Dual antiplatelet therapy with aspirin and clopidogrel is recommended treatment for percutaneous coronary intervention (PCI) (1) and acute coronary syndromes (ACS) (2,3). Whereas multidrug therapy with antiplatelet drugs, lipid-lowering and glucose-lowering agents, antihypertensive drugs, and even antidepressants has been suggested as a therapeutic strategy to reduce cardiovascular risk, multiple drug prescriptions increase the risk for drug–drug interactions. This is particularly true if more than 1 agent requires significant hepatic metabolism (4). Clopidogrel, atorvastatin, omeprazole, and many other drugs require hepatic cytochrome P450 (CYP) metabolic activation to produce the active metabolite that inhibits the platelet P2Y12 adenosine diphosphate (ADP) receptor, decreasing platelet activation and aggregation processes. Atorvastatin, omeprazole, and several other drugs have been shown in pharmacodynamic studies to competitively inhibit CYP activation of clopidogrel, reducing clopidogrel responsiveness. Conversely, other agents increase clopidogrel responsiveness by inducing CYP activity. The clinical implications of these pharmacodynamic interactions have raised concern because many of these drugs are coadministered to patients with coronary artery disease. There are multiple challenges in proving that a pharmacodynamic drug–drug interaction is clinically significant. To date, there is no consistent evidence that clopidogrel–drug interactions impact adverse cardiovascular events. Statins and proton pump inhibitors have been shown to decrease adverse clinical event rates and should not be withheld from patients with appropriate indications for therapy because of concern about potential clopidogrel–drug interactions. Clinicians concerned about clopidogrel–drug interactions have the option of prescribing either an alternative platelet P2Y12 receptor inhibitor without known drug interactions, or statin and gastro-protective agents that do not interfere with clopidogrel metabolism. (J Am Coll Cardiol 2011;57:1251–63) © 2011 by the American College of Cardiology Foundation

Drug Metabolism

The most important metabolic pathway for most medications involves oxidation by 1 or more CYP isoenzymes. These isoenzymes are generally most highly expressed in hepatocytes, but are also present in other tissues including the intestines and skin. As oxidative metabolism is the first step in the clearance of many drugs, CYP isoenzymes are central to many clinically relevant drug–drug interactions. The activity of CYP isoenzymes may also be a necessary step for conversion of a prodrug to a clinically beneficial active metabolite.

Clopidogrel bisulfate, an inactive thienopyridine prodrug, is 85% hydrolyzed in vivo by esterases to an inactive carboxylic acid derivative (Fig. 1). The remaining drug undergoes oxidative biotransformation to its active thiol metabolite by a 2-step, CYP-dependent process in which CYP3A4/5 and CYP2C19 have the greatest roles, with lesser involvement from CYP2B6, CYP1A2, and CYP2C9 (9). The active metabolite then irreversibly inhibits the platelet P2Y12 adenosine diphosphate (ADP) receptor by forming an inactivating disulfide bond with cysteine on the P2Y12 receptor (10). This blocks ADP from binding to the receptor and stimulating platelet activation and aggregation. Physical and genetic factors that induce, inhibit, or compete for CYP activity can modulate biotransformation of clopi-
Dogrel to its active metabolite and result in interindividual variability of clopidogrel responsiveness. For instance, the degree of CYP3A4 metabolic activity is inversely related to the antiplatelet effects of clopidogrel (11). CYP2C19 polymorphisms associated with enzymatic activity also impact clopidogrel metabolism and responsiveness (12).

Statins act by inhibiting 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme of cholesterol synthesis in the liver. CYP3A4 is important for the elimination of lipophilic statins (lovastatin, simvastatin, and atorvastatin), but hydrophilic statins (fluvastatin, pravastatin, and rosvastatin) are not significantly metabolized by this isoenzyme. Atorvastatin is the most commonly prescribed statin, and its extensive hepatic metabolism has the potential to result in significant interactions with other drugs (13). Atorvastatin calcium is initially converted to the acid and lactone metabolites of the parent drug. Whereas the acid form inhibits HMG-CoA reductase, the dominant pathway of elimination is through the lactone form that binds more tightly to CYP3A4 than many other substrates and competes with a large number of medications, including itraconazole, nelfinavir, ritonavir, cyclosporine, fibrates, erythromycin, amiodarone, verapamil, fluoxetine, and nefazadone, as well as grapefruit juice.

Proton pump inhibitors (PPIs) are prodrugs that are activated in gastric parietal cells. PPIs irreversibly inhibit the gastric H+\text{/}K+\text{ATPase} (the proton pump) that accomplishes the final step in acid secretion. Omeprazole, the most widely used PPI, is metabolized to hydroxyomeprazole and omeprazole sulphate primarily by CYP2C19 and CYP3A4 (14). Omeprazole has a greater affinity for CYP2C19 than CYP3A4, compared with the other PPIs that are also metabolized by these isoenzymes, and therefore

**Figure 1** Clopidogrel–Drug Interactions

After ingestion and absorption, 85% of clopidogrel bisulfate is hydrolyzed by esterases to an inactive carboxylic acid metabolite and the remaining drug is oxidized in a 2-step process by hepatic P450 cytochromes. Multiple pharmacodynamic drug interactions can influence active thiol metabolite levels. cAMP = cyclic adenosine monophosphate; PPI = proton pump inhibitor.
has a greater potential for drug–drug interactions mediated by CYP2C19. Omeprazole has been shown to reduce the clearance of diazepam, phenytoin, and warfarin. Conversely, ketoconazole and clarithromycin have a high affinity for CYP3A4 and increase omeprazole concentrations. Another mechanism by which omeprazole may induce drug interactions is by elevating gastric pH and altering drug absorption rates.

