Optimal Antithrombotic Therapy After PCI in Japan:

Why We Are Going Our Own Way?

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Disclosures

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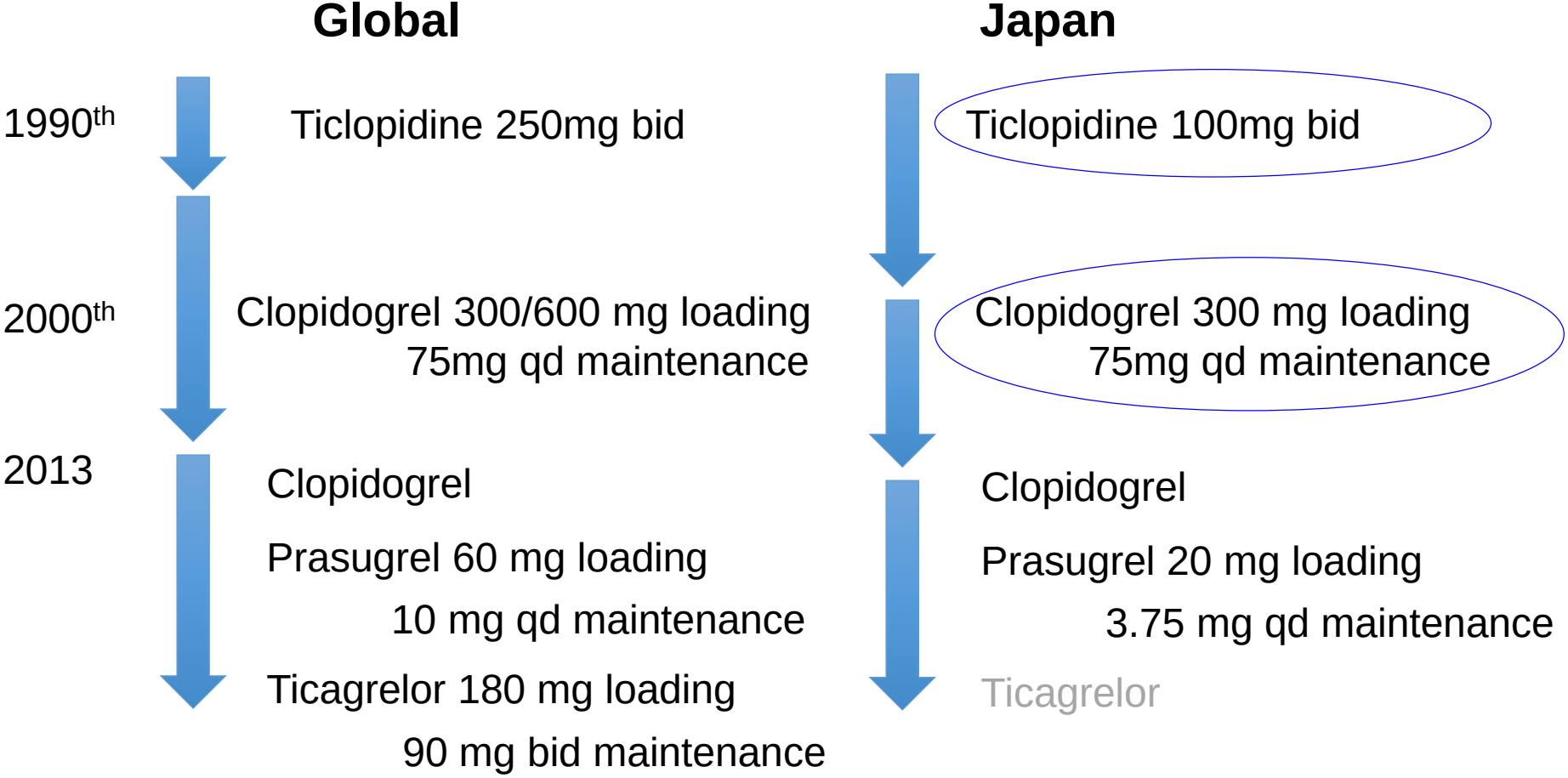
ABBOTT Vascular, Boston Scientific,

Daiichi-Sankyo, Sanofi, and Bayer

History of $P2Y_{12}$ Inhibitors in PCI

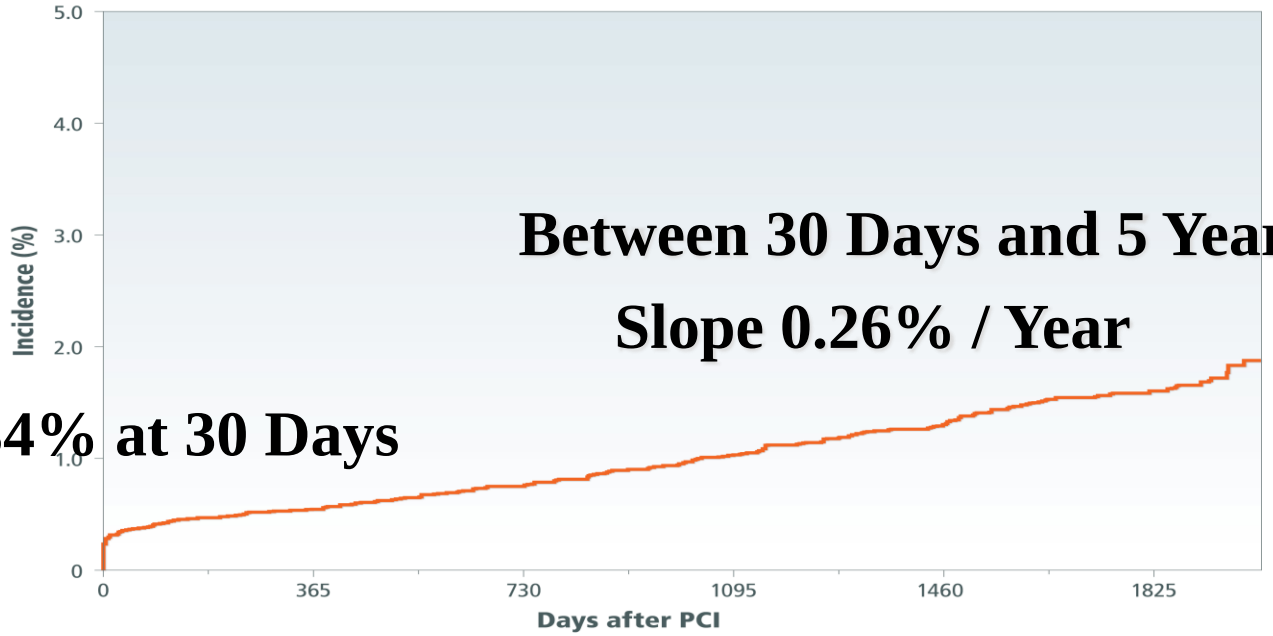


Goto S. Circulation 2019. Modified.

