Lack of Evidence of a Clopidogrel–Statin Interaction in the CHARISMA Trial

Jacqueline Saw, MD,* Danielle M. Brennan, MS,† Steven R. Steinhubl, MD,‡ Deepak L. Bhatt, MD,† Koon-Hou Mak, MD,§ Keith Fox, MB, CittB,|| Eric J. Topol, MD,# on behalf of the CHARISMA Investigators

Vancouver, British Columbia, Canada; Cleveland, Ohio; Lexington, Kentucky; Singapore; Edinburgh, Scotland, United Kingdom; and La Jolla, California

Objectives
The purpose of this study was to evaluate the potential impact of clopidogrel and statin interaction in a randomized, placebo-controlled trial with long-term follow-up.

Background
There are conflicting data regarding whether statins predominantly metabolized by CYP3A4 reduce the metabolism of clopidogrel to its active metabolite and diminish its clinical efficacy.

Methods
The CHARISMA trial was a randomized trial comparing long-term 75 mg/day clopidogrel versus placebo in patients with cardiovascular disease or multiple risk factors on aspirin. The primary end point was a composite of myocardial infarction, stroke, or cardiovascular death at median follow-up of 28 months. We performed a secondary analysis evaluating the interaction of clopidogrel versus placebo with statin administration, categorizing baseline statin use to those predominantly CYP3A4 metabolized (atorvastatin, lovastatin, simvastatin; CYP3A4-MET) or others (pravastatin, fluvastatin; non–CYP3A4-MET).

Results
Of 15,603 patients enrolled, 10,078 received a statin at baseline (8,245 CYP3A4-MET, 1,748 non–CYP3A4-MET) and 5,496 did not. For the overall population, the primary end point was 6.8% with clopidogrel and 7.3% with placebo (hazard ratio [HR] 0.93; p = 0.22). This was similar among patients on CYP3A4-MET (5.9% clopidogrel, 6.6% placebo, HR 0.89; p = 0.18) or non–CYP3A4-MET statin (5.7% clopidogrel, 7.2% placebo, HR 0.78; p = 0.19). There was no interaction between statin types and randomized treatment (p = 0.69). Patients on atorvastatin (n = 4,127) (5.7% clopidogrel, 7.1% placebo, HR 0.80; p = 0.06) or pravastatin (n = 1,440) (5.1% clopidogrel, 7.0% placebo, HR 0.72; p = 0.13) had similar event rates.

Conclusions
Despite theoretic concerns and ex vivo testing suggesting a potential negative interaction with concomitant clopidogrel and CYP3A4-MET statin administration, there was no evidence of an interaction clinically in a large placebo-controlled trial with long-term follow-up. (J Am Coll Cardiol 2007;50:291–5) © 2007 by the American College of Cardiology Foundation

Clopidogrel and 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors (statins) are frequently coadministered in patients with atherosclerosis, especially those who have undergone stent implantation. Furthermore, clopidogrel and several statins are predominantly metabolized by cytochrome P450 3A4 isoenzyme (CYP3A4) in vivo for activation and elimination, respectively (1,2). Thus, any drug–drug interactions that may adversely affect the efficacy of either drug could radically alter our standard treatment armamentarium. Such an interaction between clopidogrel and atorvastatin was first described in an ex vivo experiment using the point-of-care Plateletworks test by Lau et al. in 2003 (3). Since then, several other ex vivo studies using light transmission aggregometry and flow cytometry have yielded conflicting results (1,4–11). In addition, we and others have studied the clinical impact of such a potential interaction between clopidogrel and CYP3A4-metabolized statins and have found no adverse interaction (12–14). The major criticisms of those clinical studies were their small sample size and lack of long-term follow-up.
size and retrospective nature. Although a large randomized study comparing CYP3A4-metabolized versus non-CYP3A4-metabolized statins in patients on clopidogrel (with evaluation of platelet aggregation, activation, and clinical end points) would be ideal to solve this controversy, such a study would require tremendous resources and laboratory personnel support and, therefore, is not likely to be executed.

The CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) study (15) inclusive of 15,603 high-risk patients provided an opportunity to more definitively evaluate the clinical impact of concomitant clopidogrel and statin therapy. We therefore performed a secondary analysis of CHARISMA, stratifying patients into statins administered according to CYP3A4 metabolism.

Methods

The design, methods, and primary results of the CHARISMA study have been described in detail previously (15). To summarize, CHARISMA was a prospective, multicenter, double-blind, randomized, placebo-controlled trial comparing long-term 75 mg/day clopidogrel versus placebo in patients at high risk for cardiovascular events. All patients also received low-dose (75 to 162 mg/day) aspirin. Inclusion criteria were patients age ≥45 years with either multiple atherothrombotic risk factors or documented coronary disease, cerebrovascular disease, or symptomatic peripheral arterial disease. Patients were excluded if they were judged to have established indications for clopidogrel therapy (e.g., acute coronary syndrome, stent implantation). The follow-up was at 1 month, 3 months, 6 months, and every 6 months thereafter until the end of the trial. The primary efficacy end point was the first occurrence of myocardial infarction (MI), stroke, or cardiovascular death with the median of 28 months follow-up. The primary safety end point was major bleeding according to the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries) definition (16), which includes fatal bleeding and intracranial hemorrhage or bleeding that caused hemodynamic compromise requiring blood or fluid replacement, inotropic support, or surgical intervention.

We performed a secondary analysis of the CHARISMA trial, evaluating the differential treatment effect (interaction) of clopidogrel versus placebo according to the type of statin administration. Statin administration was nonrandomized and directed by the treating physicians. We divided patients into 2 major groups according to baseline statin administration: 1) those receiving statins that are predominantly metabolized by CYP3A4 (atorvastatin, lovastatin, simvastatin; CYP3A4-MET); and 2) those on statins that are not predominantly metabolized by CYP3A4 (pravastatin, fluvastatin; non-CYP3A4-MET). Additionally, clinical outcomes were evaluated separately in patients receiving atorvastatin or pravastatin. We compared the relative efficacy of clopidogrel versus placebo on the primary efficacy and safety end points according to the type of statin administered. The analyses were performed on the entire cohort of the CHARISMA trial patients as well as the subgroup of patients with established cardiovascular disease.

Statistics. All data analyses were performed on the intention-to-treat population. Hypothesis tests were done using 2-sided tests at the 5% significance level. Baseline characteristics were compared with chi-square tests for discrete and continuous variables. The primary efficacy of clopidogrel versus placebo was assessed with the log rank test. Statistical comparisons of the primary safety end point in the 2 treatment groups were performed with Pearson chi-square test. The treatment effect, measured by the hazard ratio (HR) and its 95% confidence interval (CI), was estimated with the Cox proportional hazards model for the primary efficacy end point and by odds ratios (OR) and 95% CI from logistic regression model for the primary safety end point. Interactions were tested in a Cox proportional hazards model, incorporating terms for randomized treatment, statin, and the treatment–by–statin interaction, to assess if treatment effect differed for CYP3A4-MET versus non–CYP3A4-MET and atorvastatin versus pravastatin. All statistical analyses were performed with SAS software (version 8.2; SAS Institute, Cary, North Carolina).

Results

Patient characteristics. The CHARISMA trial enrolled 15,603 patients, with 7,802 randomized to clopidogrel and 7,801 randomized to placebo. Of these, 10,078 (64.6%) were on a statin before randomization: 8,245 were on a CYP3A4-MET statin (4,127 on atorvastatin) and 1,748 were on a non–CYP3A4-MET statin (1,440 on pravastatin). We excluded 29 patients who were listed as being on both types of statins. The baseline demographics are described in Table 1. Patients in the CYP3A4-MET group were slightly younger, had a greater body mass index, and had a higher prevalence of hypercholesterolemia, peripheral arterial disease, prior strokes, carotid endarterectomy, and coronary artery bypass surgery. The median follow-up was 28 months.

