Developments in Secondary Stroke Prevention

a report by

Hans-Christoph Diener[1] *and* **Patrick Wong**[2]

1. Department of Neurology, University of Duisberg-Essen; 2. Senior Medical Editor, Touch Briefings

DOI:10.17925/ENR.2008.03.02.50

The Importance of Treating Stroke

Ischaemic stroke is the leading global cause of disability in the developed world, and the third leading cause of mortality. It is estimated that 8–12% of individuals die within the first 30 days of their initial stroke,[1] and patients who survive the initial attack face an increased risk of subsequent vascular events and stroke, as approximately one-quarter of all strokes occurring each year are recurrent.[2] Within the first year of survival following the initial attack, 21.5% of patients will experience a recurrent stroke or transient ischaemic attack (TIA).[2]

The severity of disability resulting from stroke depends on the size and location of the lesion, and patients can be affected physically, neurologically and emotionally. The consequences of stroke are socioeconomic: 75% of stroke survivors are afflicted with disabilities that affect their employability.[3] Furthermore, there are significant costs to the stroke patient and his/her family in terms of inpatient care, rehabilitation, care-giving and any necessary follow-up care for lasting disabilities; therefore, in light of this disease burden, prevention of initial and recurrent stroke is a major priority for healthcare providers.

Recent guidelines for primary and secondary stroke prevention suggest focusing on the reduction or control of cardiovascular risk factors such as hypertension, hyperlipidaemia, tobacco usage, diabetes and obesity.[4,5] Antiplatelet therapy is common as well, with aspirin (acetylsalicylic acid) being the most widely used due to its cost-efficiency and agreeable adverse-effect profile. However, primary prevention of stroke is generally less effective than secondary prevention, as indicated by the number of patients needed to treat in order to prevent one stroke per year.[6]

Current Options in Secondary Stroke Prevention

Antiplatelet therapy is one of the leading strategies in preventing recurrent vascular events in patients with a history of stroke or TIA. Current clinical practice guidelines by the American Heart Association (AHA), the American Stroke Association (ASA), the American College of Chest Physicians (ACCP), the American Academy of Neurology (AAN), the European Stroke Organisation (ESO) and the European Society of Cardiology (ESC) recognise the benefits of secondary stroke prevention associated with aspirin, other antiplatelet agents such as clopidogrel and combinations of antiplatelet drugs such as aspirin and extended-release dipyridamole in initial therapy.[5,7–10] The most recent recommendations from the XVII ESO released at the European Stroke Consortium in Nice, France in May 2008 advocate the use of antithrombotic therapy, where patients not requiring anticoagulation should receive antiplatelet therapy, with the combination of aspirin and dipyridamole, or clopidogrel alone where possible. Alternately, aspirin alone or trifusal alone may be used;[9] however, trifusal is available in only a few countries.

The past two decades have seen great developments in antithrombotic agents for secondary stroke prevention. The administration of aspirin in stroke patients has long since been known to have beneficial effects in reducing the risk of recurrent stroke compared with placebo:[11] recurrent vascular events can be reduced by about 13%, while the risk of recurrent stroke can be reduced by up to 23% with aspirin.[12] This protective effect was found to be independent of dosage, to the extent that a low dose can provide the same level of efficacy while offering a more favourable tolerability profile; however, the lack of an impressive risk reduction has spurred on a search for stronger antithrombotic agents.

Anticoagulants

The Stroke Prevention in Reversible Ischemia Trial (SPIRIT) was the first randomised study to compare the safety and efficacy in the prevention of recurrent cerebral ischaemia of presumed arterial (non-cardiac) origin of oral anticoagulation agents (international normalised ratio [INR] 3–4.5) with low-dose aspirin (30mg) daily.[13] However, patients treated with anticoagulants experienced a significant increase in the number of bleeding complications, inclusive of intracerebral haemorrhages, leading to the premature termination of the study. Soon after, the Warfarin-Aspirin Recurrent Stroke Study (WARSS) randomised patients with non-cardiogenic stroke to receive warfarin (INR 1.4–2.8) or aspirin (325mg/day).[14] After two years of follow-up, the investigators found no significant difference between the anticoagulant and aspirin in preventing recurrent ischaemic stroke or death. To date, the utility of anticoagulants in secondary stroke prevention remains unclear. Finally, the ESPRIT study showed that aspirin is equivalent to oral anticoagulation in patients with a non-cardiac source of embolism.[15]

Antiplatelet Studies

Various studies have aimed to improve on the efficacy and safety of aspirin by focusing on antiplatelet agents and combinations of antiplatelet drugs, with many recent trials concentrating on clopidogrel and dipyridamole. The first of these was the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, which enrolled 19,185 patients with a history of ischaemic stroke (n=6,431), myocardial infarction (n=6,302) or peripheral arterial disease (n=6,452) and randomised them to receive either clopidogrel 75mg once daily or aspirin 325mg once daily.[16] Clopidogrel offered an overall relative risk (RR) reduction in the recurrence of vascular events by 8.7% versus aspirin (95% confidence interval [CI] 0.3–16.5). However, the RR reduction between the vascular events was significantly heterogeneous (p=0.042): patients who entered the study with ischaemic stroke had an RR reduction of 7.3% and those with peripheral arterial disease had an RR reduction of 23.8%, while the patients who qualified for the study with a myocardial infarction had a 3.7% increased RR, implying that the extent of risk reduction with clopidogrel may depend on the type of arterial disease. Looking more specifically at the stroke subgroup of patients, the absolute risk reduction with clopidogrel was a modest 0.56%

per year (event rate 7.15% per year with clopidogrel and 7.71% per year with aspirin; p=0.26).[16] Furthermore, the 95% CI for the 7.3% RR reduction is wider than for all patients (-5.7–18.7), suggesting that the benefits observed with clopidogrel over aspirin for the reduction of vascular events may not be directly applicable to the specific subset of stroke. Although effective in the general study population in reducing the composite of vascular death, myocardial infarction or stroke, clopidogrel offered only a moderate benefit over aspirin in preventing stroke.

Antiplatelet Combination Therapies

To further explore the possibilities of improving antiplatelet therapy, subsequent studies examined combination therapies. Early trials validated the combination of clopidogrel plus aspirin as therapeutic strategies in acute coronary syndromes and stenting,[17,18] and in the move from coronary circulation to cerebral circulation the Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) study soon followed. This double-blind, placebo-controlled trial randomised 7,599 high-risk patients with prior ischaemic stroke or TIA and at least one additional vascular risk factor to a combination therapy of clopidogrel 75mg/day plus aspirin 75–162mg/day, or clopidogrel only 75mg/day.[19] After a mean follow-up of 18 months, there was no significant reduction in the number of ischaemic events; 15.7% of patients receiving the combination reached the composite end-point of a vascular event or re-hospitalisation for an acute ischaemic event compared with 16.7% of patients receiving clopidogrel monotherapy (RR reduction 6.4%, 95% CI -4.6–16.3; p=0.244). However, life-threatening bleeds were significantly increased in patients taking combination aspirin and clopidogrel (2.6%) compared with patients taking clopidogrel alone (1.3%; p<0.001).

