Pharmacotherapy of Stroke

a report by

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DOI:10.17925/ENR.2006.00.01.52

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Stroke is the third leading cause of death worldwide and in developed countries, it is the leading cause of disability. In developed countries, the average age-adjusted incidence of stroke is 150 per 100,000 population per year and stroke-related mortality ranges from 50 to 100 per 100,000 population per year. The non-modifiable risk factors include age, race, sex and family history of stroke or transient ischaemic attack (TIA). After the age of 55 years, each decade doubles the risk of stroke.[1] The incidence of stroke is the highest in blacks (233/100,000), followed by Hispanics (196/100,000) and whites (93/100,000).[2] Stroke is more prevalent in men (58.8/1,000 to 92.6/1,000) than in women (32.2/1,000 to 61.2/1,000).[3] A paternal history of stroke or TIA increases the risk of stroke by 2.4 (95% confidence interval (CI): 0.96–6.03) and maternal history by 1.4 (0.60–3.25).[4] The traditional modifiable vascular risk factors include hypertension, tobacco smoking, diabetes, atrial fibrillation and hypercholes-terolaemia. Hypertension was shown to increase the relative risk (RR) of stroke by up to four-fold, smoking by 1.8-fold and diabetes up to six-fold.[5,6] Atrial fibrillation increases the risk of stroke 2.6- to four-fold,[7] but the role of hyperlipidaemia in stroke is still debated.[8]

Pharmacological treatment of stroke can be divided into stroke-specific treatment in the hyperacute phase and stroke prevention. This overview concentrates on both aspects of pharmacotherapy of stroke.

Thrombolytic Therapy

Aetiological treatment of acute ischaemic stroke can be achieved by dissolving the blood clot in the affected brain artery. So far, numerous attempts have been made to find the best thrombolytic agent. The first trials tested the efficacy of intravenous (IV) streptokinase within a time window varying from three to six hours. Instead of showing benefit, this rather demonstrated an unacceptably high risk of fatal intracranial haemorrhages and death.[9–11] These results came together with those of other groups that tested the efficacy of recombinant tissue plasminogen activator (rt-PA).

The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study was a prospective randomised placebo-controlled trial on the effectiveness of IV infusion of 0.9mg/kg of rt-PA in acute ischaemic stroke. There were four inclusion criteria:

- a diagnosis of ischaemic stroke with a clearly defined time of onset;
- a presence of a neurological deficit measurable with National Institute of Health Stroke Scale (NIHSS);
- a baseline brain computed tomography (CT) scan without signs of intracerebral haemorrhage (ICH); and
- a time window shorter than three hours.

A tissue plasminogen activator did not influence the improvement during the first 24 hours. However, the long-term efficacy of rt-PA was confirmed and the odds for a favourable outcome were 1.7 (95% CI: 1.2–2.6). A 30% benefit of having minimal or no disability (modified Rankin Scale (mRS) 0–1) was demonstrated for patients in the rt-PA arm. Patients treated with rt-PA were also more likely to have symptomatic ICH (rt-PA 6.4% versus placebo 0.6%; $p<0.001$), especially those with brain oedema (9% of rt-PA-treated patients versus 4% of the whole group). There was no difference in three-month mortality (rt-PA 17% versus placebo 21%).[12] When looking at the data at six and 12 months from treatment, the odds ratio (OR) for a favourable outcome was 1.7 for rt-PA-treated patients, and these patients were 30% more likely to have minimal or no disability when compared with controls. There was no significant difference in case fatality between the two groups (24% versus 28%).[13] A *post hoc* analysis showed no correlation between the presence of early ischaemic changes and the occurrence of symptomatic ICH.[14] Based on the primary results of this trial, the treatment with rt-PA of acute ischaemic stroke within a three-hour time window was approved in the US.

