REVIEW ARTICLE

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Safety of Clopidogrel and Aspirin for Stroke Prevention

Implications of the CHARISMA trial

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Contents

Abstract

Antiplatelet therapy is universally recommended for the prevention of recurrent events in patients with noncardioembolic ischaemic stroke or transient ischaemic attack (TIA), acute and chronic coronary artery disease, or peripheral arterial disease. However, choosing which antiplatelet agents to use in these situations remains controversial. The use of aspirin, aspirin plus extended-release dipyridamole, or clopidogrel is recommended as initial therapy in patients with noncardioembolic ischaemic stroke or TIA to reduce the risk of recurrent stroke and other cardiovascular events. Based on the results of the MATCH trial, combination therapy with aspirin plus clopidogrel is not recommended for patients with ischaemic stroke or TIA due to the increased risk of haemorrhage.

The results of the CHARISMA trial support this recommendation; despite previous data demonstrating a favourable benefit-risk profile of aspirin plus clopidogrel in patients with acute coronary syndrome, this combination should not be used in patients at high risk for atherothrombosis and those with previous stroke or TIA. In these patients, the CHARISMA trial demonstrated a lack of significant clinical efficacy and an increased risk of bleeding with clopidogrel plus aspirin compared with aspirin alone.

Further research is needed to assess the benefit-risk ratio of clopidogrel plus aspirin in specific subpopulations of patients at high risk for atherothrombotic events, and to determine the role of clopidogrel plus aspirin in preventing cardioembolic stroke or early recurrent stroke after symptomatic large-vessel

atherostenosis. Recent and ongoing studies are seeking to better define the roles of different antiplatelet regimens in preventing recurrent stroke.

Atherothrombotic disorders are a leading cause of death and disability worldwide,[1-3] and it is estimated that one third of adults in the US have some form of cardiovascular disease.[4] The goal of pharmacotherapy is the prevention of recurrence of ischaemic events; a large study of patient records indicates that the 3-year rate of recurrence of ischaemic events among patients with stroke, acute myocardial infarction, or peripheral arterial disease may be as high as 18%.[5] Antiplatelet therapy is universally recommended for the prevention of recurrence of events in patients with non-cardioembolic ischaemic stroke or transient ischaemic attack (TIA),[6-8] acute and chronic coronary artery disease,[9-14] or peripheral arterial disease.[15-17] What remains controversial however, is how the available antiplatelet agents should be used for patients in these various disease states.

This paper explores the use of antiplatelet agents in the general population and in specific subsets of patients requiring secondary prevention of cardiovascular or cerebrovascular events. It also emphasizes the need to stratify the patient population more thoroughly before prescribing an antiplatelet regimen rather than to generalize treatments for all patients with atherothrombotic disorders, since the benefit-risk analysis may be quite different for different subgroups of this population. For example, the results of the CHARISMA trial (please see table I for definitions of trial acronyms) indicate that despite previous data demonstrating a favourable benefit-risk profile of aspirin (acetylsalicylic acid) plus clopidogrel in patients with acute coronary syndrome,[18-22] this form of combination antiplatelet therapy should not be extended to the general population of patients at high risk for atherothrombosis and in those patients with prior stroke or TIA.[23]

In the CURE trial, comprising 12 562 patients with acute coronary syndrome without ST-segment elevation, combination therapy with clopidogrel and aspirin (mean duration 9 months) compared with aspirin alone, significantly increased the risk of major bleeding, but also significantly decreased the risk of nonfatal myocardial infarction, stroke or death from cardiovascular causes.[18] Similar results were observed among the subpopulation of patients undergoing percutaneous coronary intervention,[19] and in a separate study of 2116 patients undergoing percutaneous coronary intervention (the CREDO trial).[20] In two more recent, short-term trials in patients with acute coronary syndrome (COMMIT and CLARITY-TIMI 28), clopidogrel plus aspirin compared with aspirin alone also demonstrated superior efficacy in preventing the recurrence of cardiovascular events.[21,22]

These results have been extrapolated to the routine use of clopidogrel plus aspirin among cardiologists, neurologists and primary care physicians for patients with all atherothrombotic disorders. However, two recent studies (the MATCH and CHARISMA trials) do not support the routine use of clopidogrel plus aspirin for the prevention of recurrent cerebrovascular events.[23,24] These studies demonstrate a lack of significant clinical efficacy and an increased bleeding risk in patients with recent ischaemic stroke or TIA, and in the more general population of patients at high risk for atherothrombotic events treated with the combination of aspirin and clopidogrel compared with those treated with either agent alone.

