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Antithrombotic Therapy

Impact of Smoking on Long-Term Outcomes in Patients With Atherosclerotic Vascular Disease Treated With Aspirin or Clopidogrel

Insights From the CAPRIE Trial (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events)

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Objectives The goal of this study was to investigate the differential efficacy of clopidogrel or aspirin monotherapy according to smoking status in patients with atherosclerotic vascular disease.

Background Smoking enhances clopidogrel-induced platelet inhibition, which may explain the higher relative benefit among smokers observed in trials evaluating dual antiplatelet therapy. Whether smoking has an impact on clinical outcomes in patients requiring a single antiplatelet agent remains unknown.

Methods This was a post-hoc analysis of the CAPRIE (Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events) trial that compared clopidogrel and aspirin monotherapy in patients (N = 19,184) with atherosclerotic vascular disease.

Results Current smokers (n = 5,688) had an increased risk of ischemic events compared with never smokers (n = 4,135; hazard ratio [HR]: 1.24 [95% confidence interval (CI): 1.08 to 1.42]) and ex-smokers (n = 9,381; HR: 1.32 [95% CI: 1.18 to 1.47]) ($p < 0.001$). Clopidogrel was associated with a reduction in ischemic events among current smokers (8.3% vs. 10.8%; HR: 0.76 [95% CI: 0.64 to 0.90]), whereas no benefit over aspirin was seen in the combined group of ex-smokers/never-smoked patients (10.4% vs. 10.6%; HR: 0.99 [95% CI: 0.89 to 1.10]; $p = 0.01$ for interaction). Among current smokers, clopidogrel also reduced myocardial infarction, vascular death, and death from any cause compared with aspirin. No interaction between smoking status and study treatment was observed for bleeding events.

Conclusions In a post-hoc analysis of the CAPRIE population, current smokers appeared to have enhanced benefit with clopidogrel therapy for secondary prevention compared with aspirin. These results should be considered hypothesis generating for future prospective studies assessing the impact of specific platelet-inhibiting strategies according to smoking status. (J Am Coll Cardiol 2014;63:769–77) © 2014 by the American College of Cardiology Foundation

Cigarette smoking is a potent inducer of the hepatic cytochrome P450 (CYP) 1A2 and 2B6 isoenzymes and can have an impact on the pharmacokinetic and pharmacodynamic profiles of drugs sharing this metabolic pathway, including clopidogrel (1–4). In particular, CYP1A2 is the predominant isoenzyme responsible for the first

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Abbreviations and Acronyms

ACS = acute coronary syndrome

CI = confidence interval

CYP = cytochrome P450

HR = hazard ratio

DAPT = dual antiplatelet therapy

MI = myocardial infarction

OR = odds ratio

PCI = percutaneous coronary intervention

oxidative step in the conversion of clopidogrel into its active metabolite and may therefore increase clopidogrel biotransformation (5). This is supported by pharmacodynamic studies, which have shown, with some exception (6), that cigarette smoking enhances clopidogrel-induced platelet inhibitory effects (7–12). These pharmacodynamic findings may explain the observations from large-scale clinical trials demonstrating that, among clopidogrel-treated patients, smokers have a higher relative clinical benefit compared with nonsmokers (13–19). However, to date, such a "smoker's paradox" has been assessed only in patients requiring dual antiplatelet therapy (DAPT) with aspirin and clopidogrel, and whether smoking impacts clinical outcomes in patients with atherosclerotic disease manifestations requiring a single antiplatelet agent for secondary prevention of ischemic events remains unknown.

The CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) trial is the only large-scale head-to-head clinical investigation comparing clopidogrel versus aspirin for secondary prevention in patients with various atherosclerotic disease manifestations (20). The trial showed clopidogrel to be modestly, and statistically significantly, more effective in reducing ischemic outcomes than aspirin, with a favorable safety profile. The objectives of the present analysis were 2-fold: first, to evaluate the relationship between smoking status and clinical outcomes in the overall CAPRIE study population; and second, to investigate the differential effects of clopidogrel or aspirin therapy according to smoking status.

