Reading List of Key Trials and Studies

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Stroke:

Endovascular Thrombectomy

2015 landmark trials:

MR CLEAN: Intra-arterial treatment in addition to usual care within 6 hours of symptom onset for proximal arterial occlusion in anterior circulation stroke. Randomized 500 patients at 16 centers in Netherlands (233 in intraarterial treatment group and 267 in usual care alone group). The adjusted common odds ratio was 1.67 (95% CI, 1.21-2.30) and absolute difference of 13.5 percentage points (95% CI, 5.9-21.2) in the rate of functional independence (defined as mRS 0-2) in favor of the intervention (32.6% vs. 19.1%). Concluded that in patients with proximal intracranial occlusion anterior circulation strokes, intra-arterial therapy within 6 hours after symptom onset improved functional independence at 90 days without increasing intracranial hemorrhage (ICH) or mortality.

REVASCAT: Patients with large-vessel occlusion acute ischemic stroke were randomized within 8 hours of symptom onset to either medical therapy (including IV alteplase when eligible) and endovascular therapy with Solitaire stent retriever (thrombectomy group) or medical therapy alone (control group) at 4 centers in Catalonia, Spain during a 2 year period. Eligible patients had proximal anterior circulation occlusion, absence of large infarct on neuroimaging, baseline mRS score ≤1 and minimum NIHSS score ≥5. Although the maximum planned sample size was 690, enrollment was halted early due to loss of equipoise after positive results for thrombectomy from other similar trials. 206 patients were randomized and the trial found that thrombectomy reduced the severity of disability over the range of mRS (adjusted odds ratio for 1 point improvement, 1.7; 95% CI, 1.05-2.8) and increased rates of functional independence (mRS 0-2) at 90 days (43.7% vs. 28.2%; adjusted odds ratio, 2.1; 95% CI, 1.1-4.0). Rates of symptomatic ICH were similar in both groups and rates of death were not statistically significant. Concluded that stent retriever thrombectomy reduced the severity of post-stroke disability and increased rate of functional

independence in patients with anterior circulation stroke within 8 hours after symptom onset.

ESCAPE: Endovascular thrombectomy in addition to standard care within 12 hours of symptom onset in acute ischemic stroke patients with small infarct core, proximal intracranial arterial occlusion, and moderate-to-good collateral circulation. Randomly assigned participants to standard care (control group) or standard care and endovascular treatment (intervention group). Enrolled 316 patients with 238 receiving IV alteplase (120 in intervention group and 118 in control group). The trial was stopped early because of efficacy. Found an increased rate of functional independence (mRS 0-2 at 90 days) with intervention (53.0% vs. 29.3% in control group; P<0.001) and reduced mortality. The rate of symptomatic ICH did not differ. Concluded that among patients with acute ischemic stroke and proximal vessel occlusion, a small infarct core, moderate-to-good collaterals, and rapid endovascular treatment improved functional outcomes and reduced mortality.

EXTEND IA: Assessed the benefit of advanced imaging selection and early endovascular thrombectomy with the Solitaire FR (Flow Restoration) device when performed within 4.5 hours. Patients with acute ischemic stroke receiving 0.9 mg/kg alteplase presenting less than 4.5 hours of symptom onset were randomized either to endovascular thrombectomy with Solitaire FR (Flow Restoration) stent retriever or to continue receiving alteplase alone. All patients had occlusion of ICA or MCA and evidence of salvageable brain tissue and ischemic core less than 70 mL on CTP imaging. 70 patients were randomized (35 in each group) before the trial was stopped early due to efficacy. Endovascular therapy increased early neurologic improvement at 3 days (80% vs. 37%, P=0.002) and improved 90 day functional outcomes with more patients achieving functional independence (mRS 0-2, 71% vs 40%; P=0.01). Concluded that in patients with proximal vessel occlusion and salvageable tissue, early thrombectomy with the Solitaire FR stent retriever improved reperfusion at 24 hours, early neurologic recovery at 3 days, and functional outcome at 90 days.

