ORIGINAL RESEARCH PAPER
Volume - 12 | Issue - 03 | March - 2023 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

TICAGRELOR VS. CLOPIDOGREL: CLINICAL OUTCOMES IN ST-ELEVATION MYOCARDIAL INFARCTION PATIENTS

Cardiology

Rafiq Ahmed Bhat	MD, PhD, Department of Intervention Cardiology, Fuwai Central China Cardiovascular Hospital, Zhengzhou University, Zhengzhou 450000, People's Republic of China
Syed Manzoor Ali	DM, Department of Cardiology, Super Speciality division, Government Medical College Srinagar J&K India.
Syed Maqbool	DM, DNB, FNB Invasive Cardiology, Government Superspeciality Hospital, Srinagar J&K India.
Akanksha Rathi	MD, Department of Community Medicine, Vedanta Institute of Medical Sciences, Palghar, India.
Md. Monowarul Islam	MD(Cardiology), MD(Internal Medicine, Phase-A), Department of Internal Medicine, Rajshahi Medical College, Rajshahi 6100, Bangladesh.
Raja Saqib Iqbal	MD, Department of Paediatrics, Batra Hospital and Medical Research Centre, New Delhi, India.
Mohammed Awadh Abdun	MD, Department of Internal Medicine, Henan Provincial People's Hospital, Zhengzhou University, Zhengzhou 450003, People's Republic of China.
Usama Bin Latief	MBBS, Acharya Shree Chander College of Medical Sciences (ASCOMS)
Atul Dwivedi	MS, PhD Department of Orthopaedics Shivaanan Polyclinic and Dental House, Bareilly, UP, India.
PengCheng Yuan	Bachelor of Psychology, University of Toronto, Canada.
Li Muwei	MD, PhD Department of Cardiology, Fuwai Central China Cardiovascular Hospital, Zhengzhou University, Zhengzhou 450000, People's Republic of China.
Zhongyu Zhu	MD, PhD Department of Cardiology, Fuwai Central China Cardiovascular Hospital, Zhengzhou University, Zhengzhou 450000, People's Republic of China.
Yongsheng Qu	MD, Department of Cardiology, Fuwai Central China Cardiovascular Hospital, Zhengzhou University, Zhengzhou 450000, People's Republic of China.
You Zhang	MD, Department of Cardiology, Fuwai Central China Cardiovascular Hospital, Zhengzhou University, Zhengzhou 450000, People's Republic of China.
Wentao Xiao	MD, Department of Cardiology, Fuwai Central China Cardiovascular Hospital, Zhengzhou University, Zhengzhou 450000, People's Republic of China.
Zhang Xingkun	Msc, Fuwai Central China Cardiovascular Hospital, Zhengzhou University, Zhengzhou 450000, People's Republic of China.
Chuanyu Gao*	MD, PhD, Department of Cardiology, Fuwai Central China Cardiovascular Hospital, Zhengzhou University, Zhengzhou 450000, People's Republic of China. *Corresponding Author

ABSTRACT

A large, randomised control trial known as PLATO study proved a turning point in the assessment of superiority of ticagrelor over clopidogrel in post- MI cases. This breakthrough in assessing the quantum of efficacy of ticagrelor over clopidogrel in post-MI patients led to changes in international guidelines. However, based on the mortality index associated with these two drugs, the outcome is not encouraging, and both ticagrelor and clopidogrel are on par in terms of efficacy or safety. Recurrent episodes of bleeding were more common in patients who were prescribed ticagrelor than in patients who were given clopidogrel. However, future trials with longer follow-up time periods may be able to answer all the remaining questions.

KEYWORDS

Ticagrelor, Clopidogrel, P2Y12 inhibitor, Acute Myocardial Infarction

BACKGROUND

Acute Coronary Syndrome (ACS) is a fatal disease, and 32% of those who suffer from it have ST-elevation myocardial infarction (STEMI), which has an in-hospital mortality rate of 5%-15% based on other factors possibly due to comorbidity [1]. Because of their efficacy, aspirin and a P2Y12 receptor antagonist, two key components of dual antiplatelet therapy (DAPT), have revolutionized the treatment of STEMI patients, particularly those undergoing percutaneous coronary intervention (PCI) [2-5]. Clopidogrel has been widely used as a dual antiplatelet therapy agent for many years; however, new drugs such as ticagrelor and prasugrel have recently been introduced to augment the treatment of STEMI and achieve faster, more potent, and life-saving antiplatelet action [6-9]. All antiplatelet drugs can be profiled in terms of their distinctive characteristics like efficacy, risk of bleeding following administration, cost, and timing of administration. As a result, physicians frequently switch between drugs based on the clinical situation [10]. Clopidogrel, a second generation thienopyridine, is sold in generic form, and given its cost-effectiveness, it is widely available. The main disadvantage of this drug is that its activation is dependent on liver metabolism. [2]. Given this serious drawback, clopidogrel does not qualify as being a potent platelet inhibitor [11]. In addition to this, most Asian patients have been reported to be poor clopidogrel metabolizers due to the prevalence of cytochrome P450 2C19 (CYP2C19) loss-of-function alleles [12]. Conversely, based on available data, some Asian countries, such as Korea and Japan, have a lower incidence of stent