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Table I. Definitions of trial acronyms used in this review

Trial acronym	Definition
CHARISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance
CURE	Clopidogrel in Unstable Angina to prevent Recurrent Events
CREDO	Clopidogrel for the Reduction of Events During Observation
COMMIT	Clopidogrel and Metoprolol in Myocardial Infarction Trial
CLARITY-TIMI 28	Clopidogrel as Adjunctive Reperfusion Therapy-Thrombolysis in Myocardial Infarction 28
MATCH	Management of Atherothrombosis with Clopidogrel in High-risk patients
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
TASS	Ticlopidine Aspirin Stroke Study
SPS3	Secondary Prevention of Small Subcortical Stroke
FASTER	Fast Assessment of Stroke and TIA to prevent Early Recurrence
ESPRIT	European/Australian Stroke Prevention in Reversible Ischaemia Trial
PRoFESS	Prevention Regimen for Effectively avoiding Second Strokes

1. Rationale for Combination Therapy with Clopidogrel and Aspirin

Platelet activation plays a central role in the pathogenesis of atherothrombosis and is an important therapeutic target.[25,26] A meta-analysis of 287 randomized trials of antiplatelet therapy including aspirin, clopidogrel, or aspirin plus dipyridamole demonstrated that in high-risk patients, antiplatelet therapy reduced the risk of any serious vascular event by one-quarter, nonfatal myocardial infarction by one-third, nonfatal stroke by one-quarter, and vascular mortality by one-sixth.[27]

Aspirin and clopidogrel inhibit platelet aggregation via distinct mechanisms.[28] Aspirin irreversibly acetylates and inactivates cyclo-oxygenase (COX)-1, the enzyme that catalyses the conversion of arachidonic acid into prostaglandin H_2, the precursor of thromboxane A_2 – a lipid synthesized by stimulated platelets that further activates platelets by binding to specific G protein-coupled 7-transmembrane-domain receptors.[26] Clopidogrel does not affect the COX pathway. Instead, clopidogrel inhibits platelet activation, after biotransformation into active metabolites, by binding and irreversibly modifying and inhibiting the G protein-coupled 7-transmembrane-domain receptor for adenosine diphosphate, a platelet activator released from red blood cells, activated platelets, and damaged endothelial cells.[29] Because platelets do not synthesize new proteins, the actions of aspirin and clopidogrel are permanent, lasting for the life of the platelet (7–10 days).[30]

The rationale for combination therapy with aspirin and clopidogrel for cardiovascular disease is to enhance platelet inhibition by two complementary mechanisms. A safety concern, however, is that excessive inhibition of platelet aggregation may lead to increased bleeding risk. This concern was realized in the CURE,[18] MATCH[24] and CHARISMA trials.[23]

2. Clinical Trials of Clopidogrel Preceding CHARISMA

Long-term clopidogrel monotherapy has demonstrated superior efficacy and comparable safety when compared with aspirin in preventing cardiovascular events in patients with recent cardiovascular disease.[31] In the CAPRIE trial, patients with recent ischaemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease were randomized to receive treatment with clopidogrel 75 mg/day or aspirin 325 mg/day.[31] At a mean treatment duration of 1.91 years, subjects who received clopidogrel (n = 9577) had a lower

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annual risk of ischaemic stroke, myocardial infarction or vascular death (the composite endpoint) compared with patients who received aspirin (n = 9546; reduction in relative risk [RR] 8.7%; p = 0.043). Both treatment groups had similar bleeding rates. Intention-to-treat (ITT) analysis showed that the clopidogrel group had an annual 5.32% risk, and the aspirin group had a 5.83% risk of the composite endpoint.