SWIFT PRIME: IV tPA and Solitaire FR stent-retriever within 6 hours of symptom onset in proximal large-vessel occlusion anterior circulation ischemic stroke. Patients who were receiving or had received IV tPA were enrolled into control group (continue with tPA alone) or intervention group (endovascular thrombectomy with Solitaire stent retriever) within 6 hours of symptom onset. Randomized 196 patients (98 in each group) at 39 centers and study was stopped early because of efficacy. Found that thrombectomy with stent retriever plus IV tPA reduced 90 day disability (P<0.001), increased rate of functional independence (mRS 0-2) in intervention group compared to control group (60% vs. 35%, P<0.001). There was no significant difference in 90-day

mortality or symptomatic ICH. Concluded that additional treatment with stent retriever within 6 hours of symptom onset in patients treated with IV tPA improved functional outcomes at 90 days.

Delayed presentation trials:

DAWN (2017): Evaluated endovascular thrombectomy for patients presenting more than 6 hours after ischemic stroke onset. Enrolled patients with intracranial ICA or proximal MCA occlusion with last known well of 6-24 hours prior who had mismatch between severity of clinical deficit and infarct volume. Patients were assigned to thrombectomy plus standard care (thrombectomy group) or to standard care alone (control group). Randomized 206 patients (107 in thrombectomy group and 99 in control group) and enrollment stopped early at 31 months due to results of prespecified interim analysis. The thrombectomy group had a higher utility-weighted mRS score at 90 days (5.5 vs 3.4 in control group) and higher 90-day functional independence rate (49% vs 13%). There was no statistically significant difference in symptomatic ICH or 90-day mortality. Concluded that endovascular thrombectomy reduced disability and improved functional recovery when performed 6 to 24 hours after symptom onset among patients with clinical deficit disproportionate to infarct volume.

DEFUSE 3 (2018): Assessed endovascular thrombectomy for eligible ischemic stroke patients with proximal ICA or MCA occlusion with salvageable brain tissue at 6 to 16 hours of symptom onset. Enrolled patients 6 to 16 hours after last known well with infarct size less than 70 mL and ratio of volume of ischemic tissue on perfusion imaging to infarct volume of 1.8 or more to either endovascular therapy (thrombectomy) plus standard medical therapy (endovascular therapy group) or standard medical therapy alone (medical-therapy group). Randomized 182 patients (92 in endovascular-therapy group and 90 in medical-therapy group) at 38 US centers and terminated early for efficacy. Found that endovascular therapy plus medical therapy was associated with favorable shift in distribution of functional outcomes on mRS at 90 days (odds ratio, 2.77; P=0.001) and higher percentage of functionally independent (mRS 0-2) patients (45% vs. 17%, P<0.001). The 90-day mortality was 14% in endovascular-therapy group and 26% in medical-therapy group (P=0.05) but there was no significant difference in symptomatic ICH or serious adverse events. Concluded that endovascular therapy plus standard medical care for ischemic stroke 6 to 16 hours after last known well yielded better functional outcomes and lower mortality rates.

Basilar/Posterior Fossa trials:

BEST (2019): Evaluated the safety and efficacy of endovascular treatment for acute ischemic stroke due to vertebrobasilar artery occlusion. Enrolled patients presenting within 8 hours of symptom onset at 28 centers in China into either endovascular therapy

plus standard medical therapy (intervention group) or standard medical therapy alone (control group). Assessed 288 patients for eligibility and randomized 131 patients (66 in intervention group and 65 in control group) but trial was terminated early due to high crossover rate and poor recruitment. Found no difference in proportion of participants with mRS 0-3 at 90 days according to treatment and 90-day mortality was similar between groups. Concluded that there was no evidence of difference in favorable outcomes in patients with vertebrobasilar occlusion receiving endovascular therapy compared to standard medical therapy alone but results may have been confounded by loss of equipoise during trial.

BASICS (2021): Evaluated effectiveness of endovascular therapy in basilar artery occlusion stroke patients within 6 hours of symptom onset. Randomized 300 patients (154 in endovascular therapy group and 146 in medical care group). Found that favorable functional outcome (mRS 0-3) occurred in 44.2% patients in endovascular group and 37.7% patients in medical care group (risk ratio, 1.18; 95% CI, 0.92-1.50). Symptomatic ICH occurred in 4.5% of patients after endovascular therapy and in 0.7% after medical therapy (risk ratio, 6.9; 95% CI, 0.9-53.0). Concluded that endovascular therapy and medical therapy did not significantly differ in terms of favorable functional outcome among patients with basilar artery occlusion stroke but had a wide confidence interval for primary outcome.

