

Randomized Clinical Stroke Trials In 2008

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Abstract: Problem statement: Stroke ranks as the third leading cause of death and the leading cause of serious, long-term disability; estimated direct and indirect cost of stroke for 2009 was \$68.9 billion. **Approach:** The objective of this review was to examine the effectiveness of emerging pharmacotherapies in patients with acute (≤ 2 weeks), sub-acute (2-12 weeks) and chronic (≥ 12 weeks) stroke studied in Randomized Control Trials (RCT's) published in 2008. Medline search was performed to identify all RCT's in acute, sub-acute and chronic stroke treatment in the year 2008. The search strategy used for PubMed included key words such as Randomized Controlled Trials (RCT), Stroke OR cerebrovascular disorders OR CVA, Ischemic stroke OR ischemia, Hemorrhage OR intraparenchymal hemorrhage OR subarachnoid hemorrhage, Thrombolytics OR tissue plasminogen activator OR alteplase OR t-PA, Diabetes mellitus OR hyperglycaemia, Hypertension OR raised blood pressure, Aspirin OR anti-platelets, Warfarin OR anticoagulant, Antidepressants, Neuroprotectants and Coiling OR stents OR endovascular. Search limits included Human, Adult (age >19 years), English language and Publication date: 1/1/2008 to 12/31/2008. **Results:** Eleven categories of 21 RCT's were found and analyzed. **Conclusion/Recommendations:** There is sufficient evidence to suggest that: (1) extending the time-window for administration of alteplase from 3-4.5 h after stroke onset does improve clinical outcome; (2) treatment of hypertension in the elderly does reduce rate of stroke, cardiac failure and death from stroke and (3) at present there are no neuroprotectants on the horizon.

Key words: Acute stroke. pharmacotherapies, endovascular

INTRODUCTION

This review focuses on the clinical usefulness of commonly used pharmacological agents, readily available to clinicians caring for stroke patients that were assessed in clinical trials published in 2008.

Acute stroke therapies:

Title: Emergency administration of abciximab for treatment of patients with acute ischemic stroke: Results of an international phase III trial.

Abciximab (a chimeric mouse/human monoclonal antibody with a high affinity for platelet glycoprotein IIb/IIIa receptor) has been found to be a safe and effective treatment of acute ischemic stroke (Abciximab in Ischemic Stroke Investigators, 2000; Abciximab Emergent Stroke Treatment Trial Investigators, 2005). This international, randomized, placebo-controlled; double-blind phase III study assessed intravenous abciximab efficacy and safety in patients with acute ischemic stroke (Adams *et al.*, 2008). The study was comprised of a primary cohort of patients treated within 5 h of onset of stroke; a companion cohort of patients treated 5-6 h after stroke and a smaller cohort of patients treated within 3 h of stroke present on

awakening. The primary efficacy measure was the modified Rankin Scale (mRS) score at 3 months adjusted to the baseline severity of stroke among subjects in the primary cohort. The primary safety outcome was the rate of symptomatic or fatal intracranial hemorrhage within 5 days of stroke. The trial was planned to enroll 1800 patients but was terminated prematurely after having enrolled 808 patients in all cohorts on the recommendation of an independent safety and efficacy monitoring board due to an unfavorable benefit-risk profile of abciximab. At 3 months, 33% of patients assigned to placebo (72/218) and 32% of patients assigned to abciximab (71/221; $p = 0.944$) in the primary cohort had a favorable treatment response on mRS. Within 5 days of enrollment, approximately 5.5% of abciximab-treated and 0.5% of placebo-treated patients in the primary cohort had symptomatic or fatal intracranial hemorrhage ($p = 0.002$). The trial did not show improvement in the primary outcome measure with abciximab among patients in the companion and wake-up cohorts. In conclusion this trial showed that intravenous abciximab for the treatment of patients with acute ischemic stroke was neither efficacious nor safe with an increased rate of symptomatic or fatal

intracranial hemorrhage in the primary and wake-up cohorts (13.6% versus 5% for placebo).

Intravenous thrombolysis with alteplase is the only FDA approved treatment for acute ischemic stroke, but its efficacy and safety when administered more than 3 h after the onset of symptoms have not been established. Two studies tested the efficacy and safety of alteplase administered 3-6 h after the onset of an ischemic stroke (Davis *et al.*, 2008; Hacke *et al.*, 2008).

Title: Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): A placebo-controlled randomized trial.

This trial tested the effectiveness of intravenous tissue plasminogen activator (alteplase) in promoting reperfusion and attenuating infarct growth when administered 3-6 h after ischemic stroke onset to patients with mismatch on Perfusion-Weighted (PWI) and Diffusion-Weighted (DWI) MRI. In this prospective randomized trial, patients either received alteplase (n = 52) or placebo (n = 49) 3-6 h after onset of ischemic stroke (Davis *et al.*, 2008). PWI and DWI were carried out before and 3-5 days after therapy, with T2-weighted MRI at 90 days. The primary endpoint was infarct growth between baseline DWI and day 90 T2 lesion in mismatch patients. Major secondary endpoints were reperfusion, good neurological outcome (measured by National Institute of Health Stroke Scale (NIHSS)) and good functional outcome (measured by modified Rankin Score (mRS)). Mean age was 71.6 years and median score on the NIHSS was 13. Mismatch on PWI and DWI was in 85 of 99 (86%) patients. The mean infarct growth (an exponential of the mean log of relative growth) was 1.24 with alteplase and 1.78 with placebo (ratio 0.69, 95% CI 0.38-1.28; Student's t-test p = 0.239); the median relative infarct growth was 1.18 with alteplase and 1.79 with placebo (ratio 0.66, 0.36-0.92; Wilcoxon's test p = 0.054). Reperfusion was commonly seen with alteplase than with placebo and was associated with less infarct growth (p = 0.001), better neurological outcome (p<0.0001) and better functional outcome (p = 0.010). This study showed alteplase increased reperfusion in patients who had mismatch, but did not lower infarct growth size. Because of reperfusion, there were improved neurological and functional outcomes. This trial highlights the need for more phase III studies beyond 3 h after onset of acute ischemic stroke.

Title: Thrombolysis with alteplase 3-4.5 h after acute ischemic stroke.

Eight hundred and twenty one patients with ischemic stroke were randomly assigned to the alteplase

(n = 418, 0.9 mg kg⁻¹ of body weight) or to the placebo (n = 403) group (Hacke *et al.*, 2008). The median time for the administration of alteplase was 3 h 59 min. The primary end point was disability at 90 days, dichotomized as a favorable outcome (a score of 0 or 1 on the modified Rankin Scale (mRS), which has a range of 0-6, with 0 indicating no symptoms at all and 6 indicating death) or an unfavorable outcome (a score of 2-6 on the mRS). The secondary end point was a global outcome analysis of 4 neurologic and disability scores combined. Safety end points included death, symptomatic intracranial hemorrhage and other serious adverse events. More patients had a favorable outcome with alteplase than with placebo (52.4 Vs 45.2%; odds ratio, 1.34; 95% Confidence Interval (CI), 1.02 to 1.76; p = 0.04) on the mRS for a score of 0 or 1. In the global analysis, outcome also improved with alteplase compared with placebo (odds ratio, 1.28; 95% CI, 1.00-1.65; p<0.05). The incidence of intracranial hemorrhage was higher with alteplase than with placebo (for any intracranial hemorrhage, 27.0 Vs 17.6%; p = 0.001; for symptomatic intracranial hemorrhage, 2.4 Vs 0.2%; p = 0.008). Mortality did not differ between the groups (7.7 and 8.4%, respectively; p = 0.68), nor the rate of other serious adverse events. In conclusion, intravenous alteplase administered between 3 and 4.5 h after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke; however, alteplase was more frequently associated with symptomatic intracranial hemorrhage.

The recanalisation rate of thrombolysis after r-TPA for acute ischemic stroke is 26% for internal carotid and 69% for middle cerebral arteries (Christou *et al.*, 2002). Various approaches are being studied to enhance this rate of thrombolysis induced recanalisation after an acute ischemic stroke (Christou *et al.*, 2002; Pancioli *et al.*, 2008; Alexandrov *et al.*, 2004).

