Comparison of Prescription and Bleeding Rates and Clinical Outcomes of Contemporary P2Y12 Inhibitors in Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention

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JCR 2018

- No conflict of intrest

Introduction

- **DAPT (aspirin and a P2Y12 inhibitor)**

  Essential strategy in ACS patients following PCI to reduce the ischemic event and stent thrombosis.

- **Limitation of clopidogrel**

  The relatively insufficient efficacy by slow onset of action

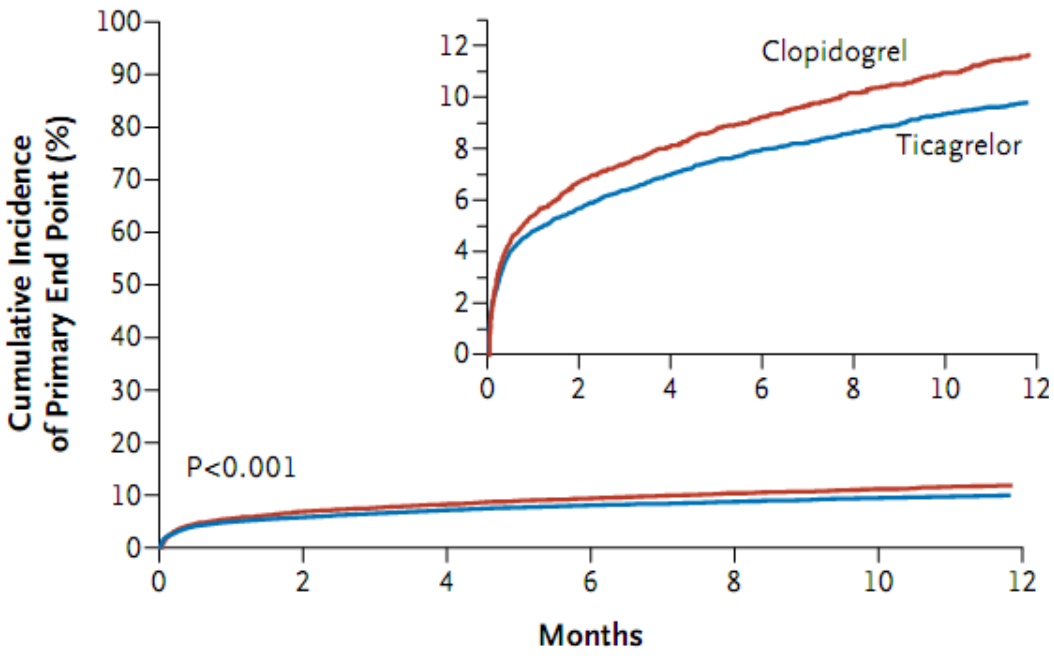
  Inter-individual variable platelet inhibition

  Poor clinical outcomes in patients with a blunted response

Introduction

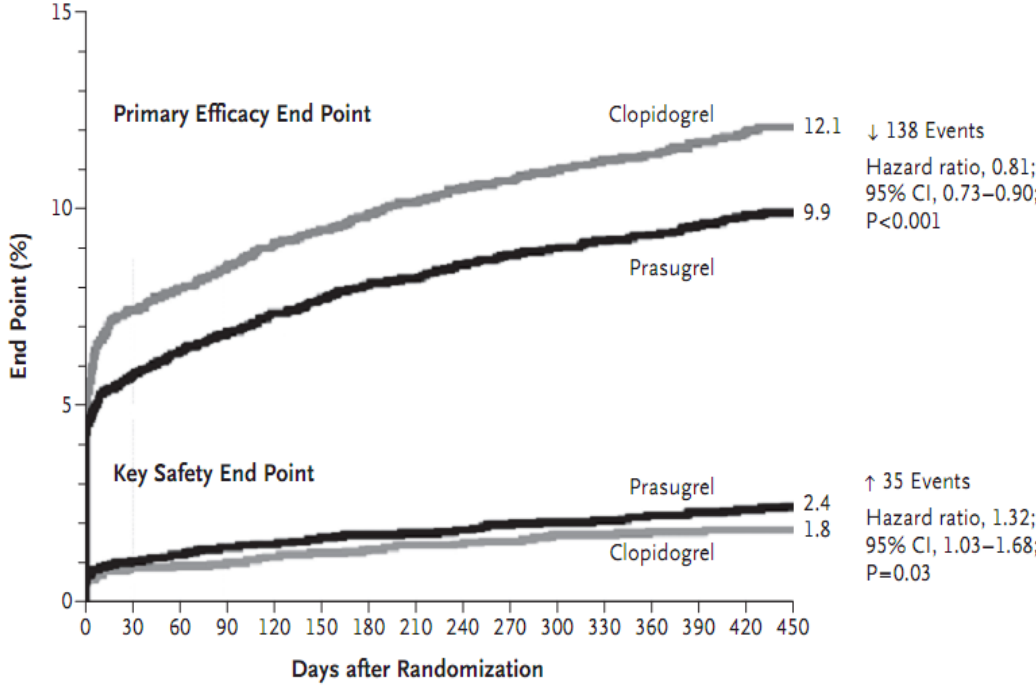
- *RCT* (New P2Y12 inhibitor vs. Clopidogrel)

PLATO trial: Ticagrelor vs. Clopidogrel



No. at Risk							
Ticagrelor	9333	8628	8460	8219	6743	5161	4147
Clopidogrel	9291	8521	8362	8124	6650	5096	4047

TRITON-TIMI38 trial: Prasugrel vs. Clopidogrel



No. at Risk							
Clopidogrel	6795	6169	6036	5835	5043	4369	3017
Prasugrel	6813	6305	6177	5951	5119	4445	3085

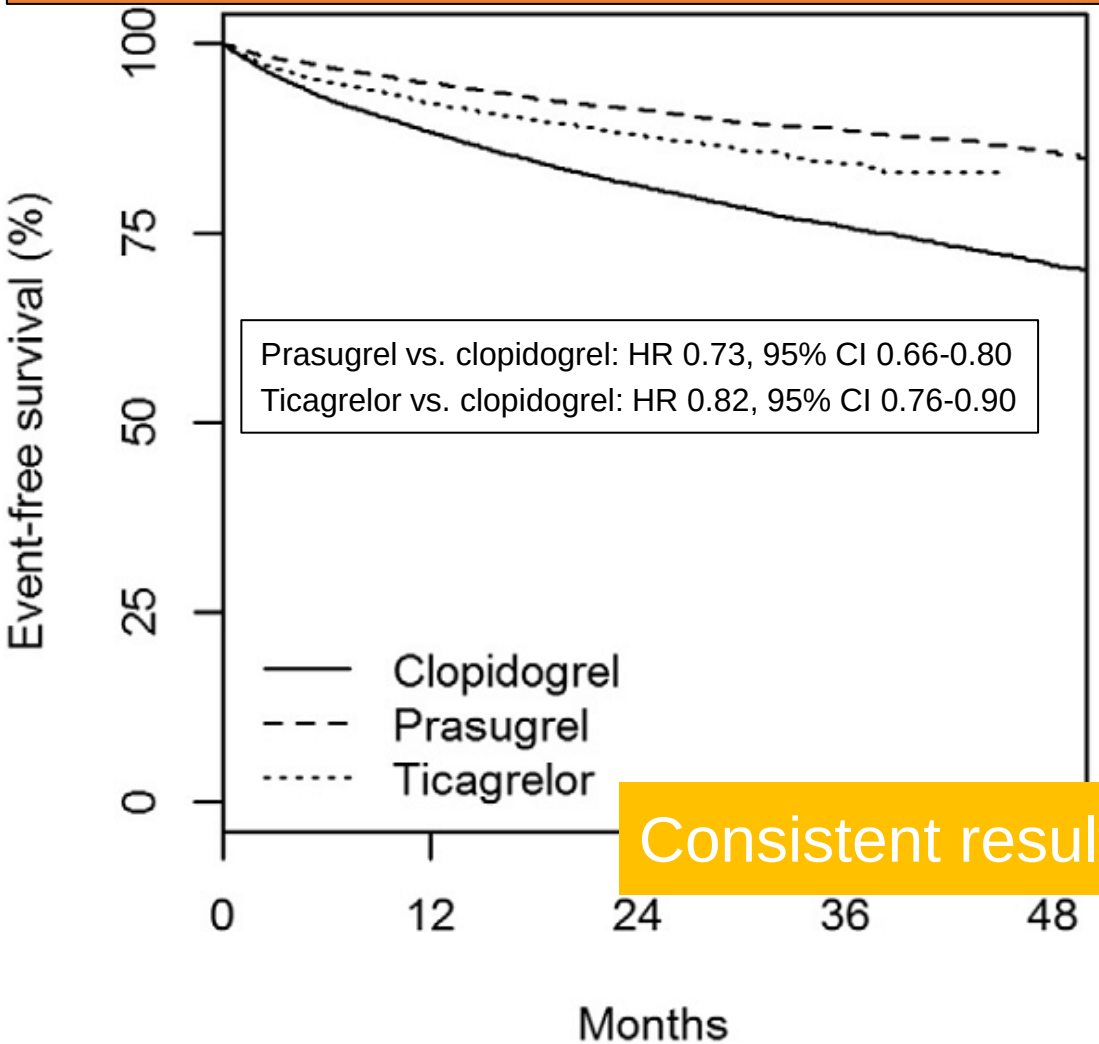
Guidelines: ticagrelor and prasugrel over clopidgrel as the preferred agent

NEJM 2007;357:2001-15.
NEJM 2009;361:1045-57.