Primary efficacy end point (MI, stroke, or cardiovascular death). In the overall study population, the primary end point was 6.8% with clopidogrel and 7.3% with placebo (HR 0.93, 95% CI 0.83 to 1.05; p = 0.23). This was similar with the use of statins (clopidogrel 5.9%, placebo 6.7%, HR 0.87, 95% CI 0.75 to 1.02; p = 0.084), irrespective of the type used (Fig. 1): CYP3A4-MET (5.9% clopidogrel, 6.6% placebo, HR 0.89, 95% CI 0.75 to 1.06; p = 0.18) or non–CYP3A4-MET (5.7% clopidogrel, 7.2% placebo, HR 0.78, 95% CI 0.54 to 1.13; p = 0.19). The interaction of the type of statin (CYP3A4-MET vs. non–CYP3A4-MET) and randomized treatment was not significant (p = 0.69).
Among patients not on a statin, the primary end point was 8.7% with clopidogrel versus 8.5% with placebo (HR 1.02, 95% CI 0.85 to 1.22; p = 0.87).

**Atorvastatin versus pravastatin.** The long-term primary end point was also similar irrespective of atorvastatin or pravastatin administration with clopidogrel. Among patients who received atorvastatin, the primary end point was 5.7% with clopidogrel, 7.1% with placebo (HR 0.80, 95% CI 0.62 to 1.01; p = 0.06). Among patients on pravastatin, the primary end point was 5.1% with clopidogrel, 7.0% with placebo (HR 0.72, 95% CI 0.47 to 1.10; p = 0.13). The interaction of atorvastatin versus pravastatin and randomized treatment was not significant (p = 0.54).

**Bleeding complications.** There was no difference in the primary safety end point of major bleeding between the groups: all patients (clopidogrel 1.6%, placebo 1.3%, OR 1.24; p = 0.11), no statin (clopidogrel 2.1%, placebo 1.7%, OR 1.29; p = 0.20), any statin (clopidogrel 1.4%, placebo 1.2%, OR 1.19; p = 0.33), CYP3A4-MET (clopidogrel 1.4%, placebo 1.2%, OR 1.19; p = 0.39), non–CYP3A4-MET (clopidogrel 1.3%, placebo 1.2%, OR 1.14; p = 0.76), atorvastatin (clopidogrel 1.2%, placebo 1.3%, OR 0.87; p =

![Figure 1

**CV Death, MI, and Stroke**](Image)

Primary end point of cardiovascular (CV) death, myocardial infarction (MI), or stroke at a median of 28 months among patients randomized to clopidogrel or placebo, according to statin administration. CYP3A4-MET = cytochrome P450 3A4-metabolized statin; HR = hazard ratio.
0.61), and pravastatin (clopidogrel 1.3%, placebo 1.3%, OR 1.04; p = 0.93).

**Patients with established cardiovascular disease.** There were 12,153 patients with established cardiovascular disease in the overall CHARISMA study. In this symptomatic subgroup, there was a marginally significant reduction in the primary end point with clopidogrel (6.9%) versus placebo (7.9%; HR 0.88, 95% CI 0.77 to 0.998; p = 0.046). Given that this prespecified cohort of patients had differential effects with clopidogrel from the asymptomatic CHARISMA population (p = 0.045 for interaction in the main CHARISMA manuscript), separate interaction analyses were performed. In the symptomatic subgroup, the interaction of the type of statin used (CYP3A4-MET or non–CYP3A4-MET) and the randomized treatment (clopidogrel vs. placebo) remained insignificant (p = 0.18). Likewise, the interaction of atorvastatin versus pravastatin and randomized treatment was not significant (p = 0.25).

