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Smoking, Clopidogrel, and Mortality in Patients With Established Cardiovascular Disease

Jeffrey S. Berger, MD, MS; Deepak L. Bhatt, MD, MPH; Steven R. Steinhubl, MD; Mingyuan Shao, MS; P. Gabriel Steg, MD; Gilles Montalescot, MD; Werner Hacke, MD; Keith A. Fox, MBChB; A. Michael Lincoff, MD; Eric J. Topol, MD; Peter B. Berger, MD; for the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) Investigators

Background—Smoking increases platelet aggregability and the degree of platelet inhibition by clopidogrel on ex vivo platelet function tests. Whether smoking status affects the relationship between clopidogrel and clinical outcomes is unknown.

Methods and Results—We evaluated the relationship between smoking status (current smoker, former smoker, or never-smoker) and treatment with clopidogrel on the risk of all-cause, cardiovascular, and cancer mortality among the 12,152 participants from the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) trial who had established cardiovascular disease. Current smoking was associated with an increase in all-cause (adjusted hazard ratio [HR] 2.58, 95% confidence interval [CI] 1.85 to 3.60), cardiovascular (HR 2.26, 95% CI 1.48 to 3.45), and cancer (HR 3.56, 95% CI 1.96 to 6.46) mortality compared with never smoking. The impact of clopidogrel on mortality differed by smoking status (P for interaction=0.018 for current smokers). Among current smokers, clopidogrel was associated with a reduction in all-cause mortality (HR 0.68, 95% CI 0.49 to 0.94); clopidogrel did not reduce all-cause mortality among former smokers (HR 0.95, 95% CI 0.75 to 1.19) or never-smokers (HR 1.14, 95% CI 0.83 to 1.58). A similar pattern was noted for cardiovascular mortality. As expected, no relationship was observed between clopidogrel and cancer mortality by smoking status. The risk of bleeding appeared to differ according to smoking status; randomized clopidogrel was associated with a significantly increased risk of severe or moderate bleeding (HR 1.62, P=0.04) among current smokers but a smaller and nonsignificant increase among never-smokers (HR 1.31, P=0.15).

Conclusions—Clopidogrel therapy may be more effective in current smokers, but it may also confer a greater bleeding risk than in nonsmokers. Further studies are needed to investigate this possibility. (Circulation. 2009;120:2337-2344.)

Key Words: smoking ■ clopidogrel ■ mortality ■ cardiovascular disease

More than 80 million people have cardiovascular disease in the United States.1 Although recent data suggest that outcomes are improving in this high-risk population,2 the overall mortality rate remains quite high, and cardiovascular disease is the number 1 killer in the United States.1 Considerable research has been directed at improving outcomes in this population.3 Because of its high associated morbidity and mortality, the influence of smoking in this population remains a major topic of interest and concern.4–6 Cigarette smoking has a number of adverse effects that influence the cardiovascular system and overall health.5 Smoking causes endothelial dysfunction, dyslipidemia, and increased platelet activation, which leads to a prothrombotic state.7–9 Smoking causes an increase in insulin resistance and the incidence of diabetes mellitus10,11 and is associated with increases in emerging biomarkers, including fibrinogen, factor VII, homocysteine, and C-reactive protein.12,13 Thus, a number of mechanisms may help explain the heightened risk of cardiovascular disease in smokers.

Clinical Perspective on p 2344

Many reports have consistently demonstrated a significant adverse relationship between smoking and mortality.14 Risk induced by smoking increases dramatically with the number

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From New York University School of Medicine (J.S.B.), New York, NY; University of Pennsylvania (J.S.B.), Philadelphia, Pa; VA Boston Healthcare System and Brigham and Women’s Hospital (D.L.B.), Boston, Mass; The Geisinger Clinic (S.R.S.), Danville, Pa; The Medicines Company (S.R.S.), Zurich Switzerland; Cleveland Clinic (M.S., A.M.L.), Cleveland, Ohio; INSERM U-698 (P.G.S.), Université Paris 7 and Assistance Publique–Hôpitaux de Paris, Paris, France; Institut de Cardiologie–Centre Hospitalier Universitaire Pitié-Salpêtrière (G.M.), Paris, France; University of Heidelberg (W.H.), Heidelberg, Germany; University and Royal Infirmary of Edinburgh (K.A.F.), Edinburgh, United Kingdom; Scripps Clinic (E.J.T.), La Jolla, Calif; and Geisinger Medical Center (P.B.B.), Danville, Pa.