Methods

The design, methods, and primary results of the CAPRIE trial have been reported previously (20). In brief, CAPRIE was a randomized, multicenter, blinded trial that compared the efficacy of clopidogrel (75 mg once daily) and aspirin (325 mg once daily) in reducing the risk of the outcome event cluster of ischemic stroke, myocardial infarction (MI), or vascular death in a population of patients with atherosclerotic vascular disease. The study population comprised subgroups of patients with either recent ischemic stroke, recent MI, or symptomatic peripheral artery disease. After a mean follow-up of 1.91 years, clopidogrel was more effective in reducing ischemic outcomes than aspirin (5.32% vs. 5.83%; $p = 0.043$). For the purpose of the present analysis, the impact of smoking status on outcomes was evaluated in the overall study population. In addition, the differential treatment effect (interaction) of clopidogrel versus aspirin according to smoking status was also evaluated. Ischemic events were defined consistent with the primary efficacy endpoint of the CAPRIE trial and included the outcome event cluster of ischemic stroke, MI, or vascular death, whichever occurred first. In addition to the components of the primary endpoint, a secondary efficacy endpoint assessed was death from any cause. Smoking status was ascertained only at a single time at the moment of enrollment, and was evaluated both as collected (never smokers, ex-smokers, and current smokers) and by combining never smokers/ex-smokers versus current smokers. A safety endpoint was also considered, and CAPRIE bleeding events were defined as any bleeding disorder, as previously described (20,21). Outcomes reported were validated by the central validation committee of the trial.

Statistical analysis. Data are presented as numbers and frequencies for categorical variables and as means ± SD for continuous variables. All data analyses were performed on the intention-to-treat population including all patients who were randomized. Baseline characteristics were compared with the chi-square test for categorical variables and analysis of variance for continuous variables. The effect of smoking status on ischemic events was evaluated using a Cox proportional hazards model, and p values were calculated using a log-rank test. For the overall population, the model was stratified by qualifying condition. Tests of interaction between smoking status and study treatment were calculated using the Cox proportional hazards model including treatment, smoking status (as a categorical variable), and the interaction; also included in the adjusted model are the covariates detailed in the following text. To take into account any imbalances in baseline variables, analyses were repeated using multivariable Cox proportional hazards model, adjusting for treatment, race, diabetes, hypercholesterolemia, congestive heart failure, cardiomegaly, atrial fibrillation, stable angina, unstable angina, previous MI, transient ischemic attack, reversible ischemic neurological deficit, previous ischemic stroke, intermittent claudication, and leg amputation (these variables were selected on the basis of a previous multivariable analysis) (22), and also for age, sex, and body mass index. The effect of smoking status and treatment on bleeding disorders was evaluated using a logistic regression model, and groups were compared using a chi-square test. A 2-tailed p value of <0.05 was considered to indicate a statistically significant difference for all of the analyses performed. Statistical analysis was performed using SAS version 9.2 software (SAS Institute, Cary, North Carolina).

Results

Study population. A total of 19,185 patients were randomized in the CAPRIE trial. Smoking status was ascertained only at the moment of enrollment and recorded in all except 1 patient who was excluded from the present analysis. Of the 19,184 patients evaluated, 5,668 (29.5%) were current smokers, 9,381 (48.9%) were ex-smokers, and 4,135 (21.6%) never smokers. Compared with

never-smokers, current smokers were younger, more frequently male, and more likely to have peripheral artery disease, but less likely to have recent ischemic stroke as qualifying conditions. Current smokers were also less likely to have a history of hypertension, diabetes mellitus, atrial fibrillation, stable angina, cardiomegaly, and congestive heart failure. Baseline demographics and clinical characteristics stratified according to smoking status (current smokers vs. the combined group of ex-smokers and never smokers) and treatment are shown in Table 1.

Effect of smoking status in the overall study population. In the overall population, current and ex-smokers had a numerically lower rate of ischemic events (primary efficacy endpoint) compared with patients who never smoked: 9.5%, 9.8%, and 12.0%, respectively ($p = 0.30$). However, after adjustment for baseline characteristics, current smokers had an increased risk of ischemic events compared with patients who never smoked (hazard ratio [HR]: 1.24 [95% confidence interval (CI): 1.08 to 1.42]) and to ex-smokers (HR: 1.32 [95% CI: 1.18 to 1.47]), achieving statistical significance ($p < 0.001$). Both unadjusted and adjusted HRs for the overall population and the study subgroups (patients with recent ischemic stroke, recent MI, or symptomatic peripheral artery disease) are reported in Table 2.

Similar results were obtained when analyzing smoking status as a dichotomous variable. Current smokers had a numerically lower rate of the primary efficacy endpoint compared with ex-smokers/never-smoked patients, which did not reach statistical significance (9.5% vs. 10.5%, HR: 0.99 [95% CI: 0.89 to 1.09]; $p = 0.82$). However, in the adjusted model, current smokers had an enhanced risk of ischemic outcomes compared with the combined group of ex-smokers/never-smoked subjects (HR: 1.30 [95% CI: 1.17 to 1.44]; $p < 0.001$).

