STROKE IN REVIEW

TM

WWW.REHABINREVIEW.COM

Volume 4 | Published by Physicians Specialization in Neurorecovery | March 5, 2024

THROMBECTOMY UP TO 24 HOURS AFTER STROKE

Previous, nonrandomized studies of patients with ischemic stroke have found that patients with a mismatch between the volume of brain tissue that may be salvaged and the volume of infarcted tissue may benefit from reperfusion. This study, the DAWN (DWI of CTP Assessment with Clinical Mismatch in the Triage of Wake-Up in Late Presenting Strokes undergoing Neurointervention with Trevo) trial, assessed the efficacy of mechanical thrombectomy up to 24 hours after stroke onset.

Subjects were 206 patients with occlusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both, all of whom had a mismatch between the severity of the clinical deficits and the infarct volume. The participants were randomized to mechanical thrombectomy plus standard medical care or to standard medical care alone. The primary endpoints were the modified Rankin scale (mRS) at 90 days, and the percentage of those patients functionally independent (mRS of zero to two) at 90 days.

At 90 days, scores on the mRS were 5.5 in the thrombectomy group and 3.4 in the control group (posterior probability of superiority>999). Functional independence at 90 days was achieved by 49% in the thrombectomy group and by 13% in the control group (posterior probability of superiority >0.999). The rate of neurologic deterioration was 14% in the thrombectomy group and 26% in the control group (p=0.04).

Conclusion: This study of patients with acute stroke, all with a mismatch between clinical deficit and infarct, found that improved outcomes could be achieved with thrombectomy if completed up to 24 hours after stroke onset.

Nogueira, R., et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. **N Engl J Med**. 2018, January 4; 378:11-21.

THROMBECTOMY AFTER TISSUE PLASMINOGEN ACTIVATOR

Studies have shown that intravenous tissue plasminogen activator (t-PA) administered within 4.5 hours of ischemic stroke symptom onset can improve outcomes. Mechanical thrombectomy can remove large, proximal clots rapidly resulting in higher rates of reperfusion than tPA alone. This study, the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) compared the relative efficacy of tPA alone versus tPA combined with stent retrieval.

This multi-center trial included 39 centers in the United States and Europe. The subjects were patients with ischemic stroke with occlusions in the proximal anterior intracranial circulation, and presenting within six hours. The patient were randomized to receive IV tPA alone, or combined with thrombectomy. The primary outcome measure was disability at 90 days as assessed by the modified Rankin scale (mRS), with secondary outcomes including death at 90 days, and the change in NIHSS scores at 27 hours after randomization.

At 90 days, the thrombectomy group had better global disability scores on the mRS (p<0.01). The portion of patients functionally independent at 90 days was higher in the intervention group with an absolute difference of 25 percentage points. Mortality at 90 days, and serious adverse events and symptomatic intracranial hemorrhage, did not differ significantly between the two groups.

Conclusion: This study of patients with acute ischemic stroke with large vessel occlusions of the anterior circulation, who received tPA, had better functional outcomes at 90 days when also treated with thrombectomy within six hours.

Saver, J et al. Stent–Retriever Thrombectomy after Intravenous t-PA vs t-PA Alone in Stroke. **N Eng J Med.** 2015, June 11; 372(24): 2285-2295.

ENDOVASCULAR TREATMENT FOR STROKE WITH LARGE MISMATCH IMAGING PROFILE

When assessing patients with ischemic stroke for endovascular therapy or tPA, the ratio of hypoperfused to nonviable ischemic tissue is determined. From previous studies, appropriate candidates for endovascular intervention have a ratio of 1.8 or greater between critically hypoperfused and ischemic core, and a volume of ischemic core of 70mL or less. This study assessed the benefits of treating patients with baseline ischemic cores of up to 150mL.

Data were reviewed from a prospectively collected large vessel occlusion stroke database for patients with intracranial internal carotid artery and/or proximal middle cerebral artery occlusion on CT angiography, with a time from last known normal of less than 12 hours, baseline ischemic cores of greater than 50 mL and an absolute mismatch volume of 40 mL-150mL. Patients undergoing endovascular treatment were compared with matched controls who did not receive this treatment. Data were included from 28 patients in the intervention group and 41 in the control group. Endovascular therapy was significantly associated with a favorable shift in the 90 day modified Rankin scores ((mRS (p=0.04)), with good outcomes in 0% of the controls and in 25% of the intervention group (p=0.04). The final infarct volumes were smaller in the intervention group (87ml) than in the control group (242 ml). For the subgroup with ischemic volumes of greater than 70ml, a significant improvement in final infarct volume was noted in the intervention group (p<0.001) with an insignificant trend towards better mRS in the treatment group. The 90 day mortality was numerically but not statistically lower in the treatment group.

Conclusion: This study of patients with ischemic stroke found that for properly selected patients, endovascular therapy may benefit those with a large ischemic core and large mismatch profiles.

Rebello, L., et al. Endovascular Treatment for Patients with Acute Stroke Who Have a Large Ischemic Core and Large Mismatch Imaging Profile. **JAMA Neurol.** 2017, January 1; 74;(1): 34-40.

MRI-GUIDED THROMBOLYSIS FOR STROKE

This study, the Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial was designed to determine whether treatment with alteplase improves functional outcomes among patients with unknown time of stroke onset and a mismatch between diffusion-weighted imaging and FLAIR findings on magnetic resonance imaging (MRI).

