Expectation of Prasugrel Use in Japanese PCI Patients

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On behalf of PRASFIT Study Investigators

Study funded by Daiichi Sankyo Company, Limited
PRASFIT-ACS:JapicCTI-No: JapicCTI-111550*
*PRASFIT-Elective**:JapicCTI-No: JapicCTI-101339*

** PRASugrel compared to clopidogrel For Japanese PatlenTs with ACS Undergoing PCI*
*** PRASugrel For Japanese PatlenTs with Coronary Artery Disease Undergoing Elective PCI*

Speaker's name: Naoto Inoue

☑ **I have the following** potential conflicts of interest to report:

Research contracts
☑ Consulting-Kaneka, Medicon, Fukuda
Employment in industry
Stockholder of a healthcare company
Owner of a healthcare company
Other(s)

I do not have any potential conflict of interest

66 y.o. Male

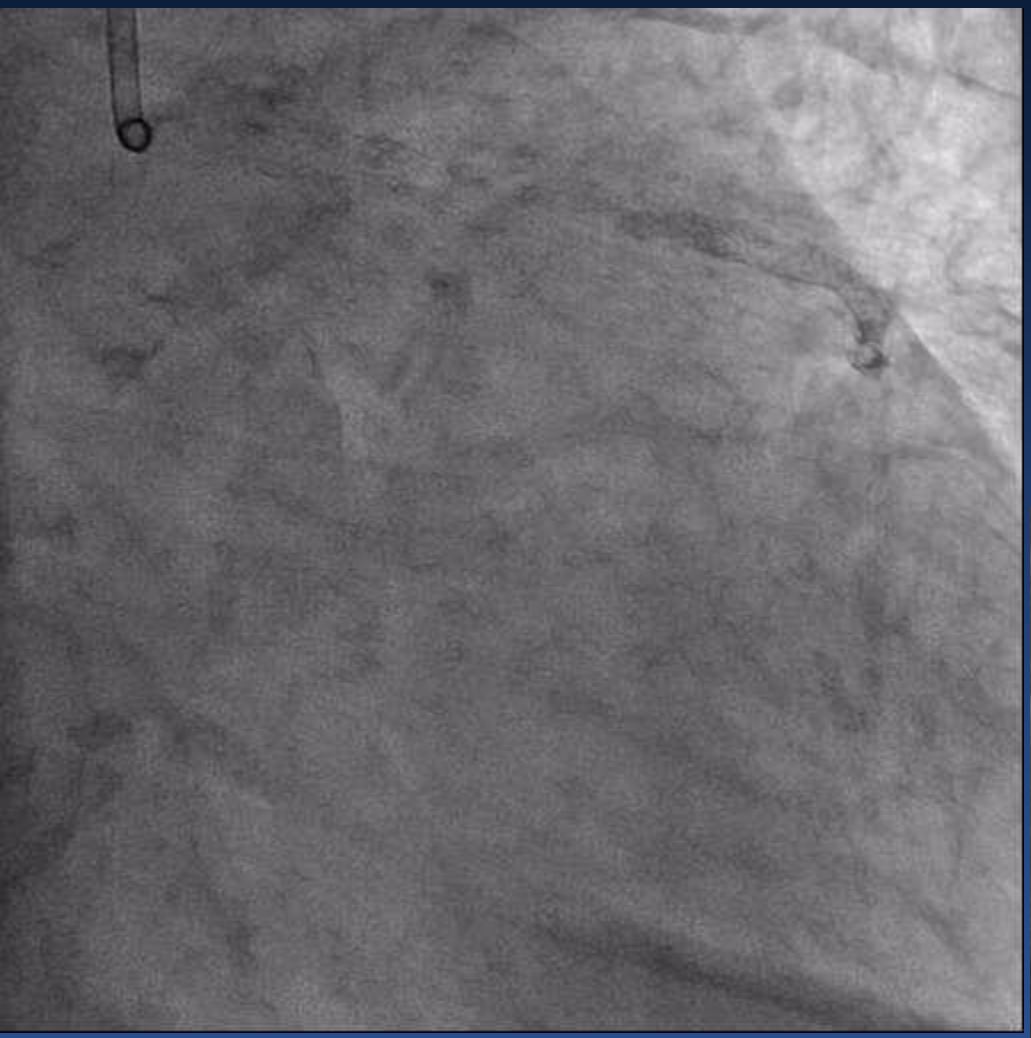
NOBORI stent was implanted in LMT in Oct. 2013

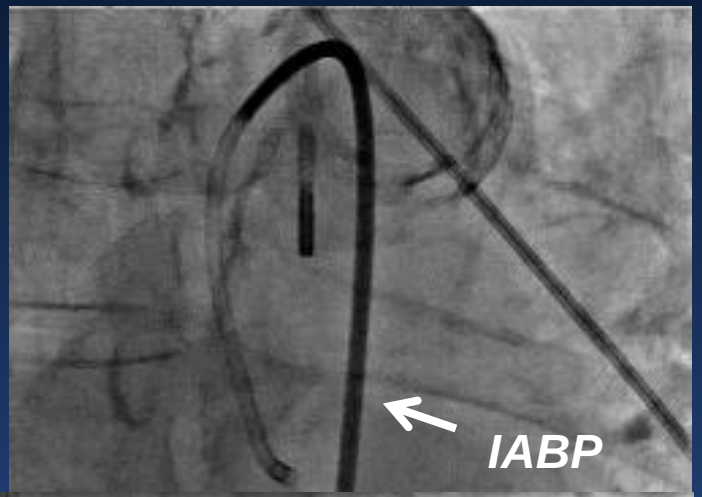
Antiplatlet regiemen

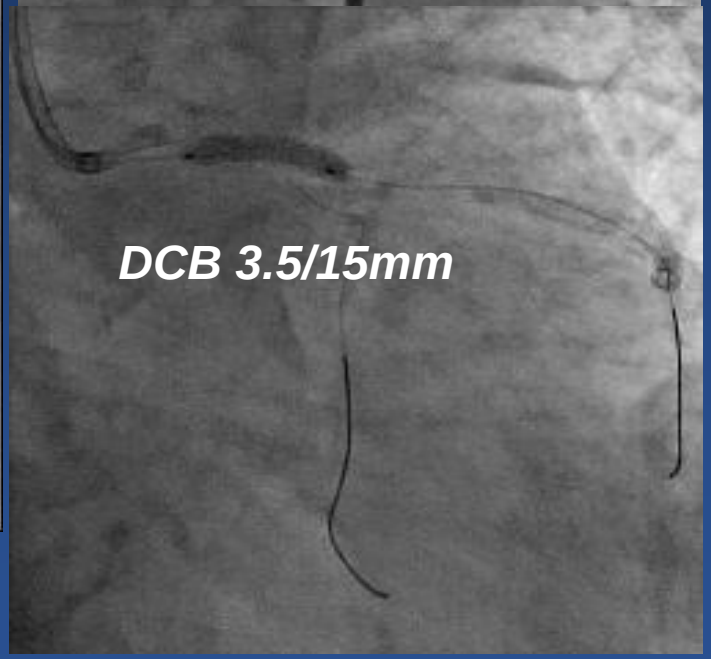
Aspirin 100mg, Clopidogrel 75mg

Chest pain and ST elevation in V1-V6 in June 8 2014

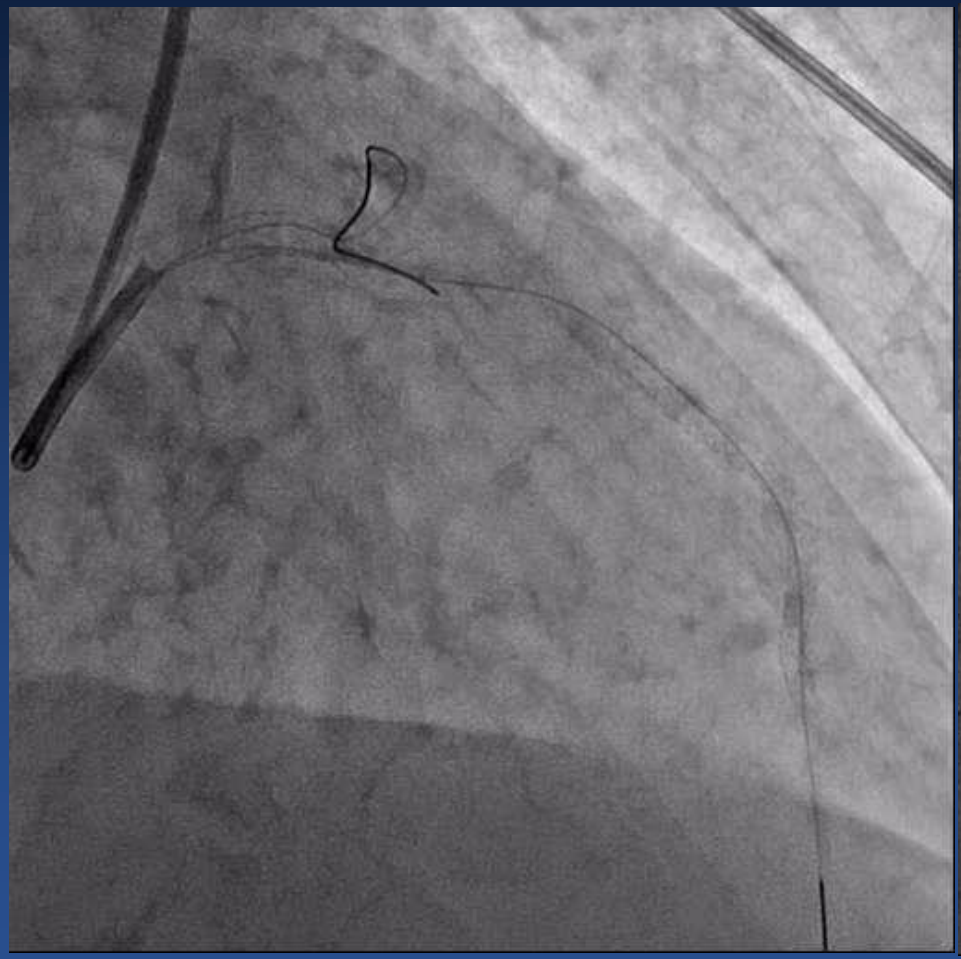
Emergent CAG was performed

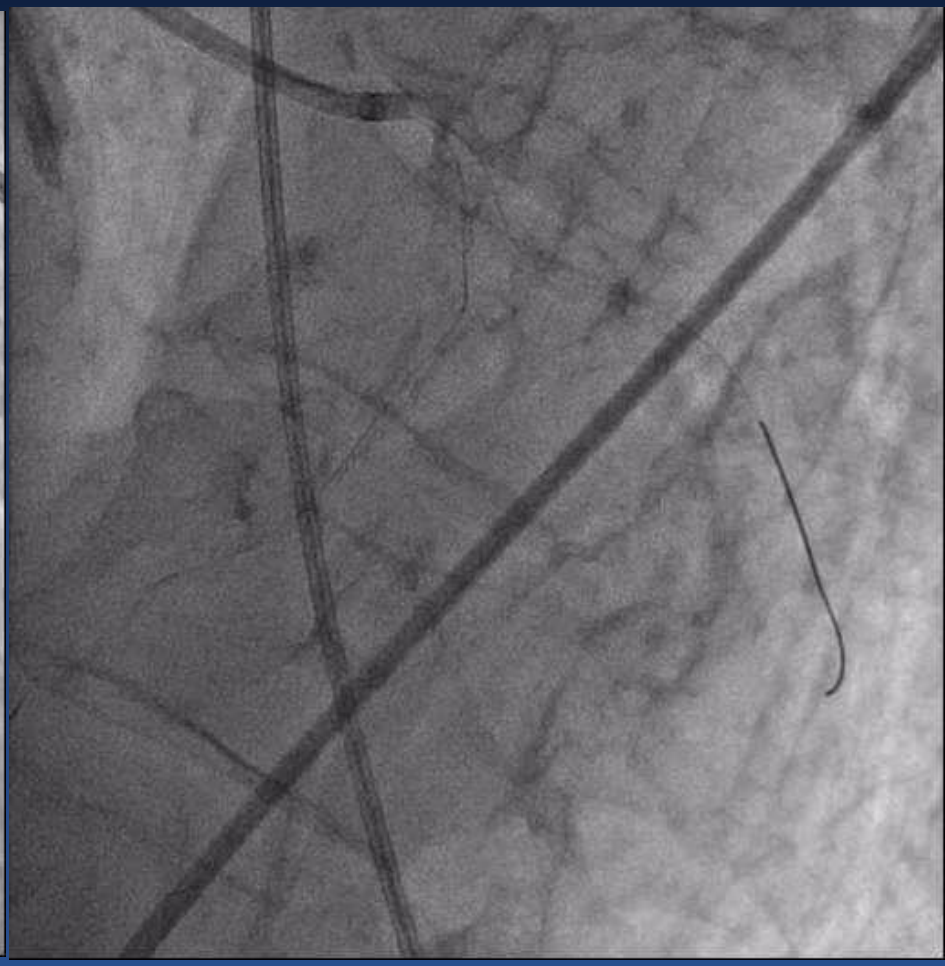






66 y.o. Male





66 y.o. Male

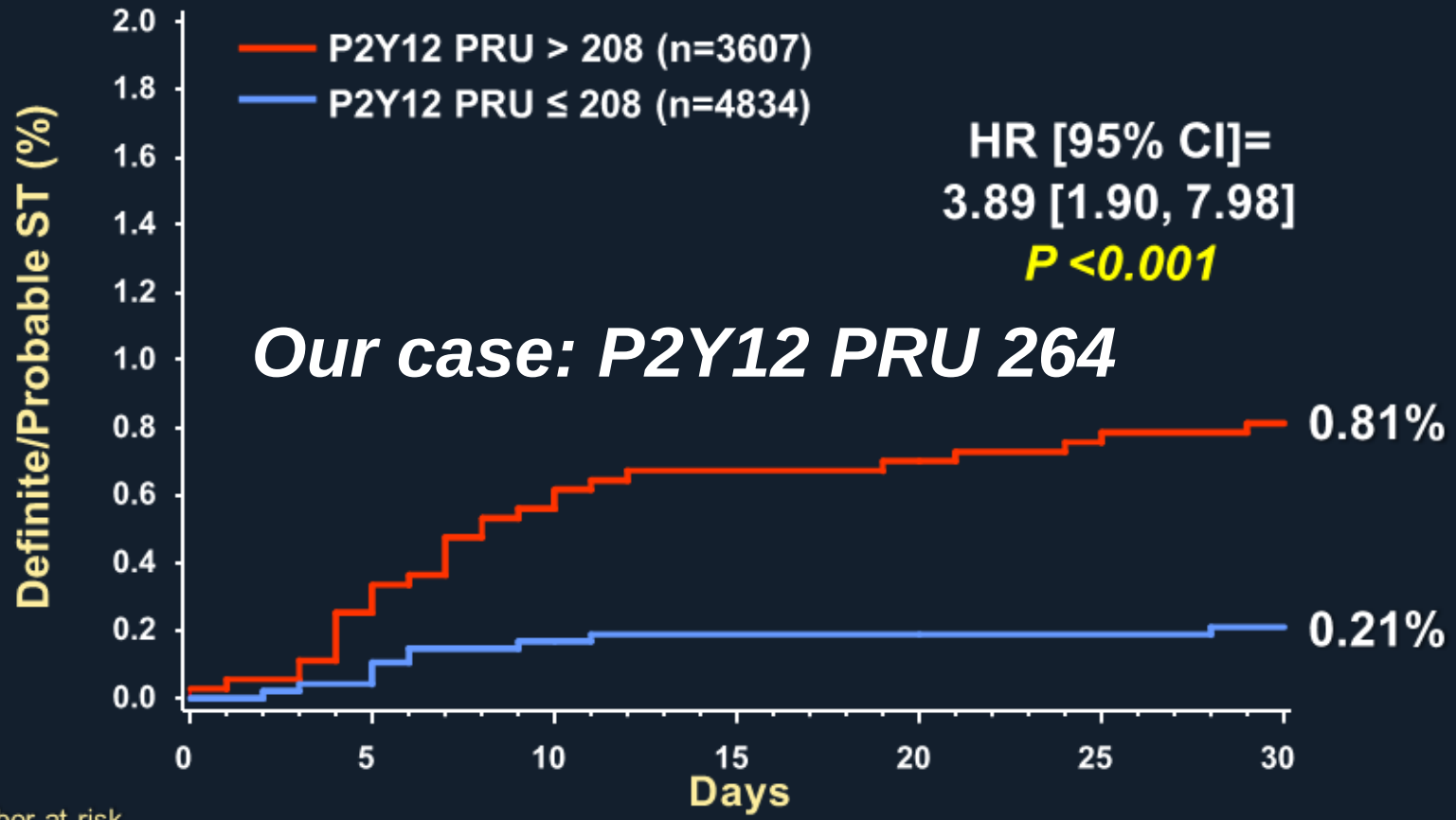
Platelet Aggregation Analysis Methods

- VerifyNow® $P2Y_{12}$ assay
  - PRU ($P2Y_{12}$ reaction unit)
  - % Inhibition