Stent Thrombosis of SES

J-CYPHER Registry

ARC Definite ST



Between 30 Days and 5 Years

Slope 0.26% / Year

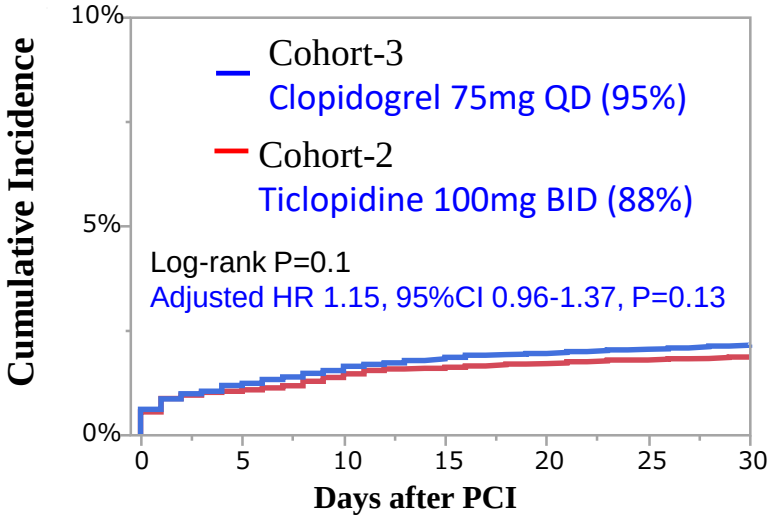
0.34% at 30 Days

		30 Days	1 Year	2 Years	3 Years	4 Years	5 Years
Cumulative incidences		0.34%	0.55%	0.76%	1.03%	1.33%	1.6%
N of events		44	70	93	121	146	164
N of patients at risk	12812	12627	11967	10813	9244	7640	4431

Kimura T, et al. Circulation 2012;125:584-591.

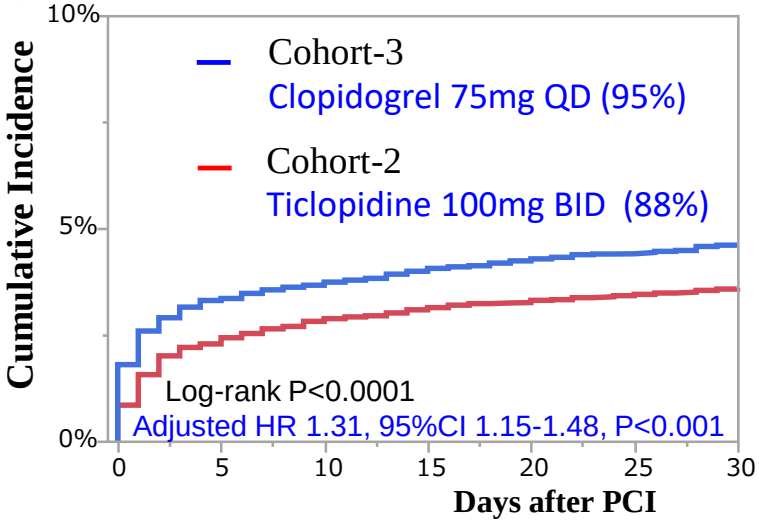
Historical Comparison of the 30-day Outcomes in PCI patients between CREDO-Kyoto Registry Cohort-2 and Cohort-3

Myocardial Infarction/Ischemic Stroke



Interval	0-day	7-day	14-day	30-day
Cohort-3				
N of patients at risk	13258	12857	12744	12602
Cumulative incidence		1.4%	1.8%	2.2%
Cohort-2				
N of patients at risk	12161	11843	11742	11638
Cumulative incidence		1.2%	1.6%	1.9%

Major Bleeding (GUSTO moderate/severe)



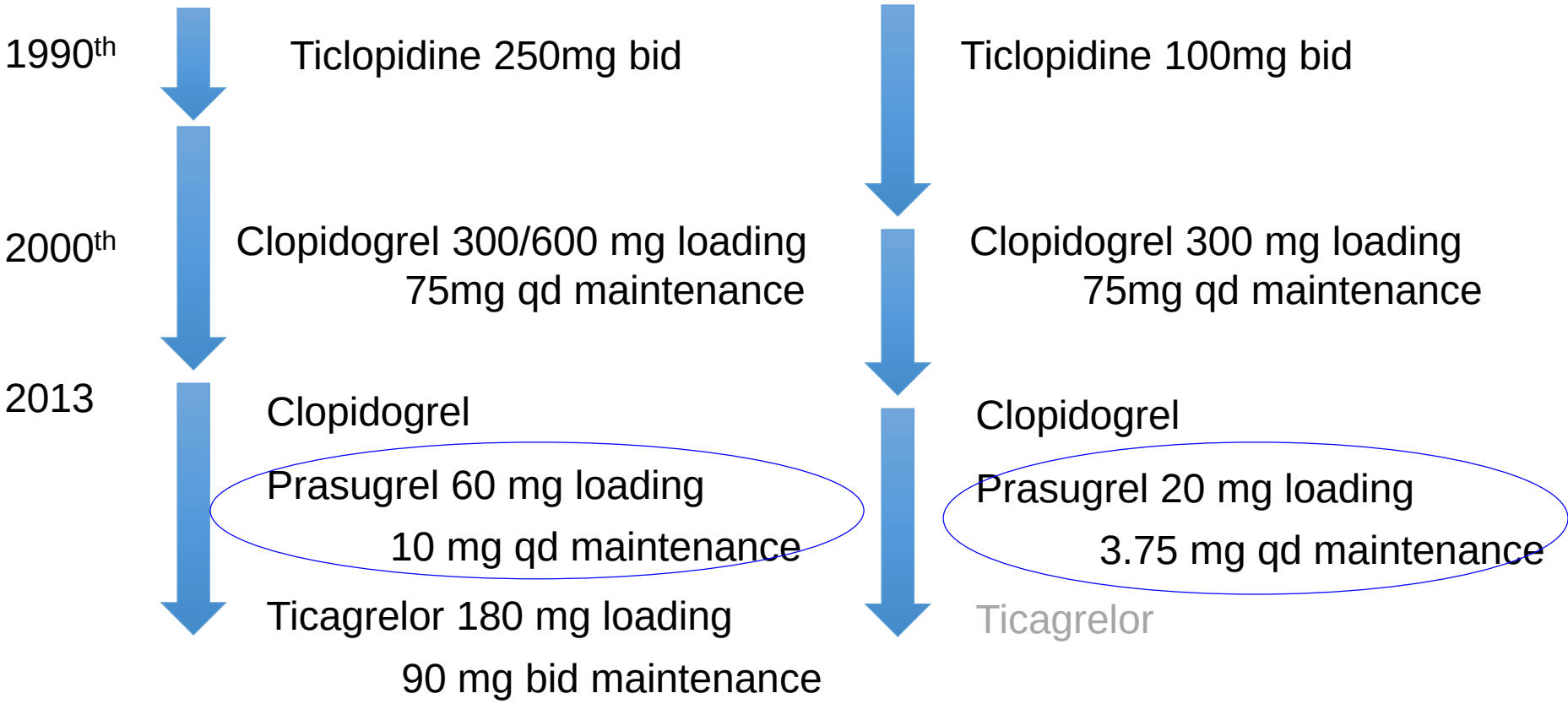
Interval	0-day	7-day	14-day	30-day
Cohort-3				
N of patients at risk	13258	12631	12531	12382
Cumulative incidence		3.6%	4.0%	4.6%
Cohort-2				
N of patients at risk	12161	11709	11614	11499
Cumulative incidence		2.6%	3.1%	3.6%

Adjusted for those factors affecting bleeding:
demographic factors, radial approach, bare-metal stent use, aspirin dose, oral anticoagulants use, cilostazole use, PPI/H2 blocker use, and DAPT discontinuation.
Not adjusted for the P2Y12 inhibitors

Japanese dose ticlopidine compared with global dose clopidogrel was associated with lower risk for major bleeding without increased ischemic risk.

