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Review article

Ticagrelor: molecular discovery to clinical evidence Ticagrelor: a novel antiplatelet agent

Nakul Sinha [a,b,*]

[a] Sr Consultant & Chief Interventional Cardiologist, Sahara Hospital, Viraj Khand, Gomti Nagar, Lucknow 226010, India
[b] Ex Prof & Head Cardiology, SGPGIMS, Lucknow, India

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ABSTRACT

Cardiovascular (CV) deaths are one of the leading cause of death, both in developed and developing countries, with acute coronary syndrome (ACS) accounting for about 50% of all CV deaths. Atherothrombosis formation is the prime reason behind ACS and platelets play a central role in formation of thrombus. Antiplatelet drugs, particularly dual antiplatelet therapy (DAPT) with Aspirin and Clopidogrel play a vital role and are widely used in the management of ACS for the past decade. However in spite of currently available options for antiplatelet therapy there remains a significant risk of arterial thrombosis and post ACS mortality grows over a period of time. Thus, there is a need for novel antiplatelet agents which can overcome some limitations of current antiplatelet therapies. Ticagrelor is a novel antiplatelet agent which has a faster onset of action, produces high level of platelet inhibition with minimal inter patient variability. This review summarizes the pharmacokinetic, pharmacodynamic characteristics and clinical evidence of ticagrelor in the management of ACS.

1. Acute coronary syndrome – global and Indian perspective

Cardiovascular death (CVD) is one of the leading causes in the non-communicable disease (NCD) deaths. According to WHO estimates around 17 million people die of CVD each year,[1] out of which coronary heart disease (CHD) accounts for 7.1 million deaths. Developing countries like India are witnessing economic transition, urbanization and industrialization resulting in major lifestyle changes like increased tobacco use, physical inactivity and unhealthy diet, that has lead to a dramatic increase in CVD and CHD.[2]

In Indian context, there are many challenges in managing patients of ACS. ACS patients in India die younger and sicker with average age at 57 years, almost 10–15 years younger than in west. Moreover, they carry high risk factor profile that includes Diabetes, Hypertension, Smoking and Dyslipidemia and close to 20% patients suffer from a 2nd heart attack in India.[3] As per CREATE registry 60% of patients in India were of STEMI whereas as per global registry data 40% patients were of STEMI. This implies that patients admitted to Indian hospitals with acute coronary syndromes are likely to have a worse prognosis than those in developed countries. In spite of being at high risk, in India, <10% ACS patients are managed through PCI with less than 15% receiving DAPT.[3]

Experience in the developed world has shown that significant reductions in CAD prevalence and mortality can be

* Sahara Hospital, Viraj Khand, Gomti Nagar, Lucknow 226010, India.
E-mail address: sinha.nakul@gmail.com.
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achieved via timely intervention and medical therapy. In spite of increasing burden of CVD, there are no definite guidelines in India to combat this serious problem. Hence there is a need for development of Indian based guidelines focused on improving compliance with evidence-based medicine. In addition to this, there is also a need to ramp up infrastructure and equip primary and secondary medical centers with increased awareness about managing first point of contact treatment better in India.

2. Role of platelets in ACS and importance of antiplatelet therapy

Platelets protect vascular integrity and play an important role in hemostasis. However, rupture of an atherosclerotic plaque causes a platelet-dependent thrombus formation leading to occlusion of a coronary artery resulting in acute myocardial infarction. Thus platelets play a central role in pathogenesis of acute myocardial infarction. Strong evidence which suggest that AMI is a platelet related disease is the capability of antiplatelet therapy to reduce morbidity and mortality in this clinical setting.[4]

Many landmark trials of aspirin and thienopyridines have established the role of oral antiplatelet agents in the management of ACS. Aspirin is the oldest of the antiplatelet drugs and has stood the test of time as an integral part of management of ACS.[5–8] The use of thienopyridines, which act by blocking the $P2Y_{12}$ receptor on the platelet surface, has shown benefit when added to aspirin in this setting.[9–12] Thus, dual antiplatelet therapy is the current standard of care for patients of ACS which is currently recommended for the period of at least 1 year. However, in spite of currently available antiplatelet therapy there remains a significant risk of arterial thrombosis and post ACS mortality grows over a period of time. Thus there is a need for novel antiplatelet agents which can overcome limitations of current antiplatelet therapies like slow onset of action, low level of platelet inhibition, high inter patient variability at the cost of clinically acceptable bleeding events.