Subjects were 18 to 80 years of age, all of whom could not report the timing of the onset of stroke symptoms, but was thought to be more than 4.5 hours. Patients were eligible who had an admission MRI revealing a mismatch between the presence of an abnormal signal on MRI diffusion-weighted imaging and no visible signal change on FLAIR in the region of the acute stroke.

Those randomized to the treatment group received 0.9 mg of alteplase per kilogram of body weight or a placebo. Clinical assessments were completed at baseline, and up to 90 days after randomization. The primary efficacy endpoint was a "favorable" clinical outcome, defined as a modified Rankin scale (MRS) score at 90 days of zero to one. The primary safety endpoints were death and a composite outcome of death or dependence, defined as an MRS of four to six at 90 days.

At 90 days, favorable outcomes were noted in 53.3% of the treatment group and 41.8% of the placebo group (p=0.02). The median scores on the MRS at 90 days were one in the alteplase group and two in the placebo group (p=0.003). Death or inability to live independently occurred in 13.5% of the alteplase group and in 18.3% of the placebo group (p=0.17). Symptomatic intracranial hemorrhage was found in two percent of the treatment group and in 0.4% in the placebo group (p=0.15).

Conclusion: This study of patients with acute stroke with an unknown time of onset found that intravenous alteplase, guided by a mismatch between diffusion-weighted imaging and FLAIR in the region of ischemia, resulted in significantly better functional outcome at 90 days.

Thomalla, G., et al. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. **N Engl J Med.** 2018, August 16; 379(7): 611-622.

INTENSIVE VERSUS STANDARD BLOOD PRESSURE CONTROL

The Systolic Blood Pressure Intervention Trial (SPRINT) was designed to assess whether a systolic blood pressure (SBP) target of less than 120 mmHg is associated with a lower rate of clinical events than a SBP target of less than 140 mmHg.

Subjects 50 years of age or older who were at increased risk for cardiovascular disease but did not have diabetes or previous stroke were assessed. Participants with a SBP of 130-180 mmHg with or without hypertensive treatment were recruited and randomized to either an intensive treatment (IT) goal of 120 mmHg or to the standard treatment (ST) goal of 140 mmHg. The primary outcome was a composite of myocardial infarction, acute coronary syndrome, stroke, acute decompensated heart failure or death from cardiovascular causes.

A total of 9,361 patients underwent randomization. The rates of the primary outcome were 1.77% per year in the IT group and 2.40% per year in the ST group (hazard ratio (HR), 0.73; p<0.001). Adverse events were more common in the IT group and included hypotension, electrolyte abnormalities, acute kidney injury and syncope. In the posttreatment phase, rates of myocardial infarction remained significantly lower in the IT group than in the ST group (HR 0.71; p=0.005).

Conclusion: This study of patients 50 years of age or older with at least one additional cardiovascular risk factor found that compared to the traditional systolic blood pressure goal of 140 mmHg or less, a goal systolic blood pressure of 120 mmHg resulted in fewer serious cardiac or cerebrovascular events.

The SPRINT Research Group. Final Report of a Trial of Intensive versus Standard Blood Pressure Control. **N Eng J Med.** 2021, May 20: 1921-1930.

INTENSIVE BLOOD PRESSURE LOWERING AFTER CEREBRAL HEMORRHAGE

After an intracerebral hemorrhage (ICH), an acute hypertensive response may be associated with hematoma expansion and an increase in mortality. This study, the Antihypertensive Treatment of Acute Cerebral Hemorrhage II (ATACH-2) was designed to determine the efficacy of an early and rapid lowering of systolic blood pressure (SBP) in patients with an ICH.

Subjects were adult patients with ICH treated within 4.5 hours of symptom onset. Eligible patients had a Glasgow Coma Scale score of five or more at the time of arrival, with a hematoma volume of less than 60 cm^3 measured on the initial CT. The patients were randomized to a standard blood pressure group to maintain systolic blood pressure at 140-179 mmHg, or to an intensive treatment group to maintain systolic blood pressure at 110-139 mmHg for 24 hours after randomization. A CT scan was obtained at 24 hours after treatment initiation. The patients were followed at one month by telephone and at three months in clinic for a disability evaluation using the modified Rankin Scale (mRS), and quality of life, assessed by the European !uality of Life–5 dimensions questionnaire. The primary outcome was the proportion of patients with

moderately severe or severe disability, or death at three months.

Of the 961 participants, moderate-severe disability was determined in 38.7% in the intensive treatment group and 37.7% in the standard treatment group (p=0.84). In addition, there was no significant difference between the groups in the rate of death or neurologic deterioration at 24 hours after randomization. The percentage of patients with treatment-related serious adverse events within 72 hours was 1.6% in the intensive treatment group and 1.2% in the standard treatment group. Adverse renal events within seven days were greater in the intensive group than in the standard treatment group (p=0.002). The trial was discontinued for futility.

Conclusion: This study of patients with acute intracerebral hemorrhage found that treatment to maintain systolic blood pressure between 110 and 139 mmHg did not result in improved outcomes compared to those with a treatment target of 140-179 mmHg.

Qureshi, A et al. Intensive Blood–Pressure Lowering in Patients with Acute Cerebral Hemorrhage. **N Eng J Med.** 2016, September; 375(11):1033 -1043.