P2Y12 PRU 264

ADAPT-DES: Relationship Between VerifyNow P2Y12 PRU and Stent Thrombosis within 30 Days

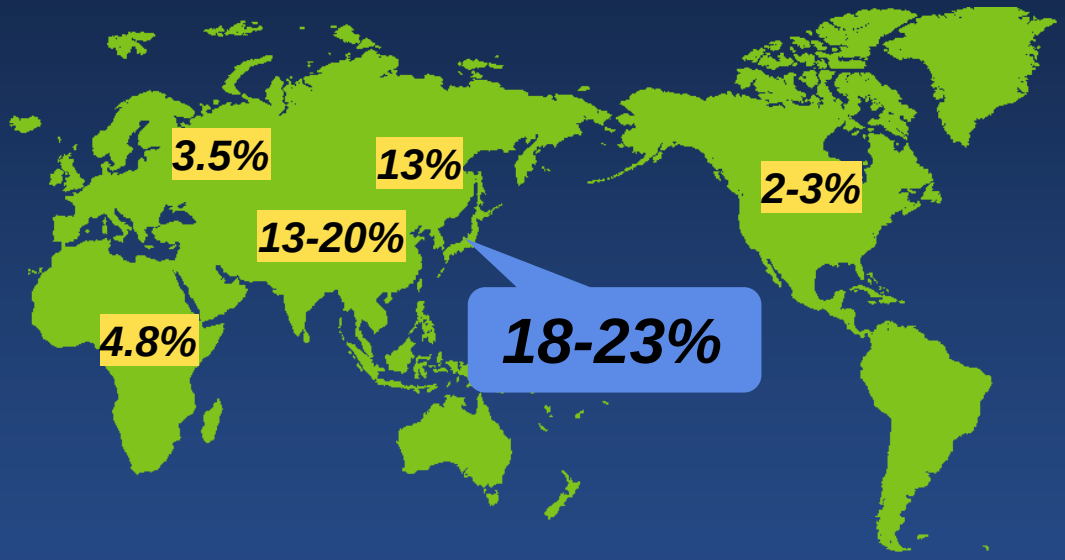
Definite or probable stent thrombosis



Stone G et al

Frequency of CYP2C19 Genetic Polymorphisms in the Japanese Population

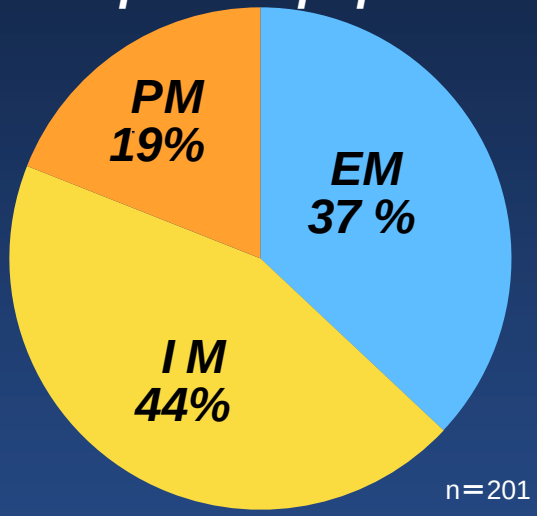
Proportion of CYP2C19 PM across the world



The proportion of CYP2C19 PM is high in Asia.

Prepared from Furuta T. et al: Drug Metab. Pharmacokinet. 20(3), 153-167, 2005

Ratio of CYP2C19 genetic polymorphism phenotypes among the Japanese population



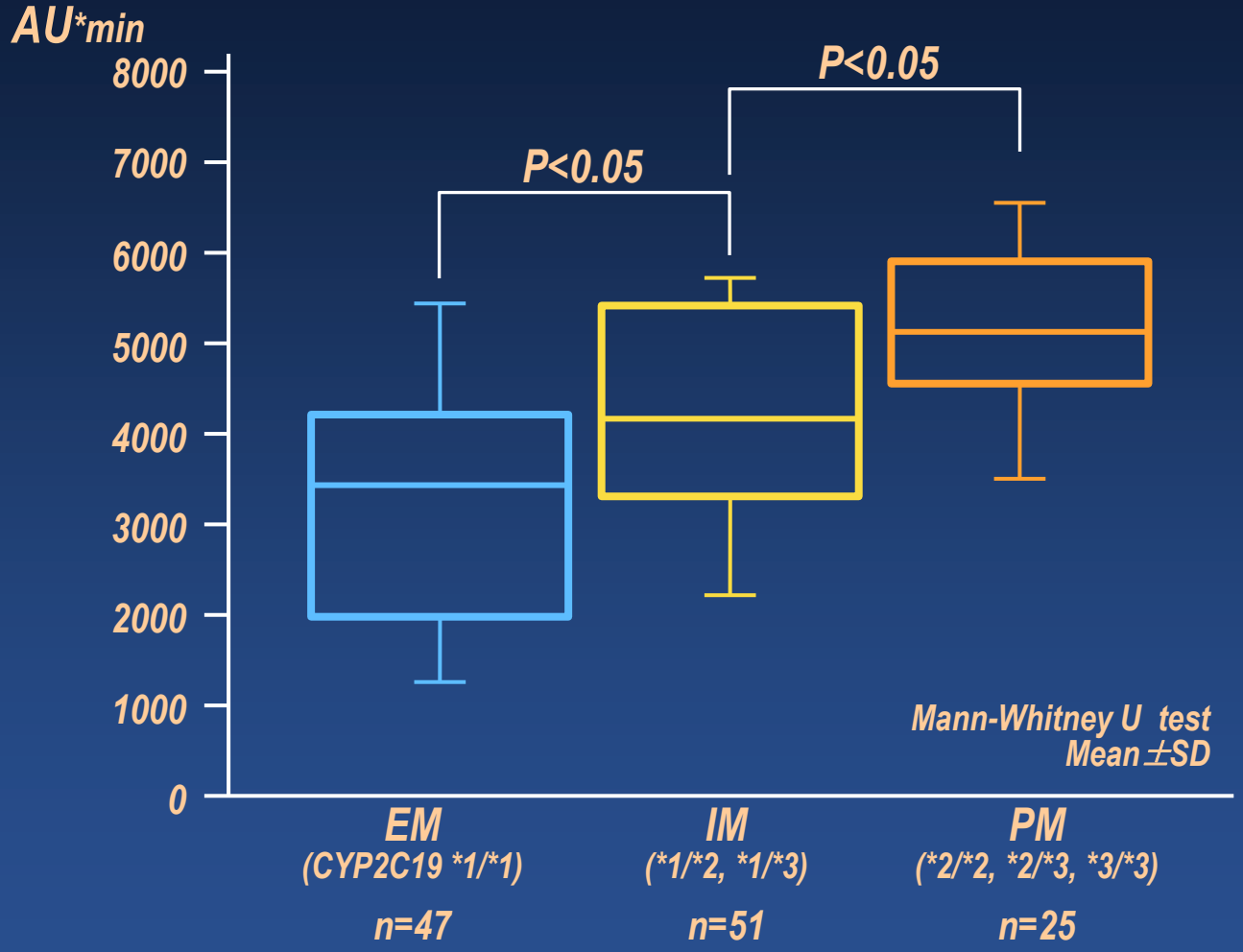
One in every 2 Japanese people have abnormal CYP2C19 metabolism.

Yamamoto K. et al: J. cardiol. 57(2), 194-201, 2011 (partly adapted)

EM (extensive metabolizer): Normal CYP2C19 metabolism type
IM (intermediate metabolizer): Underactive CYP2C19 metabolism type
PM (poor metabolizer): Inactive CYP2C19 metabolism type

EM=extensive metabolizer; IM=intermediate metabolizer; PM=poor metabolizer

Comparison of the on-treatment platelet reactivity according to CYP2C19 genotype in Japanese patients for DAPT

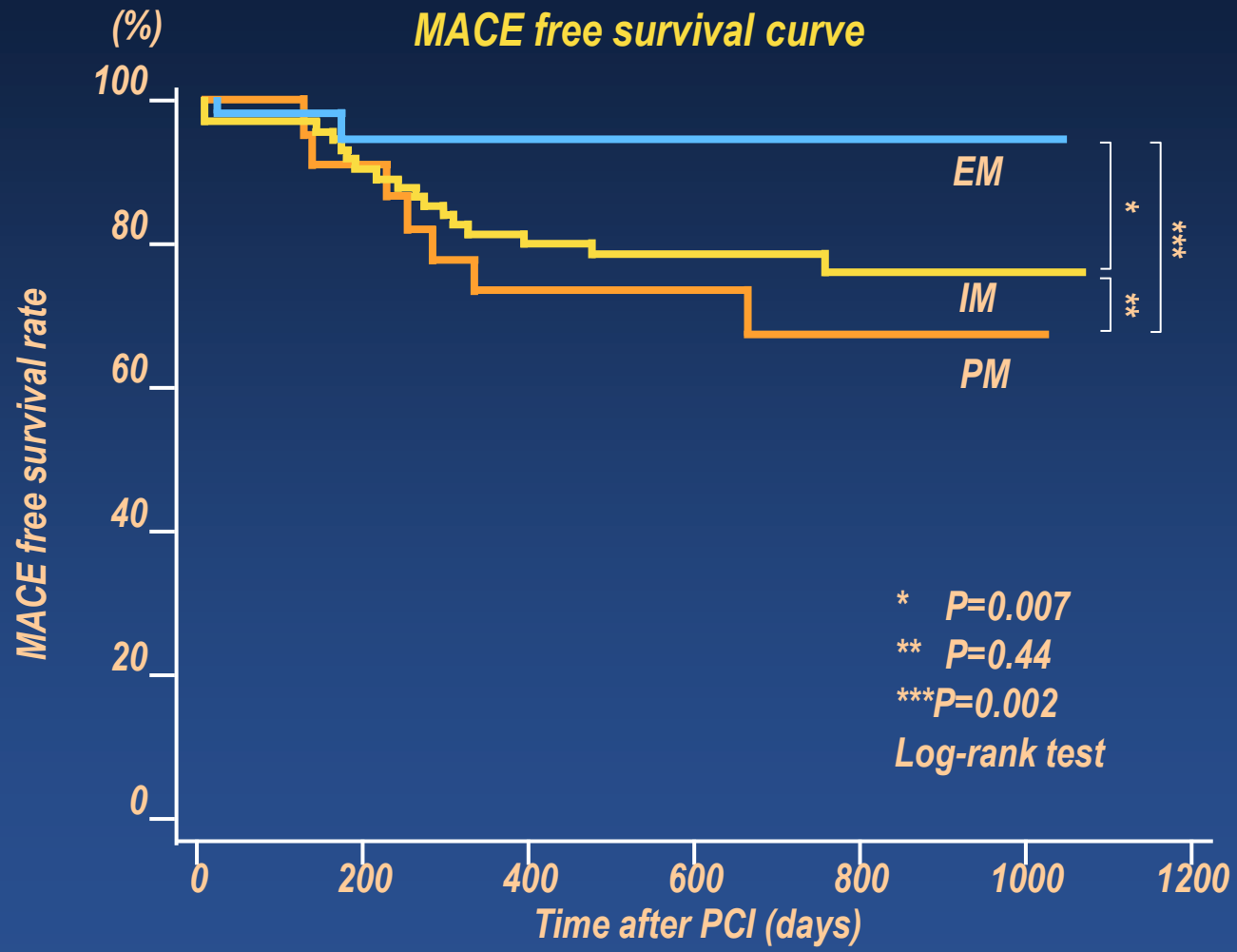


EM=extensive metabolizer; IM=intermediate metabolizer; PM=poor metabolizer

*AU:aggregation units. Platelet aggregation (AU min)induced by 20 μmol/L adenosine diphosphate was measured using a light transmission aggregometer.

Yamamoto K. et al. *J cardiol*. 2011;57:194-201.