3. Ticagrelor: molecular discovery

Adenosine triphosphate (ATP) competitively antagonize ADP-induced platelet aggregation. However unfavourable properties of ATP, such as low potency and poor stability does not allow its use as $P2Y_{12}$ receptor antagonist. Efforts were directed towards formulating ATP analogues with high potency and more stability. However because of retention of triphosphate group these agents had very short plasma half life and they need to be given intravenously. Subsequent modification of these compounds lead to discovery of selective and stable non-phosphate $P2Y_{12}$ receptor antagonist AZD6140 (ticagrelor) belonging to a new chemical class Cyclo Pentyl Triazolo Pyrimidine (CPTP). Although ATP structure was used as basis for designing of ticagrelor, it does not contain an adenosine group and therefore is distinct from true ATP analogues such as Cangrelor.[13]

4. Ticagrelor: mechanism of action

It is an oral, reversible and directly acting inhibitor of $P2Y_{12}$ receptor. Like thienopyridines, ticagrelor inhibit prothrombotic effects of ADP by blocking the platelet $P2Y_{12}$ receptor. However, unlike thienopyridines, the binding and effect is reversible and it does not require metabolic activation before its action. It has a rapid onset of action, produces high and consistent inhibition of platelet aggregation with minimal inter patient variability.[14] It binds at a site distinct from ADP binding site, causing locking of the receptor in an inactive state thereby inhibiting ADP signalling and receptor conformational changes. Unlike other thienopyridine ticagrelor is a non-competitive antagonist of $P2Y_{12}$ receptor resulting in no receptor activation in spite of increased ADP concentration.

5. Ticagrelor: pharmacological aspects

Ticagrelor is rapidly absorbed on oral administration with food intake having no appreciable effect on the absorption of ticagrelor. The T_{max} of ticagrelor is 1.3–2 h and plasma half life (t1/2) is 7–12 h.[15] It is metabolized in the liver by CYP3A4 enzyme to produce active metabolite AR-C124910XX. This metabolite is as potent as ticagrelor on $P2Y_{12}$ receptor and is present in the circulation at approximately 1/3 of the concentration of the parent drug.[16] As ticagrelor is metabolized by CYP3A4, concomitant administration of CYP3A4 inducers and inhibitors should be avoided. Elimination of ticagrelor and AR-C124910XX occurs primarily via hepatic metabolism and biliary secretion, respectively. Therefore no dose adjustment is required for renal patients.

6. Ticagrelor: clinical development

Safety and tolerability of ticagrelor was tested in various phase I and phase II trials. In phase I trial ticagrelor was tested in healthy volunteers in dosage of 50–600 mg once daily or 50–300 mg twice daily. Findings of phase I illustrated that the pharmacokinetics of ticagrelor is predictable and is associated with consistent inhibition of platelet activity. IPA with ticagrelor was greater and better sustained at high levels with twice daily ticagrelor than once daily regimens.[17]

Results of phase II DISPERSE study showed that ticagrelor 100 mg and 200 mg bd have more beneficial safety and tolerability profile and therefore these two doses were carried forward for further clinical evaluation.[18] DISPERSE II was a dose confirmation study in NSTEMI patients. Results of DISPERSE II demonstrated that protocol-defined major or minor bleeding at 4 weeks, was not different among the ticagrelor 90 mg bd, ticagrelor 180 mg bd and clopidogrel 75 mg od groups. However ticagrelor 180 mg bd was associated with increase in minor and minimal bleeds. Based on safety and efficacy profile ticagrelor 90 mg bd was selected for phase III study.[19]

Onset–Offset study illustrated that IPA with ticagrelor 180 mg loading dose was greater than clopidogrel 600 mg loading dose at all the time points. Just 30 min post loading, IPA with ticagrelor was 41% versus 8% in clopidogrel group. At

the end of 2 h IPA with ticagrelor was 88% versus 38% in clopidogrel group. At 2 h post-loading, 90% patients in ticagrelor group achieved greater than 70% IPA versus 16% in clopidogrel group. Higher level of IPA achieved with ticagrelor was maintained throughout 6 weeks of study period which indicates sustained and consistent antiplatelet action of ticagrelor. After last dose, antiplatelet effect of ticagrelor declined very rapidly as compared to clopidogrel. 24 h after last dose, IPA with ticagrelor was similar to clopidogrel. This means patients who miss 1 dose of ticagrelor will still have IPA at 24 h equivalent to patients on clopidogrel therapy. IPA at day 3 and 5 with ticagrelor were comparable to IPA at day 5 and 7 with clopidogrel respectively.[20]

