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Comparative Safety and Tolerability of Clopidogrel and Aspirin

Results from CAPRIE

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Abstract

Objective: The objective of this study was to provide a comprehensive comparison of the long term safety and tolerability of clopidogrel, a new adenosine diphosphate (ADP) receptor antagonist that inhibits platelet activation induced by ADP, and aspirin (acetylsalicylic acid).

Patients and Methods: The study population comprised 19 185 patients with symptomatic atherosclerosis manifested as recent ischaemic stroke, recent myocardial infarction or symptomatic peripheral arterial disease. Patients were randomised to receive clopidogrel 75 mg/day or aspirin 325 mg/day for a minimum of 1 year and a maximum of 3 years.

Results: Compared with aspirin, clopidogrel reduced the combined risk of ischaemic stroke, myocardial infarction or vascular death by 8.7% ($p = 0.043$). The incidence of early permanent discontinuations of the study drug due to adverse events was almost identical in both treatment groups (11.94% for clopidogrel *vs* 11.92% for aspirin). Reported neutropenia was similar in the clopidogrel and aspirin groups (0.10 *vs* 0.17%, respectively) with corresponding rates (0.05 *vs* 0.04%, respectively) for severe neutropenia. Thrombocytopenia was identical in the clopidogrel and aspirin groups (0.26%), with the rates of severe thrombocytopenia being 0.19 *vs* 0.10%, respectively. None of these observed differences was statistically significant. The overall incidence of haemorrhagic events did not differ statistically significantly between treatment groups (9.27% for clopidogrel *vs* 9.28% for aspirin; $p = 0.98$). There was a trend towards a lower incidence of intracranial haemorrhage in the clopidogrel group (0.31%) compared with the aspirin group (0.42%). Any reported gastrointestinal haemorrhage was significantly less frequent with clopidogrel (1.99%) than with aspirin (2.66%) [$p < 0.002$]. The corresponding data for severe gastrointestinal bleeding were 0.49 *vs* 0.71%; $p < 0.05$. Overall, there were significantly fewer gastrointestinal adverse events with clopidogrel than with aspirin (27.1 *vs* 29.8%; $p < 0.001$), with less abdominal pain, dyspepsia, constipation, or peptic, gastric, or duodenal ulceration with clopidogrel. Diarrhoea was significantly more common in the clopidogrel

group (4.46 *vs* 3.36%; p <0.001), although the incidence of severe diarrhoea (0.23 *vs* 0.11%) was low and was not significantly different between groups. There were significantly more patients with rash in the clopidogrel group (6.0%) compared with the aspirin group (4.6%) [p < 0.001]. However, these events were generally mild and transient in nature.

Conclusion: Given the favourable benefit/risk ratio, clopidogrel represents a clinically important advance in the treatment of patients with manifest atherosclerotic disease.

Atherosclerosis and atherothrombosis are the major pathological processes underlying stroke, coronary heart disease, and peripheral arterial disease and as such are the leading cause of death and disability in the industrialised world.[1] Atheroma formation is a long term, gradual process that involves multiple sites throughout the vasculature. Thus, symptoms originating in 1 region of the vascular system are usually indicative of widespread atherosclerotic disease and are associated with a high risk of further ischaemic events elsewhere.

Heart attacks, ischaemic strokes and peripheral arterial occlusions are generally caused by thromboocclusive episodes at sites of ruptured stenosing atheromata, leading to tissue factor–initiated platelet recruitment, fibrin synthesis and, ultimately, vascular thrombosis. Platelets have a key role in the development of atherothrombosis, prompting extensive investigation of antiplatelet agents in the prevention of vascular ischaemic events in high risk patients. A comprehensive overview is provided by the meta-analysis conducted by the Antiplatelet Trialists' Collaboration.[2] This overview included 142 randomised trials involving more than 100 000 patients at risk of vascular events which found an odds reduction of 27% in all high risk subgroups treated with antiplatelet agents. The majority of these trials were conducted with aspirin (acetylsalicylic acid), and the data support the use of aspirin for prevention of atherosclerotic complications and its current status as the reference drug. However, the therapeutic benefit of aspirin is offset to some extent by an associated increased risk of gastrointestinal discomfort and bleeding.

