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Clopidogrel and PPIs: A Final Answer at Last?

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[Authors and Disclosures](#)

Hello. I'm Dr. David Johnson, Professor of Medicine and Chief of Gastroenterology at Eastern Virginia Medical School in Norfolk, Virginia. The use of clopidogrel combined with proton pump inhibitors (PPI) has been the subject of an immeasurably controversial area of debate over the last 2 years. We've seen this to the point of product labeling changes by the makers of clopidogrel, and we've seen this by advisories at a number of major organizations, including the US Food and Drug Administration (FDA), suggesting that the two should not be combined, specifically because of potential harm that resulted in increased cardiovascular poor outcomes.

I'm happy to report to you that a consensus document^[1] has just been published in the December issues of the publications from the American College of Cardiology, the American College of Gastroenterology, and the American Heart Association. This consensus document was put together by experts. It has been endorsed by the respective boards at each of those organizations. What is the final answer? What was done in this document, which was not funded by Pharma and was not subject to any outside potential interference, is the writing committee had sole proprietary writing and the data were kept secure within the writing group.

What the writing group determined in a very extensive and exhaustive review of the literature was the following. There was pharmacologic suggestion of potential interactions between particularly omeprazole and clopidogrel, which would decrease some of the effectiveness of clopidogrel. But it did not seem to translate to cardiovascular harm, and the studies that were suggesting cardiovascular harm were all observational and retrospective studies, with very nominal odds ratios, all of which were less than 2. The only prospective trial, which was just published in November in *The New England Journal of Medicine*, was the COGENT trial.^[2] It looked at a prospective evaluation of omeprazole plus clopidogrel and showed no demonstrable cardiovascular harm. In fact, it showed a demonstrable gastrointestinal (GI) protective benefit in the patients who were prescribed with the activation omeprazole plus clopidogrel.

The consensus document determined that, at present, there's no evidence to suggest a significant cardiovascular harm, and there may be potential GI benefit, as suggested by the only randomized prospective trial we have. The group was struck at least by the potential effect of the slow metabolizers or slow bio-transformer phenotype for clopidogrel, enough to offer a caveat that this area has not been well studied and deserves further potential observation and evaluation in patients who were given PPIs with clopidogrel. In that same arena is a study^[3] that was also just published in *The New England Journal of Medicine*, which suggested that the phenotype didn't seem to make a difference, as far as the evaluation of outcomes from a cardiovascular standpoint, in patients receiving clopidogrel.

I'm not going to talk to you about outcomes with clopidogrel alone. I'm a gastroenterologist, and I'll leave that to the cardiovascular experts. Nonetheless, the point here was that the slow bio transfer and phenotype was an area that was understudied, at least in the cointeraction with PPIs, so the writing group at least left that as a point of future direction that needs further information. They did look at the effect of adding an H2 blocker instead of a PPI and suggested that first we know that between H2 blockers and PPIs, as a result of prophylaxis in patients on nonsteroidal agents, PPIs are better. And the H2 blockers are better than placebo, so perhaps in patients at low risk, H2 blockers could be substituted. But again, in patients who need the PPIs -- for example, patients with moderate to severe reflux disease or patients deemed at high risk for GI outcomes -- clearly the PPIs are still the way to go.

The issue of split dose of the PPI, potentially changing the half-life exposure from giving the PPI in the morning and the clopidogrel in the evening, was still felt not to be recommended as needed. There are still studies that need to be done here, but the only study^[4] that looked at split dosing suggested that there was a potential diminution in that cofactor interference if you split the dose. In the COGENT trial, they actually gave the trial medications at the same time. So again, the writing group left that up in the air, as far as the necessity. Certainly, from the prospective randomized trial, that was not suggested, at least in the current data.

Where are we at present? Independent of this writing, the FDA looked at the COGENT trial and looked at some of the other more recent data. On October 27, 2010, they revised their recommendation on PPI use in patients on clopidogrel, and they restricted the caveat of concern for potential adverse events only to omeprazole.^[5] At present day, even the FDA suggests that the coadministration is not to be avoided in patients deemed at risk for potential GI harm, but the restriction, or suggested restriction, is only for patients on omeprazole.

The consensus group did not come down on the side that just omeprazole should be avoided and felt that there was no significant cardiovascular risk identified for any of the PPIs when coprescribed with clopidogrel. Where are we? Do we have a final answer? I think we do, as close as we can to having one at present. Based on the evidence, I don't know that there's going to be any change emerging in the near future...in the recommendations that the consensus group has just put forward.

In patients who you feel are at risk for GI injury, I think the present data, based on the consensus recommendations from the 3 organizations and endorsed by their boards, put us back on the appropriate tact of: if they're defined to be at risk, the risk/benefit ratio should be determined, and if the patients are determined to be at significant GI risk, a PPI seems most reasonable.

Final answer: I think we can recommend that if patients are defined at GI risk, moderate-severe risk, they should be coprescribed with a PPI, and, we hope, that will put the patient back on the safest pathway that we have at present day. I don't think there will be any new noise in the future, so hopefully this will put some of this controversy to rest, and we can all be satisfied that, at least now, we have some sensible analysis of these data. I'm Dr. David Johnson, and I hope this serves you well in your patient interaction, specifically when this question comes up. I look forward to chatting with you again in the near future. Thanks for listening.