Title: The Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke: The CLEAR Stroke Trial.

Combination of a reduced-dose fibrinolytic agent and a Glycoprotein (GP) IIb/IIIa receptor antagonist has been shown to improve the rate of recanalization versus fibrinolysis alone in the treatment of myocardial infarction (Topol, 2001). This trial assessed the safety of treating acute ischemic stroke patients within 3 h of symptom onset with this combination of eptifibatide and t-PA (Pancioli *et al.*, 2008). This was a multi-center, double-blind, randomized, dose-escalation and safety study. Patients were randomized 3:1 to either low-dose t-PA (tier 1 = 0.3 mg kg⁻¹, tier 2 = 0.45 mg kg⁻¹) plus eptifibatide (75 ug kg⁻¹ bolus followed by

0.75 ug kg⁻¹ min⁻¹ infusion over 2 h) or standard-dose t-PA (0.9 mg kg⁻¹). The primary safety end point was the incidence of symptomatic intra-cerebral hemorrhage within 36 h. A secondary analysis was its clinical efficacy. Ninety-four patients (40 in tier 1 and 54 in tier 2) were enrolled. The combination group of the 2 dose tiers (n = 69) had a median age of 71 years and a median baseline National Institutes of Health Stroke Scale (NIHSS) score of 14, while the standard-dose t-PA group (n = 25) had a median age of 61 years and a median baseline NIHSS score of 10 (p = 0.01 for NIHSS score). Fifty-two (75%) of the combination treatment group and 24 (96%) of the standard treatment group had a baseline modified Rankin scale score of 0 (p = 0.04). There was 1 (1.4; 95% CI, 0-4.3%) symptomatic intracranial hemorrhage in the combination group and 2 (8.0; 95% CI, 0-19.2%) in the t-PA-only arm (p = 0.17). The study was halted by the independent data safety monitoring board because on their review the safety profile of combination therapy at the tier 2 doses suggested that further enrollment was statistically unlikely to indicate inadequate safety for the combination treatment group, the ultimate outcome of the study. The study found the combination of reduced-dose t-PA plus eptifibatid to be safe in acute ischemic stroke trials. However, there was a trend toward increased clinical efficacy of standard-dose t-PA compared with the combination treatment group. The authors speculated why combination treatment was less clinically efficacious. It may have been due to the baseline characteristics of the combination group for older age (71 years) and higher baseline median NIHSS score of 14 compared to standard t-PA group. Also, the time delay from onset to administration of medication was 2.55 h in the combination therapy group in order to maintain the double-blind drug dosing.

Title: Sonothrombolysis with transcranial color-coded sonography and recombinant tissue-type plasminogen activator in acute middle cerebral artery main stem occlusion: Results from a randomized study.

Sonothrombolysis is a new treatment approach in patients with acute ischemic stroke. CLOTBUST was the first randomized trial to show effectiveness of sonothrombolysis as a treatment modality in acute ischemic stroke patients (Alexandrov *et al.*, 2004). In this single-center trial, 37 subjects with acute middle cerebral artery main stem occlusion (no residual blood flow in the middle cerebral artery main stem (Thrombolysis in Brain Ischemia recanalization grade 0)) were randomized into an Ultrasound (US) group (n = 19) receiving 1 h transcranial continuous insonation using a 1.8-MHz Doppler US probe or a

control group (n = 18) (Eggers *et al.*, 2008). All of the subjects received standard thrombolysis with intravenous recombinant tissue-type Plasminogen Activator (tPA). The US group showed greater improvement in National Institutes of Health Stroke Scale scores at days 1 and 4 and a higher median Thrombolysis in Brain Ischemia grade 1 h after recombinant tissue-type plasminogen activator initiation compared with the control group. Recanalization (complete or partial) after 1 h occurred in 57.9% of the US group and 22.2% of the control group (p = 0.04). After 90 days, 4 subjects from the US group had a modified Rankin Score ≤1 (none from the control group; p = 0.106) and 8 had a Barthel index ≥95 (none from the control group; p = 0.003). Three subjects from the US group (15.8%) and one (5.6%) in the control group developed symptomatic intracranial hemorrhage (p = 0.60). This small randomized study reaffirmed the beneficial effect of transcranial ultrasound on recanalization and improving short-term clinical outcomes in subjects with middle cerebral artery main stem occlusion who received tPA treatment.

Title: A pilot randomized clinical safety study of sonothrombolysis augmentation with ultrasound-activated perflutren-lipid microspheres for acute ischemic stroke.

The investigators of this study, after having previously shown sonothrombolysis to be an effective alternative treatment modality for acute stroke patients (Alexandrov *et al.*, 2004); tested whether Ultrasound (US) activated perflutren-lipid microspheres (μS) induced recanalization was safe and feasible in acute stroke patients who received IV tissue Plasminogen Activator (tPA) (Alexandrov *et al.*, 2008). US is thought to transiently expand μS, thereby transmitting energy momentum to surrounding fluids accelerating residual flow and causing microfragmentation of the thrombus. Patients seen within 3 h of their acute stroke and who had on Transcranial Doppler (TCD) an abnormal residual blood flow (Thrombolysis In Brain Ischemia (TIBI) residual flow grades 0-3 before tPA, were randomized in a 3:1 ratio to either the Target (tPA + TCD + 2.8 mL μS) (n = 12) or control group (tPA + TCD) (n = 3). The primary safety end point was symptomatic Intracranial Hemorrhage (sICH) with worsening by ≥4 NIHSS points within 72 h. After treatment, asymptomatic ICH occurred in 3 Target and 1 Control subjects and sICH was not seen in any study subject. μS reached MCA occlusions at velocities higher than surrounding residual red blood cell flow: 39.8±11.3 Vs 28.8±13.8 cm sec⁻¹, p<0.001. In 75% of subjects, μS permeated to areas with no pretreatment

residual flow and in 83% residual flow velocity improved at a median of 30 min from start of μ S infusion (range 30 sec to 120 min) by a median of 17 cm sec^{-1} (118% above pretreatment values). When the current study recanalization rates were compared with the tPA control arm of the CLOTBUST trial the following results were documented: Complete recanalization occurred (50% versus 18%), partial (33% versus 21%), none (17% versus 49%), $p = 0.028$. At 2 h, sustained complete recanalization occurred in 42% versus 13% ($p = 0.003$) and NIHSS scores 0-3 were reached by 17% versus 8% ($p = 0.456$). In this study perflutren μ S reached beyond intracranial occlusion and achieved a higher recanalization rate with no increase in sICH after systemic thrombolysis. The main limitations of this study were the small numbers of patients enrolled and only those centers participated who had expertise in the use of sonothrombolysis with trained personal that could operate the TCD machine.

Stroke and hypertension: Long-term antihypertensive therapy has been shown to reduce the risk of stroke (10) and stroke recurrences.

Title: Treatment of hypertension in patients 80 years of age or older.

This study assessed whether the treatment of patients with hypertension who are 80 years of age or older is beneficial. In this multi-center, international trial of 3845 patients who were 80 years of age or older and had a sustained systolic blood pressure of 160 mm Hg or more, were randomly assigned to receive either the diuretic indapamide (sustained release, 1.5 mg) or matching placebo (Alexandrov *et al.*, 2008). The angiotensin-converting-enzyme inhibitor perindopril (2 or 4 mg), or matching placebo, was added if necessary to achieve the target blood pressure of 150/80 mm Hg. The primary end point was fatal or nonfatal stroke. There were 1933 patients in the active-treatment group and 1912 patients in the placebo group. The groups were matched for: (a) mean age, 83.6 years, (b) mean blood pressure while sitting, 173.0/90.8 mm Hg and (c) 11.8% with a history of cardiovascular disease. The median follow-up was 1.8 years. At 2 years, the mean blood pressure, while sitting, was 15.0/6.1 mm Hg lower in the active-treatment than in the placebo group. In an intention-to-treat analysis, active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% Confidence Interval (CI), -1 to 51; $p = 0.06$), a 39% reduction in the rate of death from stroke (95% CI, 1-62; $p = 0.05$), a 21% reduction in the rate of death from any cause (95% CI, 4-35; $p = 0.02$), a

23% reduction in the rate of death from cardiovascular causes (95% CI, -1 to 40; $p = 0.06$) and a 64% reduction in the rate of heart failure (95% CI, 42-78; $p < 0.001$). Fewer serious adverse events were reported in the active-treatment group (358, Vs 448 in the placebo group; $p = 0.001$). This study provides further evidence that antihypertensive treatment with indapamide (sustained release), with or without perindopril, in persons 80 years of age or older is beneficial as a primary prevention in reducing the rate of strokes, heart failure and death from stroke and all cause mortality. This study highlights the importance of hypertension control in the elderly (>80 years and older) who represent the fastest growing segment of the population.

