Interaction Between Cigarette Smoking and Clinical Benefit of Clopidogrel

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Objectives
The aim of this study was to examine the interaction between cigarette smoking and the clinical efficacy of clopidogrel in ST-segment elevation myocardial infarction (STEMI).

Background
Cigarette smoking induces cytochrome P450 (CYP)1A2, which converts clopidogrel into its active metabolite, and prior studies suggest greater inhibition of platelet aggregation by clopidogrel in smokers of ≥10 cigarettes/day.

Methods
The effect of clopidogrel compared with placebo on angiographic and clinical outcomes was examined in 3,429 STEMI patients in the CLARITY–TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28) randomized trial stratified by smoking intensity as follows: not current smokers (n = 1,732), and smokers of 1 to 9 (n = 206), 10 to 19 (n = 354), 20 to 29 (n = 715), and ≥30 cigarettes/day (n = 422). Logistic regression was used to adjust for other baseline characteristics and interaction terms to test for effect modification.

Results
Although clopidogrel reduced the rate of the primary end point of a closed infarct-related artery or death/myocardial infarction before angiography in the CLARITY–TIMI 28 trial, the benefit was especially marked among those who smoked ≥10 cigarettes/day (adjusted odds ratio [OR]: 0.49, 95% confidence interval [CI]: 0.37 to 0.66; p < 0.0001) compared with those who did not (adjusted OR: 0.72, 95% CI: 0.57 to 0.91; p = 0.006; pinteraction = 0.04). Similarly, clopidogrel was significantly more effective at reducing the rate of cardiovascular death, myocardial infarction, or urgent revascularization through 30 days among those who smoked ≥10 cigarettes/day (adjusted OR: 0.54, 95% CI: 0.38 to 0.76; p = 0.0004) compared with those who did not (adjusted OR: 0.98; 95% CI: 0.75 to 1.28; p = 0.87; pinteraction = 0.006).

Conclusions
Cigarette smoking seems to positively modify the beneficial effect of clopidogrel on angiographic and clinical outcomes. This study demonstrates that common clinical factors that influence the metabolism of clopidogrel might impact its clinical effectiveness.

Journal of the American College of Cardiology Vol. 53, No. 15, 2009
© 2009 by the American College of Cardiology Foundation ISSN 0735-1097/09/$36.00
Manuscript received September 21, 2008; revised manuscript received December 9, 2008; accepted December 16, 2008.

Clopidogrel is an oral thienopyridine inhibitor of the platelet P2Y12 adenosine diphosphate (ADP) receptor that has been shown to prevent death and adverse cardiovascular events in patients with acute coronary syndromes (ACS) (1,2). However, there is substantial interpatient variability in the response to clopidogrel (3), and several studies have demonstrated that a diminished response to clopidogrel is associated with an increased risk of ischemic events (4–7).

Clopidogrel is a pro-drug that requires 2-step oxidization by cytochrome P450 (CYP) enzymes to be transformed into its active metabolite, 2-oxoclopidogrel, with CYP1A2 and CYP3A4 being important for the first and second steps, respectively (8). Genetic and environmental influences on CYP450 enzyme activity are thought to underlie the substantial interpatient variability in the response to clopidogrel (9–13). Cigarette smoking is a known inducer of CYP1A2 (14) and is therefore potentially capable of affecting the pharmacokinetics and pharmacodynamics of clopidogrel.

To that end, a recent study published in the Journal showed that cigarette smoking was associated with increased platelet inhibition and lower aggregation in re-
Student
Baseline characteristics across groups were compared with smoking 1 to 9, 10 to 19, 20 to 29, and 30 cigarettes/day. Com-
parison of smoking (one-half pack) per day or not. The odds ratios (ORs) and 95% confidence intervals (CIs) for the effect of clopidogrel on the outcomes were calculated within each smoking intensity stratum in a logistic regression model that adjusted for age, sex, region of enrollment (on the basis of the United Nations Statistics Geographic Region Codes), hypertension, diabetes, infarct location, time to fibrinolytic therapy, and type of fibrinolytic. Interaction terms in logistic regression models were used to test for the statistical significance of effect modification by smoking on the efficacy of clopidogrel (modeled as: smoking ≥10 cigarettes × randomization to clopidogrel).

