	0.99	0.87–1.14
Left circumflex artery disease	1.43	1.23–1.65	1.30	1.14–1.49
Right coronary artery disease	1.59	1.37–1.85	1.21	1.06–1.37

## Unadjusted Kaplan-Meier Survival Curve

### PCI Stratum



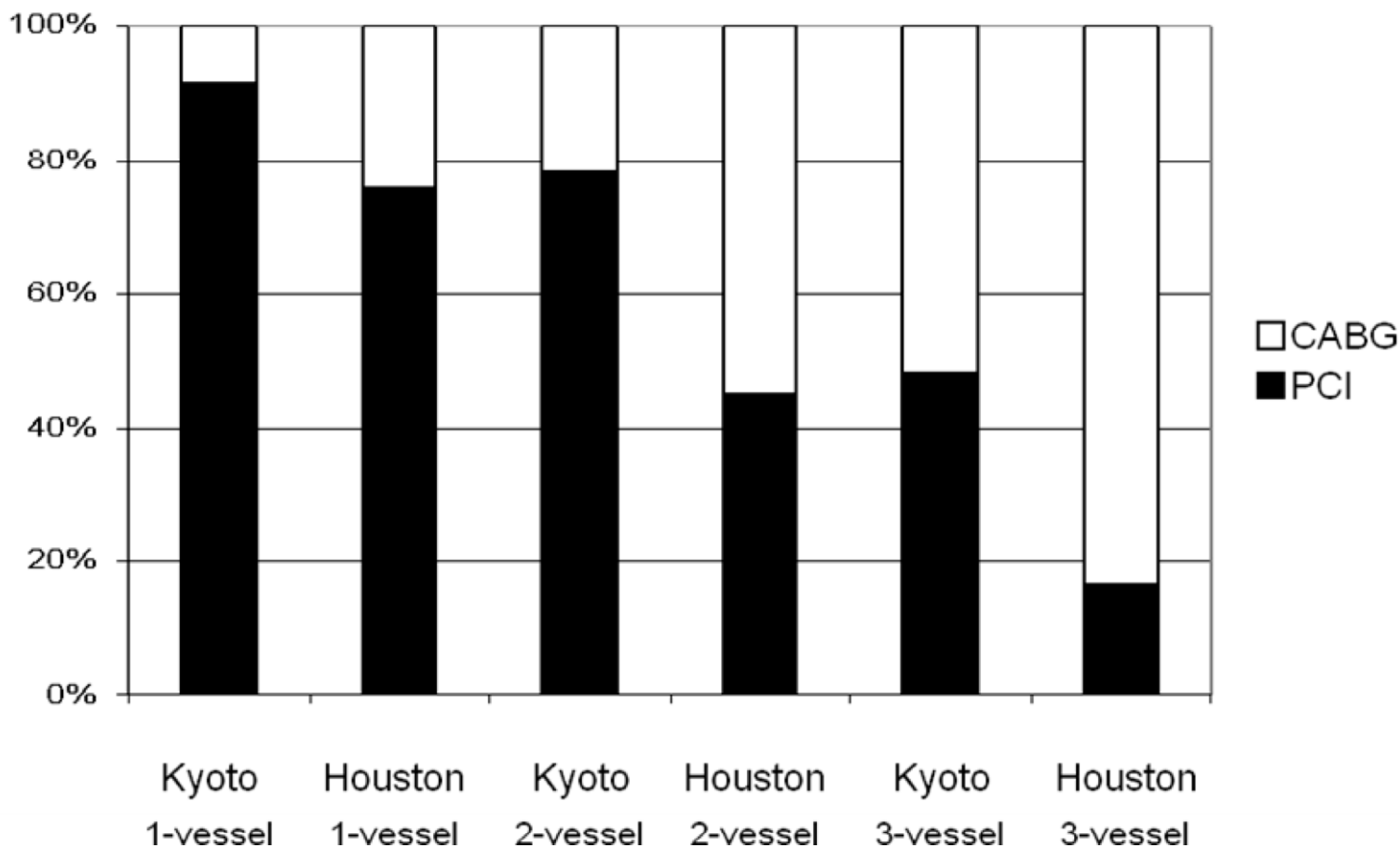
### CABG Stratum



		30 days	1 year	2 years	3 years	4 years	5 years
Kyoto		0.995	0.967	0.943	0.917	0.904	0.886
N	6,510	6,434	6,182	5,877	4,279	2,171	786
Houston		0.995	0.969	0.946	0.920	0.898	0.878
N	4,076	4,054	3,947	3,852	3,746	2,879	2,132

		30 days	1 year	2 years	3 years	4 years	5 years
Kyoto		0.984	0.956	0.930	0.912	0.895	0.858
n	2,361	2,301	2,209	2,095	1,576	909	349
Houston		0.979	0.946	0.922	0.905	0.885	0.866
n	3,153	3,090	2,981	2,905	2,855	2,364	1,808

## Selection of Revascularization Modalities According to Number of Vessels Diseased



## *Baseline Characteristics*

Variable	Missing Data	Japan (n = 8,871)	United States (n = 7,229)	p Value
Age (years)	0	67.2 ± 10.0	62.7 ± 11.1	<0.001
Women	0	29.1%	29.9%	0.28
Body mass index (kg/m <sup>2</sup> )	439	23.7 ± 3.2	29.3 ± 5.8	<0.001
Coronary artery bypass grafting	0	26.6%	43.6%	<0.001
History of myocardial infarction	80	26.3%	34.3%	<0.001
History of heart failure	99	15.4%	14.0%	0.013
New York Heart Association functional class IV	105	1.4%	7.4%	<0.001
Peripheral vascular disease	76	11.3%	14.7%	<0.001
Cerebrovascular disease	75	16.4%	5.0%	<0.001
Valve disease	85	7.6%	6.1%	<0.001
Renal insufficiency	195	6.4%	11.4%	<0.001
Hemodialysis	0	4.0%	1.1%	<0.001
Hypertension	73	69.5%	74.3%	<0.001
Diabetes mellitus	76	39.2%	31.0%	<0.001
Hyperlipidemia	87	51.3%	61.5%	<0.001
Family history of coronary artery disease	537	15.7%	33.9%	<0.001
Smoking	238	52.9%	46.0%	<0.001