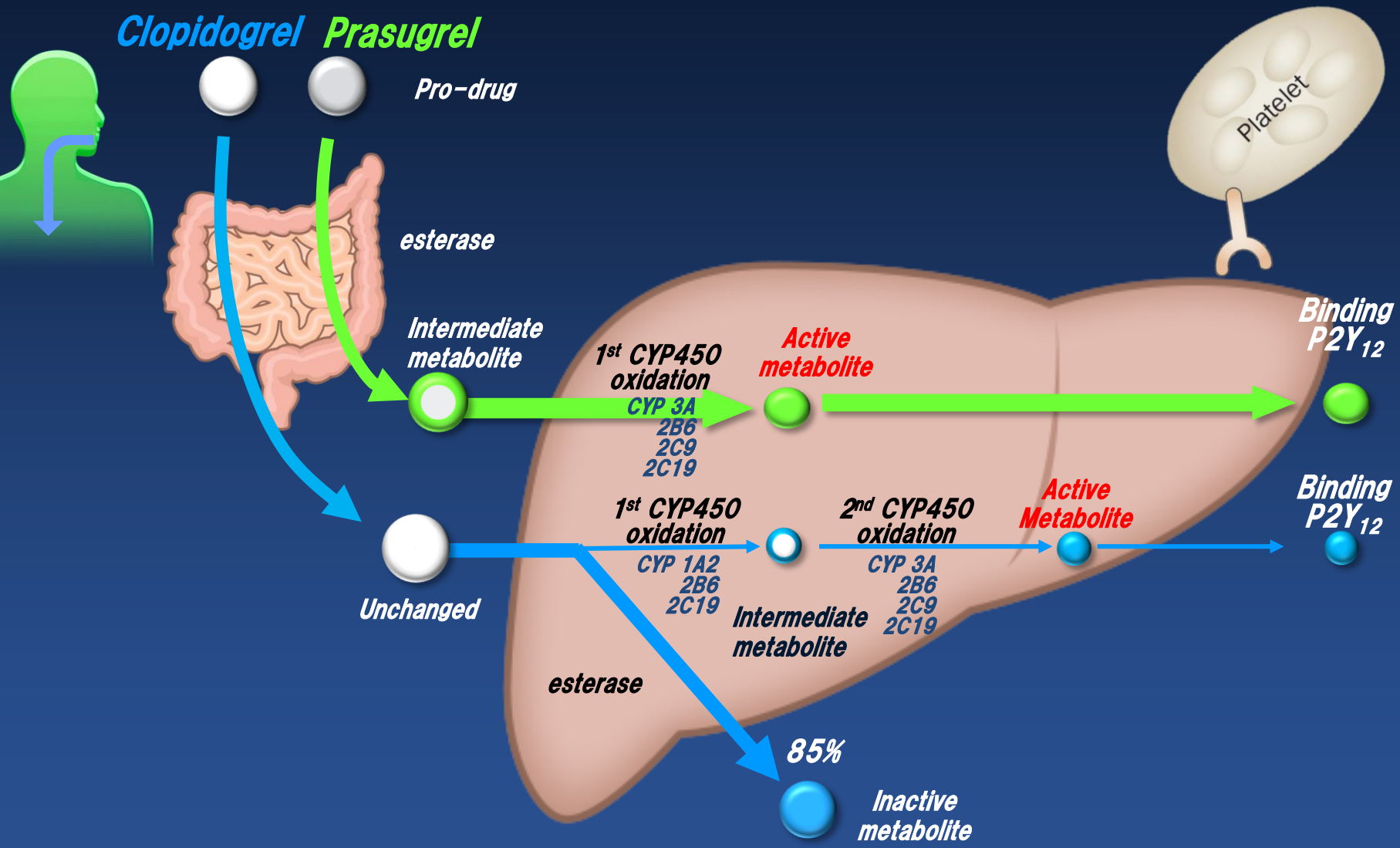
Effect of Cytochrome P450 2C19 Polymorphism on Target Lesion Outcome After Drug-Eluting Stent Implantation in Japanese Patients Receiving clopidogrel



EM=extensive metabolizer; IM=intermediate metabolizer; PM=poor metabolizer; MACE=major adverse cardiac event; TLR=target lesion revascularization; PCI=percutaneous coronary intervention

Nishio R. et al. *Circ J.* 2012;76:2348-2355.

Difference of drug metabolism

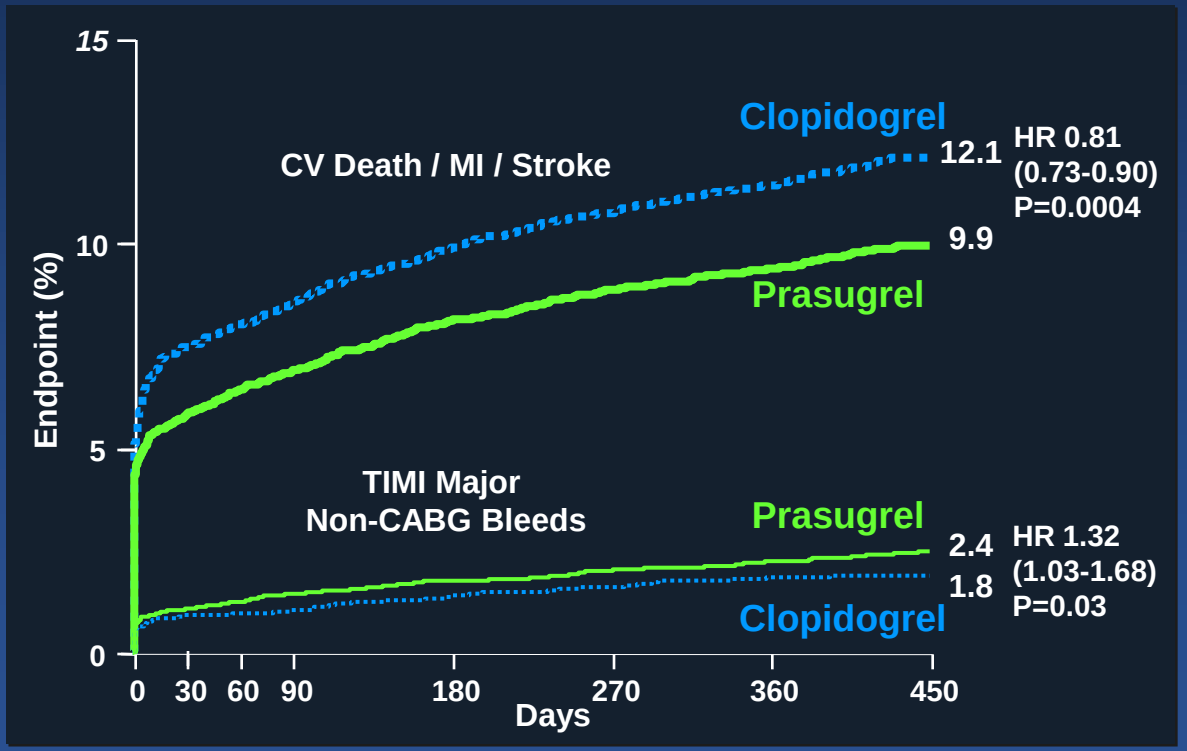


CYP=Cytochrome P450

Adapted from N.A.Farid et al. J.Clin.Pharmacol. 50, 126-142, 2010

Results of TRITON-TIMI 38

- Prasugrel 60 mg LD/10 mg MD
- Rapid onset compared to clopidogrel[1]
- Greater efficacy compared to clopidogrel[2]
- Increased TIMI Major bleeding[2]



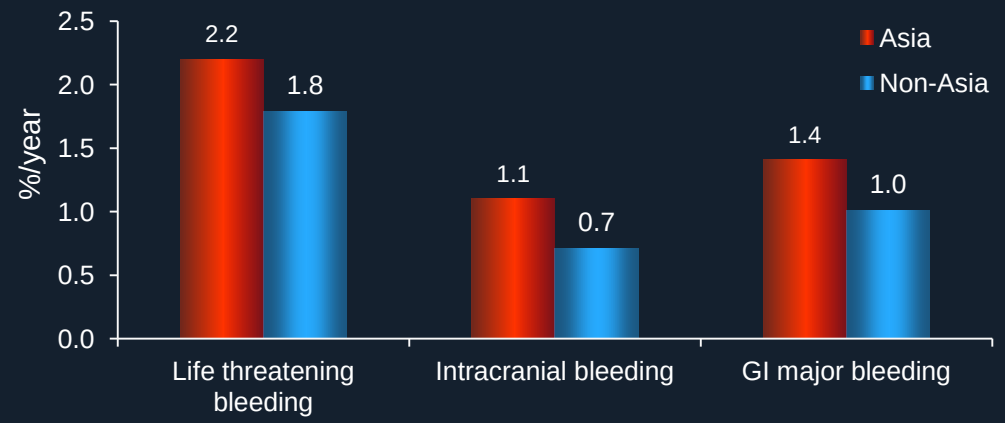
LD: Loading Dose
MD: Maintenance Dose

[1] Brandt et al. *Am Heart J*. 2007
[2] Wiviott S et al. *NEJM* 2007;357:2001-2015

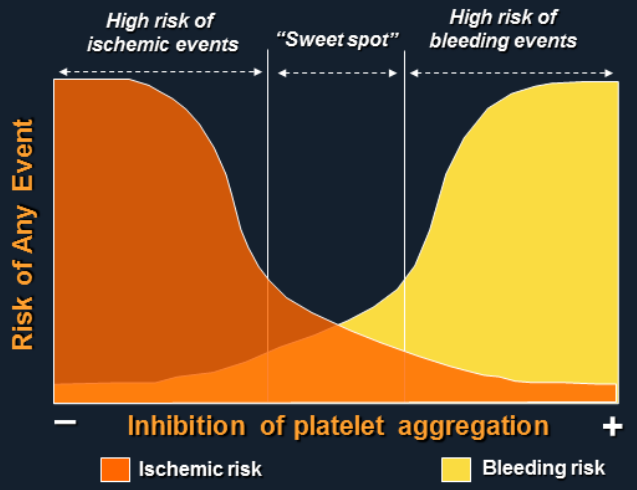
Different Characteristic in Japan and Caucasian of PCI Patients

	Japanese	Caucasian
Age	Higher (68years) [4]	Lower (61years)[2]
BMI	Lower (23.9) [4]	Higher (28.5) [2]
Body weight	Lower	Higher
CYP 2C19 IM+PM [3]	60-70%	25%
Bleeding risk for antiplatelet	Higher ?	Lower?

Bleeding in RE-LY sub analyses Warfarin arm (Asia vs. non-Asia) [5]



Platelet Inhibition Related to the Risk of Ischemic and Bleeding Events

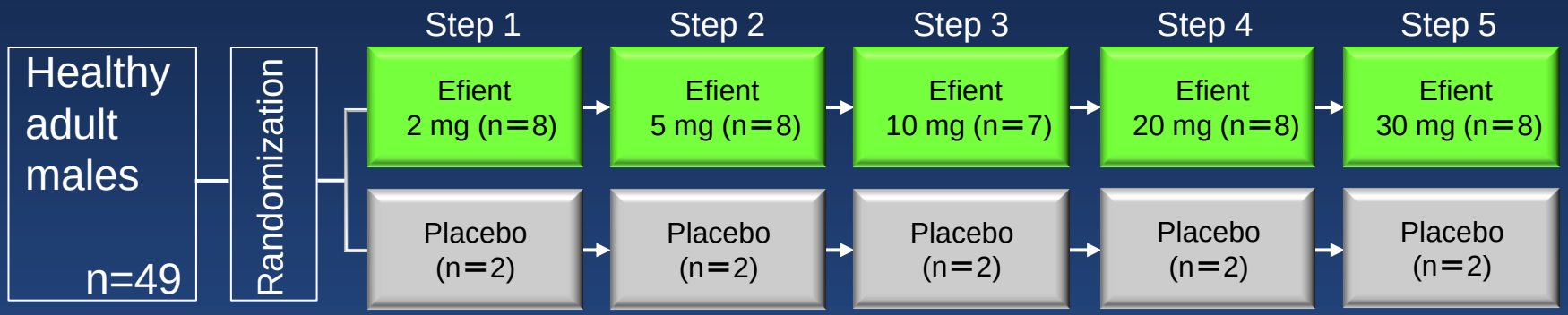


Ferreiro J.L. et al. *Thromb Haemost.* 2010;103:1-8.

[2] Wiviott S et al. *NEJM* 2007;357:2001-2015
[3] Furuta T et al. *Drug Metab. Pharmacokinet.* 2005 20(3) 153-167
[4] Kimura T et al. *Circulation.* 2009;119:987-995
[5] Hori M APSC2012

Phase 1 Single-dose Study

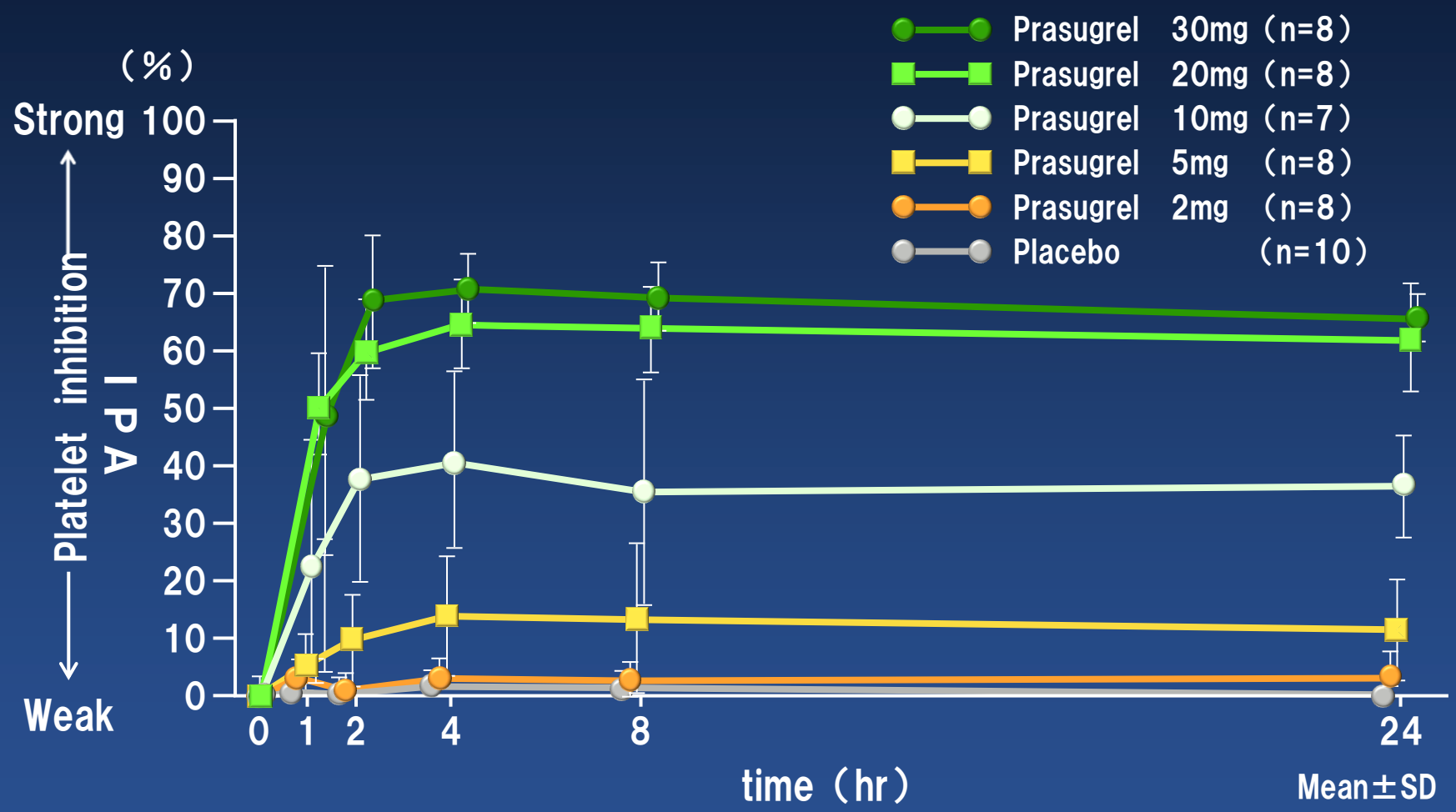
Study Design



<Endpoints>

IPA (ADP 20μM induced), bleeding time (Ivy method)