Title: Telmisartan to Prevent Recurrent Stroke and Cardiovascular Events. (Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) Study Group).

Inhibition of the renin-angiotensin system in high-risk vasculopathies has been shown to reduce the rate of cardiovascular events, including stroke (Chitravas *et al.*, 2007). In this study the effect of lowering of blood pressure was assessed using the renin-angiotensin system blocker, telmisartan, soon after a stroke. In this multicenter trial involving 20,332 patients with recent ischemic stroke, patients were randomized to receive telmisartan (80 mg daily) ($n = 10,146$) or placebo ($n = 10,186$) (Yusuf *et al.*, 2008). The primary outcome was stroke recurrence. The secondary outcome was a composite of stroke recurrence, myocardial infarction or death from vascular causes or new or worsening heart failure and new-onset diabetes. The median interval from stroke to randomization was 15 days. During a mean follow-up of 2.5 years, the mean blood pressure was 3.8/2.0 mm Hg lower in the telmisartan group than in the placebo group. A total of 880 patients (8.7%) in the telmisartan group and 934 patients (9.2%) in the placebo group had a subsequent stroke (hazard ratio in the telmisartan group, 0.95; 95% Confidence Interval (CI), 0.86-1.04; $p = 0.23$). Major cardiovascular events occurred in 1367 patients (13.5%) in the telmisartan group and 1463 patients (14.4%) in the placebo group (hazard ratio, 0.94; 95% CI, 0.87-1.01; $p = 0.11$). New-onset diabetes occurred in 1.7% of the telmisartan group and 2.1% of the placebo group (hazard ratio, 0.82; 95% CI, 0.65-1.04; $p = 0.10$). In this study telmisartan initiated soon after an ischemic stroke and continued for 2.5 years did not significantly lower the rate of recurrent stroke, major cardiovascular events, or diabetes.

Stroke and atrial fibrillation:

Title: Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: A randomised, open-label, non-inferiority trial.

Vitamin K antagonists such as warfarin, the current standard of treatment for prophylaxis against stroke and systemic embolism in patients with atrial fibrillation, require regular monitoring and dose adjustment. This randomized, open-label non-inferiority trial aimed to compare the efficacy and safety of idraparinux (a fixed-dose, unmonitored anticoagulant regimen) with warfarin (Amadeus *et al.*, 2008). Patients with atrial fibrillation at risk for thromboembolism were randomly assigned to receive either subcutaneous idraparinux (2.5 mg weekly) or adjusted-dose warfarin (target international normalised ratio of 2-3). The primary efficacy outcome was the cumulative incidence of all stroke and systemic embolism. The principal safety outcome was clinically relevant bleeding. Analyses were done by intention to treat; the non-inferiority hazard ratio was set at 1.5. The trial was stopped after randomization of 4576 patients (2283 to receive idraparinux, 2293 to receive warfarin) and a mean follow-up period of 10.7 (SD 5.4) months because of excess clinically relevant bleeding with idraparinux (346 cases Vs 226 cases; 19.7 Vs 11.3 per 100 patient-years; $p < 0.0001$). There were 21 intracranial bleeds with idraparinux and 9 with vitamin K antagonists (1.1 Vs 0.4 per 100 patient-years; $p = 0.014$); elderly patients and those with renal impairment were at greater risk of such complications. There were 18 cases of thromboembolism with idraparinux and 27 cases with vitamin K antagonists (0.9 Vs 1.3 per 100 patient-years; hazard ratio 0.71, 95% CI 0.39-1.30; $p = 0.007$), satisfying the non-inferiority criterion. There were 62 deaths with idraparinux and 61 with vitamin K antagonists (3.2 Vs 2.9 per 100 patient-years; $p = 0.49$). The study found patients with atrial fibrillation at risk for thromboembolism, long-term treatment with idraparinux was as efficacious as warfarin, however; it caused significantly more bleeding especially intracranial bleeding.

Stroke and neuroprotectants: Unfortunately at the present time there are no readily available neuroprotective agents in post-stroke to help decrease brain tissue (penumbral) injury and improve functional recovery in the short and long-term. There were 2 trials which studied the efficacy of 2 neuroprotectants after an ischemic stroke (Amadeus *et al.*, 2008; Weir *et al.*, 2003).

Title: DP-b99, a membrane-activated metal ion chelator, as neuroprotective therapy in ischemic stroke.

DP-b99, a chelator of zinc and calcium ions has been found to have neuroprotective properties in animal stroke models (Krakovsky *et al.*, 2001). This multi-center, double-blind placebo-controlled randomized phase II trial assessed the safety and potential protective effects of DP-b99 in patients with acute ischemic stroke (Diener *et al.*, 2008). Patients with signs of cortical involvement and a National Institutes of Health Stroke Scale (NIHSS) score of 7-20 received a 4 day course of intravenous $1 \text{ mg kg}^{-1} \text{ day}^{-1}$ DP-b99 ($n = 75$) or placebo ($n = 75$) within 1-9 h of an ischemic stroke. Treatment with recombinant tissue plasminogen activator was not permitted. The baseline NIHSS score was 72 for DP-b99 Vs 75 for placebo-treated patients, in the intent-to-treat cohort was (mean \pm SD) 12.2 ± 4.0 and 12.6 ± 3.3 , the time to needle (mean \pm SD) was $6:36 \pm 1:47$ and $6:28 \pm 1:33$ h and the age was 73.3 ± 9.9 and 72.0 ± 9.6 years. The 90-day median change from baseline (the primary end point) was -6.0 and -5.0 NIHSS points in the DP-b99 and placebo groups (non-significant). At 90 days, a significantly better outcome was in the DP-b99 compared with the placebo group (modified Rankin scale score of 0, 1, or same as prestroke): 30.6 and 16.0%, respectively ($p = 0.05$). The recovery rate was unaffected by the time to needle. Further analyses showed that the 90 day median change from baseline in patients with an entry NIHSS score was 8.0 and 5.0 points in the DP-b99 and placebo groups ($p = 0.03$). No major differences in mortality rate, causes of death, adverse events, safety laboratory tests and ECG parameters were found between the 2 groups. This was a negative study as the primary end point of change in NIHSS score from baseline to 90 days was the same between the 2 groups. However, secondary end points demonstrated a significantly improved 90 day recovery rate with treatment with DP-b99 compared with placebo. No major adverse events were identified.

Title: Allopurinol use yields potentially beneficial effects on inflammatory indices in those with recent ischemic stroke: A randomized, double-blind, placebo-controlled trial.