The European Cooperative Acute Stroke Study (ECASS) I was a randomised prospective placebo-controlled trial on the effectiveness of 1.1mg/kg of IV rt-PA in acute ischaemic stroke. Patients were included

if they had ischaemic stroke of a defined time of onset, moderate to severe stroke, minor signs of infarction on brain CT and could be treated no later than six hours from stroke onset. A total of 620 patients were included. A benefit of rt-PA over placebo in neurological and functional recovery was shown with an OR of 1.5 (95% CI: 1.1–2.0). There were no significant differences in mortality and frequency of ICH between the two groups but in the rt-PA group, there were significantly more large parenchymal haemorrhages than in the placebo group.[15]

In ECASS II, a lower dosage of rt-PA (0.9mg/kg) within a six-hour window was studied. The inclusion criteria were similar to those of ECASS I, but in patients with brain swelling, more than 33% of the middle cerebral artery (MCA) territory was excluded. Eight hundred patients were enrolled in the study. An absolute difference of 3.7% (rt-PA 40.3% versus placebo 36.6%; p=ns) in favourable outcome (mRS 0–1) was demonstrated. When using an extended end-point of mRS 0–2, the benefit of rt-PA becomes significant (absolute difference: 8.3%). There was no difference in case fatality and frequency of haemorrhagic infarction between the two groups. However, parenchymal haemorrhages were four-fold more common in the rt-PA group when compared with controls (11.8% versus 3.1%).[16]

The aim of the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS) study was to test the efficacy and safety of 0.9mg/kg IV rt-PA administered during one hour versus placebo in patients with acute ischaemic stroke within a time window of between three and five hours. Patients were included if they had a clinically diagnosed ischaemic stroke with a measurable neurological deficit and if they did not have signs of cerebral ischaemia in more than 33% of the MCA territory. The intent-to-treat population consisted of 613 patients; of these, 547 were treated in the predefined three- to five-hour time window. In the target population, there were no significant differences in the excellent neurological recovery at day 90, defined as an NIHSS lower than 1, between the rt-PA group (34%) and controls (32%), nor was there any improvement in functional recovery (defined as Barthel Index (BI) ≥95, mRS ≤1 and NIHSS ≤1) at days 30 and 90. In rt-PA-treated patients, there were significantly more fatal ICHs (3% versus placebo 0.3%), symptomatic ICH (7.0% versus placebo 1.1%) and asymptomatic ICH (11.4% versus placebo 4.7%). Case fatality at 90 days was higher in the rt-PA group when compared with controls (11.0% versus 6.9%; p=ns).[17]

Recently, the results of these studies were subject of a meta-analysis that showed that three-month favourable outcome (defined as mRS 0–1, BI 95–100 and NIHSS 0–1) depended on the interval from stroke onset to start of treatment. The OR for good outcome for treatment initiated from 0 to 90 minutes was 2.8 (95% CI: 1.8–4.5); from 91 to 180 minutes, it was 1.6 (1.1–2.2); from 181 to 270 minutes, it was 1.4 (1.1–1.9); and from 271 to 360 minutes, it was 1.2 (0.9–1.5). The hazard ratio (HR) for death after adjusting for baseline NIHSS did not differ for patients treated from 0 to 270 minutes and it increased to 1.45 (1.02–2.07) for those treated from 271 to 360 minutes. Haemorrhage was more frequent in the rt-PA group than in controls (5.9% versus 1.1%). What is interesting is the fact that the occurrence of haemorrhage was not influenced by the interval from stroke onset to start of treatment, but by the rt-PA treatment itself (p=0.0001) and age (p=0.0002).[18]

After the approval of rt-PA for acute stroke treatment, there were numerous phase IV reports from all over the world. Recently, phase IV data were put together in a meta-analysis to look at the real-life safety of rt-PA treatment. Data from 10 prospective (2,253 patients) and five retrospective studies were used. The rate of symptomatic ICH was 4.9% (95% CI: 4.0–5.9%). Six studies provided data on both symptomatic and asymptomatic ICH. The analysis of these reports yielded a rate of all ICH of 11.5%. In the overall analysis, the death rate was 13.4% and the rate of favourable outcome was 37.1%.[19]

Undoubtedly, these results show that rt-PA can be used safely in everyday clinical practice in experienced centres worldwide. To facilitate and enhance the efficacy of the use of rt-PA, the American Stroke Association (ASA) and the European Stroke Initiative (EUSI) issued guidelines for the use of rt-PA in acute ischaemic stroke. Both associations recommend the use of IV rt-PA (0.9mg/kg, maximum 90mg), with 10% of the dose given as a bolus followed by a one-hour infusion in carefully selected patients treated within three hours from onset of symptoms.[20,21]

