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Randomized Clinical Stroke Trials in 2009

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Abstract: Problem statement: Stroke ranks as the leading cause of serious, long-term disability and death world-wide. It is 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 pharmacotherapy's 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 2009. 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 Pub Med 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 hyperglycemia, Hypertension OR raised blood pressure, Aspirin OR anti-platelets, Warfare OR anticoagulant, Antidepressants , Neuroprotectants and Coiling OR stents OR endovascular. Search limits included Human, Adult (age>19 years), English language and Publication date: 1/1/2009-12/31/2009. **Results:** Eleven categories of 27 RCT's were found and analyzed. **Conclusion:** There was sufficient evidence to suggest that: (1) extending the time-window for administration of desmoteplase between 3-9 h after ischemic stroke onset did not improve clinical outcome; (2) at present neither lidocaine, erythropoietin or ropinotan had been effective neuroprotective agents in ischemic stroke; (3) treatment with dabigatran was associated with lower rate of stroke and systemic embolism in patients with non-valvular aerial fibrillation; (4) memantine and constraint-induced aphasia therapy were able to reduce the severity of aphasia in chronic post-stroke aphasia and (5) percutaneous closure of the left aerial appendage can be an effective alternative to chronic warfare treatment.

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 2009.

Acute stroke therapies: At present, Intravenous (IV) recombinant Tissue Plasminogen Activator (TPA) is the only FDA approved thrombolytic to be used within 3 h of stroke symptom onset (1995). The recent ECASS III study suggested IV TPA can still be effective up to 4.5 h of symptom onset (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995; Hacke *et al*., 2008). Prior studies have shown desmoteplase, a highly fibrin-specific plasminogen activator to be effective alternate Thrombolytic Agent to TPA (Hacke *et al*., 2005; Furlan *et al*., 2006). However, there have been conflicting results with Ancrod, a defibrinogenating agent derived from the Malayan pit viper as a thrombolytic agent in acute ischemic stroke (Sherman *et al*., 2000; Hennerici *et al*., 2006). Given the unmet pharmacotherapy needs in acute stroke, several agents were studied.

Title: Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): A prospective, randomized, double-blind, placebo-controlled study.

Previous studies have shown that desmoteplase, a fibrin-specific plasminogen activator, to be of clinical benefit when given 3-9 h after the onset of the stroke symptoms with brain tissue at risk identified due to mismatch on magnetic resonance Perfusion Imaging (PI) and Diffusion-Weighted Imaging (DWI) (Hacke *et al*., 2005; Furlan *et al*., 2006). In this randomized, placebo-controlled, double-blind, dose-ranging study, patients with acute ischemic stroke and tissue at risk seen on either MRI or CT imaging were randomly assigned (1:1:1) to 90 mg kg^{-1} desmoteplase, 125 mg kg^{-1} desmoteplase, or placebo within 3-9 h after the onset of

stroke symptoms (Hacke *et al*., 2009). The primary endpoint was clinical response rates at day 90, defined as a composite of improvement in National Institutes of Health Stroke Scale (NIHSS) score of 8 points or more, or an NIHSS score of 1 point or less, a modified Rankin scale score of 0-2 pointsand a Barthel index of 75-100. Secondary endpoints included change in lesion volume between baseline and day 30, rates of symptomatic intracranial hemorrhage and mortality rates. Analysis was by intention to treat. In this study 193 patients were randomized and 186 patients received treatment: 57 received 90 mg kg^{-1} desmoteplase, 66 received 125 mg kg^{-1} desmoteplase and 63 received placebo. One hundred and fifty eight patients completed the study. The median baseline NIHSS score was 9 (IQR 6-14) points and 30% (53 of 179) of the patients had an occlusion of a vessel at presentation. The core lesion and the mismatch volumes were small (median volumes were 10.6 cm^3 and 52.5 cm^3, respectively). The clinical response rates at day 90 were: 47% (27 of 57) for 90 mg kg^{-1} desmoteplase, 36% (24 of 66) for 125 mg kg^{-1} desmoteplase and 46% (29 of 63) for placebo. The median changes in lesion volume were: 14.0% (0.5 cm^3) for 90 mg kg^{-1} desmoteplase; 10.8% (0.3 cm3) for 125 mg kg^{-1} desmoteplase and -10.0% (-0.9 cm^3) for placebo. The rates of symptomatic intracranial hemorrhage were 3.5% (2 of 57) for 90 mg kg^{-1} desmoteplase, 4.5% (3 of 66) for 125 mg kg^{-1} desmoteplase and 0% for placebo. The overall mortality rate was 11% (5% for 90 mg kg^{-1} desmoteplase; 21% for 125 mg kg^{-1} desmoteplase and 6% for placebo). The DIAS-2 study did not show a benefit of desmoteplase given 3-9 h after the onset of stroke. The high response rate in the placebo group could be due to presence of mild strokes (low baseline NIHSS scores, small core lesions and small mismatch volumes that were associated with no vessel occlusions), which possibly reduced the potential to detect any effect of desmoteplase.

Title: Randomized, placebo-controlled, dose-ranging clinical trial of intravenous microplasmin in patients with acute ischemic stroke.

Microplasmin, a recombinant truncated form of human plasmin, has demonstrated efficacy in experimental animal models of stroke by reducing infarct size (Suzuki *et al*., 2004) and being well tolerated in healthy young and old volunteers (Pakola *et al*., 2009). This study tested the tolerability of microplasmin in patients with acute ischemic stroke. In this multicenter, double-blind, randomized, placebo-controlled Phase II trial, 40 patients with ischemic stroke were treated with either placebo (n = 10) or Microplasmin (n = 30) between 3 and 12 h after symptom onset and within 1 h of MRI in a dose-finding design (6 patients received a total dose of 2 mg kg^{-1}, 12 patients received a total dose of 3 mg kg^{-1} and 12 patients received a total dose of 4 mg kg^{-1} of Microplasmin) (Thijs *et al*., 2009). The radiological and biochemical markers studied were head MRI for rate of reperfusion and serum Matrix Metalloproteinase's (MMP-2, MMP-9) concentration a marker of neurovascular integrity. This study was not powered to detect clinical efficacy. Microplasmin neutralized alpha$_2$-antiplasmin by 80%. MMP-2, but not MMP-9 levels, were reduced in microplasmin-treated patients. No significant effect on reperfusion rate or on clinical outcome was observed between the 2 groups. It was well tolerated and only 1 of 30 treated patients developed a fatal symptomatic intracerebral hemorrhage. This study indicates the need for further studies to determine whether microplasmin is an effective therapeutic agent for ischemic stroke.

Title: Ancrod in acute ischemic stroke: results of 500 subjects beginning treatment within 6 h of stroke onset in the ancrod stroke program.

Given the conflicting results of multiple-day dosing with the defibrinogenating agent, ancrod, in acute ischemic stroke, the Ancrod Stroke Program tested the concept that a brief dosing regimen might improve efficacy and safety in subjects given ancrod within 6 h of the onset of acute ischemic stroke. Five hundred subjects with acute ischemic stroke within 6 h of symptom onset were infused intravenously with either ancrod (n = 253, 0.167 IU kg^{-1} per hour) or placebo (n = 247) over 2 or 3 h (Levy *et al*., 2009). The primary efficacy outcome was a dichotomized, modified Rankin score at 90 days. Safety variables included mortality, major bleeding and intracranial hemorrhage. This study was stopped prematurely for lack of efficacy based on the interim analysis for futility. Despite desired change in fibrinogen level in >90% of accord subjects, there was no difference between the groups in the primary efficacy endpoint at 90 days. Positive responder status was seen in 39.6% of ancrod and 37.2% of placebo subjects (p = 0.47). Mortality at 90 days was no different between the 2 groups (ancrod, 15.6%; placebo, 14.1%; P = 0.32) with stroke being the most common cause of death, accounting for 38% of deaths in each group. There was no difference in the incidence of symptomatic intracranial hemorrhage within the first 72 h between ancrod compared to placebo subjects (3.9% Vs 2.0%; p = 0.19). The incidence of pulmonary and upper respiratory tract infection was 38.8% Vs 29% (p = 0.023) and of renal failure was 2.7% Vs 0.4% (p = 0.034) in the ancrod Vs the placebo groups. Thus intravenous ancrod within 6 h after symptom onset in subjects with ischemic stroke did not improve their clinical outcome and showed a trend towards increased bleeding despite successfully achieving rapid initial defibrinogenation and avoiding prolonged

hypofibrinogenemia. Increase incidence of infection and renal failure in the Ancrod group is also a worrying and unexplained finding.

Title: Effectiveness and safety of transcranial laser therapy for acute ischemic stroke.

This study tested the safety and efficacy of Transcranial Laser Therapy (TLT) using near-infrared laser technology to treat acute ischemic stroke. In this Neuro there Effectiveness and Safety Trial-2 (NEST-2), 660 patients were randomized in a double-blind fashion to either TLT treatment or sham control (Zivin *et al*., 2009). Patients who received tissue plasminogen activator or had evidence of hemorrhagic infarct were excluded. The primary efficacy end point was a favorable 90-day score of 0-2 assessed by the Modified Rankin Scale (MRS). Secondary outcome measures were at 90-day: The overall shift in MRS and the change in the National Institutes of Health Stroke Scale (NIHSS) score. There were 331 patients in the TLT and 327 patients in the sham group. In the TLT group 120 (36.3%) achieved favorable outcome versus 101 (30.9%) in the sham group (odds ratio 1.38 (95% CI, 0.95-2.00, P = 0.094). Similar results were seen for the secondary outcome measures. Post hoc analysis showed patients with a baseline NIHSS score of<6 had a favorable outcome at 90 days on the primary end point (p = <0.04). Mortality rates and serious adverse events were 17.5% and 17.4% for mortality, 37.8% and 41.8% serious adverse events for TLT and sham, respectively. In this study, TLT within 24 h from stroke onset was safe but did not meet efficacy. This study was similar in design to the clinical trial (NEST-1) except that more patients were recruited in NEST-2 study (660 Vs 120) and there were more Caucasian's (77% to the 40%) (Lampl *et al*., 2007). Both studies showed TLT to be safe, but NEST-1 was the only study to show efficacy. In both studies, TLT did not adversely affect mortality and adverse event rates. The main advantage of TLT lies in its extended time window of 24 h compared to 3 h time window for TPA.