Elevated serum Uric Acid (UA) level is associated with poor outcome and increased risk of stroke recurrence (Weir *et al.*, 2003). Allopurinol, a xanthine oxidase inhibitor lowers uric acid and also attenuates expression of inflammatory adhesion molecules in murine models, reduces oxidative stress in the vasculature and improves endothelial function (Dawson *et al.*, 2007). This study sought to investigate

whether allopurinol can alter expression of inflammatory markers after acute ischemic stroke. This randomized, double-blind, placebo-controlled trial investigated the safety, tolerability and effect of 6 weeks' treatment with high- (300 mg once a day) or low- (100 mg once a day) dose allopurinol on levels of UA and circulating inflammatory markers (Intercellular Adhesion Molecule-1 [ICAM-1], C-Reactive Protein (CRP) and interleukin-6 [IL-6]) after ischemic stroke (Muir *et al.*, 2008). Fifty patients with acute ischemic stroke were enrolled (17, 17 and 16 in the high, low and placebo groups, respectively). The mean (\pm SD) age was 70 (\pm 13) years. Groups had similar characteristics at baseline. UA levels were significantly reduced at both 7 days and 6 weeks in the high-dose group (by 0.14 mmol L⁻¹ at 6 weeks, $p = 0.002$). ICAM-1 concentration (ng mL⁻¹) rose by 51.2 in the placebo group, by 10.6 in the low-dose allopurinol group, but fell in the high-dose group (by 2.6; difference between groups $p = 0.012$, Kruskal-Wallis test). The degree of change in CRP and IL-6 levels did not reach statistical significance between the 3 groups. There were no serious adverse events. Thus Allopurinol treatment was well tolerated and high dose lowered UA and ICAM-1 levels after stroke. This study suggests the need of larger future trials to evaluate the role of allopurinol as a neuroprotectant after ischemic stroke and its effect on clinical recovery.

Antiplatelets and stroke: Recurrent stroke is a frequent, disabling event after ischemic stroke. Antiplatelet agents especially aspirin has been the mainstay of secondary prophylaxis after an ischemic stroke because it is effective and cheap. Two studies compared the efficacy and safety profile of 2 different antiplatelet agents to aspirin (Dawson *et al.*, 2007; Muir *et al.*, 2008).

Title: Sarpogrelate-Aspirin Comparative Clinical Study for Efficacy and Safety in Secondary Prevention of Cerebral Infarction (S-ACCESS): A randomized, double-blind, aspirin-controlled trial.

Sarpogrelate, a selective inhibitor of 5-hydroxytryptamine receptors, is widely used in Japan, China and South Korea to treat patients with peripheral arterial disease due to its antiplatelet and vasodilator effect. This study compared the efficacy and safety of sarpogrelate to aspirin in Japanese ischemic stroke patients (Shinohara *et al.*, 2008). A total of 1510 patients with recent cerebral infarction (1 week to 6 months after onset) were randomly assigned to receive either sarpogrelate 100 mg TID ($n = 747$) or aspirin 81 mg day⁻¹ ($n = 752$), with a mean follow-up of

1.59 years. The primary efficacy end point was to demonstrate the noninferiority of sarpogrelate with respect to aspirin for recurrence of cerebral infarction. Cerebral infarction recurred in 72 patients (6.09% year⁻¹) in the sarpogrelate and in 58 (4.86% year⁻¹) in the aspirin group (hazard ratio = 1.25; 95% CI, 0.89-1.77; $p = 0.19$). Serious vascular events occurred in 90 (7.61% year⁻¹) and in 85 (7.12% year⁻¹) patients, respectively (hazard ratio = 1.07; 95% CI, 0.80-1.44; $p = 0.65$). The bleeding events were 89 (11.9%) and 131 (17.3%) respectively for sarpogrelate and aspirin ($p < 0.01$). In this study sarpogrelate was noninferior to aspirin for prevention of recurrence of cerebral infarction and had significantly fewer bleeding events than aspirin.

Title: Aspirin and Extended-Release Dipyridamole versus Clopidogrel for Recurrent Stroke. (Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) Study Group).

This study compared the efficacy and safety of two antiplatelet regimens-aspirin plus extended-release dipyridamole (ASA-ERDP) versus clopidogrel, in a double-blind, 2-by-2 factorial trial (Sacco *et al.*, 2008). Patients were randomly assigned to receive 25 mg of aspirin plus 200 mg of extended-release dipyridamole twice daily or 75 mg of clopidogrel daily. The primary outcome was first recurrence of stroke. The secondary outcome was a composite of stroke, myocardial infarction, or death from vascular causes. A total of 20,332 patients were followed for a mean of 2.5 years. Recurrent stroke occurred in 916 patients (9.0%) receiving ASA-ERDP and in 898 patients (8.8%) receiving clopidogrel (hazard ratio, 1.01; 95% Confidence Interval (CI), 0.92-1.11). The secondary outcome occurred in 1333 patients (13.1%) in each group (hazard ratio for ASA-ERDP, 0.99; 95% CI, 0.92-1.07). There were more major hemorrhagic events among ASA-ERDP (419 [4.1%]) than among clopidogrel recipients (365 [3.6%]) (hazard ratio, 1.15; 95% CI, 1.00-1.32), including intracranial hemorrhage (hazard ratio, 1.42; 95% CI, 1.11-1.83). The net risk of recurrent stroke or major hemorrhagic event was similar in the two groups (1194 ASA-ERDP [11.7%], Vs 1156 clopidogrel recipients [11.4%]; hazard ratio, 1.03; 95% CI, 0.95-1.11). This trial did not meet the predefined statistical criteria for noninferiority (margin of 1.075) and showed similar rates of recurrent stroke for the two antiplatelet agents.

Stroke and hyperglycaemia:

Title: Treatment of Hyperglycemia in Ischemic Stroke (THIS): A randomized pilot trial. Hyperglycemia

during acute cerebral infarction has been shown to worsen brain injury (Baird *et al.*, 2003). This study tested the feasibility and tolerability of aggressive hyperglycemia correction with intravenous insulin compared with usual care during acute cerebral infarction (Bruno *et al.*, 2008). This randomized, multicenter, blinded pilot trial was conducted in patients with cerebral infarction within 12 h after onset, with a baseline glucose value ≥ 8.3 mmol L⁻¹ (≥ 150 mg dL⁻¹) and a National Institutes of Health Stroke Scale (NIHSS) score of 3-22. Patients were randomized 2:1 to aggressive treatment with continuous intravenous insulin or subcutaneous insulin QID as needed (usual care). The target glucose levels were < 7.2 mmol L⁻¹ (< 130 mg dL⁻¹) in the aggressive-treatment group and < 11.1 mmol L⁻¹ (< 200 mg dL⁻¹) in the usual-care group. Glucose was monitored every 1-2 h and the protocol treatments continued for up to 72 h. Final clinical outcomes were assessed at 3 months. Thirty one patients were randomized to aggressive treatment and 15 to usual care. All of the patients in the aggressive-treatment group and 11 (73%) in the usual-care group had diabetes ($p = 0.008$). Glucose levels were significantly lower in the aggressive-treatment group throughout protocol treatment (7.4 Vs 10.5 mmol L⁻¹ (133 Vs 190 mg dL⁻¹), $p < 0.001$). Hypoglycemia < 3.3 mmol L⁻¹ (< 60 mg dL⁻¹) occurred only in the aggressive-treatment group (11 patients, (35%), 4 (13%) of whom had brief autonomic symptoms and 1 patient had cognitive-slowness which resolved with 25 mL of 50% dextrose administration. The clinical outcomes (modified Rankin scale, Barthel Index, NIHSS and Stroke Specific Quality of life Scale) were similar between the treatment groups. The authors of the study concluded that aggressive intravenous insulin corrected hyperglycemia during acute cerebral infarction was feasible without major adverse events, however; it is of questionable clinical efficacy. This trial like the recent GIST-UK study showed no significant clinical benefit is achieved in aggressively managing hyperglycaemia (Gray *et al.*, 2007).

Antibiotic prophylaxis in acute stroke: Fever after stroke is a strong predictor for a poor outcome with infections as the most common cause. Infection is a leading cause of death acutely post-stroke.

Title: The Mannheim Infection in Stroke Study (MISS).