thrombosis than people in the West, indicating that regional differences in thrombogenesis may affect the multidimensional response of clopidogrel to the onset of thrombotic events in Asian patients [13-15]. In STEMI patients, it is imperative to administer clopidogrel to achieve immediate percutaneous coronary intervention (PCI) without delay to avoid a serious or life-threatening situation, most probably due to specific circulatory conditions which may otherwise throw the whole treatment protocol off balance [16,17].

Ticagrelor, a novel, oral, reversible P2Y12 inhibitor from the cyclopentyl-triazolo-pyrimidine class, has a plasma half-life of 12 hours and is an active drug with a significantly faster onset and offset of action than clopidogrel [7,18]. A large, randomised control trial (RCT) established superiority of ticagrelor over clopidogrel in cardiac patients suffering from STEMI and non-STEMI, which led to a robust change in guidelines in favour of ticagrelor in patients with STEMI undergoing PCI [9]. Given the importance of large real-world registries in assessing the efficacy, usefulness, and outcomes of novel therapies [19-22], data on the benefits of ticagrelor in patients with STEMI in a real-world population are lacking [2]. In contrast to the large PLATO trial, a large observational registry on ticagrelor in STEMI patients found a higher rate of bleeding in the ticagrelor group with no improvement in ischemic events [23]. Table 1 summarises the comparison of various oral P2Y12 inhibitors.

Table 1. Comparison Of Oral P2y12 Inhibitors

	Clopidogrel (Plavix, Bristol-Myers Squibb/Sanofi)	Prasugrel (Effient, Eli Lilly)	Ticagrelor (Brilinta, AstraZeneca)
Initial FDA approval	1997	2009	2011
Current FDA-approved indications	ACS (invasively or noninvasively managed); recent MI or stroke; established PAD	ACS with PCI	ACS (invasively or noninvasively managed) or MI history
Mechanism of action	Bind to ADP P2Y12 receptor on platelets, preventing ADP from binding and activating the glycoprotein GPIIb/IIIa complex, which is necessary for platelet aggregation		
Binding	Irreversible	Irreversible	Reversible
Onset of action	2-8 hours	0.5-4 hours	0.5-4 hours
Half-life	Parent: 6 hours Active metabolite: 30 minutes	Active metabolite: 7 hours	Parent: 7 hours Active metabolite: 9 hours
Offset of action	5-7 days	7-10 days	3-5 days
Metabolism	Thienopyridine prodrug metabolized mostly by CYP2C19 to active metabolite	Thienopyridine prodrug metabolized mostly by esterases in GI tract to active metabolite	Nonthienopyridine metabolized by CYP3A4; parent and metabolite equally inhibit P2Y12
Dosage forms	75-mg and 300-mg tablets	5-mg and 10-mg tablets	60-mg and 90-mg tablets
Loading dose	300 mg or 600 mg	60 mg	180 mg
Maintenance dose	75 mg daily	10 mg daily (consider 5 mg daily if weight <60 kg)	90 mg twice daily for 1-year post-ACS; then 60 mg twice daily
Use in renal/hepatic impairment	No dose adjustments necessary	Use caution in moderate-to-severe renal or severe hepatic impairment	Use caution in moderate and avoid in severe hepatic impairment
Per procedural hold	5 days	7 days	5 days
Non-bleeding noteworthy side effects	None	None	Dyspnoea (14.2%); elevated serum creatinine; elevated uric acid
Boxed warnings and contraindications	Diminished antiplatelet effect in CYP2C19 poor metabolizers. Consider alternative P2Y12 inhibitor in this population. Contraindicated in active bleeding and CYP2C19 poor metabolizers.	Bleeding risk: Significant and sometimes fatal bleeding may occur; contraindicated in patients with active bleeding, stroke/TIA history, or CABG surgery within 7 days. Not recommended in patients ≥ 75 years of age unless considerable risk (diabetes or prior MI history) due to increased fatal and intracranial bleeding risk and uncertain benefit. Not recommended in patients weighing <60 kg.	Bleeding risk: Significant and sometimes fatal bleeding may occur; contraindicated in patients with active bleeding or intracranial haemorrhage history. Aspirin doses and ticagrelor effectiveness: After initial aspirin dose, give aspirin 75–100 mg daily with ticagrelor. Aspirin maintenance doses greater than 100 mg daily reduce the effectiveness of ticagrelor and should be avoided.