PFO CLOSURE OR ANTICOAGULATION VERSUS ANTIPLATELETS AFTER STROKE

Studies have shown as association between patent foramen ovale (PFO) and cryptogenic stroke, particularly among patients younger than 55 years of age, those with atrial septal aneurysm or a substantial left to right intra-atrial shunt. The Patent Foramen Ovale Closure or Anticoagulants Versus Antiplatelet Therapy to Prevent Stroke Recurrence (CLOSE) trial compared transcatheter closure of PFO plus antiplatelet therapy with antiplatelet therapy and oral anticoagulant therapy with antiplatelet therapy alone, for the prevention of stroke recurrence in adults up to 60 years of age with a recent cryptogenic stroke.

Eligible patients were randomly assigned in a 1:1:1 ratio to undergo PFO closure followed by long-term antiplatelet therapy (PFO+AP), antiplatelet therapy alone (AP), or oral anticoagulation (AC). The primary efficacy outcome was the occurrence of fatal or nonfatal stroke.

Subjects included 663 adults with 173 in the PFO, 180 in the AC, and 180 in the AP group. In follow-up, a stroke occurred in 0 patients in the PFO group and 14 in the AP group (p<0.001). A stroke occurred in 3 of the patient's in the before meals and 7 of the patients in the AP group The secondary composite outcome of stroke, transient ischemic attack, or systemic embolism occurred in significantly fewer patients in the PFO closure group than in the antiplatelet only group (3.4% vs. 8.9%;p=0.01).

Conclusion: This study of patients with a recent cryptogenic ischemic stroke attributed to PFO with associated atrial septum aneurysm or large right to left shunt found that the recurrent stroke rate was significantly lower among those with PFO closure plus long-term antiplatelet therapy than with antiplatelet therapy alone.

Mas, J et al Patent Foramen Ovale Closure or Anticoagulation Versus Antiplatelets after Stroke. **N Eng J Med.** 2017, September 14; 377: 1011 –1021

STENTING VERSUS AGGRESSIVE MEDICAL THERAPY FOR INTRACRANIAL ARTERIAL STENOSIS

Atherosclerotic intracranial arterial stenosis is one of the most common causes of stroke worldwide. Two strategies have emerged for the treatment of high-risk patients. These include aggressive medical therapy, and percutaneous transluminal angioplasty and stenting (PTAS). This study compared these two treatments in high-risk patients with intracranial arterial stenosis.

Eligible patients presented with a transient ischemic attack or non-disabling stroke within 30 days before enrollment, attributed to a 70-99% stenosis of a major intracranial artery. For both groups, medical management included aspirin 325 mg per day, clopidogrel at 75 mg per day for 90 days, and the management of primary and secondary risk factors. Those randomized the PTAS group underwent the procedure within three days of randomization. All subjects were evaluated at baseline, at four and thirty days, with follow-up every four months. The primary endpoint was stroke or death within 30 days or a revascularization procedure for the qualifying lesion beyond 30 days of enrollment. The study was terminated after 451 patients underwent randomization as the 30-day rate of stroke or death was 14.7% in the PTAS group and 5.8% in the medical management group (p=0.002). The probability of the occurrence of a primary endpoint over time was greater in the PTAS group, with a one-year occurrence of 20% in the PTAS group and 12.2% in the medical management group (p=0.009).

Conclusion: This study of patients with a recent transient ischemic attack or stroke found that medical management was superior to medical management with stenting for preventing recurrent strokes.

Chimowitz, M et al., Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis. **N Eng J Med**. 2011, Sept 15; 365 (11):993-1003.

HIGH-DOSE STATIN AFTER STROKE

Treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) has been shown to reduce the risk of stroke among patients with coronary heart disease and those at increased risk for cardiovascular disease. This study (The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) explored the efficacy of treatment with a high-dose statin to reduce the risk of fatal or nonfatal stroke among patients with a history of stroke or transient ischemic attack (TIA).

Subjects were adults with an ischemic or hemorrhagic stroke, or a TIA, 1-6 months before randomization. Subjects were randomized to receive either 80 mg of atorvastatin per day or a placebo. Follow-up visits were scheduled 1, 3, and 6 months after enrollment and every 6 months thereafter. The primary outcome was the time from randomization to a first stroke. Laboratory assessments and electrocardiograms were performed at screening and at regular intervals during the study.

A final assessment was completed using data from 4,731 subjects, at a median duration of 4.9 years follow-up. Using a pre-specified analysis, atorvastatin was associated with an 18% relative reduction in the risk of stroke as compared with placebo (p=0.03). For ischemic stroke, the adjusted hazard ratio in the atorvastatin group, compared with placebo was 0.78, and for hemorrhagic stroke was 1.66. Additional risk reductions in favor of the atorvastatin group included combined stroke or TIA (p<0.001),

major coronary event (p=0.003), and any coronary event (p<0.001).

Conclusion: This study of patients with a recent history of stroke or transient ischemic attack found that treatment with 80 mg of atorvastatin reduced the risk of subsequent stroke, TIA and coronary events.

Amarenco, P et al. High-Dose Atorvastatin after Stroke or Transient Ischemic Attack. **N Eng J Med.** 2006,Aug 10; 355(6):549-559.

FLUOXETINE FOR MOTOR RECOVERY AFTER ISCHEMIC STROKE

After an ischemic stroke, various interventions, including mono-aminergic drugs, have been shown to modulate brain plasticity, and to reduce the residual neurological deficits and subsequent disability. This study tested the effect of treatment with fluoxetine on the motor recovery of patients with an acute ischemic stroke.