Methods

Study population. The design and primary results of the CLARITY–TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis In Myocardial Infarction 28) trial have been published (2,16). In brief, 3,491 patients with ST-segment elevation myocardial infarction (STEMI) who presented within 12 h of symptom onset were to receive aspirin, a fibrinolytic, and heparin (required if they were to receive a fibrin-specific lytic) and were randomized to clopidogrel (300-mg loading dose followed by 75 mg daily) or placebo. As part of the trial protocol, patients were scheduled to undergo coronary angiography 2 to 8 days after initiation of therapy to assess for late patency of the infarct-related artery. Patients were followed for clinical outcomes and adverse events through 30 days after randomization. Smoking status and number of cigarettes smoked per day at baseline were collected on the case report form. The protocol was approved by the relevant institutional review boards, and written informed consent was obtained from all patients.

Outcomes. The primary efficacy end point was the composite of Thrombolysis In Myocardial Infarction (TIMI) flow grade (TFG) 0 or 1 or death or recurrent myocardial infarction (MI) before angiography could be performed. The 30-day clinical end point was a composite of death and primary results of the CLARITY–TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis In Myocardial Infarction 28) trial have been published (2,16). In brief, 3,491 patients with an ACS. smoking ≤10 cigarettes (one-half pack) per day or not. The odds ratios (ORs) and 95% confidence intervals (CIs) for the effect of clopidogrel on the outcomes were calculated within each smoking intensity stratum in a logistic regression model that adjusted for age, sex, region of enrollment (on the basis of the United Nations Statistics Geographic Region Codes), hypertension, diabetes, infarct location, time to fibrinolytic therapy, and type of fibrinolytic. Interaction terms in logistic regression models were used to test for the statistical significance of effect modification by smoking on the efficacy of clopidogrel (modeled as: smoking ≥10 cigarettes × randomization to clopidogrel).

Results

A total of 3,491 patients underwent randomization in the CLARITY–TIMI 28 trial, and smoking status was available for 3,429 patients. A total of 1,732 patients were not current smokers and 1,697 were, the latter consisting of 206 patients who smoked 1 to 9 cigarettes/day, 354 who smoked 10 to 19 cigarettes/day, 715 who smoked 20 to 29 cigarettes/day, and 422 who smoked ≥30 cigarettes/day. Compared with nonsmokers, smokers were younger, more likely to be men, less likely to have a history of hypertension or diabetes, and less likely to present with an anterior MI or get a fibrin-specific fibrinolytic (Table 1).

The effect of clopidogrel on the risk of the primary end point of a closed (TIMI flow grade 0 or 1) infarct-related artery or death or recurrent MI before angiography could be performed stratified by intensity of smoking is shown in Figure 1. Overall, in the trial, clopidogrel reduced the odds of the primary end point by 36% (OR: 0.64, 95% CI: 0.53 to 0.76, p < 0.001). Among nonsmokers or those who smoked less than one-half pack/day, the addition of clopi-
dogrel reduced the rate of the primary end point from 22.3% to 17.7%, with an adjusted OR of 0.72 (95% CI: 0.57 to 0.91; p = 0.006). However, among those who smoked one-half pack/day or more, the addition of clopidogrel resulted in a far greater reduction in the rate of the primary end point from 20.5% to 11.7%, with an adjusted OR of 0.49 (95% CI: 0.37 to 0.66; p < 0.0001). A test for interaction among smoking, clopidogrel treatment, and the primary efficacy end point was significant (p = 0.04), indicating a significantly greater benefit of clopidogrel in those who smoked at least one-half pack/day. Furthermore, examining the likelihood of achieving optimal epicardial flow (TFG 3), treatment with clopidogrel resulted in an adjusted OR of 1.14 (95% CI: 0.94 to 1.39; p = 0.18) among nonsmokers or those who smoked less than one-half pack/day versus 1.77 (95% CI: 1.40 to 2.22; p < 0.0001) among those who smoked one-half pack/day or more (pinteraction = 0.007), again demonstrating effect modification by smoking on clopidogrel.