Title: Transcranial Ultrasound in Clinical Sonothrombolysis (TUCSON) trial.

Microspheres (micros) reaching intracranial occlusions have been shown to promote recanalization on transmitting energy momentum from an ultrasound wave to the residual cerebral blood flow (Alexandrov *et al*., 2008). In this multi-center, phase II trial, ischemic stroke patients received 0.9 mg kg^{-1} Tissue Plasminogen Activator (TPA) were then randomized in 2:1 ratio based on proximal intracranial occlusions on Transcranial Doppler (TCD) to micros (MRX-801) infusion over 90 min (Cohort 1:1.4 mL; Cohort 2:2.8 mL) with continuous TCD insonation while controls received TPA and brief TCD assessments (Molina *et al*., 2009). The primary endpoint was Symptomatic Intracerebral Hemorrhage (SICH) within 36 h after TPA. Among the 35 patients (Cohort 1 = 12, Cohort 2 = 11, controls = 12), no SICH occurred in Cohort 1 and controls, whereas 3 (27%, 2 fatal) SICHS occurred in Cohort 2 (p = 0.028). Sustained complete recanalization/clinical recovery rates at the end of TCD monitoring at 3 month were: 67/75% for Cohort 1, 46%/50% for Cohort 2 and 33/36% for controls (p = 0.25/0.17). The median time to recanalization was shorter in Cohort 1 (30 min; Interquartile Range (IQR), 6) and Cohort 2 (30 min; IQR, 69) compared to controls (60 min; IQR, 5; p = 0.054). Patients with SICH had similar baseline and pretreatment Systolic Blood Pressure (SBP) levels while higher SBP levels were documented in SICH+ patients at 30-60 and 90-min. 24-36 h following TPA bolus. This study showed perflutren lipid micros could be safely combined with systemic tPA and ultrasound at a dose of 1.4 mL. In both dose tiers, sonothrombolysis with microS and tPA showed a trend toward higher early recanalization and clinical recovery rates compared to standard intravenous tPA therapy alone. This study main limitation is: The small number of patients recruited, the need for trained sonographers to be able to administer this technique and the lack of difference between the groups in functional outcome improvement between groups (p = 0.17).

Stroke and statins:

Title: Placebo-controlled trial of high-dose atorvastatin in patients with severe cerebral small vessel disease.

Cerebral Vasoreactivity (CVR) is a compensatory dilatory capacity of cerebral resistance vessels in response to stimuli such as carbon dioxide (Maeda *et al*., 1993). Impaired CVR has been reported in Small-Vessel Disease (SVD) (Molina *et al*., 1999). Small uncontrolled studies have shown that statins improve CVR in patients with mild SVD (Pretnar-Oblak *et al*., 2006). This study sought to determine whether high-dose atorvastatin increases CVR compared to placebo in patients with Severe SVD. In this randomized, double-blind study, 94 patients with recent lacunar stroke were allocated to 80 mg of atorvastatin daily or matching placebo after stratification for hypertensive and diabetic status (Lavallee *et al*., 2009). The primary end point was change in CVR after 3 months of treatment. Secondary outcomes were changes in brachial and carotid artery endothelial-dependent vasodilations. At baseline, all patients had a severely impaired CVR (mean, 12.1%; 95% CI, 9.5-14.7) and carotid (mean-0.25%; 95% CI-1.17-0.67) and brachial artery (mean, 2.72%; 95% CI-1.39-4.05) endothelial function. Despite 55% reduction in low-density lipoprotein cholesterol and 30% reduction in high-sensitivity C-reactive protein in the atorvastatin group

compared to placebo, atorvastatin 80 mg per day did not improve CVR or endothelial dysfunction of carotid and brachial arteries. Thus, no positive effect of 3-month treatment with atorvastatin was found on severe cerebral microvasculature endothelial dysfunction in patients with lacunar stroke.

Title: Effects of moderate-dose omega-3 fish oil on cardiovascular risk factors and mood after ischemic stroke: A randomized, controlled trial (FOILS).

Omega-3 polyunsaturated fatty acids (docosahexaenoic acid and eicosapentaenoic acid) have been associated with cardiovascular protection (Marchioli *et al*., 2002). In this trial, effects of moderate-dose omega-3 fish oil on cardiovascular risk factors and mood after ischemic stroke was assessed. One hundred and two patients with CT-confirmed ischemic stroke of >3 months were randomized to 3 g day^{-1} encapsulated fish oil containing approximately 1.2 g total omega-3 (n = 51, 0.7 g docosahexaenoic acid; 0.3 g eicosapentaenoic acid) or placebo oil (n = 51, combination palm and soy) taken daily each morning with food over 12 weeks (Poppitt *et al*., 2009) (21). The primary outcome was change in serum triglycerides after 12 weeks. The secondary outcome measures were: (i) serum total cholesterol and associated lipoproteins, (ii) selected inflammatory (C-reactive protein, sedimentation rate) and hemostatic (ferritin and fibronigen level) markers, (iii) mood (assessed by 28 items General Health Questionnaire) and iv) health-related quality of life (assessed by 36 items Short Form Questionnaire). These measures were assessed at baseline and on 12-week follow-up. Compliance was assessed by capsule count and serum phospholipid omega-3 levels. Intention-to-treat and per-protocol (>85% compliance) analyses showed no significant effect of fish oil treatment on any lipid, inflammatory, hemostatic, or composite mood parameters measured. Adherence to treatment based on pill count was good (89%) with increased serum docosahexanoic acid ($p<0.001$) and eicosapentaenoic acid ($p = 0.0006$) in the fish oil group. In this study, 12 weeks of treatment with moderate-dose fish oil supplements had no effect on cardiovascular biomarkers or mood in patients with ischemic stroke. The authors of the study concluded the negative study result to be due to low dose and short duration of treatment, moderately elevated triglyceride level and oxidation of the fish oils.

Stroke and diabetes:

Title: Glucose Regulation in Acute Stroke Patients (GRASP) trial: A randomized pilot trial.

Hyperglycemia is associated with worse outcome in patients with acute stroke. American Heart Association/American Stroke Association guidelines suggest treating hyperglycemia if levels exceed 300 mg dL^{-1} (Adams *et al*., 2005). This study assessed the feasibility and safety of insulin infusion protocols in patients with acute ischemic stroke with 3-arm trial targets (tight control, n = 24, [target 70-110 mg dL^{-1}]; loose control n = 25, [target 70-200 mg dL^{-1}] and control usual care n = 25, [70-300 mg dL^{-1}]). This prospective, randomized, multicenter trial enrolled a total of 74 subjects who received Novolin insulin in normal saline (1 U/1 mL) as a continuous infusion. Patients had Accu-checks every 1-4 h and every 15 min in hypoglyceamic patients (BS<55 mg dL^{-1}) as per protocol (Johnston *et al*., 2009). Data was available for the primary analyses in 72 subjects (97%) and 3-month clinical outcome data in 73 subjects (99%). Median age was 67 years, median National Institutes of Health Stroke Scale (NIHSS) score was 8, median glucose was 163 mg dL^{-1} and median time to randomization was 10.7 h. Fifty-nine percent of patients were diabetic, 35% received thrombolysis and 14% of subjects died within 3 months. The loose control and usual care groups had median glucose concentrations of 151 mg dL^{-1} Vs 111 mg dL^{-1} in the tight control group. The target blood sugar level in the first 24 h was achieved in 90% of the time in the loose control group and 44% of the time the tight group. There was only one symptomatic hypoglycemic patient in the loose control group (4%) and none in the tight control group. The overall rates of hypoglycemia (<55 mg dL^{-1}) were 4% in control, 4% in loose and 30% in tight. The efficacy analysis (based on modified Rankin Scale, Barthel Index and death) showed no statistically significant differences between the 3-groups. However, this was an exploratory efficacy analysis and not determined a priori. The Glucose Regulation in Acute Stroke Patients (GRASP) trial showed insulin infusion for patients with acute ischemic stroke to be feasible and safe using the insulin infusion protocol.

Stroke and atrial fibrillation:

Title: Dabigatran versus Warfarin in patients with Atrial fibrillation.

Atrial fibrillation increases the risk of stroke and death Warfarin reduces the risk of stroke and death in patients with atrial fibrillation but increases the risk of hemorrhage and needs regular blood testing to adjust its dose appropriately (Hart *et al*., 2007). Dabigatran is a new oral direct thrombin inhibitor. In this international, multi-center, noninferiority trial, 18,113 patients who had atrial fibrillation and a risk of stroke were randomly assigned to receive, in a blinded fashion, fixed doses of dabigatran (110 mg, n = 6015 or 150 mg, n = 6076) twice daily versus in an unblinded fashion, adjusted-dose warfarin (n = 6022) (Connolly *et al*., 2009). The median duration of the follow-up period was 2.0 years. The primary outcome was stroke or systemic embolism.

Rates of the primary outcome were 1.69% per year in the warfarin group compared with 1.53% per year in the 110 mg dabigatran (relative risk with dabigatran, 0.91; 95% Confidence Interval (CI), 0.74-1.11; p<0.001 for noninferiority) and 1.11% $year^{-1}$ in the 150 mg dabigatran (relative risk, 0.66; 95% CI, 0.53-0.82; p<0.001 for superiority) groups. The rate of major bleeding was 3.36% $year^{-1}$ in the warfarin group compared with 2.71% $year^{-1}$ in the 110 mg dabigatran (p = 0.003) and 3.11% $year^{-1}$ in the 150 mg dabigatran (p = 0.31) groups. The rate of hemorrhagic stroke was 0.38% $year^{-1}$ in the warfarin group compared with 0.12% per year with 110 mg dabigatran (p<0.001) and 0.10% per year with 150 mg dabigatran (p<0.001) groups. The mortality rate was 4.13% $year^{-1}$ in the warfarin group compared with 3.75% $year^{-1}$ with 110 mg dabigatran (p = 0.13) and 3.64% $year^{-1}$ with 150 mg dabigatran (p = 0.051). In patients with atrial fibrillation, dabigatran given at a dose of 110 mg was associated with rates of stroke and systemic embolism that were similar to those associated with warfarin, but with lower rates for major or minor hemorrhage. Dabigatran administered at a dose of 150 mg, as compared with warfarin, was associated with lower rates of stroke and systemic embolism but similar rates for major and minor hemorrhage.