Effect of ticagrelor in clopidogrel non-responders was studied in RESPOND study which showed that ticagrelor treatment result in consistently higher IPA in patients irrespective of responder status. Ticagrelor was found to be effective in overcoming high platelet reactivity below the ischaemic cut off points in both responders and non-responders to clopidogrel therapy. This study also showed that switching patients from clopidogrel to ticagrelor result in rapid, higher and consistent IPA.[21]

7. Ticagrelor evidence in ACS: PLATO study

Platelet inhibition and patient outcome (PLATO) trial was designed to test the hypothesis that ticagrelor is superior to clopidogrel for prevention of recurrent thrombotic events in a broad ACS population and this would be achieved with a clinically acceptable bleeding rate and overall safety profile. It was a phase III, randomized, double blind, double dummy, multicentre, multinational, event driven, parallel group study comparing efficacy and safety of ticagrelor versus clopidogrel in patients of ACS. The study was conducted across the world in 43 countries with 862 sites and 18,624 patients. India was also a part of this international trial.

PLATO was designed to reflect real world clinical practice by enrolling the full spectrum of ACS (UA, NSTEMI or STEMI) patients within 24 h of their index event based on initial presentation, and ECG irrespective of whether they are managed medically or undergoing invasive management. All patients received baseline aspirin therapy at standard doses as per local practice. In ticagrelor group, patients received 180 mg as loading dose followed by 90 mg bd as maintenance dose. In clopidogrel arm, those patients who were clopidogrel naive received 300 mg as loading dose and 75 mg as maintenance dose while in clopidogrel pre-treated patients loading dose of clopidogrel was not given. Additional 300 mg of clopidogrel was allowed pre-PCI based on physician's discretion. Randomized treatment continued from a minimum of 6 months to a maximum of 12 months. Important highlight of PLATO trial design was inclusion of broad ACS population, inclusion of patients previously treated with clopidogrel and allowing clopidogrel loading doses greater than 300 mg.[22]

Key inclusion criteria for NSTEMI were two of the three, ST-segment changes indicating ischaemia; positive biomarkers, or one of several risk factors. For STEMI patient two criteria's should be met. Persistent ST-segment elevation and the intention to perform primary PCI. Key exclusion criteria were fibrinolytic therapy within 24 h before randomization, a need for oral anticoagulation therapy, an increased risk of bradycardia, and concomitant therapy with a strong CYP3A4 inhibitor or inducer.[22]

Baseline characteristics were well balanced between two groups. Adequate representation was given to female population with 28% females in both the groups. Unlike other ACS trials, PLATO has a notable sample size in the elderly with 15.5% of patients randomized aged $\geq$75 years. Investigator-assessed compliance with study medications was greater than 80% for both ticagrelor and clopidogrel. Around 46% patients in both the groups had received open label clopidogrel before randomization. Around 20% patients in clopidogrel group had received $\geq$600 mg of clopidogrel in a loading dose. Treatment approaches planned at randomization were balanced between treatment groups. Around 64% patients in both the groups were intended to undergo PCI and around 10% were intended to undergo CABG.

The primary efficacy endpoint of PLATO was time to first occurrence of any event from the composite of death from vascular causes, myocardial infarction (MI) or stroke. At the end of 12 months ticagrelor significantly reduced the rate of the composite endpoint of CV death, MI, and stroke versus clopidogrel (Relative Risk Reduction 16%, Absolute Risk Reduction 1.9%; $P = 0.0003$). The Kaplan–Meier curves for primary endpoint separates early and continue to diverge over a period of 12 months demonstrating the fact that benefit with ticagrelor comes early and it grows over a period of time. In the first 30 days there was an RRR of 12%. From day 31 to the end of the study there was an RRR of 20%. In PLATO, for every 54 ACS patients treated with ticagrelor instead of clopidogrel one atherothrombotic event was prevented. Primary endpoint