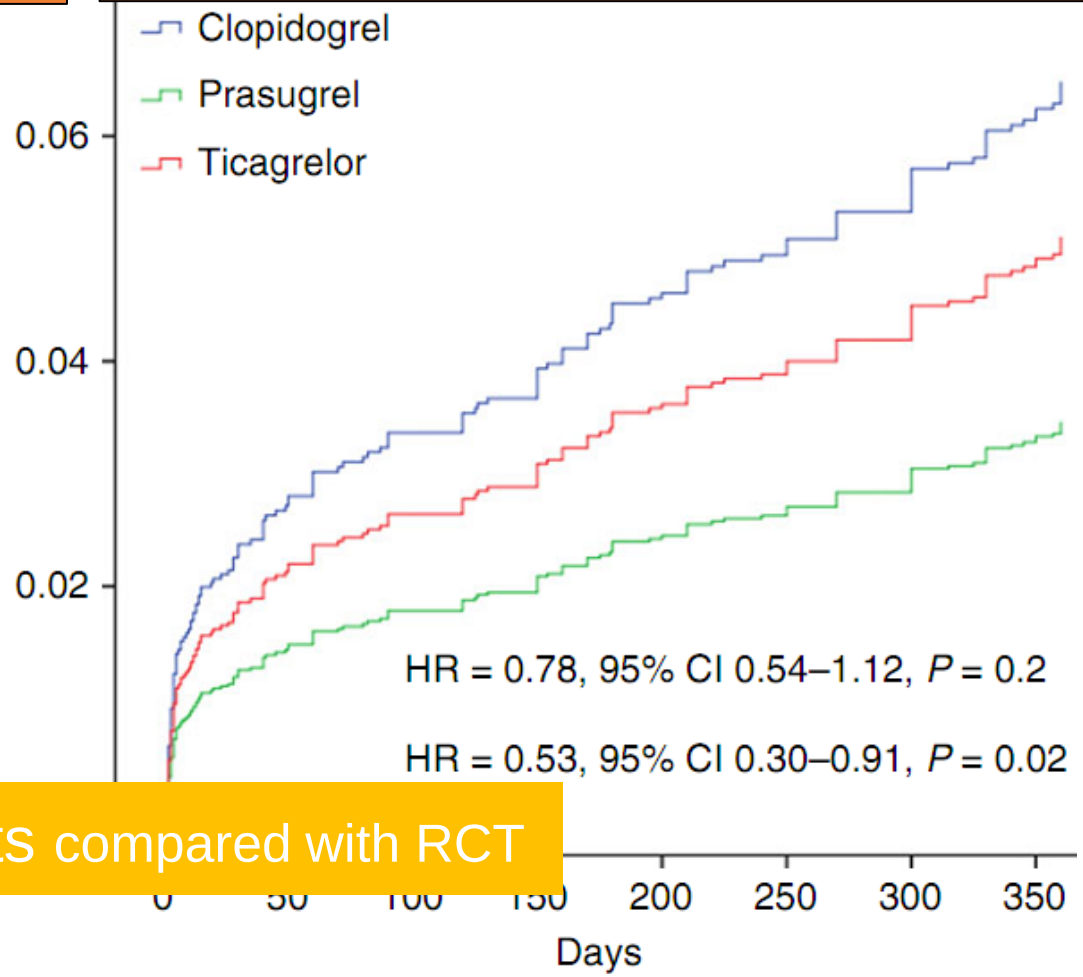
Introduction

- *Registry* (New P2Y12 inhibitor vs. Clopidogrel)

Austrian registry, 32830 ACS patients, 24.9months f/u



Greece registry, 2039 ACS patients, 1year f/u



Consistent results compared with RCT

Int J Cardiol 2017;235:61–66
J Thromb Haemost. 2016:14:1146–1154

Purpose

- The data of the prescription rate and safety and efficacy from the real-world practice, in specially East-Asian people – limited and inconsistent.

- Therefore, we compared prescription rates, bleeding events, and clinical outcomes after ticagrelor, prasugrel, or clopidogrel use in ACS patients following percutaneous coronary intervention (PCI).

Study Population

- The study population was selected from the Korea Acute Myocardial Infarction Registry-National Institutes of Health (KAMIR-NIH), which is a nationwide, prospective, multicenter online registry of patients presenting with acute MI in Korea, maintained at 20 university or community hospitals since November 2011.

- From November 2011 to June 2015, a total of 12431 consecutive patients with final diagnosis of ACS were prospectively enrolled.

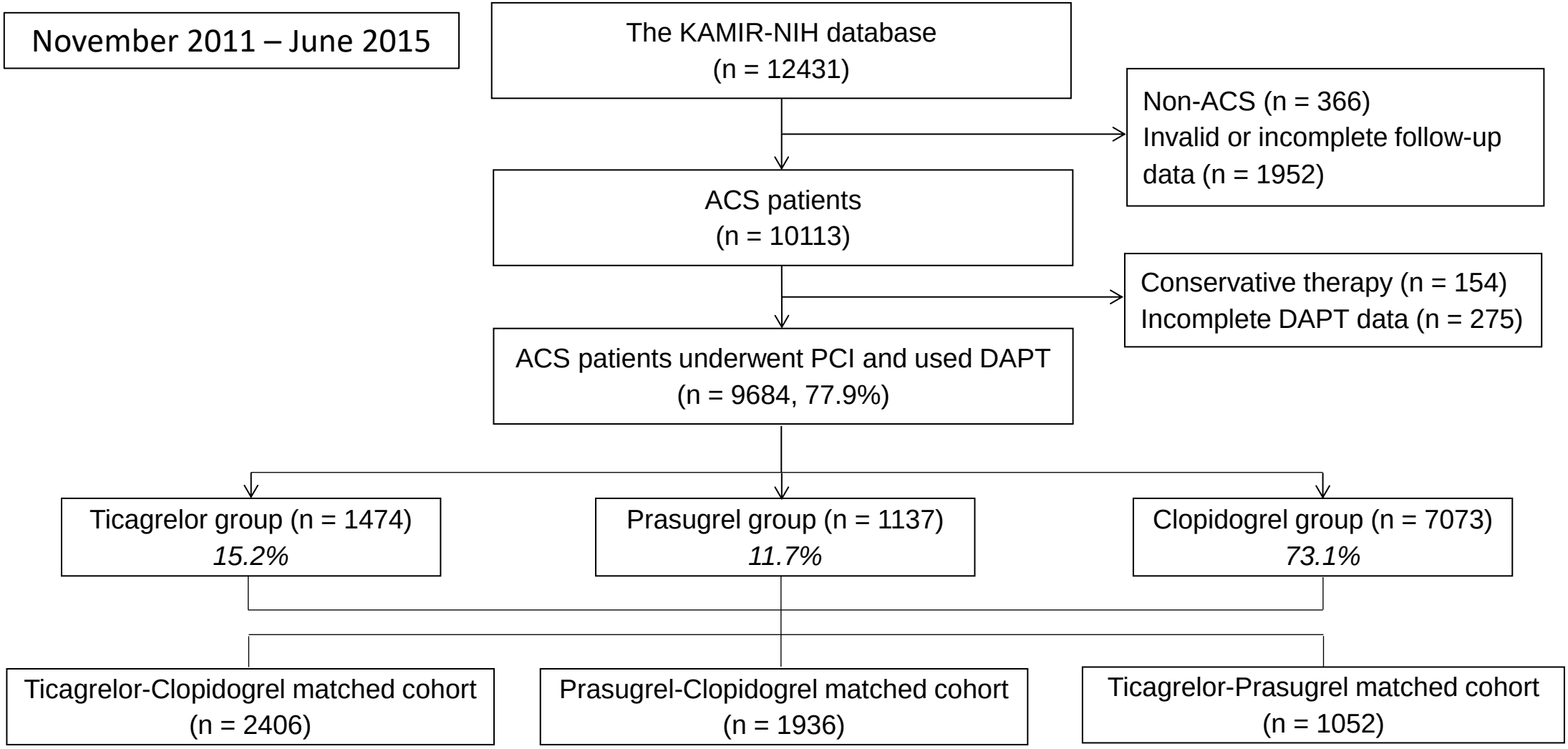
Inclusion and Exclusion Criteria

- Inclusion criteria for the present analysis were : 1) patients aged ≥18 years, 2) those with confirmed final diagnosis of ACS, 3) those who underwent PCI, and 4) those who prescribed the P2Y12 inhibitors (clopidogrel, ticagrelor, prasugrel) during hospitalization and follow-up.