Data from the Antiplatelet Trialists' Collaboration meta-analysis showed that in direct comparative trials, ticlopidine was more effective than aspirin, producing an estimated odds reduction of 10% for the combined outcome cluster of (ischaemic or haemorrhagic) stroke, myocardial infarction or vascular death.[2] This finding is supported by the higher odds reduction seen in placebo-controlled trials of ticlopidine – 33%, compared with the 25% odds reduction typically seen with aspirin.[2] Ticlopidine is associated with rash and diarrhoea, which may lead to poor patient compliance. In rare cases, ticlopidine may cause neutropenia or thrombocytopenia, necessitating regular laboratory monitoring during the first 3 months of long term therapy.[3]

Oral anticoagulants such as warfarin reduce the incidence of ischaemic stroke and recurrent myocardial infarction when used after myocardial infarction and may prevent ischaemic stroke in patients with overt cerebrovascular disease[4-6] but they require careful laboratory monitoring and carry a risk of haemorrhage, particularly intracranial and gastrointestinal haemorrhage, which is not negligible.[7] Therefore, inhibition of platelet aggregation offers a more practical and potentially safer approach to pharmacological intervention in the thrombotic process.

Clopidogrel, an adenosine diphosphate (ADP) receptor antagonist, is chemically related to ticlopidine and inhibits platelet activation induced by ADP by irreversibly inactivating ADP receptor function. In a large scale, randomised, blinded, international trial of clopidogrel *vs* aspirin in patients at risk of ischaemic events (the CAPRIE trial), clopidogrel was found to be more effective than

aspirin, reducing the combined risk of ischaemic stroke, myocardial infarction or vascular death by 8.7% ($p = 0.043$).[8] With a study sample of more than 19 000 patients, CAPRIE provides an extensive safety database, with more than 15 500 patient-years of exposure for each drug. CAPRIE was designed to include patients with atherosclerosis representative of those seen in general practice. The purpose of this article is to provide a comprehensive review, using data from CAPRIE, of the comparative safety and tolerability of clopidogrel and aspirin.

Patients and Methods

The basic methodology of CAPRIE has been published previously.[8]

Patient Eligibility

All patients enrolled in CAPRIE presented with clearly established atherosclerotic involvement of 1 or more major arterial beds and, therefore, were at high risk of an atherothrombotic event. The inclusion/exclusion criteria limited qualifying conditions to recent ischaemic stroke, recent myocardial infarction, or symptomatic atherosclerotic peripheral arterial disease. For safety reasons, patients with a history of aspirin sensitivity or intolerance were excluded from the study as were patients with past or recurrent peptic ulcer disease. Thus, the eligible population was *a priori* expected to tolerate aspirin.

Treatment and Follow-Up

Patients were randomised to receive clopidogrel 75 mg/day or aspirin 325 mg/day, using a double-dummy design. The anticipated enrolment period for the study was approximately 3 years. Study drug administration for individual patients was to be a minimum of 1 year and a maximum of 3 years, depending on the time of enrolment of the patient. Patients were permitted to discontinue permanently their study drug at any time. In addition, such discontinuation could be directed by the investigator and was deemed compulsory in certain situations: serious haemorrhage in a major organ system; development of serious adverse events, which, in the opinion of the investigator, made long term continuation of study drug medically undesirable; development of a condition which required long term use of a contraindicated therapy; patients who were randomised to study drug but were subsequently found not to have the disease of interest. If a patient permanently discontinued study drug early, he or she nevertheless remained in the study and continued to be followed until he/she would normally have stopped study drug (i.e., a maximum of 3 years or until study closure, whichever came first) and reasons for discontinuation were carefully recorded. Patients were provided with information on common over-the-counter aspirin-containing products and were instructed to avoid them.

Outcome events were defined as ischaemic stroke, myocardial infarction, leg amputation above the ankle, primary intracranial haemorrhage and death; these were recorded from initiation of treatment until the end of the study. All adverse events and laboratory test values were recorded and assessed for the duration of patients' follow-up. In cases of early permanent discontinuation of study drug, adverse experiences were counted for 28 days after discontinuation. Fatal adverse events were defined as deaths that were the outcome of an adverse event that began during study treatment or during the 28 days following early permanent discontinuation of study drug.

