RESEARCH

# Analysis of Gastrointestinal Prophylaxis in Patients Receiving Dual Antiplatelet Therapy with Aspirin and Clopidogrel

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## ABSTRACT

BACKGROUND: Dual antiplatelet therapy (DAPT) has been found to reduce the risk of cardiac death, myocardial infarction, stroke, and stent thrombosis following acute coronary syndrome and percutaneous coronary intervention. However, this therapy has also been shown to increase the risk of gastrointestinal (GI) bleeding as high as 2-fold, especially in patients with multiple risk factors. Proton pump inhibitor (PPI) therapy decreases this risk. The current consensus document on reducing GI risks associated with antiplatelet agents no longer recommends PPI therapy for all patients receiving aspirin (ASA) and clopidogrel. The consensus recommendation reserves PPI therapy for patients receiving DAPT with a history of upper GI bleeding or prespecified risk factors for GI bleeding.

OBJECTIVES: To (a) describe the use of GI prophylaxis in patients on DAPT with ASA and clopidogrel and (b) assess the incidence of adverse outcomes that occurred during readmissions within 6 months of the index hospitalization.

METHODS: A retrospective chart review of patients receiving DAPT between February 1, 2011, and October 15, 2011, was performed to assess the appropriateness of GI prophylaxis based on the current consensus document. Therapy was defined as appropriate if an indication for prophylaxis was present and PPI therapy was prescribed, or if no indication was present and no GI prophylaxis was given. Inappropriate prophylaxis was defined as no indication for GI prophylaxis yet therapy received, or prophylaxis indicated but incorrect prophylaxis prescribed. Incorrect prophylaxis included no prophylaxis, histamine H2 blocker therapy, antacid, or combination therapy. During subsequent hospitalizations in the 6-month period following discharge from the index admission, patients were assessed for the development of vascular-, GI-, and PPI-related adverse events.

RESULTS: 250 patients receiving DAPT during the study period were evaluated. Gastrointestinal prophylaxis was appropriate in 48% (119/250) of patients. Of the remaining patients, 56.4% (74/131) met guideline criteria for GI prophylaxis but did not receive a PPI at discharge, whereas 43.5% (57/131) of patients received GI prophylaxis when not indicated. Thirty-three adverse events were identified during readmissions, with the most common type being vascular followed by GI and PPI adverse events, respectively.

CONCLUSION: More than half of the patients did not receive GI prophylaxis appropriately. The most common reason for nonadherence to the consensus document was no prophylaxis when indicated. Vascular events could not be directly attributed to PPI use, and GI events occurred despite prophylaxis. Overall, there was a low incidence of adverse events related to the use of PPI therapy.

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### What is already known about this subject

- Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel reduces the risk of cardiac death, myocardial infarction, stroke, and stent thrombosis. As a result, DAPT is recommended following acute coronary syndrome and percutaneous coronary intervention.
- DAPT has been associated with an increased risk of gastrointestinal (GI) bleeding, as high as 2-fold, especially in patients with multiple risk factors. Proton pump inhibitor (PPI) use has been shown to reduce GI bleeding and is recommended in a current consensus guideline for patients with a history of upper GI bleeding or risk factors for GI bleeding (history of any type of GI bleed, peptic ulcer disease, advanced age, concurrent anticoagulants, nonsteroidal anti-inflammatory agents, steroids, and *Helicobacter pylori* infection).
- Although PPI agents are commonly prescribed and considered to be generally safe, adverse outcomes have been reported, including an increase in the rate of *Clostridium difficile* infections, fractures, acute interstitial nephritis, hypomagnesemia, and pneumonia. In addition, a potential drug interaction between PPI therapy and clopidogrel affecting clopidogrel metabolism to its active metabolite could place patients at risk for vascular events.