- Exclusion criteria for the present analysis were : 1) patients with invalid or incomplete data (patients aged <18 years, without follow-up, with inaccurate data of the coronary procedure, with dating error, and with a missing value rate >30%), 2) those without the information of P2Y12 inhibitor or the prescription of P2Y12 inhibitor, and 3) those who did not undergo PCI.

- Among the registered patients, 9684 were included in the analysis.

Study Algorithm



Study Endpoint

- primary safety endpoint: cumulative bleeding complication defined by drop of Hb or cerebral hemorrhage

- primary efficacy endpoint: major adverse cardiac events (MACE) during follow-up; cardiac death, recurrent MI, and stroke

- secondary endpoints: components of MACE, all-cause death, non-cardiac death, and any revascularization (repeat PCI and coronary artery bypass graft), during follow-up

Baseline Characteristics (1)

	Ticagrelor group (n=1474)	Prasugrel group (n=1137)	Clopidogrel group (n=7073)	P
Age (years)	63 (54-73)	57 (50-64)	67 (56-75)	**<0.001**
Male	1110 (75.3%)	997 (87.7%)	4965 (70.2%)	**<0.001**
BMI (kg/m^2)	23.9 (22.1-25.9)	24.8 (23.1-26.7)	23.7 (21.6-25.7)	0.254
Hypertension	710 (48.2%)	483 (42.5%)	3798 (53.7%)	**<0.001**
Diabetes mellitus	547 (37.1%)	424 (37.3%)	2829 (40.0%)	**0.044**
Dyslipidemia	231 (15.7%)	206 (18.1%)	1061 (15.0%)	0.056
Prior MI	152 (10.3%)	127 (11.2%)	813 (11.5%)	0.425
Current smoking	887 (60.2%)	823 (72.4%)	3841 (54.3%)	**<0.001**
Killip class III/IV	140 (9.5%)	109 (9.6%)	948 (13.4%)	**<0.001**
STEMI	1257 (85.2%)	788 (69.3%)	3729 (52.7%)	**<0.001**

Values are median (25th and 75th percentiles) or n (%).
BMI, body mass index; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction

Baseline Characteristics (2)

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	Ticagrelor group (n=1474)	Prasugrel group (n=1137)	Clopidogrel group (n=7073)	P
Max. creatine kinase-MB (ug/L)	64.2 (12.5-185.8)	79.7 (16.5-226.4)	37.4 (7.9-143.2)	**<0.001**
Max. troponin I (ng/dL)	20.6 (3.9-49.0)	23.7 (3.4-62.8)	13.9 (2.2-49.4)	**<0.001**
Brain natriuretic peptide (pg/mL)	55.6 (21.0-195.8)	42.5 (10.0-134.6)	93.9 (29.0-331.2)	**<0.001**
Baseline Creatinine (mg/dL)	0.9 (0.7-1.1)	0.9 (0.7-1.0)	0.9 (0.8-1.2)	**<0.001**
LDL-cholesterol (mg/dL)	113 (86-138)	112 (88-137)	107 (81-134)	**<0.001**
hs-CRP (mg/L)	0.22 (0.07-0.76)	0.20 (0.07-0.58)	0.30 (0.09-0.90)	**<0.001**
LVEF (%)	53.2 (46.0-60.0)	53.0 (47.0-59.7)	53.0 (45.0-60.0)	0.059
LVEF <40%	252 (17.1%)	125 (11.0%)	1148 (16.2%)	**<0.001**

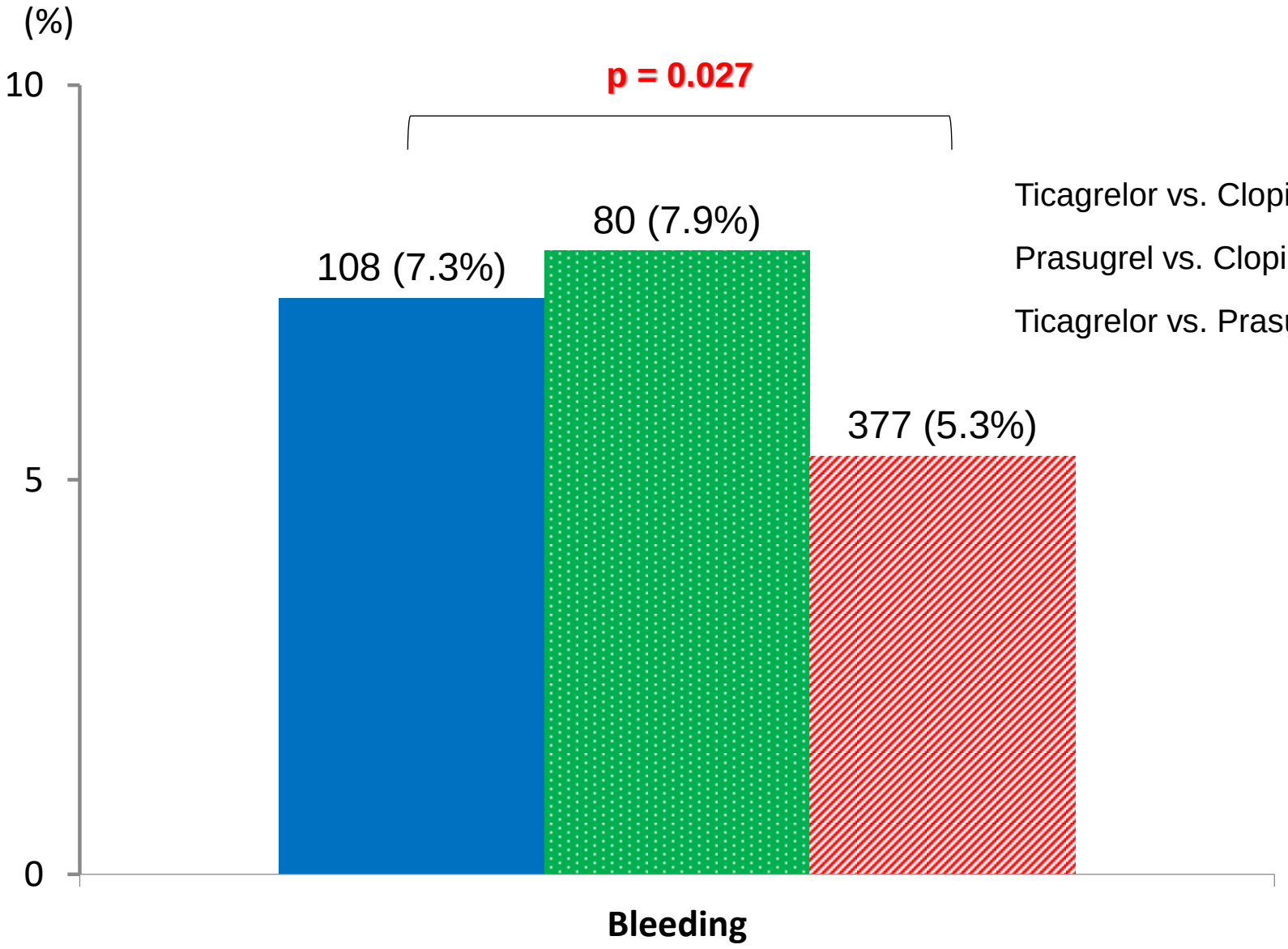
Values are median (25^{th} and 75^{th} percentiles) or n (%).
hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; LVEF, left ventricular ejection fraction.

