Title
Role of antiplatelet therapy in cardiovascular disease II: Ischemic stroke

Journal
Current Medical Research and Opinion, 20(11)

ISSN
0300-7995

Authors
Cavendish, Jeffrey J
Cramer, Steven C
Graham, Glenn D

Publication Date
2004-11-01

DOI
10.1185/030079904x10674

CURRENT MEDICAL RESEARCH AND OPINION®
VOL. 20, NO. 11, 2004, 1845–1849

0300-7995
doi:10.1185/030079904X10674

ORIGINAL ARTICLE: SUPPLEMENT

Role of antiplatelet therapy in cardiovascular disease II: Ischemic stroke

Jeffrey J. Cavendish[1], Steven C. Cramer[2] and Glenn D. Graham[3]

[1]*Department of Cardiology, Naval Medical Center, San Diego, CA, USA*

[2]*Departments Neurology and Anatomy and Neurobiology, UCI Medical Center, University of California Irvine, Orange, CA, USA*

[3]*Departments of Neurology, Radiology, and Neurosciences, Albuquerque VA and Neurology/127, VA Medical Center, University of New Mexico School of Medicine, Albuquerque, NM, USA*

Address for correspondence: **Dr Jeffrey J. Cavendish, Department of Cardiology, Building 3, 3rd Floor, Naval Medical Center, San Diego, 34800 Bob Wilson Drive, San Diego, CA 92134, USA. Tel.: +1-619-532-7421; Fax: +1-619-532-9863; email: JJCavendish@nmcsd.med.navy.mil**

Key words: **Antiplatelet – Atherothrombosis – Ischemic stroke – Transient ischemic attack**

SUMMARY

The etiology of cerebrovascular disease is heterogeneous, with the majority of strokes being of ischemic origin. Transient ischemic attack is now considered to be an important precursor and long-term risk factor for ischemic stroke. Given the lack of acute therapies for ischemic stroke, current treatments focus on secondary prevention through risk-factor management, pharmacotherapy and interventional approaches. As illustrated in this paper, antiplatelet agents (e.g. clopidogrel, aspirin, dipyridamole) are the cornerstone of therapy for prevention of recurrent ischemic stroke.

Introduction

Cerebrovascular disease is the third leading cause of mortality in the United States – accounting for over 163 000 deaths in 2001 – and the leading cause of serious, long-term disability[1]. Nearly one in every 14 deaths in the United States is due to stroke, with an average of one stroke fatality every 3 min. The prevalence of stroke is about 4.8 million, with approximately 700 000 new or recurrent cases each year[1]. The financial impact of stroke is high, with the direct and indirect cost of stroke in 2004 predicted to be US$54 billion[1].

The pathogenesis of cerebrovascular disease is heterogeneous: 80–85% of all strokes are of ischemic origin, caused by obstruction of the cerebral vasculature, while the remaining 15–20% are hemorrhagic[1–3]. The most common underlying etiology of ischemic stroke results from atherothrombotic processes leading to narrowing or blockage of arteries. Large-artery atherothrombosis accounts for 20–30%, microatheroma and other small-artery occlusive disease ('lacunar' stroke) for 20–25%, and cardiogenic embolism for 15–20% of all ischemic strokes. The remaining causes are of other (5%) or cryptogenic (30%) etiology[3].

Thrombotic and embolic strokes may be preceded by a transient ischemic attack (TIA), a mild and transitory event now recognized as an important precursor and long-term risk factor for stroke and other vascular ischemic accidents[4,5]. In the 90 days after a TIA, there is a 25% overall risk of an adverse event, including recurrent TIA (13%), stroke (11%), cardiovascular hospitalization (3%) or death (3%)[6]. More than half of these adverse events occur in the first 2 days after TIA.

Depending on the vascular bed affected, the atherothrombotic disease process can also manifest as acute coronary syndromes or peripheral arterial disease[7]. Consistent with the generalized nature of atherothrombosis, 30–50% of stroke and TIA patients have a history of coronary artery disease[8–10]. Because of this atherothrombotic cross-risk, stroke and TIA patients are not only at an increased risk of stroke, but also other ischemic vascular events, particularly myocardial infarction[11,12]. Indeed, over the 10-year period after a first ischemic stroke, the risk of death from cardiovascular events is double that from recurrent stroke[12].