### What this study adds

- This study evaluates the use of GI prophylaxis in patients receiving DAPT to assess compliance with the current consensus document as well as any potential adverse event from PPI use.
- In a sample of 250 patients, the use of GI prophylaxis was appropriate in only 48% of patients. The most common reason for inappropriate GI prophylaxis was guideline criteria for GI prophylaxis met but did not receive a PPI at discharge (56.4%; 74/131).
- During the 6-month follow-up period, 102 of the 250 patients were rehospitalized, which accounted for a total of 234 readmissions. Vascular events occurred most commonly at a rate of 58%, followed by GI events (24%) and PPI-related adverse events (18%).
- The use of GI prophylaxis is important in this population to reduce the risk of GI bleeding events, but potential adverse events associated with PPI therapy must be balanced to ensure no additional harm to the patient.

Dual antiplatelet therapy (DAPT) with aspirin and clopidogrel is commonly used in patients with cardiovascular disease to reduce vascular events. In acute coronary syndrome (ACS), DAPT reduces the risk of cardiac death, myocardial infarction, and stroke.[1,2] It is also indicated following percutaneous coronary intervention (PCI) to reduce the risk of stent thrombosis.[3] However, DAPT has also been shown to increase the risk of gastrointestinal (GI) bleeding, especially in patients with multiple risk factors. In a recent controlled trial, patients on DAPT had a 2-fold higher risk of GI bleed than those on aspirin alone.[4] Proton pump inhibitor (PPI) therapy has been shown to decrease this risk.[5]

In 2008, the American College of Cardiology (ACC) and American Heart Association (AHA) partnered with the American College of Gastroenterology (ACG) to develop a consensus document to reduce the incidence of GI events in patients receiving antiplatelet therapy and nonsteroidal anti-inflammatory agents (NSAIDs).[6] This consensus document recommended gastroprotection with a PPI for all patients receiving DAPT. However, PPI use has been associated with multiple adverse outcomes, including an increased incidence of *Clostridium difficile* infection (CDI),[7,8,9] fractures,[10,11] acute interstitial nephritis,[12] hypomagnesemia,[13] and pneumonia.[14]

In addition to adverse effects from PPI therapy, there is the potential for a drug interaction with clopidogrel. Clopidogrel is a prodrug, which requires a 2-step conversion to its active form.[15] The cytochrome P-450 *CYP2C19* enzyme is involved in both steps and is inhibited by PPIs as a class.[16] Reports of a possible drug-drug interaction between PPIs and clopidogrel began to emerge in 2008. The OCLA (Omeprazole CLopidogrel Aspirin) study found that the combination of omeprazole and clopidogrel resulted in decreased platelet inhibition.[17] Conversely, a similarly designed study found no effect with esomeprazole or pantoprazole.[18]

Population-based, retrospective trials have been published showing an increased cardiac event rate in ACS patients taking concomitant clopidogrel and PPIs.[19,20] These trials found an increase in the rate of re-infarction and the composite of all-cause mortality or rehospitalization for ACS. There are also a number of retrospective studies showing no increase in cardiovascular risk from this combination.[21,22] Interestingly, a large cohort study using Danish registry data found a similar risk of cardiovascular events in patients taking PPI therapy regardless of clopidogrel use.[23]

Two prospective studies, COGENT and a subgroup analysis of the PRINCIPLE TIMI 44/TRITON-TIMI 38 studies, have been published refuting this drug interaction as clinically meaningful.[24,25] Furthermore, a cohort study published in 2011 concluded that DAPT in combination with PPI after ACS was not associated with risk of ACS-related rehospitalization.[26] In the drug interaction section of the current package labeling for clopidogrel, which was most recently updated in late 2011, both omeprazole and esomeprazole are listed as drug interactions.[27] The labeling suggests using an alternative acid-reducing agent with less *CYP2C19* activity, such as lansoprazole, dexlansoprazole, or pantoprazole.