The effect of clopidogrel on the risk of cardiovascular death, MI, or recurrent ischemia leading to the need for urgent revascularization by 30 days stratified by intensity of smoking ≤10 cigarettes (one-half pack) per day or not. The odds ratios (ORs) and 95% confidence intervals (CIs) for the effect of clopidogrel on the outcomes were calculated within each smoking intensity stratum in a logistic regression model that adjusted for age, sex, region of enrollment (on the basis of the United Nations Statistics Geographic Region Codes), hypertension, diabetes, infarct location, time to fibrinolytic therapy, and type of fibrinolytic. Interaction terms in logistic regression models were used to test for the statistical significance of effect modification by smoking on the efficacy of clopidogrel (modeled as: smoking ≥10 cigarettes × randomization to clopidogrel).
smoking is shown in Figure 2. Overall in the trial, clopidogrel reduced the odds of the 30-day clinical end point by 20% (OR: 0.80, 95% CI: 0.65 to 0.97, p = 0.03). We observed that the magnitude of treatment benefit with clopidogrel was associated with the degree of smoking, analogous to the angiographic findings. Among nonsmokers or those who smoked less than one-half pack/day, the addition of clopidogrel had no impact on the rate of the

<table>
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<th>Variable</th>
<th>Noncurrent Smokers</th>
<th>Cigarettes/day</th>
<th>p Value</th>
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<tr>
<td></td>
<td>n</td>
<td>0–9</td>
<td>10–19</td>
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<td>Cigarettes/day, median (IQR)</td>
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<td>354</td>
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<td>Age, yrs ± SD</td>
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<td>58.3 ± 10.5</td>
<td>54.5 ± 10.5</td>
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<td>Male sex, %</td>
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<td>81.1</td>
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<td>Region, %</td>
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<td>North America and Northern and Western Europe</td>
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<td>9.3</td>
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<td>Time from symptom onset to start of fibrinolytic, h (IQR)</td>
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<td>2.9 (2.0–4.4)</td>
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<td>3.9</td>
<td>6.5</td>
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<td>Neither</td>
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<td>20.1</td>
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<td>Concurrent administration of a CYP3A4-metabolized statin*, %</td>
<td>60.6</td>
<td>57.6</td>
<td>58.5</td>
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*Includes atorvastatin, simvastatin, and lovastatin.

CYP = cytochrome P450; IQR = interquartile range; MI = myocardial infarction.
30-day clinical end point (13.7% vs. 14.3%), with an adjusted OR of 0.98 (95% CI: 0.75 to 1.28; p = 0.87). In contrast, among those who smoked one-half pack/day or more, the addition of clopidogrel reduced the rate of the 30-day clinical end point from 14.3% to 8.0%, with an adjusted OR of 0.54 (95% CI: 0.38 to 0.76; p = 0.0004). A test for interaction among smoking, clopidogrel treatment, and the 30-day clinical end point was significant (p = 0.006), indicating a significantly greater benefit of clopidogrel in those who smoked at least one-half pack/day. Similarly, treatment with clopidogrel significantly reduced the risk of cardiovascular death or MI among those who smoked one-half pack/day or more (adjusted OR: 0.57, 95% CI: 0.38 to 0.85, p = 0.006), whereas it had no effect among nonsmokers or those who smoked less than one-half pack/day (adjusted OR: 0.97, 95% CI: 0.71 to 1.32, p = 0.84) (pInteraction = 0.032).

Rates of TIMI major or minor bleeding were low (<2%) in the entire study. There was no statistically significant interaction between smoking and clopidogrel on the risk of TIMI major or minor bleeding (pInteraction = 0.90).

Discussion

In a randomized, placebo-controlled trial of clopidogrel in over 3,400 patients with STEMI, we found that cigarette smoking, which induces 1 of the key CYP450 enzymes that transforms clopidogrel into its active metabolite, was associated with the magnitude of benefit from clopidogrel on angiographic and clinical outcomes. Whereas clopidogrel had significant benefit in the entire trial cohort, treatment with clopidogrel had approximately twice the efficacy in reducing both the risk of a closed infarct-related artery or death or MI before angiography could be performed and the risk of cardiovascular death, recurrent MI, or urgent revascularization over 30 days in patients who smoked at least one-half pack of cigarettes/day. This study provides another possible link in the emerging understanding of clopidogrel pharmacology. In exploring clopidogrel resistance or hyporesponsiveness, investigators have now focused on the metabolism of clopidogrel to its active metabolite as the key factor. Building on the recent finding that cigarette smoking is an inducer of clopidogrel metabolism leading to higher degrees of platelet inhibition with clopidogrel (15), we now show that cigarette smoking, in turn, is associated with differences in the clinical effectiveness of clopidogrel.

