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TICAGRELOR VS CLOPIDOGREL THERAPY IN ST ELEVATION MYOCARDIAL INFARCTION PATIENTS

Community Medicine

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ABSTRACT

Objectives: A large randomised control trial (PLATO study) established superiority of ticagrelor over clopidogrel in post- MI cases. This led to a change in international guidelines. However, there are no large scale trials that establish these findings amongst Asian population. This study was done to assess outcomes of the two therapies in post- stenting patients. **Methods:** This study is a retrospective cohort study including all ST elevation myocardial infarct (STEMI) patients undergoing percutaneous coronary intervention (PCI) in our hospital from July 2018 to Dec 2018. Their hospital visit notes and medical records, during the period of 12 months after discharge, were also accessed to know the long-term outcomes of the study drugs. Propensity score analysis was done to take the bias into consideration, which arises as a result of not randomising the study subjects. **Results:** Out of the 270 patients admitted in the hospital due to STEMI during the study period, 250 were included in the study. Twenty patients were excluded as they did not fulfil the inclusion criteria. Out of the total participants 188 (75.2%) were males. Ninety-five patients received ticagrelor and rest 155 received clopidogrel upon discharge. The primary efficacy endpoints were death from any cause, AMI, or stroke. The safety endpoints consisted of major gastrointestinal bleeding or intracerebral haemorrhage The ticagrelor group had high procedural success rates (100% vs. 96%; p = 0.044). The incidence of primary outcomes, i.e. ischemic stroke and non-fatal AMI was 2.2% in the ticagrelor group and 2.6% in the clopidogrel group (adjusted HR, 0.86; 95% CI: 0.32–2.24, p=0.80), and 7.4% in the ticagrelor users and 9.7% in the clopidogrel users (adjusted HR, 0.975; 95% CI: 0.80–1.12, p=0.72), respectively. The incidence of any kind of bleeding was also higher in ticagrelor group (9, 9.5%) as compared to clopidogrel group (5, 3.2%) and the difference was statistically significant (adjusted HR, 1.69; 95% CI: 1.34–2.13, p<0.01). **Conclusion** We conclude that ticagrelor seems to be at par with clopidogrel as the overall mortality rate of subjects was similar on both the groups. However, bleeding episodes were more significantly associated with ticagrelor use than clopidogrel use. A larger study is, however, required to generalise the study to the whole population.

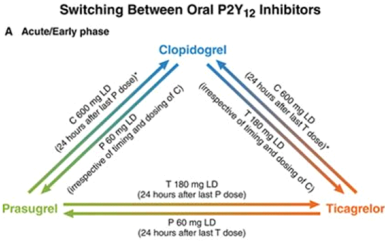
KEYWORDS

Ticagrelor, Clopidogrel, P2Y12 inhibitor, Acute Myocardial Infarction, Retrospective Cohort Study

Introduction/ Background

Acute coronary syndrome is a dreaded illness, 32% of which constitute ST elevation myocardial infarction (STEMI), which has an in-hospital mortality rate of 5%-15% basis other factors.[1] Dual antiplatelet therapy (DAPT), with aspirin and a P2Y12 receptor antagonist, is a cornerstone of therapy for patients with STEMI, especially in those undergoing percutaneous coronary intervention (PCI).[2-5] For years, clopidogrel has been extensively used throughout the world for this purpose; more recently, newer antiplatelet agents have been tested and approved for use like ticagrelor and prasugrel, in the hope of faster and more potent antiplatelet action.[6-9] Different antiplatelet drugs have different characteristics like efficacy, risk for bleeding, cost, and timing of administration, thus, physicians frequently switch among drugs according to the specific clinical scenario.[10](Figure 1)

Figure 1: Interchange between the three P2Y12 inhibitors during the early phase of an Acute Coronary Syndrome (ACS)



(Source: Ref 28)

Clopidogrel, a second generation thienopyridine, is available in generic form and has a good cost-effectiveness ration, its drawback being its dependency on liver metabolism for activation.[2] Therefore, it has a relatively slow onset and low potency of platelet inhibition.[11] Furthermore, Asian patients have been reported as poor clopidogrel metabolizers due to the prevalence of cytochrome P450 2C19 (CYP2C19) loss-of- function alleles.[12]