**TABLE 1** Consensus Document Criteria for PPI Use in Patients Receiving DAPT[28]

| |
|---|
| History of upper GI bleeding |
| Other GI bleeding |
| Advanced age |
| Concurrent use of anticoagulants or NSAIDs |
| Chronic steroid therapy |
| *Helicobacter pylori* infection/peptic ulcer disease |

*DAPT = dual antiplatelet therapy; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor.*

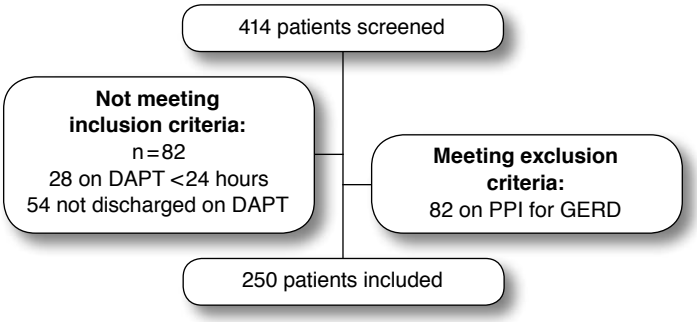
In November 2010, the ACCF/ACG/AHA published an update to the 2008 document on reducing the incidence of GI risks with antiplatelet therapy.[28] This document no longer recommends that PPI therapy be prescribed for all patients receiving aspirin and clopidogrel but reserves this therapy for patients with a history of upper GI bleeding or multiple risk factors for GI bleeding (history of any type of GI bleed, peptic ulcer disease, advanced age, concurrent anticoagulants, NSAIDs, steroids, and *Helicobacter pylori* infection; Table 1). Patients without high risk factors for GI bleeding should not receive a PPI or histamine H2 blocker, as there is no likely benefit from this therapy. Given all of the published literature surrounding a potential drug interaction between clopidogrel and PPIs, the consensus document acknowledges that although there is evidence that PPIs may impair the conversion of clopidogrel to its active form, there is no evidence that this translates into an effect on clinical outcomes. Clinicians are reminded to weigh the risks and benefits of GI prophylaxis before initiating therapy.

Although the update to the consensus document better defines the patient population that should receive a PPI, the conflicting evidence regarding the drug interaction between clopidogrel and PPIs has led to confusion with prescribers. In addition, some prescribers may not be aware that the consensus document was updated. The purpose of this study is to assess the use of GI prophylaxis in patients taking DAPT with aspirin and clopidogrel and any adverse events from the use of PPIs.

## Methods

A retrospective chart review of patients receiving DAPT with an index hospitalization between February 1, 2011, and October 15, 2011, was performed to assess the appropriateness of GI

**FIGURE 1** Patient Selection Flowchart for Identified DAPT Patients




*DAPT = dual antiplatelet therapy; GERD = gastroesophageal reflux disease; PPI = proton pump inhibitor.*

**TABLE 2** Risk Factors Meeting Criteria for GI Prophylaxis with a PPI

| Risk Factor | % | (n) |
|---|---|---|
| Advanced age | 26.8 | (67) |
| Concurrent anticoagulation | 8.0 | (20) |
| NSAID use | 5.2 | (13) |
| History of GI bleed | 3.6 | (9) |
| PUD/*Helicobacter pylori* | 3.6 | (9) |
| Chronic steroid use | 2.4 | (6) |

*GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PPI = proton pump inhibitor; PUD = peptic ulcer disease.*

prophylaxis based on the 2010 consensus document update. The study was conducted at Methodist University Hospital, a 661-bed academic medical center in Memphis, Tennessee, and was approved by the University of Tennessee Institutional Review Board. Patients were identified through a computerized report of all patients receiving concomitant aspirin and clopidogrel during the study period. Patients were included if they received concomitant aspirin and clopidogrel (DAPT) for more than 24 hours and were discharged on this regimen. Exclusion criteria included patients less than 18 years old or PPI use for a U.S. Food and Drug Administration (FDA)-approved indication, such as gastroesophageal reflux disease (GERD) or Zollinger-Ellison syndrome.