Natsuaki M, et al. Circ J. 2021.

History of $P2Y_{12}$ Inhibitors in PCI

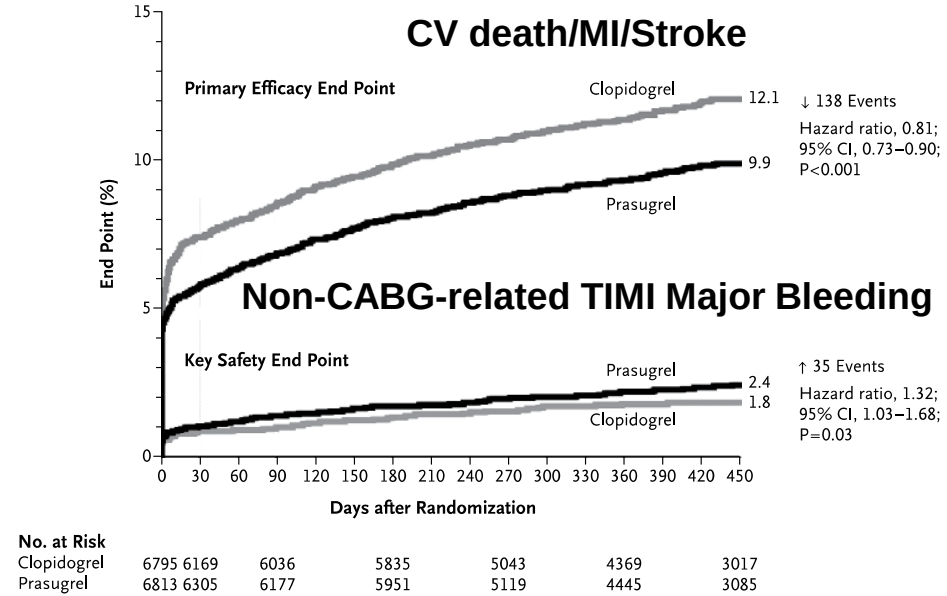


Goto S. Circulation 2019. Modified.

Prasugrel: Global dose versus Japanese dose

TRITON-TIMI 38

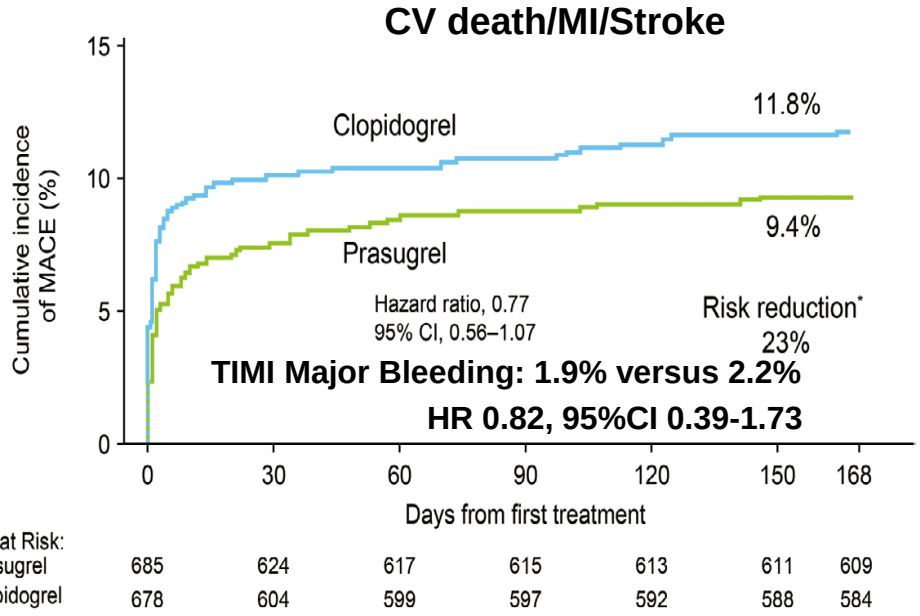
Prasugrel: 60mg loading and 10mg maintenance



Wiviott SD, et al. NEJM 2007.

PRASFIT-ACS

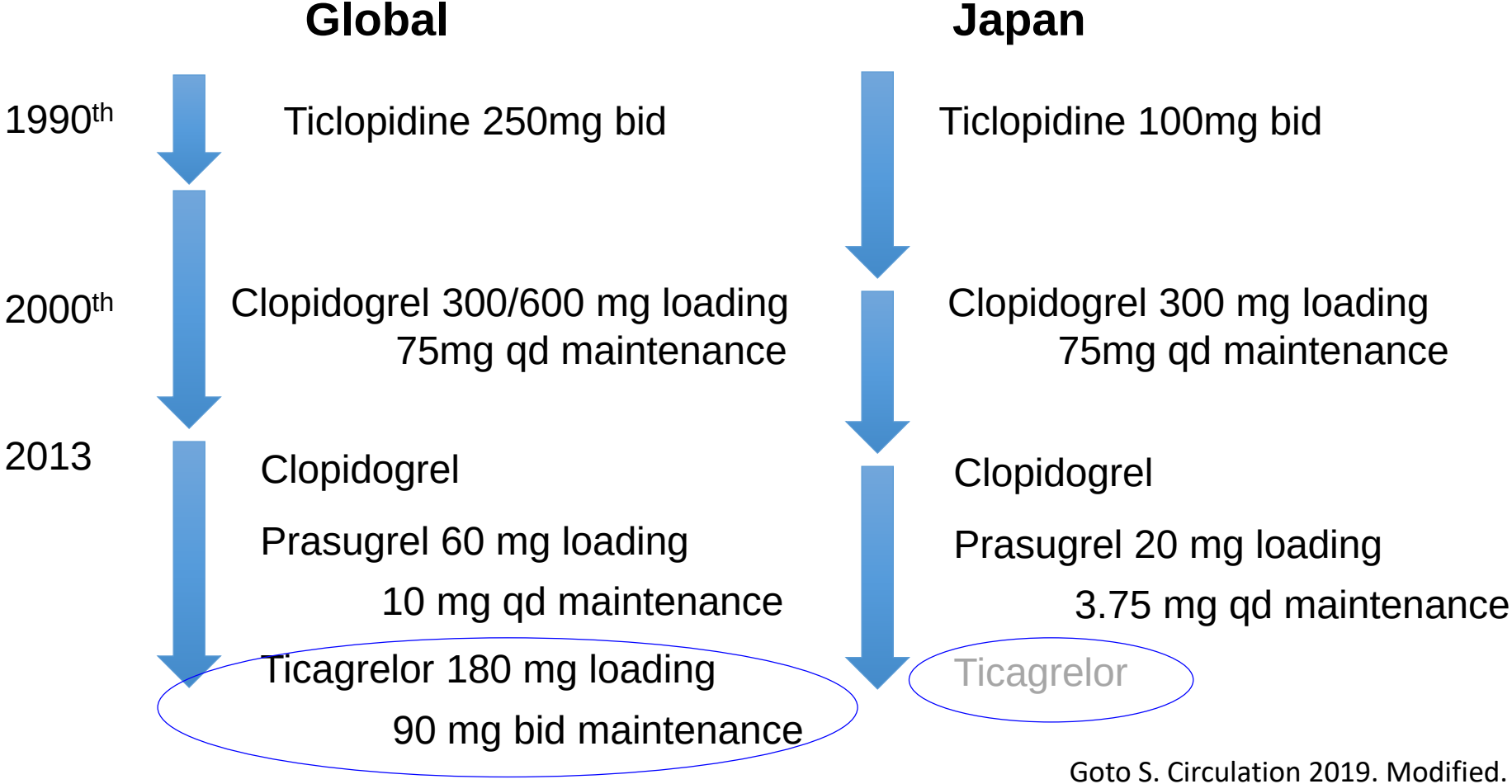
Prasugrel: 20mg loading and 3.75mg maintenance