Japanese Phase I trial: IPA for single ascending dose

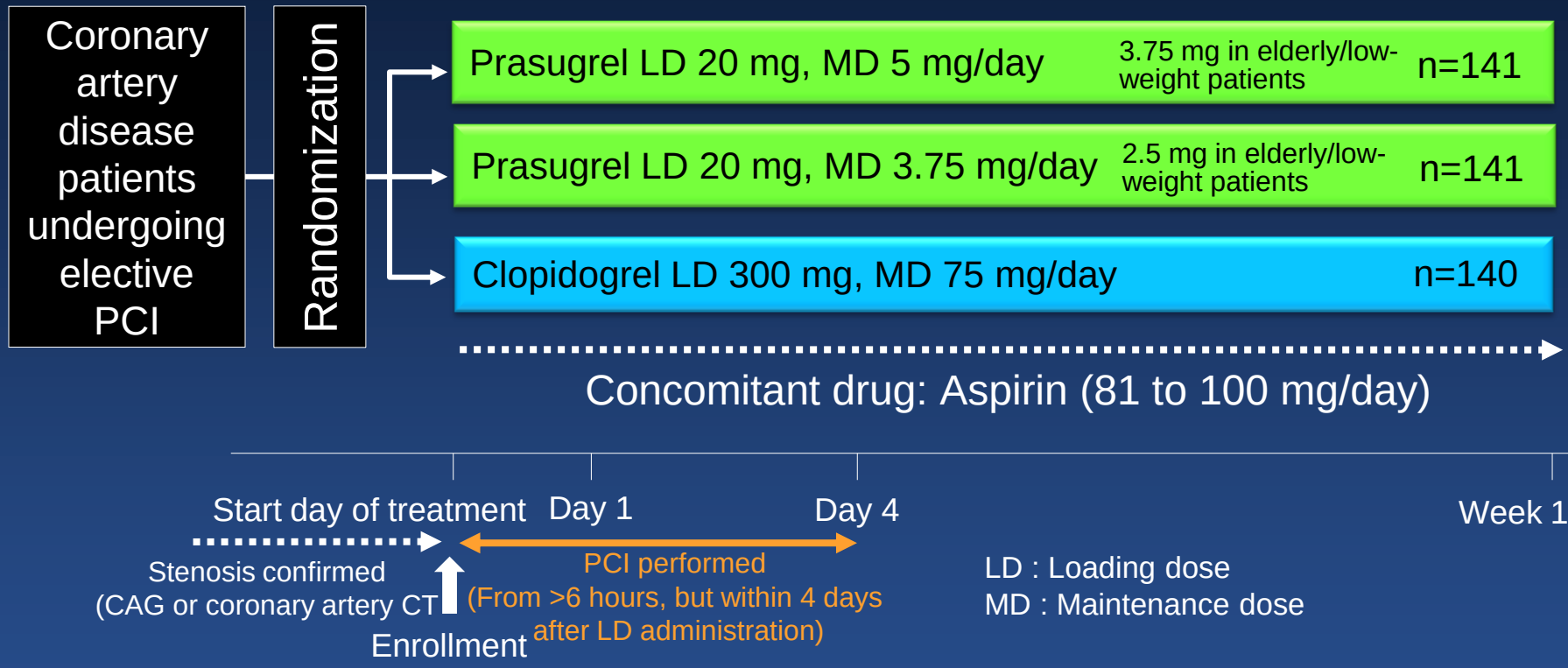


Japanese Healthy volunteers n=49

IPA = Inhibition Platelet Aggregation at ADP20 μM

Phase 2 Dose-finding Study in Patients Undergoing Elective PCI

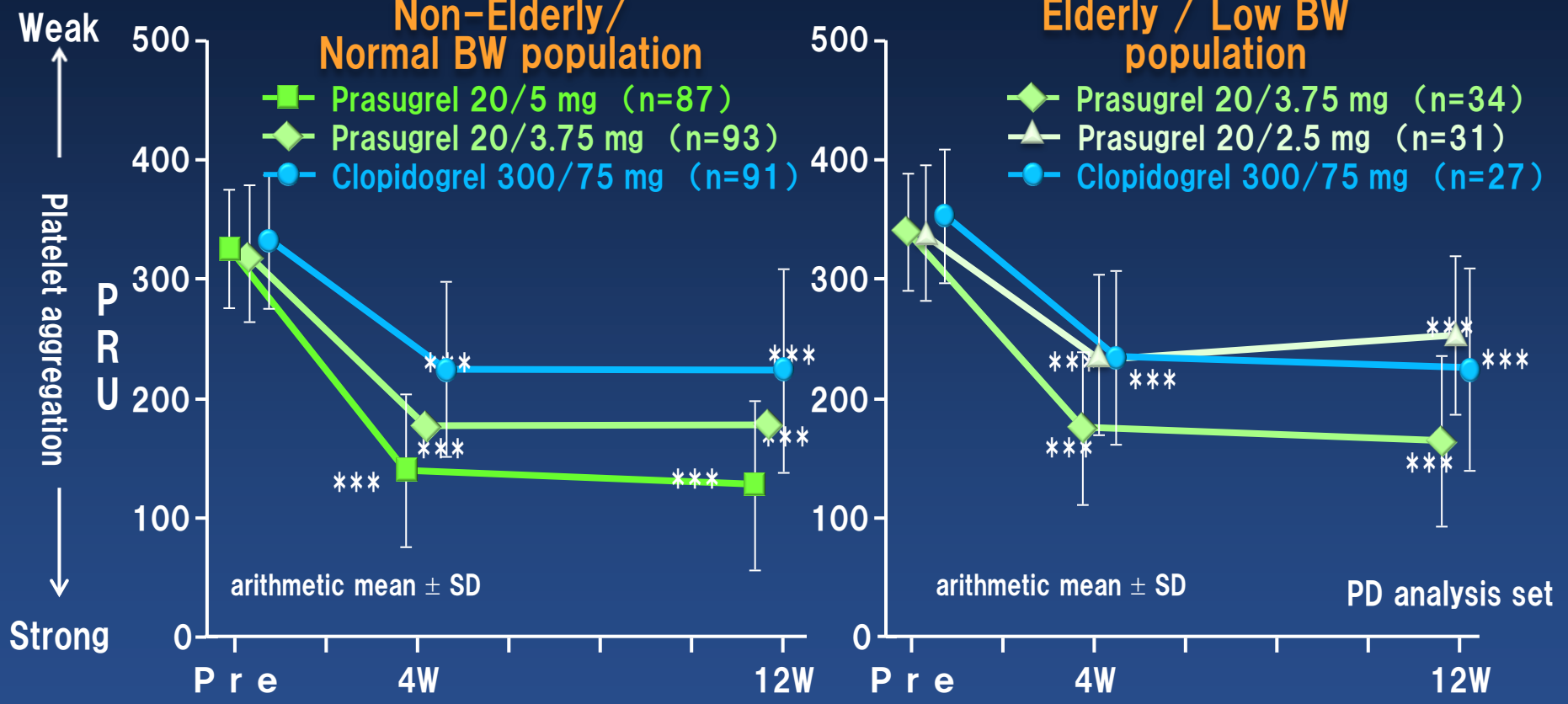
Study Design



Non-elderly/non-low weight patients: Aged <75 years and weighing >50 kg
Elderly/low-weight patients: Aged 75≤ to <85 years and weighing ≤50 but >40 kg

<Primary safety endpoint>
Non-CABG-related major bleeding and minor bleeding
<Secondary safety endpoint>
Non-CABG-related major bleeding, minor bleeding, and other clinically relevant bleeding

Platelet aggregation profile of Japanese Phase II dose finding study (Elective PCI patients)



*** p<0.0001 by paired *t* test, compared to Pre value

Low BW : BW ≤50 but >40 kg
Elderly : Aged 75≤ to <85

Subjects : CAD patients undergoing PCI (n=370

Method : LDとして、ﾌﾟﾗｽｸﾞﾚﾙ20mgまたはｸﾛﾋﾟﾄﾞｸﾞﾚﾙ300mgをPCI前に投与した。LD投与翌日以降、MDとしてﾌﾟﾗｽｸﾞﾚﾙを5.0mg/日（低体重または高齢患者では3.75mg）、3.75mg/日（低体重または高齢患者では2.5mg）、ｸﾛﾋﾟﾄﾞｸﾞﾚﾙ75mg/日なお、ｱｽﾋﾟﾘﾝ81～100mg/日を5日間以上反復投与した上で、ﾌﾟﾗｽｸﾞﾚﾙあるいはｸﾛﾋﾟﾄﾞｸﾞﾚﾙと併用投与した。

T Isshiki. et al. *CVIT* 2011

Bleeding profile of Japanese Phase II dose finding study

(Elective PCI patients)

Group (LD/MD mg)	Non-Elderly/ Normal BW population			**Elderly / Low BW population		
	Prasugrel		Clopidogrel	Prasugrel		Clopidogrel
	20/3.75 n = 104	20/5 n = 103	300/75 n = 104	20/2.5 n = 37	20/3.75 n = 37	300/75 n = 36
TIMI Major bleeding	0	0	2 (1.9%)	0	0	0
TIMI Minor bleeding	4 (3.8%)	0	1 (1.0%)	0	1 (2.7%)	1 (2.8%)
Clinically relevant bleeding	2 (1.9%)	5 (4.9%)	3 (2.9%)	1 (2.7%)	0	0
Major, minor, and clinically relevant bleeding	6 (5.8%)	5 (4.9%)	6 (5.8%)	1 (2.7%)	1 (2.7%)	1 (2.8%)

*: number of patients (%)

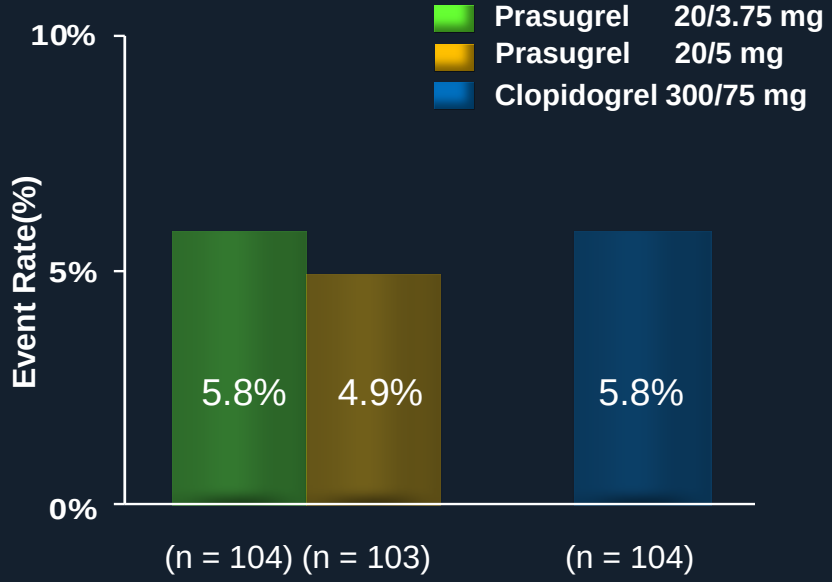
**Elderly / Low BW : ≥75year / ≤50kg

Safety analysis set

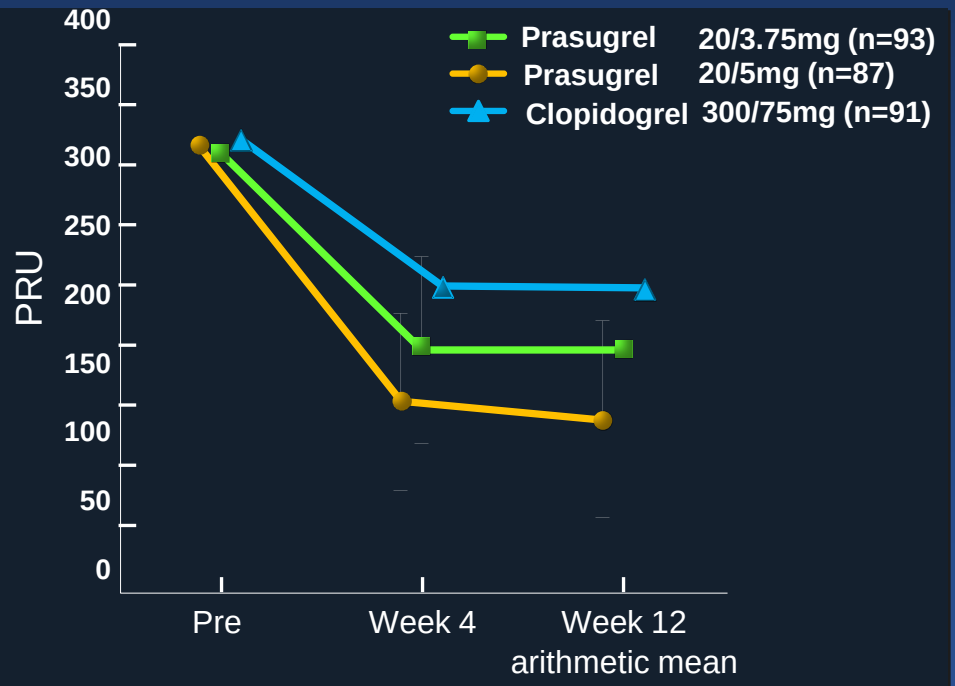
Isshiki T. et al. *CVIT* 2011

Results of Japanese Phase II Trial : Confirmed Appropriate Prasugrel Dosage

- Prasugrel dose for Phase III trial in Japan was set up at 20 mg LD/3.75 mg MD, regardless of age and body weight.
  - Clinically important bleeding events were similar in both the prasugrel and clopidogrel groups.
  - Prasugrel groups provided more potent and consistent inhibition of platelet aggregation compared with clopidogrel groups.



