Is There a Clinically Significant Interaction Between Calcium Channel Antagonists and Clopidogrel?

Results From the Clopidogrel for the Reduction of Events During Observation (CREDO) Trial

Christopher W. Good, DO; Steven R. Steinhubl, MD; Danielle M. Brennan, MS; A. Michael Lincoff, MD; Eric J. Topol, MD; Peter B. Berger, MD

Background—Clopidogrel is an inactive prodrug; it is converted to its active metabolite through the cytochrome P450 (CYP3A4) pathway, which also metabolizes calcium channel blockers (CCBs). Several studies have reported that CCBs reduce the ability of clopidogrel to inhibit platelet aggregability; one suggested that CCBs reduce the efficacy of clopidogrel.

Methods and Results—We performed a post hoc analysis of the Clopidogrel for the Reduction of Events During Observation (CREDO) study to compare the treatment effect of clopidogrel in patients on CCBs versus not on CCBs. In CREDO, 2116 patients were randomly assigned to pretreatment with 300 mg clopidogrel 3–24 hours before a planned percutaneous coronary intervention followed by 1 year of 75 mg/d clopidogrel, versus 75 mg clopidogrel at the time of the procedure and continued for 28 days only. The primary end points were a combined end point of death, myocardial infarction, and stroke at 28 days and 1 year. Among the 580 patients (27%) on CCBs at enrollment, at 28 days, the combined end point was reached in 17 patients (6%) on clopidogrel versus 28 (9%) on placebo (hazard ratio [HR], 0.71; 95% confidence interval [CI], 0.39–1.29). At 1 year, the combined end point was reached in 27 patients (10%) on clopidogrel versus 46 (15%) on placebo (HR, 0.68; 95% CI, 0.42–1.09). The treatment effect of clopidogrel was similar in patients not on CCBs at 1 year (HR, 0.78; 95% CI, 0.56–1.09). After adjustment for differences between patients on and not on CCB, there was still no evidence of an interaction between clopidogrel treatment and CCB (HR for patients not on CCBs, 0.87; 95% CI, 0.62–1.23; HR for patients on CCBs, 0.74; 95% CI, 0.45–1.21).

Conclusions—In CREDO, there was no evidence that CCBs decrease the efficacy of clopidogrel. (Circ Cardiovasc Interv. 2012;5:77-81.)

Key Words: angioplasty ■ drugs ■ platelets ■ stents ■ thrombosis

In patients with cardiovascular disease, antiplatelet medications are generally administered in addition to disease-modifying agents, most commonly antihypertensive and lipid-lowering agents. Thus, the possibility of drug-drug interactions exists.

Clopidogrel has become widely used because of its beneficial effects in patients receiving coronary, carotid, or peripheral arterial stents, acute coronary syndromes, and stable vascular disease. It is an inactive prodrug that requires conversion to its active metabolite in the liver. It is believed this occurs in part through the cytochrome P450 3A4 (CYP3A4) pathway. The active metabolite inhibits platelet activation and recruitment by blocking the adenosine diphosphate (ADP) P2Y12 receptor.

Calcium channel blockers (CCBs) are often also used in patients with cardiovascular disease for the treatment of hypertension, angina, atrial fibrillation, other arrhythmia, and other indications as well. All CCBs are believed to be primarily metabolized by the same cytochrome P450 3A system. Ex vivo studies of platelet function suggest that CCBs reduce the conversion of the clopidogrel prodrug to its active metabolite, therefore reducing the ability of clopidogrel to inhibit platelet aggregation. The clinical significance of this laboratory assessment of platelet activity, however, remains unclear. In the only study performed to determine whether there existed a clinically significant interaction between clopidogrel and CCBs, patients on both agents had a higher frequency of the combined end point of death, myocardial infarction (MI), and need for a revascularization procedure in the 6 months after a percutaneous coronary intervention (PCI) as compared with patients on clopidogrel alone, even after adjustment for differences between the 2 agents (adjusted hazard ratio [HR], 3.5; 95% confidence interval [CI], 1.4–8.6; P=0.005).
WHAT IS KNOWN

- Clopidogrel is an inactive prodrug that is converted to its active metabolite through the cytochrome P450 pathway.
- Calcium channel blockers are also metabolized by the cytochrome P450 system.
- Prior studies have reported that calcium channel blockers decrease the efficacy of clopidogrel by limiting the ability of clopidogrel to inhibit platelet aggregation.