Saito S, et al. Circ J 2014.

Japanese dose prasugrel compared with global dose prasugrel was associated with similar efficacy in reducing CV events without increased bleeding risk, although the PRASFIT-ACS was an underpowered study.

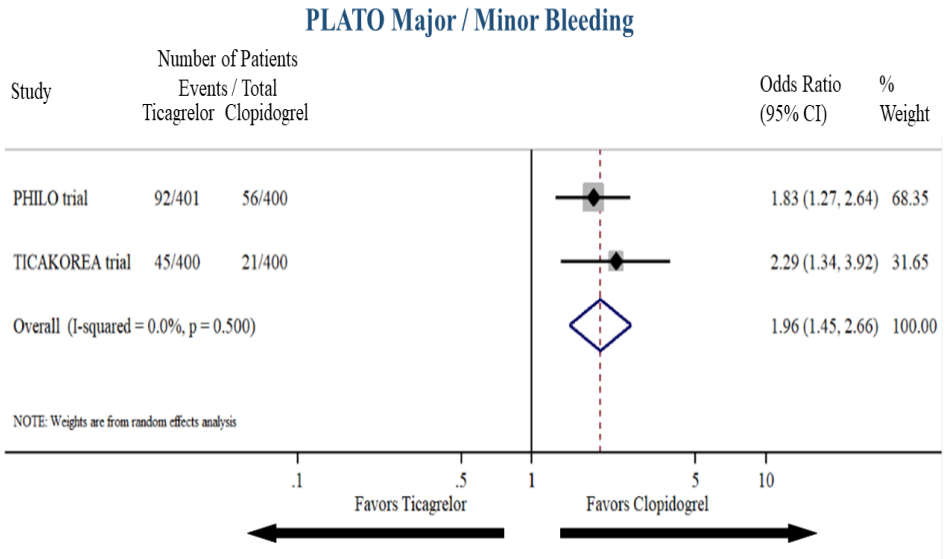
History of $P2Y_{12}$ Inhibitors in PCI

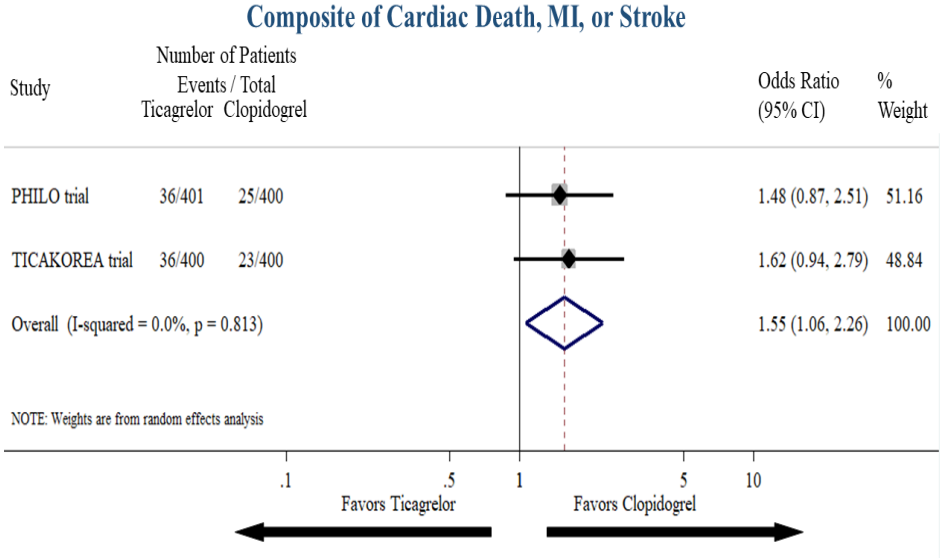


Goto S. Circulation 2019. Modified.

Pooled Analysis of PHILO and TICAKOREA

Ticagrelor versus Clopidogrel in ACS Patients





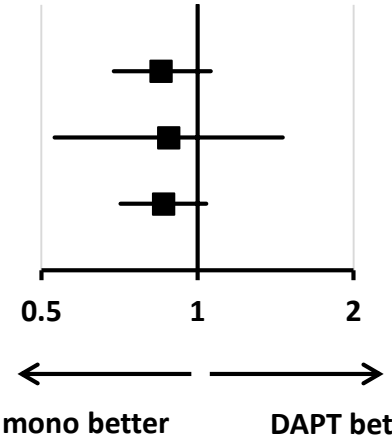
Goto S, et al. Circ J 2015.

Park DW, et al. Circulation 2019.

Metaanalysis including 5 short DAPT studies, ACS subset

Death, MI and Stroke (1-year)

	P2Y12i mono		DAPT		HR (95%CI)
P2Y12i type					
Newer P2Y12i	158/5845	(3.0%)	187/5884	(3.7%)	0.85 (0.69-1.06)
Clopidogrel	28/1103	(2.9%)	33/1134	(3.2%)	0.88 (0.53-1.46)
Overall	186/6948	(3.0%)	220/7018	(3.7%)	0.86 (0.71-1.04)