Due to their common requirement for CYP3A4 metabolism, a clopidogrel–atorvastatin interaction may exist. Similarly, due to their common requirement for CYP2C19 metabolism, a clopidogrel–omeprazole interaction may exist. These interactions could result in competitive inhibition decreasing the conversion of the clopidogrel prodrug to the active metabolite and could potentially translate into an increased risk for cardiovascular events because of inadequate platelet P2Y₁₂ receptor inhibition. This is a particularly important issue since many patients receiving treatment to prevent recurrent cardiovascular events are suitable candidates for all 3 drugs.

Pharmacodynamic Studies
The clopidogrel–atorvastatin interaction. We initially surmised that clopidogrel was metabolized in humans by CYP3A4, not CYP1A2 as described in the rat (15), when we serendipitously noted that patients on atorvastatin were not achieving the expected platelet inhibition with a clopidogrel 300-mg loading dose (5), an observation confirmed by Neubauer et al. (16). Responding to criticism that our initial study was observational and used a point-of-care platelet aggregometer, we subsequently performed a prospective randomized trial with standard light transmission aggregometry and demonstrated an interaction with a 300-mg, but not a 600-mg, clopidogrel loading dose (17). Consistent with these findings, results from an in vitro study using human microsomes containing single CYP isozymes indicated that both CYP3A4 and CYP3A5 were primarily responsible for oxidation of clopidogrel to its active metabolite. Exposure of human microsomes to clopidogrel and atorvastatin lactone at equimolar concentrations resulted in a >90% inhibition of clopidogrel metabolism (18).

However, other studies (Table 1) have shown no impact with clopidogrel and atorvastatin coadministration (19–22), especially when a higher clopidogrel loading dose (600 mg) was tested (23–26), when measurements were made several weeks later (21,27–29), or when atorvastatin was added to clopidogrel (31–32). Limitations of the ex vivo platelet aggregation studies include small sample sizes, different drug doses, heterogeneous patient populations on multiple medications, and differences in measurement techniques and protocols. Moreover, it is unknown how the variability in clopidogrel metabolism due to CYP2C19 polymorphisms and CYP3A4 expression might have impacted the results. Expression of CYP3A4 varies 40-fold in humans, and metabolism of CYP3A4 substrates varies 10-fold in vivo (33).

In summary, no one disputes our initial finding that clopidogrel is metabolized by CYP3A4, recognized by platelet aggregometry because of a presumed clopidogrel–atorvastatin interaction, but many other reports have not been able to confirm this interaction for various reasons. The clopidogrel–omeprazole interaction. Gilard et al. (6) initially observed an association between PPI use and poor clopidogrel response (Table 2). They subsequently demonstrated that more patients on omeprazole than placebo were nonresponders after clopidogrel administration (34). Cuisset et al. (35) found more nonresponders on omeprazole compared with pantoprazole despite a high clopidogrel maintenance dose of 150 mg/day. Sibbing et al. (36) demonstrated less platelet inhibition and more nonresponders in patients taking omeprazole compared with non-PPI users or those given esomeprazole or pantoprazole. Neubauer et al. (37) also found more clopidogrel nonresponders with omeprazole, but no interaction with pantoprazole. Staggering the administration times of clopidogrel and omeprazole does not decrease the interaction (38).

O’Donoghue et al. (39) measured decreased platelet inhibition after a clopidogrel loading dose in patients taking PPIs. Likewise, Zuern et al. (40) noted less platelet inhibition in patients on PPIs, but no difference between agents, although only 36 of 1,425 patients were given omeprazole. Sibbing et al. (36) and Siller-Matula et al. (41) found no impairment of clopidogrel responsiveness with pantoprazole or esomeprazole. Similarly, Small et al. (42) described no overall impact of coadministration with lansoprazole in 24 healthy volunteers, although there was decreased clopidogrel responsiveness in 8 high clopidogrel responders. Recently, Angiolillo et al. (43) confirmed a pharmacokinetic/pharmacodynamic interaction between clopidogrel (administered at both standard and double loading/maintenance dose regimens) and omeprazole (administered concomitantly or staggered), but found no interaction between clopidogrel and pantoprazole.

In summary, omeprazole has consistently been shown to attenuate clopidogrel responsiveness (34–38,43), whereas no or limited interaction has been shown with pantoprazole (35–37,41,43) and other PPIs.