At each clinical follow-up visit, patients were asked about the occurrence of any adverse events and blood was taken for haematological and biochemical assessments. Except in the early stages of the study (see Safety Evaluation), follow-up visits took place monthly for the first 4 months of each patient's follow-up and every 4 months thereafter.

Safety Evaluation

As only a limited amount of human safety data on clopidogrel was available at the start of the study, stringent procedures were implemented for efficient and timely monitoring of all serious ad-

verse events and deaths. Thus, the External Safety and Efficacy Monitoring Committee (ESEMC) monitored all data supplied by the individual clinical centres on an ongoing basis. Safety assessments were based on the data derived from clinical laboratory tests conducted at central laboratories and adverse event reports. All clinical events that occurred during the study were recorded and documented when they were thought by the reporting investigator to be a potential study outcome event, and validated by an independent Central Validation Committee (which remained blind with regard to treatment group).

Since ticlopidine can be associated with neutropenia and thrombocytopenia, surveillance for these adverse events was of particular importance. Follow-up for the first 500 patients enrolled included weekly haematological assessments and 2-weekly assessments of biochemistry during the first 3 months. A nonblinded review of these data by the ESEMC and a blinded review by the CAPRIE Steering Committee revealed no cause for concern and thereafter the frequency of these assessments was halved. After 3-month follow-up data had been collected for the first 1000 patients, the Steering Committee received a report on these laboratory results prepared by the ESEMC, classified by treatment A or B. On the basis of these results, the follow-up schedule for subsequent patients was relaxed to that stated above.

In addition, investigators were required to report as a serious adverse event all cases where the neutrophil or platelet count fell below prespecified alert values ($<1.2 \times 10^9$/L for neutrophils and $<100 \times 10^9$/L for platelets), unless a repeat test within 7 days was above the alert value. All events of this type were validated on a blinded basis by a consultant haematologist, to identify any that were due to sampling or laboratory errors, or represented clinically insignificant fluctuations around an inherently low baseline.

Haemorrhagic events were classified into 3 categories; intracranial haemorrhages, gastrointestinal bleeds, and other bleeds (such as epistaxis, ocular bleeding, haematoma, haematuria) as reported by the investigator.

Primary intracranial haemorrhage, including intracerebral haemorrhage, subarachnoid haemorrhage, and subdural haematoma, as well as death due to haemorrhage were included as outcome events, in addition to being included in the overall safety evaluation. Full details of each case were reviewed on a blinded basis by the Central Validation Committee.

Statistical Analysis

The overall frequency of adverse events, the frequency of events by body system, and the frequency of specific events were summarised using counts and percentages, and the 2 treatment groups compared using Pearson's Chi-squared test. The baseline laboratory test value for each patient was defined as the last available value prior to randomisation. Laboratory parameters at each time point, and their changes from baseline, were summarised using means, standard deviations, and ranges. The incidence of adverse events was analysed in a model which included as covariables age, gender, race, specific concomitant medications, bodyweight, body mass index, smoking status, alcohol use, qualifying condition, history of atherothrombotic events, and history of related events or risk factors. Each of these factors was analysed using a logistic regression model incorporating terms for treatment, the covariate, and the treatment-by-covariate interaction.

Results

The baseline characteristics of the patients in the clopidogrel and aspirin groups were similar and well balanced. The mean age (62.5 ± 11.1 years), percentage of male participants (72%) and percentage of Caucasians (95%) were the same for both groups. A high proportion of the total study group had pre-existing risk factors for vascular ischaemic events at baseline. More than half (51%) of the patients had hypertension, 20% had diabetes mellitus, and a substantial proportion of patients had a prior history of ischaemic stroke (9%), transient isch-

Table I. Overall safety analysis

Event	Clopidogrel (n = 9599)	Aspirin (n = 9586)
Early permanent discontinuation of study drug due to adverse event[a] (%)	11.94	11.92
Gastrointestinal disorders (%)	3.21	4.02*
Skin and appendage disorders (%)	1.52**	0.76
Fatal adverse event during study drug treatment + 28 days after stopping drug (%)	4.15	4.39
Fatal adverse event judged to be drug related by the investigator (%)	0.11	0.14

a Patients may be counted in more than 1 body system, but appear only once in the total.