ATTENTION (2022): Assessed the effects and risks of endovascular thrombectomy for basilar artery occlusion stroke at 36 centers in China. Patients were assigned in a 2:1 ratio within 12 hours after symptom onset to endovascular thrombectomy group or best medical care (control) group. 507 patients were screened, 340 included in intention-to-treat population with 226 assigned to thrombectomy group and 114 to control group. Found good functional outcome at 90 days in 46% of patients in thrombectomy group and 23% of patients in control group (adjusted rate ratio, 2.06, 95% CI, 1.46-2.91, P<0.001). There was symptomatic ICH in 5% of patients in the thrombectomy group but none in the control group. Concluded that in Chinese patients with basilar artery occlusion with one third receiving IV thrombolysis, endovascular thrombectomy within 12 hours after symptom onset resulted in better functional outcomes at 90 days but was associated with procedural complications and intracerebral hemorrhage.

BAOCHE (2022): Evaluated the efficacy and safety of endovascular thrombectomy 6 to 26 hours after symptom onset in patients with basilar artery occlusion ischemic stroke. Patients in China were assigned to either medical therapy plus thrombectomy or medical therapy only (control) group. Included 217 patients (110 in thrombectomy group and 107 in control group) in the analysis with enrollment halted at prespecified interim analysis because of the superiority of thrombectomy. Found that mRS 0-3 occurred in

46% of the thrombectomy group and 24% in the control group (adjusted rate ratio, 1.81; 95% CI, 1.26-2.60; P<0.001). Concluded that in patients with basilar artery occlusion stroke who presented 6 to 24 hours after symptom onset, thrombectomy resulted in higher percentage of good functional status at 90 days but had procedural complications and more intracranial hemorrhage rates.

Large core trials:

RESCUE-Japan LIMIT (2022): Endovascular treatment for Japanese patients with large vessel occlusion and large ischemic core presenting within 24 hours with ASPECTS score of 3-5. Patients were assigned in 1:1 ratio to endovascular therapy with medical care or medical care alone within 6 hours of last known well or within 24 hours if there was no early change on FLAIR images. Inclusion criteria were LVO from ICA or M1 segment occlusion, ASPECTS 3-5 (CT or DWI), 18 yo or older, NIHSS at least 6, pre-stroke mRS of 0-1, lack of mass effect or ICH. Randomized 203 patients (101 in thrombectomy group and 102 in medical-care group). At 90 days, the percentage of patients with mRS 0-3 was 31% in thrombectomy group and 12.7% in medical care group (relative risk, 2.43; 95% CI, 1.35-4.37; P=0.002). Ordinal shift across range of mRS scores generally favored thrombectomy. ICH occurred in 58.0 % of patients in thrombectomy group and 31.4% of patients in medical care group (p<0.001) however symptomatic ICH was similar (9% in EVT vs. 5% in medical care group). Concluded that Japanese patients with large cerebral infarctions had better functional outcomes following endovascular therapy but more intracranial hemorrhages.

ANGEL-ASPECT (2023): Evaluated the role of endovascular therapy for Chinese patients with anterior circulation large vessel occlusion and large infarction defined as ASPECTS 3-5 or infarct-core volume of 70-100 mL on CTP imaging within 24 hours of symptom onset. Patients were assigned to thrombectomy plus medical care group or medical care alone group. Inclusion criteria were ages 18-80, LKN within 24 hours, pre-stroke mRS 0-1, LVO from intracranial ICA or M1 segment, NIHSS 6-30. and imaging (ASPECTS 3-5 within 24 hours with no core limitation, ASPECTS 0-2 within 24 hours and core of 70-100 mL, ASPECTS >5 between 6-24 hours with core of 70-100 mL). Randomized 456 patients with 231 in endovascular-therapy group and 225 in medical-management group. Trial was stopped early due to efficacy of endovascular therapy after second interim analysis. Found a shift in distribution of 90 day mRS scores in favor of thrombectomy group over medical management alone (generalized odds ratio, 1.37; 95% CI, 1.11-1.69; P=0.004). Symptomatic ICH occurred in 6.1% of patients in the thrombectomy group and 2.7% of patients in the medical care group. Concluded that Chinese patients with large infarctions due to anterior large vessel occlusion had better outcomes with endovascular therapy within 24 hours compared to medical care alone.