Data from the CAPRIE trial suggest strikingly dissimilar effects among subgroups. In subjects with peripheral arterial disease, there was a reduction in RR for cardiovascular events with clopidogrel versus aspirin of 23.8% (p = 0.0028). There was no difference between treatment groups for subjects with stroke (RR reduction 7.3%; p = 0.26) or myocardial infarction (RR reduction 3.7%; p = 0.66). A test of heterogeneity of these treatment effects was significant, suggesting that the observed subgroup differences in cardiovascular risk reduction were not likely to be due to chance.[31]

Whereas studies in patients with acute coronary syndrome or stents demonstrate a therapeutic benefit to adding clopidogrel to standard treatment with aspirin,[18-22] the MATCH trial demonstrated that the long-term addition of clopidogrel to aspirin does not decrease cardiovascular risk and that it significantly increases bleeding risk compared with clopidogrel alone in patients with recent cerebrovascular events. Patients with recent ischaemic stroke or TIA and additional vascular risk factor(s) [previous ischaemic stroke, previous myocardial infarction, angina pectoris, diabetes mellitus, or symptomatic peripheral arterial disease] were randomized to receive clopidogrel 75 mg daily plus placebo or clopidogrel 75 mg plus aspirin 75 mg daily. At 18 months, combination therapy with clopidogrel plus aspirin, compared with clopidogrel alone, did not reduce the risk of ischaemic stroke, myocardial infarction, vascular death or rehospitalization for acute ischaemia. Furthermore, combination therapy, compared with clopidogrel monotherapy, significantly increased the risk of 'life-threatening' bleeding (defined as a fatal bleeding event, decrease in haemoglobin ≥50 g/L, significant hypotension with the need for inotropes, symptomatic intracranial haemorrhage, or transfusion of equivalent of ≥4 units of red blood cells) or 'major bleeding' (defined as significantly disabling with persistent sequelae, intraocular bleeding leading to significant loss of vision, or transfusion of equivalent of ≤3 units of red blood cells). In patients treated with clopidogrel plus aspirin, the incidence of life-threatening bleeding was 2.53% and the incidence of major bleeding (1.94%) was similar to that observed with clopidogrel plus aspirin in the CURE trial. Together, the incidence of serious bleeding in the clopidogrel plus aspirin group was nearly 2.5 times that seen with clopidogrel alone (4.47% versus 1.88%; p < 0.001).[24]

3. The CHARISMA Trial

The CHARISMA trial was designed to test the hypothesis that long-term treatment with clopidogrel plus aspirin would be more beneficial than aspirin alone across the spectrum of high-risk patients with atherothrombosis.[32] The trial included 15 603 patients aged ≥45 years from 768 centres in 32 countries. Patients were 'symptomatic' (those with established coronary, cerebral or peripheral arterial disease), or 'asymptomatic' (those with multiple risk factors for atherothrombosis without documented cardiovascular disease) [see table II].[23] Approximately 80% of subjects had documented vascular disease, including 35% with prior myocardial infarction, 25% with prior stroke, 12% with prior TIA, and 23% with peripheral arterial disease. Subjects were randomized to receive clopidogrel 75 mg daily plus aspirin 75–162 mg daily or placebo plus aspirin 75–162 mg daily, and were assessed at months 1, 3, 6 and 12 and every 6 months thereafter until trial completion (see figure 1). The primary

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Table II. Inclusion criteria for subjects in the CHARISMA trial (reproduced from Bhatt et al.,[23] with permission. Copyright© 2006. Massachusetts Medical Society. All rights reserved)

Asymptomatic patients with high risk for atherothrombotic events: patients with two major or three minor, or one major plus two minor atherothrombotic risk factors
Major atherothrombotic risk factors
type 1 or 2 diabetes mellitus
diabetic nephropathy
ankle brachial index <0.9
asymptomatic carotid stenosis ≥70%
at least one carotid plaque as evidenced by intima-media thickness
Minor atherothrombotic risk factors
systolic blood pressure ≥150 mmHg despite at least 3 months of therapy
primary hypercholesterolaemia
smoking >15 cigarettes per day
male ≥65 years of age or female ≥70 years of age
Symptomatic patients with established cardiovascular disease: patients with documented coronary, cerebrovascular or peripheral arterial disease
Documented coronary disease
angina with documented multivessel coronary disease
history of multivessel percutaneous coronary intervention
history of multivessel coronary artery bypass grafting
myocardial infarction
Documented cerebrovascular disease
transient ischaemic attack during previous 5 years
ischaemic stroke during previous 5 years
Documented peripheral arterial disease
current intermittent claudication and ankle brachial index ≤0.85
history of intermittent claudication and previous intervention (amputation, peripheral bypass or angioplasty)