Stroke and neuroprotection:

Title: Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery.

Cognitive decline after cardiac surgery is common and affects patients' quality of life. This study was based on experimental and clinical evidence that intravenously administered lidocaine reduces postoperative cognitive dysfunction after cardiac surgery using cardiopulmonary bypass (Niiyama *et al*., 2005). Two hundred and seventy-seven patients undergoing cardiac surgery were prospectively randomized in a double-blind fashion to either the lidocaine group (n = 114, 1 mg kg^{-1} bolus followed by a continuous infusion through 48 h postoperatively), or placebo group (n = 127, bolus and infusion of normal saline at a similar rate as the treatment group) (Mathew *et al*., 2009). Cognitive function was assessed preoperatively and again at 6 weeks and 1 year postoperatively. The effect of lidocaine on postoperative cognition was tested using multivariable regression modeling; alpha was p<0.05. The incidence of cognitive deficit in the lidocaine group was 45.5% versus 45.7% in the placebo group (p = 0.97). Multivariable analysis revealed a significant interaction between treatment group and diabetes, such that diabetic subjects receiving lidocaine were more likely to suffer cognitive decline (p = 0.004). Secondary analysis identified total lidocaine dose (mg kg^{-1}) to be a significant predictor of cognitive decline and showed a protective effect of lower dose lidocaine in nondiabetic subjects. This study found lidocaine administered during and after cardiac surgery did not reduce the high rate of postoperative cognitive dysfunction. However, higher doses of lidocaine and diabetic status were independent predictors of cognitive decline. Protective effect of lower dose lidocaine in nondiabetic subjects found in this study needs to be further evaluated.

Erythropoietin (Epo) and its receptor are expressed by astrocytes and neuron in response to hypoxia, oxidative stress, hypoglycaemia and glutamate toxicity by upregulating Hypoxia Inducing Factor-1 (HIF-1) (Morishita *et al*., 1997). Animal models suggest both exogenous and endogenous Epo to be neuroprotective (Siren *et al*., 2001). Epo exerts its neuroprotective effect by specifically binding to neuronal Epo receptors and induces anti-apoptotic, antioxidant, anti-inflammmatory, neurotropic, neural stem-cell modulation and enhance neural plasticity. A clinical pilot study suggested Epo's neuroprotective effects may be beneficial in the treatment of patients with ischemic stroke (Ehrenreich *et al*., 2002).

Title: The Erythropoietin Neuroprotective Effect: Assessment in CABG Surgery (TENPEAKS): A randomized, double-blind, placebo controlled, proof-of-concept clinical trial.

Neurocognitive dysfunction complicates coronary artery bypass surgery (Newman *et al*., 2001). This study sought to determine whether human recombinant erythropoietin would reduce the incidence of neurocognitive dysfunction after surgery. Thirty two elective first-time Coronary Artery Bypass Graft (CABG) patients were randomly assigned to receive placebo or graduated doses of recombinant human erythropoietin (375, 750, or 1500 U kg^{-1}) in 3 daily divided doses, starting the day before surgery (Haljan *et al*., 2009). Primary outcomes were feasibility and safetyand secondary outcomes were neurocognitive dysfunction at discharge and 2 months. All subjects were male, mean age 60 years (range 46-73). No significant differences were found in pump time, cross-clamp time, or hospital length of stay. Neurocognitive dysfunction occurred in 21/32 (66%) of patients at discharge and 5/32 (16%) at 2 months. Neurocognitive dysfunction at discharge by group was: Placebo 6/8 (75%), 375 U kg^{-1} 4/8 (50%), 750 U kg^{-1} 6/8 (75%) and 1500 U kg^{-1} 5/8 (63%). Neurocognitive dysfunction at 2 months by group was: Placebo 3/8 (38%), 375 U kg^{-1} 1/8 (13%), 750 U kg^{-1} 1/8 (13%) and 1500 U kg^{-1} 0/8 (0%). Neurocognitive dysfunction at 2 months for erythropoietin at any dose was 2/24 (8.3%) versus 3/8 (38%) for placebo (p = 0.085). One patient in the 375 U kg^{-1} group had ST changes compatible with myocardial injury immediately

postoperative, but no other thrombotic complications were observed. This study demonstrated feasibility and safety for the use of human recombinant erythropoietin as a neuroprotectant in coronary artery bypass graft surgery. A multicenter randomized controlled trial is warranted to confirm this impression that erythropoietin use is associated with the reduction of neurocognitive dysfunction at 2 months. This study main limitations were the small sample size and single sex (all males).

Title: Recombinant human erythropoietin in the treatment of acute ischemic stroke.

Although Epo is considered to be a safe and well-tolerated drug, recent studies have identified increased thromboembolic complications and/or mortality risks on Epo administration to patients with cancer or chronic kidney disease. This double-blind, placebo-controlled, randomized German Multicenter EPO Stroke Trial (Phase II/III) evaluated efficacy and safety of recombinant Epo in stroke. The clinical trial enrolled 522 patients with acute ischemic stroke in the middle cerebral artery territory (intent-to-treat population) with 460 patients treated as planned (per-protocol population). Within 6 h of symptom onsetand at 24-48 h, Epo was infused intravenously (40,000 IU in 50 mL normal saline over 30 min.) for a total dose of 120,000 IU per patient (Ehrenreich *et al*., 2009). Systemic thrombolysis with recombinant Tissue Plasminogen Activator (TPA) was allowed. On analysis of total intent-to-treat and per-protocol populations, neither primary outcome Barthel Index on Day 90 ($p = 0.45$) nor any of the secondary outcome measures (National Institute of Health Stroke Scale, modified Rankin Scale and head MRI for lesion size) showed favorable effects of Epo. Overall death rate was 16.4% (n = 42 of 256) in the Epo and 9.0% (n = 24 of 266) in the placebo group ($p = 0.01$). The highest death rate was in the first week mainly attributable to intra-cerebral hemorrhage, brain edemaand thrombo-embolic events. Based on analysis of total intent-to-treat and per-protocol populations, this was a negative trial. It also raises safety concerns, particularly in patients receiving systemic thrombolysis in addition to Epo. Surprisingly a very high number of patients received recombinant tissue plasminogen activator (63.4%) in this study.

Title: A randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety, tolerability and pharmacokinetic/pharmacodynamic effects of a targeted exposure of intravenous repinotan in patients with acute ischemic stroke: Modified Randomized Exposure Controlled Trial (MRECT).

Repinotan hydrochloride is a serotonin ($5\text{-}HT_{1A}$) receptor agonist with neuroprotective effects in animal models of permanent and transient focal ischemia (Mauler and Horvath, 2005; Teal *et al*., 2005). This Phase II study investigated the efficacy, safety and tolerability of a targeted exposure to repinotan in patients with acute ischemic stroke. In this double-blind, placebo-controlled, parallel-group, multi-center study, 681 patients were stratified according to whether or not tissue plasminogen activator was administered and then randomly assigned to either treatment with repinotan (n = 342; loading dose 0.1 mg h^{-1} [40 mL h^{-1}] for first 2 h followed by infusion rate of 0.05 mg h^{-1} [20 mL h^{-1}] over the next 4 h or placebo (n = 284) (Teal *et al*., 2009). A continuous 72 h intravenous infusion of repinotan or placebo was started within 4.5 h from the onset of ischemic symptoms. A Point-of-Care test was used to adjust the infusion rate if repinotan plasma concentration reached or exceeded predefined threshold. The goal of Modified Randomized Exposure Controlled Trial (MRECT) was designed to show whether repinotan was statistically superior to placebo (alpha ≤ 0.10) as measured by the response rate on the primary efficacy variable, Barthel Index ≥ 85) at 3 months, using a Cochran-Mantel-Haenszel test. For the intention-to-treat population at 3 months, the response rate on the Barthel Index ≥ 85 was 37.1% (127/342) for patients on repinotan and 42.4% (143/337) for patients taking the placebo (Cochran-Mantel-Haenszel p-value = 0.149). No apparent adverse events were identified. This study failed to demonstrate a clinical benefit of repinotan in acute ischemic stroke as a neuroprotective agent. This trial result led the drug manufacture to discontinue this medication.

Stroke prevention:

Title: High-dose B-vitamin supplementation and progression of subclinical atherosclerosis: a randomized controlled trial.

Although plasma total Homocysteine (tHcy) levels are associated with cardiovascular disease, it is unclear whether homocysteine is a cause or a marker of atherosclerotic vascular disease. Recent trials have failed to show reduction in cardiovascular events with homocysteine lowering therapies such as folic acid and vitamin B12 (Toole *et al*., 2004). This study tried to determine whether reduction of tHcy levels with B vitamin supplementation reduced subclinical atherosclerosis progression. In this double-blind clinical trial, 506 participants 40-89 years of age with an initial tHcy >8.5 micromole L^{-1} without diabetes and cardiovascular disease were randomly assigned to either high-dose B vitamin supplementation (5 mg folic acid +0.4 mg vitamin B12 +50 mg vitamin B6) or matching placebo for 3.1 years (Hodis *et al*., 2009). Subclinical atherosclerosis progression across 3 vascular beds was assessed using high-resolution B-mode ultrasonography measuring carotid artery intima media thickness (primary outcome) and multidetector spiral CT to measure aortic and coronary artery calcium (secondary

outcome). The overall carotid artery intima media thickness progression rate was lower with B vitamin supplementation than with placebo, however; between-group differences was not found (p = 0.31). Subjects with baseline tHcy ≥9.1 mL L^{-1}, randomized to B vitamin supplementation had a significantly lower rate of carotid artery intima media thickness progression compared with placebo (p = 0.02), while in subjects with a baseline tHcy <9.1 mL L^{-1}, there was no significant treatment effect. B vitamin supplementation had no effect on progression of aortic or coronary artery calcification overall or within subgroups. This was a negative study as the progression rate of intima media thickness was similar between the 2 groups. However, the high-dose B vitamin supplementation managed to reduce the progression of early-stage subclinical atherosclerosis (carotid artery intima media thickness) in well-nourished healthy individuals at low risk for cardiovascular disease with a fasting tHcy ≥9.1 mL L^{-1}.