There is some evidence available, however, from other Asian countries like Korea and Japan that Asians have a lower incidence of stent thrombosis as compared to the western population. This suggests that regional differences in thrombogenesis may affect the altered response of clopidogrel to the onset of thrombotic events in Asian patients.[13-15]

In patients of STEMI, an expeditious percutaneous coronary intervention (PCI) is imperative, thus a delayed effect of the drug, due to specific circulatory conditions, might throw the whole treatment protocol off balance.[16,17] Ticagrelor, a novel, oral, reversible, P2Y12 inhibitor, from the class of cyclopentyltriazolopyrimidine, has a plasma half-life of 12 hrs, is an active drug with more rapid onset and offset of action than clopidogrel.[7,18]

A large randomised control trial (RCT) proved superiority of ticagrelor over clopidogrel in cardiac patients suffering from STEMI and non-STEMI, which led to the change in guidelines in favour of ticagrelor in patients with STEMI undergoing PCI.[9] Keeping in mind that large real-world registries are imperative to establish the effectiveness, usefulness and outcomes of novel therapies [19-22], data on the benefits of ticagrelor in a real world population of patients with STEMI are lacking.[2] On the other hand, a large observational registry about ticagrelor in STEMI population observed findings in contrast with the large PLATO trial that changed guidelines, with no improvement in ischemic events and a higher rate of bleeding in the ticagrelor

group.[23] We thus performed the current study to compare effects of ticagrelor and clopidogrel in a real world population of Asian patients with STEMI.

Materials & Methods

Study design

We retrospectively studied the patients admitted in our hospital due to STEMI between July 2018 to Dec 2018, who were later followed up till 12 months. The outcomes of ticagrelor and clopidogrel among these patients were compared.

Subjects

All adult patients (>18 years) admitted in the hospital between the study period were included in the study.(Figure 2) Case definition (STEMI case) was any patient hospitalised and discharged with a primary or secondary discharge diagnosis code of ICD9-CM 410.x. The exclusion criteria was death within 30 days of procedure, contraindication to the study drug and administration of more than one kind of P2Y12 receptor antagonist. Co-morbidities were retrieved from the inpatient and outpatient database.

A semi-structured questionnaire was prepared to collect the data, consisting of three parts. One part was demographic details and morbidity profile of the patient, second part consisted the procedural details and third part included the drugs taken by the patient. Information like age, gender, ethnicity, comorbidities, days of hospitalisation, use of AMI-related interventions like PCI, use of circulatory support devices like intra- aortic balloon pump (IABP), and extracorporeal membrane oxygenation (ECMO), and medications used (within 3 months of the index date). Index date was taken as one month after the first AMI discharge after July 2018 in both the groups. The follow up period was defined as the period from the index date until the first occurrence of any study outcome or the end of the study period (Dec 2019), whichever came first.

Treatment

In the ticagrelor group, patients received a loading dose of 180 mg followed by 90 mg twice daily and in the clopidogrel group, they received a loading dose of 300 mg followed by a 75 mg tablet once daily. All patients were on 75 mg of aspirin daily, as well. We excluded the patients who were on varying doses or varying types of platelet inhibitors.

Study Endpoints/ Outcomes

The primary outcomes studied was a major adverse cardiac event i.e. death from any cause, non-fatal AMI and/or non-fatal stroke during follow up period. The primary safety endpoint was major bleeding episode followed by hospitalisation, and secondary safety endpoints were individual components of the same.

Statistical Analysis

The demographic data was expressed as mean and standard deviation or percentage. Chi square test/ Fischer's test and student T test were used to analyse discrete and continuous variables, respectively. To minimise the bias in the study that arises due to non-randomisation, we used propensity score analysis.

Ethical Consideration

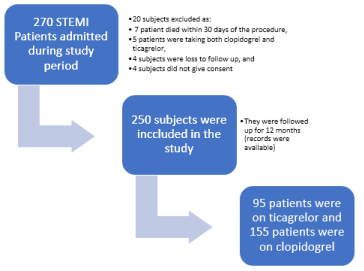
The study was prior approved by the institutional review board of the hospital.