Bleeding disorders occurred in 8.6% of current smokers, 9.7% of ex-smokers, and 9.1% of never-smoked patients ($p = 0.07$). When evaluating smoking status as a dichotomous variable, current smokers had a lower rate of bleeding events compared with ex-smokers/never-smoked subjects (8.6% vs. 9.6%; odds ratio [OR]: 0.89 [95% CI: 0.80 to 0.99]; $p = 0.04$). In the adjusted model, the ratio was inverted, indicating that current smokers had a significantly increased risk of bleeding events compared with patients who had never smoked (OR: 1.23 [95% CI: 1.04 to 1.46]; $p = 0.02$) and similar when compared with ex-smokers (OR: 0.93 [95% CI: 0.83 to 1.05]; $p = 0.25$). No difference was seen between current smokers and the combined group of ex-smokers/never-smoked patients (OR: 1.01 [95% CI: 0.90 to 1.13]; $p = 0.93$).

Table 1 Baseline Demographic Data and Clinical Characteristics Stratified According to Smoking Status and Treatment

	Aspirin Current Smokers (n = 2,860)	Clopidogrel Current Smokers (n = 2,808)	p Value	Aspirin Ex/Never Smokers (n = 6,726)	Clopidogrel Ex/Never Smokers (n = 6,726)	p Value
Age, yrs	58.6 ± 10.9	58.3 ± 10.8	0.3933	64.2 ± 10.7	64.1 ± 10.8	0.8294
Male	2,174 (76.0)	2,145 (76.4)	0.7404	4,731 (70.3)	4,804 (70.8)	0.5992
BMI, kg/m^2	25.9 ± 4.4	25.9 ± 4.3	0.8158	26.7 ± 4.4	26.7 ± 4.4	0.7273
Race			0.5564			0.0025
Caucasian	2,718 (95.0)	2,665 (94.9)		6,378 (94.8)	6,415 (94.5)	
Black	92 (3.2)	81 (2.9)		169 (2.5)	210 (3.1)	
Asian	13 (0.5)	15 (0.5)		65 (1.0)	35 (0.5)	
Other	37 (1.3)	47 (1.7)		114 (1.7)	130 (1.9)	
Risk factors						
Hypertension	1,225 (42.8)	1,187 (42.3)	0.6698	3,679 (54.7)	3,793 (55.9)	0.1738
Diabetes mellitus	451 (15.8)	425 (15.1)	0.5092	1,510 (22.5)	1,494 (22.0)	0.5318
Dyslipidemia	1,132 (39.6)	1,156 (41.2)	0.2232	2,845 (42.3)	2,770 (40.8)	0.0762
Medical history						
Stable angina	510 (17.8)	525 (18.7)	0.3997	1,561 (23.2)	1,575 (23.2)	0.9862
Unstable angina	207 (7.2)	208 (7.4)	0.8063	617 (9.2)	629 (9.3)	0.8561
Atrial fibrillation	56 (2.0)	87 (3.1)	0.0062	337 (5.0)	331 (4.9)	0.7161
Cardiac surgery	142 (5.0)	157 (5.6)	0.2917	566 (8.4)	623 (9.2)	0.1188
Other cardiac arrhythmia	242 (8.5)	246 (8.8)	0.6881	734 (10.9)	821 (12.1)	0.0318
Cardiac valve disease	79 (2.8)	81 (2.9)	0.7809	282 (4.2)	305 (4.5)	0.3935
Cardiomegaly	83 (2.9)	108 (3.8)	0.0489	333 (5.0)	361 (5.3)	0.3355
Congestive heart failure	110 (3.8)	116 (4.1)	0.5836	414 (6.2)	433 (6.4)	0.5947
Qualifying condition			0.8084			0.8961
Ischemic stroke	719 (25.1)	708 (25.2)		2,479 (36.9)	2,525 (37.2)	
Peripheral artery disease	1,235 (43.2)	1,232 (43.9)		1,994 (29.6)	1,991 (29.3)	
Myocardial infarction	906 (31.7)	868 (30.9)		2,253 (33.5)	2,274 (33.5)	

Values are mean ± SD or n (%).
BMI = body mass index.

Table 2 Summary of Patients With Ischemic Events and Unadjusted and Adjusted HRs for the Primary Efficacy Endpoint According to Smoking Status

	Never Smokers (n = 4,135)	Ex-Smokers (n = 9,381)	Current Smokers (n = 5,668)	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)
Overall (N = 19,184)	496 (12.0)	921 (9.8)	541 (9.5)	0.92 (0.82–1.03)	0.94 (0.83–1.06)
				0.93 (0.82–1.06)	1.24 (1.08–1.42)
				1.02 (0.91–1.13)	1.32 (1.18–1.47)
Ischemic stroke (n = 6,431)	296 (13.4)	383 (13.7)	215 (15.1)	1.01 (0.87–1.18)	0.98 (0.83–1.15)
				1.11 (0.93–1.32)	1.34 (1.10–1.62)
				1.09 (0.93–1.29)	1.37 (1.15–1.63)
Myocardial infarction (n = 6,301)	139 (10.3)	290 (9.1)	143 (8.1)	0.87 (0.71–1.07)	1.00 (0.81–1.24)
				0.78 (0.62–0.98)	1.18 (0.91–1.52)
				0.89 (0.73–1.09)	1.18 (0.96–1.45)
Peripheral artery disease (n = 6,452)	61 (10.6)	248 (7.3)	183 (7.4)	0.65 (0.49–0.86)	0.71 (0.53–0.96)
				0.68 (0.51–0.91)	1.02 (0.74–1.41)
				1.05 (0.87–1.28)	1.43 (1.18–1.75)