Considering the substantial mortality, morbidity and economic cost of stroke, there is a clear need for improved strategies to prevent new and recurrent stroke. Existing approaches include lifestyle modifications and management of risk factors (e.g. hypertension, hyperlipidemia, obesity, smoking), pharmacotherapy, and interventional approaches (e.g. endarterectomy, carotid stenting). Several important pharmacologic therapies can be considered, including treatment with anticoagulants (particularly in patients with atrial fibrillation), HMG-CoA reductase inhibitors (statins; particularly in coronary artery disease patients with elevated cholesterol) and antiplatelet agents.

As the majority of all strokes are ischemic in etiology, most stroke patients are suitable candidates for antiplatelet therapy, the benefits of which have been firmly established[13]. Aspirin remains the mainstay of antithrombotic therapy for the secondary prevention of stroke, reducing the relative risk of stroke recurrence by 13–18%[3,8,14]. Further benefits may be realized when low-dose aspirin is combined with extended-release dipyridamole (37% relative risk reduction vs placebo)[8].

Studies have demonstrated that the ADP receptor antagonist clopidogrel effectively prevents secondary stroke. In the CAPRIE study involving 19 185 patients with recent ischemic stroke, myocardial infarction or peripheral arterial disease, there was a significant advantage of clopidogrel over aspirin, based on a 8.7% relative risk reduction ($p = 0.043$) in the composite endpoint of ischemic stroke, myocardial infarction or vascular death[9]. In CAPRIE, the average yearly risk of this composite endpoint was 5.32% with clopidogrel and 5.83% with aspirin. This advantage is amplified in patients with a history of ischemic events[15]. Results of the recently completed MATCH study[16] confirm the benefit of clopidogrel monotherapy in high-risk ischemic stroke/TIA patients[17]; however, in this high-risk population, adding aspirin to a baseline therapy of clopidogrel increased the rate of serious bleeding without significantly improving efficacy[18].

The following collection of case studies is the second of a three-part set illustrating the role of antiplatelet therapy in current treatment strategies for various manifestations of atherothrombosis. The topic of the case reports presented in this article is ischemic stroke, with case reports on acute coronary syndromes[19] and peripheral arterial disease[20] presented in the accompanying articles.

Case studies

1. Cryptogenic Stroke in a Healthy 40-Year-Old Woman

A 40-year-old woman presented with right arm and leg heaviness and numbness of 1 days duration. For the previous 2 months she had noticed intermittent, isolated right hand 'tingling' that occurred only during exercise and abated shortly after stopping, but she had not sought medical attention. However, for the past day, she had also noted numbness of the leg and arm that began while she was at rest.

The patient was generally in good health, and her past medical history was limited to recurrent sinus infections. She was told at the age of 16 years that she had a heart murmur, but no additional testing was performed, and this has not been mentioned during subsequent medical checkups. She previously smoked one pack of cigarettes per day for 8 years, but quit 10 years ago. She regularly consumed 1–2 glasses of wine with dinner.

At presentation, her vital signs were: blood pressure 119/72 mmHg; pulse 71 beats/min and regular; respirations 18 breaths/min; and temperature 37.6 °C. General physical examination was unremarkable, with no carotid bruits or cardiac murmurs. On neurological examination, the patient was alert with normal speech and recall. The fundoscopic exam was normal. Cranial nerves 2–12 were intact, without facial asymmetry or sensory loss. Muscle strength was 5/5 throughout (Medical Research Council scale), with normal muscle bulk and tone. Coordination in the arms and legs was intact. There was a subjective dulling of touch and pin sensation in the right upper and lower extremities, but position sense was preserved in the hands and feet. Reflexes were 2+ throughout and plantar response was flexor bilaterally.

Routine laboratory parameters were within normal limits, and the electrocardiogram showed normal sinus rhythm. However, head computed tomography (CT) revealed a lucency in the left parietal region.

The patient was hospitalized for further testing. Magnetic resonance imaging (MRI) including diffusion-weighted and fluid-attenuated inversion recovery (FLAIR) sequences confirmed an acute left parietal ischemic stroke, while magnetic resonance angiography of the circle of Willis and carotid arteries was normal. Carotid ultrasound revealed very mild, hemodynamically

insignificant stenosis on both sides. A hypercoagulability screen was negative. The transesophageal echocardiogram identified a patent foramen ovale (PFO) with spontaneous left to right shunting, and documented right to left shunting on a bubble study with cough. The ejection fraction was 65%, and no atrial septal aneurysm or other abnormality was identified. Doppler ultrasound of the legs revealed no deep venous thrombosis.