This pilot study evaluated the effects of prophylactic antibiotic therapy on the incidence and degree of fever after acute ischemic stroke. In this randomized study patients with ischemic stroke were enrolled within 24 h from clinical onset who were

severely disabled (modified Rankin Scale (mRS) score > 3) with no infection (Schwarz *et al.*, 2008). Interventions included prophylactic mezlocillin plus sulbactam (2 g plus 1 g IV over 20 min every 8 h for 4 days) or conventional management. Over 10 days, body temperature was continuously monitored and the presence of infection was daily assessed. Primary end points were incidence and degree of fever; secondary end points included rate of infection and clinical outcome. There were 60 patients with a mean age of 75 years and median National Institutes of Health Stroke Scale score of 16. Over the first 3 days, patients in the intervention group had lower mean body temperatures and lower daily peak temperatures ($p < 0.05$). Throughout the 10 days observation period, 15 of 30 patients in the intervention group Vs 27 of 30 patients in the conventionally treated group developed an infection ($p < 0.05$). Mean interval until the diagnosis of infection was 5.1 days in the intervention group and 3.3 days in the control group ($p < 0.05$). Clinical outcome (defined by the mRS) favored patients with prophylactic antibiotic therapy ($p = 0.01$). This study concluded that in patients with acute severe stroke, prophylactic administration of mezlocillin plus sulbactam over 4 days decreased body temperature, lowered the rate of infection and was associated with a better clinical outcome.

Title: Preventive ANTibacterial THERapy in acute Ischemic Stroke (PANTHERIS): A randomized controlled trial.

In a mouse model, preventive antibacterial therapy with moxifloxacin prevented the development of post-stroke infections, reduced mortality and improved neurological outcome significantly. This study investigated whether this approach was effective in stroke patients. In this randomized, double-blind, placebo-controlled trial in 80 patients with severe, Non-Lacunar, Ischemic Stroke (NIHSS > 11) in the Middle Cerebral Artery (MCA) territory, patients received either intravenous moxifloxacin (400 mg daily) or placebo for 5 days starting within 36 h after stroke onset. Primary endpoint was infection within 11 days. Secondary endpoints included neurological outcome, survival, development of stroke-induced immunodepression and induction of bacterial resistance. On intention-to treat analysis (79 patients), the infection rate at day 11 in the moxifloxacin treated group was 15.4% compared to 32.5% in the placebo treated group ($p = 0.114$). On per protocol analysis ($n = 66$), moxifloxacin significantly reduced infection rate from 41.9-17.1% ($p = 0.032$). Stroke associated infections were associated with a lower survival rate. In

this study, neurological outcome and survival were not influenced by treatment with moxifloxacin. On logistic regression analysis, treatment arm as well as the interaction between treatment arm and monocytic HLA-DR expression (a marker for immunodepression) at day 1 after stroke onset was independently and highly predictive for post-stroke infections. This study suggests that preventive administration of moxifloxacin was superior in reducing infections after severe non-lacunar ischemic stroke compared to placebo. In addition, the results emphasize the pivotal role of immunodepression in developing post-stroke infections.

Post-stroke depression:

Title: Escitalopram and problem-solving therapy for prevention of poststroke depression: a randomized controlled trial.

Depression occurs in a third of patients post stroke (Goodwin and Devanand, 2008; Rabadi *et al.*, 2008). Since poststroke depression has been associated with both impaired recovery in activities of daily living and increased mortality, prevention of depression represents an important goal. This study tried to determine whether treatment with escitalopram or problem-solving therapy in non-depressed stroke patients during their first year following acute stroke will decrease the number of depression cases compared to placebo (Robinson *et al.*, 2008). In this multi-center randomized, double-blind, placebo-controlled trial of 176 non-depressed patients conducted within 3 months following acute stroke there were 3 groups: Escitalopram (n = 59), placebo (n = 58) and a nonblinded problem-solving therapy group (n = 59). The main outcome measure was the development of major or minor poststroke depression based on symptoms elicited by the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) (DSM-IV) and the diagnostic criteria from DSM-IV for depression due to stroke with major depressive-like episode or minor depression (i.e., research criteria). Patients in the placebo group developed more depression than individuals who received escitalopram (11 major and 2 minor cases of depression [22.4%] Vs 3 major and 2 minor cases of depression [8.5%], adjusted Hazard Ratio (HR), 4.5; 95% Confidence Interval (CI), 2.4-8.2; p<0.001) and individuals who received problem-solving therapy (5 major and 2 minor cases of depression [11.9%], adjusted HR, 2.2; 95% CI, 1.4-3.5; p<0.001). These results were unchanged after accounting for confounders such as age, sex, treatment site, prior history of mood disorders and severity of stroke impairment. On an intention-to-treat basis, which

assumed that all 27 patients who did not start randomized treatment would develop depression and controlling for prior history of mood disorders, escitalopram was superior to placebo (23.1% Vs 34.5%; adjusted HR, 2.2; 95% CI, 1.2-3.9; p = 0.007), while problem-solving therapy was no different than placebo (30.5 Vs 34.5%; adjusted HR, 1.1; 95% CI, 0.8-1.5; p = 0.051). Adverse events, including all-cause hospitalizations, nausea and adverse effects associated with escitalopram were not different between the 3 groups. In this study of non-depressed patients with recent stroke, the use of escitalopram or problem-solving therapy significantly lowered the incidence of depression over 12 months of treatment compared with placebo, but problem-solving therapy did not achieve significant results over placebo on the intention-to-treat method of analysis.

Vascular dementia:

Title: Donepezil in patients with subcortical vascular cognitive impairment: a randomized double-blind trial in CADASIL.

Vascular cognitive impairment may be due to cholinergic deficits. Trials of cholinesterase inhibitors in patients with vascular dementia have been difficult because of the heterogeneous disease mechanisms and overlap between vascular and Alzheimer's Disease (AD) pathology in the age-group recruited. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy (CADASIL), a genetic form of subcortical ischemic vascular dementia represents a homogeneous disease process and because of CADASIL's early onset co-morbid AD pathology is rare. In this multicentre, 18 week, placebo-controlled, double-blind, randomized parallel-group trial determined whether the cholinesterase inhibitor donepezil improved cognition in patients with CADASIL (Dichgans *et al.*, 2008). One hundred and sixty eight patients with CADASIL (mean age 54.8 years) were randomly assigned to either 10 mg donepezil day⁻¹ (n = 86) or placebo (n = 82) by a computer-generated protocol. Inclusion criteria included a Mini-Mental State Examination (MMSE) score of 10-27 or a Trail Making Test (TMT) B time score at least 1.5 SD below the mean, after adjustment for age and education. The primary endpoint was change from baseline in the score on the vascular AD assessment scale cognitive subscale (V-ADAS-cog) at 18 weeks. Secondary endpoints included scores on the ADAS-cog, MMSE, TMT A time and B time, Stroop, executive interview-25 (EXIT-25), CLOX, disability assessment for dementia and sum of boxes of the clinical dementia rating scale. Analysis was by

intention to treat. There was no significant difference between donepezil (n = 84) and placebo (n = 77) in the primary endpoint (V-ADAS-cog score). The least-squares mean change from baseline score was -0.81 (SE 0.59) in the placebo and -0.85 (SE 0.57) in the donepezil group (p = 0.96). There was a significant treatment effect favoring donepezil on the following secondary outcomes: TMT B time (p = 0.02), TMT A time (p = 0.015) and EXIT-25 (p = 0.02). Ten donepezil-treated patients discontinued treatment due to adverse events compared to seven placebo-treated patients. Thus donepezil had no effect on the primary endpoint (the V-ADAS-cog score) in CADASIL patients with cognitive impairment. Improvements were noted on several measures of executive function but the clinical relevance of these findings is unclear.

Stroke and subarachnoid hemorrhage: Cerebral infarction secondary to vasospasm after an aneurysmal rupture is a dreaded complication. It is responsible for poor functional outcome in these patients. Three studies tried to address how best to prevent this delayed cerebral artery vasospasm (Chou *et al.*, 2008; Macdonald *et al.*, 2008; Ryttefors *et al.*, 2008).

Title: A randomized, double-blind, placebo-controlled pilot study of simvastatin in aneurysmal subarachnoid hemorrhage.

