

Benefit of Clopidogrel Over Aspirin Is Amplified in Patients With a History of Ischemic Events

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Background and Purpose—The goal of this study was to examine the influence of preexisting symptomatic atherosclerotic disease on subsequent ischemic event rates and compare the efficacy of clopidogrel versus aspirin (acetylsalicylic acid, ASA) in patients with such disease.

Methods—Using the CAPRIE database, we performed multivariate analyses for patients who had symptomatic atherosclerotic disease (ischemic stroke [IS] or myocardial infarction [MI]) in their medical history before enrollment in the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial. Two composite end points were used: (1) IS, MI, or vascular death and (2) IS, MI, or rehospitalization for ischemia.

Results—In the CAPRIE population, prior IS and MI each were statistically significant predictors of subsequent ischemic events. Compared with the overall population, patients with preexisting symptomatic atherosclerotic disease had elevated event rates for the end point of IS, MI, or vascular death; 3-year rates were 20.4% with clopidogrel and 23.8% with ASA (absolute risk reduction, 3.4%; 95% CI, -0.2 to 7.0 ; number needed to treat, 29; relative risk reduction, 14.9%; $P=0.045$). Similar results were obtained for the end point of IS, MI, or rehospitalization for ischemia; 3-year event rates were 32.7% with clopidogrel and 36.6% with ASA (absolute risk reduction, 3.9%; 95% CI, -0.4 to 8.1 ; number needed to treat, 26; relative risk reduction, 12.0%; $P=0.039$).

Conclusions—CAPRIE patients with a history of prior symptomatic atherosclerotic disease had a high rate of subsequent ischemic events. The absolute benefit of clopidogrel over ASA seemed to be amplified in such high-risk patients. (*Stroke*. 2004;35:528-532.)

Key Words: aspirin ■ clopidogrel ■ patients ■ randomized controlled trials

Ischemic events affecting the cerebral, coronary, and peripheral arteries are different manifestations of a common pathophysiological process, namely atherothrombosis, or thrombus formation superimposed on preexisting atherosclerosis.¹ Such events are the leading cause of death and disability in the industrialized world and result in a considerable burden of disease to society.² The platelet is a pivotal mediator in the initiation and propagation of thrombus formation.³ Thus, antiplatelet agents have a key role in preventing further ischemic events. Aspirin (acetylsalicylic acid, ASA), an inhibitor of the thromboxane A₂ pathway of platelet activation,⁴ can be regarded as the prototype inhibitor of platelet aggregation. However, unsatisfactory effectiveness and existing side effects led to the development of newer antiplatelet agents such as the ADP receptor antagonist clopidogrel.⁵

The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study was a randomized, blinded trial of clopidogrel versus ASA in patients with symptomatic

atherosclerosis.⁶ The rationale for CAPRIE was based on the following tenets: (1) patients with a wide spectrum of atherosclerotic disease are at risk of all major atherothrombotic events; (2) biological and clinical evidence suggests that the atherothrombotic process is similar, regardless of the clinical manifestation of underlying atherosclerosis; and (3) clopidogrel can be expected to benefit the entire spectrum of patients with symptomatic atherosclerosis.⁷

Patients were enrolled in CAPRIE on the basis of recent myocardial infarction (MI), recent ischemic stroke (IS), or established atherosclerotic peripheral arterial disease. In addition to the qualifying condition, a substantial proportion of patients in each treatment arm had prior symptomatic atherosclerotic disease.⁸ The primary analysis of efficacy, based on a composite end point of IS, MI, or vascular death (VD), showed that clopidogrel provided a relative risk reduction (RRR) of 8.7% ($P=0.043$) over and above the 25% odds reduction for a similar outcome cluster shown by the Antiplatelet Trialists' Collaboration⁷ to be provided by ASA over