Each patient was assessed for clinical characteristics that increase the risk of GI bleeding as outlined in the consensus document. Advanced age and chronic steroid therapy is not defined, so we defined advanced age as greater than or equal to 75 years and chronic steroid therapy as steroid use for greater than or equal to 14 days. For this study, appropriate prophylaxis was defined as the following: indicated for GI prophylaxis and received PPI monotherapy or no indication and did not receive GI prophylaxis. Inappropriate prophylaxis was defined as no indication yet received GI prophylaxis or indicated but received incorrect prophylaxis. Incorrect prophylaxis was defined as no prophylaxis, H2 blocker, antacid, or combination therapy.

During subsequent hospitalizations in the 6-month period following discharge from the index admission, patients were assessed for the development of vascular, GI, or PPI adverse events. Vascular events were defined as myocardial infarction (MI), in-stent thrombosis, revascularization, or stroke documented by a physician in a progress note. ACS, unstable angina, non-ST segment elevation MI, and ST segment elevation MI were all categorized as myocardial infarction. Gastrointestinal adverse events included GI bleed or newly diagnosed ulcer or perforation by upper endoscopy (EGD) or colonoscopy. PPI adverse outcomes were defined as hypomagnesemia (magnesium level less than or equal to 1.5 millegrams per deciliter [mg/dl]), CDI, new fracture, acute interstitial nephritis, or pneumonia. An additional analysis was performed to evaluate the rate of vascular and GI events with or without PPI use.

## Results

Patients screened for enrollment totaled 414. Of these, 28 were on DAPT for less than 24 hours, and 54 were not discharged on DAPT, thus, not meeting criteria for inclusion. Eighty-two patients were receiving a PPI for GERD and were excluded. Patients included for evaluation totaled 250 (Figure 1).

The average patient was aged 68 years (± 12 years). Fifty percent of patients were male, and 67% were African American. The indications for GI prophylaxis based on patient risk factors are reported in Table 2. Fifty-nine percent (147/250) of patients had no risk factors, while 8% (21/250) of patients had 2 or more risk factors present. The most common risk factor was advanced age (26.8%), followed by concurrent anticoagulation (8%) and NSAID use (5.2%).

Gastrointestinal prophylaxis was considered appropriate in 48% (119/250) of patients (Table 3). Of the remaining patients who received inappropriate prophylaxis, 56.4% (74/131) of patients met guideline criteria for prophylaxis but did not receive a PPI at discharge, whereas 43.5% (57/131) of patients had no indication yet were prescribed GI prophylaxis at discharge. In the group who met criteria for prophylaxis and should have received a PPI, 68.9% (51/74) received no prophylaxis, and 25.7% (19/74) received an H2 blocker. The remaining patients were prescribed a PPI combination regimen (2.7%; 2/74), a combination regimen not including a PPI (1.4%; 1/74), or a scheduled antacid (1.4%; 1/74). For patients who did not have an indication for GI prophylaxis yet received prophylaxis, the most commonly used agent was a PPI (60%; 34/57), followed by an H2 blocker (35%; 20/57).

**TABLE 3** GI Prophylaxis: Appropriate and Inappropriate

| | % | (n) |
|---|---|---|
| **Appropriate GI prophylaxis** | **47.6** | **(119)** |
| PPI indicated: received PPI monotherapy | 25.2 | (30) |
| No indication: did not receive GI prophylaxis | 74.8 | (89) |
| **Inappropriate GI prophylaxis** | **52.4** | **(131)** |
| PPI indicated: received alternate or no GI prophylaxis | 56.4 | (74) |
| No GI prophylaxis | 68.9 | (51) |
| H2 blocker | 25.7 | (19) |
| Combination drug regimen with PPI | 2.7 | (2) |
| Combination drug regimen without PPI | 1.7 | (1) |
| Antacid | 1.7 | (1) |
| No GI prophylaxis indicated: received GI prophylaxis | 43.5 | (57) |

