



**EDUCATIONAL OBJECTIVE:** Readers will appropriately prescribe proton pump inhibitors to patients receiving dual antiplatelet therapy who are at high risk of gastrointestinal bleeding

**JEREMIAH P. DEPTA, MD**

Department of Internal Medicine,  
Medicine Institute, Cleveland Clinic

**DEEPAK L. BHATT, MD, MPH\***

Chief of Cardiology, VA Boston Healthcare System;  
Director, Integrated Interventional Cardiovascular  
Program, Brigham and Women's Hospital; Associate  
Professor of Medicine, Harvard Medical School;  
Senior Investigator, TIMI Study Group; Boston, MA

# Omeprazole and clopidogrel: Should clinicians be worried?

## ABSTRACT

The US Food and Drug Administration has issued a warning that omeprazole (Prilosec) reduces the antiplatelet activity of clopidogrel (Plavix) by about 50%. However, the warning is based largely on ex vivo data. Preliminary results from a randomized clinical trial revealed no effect on cardiovascular outcomes when omeprazole was given with clopidogrel. We recommend that physicians continue to prescribe a proton pump inhibitor for patients receiving dual antiplatelet therapy who are at risk of gastrointestinal bleeding or have an indication for use of a proton pump inhibitor.

## KEY POINTS

Proton pump inhibitors such as omeprazole reduce the risk of gastrointestinal bleeding in patients on antiplatelet therapy after an acute coronary syndrome or percutaneous coronary intervention.

Omeprazole diminishes the antiplatelet activity of clopidogrel by inhibiting the CYP2C19 isoenzyme.

Although the interaction between omeprazole and clopidogrel can be demonstrated on platelet function studies, the clinical significance of this interaction is not clear.

\*Dr. Bhatt has disclosed that he has received institutional research grants from Astra Zeneca, Bristol-Myers Squibb, Eisai, Ethicon, HeartScape, Sanofi Aventis, and The Medicines Company.

doi:10.3949/ccjm.77a.09173

**M**ANY CLINICIANS are concerned about a possible interaction between the proton pump inhibitor omeprazole (Prilosec) and the antiplatelet drug clopidogrel (Plavix), which is often given to patients as part of dual antiplatelet therapy after an acute coronary syndrome or a percutaneous coronary intervention. Indeed, the US Food and Drug Administration (FDA) has warned that omeprazole reduces the antiplatelet effect of clopidogrel.

Although we should not take such warnings lightly, we also should not be alarmed. The data on which the FDA warning was based came mostly from laboratory assays of platelet function. Preliminary results from a randomized, controlled clinical trial with hard end points show that, for the time being, we should not change the way we manage patients.

## PROTON PUMP INHIBITORS DECREASE GASTROINTESTINAL BLEEDING

Dual antiplatelet therapy with aspirin and clopidogrel decreases the risk of major adverse cardiac events after an acute coronary syndrome or a percutaneous coronary intervention compared with aspirin alone.<sup>1</sup> However, it also increases the risk of gastrointestinal bleeding. A recent analysis determined that dual antiplatelet therapy was the most significant risk factor associated with serious or fatal gastrointestinal bleeding in high-risk survivors of myocardial infarction.<sup>2</sup>

Given the risks of significant morbidity and death in patients on dual antiplatelet therapy who develop gastrointestinal bleeding, an expert consensus panel recommended the use of proton pump inhibitors in patients on dual

antiplatelet therapy who have risk factors for gastrointestinal bleeding.<sup>3</sup> Accordingly, these drugs are commonly used for gastrointestinal protection in patients requiring dual antiplatelet therapy.

## A POSSIBLE CYP450 INTERACTION

Clopidogrel is metabolized from a prodrug to its active metabolite by the cytochrome P450 (CYP450) system. Proton pump inhibitors also are metabolized by the CYP450 system.<sup>4</sup> Proton pump inhibitors are thought to diminish the activity of clopidogrel via inhibition of the CYP2C19 isoenzyme. However, the clinical significance of this inhibition is not clear. Different drugs of this class inhibit the CYP450 system to varying degrees.

The potential interaction between proton pump inhibitors and clopidogrel is worrisome for many physicians, since adverse cardiovascular outcomes are more common in patients in whom the antiplatelet response to clopidogrel is impaired.<sup>1</sup> This interaction led to the publication of numerous articles, and prompted the FDA to carefully analyze the potential clinical implications.

In several randomized trials, omeprazole diminished the response to clopidogrel (measured via platelet function assays).<sup>5,6</sup> It is unclear if this is a class effect, as proton pump inhibitors other than omeprazole have not consistently been shown to have this effect.<sup>6,7</sup> Observational studies of the effect of co-administration of a proton pump inhibitor and clopidogrel on cardiovascular outcomes following acute coronary syndromes have had conflicting findings.<sup>8-11</sup>

## THE FDA ISSUES AN ADVISORY

Given the reports of an impaired platelet response to clopidogrel with omeprazole, the FDA asked the manufacturer for data on this potential interaction. The data showed diminished platelet inhibition when clopidogrel was co-administered with omeprazole or when the two were taken 12 hours apart.

