

Proton Pump Inhibitors and Clopidogrel – What is the current status?

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- It is increasingly recognized that anti-platelet agents such as clopidogrel are associated with increased rates of GI bleeding, similar to that seen with cardioprotective doses of ASA.
- When administered in combination with ASA, clopidogrel is particularly potent in increasing the risk for upper GI bleedingⁱ.
- Consequently, proton pump inhibitors (PPIs) are frequently prescribed to reduce bleeding risk.
- Clopidogrel is a pro-drug, which requires cytochrome P-450 metabolism (specifically via the iso-enzyme CYP2C19) to an active form.
- CYP2C19 can be inhibited by PPI's thereby reducing the formation of the active clopidogrel metabolite. Reduced clopidogrel platelet inhibition is associated with an increased risk for cardiovascular events. There appear to be differences between PPIs in their ability to inhibit the CYP2C19 enzyme when assessed *in vitro*ⁱⁱ.
- An example of this drug-drug interaction is seen in the OCLA study where omeprazole significantly decreased the clopidogrel inhibitory effect on platelet functionⁱⁱⁱ.
- Because of this and other reports, the FDA has requested additional studies to further characterize this potential interaction.
- More recent studies have demonstrated that pantoprazole and esomeprazole have no observable effect on the clopidogrel inhibitory effect of platelet function^{iv,v}.
- Several recent studies using administrative data have examined this interaction:
 - A recent Canadian investigation examined provincial hospital discharge data after treatment for myocardial infarction. The investigators found that readmission rates for cardiovascular events within 90 days were statistically higher in those patients taking PPI's in addition to clopidogrel (adjusted odds ratio 1.27, 95% CI 1.03 – 1.57)^{vi}. This interaction was not seen with pantoprazole.
 - A similar American study using Veteran's Affairs data identified an increased risk for cardiovascular events of 1.86 (95% CI, 1.57-2.20) for patients taking PPI and clopidogrel together^{vii}. The investigators did not examine differences among various PPIs
- One factor that may influence future conclusions is the issue of reduced-function CYP2C19 alleles. It has now been shown that carriers of the reduced-function allele have significantly lower levels of the active metabolite of clopidogrel, diminished platelet inhibition, and a higher rate of major adverse cardiovascular events than do non-carriers^{viii}. To date, there are no published reports of the interaction between these alleles and PPI's. The distribution of these reduced function alleles in the general population and in various disease states is unknown.

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- **Summary:**

- There is biologic plausibility for an interaction between PPIs and clopidogrel based on inhibition of the CYP2C19 enzyme.
- There is also *in vitro* evidence that significant differences exist between PPI's and their ability to interfere with clopidogrel metabolism.
- While the best available clinical evidence is weak (observational studies only) there is a consistent signal in the same direction.
- The most recent evidence would suggest that pantoprazole and esomeprazole do not appear to have a significant drug-drug interaction with clopidogrel.
- It should be kept in mind that these conclusions are based on the best current evidence which is somewhat circumstantial.

- **Recommendations:**

- Patients at high risk of GI bleeding (e.g. previous peptic ulcer disease, multiple medical co-morbidities) in the setting of clopidogrel use require some form of prophylaxis as they are at increased risk of mortality from GI bleeding.
- H₂ receptor antagonists are ineffective in this setting and should not be used^{ix}.
- PPI use should be restricted to clopidogrel using subjects who are at significantly increased risk of adverse GI events or who have absolute indications for PPI, and in patients who cannot achieve satisfactory symptom control on alternate acid-reducing strategies.
- Given the current evidence, it is reasonable for clinicians to consider using pantoprazole or esomeprazole or separating the dosing of the PPI and clopidogrel by at least 5 hours.

ⁱ Lanas A, Garcia-Rodriguez LA, Arroyo MP et al. Risk Of Upper Gastrointestinal Ulcer Bleeding Associated With Selective Cyclo-Oxygenase-2 Inhibitors, Traditional Non Steroidal Non Aspirin Anti-Inflammatory Drugs, Aspirin and Combinations. *Gut* 2006; 55:1731-1738.

ⁱⁱ Li X-Q, Andersson TB, Ahlstrom M, Weidolf L. Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. *Drug Metabolism and Disposition* 2004; 32: 821-7.

ⁱⁱⁱ Gilard M et al. Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: a randomized, double-blind OCLA (Omeprazole Clopidogrel Aspirin) Study. *J Am Coll Cardiol* 2008; 51:256-60.

^{iv} Siller-Matula JM et al. Effects of pantoprazole and esomeprazole on platelet inhibition by clopidogrel. *Am Heart J* 2009; 157:148e1-148.e5.

^v Sibbing D, Morath T, et al. Impact of proton pump inhibitors on the antiplatelet effects of clopidogrel. *Thromb Haemost.* 2009 Apr;101(4):714-9.

^{vi} Juurlink, DN, Gomes T, Ko DT, Szmítka PE, Austin PC et al. A Population Based Study Of The Drug Interaction Between PPI's And Clopidogrel. *CMAJ* 2009; 180(7):713-718

^{vii} Ho MP, Maddox TM, Wang L, Fihn SD, Jesse RL et al. Risk of adverse outcomes associated with concomitant use of clopidogrel and proton pump inhibitors following acute coronary syndrome. *JAMA* 2009; 301: 937-44.

^{viii} Mega JL, Close SL, Wiviott SD et al. Cytochrome P-450, Polymorphisms And Response To Clopidogrel. *NEJM* 2009; 360:354-362.

^{ix} Lanas A, García-Rodríguez LA, Arroyo MT et al. Effect of antisecretory drugs and nitrates on the risk of ulcer bleeding associated with nonsteroidal anti-inflammatory drugs, antiplatelet agents, and anticoagulants. *Am J Gastroenterol.* 2007 Mar;102(3):507-15.