The clinical significance of a small PFO is controversial, and the optimal treatment of patients with small PFO, stroke, and emboli of unknown source is uncertain[21]. Possible treatments options include closure of the PFO by an open surgical procedure or with an endovascular closure device, anticoagulation, and antiplatelet therapy. After discussions between the cardiology and neurology consultants, it was decided to use aggressive antiplatelet therapy with clopidogrel 75 mg daily and aspirin 81 mg daily. This choice satisfied the patient's desire to avoid invasive procedures or chronic warfarin therapy. The patient was started on the antiplatelet combination prior to hospital discharge and has subsequently remained free of recurrent events or any complications of therapy.

2. Multiple Procedures to Prevent Stroke in a 53-Year-Old Man

A 53-year-old man, well known to our department, with a long history of atherosclerotic coronary, cerebrovascular and peripheral vascular disease presented after undergoing a routine follow-up Doppler ultrasound of his carotid arteries. Three years prior to this presentation, he had developed classic symptoms of amaurosis fugax in the left eye, despite being on aspirin. Severe bilateral internal carotid artery stenoses were discovered and he underwent left carotid endarterectomy. Post-operatively he had severe chest pain, nausea, vomiting and developed a left cervical nerve injury. He therefore refused surgery on the stenosis in the right internal carotid artery and opted for carotid stenting. The patient had also undergone multiple coronary angioplasty procedures and renal artery stenting for severe bilateral renal artery stenosis, which was causing severe renovascular hypertension. The patient had been doing quite well for the past 3 years on chronic aspirin and clopidogrel; he had also been taking atenolol, lisinopril, nicotinic acid, and clonidine.

The carotid ultrasound showed severely elevated velocities in the left internal carotid artery: the peak velocity was 499 cm/sec and the left common carotid velocity was 75 cm/sec. Estimated stenosis severity in the left internal carotid artery was greater than 90%. The right carotid stent had normal velocities. The patient was referred for angiography.

Aortic arch angiography and selective carotid angiography revealed 90% stenosis in the proximal left internal carotid artery at the distal margin of the endarterectomy site (Figure 1a). Carotid angioplasty and stenting was then performed. A 3000 unit heparin bolus was given intravenously; the patient continued to take aspirin and clopidogrel, including on the morning of the procedure. The stenosis was initially dilated with a 4.0 × 30 mm Opensail balloon (Guidant, Temecula, CA), and an 8.0 × 30 mm SMART Stent (Cordis, Miami, FL) was deployed and post-dilated with a 5.5 × 40 mm Savvy balloon (Cordis). Post-procedure angiography demonstrated an excellent result (Figure 1b). In the absence of any change in baseline neurologic findings after overnight monitoring, the patient was discharged the next day on indefinite aspirin (325 mg) and clopidogrel (75 mg) therapy, in addition to his other outpatient medications.

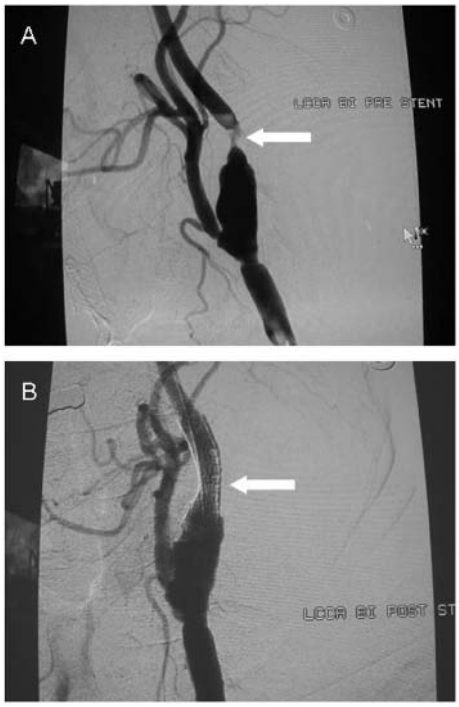

Figure 1. *Selective carotid angiograms illustrating near complete (90%) stenosis in the proximal left internal carotid artery (depicted by the white arrow) before (a) and after (b) carotid angioplasty and stenting*

At his 6-month follow-up exam, the patient continued to do well with no further episodes of amaurosis fugax. The patient remains on an aggressive medical regimen for risk factor reduction with lifelong aspirin and clopidogrel, as well as atorvastatin, nicotinic acid, atenolol and fosinopril.

3. Ischemic Infarct in a 68-Year-Old Man

A 68-year-old man presented to the emergency room with left arm and leg weakness of 9 hours duration. He had no history of stroke or TIA. That morning, he had felt 'funny' while shaving, and thought that his face was possibly drooping when he looked in the mirror. He also

noted clumsiness when using his left hand to apply the shaving cream. Shortly thereafter, his left arm and leg grew weaker. He sat and watched television for most of the day; by dinner time, his weakness was substantial and the paramedics were phoned.