Subsequently, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stablization, Management, and Avoidance (CHARISMA) study that followed enrolled 15,603 patients with clinically evident cardiovascular disease or multiple risk factors and compared the combination of clopidogrel 75mg/day and aspirin 75–162mg/day versus aspirin 75–162mg/day; these patients were followed up for a median duration of 28 months.[20] The rate of the primary composite end-point of myocardial infarction, stroke or vascular death was 6.8% in the combination arm and 7.3% in the aspirin arm (RR 0.93, 95% CI 0.83–1.05; p=0.22). Furthermore, patients treated with clopidogrel plus aspirin experienced a trend towards increased risk of severe bleeding complications (1.7 versus 1.3%, RR 1.25, 95% CI 0.97–1.61) and significantly greater moderate bleeding episodes (2.1 versus 1.3%, RR 1.62, 95% CI 1.27–2.08) compared with patients receiving aspirin only. *Post hoc* subgroup analysis of 'CAPRIE-like' patients with prior myocardial infarction, stroke or peripheral arterial disease indicated a possible benefit for the combination in reducing the risk of serious vascular events by 17% (95% CI 0.72–0.96; p=0.01), warranting further investigation.[21] As before, patients receiving the combination therapy were more prone to bleeding complications. Therefore, the data from MATCH and CHARISMA indicated no significant benefit for the combination of clopidogrel plus aspirin over clopidogrel, but a possible advantage over aspirin monotherapy. However, the use of this combination in secondary stroke prevention is precluded by the significantly increased risk of bleeding complications in patients.

The combination of aspirin plus dipyridamole has also been studied in the setting of secondary stroke prevention. The placebo-controlled, double-blind European Stroke Prevention Study 2 (ESPS-2) compared the effects of low-dose aspirin (25mg twice daily), extended-release dipyridamole (200mg twice daily) and a combination of the two drugs versus placebo in 6,602 patients with prior stroke or TIA.[22] Compared with placebo, stroke risk was significantly reduced by 18.1% with aspirin alone (p=0.013), by 16.3% with dipyridamole alone (p=0.039) and by 37% with the combination (p<0.001); RR reduction for combination therapy over aspirin monotherapy was a significant 23.1% (p=0.006). The risk of stroke or death was reduced by 13% with aspirin (p=0.016), by 15% with dipyridamole and by 24% with the combination (p<0.001). However, none of the active treatments evaluated was able to significantly reduce the risk of death alone or fatal stroke, although it is worth mentioning that there were only 90 fatal strokes among the entire study population (20 in the aspirin group, 28 in the dipyridamole group, 20 in the combination group and 22 in the placebo group).

Four earlier smaller studies with patient enrolment between 88 and 448 had also compared the efficacy of the combination therapy of aspirin and the immediate-release formulation of dipyridamole versus aspirin monotherapy ranging from doses of 900 to 1,300mg daily; the results showed minimal difference between the treatments.[23–26] The study by Kaye enrolled stroke patients and studied deep venous thrombosis as a primary outcome and vascular events as a secondary outcome.[26] A systematic review of these four studies for the composite outcome of vascular death, stroke or myocardial infarction led to an RR of 0.97 (95% CI 0.78–1.22).[27] The omission of Kaye's small study led to a cumulative RR of 0.95 (95% CI 0.75–1.19). These results are strikingly different from those obtained in ESPS-2. Furthermore, the primary outcome measure of stroke or death in ESPS-2 showed a similar discrepancy, with an RR of 1.01 (95% CI 0.82–1.25) for the four earlier studies and 0.87 (95% CI 0.75–1.00) for ESPS-2. Combining the results of all five trials then leads to a relative risk ratio of 16% (95% CI 5–26%).[27] There was no benefit for the combination therapy of aspirin and dipyridamole over aspirin monotherapy for total deaths (RR 1.02) or vascular death (RR 0.99, 95% CI 0.77–1.27), suggesting that the combination may confer some advantage, if any, to non-fatal events.

In response to the discrepancies between the earlier studies and ESPS-2, researchers embarked on the European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT) to further compare the effects of aspirin (median dose 75mg, range 30–325mg) with or without dipyridamole 200mg twice daily in 2,739 patients with a TIA or stroke of non-cardiac origin.[28] The study design was open and non-blinded in order to assess treatment strategies in real-life clinical settings. The distribution of aspirin doses was similar between groups, with the most common dose being 30mg (in 42% of patients receiving the combination and 46% of patients receiving aspirin alone). After a mean follow-up of 3.5 years, 13% of the patients receiving combination therapy had fewer non-fatal strokes, non-fatal myocardial infarctions, bleeding complications and vascular events leading to death compared with 16% of those receiving aspirin alone, leading to an RR reduction of 20% with the combination over aspirin (95% CI 0.66–0.98) and an absolute risk reduction of 1% per year with the combination (95% CI 0.1–1.8). These results affirm those of ESPS-2 and provide support for the combination of aspirin plus dipyridamole over aspirin as antithrombotic therapy in secondary stroke prevention. Notably, all patients receiving combination therapy in ESPS-2 and 83% of the patients receiving combination therapy in ESPRIT used extended-release dipyridamole, which is more readily bioavailable than the immediate-release formulation used in the four earlier smaller trials, which may account for the observed lack of benefit in the latter.

Table 1: Prevention Regimen for Effectively Avoiding Second Strokes Trial 2x2 Factorial Study Design

	ASA + ER-DP	Clopidogrel
Telmisarten	ASA + ER-DP + clopidogrel placebo + telmisartan	Clopidogrel + ASA + ER-DP placebo + telmisartan
Telmisarten placebo	ASA + ER-DP + clopidogrel placebo + telmisartan placebo	Clopidogrel + ASA + ER-DP placebo + telmisartan placebo

ASA = aspirin; ER-DP = extended-release dipyridamole.
The original study design was amended to remove aspirin from the clopidogrel comparator following the publication of the results of Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) in May 2004, at which point only 2,027 study subjects had received a maximum of eight months' treatment with clopidogrel plus aspirin.

Antihypertensive Agents

Blood pressure is the strongest risk factor in stroke. With a direct relationship between blood pressure and the risk of stroke,[29] even minor decreases in blood pressure can reduce the risk of stroke.[30] Current ESO guidelines recommend regular monitoring of blood pressure as well as lowering of blood pressure following stroke.[6] Using an angiotensin-converting enzyme (ACE) inhibitor and a diuretic has been shown to reduce the rate of recurrent stroke in the Perindopril Protection against Recurrent Stroke Study (PROGRESS).[31] However, several studies have suggested that a system independent of blood pressure lowering may also benefit stroke patients. The use of ACE-inhibitor therapy (ramipril) in the Heart Outcomes Prevention Evaluation (HOPE) trial was effective in reducing the rate of stroke in patients with previous cardiovascular events or high-risk diabetes, despite only a small reduction in blood pressure.[32]