Results

Baseline characteristics

Out of the 270 patients admitted in the hospital due to STEMI during the study period, 250 were included in the study. Twenty patients were excluded as they did not fulfil the inclusion criteria.(Figure 2) Ninety-five patients received ticagrelor and rest 155 received clopidogrel upon discharge, while all of them received aspirin. Out of the total participants 188 (75.2%) were males. Other baseline characteristics are listed in Table 1. It was noted that the patients who received ticagrelor were more often females, younger in age and having lesser comorbid conditions (like hypertension, diabetes, asthma, h/o stroke, h/o kidney disease) than those receiving clopidogrel, however, the difference was not statistically significant. The groups also differed with respect to the medications they were consuming before the admission. The mean exposure time to the study drugs in the two groups was also different, as ticagrelor group took ticagrelor for 223 +/- 109 days and subjects in clopidogrel group took clopidogrel for 260 +/- 104 days (p value <0.001). To take care of the differences, propensity scoring was done.

Figure 2: Study subject selection and methodology of the study



(Source: Original)

Table 1: Baseline Characteristics of study subjects (N=250):

Characteristics	Ticagrelor group (n=95)	Clopidogrel group (n=155)
Age	57.0 (Range: 51.7-65.4)	58.7 (Range: 51.6-65.2)
Females	25 (26.3)	37 (23.8)
Males	70 (73.7)	118 (76.2)
BMI	26.5 (Range: 24.0-29.8)	26.4 (Range: 24.0-28.9)
Smoking	45 (47.4)	73 (47.1)
Hypertension	52 (54.7)	92 (59.3)
Dyslipidemia	24 (25.2)	36 (23.2)
Diabetes mellitus	14 (14.7)	24 (15.5)
COPD	3 (3.1)	5 (3.2)
Peripheral artery disease	-	1 (0.6)
Asthma	1 (1.1)	4 (2.6)
MI	9 (9.5)	16 (10.3)
Stroke	3 (3.1)	6 (3.9)
CABG	1 (1.1)	1 (0.6)
PCI	6 (6.3)	10 (6.4)
Kidney disease	4 (4.2)	8 (5.2)
Positive Troponin I test at study entry	84 (88.4)	132 (85.2)

Values are n (%) unless otherwise indicated.
Source: Original

Clinical outcomes

The ticagrelor group had high procedural success rates (100% vs. 96%; p = 0.044). The incidence of primary outcomes, i.e. ischemic stroke and non-fatal AMI was 2.2% in the ticagrelor group and 2.6% in the clopidogrel group (adjusted HR, 0.86; 95% CI: 0.32–2.24, p=0.80), and 7.4% in the ticagrelor users and 9.7% in the clopidogrel users (adjusted HR, 0.975; 95% CI: 0.80–1.12, p=0.72), respectively. The number of patients having major bleeding requiring medical attention were five (5.3% & 3.2%) in each group and the difference was statistically significant (adjusted HR, 1.39; 95% CI: 1.02–1.89, p=0.03). The incidence of a major gastrointestinal bleeding or intracerebral haemorrhage in the ticagrelor and clopidogrel groups was 5.2% and 3.8%, respectively (adjusted HR, 1.45; 95% CI: 0.43–5.19). The incidence of any kind of bleeding was also higher in ticagrelor group (9, 9.5%) as compared to clopidogrel group (5, 3.2%) and the difference was statistically significant (adjusted HR, 1.69; 95% CI: 1.34–2.13, p<0.01). The details of efficacy events at 12 months has been given in Table 2.

Table 2: Outcome Events at 12 months:

Outcomes at 12 months		Ticagrelor group (n=95)	Clopidogrel group (n=155)	HR (95% CI)	P value
Primary Outcomes					
Death from vascular event	6 (6.3)	11 (7.2)	0.92 (0.77-1.20)	0.50	

Deaths due to	Fatal MI	1 (1.1)	2 (1.2)	0.94 (0.52–2.14)	0.73
	Non-fatal MI	7 (7.4)	15 (9.7)	0.97 (0.80–1.12)	0.72
	Ischemic Stroke	2 (2.2)	4 (2.6)	0.86 (0.32–2.24)	0.80
TIA	0.0	0.0			
Severe Recurrent Ischemia	1 (1.1)	2 (1.2)	0.94 (0.52–2.14)	0.73	
Other arterial thrombotic events	1(1.1)	4(2.6)	0.47 (0.08–2.66)	0.39	
Death from any cause	4 (4.2)	7 (4.5)	0.89 (0.66–1.19)	0.55	
Secondary Outcomes					
Major bleeding requiring medical attention	5 (5.3)	5 (3.2)	1.39 (1.02–1.89)	0.03	
Minor bleeding	3 (3.1)	6 (3.8)	0.92 (0.42–2.17)	0.96	
Gastrointestinal/ Intracranial Bleeding	5 (5.2)	6 (3.8)	1.45 (0.43–5.19)	0.54	
Any bleeding	9 (9.5)	5 (3.2)	1.69 (1.34–2.13)	<0.01	