The patient's medical history was remarkable for peptic ulcer disease, which had been symptomatic 10 days previously, and he was taking lansoprazole 30 mg daily. The patient had hypertension of 8 years duration, for which he was treated with hydrochlorothiazide 25 mg/day. The patient had no drug allergies. On the evening of admission, the patient's blood pressure was 188/92 mmHg, his pulse was 80 beats/min and regular, and he was afebrile. General medical examination was unremarkable. On neurological examination, the patient had mild-moderate left hemispatial neglect. Language and attention were unremarkable. Cranial nerve examination disclosed no gaze preference and mild left facial weakness. Mild copper wiring was present bilaterally on fundoscopic examination. The left arm and leg were 2/5 proximally and distally, though with prompting, but strength was closer to 4–/5 on the Medical Research Council scale. Sensory examination showed no deficits apart from extinction to double simultaneous stimulation on the face and dorsum of the hand. Reflex testing was unremarkable, as was cerebellar examination; no gait examination was performed.

On admission, the patient's blood chemistry, complete blood count, and activated partial thromboplastin time were unremarkable. Total blood cholesterol was 196 mg/dL (5.1 mmol/L), with low density lipoprotein = 84 mg/dL (2.2 mmol/L) and high density lipoprotein = 46 mg/dL (1.3 mmol/L). The electrocardiogram showed voltage criteria suggestive of left ventricular hypertrophy. Cranial CT showed early edema in the right frontoparietal cortex/subcortical white matter of the middle cerebral artery territory, which was confirmed by subsequent diffusion-weighted MRI. Doppler studies identified no significant intracranial or extracranial cerebral artery disease. Transesophageal echocardiography revealed slight wall thickening without other abnormalities apart from a moderate patent foramen ovale, which was demonstrated by performing the Valsalva maneuver after injection of agitated saline contrast medium into the antecubital vein.

Blood pressure returned to normal on day 3 of admission. Due to the history of peptic ulcer disease and risk of gastrointestinal bleeding, the patient was placed on clopidogrel 75 mg monotherapy once daily for secondary stroke prevention. On day 4 of admission, the patient was transferred to an acute rehabilitation ward. Steady gains were seen in the patient's motor function over the subsequent 9 weeks, and in his attentional examination over the subsequent 12 months. At 1-year follow-up exam, there was no evidence of any further arterial events. The patient is scheduled to be on clopidogrel indefinitely.

Conclusions

The goals of treatment after ischemic stroke or TIA are multifaceted. In the short term, objectives are to treat stroke symptoms, to re-establish blood flow and to restrict brain damage. However, acute therapies for ischemic stroke are limited: tissue plasminogen activator is the only approved agent in North America, but the short 3 h post-stroke therapeutic window and bleeding concerns effectively restrict its use to 1.6–3% of patients[22,23]. Research into other treatment strategies such as neuroprotection or neurorestoration is ongoing.

For the long-term treatment of ischemic stroke, goals are to reduce the risks of recurrent stroke and of ischemic events at other vascular sites. This can be achieved by identification and treatment of modifiable risk factors through life-style changes and pharmacologic intervention. As stroke and TIA patients are at long-term risk of future ischemic episodes, antiplatelet therapy is desirable in ischemic stroke patients. Antiplatelet drugs target not only the thrombosis responsible for the ischemic cerebrovascular event, but also the common underlying pathophysiology of atherothrombosis that increases the risk of ischemic events in other vascular beds.

The American College of Chest Physicians' 2004 Guidelines[3] recommend antiplatelet therapy to reduce the risk of secondary stroke and other ischemic events following an ischemic stroke or TIA. Treatment with aspirin (50-325 mg) once daily, low-dose aspirin (25 mg) plus extended-release dipyridamole (200 mg) twice daily, or clopidogrel (75 mg) once daily are acceptable initial therapies.

Two of the case studies presented here illustrate the safety and efficacy of clopidogrel plus aspirin dual therapy. It is appropriate to mention that these patients were treated before the results of MATCH[17] were available. While MATCH in general does not support the routine use of clopidogrel plus aspirin combination in the high-risk stroke patients investigated in the trial, the patients in the first two case reports fall outside the MATCH population[16,17]. The patient in case study 1 had a presumed (or at least possible) cardiogenic event and did not exhibit any of the MATCH inclusion criteria regarding risk factors (e.g. diabetes, prior ischemic stroke, prior myocardial infarction, angina pectoris, or symptomatic peripheral arterial disease)[16,17]. In case study 2, the patient had not suffered from prior ischemic stroke or TIA. Therefore, combination therapy

with clopidogrel plus aspirin may be appropriate for some patients, although clinicians must weigh the clinical benefits against the potential increased risk of bleeding complications.