* = $p < 0.01$; ** = $p < 0.001$ clopidogrel *vs* aspirin (other observed differences were not statistically significant: $p > 0.05$).

aemic attack (8%), myocardial infarction (17%) or stable angina (22%).

An overall analysis of safety is given in table I. A comparable rate of adverse events was reported under the 2 study treatments; 86.25% of patients receiving clopidogrel and 86.48% of those receiving aspirin ever reported at least 1 adverse event. The incidence of early permanent discontinuations of the study drug due to adverse events was essentially identical in both treatment groups (11.94% for clopidogrel *vs* 11.92% for aspirin). The most common reason for an adverse event-related early permanent discontinuations was a gastrointestinal event; such events were responsible for early permanent discontinuations in 3.21% of patients receiving clopidogrel and 4.02% of patients receiving aspirin. For the body system of skin and appendage disorders, early permanent discontinuations were more frequent with clopidogrel than with aspirin (1.52 *vs* 0.76%). The incidence of death resulting from an adverse event that began under treatment (including the 28-day period following early permanent discontinuations) was similar in the 2 treatment groups: 4.15 and 4.39% for clopidogrel and aspirin, respectively. Fatal adverse events were judged by the investigator to be drug-related in 0.11% of clopidogrel patients and 0.14% of aspirin patients.

Neutropenia and Thrombocytopenia

Similar incidences of neutropenia were reported by the investigators for patients receiving clopidogrel or aspirin (0.27 *vs* 0.24%) and these cases occurred throughout the treatment period. After blinded evaluation by a consultant haematologist, neutropenia or thrombocytopenia for both clopidogrel and aspirin patients was very low (table II). Neutropenia was seen in 0.10% of patients receiving clopidogrel and in 0.17% of those receiving aspirin. Only 5 patients (0.05%) receiving clopidogrel and 4 (0.04%) receiving aspirin showed severe neutropenia ($<0.45 \times 10^9$/L). In the clopidogrel group, 1 of the 5 cases of severe neutropenia was due to aplastic anaemia.[9] However, this event occurred 17 months after the initiation of clopidogrel, and throughout this period the patient was concurrently taking phenytoin, which is associated with aplastic anaemia.[10] Similarly, of the 4 validated cases of severe neutropenia within the aspirin group, 1 case was assessed to be due to acute leukaemia and 1 to myelogenous leukaemia. Although the number of events was very small, there did not appear to be any differences in incidence with respect to age or gender. No significant difference between clopidogrel and aspirin was found for the frequency of thrombocytopenia ($<100 \times 10^9$/L; 0.26% in both groups) or severe thrombocytopenia ($<80 \times 10^9$/L; 0.19% *vs* 0.10%). No

Table II. Number of cases (percentage) of validated neutropenia and thrombocytopenia[a]

Event	Clopidogrel (n = 9599)	Aspirin (n = 9586)
Neutropenia ($<1.2 \times 10^9$/L)	10 (0.10%)	16 (0.17%)
severe neutropenia ($< 0.45 \times 10^9$/L)	5[b] (0.05%)	4[c] (0.04%)
Thrombocytopenia ($< 100 \times 10^9$/L)	25 (0.26%)	25 (0.26%)
severe thrombocytopenia ($< 80 \times 10^9$/L)	18 (0.19%)	10 (0.10%)

a None of the observed differences was statistically significant: $p > 0.05$.

b Includes 1 case which was judged to be due to underlying aplastic anaemia.

c Includes 2 cases that were judged to be due to underlying disorders (acute leukaemia and myelogenous leukaemia, respectively).