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of cigarettes smoked daily. Data from several reports noted a significant relationship between total and cause-specific mortality in male and female smokers. A recent report from the Nurses Health Study demonstrated that excess vascular mortality may decrease rapidly after smoking cessation, but lung disease mortality may take up to 20 years to demonstrate a decline. The relationship between smoking status, total mortality, and cause-specific mortality in patients with established cardiovascular disease in the current era is less well established.

Recent laboratory data suggest that smoking influences the antiplatelet effect of clopidogrel. Cigarette smoking is an inducer of cytochrome P450 1A2 (CYP1A2), a hepatic enzyme involved in the metabolism of clopidogrel. Clopidogrel has been reported to result in greater inhibition of platelet aggregation in smokers than nonsmokers, which suggests that the pharmacodynamic response to clopidogrel may be modified by smoking. In studies that assessed the variability of platelet response to clopidogrel, smokers were less likely than nonsmokers to be hyporesponders. Whether smoking affects clinical outcomes in patients receiving clopidogrel remains uncertain.

The objectives of the present study were 2-fold: First, to evaluate the relationship between smoking status (current, former, and never) and all-cause, cardiovascular, and cancer mortality in patients with established cardiovascular disease, and second, to investigate the safety and efficacy of clopidogrel versus placebo according to smoking status. We hypothesized that in patients with established cardiovascular disease, current smokers would be at greatest risk for all-cause, cardiovascular, and cancer mortality. Because smoking appears to augment the antiplatelet effects of clopidogrel, we postulated that clopidogrel would have a greater benefit and higher bleeding risk than placebo in current smokers than in former smokers or those who had never smoked.

Methods

The design, methods, and primary results of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial have been described in detail previously. To summarize, CHARISMA was a prospective, multicenter, double-blind, randomized, placebo-controlled trial that compared clopidogrel 75 mg/d versus placebo long-term in patients at high risk for cardiovascular events. All patients also received aspirin (75 to 162 mg/d). After a median follow-up of 28 months, clopidogrel was no more effective than placebo in reducing the rate of myocardial infarction (MI), stroke, or cardiovascular death.

For the present study, we analyzed the impact of smoking status on mortality, cardiovascular events, and severe or moderate bleeding in subjects with established cardiovascular disease. Additionally, we evaluated the differential treatment effect (interaction) of clopidogrel versus placebo according to smoking status. Because smoking status was also used as an entry criterion for inclusion into the study for patients without established cardiovascular disease, patients without established cardiovascular disease were excluded from the present analysis. We divided the remaining 12,152 patients with established cardiovascular disease into 3 groups, according to smoking status: Current smokers, former smokers, and patients who had never smoked. Current smokers were defined as those who smoked at least 1 cigarette per day during the month before enrollment. Former smokers were defined as those who had smoked at least 1 cigarette per day at any time prior to the month before enrollment. Rates of permanent discontinuation of clopidogrel did not differ by smoking status (current smokers 19.4%, former smokers 18.9%, and never-smokers 18.2%; \( \chi^2 P = 0.51 \)). The median follow-up time was the same as in the main study (28 months).

We compared the relationship between current smokers and never-smokers, between former smokers and never-smokers, and between current smokers and former smokers for all-cause mortality, mortality subtype, cardiovascular events, and risk of severe or moderate bleeding. In addition, we compared the relative efficacy of clopidogrel versus placebo for all-cause, cardiovascular, and cancer mortality according to smoking status. We also compared the relative safety of clopidogrel versus placebo with regard to severe or moderate bleeding (determined by the GUSTO [Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries] criteria) according to smoking status. These events were adjudicated by the Cleveland Clinic Clinical Events Adjudication Committee.

Statistical Analysis

All data analyses were performed on the intention-to-treat population. Hypothesis tests were performed with 2-sided tests at the 5% significance level. Baseline characteristics were compared with \( \chi^2 \) tests for discrete variables and ANOVA for continuous variables. Adverse outcomes were compared with a 2-sided log-rank test and were plotted with cumulative Kaplan–Meier estimates of the event rates. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were estimated with the Cox proportional hazards model.