efficacy outcome measure was the rate of myocardial infarction, stroke or death from cardiovascular causes. The primary safety outcome measure was the rate of 'severe bleeding', defined as fatal bleeding and intracranial haemorrhage, or bleeding that causes haemodynamic compromise requiring blood or fluid replacement, inotropic support or surgical intervention. Furthermore, pre-specified subgroups of subjects, classified according to prior cardiovascular events, prior use of cardiovascular medication, risk factors, or criteria for enrolment in the trial, were analysed for primary endpoints.[23]

At trial completion (median follow-up 28 months), ITT analysis showed that clopidogrel plus aspirin had similar efficacy compared with placebo plus aspirin (figure 2).[23] There were similar rates of the primary efficacy endpoint: myocardial infarction, stroke or death from cardiovascular causes occurred in 6.8% of patients treated with aspirin plus clopidogrel and 7.3% of those treated with aspirin plus placebo (RR 0.93; p = 0.22) In an analysis of the secondary efficacy endpoint, there was a marginally lower rate of first occurrence of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for unstable angina, a TIA, or revascularization (coronary, cerebral or peripheral), with rates of 16.7% with clopidogrel plus aspirin versus 17.9% with placebo plus aspirin (RR 0.92; p = 0.04). In individual components of these composite endpoints there were significantly lower rates of nonfatal stroke and hospitalization for unstable angina, TIA or revascularization with clopidogrel plus aspirin versus placebo plus aspirin.[23]

Clopidogrel plus aspirin had an inferior safety profile compared with placebo plus aspirin (figure 3).[23] There were similar rates of severe bleeding compared with placebo plus aspirin: 1.7% with clopidogrel plus aspirin and 1.3% with placebo plus aspirin (RR 1.25; p = 0.09). Both treatment groups also had similar rates of fatal bleeding and primary intracranial haemorrhage. However, treatment with clopidogrel plus aspirin resulted in a significantly higher rate of 'moderate bleeding', defined as bleeding that led to transfusion but did not meet the criteria for severe bleeding (2.1% with clopidogrel plus aspirin versus 1.3% with placebo plus aspirin [RR 1.62; p < 0.001]).[23]

Comparing moderate and severe bleeding occurrences with the overall efficacy endpoints, bleeding occurrences for those on clopidogrel plus aspirin outweighed the primary efficacy endpoint reduction by 2.3-fold (89 more bleeding complications versus 39 fewer myocardial infarctions, strokes or cardio-

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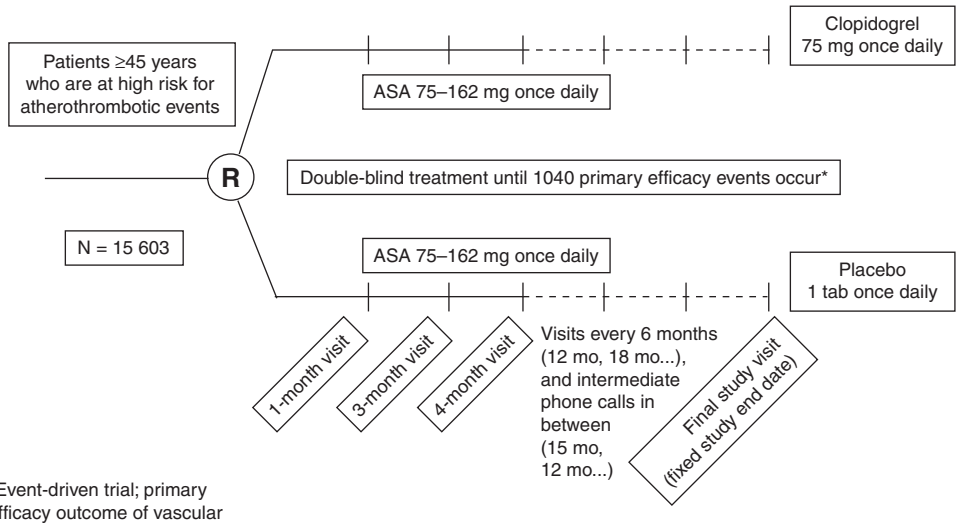