Non-CABG TIMI Major, Minor bleeding,
Clinically relevant bleeding Bleeding in Phase II



PRU: $P2Y_{12}$ Reaction Unit

Study Design

PRASFIT ACS

ACS (STEMI, NSTEMI, UA) patients undergoing PCI

Inclusion criteria
- chest discomfort or ischemic symptoms lasting 10 min or more within 72 hours before randomization
- ST-segment deviation of 1 mm or more, or T-wave inversion of 3 mm or more, or elevated levels of a cardiac biomarker of necrosis

Major exclusion criteria
- *History of intracranial bleeding or increased bleeding risk*
- *Stroke/TIA*
- *Thienopyridine use within 5 days before enrollment*

Randomized **N=1,363**

Prasugrel	**Clopidogrel**
20 mg LD/ 3.75 mg MD	**300 mg LD/ 75 mg MD**

Treatment duration: 24 to 48 weeks

Primary Efficacy Endpoint:
MACE：Cardiovascular(CV) death, Nonfatal MI and Nonfatal ischemic stroke

Safety Endpoints:
Non-CABG TIMI major bleed

LD: Loading Dose MD: Maintenance Dose

Study Design

PRASFIT Elective

CAD patients (Stable angina, Previous myocardial infarction, Silent myocardial ischemia) undergoing elective PCI

Major exclusion criteria
- Unstable angina (within 72 hours after the onset), or acute MI
- History of intracranial bleeding or increased bleeding risk
- *Ischemic stroke with one or more of the following conditions,*

1) Required to receive anticoagulation therapy
2) Age 75 years or older
3) Within 6 months after the onset of cerebral infarction

Preoperative Examination† Randomized

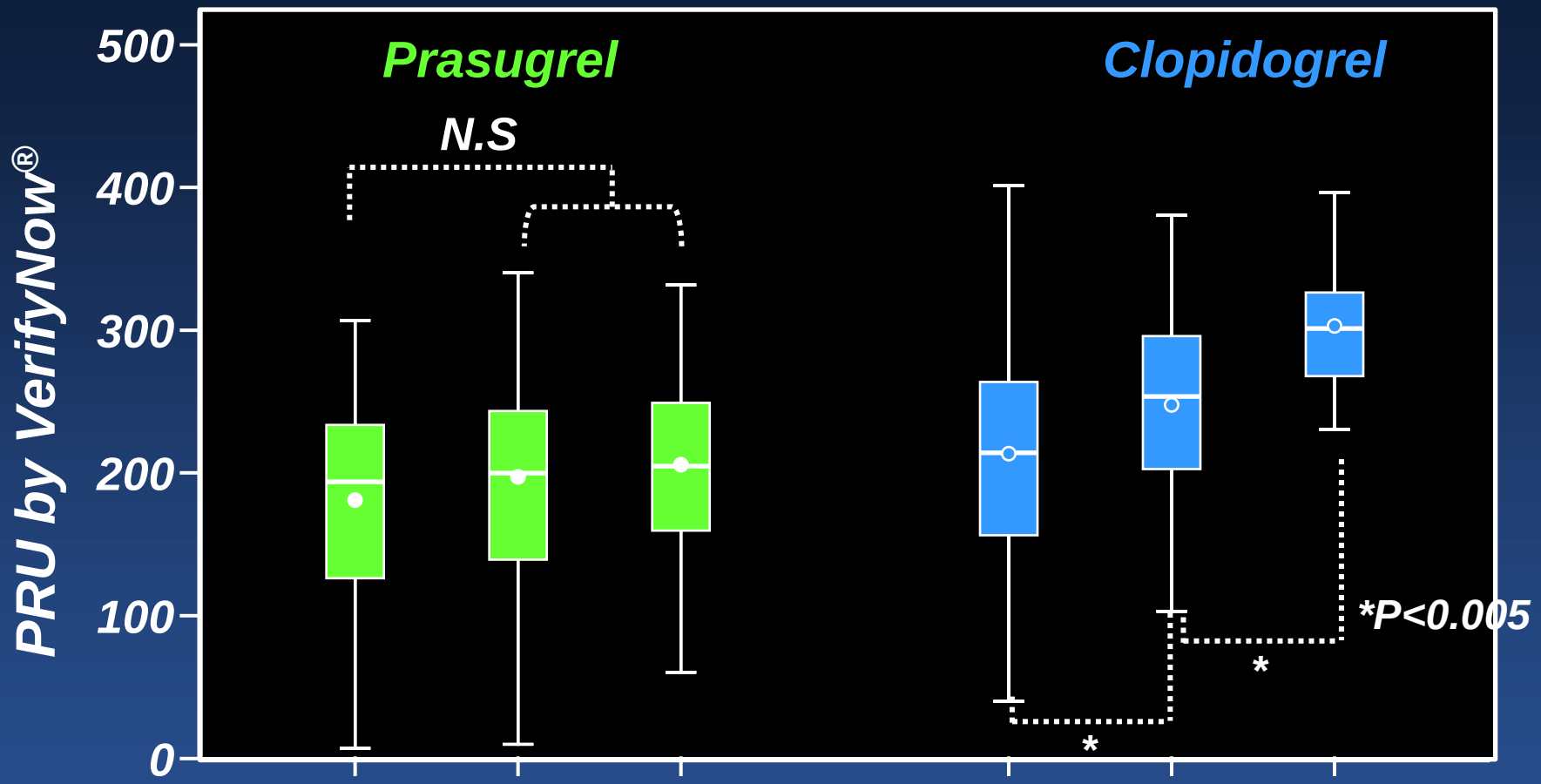
Prasugrel	Clopidogrel
LD 20mg【before PCI】or MD 3.75mg 14-21days	LD 300mg【before PCI】or MD 75mg 14-21days
PCI	PCI
Prasugrel 3.75 mg MD	**Clopidogrel 75 mg MD**

Treatment duration: 24 to 48 weeks

LD: loading dose, MD: maintenance dose
†: after preoperative examination, LD(+)/LD(-) selection was determined by investigators

Platelet Aggregation (PRU) at 4w: Impact of CYP2C19 phenotype

PRASFIT Elective



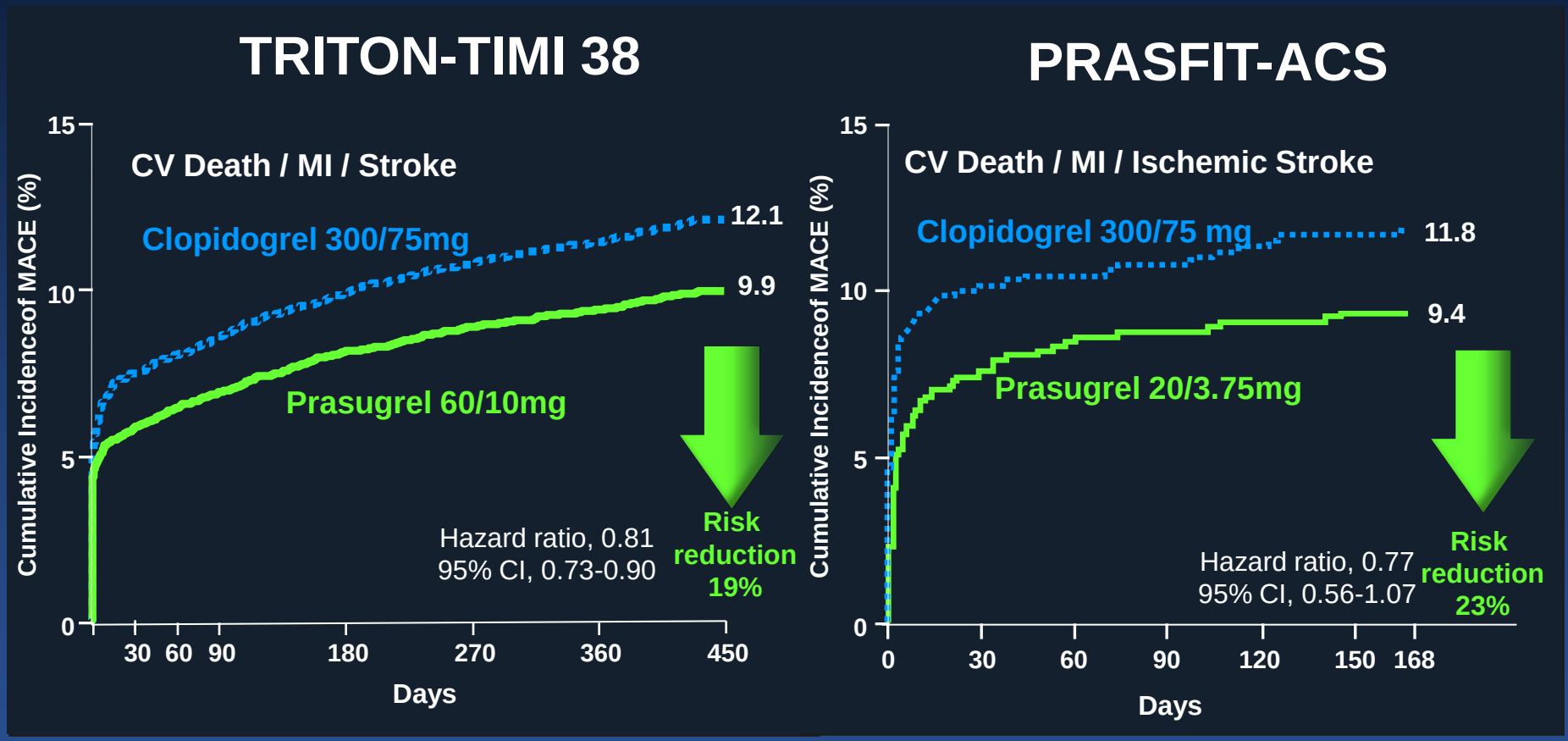
	Prasugrel			Clopidogrel		
	EM	IM	PM	EM	IM	PM
	n=78	n=116	n=46	n=76	n=118	n=42
mean	181.2	195.0	205.2	212.7	247.5	303.9
SD	68.63	69.98	74.95	79.41	65.13	41.43

Based on Pharmacodynamics Analysis Set

PRU: $P2Y_{12}$ Reaction Unit

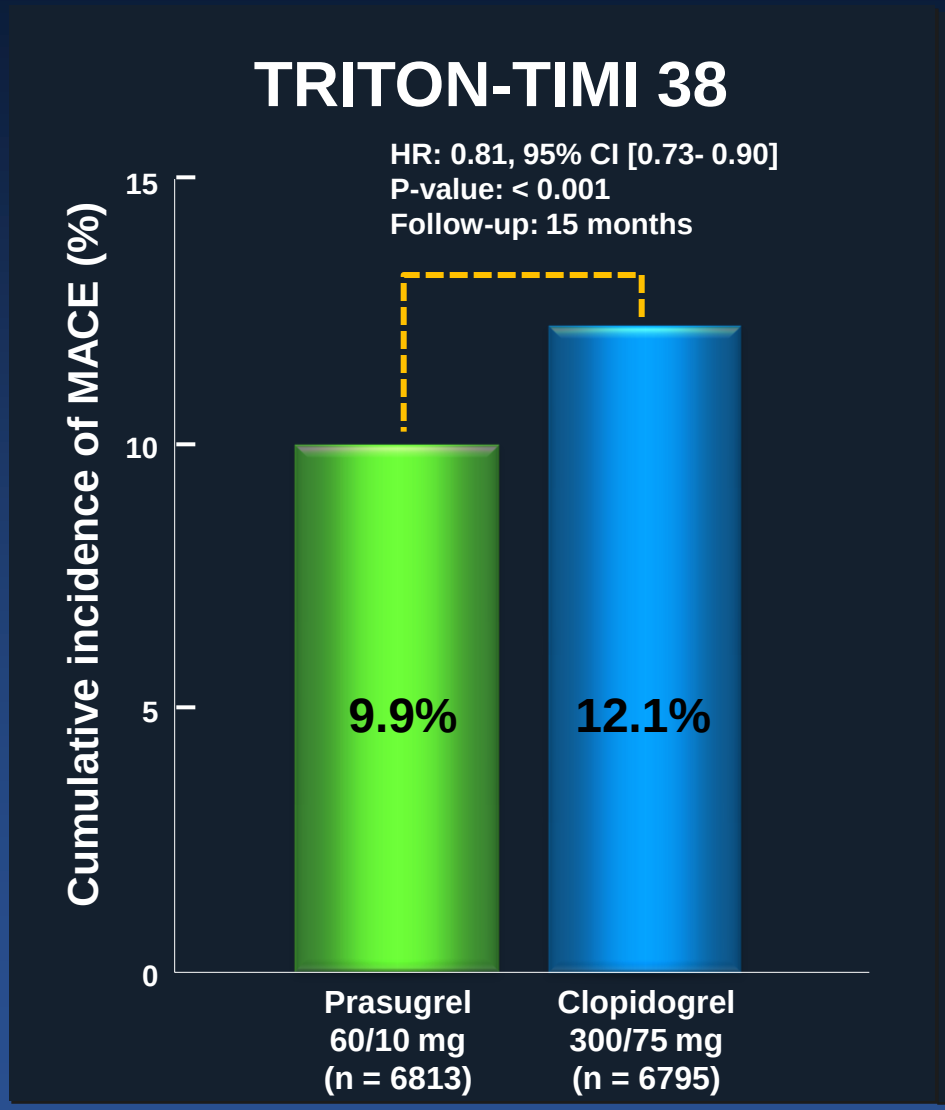
Efficacy Results

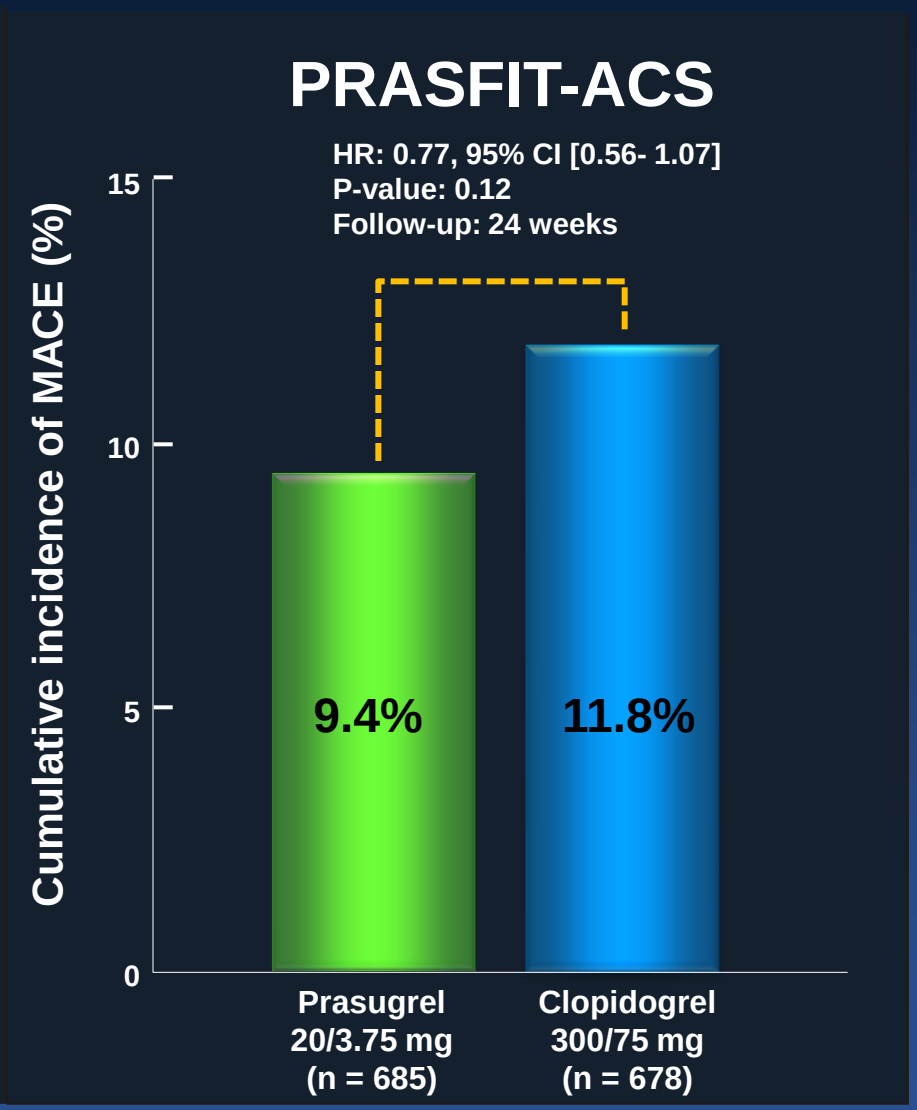
Primary Efficacy Endpoint of TRITON-TIMI 38 and PRASFIT-ACS