The SPICE (Evaluation of the Influence of Statins and Proton Pump Inhibitors on Clopidogrel Antiplatelet Effects) trial. The SPICE trial (44) is enrolling 320 patients treated with dual antiplatelet therapy for at least 60 days after bare-metal stent implantation. Patients will receive either atorvastatin 80 mg or the comparator rosuvastatin 20 mg daily for 12 months. After 1 month, they will also receive either omeprazole 20 mg, pantoprazole 40 mg, esomeprazole 40 mg, or the histamine₂-receptor antagonist (H₂RA) comparator ranitidine 300 mg daily for 11 months. Percentage change in residual platelet aggregation by light transmittance aggregometry and percentage change in platelet reactivity index by flow cytometry will be measured...
Table 1  Pharmacodynamic Studies That Evaluated the Administration of Clopidogrel to Subjects Receiving Atorvastatin

<table>
<thead>
<tr>
<th>First Author (Ref. #)</th>
<th>(Year)</th>
<th>Population</th>
<th>Clopidogrel Dose</th>
<th>Atorvastatin Dose</th>
<th>Main Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lau et al. (5)</td>
<td>2003</td>
<td>19 pts, 16 controls undergoing PCI</td>
<td>300 mg</td>
<td>10-40 mg/day</td>
<td>Atorvastatin dose-related decrease of platelet aggregation inhibition by clopidogrel at 24 h</td>
<td>First demonstration that clopidogrel is activated by CYP3A4</td>
</tr>
<tr>
<td>Neubauer et al. (16)</td>
<td>2003</td>
<td>17 pts, 22 controls undergoing PCI</td>
<td>300 mg then 75 mg/day</td>
<td>20-40 mg/day</td>
<td>Dose-related decrease of platelet aggregation inhibition by atorvastatin at 5 and 48 h</td>
<td>Diminished interaction at 48 h compared with 5 h</td>
</tr>
<tr>
<td>Muller et al. (23)</td>
<td>2003</td>
<td>7 pts, 12 controls undergoing angiography</td>
<td>600 mg</td>
<td>20 mg/day</td>
<td>No inhibition of platelet aggregation at 2-4 h</td>
<td>No inhibition with high clopidogrel loading dose</td>
</tr>
<tr>
<td>Mitsios et al. (27)</td>
<td>2004</td>
<td>13 pts, 8 controls with ACS</td>
<td>375 mg then 75 mg/day</td>
<td>10 mg/day</td>
<td>No inhibition of platelet aggregation at 5 weeks</td>
<td>No inhibition with sustained coadministration</td>
</tr>
<tr>
<td>Piorowski et al. (19)</td>
<td>2004</td>
<td>17 volunteers, 15 pts with CAD, 17 controls</td>
<td>300 mg then 75 mg/day</td>
<td>20 mg/day</td>
<td>No inhibition of platelet aggregation at 4, 24, and 96 h</td>
<td>No inhibition with standard clopidogrel loading dose</td>
</tr>
<tr>
<td>Serebruany et al. (20)</td>
<td>2004</td>
<td>25 pts, 25 controls undergoing PCI</td>
<td>300 mg</td>
<td>10-40 mg/day</td>
<td>No inhibition of platelet aggregation at 24 h</td>
<td>No inhibition with standard clopidogrel loading dose</td>
</tr>
<tr>
<td>Gorchakova et al. (24)</td>
<td>2004</td>
<td>58 pts, 90 controls undergoing PCI</td>
<td>600 mg</td>
<td>10-40 mg/day</td>
<td>No inhibition of platelet aggregation at 2 h</td>
<td>No inhibition with high clopidogrel loading dose</td>
</tr>
<tr>
<td>Smith et al. (21)</td>
<td>2004</td>
<td>20 pts, 5 controls undergoing PCI</td>
<td>300 mg then 75 mg/day</td>
<td>Not stated</td>
<td>No inhibition of platelet aggregation at 4 h, 10 days, and 28 days</td>
<td>No inhibition with standard clopidogrel loading dose and sustained coadministration</td>
</tr>
<tr>
<td>Mitsios et al. (28)</td>
<td>2005</td>
<td>26 pts, 25 controls undergoing PCI for ACS</td>
<td>375 mg then 75 mg/day</td>
<td>20 mg/day</td>
<td>No inhibition of platelet aggregation at 5 weeks</td>
<td>No inhibition with sustained coadministration</td>
</tr>
<tr>
<td>Lau et al. (17)</td>
<td>2005</td>
<td>36 volunteers, 24 controls</td>
<td>300, 450, 600 mg</td>
<td>40 mg/day</td>
<td>Dose related decrease of platelet inhibition by atorvastatin at 2, 4, 6, and 8 h</td>
<td>Inhibition with 300 mg, less inhibition with 450 mg, no inhibition with 600 mg</td>
</tr>
<tr>
<td>Trenk et al. (25)</td>
<td>2008</td>
<td>255 pts, 682 controls undergoing angiography</td>
<td>600 mg</td>
<td>Not stated</td>
<td>No inhibition of platelet aggregation at 2 h</td>
<td>No inhibition with high clopidogrel loading dose</td>
</tr>
<tr>
<td>Geisler et al. (26)</td>
<td>2008</td>
<td>262 pts, 142 controls undergoing PCI</td>
<td>600 mg</td>
<td>Not stated</td>
<td>No inhibition of platelet aggregation at 6 h</td>
<td>No inhibition with high clopidogrel loading dose</td>
</tr>
<tr>
<td>Farid et al. (22)</td>
<td>2008</td>
<td>31 volunteers</td>
<td>300 mg</td>
<td>80 mg/day</td>
<td>No inhibition of platelet aggregation at 2-24 h</td>
<td>No inhibition with standard clopidogrel loading dose</td>
</tr>
<tr>
<td>Malmstrom et al. (29)</td>
<td>2009</td>
<td>22 pts with CAD</td>
<td>75 mg/day</td>
<td>20-80 mg/day</td>
<td>No inhibition of platelet aggregation at 2 weeks</td>
<td>No inhibition with sustained coadministration</td>
</tr>
</tbody>
</table>