Studies suggest statins ameliorate aneurysmal Subarachnoid Hemorrhage (SAH)-induced cerebral vasospasm and ischemic complications. This study tested the safety and feasibility of simvastatin 80 mg day⁻¹ for vasospasm prevention in SAH patients (Chou *et al.*, 2008). Thirty-nine statin-naïve Fisher grade 3 SAH subjects were double-blind randomized to receive simvastatin 80 mg day⁻¹ (n = 19) or placebo (n = 20), stratified by Hunt and Hess grade. Primary end points were death and drug morbidity. Angiographically-confirmed vasospasm occurred in 8/20 placebo and 5/19 simvastatin-treated subjects. Vasospasm-related ischemic infarcts developed in 5/20 placebo and 2/19 simvastatin-treated subjects. Death was 3/20 in the placebo and 0/19 in the simvastatin group. Study drug was withdrawn in 1 subject in each treatment group for reversible liver enzyme or creatine phosphokinase elevation. Simvastatin was found to be safe and feasible after SAH in preventing vasospasm-related delayed cerebral ischemia. However, a larger study is needed to test its efficacy in preventing SAH-induced vasospasm.

Title: Clazosentan to Overcome Neurological Ischemia and Infarction Occurring after Subarachnoid

Hemorrhage (CONSCIOUS-1): Randomized, double-blind, placebo-controlled phase 2 dose-finding trial.

This randomized, double-blind, placebo-controlled, dose-finding study assessed efficacy and safety of 1, 5 and 15 mg h⁻¹ intravenous clazosentan, an endothelin receptor antagonist, in preventing vasospasm after aneurysmal subarachnoid hemorrhage (Macdonald *et al.*, 2008). Four hundred and thirteen patients were randomized to placebo or clazosentan within 56 h and continued up to 14 days after initiation of treatment. The primary end point was moderate or severe angiographic vasospasm based on centrally read, blinded evaluation of digital subtraction angiography at baseline and 7-11 days post-subarachnoid hemorrhage. The secondary end point, included all-cause mortality, new cerebral infarct from any cause, delayed ischemic neurological deficit due to vasospasm, or use of rescue therapy. Clinical outcome was assessed by the extended Glasgow Outcome Scale at 12 weeks. Moderate or severe vasospasm was reduced in a dose-dependent fashion from 66% in the placebo group to 23% in the 15 mg h⁻¹ clazosentan group (risk reduction, 65; 95% CI, 47-78%; p<0.0001). No significant effects were seen on secondary end points. On post hoc analysis for cerebral infarcts and delayed ischemic neurological deficit due to vasospasm on central review a trend favoring clazosentan (37, 28 and 29% in the 1, 5 and 15 mg h⁻¹ groups versus 39% in the placebo group, non-significant) was seen. Clazosentan had increased rates of pulmonary complications, hypotension and anemia. The study concluded that clazosentan significantly decreased moderate and severe vasospasm in a dose-dependent manner and there was a trend for reduction in vasospasm-related morbidity/mortality in patients with aneurysmal subarachnoid hemorrhage when centrally assessed. Overall, the adverse effects were not serious.

Title: Effect of prophylactic transluminal balloon angioplasty on cerebral vasospasm and outcome in patients with Fisher grade III Subarachnoid Hemorrhage (SAH): Results of a phase II multicenter, randomized, clinical trial.

Prophylactic Transluminal Balloon Angioplasty (pTBA) has been shown to prevent delayed ischemic neurological deficit in a pilot study (Muizelaar *et al.*, 1999). In this phase II multicenter randomized clinical trial of 170 patients with Fisher Grade III Subarachnoid Hemorrhage (SAH), 85 patients were randomized to the treatment group and underwent pTBA within 96 h after SAH (Zwienenberg-Lee *et al.*, 2008). The primary outcome measures were: Glasgow Outcome Score (GOS) at 3 months, development of Delayed Ischemic Neurological Deficit (DIND), occurrence of

Transcranial Doppler (TCD) vasospasm and length of stay in the ICU and hospital. Overall pTBA resulted in an absolute risk reduction of 5.9% and a relative risk reduction of 10.4% unfavorable outcome ($p = 0.54$). Good grade patients had absolute and relative risk reductions of respectively 9.5 and 29.4% ($p = 0.73$). The incidence of DIND was lower in the pTBA group ($p = 0.30$) and fewer patients required therapeutic angioplasty to treat DIND ($p = 0.03$). Length of stay in ICU and hospital was similar in both treated and the control groups. 4 patients had a procedure-related vessel perforation, of which 3 patients died. This trial was unsuccessful as defined by the primary end point (GOS). Fewer patients developed vasospasm after treatment with pTBA and significantly decreased the need for therapeutic angioplasty. Thus pTBA was unable to improve the poor outcome of patients with Fisher grade III SAH.

Stroke and surgery:

Title: International subarachnoid aneurysm trial of neurosurgical clipping versus endovascular coiling: Subgroup analysis of 278 elderly patients.

It is often thought that elderly patients in particular would benefit from endovascular aneurysm treatment. This study compared the efficacy and safety of endovascular coiling (EVT) with neurosurgical clipping (NST) in the subgroup of elderly SAH patients in the

International Subarachnoid Aneurysm Trial (ISAT)^[36]. A cohort 278 SAH patients, 65 years or older, were enrolled in the ISAT. The patients were randomly allocated to EVT ($n = 138$) or NST ($n = 140$). The primary outcome was the proportion of patients with a modified Rankin scale score of 0-2 (independent survival) at 1 year after the SAH. The rates of procedural complications and adverse events were also recorded. Of the patients allocated to EVT 83 of 138 (60.1%) were independent compared to 78 of 140 (56.1%) allocated NST (NS). Of the patients with internal carotid and posterior communicating artery aneurysms allocated to EVT 36 of 50 (72.0%) were independent compared to 26 of 50 (52.0%) allocated NST ($p < 0.05$). Of the patients with middle cerebral artery aneurysms allocated to EVT 10 of 22 (45.5%) were independent compared to 13 of 15 (86.7%) allocated NST ($p < 0.05$). The epilepsy frequency was 0.7% in the EVT compared to 12.9% in the NST group ($p < 0.001$). The study concluded that in good grade elderly SAH patients with small anterior circulation aneurysms, EVT is probably the favored treatment for ruptured internal carotid and posterior communicating artery aneurysms, while elderly patients with ruptured middle cerebral artery aneurysms benefit from NST. EVT results in a lower epilepsy frequency than NST.

A summary of these RCTs in acute Stroke in 2008 is presented in Table 1.

Table 1: Summary of the randomized control trials undertaken in stroke in 2008

| References | Time to randomization post-stroke | Set-up | Sample size | Invention | Main findings |
|--------------------------------|---|-----------------------|---|--|--|
| Thrombolytic and stroke | | | | | |
| Adams <i>et al.</i> (2008) | On awakening (<3 h) Vs mainly within 5 h of acute is chemic stroke VS between 5-6 h of an acute ischemic stroke | Acute hospitalization | Planned enrollment 1800 patients; Enrolled 801. Abciximab = 403 Placebo = 398 On awakening: A = 22, p = 21 within 5 h: A = 221, p = 218 between 5-6: A = 160, p = 159 | Intravenous abciximab: Bolus 0.25 mg kg ⁻¹ followed by 12 h infusion (0.125 µgm kg ⁻¹ min ⁻¹ to max 10 µgm min ⁻¹ VS placebo | The trial was halted after having enrolled 808 patients in all cohorts by the independent safety and efficacy monitoring board as risk outweighed the benefit for abciximab. Within 5 days of enrollment, 5.5% of abciximab-treated and 0.5% of placebo-treated patients had symptomatic or fatal intracranial hemorrhage ($p = 0.002$). The trial did not show improvement in the primary outcome measure with abciximab. |
| Davis <i>et al.</i> (2008) | 3-6 h of an acute ischemic stroke | Acute hospitalization | 101; Alteplase = 52 Placebo = 49 | IV Alteplase 0.9 mg kg ⁻¹ to max 90 mg; 10% as bolus and reminder over 1 h Vs placebo | The mean infarct growth was 1.24 with alteplase and 1.78 with placebo (ratio 0.69, $p = 0.239$); the median relative infarct growth was 1.18 with alteplase and 1.79 with placebo (ratio 0.66, $p = 0.054$). With alteplase reperfusion was commonly seen with less infarct growth ($p = 0.001$), better neurological outcome ($p < 0.0001$) and better functional outcome ($p = 0.010$). |
| Hacke <i>et al.</i> (2008) | Between 3 and 4.5 h after the onset of a stroke | Acute hospitalization | 821; Alteplase = 418 Placebo = 403 | IV Alteplase 0.9 mg kg ⁻¹ to max 90 mg; 10% as bolus and reminder over 1 h Vs placebo | Patients with alteplase had a favorable outcome than with placebo (52.4% Vs 45.2%; $p = 0.04$) on the mRS score of 0 to 1. The incidence of intracranial hemorrhage was higher with alteplase than with placebo (27.0% VS 17.6%; $p = 0.001$; for symptomatic intracranial hemorrhage, 2.4% Vs 0.2%; $p = 0.008$). Mortality did not differ between the two groups (7.7 and 8.4%, respectively; $p = 0.68$) |

