

**INTRODUCTION**

Low dose aspirin (75 to 325mg/d) alone or in combination with second generation thienopyridine clopidogrel is now frequently prescribed anti-thrombotics in patients with ischaemic stroke, Ac Myocardial infarction, Acute coronary syndrome and after per-cutaneous coronary interventions (PCI) to minimize re-thrombosis risk. While these reduce the risk of CV events there is increased risk of GI bleeding. There is higher risk with dual antiplatelet agents and when corticosteroids, NSAIDs or anticoagulants are co-prescribed as shown in the figure below.

Previous history of GI bleed, h/o peptic ulcer disease and age above 60 years are strong risk factors for bleeding due to antiplatelet therapy. Aspirin causes direct mucosal injury in the GI tract causing ulcerations but Theinopyridines increase the risk of GI bleed by anti-thrombotic action and delay healing of pre-existing erosions and ulcers.

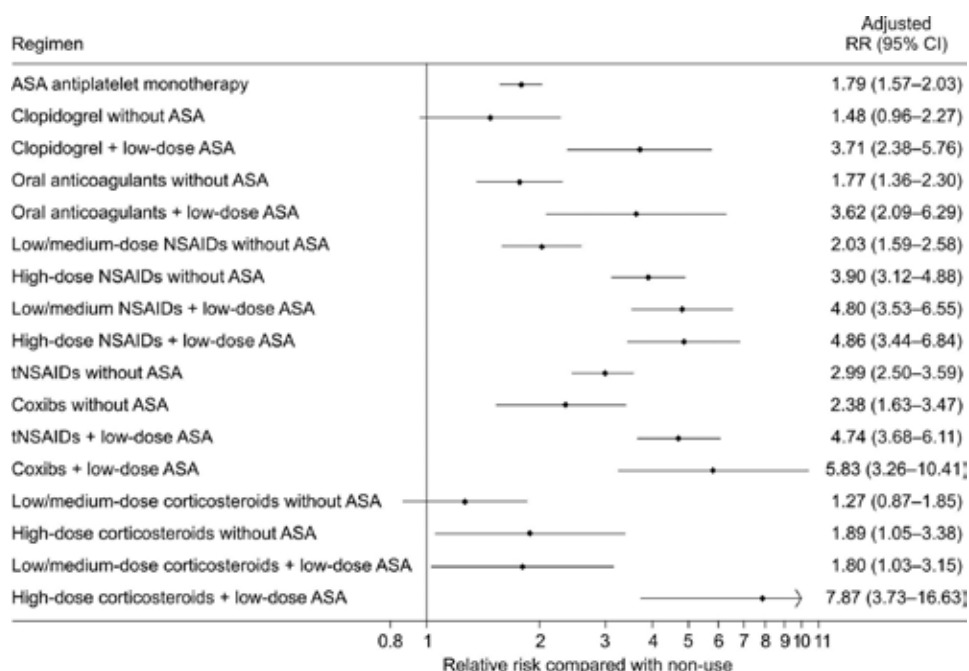
**RISK OF GI BLEED WITH ANTIPLATELETS**

Gastric acid suppression effectively reduces the risk of GI bleed by stabilization of platelet clot and healing of ulcers. H2RAs and PPIs are both effective in gastric acid suppression and ulcer healing. H2RAs are more effective than placebo in prevention of aspirin induced ulcers but PPIs cause more profound acid suppression and ulcer healing compared to H2RAs with significant risk