Table 1 – Outcome Events in PLATO

All patients	Ticagrelor ($n = 9333$)	Clopidogrel ($n = 9291$)	HR for (95% CI)	P-value
Primary endpoint, *n* (%) CV death + MI + stroke	864 (9.8)	1,014 (11.7)	0.84 (0.77–0.92)	0.0003
Secondary endpoint, *n* (%) Total death + MI + stroke	901 (10.2)	1,065 (12.3)	0.84 (0.77–0.92)	0.0001
CV death + MI + stroke + ischemia + TIA + arterial thrombotic events	1290 (14.6)	1456 (16.7)	0.88 (0.81–0.95)	0.0006
Myocardial infarction	504 (5.8)	593 (6.9)	0.84 (0.75–0.95)	0.0045
CV death	353 (4.0)	442 (5.1)	0.79 (0.69–0.91)	0.0013
Stroke	125 (1.5)	106 (1.3)	1.17 (0.91–1.52)	0.2249
Total death	399 (4.5)	506 (5.9)	0.78 (0.69–0.89)	0.0003

was mainly driven by reduction in MI and cardiovascular death with no difference in stroke.[23]

Analysis of secondary efficacy endpoints showed that ticagrelor treatment resulted in a statistically significant reduction in both cardiovascular mortality (4.0% vs 5.1%; HR = 0.79; 95% CI: 0.69–0.91) and all-cause mortality (4.5% vs 5.9%; HR = 0.78; 95% CI: 0.69–0.98; $P = 0.001$). This mortality benefit compared with clopidogrel is similar in magnitude to other major advances, such as streptokinase or aspirin versus placebo, tissue plasminogen activator versus streptokinase, and primary PCI versus tissue plasminogen activator, in care of patients with ST-elevation myocardial infarction. The mortality benefit was more notable in patients with non-ST-elevation acute coronary syndromes, when previous antithrombotic treatments were unsuccessful in improving survival by a reduction in ischaemic events. Thus, platelet inhibition with aspirin, clopidogrel, prasugrel, glycoprotein IIb/IIIa inhibitors, or treatment with unfractionated or low-molecular-weight heparins, or an early invasive strategy have not had any consistent effects on overall mortality in the setting of non-ST-elevation acute coronary syndromes.

The incidence of definite stent thrombosis was also reduced with ticagrelor as compared to clopidogrel (1.3% vs 1.9%; HR = 0.68; 95% CI: 0.50–0.91; $P = 0.009$).

Primary safety endpoint of PLATO was time to occurrence of first PLATO-defined major bleeding event. PLATO bleeding scale which was used in this trial takes into consideration both laboratory and clinical parameters for capturing bleeding events. There was no significant difference in the rate of major bleeding between ticagrelor and clopidogrel group (11.6% and 11.2%, respectively; $P = 0.43$). There was also no significant difference in the rate of fatal/life threatening bleeding between two treatment groups (5.8% in both groups, $P = 0.70$). There was increased fatal intracranial bleeding with ticagrelor as compared to clopidogrel (11 [0.1%] vs 1 [0.01%], $P = 0.02$). However, there were fewer episodes of fatal gastro intestinal and other fatal bleeding in the ticagrelor group than clopidogrel group (9 [0.1%], vs 21 [0.3%], $P = 0.03$). There was no significant difference in the rates of CABG-related major bleeding between two treatment groups. However, in the ticagrelor group, there was a higher rate of non-CABG-related major bleeding (4.5% vs 3.8%, $P = 0.03$).

Dyspnoea occurred more frequently in ticagrelor group than clopidogrel group (13.8% vs 7.8%).[23] However this dyspnoea was usually mild to moderate and in majority of the cases it resolved spontaneously. Most importantly, mortality benefit of ticagrelor was maintained irrespective of dyspnoea status. This dyspnoea is thought to be caused by increase in adenosine level in blood due to inhibition of re-uptake of adenosine in RBC by ticagrelor.

In PLATO study Holter monitoring was performed in 2866 patients and was repeated at 30 days in 1991 patients. There was a higher incidence of ventricular pauses of $\geq$3 s during first week in the ticagrelor group than in the clopidogrel group, however they resolved spontaneously and there was no difference in ventricular pauses at day 30.[23] Ventricular pauses were mostly sinoatrial in origin, asymptomatic and did not correlate with any clinical bradycardia adverse events. The efficacy of ticagrelor was not affected by ventricular pause status and reduction in overall mortality with ticagrelor was consistent with entire PLATO trial. Creatinine and uric acid levels increased slightly more in ticagrelor group than clopidogrel group.[23] This increase in creatinine and uric acid with ticagrelor was non-progressive and there was no significant difference in clinical adverse events due to increased creatinine and uric acid in two treatment groups.