[2] Wiviott S et al. *NEJM* 2007;357:2001-2015

Primary Endpoint of TRITON-TIMI 38 and PRASFIT-ACS

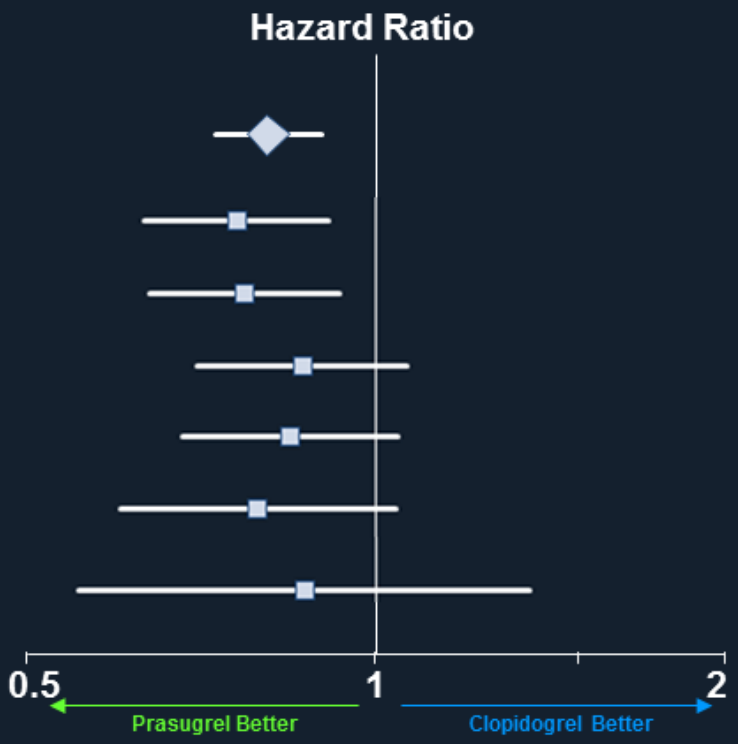




[2] Wiviott S et al. *NEJM* 2007;357:2001-2015

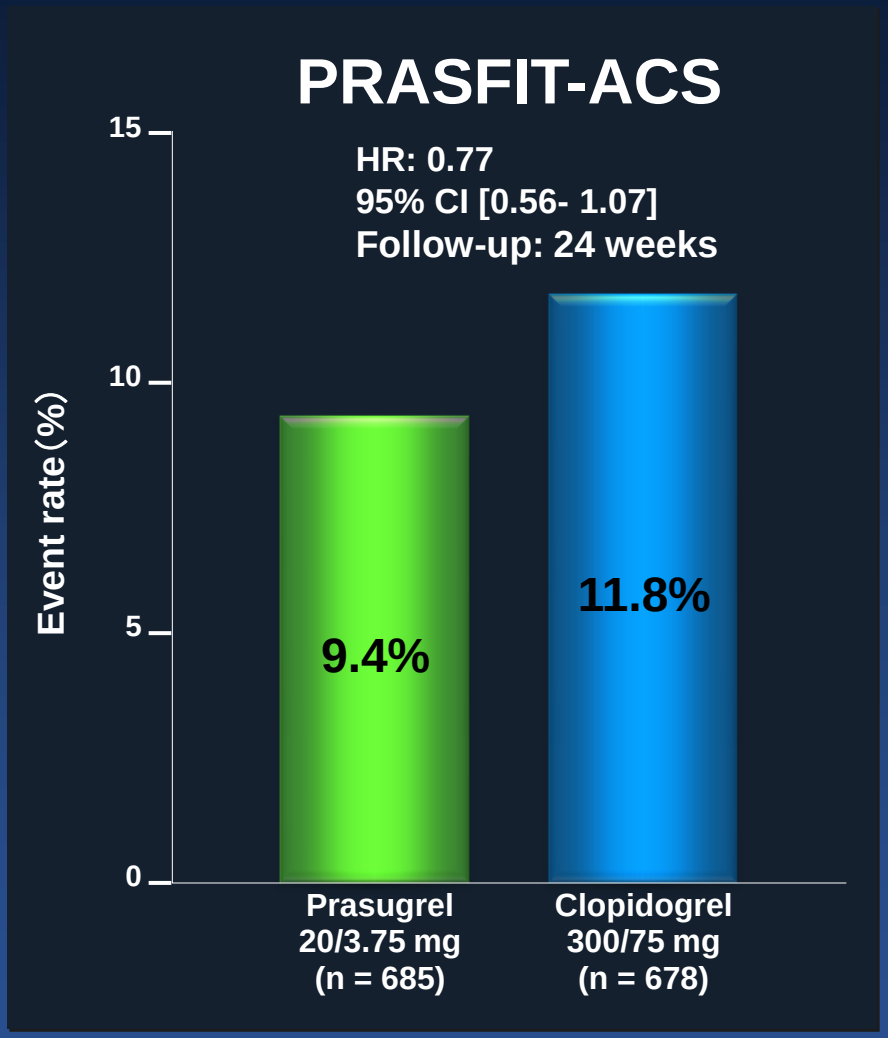
TRITON-TIMI 38 / PRASFIT-ACS
Consistency of Primary Endpoint

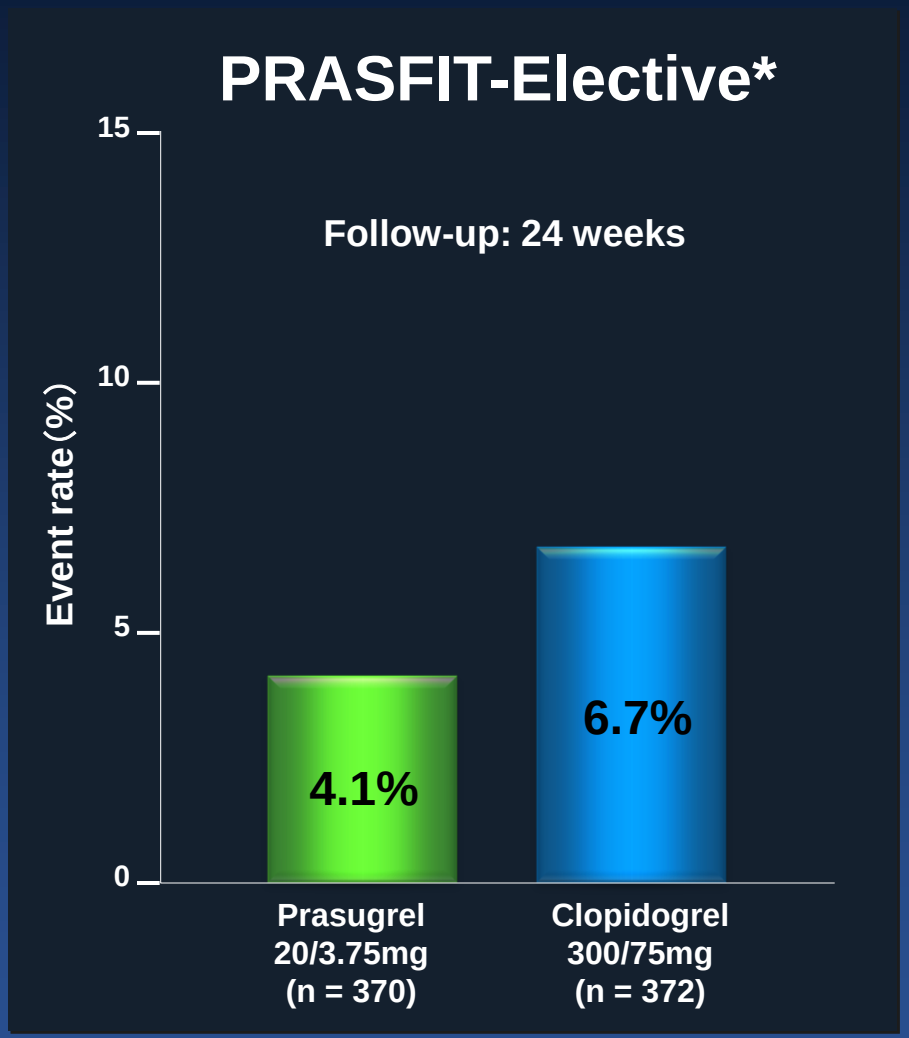
TRITON-TIMI38	N	Incidence of MACE (%)	
		Prasugrel	Clopidogrel
All Regions	13608	9.9	12.1
North America	4310	9.2	12.0
United States	4059	9.4	12.1
Western Europe	3553	9.2	10.6
Eastern Europe	3322	9.2	10.9
Rest of World	1889	9.7	12.1
South America	534	13.3	15.2



PRASFIT-ACS	N	Prasugrel	Clopidogrel
Japan	1363	9.4	11.8

Primary Endpoint of PRASFIT-ACS and PRASFIT-Elective



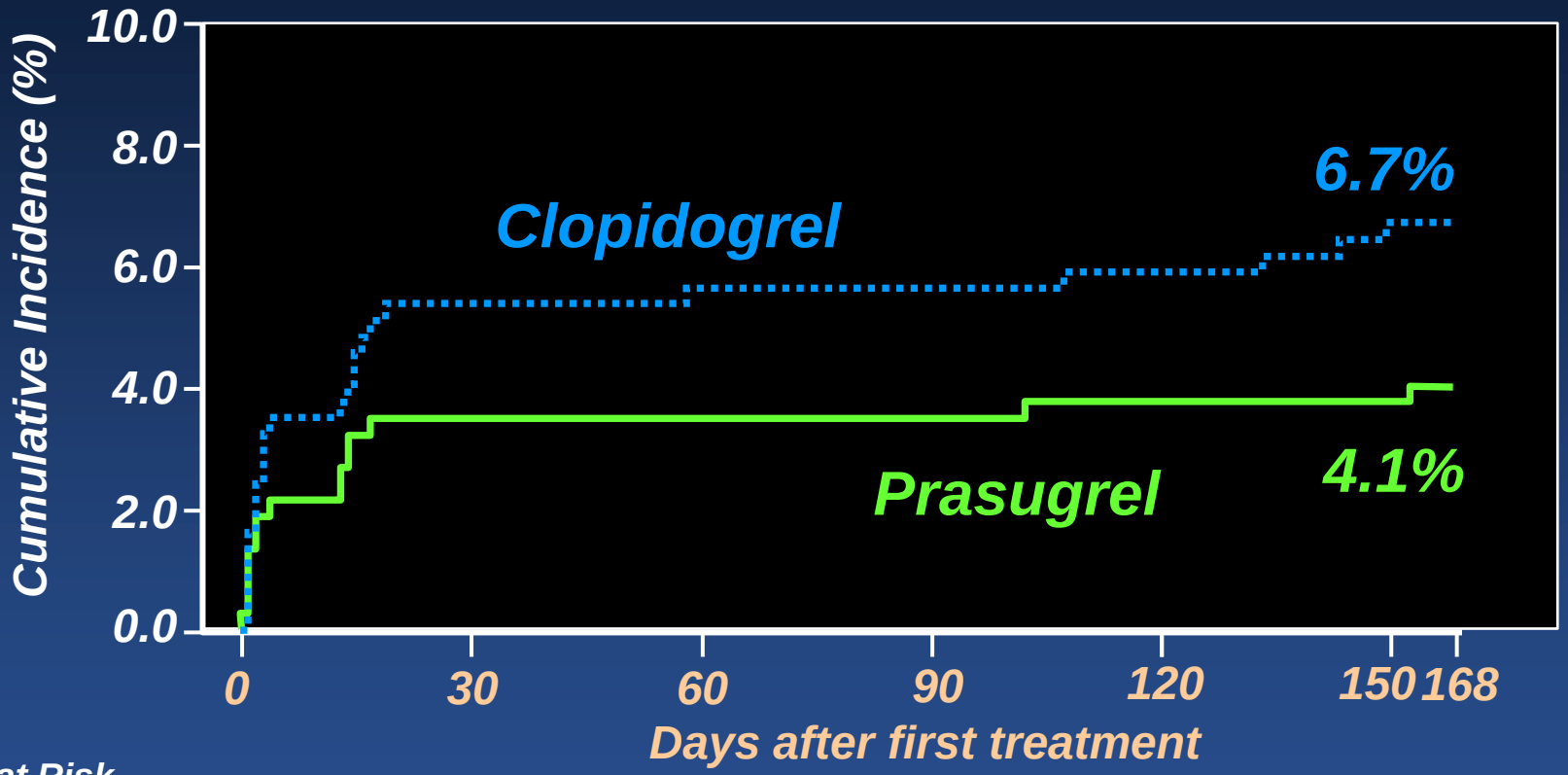


[2] Wiviott S et al. *NEJM* 2007;357:2001-2015

Based on Full Analysis Set

PRASFIT-Elective * : Test for statistical significance was not conducted

Primary Efficacy Endpoint
MACE at 24 weeks: Overall



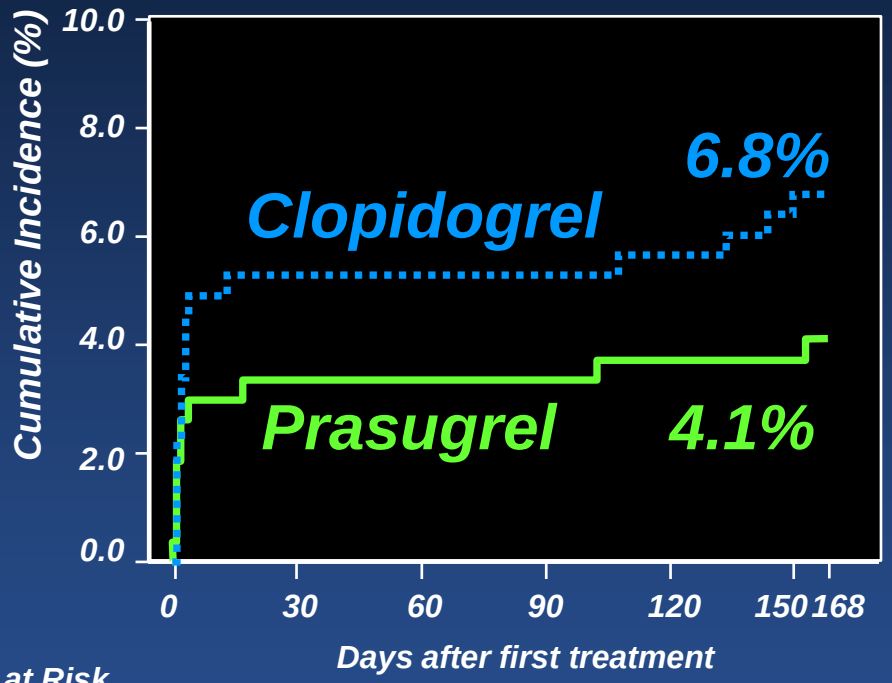
No. at Risk						
Prasugrel	370	356	356	356	355	355 353
Clopidogrel	372	351	350	350	349	346 345

Based on Full Analysis Set
Test for statistical significance was not conducted

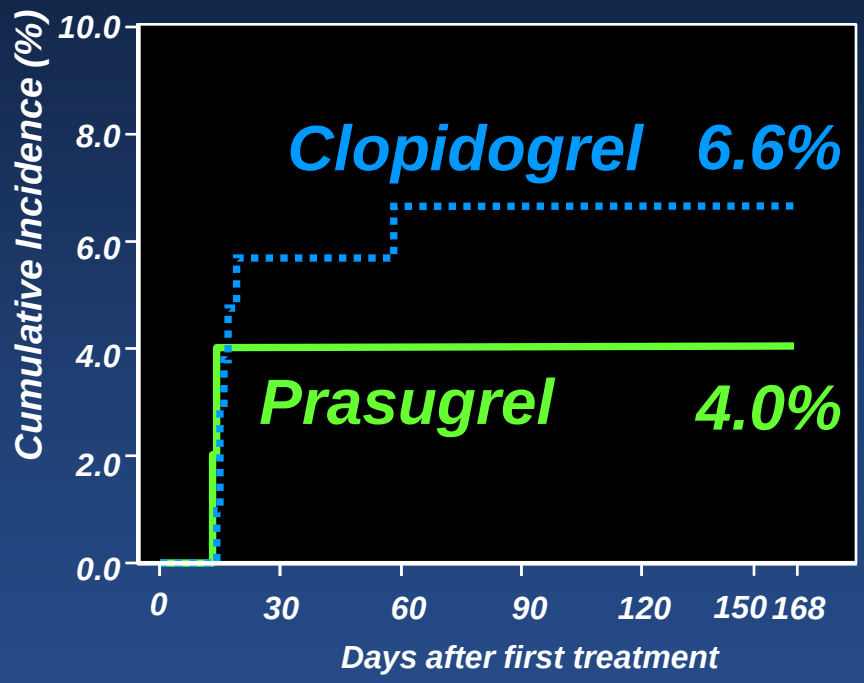
Primary Efficacy Endpoint
MACE at 24 weeks: LD (+)/(-)