WHAT THE STUDY ADDS

- This article provides evidence to refute the findings from earlier studies by demonstrating that patients taking calcium channel blockers do not derive any less clinical benefit from clopidogrel compared with patients not taking these agents.

Methods

The full details of the design, methods, and findings for the Clopidogrel for the Reduction of Events During Observation (CREDO) trial have previously been published. Briefly, CREDO was a prospective, multicenter, double-blind, randomized, placebo-controlled trial comparing 2 dosage regimens of clopidogrel among patient planned for PCI: a 300-mg loading dose administered 3–24 hours before PCI followed by 75 mg daily for 1 year, versus 75 mg daily for 28 days without a loading dose. Eligible patients were those not taking these agents.

Table. Baseline Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>CCB (n=580)</th>
<th>No CCB (n=1536)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo,  n (%)</td>
<td>Clopidogrel, n (%)</td>
</tr>
<tr>
<td>Total No.</td>
<td>312</td>
<td>268</td>
</tr>
<tr>
<td>Age &gt;65 y</td>
<td>151 (48)</td>
<td>132 (49)</td>
</tr>
<tr>
<td>Male</td>
<td>212 (68)</td>
<td>181 (68)</td>
</tr>
<tr>
<td>Body mass index &gt;30</td>
<td>151 (49)</td>
<td>125 (47)</td>
</tr>
<tr>
<td>Smoking within 1 year</td>
<td>86 (28)</td>
<td>74 (28)</td>
</tr>
<tr>
<td>Stable angina</td>
<td>84 (27)</td>
<td>82 (31)</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>182 (59)</td>
<td>139 (52)</td>
</tr>
<tr>
<td>History of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>272 (87)</td>
<td>234 (88)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>243 (81)</td>
<td>214 (81)</td>
</tr>
<tr>
<td>CHF</td>
<td>31 (10)</td>
<td>23 (9)</td>
</tr>
<tr>
<td>MI</td>
<td>117 (40)</td>
<td>82 (32)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>14 (5)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>91 (29)</td>
<td>85 (32)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>34 (11)</td>
<td>20 (8)</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>40 (13)</td>
<td>34 (13)</td>
</tr>
<tr>
<td>CABG</td>
<td>61 (20)</td>
<td>49 (19)</td>
</tr>
<tr>
<td>PCI</td>
<td>111 (37)</td>
<td>88 (34)</td>
</tr>
<tr>
<td>Baseline ACE inhibitor</td>
<td>200 (35)</td>
<td>92 (34)</td>
</tr>
<tr>
<td>Baseline aspirin</td>
<td>192 (33)</td>
<td>88 (33)</td>
</tr>
<tr>
<td>Baseline β-blocker</td>
<td>331 (57)</td>
<td>141 (53)</td>
</tr>
<tr>
<td>Baseline statin</td>
<td>367 (63)</td>
<td>169 (63)</td>
</tr>
</tbody>
</table>

CCB indicates calcium channel blocker; CHF, congestive heart failure; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; and ACE, angiotensin-converting enzyme.

for patients on a CCB and those not on a CCB. All probability values <0.05 are considered statistically significant. No adjustments were made for multiple comparisons. Analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC).

Results

Baseline Characteristics

Of the 2116 patients enrolled in CREDO, 580 patients (27%) were on CCBs and 1536 (73%) patients were not on CCB at the time of enrollment in the trial. Baseline characteristics based on CCB use at study entry are shown in the Table. Patients on CCBs tended to be older, were more commonly female, more frequently had a body mass index >30, diabetes mellitus, hypertension, hyperlipidemia, cerebrovascular disease, and peripheral vascular disease. They also had more commonly undergone previous coronary artery bypass grafting and a prior PCI.