The actions of angiotensin II, a major effector of the renin–angiotensin system (RAS), can induce vasoconstriction, ultimately resulting in increased blood pressure.[33] Angiotensin II has also been implicated in organ damage via oxidative, proliferative, inflammatory and fibrotic pathways.[34,35] Although ACE inhibitors are effective in lowering blood pressure, humans can generate angiotensin II independently of ACE inhibition, such that not all angiotensin II is blocked. In these terms, it is logical to block the action of angiotensin II at its receptor. Indeed, while some angiotensin II receptor blockers (ARBs) can reduce blood pressure as well as cardiovascular events,[36] studies have also shown that ARBs are able to reduce the frequency of recurrent stroke.[37,38]

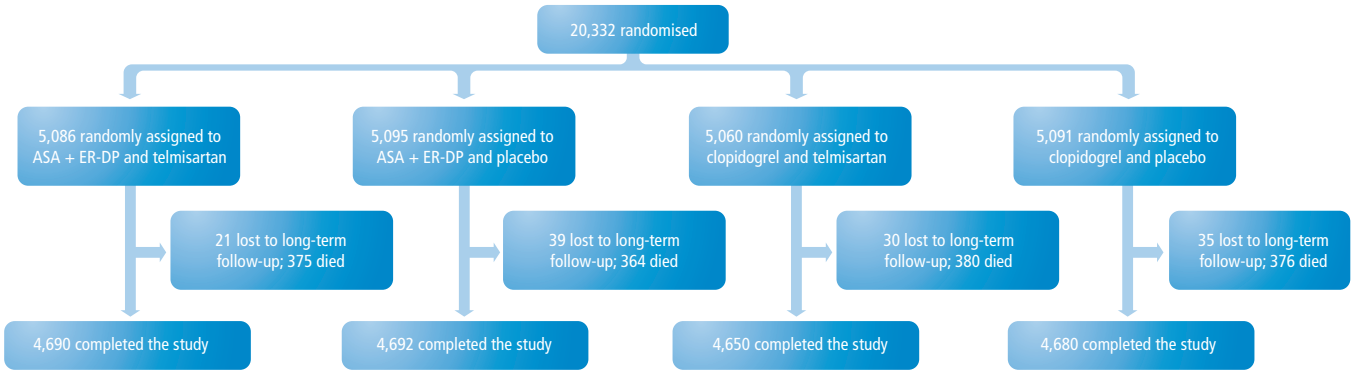
ACE inhibitors have proved highly beneficial in reducing mortality, myocardial infarction, stroke and heart failure in high-risk patients with heart failure, left ventricular dysfunction, prior vascular diseases or diabetes, but these drugs also increase the rates of cough and angioedema as a result of reduced bradykinin degradation and enhanced vasodilation. The Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) was the first study to compare ARBs versus ACE inhibitors. This trial evaluated how an alternative agent such as the ARB telmisartan would compare with the ACE inhibitor ramipril in terms of safety and efficacy in preventing cardiovascular events, and tested whether the combination of an ACE and ARB together would be superior to either drug alone.[39] Patients with vascular disease or high-risk diabetes were randomised to receive ramipril (10mg/day; n=8,576), telmisartan (80mg/day; n=8,542) or a combination of the two drugs (n=8,502), and were followed up for a median of 56 months. Telmisartan demonstrated statistical non-inferiority compared with ramipril in reducing the composite outcome of death from cardiovascular causes, myocardial infarction, stroke or hospitalisation. Furthermore, patients treated with telmisartan had significantly lower rates of cough (1.1 versus 4.2%; p<0.001) and angioedema (2.6 versus 1.7%; p=0.01) compared with those receiving ramipril. However, this benefit was offset by an increase in hypertensive symptoms (2.6 versus 1.7%; p<0.001). There was no difference in the rate of syncope between the two groups (0.2%). The combination therapy of telmisartan plus ramipril showed no benefit over ramipril or telmisartan monotherapy; rather, combination therapy was associated with an increased risk of syncope (0.3 versus 0.2%; p=0.03), hypotensive symptoms (4.8 versus 1.7%; p<0.001) and renal dysfunction (13.5 versus 10.2%; p<0.001). This phenomenon had previously been observed where the combination of the ARB valsartan and the ACE inhibitor captopril led to an increased incidence of hypotension without demonstrating any additive effect in reducing the occurrence of the primary outcome.[40] Data from ONTARGET therefore offer an alternative to ramipril with decreased risk of developing angioedema in telmisartan, providing patients and physicians with an additional option in preventing vascular events depending on the patient's inclination to adverse events.

The Rationale and Results of Prevention Regimen for Effectively Avoiding Second Strokes Study

In May 2008, results from the highly anticipated Prevention Regiment for Effectively avoiding Second Strokes (PRoFESS) study were presented at the XVII European Stroke Conference (ESC) in Nice, France. As the largest-ever recurrent stroke prevention trial, PRoFESS was a double-blind, placebo-controlled trial that took place at 695 sites in 35 countries, with 20,332 patients randomised to receive a combination of 200mg extended-release dipyridamole plus 25mg aspirin twice daily, or 75mg of daily clopidogrel, while also undergoing simultaneous randomisation to 80mg telmisartan or placebo in a 2x2 factorial study design (see *Table 1*).[41] The original study design had a combination of clopidogrel plus aspirin, but aspirin was discontinued in the comparator arm shortly after the data from MATCH were made available, and the study continued with clopidogrel monotherapy. A test for treatment interaction found that there was no interaction between the antiplatelet and telmisartan arms (p=0.35).[42] Patients 55 years of age or older who experienced an ischaemic stroke within 90 days prior to randomisation were eligible to participate in the study. The criteria were revised after the enrolment of approximately 6,000 patients to allow for the inclusion of younger patients from 50 to 54 years of age, and patients with less recent strokes ranging from 90 to 120 days if at least two other risk factors were present. Patients were excluded if they had experienced a primary haemorrhagic stroke or severe disability stemming from the qualifying stroke, if they were contraindicated to any of the antiplatelets in the study or if they possessed any other factors that would make them unsuitable for randomisation.[41] This trial randomised patients extremely early at a median of 15 days; nearly 40% of all patients were randomised within 10 days of stroke.[42] Patients were followed up for a mean duration of 2.5 years; 1,495 patients (7.4%) died during the study, and 125 patients (0.6%) were lost to follow-up (see *Figure 1*). PRoFESS was a truly novel study; prior to PRoFESS there had been no direct head-to-head comparisons between the available antiplatelet options, nor had there been any information available as to the safety and efficacy of antithrombotic therapy in combination with additional RAS inhibition. The study also endeavoured to assess the effects of these treatments on cognition and disability.

PRoFESS was the first trial to directly compare the safety and efficacy of two different antiplatelet agents following non-cardioembolic stroke. While the pre-specified criteria for non-inferiority were not met in the comparison of aspirin plus extended-release dipyridamole versus the active comparator

Figure 1: Trial Profile and Patient Distribution[40]



ASA = acetylsalicylic acid; ER-DP = extended-release dipyridamole.