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placebo.⁶ Compared with ASA, clopidogrel demonstrated a favorable safety-tolerability profile, with a significantly lower overall incidence of gastrointestinal hemorrhage, abnormal liver function, and indigestion but an increase in the rate of skin rash and diarrhea.^{6,9} Furthermore, clopidogrel was not associated with hematological side effects that limit the use of the ADP receptor antagonist ticlopidine.^{6,10}

The availability of the extensive CAPRIE database presents an important opportunity to study risk and efficacy in symptomatic atherosclerotic patients. The purpose of the present analyses was to define the role of preexisting symptomatic atherosclerotic disease in predicting further atherothrombotic events and to assess the absolute risk reduction (ARR) and RRR for clopidogrel (compared with ASA) in such patients.

Methods

Study Population

Details of the CAPRIE study design and main findings have been reported elsewhere.⁶ Briefly, patients were randomized on a double-blind basis to receive clopidogrel 75 mg/d or ASA 325 mg/d if they had 1 of 3 qualifying conditions: recent IS (≥ 1 week and ≤ 6 months before randomization), recent MI (≤ 35 days before randomization), and established peripheral arterial disease (PAD; either intermittent claudication and an ankle-brachial index of ≤ 0.85 in either leg at rest on 2 separate occasions or previous leg amputation or angioplasty of a peripheral artery).

Patients received study medication for up to 3 years (mean duration of treatment, 1.6 years; 12.8% of all patients received medication for 3 years). Patients who were enrolled in the study were stratified according to qualifying condition but may have had a medical history of symptomatic atherosclerotic disease. Exclusion criteria included uncontrolled hypertension, severe renal or hepatic insufficiency, and history of bleeding disorders or abnormal blood cell counts.

For the purpose of this subgroup analysis, patients with preexisting symptomatic atherosclerotic disease were selected from the overall CAPRIE population. This was defined as a self-reported history of IS and/or MI before the qualifying event for enrollment in CAPRIE. The data concerning such events had been routinely collected in the case record forms. However, no standard procedures to prove such a preexisting event were defined.

Statistical Analyses

Multivariate analyses were conducted with a Cox proportional-hazards model run on the entire on-treatment population (patients receiving at least 1 dose of study drug) from the CAPRIE study (19 099 patients). Initially, a model including all baseline factors collected in the CAPRIE study (30 in total) plus study drug treatment (clopidogrel or aspirin) was run (full model). This included all specific factors collected under previous history of atherothrombotic events and history of related events or associated risk factors on the CAPRIE case record form (20 in total). In addition, 7 demographic or habit factors were included. Finally, a factor for MI location, IS type (lacunar or nonlacunar), and PAD eligibility (current claudication or arterial intervention) was included. Thus, the model basically included all relevant baseline factors. Data collected under "general" medical history and prior medications were not included because they would be related to the underlying condition already included in the model. The type of qualifying event was not included as a factor in any model used for analyses for this article. Hence, factors related to the various qualifying events were included in the full model (ie, IS type, MI location, and PAD eligibility); however, the multivariate analysis itself was stratified by qualifying condition, allowing the shape of the hazard function to differ for the different conditions. The unadjusted analyses performed for the subgroup of patients with a history of symptomatic atherosclerotic disease were run both with

and without qualifying condition as a stratification factor. The stratified analysis is consistent with the methods used for the primary CAPRIE analyses.

Two different end points were evaluated with this full model: (1) IS, MI, or VD and (2) IS, MI, or hospitalization for ischemia (angina/claudication/peripheral ischemia/transient ischemic attack/MI).¹¹ The outcome events were collected prospectively and evaluated carefully with the use of standardized criteria predefined in the study protocol. This model was used to examine the role of preexisting symptomatic atherosclerotic disease in predicting further ischemic events. The first of these is the primary end point in CAPRIE; it was used to be consistent with the original publication. The second end point is likely to have a major health benefit and has important implications for the practitioner.¹¹

After calculation of the full model with all medical variables recorded at study entry (31), factors leading to a value of $P < 0.1$ were used to build a reduced model. Although in some cases a particular factor had a lower probability value for 1 end point than the other, a final reduced model was selected, and the same model was used for both end points. No multivariate analyses were run for this subgroup of patients; thus, adjusted results are not presented.