The search for the most efficacious treatment has not stopped since the approval of rt-PA in the three-hour time window. Major efforts have been carried out to find supplementary parameters that would allow extending the time window for the use of thrombolytic treatment, as the results of other studies with longer time windows (ATLANTIS and ECASS I and II) did not show a significant benefit beyond three hours. Most recently, a study based on penumbra imaging with magnetic resonance (MR) was completed. The Desmoteplase in Acute Ischemic Stroke (DIAS) trial was a randomised double-blind placebo-controlled study that tested safety and efficacy of IV desmoteplase – a highly fibrin-specific and non-neurotoxic thrombolytic agent – within three to nine

hours after acute ischaemic stroke in patients with MRI perfusion/diffusion mismatch. This study consisted of two parts: in the first, fixed doses of desmoteplase were studied (25mg, 37.5mg and 50mg, respectively); and in the second, escalating weight-adjusted doses were investigated (62.5µg/kg, 90µg/kg and 125µg/kg, respectively). Part one was prematurely terminated due to a high rate of symptomatic ICH (23.5% in the low-dose group and 30.8% in the high-dose group versus 0% in controls). In part two, higher reperfusion rates were seen with increasing doses of desmoteplase (23.1%, 46.7% and 71.4%, respectively) and were significantly higher (20%) than in the placebo group for the two highest weight-adjusted doses – 90µg/kg and 125µg/kg. The same was true for favourable outcome at 90 days, as the percentage of patients with good recovery increased with rising weight-adjusted doses of desmoteplase from 13.3% to 60% (placebo 18.2%). Statistical significance was shown only for the 125µg/kg group (p=0.009). Overall, the importance of reperfusion in an extended time window was confirmed by the fact that favourable outcome occurred in 52.5% of patients with reperfusion and in 24.6% of those without.[22]

In parallel with IV administration of thrombolytic agents, there have been attempts on intra-arterial (IA) *in situ* thrombolysis. Several thrombolytic agents have been tested, such as urokinase (UK), streptokinase (SK) and rt-PA, in a wide variety of patients with different arterial occlusions.

Prolyse in Acute Cerebral Thromboembolism (PROACT) I was a randomised placebo-controlled study that tested the safety and recanalisation efficacy of IA 6mg of recombinant pro-UK (r-pro-UK) delivered over 120 minutes in the proximal thrombus site. Patients were enrolled if they had a new onset of focal neurological signs in the MCA distribution (<6 hours, NIHSS 4–30) and an angiographically documented occlusion of proximal MCA. Evidence of haemorrhage and significant mass effect with mid-line shift were CT exclusion criteria. A strict blood pressure limit of 180/100 millimetres of mercury (mmHg) was obligatory. Forty patients met the inclusion criteria and were randomised; 26 of them were treated with r-pro-UK. During angiographical identification of an occluding thrombus, both the treatment and placebo group received an IV heparin infusion in two doses: a high dose (100IU/kg bolus followed by 1,000IU/h over four hours) and a low dose (2,000IU/kg bolus followed by 500IU/h over four hours). IA r-pro-UK treatment significantly improved the recanalisation rates when compared with placebo (57.7% versus 14.3%). This benefit was even more significant in patients receiving a high dose of heparin (81.8% versus 0%). However, in the treatment arm, there were significantly more ICHs at 24 hours (42.3% versus 7.1%), including symptomatic ICH (15.4% versus 7.1%). A correlation between the frequency of ICH and higher heparin doses was also demonstrated, as ICH was present in three of 15 (20%) in the low-dose group and in eight of 11 (72.7%) in the high-dose group. When compared with placebo the case fatality at 90 days was insignificantly lower in the treatment group (42.9% versus 26.9%), and the clinical outcome was insignificantly better (mRS 0–1: 21.4% versus 30.8%; NIHSS 0–1: 7.1% versus 19.2%).[23]

These promising results prompted the launch of another trial – PROACT II. In this open-label trial, a higher dose of r-pro-UK (9mg) and a lower dose of heparin (i.e. 2,000IU/kg bolus, followed by 500IU/h over four hours) were used. Inclusion and exclusion criteria were comparable with those used at PROACT I. In total, 180 patients were randomised (121 into the treatment arm). Recanalisation rates were higher in the treated group when compared with controls (66% versus 18%). A clear 15% absolute benefit in favourable outcome (mRS 0–2) of r-pro-UK over placebo (40% versus 25%) was demonstrated at 90 days (OR 2.13; 95% CI: 1.02–4.42) with a number needed to treat (NNT) equal to seven. Patients treated with r-pro-UK also had better functional outcome (BI >90) at seven to ten days when compared with controls (22% versus 10%). Treatment with r-pro-UK significantly increased the risk of ICH within 24 hours when compared with placebo (35% versus 13%). The frequency of symptomatic ICH was also higher in the treatment arm (10% versus 2%), with a number needed to harm (NNH) equal to 12. Symptomatic ICH occurred only in patients with moderate and severe strokes (baseline NIHSS >10). No significant difference in case fatality was observed between groups (r-pro-UK 25% versus placebo 27%).[24]