Angiographic Characteristics

	Ticagrelor group (n=1474)	Prasugrel group (n=1137)	Clopidogrel group (n=7073)	P
Left main or 3-vessel disease	305 (20.7%)	174 (15.3%)	1591 (22.5%)	**<0.001**
Culprit lesion: Left main or LAD	716 (48.6%)	571 (50.2%)	3437 (48.6%)	0.554
ACC/AHA Lesion type: B2 or C	1337 (90.7%)	1028 (90.4%)	5970 (84.4%)	0.092
Transfemoral approach	738 (50.1%)	773 (68.0%)	4109 (58.1%)	**<0.001**
Multiple treated vessels (≥2)	308 (20.9%)	224 (19.7%)	1471 (20.8%)	0.626
Multiple stents (≥2)	479 (32.5%)	317 (27.9%)	1674 (23.7%)	**0.024**
IVUS use	522 (35.4%)	187 (16.4%)	1389 (19.6%)	**<0.001**
Procedural success	1468 (99.6%)	1130 (99.4%)	7031 (99.4%)	0.658
Procedural complications	295 (20.0%)	248 (21.8%)	1400 (19.8%)	0.224

Values are median (25^{th} and 75^{th} percentiles) or n (%).
IVUS, intravascular ultrasound; LAD, left anterior descending.

Primary Safety Endpoint: Bleeding



	OR (95% CI), p
Ticagrelor vs. Clopidogrel	**1.32 (1.08-1.61), 0.008**
Prasugrel vs. Clopidogrel	**1.17 (1.02-1.89), 0.026**
Ticagrelor vs. Prasugrel	0.79 (0.59-1.09), 0.159

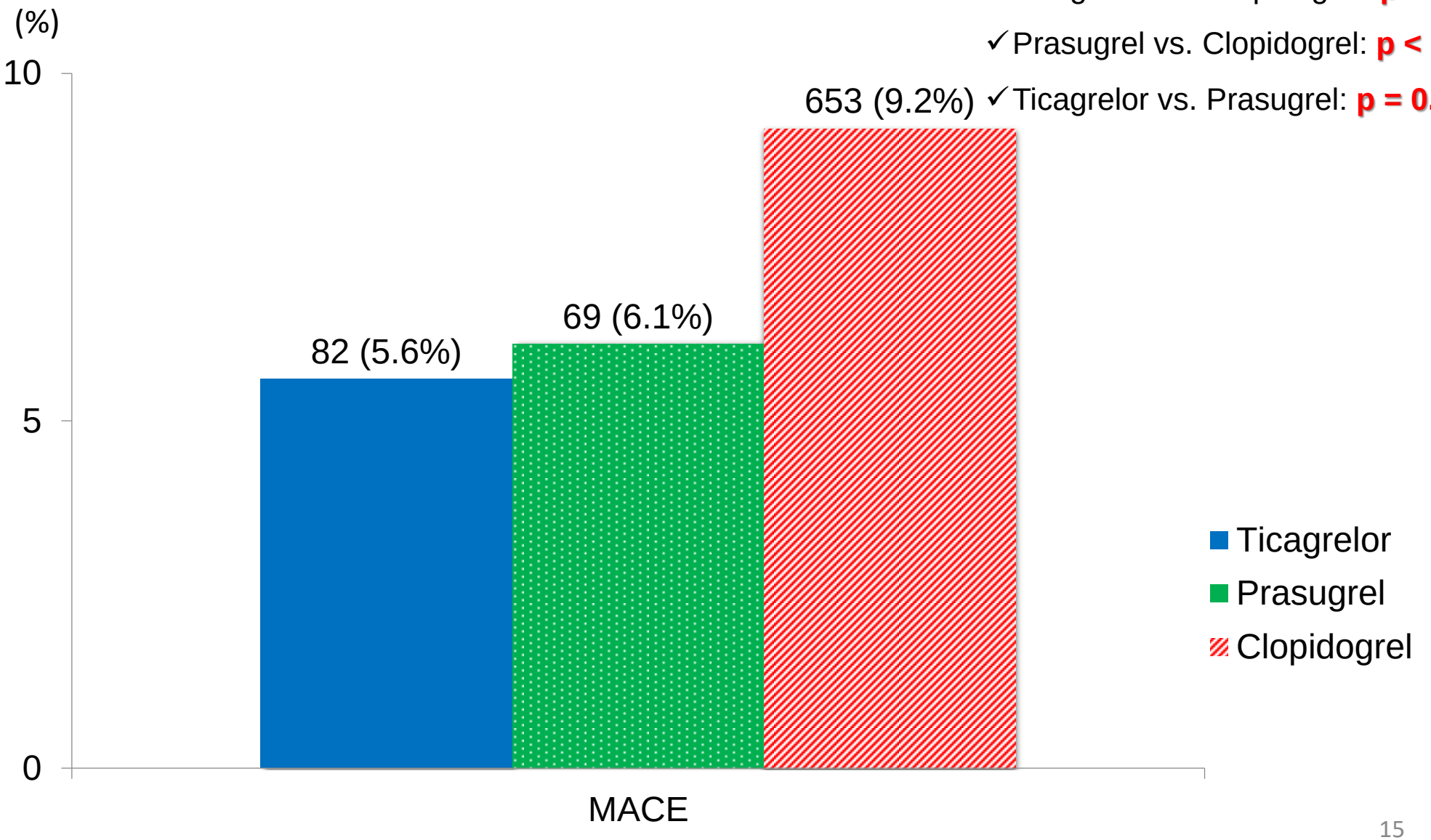
- Ticagrelor
- Prasugrel
- Clopidogrel

Primary Efficacy Endpoint: MACE

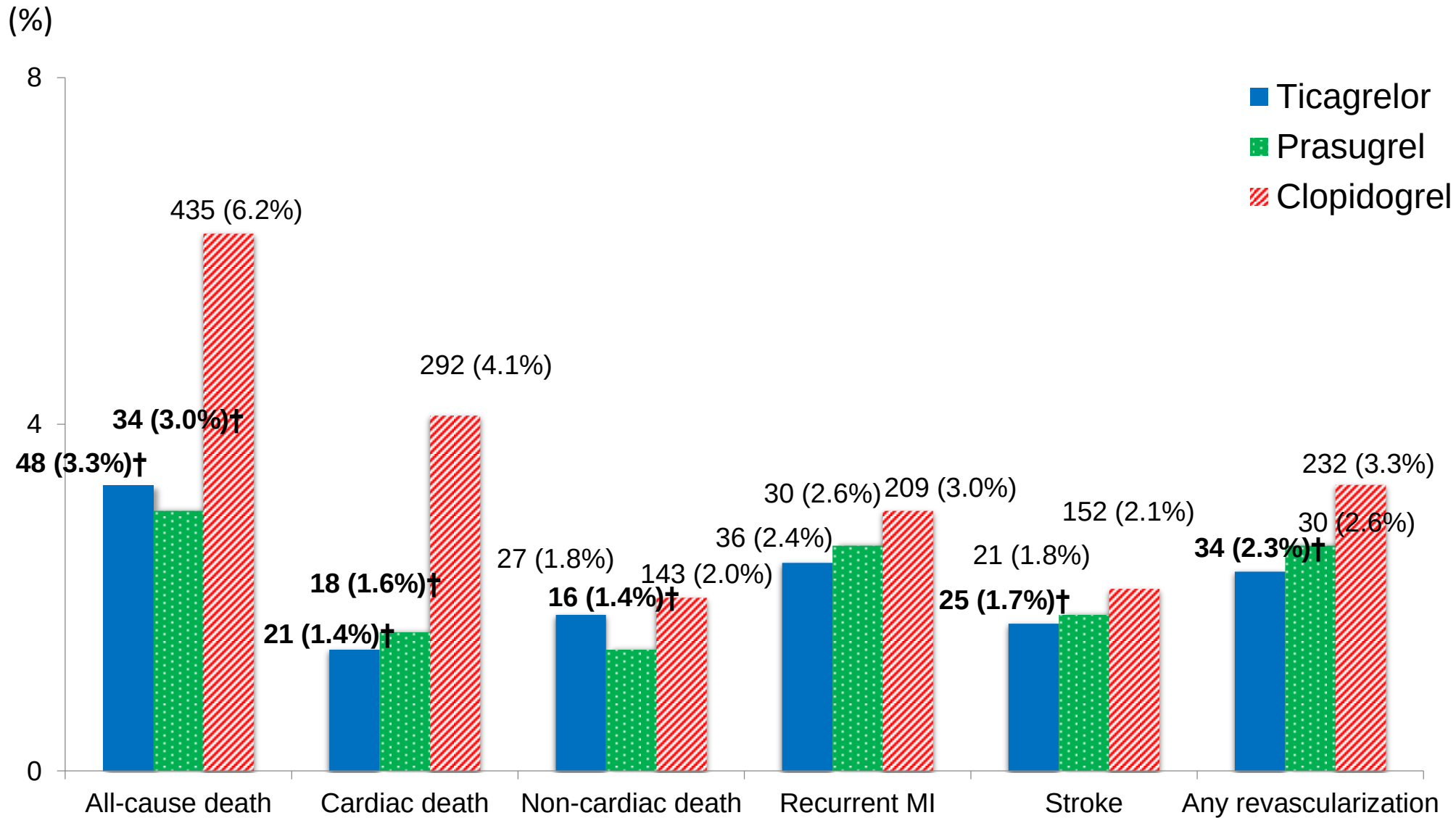
✓Ticagrelor vs. Clopidogrel: **p < 0.001**