Table III. Number of cases (percentage) of gastrointestinal haemorrhage

Adverse event[a]	Clopidogrel (n = 9599)				Aspirin (n = 9586)			
	all	severe	hospitalised	fatal	all	severe	hospitalised	fatal
Any gastrointestinal bleed	191 (1.99%)	47 (0.49%)	71 (0.74%)	1 (0.01%)	255* (2.66%)	68 (0.71%)	104** (1.08%)	2 (0.02%)
Bloody diarrhoea	3	0	0	0	5	2	3	0
Haemorrhagic duodenal ulcer	17	12	17	0	14	10	13	0
Haemorrhagic gastric ulcer	8	5	6	0	12	7	11	0
Haemorrhagic gastritis	4	3	4	0	4	2	3	0
Gastrointestinal haemorrhage	32	17	24	1	51	30	39	1
Haematemesis	22	5	9	0	20	7	12	1
Rectal haemorrhage	52	2	4	0	75	5	13	0
Melena	58	2	4	0	75	5	8	0
Haemorrhagic oesophageal ulceration	3	3	3	0	4	2	4	0
Oral haemorrhage	2	0	0	0	5	0	1	0

a Table is based on World Health Organization system of nomenclature for adverse events.

***** = $p < 0.002$; ****** = $p = 0.012$ clopidogrel *vs* aspirin (other observed differences were not statistically significant: $p > 0.05$).

cases of thrombotic thrombocytopenic purpura were reported with either clopidogrel or aspirin.

Haemorrhagic Events

The overall incidence of haemorrhagic events did not differ statistically significantly between treatment groups (9.27% in the clopidogrel group *vs* 9.28% in the aspirin group; $p = 0.98$). Overall, there was a trend towards a lower frequency of primary intracranial haemorrhages in the clopidogrel group compared with the aspirin group [30 (0.31%) *vs* 40 (0.42%) cases, respectively, as judged by the Central Validation Committee]. In the clopidogrel group, 16 (0.17%) intracranial haemorrhages were fatal and 14 (0.15%) were nonfatal. In the aspirin group, 16 (0.17%) were fatal and 24 (0.25%) were nonfatal. Other haemorrhagic deaths were also less frequent in the clopidogrel group than in the aspirin group [7 (0.07%) *vs* 11 (0.11%), respectively]; the difference was not statistically significant.

Table III shows data on the incidence of gastrointestinal bleeding in the 2 treatment groups. Overall, there was a significantly lower incidence of gastrointestinal bleeding with clopidogrel than with aspirin ($p < 0.002$); 0.49% of clopidogrel cases were severe, as judged by the reporting investigator, compared with 0.71% of aspirin cases, and 0.74% of clopidogrel cases required hospitalisation compared with 1.08% of aspirin cases ($p = 0.012$). There was 1 death (0.01%) due to gastrointestinal haemorrhage in the clopidogrel group compared with 2 (0.02%) in the aspirin group. The most frequent types of gastrointestinal haemorrhage were rectal haemorrhage and melena, which were both more common in patients who received aspirin than in those who received clopidogrel.

Gastrointestinal Tolerability

Patients with aspirin sensitivity or intolerance, or with a history of peptic ulceration were excluded from CAPRIE. Nonetheless, the gastrointestinal tolerability of clopidogrel was significantly better than that of aspirin. Thus, gastrointestinal adverse events were significantly more frequent in the aspirin group (29.82%) than in the clopidogrel group (27.14%) [$p < 0.001$] (table IV). Only diarrhoea was reported at a significantly higher frequency in patients receiving clopidogrel (4.46 *vs* 3.36%; $p < 0.001$). The median time to onset of diarrhoea from the start of treatment was 78 days in the clopidogrel group and 105 days in the aspirin group, with a median duration of 10 days for clopidogrel and 5 days for aspirin. The number of cases of severe diarrhoea was low (0.23% for clopidogrel and 0.11% for aspirin; not statistically significant). In contrast, dyspepsia, abdominal pain, constipation, gastritis and ulcers were all more frequent in pa-

Table IV. Incidence of gastrointestinal adverse events

Event	Clopidogrel (n = 9599)		Aspirin (n = 9586)	
	all (%)	severe (%)	all (%)	severe (%)
Any gastrointestinal adverse event	27.14	2.98	29.82**	3.60
Abdominal pain	5.64	0.38	7.14**	0.64
Dyspepsia	5.22	0.19	6.10*	0.25
Diarrhoea	4.46**	0.23	3.36	0.11
Constipation	2.38	0.08	3.33**	0.09
Gastritis	0.75	0.08	1.32**	0.07
Ulcer (gastric, duodenal, peptic)	0.68	0.25	1.15**	0.38

* = $p < 0.01$; ** = $p < 0.001$ clopidogrel *vs* aspirin (other observed differences were not statistically significant: $p > 0.05$).

tients receiving aspirin relative to patients receiving clopidogrel. The number of patients experiencing peptic, gastric, or duodenal ulcers was 65 (0.68%) for clopidogrel and 111 (1.15%) for aspirin ($p < 0.001$).