Efficacy And Safety: Key Clinical Trials

Clopidogrel

Prior to the discovery of P2Y12 inhibitors, aspirin alone was the standard antiplatelet regimen post-MI. The CURE trial compared clopidogrel and aspirin (DAPT) to aspirin with or without revascularization in patients with ACS without ST elevation, and the COMMIT trial compared them post-STEMI. Patients undergoing primary PCI were excluded from the COMMIT trial. DAPT reduced the risk of adverse cardiovascular events compared with aspirin alone in both trials [24, 25]. There was an increase in major bleeding with clopidogrel only in the CURE trial [24]. The CLARITY-TIMI 28 trial discovered that clopidogrel plus aspirin (DAPT) reduced adverse cardiovascular events without increasing major bleeding compared to aspirin alone, with or without angiography, in patients with STEMI receiving fibrinolytic therapy. [26]. This trial established the safety and efficacy of DAPT plus a fibrinolytic post-STEMI.

Clopidogrel Versus Prasugrel

The TRITON-TIMI 38 trial compared DAPT with clopidogrel or prasugrel in patients with ACS undergoing PCI. There was a significant decrease seen in adverse cardiovascular events and an increase in major bleeding with prasugrel compared with clopidogrel. A subset of patients, including diabetics, those under the age of 75, those weighing less than 60 kg, and those with no history of stroke or transient ischemic attack (TIA), saw a reduction in adverse cardiac events when given prasugrel [27]. This trial led to prasugrel's approval by the US Food and Drug Administration (FDA). A post-hoc subgroup analysis of patients with STEMI undergoing PCI found a decrease in the primary endpoint without an increased risk of bleeding in the prasugrel versus clopidogrel group [28]. In a recent multicenter, double-blind, phase III study, prasugrel had an observed risk of 5% when compared to clopidogrel demonstrating that prasugrel has a slighter advantage over clopidogrel with no significant problems with regards to the safety of the drug [29].

Clopidogrel Versus Ticagrelor

In the final assessment, PLATO trial formally established that adverse cardiovascular events occurred less often following the administration of ticagrelor than that of clopidogrel and there was not any marked or significant difference in major bleeding [30]. This discovery led to ticagrelor's FDA approval. A post-hoc subgroup analysis found no

difference in the primary efficacy or safety endpoints between the two groups in patients with STEMI undergoing PCI [31].

Guan et al. [32] reported that all-cause mortality, major adverse cardiovascular events (MACEs), MI, stroke, and stent thrombosis were not significantly different with clopidogrel versus ticagrelor, and they assessed the safety of ticagrelor and clopidogrel based on various secondary outcomes such as:

- Major bleeding including intraocular bleeding resulting in complete blindness or visual loss, or bleeding that resulted in a drop in the haemoglobin level of ≥3 g per decilitre but < 5 g per decilitre or bleeding that required blood transfusion of 2 to 3 units of red cells, was defined as bleeding that led to a significantly high level of disability.
- Minor bleeding was defined as mild bleeding that did not require intervention or bleeding that required intervention but did not satisfy the criteria for major bleeding or bleeding that was too mild to be compared with major bleeding.
- Life-threatening bleeding which included intracranial bleeding, intra-pericardial bleeding with cardiac tamponade, a decrease in haemoglobin level of 5.0 g or more per decilitre, or bleeding that required blood transfusion of at least 4 units of red cells, and bleeding which resulted in severe hypotension or hypovolemic shock and bleeding requiring immediate intervention (surgery) was defined as the most fatal bleeding.
- Adverse drug events including dyspnoea, bradycardia, diarrhoea, ventricular tachycardia, and drug discontinuation especially due to dyspnoea.

It was demonstrated that ticagrelor was associated with a significantly higher rate of overall bleeding, both major and minor, (OR: 1.38, 95% CI: 1.13-1.70; P=.002) when compared to clopidogrel. However, life-threatening bleeding (OR: 1.00, 95% CI: 0.79–1.27; P=.98) was not significantly different between these 2 antiplatelet drugs. Furthermore, patients taking ticagrelor experienced more adverse events, such as dyspnea, and were more likely to discontinue the medication.