ACS = acute coronary syndrome; CAD = coronary artery disease; PCI = percutaneous coronary intervention; pts = patients.
Table 2 Pharmacodynamic Studies That Evaluated the Administration of Clopidogrel to Subjects Receiving Proton Pump Inhibitors

<table>
<thead>
<tr>
<th>First Author (Ref. #) (Year)</th>
<th>Design</th>
<th>Population</th>
<th>End Point</th>
<th>Clopidogrel Dose</th>
<th>n</th>
<th>Main Outcome</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gilard et al. (6) (2006)</td>
<td>Cohort</td>
<td>High-risk PCI</td>
<td>VASP (PRI)</td>
<td>300 mg then 75 mg/day</td>
<td>No PPI: 81 PPI: 24</td>
<td>No PPI: 49.5% PPI: 61.4% p = 0.007</td>
<td>PPI decreased platelet inhibition</td>
</tr>
<tr>
<td>Gilard et al. (34) (2008)</td>
<td>Prospective, Double-blind RCT</td>
<td>Elective coronary stent implantation</td>
<td>VASP (PRI) at 7 day</td>
<td>Placebo: 60 Omeprazole: 64</td>
<td>Placebo: 39.9% Omeprazole: 51.4% p &lt; 0.0001</td>
<td>Omeprazole decreased platelet inhibition</td>
<td></td>
</tr>
<tr>
<td>Cuisett et al. (35) (2009)</td>
<td>Prospective RCT</td>
<td>PCI for ACS</td>
<td>VASP (PRI) at 1 month</td>
<td>Pantoprazole: 52 Omeprazole: 52</td>
<td>Pantoprazole: 36% Omeprazole: 48% p = 0.007</td>
<td>Omeprazole decreased platelet inhibition vs. pantoprazole</td>
<td></td>
</tr>
<tr>
<td>Sibbing et al. (36) (2009)</td>
<td>Cohort</td>
<td>Prior coronary stent implantation</td>
<td>Platelet aggregation</td>
<td>75 mg/day</td>
<td>No PPI: 732 Esomeprazole: 42 Pantoprazole: 162 Omeprazole: 64</td>
<td>No PPI: 220 AU×min Esomeprazole: 209 AU×min Pantoprazole: 226 AU×min Omeprazole: 296 AU×min p = 0.001 vs. omeprazole</td>
<td>Omeprazole decreased platelet inhibition; esomeprazole and pantoprazole did not decrease platelet inhibition</td>
</tr>
<tr>
<td>Siller-Matula et al. (41) (2009)</td>
<td>Cohort</td>
<td>Undergoing PCI</td>
<td>VASP (PRI) after PCI</td>
<td>600 mg then 75 mg/day</td>
<td>No PPI: 74 Esomeprazole: 74 Pantoprazole: 152</td>
<td>No PPI: 49% Esomeprazole: 54% Pantoprazole: 50%</td>
<td>Esomeprazole and pantoprazole did not decrease platelet inhibition</td>
</tr>
<tr>
<td>O’Donoghue et al. (39) (2009)</td>
<td>Retrospective RCT cohort</td>
<td>ACS with planned PCI</td>
<td>Inhibition of platelet aggregation at 6 h</td>
<td>600 mg then 150 mg/day</td>
<td>No PPI: 71 PPI: 28</td>
<td>No PPI: 35.2% PPI: 23.2% p = 0.02</td>
<td>PPI decreased platelet inhibition</td>
</tr>
<tr>
<td>Zuern et al. (40) (2009)</td>
<td>Cohort</td>
<td>Undergoing PCI</td>
<td>Platelet aggregation at 20 h</td>
<td>600 mg then 75 mg/day</td>
<td>No PPI: 1.001 Esomeprazole: 108 Pantoprazole: 280 Omeprazole: 36</td>
<td>No PPI: 29.8% PPI: 34% p = 0.001</td>
<td>PPI decreased platelet inhibition</td>
</tr>
<tr>
<td>Neubauer et al. (37) (2010)</td>
<td>Cohort</td>
<td>Undergoing PCI</td>
<td>Platelet aggregation at 48 h</td>
<td>600 mg then 75 mg/day</td>
<td>No PPI: 188 Esomeprazole or omeprazole: 26 Pantoprazole: 122</td>
<td>No PPI: 2.75 † Esomeprazole or omeprazole: 3.00 † Pantoprazole: 2.33 †</td>
<td>Nonresponders: no PPI, 21.9%, esomeprazole or omeprazole, 30.8%, pantoprazole, 16.4%.</td>
</tr>
</tbody>
</table>

AU = aggregation unit; PPI = proton pump inhibitor; PRI = platelet reactivity index; RCT = randomized clinical trial; VASP = vasodilator-stimulated phosphoprotein; other abbreviations as in Table 1.
at 30 and 60 days. Death, myocardial infarction (MI), ischemia-driven repeat revascularization, stroke, gastrointestinal bleeding, and peptic ulcer disease will be documented at 30 days, 60 days, and 1 year. Unfortunately, this protocol will not evaluate the interaction we described when a loading dose of clopidogrel is given to a patient on chronic atorvastatin therapy, nor will it measure the early potential interaction between omeprazole and clopidogrel.

