

The Ohio State University College of Pharmacy

DRUG INFORMATION RESPONSE FORM

<b>Requested by:</b> CPCO		<b>Name:</b> Dr. Ronni Elhers		<b>Title:</b> Pharmacist	
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<b>Received by:</b> Aaron Bridges		<b>Date Received:</b> 07.16.21		<b>Date Returned:</b> 07.19.21	

**Question:** Is there a preferred PPI for patients who are also taking Plavix? Why can certain PPIs not be used?

How Requested: Written	Type of Request: Drug Information
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<b>Patient Information (N/A)</b> Age: Gender: Diagnosis:	Pertinent Lab Values: Pertinent Medical History: Miscellaneous Information:
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<b>Resources Used</b> <input type="radio"/> Micromedex <input type="radio"/> Lexi-Comp <input type="radio"/> Drug Facts & Comparisons <input type="radio"/> AHFS Drug Information <input type="radio"/> Dipro's Pharmacotherapy <input type="radio"/> Clinical Key <input type="radio"/> Brigg's Drugs in Pregnancy & Lactation <input type="radio"/> Trissel's Handbook on Injectable Drugs	<input type="radio"/> Natural Medicines Comprehensive Database <input type="radio"/> National Guidelines: <input checked="" type="checkbox"/> Pubmed (search terms): PPI, Clopidogrel, Dose-response relationship, pantoprazole <input type="radio"/> International Pharmaceutical Abstracts (search terms): <input type="radio"/> Internet: <input type="radio"/> Other:
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**Time Spent to Answer Question:** 60 minutes

**Response provided by:** Aaron Bridges

**Please provide response below (with citations) or attach response to this sheet:**

CYP450 enzymes, specifically 2C19, are required to metabolize clopidogrel into the active form. PPIs may reduce the concentration of the active metabolite through 2C19 inhibition. All PPIs inhibit CYP to varying degrees. Omeprazole and esomeprazole have been the most scrutinized. The FDA has issued an update to the clopidogrel package insert stating to avoid the concomitant use of clopidogrel with omeprazole and esomeprazole. A randomized crossover study assessed the PK and PD interaction of varying PPIs and clopidogrel in healthy subjects. All PPIs were shown to diminish the peak plasma concentration of clopidogrel. Omeprazole and esomeprazole being the worst offenders followed by lansoprazole and dexlansoprazole. Furthermore, lansoprazole and dexlansoprazole did not significantly reduce the AUC.<sup>3</sup> A meta-analysis was completed in 2019 and found those who were in the clopidogrel + PPI group suffered a statistically significant increase in MACE, MI recurrence, stent thrombosis and stroke. However, there was no statistically significant difference between all cause death, cardiovascular death and major bleeding events.<sup>2</sup> Another similar result was seen in a meta-analysis among PCI-treated patients. Clopidogrel + PPIs had no statistically significant impact on all-cause mortality, cardiovascular death and stent thrombosis. However, the study group had a statistically significant higher risk of recurrent MI, stroke and MACE.<sup>1</sup>

Based on the available literature, all PPIs interfere with clopidogrel's metabolism to a varying degree. It is important to note that while PPIs interfere with clopidogrel's activation, there has not been any evidence that certain PPIs can cause a statistically significant increase in mortality. PPIs to use with great caution would be omeprazole and esomeprazole due to their greater affinity of inhibition. Dexlansoprazole, lansoprazole and pantoprazole would be the preferred agent because these three have been shown to affect clopidogrel's metabolism the least.

1. Serbin MA, Guzauskas GF, Veenstra DL. Clopidogrel-Proton Pump Inhibitor Drug-Drug Interaction and Risk of Adverse Clinical Outcomes Among PCI-Treated ACS Patients: A Meta-analysis. J Manag Care Spec Pharm. 2016;22(8):939-947. doi:10.18553/jmcp.2016.22.8.939.

2. Pang J, Wu Q, Zhang Z, et al. Efficacy and safety of clopidogrel only vs. clopidogrel added proton pump inhibitors in the treatment of patients with coronary heart disease after percutaneous coronary intervention: A systematic review and meta-analysis. *Int J Cardiol Heart Vasc.* 2019;23:100317. Published 2019 Apr 2. doi:10.1016/j.ijcha.2018.12.016.
3. Frelinger AL 3rd, Lee RD, Mulford DJ, et al. A randomized, 2-period, crossover design study to assess the effects of dexlansoprazole, lansoprazole, esomeprazole, and omeprazole on the steady-state pharmacokinetics and pharmacodynamics of clopidogrel in healthy volunteers [published correction appears in *J Am Coll Cardiol.* 2012 Aug 7;60(6):566-7]. *J Am Coll Cardiol.* 2012;59(14):1304-1311. doi:10.1016/j.jacc.2011.12.024.
4. Bundhun PK, Teeluck AR, Bhurtu A, Huang WQ. Is the concomitant use of clopidogrel and Proton Pump Inhibitors still associated with increased adverse cardiovascular outcomes following coronary angioplasty?: a systematic review and meta-analysis of recently published studies (2012 - 2016). *BMC Cardiovasc Disord.* 2017;17(1):3. Published 2017 Jan 5. doi:10.1186/s12872-016-0453-6