One of the phase IV studies on IA thrombolysis that have been published includes 100 patients with acute ischaemic stroke due to MCA occlusion who were treated with IA r-pro-UK within a six-hour time window. At three months, 47% of patients had an excellent outcome (mRS 0–1) and 10% died. Distal MCA occlusion, i.e. M3 or M4, correlated with an excellent outcome (63% at three months) and lower case fatality (5% at three months), while proximal MCA occlusion was linked with lower frequency of excellent outcome (42%) and higher case fatality (13%). Complete recanalisation was achieved in 20% and partial in 56% of patients. In patients with proximal occlusion, the combined recanalisation rate was higher than in those with distal occlusion (79% versus 64%). There were 7% of symptomatic ICH, all in patients with proximal occlusion, and two were fatal (2%).[25] Both in North America and Europe, IA thrombolysis is considered as a possible option for

treatment in selected stroke patients with proven large intracranial vessel occlusion (MCA, basilar artery).[20,21]

The Emergency Management of Stroke (EMS) bridging trial tested combined use of IV and IA rt-PA in acute ischaemic stroke. It was a double-blind randomised placebo-controlled phase I trial. Patients were randomised to receive either IV rt-PA (0.6mg/kg, 60mg maximum – 10% as a bolus over one minute and the rest in a 30-minute infusion) or placebo. After IV infusion, an immediate angiography was performed in all patients and IA rt-PA was administered with 1mg rt-PA delivered directly into the thrombus, followed by an rt-PA infusion of 10mg/h during maximum two hours. In total, 35 patients were randomised, including 17 into the IV/IA arm. Combined IV/IA thrombolysis was significantly more efficient in recanalisation when compared with IA treatment (53% versus 10%; p=0.03). However, there was no difference in clinical outcome between both groups, neither in the acute phase nor at 90 days. Case fatality at 90 days was higher in the IV/IA arm (29% versus 5.5%; p=0.06). Extracranial life-threatening bleeding complications were present only in the combined treatment arm. There were two symptomatic ICH in the combined treatment arm and one in the placebo group (11.8% versus 5.5%; p=ns).[26]

Stroke Prevention

Treatment of Hypertension

Treating hypertension in stroke prevention has been the subject of multiple reviews.[27] The RR of stroke rises proportionately to the level of systolic blood pressure (SBP) for both ischaemic and haemorrhagic stroke. The RR of ischaemic stroke approaches 4 and the RR for haemorrhagic stroke reaches almost 8 when systolic pressure is higher than 160mmHg.[28] The difference in the risk of death of vascular causes – such as stroke or ischaemic heart disease associated with a given absolute difference in usual blood pressure – was shown to be approximately the same, at least down to 115mmHg SBP and 75mmHg diastolic blood pressure (DBP). For patients of 40–69 years of age, each difference of 20mmHg usual SBP or 10mmHg usual DBP caused more than a two-fold increase in the stroke death rate. Lowering the usual SBP by 20mmHg decreased stroke-related mortality in all major aetiological subtypes of stroke, including subarachnoidal haemorrhage, ICH and ischaemic stroke.[29] The Heart Outcomes Prevention Evaluation (HOPE) study investigated high-vascular-risk patients with coronary artery disease, ischaemic stroke or peripheral artery disease and other risk factors, such as hypertension, hyperlipidaemia, smoking or microalbuminuria. In this trial, an angiotensin-converting enzyme inhibitor (ACEI), ramipril 10mg, versus placebo was used in preventing myocardial infarction (MI), ischaemic stroke or vascular death, irrespective of baseline blood pressure levels. A mean blood pressure reduction of 9mmHg/4mmHg (SBP/DBP) gave an RR of stroke of 0.68 (95% CI: 0.56–0.84).[30] Another trial assessed the efficacy of perindopril 4mg versus placebo, with additional randomisation into indapamide versus placebo in 6,105 patients with a history of stroke, TIA or amaurosis fugax in preventing fatal or non-fatal stroke. The combination of perindopril and indapamide diminished the risk of stroke by 43% (30–54%) and reduced blood pressure by 12mmHg/5mmHg. The single drug therapy did not change the risk of stroke, but it reduced blood pressure by 5mmHg/3mmHg. When compared with placebo, an average blood pressure reduction of 3mmHg/1mmHg lowered the RR of stroke in the perindopril arm by 28% (17–38%). This effect was more evident in haemorrhagic stroke with the risk decreased by 50% (26–67%), when compared with the risk reduction of 24% (10–35%) in ischaemic stroke. In this trial, the effects of treatment were not related to the presence or absence of hypertension. In the hypertensive group, the risk of stroke was decreased by 32% (17–44%), while it was lowered by 27% (8–42%) in the normotensive group.[31]