Fig. 1. Design of the CHARISMA trial (reproduced from Bhatt and Topol,[32] with permission). **ASA** = aspirin; **MI** = myocardial infarction; **mo** = month; **R** = randomization; **tab** = tablet.

vascular deaths) and were similar compared with the secondary endpoint reduction (94 fewer primary efficacy endpoints or hospitalization for unstable angina, TIAs or revascularization procedures).[23]

In the subgroup analyses, no differences were detected between the treatment responses of subjects with and without a history of diabetes, hypertension, hypercholesterolaemia, peripheral arterial disease, prior cardiac or vascular surgery, prior myocardial infarction, prior stroke, prior TIA, or prior use of other antiplatelet agents, ACE inhibitors, HMG-CoA reductase inhibitors, α-adrenergic receptor antagonists, calcium channel antagonists, antidiabetic agents, angiotensin II receptor antagonists, COX-2 inhibitors and anticoagulants.[23] However, differences in treatment response were found between 'symptomatic' patients, enrolled in the trial on the basis of established cardiovascular disease, and 'asymptomatic' patients, enrolled on the basis of multiple atherothrombotic risk factors (figure 4). In symptomatic patients but not asymptomatic patients, the addition of clopidogrel to aspirin therapy marginally reduced the risk of myocardial infarction, stroke or death from cardiovascular cause (63 fewer events; $p = 0.046$) [figure 4a]. However, this benefit in symptomatic patients was offset by the risk of moderate bleeding (2.1% for clopidogrel plus aspirin vs 1.3% for placebo plus aspirin; $p < 0.001$) or severe (1.6% clopidogrel plus aspirin vs 1.4% placebo plus aspirin; $p < 0.39$) bleeding events (60 more events).

The results of the myriad subgroup analyses in the CHARISMA trial should be interpreted with caution.[33] Subgroup analyses are generally inconclusive. Their value lies in their potential to generate hypotheses, which require validation in trials specifically designed to examine them directly.[34] For example, a subgroup analysis of the TASS study suggested that among non-White patients, ticlopidine has a more favourable benefit-risk profile than aspirin;[35] however, in a subsequent trial designed to directly compare these agents in Black patients, ticlopidine did not prove superior to aspirin for preventing recurrent stroke, myocardial infarction or vascular death.[36]

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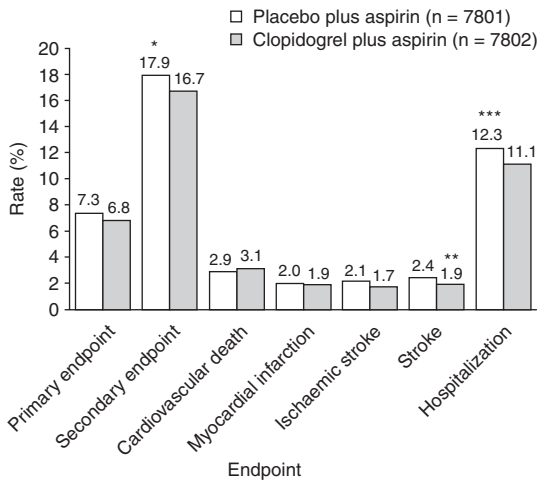

Fig. 2. Efficacy of clopidogrel plus aspirin and placebo plus aspirin in the CHARISMA trial: primary and secondary endpoints and their components. Hospitalization represents hospitalization for unstable angina, transient ischaemic attack or revascularization. The primary endpoint is the rate of myocardial infarction, stroke or death from cardiovascular causes. The secondary endpoint is first occurrence of myocardial infarction, stroke, death from cardiovascular causes, or hospitalization for unstable angina, a transient ischaemic attack, or a revascularization procedure (coronary, cerebral or peripheral). Data from Bhatt et al.[23] * p = 0.04, ** p = 0.03, *** p = 0.02.