SELECT 2 (2023): Evaluated the safety and efficacy of endovascular thrombectomy in patients with large ischemic strokes from anterior circulation LVO presenting within 24 hours and ASPECTS of 3-5 or core volume of at least 50 mL on CT Perfusion or diffusion weighted MRI. Patients were assigned to endovascular therapy plus medical care group or to medical care alone group. Inclusion criteria were ages 18-85, pre-stroke of mRS 0-1, no evidence of ICH, and anterior circulation ICA or M1 occlusion (tandem or isolated). Randomized 352 patients in total with 178 in thrombectomy group and 174 in medical care group. Trial was stopped early because of efficacy. Found a generalized odds ratio for shift in distribution of mRS scores toward better outcomes in favor of thrombectomy was 1.51 (95% CI, 1.20-1.89; P<0.001) and 20% of patients in thrombectomy group and 7% in medical-care group had functional independence (relative risk, 2.97; 95% CI, 1.60-5.51). There was similar mortality between groups with symptomatic ICH in 1 patient in the thrombectomy group and 2 patients in the medical-care group. Concluded that in patients with large ischemic strokes, endovascular therapy resulted in better functional outcomes than medical care alone but was associated with vascular complications.

LASTE (2024): Endovascular thrombectomy in patients with proximal vessel occlusion in anterior circulation with large infarct (ASPECTS ≤5) detected on MRI or CT within 6.5 hours of symptom onset. Assigned to either endovascular thrombectomy and medical care (thrombectomy group) or medical care alone (control group). Randomized a total of 333 patients with 166 in thrombectomy group or 167 in control group. Trial was stopped early because results of similar trials favored thrombectomy. Found a median mRS at 90 days was 4 in thrombectomy group and 6 in control group (generalized odds ratio, 1.63; 95% CI, 1.29-2.06; P<0.001) Symptomatic ICH at 24 hours occurred in 9.6% of patients in thrombectomy group and 5.7% of patients in control group (adjusted relative risk, 1.73; 95% CI, 0.78-4.68). Concluded that patients with acute stroke from proximal large vessel occlusion and large infarct of unrestricted size, thrombectomy plus medical care yielded better functional outcomes and lower mortality than medical care alone but higher incidence of symptomatic ICH.

TENSION (2024): Evaluated patients with acute ischemic stroke due to anterior circulation large vessel occlusion and large established infarct (ASPECTS of 3-5). Assigned patients to either endovascular therapy with medical treatment or medical treatment (standard of care) up to 12 hours of symptom onset across 40 hospitals in Europe and one in Canada. Randomized 253 patients with 125 in the endovascular thrombectomy group and 128 in the medical treatment alone group. Trial was stopped early due to efficacy after the first pre-planned interim analysis. Found a shift in distribution of scores on mRS at 90 days towards better outcome (adjusted common odds ratio 2.58; 95% CI, 1.60-4.15; P=0.0001) and lower mortality (hazard ratio 0.67;

95% CI, 0.46-0.98; p=0.038) in endovascular thrombectomy group. Symptomatic ICH occurred in 6% of thrombectomy patients and 5% of medical treatment group patients. Concluded that thrombectomy improved functional outcome and had lower mortality in large vessel occlusion acute ischemic stroke patients with established large infarct using non-contrast CT imaging for patient selection.