Values are n (%). In the Unadjusted and Adjusted HR columns, the first hazard ratio (HR) is for ex-smokers versus never smokers, the second hazard ratio is for current smokers versus never smokers, and the third hazard ratio is for current smokers versus ex-smokers. *Model adjusted for treatment, age, sex, body mass index, race, diabetes, hypercholesterolemia, congestive heart failure, cardiomegaly, atrial fibrillation, stable angina, unstable angina, previous myocardial infarction, transient ischemic attack, reversible ischemic neurological deficit, previous ischemic stroke, intermittent claudication, and leg amputation.

CI = confidence interval.

Effect of smoking status on study treatment: clopidogrel versus aspirin. In aspirin-treated patients, the unadjusted analysis showed no significant difference according to smoking status (current smokers vs. ex-smokers/never-smoked subjects) in the overall population (10.8% vs. 10.6%, HR: 1.11 [95% CI: 0.97 to 1.27]; p = 0.14). However, in the adjusted model, current smokers had a higher risk of ischemic outcomes (HR: 1.39 [95% CI: 1.20 to 1.60]; p < 0.001), an effect that was consistent among all qualifying conditions. Similarly, the impact on ischemic outcomes in clopidogrel-treated patients was not observed in the unadjusted model (8.3% vs. 10.4%, HR: 0.87 [95% CI: 0.75 to 1.01]; p = 0.07), but it reached significance in the adjusted analysis (HR: 1.19 [95% CI: 1.02 to 1.39]; p = 0.03).

A significant interaction between study treatment and smoking status was found (p = 0.01 for interaction) when evaluated as a dichotomous variable (current smokers vs. ex-smokers/never-smoked patients). In particular, clopidogrel-treated patients had no reduction in the incidence of the primary efficacy outcome compared with aspirin-treated patients in the combined group of ex-smokers/never-smoked patients (10.4% vs. 10.6%; HR: 0.99 [95% CI: 0.89 to 1.10]; p = 0.73), whereas patients treated with clopidogrel in the current smoker group had a significantly lower rate of ischemic events (8.3% vs. 10.8%; HR: 0.76 [95% CI: 0.64 to 0.90]; p = 0.001) than aspirin-treated patients (Fig. 1). This trend toward a lower risk of ischemic events among clopidogrel-treated subjects was observed in all qualifying conditions (recent ischemic stroke: 14.0% vs. 16.1%, HR: 0.88 [95% CI: 0.67 to 1.16]; recent MI: 7.4% vs. 8.7%, HR: 0.88 [95% CI: 0.63 to 1.22]; and peripheral artery disease: 5.7% vs. 9.1%, HR: 0.60 [95% CI: 0.44 to 0.81]). The benefit of the clopidogrel-treated current smokers subgroup compared with the other 3 subgroups (clopidogrel-treated ex-smokers/never smoked, aspirin-treated current smokers, and aspirin-treated ex-smokers/never smoked) was observed during the entire study follow-up (Fig. 2A). Among current smokers, in addition to the benefit observed in the combined primary efficacy endpoint, clopidogrel was associated with a reduction in MI, vascular death, or death from any cause compared with aspirin, with the interaction mainly due to the difference in the rates of vascular death (Fig. 3).

When evaluating smoking status as a variable with 3 categories (current smokers, ex-smokers, and never smokers), a significant interaction (p < 0.01) with study treatment for the primary efficacy endpoint was observed in the overall population due to no observed efficacy in ex-smokers (clopidogrel vs. aspirin: 8.3% vs. 10.8% in current smokers, HR: 0.76 [95% CI: 0.64 to 0.90], p = 0.002; 10.1% vs. 9.5% in ex-smokers, HR: 1.10 [95% CI: 0.97 to 1.26], p = 0.14; 10.9% vs. 13.1% in patients who never smoked, HR: 0.79 [95% CI: 0.66 to 0.94]; p < 0.01).