Conclusions based on the results of the subgroup analyses in the CHARISMA trial are undermined by marginal statistical significance, the absence of statistical adjustment for multiple analyses, and the large number of subanalyses made, which increases the odds of finding a significant result by chance.[37] Furthermore, the value of categorizing patients as symptomatic and asymptomatic is unclear. Patients may not be clearly distinguished based on the current presence of cardiovascular disease or cardiovascular symptoms alone. In the CHARISMA trial, for example, some patients classified as asymptomatic had reported a history of cardiovascular events, including 10% with prior myocardial infarction, 6% with prior stroke, 5% with prior TIA, 8% with prior percutaneous coronary intervention, and 10% with prior coronary artery bypass grafting.

4. Conclusions

The results of the CHARISMA trial have better defined the role of clopidogrel in preventing secondary cardiovascular events. Previous studies support therapy with clopidogrel plus aspirin for about 1 year in patients with acute coronary syndrome and following coronary stent deployment.[7-9,11-13,18-22] However, the results of the CHARISMA trial indicate that the benefits of combination therapy with clopidogrel plus aspirin seen in these patient populations do not extend to all patients at high risk for atherothrombosis, including those with a prior cerebrovascular event; there is no evidence of therapeutic benefit to outweigh the increased bleeding risk in these patients. The American Heart Association, the American Stroke Association and the American College of Chest Physicians recommend aspirin, aspirin plus extended-release dipyridamole, or clopidogrel as initial therapy in patients with non-cardioembolic ischaemic stroke or TIA to reduce the risk of recurrent stroke and other cardiovascular events.[6,15] Based on the results of the MATCH

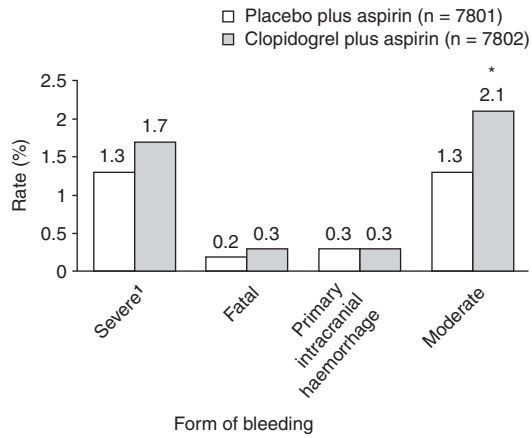

Fig. 3. Safety of clopidogrel plus aspirin and placebo plus aspirin in the CHARISMA trial. Severe bleeding is fatal bleeding and intracranial haemorrhage, or bleeding that causes haemodynamic compromise requiring blood or fluid replacement, inotropic support or surgical intervention. Moderate bleeding is bleeding that leads to transfusion but does not meet the criteria for severe bleeding. **1** Severe bleeding is the primary safety endpoint. Data from Bhatt et al.[23] * p < 0.001.

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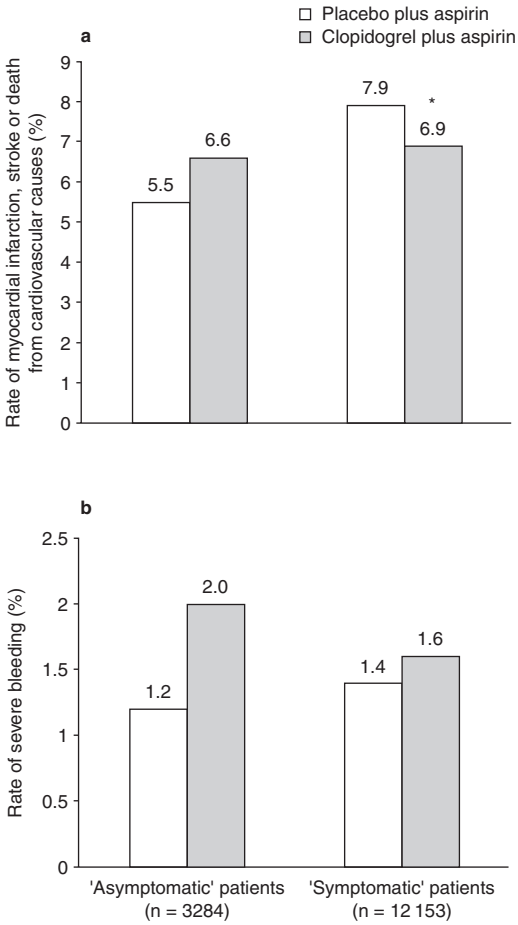