This multicenter French study included patients who were 18-85 years of age, within 5-10 days of an ischemic stroke. All subjects had a Fugl-Meyer motor scale (FMMS) score of 55 or less at baseline. The patients were randomized to receive either a placebo or fluoxetine at 20 mg per day. All patients were involved in physiotherapy throughout the trial. The primary outcome was the mean change in FMMS scores between the day of inclusion and day 90.

At 90 day follow up, FMMS score improvement was significantly greater in the fluoxetine group than in the placebo group (p=0.003). Activities of daily living, measured by the modified Rankin scale (mRS) score improved in both groups, while the proportion of independent patients (mRS scores 0-2) at day 90 was higher in the fluoxetine group than in the control group (p=0.021).

Conclusion: This study of patients with acute ischemic stroke found that treatment with fluoxetine at 20 mg per day resulted in improved motor recovery at 90 days as compared with a placebo.

Chollet, F et al. Fluoxetine for Motor Recovery after Acute Ischemic Stroke (FLAME): A Randomized Placebo Controlled Trial. **Lancet Neurol.** 2011, Feb 1; 10(2):123-130.

ASPIRIN AND EXTENDED–RELEASE DIPYRIDAMOLE VERSUS CLOPIDOGREL FOR RECURRENT STROKE

A number of studies have demonstrated the efficacy of antiplatelet agents for the prevention of recurrent stroke after a non-cardioembolic stroke. Studies have also shown that combining two antiplatelet agents with different mechanisms of action, aspirin and extended-release dipyridamole, is better than aspirin alone for the prevention of recurrent stroke. This study compared the efficacy of aspirin plus extended release dipyridamole with that of clopiogrel for the treatment of ischemic stroke.

This study, the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) included patients 55 years of age or older with an ischemic stroke within 90 days. The subjects were randomized to receive either aspirin (25 mg) plus extended-release dipyridamole (200 mg) twice daily or clopidogrel (75 mg daily) and telmisartan (80 mg daily) or placebo. The patients were evaluated during hospitalization, within one week after discharge and then at 1, 3 and 6 months, and then every 6 months after discharge. The primary outcome measure was a recurrent stroke of any type.

Data were available for analysis from 20,332 patients from 35 countries. The primary outcome of recurrent stroke occurred in 7.6% of those treated with aspirin plus dipyridamole and 7.7% of those treated with clopidogrel group, with a hazard ratio (HR) of 1.07. The occurrence of the secondary outcome of a composite of stroke, myocardial infarction or death from vascular causes did not differ between the two groups (HR 0.99). The number of patients with fatal or disabling stroke at 3 months was also similar between the two groups (HR 1.05). The rate of new or worsening congestive heart failure was significantly lower in the aspirin plus dipyridamole group than in the clopidogrel plus telmisartan group (HR 0.78). Major hemorrhagic events occurred more frequently in the aspirin plus dipyridamole group than in the clopidogrel group.

Conclusion: This study of patients with ischemic stroke found no clinically significant difference in the occurrence of recurrent strokes between patients treated with aspirin plus extended release dipyridamole and those treated with clopidogrel.

Sacco, R., et al. Aspirin and Extended–Release Dipyridamole versus Clopidogrel for Recurrent Stroke. **N Eng J Med**. 2008, September 18:359 ;(12): 1238-1251.

RIVAROXABAN VS WARFARIN IN ATRIAL FIBRILLATION

Studies have shown that atrial fibrillation (AF) is associated with an increased risk of ischemic stroke by a factor of 4-5. While the use of vitamin K antagonists has been shown to be effective, food and drug interactions make it difficult for patients to use these medications in clinical practice. This study compared the efficacy of warfarin with that of rivaroxaban, a direct factor Xa inhibitor, as a prophylactic treatment for patients with nonvalvular AF.

This study, the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), was a randomized double-blind trial conducted in 45 countries. Eligible patients included those with nonvalvular AF with elevated risk indicated by history of stroke. The patients were randomized to receive Rivaroxaban at 20 mg per day, or warfarin adjusted to an international normalized ratio of 2–3. The primary efficacy endpoint was composite of stroke or systemic embolism. Secondary endpoints included a composite of stroke, systemic embolism or death from cardiovascular causes.

Between 2006 and 2009, 14,264 patients were randomized. In the per–protocol population, stroke or systemic embolism occurred in 1.7% per year in the Rivaroxaban group and in 2.2% per year in the warfarin group (p<0.001 for non-inferiority). In the intention to treat population, this difference remained significant (p=0.02). No significant difference was found between groups in the rate of myocardial infarction or death (p=0.12 and p=0.07, respectively).

Conclusion: This study of patients with nonvalvular atrial fibrillation who were at moderate–to–higher risk for stroke, found that the factor X inhibitor Rivaroxaban was not inferior to warfarin for the prevention of subsequent stroke or systemic embolism.

Patel, M et al. Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. **N Engl J Med**. 2011, September 8; 365(10):883-891.

EVOLOCUMAB AND CARDIOVASCULAR DISEASE

Low-density lipoprotein is a known risk factor for cardiovascular disease. Monoclonal antibodies that inhibit proprotein convertase subtilisin–kexin type 9 (PCSK9) have emerged as a new class of drugs that effectively lower LDL cholesterol levels. The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) compared the clinical efficacy of evolocumab to statin therapy in patients with atherosclerotic cardiovascular disease.