Title: Homocysteine-lowering therapy and stroke risk, severityand disability: Additional findings from the HOPE 2 trial.

Elevated total homocysteine is associated with a higher risk of cerebrovascular disease (Kittner *et al*., 1999). This study aimed to determine whether lowering homocysteine by vitamin therapy reduced the severity and incidence of stroke subtypes (ischemic Vs hemorrhagic). The Heart Outcomes Prevention Evaluation 2 (HOPE 2) trial randomized 5522 adults with known cardiovascular disease to a daily combination of 2.5 mg of folic acid, 50 mg of vitamin B6and 1 mg of vitamin B12, or matching placebo, for 5 years. Among 5522 participants, stroke occurred in 258 (4.7%) individuals during a mean of 5 years of follow-up (Saposnik *et al*., 2009). The mean homocysteine concentration decreased by 2.2 mL L^{-1} in the vitamin therapy group and increased by 0.80 mL L^{-1} in the placebo group. The incidence rate of stroke was 0.88 per 100 person-years in the vitamin therapy group and 1.15 per 100 person-years in the placebo group (Hazard Ratio (HR), 0.75; 95% CI, 0.59-0.97). Vitamin therapy reduced the risk of nonfatal stroke (HR, 0.72; 95% CI, 0.54-0.95) but had no impact on neurological deficit at 24 h (p = 0.45) or functional independence at discharge or at day 7 (OR, 0.95; 95% CI, 0.57-1.56). In subgroup analysis, patient's aged≤69 years, from regions without folic acid food fortification, with higher baseline cholesterol and homocysteine levels and those not receiving antiplatelet or lipid-lowering drugs at enrollment had the largest treatment benefit. Thus lowering of homocysteine with folic acid and vitamins B 6 and B 12 did reduce the risk of overall stroke, but not stroke severity or disability.

Stroke and fever: Fever, defined as elevation of body core temperature (>38°C) is common in critically ill patients (Diringer *et al*., 2004). Multiple pathophysiologic mechanisms of hyperthermia have been hypothesized to be potentially harmful: (i) enhanced release of excitatory neurotransmitters, (ii) exaggerated free oxygen-radical production, (iii) blood-brain barrier breakdown, (iv) increased ischemic depolarization in the focal ischemic penumbra, (v) enhanced inhibition of protein kinasesand (iv) worsening of cytoskeletal proteolysis leading to secondary and worsening primary (neuronal) injury (Ginsberg and Busto, 1998). A temperature beyond 40°C causes transient vasoparalysis in humans, resulting in cerebral metabolic uncoupling and loss of pressure-flow autoregulation (Cremer and Kalkman, 2007). In many diseases, fever is an independent predictor of unfavorable outcome and therefore; early treatment of hyperthermia is the standard of care (Schmutzhard *et al*., 2002). Currently, various techniques including antipyretic drugs, surface cooling and intravascular devices are used alone or in combination to treat fever (Schmutzhard *et al*., 2002). Due to the adverse effects of mild to moderate hypothermia (body core temperature 33-35°C) outweighing its beneficial effects in ICU patients with various diseases, the therapeutic use of hypothermia is still debated (Clifton *et al*., 2001). Given this uncertainty, 2 recent studies evaluated whether maintaining prophylactic normothermia to be both efficacious and safe.

Title: The Paracetamol (Acetaminophen) In Stroke (PAIS) trial: A multicentre, randomized, placebo-controlled, phase III trial.

Fever in the first 12-24 h after stroke onset has been associated with poor functional outcome (Azzimondi *et al*., 1995; Boysen and Christensen, 2001). The odd of this poor outcome doubles for every degree increase in body temperature in the initial 12 h stroke onset (Reith *et al*., 1996). Guidelines for treatment of acute ischemic and hemorrhagic stroke recommend use of antipyretic drugs in patients with fever (Adams *et al*., 2007a; Broderick *et al*., 2007). The Paracetamol (Acetaminophen) In Stroke (PAIS) trial aimed to assess whether early treatment with paracetamol improves functional outcome in patients with acute stroke by reducing body temperature and preventing fever. In this multicentre, randomized, double-blind, placebo-controlled trial, patients with ischemic stroke or intracerebral hemorrhage and body temperature between 36-39 degrees C were randomly assigned treatment with paracetamol (6 g daily; n = 697) or placebo (n = 703) within 12 h from symptom onset (Den Hertog *et al*., 2009). The primary outcome was improvement beyond expectation on the modified Rankin scale at 3 months. This trial was stopped after 1400 patients were enrolled as it ran out of funding. 260

(37%) patients receiving paracetamol and 232 (33%) receiving placebo improved beyond expectation (adjusted Odds Ratio (OR) 1.20, 95% CI 0.96-1.50). In a post-hoc analysis of patients with baseline body temperature 37-39°C, treatment with paracetamol was associated with improved outcome (1.43, 1.02-1.97). There were 55 serious adverse events in the paracetamol group (8%) and 70 in the placebo group (10%). Routine use of high-dose paracetamol in patients with acute stroke cannot be suggested based on the results of this study as it did not improve functional outcome at 3-months. However, paracetamol might have a beneficial effect on functional outcome in patients admitted with a body temperature 37-39°C, based on the post-hoc findings. This post-hoc finding needs further study.

Title: Prophylactic, endovascularly based, long-term normothermia in ICU patients with severe cerebrovascular disease: Bicenter prospective randomized trial.

This prospective, randomized, controlled trial sought to assess the effectiveness and safety of catheter-based normothermia (CoolGard; i.e., body core temperature 36.5°C) to conventional, stepwise fever management with anti-inflammatory drugs and surface cooling. Patients admitted to the neurointensive care units were eligible for study inclusion if they had a (1995) spontaneous subarachnoid hemorrhage with Hunt and Hess grade between 3 and 5, (Hacke *et al*., 2008) spontaneous intracerebral hemorrhage with a Glasgow Coma Scale score ≤10, or (Hacke *et al*., 2005) complicated cerebral infarction requiring intensive care unit treatment with a National Institutes of Health Stroke Scale score ≥15. One hundred and two patients (56 female) were enrolled during a 3.5 year period (Broessner *et al*., 2009). Body core temperature was measured in the urinary bladder by a Foley catheter. In both treatment arms, the fever threshold was set at a temperature >37.9°C for >1 h and exceeding this threshold led to additional predefined conventional, stepwise fever management. The standardized, stepwise fever management started with acetaminophen 500 mg PO or by nasogastric tube. If the temperature remained above the threshold for another hour, patient's received on an hourly basis ibuprofen 500 mg PO, followed by pethidine 100 mg IV and finally with a surface cooling blanket (Blanketrol, Cincinnati Sub-Zero). When the temperature dropped below 37.9°C at any time, the stepwise management was stopped. For patients who did not respond to this fever management, the entire procedure was repeated again, starting with acetaminophen. The intravascular device (Cool Line) was inserted into the subclavian vein and positioning was verified by chest x-ray. Target temperature was set at 36.5°C to maintain normothermia and endovascular treatment was strictly adhered to for the pre-defined period. There were 51 patients in the Cool Gard and 51 patients in the conventional control group. Fifty percent had a spontaneous subarachnoid hemorrhage, 40% had a spontaneous intracerebral hemorrhage and 10% had a complicated cerebral infarction. Overall median total fever burden during the course of treatment was 0.0°C h in the catheter and 4.3°C h in the conventional groups (p = <0.0001). Infectious adverse event rate reported for 49 CoolGard and 41 control patients was 96% and 80% respectively (p = 0.03). Bacteremia and pneumothorax were each reported for ≤10% patients in each group. Prophylactic normothermia did not lead to an increase in the number of major adverse events. No significant difference was found in mortality and neurological outcomes based on Glasgow Outcome Scale and modified Rankin Scale scores at 6 month follow-up. Thus long-term, catheter-based, prophylactic normothermia significantly reduced fever burden in neurointensive care unit patients with severe stroke without any increase in major adverse events, mortality and neurological outcomes.

Stroke and deep vein thrombosis:

Title: Effectiveness of thigh-length graduated compression stockings to reduce the risk of deep vein thrombosis after stroke (CLOTS trial 1): A multicentre randomized controlled trial.

Deep Vein Thrombosis (DVT) develops in up to 42% of patients admitted with stroke due mainly to immobility (Kelly *et al*., 2004). Most national guidelines recommend use of graduated compression stockings in patients with acute stroke (Adams *et al*., 2007b). In small trials of patients undergoing surgery, Graduated Compression Stockings (GCS) has reduced the risk of DVT (Kierkegaard and Norgren, 1993). This study assessed the effectiveness of thigh-length GCS to reduce DVT after stroke. Two thousand five hundred and eighteen patients were admitted to hospital within 1 week of an acute stroke; those who were immobile were randomized to routine care plus thigh-length GCS (n = 1256) or to routine care only (n = 1262) (Dennis *et al*., 2009). A technician blinded to treatment allocation undertook compression Doppler ultrasound of both legs at about 7-10 days and again at 25-30 days after enrolment. Analyses were by intention to treat. The primary outcome (occurrence of symptomatic or asymptomatic DVT in the popliteal or femoral veins) occurred in 126 (10.0%) patients allocated to thigh-length GCS and in 133 (10.5%) allocated to routine care only, resulting in a non-significant absolute reduction in risk of 0.5% (95% CI-0.9%-2.9%). Skin breaks, ulcers, blisters and skin necrosis were significantly more common in patients allocated to GCS than in those allocated to routine care only (64 (5%) Vs 16 (1%); odds ratio 4.18, 95% CI 2.40-7.27).