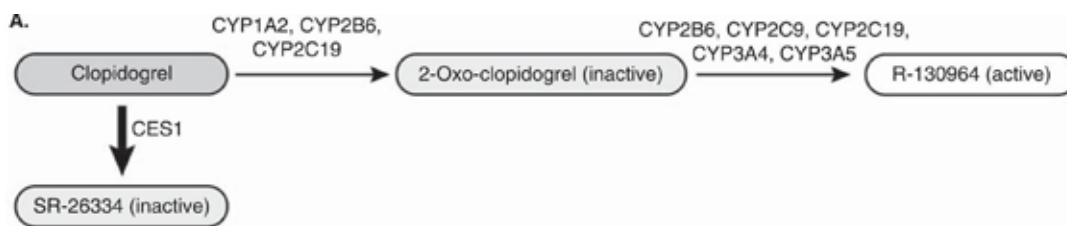
reduction for an UGI bleed. In a large case-control study in 2007 comparing 2779 patients of upper GI bleeding on endoscopy with 5532 controls, PPI use along with clopidogrel resulted in less upper GI bleeding (RR: 0.19; 95% CI: 0.07 to 0.49) than clopidogrel alone (Figure 1). A recent (2010) RCT demonstrated that co-prescription of Omeprazole with clopidogrel resulted in nearly 66% reduced risk of GI events including overt or obscure GI bleed and gastro-duodenal ulcers as compared to clopidogrel alone. Because of these benefits PPIs are often prescribed along with antiplatelets particularly in high risk patients.

Clopidogrel and several PPIs share a common hepatic metabolic pathway through cytochrome-P450 (CYP450) enzymes CYP2C19 and CYP3A4, suggesting the potential for drug interaction and reduced efficacy and adverse CV outcomes. This resulted in 2009 a FDA warning on co-prescription of Omeprazole with Clopidogrel.

There has been intensive study of pharmacological interaction and clinical outcomes with conflicting data since then. To understand the intricacies of this drug drug interaction we need to understand metabolism and mechanism of both the molecules



**Fig. 1: Case Control Study showing risk of GI Bleed with Antiplatelets**



**Fig. 2: Clopidogrel Metabolism**

## DRUG METABOLISM AND INTERACTION

Clopidogrel is a pro-drug and its active metabolite binds irreversibly to purinergic P2Y receptor causing inhibition of ADP mediated platelet activation and aggregation.

Nearly 85% of pro-drug is hydrolysed by esterases into an inactive metabolite and rest is converted to its active metabolite through two step sequential oxidative pathway involving CYP 450 enzymes as shown below.

### CLOPIDOGREL METABOLIC PATHWAY (FIGURE 2)

PPIs are weak bases which are activated in the highly acidic environment of gastric parietal cell and metabolized in the liver by CYP 450 enzymes mainly CYP2C19 and CYP3A4 which it shares with Clopidogrel oxidation pathway. There are some differences in degree of CYP2C19 dependent metabolism of various PPIs but pharmacokinetic studies have been inconsistent and do not show superiority of one PPI over other. However Omeprazole and Esomeprazole have strongest competitive.

CYP2C19 inhibition with resultant pharmacokinetic outcomes of decreased levels of clopidogrel active metabolite and preserved platelet reactivity *ex vivo*. Some studies have shown lesser competitive inhibition of CYP2C19 with Pantoprazole and Rabeprazole.

### HEPATIC METABOLIC PATHWAY OF OMEPRAZOLE (FIGURE 3)

Clopidogrel biological activity will also depend upon

- Intestinal absorption of pro-drug which may vary with ABCB 1 polymorphism
- Genetic polymorphism of CYP2C19. Three alleles; 2,3 and 4 have decreased

activity and produce less amount of active metabolite and therefore decreased anti-platelet activity. Competitive inhibition by Omeprazole will have maximum impact on individuals with such polymorphism. CYP2C19\*2 is present in >50% asian, >33% African Americans and 24% Caucasians. However these factors influence only 12% in variation of platelet aggregability in response to ADP while Obesity, Diabetes and acute Ischaemia may have much greater effect.

Recent SPICE trial (evaluation of influence of statins and PPIs on Clopidogrel anti-platelet activity) on 350 post PCI patients on aspirin and clopidogrel shows that 35 to 50% patients taking esomeprazole had >10% effect on antiplatelet effect of Clopidogrel while Pantoprazole and H2RAs and statins had no significant effect.

## NEWER ANTIPLATELET AGENTS

Prasugrel and Ticagrelor are new antiplatelet agents approved for ACS patients undergoing PCI. Prasugrel is a third generation thienopyridine which is a pro-drug and needs one step of CYP 450 dependent hepatic metabolism to active metabolite conversion. In PRINCIPLE-TIMI 44 a study comparing anti-thrombotic activity, post PCI for ACS in patients taking Clopidogrel or Prasugrel with PPIs showed much less effect on anti-platelet activity of PPIs on Prasugrel compared to Clopidogrel.