Acknowledgements

This project was supported by Bristol-Myers Squibb/ Sanofi-Synthélabo Pharmaceutical Partnership.

Case study 1 was contributed by G. Graham, case study 2 by J.J. Cavendish and case study 3 by S.C. Cramer.

References

1. American Heart Association. Heart Disease and Stroke Statistics – 2004 Update. Report available online at: http://www.americanheart.org/downloadable/heart/1079736729696HDSStats2004UpdateREV3-19-04.pdf [accessed 1 Sept 2004]
2. Rosamond WD, Folsom AR, Chambless LE, et al. Stroke incidence and survival among middle-aged adults: 9-year follow-up of the Atherosclerosis Risk in Communities (ARIC) cohort. Stroke 1999;30:736-43
3. Albers GW, Amarenco P, Easton JD, et al. Antithrombotic and thrombolytic therapy for ischemic stroke. Chest 2004;126: 483S-512S
4. Albers GW, Caplan LR, Easton JD, et al. Transient ischemic attack: proposal for a new definition. N Engl J Med 2002;347:1713-6
5. Hankey GJ. Long-term outcome after ischaemic stroke/transient ischaemic attack. Cerebrovasc Dis 2003;16(Suppl. 1):14-9
6. Johnston SC, Gress DR, Browner WS, et al. Short-term prognosis after emergency department diagnosis of TIA. JAMA 2000;284:2901-6
7. Munger MA, Hawkins DW. Atherothrombosis: epidemiology, pathophysiology, and prevention. J Am Pharm Assoc 2004;44: S5-12;quiz S12-3
8. Diener HC, Cunha L, Forbes C, et al. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996;143:1-13
9. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348:1329-39
10. Ness J, Aronow WS. Prevalence of coexistence of coronary artery disease, ischemic stroke, and peripheral arterial disease in older persons, mean age 80 years, in an academic hospital-based geriatrics practice. J Am Geriatr Soc 1999; 47:1255-6
11. Sacco RL, Shi T, Zamanillo MC, et al. Predictors of mortality and recurrence after hospitalized cerebral infarction in an urban community: the Northern Manhattan Stroke Study. Neurology 1994;44:626-34
12. Hardie K, Hankey GJ, Jamrozik K, et al. Ten-year survival after first-ever stroke in the Perth community stroke study. Stroke 2003;34:1842-6
13. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86
14. Algra A, van Gijn J. Cumulative meta-analysis of aspirin efficacy after cerebral ischaemia of arterial origin. J Neurol Neurosurg Psychiatry 1999;66:255
15. Ringleb PA, Bhatt DL, Hirsch AT, et al. Benefit of clopidogrel over aspirin is amplified in patients with a history of ischemic events. Stroke 2004;35:528-32
16. Diener HC, Bogousslavsky J, Brass LM, et al. Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischaemic Attack or Ischaemic Stroke (MATCH): Study Design and Baseline Data. Cerebrovasc Dis 2004;17:253-61
17. Diener HC, Bogousslavsky J, Brass LM, et al. MATCH investigators. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. Lancet 2004;364: 331-7
18. Amarenco P, Donnan GA. Should the MATCH results be extrapolated to all stroke patients and affect ongoing trials evaluating clopidogrel plus aspirin? Stroke 2004;35:2606-8
19. Cavendish JJ, Fugit RV, Safani M. Role of antiplatelet therapy in cardiovascular disease I: acute coronary syndromes. Curr Med Res Opin 2004;20(11):1839-43
20. Cavendish JJ, Safani M. Role of antiplatelet therapy in cardiovascular disease III: Peripheral arterial disease, Curr Med Res Opin 2004;20(11):1851-55
21. Mas JL, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. N Engl J Med 2001;345:1740-6
22. Alberts MJ. Hyperacute stroke therapy with tissue plasminogen activator. Am J Cardiol 1997;80:29D-34D;discussion 5D-9D
23. Reed SD, Cramer SC, Blough DK, et al. Treatment with tissue plasminogen activator and inpatient mortality rates for patients with ischemic stroke treated in community hospitals. Stroke 2001;32:1832-40

CrossRef links are available in the online published version of this paper:
http://www.cmrojournal.com
Paper CMRO-2728B_4, *Accepted for publication*: 23 September 2004
Published Online: 26 October 2004
doi:10.1185/030079904X10674