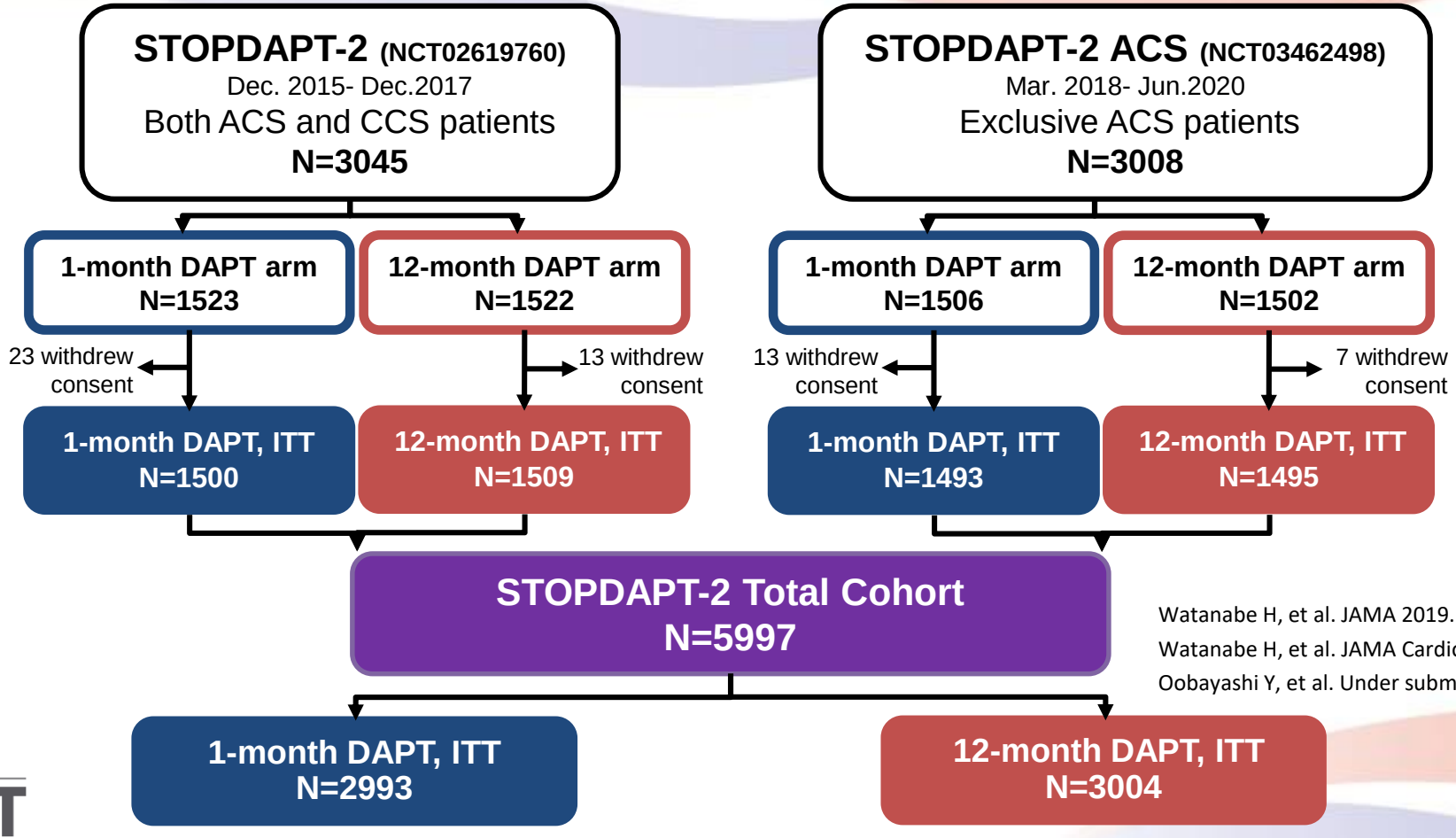


However, monotherapy with newer P2Y12i was the dominant strategy in ACS patients in these very short DAPT studies. Global doses of newer P2Y12i are never used in Japan, and therefore, we have to generate our own data supporting further de-escalation of antithrombotic therapy to guide the practice in Japan.

Valgimigli M, et al. BMJ 2021.

STOPDAPT-2 Total cohort

STOPDAPT-2 Total Cohort

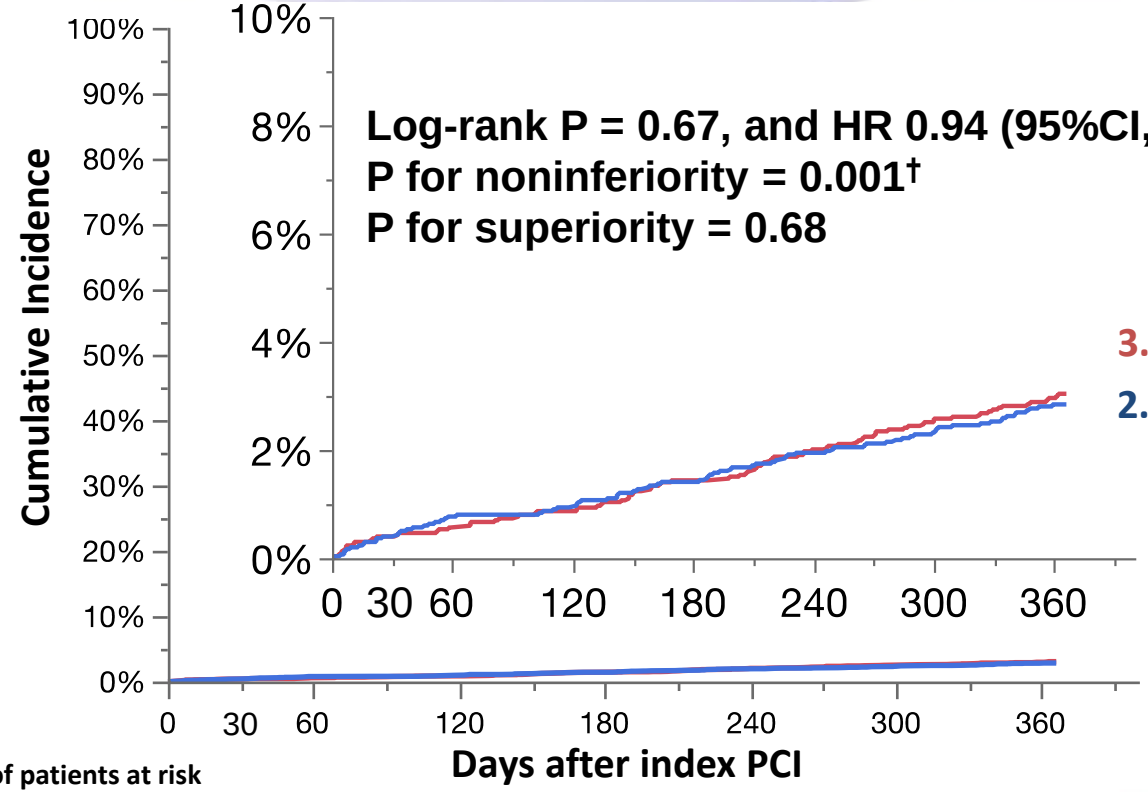


Watanabe H, et al. JAMA 2019.
Watanabe H, et al. JAMA Cardiol (In-press).
Oobayashi Y, et al. Under submission.

CRF TCT

Primary Endpoint

CV death/MI/ST/Stroke/TIMI major/minor bleeding



*Adjusted by ACS and study (STOPDAPT-2 vs. STOPDAPT-2 ACS).