In PLATO study, subgroup analysis was conducted to evaluate the robustness and consistency of the overall benefit. The benefit of ticagrelor over clopidogrel was found to be consistent in patients who had an ACS with or without ST-segment elevation, irrespective of the planned treatment approach, TIMI risk score, prior medical or revascularization history, age group, sex, weight, waist circumference, BMI group, and prior use of antiplatelet therapy.

In PLATO at randomization, an invasive strategy was planned for 13,408 (72.0%) of 18,624 patients hospitalised for acute coronary syndromes. The primary composite endpoint occurred in fewer patients in the ticagrelor group than in the clopidogrel group (9.0% vs 10.7%, hazard ratio 0.84, 95% CI 0.75–0.94; $P = 0.0025$).[24] A predefined subgroup analysis of patients in PLATO who were treated medically ($n = 5216$ intention to treat population) reported that patients who received ticagrelor had a lower rate of the composite primary endpoint than patients who received clopidogrel (12.0% vs 14.3%; $P = 0.045$).[25]

Diabetes mellitus (DM) is one of the important risk factor for recurrent cardiovascular (CV) events including death in patients of acute coronary syndromes (ACSs). Although clopidogrel is effective in treatment of ACS with diabetes, there are incidences of higher on-treatment platelet reactivity and worse clinical outcomes. The mechanisms leading to poor response to clopidogrel in diabetic patients are multifactorial including genetic, metabolic, cellular, and clinical factors. Diabetic subgroup analysis showed that primary endpoint benefit with ticagrelor was consistent with the overall PLATO trial results and no interaction between diabetic status and treatment was found.[26]

A subgroup analysis patients from the PLATO study with chronic kidney disease (creatinine clearance <60 mL/min; $n = 3237$) has shown that ticagrelor reduced the primary composite endpoint compared with clopidogrel (17.3% vs 22.0%; HR: 0.77; 95% CI: 0.65–0.90), with an ARR greater than that of patients with normal renal function ($n = 11,965$; 7.9% vs 8.9%; HR: 0.90; 95% CI: 0.79–1.02). Thus in patients of chronic kidney disease, benefit with ticagrelor was again consistent and there was no interaction between treatment and renal function.[27]

The consistency of benefit with ticagrelor was maintained in 33 subgroups, with three exceptions. These three subgroups were, patients weighing less than the median weight for their sex ($P = 0.04$ for the interaction), those not taking lipid-lowering drugs at randomization ($P = 0.04$ for the interaction), and those enrolled in North America ($P = 0.045$ for the interaction). Inconsistent benefit in North American population could be because of the use of higher maintenance dose of aspirin as this was the only variable that correlated with different outcomes between the US and non-US patients. As a result, ACS guidelines recommend that Ticagrelor should be used with low maintenance dose of aspirin (75–100 mg).[28,29]

To summarize, PLATO was designed to reflect current medical practice by enrolling the full spectrum of ACS (UA, NSTEMI or STEMI) patients and following them whether they

were medically managed or undergoing an invasive management. Results demonstrated that ticagrelor achieved greater efficacy in the primary endpoint (composite of CV death, MI and stroke) over clopidogrel without an increase in major bleeding The results of the PLATO trial indicate that treating 1000 patients over 12 months with ticagrelor instead of clopidogrel will result in 14 fewer deaths, 11 fewer MIs, or 6 fewer stent thrombosis.

8. Guideline recommendations for the use of OAPs

There are various international guidelines for the management of ACS. These guidelines evaluate available evidence and are intended to assist healthcare providers in clinical decision making for the management of ACS. Adherence to these evidence based guidelines can lead to better patient outcome. The increasing rates of ACS mortality and the projected rise in ACS mortality for 2020 in India necessitate implementation of these guidelines in day today clinical practice.