✓Prasugrel vs. Clopidogrel: **p < 0.001**

✓Ticagrelor vs. Prasugrel: **p = 0.578**



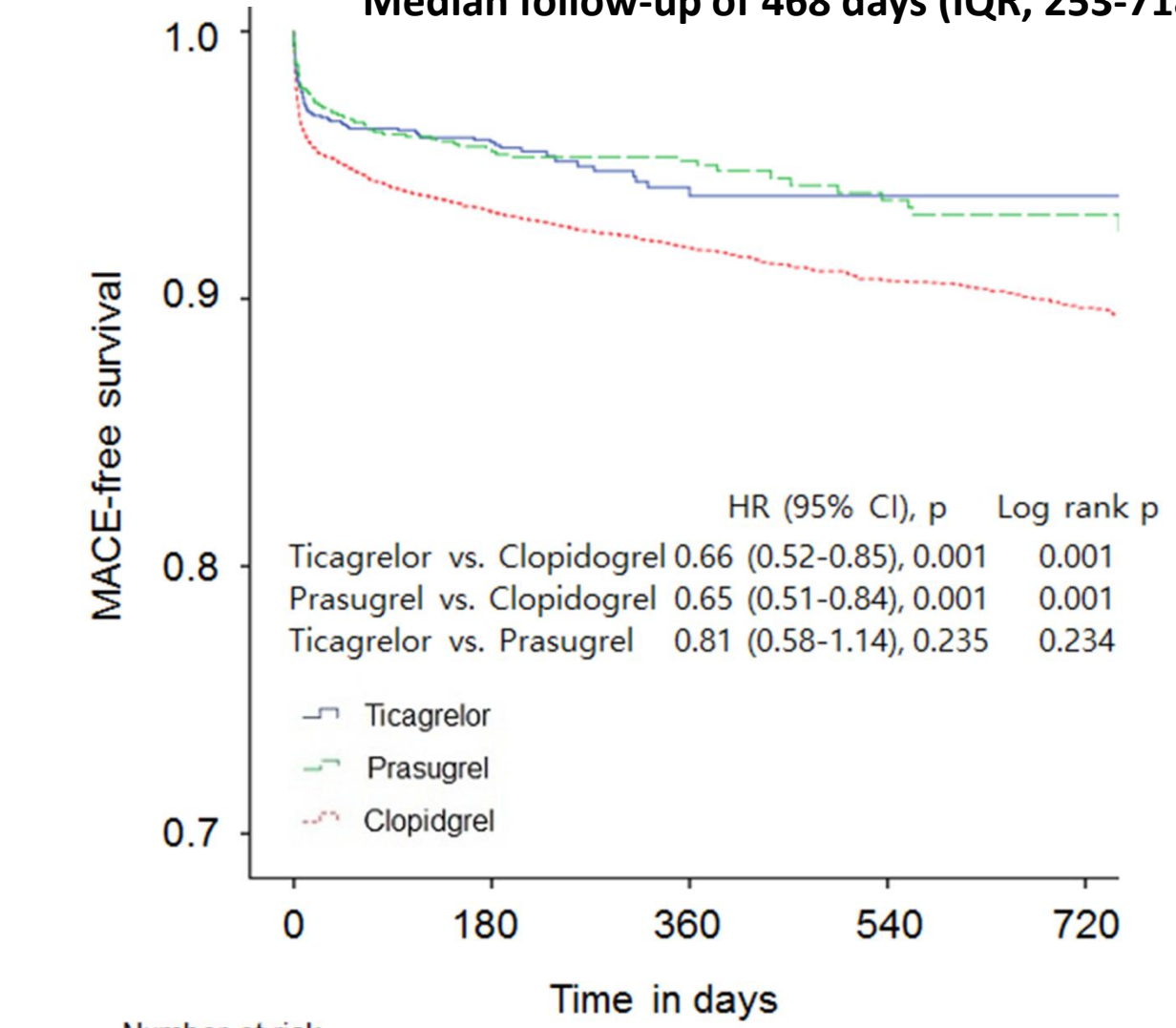
Secondary Endpoints



*significant p value compared with Prasugrel. † significant p value compared with Clopidogrel.

MACE-free survival

Median follow-up of 468 days (IQR, 253-718 days)



Number at risk					
Ticagrelor	1474	1312	1132	952	772
Prasugrel	1137	939	759	579	399
Clopidgrel	7073	6893	6713	6533	6353

Cox regression hazard analysis (1)

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Standard Cox regression analysis

	Ticagrelor vs. Clopidogrel	Prasugrel vs. Clopidogrel	Ticagrelor vs. Prasugrel
	Adjusted HR (95% CI), p	Adjusted HR (95% CI), p	Adjusted HR (95% CI), p
All-cause death	**0.71 (0.43-0.89), 0.033**	**0.67 (0.49-0.83), 0.026**	1.11 (0.38-4.19), 0.748
Cardiac death	**0.59 (0.45-0.79), <0.001**	**0.54 (0.39-0.74), <0.001**	0.81 (0.34-2.62), 0.706
Non-cardiac death	0.91 (0.61-1.38), 0.664	**0.50 (0.29-0.85), 0.010**	1.51 (0.35-5.27), 0.348
MI	0.81 (0.54-1.47), 0.656	0.89 (0.65-1.54), 0.979	0.71 (0.22-3.12), 0.084
Stroke	0.76 (0.68-2.37), 0.456	0.88 (0.46-1.56), 0.141	0.82 (0.35-4.29), 0.328
Any revascularization	**0.81 (0.52-0.97), 0.023**	**0.85 (0.61-0.98), 0.035**	0.79 (0.25-5.31), 0.569
Re-PCI	**0.79 (0.53-0.89), 0.034**	**0.88 (0.52-0.95), 0.041**	0.84 (0.41-5.58), 0.156
CABG	0.40 (0.10-1.68), 0.213	0.59 (0.18-1.93), 0.385	0.97 (0.12-1.29), 0.659
Cardiac death, MI, or stroke	**0.66 (0.52-0.85), 0.001**	**0.65 (0.51-0.84), 0.001**	0.81 (0.58-1.14), 0.235

Cox regression hazard analysis (2)

Propensity Score-matched analyses

	Ticagrelor vs. Clopidogrel	Prasugrel vs. Clopidogrel	Ticagrelor vs. Prasugrel
	Adjusted HR (95% CI), p	Adjusted HR (95% CI), p	Adjusted HR (95% CI), p
All-cause death	**0.61 (0.34-0.93), 0.032**	**0.53 (0.38-0.96), 0.041**	1.02 (0.59-6.29), 0.759
Cardiac death	**0.56 (0.35-0.91), 0.012**	**0.49 (0.23-0.83), 0.007**	0.62 (0.05-1.30) 0.358
Non-cardiac death	0.89 (0.59-2.24), 0.247	0.93 (0.74-4.19), 0.422	1.11 (0.72-5.88), 0.649
MI	0.70 (0.34-1.43), 0.416	0.68 (0.32-1.46), 0.249	0.87 (0.05-8.31), 0.843
Stroke	0.61 (0.47-2.61), 0.219	0.38 (0.12-1.19), 0.157	0.78 (0.22-4.84), 0.469
Any revascularization	0.71 (0.42-1.61), 0.194	0.82 (0.48-2.03), 0.689	0.81 (0.35-6.92), 0.786
Re-PCI	0.82 (0.67-1.72), 0.258	0.98 (0.59-1.64), 0.428	0.76 (0.24-3.27), 0.512
CABG	0.19 (0.02-1.57), 0.648	0.50 (0.09-2.75), 0.785	0.92 (0.22-5.12), 0.611
Cardiac death, MI, or stroke	**0.68 (0.47-0.97), 0.025**	**0.55 (0.33-0.90), 0.017**	0.39 (0.12-1.29), 0.327

Summary

- From a recent, nationwide, prospective, multicenter registry
- 9684 ACS patients who underwent PCI during the median follow-up of 468 days Bleeding, Clinical outcomes: Ticagrelor (15%) vs. Prasugrel (12%) vs. Clopidogrel (73%)
- compared to clopidogrel use, bleeding rates were significantly higher in ticagrelor and prasugrel groups but not different significantly between ticagrelor and prasugrel uses
- Ticagrelor and prasugrel vs. Clopidogrel: lower risks of MACE, all-cause death, and cardiac death, whereas the differences between ticagrelor and prasugrel use for lower rates of MACE, all-cause death, and cardiac death were not significant.