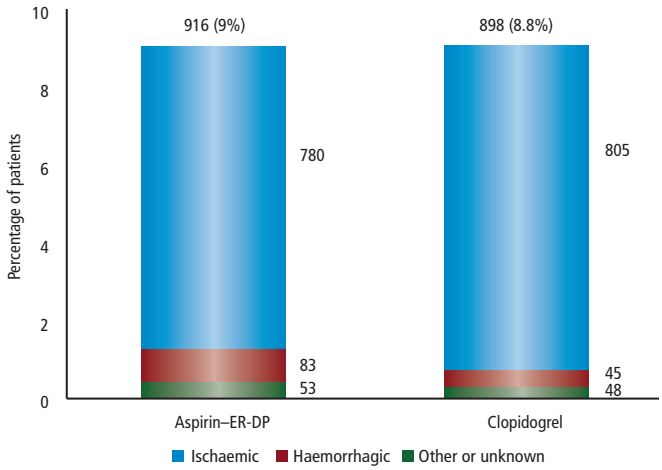
clopidogrel, the authors of the study[42] note that neither drug could be shown to be superior in secondary stroke prevention. Rather, results indicate that the two drugs have similar rates of recurrent stroke and effects in reducing the composite outcome of vascular events following stroke. Although the combination therapy was associated with increased incidence of major haemorrhagic events and intracranial bleeds, the absolute risks were low and partially offset by a lack of ischaemic events in the primary outcome. The results of this study highlight the importance of conducting direct comparisons in the context of secondary stroke prevention in lieu of relying on indirect comparisons that can be limited by trial design, patient populations, comparator drugs and definitions of study outcomes. The authors of the study have also noted that the trial was considerably underpowered to show non-inferiority at 30% power, given the study outcome of equivalency between the antiplatelet regimens. Although no significant difference could be found between the antiplatelet agents in question in terms of their ability to prevent secondary stroke, study results suggest a significant benefit for aspirin plus extended-release dipyridamole in reducing the risk of new or worsening congestive heart failure, the reason for which has been purported to be related to increased adenosine levels and coronary collateralisation.[43] The study also disproved the frequently quoted hypothesis that clopidogrel is the drug of choice for large-vessel disease and will decrease the rate of cardiac events while aspirin plus dipyridamole is preferred in patients with small-vessel disease and will reduce primary strokes.

Aspirin plus Extended-release Dipyridamole versus Clopidogrel

Although aspirin is known to confer a benefit in terms of reducing the risk of recurrent stroke, clopidogrel has also been implicated in a role for reducing stroke recurrence by approximately 8% compared with aspirin,[16] while the combination of aspirin plus extended-release dipyridamole compared with aspirin have indicated an RR reduction of 20–23%[22,28] From indirect comparisons alone, one would gather that aspirin plus extended-release dipyridamole would be superior to clopidogrel in secondary stroke prevention. With no guideline recommendations for any one of these therapies over the other,[5,6,44] the antiplatelet segments of the PRoFESS study aimed to compare the efficacy and safety of aspirin plus extended-release dipyridamole versus clopidogrel in patients who had recently suffered an ischaemic stroke.[41]

The primary outcome of first recurrent stroke was not significantly different between the treatments, occurring in 916 patients (9%)

Figure 2: Distribution of Types of Recurrent Stroke Under Antiplatelet Therapy[41]



ER-DP = extended-release dipyridamole.

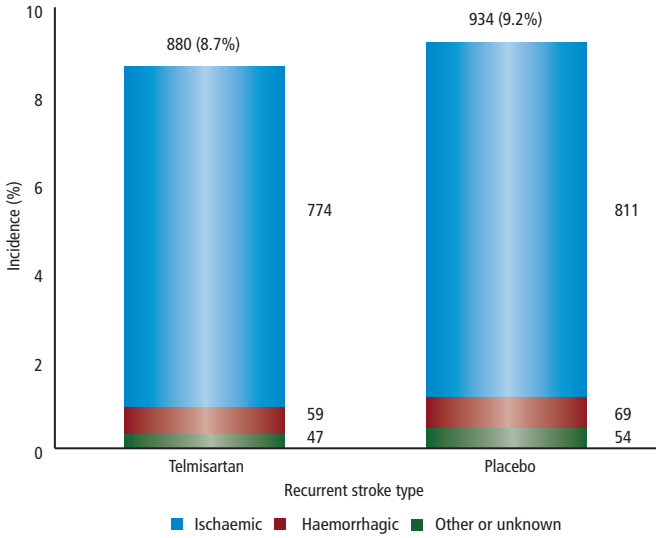
receiving aspirin plus extended-release dipyridamole and 898 (8.8%) receiving clopidogrel (hazard ratio [HR] 1.01, 95% CI 0.92–1.11).[42] Being close to 1.00, the HR indicated that the rates of primary outcome were essentially identical. However, due to the study's statistical design, the upper boundary of the 95% CI for the HR was required to lie below the value of 1.075 in order to demonstrate non-inferiority of aspirin plus extended-release dipyridamole compared with clopidogrel – a requirement that was not met in this case. Of these first recurrent strokes, there were 25 fewer ischaemic strokes, 38 more haemorrhagic strokes and five more strokes of other or unknown causes with combination therapy compared with clopidogrel (see *Figure 2*). This overall difference of 16 increased strokes was not significant between the two treatment arms. The secondary outcome of stroke, myocardial infarction or death from vascular causes were nearly identical, occurring in 1,333 patients (13.1%) from each treatment group (HR for combination versus clopidogrel 0.99, 95% CI 0.92–1.07). The rates of tertiary outcomes of myocardial infarction, deaths and other designated vascular events were similar between the two groups. No significant difference was found in the rates of recurrent stroke or major haemorrhagic event between patients treated with aspirin plus extended-release dipyridamole (1,194 [11.7%]) compared with those receiving clopidogrel (1,156 [11.4%], HR 1.03, 95% CI 0.95–1.11). Interestingly enough, the researchers found that there was a significant

Table 2: Use of Blood-pressuring-lowering Agents at Study End by Treatment Group[43]

Blood-pressure-lowering Agent	Telmisartan (%)	Placebo (%)
Diuretics	22.6	28.2
ACE inhibitors	28.4	33.9
Calcium-channel blockers	26.5	30.9
Beta blockers	22.3	25.4

ACE = angiotensin-converting enzyme.

Figure 3: Distribution of Types of Recurrent Stroke Under Angiotensin Receptor Blocker Therapy or Placebo



advantage for the combination of aspirin plus extended-release dipyridamole in lowering the rate of new or worsening congestive heart failure (144 [1.4%] versus 182 [1.8%], HR 0.78, 95% CI 0.62–0.96).

Patients receiving aspirin plus extended-release dipyridamole were more likely to experience major haemorrhagic events (419 [4.1%]) than those receiving clopidogrel (365 [3.6%], HR 1.15, 95% CI 1.00–1.32), inclusive of intracranial haemorrhages (HR 1.42, 95% CI 1.11–1.83), although there was no significant difference between the two treatments in terms of frequency of death, total haemorrhagic events, thrombotic thrombocytopenic purpura or neutropenia. An increased number of patients being treated with aspirin plus extended-release dipyridamole were more likely to permanently discontinue therapy due to adverse events (1,650 [16.4%]), and earlier on in their treatment course compared with patients receiving clopidogrel (1,069 [10.6%]); headache leading to permanent discontinuation was greater in the combination group (593 [5.9%] versus 87 [0.9%]).