Switching Between P2Y12 Inhibitors

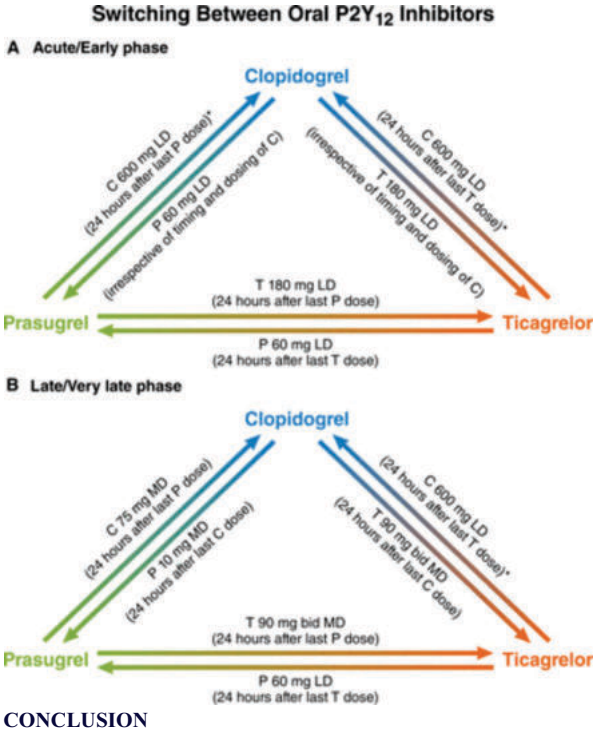
Patients may need to switch from one P2Y12 inhibitor to another for a variety of reasons, including treatment failure, side effects, cost, non-adherence, and contraindications. Registries and pharmacodynamics studies have thoroughly evaluated the need of switching between various inhibitors under both emergent and non-emergent circumstances. According to these studies, a one-time loading dose of the new agent (clopidogrel 600 mg, prasugrel 60 mg, ticagrelor 180 mg) is recommended to avoid a gap in adequate platelet inhibition in the acute/early phase (30 days or less after the index event). The loading dose should be administered within 24 hours after the last dose of the initial P2Y12 inhibitor for all situations, except in case of switching from clopidogrel to ticagrelor or prasugrel, where the timing of the loading dose is irrespective of the timing and dosing of clopidogrel. In the late or very late phase (more than 30 days from the index event), no loading dose of the new agent is recommended, except when switching from ticagrelor to clopidogrel or prasugrel, when a 600-mg or 60-mg loading dose, respectively, is recommended 24 hours after the last ticagrelor dose [33-37]. When switching to ticagrelor, the daily aspirin dose should not exceed 100 mg [38] Figure 1 depicts the interaction of the three P2Y12 inhibitors during the early and late stages of an ACS.

Two recent, randomized, open-label trials studied the efficacy and safety of initiating prasugrel in TROPICAL-ACS trial and prasugrel or ticagrelor (TOPIC trial) post-ACS and switching to clopidogrel one week (TROPICAL-ACS) or one month (TOPIC) later and continuing them for one year. In TROPICAL-ACS, patients were assessed for high on-treatment platelet reactivity (HPR) two weeks after initiation. If they were on clopidogrel and HPR was noted, patients were switched back to prasugrel. HPR was found in 39% of patients taking clopidogrel and 14% of patients taking prasugrel. This study finding guided the de-escalation to clopidogrel to be superior to continued prasugrel for both ischemic and bleeding outcomes. TOPIC found de-escalation to clopidogrel to be superior to continued prasugrel or ticagrelor in preventing bleeding complications without increasing ischemic events [39, 40].

Gaps In Knowledge

As opposed to clopidogrel, ticagrelor is not known to be sensitive to individual variations and has been reported to quickly inhibit platelet action [41]. The findings of PLATO study conclude 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 on its trial list. Hence, there is a scarcity of data on the comparative effects of ticagrelor and clopidogrel among Asians [41-44]. The PHILO trial was carried out in Japan and other East Asian countries in the same manner as the PLATO trials, but the results were inconclusive [43]. Another study among Korean AMI patients found no significant difference in the incidence of primary efficacy endpoints between ticagrelor and clopidogrel, but ticagrelor had a higher incidence of bleeding events [13]. Another Asian trial, the ESTATE study [42], was conducted among Taiwanese people and reported that at 5.5-month follow-up, ticagrelor was associated with a lower incidence of composite PLATO efficacy endpoints when compared to clopidogrel (7.1% vs. 11.6%, P=0.07). Ticagrelor was associated with similar rates of in-hospital major bleeding when compared to clopidogrel (4.5% vs. 6.3%, P=0.4). These results were probably influenced by the small sample size of the ESTATE trial. A meta-analysis performed by Misumida et al. has also produced results like that found in our study [45]. Misumida et al. demonstrated that ticagrelor was associated with a higher risk of major bleeding compared to clopidogrel in East Asian patients with ACS. According to Wang et al.'s study of a Chinese population, while ticagrelor appears to have superior efficacy to clopidogrel, it loses its superiority in patients with moderate to high bleeding potential [46]. Another study 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 [47]. The increased bleeding in the clopidogrel group in the Swedish study could be attributed to the subjects' poor clinical profiles and the use of warfarin prior to surgery.

