CORRESPONDENCE

Clopidogrel with or without Omeprazole in Coronary Disease

TO THE EDITOR: The conduct of the Clopidogrel and the Optimization of Gastrointestinal Events Trial (COGENT) by Bhatt and colleagues (Nov. 11 issue)[1] is timely. Previous nonrandomized studies have suggested an association between the use of proton-pump inhibitors (PPIs) and adverse cardiovascular outcomes in patients receiving clopidogrel.[2,3] These studies have led to concerns that PPIs are blunting the efficacy of clopidogrel.

COGENT showed significant reductions in overt gastrointestinal hemorrhages with a combination of omeprazole and clopidogrel compared with clopidogrel alone, with a number needed to treat of 98. Cardiovascular events were not more common with omeprazole.

We would like to put the COGENT findings into an economic context. In the United Kingdom, the cost of PPIs is low. A 6-month course of generic omeprazole, at a dose of 20 mg once daily, costs approximately £12.[4] The cost of preventing one overt gastrointestinal hemorrhage would therefore be approximately £1,180, which is likely to be lower than the cost of treating such an event.

These data suggest that the omission of PPI coprescribing in patients receiving dual antiplatelet therapy is a strategy that is likely to both increase patients' morbidity and mortality and lead to increased costs to the health care system.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: In their discussion of COGENT, Bhatt and colleagues note that the intervention (CGT-2168) differs from commercially available omeprazole. In fact, as its patent application indicates, the product was purposefully formulated to retard the dissolution and absorption of omeprazole, thereby averting any interaction with clopidogrel.[1] It is therefore not surprising that the study found no increased risk of cardiovascular events in patients receiving this unique formulation of clopidogrel and omeprazole. Clinicians should not assume that these findings can be safely generalized to other omeprazole products in widespread clinical use when they are taken with clopidogrel.

THIS WEEK'S LETTERS

COGENT nicely shows the gastrointestinal benefits of using a PPI with clopidogrel in appropriately selected patients. Pantoprazole is a safer choice than omeprazole for this purpose, because it does not interfere with the antiplatelet effect of clopidogrel.[2-4] Notwithstanding uncertainty about the clinical relevance of ex vivo platelet-aggregation studies, there is no compelling reason to use omeprazole rather than pantoprazole in patients receiving clopidogrel.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Although we did not perform a formal cost-effectiveness analysis, we agree with Sadek and Ford that on the basis of COGENT, prophylactic therapy with a generic PPI is likely to be cost-effective in patients receiving dual antiplatelet therapy.

Juurlink is correct in stating that the formulation of omeprazole studied in COGENT was not the same as that used in current clinical practice. Therefore, we cannot be certain that our results regarding cardiovascular safety can be extrapolated to other formulations or higher doses of omeprazole. However, the significant reduction in gastrointestinal events suggests that adequate absorption of omeprazole occurred, and the clopidogrel–omeprazole pharmacodynamic interaction has been reported even when the two medications are given at widely separated times. The choice of PPI is uncertain on the basis of current evidence. A pharmacodynamic interaction has not been clearly documented with PPIs other than omeprazole, but observational studies showing an association between PPIs and cardiovascular events in clopidogrel users have implicated all PPIs evaluated.[1,2]

Platelet-function tests have shown that use of PPIs decreases the platelet inhibition caused by clopidogrel by approximately 10%. Recent data show that improving residual platelet reactivity, from 60% to 40%, did not improve clinical outcomes.[3] Thus, relatively small changes in platelet function may not be enough to translate into clinical-event differences. Furthermore, new research suggests that paraoxonase-1 may be the major enzyme determining clopidogrel efficacy, more so than *CYP2C19*.[4]

Although COGENT did not resolve all the complex issues with respect to improving the gastrointestinal safety of antithrombotic medications, it did show that prophylactic PPIs given to a general population receiving dual antiplatelet therapy could reduce clinical gastrointestinal bleeding. Furthermore, there was no evidence of excess ischemic events. Thus, randomized trial results for omeprazole in clopidogrel users reveal a small change in platelet function, no difference in cardiovascular events, and a 66% reduction in gastrointestinal events (with an 87% reduction in overt upper gastrointestinal bleeding), supporting current American College of Cardiology–American Heart Association–American College of Gastroenterology consensus recommendations to provide PPI therapy to patients with cardiovascular disease who are at increased gastrointestinal risk (e.g., those receiving dual antiplatelet therapy). Future research will need to determine the optimal gastroprotective strategy in patients with cardiovascular disease who are receiving increasingly potent antithrombotic agents.

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Since publication of their article, Dr. Bhatt reports being an unpaid research collaborator with Takeda. No further potential conflict of interest relevant to this letter was reported.

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Outcomes of Kidney Transplantation in HIV-Infected Recipients

TO THE EDITOR: Stock and colleagues (Nov. 18 issue)[1] describe a successful trial exploring the feasibility of kidney transplantation in patients infected with the human immunodeficiency virus (HIV). Initially, there was great uncertainty regarding the wisdom of immunosuppression in such patients. Many physicians treating patients with HIV and advanced chronic kidney disease initially favored recruitment of only patients with an overall poor prognosis for studies on the feasibility of kidney transplantation. Stock et al. focused on patients with optimal immunologic factors and good HIV control, both to reduce individual risk and to increase the likelihood of an interpretable study result. That approach required courage, and the authors are to be commended for having pursued it. However, it is important to recognize that those stringent eligibility criteria also limit the generalizability of the study results. Although patient survival was only slightly lower than that reported based on data from the U.S. Scientific Registry of Transplant Recipients for the most directly relevant 35- to 49-year age bracket,[2] the same may not be true among patients with lower CD4 counts or poorer HIV control. Further, the higher-than-expected rejection rate in this trial will probably prompt intensification of immunosuppressive regimens.

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Stock et al. report on a disturbingly higher rejection rate among HIV-infected kidney-transplant recipients than among the general population of patients who have undergone kidney transplantation in the United States. They suggest this outcome is partly caused by the profound pharmacokinetic interaction between immunosuppressants and protease inhibitors.

Dosing of tacrolimus in transplant recipients is ideally based on a 12-hour area under the curve (AUC). In clinical practice, trough levels are usually monitored, assuming a correlation with AUCs.[1] However, the pharmacokinetic curve of tacrolimus in HIV patients receiving protease inhibitors does not show the normal peak-and-trough pattern but rather resembles a flat line with a half-life of up to 20 days as a result of extremely strong inhibition of CYP3A.[2] Therefore, and based on our findings, trough levels of tacrolimus in patients receiving protease inhibitors should be higher (17.5 ng per milliliter at 1 month and 10 ng per milliliter at 1 year after transplantation) than the trough levels reported by Stock et al. (9.1 ng per milliliter and 7.2 ng per milliliter, respectively) to achieve AUCs that are equal to those in patients who are not receiving protease inhibitors.[3]

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