Based on the results of this study the national guidelines for prevention of DVT in patients after stroke need to be revised as this study does not support the use of thigh-length GCS in patients admitted to hospital with an acute stroke.

Stroke and depression:

Title: Brief psychosocial-behavioral intervention with antidepressant reduces poststroke depression significantly more than usual care with antidepressant: Living Well With Stroke (LWWS): Randomized, controlled trial.

Depression post-stroke is prevalent and is usually associated with poor functional recovery and quality of life. This study evaluated short- and long-term efficacy of brief behavioral intervention, adjunctive to antidepressant therapy in patients with poststroke depression. One hundred one clinically depressed patients with ischemic stroke within 4 months of index stroke were randomly assigned to an 8-week brief psychosocial-behavioral intervention plus antidepressant (n = 48) or usual care including antidepressant (n = 53) (Mitchell *et al*., 2009). The primary end point was reduction in depressive symptom severity at 12 months after entry based on the Hamilton Rating Scale (HRS). The HRS for Depression raw score in the intervention group was significantly lower immediately post-treatment ($p<0.001$) and at 12 months ($p = 0.05$) compared with control subjects. Remission (HRS for Depression <10) was significantly greater immediately post-treatment and at 12 months in the intervention group compared with the usual care control. The mean percent decrease (47±26% intervention versus 32±36% control, $p = 0.02$) and the mean absolute decrease (-9.2 ± 5.7 intervention versus-6.2±6.4 control, $p = 0.023$) in HRS for depression at 12 months were clinically important and statistically significant in the intervention group compared with control. This study concluded brief psychosocial-behavioral intervention to be highly effective in reducing depression in both the short and long term.

Stroke and aphasia:

Title: Memantine and constraint-induced aphasia therapy in chronic poststroke aphasia.

Aphasia occurs in one third of stroke patients and resolves spontaneously in only one third of these affected patients (Engelter *et al*., 2006). This randomized, double-blind, placebo-controlled, parallel-group studied both memantine and Constraint-Induced Aphasia Therapy (CIAT) on chronic poststroke aphasia followed by an open-label extension phase. CIAT is an intensive form of language therapy for aphasia performed in small group settings of 2-3 patients with a speech therapist. In this therapy patients are encouraged to communicate by asking questions, requesting picture cards from each other by providing descriptions of the objects. Other forms of communications (gesturing, drawing or writing) are actively discouraged. In this study, patients were randomized to memantine (20 mg day^{-1}) or placebo alone during 16 weeks, followed by combined drug treatment with CIAT (weeks 16-18), drug treatment alone (weeks 18-20) and washout (weeks 20-24) and finally, an open-label extension phase of memantine (weeks 24-48) (Berthier *et al*., 2009). Patients received 30 h of CIAT in 2 weeks (3 h day^{-1}). After baseline evaluations, clinical assessments were done at two end points (weeks 16 and 18) and at weeks 20, 24 and 48. Outcome measures were changes in the Western Aphasia Battery-Aphasia Quotient and the Communicative Activity Log. Twenty-eight patients were included and 27 completed both treatment phases. The memantine group (n = 14) showed significantly better improvement on Western Aphasia Battery-Aphasia Quotient compared with the placebo group (n = 14) while the drug was being taken (week 16, $p = 0.002$; week 18, $p = 0.0001$; week 20, $p = 0.005$) and at the washout assessment ($p = 0.041$). A significant increase in Communicative Activity Log was found in favor of memantine-CIAT relative to placebo-CIAT (week 18, $p = 0.040$). CIAT treatment led to significant improvement in both groups ($p = 0.001$), which was even greater in the memantine treatment ($p = 0.038$). Beneficial effects of memantine were maintained in the long-term follow-up evaluationand patients who switched to memantine from placebo experienced a benefit ($p = 0.02$). Thus both memantine and CIAT individually improved aphasia severity, but best outcomes were achieved when memantine and CIAT were combined. This beneficial effect of memantine and CIAT persisted on long-term follow-up. However, this was a small study. Since patients recruited were from aphasia support groups and local advertisement there is an inherent bias as motivated patients were likely to have been enrolled.

Stroke and surgery:

Title: Protection or nonprotection in carotid stent angioplasty: The influence of interventional techniques on outcome data from the SPACE Trial.

SPACE, an independent investigator driven study, tried to address the benefit of Protection Devices (PDs) in stents with different cell designs in Carotid Artery Stinting (CAS). In the secondary analysis of this prospective randomized trial, 563 patients were randomized to CAS and treated per protocol. A total of 145 patients were treated with a PD and 418 without. There were 436 patients treated with an open cell stent and 127 with a closed cell stent. The use of PDs and choice of device was at the individual discretion of the intervention list (Jansen *et al*., 2009). The main

Outcome Event (OE) of the analysis (ipsilateral stroke or stroke death within 30 days) was reached in 26/418 patients (6.2 and 95% CI: 4.1-9.0%) in the PD group and in 12/145 patients (8.3 and 95% CI: 4.3-14.0%) in the non-protection group (p = 0.40). The OE rate was significantly lower in patients treated with a closed cell stent (5.6% [95% CI: 3.7-8.2%]) than in those treated with an open cell stent (11.0 and 95% CI: 6.2-17.8%; p = 0.029). Of all OEs 49% occurred during the intervention, 10% during the navigation procedure and 41% after the intervention, including 10% of hyperperfusion syndromes. The events were not influenced by the use of a PD. This secondary analysis of data from the SPACE trial did not support the use for a PD in CAS. It did demonstrate that stent design impacted the OE rate and the development of specific stent designs for the treatment of carotid stenosis is may reduce the complication rate significantly.

Title: Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): Long-term follow-up.

The International Subarachnoid Aneurysm Trial (ISAT) reported that coiling was associated with a reduction in the risk of death or dependency at 1 year, 24% compared to 31% in the clipping group (Molyneux *et al*., 2005). Since individuals with ruptured intracranial aneurysms frequently occur in the young (mean age in this trial was 52 years), the potential long-term risks of death, disability and rebleeding in this group of patients was not known. A total of 2143 patients with ruptured intracranial aneurysms enrolled between 1994 and 2002 (endovascular group n = 1073 and clipping group n = 1070) with an annual follow-up for a minimum of 6 years and a maximum of 14 years (mean follow-up 9 years) (Molyneux *et al*., 2009). Analysis of recorded rebleeding and death was by the treatment received. Twenty four rebleeds occurred more than 1 year after treatment. Of these, 13 were from the treated aneurysm (10 in the coiling group and 3 in the clipping group; log rank p = 0.06 by intention-to-treat analysis). Four rebleeds occurred from a pre-existing aneurysm and six from new aneurysms. At 5 years, 11% (112 of 1046) of the patients in the endovascular group and 14% (144 of 1041) of the patients in the neurosurgical group had died (log-rank p = 0.03). The risk of death at 5 years was significantly lower in the coiling group than in the clipping group (relative risk 0.77, 95% CI 0.61-0.98; p = 0.03). The proportion of survivors at 5 years who were independent did not differ between the two groups: endovascular 83% (626 of 755) and neurosurgical 82% (584 of 713). The standardized mortality rate, conditional on survival at 1 year, was increased for patients treated for ruptured aneurysms compared with the general population (1.57, 95% CI 1.32-1.82; p<0.0001). Long-term follow-up showed an increased risk of recurrent bleeding from a coiled aneurysm compared with a clipped aneurysm, but this risk was small. However, the risk of death at 5 years was significantly lower in the coiled than it was in the clipped group. The standardized mortality rate for patients treated for ruptured aneurysms was increased compared with the general population.

Title: General Anesthesia versus Local Anesthesia for carotid surgery (GALA).

The Carotid End Arterectomy (CEA) has been shown to lower the risk of stroke ipsilateral to severe atherosclerotic carotid-artery stenosis. This effect is offset by complications during or soon after surgery. This study compared surgery under general anesthesia with that under local anesthesia because prediction and avoidance of perioperative strokes would be easier under local anesthesia than under general anesthesia. In this international, multicentre, randomized controlled trial of 3526 patients with symptomatic or asymptomatic carotid stenosis, subjects were randomly assigned to surgery under general (n = 1753) or local (n = 1773) anesthesia (Lewis *et al*., 2008). The primary outcome was the proportion of patients with stroke (including retinal infarction), myocardial infarction, or death between randomization and 30 days after surgery. Analysis was by intention to treat. The primary outcome occurred in 84 (4.8%) patients assigned to surgery under general anesthesia and 80 (4.5%) of those assigned to surgery under local anesthesia; three events per 1000 treated were prevented with local anesthesia (95% CI -11 to 17; Risk Ratio (RR) 0.94 [95% CI 0.70-1.27]). The two groups did not significantly differ for quality of life, length of hospital stay, or the primary outcome in the prespecified subgroups of age, contralateral carotid occlusion and baseline surgical risk. This study did not show difference in outcomes between general and local anesthesia for carotid surgery. The study once again highlights that per-and post-operative CEA risks are surgeon skill dependent.

Title: Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: A randomized non-inferiority trial.