PRASFIT Elective

LD (+)



LD (-)



No. at Risk							
Prasugrel	269	259	259	259	258	258	257
Clopidogrel	266	251	251	251	250	247	246

101	97	97	97	97	97	96
106	100	99	99	99	99	99

Based on Full Analysis Set
Test for statistical significance was not conducted

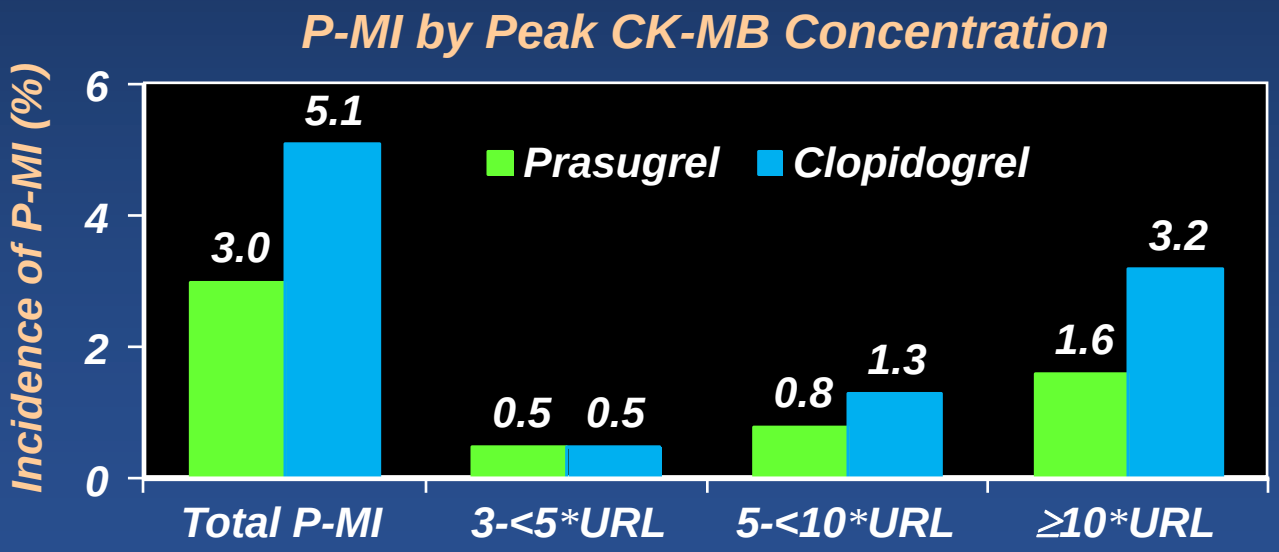
Efficacy Component Endpoints Through 24 weeks

Endpoints	Prasugrel N=370 n (%)	Clopidogrel N=372 n (%)
MACE	15 (4.1)	25 (6.7)
CV death	0 (0.0)	0 (0.0)
Nonfatal MI	12 (3.2)	24 (6.5)
Nonfatal ischemic stroke	3 (0.8)	1 (0.3)
All cause death	0 (0.0)	0 (0.0)
Nonfatal stroke	3 (0.8)	2 (0.5)
Hospitalization for angina	0 (0.0)	1 (0.3)
Revascularization	8 (2.2)	9 (2.4)
Stent thrombosis	0 (0.0)	1 (0.3)

Based on Full Analysis Set
Test for statistical significance was not conducted
Percentage: (n / n) x 100%

Nonfatal myocardial infarction Characteristics

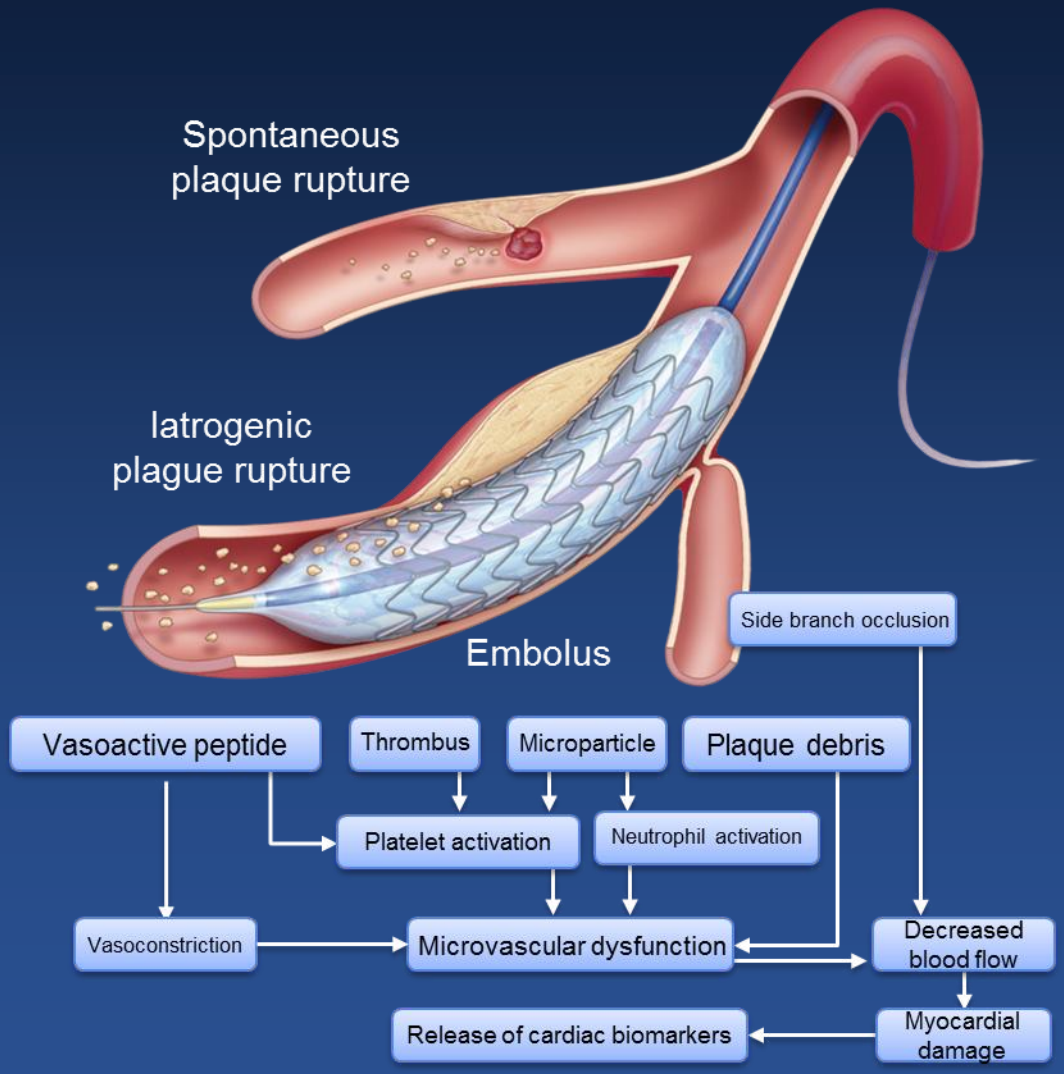
Endpoints	Prasugrel N=370 n (%)	Clopidogrel N=372 n (%)
Nonfatal MI	12 (3.2)	24 (6.5)
Periprocedural (P-MI)	11 (3.0)	19 (5.1)
Spontaneous	1 (0.3)	5 (1.3)



Based on Full Analysis Set
Test for statistical significance was not conducted
Percentage: (n / n) x 100%

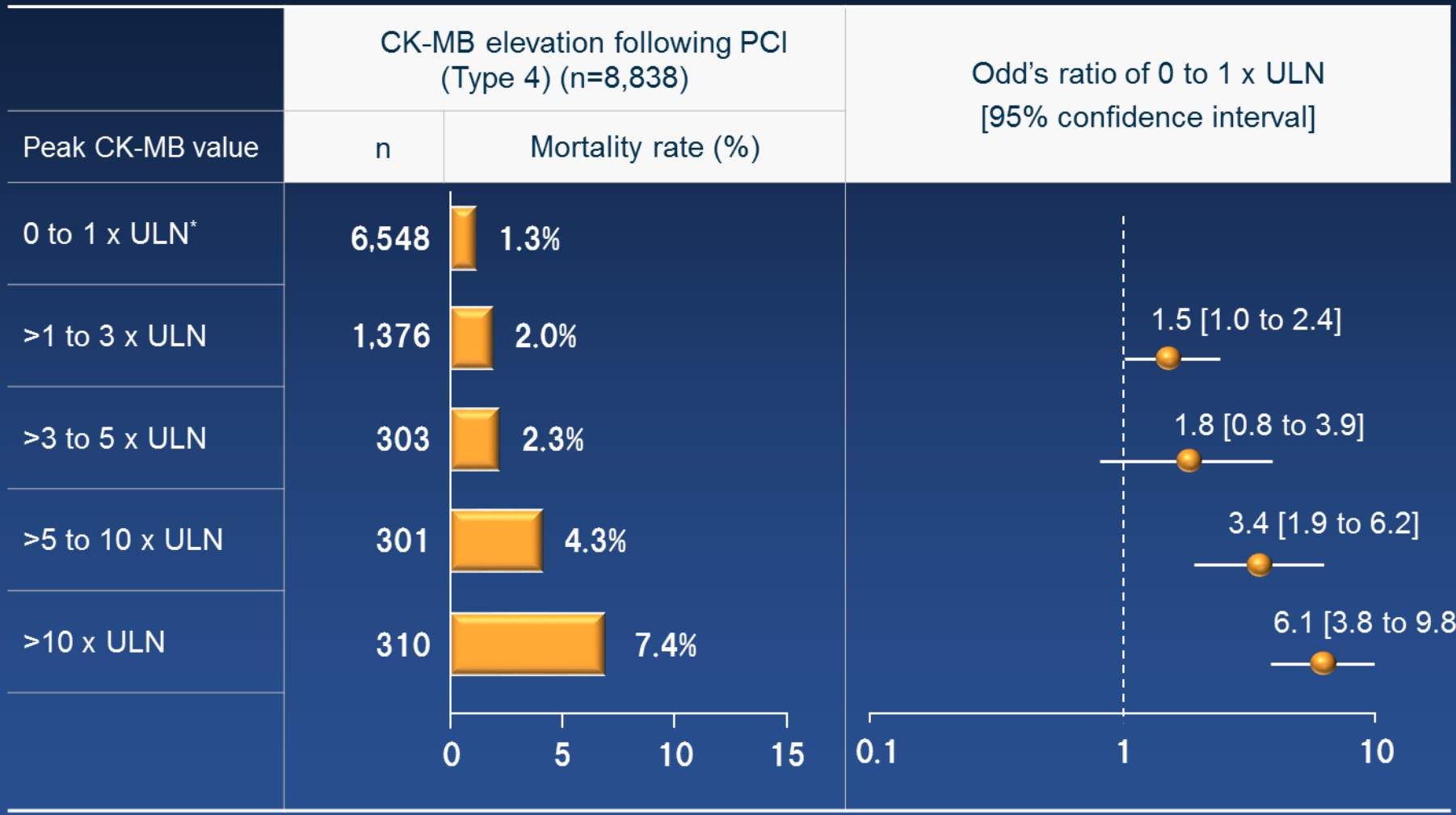
P-MIs were adjudicated according to 3rd universal definition of myocardial infarction.

Relationship between Stenting and Myocardial Infarction



Prasad A. et al：N. Engl. J. Med. 364(5), 453-464, 2011

Peak CK-MB Value and Mortality Rate (At 6-Month Observation)