Skin and Appendage Disorders

Skin and appendage disorders were significantly more frequent in the clopidogrel group than in the aspirin group (15.81 *vs* 13.08%; $p < 0.001$) [table V]. However, few of these were classified by the reporting investigator as severe. Rashes were experienced by significantly more patients in the clopidogrel group than in the aspirin group ($p < 0.001$). Rashes appeared to occur throughout the study period, with the median time of onset being 77 days in the clopidogrel group and 103 days in the aspirin group. The median duration of rash was similar for the 2 treatment groups (21 days for clopidogrel *vs* 25 days for aspirin), and the incidence of rash was independent of age, gender or race. Pruritus was also more common in the clopidogrel group ($p < 0.001$). There was no statistically significant difference in the incidence of allergic reaction, which was low in both treatment groups (0.92 *vs* 1.01%). No cases of epidermal necrolysis, necrotising dermatitis, Stevens Johnson syndrome or erythema multiforme were reported.

Central and Peripheral Nervous System Disorders

These events were reported at a statistically significantly lower frequency in the clopidogrel group than in the aspirin group (22.3 *vs* 23.8%; $p = 0.05$), although the overall frequencies were close and the most frequent central nervous system events, i.e., headache, dizziness and vertigo, were reported at similar frequency (7.6 *vs* 7.2%, 6.2 *vs* 6.7%, and 2.2 *vs* 2.1%, respectively).

Cardiovascular Events

Overall, the cardiovascular tolerability of clopidogrel was statistically significantly greater than that of aspirin. Apart from efficacy outcome events, cardiovascular adverse events were slightly but significantly less frequent overall for patients receiving clopidogrel than for patients receiving aspirin ($p = 0.002$). Statistically significant differences between the clopidogrel and aspirin groups were observed for hypertension (4.3 *vs* 5.1%; $p = 0.013$) and peripheral oedema (1.2 *vs* 1.6%; $p = 0.012$). Heart rate and rhythm adverse events were overall statistically significantly more frequent in the aspirin group than in the clopidogrel group (5.0 *vs* 4.3%; $p = 0.011$). However, there were no specific heart rate and rhythm adverse events that were experienced statistically significantly more by 1 group than by the other.

Adverse Events by Concomitant Medication, Demographic Factors or Concurrent Medical Condition

The large number of patients enrolled in CAPRIE permitted statistical testing for potential interactions between the study treatments and a variety of concomitant medications (ACE inhibitors, antidiabetic, anticonvulsant, anti-inflammatory or antithrombotic drugs, β-blockers, calcium antagonists, coronary vasodilators, cardiac glycosides, diuretics, hormone therapy, estrogen, peripheral

Table V. Incidence of skin and appendage disorders

Event	Clopidogrel (n = 9599)		Aspirin (n = 9586)	
	all (%)	severe (%)	all (%)	severe (%)
Any skin and appendage disorders	15.81*	0.71	13.08	0.47
Pruritus	3.26*	0.14	1.63	0.0
Rash (any)	6.02*	0.26	4.61	0.10
Allergic reaction (any)	0.92	0.08	1.01	0.11

***** = $p < 0.001$ clopidogrel *vs* aspirin (other observed differences were not statistically significant: $p > 0.05$).

vasodilators), demographic factors, or concurrent medical conditions. Patients receiving anticonvulsant medication were at greater risk of adverse events if they received aspirin rather than clopidogrel (95.7 *vs* 90.6%; p = 0.007 for interaction); no other such interactions were noted. There was no evidence that the incidence of adverse events varied with race or bodyweight, although it did increase slightly with age, in female participants, and in nonsmokers. However, these effects were seen in both treatment groups. Patients who consumed alcohol regularly were at a statistically significantly greater risk of adverse events if they took aspirin rather than clopidogrel (85.8 *vs* 83.2%; p = 0.001). The presence of a variety of concurrent medical conditions slightly increased the probability of patients experiencing an adverse event, but no difference was detected for those receiving clopidogrel relative to those receiving aspirin.