In patients with non-alular aerial fibrillation, embolic stroke is associated with Left Atrial Appendage (LAA) thrombi. This study assessed the efficacy and safety of percutaneous closure of the LAA for prevention of stroke compared with warfare treatment in patients with aerial fibrillation. In this multicentre, randomized, non-inferiority trial adult patients with non-alular aerial fibrillation were eligible if they had at least one of the following: Previous stroke

or transient ischemic attack, congestive heart failure, diabetes, hypertension, or were 75 years or older. There were 707 eligible patients randomly assigned in a 2:1 ratio to either percutaneous closure of the LAA by use of a WATCHMAN device (Atritech, Plymouth, MN, US) implanted by a catheter-based delivery system implanted by a trans-septal approach under fluoroscopy guidance and subsequent discontinuation of warfarin (intervention; n = 463) or to warfare treatment with a target international normalized ratio between 2.0 and 3.0 (control; n = 244) (Holmes *et al*., 2009). Efficacy was assessed by a primary composite endpoint of stroke, cardiovascular death and systemic embolism. The criterion of non-inferiority for the intervention was 97.5% by use of a two-fold non-inferiority margin. Serious adverse events that constituted the primary endpoint for safety included major bleeding, pericardial effusion and device embolisation. Analysis was by intention to treat. At 1065 patient-years of follow-up, the primary efficacy event rate was 3.0 per 100 patient-years (95% Credible Interval (CrI) 1.9-4.5) in the intervention group and 4.9 per 100 patient-years (2.8-7.1) in the control group (Rate Ratio (RR) 0.62, 95% CrI 0.35-1.25). The probability of non-inferiority of the intervention was more than 99.9%. Adverse safety events were more frequent in the intervention group than in the control group (7.4 per 100 patient-years, 95% CrI 5.5-9.7, Vs 4.4 per 100 patient-years, 95% CrI 2.5-6.7; RR 1.69, 1.01-3.19) and included serious pericardial effusion, major bleeding and hemorrhagic stroke. In this study, the percutaneous closure of the LAA with this device was efficacious and non-inferior to that of warfare therapy. There was a higher rate of adverse safety events in the intervention than in the control group mainly a result of peri-procedural complications. Thus closure of the LAA provides an alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with non-valvular atrial fibrillation. The main limitations of this study is it is difficult to judge the true efficacy of the device given that the patients continued to be on warfarin for 45 days in 14% cases and for 6-months in 8% cases. Second, in the warfarin group patients had a therapeutic INR (between 2.0 and 3.0) only 66% of the time.

Title: Long-term risk of carotid restenosis in patients randomly assigned to endovascular treatment or endarterectomy in the Carotid and Vertebral Artery Tran luminal Angioplasty Study (CAVATAS): Long-term follow-up of a randomized trial.

Table 1: Summary of the randomized control trials undertaken in stroke in 2009

References	Time to randomization post-stroke	Set-up	Sample size	Intervention	Main findings
Thrombolytics and stroke					
Hacke *et al*. (2009)	Within 3-9 h of ischemic stroke		186; 90 µg kg^{-1} desmoteplase = 57, 125 µg kg^{-1} desmoteplase = 66, Placebo = 63	Desmoteplase Vs placebo	The clinical response rates at day 90 were: 47% (27 of 57) for 90 microg kg^{-1} desmoteplase, 36% (24 of 66) for 125 microg kg^{-1} desmoteplase and 46% (29 of 63) for placebo. The median changes in lesion volume were: 14.0% (0.5 cm^3) for 90 microg kg^{-1} desmoteplase; 10.8% (0.3 cm^3) for 125 microg kg^{-1} desmoteplase and -10.0% (-0.9 cm^3) for placebo. The rates of symptomatic intracranial hemorrhage were 3.5% for 90 mg kg^{-1} desmoteplase, 4.5% for 125 mg kg^{-1} desmoteplase and 0% for placebo. The overall mortality rate was 11% (5% for 90 mg kg^{-1} desmoteplase; 21% for 125 mg kg^{-1} desmoteplase and 6% for placebo).
Thijs *et al*. (2009)	Between 3 and 12 h of ischemic stroke	Acute hospitalization	40 patients; Microplasmin = 30 Placebo = 10	Microplasmin (6 patients received a total dose of 2 mg kg^{-1}, 12 patients received a total dose of 3 mg kg^{-1} and 12 patients received a total dose of 4 mg kg^{-1}) or placebo.	Microplasmin neutralized alpha$_2$-antiplasmin by 80%. No significant effect on reperfusion rate or on clinical outcome was observed between the 2 groups. MMP-2 levels were reduced in microplasmin-treated patients but not MMP-9 levels. Microplasmin was well tolerated with only1 of 30 treated patients developing a fatal symptomatic intracerebral hemorrhage.
Levy *et al*. (2009)	< 6 h of ischemic Stroke		500 patients; Ancrod = 253 Placebo = 247	Ancrod (0.167 IU kg^{-1} h^{-1}) or placebo over 2 or 3 h	This study was stopped prematurely for lack of efficacy based on the interim analysis for futility. Despite desired change in fibrinogen level in >90% of ancrod subjects there was no difference between the groups on the modified Rankin Scale at 90 days. Mortality at 90 days was the same between the 2 groups (P = 0.32) with stroke being the most common cause of death, accounting for 38% of deaths in each group There was no difference in the incidence of symptomatic intracranial hemorrhage within the first 72 h between 2 groups (3.9% Vs 2.0%; P = 0.19).
Zivin *et al*. (2009)	Within 24 h of ischemic stroke		660; Transcranial Laser Therapy (TLT) = 331 Sham control = 327	Transcranial Laser Therapy (TLT) Vs sham control	In the TLT group 120 (36.3%) achieved favorable outcome versus 101 (30.9%), in the sham group (p = 0.094). Post hoc analysis showed patients with a baseline NIHSS score of <16 had a favorable outcome at

Table 1: Continued

					90 days on the primary end point (p<0.044). Mortality rates were 17.5% and17.4% and serious adverse events were 37.8% and 41.8% for TLT and sham respectively
Molina *et al*. (2009)	< 3 h of ischemic stroke	Acute hospitalization	35 patients; Cohort 1 = 12, Cohort 2 = 11, Controls = 12	tPA plus micros (MRX-801) infusion over 90 min (Cohort 1 = 1.4 mL; Cohort 2 = 2.8 mL with continuous TCD insonation; Controls received tPA and brief TCD assessments.	No symptomatic Intracerebral Hemorrhage (sICH) within 36 h after tPA occurred in Cohort 1 and controls, whereas 3 (27%) occurred in Cohort 2 (p = 0.028). Sustained complete recanalization/clinical recovery rates at the end of TCD monitoring at 3 month were: 67/75% for Cohort 1, 46/50% for Cohort 2 and 33/36% for controls (p = 0.25/0.17). The median time to recanalization was shorter in Cohort 1 (30 min) and Cohort 2 (30 min) compared to controls (60 min) (p = 0.054).
Statins and stroke					
Lavallee *et al*. (2009)			94; Atorvastatin = 47 Placebo = 47	Atorvastatin 80 mg daily or matching placebo.	Atorvastatin 80 mg day^{-1} did not improve CVR or endothelial dysfunction of carotid and brachial arteries at 3 months in patients with lacunar stroke.
Poppitt *et al*. (2009)	>3 months of ischemic stroke	On acute hospitalization.	102; Omega-3 = 51, Placebo oil = 51	3 g day^{-1} encapsulated fish oil containing ≈ 1.2 g total omega-3 (0.7 g docosahexaenoic acid; 0.3 g eicosapentaenoic acid) or placebo oil (combination palm and soy) taken daily each morning with food over 12 weeks.	Twelve weeks of treatment with moderate-dose fish oil supplements had no effect on cardiovascular biomarkers or mood in patients with ischemic stroke.
Hyperglycaemia and stroke					
Johnston *et al*. (2009)			74; Tight control, = 24, Loose control = 25, Control usual care = 25	Subjects who received Novolin insulin in normal saline (1 U/1 mL) as a continuous infusion were randomized to tight control target 70-10 mg dL^{-1} vs. loose control target 70-200 mg dL^{-1} vs. control usual care 70-300 mg dL^{-1}	The target blood sugar level was achieved in the first 24 h in 90% of the time in the loose control group and 44% of the time the tight group. The overall rates of hypoglycemia (<55 mg dL^{-1}) were 4% in control, 4% in loose and 30% in tight. The efficacy analysis based on modified Rankin Scale, Barthel Index and death showed no statistically significant differences between the 3-groups.
Atrial fibrillation and stroke					
Connolly *et al*. (2009)		Out-patient setting	18,113 patients; Dabigatran- 110 mg = 6015, 150 mg = 6076, Warfarin = 6022	Fixed doses of dabigatran-110 mg or 150 mg twice daily or adjusted-dose warfarin	Rates of the stroke or systemic embolism were 1.69% $year^{-1}$ in the warfarin group compared with 1.53% $year^{-1}$ in the 110 mg dabigatran (p<0.001 for noninferiority) and 1.11% $year^{-1}$ in the 150 mg dabigatran group (p<0.001 for superiority). The rate of major bleeding was 3.36% $year^{-1}$ in the warfarin group compared with 2.71% $year^{-1}$ in the 110 mg dabigatran (p = 0.003) and 3.11% $year^{-1}$ in the 150 mg dabigatran group (p = 0.31). The rate of hemorrhagic stroke was 0.38% $year^{-1}$ in the warfarin group compared with 0.12% $year^{-1}$ with 110 mg dabigatran (p<0.001) and 0.10% $year^{-1}$ with 150 mg of dabigatran (p<0.001). The mortality rate was 4.13% $year^{-1}$ in the warfarin group vs. 3.75% $year^{-1}$ with 110 mg dabigatran (p = 0.13) and 3.64% $year^{-1}$ with 150 mg dabigatran (p = 0.051).
Neuroprotection and stroke					
Mathew *et al*. (2009)			277; Lidociane = 114 Placebo = 127	Lidocaine group (1 mg kg^{-1} bolus followed by a continuous infusion through48 h postoperatively), or placebo group (bolus and infusion of normal saline at a similar rate as the treatment group)	The incidence of cognitive deficit in the lidocaine group was 45.5% versus 45.7% in the placebo group (p = 0.97). Multivariable analysis revealed a significant interaction between treatment group and diabetes, such that diabetic subjects receiving lidocaine were more likely to suffer cognitive decline (p = 0.004). Secondary analysis showed protective dose effect of lower dose lidocaine in non-diabetics.
Haljan *et al*. (2009)	Before undergoing CABG surgery	Academic Hospital	32; Erythropoietin = 24 (375 U kg^{-1} = 8, 750 U kg^{-1} = 8, 1500 U kg^{-1} = 8), Placebo = 8	375 U kg^{-1}, 750 U kg^{-1}, or 1500 U kg^{-1} of recombinant human erythropoietin divided in 3 daily doses, starting the day before surgery or placebo	Neurocognitive dysfunction at discharge by group was: placebo 6/8 (75%), 375 U kg^{-1} 4/8 (50%),750 U kg^{-1} 6/8 (75%) and 1500 U kg^{-1} 5/8 (63%). Neurocognitive dysfunction at 2 months by group was: placebo 3/8 (38%), 375 U kg^{-1} 1/8 (13%), 750 U kg^{-1} 1/8 (13%) and 1500 U kg^{-1} 0/8 (0%).
Ehrenreich *et al*. (2009)	6 h of symptom onset, at 24 and 48 h	Acute hospitalization	522; Epo = 256 Placebo = 266	Epo was infused intravenously (40,000 IU in 50 mL normal saline over	On analysis of intention-to-treat and per-protocol populations, neither primary outcome Barthel Index on Day 90 (p = 0.45) nor any of the secondary outcome measures (NIHSS, m Rankin Scale and HMRI for lesion