Clinical Studies
The clopidogrel–atorvastatin interaction. REGISTRY REPORTS. The MITRA-Plus (Maximal Individual Therapy of Acute Myocardial Infarction PLUS) registry (45) reported no significant difference in mortality in 2,086 patients who received clopidogrel for ACS with atorvastatin versus other statins (3.2% atorvastatin, 2.7% other statins) (Table 3). A registry report (46) from Nova Scotia including 1,537 patients with PCI found no significant difference in death, MI, or unstable angina rates (4.6% atorvastatin, 3.5% pravastatin). A single-center study (47) with 211 patients undergoing coronary stenting receiving pretreatment with clopidogrel described a lower rate of periprocedural MI for patients on pravastatin and fluvastatin compared with atorvastatin and simvastatin.

ADMINISTRATIVE DATABASE REPORTS. Brophy et al. (50) reported on 2,927 consecutive patients discharged after PCI on clopidogrel and found a significantly increased risk for the 30-day composite outcome of death, MI, unstable angina, cerebrovascular events, and repeat revascularization for those treated with atorvastatin (4.54% vs. 3.0%). Risk was also increased with other prescriptions for drugs inhibiting CYP3A4 enzyme activity (odds ratio [OR]: 1.56, 95% confidence interval [CI]: 1.02 to 2.37) and for those who delayed filling the clopidogrel prescription. A subsequent report (51) on 10,491 patients, with a different reference group (nonstatin users) and 62-day follow-up, found no significant risk for adverse outcomes with CYP-metabolized statins compared with non–CYP-metabolized statins, but could not exclude a small risk (hazard ratio [HR]: 1.16; 95% CI: 0.91 to 1.47).

POST HOC RANDOMIZED CLINICAL TRIAL REPORTS. A report from the CREDO (Clopidogrel for the Reduction of Events During Observation) trial (52) concluded that there was no statistically significant interaction on the 1-year
composite end point of death, MI, and stroke with clopidogrel and statin coadministration (7.6% CYP3A4 statins, 5.4% non-CYP3A4 statins) or atorvastatin (6.5% atorvastatin, 4.6% pravastatin). Similar findings were found in a post hoc analysis of the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial (5.9% CYP3A4 statins, 5.7% non-CYP3A4 statins; 5.7% atorvastatin, 5.1% pravastatin) (53). A post hoc analysis from the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial (54) addressed a different question and found no impact of adding atorvastatin to patients already on clopidogrel.

In summary, increased risk was seen in 2 studies (47,50), but not in 3 studies (25,26,48), 2 of which used a high clopidogrel loading dose (25,26). In other studies, there was an insignificant trend for worse outcomes with atorvastatin compared with pravastatin or no statin (45,46,52,53) and with CYP-metabolized statins compared with non-CYP-metabolized statins (51–53), but no consistent signal for increased cardiovascular risk with drug coadministration.

**The clopidogrel–omeprazole interaction. REGISTRY REPORTS.** A letter to the editor first suggested that PPI exposure increased the rate of MI in patients on clopidogrel (55). Two small (56,57) and 1 large (58) single-center reports supported increased adverse cardiac events in patients discharged on a PPI after PCI. Conversely, omeprazole and other PPIs had no effect on the clinical response to clopidogrel in the FAST-MI (French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction) registry that enrolled 2,208 patients with MI and assessed 1-year risk for death, MI, and stroke (59).

**ADMINISTRATIVE DATABASE REPORTS.** Ho et al. (60) studied 8,205 veterans discharged after hospitalization for ACS and found an increased risk for mortality or rehospitalization for ACS for patients treated with clopidogrel plus PPI compared with clopidogrel without PPI (OR: 1.25, 95% CI: 1.11 to 1.41). The increased risk was present in patients taking omeprazole (Table 4). Similarly, Juurlink et al. (61) conducted a nested case-control study including 782 elderly Canadian patients readmitted to the hospital for recurrent MI within 90 days following hospital discharge for MI, of whom 46 were taking pantoprazole and 148 were taking omeprazole, lansoprazole, or rabeprazole. Risk was increased with PPI use (OR: 1.27, 95% CI: 1.03 to 1.57), but not with pantoprazole or H2RAs. Kreutz et al. (62) studied 16,690 patients with commercial insurance in the Medco Health Solutions, Inc. (Franklin Lakes, New Jersey) database after coronary stent implantation and described an increased 1-year risk for the composite outcome of hospitalization for cardiovascular death, ACS, cerebrovascular event, or revascularization in patients prescribed a PPI (HR: 1.51, 95% CI: 1.39 to 1.64). Risk was increased for all PPIs, but not with H2RAs. Huang et al. (63) also noted an increased risk of rehospitalization and death in East Asian patients prescribed PPIs after PCI. Stockl et al. (64) attempted to address some of the limitations of performing an administrative claims-based analysis by using propensity scoring, but the results illustrate the analytical challenges. The negative impact of PPIs on risk (HR: 1.93, 95% CI: 1.05 to 3.54) was greater than the incremental benefit of adding clopidogrel to aspirin in any randomized clinical trial, and risk was demonstrated with pantoprazole (HR: 1.91, 95% CI: 1.19 to 3.06), despite no prior pharmacodynamic evidence of a clopidogrel–pantoprazole interaction.