The quest for the most effective pharmacological treatment of hypertension in stroke prevention is on-going. According to a recent systematic review, β-blockers or diuretics yielded a 35% RR reduction (RRR) with a net difference in SBP/DBP of 13mmHg/6mmHg when compared with placebo or no treatment. The ACEIs versus placebo or no treatment showed a benefit of 28% in decreasing the risk of stroke (absolute blood pressure difference: 5mmHg/2mmHg), and calcium blockers versus placebo or no treatment yielded an RR of 0.61, with a net difference in blood pressure of 10mmHg/5mmHg.[32] When comparing different age groups, the effect of anti-hypertensive treatment was most pronounced in patients younger than 60 years (RRR 40%; 95% CI: 26–52%). The mean baseline SBP seemed not to influence this effect.

Comparing the efficacy of different types of blood-pressure-lowering agents is of great clinical interest. Diuretics were shown to be more efficacious than β-blockers (RRR 31%; 95% CI: 3–51%).[33] Composite data from five randomised trials that included more than 46,000 of patients (absolute blood pressure difference: 2mmHg/1mmHg) showed that β-blockers and/or diuretics were more efficient than ACEIs (RR 0.91; 95% CI: 0.83–0.99).[32] Ten randomised trials tested β-blockers and/or diuretics versus calcium blockers (n=68,000; absolute blood pressure difference: 1mmHg/1mmHg), and the results were slightly in favour of the latter (RR 1.08; 95% CI:

0.99–1.16). Based on the results of four randomised trials (n=23,000), an advantage of calcium blockers over ACEI with an RR of 0.89 was demonstrated (95% CI: 0.80–0.99) (absolute blood pressure difference: 1mmHg/1mmHg). A comparison of more intensive versus less intensive anti-hypertensive treatment (three randomised trials; n=20,000) showed that a more intensive approach was more efficient with an RR of 0.80 (95% CI: 0.65–0.99).[32] Lowering the SBP was shown to proportionately increase the RRR of stroke.[32]

In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study, the efficacy of losartan versus atenolol was compared in 9,193 patients with essential hypertension and an RR of stroke of 0.75 (0.63–0.89) was found.[34] The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial compared valsartan with amlodypine in 15,245 patients with treated and untreated hypertension. Valsartan was slightly less efficient in preventing strokes with an HR of 1.15 (95% CI: 0.98–1.35).[35] The Study on Cognition and Prognosis in the Elderly (SCOPE) assessed the efficacy of candesartan versus placebo in elderly patients (n=4,937) with mildly to moderately elevated blood pressure in reducing the rate of cardiovascular events, cognitive decline and dementia. The treatment with candesartan was shown to modestly decrease the rate of stroke (RR 0.24; -0.7–42.1).[36] Currently, there are three on-going randomised studies on angiotensin receptor blockers (ARBs) and stroke prevention. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) compares telmisartan 80mg and ramipril 10mg with monotherapies and placebo in the prevention of stroke, MI, cerebrovascular disease (CVD) death and hospitalisation for cardiac failure in patients older than 55 years with coronary artery disease, ischaemic stroke or TIA, peripheral artery disease or diabetes mellitus (DM). Another trial, the Telmisartan Randomised Assessment Study in ACE-intolerant Subjects with Cardiovascular Disease (TRANSCEND), compares telmisartan 80mg with placebo in ACEI-intolerant patients with the same risk factors and end-points as ONTARGET.[37] The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) study is a randomised parallel-group double-blind double-dummy placebo-controlled study on stroke prevention in patients over 55 years of age who have had a stroke within 90 days. There are 15,500 patients to be randomised. Half of the active group participants will receive a combination of acetylsalicylic acid (ASA) and dipiridamole and telmisartan, while the other half will receive clopidogrel, aspirin and telmisartan. The placebo group will also be divided into one-half receiving a combination of ASA, dipiridamole and placebo, and the one-half receiving clopidogrel, aspirin and placebo. The primary outcome is time to first recurrent stroke.[38]