In this subgroup analysis, 1- and 3-year event rates based on Kaplan-Meier survival curves¹² were estimated for both end points for patients with symptomatic atherosclerotic disease (IS or MI) before the qualifying event that led to their enrollment in CAPRIE. These are nonparametric estimates at these specific time points and are not obtained from different models fit for different time points. One-year event rates were calculated for comparison with the overall CAPRIE population and the original publication.⁶ The 3-year event rates were calculated to demonstrate whether a positive effect is stable over a longer time period.

The average event rate per year is calculated as the number of events divided by the patient-years at risk. The ARR is thus the difference between the aspirin rate and the clopidogrel rate. The number of patients needed to be treated (NNT; reciprocal of ARR) to prevent 1 event was calculated from the 1- and 3-year event rate estimates. The RRR in our model is not specifically related to a particular time point. It is an overall measure of how much the risk is reduced in the experimental group (clopidogrel) compared with the control group (ASA). This estimate is obtained from the Cox proportional-hazards model, which assumes that the hazard ratio is constant over time.

A significance level of 0.05 was used for all analyses. Statistical analyses were performed with SAS software, version 6.12 (SAS Institute Inc).

Results

The results presented in Table 1 are intended to show the relative risk of subsequent ischemic events in patients having a particular risk factor compared with those not having the risk factor in the reduced multivariate model when other covariates, including study drug treatment for both end points analyzed, are controlled for. On one hand, it shows that patients with a prior IS (qualifying event or history) or prior MI (qualifying event or history) have an increased risk of having a subsequent ischemic event. On the other hand, it shows that patients with PAD leading to leg amputation had the highest risk for revealing further ischemic events. For 1 end point, coexisting hypercholesterolemia seems to have a protective effect. Variables from the full model that had a value of $P > 0.1$ and thus were not included in the reduced model were alcohol consumption, amaurosis fugax, angioplasty, body mass index, cardiac surgery, cardiac valvular disease, sex, hypertension, type of ischemic stroke, location of MI, other cardiac arrhythmia, PAD eligibility, reconstructive surgery, surgical intervention, and weight.

TABLE 1. Risk Ratios for Factors in the Multivariate Model for Both End Points

Factor	End Point			
	IS, MI, VD		IS, MI, Rehospitalization for Ischemia*	
	RR	<i>P</i>	RR	<i>P</i>
Age	1.372/10 yrs	<0.001	1.11/10 yrs	<0.001
Race	1.278	0.015	1.073	0.393
Cigarette smoking	1.288	0.001	1.101	0.081
Diabetes mellitus	1.445	<0.001	1.266	<0.001
Hypercholesterolemia	0.848	0.002	0.950	0.164
Congestive heart failure	1.288	0.005	1.070	0.340
Cardiomegaly	1.405	<0.001	1.092	0.273
Atrial fibrillation	1.187	0.094	1.106	0.208
Stable angina	1.363	<0.001	1.592	<0.001
Unstable angina	1.269	0.004	1.340	<0.001
Previous MI	1.380	<0.001	1.261	<0.001
TIA	1.189	0.029	1.220	0.002
RIND	1.486	0.005	1.348	0.013
Previous IS	1.478	0.004	1.264	0.012
Intermittent claudication†	1.383	<0.001	1.425	<0.001
Leg amputation	1.790	0.028	1.742	0.017

RR indicates risk ratio (model containing all factors); TIA, transient ischemic attack; and RIND, reversible ischemic neurological deficit.

*Including peripheral ischemia, intermittent claudication, angina, MI, and TIA.

†Includes all patients with the qualifying condition and any other patients with a history of the condition.