Multivariable Cox proportional hazards models were created to assess the relationship of smoking status and adverse outcomes after adjustment for baseline demographic and clinical history variables. Indicator variables of current smoker, former smoker, and never-smoker were created to represent the smoking data. An indicator variable of Europe versus all other locations was created for geographic region. Demographic data and baseline characteristics were entered into a multivariable Cox model for variable selection with bootstrap resampling (500 iterations and a \( P \) value criterion of 0.1 for retention). Those variables having a 50% or more probability of retention were considered reliable and were entered into a second Cox model with the model-selection procedure of stepwise selection or backward elimination. The significance level to enter and keep a variable was set at 0.05. These risk factors and the smoking indicator variables met the proportional hazards assumption by plotting the log of the negative log of their estimated survival distribution, \( \log(-\log(S(t))) \), versus time. The linearity assumption was assessed and satisfied for all continuous variables by plotting the log of the events against the continuous variable. The selected covariates from the 2 model-selection methods were compared to choose an optimal multivariable Cox model for each individual clinical end point.

Univariable interactions were tested in a Cox proportional hazards model that incorporated terms for randomized treatment, smoking status, and the treatment-by–smoking status interaction to assess whether treatment effect differed for current smokers versus never-smokers and former smokers versus never-smokers. Multivariable interactions were further analyzed by the addition of covariates of baseline characteristics into the model.

Because the present analysis was exploratory and primarily meant to be hypothesis generating, no adjustments for multiple comparisons were made. All statistical analyses were performed with SAS software (version 9.1.3; SAS Institute, Cary, NC).

Results

Of the 12,152 patients included in the present analysis, 2419 (19.9%) were current smokers, 6260 (51.5%) were former smokers, and 3473 (28.6%) never smoked. The median time of quitting smoking for former smokers was 11 years (range 0 to 69 years, mean 14.3 ± 13.4 years). Table 1 shows the baseline characteristics of the study participants by smoking status. Compared with never-smokers, current smokers were younger, less frequently female, and more likely to be white. Current smokers were less likely to have a history of
Smokers compared with those who had never smoked did not differ (HR 0.93, 95% CI 0.78 to 1.11, P=0.42). After multivariable adjustment, current smokers had a greater risk of stroke (HR 1.39, 95% CI 0.96 to 2.01) than never-smokers. No statistically significant increased risk for severe or moderate bleeding was observed for former smokers (HR 1.10, 95% CI 0.87 to 1.40, P=0.42).

**Current Versus Former Smokers**

After removing all patients who never smoked from the analysis, we performed multivariable adjustments to compare current versus former smokers. Current smokers were at increased risk for all-cause mortality (HR 1.75, 95% CI 1.39 to 2.19, P<0.01), cardiovascular mortality (HR 1.62, 95% CI 1.23 to 2.13, P<0.01), cancer mortality (HR 2.26, 95% CI 1.08 to 4.80, P<0.01), cardiovascular events (HR 1.56, 95% CI 1.08 to 2.26, P<0.01), and severe or moderate bleeding (HR 1.38, 95% CI 1.05 to 1.83, P=0.02) compared with former smokers (Figure 2).

**Clopidogrel**

Finally, we assessed whether smoking status had any influence on the effect of clopidogrel. In the overall cohort, rates of all-cause mortality were 4.9% with clopidogrel and 5.0% with placebo (HR 0.91, 95% CI 0.78 to 1.07, P=0.27). A significant interaction existed between current smokers and clopidogrel use for the outcome of all-cause mortality (P=0.018). Among current smokers, clopidogrel was associ-
ated with a reduction in all-cause mortality (HR 0.68, 95% CI 0.49 to 0.94). No reduction in all-cause mortality was noted for either former smokers (HR 0.95, 95% CI 0.75 to 1.19) or patients who had never smoked (HR 1.14, 95% CI 0.83 to 1.58). Similarly, a significant interaction existed between current smokers and clopidogrel for the outcome of cardiovascular mortality ($P_{\text{for interaction}}=0.037$; Figure 3). As would be expected, no significant interaction was noted for cancer mortality ($P_{\text{NS}}$).

The effect of clopidogrel on reducing cardiovascular events (MI, stroke, or cardiovascular death) did not differ according to smoking status ($P_{\text{for interaction}}=\text{NS}$). Clopidogrel was associated with a nonsignificant reduction in cardiovascular events in current smokers (HR 0.93, 95% CI 0.71 to 1.22), former smokers (HR 0.83, 95% CI 0.69 to 1.00), and never-smokers (HR 0.92, 95% CI 0.72 to 1.17). Although no significant interaction was noted, the benefit of clopidogrel versus placebo on the risk of cardiovascular death or MI was greater in current smokers (HR 0.82, 95% CI 0.58 to 1.15) than in former smokers (HR 0.92, 95% CI 0.74 to 1.15) or those who had never smoked (HR 1.01, 95% CI 0.74 to 1.37).