Values are n (%) unless otherwise indicated. *p values and hazard ratios were calculated by Cox regression analysis.
CI - confidence interval; HR - hazard ratio; MI - myocardial infarction. TIA - transient ischemic attack.
Source: Original

Other adverse events

Dyspnoea was seen more commonly in the ticagrelor group than in the clopidogrel group (in 20.0% vs. 9.6% of patients, respectively). One patient left the study in ticagrelor group due to dyspnoea, but no patient left the study in clopidogrel group. The frequencies of other serious adverse events were comparable between groups.(Table 3)

Table 3: Reported Adverse and Serious Adverse Events at 12 months:

Adverse Events at 12 months follow up	Ticagrelor group (n=95)	Clopidogrel group (n=155)
Dyspnoea	19 (20.0)	15 (9.6)
Dyspnoea resulting in permanent discontinuation of drug	1 (1.1)	-
Atrial fibrillation	1 (1.1)	2 (1.3)
Ventricular tachycardia	2 (2.1)	2 (1.3)
Pericarditis	1 (1.1)	-
Kidney injury	1 (1.1)	1 (0.6)
Pneumonia	2 (2.1)	3 (1.9)
Allergic reaction	1 (1.1)	-
Others	2 (2.1)	1 (0.6)

Values are n (%) unless otherwise indicated.
Source: Original

Discussion

This study was done to assess the safety and compare the outcomes of a newer drug, ticagrelor, as compared to the conventional pharmacotherapy with clopidogrel, in an Asian population. We observed that though the primary outcomes were similar in the two groups, there was an increased risk of bleeding with ticagrelor use. Ticagrelor can, thus, be used in AMI patients but one should be cautious of the bleeding profile of the patients. Overall, efficacy, superiority or safety of ticagrelor as compared to clopidogrel should be established in this population with the help of a large population-based randomised control trial. In contrast to clopidogrel, ticagrelor has been reported to inhibit platelet action swiftly and is not known to be susceptible to individual variations.[24] The PLATO study has reported that ticagrelor is associated with lower deaths but increased chances of major bleeding episodes among AMI patients.[9] However, the findings cannot be generalised to Asian patients as the PLATO study had just 6% Asian subjects. Hence, there is a scarcity of data on the comparative effects of ticagrelor and clopidogrel among Asians.[24-27] PHILO trial was conducted in Japan and other east Asian countries, on the lines of PLATO trials but the results were inconclusive.[26] Another study amongst Korean AMI patients reported that upon comparing the incidence of primary efficacy endpoints between ticagrelor and clopidogrel, no significant difference was observed, rather a higher incidence of bleeding events was reported with ticagrelor.[13] One more Asian trial, ESTATE study [25], was done amongst Taiwanese population and it reported that at 5.5-month follow-up, ticagrelor, compared with clopidogrel, was associated with a lower incidence of composite PLATO efficacy endpoint (7.1% vs. 11.6%, P=0.07). Ticagrelor, compared with clopidogrel, was associated with similar incidences of in-hospital major bleeding (4.5% vs. 6.3%, P=0.4). These results were probably influenced by a small sample size of the ESTATE trial. A meta-analysis done by Misumida et al has also produced results similar to that found in our study.[28] Misumida demonstrated that ticagrelor was associated with a higher risk of major bleeding compared to clopidogrel in East Asian patients with ACS. A study done by Wang et al among Chinese population reported that though ticagrelor seem to have superior efficacy as compared to clopidogrel, it loses its superiority in patients having moderate to high bleeding potential.[29] A study done by Hansson et al in Sweden has stated contrary findings to all the above studies, as it reported that overall risk of major CABG-related bleeding complications was lower with ticagrelor than with clopidogrel.[30] The reasons for the increased bleeding in the clopidogrel group in the Swedish study might be worse clinical profile of the subjects and use of warfarin before surgery.