Table 1: Continued

				30 min) for a total dose of 120,000 IU vs. placebo	lesion size) showed favorable effects of Epo. Overall death rate was 16.4% in the Epo and 9.0% in the placebo group ($p = 0.01$).
Teal *et al*. (2009)	4.5 h of ischemic stroke	Acute hospitalization	681; Repinotan = 342, Placebo = 284	Repinotan (loading dose 0.1 mg h^{-1} [40 mL h^{-1}] for first 2 h followed by infusion of 0.05 mg h^{-1}\ [20 mL h^{-1}] over the next 4 h or placebo. Continuous IV infusion of repinotan or placebo started within 4.5 h from the onset of ischemic symptoms.	At 3 months, the response rate on the Barthel Index ≥ 85 was 37.1% (127/342) for patients on repinotan and 42.4% (143/337) for patients taking the placebo (Cochran-Mantel-Haenszel probability value = 0.149).
Stroke prevention					
Hodis *et al*. (2009)			506; High dose vitamin B = 254 Placebo = 252	High-dose vitamin B supplementation (5 mg folic acid + 0.4 mg vitamin B12 + 50 mg vitamin B6) or matching placebo for 3.1 years	Subjects with baseline tHcy ≥9.1 micromol L^{-1}, randomized to B vitamin supplementation had a significant lower rate of carotid artery intima media thickness progression compared with placebo ($p = 0.02$); while in subjects with a baseline tHcy <9.1 micromol L^{-1}, there was no significant treatment effect. B vitamin supplementation had no effect on progression of aortic or coronary artery calcification overall.
Saposnik *et al*. (2009)			5522; Vitamins = 2758 Placebo = 2764	Vitamins (daily combination of 2.5 mg of folic acid, 50 mg of vitamin B6 and 1 mg of vitamin B12) or matching placebo, for 5 years	The mean homocysteine concentration decreased by 2.2 mmol L^{-1} in the vitamin therapy group and increased by 0.80 mmol L^{-1} in the placebo group. The incidence rate of stroke was 0.88/100 person-years in the vitamin therapy group and 1.15/100 person-years in the placebo group. Vitamin therapy did not impact on neurological deficit at 24 h ($p = 0.45$) or functional dependence at discharge or at day 7. In subgroup analysis, patients aged ≤69 years, from regions without folic acid food fortification, with higher baseline cholesterol and homocysteine levels and those not receiving antiplatelet or lipid-lowering drugs at enrollment had a larger treatment benefit.
Fever in acute stroke					
Den Hertog *et al*. (2009)	Within 12 h of an acute stroke	Acute hospitalization	1400; Paracetamol = 697 Placebo = 703	Paracetamol 6 g daily or placebo	37% patients receiving paracetamol and 33% receiving placebo improved. In a post-hoc analysis of patients with baseline body temperature 37-39°C, treatment with paracetamol was associated with improved outcome. The serious adverse events in the paracetamol was 8% vs. 10% in the placebo group.
Broessner *et al*. (2009)		Neurointensive care unit	102; CoolGard = 51 Control = 51	CoolGard Vs conventional, stepwise fever management with acetaminophen 500 mg followed by anti-inflammatory drugs (an hourly ibuprofen 500 mg po, followed by pethidine 100 mg IV) and finally a surface cooling blanket (Blanketrol, Cincinnati Sub-Zero).	Fever burden during the course of treatment was 0.0 and 4.3°C h in the catheter and conventional groups, respectively ($p<0.0001$). There was at least 1 infectious adverse event reported for 49 (96%) CoolGard and 41 (80%) control patients ($p = 0.03$). There was no significant difference in mortality and neurological outcomes (Glasgow outcome scale and modified Rankin Scale scores) at 6-month follow-up between the 2 groups.
Stroke and deep vein thrombosis					
Dennis *et al*. (2009)	Within 1 week of acute hospitalization	Acute hospitalization	2518; Graduated Compression Stockings (GCS) = 1256, No GCS = 1262)	Thigh-length GCS Vs no GCS	The primary outcome (occurrence of symptomatic or asymptomatic DVT in the popliteal or femoral veins) occurred in 10.0% patients allocated to thigh-length GCS and in 10.5% allocated to avoid GCS, resulting in a non-significant absolute risk reduction of 0.5%. Skin breaks, ulcers, blisters and skin necrosis were more common in patients allocated to GCS 5% vs.1% in those allocated to avoid their use.
Stroke and depression					
Mitchell *et al*. (2009)	Within 12 week of an acute stroke	Out-patient setting	101; Psychosocial-behavioral intervention plus antidepressant = 48, Usual care including antidepressant = 53	9 sessions of brief psychosocial-behavioral intervention plus antidepressant Vs usual care including antidepressant over an 8 week period.	The Hamilton Rating Scale (HRS) for Depression raw score in the intervention group was significantly lower immediately post-treatment ($p<0.001$) and at 12 months ($p = 0.05$) compared with control subjects. Remission (HRS for Depression <10) was significantly greater immediately post-treatment and at 12 months in the intervention group compared with the usual care control.

Table 1: Continued

Stroke and aphasia					
Berthier *et al*. (2009)	Post-stroke aphasia for 2-6 years.	Out-patient setting	28; Memantine = 14 Placebo = 14	Memantine 20 mg day^{-1} Vs placebo alone during 16 weeks, followed by combined drug treatment with CIAT (weeks 16-18), drug treatment alone (weeks 18-20) and washout (weeks 20-24) and finally, an open-label extension phase of memantine (weeks 24-48).	The memantine group showed significantly better improvement on Western Aphasia Battery-Aphasia Quotient compared with the placebo group during week 16, p = 0.002; week 18, p = 0.0001; week 20, p = 0.005 and at the washout assessment p = 0.041. A significant increase in Communicative Activity Log was found in favor of memantine-CIAT relative to placebo-CIAT (week 18, p = 0.040). CIAT treatment led to improvement in both groups (p = 0.001), which was even greater in the memantine treatment (p = 0.038). Beneficial effects of memantine were maintained in the long-term follow-up evaluation and patients who switched to memantine from placebo also experienced a benefit (p = 0.02).
Surgery and stroke					
Jansen *et al*. (2009)			563; Protective Device (PD) = 145 No PD = 418	Carotid A stents with PD Vs no PD.	The main Outcome Event (OE) of the analysis (ipsilateral stroke or stroke death within 30 days) was reached in 6.2%) in the PD group and in 8.3%) in the non-protection group (p = 0.40). The OE rate was significantly lower in patients treated with a closed cell stent (5.6%) than in those treated with an open cell stent (11.0%) (p = 0.029). Secondary analysis of the data from the SPACE trial did not support the use for a PD in CAS.
Molyneux *et al*. (2009)			2143; Endovascular = 1073 Clipping = 1070	Endovascular Vs Clipping	There were 10 rebleeds in the coiling group and 3 in the clipping group; log rank p = 0.06 by intention-to-treat analysis. At 5 years, 11% of the patients in the endovascular group and 14% of the patients in the neurosurgical group had died log-rank p = 0.03. The risk of death at 5 years was lower in the coiling group than in the clipping group (p = 0.03). The proportion of survivors at 5 years who were independent did not differ between the 2 groups: endovascular 83% and neurosurgical 82%.
Lewis *et al*. (2008)			3526; Surgery under general anesthesia = 1753, Local anesthesia = 1773	Surgery under general Vs local anesthesia	The primary outcomes (stroke, retinal and myocardial infarctions and death) occurred in 4.8% patients assigned to surgery under general anesthesia and 4.5% of those assigned to surgery under local anesthesia. Three events per 1000 treated were prevented with local anesthesia. The two groups did not differ for quality of life, length of hospital stay or the primary outcome.
Holmes *et al*. (2009)		Out-patient setting	707; Percutaneous closure of the LAA by device = 463 Warfarin (control) = 244	Percutaneous closure of the LAA by use of a WATCHMAN device and subsequent discontinuation of warfarin Vs warfarin treatment with a target INR ratio between 2.0 and 3.0	The primary efficacy event rate (stroke, systemic embolisation, cardiovascular death) was 3.0/100 patient-years in the intervention group and 4.9/100 patient-years. in the control group. Primary safety events were more in the intervention than in the control group (7.4/100 patient-years vs. 4.4/100 patient-years) and included serious pericardial effusion, major bleeding and hemorrhagic stroke.
Bonati *et al*. (2009)			413; Endovascular treatment = 200 Endarterectomy = 213	Endovascular treatment Vs carotid endarterectomy	Severe carotid restenosis (≥ 70%) or occlusion occurred significantly more often in patients in the endovascular (CAS) than in patients in the endarterectomy (CEA) group (p<0.0001). The estimated 5 year incidence of restenosis was 30.7% in the CAS vs. 10.5% in the (CEA). Patients in the CAS who were treated with a stent (n = 50) had a lower risk of developing restenosis of ≥ 70% compared with those treated with balloon angioplasty alone (n = 145; p = 0.04). Ipsilateral non-perioperative stroke or TIA occurred more often in patients in whom restenosis of ≥ 70% was diagnosed in the 1st year after treatment compared with patients without restenosis of ≥ 70% (5-year incidence 23% vs 11%; p = 0.04), but the increase in ipsilateral stroke alone was not significant (10%vs 5%).
Ederle *et al*. (2009)			504; Endovascular treatment = 251, CEA surgery = 253	Patients with stenosis of the carotid artery (90% symptomatic) were randomly assigned to endovascular treatment or CEA surgery.	Within 30 days of treatment, there were more minor strokes that lasted ≤ 7 days in the endovascular (CAS) group (8 Vs 1) but the number of other strokes that lasted ≥7 days in any territory (9 Vs 10) or death was the same between the two groups (25 Vs 25). There were more cranial nerve palsies (22 Vs 0) in the CEA than in the CAS group. The estimated 8 year risk for any stroke or perioperative death was more frequent in the CAS than in the CEA treatment group 29.7% vs. 23.5%.
Santarius *et al*. (2009)			215; Drain inserted = 108, No drain inserted = 107	Drain inserted into the subdural space Vs no drain after evacuation	The trial was stopped early because of a significant benefit in reduction of SDH recurrence in drain inserted group. Recurrence occurred in 10 of 108 (9.3%) people with a drain Vs 26 of 107 (24%) without (p = 0.003). At 6 months mortality was nine of 105 (8.6%) and 19 of 105 (18.1%), respectively (p = 0.042). Medical and surgical complications were the same between the groups.