The FOURIER trial included adults 40-85 years of age with clinically evident atherosclerotic cardiovascular disease with fasting LDL cholesterol levels of 70 mg/ADL or higher, or a non-high-density lipoprotein cholesterol level >-100 mg/DL while optimized on lipid-lowering therapy. The subjects were randomized to receive either subcutaneous evolocumab 140 mg every two weeks or 420 mg every month. The primary efficacy and point of major cardiovascular events was defined as the composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, or coronary revascularization.

The primary endpoint occurred in 9.8% of the evolocumab group and 11.3% in the placebo group ($p<0.001$). In addition evolocumab reduced the risk of cardiovascular death, myocardial infarction or stroke, occurring in 5.9% of the treatment group and 7.4% of the placebo group ($p<0.001$).

Conclusion: This trial of patients with recalcitrant LDL cholesterol levels demonstrated that the monoclonal antibody evolocumab could lower LDL levels and reduce the risk of cardiovascular events.

Sabatine, M., et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. **N Engl J Med.** 2017, May 4; 376(18): 1713-1722.

CRYPTOGENIC STROKE AND ATRIAL FIBRILLATION

The etiology of ischemic strokes is unclear in 20-40% of cases and consequently labeled cryptogenic. Given the often paroxysmal and asymptomatic nature of atrial fibrillation (AF), it is often undetected and thus untreated. This study was designed to determine whether long-term ECG monitoring may improve the ability to detect AF in patients with cryptogenic stroke.

The Cryptogenic Stroke and Underlying AF (CRYSTAL AF) trial included patients 40 years of age or older with ischemic cryptogenic stroke within the previous 90 days. After a traditional stroke workup, including 24 hours or more of ECG monitoring, those with no clear etiology were randomized to receive either an implantable cardiac monitor (ICM) for automatic detection of AF or to a control group who had ECG monitoring performed at the discretion of the site investigator. Follow-ups were scheduled at one, six and 12 months, and every six months thereafter until study completion. The primary end point was the time to first detection of AF at six months follow-up.

The rate of AF detection at six months in the 208 patients in the ICM group was 8.9%, as compared to 1.4% among those in the control group ($p<0.001$). At one year AF was detected in 12.4% of those in the ICM group compared to 2% in the control group ($p<0.001$). The median time to detection of AF in the ICM group was 41 days.

Conclusion: This study of patients with cryptogenic stroke found that cardiac monitoring over 30 days resulted in a significantly higher detection of atrial fibrillation when compared with conventional evaluation.

Sanna, T et al. Cryptogenic Stroke and Underlying Atrial Fibrillation. **N Engl J Med**. 2014, June 26: 370; 26:2478-2486.

TICAGRELOR VERSUS ASPIRIN FOR ISCHEMIC STROKE

After an ischemic stroke or transient ischemic attack, the risk of subsequent ischemic events is particularly high during the first 90 days. The role of aspirin for the secondary prevention of ischemic stroke has been found to be limited. As more intensive antiplatelet therapy through a different mechanism of action may be more effective than aspirin, this study compared ticagrelor (an antiplatelet agent that reversibly binds and inhibits the platelet P2Y12 receptor) with aspirin for their effectiveness in preventing major vascular events.

This multiple center, randomized, double-blind study enrolled subjects at 674 sites in 33 countries. Eligible patients presented with an acute ischemic stroke, with a National Institutes of Health Stroke Scale (NIHSS) score of five or lower or a high-risk transient ischemic attack, with an $ABCD^2$ stroke risk score of greater than or equal to four. Subjects who underwent thrombolysis or mechanical thrombectomy within 24 hours before randomization were excluded. The participants were randomly assigned to receive either ticagrelor, 90 mg twice per day, or aspirin, 100 mg per day. The primary endpoint was the time from randomization to the first occurrence of any stroke, myocardial infarction or death.

The primary composite endpoint occurred in 6.7% of the patients receiving ticagrelor and 7.5% of those receiving aspirin ($p=0.07$). Ischemic stroke occurred in 5.8% of the ticagrelor group and 6.7% of the aspirin group ($p=0.046$).

Conclusion: This study of patients with acute ischemic stroke or transient ischemic attack found that the primary endpoint, a composite of stroke, myocardial infarction or death, was not significantly less common among patients who received ticagrelor than among patients who received aspirin during a 90-day follow-up period.

Johnston, S., et al. Ticagrelor versus Aspirin in Acute Stroke or Transient Ischemic Attack. **N Eng J Med.** 2016, July 7; 375 (1): 35-43.

SURGICAL RESULTS OF THE CAROTID OCCLUSION SURGERY STUDY

The International Study of Extracranial-to-Intracranial Arterial Anastomosis (STA-MCA bypass trial) tested the usefulness of STA-MCA bypass surgery, as a prophylaxis against stroke, finding better outcomes with medical treatment. Based on the results of this trial, extracranial-intracranial (EC-IC) arterial bypass was generally abandoned as a treatment for symptomatic complete ICA occlusion. The carotid occlusion surgery study (COSS) was a randomized open label blinded trial involving patients with recent internal carotid artery occlusion, comparing bypass surgery with and without medical intervention. This study reports on the outcomes of the surgical arm of the COSS.