Clinical Outcome

Among the 580 patients on CCBs on enrollment in the trial, 268 (46%) were randomly assigned to pretreatment with a loading dose of clopidogrel and treatment for 1 year, and 312 (54%) received no pretreatment and received clopidogrel for 28 days only. In patients on CCBs at study entry, the 1-year...
combined end point of death, MI, and stroke was reached in 27 patients (10%) on 1 year of clopidogrel versus 46 patients (15%) on placebo (HR, 0.68; 95% CI, 0.42–1.09) (Figure 1). Among patients not on CCBs at study entry, the 1-year combined end point was reached in 62 patients (8%) on clopidogrel versus 76 (10%) on placebo HR, 0.78; 95% CI, 0.56–1.09). This primary combined end point in patients on CCBs at study entry was driven by a large reduction in MI (Figure 2). Analysis to determine whether there was an interaction between clopidogrel treatment effect and CCBs revealed that there was not a significant interaction (Wald $\chi^2$ $P$ = 0.64). To eliminate potential confounders, the model was adjusted for the differences between patients on CCBs and those not on CCBs found in the Table. After adjustments for these variables, the lack of an interaction between clopidogrel treatment effect and CCBs revealed that there was not a significant interaction (Wald $\chi^2$ $P$ = 0.58; HR for patients not on CCBs, 0.87; 95% CI, 0.62–1.23; HR for patients on CCBs, 0.74; 95% CI, 0.45–1.21).

Among patients on a CCB, the 28-day combined end point was reached in 17 patients (6%) on clopidogrel versus 28 patients (9%) on placebo (HR, 0.71; 95% CI, 0.39–1.29) (Figure 3). Among those patients not on CCBs, the 28-day combined end point was reached in 41 patients (5%) on clopidogrel versus 45 patients (6%) on placebo (HR, 0.87; 95% CI, 0.57–1.33).

**Discussion**

In this post hoc analysis of the CREDO trial, we found no evidence that patients on CCBs derive less benefit from clopidogrel. In fact, the relative risk reduction associated with pretreatment with a loading dose and long-term clopidogrel was numerically greater among those patients on a CCB than among those who were not on a CCB.

**Background**

The possibility that other drugs that require the CYP 3A4 metabolic pathway might interfere with the conversion of clopidogrel prodrug to its active metabolite first surfaced with atorvastatin. Many preclinical studies suggested that atorvastatin reduced the inhibition of platelet aggregation by clopidogrel using ADP-stimulated expression of P-selectin by flow cytometry, platelet aggregation measured by the point-of-care MICROs cell counter, and optical aggregometry.5–7 Subsequently, several confounded registry analyses suggested that indeed there might be a negative interaction. However, retrospective analyses of unbiased clinical trials subsequently proved strong evidence against such an interaction.8–10

**Prior Studies of CCBs**

The concern that an interaction between clopidogrel and CCBs might exist also stems from their common metabolism through the CYP 3A4 pathway. A study by Siller-Matula et al2 used flow cytometry to assess VASP phosphorylation, which is believed to be an excellent measure of P2Y12 inhibition. They found that the patients on both CCBs and clopidogrel had a higher platelet reactivity index, suggesting less inhibition of aggregation from clopidogrel than patients not on CCBs. They also found that ADP-induced platelet aggregation was greater in patients not on CCBs than in those on CCBs. In the only study evaluating a possible interaction...
between CCBs and clopidogrel using clinical end points, these same investigators evaluated the 6-month clinical outcomes of 200 patients who underwent a PCI and were treated with clopidogrel. Using a composite end point of cardiovascular death, MI, and revascularization, they found that the 45 patients (23%) on a CCB had a higher event rate than those not on a CCB; the adjusted HR was 3.5 (95% CI, 1.4–8.6; P = 0.005) for CCB use. The study, however, was limited by its small sample size, the inability of even complex statistical methods to adjust for many important differences between groups, and that the end point was driven by a difference in revascularization between days 100–200, which probably was due to restenosis, a phenomenon not believed to be reduced by clopidogrel. A more recent study by Gremmel et al\(^1\) used light transmission aggregometry and the VerifyNow P2Y12 assay and also identified a negative interaction between CCBs and clopidogrel. They found higher on-treatment platelet reactivity in patients who were on concomitant CCB therapy as opposed to those who were not, by both laboratory tests. However, they did not assess the impact of the interaction on clinical outcomes.