TESLA (2024): Assessed the effect of endovascular thrombectomy with medical care compared to medical care alone among patients with large vessel occlusion anterior circulation stroke and large infarct (ASPECTS 2-5 detected on noncontrast CT imaging) within 24 hours of symptom onset. Randomized a total of 300 patients (152 in intervention group and 148 in control group) with 297 patients completing 90 day follow-up. Found that mean 90-day utility weighted mRS was 2.93 for intervention group versus 2.27 for control group. The 90-day mortality was similar between groups and there was slightly larger percentage of symptomatic ICH at 24 hours (4% vs. 1.3%) in the thrombectomy group, type 1 parenchymal hemorrhage (9.5% vs. 2.7%), and SAH (16.2% vs. 6.2%). Concluded that thrombectomy did not demonstrate improvement in functional outcomes among patients with large infarct on noncontrast CT within 24 hours of symptom onset but interval around effect estimates includes possibility of both no important effect and a clinically relevant benefit of thrombectomy indicating more study required.

Intracranial Atherosclerosis:

WASID (2005): Compared warfarin and aspirin in patients with TIA or stroke caused by intracranial arterial stenosis (50-99%). Enrolled patients with TIA or stroke caused by angiographically verified 50-99% stenosis of a major intracranial artery to warfarin (target INR 2-3) group or aspirin (1300 mg/day) group. Randomized 569 patients and stopped after due to concerns about safety of patients who were assigned to the warfarin group. Found that adverse events included death (4.3% in aspirin group vs. 9.7% in warfarin group; hazard ratio 0.46; 95% CI, 0.23-0.90; P=0.02), major hemorrhage (3.2% vs. 8.3%; hazard ratio, 0.39; 95% CI, 0.18-0.84; P=0.01), and myocardial infarction or sudden death (2.9% vs. 7.3% respectively; hazard ratio, 0.40; 95% CI, 0.18-0.91; P=0.02). Concluded that Warfarin had significantly higher rates of adverse events and showed no benefit over aspirin for patients with intracranial arterial stenosis.

SAMMPRIS (2011): Assessed whether percutaneous transluminal angioplasty and stenting (PTAS) plus aggressive medical treatment is more effective than aggressive medical treatment alone in high-risk patients with atherosclerotic intracranial arterial stenosis. Enrolled patients with recent TIA or stroke attributed to 70-99% stenosis of major intracranial artery to aggressive medical management alone (aspirin 325 mg/day

and clopidogrel 75 mg/day for 90 days) or aggressive medical management plus PTAS with use of Wingspan stent. Medical arm consisted of a lifestyle modification program with management of secondary risk factors (diabetes, elevated non-HDL cholesterol levels, smoking excess weight, insufficient exercise) as well as rosuvastatin and blood pressure control (SBP <140 mmHg or <130 mmHg in diabetic patients). Randomized 451 patients before enrollment was stopped because the 30-day rate of stroke or death was 14.7% in the PTAS group (nonfatal stroke, 12.5%; fatal stroke, 2.2%) and 5.8% in the medical-management group (nonfatal stroke, 5.3%; non-stroke-related death, 0.4%) (P=0.002). Concluded that aggressive medical management was superior to PTAS with the use of the Wingspan stent system in patients with intracranial arterial stenosis because the risk of early stroke after PTAS was high and risk of stroke with aggressive medical treatment alone was lower than expected.

VISSIT (2015): Evaluated the efficacy and safety of balloon-expandable stent plus medical therapy versus medical therapy alone in patients with symptomatic intracranial stenosis (≥70%). Randomized 112 patients to either balloon-expandable stent plus medical therapy group (59 patients) or medical therapy alone group (53 patients). Enrollment was halted after negative results from another trial resulted in early analysis of outcomes, which suggested futility. The 30-day primary safety endpoint (composite of any stroke, death, or intracranial hemorrhage and any hard TIA) occurred in more patients in the stent group (14/58; 24.1%; 95% CI, 13.9%-37.2%) vs the medical group (5/53; 9.4%; 95% CI, 3.1%-20.7%; P=0.05). Concluded that the use of balloon-expandable stent compared to medical therapy increased the 12-month risk of added stroke or TIA in the same territory, increased 30-day risk of any stroke or TIA among patients with symptomatic intracranial arterial stenosis.