Subjects included adults with complete occlusion of the ICA

causing either a transient ischemic attack or ischemic stroke within 120 days as well as hemodynamic cerebral ischemia, as measured by a positron emission tomography (PET). Those in the neurosurgical group underwent arterial bypass surgery using a STA-MCA cortical branch and anastomosis. Following surgery patients were given aspirin at 81 or 325 mg for at least 30 days. The primary endpoint was stroke at two years

At follow-up, the graft patency rate was 98% at 30 days, and 96% at 605 days. In the intention to treat analysis, the primary endpoint rate was 0.210 in the surgical group and 0.227 in the medical group (p=0.78). At 30-60 days, the mean OEF (oxygen extraction fraction) ratio in the surgical group improved from 1.258 at baseline to 1.1.

Conclusion: The COSS study found that, compared with medical treatment, surgical STA-MCA anastomosis did not provide a better stroke risk reduction as compared medical intervention, primarily due to a high perioperative stroke risk.

Grubb, R et al. Surgical Results of the Carotid Occlusion Surgery Study. **J Neurosurg.** 2013, January; 118 (1):2533.

THE NORTH AMERICAN SYMPTOMATIC CAROTID ENDARTECTOMY TRIAL

Carotid endarterectomy (CE) was introduced in 1954 as a procedure to prevent ischemic stroke distal to carotid artery stenosis. With regional variations and uncertainties in outcome, the North American Symptomatic Carotid Endarterectomy Trial (NASCET) was initiated to better understand the efficacy of this procedure.

Subjects were from 50 clinical sites, admitted with hemispheric transient ischemic attack (TIA), or nondisabling stroke associated with an ipsilateral carotid stenosis of 30% to 90%. Subjects were randomized to receive either medical treatment (antiplatelets, antihypertensives, antiplatelet lipids and antidiabetic therapy), or CE plus medical treatment. Patients were followed for perioperative events and functional outcome as assessed with the modified Rankin Disability Score (mRS).

At two years after randomization, the life-table estimate of the risk of any fatal or nonfatal ipsilateral stroke was 26% in the medical group and 9% in the CE group, with an absolute risk reduction of 17%. Of the 1,415 patients undergoing surgery, 92 had perioperative outcome events (6.5%), with the 30-day risk of disabling stroke and death of 2.9%. At 8-year follow-up, those in the surgical group with a 70% or greater stenosis had a risk of ipsilateral stroke, any stroke, or death of 46.6%. The corresponding risk for those with < 70% stenosis was 48.7%. In a multivariate analysis of baseline variables, those associated with an increased risk of 30-day stroke and death were hemispheric TIA (rather than a retinal TIA), a left-sided procedure, the presence of contralateral carotid occlusion, ipsilateral ischemic lesion on admission CT, and irregular or ulcerated ipsilateral plaque.

Conclusion: This study demonstrates that carotid endarterectomy is safe and effective in preventing the recurrence of ipsilateral carotid ischemia and disabling ipsilateral stroke.

Ferguson, G et al. The North American Symptomatic Carotid Endarterectomy Trial. Surgical Results in 1415 Patients. **Stroke.** 1999 Sept; 30 (9):1751-1758.

BYPASS SURGERY FOR STROKE PREVENTION IN HEMODYNAMIC CEREBRAL ISCHEMIA

Atherosclerotic internal carotid occlusion causes approximately 10% of transient ischemic attacks (TIAs) and up to 25% of ischemic strokes in the carotid artery territory. This study of patients with symptomatic atherosclerotic internal carotid artery occlusion (AICAO) and hemodynamic cerebral ischemia, was conducted to determine if extracranial-intracranial (EC-IC) arterial bypass surgery, could reduce subsequent ipsilateral ischemic stroke as compared with medical therapy.

This multicenter blinded parallel group randomized open label study, the Carotid Occlusion Surgery Study (COSS), included patients who had a TIA or ischemic stroke in the hemispheric territory of an occluded internal carotid artery within the preceding 120 days. All were assessed for hemodynamic cerebral ischemia as identified by ipsilateral increased oxygen extraction fraction (OEF) ratio as measured by PET. The subjects were randomized to a nonsurgical group that received medical (including antithrombotic) treatment, chosen by the referring physician, or to an endarterectomy group to undergo microsurgical end-to-side anastomosis of a superficial temporal artery branch to a cortical branch of the middle cerebral artery. The primary endpoint was the combination of all stroke and death from surgery to 30 days, and ipsilateral ischemic stroke within two years of randomization.

At two-year follow-up, the primary endpoint occurred in 21% of the surgical group and 22.7% of the nonsurgical group (p=0.78). Ipsilateral stroke at 30 days occurred in 14.4% of the surgical group and 2% of the nonsurgical group. In the surgical group the mean OEF ratio improved from 1.258 at baseline to 1.109 at the 30-60 day postoperative repeat PET scan.

Conclusion: This study of patients with symptomatic atherosclerotic internal carotid artery occlusion and hemodynamic cerebral ischemia found that bypass surgery, while improving cerebral perfusion, did not reduce the recurrence of ipsilateral ischemic stroke at two years.

Powers, W et al. Extracranial–Intracranial Bypass Surgery for Stroke Prevention in Hemodynamic Cerebral Ischemia: The Carotid Occlusion Surgery Study Randomized Trial. **JAMA** 2011, Nov 9; 306(18):1983-1992.

LOW-DENSITY LIPOPROTEIN TARGETS AFTER ISCHEMIC STROKE

The Stroke Prevention by Aggressive Reduction in Cholesterol Level (SPARCL) trial established the basis for recommendations of intensive therapy to lower serum lipid levels after a transient ischemic attack (TIA) or ischemic stroke (IS). There was, however, no target low density lipoprotein (LDL) level in these recommendations. This study compared the outcomes of patients with a target level of LDL cholesterol < 70 mg/dL to those of patients with a higher target range of 90 to 100 mg/dL.