**Proton Pump Inhibitors**

Currently, similar concerns have been raised about proton pump inhibitors interfering with the metabolic activation of clopidogrel.\(^11\)^\(^12\) Registries have suggested that patients who are on clopidogrel and proton pump inhibitors have worse outcomes than patients on clopidogrel but not on proton pump inhibitors.\(^13\) A preliminary report from the CREDO trial suggested that this, too, may be due to confounding.\(^14\) Further studies are ongoing.

**Implications**

The current study raises questions about the appropriateness of clinical decision-making based on ex vivo measures of platelet function. Though several ex vivo platelet function tests have correlated with clinical outcome in clinical studies,\(^15\)^\(^17\) they have been misleading in terms of the ability to predict benefit from clopidogrel in patients treated with medications that reportedly reduce the ability of the liver to convert clopidogrel to its active metabolite. Until prospective, randomized studies, like The Gauging Responsiveness with A VerifyNow assay-Impact on Thrombosis And Safety (GRAVITAS) trial are completed, we would recommend that ex vivo platelet function tests not be used to guide clinical practice.\(^18\)

**Limitations**

Our analysis has some important limitations. This was a post hoc analysis of a randomized trial. The fact that patients on CCBs have more adverse events than patients not on CCBs supports the hypothesis that confounding may contribute to the prior clinical study that did suggest an interaction between CCBs and clopidogrel. The type of CCB was not recorded in the CREDO database; however, all are believed to be primarily metabolized by the same CYP3A4 pathway.\(^19\)

Two other limitations are potentially important, however. In CREDO, it was known if patients were on CCBs at the time of enrollment into the trial, but subsequent prescription of and adherence to CCB therapy was not evaluated. Therefore, it is possible that some patients stopped their CCB after enrollment and others began treatment with them after enrollment during the course of the 1-year follow-up period. However, approximately 87% of patients on CCBs had hypertension, and 30% had diabetes mellitus; these conditions likely would not have been influenced by the index PCI procedure, so that nearly all patients on CCBs had continued indications for the drug and probably were continued on it. Additionally, the 28-day combined end point was primarily affected by the difference in treatment between the 2 arms within the 3–24 hours after enrollment, before any changes in medication were likely to have occurred. In that analysis, patients on CCBs continued to have greater risk reduction with clopidogrel than patients not on CCBs. The other potentially important limitation is that the study included a relatively small number of patients (n=2116), limiting its power to detect a difference in therapeutic effect of clopidogrel in patients on and those not on CCBs. However, the risk reduction with clopidogrel in patients on CCBs for both the 1-year and 28-day end points was paradoxically greater than for patients not on CCBs. Given this observation, the likelihood that CCBs actually do reduce the therapeutic benefits of clopidogrel is remote. Furthermore, the current study is more than 10 times the size of the only prior study evaluating the clinical impact of CCBs potential interaction with clopidogrel.\(^2\)

**Conclusions**

In the CREDO trial, there was no evidence that CCBs decrease the efficacy of clopidogrel in the year after a PCI. These data raise questions about the appropriateness of clinical decision-making based on ex vivo measures of platelet function.

**Disclosures**

Dr Steinh Dubl is currently an employee of The Medicines Company. Dr Lincoff has research funding with BMS, Sanofi, Schering-Plough, Medicines Company, Takeda, Roche, and Kai Therapeutics. Dr Topol serves as a consultant to Sanofi-Aventis and Daiichi-Sankyo. Dr Berger serves as a consultant to Accumetrics, Boehringer Ingelheim, Eli Lilly/Daiichi Sankyo, Novartis/Portola, and AstraZeneca; he has research funding from Thrombosis Prevention, Helena, Accumetrics, AstraZeneca, Hemoscope, The Medicines Company, Corgenix/Aspirininworks, and Eli Lilly/Daiichi-Sankyo.

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