Limitation of study

- Definition and event occured time of Bleeding event?? It's only in-hospital bleeding event recorded, even not using international bleeding criteria

- No data about prescription rate for the maintenance therapy during follow-up period

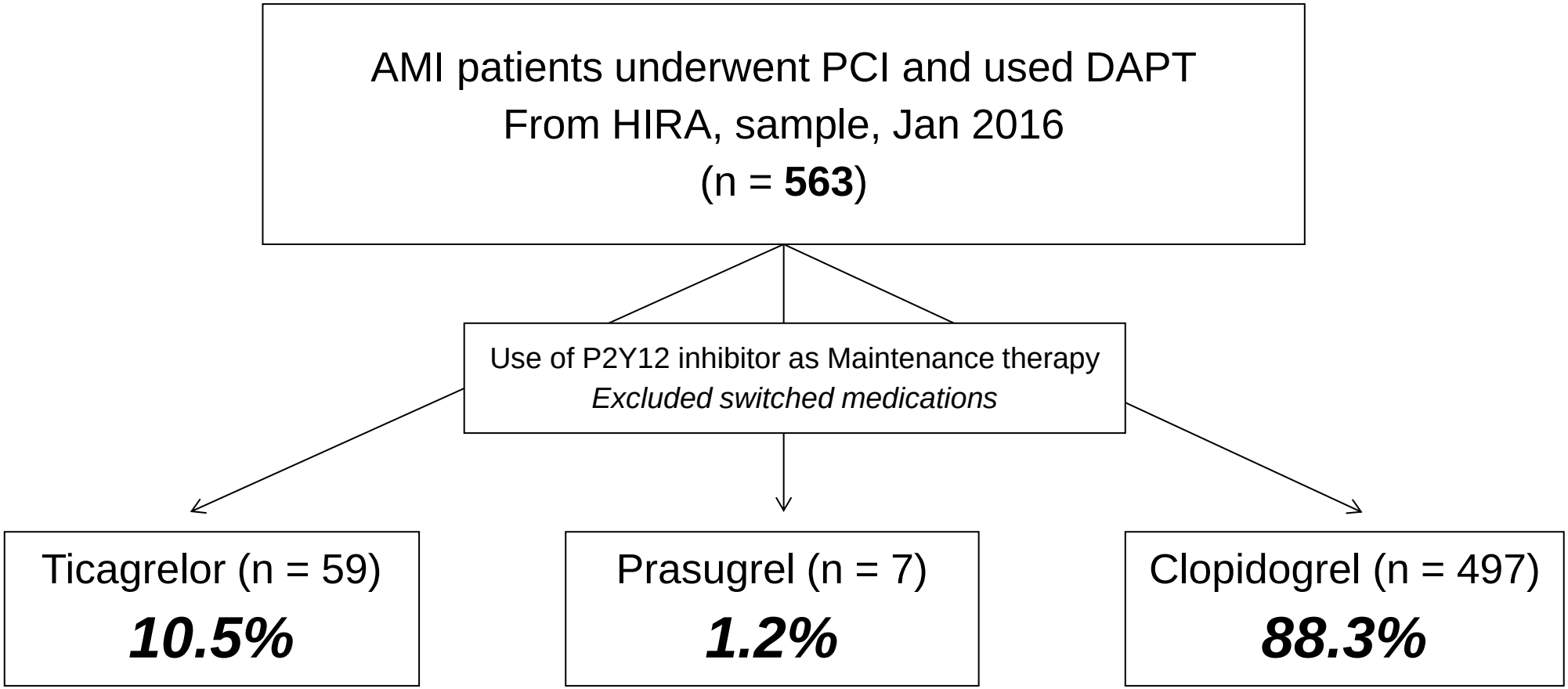
"How about the real bleeding and ischemic evnets during prescribed P2Y12 inhibitors continously?"

Study using HIRA

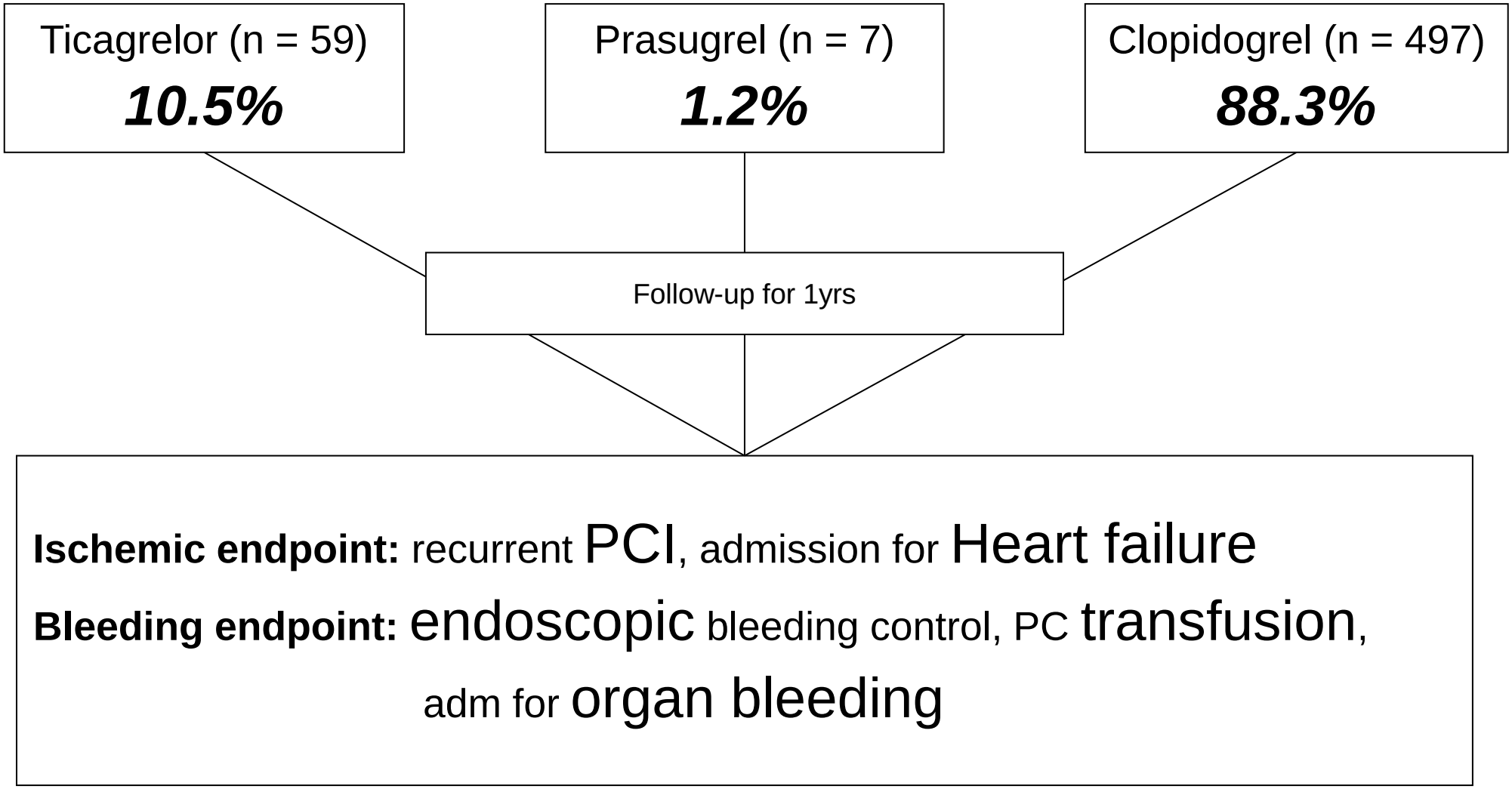
- Data provided by HEALTH INSURANCE REVIEW & ASSESSMENT (HIRA) SERVICE, including all assets related to the medical services, such as, prescribed medication, code of diagnosis, all kind of medical behavior...