On November 17, 2009, the FDA issued a patient advisory and updated the patient safety information on the package insert for clopidogrel about this drug interaction.<sup>12</sup> Specifically, the FDA warns that omeprazole re-

duces the antiplatelet effect of clopidogrel by about 50%. The FDA warning sparked debate in the medical community, as the decision was based in part on ex vivo data.

## POST HOC ANALYSES FROM RANDOMIZED CONTROLLED TRIALS

Several post hoc analyses of large randomized clinical trials have studied the potential interaction between proton pump inhibitors and clopidogrel.

In the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, clopidogrel reduced the incidence of death, myocardial infarction, or stroke to a similar extent regardless of baseline use of a proton pump inhibitor.<sup>13</sup>

In patients undergoing percutaneous coronary intervention, the Prasugrel in Comparison to Clopidogrel for Inhibition of Platelet Activation and Aggregation—Thrombolysis in Myocardial Infarction 44 (PRINCIPLE-TIMI 44) trial found that those taking a proton pump inhibitor had significantly less platelet inhibition with clopidogrel compared with those not on one.<sup>14</sup> However, patients taking prasugrel (Effient) and a proton pump inhibitor only had a slight trend towards diminished platelet inhibition.<sup>14</sup>

The Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel—Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) found that proton pump inhibitors did not influence the long-term outcome of cardiovascular death, myocardial infarction, or stroke for patients on clopidogrel or prasugrel after an acute coronary syndrome.<sup>14</sup> A subanalysis did not reveal any differences between omeprazole or other drugs of this class as to an effect on the primary outcome.

Though informative, the results of these post hoc analyses need to be validated with data from randomized clinical trials.

## 'COGENT' TRIAL HALTED EARLY, BUT PRELIMINARY RESULTS AVAILABLE

The Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) trial was the first randomized clinical study of the effect of the interaction between clopidogrel

and omeprazole on cardiovascular and gastrointestinal outcomes.<sup>15</sup> In a double-blind fashion, patients with acute coronary syndromes or undergoing percutaneous coronary interventions were randomized to receive a fixed-dose combination pill containing either clopidogrel and delayed-release omeprazole or clopidogrel alone. All patients also received aspirin.

Unfortunately, the trial was stopped early because the sponsor declared bankruptcy. However, preliminary results revealed no significant difference in cardiovascular outcomes for patients on clopidogrel and omeprazole compared with clopidogrel alone.<sup>15</sup> Furthermore, adverse gastrointestinal events were significantly fewer in patients on clopidogrel and omeprazole.

Thus, omeprazole appears to be safe and may offer gastrointestinal protection to patients on dual antiplatelet therapy, though we need to await publication of the full results.

### ■ 'SPICE' TRIAL TO EVALUATE POSSIBLE MECHANISMS OF INTERACTION

The Evaluation of the Influence of Statins and Proton Pump Inhibitors on Clopidogrel Antiplatelet Effects (SPICE) trial is a mechanistic study that will evaluate platelet function and genetic polymorphisms in patients on clopidogrel and aspirin after a percutaneous coronary intervention. They will be randomized to statin therapy plus different proton pump inhibitors.<sup>16</sup> Prior concerns about an ex vivo interaction between clopidogrel and certain statins were not validated by clinical data.<sup>17</sup>

### ■ OUR RECOMMENDATIONS

Based on the current evidence, patients on aspirin and clopidogrel who have an indication

for a proton pump inhibitor or who are at risk of gastrointestinal bleeding can continue or start taking a proton pump inhibitor, including omeprazole.

Switching to another proton pump inhibitor is not currently supported by any randomized clinical trial, nor is changing to a histamine H<sub>2</sub>-receptor antagonist. The effect of proton pump inhibitors other than omeprazole on clopidogrel is unclear, and it is not known if the interaction with clopidogrel is a class effect or specific to certain drugs of this class.<sup>18</sup> On the other hand, we still have no compelling evidence of any major clinical interaction between alternative proton pump inhibitors and clopidogrel.<sup>18</sup>

Also, separating the dosing times of clopidogrel and omeprazole by 12 hours is not supported by any randomized clinical trial, and runs contrary to at least some ex vivo data.

It is important that all physicians assess the need for a proton pump inhibitor in their patients, as overuse of these drugs has been documented in certain settings.<sup>19</sup>

Clopidogrel and omeprazole share a common metabolic link via CYP2C19. Omeprazole, along with some other proton pump inhibitors, interacts with clopidogrel at the level of the CYP450 system. Platelet function studies show that platelet inhibition by clopidogrel is impaired, though the astute clinician should be aware of the wide variability associated with platelet function assays and clopidogrel.<sup>1,20</sup> However, what may appear to be an interaction at the enzymatic level does not necessarily translate into worse clinical outcomes. Additionally, reliance on nonrandomized studies rather than on randomized clinical trials can be misleading.

**COGENT preliminary results: omeprazole appears safe and may protect against bleeding in those on dual antiplatelet therapy**

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**ADDRESS:** Deepak L. Bhatt, MD, MPH, VA Boston Healthcare System, 1400 VFW Parkway, Boston, MA 02132; e-mail [dlb-hattmd@post.harvard.edu](mailto:dlb-hattmd@post.harvard.edu).