Figure 1. Interchange between the three P2Y12 inhibitors during the acute/early and late/very late phase of an Acute Coronary Syndrome (ACS) (Source: Ref 35)



CONCLUSION

Ticagrelor and clopidogrel exhibited similarities in their known properties, as the overall mortality rate of subjects in both of the treatment groups was the same. However, ticagrelor use is significantly associated with bleeding episodes rather than clopidogrel use. Future trials with longer follow-up periods could provide answers to all the remaining issues related to this drug.

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. Vercelli no, M., Sanchez, 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. Angiolillo, Dominick J et al. "International Expert Consensus on Switching Platelet $P2Y_{12}$ Receptor-Inhibiting Therapies." Circulation vol. 136,20 (2017): 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. Euro intervention 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 implant- 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. CURE Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001; 345:494-502.
25. COMMIT Collaborative Group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. Lancet. 2005; 366:1607-1621.
26. Sabatini MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. CLARITY-TIMI28. N Engl J Med. 2005; 352:1179-1189.
27. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes (TRITON-TIMI 38) N Engl J Med. 2007;357(20):2001-2015.
28. Montalescot G, Wiviott SD, Braunwald E, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet. 2009; 373(9665):723-731.
29. Kitazono, Takanari et al. "Efficacy and Safety of Prasugrel vs Clopidogrel in Thrombotic Stroke Patients with Risk Factors for Ischemic Stroke Recurrence: A Double-blind, Phase III Study (PRASTRO-III)." Journal of atherosclerosis and thrombosis, 10.5551/jat.63473. 21 May. 2022.
30. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. N Engl J Med. 2009; 361(11):1045-1057.
31. 23. Velders MA, Abtan J, Angiolillo DJ, et al. Safety and efficacy of ticagrelor and clopidogrel in primary percutaneous intervention. Heart. 2016; 102:617-625.
32. Guan W, Lu H, Yang K. Choosing between ticagrelor and clopidogrel following percutaneous coronary intervention: A systematic review and Meta-Analysis (2007-2017). Medicine (Baltimore). 2018; 97(43): e12978.
33. Bagai A, Chua D, Cohen EA, et al. Pharmacodynamics and clinical implications of switching between $P2Y_{12}$ receptor antagonists: considerations for practice. Crit Pathw Cardiol. 2014; 13(4):156-158.
34. 38. De Luca L, Capranzano P, Patti G, et al. switching of platelet $P2Y_{12}$ receptor inhibitors in patients with acute coronary syndromes undergoing percutaneous coronary intervention: review of the literature and practical considerations. Am Heart J. 2016; 176:44-52.
35. Angiolillo DJ, Rollini F, Storey RF, et al. International expert consensus on switching platelet $P2Y_{12}$ receptor-inhibiting therapies. Circulation. 2017; 136(20):1955-1975.
36. Chandrasekhar J, Hibbert B, Froeschl M, et al. The impact of switching $P2Y_{12}$ receptor inhibitor therapy during index hospitalization: a systemic review. Eur J Clin Pharmacol. 2016; 72:83-91.
37. Biscaglia S, Campo G, Pavasini R, et al. Occurrence, causes, and outcomes after switching from ticagrelor to clopidogrel in a real-life scenario: data from a prospective registry. Platelets. 2016; 27(5):484-487.
38. Brilinta (ticagrelor) prescribing information. Wilmington, Delaware: AstraZeneca; 2015.
39. Sibbing D, Jacobs Hagen C, Gross L, et al. Guided de-escalation of antiplatelet treatment in patients with acute coronary syndrome undergoing percutaneous coronary intervention (TROPICAL-ACS): a randomized, open-label treatment. Lancet. 2017; 390:1747-1757.
40. Cuisset T, Deharo P, Quilici J, et al. Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J. 2017; 38:3070-3078.
41. 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.
42. 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 multicentre retrospective pilot study. J Chin Med Assoc. 2016; 79:521-30.
43. 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.
44. 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.
45. 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.
46. 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.
47. 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.