In the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), early recurrent carotid stenos is was more common in patients assigned to endovascular treatment than in patients assigned to Carotid Endarterectomy (CEA) (Brown *et al*., 2001). This raised the concern about the long-term effectiveness of endovascular treatment. This study investigated the long-term risks of carotid rest enosis after endovascular treatment and endarterectomy, the effect of the use of stents on rest enosis after endovascular treatment, risk factors for the development of rest enosis and the effect of carotid rest enosis on the risk of recurrent cerebrovascular events in patients who were enrolled in the CAVATAS. Of the 413 patients in the CAVATAS, 200 patients had endovascular treatment and 213 patients had endarterectomy with prospective clinical follow-up at a median of 5 years and carotid duplex ultrasound at a median of 4 years (Bonati *et al*., 2009). Analysis was by intention to treat. Severe carotid resents is (≥70%) or occlusion occurred significantly more often in patients in the endovascular than in patients in the endarterectomy group (adjusted Hazard Ratio (HR) 3.17, 95% CI 1.89-5.32; p<0.0001). The estimated 5-year incidence of rest enosis was 30.7% in the endovascular and 10.5% in the endarterectomy group. Patients in the endovascular group who were treated with a stent (n = 50) had a significantly lower risk of developing rest enosis of ≥70% compared with those treated with balloon angioplasty alone (n = 145; HR 0.43, 0.19-0.97; p = 0.04). Current smoking or a history of smoking was a predictor of restenosis of ≥70% (2.32, 1.19-4.54; p = 0.01) and the early finding of moderate stenos is (50-69%) up to 60 days after treatment was associated with the risk of progression to rest enosis of ≥70% (3.76, 1.88-7.52; p = 0.0002). The composite endpoint of ipsilateral non-perioperative stroke or transient ischemic attack occurred more often in patients in whom restenosis of ≥70% was diagnosed in the first year after treatment compared to patients without rest enosis of ≥70% (5-year incidence 23% Vs 11%; HR 2.18, 1.04-4.54; p = 0.04), but this increase in ipsilateral stroke alone was not significant (10% Vs 5%; 1.67, 0.54-5.11). In this study long-term risk of carotid rest enosis is three times more common after endovascular treatment than after endarterectomy and is associated with recurrent ipsilateral cerebrovascular symptoms; however, the risk of recurrent ipsilateral stroke is low.

Title: Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid and Vertebral Artery Tran luminal Angioplasty Study (CAVATAS): Long-term follow-up of a randomized trial.

Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) was a randomized controlled trial of endovascular treatment (angioplasty with or without stenting) compared to Carotid Endarterectomy (CEA) for the treatment of mainly symptomatic carotid artery stenosis. The initial short-term data as to the safety of endovascular Vs CEA treatment was published in (Brown *et al*., 2001). This article reports the long-term follow-up results of the CAVATAS (Ederle *et al*., 2009). There were 504 patients with stenosis of the carotid artery (90% symptomatic) randomly assigned to endovascular treatment (n = 251) or CEA surgery (n = 253). Within 30 days of treatment, there were more minor strokes that lasted ≤7 days in the endovascular group (8 Vs 1) but the number of other strokes that lasted ≥7 days in any territory (9 Vs 10) or death was the same between the two groups (25 Vs 25). There were more cranial nerve palsies in the CEA than in the endovascular group (22 Vs 0). The 8-year cumulative incidence of disabling stroke or death was 45.2% (SE 4.0%) in the endovascular group Vs 50.4% (4.1%) in the CEA group. The estimated 8-year risk for any stroke or perioperative death was more frequent in the endovascular than in the CEA treatment group 29.7% (SE 3.4%) Vs 23.5% (3.5%). Thus more patients had stroke during follow-up in the endovascular group than in the CEA surgical group, but the rate of ipsilateral non-perioperative stroke was low in both groups and none of the differences in the stroke outcome measures was significant. However, this study was underpowered and the confidence intervals were wide. Additionally, improvement in the technical equipment used in endovascular treatment has occurred since the CAVATAS study was undertaken and the results today would be quite different. This study highlights the low rate of stroke, long-term, after endovascular treatment, making it an acceptable approach for patients in whom CEA is contraindicated or who prefer endovascular treatment over CEA surgery.

Title: Use of drains versus no drains after burr-hole evacuation of chronic subdural hematoma: A randomized controlled trial.

Chronic subdural hematoma causes serious morbidity and mortality especially in the elderly (Weigel *et al*., 2003). It recurs after surgical evacuation in 5-30% of patients (Santarius and Hutchinson, 2004). Drains might reduce recurrence but are not used routinely. This study aimed to investigate the effect of drains on recurrence rates and clinical outcomes. In this single center randomized controlled trial, 269 patients aged >18 years with a chronic subdural hematoma were assessed for eligibility for burr-hole drainage (Santarius *et al*., 2009). By block randomization drain was inserted into the subdural space in 108 patients and no drain after evacuation in 107 patients. The primary endpoint was recurrence needing re-drainage. Analyses were on an intention-to-

treat basis. The trial was stopped early because of a significant benefit in reduction of recurrence. Recurrence occurred in ten of 108 (9.3%) people with a drain and 26 of 107 (24%) without (p = 0.003; 95% CI 0.14-0.70). At 6 months, mortality was 9 of 105 (8.6%) and 19 of 105 (18.1%), respectively (p = 0.042; 95% CI 0.1-0.99). Medical and surgical complications were the same between the study groups. Thus in this study use of a drain after burr-hole drainage of chronic subdural hematoma was safe and associated with reduced recurrence and mortality at 6 months.

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

CONCLUSION

The following conclusions can be drawn from the studies summarized here: (1) Desmoteplase given 3-9 h after the onset of stroke has no clinical benefit. (2) Microplasmin is well tolerated but its therapeutic efficacy in ischemic stroke needs to be confirmed. (3) IV accord within 6 h of the onset of acute ischemic stroke does not improve clinical outcome, with a trend towards increased intracranial bleeding. (4) Tran cranial Laser Therapy (TLT) using near-infrared laser technology is safe in the treatment of acute ischemic stroke but of questionable efficacy. (5) Atorvastatin 80 mg day^{-1} does not affect cerebral vasoreactivity or endothelial dysfunction of carotid and brachial arteries. (6) Moderate-doses of omega-3 fish oil supplements had no effect on cardiovascular biomarkers or mood in patients with ischemic stroke. (7) Aggressive blood sugar control with insulin infusion, though achievable, does not improve functional outcome. (8) Dabigatran administered at a dose of 150 mg, is effective in lowering rates of stroke and systemic embolism but has similar rates of major and minor hemorrhage to warfare. (9) Agents such as Repinotan, lidocaine and erythropoeitin have not been found to be effective neuroprotectants in patients with acute ischemic stroke. (10) High-dose vitamin B supplementation is unable to slow the progression of atherosclerosis in the carotid and coronary arteries. (11) Routine use of high-dose paracetamol in patients with acute stroke does not improve functional outcome at 3 months. (12) Prophylactic, endovascular-based long-term normothermia in ICU patients with severe cerebrovascular disease, despite significantly reducing fever is not associated with an increase in adverse events, mortality and neurological outcomes. (13) Thigh-high compression stockings do not reduce the risk of deep vein thrombosis in patients with ischemic stroke. They are however, associated with increase skin breakdown. (14) Memantine and constraint-induced aphasia therapy were effective in decreasing aphasia severity in chronic poststroke aphasia both in short-and long-term duration. (15) Long-term follow-up (mean 9 years) show an increased risk of recurrent bleeding from a coiling compared to clipping an aneurysm, but this risk is small. However, the risk of death at 5 years is significantly lower in the coiled than in the clipped group. (16) Percutaneous closure of the left atrial appendage can be an effective alternative strategy to chronic warfarin therapy for stroke prophylaxis in patients with non-valvular atrial fibrillation. (17) Long-term risk of carotid restenosis is three times more common after endovascular treatment than after endarterectomy with recurrent ipsilateral cerebrovascular symptoms; however, the risk of recurrent ipsilateral stroke is low. (18) Drain after burr-hole drainage of chronic subdural hematoma is safe and associated with reduced recurrence and mortality at 6 months.

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