No interaction between smoking status and study treatment was observed for bleeding events when considering the variable smoking status with 3 categories (current smokers, ex-smokers, and never smokers) or dichotomous (current smokers vs. ex-smokers/never-smoked patients): p = 0.35 and p = 0.73 for interaction, respectively. The incidence of bleeding events in the 4 subgroups of subjects evaluated according to smoking status and treatment (clopidogrel-treated current smokers, clopidogrel-treated ex-smokers/never smokers, aspirin-treated current smokers, and aspirin-treated ex-smokers/never smokers) was similar, as illustrated in Figure 2B.

Discussion

The present analysis of the CAPRIE trial showed that: 1) current smokers, despite being younger and with fewer comorbidities, presented in the adjusted model with an

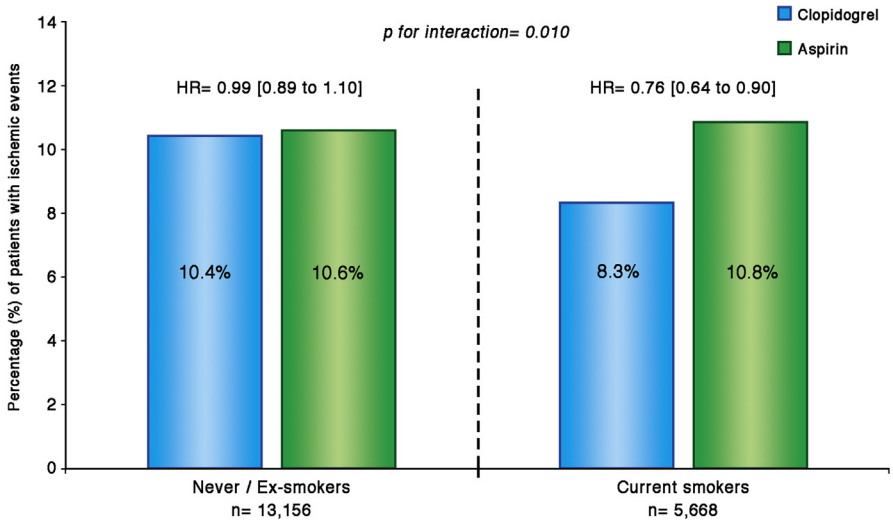

Figure 1 **Ischemic Events According to Smoking Status and Study Treatment**

Percentage of patients with ischemic events according to smoking status (never/ex-smokers vs. current smokers) and study treatment (aspirin vs. clopidogrel) is shown. HR = hazard ratio.

increased risk of long-term ischemic events; 2) among current smokers, clopidogrel therapy achieved a reduction in ischemic events, whereas no difference between aspirin and clopidogrel treatment was observed in the combined group of ex-smokers/never smokers; and 3) no significant interaction was seen between treatment and smoking habit for bleeding events. Although smoking cessation represents the optimal healthcare goal, these findings suggest that clopidogrel may offer greater ischemic protection and potentially be preferred over aspirin for smokers with stable atherosclerotic vascular disease and requiring a single antiplatelet drug regimen. Indeed, the availability of clopidogrel in a generic formulation with contained costs, which in the past had limited its more broad-scale use, makes this an appealing treatment option in subsets of patients in which clopidogrel may improve outcomes when compared with aspirin.

Smoking is an established major risk factor for all-cause and cardiovascular mortality, as well as for ischemic and bleeding outcomes, and smoking cessation is a Class I recommendation (Level of Evidence: A) for secondary prevention in patients with atherosclerotic vascular disease (23). Although the optimal healthcare goal is to reinforce the importance of smoking cessation, this is not achieved in many patients, as also reflected by the slowing in the decline in adult smoking (24). These observations underscore the importance of defining more-effective secondary prevention treatment strategies for patients who continue to smoke and thus remain at increased risk for ischemic recurrences.

DAPT with aspirin and clopidogrel represents the most broadly utilized treatment for patients presenting with an acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI). Despite having increased rates of adverse events, smokers have been shown to have a higher relative clinical benefit of DAPT compared with nonsmokers (13–19). Importantly, for patients requiring DAPT, more-potent antiplatelet treatment strategies (e.g., prasugrel, ticagrelor) are currently available, and may therefore be considered in patients requiring more effective platelet blockade because of their high-risk profile (25,26). These agents have a more favorable pharmacokinetic and pharmacodynamic profile compared with clopidogrel, and outcomes of patients treated with these agents are not affected by smoking (6,27). This is supported also in the recently reported PARADOX (Influence of Smoking Status on Prasugrel and Clopidogrel Treated Subjects Taking Aspirin and Having Stable Coronary Artery Disease) trial, which showed that the antiplatelet efficacy of clopidogrel is reduced in nonsmokers, whereas prasugrel-mediated platelet inhibition is not influenced by smoking status (28). In addition, in the large-scale TRILOGY ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) clinical trial that randomized ACS patients not undergoing revascularization to long-term therapy with prasugrel versus clopidogrel (29), there was a significant interaction between treatment and smoking, showing almost a 50% relative reduction in ischemic events with prasugrel versus clopidogrel treatment among smokers. Because smoking had no significant impact on prasugrel efficacy, this differential effect might be due to an increased risk of adverse outcomes of smokers compared with nonsmokers among clopidogrel-treated patients (30). Because smokers have an increased density of $P2Y_{12}$ receptors on the platelet surface (31),

