Ticagrelor

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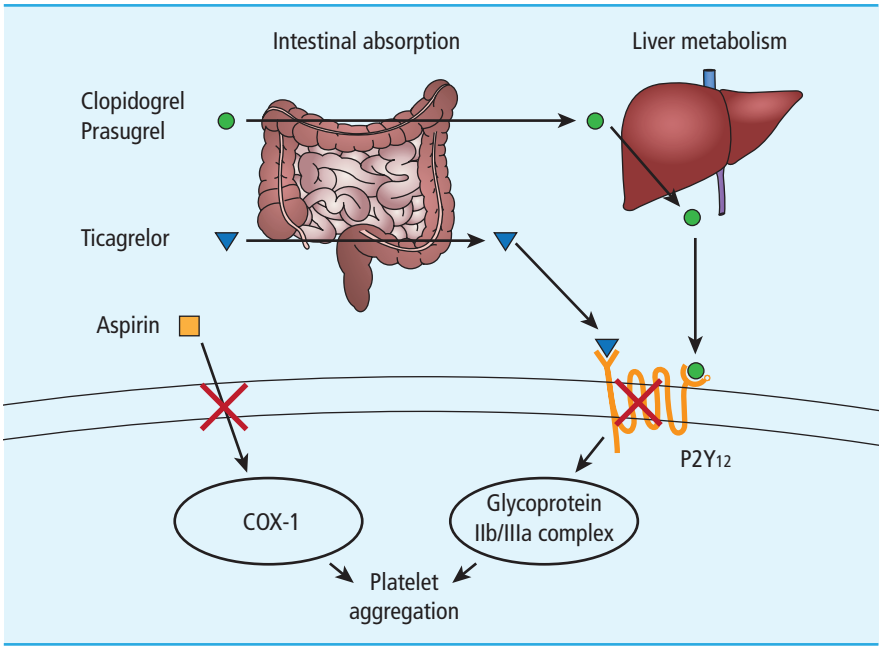

Figure 1. Ticagrelor binds reversibly to the P2Y12 receptor and, although at a different binding site from adesonine diphosphate (ADP), it leads to inhibition of ADP-mediated signal transduction and prevention of platelet activation

Introduction

Acute coronary syndrome (ACS) is a leading cause of mortality and morbidity in people with diabetes. The majority of ACS cases are due to rupture of an atherosclerotic plaque within a coronary artery, leading to platelet aggregation and thrombus formation. Diabetes leads to high platelet activity and adhesiveness, and an increased risk of ischaemic events and bleeding post ACS. Dual antiplatelet therapy of low-dose aspirin in combination with one of the P2Y12 receptor antagonists is the standard of care for ACS patients. There are multiple P2Y12 receptor antagonists available, such as the thienopyridines clopidogrel and prasugrel. Ticagrelor is a P2Y12 receptor antagonist which has a different mechanism of action compared to thienopyridines.

Pharmacology

Ticagrelor is the first P2Y12 receptor antagonist that has a binding site different from adesonine diphosphate (ADP), but leads to inhibition of ADP-mediated signal transduction and prevention of platelet activation. (Figure 1.) Clopidogrel is associated with a number of limitations including delayed onset and prolonged recovery of platelet function due to metabolic activation and irreversible binding and reduced antiplatelet effect in certain genotypes. Unlike thienopyridines, ticagrelor binds reversibly to the P2Y12 receptor, in a non-competitive manner, and does not require metabolic activation. The antiplatelet effect also does not appear to be affected in CYP2C19 and ABCB1 genotypes.[1]

Ticagrelor is taken orally, and is absorbed quickly from the gut, with a bioavailability of 36% reaching peak plasma concentration in 1.5 hours. Its active metabolite (AR-C124910XX) is formed quickly via the liver enzyme CYP3A4 and peaks after 2.5 hours. As it is a weak inhibitor of CYP3A4, concomitant use of other drugs metabolised by CYP3A4 such as simvastatin, particularly at high doses, shows increased levels and subsequent increased risk of statin-related side effects. Inhibitors of liver enzyme CYP3A4, such as ketoconazole, lead

to increased plasma levels and worsening of side effects – including bleeding – and strong inducers, which include rifampicin, decrease the effectiveness of ticagrelor.

It has a half-life of 7 hours (7.7–13 hours) and is excreted mainly in faeces, likely by biliary secretion. As ticagrelor is metabolised in the liver, it is contraindicated in severe hepatic impairment. It produces a faster onset of inhibition of platelet aggregation, reaching maximum inhibition after 2 hours.