A substantial proportion of the CAPRIE population had experienced symptomatic atherosclerotic disease before the qualifying event. A total of 4496 patients, 23.4% of the total study population, had suffered an IS or MI before entry into the study. Of these, 1681 had suffered an IS before the qualifying event for the CAPRIE trial. In this CAPRIE subpopulation, demographic parameters and atherosclerosis risk factors were well balanced, with no major differences between treatment groups (Table 2). The only significant difference was ethnicity; there was a slightly lower percentage of white patients in the clopidogrel group ($P=0.02$).

For the primary CAPRIE end point (IS, MI, or VD), the risk ratio for patients with preexisting IS compared with those without prior IS was 1.48 ($P=0.004$); for those with preexisting MI, it was 1.38 ($P<0.001$). In the overall CAPRIE population, the 1-year event rates for the primary end point were 5.3% for clopidogrel and 5.8% for ASA.

For such patients with preexisting symptomatic atherosclerotic disease, the 1-year event rates for the primary outcome cluster (IS, MI, Vd) were 8.8% for clopidogrel and 10.2% for ASA, corresponding to an ARR of 1.4%. The 3-year event rates for this primary outcome cluster were 20.4% for clopidogrel and 23.8% for ASA, corresponding to an ARR of 3.4% (95% CI, -0.2 to 7.0). The RRR was 14.9% (95% CI, 0.3 to 27.3; $P=0.045$). Thus, 71 of these patients would need to be treated for 1 year or 29 patients for 3 years with

TABLE 2. Demographic Parameters and Clinical Characteristics of the CAPRIE Subpopulation With a Preexisting Symptomatic Atherosclerotic Disease Split by Treatment

Parameter	Treatment		
	Clopidogrel	Aspirin	<i>P</i>
n	2249	2247	
Enrolling event status (IS/MI/PAD), n	862/568/819	863/573/811	0.97
Age (mean), y	65	65	1.00
Male, n (%)	1754 (78.0)	1697 (75.5)	0.06
White, n (%)	2084 (92.7)	2122 (94.4)	0.02
Body mass index, kg/m ²	26.6	26.6	1.00
Current smoker, n (%)	598 (26.6)	612 (27.2)	0.65
Ex-smoker, n (%)	1194 (53.1)	1202 (53.5)	0.79
Regular alcohol consumption, n (%)	320 (14.2)	340 (15.1)	0.39
Amaurosis fugax, n (%)	55 (2.5)	45 (2.0)	0.31
Leg amputation, n (%)	10 (0.4)	8 (0.4)	0.64
Intermittent claudication, n (%)	166 (7.4)	156 (6.9)	0.57
Previous IS, n (%)	815 (36.2)	866 (38.5)	0.12
Previous MI, n (%)	1621 (72.1)	1571 (69.9)	0.11
RIND, n (%)	85 (3.8)	78 (3.5)	0.58
TIA, n (%)	301 (13.4)	319 (14.2)	0.43
Atrial fibrillation, n (%)	149 (6.6)	153 (6.8)	0.81
Diabetes mellitus, n (%)	633 (28.2)	612 (27.2)	0.50
Hypercholesterolemia, n (%)	1090 (48.5)	1066 (47.4)	0.49
Hypertension, n (%)	1400 (62.3)	1378 (61.3)	0.52

Abbreviations as in Table 1. Probability value by χ^2 test except for age and body mass index (*t* test).

clopidogrel instead of ASA to prevent 1 ischemic event (Table 3 and the Figure).

For the combined end point of IS, MI, or rehospitalization for ischemia, patients with preexisting IS or preexisting MI had risk ratios of 1.26 ($P=0.012$) and 1.26 ($P<0.001$), respectively. For this end point, the 1-year event rates were 16.1% for clopidogrel and 18.5% for ASA (ARR, 2.4%), and the 3-year event rates were 32.7% for clopidogrel and 36.6% for ASA (ARR, 3.9%; 95% CI, -0.4 to 8.1), corresponding to an RRR of 12.0% (95% CI, 0.6 to 22.1; $P=0.039$). Thus, 42 of these patients would need to be treated for 1 year or 26 patients for 3 years with clopidogrel instead of ASA to prevent 1 ischemic event or hospitalization for ischemia in the high-risk cohort (Table 3 and the Figure).