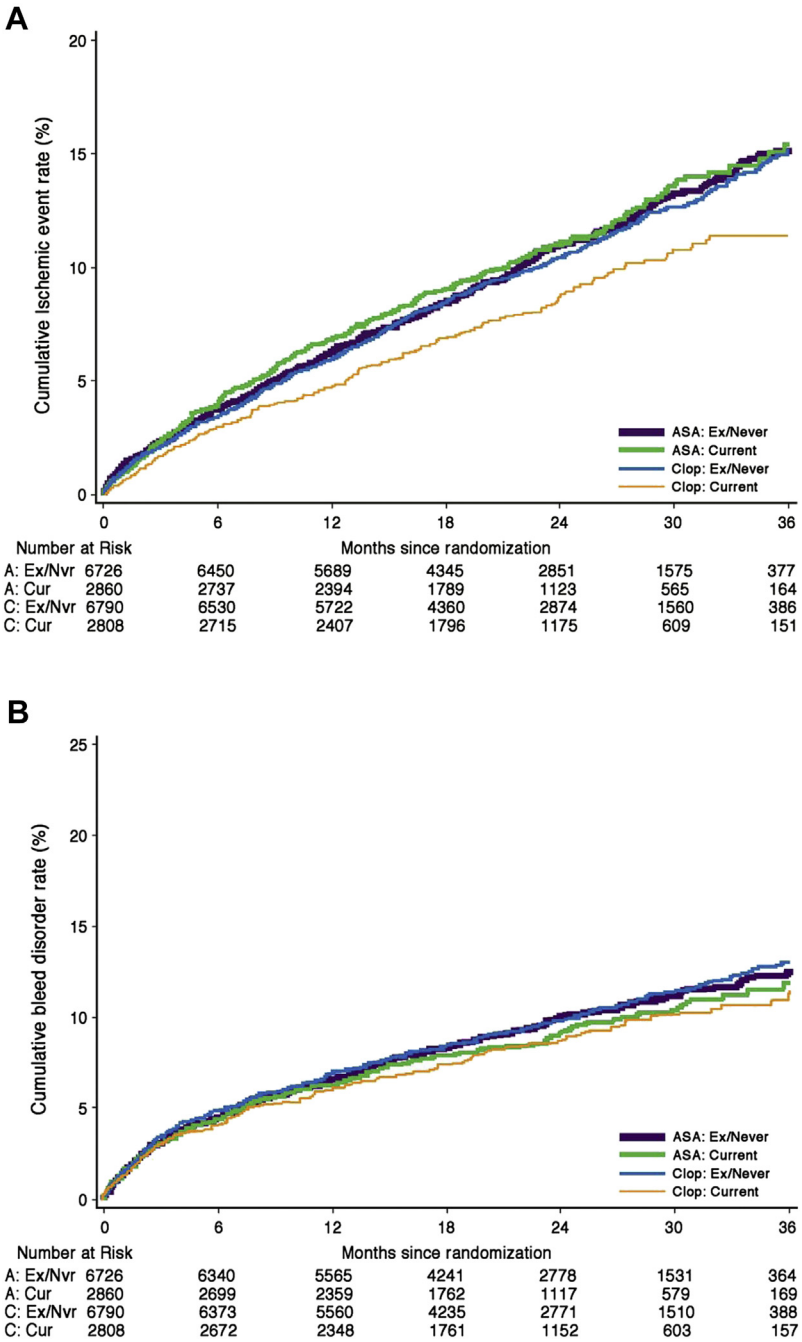

Figure 2 **Kaplan-Meier Curves of Ischemic and Bleeding Events Stratified According to Smoking Status and Study Treatment**

(A) The cumulative ischemic event rates, expressed as percentages, according to smoking status (never [Nvr]/ex-smokers [Ex] and current [Cur] smokers) and study treatment (aspirin [ASA] and clopidogrel [Clop]). **(B)** The cumulative bleeding event rate, expressed as percentages, according to smoking status (never/ex-smokers and current smokers) and study treatment (aspirin and clopidogrel).

this may also have played a role in the observed benefit of prasugrel over clopidogrel in this subgroup analysis (30).