Rasen et al. (65) noted low event rates in 18,565 elderly patients with ACS or PCI followed for MI hospitalization or death. The excess risk with PPI therapy (risk ratio [RR]: 1.22, 95% CI: 0.99 to 1.51) was progressively reduced with additional statistical analyses that controlled for confounding variables and was considered inconclusive. Ray et al. (66) studied 20,596 Medicaid patients hospitalized for ACS or revascularization. There was no cardiovascular risk during follow-up with PPI use (HR: 0.99; 95% CI: 0.82 to 1.19), but hospitalizations for gastroesophageal bleeding were 50% lower than in nonusers. Charlot et al. (67) described increased risk for PPI use regardless of clopidogrel use in 56,406 Danish patients, but no risk with individual PPIs. A recent meta-analysis (68) of 23 studies on clopidogrel–PPI interactions, many unpublished, further describes the limitations of observational study design on accurately determining risk. Another meta-analysis concluded that patient risk for cardiovascular events impacted PPI risk (69).

**POST-HOC RANDOMIZED CLINICAL TRIAL REPORTS.** Dunn et al. (70) reported preliminary results in 366 patients from the CREDO trial and found no difference in the 1-year risk of death, stroke, or MI when PPI was added to clopidogrel. O’Donoghue et al. (39) studied 13,608 patients in the TRITON–TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction 38), 4,529 of whom were taking a PPI. No risk was found for the composite end point of cardiovascular death, MI, or stroke compared with the no PPI group (HR: 0.94, 95% CI: 0.80 to 1.11). Both studies showed higher risk for patients on PPIs, suggesting that comorbidities, rather than a clopidogrel–PPI interaction, may make patients higher risk for adverse cardiac events.

**RANDOMIZED CLINICAL TRIAL.** The COGENT (Clopidogrel and the Optimization of Gastrointestinal Events Trial) randomized 3,627 patients with ACS or PCI to a fixed-dose combination of controlled-release omeprazole 20 mg–clopidogrel 75 mg/day or clopidogrel alone, but was terminated early because of sponsor bankruptcy (71). Although underpowered, the secondary combined cardiovascular end point of cardiovascular death, ischemic stroke, nonfatal MI, or revascularization was not different (HR: 1.02, 95% CI: 0.70 to 1.51), but the composite primary gastrointestinal event rate was reduced with PPI use (HR: 0.55, 95% CI: 0.36 to 0.85).
Table 4  Clinical Studies That Evaluated the Coadministration of Clopidogrel and Omeprazole

<table>
<thead>
<tr>
<th>First Author (Ref. #) (Year)</th>
<th>Design</th>
<th>Population</th>
<th>End Point</th>
<th>n</th>
<th>Results, RR/OR/HR (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simon et al. (49) (2009)</td>
<td>Retrospective registry cohort</td>
<td>Acute MI</td>
<td>Death, MI, stroke at 1 yr</td>
<td>Omeprazole: 1,147 No PPI: 602</td>
<td>RR: 0.85 (0.69–1.05)</td>
<td>No risk</td>
</tr>
<tr>
<td>Ho et al. (60) (2009)</td>
<td>Retrospective administrative database cohort</td>
<td>Hospital discharge for ACS</td>
<td>Death or rehospitalization for UA/MI at 17 months</td>
<td>Omeprazole: 3,132 No PPI: 2,961</td>
<td>OR: 1.24 (1.08–1.41)</td>
<td>Increased risk in male veterans</td>
</tr>
<tr>
<td>O’Donoghue et al. (39) (2009)</td>
<td>Retrospective RCT cohort</td>
<td>ACS undergoing PCI</td>
<td>CV death, MI, stroke at 15 months</td>
<td>Esomeprazole: 613</td>
<td>Lansoprazole: 441</td>
<td>Omeprazole: 1,675</td>
</tr>
<tr>
<td>Rassen et al. (65) (2009)</td>
<td>Retrospective administrative database cohort</td>
<td>ACS or PCI</td>
<td>Death, MI hospitalization at 30 days</td>
<td>Omeprazole: NA</td>
<td>Pantoprazole: NA No PPI: NA</td>
<td>RR: 1.17 (0.68–2.01)</td>
</tr>
<tr>
<td>Ray et al. (66) (2010)</td>
<td>Retrospective administrative database cohort</td>
<td>UA, MI, PCI, CABG</td>
<td>CV death, MI, stroke</td>
<td>Esomeprazole: 690</td>
<td>Lansoprazole: 1,042</td>
<td>Omeprazole: 660</td>
</tr>
<tr>
<td>Kreutz et al. (62) (2010)</td>
<td>Retrospective administrative database cohort</td>
<td>Stent implantation</td>
<td>Hospitalization for CV death, ACS, cerebrovascular event, revascularization at 1 yr</td>
<td>Esomeprazole: 3,257</td>
<td>Lansoprazole: 785</td>
<td>Omeprazole: 2,307</td>
</tr>
<tr>
<td>Charlot et al. (67) (2010)</td>
<td>Retrospective administrative database cohort</td>
<td>30 days after MI</td>
<td>CV death or rehospitalization for MI or stroke</td>
<td>Esomeprazole: 5,316</td>
<td>Lansoprazole: 2,798</td>
<td>Omeprazole: 2,717</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass graft; HR = hazard ratio; RR = risk ratio; other abbreviations as in Tables 1, 2, and 3.
In summary, patients who receive PPIs are older and have more comorbidity, making confounding and selection bias a likely explanation for increased clinical risk in some observational studies. Whereas observational studies have produced discordant results for a clopidogrel–omeprazole interaction, post hoc randomized clinical trial reports (39,70) and 1 randomized clinical trial (71) have shown no signal for increased cardiovascular risk with drug coadministration.