The guidelines for treatment of hypertension in prevention of stroke state that in primary prevention of stroke, normal blood pressure limit should be set at a level lower than 149mmHg/90mmHg and lower than 130mmHg/85mmHg in diabetics. Normal blood pressure values should be reached first with modification of lifestyle, and if the former is unsuccessful a medical treatment should be considered. Lowering blood pressure, irrespective of baseline level, is recommended in secondary stroke prevention. The first-line agents should be diuretics and/or ACEI.[39] In patients with severe pre-cerebral artery stenosis, intensive blood pressure lowering in the secondary prevention of stroke should be started with caution, if at all.[40,41]

Hypercholesterolaemia

The relation between the serum level of cholesterol and stroke occurrence is debated in the literature, although the correlation between increased total blood cholesterol levels and risk of MI is well known.[42,43] One trial observed a positive correlation between total cholesterol levels and stroke-related mortality in young women, while an inverse correlation between these parameters was demonstrated in elderly subjects.[43] In a combined analysis, no significant association between the increased level of serum cholesterol and stroke rate was found, except for in subjects younger than 45 years.[44] However, this analysis did not include a stratification into stroke subgroups and, possibly, a positive association with ischaemic stroke might be counterbalanced by a negative association with haemorrhagic stroke. This finding was confirmed in another study in which a positive correlation between total cholesterol levels and ischaemic stroke risk was demonstrated. The risk of fatal ischaemic stroke rose when the serum cholesterol levels were higher than 7.23mmol/litre.[45] A lowered cholesterol level was shown to decrease the risk of ischaemic stroke, but this correlation was statistically non-significant (ns).[46] A positive correlation between total cholesterol levels higher than 8mmol/litre and the risk of non-haemorrhagic stroke was demonstrated in a different study.[47]

The Heart Protection Study assessed the efficacy of simvastatin in patients with coronary disease, other occlusive disease or diabetes and low-density lipoprotein (LDL) cholesterol levels of at least 3.5mmol/litre in reducing vascular events.[48] A 24% reduction in the rate of all-cause mortality, fatal or non-fatal vascular events was shown in patients treated with simvastatin when compared with those treated with placebo. A 25% reduction in total stroke

incidence rate and a 30% reduction in the ischaemic stroke incidence rate were observed. In the simvastatin-treated group, transient ischaemic attacks were significantly less frequent than in the placebo group (2% versus 2.4%). In this trial, there was no stratification for past medical events, thus rendering the interpretation of the effects of simvastatin in subgroups untrustworthy, as there was a subgroup of patients with the history of CVD without coronary heart disease. In this subgroup, a 21% RRR of major vascular events was demonstrated, but no effect of simvastatin on stroke recurrence was observed.

A few meta-analyses on lipid lowering and ischaemic heart disease prevention have been published in the past decade. One included all randomised trials that were published between 1966 and 2001, testing statins, resins, fibrates, niacin, surgical interventions and diet.[49] There were 10 primary and 28 secondary prevention trials. This analysis showed a significant 17% RRR of stroke incidence. There was no significant heterogeneity between trials, either in intervention tested (primary versus secondary prevention) or in the type of lipid-lowering therapy examined. When comparing different pharmacological agents, only statins yielded a significant 24% RRR of stroke. When analysing by type of intervention, the significant effect of statins on stroke incidence was present only in secondary prevention, with a 26% RRR of stroke. Lipid-lowering therapy, however, did not influence the incidence of fatal strokes and did not change the incidence of haemorrhagic stroke. A strong evidence for the role of cholesterol in the pathogenesis of stroke is based on the correlation of stroke incidence and the degree of cholesterol reduction, baseline cholesterol level and final cholesterol level, as the target cholesterol level around 6mmol/litre (232mmol/litre) is the divide between absence and presence of stroke RR.