Subjects were adult patients who had sustained an ischemic stroke within the past three months, all with a modified Rankin Scale score of zero to three. The participants were randomized to a target LDL cholesterol of less than 70 mg/dL or a target range of 90 to 100 mg/dL. Investigators were allowed to prescribe any type and dose of statin to reach these targets. The composite

primary endpoint was major cardiovascular events.

At a median follow-up of 3.5 years, the mean LDL cholesterol levels were 65 mg/dL in the lower target group and 96 mg/dL in the higher target group. The primary endpoint occurred in 0.5% of the lower target group and in 10.9% of the higher target group (Hazard Ratio 0.78; p=0.04). The majority of the endpoint events were cerebral infarctions or strokes of undetermined origin.

Conclusion: This study involving patients with recent ischemic stroke or transient ischemic attack, found that those assigned a target low density lipoprotein cholesterol of less than 70 mg/dL had fewer major cardiovascular events than did those with a target of 90-110 mg/dL.

Amarenco, P., et al. A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. **N Engl J Med**. 2020, January 2; 382 (1): 9-19.

ORAL ANTICOAGULANTS AFTER STROKE IN THE OLDEST OLD WITH ATRIAL FIBRILLATION

As the population ages, the number patients 85 years of age and older is steadily growing. Increasing age and atrial fibrillation (AF) are both risk factors for ischemic stroke (IS). This study compared the efficacy of direct oral anticoagulants (DOACs) with vitamin K antagonist (VKA) for patients 85 years of age and older with AF and a recent IS.

Subjects were consecutive patients with an IS or a transient ischemic attack (TIA) within three months, with concurrent nonvalvular AF, who were treated with a DOAC or VKA, initiated after the index event. The primary outcome variable was time to occurrence of the composite of recurrent IS, intracerebral hemorrhage (ICH) or all-cause death.

Data were obtained concerning 5,593 patients with an IS and 391 with a TIA, with a median age of 78 years and a follow-up of 2.5 years. Of these, 1,380 were ≥85 years of age and 4,604 were <85 years of age. Events during the follow-up included 279 recurrent IS events, 69 ICH events and 737 deaths. The risk of a primary event was less in among those treated with DOAC in both patients ages ≥85 years (HR 0.46) and those ages <85 years (HR 0.74). These findings were maintained in the adjusted analysis (HR 0.70 for those >85 years and HR 0.87 for those <85 years).

Conclusion: This study of patients with a recent ischemic stroke found that treatment with a direct oral anticoagulant was superior to treatment with a vitamin K antagonist for the prevention of recurrent stroke, intracerebral hemorrhage, or death.

Polymeris, A., et al. Oral Anticoagulants in the Oldest Old with Recent Stroke and Atrial Fibrillation. **Annals Neurol.** 2021, January: 78-88.

META-ANALYSIS OF THERAPIES FOR POSTSTROKE UPPER LIMB IMPAIRMENT

Recovery of upper extremity (UE) movement after a cerebral vascular accident (CVA) is thought to be mainly due to spontaneous neurobiological recovery. While many individuals participate in stroke rehabilitation, roughly 36% of survivors continue to have significant upper limb disabilities for five years post-stroke. This study evaluated the relative efficacy of interventions designed to improve stroke recovery.

A literature review was performed to identify randomized, clinical trials of adult patients who had experienced a stroke and were treated with an unconventional therapy. The primary outcome of interest was the Fugl-Meyer, UE (FMUE). Data were analyzed from 176 randomized, controlled trials, including 6,781 participants and examining 20 non-conventional interventions. Compared with conventional care, eleven of the interventions were found to result in significantly better UE function. These included constraint induced movement therapy (mean difference (MD) 6.7), high frequency repetitive transcranial magnetic stimulation (MD 5.4), mental imagery (MD 5.4), bilateral arm training (MD 5.1), intermittent theta burst stimulation (MD 5.1), cathodal transcranial direct current stimulation (MD 4.8), neuromuscular electrical stimulation (MD 4.4), action observation (MD 4), low frequency repetitive transcranial magnetic stimulation (MD 3.5), mirror therapy (MD 3.2), and electromyography triggered neuromuscular electrical stimulation (MD 3).

Conclusion: This meta-analysis identified therapeutic interventions that were found to be more effective than conventional care for the treatment of acute stroke.

Saikaley, M., et al. Network Meta Analysis of Non-Conventional Therapies for Improving Upper Limb Motor Impairment Post-Stroke. **Stroke.** 2022, December; 53(12): 3717-3727.

THROMBOLYSIS FOR ISCHEMIC STROKE IN NONAGENARIANS

Current intravenous thrombolysis (IVT) guidelines recommend IVT for patients 80 years of age or older with ischemic stroke. However, the Data for this study were prospectively collected for the Thrombolysis in Ischemic Stroke Patients (TRIST) study, conducted at 20 separate centers. Subjects were patients presenting to the hospital with symptoms of acute ischemic stroke, with data collection including the National Institute of Health Stroke Scale (NIHSS) score before treatment, as well as medical and functional outcomes. Intracranial hemorrhage was monitored by follow-up using computed tomography or magnetic resonance imaging. Early functional improvement was a secondary outcome defined as any decrease in the NIHSS score after 24 hours as compared to baseline.