- Using Sample data inside HIRA, patients with diagnosis of AMI underwent PCI for 1month, Jan. 2016 were analysed according to the ticagrelor, prasugrel, clopidogrel use as maintenance therapy during 1 yr of follow-up period

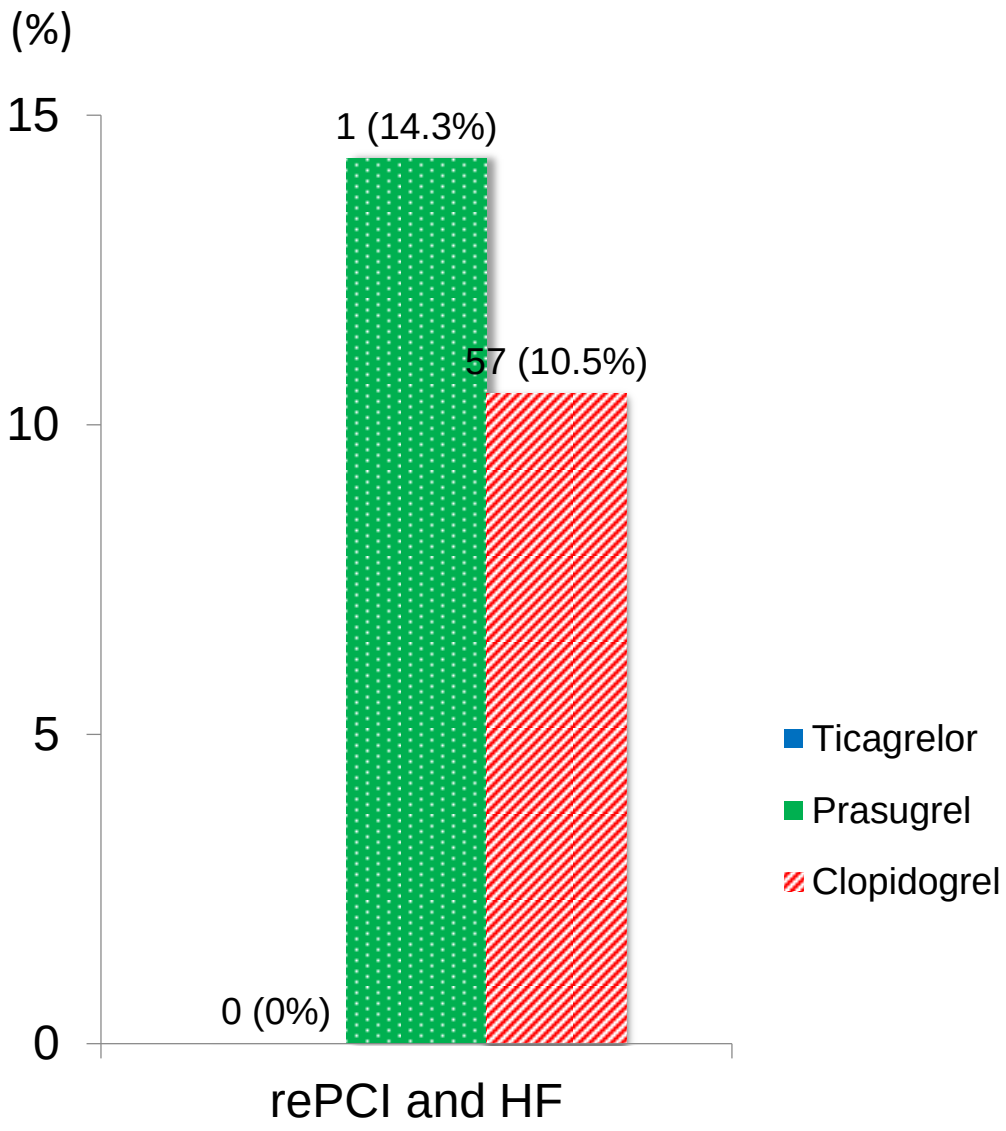
Results from HIRA

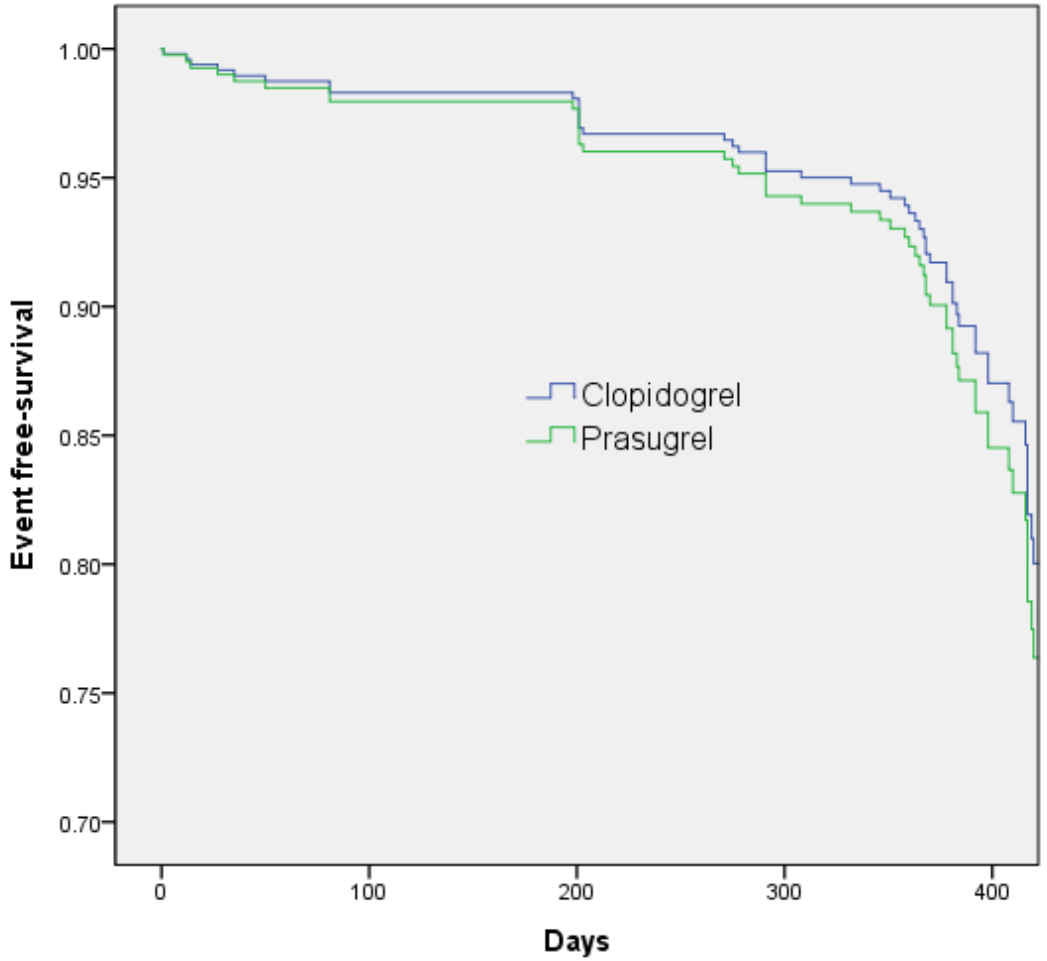


Results from HIRA



Ischemic endpoint from HIRA



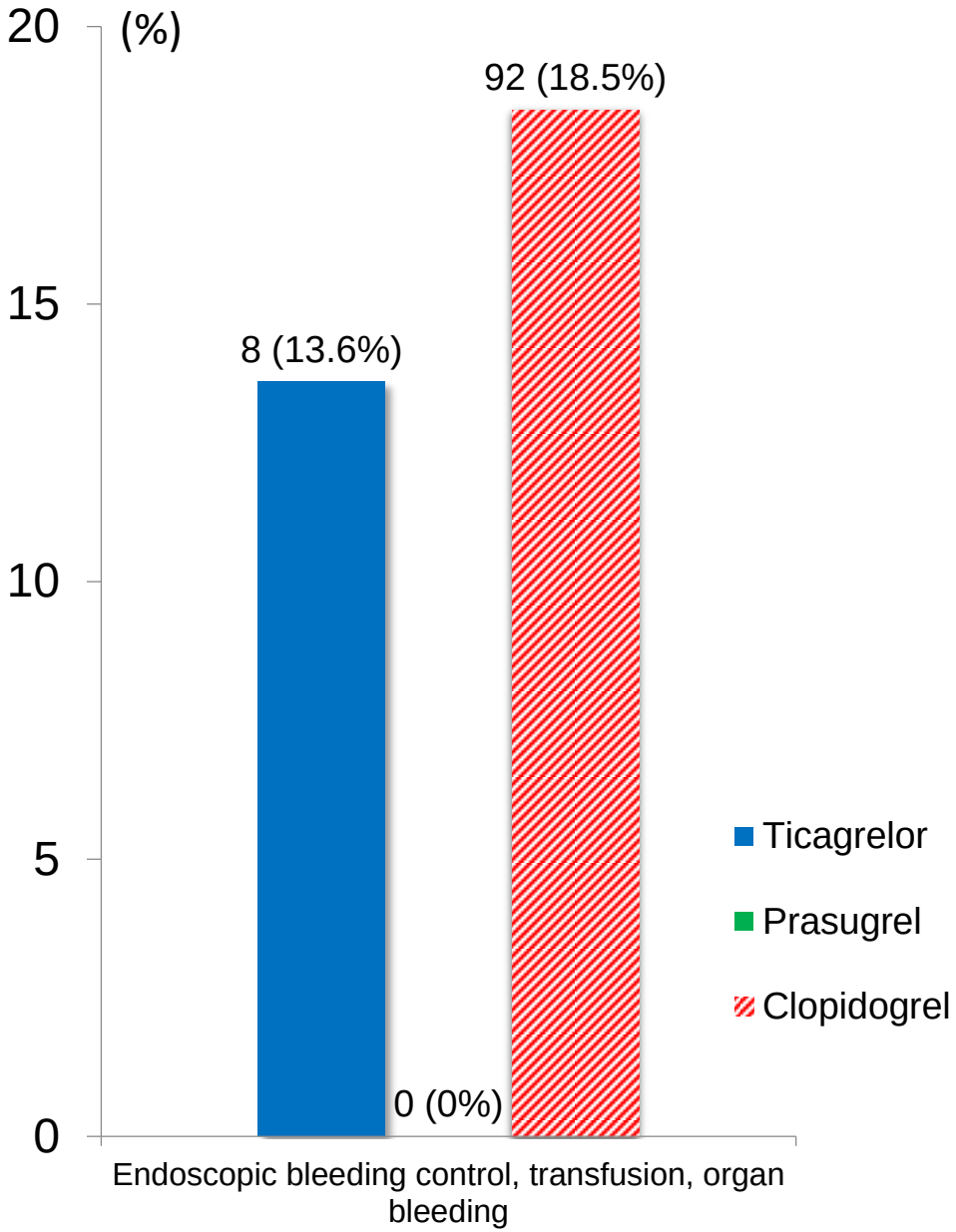


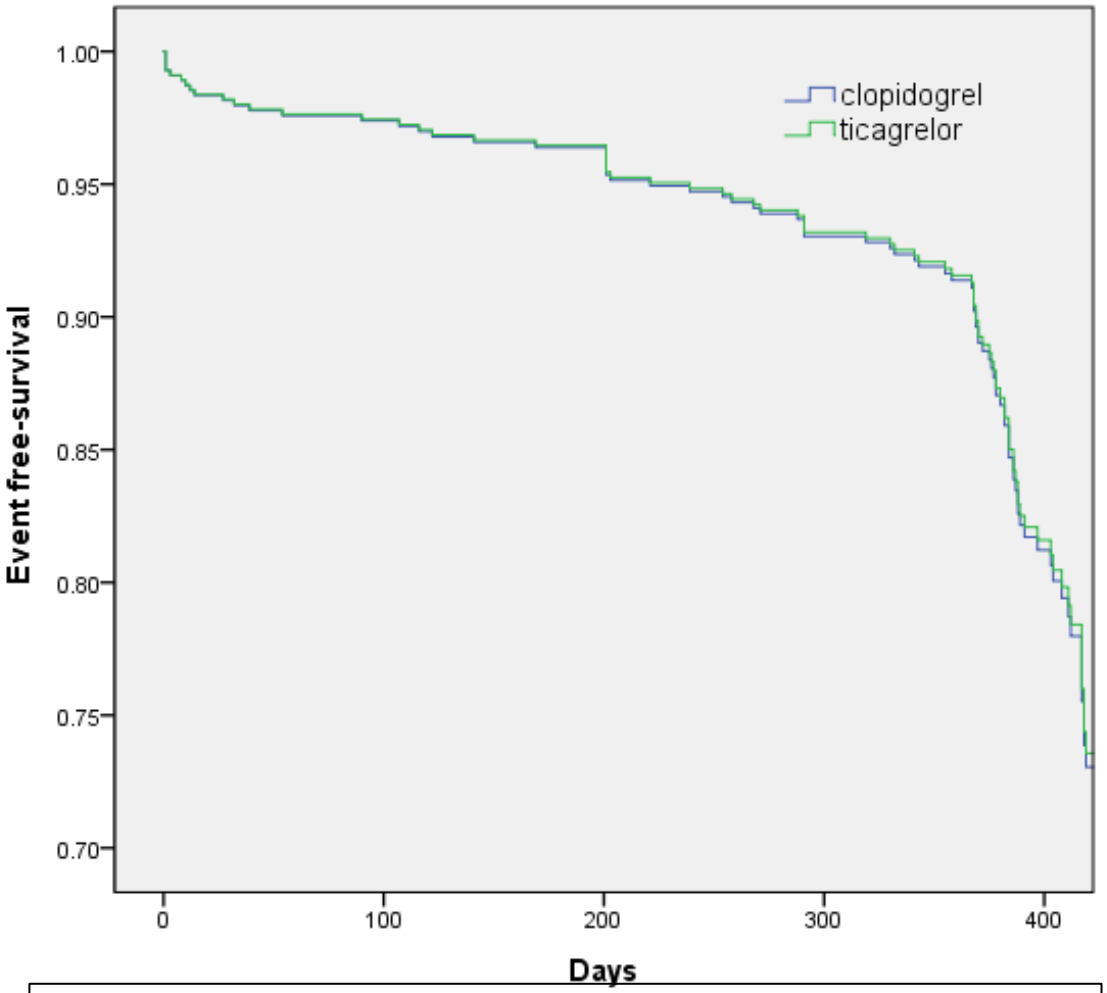
No event occur in Ticagrelor

Prasugrel vs. clopidogrel:

HR 1.211, 95% CI 0.167-8.776, p=0.850

Bleeding endpoint from HIRA