The most recent systematic review analysed all randomised trials testing statin drugs published before 2003. The RRR for stroke in patients on statins was 21% (OR 0.79; 95% CI: 0.73–0.85), the rate of fatal strokes was insignificantly reduced by 9% (OR 0.91; 0.76–1.10) and there was no increase in the frequency of haemorrhagic strokes. The effect of statins was closely linked to LDL-C reduction, as each 10% reduction in LDL-C reduced the risk of all strokes by 15.6% (95% CI: 6.7–23.6%).[50]

An additive effect of ASA and pravastatin was assessed in one meta-analysis that included five randomised trials of secondary prevention with pravastatin 40mg/day and ASA (73,900 patient years of observation). The RR of ischaemic stroke was reduced by 39% in patients treated with pravastatin and ASA when compared with placebo. The combination of pravastatin and ASA was shown to be more efficient than aspirin and pravastatin alone (RRR 29% and RRR 31%, respectively).[51]

The Collaborative Atorvastatin Diabetes Study (CARDS) evaluated the effectiveness of atorvastatin 10mg/day versus placebo in the primary prevention of coronary artery disease and stroke in 2,838 patients with type 2 diabetes without increased cholesterol levels. The RR of stroke was lowered by 52% in the group treated with atorvastatin (RR 48%; 95% CI: 11–69%).[52] Cholesterol-lowering therapy is recommended in primary stroke prevention in high-risk patients with coronary artery disease, hypertension or DM. All patients with a history of ischaemic stroke or TIA may be considered for statin therapy, which may be started already during the hospitalisation.[39,53]

The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial evaluates the effects of atorvastatin 80mg/day in secondary prevention of stroke in patients without a history of coronary artery disease. A total of 4,732 patients have been enrolled. This is the first study primarily designed to prospectively evaluate the effect of statin treatment in secondary stroke prevention, so its results will be of great clinical interest.[50]

Antiplatelet and Anticoagulant Therapy

Acute Phase of Stroke

Patients treated with thrombolytic therapy or ineligible for this treatment should be started on early secondary prevention, as the risk of stroke recurrence is the highest in the acute phase of stroke. Two large randomised non-blinded trials tested the use of ASA in the acute phase of stroke.[54,55] The Chinese Acute Stroke Trial (CAST) tested 160mg of ASA per day in patients suspected to have an ischaemic stroke and showed that this treatment reduces mortality from 3.9% to 3.3% and recurrent stroke rate from 2.1% to 1.6%, but increases the rate of haemorrhagic strokes from 0.9% to 1.1%. For the combined in-hospital end-point of death or non-fatal stroke, there was a 12% reduction with ASA. In this trial, ASA was shown to give a small but significant benefit, with nine fewer deaths or non-fatal strokes per 1,000 treated in the first weeks and 13 fewer dead or dependent per 1,000 treated after a few months of follow-up.[54]

The International Stroke Trial (IST) tested two doses of unfractionated heparin or 300mg of ASA started as soon as possible after stroke onset. After adjustment for baseline prognosis, ASA was shown to decrease the odds of being dead or dependent. Patients treated with ASA had fewer recurrent events (ASA 2.8% versus placebo 3.9%) and no increase in haemorrhagic

strokes, which yielded an absolute decrease in death or non-fatal recurrent events of 1.1% (11.3% versus 12.4%). Here, ASA was shown to result in a reduction of 10 deaths or recurrent strokes per 1,000 treated in the first few weeks.[55]

The recent meta-analysis of randomised trials of antiplatelet therapy for prevention of death, MI and stroke confirmed the effectiveness of ASA in acute stroke treatment. The randomised evidence was available from approximately 40,000 patients with acute stroke. Treatment with ASA increased the number of major extracranial bleeds by two per 1,000 treated. However, ASA was shown to decrease the number of non-fatal strokes by four per 1,000 treated and, additionally, to decrease the number of all vascular deaths by five per 1,000 treated, giving a net benefit of nine events prevented per 1,000 patients treated.[56] ASA 100mg to 300mg is a recommended treatment within 48 hours after ischaemic stroke.[39]