The Role of Telmisartan in the Prevention of Secondary Stroke and Cardiovascular Events

Studies have shown that administering the combination of an ACE inhibitor and diuretic following the event of a stroke has a beneficial effect in reducing the rate of recurrent stroke by decreasing blood pressure levels.[31] ARBs have also proved effective in reducing the rate of recurrent strokes compared with placebo or a calcium channel blocker.[37,38] However, these studies enrolled patients after several months to years of their stroke occurrence, and did not address the role of blood-pressure lowering or blockage of RAS soon after the occurrence of stroke. In PRoFESS, patients were randomised to receive 80mg/day of the ARB telmisartan or placebo within four months of their initial stroke to determine the effect of blocking RAS on reducing the risk of recurrent stroke.[45] It was also the intent of the PRoFESS study group to investigate the effect of telmisartan compared with placebo in reducing the composite outcome of recurrent stroke, myocardial infarction, vascular death and new or worsening heart failure. Based on previous evidence that blockers of RAS can reduce the occurrence of new diabetes,[46–48] telmisartan was also evaluated for this benefit over placebo.

While participating in the study, all patients were provided with medication to maintain good control of blood pressure at the discretion of the investigators. After a mean follow-up of 2.5 years, the mean blood pressure of patients treated with telmisartan was 3.8/2mmHg lower than that of the placebo group, despite the fact that the placebo group used blood-pressure-lowering agents more frequently (see *Table 2*).[45] Recurrent stroke occurred in 880 patients (8.7%) in the telmisartan group and 934 (9.2%) in the placebo group (HR 0.95, 95% CI 0.86–1.04; p=0.23); the potential benefits of telmisartan was observed across the distribution of ischaemic and haemorrhagic strokes, as well as strokes of other or unknown aetiology (see *Figure 3*). However, the effect of each respective treatment appeared to vary significantly by time (p=0.04). *Post hoc* analyses showed that secondary stroke during the first six months of treatment was greater in the telmisartan group (n=347 [3.4%]) compared with the placebo group (326 [3.2%], HR 1.07, 95% CI 0.92–1.25), while 533 (5.3%) patients had a recurrent stroke in the telmisartan group compared with 608 (6%) in the placebo group after six months (HR 0.88, 95% CI 0.78–0.99). The rate of major cardiovascular events was comparable between the study groups as well, occurring in 1,367 patients (13.5%) receiving telmisartan and 1,463 patients (14.4%) receiving placebo (HR 0.94, 95% CI 0.87–1.01; p=0.11). Similar to the rate of recurrent stroke, the number of cardiovascular events within the first six months following randomisation was greater in the telmisartan group (474 [4.7%]) compared with placebo (433 [4.3%]), with a reversal after six months, where the events were lower in the telmisartan group (893 [8.8%]) than in the placebo group (1,030 [10.1%], HR 0.87, 95% CI 0.80–0.95; p=0.004). The onset of new diabetes occurred in 1.7% of patients on telmisartan and 2.1% of those on placebo (HR 0.82, 95% 0.65–1.04; p=0.10). No significant differences were found between the telmisartan group and the placebo group in terms of the number of deaths (755 versus 740), major haemorrhages (385 versus 399), migraines within the first six months (429 versus 447) or headaches within the first seven days of treatment (2,006 versus 2,102). Intracranial bleeding was also similar between patients on telmisartan (112 [1.1%]) and placebo (138 [1.4%], HR 0.81, 95% CI 0.63–1.05).

Results from the ARB segment of the PRoFESS trial were unable to show any significant reduction in the risk of a subsequent stroke, of the composite outcome of major cardiovascular events or of new-onset diabetes with telmisartan use.[45] However, the *post hoc* analyses in event rates prior to and following six months of randomisation are suggestive of a time-dependent effect of telmisartan, where the initial six months of therapy may be associated with a slight increase in risk, possibly because treatment may not have full efficacy at an early stage, followed by a more beneficial outcome of lowered rates of stroke and major cardiovascular events that emerges gradually with longer ARB therapy. In this respect, the authors of the study note that the mean duration of 2.5 years of follow-up in PRoFESS may have been too short to demonstrate any significant benefit with telmisartan, as HOPE and PROGRESS had mean follow-up durations of 4.5 and four years, respectively. A trend was also

observed towards a decreased rate of new-onset diabetes in patients receiving telmisartan therapy.

This segment of PRoFESS faced quite a few limitations that may have led to the observed results. Not only might the trial duration have been too short, but adherence to telmisartan was not ideal either; at three months into the study, adherence was 85% in the telmisartan group compared with 87% in the placebo group. By 12 months, adherence had dropped to 77 and 80%, respectively, and by 36 months to 68 and 71%, respectively, and these levels of adherence were much lower than what was previously observed in ONTARGET.[39] The authors of the study attribute this decreased adherence to a lack of a run-in period in the ARB segment, and to the fact that any headache experienced as a side effect of aspirin plus extended-release dipyridamole may have caused patients to stop taking both blinded medications as a result.[45] Another limitation is the use of external blood-pressure-lowering medications by patients, which was greater in the placebo group than in the telmisartan group in all categories of blood-pressure-lowering medications. As patients were encouraged to maintain good blood-pressure control, the authors of the study propose that these additional medications could have interfered with the study results in minimising the blood pressure differential between the treatment groups and therefore leading to a lack of significance in the study outcomes.

Effect on Disability and Neuroprotection

Stroke has the potential to be a highly debilitating event physically, mentally and emotionally. Physical disabilities can lead to neuro-psychological deficits including aphasia, apraxia and overall difficulties in performing daily tasks, and may encompass paralysis or numbness, pain, incontinence and loss of speech and vision. Cognitive deficits are also common in stroke patients, including dementia, problems with memory and attention and speech problems. Patients may also experience emotional difficulties such as anxiety, panic attacks, apathy or even emotional lability, in which patients are unable to express the emotion appropriate to a situation.[3] Depression can also present as a problem in 20–60% of stroke patients.[49] With these factors as a significant threat to patient quality of life, it is necessary to explore options that can reduce, if not prevent, the onset of disability and loss of cognitive function.

Randomised trials investigating the use of neuroprotective drugs in the treatment of ischaemic stroke have failed to show any benefit in the past,[50–52] although it is purported that the reason for this may be the time delay between the stroke and the application of the drug. Experiments in animal models and cell cultures have suggested a role for dipyridamole,[53,54] aspirin[55,56] and ARBs[57–62] in neuroprotection, while there has been no evidence of such a benefit with clopidogrel.[63] However, neuroprotective studies with aspirin and dipyridamole have presented conflicting data.[64–66] Studies have also suggested that antihypertensive drugs can decrease the risk of stroke-based dementia.[67–70] Given the current evidence for antiplatelets and ARBs in neuroprotection, the efficacy of prophylactic aspirin plus extended-release dipyridamole was compared with that of clopidogrel for the reduction of disability following recurrent strokes in PRoFESS.[71] Furthermore, the study hypothesised that telmisartan would have a benefit in reducing disability or cognitive performance resulting from recurrent stroke. As a time delay has been insinuated as a possible cause for the failure of neuroprotective drugs in treating ischaemic strokes, patients in PRoFESS were receiving the prophylactic treatment of an antiplatelet agent or telmisartan present at the time of the recurrent stroke.

