

## Clopidogrel and proton-pump inhibitors

Clopidogrel is part of standard care for various cardiovascular atherothrombotic diseases. It is an inactive pro-drug that requires conversion to its active compound to have an antiplatelet effect. Recent data suggests that proton pump inhibitors (PPIs) may inhibit this conversion and reduce the effectiveness of clopidogrel.

The aim of this bulletin is to provide an overview of the clopidogrel/PPI interaction and suggest management strategies when faced with co-prescription of these drugs.

### Overview of clopidogrel-PPI data

The cytochrome P450 2C19 (CYP2C19) isoenzyme appears to be particularly important in the conversion of clopidogrel to the active metabolite. Patients with reduced function of CYP2C19 due to genetic polymorphisms (e.g. 15% of Caucasians) have significantly lower concentrations of the active metabolite of clopidogrel and higher rates of adverse cardiovascular outcomes compared to normal metabolisers. Drugs that are metabolised by CYP2C19 may competitively inhibit the conversion of clopidogrel to its active metabolite. There is a rapidly growing body of data that examines the possibility that PPIs interact with clopidogrel via this mechanism.

### In vitro data

*In vitro* studies show that the different PPIs inhibit CYP2C19 to different extents. For example, lansoprazole and omeprazole have been found to be significant inhibitors, whereas pantoprazole was shown to be a very weak inhibitor of CYP2C19.

### Platelet aggregation data

Platelet aggregation studies are surrogate pharmacodynamic markers for the effectiveness of clopidogrel, with increased aggregation being predictive of poorer cardiovascular outcomes. An observational study of clopidogrel users showed that those on omeprazole had a ~20% increase in platelet aggregation compared to non-users ( $p=0.007$ ). A subsequent randomised controlled trial of patients undergoing coronary artery stenting who were given aspirin and clopidogrel found a similar increase in platelet aggregation in those given omeprazole (20mg/day) compared with placebo ( $p<0.0001$ ). Similar studies with pantoprazole have found conflicting results.

### Clinical data

This is largely limited to observational studies, which have reported conflicting results regarding:

- the presence of a clopidogrel-PPI interaction leading to increased adverse cardiovascular outcomes and
- the specificity of the interaction to PPIs that are potent CYP2C19 inhibitors.

There have been six observational studies published as original articles, including five retrospective cohort studies and one

nested case-control study. Endpoints have included serious cardiovascular events such as myocardial infarction and stroke.

Two have concluded, with statistical significance, that combining PPIs with clopidogrel increases the risk of serious cardiovascular events by around 25%. Omeprazole was the predominant PPI in both of these studies. In one of these two studies, stratified analysis found an absence of increased risk with pantoprazole. Three other studies did not show an association between PPI and cardiovascular events in the setting of clopidogrel use. In two of these, pantoprazole was the predominant PPI, whilst no breakdown of specific PPIs was provided in the third. It may therefore be argued that these five studies reflect the *in vitro* data, highlighting the difference between omeprazole and pantoprazole in terms of CYP2C19 inhibitory potency.

The results of a sixth study are at odds with the other five as pantoprazole was the main PPI and the study showed a statistically significant adverse cardiovascular interaction with clopidogrel.

Observational studies are inherently limited by the presence of residual confounding, which may have led to the findings in favour of an interaction being present. However, observational medication exposure typically causes a bias towards the null hypothesis as a result of non-adherence and over-the-counter medication exposure. Randomised controlled studies are therefore important in providing more definitive evidence. Of note, there has been one randomised controlled trial of a fixed-dose combination of omeprazole and clopidogrel compared with clopidogrel alone. The data from this study has been provisionally reported as showing an absence of an adverse cardiovascular interaction between omeprazole and clopidogrel and a protective effect in terms of gastrointestinal bleeding. Formal publication of this study is awaited.

### Conclusion and management strategies

The currently available data are strongly suggestive of a significant adverse interaction at the molecular level between clopidogrel and some PPIs (such as omeprazole), but is inconclusive at the clinical level. Until more definitive evidence is available, the possible risk posed by this interaction should be taken into account when contemplating co-prescription of clopidogrel with a PPI.

In this setting, the individual gastrointestinal benefit needs to be balanced against the cardiovascular risk. For example, a PPI may, overall, be beneficial where there is a low risk of cardiovascular events but a high risk of haemorrhagic gastrointestinal events. When faced with co-prescription of clopidogrel and PPIs, an algorithm based on both PPI and non-PPI alternatives to those PPIs that are significant *in vitro* CYP2C19 inhibitors may be considered (see figure below).