**Statins versus no statins.** The use of any statins at randomization was associated with a lower primary end point for both patients randomized to clopidogrel (5.9% statins, 8.7% no statins; p < 0.001) and to placebo (6.7% statins, 8.5% no statins; p < 0.001). However, there was no significant interaction between the use of statins (vs. no statins) and randomized treatment (clopidogrel vs. placebo; p = 0.21).

**Discussion**

The CHARISMA trial was a large randomized prospective trial comparing long-term clopidogrel therapy with placebo in patients deemed at high risk for atherothrombotic events receiving concomitant aspirin. The design of the study allowed us to evaluate if there were any clinically relevant interactions with long-term concomitant clopidogrel and statin therapy. The present study is not only the largest to-date, but it is also the only one that studied the clinical impact of long-term (>1 year) coadministration of clopidogrel and statins. We stratified the CHARISMA patients according to the statin administered: no statin, any statin, CYP3A4-MET, non–CYP3A4-MET, atorvastatin, or pravastatin. We found no difference in the relative efficacy of clopidogrel compared with placebo at 28 months, irrespective of the type of statin administered (CYP3A4-MET or non–CYP3A4-MET, atorvastatin or pravastatin). Therefore, there is no clinically apparent adverse interaction between long-term administration of clopidogrel and statins that are predominantly CYP3A4 metabolized (i.e., atorvastatin, simvastatin, lovastatin).

Clopidogrel is an inactive prodrug that is metabolized to its active form in the liver by the cytochrome P450 enzyme, primarily by the CYP3A4 isoenzyme. Other isoenzymes involved to lesser degrees include CYP3A5, CYP2B6, and CYP1A2 (1). Several statins are also metabolized in the liver by CYP3A4 for elimination. Although 2 ex vivo studies showed that atorvastatin inhibited clopidogrel’s antiplatelet activity (3,5), both of those studies did not use the gold-standard light transmission aggregometry. In the study by Lau et al. (3), platelet aggregation was assessed by the bedside Plateletworks test, which indirectly measures platelet aggregation using a cell counter to measure objects exceeding the threshold platelet size. Likewise, Neubauer et al. (5) used flow cytometry to evaluate ADP-stimulated expression of P-selectin as a marker of platelet activation, without correlating to light transmission aggregometry.

In fact, all ex vivo studies using light transmission aggregometry have contradicted the clopidogrel and statin interaction (4,6–11). For instance, in the INTERACTION (Interaction of Atorvastatin and Clopidogrel) study, Serebruany et al. (8) prospectively assessed platelet function in 75 patients undergoing coronary stenting (pretreated with 325 mg/day aspirin and 300 mg loading clopidogrel) who had been taking atorvastatin, other statins, or no statins for at least 30 days. They found similar platelet inhibition at 4 h and at 24 h, assessed by light transmission aggregometry and flow cytometry (e.g., PECAM–1, P-selectin, CD40 ligand), irrespective of atorvastatin or other statin administration. In the study by Mitsios et al. (7), patients with acute coronary syndrome undergoing percutaneous coronary intervention (n = 30) were administered 375 mg loading clopidogrel (followed by 75 mg/day) and randomized to 10 mg atorvastatin or 40 mg pravastatin. Neither statin adversely affected clopidogrel’s platelet inhibition when assessed with light transmission aggregometry and flow cytometry expressions of P-selectin and CD40 ligand. Furthermore, in the largest relevant laboratory study to date (539 of 1,001 patients undergoing catheterization were on statins), Hochholzer et al. (10) found that the use of CYP3A4-MET statins did not adversely affect platelet aggregation with clopidogrel as assessed by light transmission aggregometry and flow cytometry surface expressions of P-selectin and activated glycoprotein IIb/IIIa. Of note, these studies were performed during the acute loading phase of clopidogrel administration, whereas steady state may not have been achieved in all patients, given the individual variability of response to clopidogrel. However, in the study by Vinholt et al. (9), in which patients with stable ischemic heart disease (n = 66) had been on 75 mg/day clopidogrel for at least 10 weeks, there also was no adverse laboratory interaction with statins (irrespective of CYP3A4 metabolism) when assessed with light transmission aggregometry.