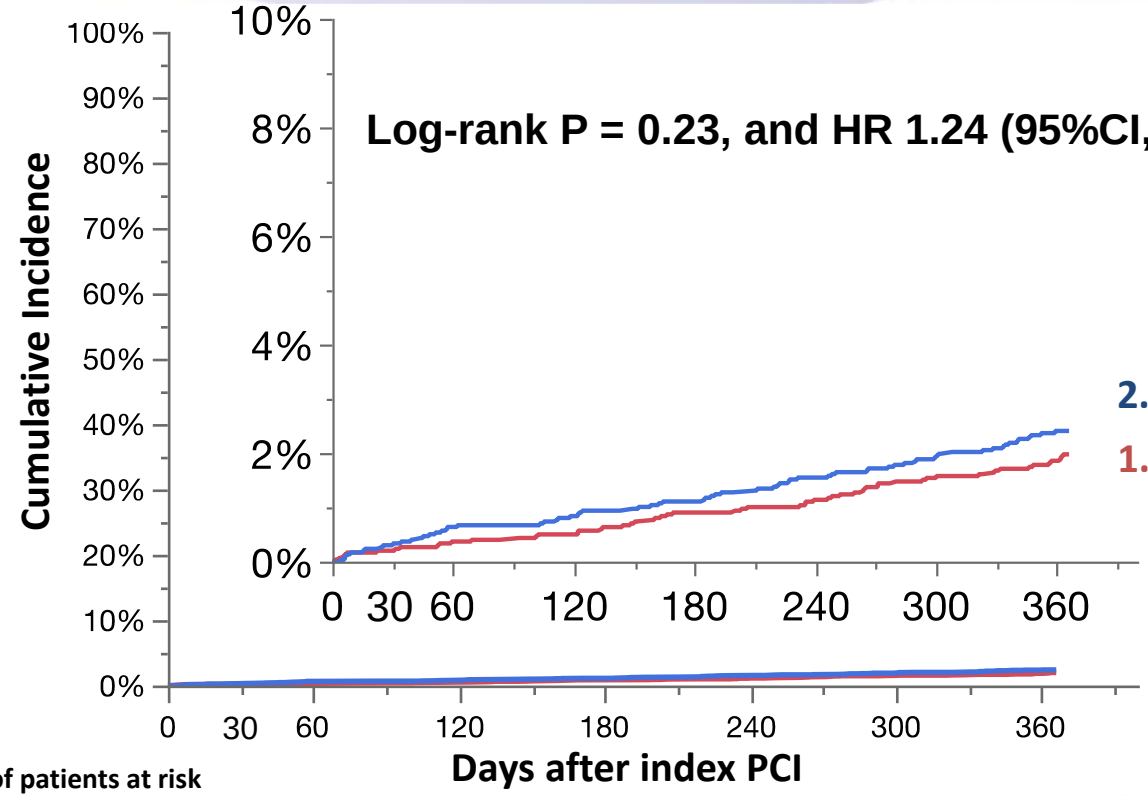
†Non-inferiority margin: 50% on the hazard ratio scale

Number of patients at risk

12-month DAPT	3004	2991	2970	2959	2941	2922	2902	2327
1-month DAPT	2993	2980	2956	2946	2928	2905	2885	2357

Major Secondary CV Endpoint

CV death/MI/ST/Stroke



Log-rank P = 0.23, and HR 1.24 (95%CI, 0.88–1.75)*

2.40% 1-month DAPT

1.97% 12-month DAPT

*Adjusted by ACS and study (STOPDAPT-2 vs. STOPDAPT-2 ACS).

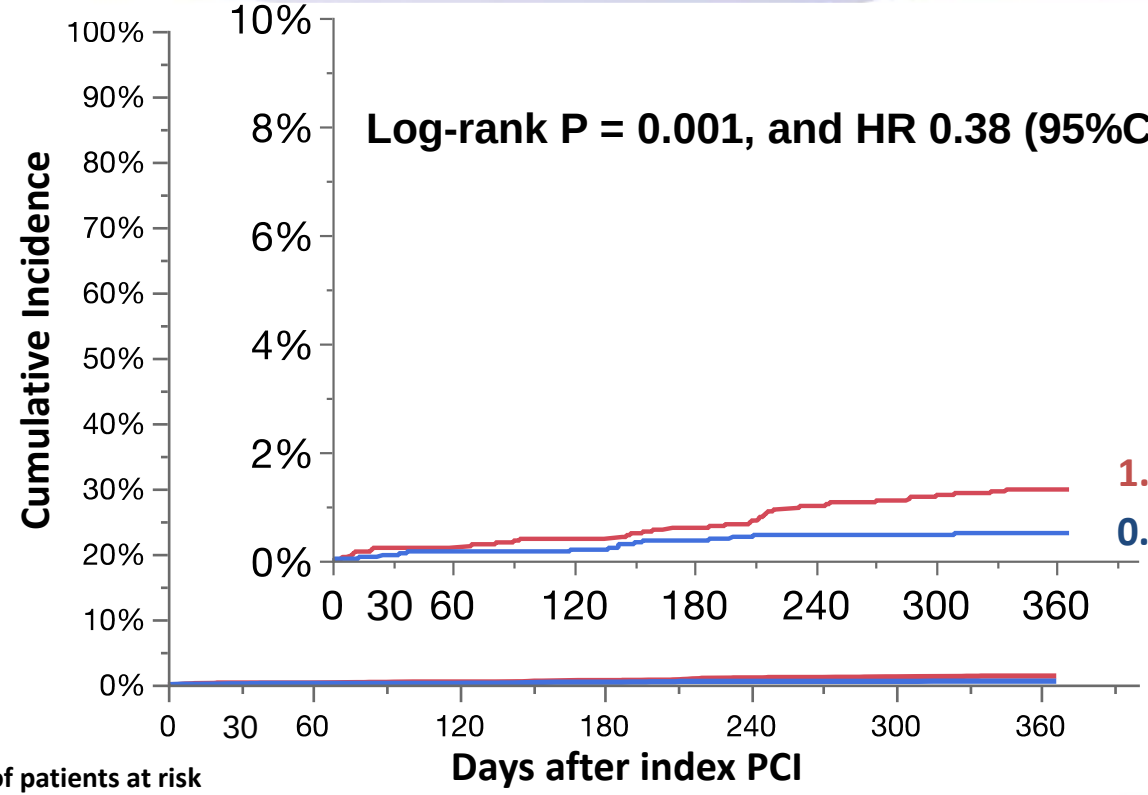
Number of patients at risk

12-month DAPT	3004	2997	2977	2970	2957	2947	2930	2352
1-month DAPT	2993	2983	2960	2950	2937	2917	2897	2369

STOPDAPT-2 Total cohort

Major Secondary Bleeding Endpoint

TIMI major/minor bleeding



Log-rank P = 0.001, and HR 0.38 (95%CI, 0.21–0.70)*

1.31% 12-month DAPT

0.50% 1-month DAPT

*Adjusted by ACS and study (STOPDAPT-2 vs. STOPDAPT-2 ACS).