Table 1: Continued

| | | | | | |
|---------------------------------------|---|--|---|---|---|
| Christou <i>et al.</i> (2002) | Within 3 h of an acute ischemic stroke | Acute hospitalization | 94; Tier 1 = 40 Tier 2 = 54 the combine group of the 2 dose tiers (n = 69) t-PA group = 25 | Low-dose t-PA (tier 1 = 0.3 mg kg ⁻¹ , tier 2 = 0.45 mg kg ⁻¹) plus eptifibatide (75 mug kg ⁻¹ bolus followed by 0.75 mug kg ⁻¹ per min infusion for 2 h) Vs standard-dose rt-PA (0.9 mg kg ⁻¹). | The study was halted by the independent data safety monitoring board because on their review the safety profile of combination therapy (reduced-dose t-PA plus eptifibatide) to be safe in acute ischemic stroke trials. However, there was a trend toward increased clinical efficacy in the standard-dose t-PA compared to the combination treatment group. |
| Pancioli <i>et al.</i> (2008) | Within 3 h of an acute stroke | Acute hospitalization | 37; Doppler U. Sound = 19 Control = 18 | Effectiveness of sonothrombolysis with 1.8 Hz doppler ultrasound for 1 h transcranially | Recanalization (complete or partial) after 1 h occurred in 57.9% of the US and 22.2% of the control group (p = 0.04). After 90 days, 4 subjects from the US had a modified rankin score ≤1 (none from the control group; p = 0.106) and 8 had a Barthel Index ≥95 (none from the control group; p = 0.003). Three subjects from the US (15.8%) and one (5.6%) in the control group (p = 0.60) developed symptomatic intracranial bleed. |
| Alexandrov <i>et al.</i> (2004) | Within 3 h of their acute stroke | Acute hospitalization | 15; Experimental group tPA + TCD + 2.8 mL μS) = 12 Control group (tPA + TCD) = 3 | Ultrasound activated perflutren-lipid microspheres (μS) induced recanalization with IV tissue plasminogen activator (t-PA) Vs t-PA only | Perflutren μS was able to reach beyond intracranial occlusions, achieve a higher recanalization rate (42%) with no increase in symptomatic intracraia hemorrhage after systemic thrombolysis. |
| Hypertension and stroke | | | | | |
| Alexandrov <i>et al.</i> (2008) | Patients ≥ 80 years with sustained SBP > 160 mmHg | Outpatient setting | 3845; Treatment = 1933 Placebo = 1912 | Indapamide SR 1.5 mg with or without perindopril (2mg or 4 mg) daily or placebo | At 2 years, the mean BP sitting was 15.0/6.1 mm Hg lower in the active than in the placebo group. In an intention-to-treat analysis, active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (p = 0.06). Reduction in the rate of death was: 39% from stroke (p = 0.05), 21% from any cause (p = 0.02), 23% from cardiovascular causes (p = 0.06). A 64% reduction in the rate of heart failure (p<0.001). Fewer adverse events were reported in the active-treatment (358, Vs 448 in the placebo group; p = 0.001). |
| Chitravas <i>et al.</i> (2007) | ≤ 15 days of an acute ischemic stroke | Acute hospital followed by out-patient setting | 20,332; Telmisartan = 10,146) Placebo = 10,186 | Telmisartan 80 mg daily Vs placebo | During a mean follow-up of 2.5 years, the mean BP was 3.8/2.0 mm Hg lower in the telmisartan than in the placebo group. A total of 880 patients (8.7%) in the telmisartan and 934 patients (9.2%) in the placebo group had a subsequent stroke (p = 0.23). Major cardiovascular events occurred in 1367 patients (13.5%) in the telmisartan and 1463 patients (14.4%) in the placebo group (p = 0.11). New-onset diabetes occurred in 1.7% of the telmisartan and 2.1% of the placebo group (p = 0.10). |
| Atrial fibrillation and stroke | | | | | |
| Beckett <i>et al.</i> (2008) | Patients with atrial fibrillation | Out-patient setting | 4576; Idraparinux = 2283 Warfarin = 2293 | Idraparinux S/c 2.5 mg weekly Vs warfarin) (INR 2-3 | The trial was stopped after a mean follow-up period of 10.7 (SD 5.4) months because of excess clinically relevant bleeding with idraparinux (346 Vs 226 cases; p<0.0001). There were 21 intracranial bleeding with idraparinux and 9 with vitamin K antagonists (p = 0.014) sp. in elderly patients and those with renal impairment were at greatest risk. There were 18 cases of thromboembolism with idraparinux and 27 cases with vitamin K antagonists (p = 0.007) and 62 deaths with idraparinux and 61 with vitamin K antagonists (p = 0.49). |
| Neuroprotection and stroke | | | | | |
| Amadeus <i>et al.</i> (2008) | ≤9 h of ischemic stroke | Acute hospitalization | 150; DP-b99 = 75 Placebo = 75 | DP-b99 intravenous 1 mg kg ⁻¹ per day as a 2 h infusion for 4 days VS placebo | The 90-day median change from baseline was similar for NIHSS score for the 2 groups. At 90 days, a significantly better outcome was in the DP-b99 on the modified Rankin scale score of 0, 1, or same as prestroke (p = 0.05). The recovery rate was unaffected by the time to needle. |