Functional outcome was evaluated using the modified Rankin scale (mRS)[72] and the Barthel index[73] three months after a recurrent stroke, the former being a measure of global disability, while the latter measures are activities of daily living. The mini-mental state examination (MMSE)[74] was used as a measure of cognitive function, having been performed in patients one month after randomisation, after two years and at the end of the trial. There were no significant differences present in patients receiving aspirin plus extended-release dipyridamole, clopidogrel, telmisartan or placebo in mRs scores at baseline or three months following recurrent stroke.[42] No significant difference was shown in the Barthel index measurements between clopidogrel and aspirin plus extended-release dipyridamole or telmisartan and placebo. Based on measures from the mRS and the Barthel index, there is no difference between either antiplatelet therapy with respect to recovery from current stroke, and no benefit for telmisartan in reducing the functional deficit acquired in recurrent stroke; a neuroprotective effect with the antiplatelet treatments or the ARB telmisartan is therefore unlikely. There was no significant difference in MMSE scores between the two antiplatelet agents or between telmisartan and placebo, and no change in MMSE scores from the initial score at one month to the penultimate examination. Subgroup analysis of patients with an MMSE score indicative of cognitive impairment (MMSE ≤24) showed similar results, with no significant difference from one month to the penultimate visit in the antiplatelet comparison or ARB comparison. No significant difference was found in the number of patients with dementia among the treatment groups. Therefore, results showed no benefit for the antiplatelet regimens or the ARB telmisartan in reducing stroke-based disability or restoring cognition in patients.

In light of these results, the authors of the study emphasise that results from animal experiments cannot be extrapolated to human studies; although previous animal experiments may have indicated neuro-protective advantages with antiplatelet agents, it may very well be the case that such a benefit is lacking in humans.[64] However, it may also be that the average 2.5 years of follow-up was too short to demonstrate any effects of the treatment regimes on cognition, as candesartan had previously been shown to reduce cognitive decline in the Study on Cognition and Prognosis in the Elderly (SCOPE) trial, a study with a mean follow-up of 3.5 years.[70]

Implications of Recent Trials for Secondary Stroke Prevention

The past few years have seen a series of trials in stroke prevention with antiplatelets and blockers of RAS. CAPRIE has shown that clopidogrel can better reduce the rate of ischaemic events and vascular events than aspirin.[16] Combination therapies have demonstrated that two antiplatelet drugs are more effective than one when it comes to reducing ischaemic events, as in the case of aspirin plus clopidogrel or aspirin plus dipyridamole.[19–22,28] However, the use of aspirin plus clopidogrel has repeatedly been shown to increase the occurrence of bleeding complications than either drug as monotherapy, thereby negating any benefit that may arise.[19–21] The recent release of results from the PRoFESS trial has served only to reinforce the available knowledge about antiplatelet use in secondary stroke prevention. The much anticipated head-to-head comparison between aspirin plus

extended-release dipyridamole and clopidogrel demonstrated comparable efficacy in secondary stroke prevention, with similar ability in preventing cardiovascular events, contrary to any advantage that may have been assumed through indirect comparisons. Despite the modest effect of aspirin in preventing recurrent stroke and vascular events, the big advantage is its cost-effectiveness and worldwide availability. Although it is necessary for better and improved pharmaceuticals, it is also necessary to have affordable treatments for patients worldwide.

Previous studies had shown evidence in support of ARBs in reducing the frequency of recurrent stroke independent of blood-pressure lowering. Patients in PRoFESS receiving telmisartan did experience a greater decrease in blood pressure relative to patients in the placebo group, but telmisartan could not be shown to have any significant benefit in reducing recurrent stroke or cardiovascular events by study end, although a number of limiting factors have been implicated in these results.

PRoFESS was also unable to demonstrate any advantage with the antiplatelet therapies and prophylactic telmisartan in reducing stroke-based disability and restoration of cognitive function. However, recent stroke research has revealed new developments where the cerebral endothelium has been shown to secrete neuroprotective trophic factors that protect against stressful and damaging conditions.[75] This information suggests that targeting the cerebral endothelium to salvage the trophic signals originating from the matrix-trophic coupling between neurons and the cerebral endothelium may provide novel therapeutic opportunities within stroke and neurodegenerative diseases.

What Have We Learned from the Prevention Regimen for Effectively Avoiding Second Strokes Study?

From the information available from historical antiplatelet studies alone, it was likely that many favoured low-dose aspirin plus extended-release dipyridamole over clopidogrel in secondary stroke prevention. However, the results from the first ever head-to-head comparison between the two antiplatelet agents in PRoFESS emphasised the need for direct studies, a clear demonstration of the unreliability of indirect comparisons. Contrary to what many had expected based on indirect comparisons alone, PRoFESS not only failed to show the superiority of aspirin plus extended-release dipyridamole over clopidogrel, but was also unable to reach the non-inferiority margin in spite of the global enrolment of over 20,000 patients. Indeed, the study and methodology of PRoFESS clearly show that non-inferiority analyses are valid only if the prior assumptions are met. Although the primary outcome of recurrent stroke was essentially identical between the treatment groups, the failure to demonstrate non-inferiority is attributed to the stringent and conservative non-inferiority margin of 7.5%, selected under the initial assumptions of the trial design that the use of aspirin plus extended-release dipyridamole would be superior to clopidogrel. However, it is necessary to take the results of PRoFESS and compare them with previous evidence suggestive of clear superiority for aspirin plus extended-release dipyridamole over aspirin, the latter of which had similar efficacy in secondary stroke prevention of clopidogrel.

The efforts of PRoFESS investigators were not in vain. Although their desired outcome was not achieved in the study, the information provided does add a positive feature in secondary stroke prevention, where the comparable efficacy between the antiplatelet treatments has reinforced the availability of options within the armamentarium against recurrent stroke. With this in mind, patients and physicians have a choice in their antiplatelet therapy after initial stroke, and may not have to base their decisions on efficacy alone, but possibly also on frequency of dosing, tolerability, adverse effects and cost. Notably, aspirin plus extended-release dipyridamole conferred a significant advantage over clopidogrel in reducing the risk of new or worsening congestive heart failure, an unexpected but welcome benefit that warrants further research.

In the ARB segment of PRoFESS, telmisartan demonstrated only a non-significant trend towards a benefit, appearing only in the later stages of the follow-up period; factors such as sub-optimal adherence, the use of counterbalancing blood-pressure-lowering agents and a short follow-up period have been implicated in this result. Also observed was a small trend towards a lower rate of new-onset diabetes. To further evaluate the role of ARBs in the prevention of recurrent stroke, two large trials are currently under way with expected mean follow-ups of more than four years.[76,77] ■

This work was supported by Boehringer Ingelheim Pharmaceuticals, Inc. The author had full control over content and received editorial assistance from Patrick Wong, PhD, Touch Briefings.