Other Safety Data

Hepatic and biliary disorders were reported with a low frequency in both the clopidogrel and aspirin groups. Liver function tests showed no clinically significant mean changes, and the incidence of severe hepatic enzyme increase was very low (0.03% for clopidogrel *vs* 0.05% for aspirin). Renal impairment was reported at a similar low frequency (1.9% average) in the treatment groups, with 0.2% of cases classified as severe. Since ticlopidine, which is chemically related to clopidogrel, is known to increase cholesterol levels slightly,[11] and as a large proportion of the patients in CAPRIE had a history of hypercholesterolaemia at study entry, special attention was paid to cholesterol changes during the study. However, laboratory monitoring showed no significant differences for any lipid parameters (cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol or triglycerides) between the 2 groups. Indeed, both groups showed a similar decrease in mean cholesterol levels over the course of the study.

Discussion

There is currently a need for better antithrombotic agents for the prevention of vascular ischaemic events in patients with symptomatic atherosclerosis. Compared with placebo, aspirin reduces the risk by about 25%.[2] Although ticlopidine has higher efficacy than aspirin in those patient groups (ischaemic stroke/transient ischaemic attack, peripheral arterial disease and angina) in which it has been tested, its use is limited by frequent diarrhoea and rash, and the rare occurrence of neutropenia and thrombocytopenia.[3]

CAPRIE has provided an extensive database with which to assess the relative safety and tolerability of clopidogrel *vs* aspirin. With a sample size of 19 185 patients, and a mean follow-up period of 1.91 years (mean duration of study drug treatment = 1.62 years), over 15 500 patient-years of exposure were obtained for each drug. Moreover, the broad entry criteria meant that the study population was representative of that normally seen in everyday clinical practice, with the exception of the exclusion of patients sensitive to, or intolerant of, aspirin. Given the length of treatment, the severity of the underlying condition of study participants, and the fact that most patients were either middle-aged or elderly, a high overall incidence of adverse events was expected. Moreover, the high reported adverse event rates indicate the thoroughness of safety data collection. During CAPRIE, a similar frequency of adverse events was observed in each treatment group for total events (86.25 *vs* 86.48%), reflecting the favourable tolerability profile of

clopidogrel compared with a long established drug such as aspirin.

In view of the known safety profile of ticlopidine,[3] particular attention was given to the possible development of haematological disorders, with patients' blood cell parameters being carefully monitored. Specifically, an independent haematologist reviewed on a blinded basis all reported cases of abnormal neutrophil and platelet counts. Results indicated that an excess of neutropenia and thrombocytopenia did not occur with long term clopidogrel therapy during the CAPRIE trial, during which time haematological parameters were frequently and stringently monitored. Thus, unlike ticlopidine, there is no need for routine haematological monitoring with clopidogrel in clinical practice. Thrombotic thrombocytopenic purpura is a concern with ticlopidine use.[12,13] However, as reported, there were no such cases among clopidogrel treated patients in CAPRIE.

Overall, clopidogrel caused fewer gastrointestinal adverse events than aspirin, as reflected in the statistically significantly lower frequencies of abdominal pain, dyspepsia, constipation, gastritis or ulcers in the clopidogrel group. Moreover, since patients with a history of aspirin sensitivity or intolerance were also excluded from the study, this is likely to have produced a more favourable tolerability profile for aspirin than that which would be obtained in a completely unselected population. Although diarrhoea was significantly more frequent in those receiving clopidogrel (4.5 *vs* 3.4%), this incidence is substantially lower than the 20.7% reported with long term ticlopidine treatment.[3]

Adverse events of bleeding are sometimes reported during antiplatelet therapy, as would be expected from the pharmacology of these compounds. In CAPRIE, the overall incidence of haemorrhagic events did not differ significantly between treatment groups. However, the frequency of gastrointestinal haemorrhage was significantly higher in patients receiving aspirin compared with patients receiving clopidogrel, despite the exclusion of patients with past or recurrent peptic ulcer disease from the trial. There was also a trend for more primary intracranial haemorrhages and haemorrhagic deaths in the aspirin group compared with the clopidogrel group, although these differences were not statistically significant. Primary intracranial haemorrhages, as might be expected, were more common among patients presenting with stroke.