The relationship between clopidogrel or placebo and severe or moderate bleeding is illustrated in Figure 4. The risk of severe or moderate bleeding was increased in all smoking categories; however, despite the lack of a significant interaction between smoking and bleeding, the magnitude of the risk of severe or moderate bleeding with clopidogrel appeared to be related to smoking status. Specifically, clopidogrel was associated with a statistically significant increase in the risk of bleeding in current smokers (HR 1.62, 95% CI 1.02 to 2.58, $P=0.04$). Among those who never smoked, however, the increase in risk associated with clopidogrel was not statistically significant (HR 1.31, 95% CI 0.90 to 1.90, $P=0.15$).

**Discussion**

Among patients with established cardiovascular disease, smoking status is a strong independent risk factor for all-cause mortality, cardiovascular mortality, cancer mortality, cardiovascular events, and bleeding risk. Current smokers were at higher risk for each end point analyzed than former smokers or those who had never smoked. Interestingly, former smokers had similar outcomes as those who had never smoked, except for higher cancer mortality. These data also indicate that the benefit and risk of clopidogrel may be related to smoking status. Clopidogrel was most effective in reducing all-cause and cardiovascular mortality, while simultaneously causing an increase in the risk of bleeding in current smokers, a finding not observed in former smokers or never-smokers.

We believe the present data have clinical relevance for several reasons. Although smoking is known to influence total and cause-specific mortality in the general population, data in patients with cardiovascular disease are inconsistent. In fact, several reports have described a lower adverse event rate among smokers after an MI or

![Figure 1](circ.ahajournals.org) Kaplan–Meier curves of cardiovascular events stratified by smoking status. Cumulative incidence of all-cause mortality, cardiovascular mortality, and cancer mortality stratified by smoking status.
percutaneous revascularization, described as the “smoker’s paradox.”27–29 Nevertheless, despite the younger age and considerably lower risk of current smokers at the time of enrollment in the present study, smoking has a widespread negative effect on their health. The present analysis extends and reinforces evidence of an increase in total and cause-specific mortality caused by smoking, as well as the increase in bleeding in a population with established cardiovascular disease.

In the present analysis, former smokers had a risk of all-cause mortality, cardiovascular mortality, and bleeding similar to that for those who had never smoked. In contrast, the risk of cancer mortality remained elevated in former smokers compared with those who had never smoked. These data suggest that the high risk of all-cause and cardiovascular mortality and severe or moderate bleeding subsides after smoking cessation, whereas the risk of cancer mortality persists for a longer period of time. Recent data from the Nurses Health Study are consistent with this idea, with the finding that cardiovascular mortality decreases rapidly on smoking cessation, whereas cancer-related mortality may take up to 20 years to show a decline.19

The data suggest an important relationship between smoking status and the safety and efficacy of clopidogrel therapy. A formal test of heterogeneity of the treatment effect of clopidogrel on all-cause mortality and cardiovascular mortality was statistically significant, which suggests that the benefit of clopidogrel may not be identical across smoking categories. The present finding indicates that the effect of clopidogrel in reducing all-cause and cardiovascular mortality, MI, or stroke was greatest among current smokers, and the benefit diminished significantly in former smokers and never-smokers. As expected, the effect of clopidogrel on cancer mortality was neutral, with cancer mortality not modified by clopidogrel use. Surprisingly, the relationship between clopidogrel and cardiovascular events was not significantly modified by smoking. Nevertheless, the apparent

<table>
<thead>
<tr>
<th>Smoking Status</th>
<th>Unadjusted* HR (95% CI)</th>
<th>Fully Adjusted HR (95% CI)†</th>
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<td>All-cause mortality</td>
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<td>1.25 (0.93–1.68)</td>
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<td>Cardiovascular mortality</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>1.00</td>
</tr>
<tr>
<td>Former smoker</td>
<td>1.16 (0.81–1.65)</td>
<td>1.29 (0.90–1.84)</td>
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<td>2.26 (1.48–3.45)</td>
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<tr>
<td>Cancer mortality</td>
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<td>3.56 (1.96–6.46)</td>
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<td>Cardiovascular mortality or MI</td>
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<td>Nonsmoker</td>
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<td>1.00</td>
</tr>
<tr>
<td>Former smoker</td>
<td>0.95 (0.82–1.11)</td>
<td>1.00 (0.84–1.17)</td>
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<td>1.46 (1.14–1.88)</td>
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<td>Current smoker</td>
<td>0.97 (0.73–1.30)</td>
<td>1.48 (1.09–2.00)</td>
</tr>
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</table>