The emerging recognition that factors influencing the metabolism of clopidogrel can impact its pharmacologic and now clinical efficacy is supported by multiple pharmacologic observations. First, CYP1A2 is the predominant enzyme responsible for the first oxidative step in the conversion of clopidogrel to its active metabolite (8). Accelerating the first step would help prevent the pro-drug from being shunted down an esterase-mediated pathway that leads to pharmacologically inactive metabolites. Second, cigarette smoke in general and its polycyclic aromatic hydrocarbons in particular are known to induce CYP1A2 (14). A study comparing those who smoked one-half pack/day or more with nonsmokers found a 66% increase in CYP1A2 activity among smokers (17). Third, among heavy smokers, the half-life for dissipation of CYP1A2 induction upon discontinuation of smoking has been estimated to be 38.6 h, which would easily cover the time frame from symptom onset to clopi-
Clopidogrel pharmacology such as statins metabolized by for medications that have been associated with altered unmeasured or unknown variables. Five, we did not adjust justment, we cannot exclude residual confounding due to subgroups. Although the effect modification of smoking on allocated clopidogrel therapy on outcomes within smoking reason, we did not examine the association between smok-mates for clopidogrel in this group were wide. Four, relatively small; hence the CIs surrounding the effect esti-mented in CLARITY–TIMI 28, a large multinational sample handling and assay complexity necessary for platelet data from recent platelet aggregation studies, within our clinical trial. Thus, although our findings are consistent with the presence of an interaction between clopidogrel and smoking. Specifically, analyses comparing smokers and non-smokers that include predominantly light smokers might fail to show a significant interaction.

It also is possible that smoking is associated with the magnitude of clinical benefit of clopidogrel for reasons in addition to or other than altering clopidogrel biotransformation into an active metabolite. There are data that smoking is associated with platelet activation in vivo and ex vivo (21–24). Thus, if they had more active platelets, smokers might stand to gain greater benefit from more intensive antiplatelet therapy. However, we should note that we did not see any significant difference in angiographic or clinical events in the placebo arm across smoking categories.

**Study limitations.** First, this was a post hoc analysis of a completed clinical trial. However, as we have noted in the preceding text, there are multiple pharmacologic studies that formed the basis for our hypothesis. Second, due to the sample handling and assay complexity necessary for platelet aggregation studies, these evaluations could not be implemented in CLARITY–TIMI 28, a large multinational clinical trial. Thus, although our findings are consistent with data from recent platelet aggregation studies, within our dataset the mechanistic link between smoking and the efficacy of clopidogrel remains speculative. Third, the subgroup of those who smoked 1 to 9 cigarettes/day was relatively small; hence the CIs surrounding the effect estimates for clopidogrel in this group were wide. Four, smoking status was, of course, not randomized. For that reason, we did not examine the association between smoking status and outcomes but rather the effect of randomly allocated clopidogrel therapy on outcomes within smoking subgroups. Although the effect modification of smoking on clopidogrel efficacy persisted after careful multivariable ad-justment, we cannot exclude residual confounding due to unmeasured or unknown variables. Five, we did not adjust for medications that have been associated with altered clopidogrel pharmacology such as statins metabolized by CYP3A4 or proton pump inhibitors (25,26). Use of proton pump inhibitors was not collected on the case report form. Use of statins was collected, but administration of CYP3A4-metabolized statins was not imbalanced across smoking categories. Furthermore, data from 3 randomized trials of clopidogrel (including ours, data not shown) have shown no clinical effect modification by statin therapy (27,28).

**Conclusion**

Cigarette smoking seems to positively modify the beneficial effect of clopidogrel on both angiographic and clinical outcomes. These data highlight the contribution of envi-ronmental factors to the interpatient variability in response to clopidogrel.

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**REFERENCES**


**Key Words:** clopidogrel • cytochrome P450 • smoking.