Table 1: Continued

| | | | | | |
|---|--|---|--|--|---|
| Weir <i>et al.</i> (2003) | Within 3 days of an acute ischemic stroke | Acute hospitalization | 50; Allopurinol high dose = 17 Allopurinol low dose = 17 Placebo = 16 | Treatment with high -300 mg once a day or low -100 mg once a day dose of Allopurinol Vs placebo | Uric acid levels were significantly reduced at 7 days and 6 weeks in the high-dose group (by 0.14 mmol L ⁻¹ at 6 weeks, p = 0.002). ICAM-1 concentration (ng mL ⁻¹) rose by 51.2 in the placebo, by 10.6 in the low-dose Allopurinol, but fell in the high-dose group (by 2.6; p = 0.012). The degree of change in CRP and did not reach statistical significance between IL-6 levels the 3 groups. There were no serious adverse events. |
| Antiplatelets and stroke | | | | | |
| Dawson <i>et al.</i> (2007) | ≤ 24 weeks after an acute ischemic stroke | Out-patient setting | 1510; Sarpogrelate = 752 Aspirin = 758 | Sarpogrelate 100 mg TID Vs aspirin 81 mg day ⁻¹ | Cerebral infarction recurred in 72 patients in the sarpogrelate and in 58 in the aspirin group (p = 0.19). Serious vascular events occurred in 90 and in 85 patients respectively (p = 0.65). The incidence of bleeding events were 89 and 131 respectively (p<0.01). |
| Muir <i>et al.</i> (2008) | Within 3 months of an acute ischemic stroke | Acute hospitalization followed by out-patient setting | 20,332; ASA-ERDP = 10,181 Clopidogrel = 10,151 | 25 mg of aspirin plus 200 mg of extended-release dipyridamole twice daily (ASA-ERDP) VS 75 mg of clopidogrel daily | Recurrent stroke occurred in 916 patients (9.0%) receiving ASA-ERDP and in 898 patients (8.8%) receiving clopidogrel. The secondary outcome occurred in 1333 patients (13.1%) in each group. There were more major hemorrhagic events in ASA-ERDP (419 [4.1%]) than in the clopidogrel recipients (365 [3.6%]), including intracranial emorrhage. |
| Hyperglycaemia and stroke | | | | | |
| Sacco <i>et al.</i> (2008) | Within 12 h of an acute ischemic stroke | Acute hospitalization | 46; Aggressive = 31 Usual care = 15 | Aggressive treatment with continuous IV insulin Vs Usual care with subcutaneous insulin QID as needed | Glucose levels were significantly lower in the aggressive-treatment group throughout protocol treatment (7.4 Vs 10.5 mmol L ⁻¹ [133 Vs 190 mg dL ⁻¹], p<0.001). Hypoglycemia <3.3 mmol L ⁻¹ (<60 mg dL ⁻¹) occurred only in the aggressive-treatment group (11 patients, 35%). The clinical outcomes (modified Rankin scale, Barthel index, NIHSS and stroke specific quality of life Scale) were similar between the treatment groups. |
| Antibiotic prophylaxis in acute stroke | | | | | |
| Bruno <i>et al.</i> (2008) | Within 24 h of ischemic stroke | Acute hospitalization | 60; Intervention = 30 Conventional = 30 | Mezlocillin + sulbactam (2 g +1 g IV infusion over 20 min every 8 h for 4 days) VS conventional management. | In the 10 days observation period, 15 of 30 patients in the intervention Vs 27 of 30 patients in the conventionally treated group developed an infection (p<0.05). Mean interval until the diagnosis of infection was 5.1 days in the intervention group and 3.3 days in the control group (p<0.05). Clinical outcome (modified rankin scale) favored patients with prophylactic therapy (p = 0.01). |
| Schwarz <i>et al.</i> (2008) | Within 36 h of ischemic stroke | Acute hospitalization | 80; Moxifloxacin = 40 Placebo = 40 | Moxifloxacin 400 mg daily or placebo for 5 days | On intention-to-treat analysis (79 patients), the infection rate at day 11 in the moxifloxacin was 15.4% compared to 32.5% in the placebo group (p = 0.114). On per-protocol-analysis (n = 66), moxifloxacin significantly reduced infection rate from 41.9% to 17.1% (p = 0.032). |
| Post-stroke depression | | | | | |
| Harms <i>et al.</i> (2008) | Within 3-months of their acute ischemic/hemorrhagic stroke | Out-patient setting | 176; Escitalopram = 59 Problem-solving therapy = 59 Placebo = 58 | Escitalopram (10 mg for pts < 65 years and 5 mg for pts > 65 years) VS problem-solving therapy VS control | Patients in the placebo group had more depression than individuals who received escitalopram (11 major and 2 minor cases of depression [22.4%] Vs 3 major and 2 minor cases of depression [8.5%], (p<0.001) and individuals who received problem-solving therapy (5 major and 2 minor cases of depression [11.9%], (p<0.001). On an intention-to-treat basis, escitalopram was superior to placebo (23.1% Vs 34.5%; p = 0.007), while problem-solving therapy was no different than placebo (30.5% Vs 34.5%; p = 0.51). |
| Vascular dementia | | | | | |
| Goodwin and Devanand (2008) | Patients with CADASIL syndrome | Out-patient setting | 168; Donepezil = 86 Placebo = 82 | Donepezil 10 mg daily Vs placebo for 18 weeks | There was no significant difference between donepezil (n = 84) and placebo (n = 77) in the primary endpoint (V-ADAS-cog) (p = 0.96). There was a significant treatment effect favoring donepezil on the secondary outcomes: TMT B time (p = 0.02), TMT A time (p = 0.015) and EXIT-25 (p = 0.02). |

Table 1: Continued

| Subarachnoid Hemorrhage (SAH) and stroke | | | | | |
|---|---|-----------------------|---|---|---|
| Rabadi <i>et al.</i> (2008) | Within 4 days of fisher grade III SAH | Acute hospitalization | 39; Simvastatin = 19 Placebo = 20 | Simvastatin 80 mg day ⁻¹ or placebo | Angiographically-confirmed vasospasm occurred in 8/20 placebo and 5/19 simvastatin-treated subjects. Vasospasm-related ischemic infarcts developed in 5/20 placebo and 2/19 simvastatin-treated subjects. Death was 3/20 in the placebo and 0/19 in the simvastatin group. |
| Robinson <i>et al.</i> (2008) | Within 56 h to 14 days of their SAH | Neurosurgical center | 413; Clazosentan = 317 (1 mg h ⁻¹ = 108, 5 mg h ⁻¹ = 111, 15 mg h ⁻¹ = 98) Placebo = 96 | Clazosentan IV in 1, 5 and 15 mg h ⁻¹ Vs placebo | Moderate or severe vasospasm was reduced in a dose-dependent fashion from 66% in the placebo to 23% in the 15 mg h ⁻¹ clazosentan group (p<0.0001). On post hoc analysis for cerebral infarcts and delayed ischemic neurological deficit due to vasospasm on central review a trend favored clazosentan (37, 28 and 29% for the 1, 5 and 15 mg h ⁻¹ groups versus 39% in the placebo group) was seen. |
| Chou <i>et al.</i> (2008) | Within 4 days of fisher Grade III (and IV) SAH | Acute hospitalization | 170; TBA = 85 Control = 85 | Prophylactic Transluminal balloon angioplasty (TBA) under general anesthesia VS control | pTBA had an absolute risk reduction of 5.9% and a relative risk reduction of 10.4% unfavorable outcome (p = 0.54). The incidence of vasospasm related cerebral ischemia was lower in the pTBA group (p = 0.30) and fewer patients required therapeutic angioplasty to treat vasospasm (p = 0.03). 4 patients had a procedure-related vessel perforation, of which 3 patients died. This was a negative trial as fewer patients developed vasospasm after treatment with pTBA. |
| Surgery and stroke | | | | | |
| Macdonald <i>et al.</i> (2008) | Within 28 days of SAH on head CT or lumbar puncture | Neurosurgical centers | 278; NST = 140 EVT = 138 | Neurosurgical clipping (NST) VS endovascular coiling (EVT) | Of the patients allocated to EVT 83 of 138 (60.1%) were independent compared to 78 of 140 (56.1%) allocated NST. In patients with internal carotid and posterior communicating artery aneurysms EVT 36 of 50 (72.0%) was superior to 26 of 50 (52.0%) allocated NST (p<0.05). In patients with middle cerebral artery aneurysms NST 13 of 15 (86.7%) was superior to EVT 10 of 22 (45.5%) (p<0.05). The frequency of epilepsy was 0.7% in the EVT compared to 12.9% in the NST group (p<0.001). |

CONCLUSION

The following conclusions can be drawn from the studies summarized here: (1) extending the time-window for administration of alteplase from 3-4.5 h after stroke onset improved clinical outcome; (2) treatment of hypertension in the elderly does reduce rate of stroke, cardiac failure and death from stroke; (3) fixed dose unmonitored idraparinux was as effective as warfarin in primary stroke prevention, however, was associated with increase bleeding risk; (4) neither DP-b99 nor allopurinol proved to be an effective neuroprotectant; (5) anti-platelet agent Sarpogrelate was as effective as aspirin in secondary stroke prevention, hence a new anti-platelet to the growing list of effective anti-platelet agents; (6) aggressive management of hyperglycaemia does not improve clinical outcome; (7) prophylactic antibiotic use after an acute stroke reduced the rate of secondary infection with improved clinical outcome; (8) prophylactic anti-depressant use lowers the incidence of depression for 12 months post-stroke; (9) though

donepezil improved measures of executive function it did not translate into clinical improvement; (10) both statins and clazosentan in reduced subarachnoid hemorrhage induced vasospasm and delayed cerebral infarction, and finally (11) non-pharmacotherapies such as clips were safe to use in patient's with subarachnoid hemorrhage in the internal carotid and posterior communicating artery aneurysm while middle cerebral artery aneurysm benefited from coils.

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