* Treatment allocation (clopidogrel vs placebo) was forced into the model. All-cause mortality and cardiovascular mortality were also adjusted for the interaction term between treatment allocation and smoking status.
†Adjusted for model-selected covariates from the pool of age; sex; ethnicity; geographic region (Europe vs all others); body weight; history of heart failure, hypercholesterolemia, hypertension, diabetes mellitus, diabetic nephropathy, transient ischemic attack, MI, stroke, peripheral arterial disease, percutaneous coronary intervention, or coronary artery bypass graft; and baseline medications (aspirin, β-blocker, angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, oral hypoglycemic). Treatment allocation (clopidogrel vs placebo) was forced into the model. All-cause mortality and cardiovascular mortality were also adjusted for the interaction term between treatment allocation and smoking status.
benefit of clopidogrel in reducing fatal cardiovascular events in current smokers suggests a real and plausible association. Overall, these data are in accordance with others and support recent ex vivo data that showed greater platelet inhibition by clopidogrel in current smokers than in never-smokers. These data, combined with the present clinical analysis, suggest that factors such as smoking modify the benefit of clopidogrel. Cigarette smoking induces activity of CYP1A2, a hepatic enzyme involved in the metabolism of clopidogrel. Thus, the greater platelet inhibition demonstrated by Blijden and colleagues and the clinical differences observed in the present study may be explained via the induction of CYP1A2. An alternative explanation for the association between smoking and clopidogrel may be explained in part by the lower release of tissue plasminogen activator in current smokers. Current smokers with impaired endogenous fibrinolysis may benefit the most from antiplatelet therapy, an observation noted in thrombolytic therapy and termed the "smoker's paradox." Because clopidogrel is known to increase bleeding, we evaluated whether smoking would modulate the excess bleeding risk with clopidogrel. Although no significant interaction was detected for bleeding risk and smoking, current smokers had the greatest risk of bleeding with clopidogrel use. This excess risk was attenuated in a stepwise fashion among former and current smokers.

Study Limitations

There are several important limitations of the present analysis. First, this post hoc subgroup analysis should be considered hypothesis generating. The present analyses of smoking status are based on a single baseline determination that may have changed over the study period; we did not have data on smoking after enrollment. However, misclassifications of smoking status would probably have attenuated the true association between current smokers and adverse events; thus, these results may represent an underestimate of the risk associated with current smoking.

Conclusions

Among patients with established cardiovascular disease, current smokers are at increased risk for all-cause, cardiovascular, and cancer-specific mortality, cardiovascular events, and severe or moderate bleeding. These data also suggest that the benefit and risk of clopidogrel may be modified by smoking status, thus providing additional evidence to support the hypothesis that the antiplatelet effect of clopidogrel may be enhanced in current smokers.

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Disclosures

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**CLINICAL PERSPECTIVE**

Clopidogrel is metabolized in the cytochrome P450 pathway to its active metabolite, and smoking is an inducer of CYP1A2. Recent in vitro data suggest that smoking influences the platelet inhibitory effect of clopidogrel, yet the relationship between clopidogrel, smoking, and clinical outcomes is incompletely understood. The objectives of this study were 2-fold: First, to evaluate the relationship between smoking status (current, former, or never) and all-cause, cardiovascular, and cancer mortality in patients with established cardiovascular disease, and second, to investigate the safety and efficacy of clopidogrel versus placebo stratified by smoking status. Among patients with established cardiovascular disease, smoking status is a strong independent risk factor for all-cause mortality, cardiovascular mortality, cancer mortality, cardiovascular events, and bleeding risk. A significant interaction existed between current smokers and clopidogrel use for the outcomes of all-cause and cardiovascular mortality. Clopidogrel was most effective in reducing all-cause and cardiovascular mortality, while simultaneously increasing the risk of bleeding in current smokers, a finding not observed in former or never-smokers. The present analysis extends and reinforces evidence of the increase in total and cause-specific mortality caused by smoking, as well as the increase in bleeding in a population with established cardiovascular disease. The data suggest an important relationship between smoking status and the safety and efficacy of clopidogrel therapy. Further studies are needed to investigate this possibility.