Fig. 4. Subgroup analyses: efficacy in preventing cardiovascular events in asymptomatic and symptomatic patients (**a**) and rates of severe bleeding (**b**). Asymptomatic patients were enrolled in the CHARISMA trial on the basis of multiple atherothrombotic risk factors. Symptomatic patients were enrolled on the basis of established cardiovascular disease. For differential interaction between subgroup and treatment response, p = 0.045. Severe bleeding is fatal bleeding and intracranial haemorrhage, or bleeding that causes haemodynamic compromise requiring blood or fluid replacement, inotropic support, or surgical intervention. Data from Bhatt et al.[23]
* p = 0.046.

trial, combination therapy with aspirin plus clopidogrel is not recommended for patients with ischaemic stroke or TIA, due to an increased risk of haemorrhage. The results of the CHARISMA trial further support this recommendation.

Future directions for research include assessing the benefit-risk ratio of clopidogrel plus aspirin therapy in specific subpopulations of patients at high risk for atherothrombotic events. An ongoing phase 3 trial, the SPS3 trial, is designed to assess whether aspirin plus clopidogrel is more effective than aspirin alone for preventing recurrent stroke and cognitive decline in patients with lacunar stroke and whether outcomes are affected by blood pressure control.[37] Also, the role of clopidogrel plus aspirin in preventing cardioembolic stroke or early recurrent stroke after symptomatic large-vessel atherostenosis is not currently known.

Of all stroke aetiologies, the pathophysiology of cervical internal carotid artery disease most closely resembles that of acute coronary syndrome. Unstable plaque is prone to rupture with subsequent thrombosis and distal embolization.[38] In this situation, acute treatment with clopidogrel plus aspirin to prevent early recurrence may warrant future study. However, this paradigm may suffer from insurmountable study design limitations due to the trend towards earlier carotid revascularization and the higher surgical bleeding associated with clopidogrel.

Acute clopidogrel loading plus aspirin was investigated in the FASTER study.[39] This study was prematurely halted due to slow recruitment after enrolling 396 subjects. Patients with acute presumed noncardioembolic ischaemic stroke or TIA were randomized in a 2 × 2 factorial design to receive clopidogrel (300 mg loading dose and 75 mg daily thereafter) or placebo and simvastatin or placebo within 24 hours of symptom onset. All subjects received aspirin 81 mg daily. The primary outcome, any stroke within 90 days, occurred in 14 subjects in the clopidogrel group and 21 in the group without clopidogrel. This was offset by five moderate or severe bleeding events, including two intracranial haemorrhages in the clopidogrel group versus none in the group without clopidogrel. These data must be interpreted with caution considering the low sample size and few primary outcomes during follow-up.

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Other future directions include examining other combination therapies for preventing recurrent cerebrovascular events. The recently published results of the ESPRIT trial demonstrate that within 6 months of TIA or minor stroke of arterial origin, long-term treatment with aspirin plus dipyridamole is superior to aspirin alone in reducing the risk of death from vascular causes, nonfatal stroke, nonfatal myocardial infarction or major bleeding.[40] An ongoing phase 4 trial, the PRoFESS trial, is designed to compare aspirin plus dipyridamole and clopidogrel for preventing recurrent strokes in over 20 333 patients with a recent stroke.[41] Results are expected later in 2008.

In lieu of ongoing and future trial data, adherence to published guidelines for antiplatelet agent selection and avoidance of the routine use of clopidogrel plus aspirin for stroke prevention as discussed above is recommended.

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