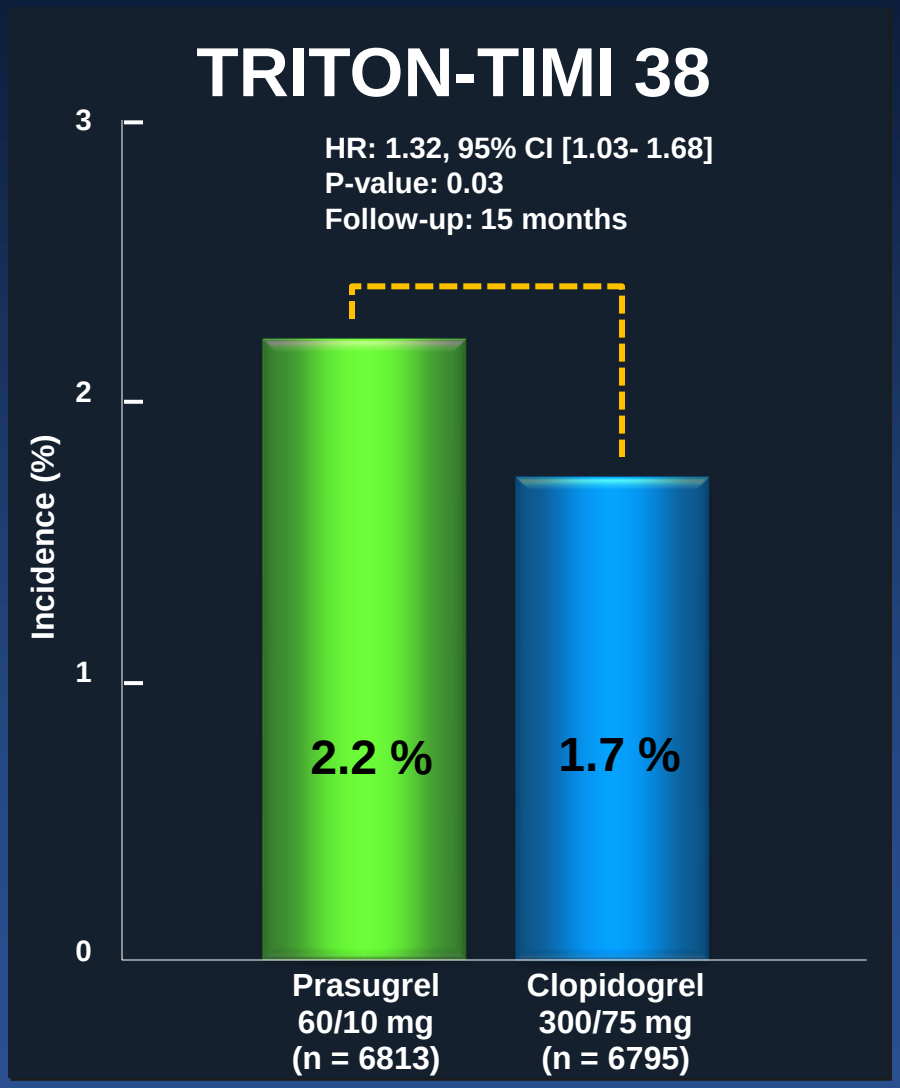


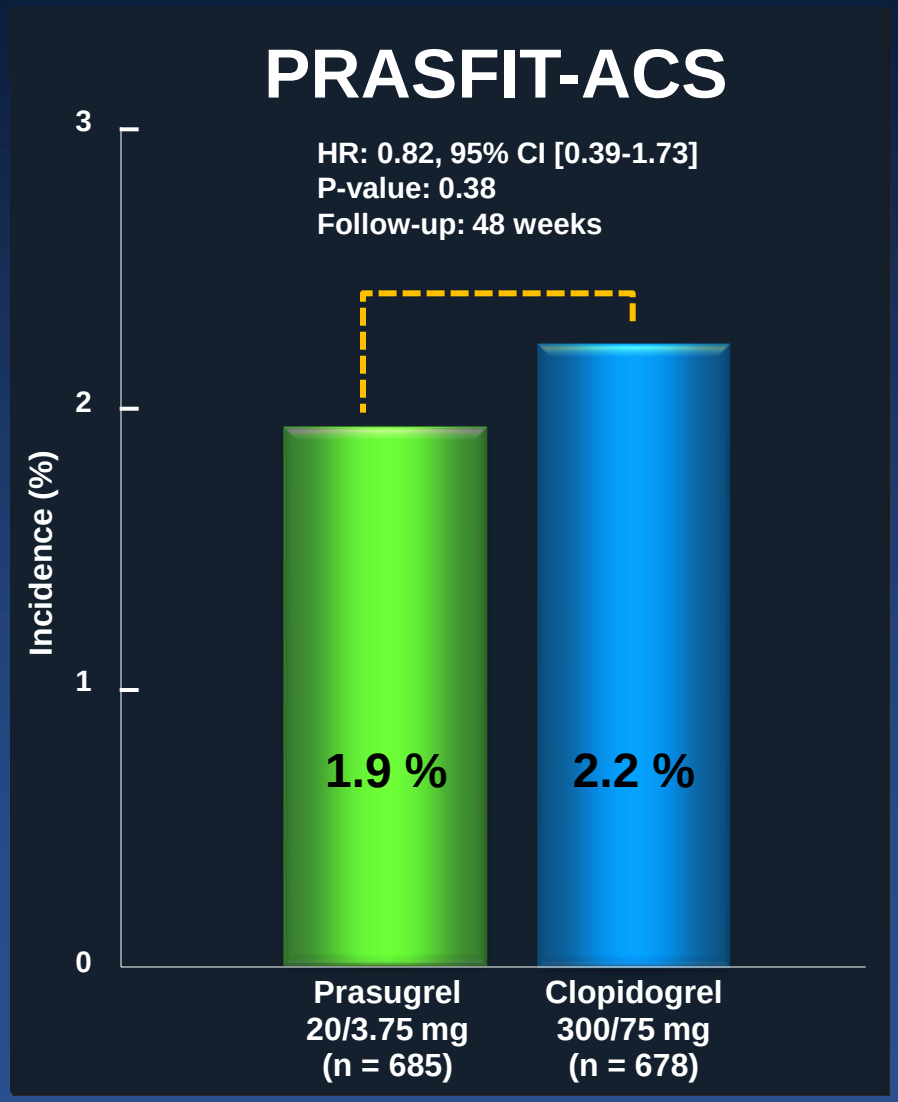
* ULN: Upper limit of normal

Prepared from Akkerhuis K. M. et al: Circulation 105(5), 554-556, 2002

Safety Results

Non-CABG TIMI-Major Bleeding Events of TRITON-TIMI 38 and PRASFIT-ACS

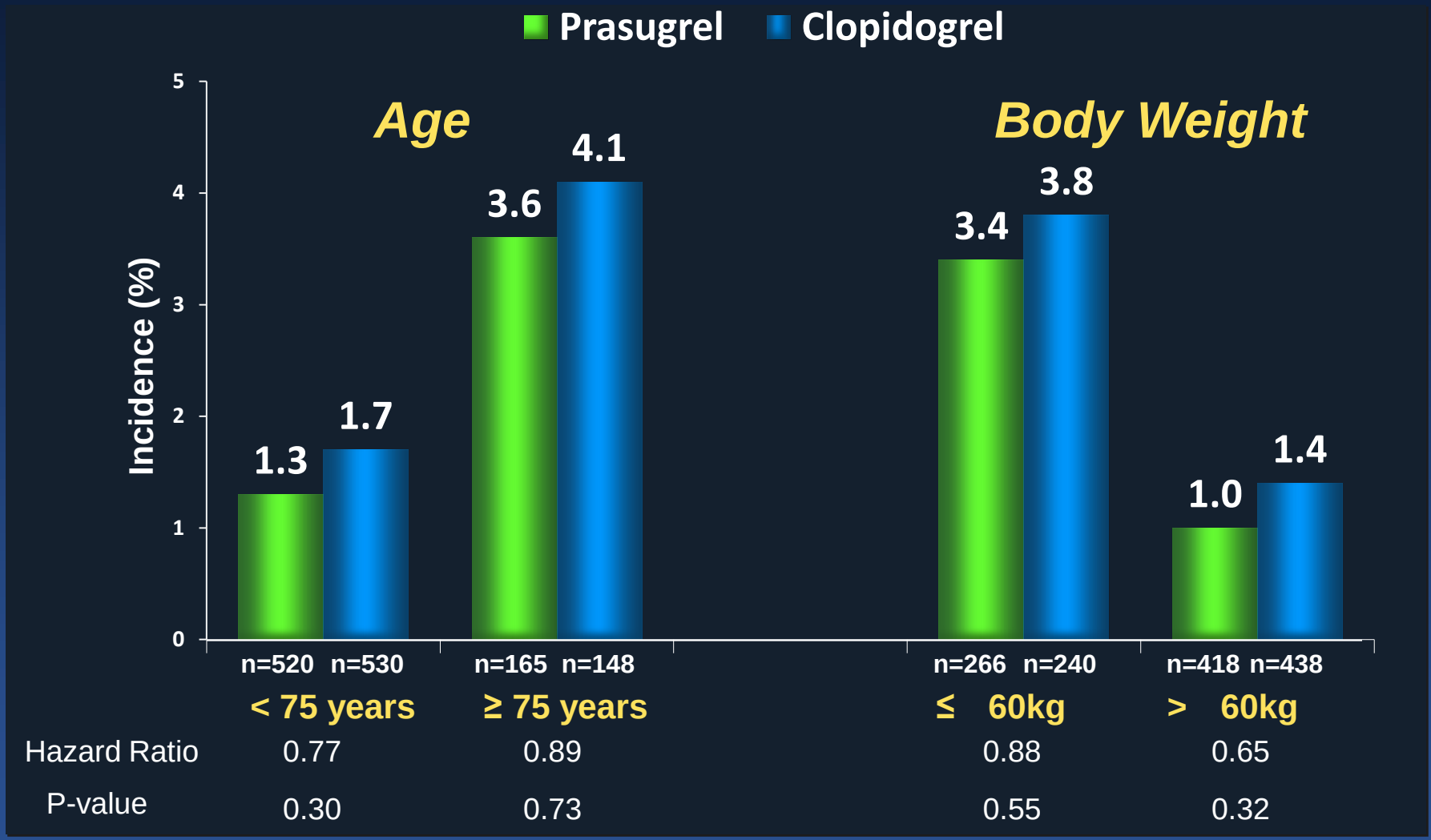




[2] Wiviott S et al. *NEJM* 2007;357:2001-2015

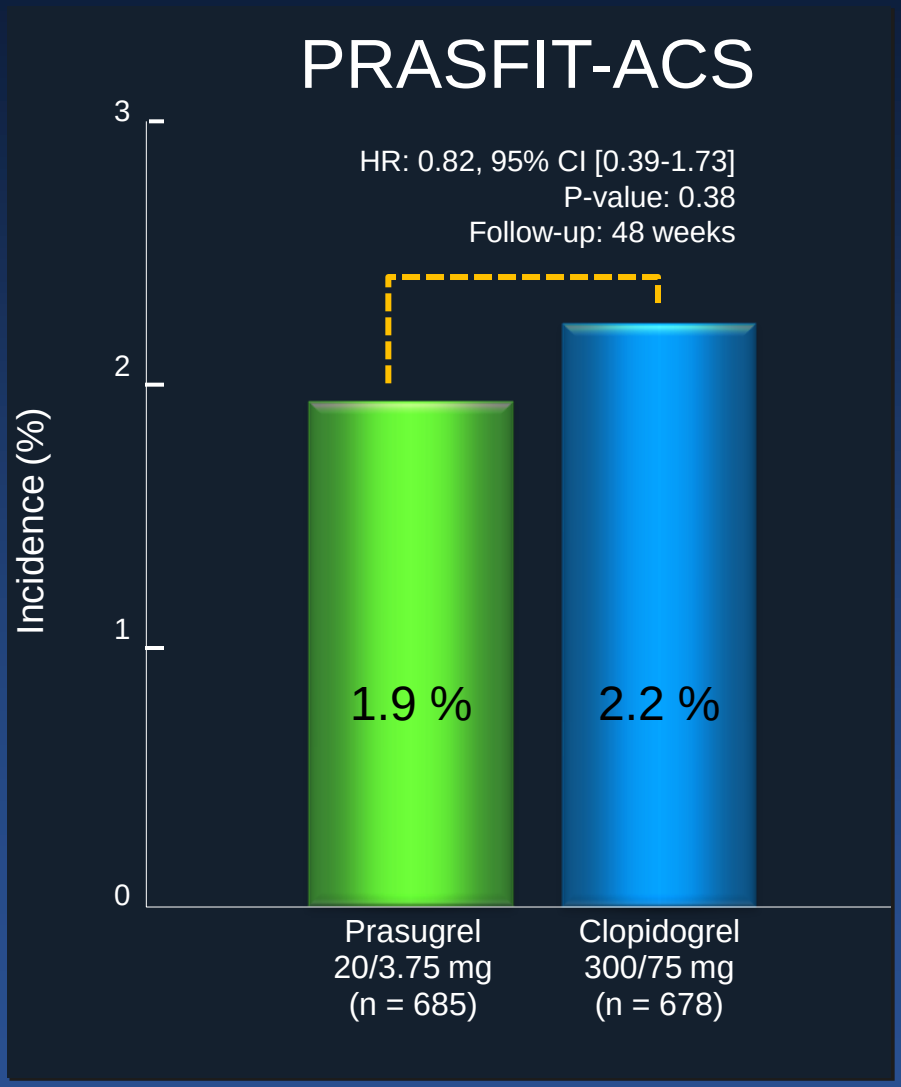
Based on Safety Analysis Set
Incidence: (n / n) x 100%

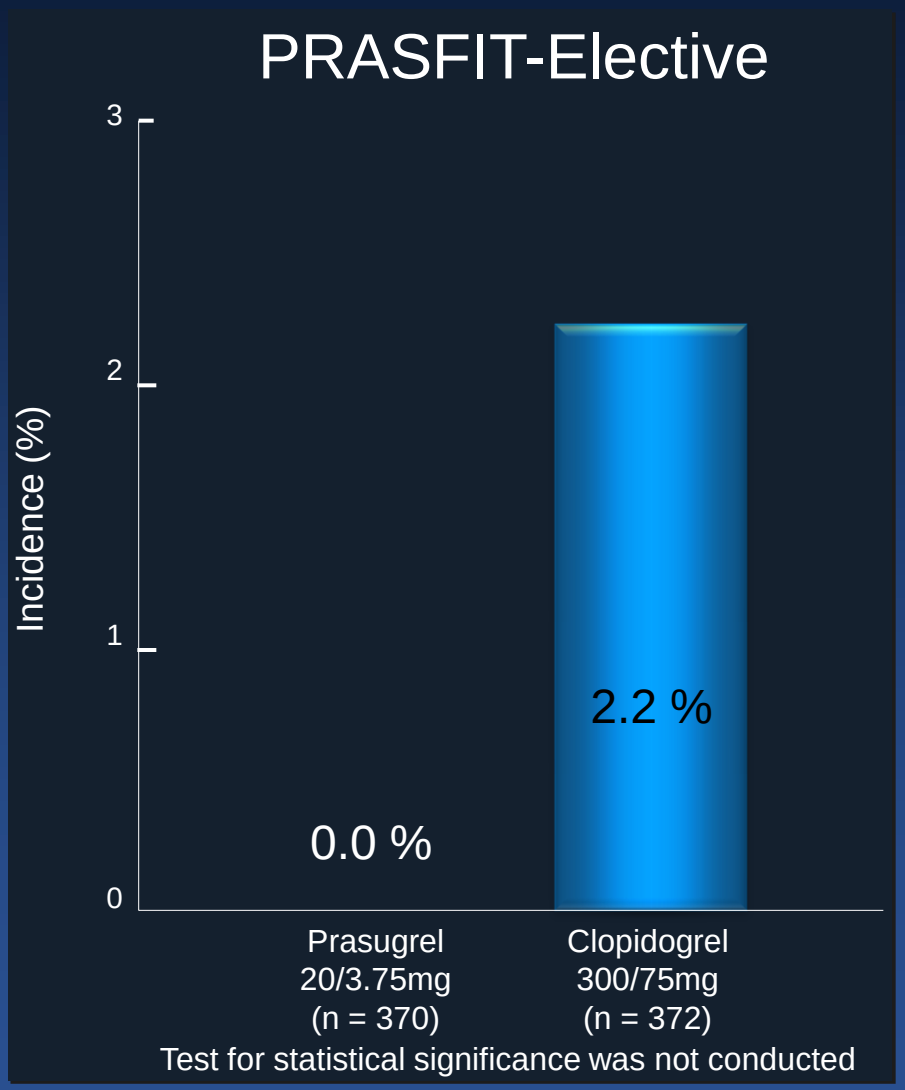
Non-CABG TIMI Major Bleeding Subgroup Analysis in PRASFIT-ACS



Based on Safety Analysis Set
Incidence: (n / n) x 100

Non-CABG TIMI-Major Bleeding Events of PRASFIT-ACS and PRASFIT-Elective





Based on Safety Analysis Set
Percentage: (n / n) x 100%

Summary of Efficacy and Safety

- **Ph III trials for Japanese ACS and elective-PCI patients with 20mg LD/ 3.75 mg MD of prasugrel were conducted.**
- **Efficacy**
  - In PRASFIT-ACS, the incidence of MACE at 24 weeks in Prasugrel 20 mg LD/3.75 mg MD group was 9.4%, while 11.8% in Clopidogrel group. (Risk reduction*: 23%)
  - In PRASFIT-Elective, the incidence of MACE at 24 weeks was 4.1% in the prasugrel group, and 6.7 % in the clopidogrel group.
- **Safety**
  - In PRASFIT-ACS, the incidence of Non-CABG TIMI major bleeding, and the incidence of TIMI major or minor bleeding or clinically relevant bleeding, were similar in the prasugrel and clopidogrel groups.
  - PRASFIT-Elective study provided efficacy and safety results in CAD with PCI consistent with the results seen in the PRASFIT-ACS study in ACS-PCI.

LD: Loading Dose MD: Maintenance Dose
MACE: Major adverse cardiovascular event
**Risk reduction: 1- HR (Hazard Ratio)*

Conclusions

- Prasugrel (20mg/3.75mg) demonstrated a favorable clinical benefit in Japanese patients with ACS or stable CAD treated with PCI.

Thank you very much!