Ticagrelor is a non thienopyridine antiplatelet agent which does not need hepatic metabolism for conversion into active metabolite. It has rapid onset of action and more profound antiplatelet action and has similar risk of major bleeds as Clopidogrel. Its interaction with PPIs is not known.

## CLINICAL EVIDENCE OF PPI AND ANTIPLATELETS INTERACTION

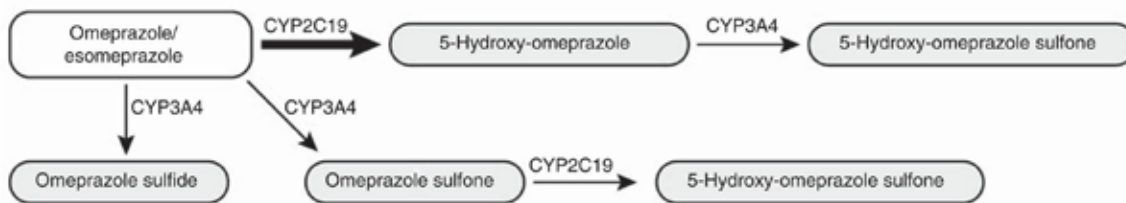
There has been inconsistent results of various clinical studies looking at the effect of PPIs co-prescription with thienopyridines on adverse CV events.

Studies which have shown positive association are mostly observational and are likely to be influenced by selection bias and other confounding factors. In a study of 13608 post PCI patients (Lancet 2009) randomized to either Clopidogrel or Prasugrel, addition of PPIs did not effect cardio-vascular events or incidence of stroke. In the only RCT (COGENT) comparing fixed dose Clopidogrel and Omeprazole (75/20) combination with clopidogrel alone there was no effect of PPIs on adverse CV events. There were significantly less adverse GI events (HR .34). However this trial fell short on enrolment numbers planned and was interrupted. Two recent meta-analysis also found no adverse effect of PPIs on CV events.

There is no evidence of superiority of one PPI over other in clinical CV outcomes inspite of pharmacokinetic advantage of Pantoprazole and Rabeprazole over other PPIs. In a retrospective analysis of 20956 patients taking Clopidogrel PPIs did not influence CV events and all PPIs were same.

## STRATEGIES TO MINIMISE INTERACTION

There have been various strategies to reduce PPI, anti-platelet agent interaction. Giving Pantoprazole or Rabeprazole instead of Omeprazole or eso-omeprazole or substituting Clopidogrel with Prasugrel may minimize potential pharmacokinetic interaction. Split dosing of PPIs and Clopidogrel at different time of the day also has inconsistent results.



**Fig. 3: Omeprazole Metabolism**

## RECOMMENDATIONS

There is evidence of pharmacokinetic interaction and measurable decreased anti-platelet activity (ex vivo) of Clopidogrel prescribed with PPIs. There are safety concerns of PPIs co-prescription with anti-platelet agents based on observational studies which only show mild to moderate clinical impact with HR <2. This may be due to study population heterogeneity and other confounding factors. Only RCT till date and two meta-analysis do not show clinically significant adverse CV events.

However it is prudent to be cautious till more definitive evidence of safety emerges. Various cardiology and GI society guidelines recommend risk assessment of GI complications and potential risk of PPI co-administration. Routine use of PPIs in all patients on theinopyridines or even dual antiplatelets is not recommended. However PPIs must be given to patients at higher risk of GI complications and these are

- a. Old age > 60 years
- b. History of previous GI bleed on DAPT
- c. Concomitant use of NSAIDS
- d. Concomitant use of anti-coagulants
- e. Patients with H. Pylori infection

In this group of patients risk of adverse GI events outweighs potential risk of decreased anti-thrombotic activity. There is unsubstantiated evidence that Pantoprazole or Rabeprazole may be safer and given short half life of most PPIs and Clopidogrel, dosing them at different time of the day may have un-proven but potential benefit in further reducing adverse drug drug interaction.

## REFERENCES

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