As anticoagulants have been used quite frequently in the acute phase of ischaemic stroke, it is of use to mention that none of the acute-phase anticoagulant trials showed any overall benefit of treatment. The beneficial effects of early anticoagulation were counterbalanced by an increased frequency of haemorrhages. The IST showed that in patients on unfractionated heparin, there were insignificantly fewer deaths within two weeks (three per 1,000 treated), and at six months of follow-up, this benefit was no longer present. Patients treated with heparin had fewer recurrent strokes within two weeks (absolute decrease: 0.9%), but this effect was outweighed by a similar increase in haemorrhagic strokes, so the difference in death or non-fatal recurrent stroke was insignificant (absolute decrease: 0.3%). Moreover, higher doses of heparin were associated with more serious or fatal extracranial bleeds and more haemorrhagic strokes within two weeks (absolute increase: 1.8%).[55] Full-dose heparin may be used in selected patients with cardiac sources with high embolic potential, extracranial arterial dissection or high-grade arterial stenosis prior to surgery.[39]

Post-acute Phase of Stroke

The subject of the use of antithrombotic treatment in stroke prevention in the chronic phase of the disease, particularly in high-risk subgroups of patients, is widely discussed in the literature.[57] The effectiveness of antiplatelet agents for the prevention of ischaemic events has been established in patients with a history of coronary heart disease, peripheral arterial disease (PAD) and stroke. In a recent meta-analysis, antiplatelet therapy reduced the odds of serious vascular events (non-fatal MI, non-fatal stroke or vascular death) in high-risk vascular patients (with acute or previous vascular disease) by 22% ($p<0.05$), and in a subgroup of patients with DM (n=4,961) by 7% (p=ns).[56]

The superiority of clopidogrel versus placebo on top of standard therapy, including ASA, was demonstrated for the prevention of cardiovascular death, MI or stroke in patients with acute coronary syndromes in the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events (CURE) study. The benefit of clopidogrel was consistent across a range of pre-specified subgroups.[58] The efficacy of clopidogrel and ASA in reducing the risk of a composite end-point of ischaemic stroke, MI or vascular death in patients with recent ischaemic stroke, recent MI or established PAD was assessed in the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, which included a broad population of patients with a history of atherothrombosis. Clopidogrel was shown to be superior to ASA by significantly lowering the risk of the primary end-point by an additional 8.7% (95% CI: 0.3–16.5) compared with ASA. In a subgroup of patients who qualified for CAPRIE on the basis of a recent ischaemic stroke, the RRR in favour of clopidogrel was 7.3% (95% CI: -5.7–18.7%).[59]

Management of Atherothrombosis with Clopidogrel in High-risk Patients (MATCH) was a randomised placebo-controlled double-blind multinational trial that studied the effectiveness of adding ASA 75mg/day to clopidogrel 75mg/day in high-risk patients with symptomatic CVD and included 7,599 patients with ischaemic stroke or TIA in the previous three months and at least one of the following risk factors:

- previous ischaemic stroke;
- previous MI;
- angina pectoris;
- symptomatic PAD; or
- DM.[60,62]

The RRR of first occurrence of ischaemic stroke, MI, vascular death (including haemorrhagic death of any aetiology) or rehospitalisation for an acute ischaemic event was 6.4% (95% CI: -4.6–16.3%) in favour of combined therapy. However, adding ASA to clopidogrel led to more bleeding complications than monotherapy with clopidogrel. There were significantly more life-threatening events in the ASA group than in the placebo group (2.6% versus 1.3%; $p<0.001$). Life-threatening bleedings were more frequent in the ASA than in the placebo group irrespective of whether they were gastrointestinal (1.4% versus 0.6%) or intracranial (1.1% versus 0.7%). Despite these bleeding data, there was no difference in overall mortality between the two treatment groups.

Currently, the Clopidogrel for High Athero-thrombotic Risk and Ischemic Stabilization,

Management and Avoidance (CHARISMA) study is on-going and has enrolled patients (n=15,603) with coronary, cerebrovascular or peripheral arterial disease, as well as those with multiple cardiovascular risk factors. Patients were randomised to clopidogrel and aspirin or placebo and aspirin (low- or moderate-dose aspirin).[62,63] Results of this trial are expected with great attention, as they may expand the knowledge of the effectiveness of combination therapy with antiplatelet agents in patients with multiple cardiovascular risk factors or established vascular disease.

Conclusion

Pharmacotherapy of stroke does not have a solid ground in the clinical practice, mainly due to therapeutic nihilism and scepticism. However, there are some very solid and evidence-based data on the effectiveness of stroke treatment in both the acute and chronic phase. It is in the hands of clinicians to use the available information to educate stroke victims and health authorities to diminish the burden of stroke. ■

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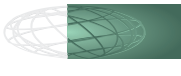

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