Canterbury District Health Board
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A brief overview of ticagrelor

Ticagrelor is a new antiplatelet agent with the same mechanism of action as clopidogrel. One of the proposed advantages is that it is not a prodrug and does not have an activation step that can be affected by genetics / interactions. It has been recently introduced to the CDHB (Cardiology), as an alternative to clopidogrel, for the treatment of acute coronary syndromes in conjunction with aspirin. Ticagrelor is being supplied free of charge by the manufacturers for up to one year. The initial supply is provided in hospital with further supplies sent directly to the patient following a faxed prescription from their GP to a supplier in Auckland (unlikely to be listed on community pharmacy medication records).

Pharmacodynamics: Ticagrelor is a reversible adenosine phophate (ADP) receptor antagonist and acts on the $P2Y_{12}$ ADP receptor inhibiting ADP-mediated platelet activation and aggregation. It has a fast onset of action (0.5 hours; peak 2 to 4 hours) and a shorter time of offset than clopidogrel (stop 5 days prior to surgery compared to 7 days for clopidorel).

Pharmacokinetics: Absorption: Undergoes first pass metabolism with a mean oral bioavailability of 36%.
Metabolism: Ticagrelor and its equipotent active metabolite are extensively metabolised by CYP3A4 with <1% being cleared unchanged by the kidneys.
Elimination half-life: Ticagrelor 7 hours, metabolite 9 hours.
Interactions: Ticagrelor (and active metabolite) is a CYP3A4 and p-glycoprotein substrate and inhibitor (mild). See table 1 below for examples. Additive risk of bleeding is expected with other antiplatelets or anticoagulants.

Contraindications: Severe hepatic impairment (increased risk of bleeding), history of intracranial bleeding (risk of recurrence) and pathological bleeding e.g. active peptic ulcer.

Adverse effects: The adverse effects of ticagrelor are similar to those reported with clopidogrel. These similarities include major bleeding (7.9% vs. 7.7%, respectively), total major and minor bleeding (11.4% vs. 10.9%), cardiovascular side effects e.g. atrial fibrillation, bradycardia, chest pain etc and gastrointestinal effects. However, ticagrelor is associated with greater increases in uric acid concentrations compared to baseline (14% increase vs. 7%) and a greater incidence of dyspnoea (13.8% vs. 7.8%) than clopidogrel. [1]
[1] PLATO (NEJM 2009; 361: 1045-57)

Summary: Ticagrelor has some advantages over clopidogrel; the main one being that ticagrelor is the active agent, whereas clopidogrel requires an activation step. However, both are associated with significant interactions; for ticagrelor these can significantly alter serum concentrations and increase the risk of bleeding or decrease the response; for clopidogrel these can prevent activation, resulting in loss of efficacy. Both drugs have a similar adverse effect profile with the exceptions of greater increases in uric acid concentrations and a higher incidence of dyspnoea with ticagrelor. The other issue with ticagrelor is the current provision of free supply by the manufacturer, which is of a promotional nature and designed to influence prescribing.

Table 1: Examples of pharmacokinetic interactions with ticagrelor

Effects of other drugs on ticagrelor		**Comments**
CYP3A4 inhibitors: strong	Ketoconazole increases Cmax and AUC of ticagrelor by 2.4-fold and 7.3-fold, respectively. Other strong inhibitors are expected to have similar effects. (see Pink Book) e.g. clarithromycin, itraconazole and some antiretrovirals	Use contraindicated. Consider alternative agent.
moderate	Diltiazem increases the Cmax and AUC of ticagrelor by 69% and 2.7-fold, respectively. Other moderate inhibitors are expected to have similar effects. (see Pink Book) e.g. verapamil, erythromycin, fluconazole and grapefruit juice	Use not contraindicated; however, likely increased risk of ADRs. Consider alternative agent.
others	Amiodarone and ciprofloxacin (see Pink Book)	Monitor for increased ADRs.
CYP3A4 inducers: strong	Rifampicin decreases Cmax and AUC of ticagrelor by 73% and 86%, respectively. Other strong inducers would be expected to have a similar effect. (see Pink Book)	Concomitant use may reduce the efficacy of ticagrelor. Consider alternative agent.
others	Dexamethasone, phenytoin, carbamazepine, phenobarbitone and St John's wort (see Pink Book)	Monitor for reduced efficacy.
Effects of ticagrelor on other drugs		**Comments**
CYP3A4 substrates	**Ticagrelor is a mild CYP3A4 inhibitor** – coadministration increases simvastatin AUC by a mean of 56% (up to 3-fold in some).	Maximum dose of 40mg simvastatin.
	Others: amlodipine, felodipine, verapamil, atorvastatin and propranolol (see Pink Book)	Monitor for increased ADRs.
P-glycoprotein substrates	**Ticagrelor is a p-glycoprotein inhibitor** – coadministration increases digoxin AUC and serum concentrations by a mean of 30% (up to 2-fold in some)	Monitor serum digoxin concentrations.
	Others: dabigatran etexilate (see Pink Book).	Monitor for increased ADRs.