Whether this controversial laboratory interaction translates to adverse clinical events had been previously evaluated in several studies. In a post hoc analysis of the CREDO (Clopidogrel for the Reduction of Events During Observation) study (n = 2,116), we showed no statistical interaction in the 28-day or 1-year composite death, MI, and stroke event rates with coadministration of clopidogrel and a CYP3A4-MET statin in patients who underwent coronary stenting (12). Wienbergen et al. (13) analyzed the MITRA-PLUS (Maximal Individual Therapy of Acute Myocardial Infarction Plus) registry of acute coronary syndrome patients on clopidogrel (n = 2,086),
segregating patients into those receiving atorvastatin versus other statins (including both CYP3A4-MET and non–CYP3A4-MET statins). They found no difference in mortality or stroke events between the 2 groups at a median follow-up of 14 months. In a single-center experience, Mukherjee et al. (14) also evaluated acute coronary syndrome patients (n = 1,691) on clopidogrel and found no difference in major adverse cardiac events at 6 months when they stratified patients according to the use of CYP3A4-MET statin. In contrast, in the observational study of the Quebec universal insurance database by Brophy et al. (17) of 2,927 patients who underwent percutaneous coronary interventions and received clopidogrel, those who were prescribed atorvastatin had worse 30-day outcomes than control subjects. However, there was no dose-dependent relationship with atorvastatin administration, and patients who were prescribed atorvastatin were likely a higher-risk cohort, thus introducing bias into the analysis (18).

The present study confirms the results of the 3 previous post hoc analyses showing lack of clinical interaction between clopidogrel and statins, extending the findings out beyond 2 years of concomitant therapy. The other major strength of the present study is the large patient population of the CHARISMA study. Excluding the MITRA–PLUS registry (which did not stratify patients according to CYP3A4 metabolism), we now have 3 studies concluding that the treatment benefit of clopidogrel is similar in patients on concomitant CYP3A4-MET statin or non–CYP3A4-MET statin. Furthermore, the present study suggests that this high-risk patient cohort benefited from statin administration, with lower clinical event-rates compared with those not on statins.

Study limitations. The major limitations of the present study include its retrospective post hoc design, which precludes definitive conclusions. The choice of statin administered was at the discretion of treating physicians, and thus potential selection bias may exist. However, clopidogrel allocation was randomized and blinded; therefore, any bias introduced by statin choice should be well balanced between clopidogrel and control groups. We did not perform laboratory assessments of platelet aggregation or activation, and the dose of statins administered and compliance with statins were not known. Our analyses were based upon baseline statin use, which is subject to error if there were major changes in statin prescription. However, when we evaluated statin usage over the study time period, we found an overall absolute 6% increase in statin use that was spread evenly between the different types of statins. Furthermore, when we reanalyzed the data including only patients on the same statin throughout the study, the results and conclusions remained unchanged (data not shown).

Conclusions

Our secondary analysis of a large randomized placebo-controlled trial with long-term follow-up showed no adverse clinical interaction with coadministration of clopidogrel and statins, irrespective of CYP3A4 metabolism. The concordant results from this study and other clinical analyses solidify the recommendation that clinicians need not choose statins on the basis of CYP3A4 metabolism when clopidogrel coadministration is necessary.

Reprint requests and correspondence: Dr. Eric J. Topol, Director, Scripps Translational Science Institute, Chief Academic Officer, Scripps Health, Professor of Translational Genomics, The Scripps Research Institute, Scripps Clinic, Division of Cardiovascular Diseases, 10666 North Torrey Pines Road, Mail Drop SW206, La Jolla, California 92037. E-mail: etopol@scripps.edu.

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