For both end points, the results were not different after stratification for qualifying event.

Discussion

To date, CAPRIE is the largest prospective evaluation of antiplatelet agents and the first study to include patients with all of the main clinical manifestations of atherothrombosis in a single clinical trial. The size of the CAPRIE population, its study design, and the robustness of the data set provided a unique opportunity to define high-risk subpopulations of patients with symptomatic atherosclerosis and to assess the magnitude of the absolute benefit of clopidogrel over ASA in

TABLE 3. Efficacy of Clopidogrel Over ASA in Patients With Previous Acute Events

IS, MI, VD	IS, MI, VD					IS, MI, Rehospitalization				
	Event Rate, %	ARR (95% CI), %	NNT	RRR (95% CI), %	P	Event Rate, %	ARR (95% CI), %	NNT	RRR (95% CI), %	P
Previous Acute Events (IS or MI)										
1-y										
Clopidogrel (n=2249)	8.8	1.4	71	14.9	0.045*	16.1	2.4	42	12.0	0.039†
Aspirin (n=2247)	10.2	(-0.3%, 3.0%)		(0.3-27.3)		18.5	(0.3%, 4.6%)		(0.62, 22.1)	
3-y										
Clopidogrel (n=2249)	20.4	3.4	29			32.7	3.9	26		
Aspirin (n=2247)	23.8	(-0.2%, 7.0%)				36.6	(-0.4%, 8.1%)			
Average per year										
Clopidogrel (n=2249)	8.3	1.5	67			15.4	2.2	45		
Aspirin (n=2247)	9.8	(0.03%, 2.7%)				17.6	(0.1%, 3.9%)			

*14.4% (95% CI, -0.3-26.9), P=0.054 based on analysis stratified by qualifying event.

†11.9% (95% CI, 0.5-22.0) P=0.041, based on analysis stratified by qualifying event.

these patients. Cox regression analysis was run on the entire population of the CAPRIE study (19 099 patients), not just the subgroup of patients with previous ischemic events. Of these, 775 had a primary event. Thus, the so-called rule of 10s has not been violated. This rule stipulates that for regression modeling, the maximum number of degrees of freedom should not exceed 1/10th of the least frequent outcome. We used 31 factors (1 df each) for the full and 16 factors for the reduced model, much less than the possible 78.

Our study defined a subpopulation presumed to have a higher risk of experiencing a further ischemic event compared with the overall CAPRIE population. We analyzed event rates for clopidogrel and ASA treatment groups for 2 composite end points. The rationale for using 2 composite end points and evaluating 2 time intervals is explained earlier.

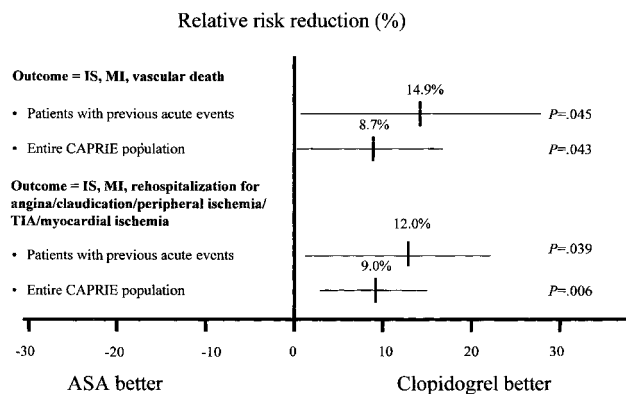
The CAPRIE cohort with a prior history of symptomatic atherosclerotic disease (IS or MI) had high event rates for both end points examined in our study. For example, for the primary end point, the 3-year event rates were 20.4% with clopidogrel and 23.8% with ASA in patients with preexisting symptomatic atherosclerotic disease compared with 14.1% with clopidogrel and 15.2% with ASA for the overall CAPRIE population. This difference increases even more if a