Most patients with atherosclerotic manifestations do not have a clinical indication to be on DAPT, which is generally recommended for up to 1 year in the settings of ACS and PCI, and the use of DAPT has been shown to be potentially harmful outside of these clinical presentations (32). Therefore, defining the optimal treatment for patients requiring only a single antiplatelet agent, either aspirin or clopidogrel, for secondary prevention of ischemic events is of paramount importance. Overall, the results of the present investigation may have practical implications

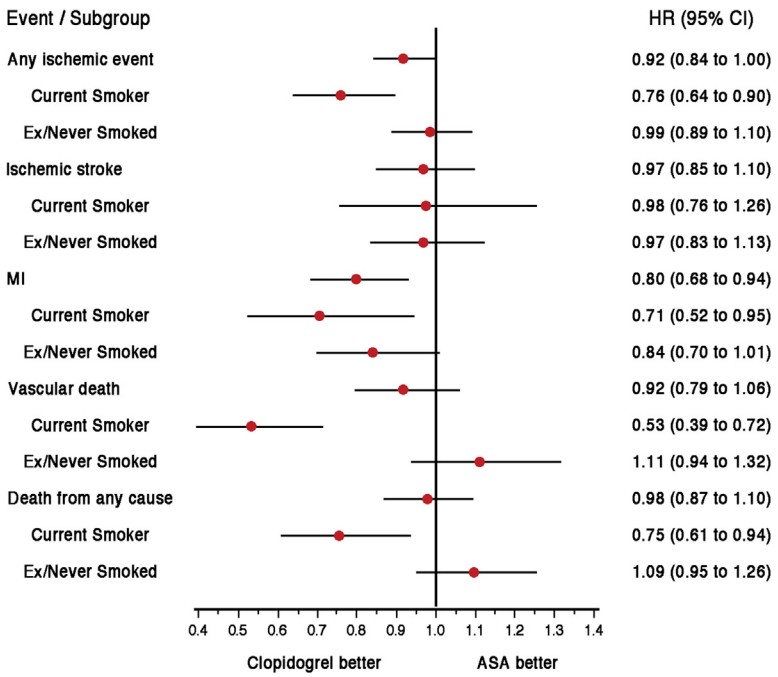

Figure 3 **HRs for Cardiovascular Events**

Hazard ratios (HRs) and 95% confidence intervals (CIs) for cardiovascular events in clopidogrel-versus aspirin-treated patients (adjusted model) are shown. ASA = aspirin; MI = myocardial infarction.

for current clinical practice. In particular, one might consider recommending clopidogrel therapy for smokers and aspirin for nonsmokers when a single antiplatelet agent is required in patients with atherothrombotic diseases, such as for secondary prevention in patients with peripheral artery disease, a prior stroke, or in those with ACS or PCI after completing 1 year of DAPT. Further, the use of clopidogrel must be also considered in nonsmoking, aspirin-intolerant patients, because no other option (e.g., prasugrel, ticagrelor) has been tested for monotherapy. If $P2Y_{12}$ blockade is clinically superior to aspirin, as it appears to be in clopidogrel-treated smokers, the findings of this study also pose the question of whether monotherapy with the more potent $P2Y_{12}$ antagonist prasugrel or ticagrelor would be even superior to both aspirin and clopidogrel. This concept is currently being evaluated in the GLOBAL LEADERS (A Clinical Study Comparing Two Forms of Anti-platelet Therapy After Stent Implantation) trial (NCT01813435) that aims to enroll approximately 16,000 patients from an "all-comers" population undergoing PCI with a drug-eluting stent with an abluminally-coated biodegradable polymer. Patients will be followed for 2 years after being randomized to either: 1) a study treatment strategy of 1 month of aspirin plus ticagrelor followed by 23 months of ticagrelor monotherapy; or 2) a reference treatment strategy of 12 months of DAPT (aspirin plus ticagrelor for ACS patients; aspirin plus clopidogrel for elective patients) followed by 12 months of aspirin monotherapy.

CAPRIE is the only large-scale investigation to our knowledge to assess differences in safety and efficacy between aspirin and clopidogrel monotherapy for secondary prevention of ischemic events in patients with atherosclerotic disease manifestations. Although clopidogrel was associated with a favorable safety profile, including bleeding and nonbleeding side effects, and reduced ischemic event rates compared with aspirin, a finding that was of even greater magnitude in higher-risk subgroups, aspirin has represented the mainstay of treatment for these patients (20,33). Indeed, costs may have contributed to this practice pattern, given that clopidogrel has only recently become available in a generic formulation. Importantly, the findings of the present investigation also suggest that the benefit of clopidogrel over aspirin can be attributed in part to its effect among smokers. The greater magnitude of benefit of clopidogrel among smokers (smoker's paradox) is likely attributed to the more effective platelet inhibition that is achieved in these patients, as demonstrated by the higher rates of reperfusion observed in patients with ST-segment elevation MI undergoing routine angiography (13), and also consistently shown in various pharmacodynamic investigations (13–16). However, this greater effect of clopidogrel among smokers must not be overstated, and it must not be concluded from the results of our study that clopidogrel is

not effective in patients that do not currently smoke. In fact, in the present analysis, patients who were "never smokers" (when not combined with ex-smokers) also obtained a benefit from clopidogrel therapy compared with aspirin.