**Other Clopidogrel–Drug Interactions**

We initially demonstrated that CYP3A4 inhibitors (erythromycin, troleandomycin, ketoconazole) decreased and CYP3A4 inducers (rifampin) increased the antiplatelet activity of clopidogrel (5,11). Several other clopidogrel–drug interactions have subsequently been described (Fig. 1). **CYP inhibitors.** Ketoconazole is a potent inhibitor of both CYP3A4 and CYP3A5. Healthy subjects given loading and maintenance doses of clopidogrel had decreased production of active metabolite and significantly reduced platelet inhibition on ketoconazole compared with control (72). Similarly, the CYP3A inhibitor irtraconazole significantly decreased the ability of clopidogrel to inhibit platelet aggregation (73).

Dihydropyridine calcium channel blockers (nifedipine, amlodipine) also inhibit CYP3A4. In observational studies, they have been shown to decrease clopidogrel responsiveness as measured by the vasodilator-stimulated phosphoprotein (VASP) assay and electrical impedance aggregometry (74) and by light transmission aggregometry and the VerifyNow P2Y12 assay (Accumetrics, San Diego, California) (75).

Phenprocoumon, an oral anticoagulant used in Europe, is a coumarin derivative metabolized by CYP3A4 and CYP2C9. Concomitant treatment with clopidogrel attenuated the antiplatelet effect of clopidogrel and increased the number of nonresponders (76).

Cangrelor, an ATP analogue, is a parenteral reversible P2Y12 receptor inhibitor with a short half-life that results in normalization of platelet aggregation approximately 30 min after discontinuation of the infusion. When clopidogrel was given simultaneously with cangrelor and cangrelor was continued for 2 h, there was no inhibition of the P2Y12 receptor by clopidogrel after the infusion was stopped because the clopidogrel active metabolite was unavailable for binding due to its short half-life (77). When clopidogrel was started at the time the cangrelor infusion was discontinued, there was inhibition of the P2Y12 receptor. Importantly, it takes 2 to 4 h for clopidogrel to reach maximal effect. Therefore, there could be an important gap in platelet inhibition while the patient transitions from cangrelor to clopidogrel.

**CYP inducers.** We initially demonstrated that clopidogrel responsiveness could be increased by coadministration with rifampin, a CYP3A4 and CYP2C19 inducer, and that nonresponders could become responsive (5,11). Judge et al. (78) have recently proven that this response is due to increased production of the clopidogrel active metabolite and increased P2Y12 receptor blockade.

By inhibiting the platelet P2Y12 receptor, clopidogrel increases intracellular cyclic adenosine monophosphate (cAMP), a key signaling molecule in inhibiting platelet aggregation. Caffeine also increases cAMP levels and has been shown to enhance platelet inhibition by clopidogrel (79). Other methylxanthines (theophylline) and phosphodiesterase inhibitors (cilostazol) also increase platelet cAMP levels (80).

Smoking is a known CYP1A2 inducer, and several studies have demonstrated increased platelet inhibition (81), fewer ischemic events (82,83), and increased bleeding risk (83) in smokers following clopidogrel administration.

Omega-3 polyunsaturated fatty acids (PUFA) were shown in 1 small prospective randomized trial to increase clopidogrel responsiveness, but the mechanism is unclear (84).

St. John’s wort (*Hypericum perforatum*) is an herbal product used to treat depression. It also induces CYP3A4 activity. In healthy volunteers who were nonresponders to clopidogrel, St. John’s wort 300 mg thrice daily for 14 days improved the platelet inhibitory activity of clopidogrel by increasing CYP3A4 metabolic activity (85).

**Confounding Variables in the Drug Interaction Debate**

There are many confounding variables that have contributed to the discordant results regarding potential clopidogrel–drug interactions:

1. **Dose effect.** Inhibition of clopidogrel activation by atorvastatin appears to be dose-dependent (5), consistent with the hypothesis that atorvastatin is a competitive inhibitor of CYP3A4. Studies with high loading doses of clopidogrel (600 mg) and lower doses of atorvastatin (10 to 20 mg) could miss the inhibitory effect of high-dose atorvastatin on a lower clopidogrel loading dose (17).