1. 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; 4:736–43.
2. American Heart Association. Heart Disease and Stroke Statistics: 2008 Update. Available at: www.circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.107.187998v1
3. Coffey CE, Cummings JL, Starkstein S, et al., *Stroke—The American Psychiatric Press Textbook of Geriatric Neuropsychiatry, Second Edition*, Washington DC: American Psychiatric Press, 2000; 601–17.
4. Goldstein LB, Adams R, Alberts MJ, et al., Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the Atherosclerotic Peripheral Vascular Disease Interdisciplinary Working Group; Cardiovascular Nursing Council; Clinical Cardiology Council; Nutrition, Physical Activity, and Metabolism Council; and the Quality of Care and Outcomes Research Interdisciplinary Working Group: the American Academy of Neurology affirms the value of this guideline, *Stroke*, 2006;37 (6):1583–1633.
5. Sacco RL, Adams R, Albers G, et al., Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke, Co-sponsored by the Council on Cardiovascular Radiology and Intervention: The American Academy of Neurology affirms the value of this guideline, *Stroke*, 2006;37:577–617.
6. The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee, Guidelines for management of ischaemic stroke and transient ischaemic attack 2008, *Cerebrovasc Dis*, 2008;25(5):457–507.
7. Straus SE, Majumdar SR, McAlister FA, New evidence for stroke prevention: scientific review, *JAMA*, 2002;288(11):1388–95.
8. Albers GW, Amarenco P, Easton JD, et al., Antithrombotic and thrombolytic therapy for ischemic stroke. The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy, *Chest*, 2004;126(Suppl.):483S–512S.
9. Guyatt G, Schunëmann H, Cook D, et al., Grades of recommendation for antithrombotic agents, *Chest*, 2001;119 (Suppl 1):3S-7S.
10. Patrono C, Bachmann F, Baigent C, et al., Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European society of cardiology, *Eur Heart J*, 2004;25(2):166–81.
11. Algra A, van Gijn J, Cumulative meta-analysis of aspirin efficacy after cerebral ischaemia of arterial origin, *J Neurol Neurosurg Psychiatry*, 1999;65:255.
12. Antithrombotics 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.
13. The Stroke Prevention In Reversible Ischemia Trial (SPIRIT) Study Group, A randomized trial of anticoagulants versus aspirin after cerebral ischemia of presumed arterial origin. The stroke prevention in reversible ischemia trial (SPIRIT) study group, *Ann Neurol*, 1997;42(6):857–65.
14. Mohr JP, Thompson JLP, Lazar RM, et al., A comparison of warfarin and aspirin for the prevention of recurrent ischemic