*GI = gastrointestinal; PPI = proton pump inhibitor.*

**TABLE 4** Adverse Events Identified at Readmission

| Event | % | (n) |
|---|---|---|
| Vascular | | |
| Revascularization | 21 | (7) |
| MI & revascularization | 18 | (6) |
| MI | 3 | (1) |
| Stroke | 15 | (5) |
| GI | | |
| GI bleed | 9 | (3) |
| New ulcer | 6 | (2) |
| New ulcer & GI bleed | 9 | (3) |
| PPI | | |
| Hypomagnesemia | 6 | (2) |
| CDI | 3 | (1) |
| Pneumonia | 3 | (9) |

*CDI = Clostridium difficile infection; GI = gastrointestinal; MI = myocardial infarction; PPI = proton pump inhibitor.*

Of the 51 patients who did not receive prophylaxis when it was indicated, the most common risk factors were advanced age 68.6% (35/51), NSAID use 17.6% (9/51), and concurrent anticoagulation 13.8% (7/51). Peptic ulcer disease and history of GI bleed were uncommon, at 7.8% and 3.9%, respectively. Six of these patients had more than 1 risk factor yet did not receive appropriate prophylaxis. Advanced age was a common risk factor, seen in 5 of these 6 patients.

Forty-one percent of patients (102/250) were readmitted during the 6-month follow-up period for a total of 234 readmissions. During these readmissions, 33 adverse events occurred. Vascular events were the most common (58%; 19/33), followed by GI (24%; 8/33) and PPI related (18%; 6/33; Table 4).

When evaluating vascular events by PPI use versus no PPI use, a greater number of events occurred in the no PPI group (4 vs. 15 events). Four patients at risk for GI adverse outcomes experienced GI events despite appropriate prophylaxis with a PPI. Gastrointestinal events were numerically similar in patients who did not receive a PPI when indicated and patients who were on a PPI or other inappropriate GI prophylaxis when not indicated. Two patients inappropriately receiving a PPI, and 2 patients who were candidates to receive a PPI but did not, experienced GI adverse outcomes.

## Discussion

It is apparent from this study that prescribing habits at our institution are inconsistent with the most recent consensus document recommendations. Given the increased risk of GI events associated with DAPT in high-risk patients, this deviation could lead to adverse patient outcomes.[4] Alternatively, the inappropriate use of GI prophylaxis in patients without an indication could be subjecting patients to a potential increased risk of adverse PPI outcomes as noted in previous studies.[7-14] Inappropriate PPI prescribing is also associated with an increased cost burden to the health care system.[29] In patients who received no prophylaxis at discharge when therapy was indicated, advanced age appears to be the risk factor most commonly overlooked or disregarded.

The number of adverse events within the 6-month follow-up period was low. This could be because the period of evaluation was too short for adverse events to have occurred or may be because of lack of follow-up for adverse events in the patient population. Since our hospital is not a closed system, patients are able to seek care at any facility. It is possible that additional adverse events may have occurred outside of our hospital system.

Although retrospective studies have shown an association between PPI use and increased rate of vascular events, this was not evident in our study. Overall, 19 vascular events were observed, and there was no correlation with PPI use. This is consistent with the results of prospective trials.[30] We were unable to accurately collect data regarding medication compliance or over-the-counter PPI use. Therefore, it is possible that additional vascular events may have occurred in cases where the medication history was not accurate. Home medication reconciliation was based on retrospective chart review, patient self-reporting, and practitioner documentation.

Observed GI adverse outcomes were low overall. Four patients who were indicated for and received PPI therapy experienced a GI event despite receiving appropriate therapy. This is likely due to the patients' underlying risk for GI adverse outcomes, which was not negated by PPI use; all 4 of these patients had advanced age. One of these patients had advanced age and anticoagulation as risk factors; another had advanced age and anticoagulation plus a third indication of GI bleed. Contrary to expectation, patients receiving a PPI without an indication and those indicated for PPI yet not receiving one had similar GI outcomes. This is likely because of the low incidence

of adverse outcomes overall and incomplete follow-up. In our study, the incidence of GI bleeding of 2.4% (6/250) is similar to rates found in other studies, which varied from 1.3%-3.5% in patients receiving DAPT.[4,30,31]

