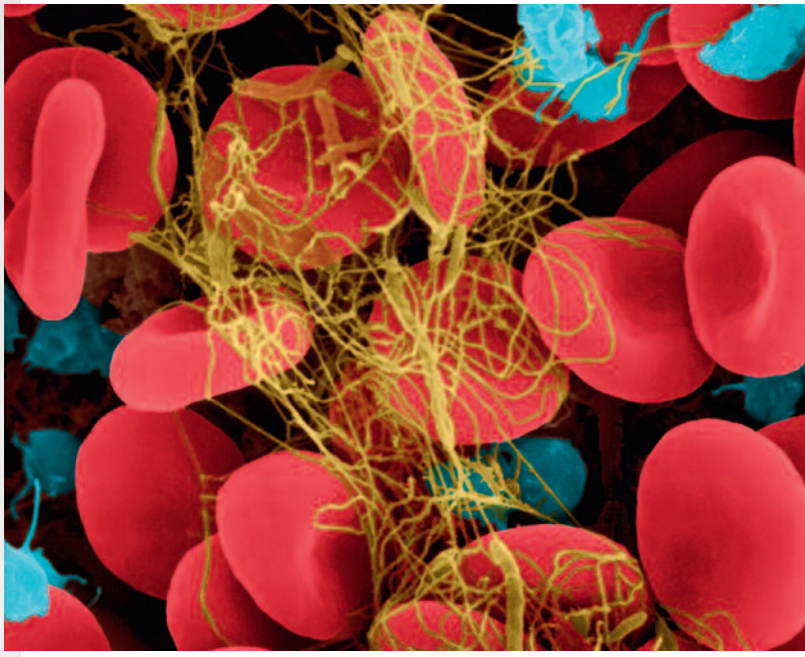

Ticagrelor – a new player in the antiplatelet therapy field

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Ticagrelor is a promising new first-line antiplatelet agent for use with aspirin in the treatment of acute coronary syndromes.

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In patients with acute coronary syndromes or who have had percutaneous coronary intervention, effective antiplatelet therapy is essential to reduce the risk of thrombus formation and consequent vascular events (recurrent angina and re-infarction in the case of ACS, and stent thrombosis and restenosis after coronary stent implantation). Dual antiplatelet therapy is often required to inhibit platelet function in such patients, and there is now a choice of three agents that can be used with aspirin: clopidogrel, prasugrel and ticagrelor.

Ticagrelor has recently been PBS listed (August 2012) for the treatment of acute coronary syndromes (myocardial infarction or unstable angina) in combination with aspirin. This article reviews ticagrelor, including the evidence for its efficacy and its side effects.

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WHAT IS TICAGRELOR?

Ticagrelor is an oral, reversibly binding inhibitor of the adenosine diphosphate receptor P2Y12 on platelets. P2Y12 is important for platelet activation and aggregation, and drugs that inhibit this receptor (clopidogrel, prasugrel and ticagrelor) are major therapeutic tools for acute coronary syndromes.

The level of P2Y12 inhibition by ticagrelor is determined by its plasma level and, to a lesser extent, that of an active metabolite. Ticagrelor has a more rapid and consistent onset of action than clopidogrel, and also a quicker offset of action (since it binds reversibly, unlike clopidogrel and prasugrel, and hence recovery of platelet function is not dependent on platelet replacement).

The features of clopidogrel, prasugrel and ticagrelor are listed in the Table.[1]

EVIDENCE FOR ITS USE

One of the largest trials that has been performed for acute coronary syndromes is the PLATO trial (the Study of Platelet Inhibition and Patient Outcomes), which provided evidence for superiority of ticagrelor over clopidogrel.[2] This multicentre, double-blind, randomised trial compared ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300 to 600 mg loading dose, 75 mg daily thereafter), given in combination with aspirin and other standard therapy, for the prevention of cardiovascular events in 18,624 patients admitted to hospital with an acute coronary syndrome, with or without ST-segment elevation.

At 12 months in this trial, the primary endpoint (death from vascular causes, myocardial infarction or stroke) had occurred

in 9.8% of patients receiving ticagrelor compared with 11.7% of those receiving clopidogrel (hazard ratio [HR] 0.84; 95% confidence interval 0.77 to 0.92, p<0.001).[2] Surprisingly, this was the first study to show a mortality benefit with an alternative antiplatelet agent (death from any cause, ticagrelor 4.5% *v.* clopidogrel 5.9%, p<0.001). There were also significant reductions in rates of myocardial infarction (ticagrelor 5.8% *v.* clopidogrel 6.9%, p=0.005) and stent thrombosis (ticagrelor 1.3% *v.* clopidogrel 1.9%, p=0.009), but not in rates of stroke. The benefit of ticagrelor extended to patients treated invasively (percutaneous intervention or coronary artery bypass grafting) or noninvasively, as well as to people with diabetes.

In the overall group in PLATO, there was no difference in rates of major bleeding (ticagrelor 11.6% *v.* clopidogrel 11.2%, p=0.43).[2] However, in the non-coronary artery bypass graft patients there was an increase in major bleeding with ticagrelor (ticagrelor 4.5% *v.* clopidogrel 3.8%, p=0.03).

TABLE. P2Y12 INHIBITORS

	Clopidogrel	Prasugrel	Ticagrelor
Class	Thienopyridine	Thienopyridine	Triazolopyrimidine
Reversibility	Irreversible	Irreversible	Reversible
Activation	Prodrug, not limited by metabolism	Prodrug, limited by metabolism	Active drug
Onset of effect*	2 to 4 hours	30 minutes	30 minutes
Duration of effect	3 to 10 days	5 to 10 days	3 to 4 days
Withdrawal before major surgery	5 days	7 days	5 days

* 50% inhibition of platelet aggregation.

Reproduced with permission of Oxford University Press from *Eur Heart J* 2011; 32: 2999-3054.[1]

HOW IS IT USED?

Ticagrelor is given orally in a loading dose of 180 mg followed by a twice-daily dose of 90 mg. A similar dose is given even if patients have been pre-treated with clopidogrel. Patients should also be taking aspirin daily. Therapy should continue for 12 months after the index event.

Dose adjustment in patients with renal impairment is unnecessary because ticagrelor is not renally excreted. However, it is hepatically excreted and so is contraindicated in patients with moderate or severe hepatic impairment.

SIDE EFFECTS

Side effects not seen with clopidogrel or prasugrel have been seen with ticagrelor.[1,2] These include dyspnoea, bradyarrhythmia and increased levels of uric acid and creatinine. These side effects possibly relate to structural similarities of ticagrelor and adenosine. While these side effects have a negative effect on quality of life, they did not put patients at higher risk for death.[2]

A NEW TAILORED THERAPY?

When dual antiplatelet therapy is indicated, there is now a choice of three agents that can potentially be used with aspirin. The advantage of ticagrelor is its clinical utility in the broad range of patients with acute coronary syndromes, including those who receive stenting or are managed medically.

Ticagrelor may be preferred in patients requiring cardiac bypass graft surgery or where the coronary anatomy is unknown.[3] Prasugrel has mainly been studied in patients undergoing stenting and is discouraged in patients with a history of stroke or transient ischaemia attacks. Clopidogrel resistance is a real entity and limits the widespread application of this drug.

SUMMARY

Ticagrelor is a promising new first-line antiplatelet agent for use with aspirin in patients presenting with an acute coronary syndrome. An advantage is the consistent degree of platelet inhibition reducing ischaemic events, associated with an acceptable safety profile. MT

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