Trials of safety and efficacy

The PLATelet inhibition and patient Outcomes (PLATO) trial was a multicentre, double-blind, randomised trial involving over 18 000 patients comparing ticagrelor and clopidogrel, with a 12-month primary endpoint of major adverse cardiovascular events (death from cardiovascular causes, non-fatal myocardial infarction [MI], non-fatal stroke).[2] Ticagrelor showed a significant reduction in the rates of the primary endpoint compared to clopidogrel (HR 0.84, 95% CI 0.77–0.92, p<0.001). It also showed a reduction in the primary endpoint in patients for whom invasive treatment was planned (PCI or CABG); (8.9% vs 10.6%, p=0.003).

Regarding secondary endpoints, ticagrelor patients compared to patients given clopidogrel had significant reductions in all-cause mortality (4.5% vs 5.9%, p<0.001), a wider composite endpoint including MI, stroke, recurrent ischaemia, TIA (14.6% vs 16.7%), MI alone, and death from vascular causes. The numbers of haemorrhagic strokes were slightly higher in ticagrelor patients but this was not statistically significant (0.2% vs -0.1%, p<0.1).

The primary safety endpoint of first occurrence of major bleeding showed similar rates when ticagrelor was compared to clopidogrel (11.6% vs 11.2%, p=0.43). Other safety endpoints showed that fatal intracranial bleeding was common with ticagrelor (0.1% vs 0.01%, p=0.02) but other types of fatal bleeding were less common (0.1% vs 0.4%, p=0.03) when compared to clopidogrel. There were increased rates of dyspnoea and increased numbers of discontinuation due to dyspnoea with ticagrelor than there were with clopidogrel, and most of the episodes lasted less than a week. Of note, ventricular pauses were more common within the first week with ticagrelor but were rarely symptomatic, and creatinine and uric acid levels increased significantly during ticagrelor treatment.

Specific evidence for use in diabetes

A quarter of the subjects in PLATO were recorded as having diabetes at baseline (n=4662). Diabetes was associated with significantly higher incidences of the primary composite outcome, mortality and major bleeding, compared to subjects without diabetes. In the substudy of subjects with diabetes,[3] the reduction in the primary composite endpoint with ticagrelor compared to clopidogrel (HR 0.88, 95% CI 0.76–1.03), all-cause mortality (HR 0.82, 95% CI 0.66–1.01) and stent thrombosis (HR 0.65, 95% CI 0.36–1.17) with no increase in major bleeding (HR 0.95, 95% CI 0.81–1.12) was consistent with the findings in the overall cohort, and without significant diabetes status-by-treatment interactions; however, this did not reach nominal statistical significance. These findings were consistent independently of type of ACS, renal function or invasive treatment. There was no heterogeneity between patients with or without insulin therapy.

Higher levels of baseline HbA_{1c} and higher levels of glucose were both strongly associated with a higher incidence of all evaluated ischaemic outcomes and major bleeding. For patients with an HbA_{1c} or blood glucose above the median, the primary composite outcome was reduced with ticagrelor versus clopidogrel but with similar bleeding rates, and there were no significant interactions for treatment-by-glucose or HbA_{1c} level.

Discussion

In patients with ACS, ticagrelor significantly reduced cardiovascular death and total mortality without an increase in major bleeding when compared to clopidogrel. A similar reduction was found in subjects with diabetes although not nominally statistically significant.

A series of critical articles, largely by the same two authors, and refuted by the PLATO investigators, have raised a multitude of concerns regarding the PLATO trial, including: worse outcome for US patients which were monitored by an independent organisation; higher rate of all-cause death in clopidogrel-treated patients compared to previous studies; obvious differences in the shape of the tablets which may have led to unblinded bias; and differences in the classification of diagnosis of MI.[4]

The PLATO trial controversy is still ongoing and is likely to continue until more data are available. In addition to any further sources of bias, it highlights some potential limitations of peer-review processes, and problems in free access to clinical trial data and data sharing.[4]

Key points

- Ticagrelor is indicated for patients with an acute coronary syndrome as dual antiplatelet therapy in combination with low-dose aspirin, including in people with diabetes
- Due to its quicker onset of action compared to clopidogrel, ticagrelor may be more useful before surgery and CABG; however, it requires to be taken twice daily which may lead to issues with adherence in the long term
- It is contraindicated in patients with a history of intracranial haemorrhage due to an increased rate with ticagrelor compared to clopidogrel, but overall has less major bleeding events

Declaration of interests

Professor Fisher has received payment for lectures and advisory boards from AstraZeneca. Professor McKay has received payment for lectures from AstraZeneca.

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