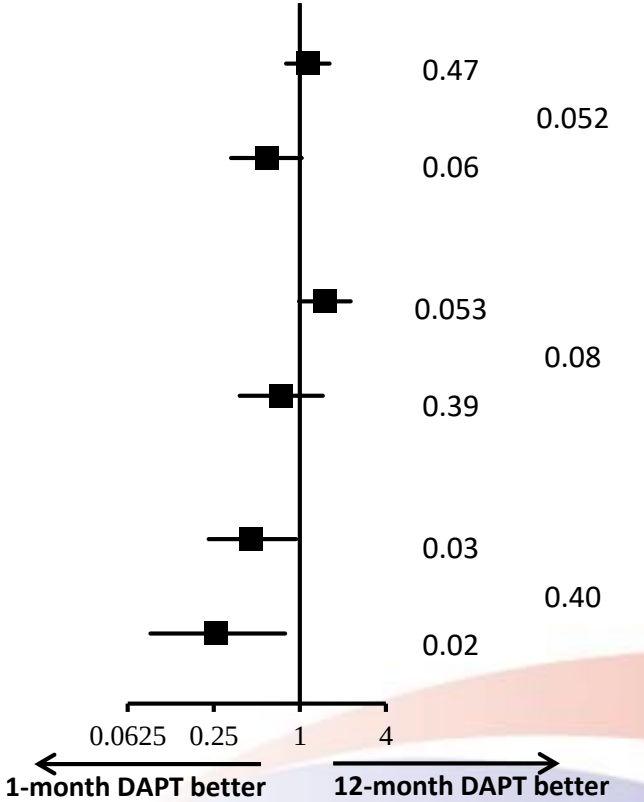
Number of patients at risk

12-month DAPT	3004	2995	2977	2968	2957	2941	2929	2360
1-month DAPT	2993	2985	2970	2965	2955	2941	2927	2400

CRF TCT

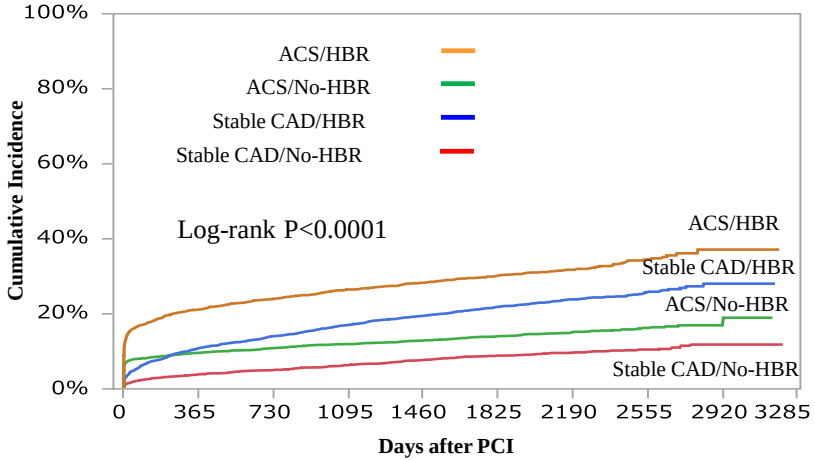
ACS/CCS Subgroup Analysis

	1-year incidence (N with event/subtotal N)				P value	$P_{interaction}$
	1-month DAPT (N=2993)	12-month DAPT (N=3004)	Absolute difference (95%CI)	Hazard Ratio (95%CI)		
Primary Endpoint						
ACS	3.20% 65/2058	2.83% 58/2078	0.40% (-0.68% to 1.42%)	1.14 (0.80-1.62)	0.47	0.052
CCS	2.05% 19/935	3.49% 32/926	-1.44% (-2.95% to 0.07%)	0.59 (0.33-1.03)	0.06	
Major Secondary Cardiovascular Endpoint						
ACS	2.76% 56/2058	1.86% 38/2078	0.90% (-0.02% to 1.82%)	1.50 (0.99-2.27)	0.053	0.08
CCS	1.62% 15/935	2.21% 20/926	-0.59% (-1.85% to 0.67%)	0.74 (0.38-1.45)	0.39	
Major Secondary Bleeding Endpoint						
ACS	0.54% 11/2058	1.17% 24/2078	-0.63% (-1.20% to -0.06%)	0.46 (0.23-0.94)	0.03	0.40
CCS	0.43% 4/935	1.63% 15/926	-1.20% (-2.13% to -0.27%)	0.26 (0.09-0.79)	0.02	



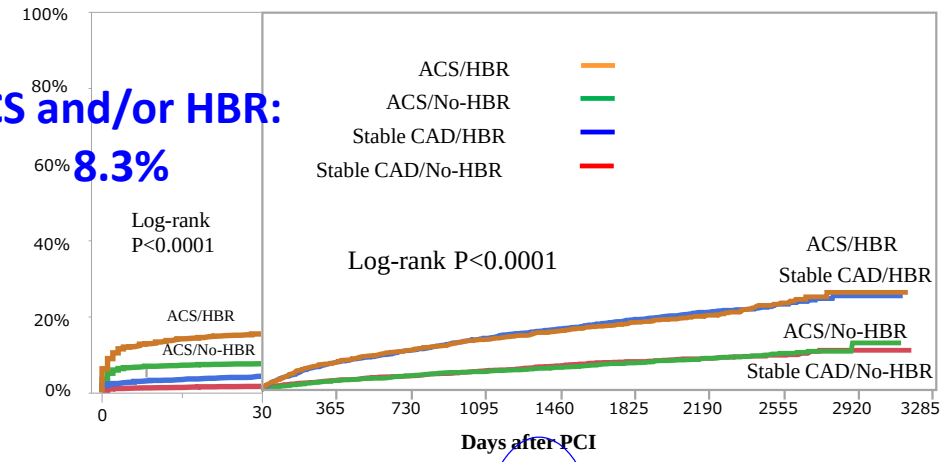
CREDO-Kyoto PCI/CABG Registry Cohort-3 ACS/HBR Analysis

Major Bleeding (BARC type 3 or 5)



Interval	0-day	30-day	1-year	3-year	5-year
ACS/HBR group					
N of patients with event		377	504	608	668
N of patients at risk	2502	1965	1639	1339	973
Cumulative incidence		15.4%	21.2%	26.5%	30.1%
ACS/No-HBR group					
N of patients with event		230	287	354	408
N of patients at risk	3019	2738	2616	2445	2007
Cumulative incidence		7.7%	9.6%	12.0%	14.0%
Stable CAD/HBR group					
N of patients with event		168	415	628	770
N of patients at risk	3905	3692	3246	2691	1952
Cumulative incidence		4.3%	10.9%	17.1%	21.9%
Stable/No-HBR group					
N of patients with event		62	148	239	326
N of patients at risk	3832	3760	3606	3394	2784
Cumulative incidence		1.6%	3.9%	6.4%	8.8%

ACS and/or HBR: 8.3%



Interval	0-day	7-day	30-day	1-year	3-year	5-year
ACS/HBR group						
N of patients with event		313	377	127	231	291
N of patients at risk	2502	2088	1965	1639	1339	973
Cumulative incidence		12.7%	15.4%	6.9%	13.2%	17.4%
ACS/No-HBR group						
N of patients with event		206	230	57	124	178
N of patients at risk	3019	2783	2738	2616	2445	2007
Cumulative incidence		6.8%	7.7%	2.1%	4.7%	6.9%
Stable CAD/HBR group						
N of patients with event		116	168	247	460	602
N of patients at risk	3905	3768	3692	3246	2691	1952
Cumulative incidence		3.0%	4.3%	6.9%	13.3%	18.3%
Stable/No-HBR group						
N of patients with event		45	62	86	177	264
N of patients at risk	3832	3782	3760	3606	3394	2784
Cumulative incidence		1.2%	1.6%	2.3%	4.8%	7.3%

Natsuaki M, et al. Circ J. 2021.