Our study shows that ticagrelor was associated with a worse bleeding outcomes for patients, though the primary outcomes like death remain comparable to the clopidogrel group. The results of this study are not consistent with the results of the study done in western population, as many studies have mentioned that the bleeding profiles, and the way anti-platelet drugs act in the body differs in Asian and Caucasian race.[29,31,32]

Study limitations

Various limitations of the study are its small sample size, non-randomised study design, and a relatively shorter period of follow up. Being a retrospective cohort study, it is susceptible to bias. Also, the database did not include some variables such as coronary artery disease extension and revascularization details. It is a hospital based study, and generalisation to the whole population seems unjust.

Conclusion

We conclude that ticagrelor seems to be at par with clopidogrel as the overall mortality rate of subjects was similar on both the groups. However, bleeding episodes were more significantly associated with ticagrelor use than clopidogrel use. A larger study is, however, required to generalise the study to the whole population.

Conflict of interest

The authors declare no conflict of interest.

References

1. André R, Bongard V, Elosua R, Kirchberger I, Farmakis D, Häkkinen U, et al. International differences in acute coronary syndrome patients' baseline characteristics, clinical management and outcomes in Western Europe: the EURHOBOP study. Heart Br Card Soc. 2014;100:1201–7.
2. Vercellino, M., Sánchez, F.A., Boasi, V. et al. Ticagrelor versus clopidogrel in real-world patients with ST elevation myocardial infarction: 1-year results by propensity score analysis. BMC Cardiovasc Disord 17, 97 (2017).
3. Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al; ESC Committee for Practice Guidelines. ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the Management of Acute Coronary Syndromes (ACS) in Patients Presenting Without Persistent ST-segment Elevation of the European Society of Cardiology (ESC). Eur Heart J 2011; 32: 2999 – 3054.
4. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2015 ACC/AHA/SCAI Focused Update on Primary Percutaneous Coronary Intervention for Patients With ST-Elevation Myocardial Infarction: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention and the 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction. J Am Coll Cardiol 2016; 67: 1235 – 1250.
5. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al;