9. ESC guidelines for the management of NSTE–ACS (2011)

The ESC guidelines recommend using aspirin in all patients of ACS at a loading dose of 150–300 mg, and at a maintenance dose of 75–100 mg daily long term (Class I A). $P2Y_{12}$ inhibitor should be added to aspirin for duration of 12 months (Class I A). Among the different $P2Y_{12}$ inhibitors Ticagrelor is recommended to all patients of ACS at moderate to high risk of ischaemic events regardless of initial treatment strategy including those pre-treated with clopidogrel (Class I B). The guideline recommends the use of prasugrel in patients who are planned for PCI and whose coronary anatomy is known (Class I B). Clopidogrel is recommended only in patients who cannot receive ticagrelor or prasugrel (Class I A). In patients undergoing CABG or any other major surgery the guideline recommends stopping clopidogrel or ticagrelor 5 days before and prasugrel 7 days before the surgery (Class IIa C).[28]

10. ESC guidelines for the management of STE–ACS (2012)

Recently published ESC guidelines for STEMI recommends aspirin loading dose of 150–300 mg followed by maintenance dose of 75–100 mg daily long term (Class I B). ADP receptor blocker should be added to aspirin for duration of 12 months (Class I A). For patients undergoing primary PCI options include ticagrelor 180 mg loading dose, 90 mg bd maintenance dose (Class I B); Prasugrel 60 mg loading dose, 10 mg od maintenance dose in clopidogrel-naive patients with no history of prior stroke/TIA and age <75 years (Class I B); clopidogrel 600 mg loading dose, 75 mg maintenance dose preferably when prasugrel or ticagrelor are either not available or contraindicated (Class I C). For patients receiving fibrinolytic therapy, clopidogrel loading dose 300 mg followed by maintenance dose 75 mg daily should be given along with aspirin.[29]

11. American college of cardiology foundation (ACCF)/American heart association (AHA) guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (2012)

The ACCF/AHA guidelines recommend the use of aspirin to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients who tolerate it (Class I A). In patients in whom an initial conservative management is selected clopidogrel or ticagrelor (loading dose followed by daily maintenance dose) should be added to aspirin and anticoagulant therapy as soon as possible after admission and administered for up to 12 months (Class I B).

In patients where initial invasive strategy is selected, either ticagrelor or clopidogrel or IV GP IIb/IIIa inhibitor before PCI is recommended, or ticagrelor or prasugrel or clopidogrel is recommended at the time of PCI (Class I B). In patients who are intolerant to aspirin the guidelines recommend the use of clopidogrel or ticagrelor (in all UA/NSTEMI patients) or prasugrel (in PCI patients).[30]

12. ACC/AHA – PCI 2011

Patients already on aspirin therapy should take 81 mg–325 mg aspirin before PCI (Class I B).

A loading dose of a $P2Y_{12}$ receptor inhibitor should be given to patients undergoing PCI, options include: clopidogrel 600 mg, prasugrel 60 mg or ticagrelor 180 mg (Class I B).

In patients receiving a stent (BMS or DES) during PCI for ACS, $P2Y_{12}$ inhibitor therapy should be given for at least a year. Options include: clopidogrel 75 mg daily, prasugrel 10 mg daily or ticagrelor 90 mg twice daily (Class I B).[31]

13. Conclusion

Taking into consideration the dramatic increase in the incidence of and mortality from ACS, there is a dire need for optimizing management strategy of ACS. Platelets play a central role in pathogenesis of ACS and dual antiplatelet therapy is an important cornerstone of ACS therapy. There remains a significant incidence of arterial thrombosis in patients treated with currently available antiplatelet therapy. Novel $P2Y_{12}$ antagonist ticagrelor represents advancement over currently available oral antiplatelet agents. Its advantages include rapid onset of action, high and consistent platelet inhibition, a lack of need for metabolic conversion, an acceptable safety profile, and documented evidence in reducing cardiovascular events and mortality in broad-spectrum ACS patients.

Conflicts of interest

The author has none to declare.