stroke, *N Engl J Med*, 2001;345:1444–51.
15. The ESPRIT Study Group, Medium intensity oral anticoagulants versus aspirin after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial, *Lancet Neurol*, 2007;6(2):115–24.
16. CAPRIE Steering Committee, A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE), *Lancet*, 1996;348:1329–39.
17. The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators, Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation, *N Engl J Med*, 2001;345:494–502.
18. Steinhubl SR, Berger PB, Mann JT III, et al., Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial, *JAMA*, 2002;288: 2411–20.
19. Diener H-C, Bogousslavsky J, Brass LM, et al., 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.
20. Bhatt DL, Fox KA, Hacke W, et al., Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events, *N Engl J Med*, 2006;354:1706–17.
21. Bhatt DL, Flather MD, Hacke W, et al., Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial, *J Am Coll Cardiol*, 2007;49: 1982–8.
22. 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.
23. Guiraud-Chaumeil B, Rascol A, David J, et al., Prévention des récidives des accidents vasculaires cérébraux ischémiques par les anti-agrégants plaquettaires Résultats d'un essai thérapeutique controlé de 3 ans, *Rev Neurol (Paris)*, 1982;138:367–85.
24. Bousser MG, Eschwege E, Haguenau M, et al., 'AICLA' controlled trial of aspirin and dipyridamole in the secondary prevention of atherothrombotic cerebral ischemia, *Stroke*, 1983;14:5–14.
25. American-Canadian Co-operative Study Group, Persantin aspirin trial in cerebral ischemia. Part II: Endpoint results, *Stroke*, 1985; 16:406–15.
26. Kaye J, *A trial to evaluate the relative roles of dipyridamole and aspirin in the prevention of deep vein thrombosis in stroke patients*, Bracknell, Berkshire: Boehringer Ingelheim, 1990.
27. Algra A, Van Gijn J, Algra A, et al.,Secondary prevention after cerebral ischaemia of presumed arterial origin: is aspirin still the touchstone?, *J Neurol Neurosurg Psychiatry*, 1999;66(5):557–9.
28. The ESPRIT Study Group, Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial, *Lancet*, 2006;1367: 1665–73.
29. Rodgers A, MacMahon S, Gamble G, et al., Blood pressure and risk of stroke in patients with cerebrovascular disease, The United Kingdom Transient Attack Collaborative Group, *BMJ*, 1996;313: 147.
30. Blood Pressure Lowering Treatment Trialists' Collaboration, Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively designed overviews of randomised trials, *Lancet*, 2003;362:1527–35.
31. PROGRESS Collaborative Group, Randomised trial of a perindopril-based blood-press-lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack, *Lancet*, 2001;358: 1033–41. Errata, *Lancet*, 2001;358:1556, 2002;359:2120.
32. The Heart Outcomes Prevention Evaluation Study Investigators, Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients, *N Engl J Med*, 2000; 342:145–53. Errata, *N Engl J Med*, 2000;342:748, 1736.
33. Kaschina E, Unger T, Angiotensin AT1/AT2 receptors: regulation, signalling and function, *Blood Press*, 2003;12: 70–88.
34. Schmieder RE, Mechanisms for the clinical benefits of angiotensin II receptor blockers, *Am J Hypertens*, 2005;18: 720–30.
35. Brewster UC, Setaro JF, Perazella MA, The renin-angiotensin-aldosterone system: cardiorenal effects and implications for renal and cardiovascular disease states, *Am J Med Sci*, 2003;326:15–24.
36. Dahlöf B, Devereux RB, Kjeldsen SE, et al., Cardiovascular morbidity and mortality in the Losartan Intervention for Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol, *Lancet*, 2002;359:995–1003.
37. Schrader J, Lüders S, Kulschewski A, et al., Morbidity and Mortality after Stroke, Eprosartan compared with nitrendipine for secondary prevention: principal results of a prospective randomized controlled study (MOSES), *Stroke*, 2005;36:61218–26.
38. Schrader J, Lüders S, Kulschewski A, et al., The ACCESS Study: evaluation of acute candesartan cilexetil therapy in stroke survivors, *Stroke*, 2003;34:2699–703.
39. The ONTARGET Investigators, Telmisartan, ramipril, or both in patients at high risk for vascular events, *N Engl J Med*, 2008;358: 1547–59.
40. Pfeffer MA, McMurray JJV, Velazquez EJ, et al., Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both, *N Engl J Med*, 2003; 349:1893–1906.
41. Diener HC, Sacco R, Yusuf S for the Steering Committee and PRoFESS Study Group, Rationale, design and baseline data of a randomized, double-blind, controlled trial comparing two antithrombotic regimens (a fixed-dose combination of extended-release dipyridamole plus ASA with clopidogrel) and telmisartan versus placebo in patients with strokes: The Prevention Regimen for Effectively Avoiding Second Strokes Trial (PRoFESS), *Cerebro Dis*, 2007;23:368–380.
42. Sacco RL, Diener H-C, Yusuf S, et al., Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke, *N Engl J Med*, 2008;359(12):1238–51.
43. Akhtar M, Ordovas K, Martin A, et al., Effect of chronic sustained-release dipyridamole on myocardial blood flow and left ventricular function in patients with ischemic cardiomyopathy, *Conges Heart Fail*, 2007;13:130–35.
44. Hirsh J, Guyatt G, Albers GW, et al.,The seventh ACCP conference on antithrombotic and thrombolytic therapy: evidence-based guidelines, *Chest*, 2004;126(Suppl. 1): S172–3.
45. Yusuf S, Phil D, Diener H-C, et al., Telmisartan to prevent recurrent stroke and cardiovascular events, *N Engl J Med*, 2008;359 (12):1225–37.
46. Jandeleit-Dahm KA, Tikellis C, Reid CM, et al., Why blockade of the renin-angiotensin system reduces the incidence of new-onset diabetes, *J Hypertens*, 2005;23:463–73.
47. Ruilope LM, Segura J, Losartan and other angiotensin II antagonists for nephropathy in type 2 diabetes mellitus: a review of the clinical trial evidence, *Clin Ther*, 2003;25: 3044–64.
48. Silverstein RL, Fenves AZ, Ram CV, ARBs and target organ protection. Exploring benefits beyond their antihypertensive effects, *Postgrad Med*, 2004;116:31–8.
49. Lenzi GL, Altieri M, Maestrini I, Post-stroke depression, *Rev Neurol (Paris)*, 2008;164(10):837–40.
50. De Keyser J, Uyttenboogaart M, Koch MW, et al., Neuroprotection in acute ischemic stroke, *Acta Neurol Belg*, 2005;105:144–48.
51. Schabitz WR, Fisher M, Perspectives on neuroprotective stroke therapy, *Biochem Soc Trans*, 2006;34:1271–6.
52. Hill MD, Stroke: the dashed hopes of neuroprotection, *Lancet Neurol*, 2007;6:2–3.
53. Blake AD, Dipyridamole is neuroprotective for cultured rat embryonic cortical neurons, *Biochem Biophys Res Commun*, 2004; 314(2):501–4.
54. Farinelli SE, Green LA, Friedman WJ, Neuroprotective actions of dipyridamole on cultured CNS neurons, *J Neurosci*, 1998;18(14): 5112–23.
55. Zheng Z, Schwab S, Grau A, et al., Neuroprotection by early and delayed treatment of acute stroke with high dose aspirin, *Brain Res*, 2007;1186:275–80.
56. Gomes I, Aspirin: a neuroprotective agent at high doses?, *Natl Med J India*, 1998;11(1):14–17.
57. Krikov M, Thone-Reineke C, Müller S, et al., Candesartan but not ramipril pretreatment improves outcome after stroke and stimulates neurotrophin BNDF/TrkB system in rats, *J Hypertens*, 2008;26(3):544–52.
58. Fagan SC, Kozak A, Hill WD, et al., Hypertension after experimental cerebral ischemia: candesartan provides neurovascular protection, *J Hypertens*, 2006;24:535–9.
59. Faure S, Oudart N, Javellaud J, et al., Synergistic protective effects of erythropoietin and olmesartan on ischemic stroke survival and post-stroke memory dysfunctions in the gerbil, *J Hypertens*, 2006;24:2255–61.
60. Engelhorn T, Doerfler A, Heusch G, et al., Reduction of cerebral infarct size by the AT1-receptor candesartan, the HMG-CoA reductase inhibitor rosuvastatin and their combination, An experimental study in rats, *Neurosci Lett*, 2006;406:92–6.
61. Groth W, Blume A, Gohlke P, et al., Chronic pre-treatment with candesartan improves recovery from focal cerebral ischaemia in rats, *J Hypertens*, 2003;21:2175–82.
62. Thone-Reineke C, Zimmermann M, Neumann C, et al., Are angiotensin receptor blockers neuroprotective?, *Curr Hypertens Rep*, 2004;6:257–66.
63. Lee JH, Lack of antiapoptotic effects of an antiplatelet drug, aspirin and clopidogrel, and antioxidant, MCI-186, against focal ischemic brain damage in rats, *Neurol Res*, 2005;27: 483–92.
64. Paciaroni M, Agnelli G, Caso V, et al., Prior use of antithrombotic agents and neurological functional outcome at discharge in patients with ischemic stroke, *J Thromb Haemost*, 2006;4: 1957–61.
65. Sivenius J, Cunha L, Diener HC, et al., Antiplatelet treatment does not reduce the severity of subsequent stroke. European Stroke Prevention Study 2 Working Group, *Neurology*, 1999;53(4):825–9.
66. Aldandashi S, Noor R, Wang CX, et al., Combination treatment with dipyridamole, aspirin, and tPA in an embolic model of stroke in rats, *Exp Neurol*, 2007;205:563–8.
67. Feigin V, Ratnasabapathy Y, Anderson C, Does blood pressure lowering treatment prevents dementia or cognitive decline in patients with cardiovascular and cerebrovascular disease?, *J Neurol Sci*, 2005;229–230:151–5.
68. The PROGRESS Collaborative Group, Effects of blood pressure lowering with perindopril and indapamide therapy on dementia and cognitive decline in patients with cerebrovascular disease, *Arch Intern Med*, 2003;163: 1069–75.
69. Forette F, Seux M, Staessen J, et al., Prevention of dementia in randomised double-blind placebo-controlled Systolic Hypertension in Europe (Syst-Eur) trial, *Lancet*, 1998;352:1347–51.
70. Lithell H, Hansson L, Skoog I, et al., for the SCOPE Study Group, The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomised double-blind intervention trial, *J Hypertens*, 2003;21:875–86.
71. Diener H-C, Sacco RL, Yusuf S, et al., Effects of aspirin plus extended-release dipyridamole versus clopidogrel and telmisartan on disability and cognitive function after recurrent stroke in patients with ischaemic stroke in the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial: a double-blind, active and placebo-controlled study, *Lancet Neurol*, 2008; 7(10):875–84.
72. Rankin J, Cerebral vascular accidents in patients over the age of 60, II: prognosis, *Scot Med J*, 1957;2:200–15.
73. Mahoney FI, Barthel DW, Functional evaluation: The Barthel Index, *Md State Med J*, 1965;14:61–5.
74. Folstein M, Folstein S, McHugh PR, Mini-mental state: a practical method for grading the cognitive state of patients for the clinician, *J Psychiatr Res*, 1975;12:189–98.
75. Guo S, Kim WJ, Lok J, et al., Neuroprotection via matrix-trophic coupling between cerebral endothelial cells and neurons, *Proc Natl Acad Sci U S A*, 2008;105:7582–7.
76. The ACTIVE Steering Committee, Rationale and design of ACTIVE: the atrial fibrillation clopidgrel trial with irbesartan for prevention of vascular events, *Am Heart J*, 2006;151:1187–93.
77. Teo K, Yusuf S, Sleight P, et al., Rationale, design and baseline characteristics of two large, simple randomized trials evaluating telmisartan, ramipril and their combination in high-risk patients: the Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials, *Am Heart J*, 2004;148:52–61.