2. **Time effect.** Suboptimal production of active metabolite following clopidogrel loading dose administration could eventually be overcome as active metabolite production eventually accumulates from maintenance dosing and binds to initially unblocked platelet receptors. Moreover, only 10% to 15% of the platelet pool is regenerated daily and platelet reactivity decreases with time after the initiating event, making it unlikely that a sustained inhibition of platelet aggregation could be maintained by a drug interaction. Additionally, 3 recent reports suggest that the interaction between CYP2C19 polymorphisms and the effect of clopidogrel on clinical events is limited to a few weeks (86–88).

3. **Class effect.** Only clopidogrel interactions with a single statin (atorvastatin) and a single PPI (omeprazole) appear to be important. Studies that evaluate clopidogrel–statin and clopidogrel–PPI interactions miss the point that these drug–drug interactions do not appear to be a
class effect because of pharmacokinetic and pharmacodynamic differences between agents within a drug class.

4. Clopidogrel response variability. Genetic, cellular, and metabolic factors influence clopidogrel responsiveness (89). Drug interactions may only be important in patients with borderline platelet inhibition, where small reductions in platelet inhibition might result in post-treatment platelet reactivity above therapeutic thresholds. Additionally, alternative CYP isoenzyme pathways may become more active in patients with concomitant treatment of competing agents.

5. Ex vivo platelet function testing. The role of platelets in thrombosis is complex; platelet function tests on isolated platelets measure only part of this process. Test heterogeneity, lack of standardization, operator dependency, and lack of an accepted gold standard challenge the accurate measurement of variable platelet reactivity.

6. Offsetting clinical effects. Atorvastatin has a number of beneficial pleiotropic effects (LDL reduction, decreased inflammation, plaque stabilization, fibrinolysis stimulation, improved endothelial function), including platelet inhibition, associated with decreased MI and death rates that could offset the negative clinical effect of any potential reduction in platelet inhibition with clopidogrel. Likewise, omeprazole reduces bleeding events, linked to risk for acute and future ischemic events, potentially neutralizing an adverse clinical effect on platelet inhibition.

**Research Challenges in the Drug Interaction Debate**

There are many research challenges in scientifically measuring the clinical importance of drug–drug interactions.

1. **Study design.** Treatment in observational studies is based on clinical need or physician preference, creating selection bias, so these studies can only suggest association, not conclude causality. Claims-based studies are particularly limited by missing or misclassified data. Outcome events in randomized trials are often adjudicated, but multivariable or propensity score analyses in post hoc studies cannot completely adjust for differences in unknown or unmeasured confounders. Only a randomized clinical trial could confirm the importance of a drug–drug interaction at the population level, although the generalizability of the results would be modified by inclusion and exclusion criteria and the potential cost of such a trial would probably be prohibitive.

2. **Sample size.** The published studies have not been appropriately powered to address clopidogrel–drug interactions. The absolute reduction in major adverse cardiac events at 30 days when clopidogrel is added to aspirin compared with aspirin monotherapy is only 1% (90), making it possible that studies demonstrating no clopidogrel–drug interactions were insufficiently powered to detect a small, but clinically meaningful, difference in event rates when millions of patients are prescribed these drugs.

3. **Composite primary end point.** Increased individual events related to attenuation of platelet inhibition by a drug–drug interaction (MI, transient ischemic attack) might be neutralized by other events not mediated by platelet aggregation (noncardiac death, target vessel revascularization), producing a net effect that obscures a potential drug interaction.

4. **Clinical risk.** Only specific patient subgroups may have clinical risk. Low CYP 3A4 metabolic activity, CYP2C19 polymorphisms, age, sex, diabetes mellitus, increased body mass index, and renal insufficiency also decrease clopidogrel responsiveness. Drug–drug interactions in subgroups of patients may not be recognized in population analyses. Moreover, the small reduction in platelet aggregation (10% to 15%) with clopidogrel–drug interactions may not be clinically significant in many subgroups.

5. **Patient compliance.** A major obstacle to finding a clinical clopidogrel–drug interaction is assuring patient compliance with coadministration of both medications during the study period. Measuring medication use at 1 point in time does not assure continued use of both medications.

**Conclusions**

There are many pharmacodynamic clopidogrel–drug interactions, but there is no consistent evidence that these interactions have clinical significance. Because the benefit of dual antplatelet therapy is well established and the existing clinical data on clopidogrel–drug interactions are inconclusive, clinicians should concentrate on initiating proper statin therapy in patients with coronary artery disease and prescribing PPIs for patients at increased risk for gastroesophageal bleeding. The therapeutic benefit of coadministering these medications to appropriate patients should greatly exceed any theoretical harm from clopidogrel–drug interactions that appear to be dose-dependent, time-dependent, and mild compared with the larger challenges of patient compliance and interindividual variability in clopidogrel responsiveness. Clinicians concerned about these interactions have the option of prescribing a different platelet P2Y12 receptor inhibitor without known drug interactions (39,72,91). Another option is to prescribe a hydrophilic statin in place of atorvastatin; or pantoprazole or ranitidine, an H2RA not metabolized by CYP isoenzymes, in place of omeprazole (92).

**Reprint requests and correspondence:** Dr. Eric R. Bates, CVC Cardiovascular Medicine, 1500 East Medical Center Drive, SPC 5869, Ann Arbor, Michigan 48109-5869. E-mail: ebates@umich.edu.

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