comparison with the CAPRIE subpopulation without any preexisting symptomatic atherosclerotic disease in the history is performed. For these patients, the 3-year event rates were 10.2% with clopidogrel and 11.3% with ASA. Therefore, the patients evaluated in this analysis represent a population that is at high risk for subsequent ischemic events, about twice that of patients without this disease history. Coexisting hypercholesterolemia seems to be protective regarding 1 end point. This might be explained by an additional treatment with statins, but because comedication was not included in the multivariate model, this explanation is only hypothetical.

The clinical benefit of a drug may be expressed in several different ways, including relative risk, RRR, ARR, odds ratio, and NNT. For the medical decision maker, NNT¹³ is a convenient and informative way to compare the clinical benefits of different therapeutic interventions. NNT denotes the number of patients who must receive a given treatment in a specified population to prevent 1 clinical event.

The key finding of this study is that the NNT for prevention of 1 ischemic event in patients with preexisting symptomatic atherosclerotic disease is lower than that for the total CAPRIE population. Thus, in the overall study cohort, the NNT for prevention of 1 IS, MI, or VD is 200 patients per year of treatment with clopidogrel instead of ASA compared with 71 in those patients with a prior IS or MI in their pre-CAPRIE history. For a treatment period of 3 years, the NNT to prevent such an event is 91 in the overall CAPRIE population compared with 29 for patients with preexisting acute symptomatic atherosclerotic disease. Comparable reductions in the NNT to prevent 1 IS, MI, or hospitalization for ischemia were also observed.

These data seem to indicate an amplification of the absolute benefit of clopidogrel over ASA in patients with a history of symptomatic atherosclerotic disease. This is consistent with other analyses showing that patients with increased risk for ischemic events like previous cardiac surgery or unstable angina benefit from more potent antithrombotic treatment.¹⁴⁻¹⁶ This issue will be tested prospectively in the running CHARISMA and the PROFESS trials. Considering economic aspects, such information can be helpful in identi-



Benefit of clopidogrel over ASA in patients with previous acute events expressed as RR (%). Shown are both composite end points compared with the entire CAPRIE population.

fying patients who have the most benefit from a more expensive therapy.

Findings from the present study should be considered in the context of the nature of the CAPRIE data set. The cohorts analyzed in our study are not large enough to detect differences between the relative potencies of cerebrovascular, coronary, and peripheral arterial events as predictors of further events. That is, the subgroup of patients with a qualifying event ischemic stroke and a history of another cerebrovascular accident had event rates for IS, MI, and Vd of 10.6% for ASA treatment compared with 9.6% with clopidogrel. This led to a statistically insignificant RRR of 11.8% (95% CI, -8.1 to 28.1; $P=0.226$). The results are also limited by the nature of a posthoc analysis with a nonpredefined subgroup because of the risks of incomplete historical data and an imbalance between observation arms. On the other hand, our high-risk subgroup contains nearly 4500 patients, and the basic clinical criteria are well balanced between treatment arms. We did not include information on prior medication in our analyses. However, to be enrolled in CAPRIE, patients were not allowed to take warfarin or any other antithrombotic agent except ASA. Thus, the preexisting events could have occurred while patients were taking no antithrombotic medication or ASA.

In conclusion, this study demonstrates an increased risk of ischemic events in patients with a history of symptomatic atherosclerotic disease. Moreover, different manifestations of atherosclerotic disease represent separate risk factors for recurrent vascular ischemic events. Finally, the absolute benefit of clopidogrel over ASA seems to be amplified in high-risk patients, whereas the relative benefit is similar across end points related to vascular ischemia.

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