ACC/AHA Task Force Members; Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coro- nary syndromes: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines. Circulation 2014; 130: 2354 – 2394.
6. Wallentin L, Varenhorst C, James S, Erlinge D, Braun OO, Jakubowski JA, et al. Prasugrel achieves greater and faster P2Y12 receptor-mediated platelet inhibition than clopidogrel due to more efficient generation of its active metabolite in aspirin-treated patients with coronary artery disease. Eur Heart J. 2008;29:21–30.
7. Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, et al. Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. Circulation. 2009;120:2577–85.
8. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2007;357:2001–15.
9. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009;361:1045–57.
10. Dominick J. Angiolillo et al. Circulation. 2017;136:1955-1975.
11. Tantry US, Bonello L, Aradi D, Price MJ, Jeong YH, Angiolillo DJ, et al; Working Group on On-Treatment Platelet Reactivity. Consensus and update on the definition of on-treatment platelet reactivity to adenosine diphosphate associated with ischemia and bleeding. J Am Coll Cardiol 2013; 62: 2261 – 2273.
12. Liang ZY, Han YL, Zhang XL, Li Y, Yan CH, Kang J. The impact of gene polymorphism and high on-treatment platelet reactivity on clinical follow-up: Outcomes in patients with acute coronary syndrome after drug-eluting stent implantation. Eurointervention 2013; 9: 316 – 327.
13. Park DW, Yun SC, Lee SW. Stent thrombosis, clinical events, and influence of prolonged clopidogrel use after placement of drug eluting stent data from an observational cohort study of drug eluting vs bare-metal stents. JACC Cardiovasc Interv 2008; 1: 494 – 503.
14. Kimura T, Morimoto T, Nakagawa Y, Tamura T, Kadota K, Yasumoto H, et al; j-Cypher Registry Investigators. Antiplatelet therapy and stent thrombosis after sirolimus-eluting stent implan- tation. Circulation 2009; 119: 987 – 995.
15. Kumar RS, Douglas PS, Peterson ED, Anstrom KJ, Dai D, Brennan JM, et al. Effect of race and ethnicity on outcomes with drug-eluting and bare metal stents: Results in 423,965 patients in the linked National Cardiovascular Data Registry and centers for Medicare & Medicaid services payer databases. Circulation 2013; 127: 1395 – 1403.
16. Morici N, Colombo P, Mafrici A, Oreglia JA, Klugmann S, Savonitto S. Prasugrel and ticagrelor: is there a winner? J Cardiovasc Med. 2014;15:8–18.
17. Alexopoulos D, Xanthopoulou I, Goudevenos J. Effects of P2Y12 receptor inhibition in patients with ST-segment elevation myocardial infarction. Am J Cardiol. 2014;113:2064–9.
18. Parodi G, Valenti R, Bellandi B, Migliorini A, Marcucci R, Comito V, et al. Comparison of prasugrel and ticagrelor loading doses in ST-segment elevation myocardial infarction patients. J Am Coll Cardiol. 2013;61:1601–6.
19. Damman P, Varenhorst C, Koul S, Eriksson P, Erlinge D, Lagerqvist B, et al. Treatment patterns and outcomes in patients undergoing percutaneous coronary intervention treated with prasugrel or clopidogrel (from the Swedish Coronary Angiography and Angioplasty Registry [SCAAR]). Am J Cardiol. 2014;113:64–9.
20. Bhatt DL. Prasugrel in clinical practice. N Engl J Med. 2009;361:940–2.
21. Bae JP, Faries DE, Ernst FR, Lipkin C, Zhao Z, Moretz C, et al. Real-world observations with prasugrel compared to clopidogrel in acute coronary syndrome patients treated with percutaneous coronary intervention in the United States. Curr Med Res Opin. 2014;30:2207–16.
22. Klingenberg R, Heg D, Räber L, Carballo D, Nanchen D, Gencer B, et al. Safety profile of prasugrel and clopidogrel in patients with acute coronary syndromes in Switzerland. Heart Br Card Soc. 2015;101:854–63.
23. Park K-H, Jeong MH, Ahn Y, Ahn TH, Seung KB, Oh DJ, et al. Comparison of short-term clinical outcomes between ticagrelor versus clopidogrel in patients with acute myocardial infarction undergoing successful revascularization; from Korea Acute Myocardial Infarction Registry-National Institute of Health. Int J Cardiol. 2016;215:193–200.
24. Storey RF, Husted S, Harrington RA, Heptinstall S, Wilcox RG, Peters G, et al. Inhibition of platelet aggregation by AZD6140, a reversible oral P2Y12 receptor antagonist, compared with clopi- dogrel in patients with acute coronary syndromes. J Am Coll Cardiol. 2007;50:1852 – 6.
25. Chen IC, Lee CH, Fang CC, Chao TH, Cheng CL, Chen Y, et al; ESTATE Investigators. Efficacy and safety of ticagrelor versus clopidogrel in acute coronary syndrome in Taiwan: A multicenter retrospective pilot study. J Chin Med Assoc. 2016; 79:521 – 30.
26. Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome: Randomized, double- blind, phase III PHILO study. Circ J. 2015;79:2452 – 60.
27. Saito S, Isshiki T, Kimura T, Ogawa H, Yokoi H, Nanto S, et al. Efficacy and safety of adjusted-dose prasugrel compared with clopidogrel in Japanese patients with acute coronary syndrome: The PRASFIT-ACS study. Circ J. 2014;78: 684 – 92.
28. Misumida, Naoki, et al. "Ticagrelor Versus Clopidogrel in East Asian Patients With Acute Coronary Syndrome: Systematic Review and Meta-analysis." Cardiovascular Revascularization Medicine : Including Molecular Interventions. 2018; 19(6):689-94.
29. Wang HY, Li Y, Xu XM, Li J, Han YL. Impact of Baseline Bleeding Risk on Efficacy and Safety of Ticagrelor versus Clopidogrel in Chinese Patients with Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. Chin Med J (Engl). 2018;131(17):2017-2024.
30. Hansson EC, Jidéus L, Åberg B, Bjursten H, Dreifaldt M , Holmgren A, et al. Coronary artery bypass grafting-related bleeding complications in patients treated with ticagrelor or clopidogrel: a nationwide study. European Heart Journal. 2016 Jan;37(2):189-97.
31. Teng R, Butler K. Pharmacokinetics, pharmacodynamics, and tolerability of single and multiple doses of ticagrelor in Japanese and caucasian volunteers. Int J Clin Pharmacol Ther. 2014;52:478–91.
32. Kwon TJ, Tantry US, Park Y, Choi YM, Ahn JH, Kim KH, et al. Influence of platelet reactivity on BARC classification in East Asian patients undergoing percutaneous coronary intervention. Results of the ACCEL-BLEED study. Thromb Haemost. 2016;115:979–92.