Despite new information linking PPI use to numerous adverse events, the rate of events in this study was low, which affirms the historic tolerability of these agents. The incidence of pneumonia in patients receiving PPI was similar to that reported for patients receiving acid suppressive therapy in the study by Laheij et al. (2004), with 2.4 versus 2.45 per 100 person-years.[14] No PPI-related fractures were observed, which may be related to the short period of observation. Fractures from PPI use has been associated with long-term, high dose PPI therapy, and the strength of association increases with an increased duration of therapy.[10] The incidence of CDI infection was similar in patients receiving and not receiving PPI. The national point prevalence of CDI in U.S. health care facilities in 2008 was reported as 13.1 per 1,000 inpatients.[32] In this study, the rate was similar at 1.2% (3/250) of patients or 12.0 per 1,000 inpatients. However, we observed a higher incidence of CDI in patients not receiving PPI. This may be due to the overall larger number of patients not receiving PPI (168/250) or the overall incidence of inpatient CDI versus the incidence of community-acquired CDI associated with PPI use that has been reported in the literature.[7-9,33] The incidence of PPI-induced interstitial nephritis was unreportable due to infrequency of diagnosis.

Hypomagnesemia occurred in 2 patients receiving PPI with magnesium levels of 0.7 and 0.9 mg/dl, respectively. No data were available on magnesium urinary excretion or other causative agents, so it is difficult to definitively associate the hypomagnesemia to PPI use versus other unknown etiologies. However, the incidence has been estimated at 1% or less by postmarketing surveillance, with 38 cases from the FDA Adverse Event Reporting system and 23 cases from the medical literature, although the actual incidence cannot be quantified due to underrecognition and underreporting.[34] This estimate correlates with the 0.8% incidence observed in our study.

Given the results found in this study, there is an opportunity to improve compliance with the consensus document recommendations. Following completion of this study, the results were presented to the medical community at our facility in the Pharmacy and Therapeutics (P&T) Committee meeting. In addition, since many patients are started on DAPT following PCI, a revision to the PCI order set is planned to provide physicians with the clinical characteristics indicated as high risk so appropriate GI prophylaxis can be ordered. Due to the general overuse of PPI therapy in our hospital, a proposal will be taken to the P&T Committee to require prescribers to check an indication box when ordering PPI therapy. Another opportunity is prescriber education provided by clinical pharmacists during patient rounding. This approach has been proven to reduce inappropriate prescribing.[35] These suggestions for improvement through education, changes to order sets, and prescribing restrictions can be done at any hospital facility.

### Limitations

The limitations of this study are primarily due to its retrospective nature. These include difficulty establishing causal relationships and unavailable data. In addition, we designed a 6-month follow-up period to complete the study in a 1-year time frame. It is possible that there would have been additional adverse events identified if patients had been followed for a longer time period, since most patients on DAPT receive therapy for a minimum of 12 months. Another limitation previously stated is the single-center, open-system of the study site. Patients were not contacted via phone to determine if additional hospital admissions could have occurred outside of our facility. Although this would have allowed for a more complete analysis of readmissions during the 6-month time period, it is possible that patients would not have been able to correctly describe any adverse events that may have occurred.

## Conclusion

Despite the consensus document recommendations for GI prophylaxis in high-risk patients on DAPT, more than half of the patients at our institution did not receive appropriate GI prophylaxis. The most common reason for nonadherence was no prophylaxis when indicated, which could predispose patients to adverse GI outcomes. Although there was a low occurrence of adverse events, the incidence was similar to those reported in larger studies.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## DISCLOSURES

The authors have no financial or intellectual conflicts of interest to disclose.

Concept and design were contributed by Morneau, Oliphant, Reaves, and Martin. Morneau was responsible for data collection, which was interpreted by Morneau, Oliphant, Reaves, and Martin. The manuscript was written by Morneau, Oliphant, Reaves, and Martin, and all authors contributed equally to the revision of the manuscript. At the time of writing, Morneau was a PGY-1 Resident, and Martin was a Clinical Pharmacist at Methodist University Hospital, Memphis, Tennessee.

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