Data from CAPRIE are consistent with the well documented gastrointestinal toxicity of aspirin. A meta-analysis of 9 trials that used aspirin (dose range 75 to 325 mg/day) for prevention of arterial occlusive events reviewed data on more than 14 000 patients.[14] Results showed that compared with placebo, the relative risk for the occurrence of peptic ulcer bleeding in the aspirin group was 1.5. This value is lower than that obtained in 2 large UK multicentre studies, 1 of them a case-control study, which found relative risks of hospitalisation for bleeding peptic ulcer of 3.6[15] and 3.9[16] respectively, for those taking aspirin 300 mg/day. Weil et al.[16] also studied aspirin doses of 75 mg/day and 150 mg/day and found odds ratios of 2.3 and 3.2, respectively. The difference in magnitude of the relative risk between the meta-analysis and the multicentre studies may reflect the fact that the trials in the meta-analysis did not include patients with a history of ulcer.

Aspirin has an ulcerogenic effect, which occurs both through direct contact of ingested aspirin with the gastric mucosa and through its ability to reduce levels of gastric prostaglandin E_2, which has cytoprotective properties.[17] In addition, it increases the propensity of any gastrointestinal lesion to bleed, through impaired homeostasis. The antiplatelet activity of aspirin appears to be mediated through irreversible inactivation of the synthesis of platelet thromboxane A_2,[18] a potent inducer of platelet aggregation. In contrast, clopidogrel does not cause gastric mucosal injury through direct exposure and does not affect prostaglandin E_2 production. Moreover, clopidogrel is an ADP receptor antagonist, preventing initiation of intracellular signalling and expression of the glycoprotein IIb/IIIa receptor and subsequent binding of fibrinogen to this receptor.[19] These mechanistic differ-

ences are likely to contribute to the superior antithrombotic activity and gastrointestinal tolerability of clopidogrel over aspirin.

Cappelleri et al.[20] analysed 36 randomised, controlled trials of the use of aspirin for secondary prevention of vascular events in high risk patients. For all patients, a dose-response relationship was observed for gastrointestinal symptoms and early permanent discontinuations of aspirin due to adverse effects. In contrast, there was no apparent relationship between aspirin dose and the incidence of gastrointestinal haemorrhage or haemorrhagic stroke. This finding is supported indirectly by results from the European Stroke Prevention Study (ESPS-2), which compared low dose aspirin (25mg twice daily), dipyridamole (200mg twice daily) or both against placebo in the secondary prevention of ischaemic stroke.[21] Thus, in patients receiving aspirin alone, 3.21% experienced moderate to severe/fatal bleeds, compared with 1.33% of those in the placebo group. Although separate figures for the incidence of gastrointestinal haemorrhage or intracerebral haemorrhage were not reported for ESPS-2, the data indicate that aspirin 50 mg/day is not free from haemorrhagic complications. Based on these findings, it seems unlikely that an aspirin dosage of less than 325 mg/day would have reduced the frequency of gastrointestinal bleeds or intracerebral haemorrhages relative to those seen in CAPRIE.

There is considerable interest in the potential benefit of combining clopidogrel with aspirin and ongoing trials are looking at this combination in coronary patients. The relative efficacy and safety of the combination may subsequently need to be compared with oral glycoprotein IIb/IIIa receptor antagonists.

Conclusion

The data from CAPRIE reviewed here indicate that clopidogrel has an excellent overall safety and tolerability profile. The benefit afforded by clopidogrel in reducing vascular ischaemic events by 8.7% compared with aspirin is achieved with no evidence of excess neutropenia and with better gastrointestinal tolerability than aspirin. Indeed, the risk of clinically relevant bleeding with clopidogrel is less than that of aspirin 325 mg/day. No other toxicity of concern has been demonstrated. The antithrombotic superiority of clopidogrel over aspirin is therefore reinforced by such a profile. These findings further support the use of clopidogrel, an ADP receptor antagonist, for the prevention of vascular ischaemic events (myocardial infarction, stroke or vascular death) in patients with a history of symptomatic atherosclerosis.

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