Data were available for 16,974 patients including 978 patients ≥90 years of age. After adjusting for potential confounders, the probability of sICH and the probability of early functional improvement did not differ significantly between patients ≥90 years of age and those in the younger cohort. The probability of death and poor functional outcome remained significantly higher in patients ≥90 years or older, though this was not correlated with IVH.

Conclusion: This study of patients admitted with acute ischemic stroke did not find that age should be a reason for withholding intravenous thrombolysis.

Altersberger, V., et al. Intravenous Thrombolysis in Patients with Ischemic Stroke Aged ≥90 Years: A Cohort Study from The TRISP Collaboration. **Stroke.** 2022, December; 53 (12): 3557-3563.

AGATROBAN FOR ISCHEMIC STROKE WITH EARLY NEUROLOGIC DETERIORATION

Early neurologic deterioration (END) after an acute ischemic stroke (AIS) is relatively common and is associated with an increased risk of intracranial hemorrhage. Therefore,

guidelines recommend against urgent anticoagulation with AIS. As agatroban is a rapid but short acting direct thrombin inhibitor, this study evaluated the efficacy of agatroban for END in AIS

Subjects were 628 adults with an AIS and experiencing END. Both the control and treatment groups received standard therapy, including oral mono or dual antiplatelet therapy such as aspirin and/or clopidogrel, according to Chinese Stroke Association guidelines. Those randomized to the treatment group also received agatroban 60mg/day for two days, followed by 20 mg/day for seven days. The primary endpoint was a good functional outcome at 90 days (modified Rankin Scale (mRS) score of zero to two).

The primary outcome measure was realized at 90 days in 80.5% of the treatment group and 73.3% of the control group (p=0.04). This difference remained in the adjusted analysis (p=0.03). The occurrence of symptomatic intracranial hemorrhage was 0.9% in the agatroban and 0.7% of the control group (p=0.78).

Conclusion: This study of patients with acute ischemic stroke followed by early neurologic

Rehab in Review (RIR) **is produced monthly by physicians in the field of Physical Medicine and Rehabilitation (PM&R), with the cooperation and assistance of Emory University School of Medicine, Department of Rehabilitation Medicine. The summaries appearing in this publication are intended as an aid in reviewing the broad base of literature relevant to this field. These summaries are not intended for use as the sole basis for clinical treatment, or as a substitute for the reading of the original research.**

The Emory University School of Medicine designates this journal based activity for a maximum of 3 AMA PRA Category 1 Credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity. The Emory University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

RIR **is affiliated with the Association of Academic Physiatrists, the World Health Organization, and the Chinese and Indian Societies of PM&R and endorsed by the International Society of Physical and Rehabilitation Medicine.**

Private subscriptions are available by email at rehabinreview@aol.com or by fax or phone at (800) 850-7388.

ISSN # 1081-1303

www.rehabinreview.com

deterioration found that adding seven days of agatroban to traditional antiplatelet therapy resulted in a greater likelihood of a good functional outcome at 90 days.

Zhang, X., et al. Agatroban in Patients with Acute Ischemic Stroke with Early Neurological Deterioration. **JAMA Neurol**. 2024. doi: 10.1001/ jamaneurol. 2023. 5093.

SUBLINGUAL EDARAVONE DEXBORNEOL FOR ACUTE ISCHEMIC STROKE

The Efficacy and Safety of Nerinetide for the Treatment of Acute Ischemic Stroke (ESCAPE-NA1) trial reported that eicosapeptide nerinetide had a potentially cytoprotective effect via inhibition of neuronal excitotoxicity, and decreased production of nitric oxide among patients with acute ischemic stroke. Sublingual edaravone dexborneol, composed of edaravone and dexborneol, can rapidly diffuse and be absorbed through the oral mucosa after sublingual exposure. Therefore, the Treatment of Acute Ischemic Stroke (AIS) with Sublingual Edaravone Dexborneol (TASTE-SL) trial investigated the effects of sublingual edaravone dexborneol on 90-day functional outcomes in patients with AIS.

This phase three, double-blind, placebo-controlled, multicenter, parallel group, randomized, clinical trial was completed in 33 centers in China between June of 2021 and August of 2022. The subjects presented to the centers with AIS symptoms and NIHSS scores of between six and 20. Within 48 hours of symptom onset, the eligible patients were randomized to receive either a sublingual placebo or sublingual edaravone dexborneol, 36 mg (edaravone, 30 mg; dexborneol, six mg), twice a day for 14 consecutive days. The primary efficacy outcome was the proportion of patients with a Modified Rankin Scale (mRS) score of one or less at 90 days after randomization.

A favorable outcome of an mRS score of one or less on day 90 occurred in 290 of 450 patients (64.4%) in the edaravone dexborneol group and in 254 of 464 patients (54.7%) in the placebo group (p=0.003). Edaravone dexborneol did not have a positive effect on the proportion of scores with a mRS score of two or less or changes in NIHSS scores to day 14.

Conclusion: This prospective study of adult patients hospitalized with acute ischemic stroke within 48 hours of symptom onset found that sublingual edaravone dexborneol can improve the proportion of patients achieving a good functional outcome on day 90, without increasing the risk of adverse events.

Fu, Y., et al. Sublingual Edaravone Dexborneol for the Treatment of Acute Ischemic Stroke. The TASTE-SL Randomized, Clinical Trial. **JAMA Neurol**. 2024. doi:10.1001/ jamaneurol.2023.5716.