No event occur in prasugrel

Ticagrelor vs. clopidogrel:

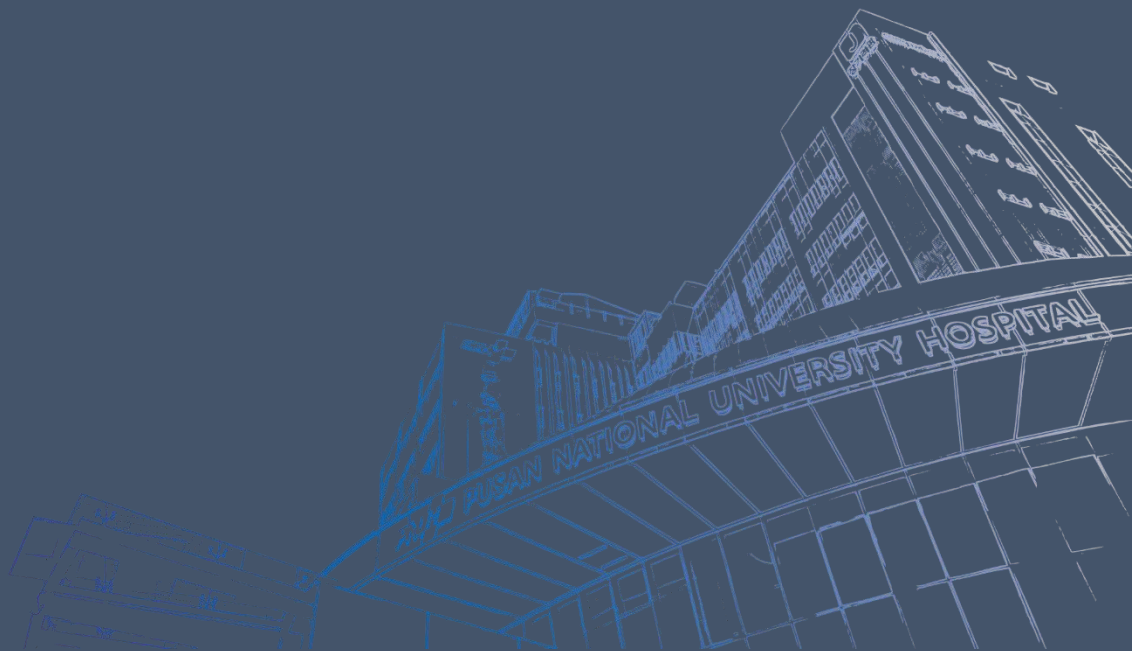
HR 0.978, 95% CI 0.473-2.021, p=0.951

Summary

- From sample data from HIRA
- Use of new P2Y12 inhibitor were relatively low compared to clopidogrel
- Ticagrelor showed better efficacy and comparable bleeding outcome compared to clopidogrel
- Prasugrel showed comparable efficacy and lowere bleeding outcome compared to clopidogrel

"This is just sample data, Do not be serious!!"

Thank you for your attention



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