REFERENCES

1. WHO. *Cardiovascular Diseases – Prevention and Control*; 2001.
2. *Global Atlas on Cardiovascular Disease Prevention and Control*. WHO [Internet] Available from: www.who.int/ncd/cvd; 2012.
3. Xavier Denis, Pais P, Devereaux PJ, et al. Treatment and outcomes of acute coronary syndromes in India (CREATE): a prospective analysis of registry data. *Lancet*. 2008;371:1435–1442.
4. Michelson AD, ed. *Platelets*. 2nd ed. San Diego: Elsevier/ Academic Press; 2007.
5. Cairns JA, Gent M, Singer J, et al. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. *N Engl J Med*. 1985;313:1369–1375.
6. Lewis Jr HD, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1983;309:396–403.
7. Théroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med*. 1988;319:1105–1111.
8. Wallentin LC. Aspirin (75 mg/day) after an episode of unstable coronary artery disease: long-term effects on the risk for myocardial infarction, occurrence of severe angina and the need for revascularization. Research Group on Instability in Coronary Artery Disease in Southeast Sweden. *J Am Coll Cardiol*. 1991;18:1587–1593.
9. Fox KAA, Mehta SR, Peters R, et al. Benefits and risks of the combination of clopidogrel and aspirin in patients undergoing surgical revascularization for non-ST-elevation acute coronary syndrome: the clopidogrel in unstable angina to prevent recurrent ischemic events (CURE) trial. *Circulation*. 2004;110:1202–1208.
10. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366: 1607–1621.
11. Sabatine MS, Cannon CP, Gibson CM, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA*. 2005;294:1224–1232.
12. Wang TH, Bhatt DL, Fox KAA, et al. An analysis of mortality rates with dual-antiplatelet therapy in the primary prevention population of the CHARISMA trial. *Eur Heart J*. 2007;28:2200–2207.
13. Storey Robert F. Pharmacology and clinical trials of reversibly-binding P2Y12 inhibitors. *Thromb Haemost*. 2011;105(suppl 1):S75–S81.
14. Storey RF, Husted S, Harrington RA, et al. Inhibition of platelet aggregation by AZD6140, reversible oral P2Y12 receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol*. 2007;50:1852–1856.
15. Van Giezen JJ, Humphries RG. Preclinical and clinical studies with selective reversible direct P2Y12 antagonists. *Semin Thromb Hemost*. 2005;31:195–204.
16. Butler K, Mitchell PD, Teng R. No significant food effect on the pharmacokinetics of AZD6140, the first reversible oral P2Y12 receptor antagonist, in healthy subjects [abstract PI-39]. *Clin Pharmacol Ther*. 2009;85:S20.
17. Butler K, Teng R. Pharmacokinetics, pharmacodynamics, safety and tolerability of multiple ascending doses of ticagrelor in healthy volunteers. *Br J Clin Pharmacol*. 2010;70(1):65–77.
18. Husted S, Emanuelsson H, Heptinstall S, et al. Pharmacodynamics, pharmacokinetics, and safety of the oral reversible P2Y12 antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J*. 2006;27:1038–1047.
19. Cannon CP, Husted S, Harrington RA, et al. Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol*. 2007;50:1844–1851 [Erratum, *J Am Coll Cardiol*. 2007;50:2196].
20. Gurbel PA, Bliden KP, Butler K, 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;120:2577–2585.
21. Gurbel PA, Bliden KP, Butler K, et al. Response to ticagrelor in clopidogrel nonresponders and responders and effect of switching therapies. The respond study. *Circulation*. 2010;121:1188–1199.
22. James S, Akerblom A, Cannon CP. Comparison of ticagrelor, the first reversible oral P2Y(12) receptor antagonist, with clopidogrel in patients with acute coronary syndromes: rationale, design, and baseline characteristics of the platelet inhibition and patient Outcomes (PLATO) trial. *Am Heart J*. 2009;157:599–605.
23. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045–1057.
24. Cannon CP, Harrington RA, James S, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. *Lancet*. 2010;375: 283–293.
25. James SK, Roe MT, Cannon CP, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes intended for non-invasive management: substudy from prospective randomised platelet inhibition and patient outcomes (PLATO) trial. *BMJ*. 2011;342:d3527.
26. James S, Angiolillo DJ, Cornel JH, et al. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the platelet inhibition and patient outcomes (PLATO) trial. *Eur Heart J*. 2010;31:3006–3016.
27. James S, Budaj A, Aylward P, et al. Ticagrelor versus clopidogrel in acute coronary syndromes in relation to renal function: results from the platelet inhibition and patient outcomes (PLATO) trial. *Circulation*. 2010;122:1056–1067.
28. Hamm CW, Bassand J-P, Agewall S, et al. 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.
29. Steg Ph G, James SK, Atar D, et al. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J*; 2012 [Epub ahead of print].
30. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. *Circulation*; 2012 [Epub ahead of print].
31. Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/ SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/ American Heart Association task force on practice guidelines and the Society for Cardiovascular Angiography and Interventions. *Circulation*. 2011;124:e574–e651.