STOPDAPT-3 Trial Exploring Completely Aspirin-free Strategy

＜Entry Criteria＞

1. **PCI with planned exclusive use of CoCr-EES (XIENCE)**
2. **ARC-HBR or ACS presentation**
3. **Eligible for DAPT (Aspirin/$P2Y_{12}$ inhibitor) for 1 month**

No Exclusion Criteria

Informed Consent Before Angiography

Randomization After Angiography, but Before PCI

Loading: Prasugrel 20mg

No aspirin Group

1500 Patients

Prasugrel Monotherapy for 1M

1-month DAPT Group

1500 Patients

Loading Aspirin also, if Aspirin naïve

DAPT (Aspirin and Prasugrel) for 1M

Primary Analysis at 1-Month

Co-primary Bleeding Endpoint：BARC 3 or 5 bleeding at 1M (Superiority)

Co-primary Cardiovascular Endpoint : CV death/MI/Ischemic Stroke/ST at 1M (Non-inferiority)

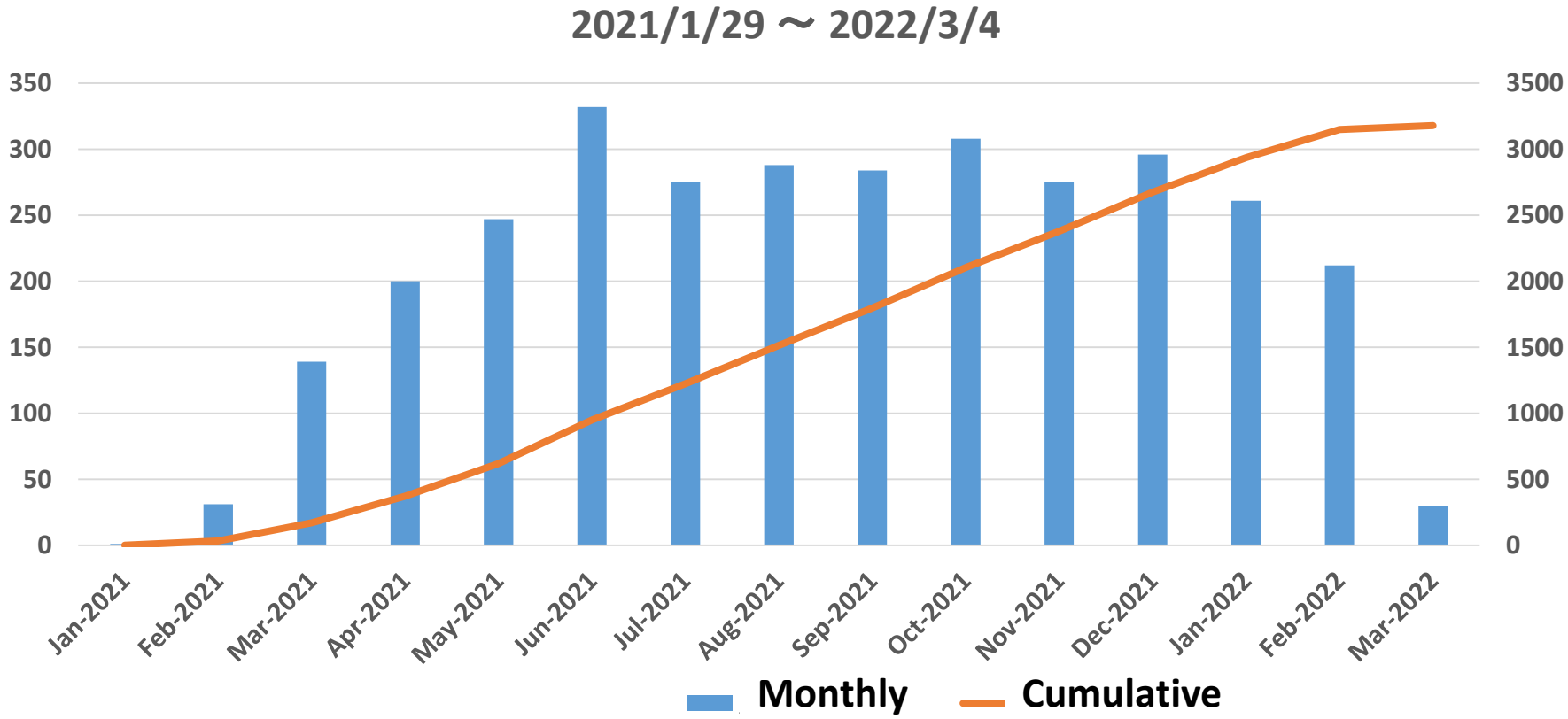
Clopidogrel Monotherapy
Between 1M and 12 M

Exploratory Analysis

Aspirin Monotherapy
Between 1M and 12 M

STOPDAPT-3 Enrollment Status (Target: 3110 patients)

2022. 3. 4 **3179 patients (ACS N=2248, Non-ACS HBR N=931)**



STOPDAPT-3: Event rates at 30-day in the initial 1200 patients (Blinded evaluation, Adjudicated)

Outcome	N (%)	Assumed event rate
Co-primary bleeding endpoint (BARC 3 or 5 Bleeding)	50 (4.2%)	5.8%
Co-primary CV endpoint (CVD, MI, Definite ST, Ischemic Stroke)	39 (3.3%)	6.2%
Death	23 (1.9%)	
CVD	23 (1.9%)	
MI	9 (0.8%)	
Definite ST	3 (0.3%)	
Stroke	9 (0.8%)	
Ischemic	7 (0.6%)	
Hemorrhagic	2 (0.2%)	
BARC 3	45 (3.8%)	
BARC 5	5 (0.4%)	

Conclusions

Antithrombotic therapy in ACS patients in Japan as compared with outside Japan has already been de-escalated with use of low intensity $P2Y_{12}$ inhibitor. Therefore, we have to generate our own data supporting further de-escalation of antithrombotic therapy to guide the clinical practice in Japan.

The STOPDAPT-2 trial has suggested safety and efficacy of 1-month DAPT followed by clopidogrel monotherapy after PCI in Japanese patients.

We are currently conducting the STOPDAPT-3 trial, which would be an adequately powered trial exploring completely aspirin-free strategy without any DAPT background in an attempt to reduce major bleeding early after PCI in ACS and/or HBR patients.