Pharmacodynamic studies have shown a broad range in the interindividual response profile among clopidogrel-treated patients, and those who have high on-treatment platelet reactivity have an increased risk of ischemic recurrences, including stent thrombosis (34,35). Cigarette smoking is a strong inducer of the activity of CYP1A2 and CYP2B6, which are involved in the hepatic transformation of clopidogrel (1,2), thus leading to an enhanced production of its active metabolite (5). The greater clopidogrel-induced platelet inhibition observed in current smokers compared with nonsmokers was first demonstrated by Bliden et al. (7) in a cohort of patients on DAPT undergoing elective coronary stenting, and later confirmed in other settings (8,9), notably showing a dose–response effect according to the intensity of smoking (9). Although some studies have not found an association between smoking and clopidogrel efficacy (6), a causal relationship between smoking and degree of clopidogrel-induced antiplatelet effects is also supported by the observation that the enhanced platelet inhibitory effects among smokers diminished with smoking discontinuation (36). Other studies suggest that this benefit may occur in patients more likely to have reduced clopidogrel response, based on clinical presentation (e.g., diabetic status) or CYP1A2 polymorphisms (9,37).

In addition to a more favorable metabolism of clopidogrel due to enhanced CYP enzymatic activity, other mechanisms may contribute to the benefit among smokers. Nicotine has been shown to be associated with higher platelet $P2Y_{12}$ receptor expression in platelet lysates compared with that of nonsmokers (31). Therefore, it may be hypothesized that the benefit of clopidogrel over aspirin may be due to the fact that smokers have higher platelet surface $P2Y_{12}$ density, contributing to their higher risk for recurrent events, which can be suppressed by clopidogrel, but not by aspirin (31). Also, smoking has been associated with less biological efficacy of aspirin, also coined "aspirin resistance," as determined by increased platelet reactivity and incomplete inhibition of thromboxane biosynthesis compared with that of smokers (38). However, in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) trial, randomization to clopidogrel versus placebo did not reduce the hazard of cardiovascular events in low-risk aspirin-treated patients in the highest quartile of urinary 11-dehydro-thromboxane B2 levels (39).

Study limitations. The major limitation is that the present study is a post-hoc subgroup analysis of a large-scale clinical trial and, thus, there is potential for bias because the study was not designed and powered for subgroup analyses. Indeed, the more subgroup analyses of a given trial that are performed, the more likely that a positive finding in 1 of them may be due to the play of chance. Therefore, the results observed in the present investigation must be considered only hypothesis generating. For instance, the fact that the benefit observed for clopidogrel therapy among current smokers mainly depended on the individual endpoint of vascular death, whereas no relevant interaction was seen for stroke or MI, urges caution with the conclusions derived regarding a different clopidogrel benefit depending on smoking status. This is also in line with the observation from the present analysis that patients who were never smokers (when not combined with ex-smokers) also obtained a benefit from clopidogrel therapy compared with aspirin. Further, the CAPRIE trial was published in 1996, which may limit the clinical significance of the present analysis because clinical practice has evolved and differs from standards used when patients were recruited in this trial. However, this is the first study to assess the impact of smoking in patients requiring single antiplatelet therapy for secondary prevention of ischemic events, which in addition to the consistent findings with DAPT trials (13–16) and the plausible biological explanations based on a multitude of pharmacodynamic studies, is reassuring (7–12). Finally, smoking status was based on a single determination at enrollment that may have changed over the study period. However, misclassification of smoking status would more likely have attenuated the strength of the association between current smokers and adverse outcomes.

Conclusions

In a population of patients with stable atherosclerotic vascular disease, smoking is associated with an increased risk of adverse ischemic outcomes, both in aspirin- and clopidogrel-treated patients. Current smokers treated with clopidogrel for the secondary prevention of ischemic recurrences had a greater reduction in events compared with those treated with aspirin, whereas no clear benefit of clopidogrel over aspirin was seen in the combined group of ex-smokers/never smokers. Although smoking cessation represents the optimal healthcare goal, these findings suggest that clopidogrel may offer greater ischemic protection and potentially be preferred over aspirin for smokers with stable atherosclerotic vascular disease requiring a single antiplatelet drug.

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