WEAVE (2019): Post-market surveillance study mandated by the FDA to assess the periprocedural safety of the Wingspan Stent system. Enrolled 152 patients at 24 hospitals who underwent angioplasty and stenting with the Wingspan stent. Inclusion criteria were age 22-80, symptomatic intracranial atherosclerotic stenosis 70-99%, baseline mRS score ≤, ≥2 strokes in vascular territory of stenotic lesion with at least 1 stroke while on medical therapy, and stenting of lesion ≥8 days after last stroke. Trial was stopped early after interim analysis showed lower than expected 2.6% periprocedural stroke, bleed, and death rate. Concluded that the use of Wingspan stent for intracranial atherosclerotic disease demonstrated low periprocedural complication rate and excellent safety profile with proper patient selection and experienced interventionalists.

BASIS (2024): Determined whether balloon angioplasty plus aggressive medical management is superior to aggressive medical management alone for patients with

symptomatic atherosclerotic stenosis (70-99%) of a major intracranial artery receiving treatment with at least 1 antithrombotic drug and/or standard risk factor management. Randomized 512 patients at 31 centers across China, of whom 501 were eligible and completed the trial. The incidence of primary outcome (composite of any stroke or death within 30 days after enrollment or after balloon angioplasty or any ischemic stroke in qualifying artery territory or revascularization after 30 days -12 months after enrollment) was lower in the balloon angioplasty group than medical management group (4.4% vs 13.5%; hazard ratio, 0.32; 95% CI, 0.16-0.63; P<0.001). Concluded that balloon angioplasty plus aggressive medical management compared to medical management alone in patients with symptomatic ICAS statistically lowered the risk of a composite outcome of any stroke or death within 30 days or an ischemic stroke or revascularization of qualifying artery between 30 days to 12 months.

Carotid Revascularization:

ACAS (1995): Assessed carotid endarterectomy (CEA) and aggressive medical therapy in reducing incidence of cerebral infarction over 5 years in patients with asymptomatic carotid artery stenosis. Randomized 1662 patients across 39 clinical sites in the United States and Canada between December 1987 and December 1993. Found that after a median follow-up of 2.7 years, the aggregate risk over 5 years for ipsilateral stroke and any perioperative stroke or death was estimated as 5.1% for surgical patients and 11.0% for medically treated patients (aggregate risk reduction 53% (95% CI, 22%-72%). Concluded that patients with asymptomatic carotid artery stenosis of 60% or greater reduction in diameter who are good elective surgical candidates will have a lower 5-year risk of ipsilateral stroke if CEA is performed with less than 3% perioperative morbidity or mortality.

NASCET (1998): Assessed the benefit of carotid endarterectomy in patients with symptomatic moderate carotid stenosis (<70%). Patients with moderate carotid stenosis and TIAs or non disabling strokes on ipsilateral side as stenosis within 180 days were stratified by degree of stenosis (50-69% or <50%) and assigned to either carotid endarterectomy group (1108 patients) or to medical care alone (1118 patients). Found that the 5-year rate of ipsilateral stroke (failure rate) was 15.7% among surgical group patients and 22.2% among medical group patients (P=0.045) in patients with 50-69% stenosis. Concluded that endarterectomy in patients with symptomatic moderate carotid stenosis 50-69% yielded a moderate reduction in stroke risk while patients with stenosis of <50% did not benefit from surgery. Patients with severe stenosis (≥70 percent) had durable benefit from endarterectomy at 8 years follow-up.

CREST (2010): Compared carotid artery stenting to carotid endarterectomy in management of symptomatic and asymptomatic carotid artery stenosis. Assigned

patients with symptomatic or asymptomatic carotid stenosis to undergo carotid-artery stenting or carotid endarterectomy. In 2502 patients, there was no significant difference in estimated 4-year rates of primary end point between stenting group and endarterectomy group (7.2% and 6.8% respectively; hazard ratio with stenting, 1.11; 95% CI, 0.81-1.51; P=0.51). The 4-year rate of stroke or death was 6.4% with stenting and 4.7% with CEA (hazard ratio, 1.50; P=0.03); the rates among symptomatic patients were 8.0% and 6.4% (hazard ratio, 1.37; P=0.14), and the rates among asymptomatic patients were 4.5% and 2.7% (hazard ratio, 1.86; P=0.07) respectively. Concluded that in patients with symptomatic or asymptomatic carotid stenosis, the risk of composite primary outcome of stroke, myocardial infarction, or death did not significantly differ in the group undergoing carotid-artery stenting and group undergoing carotid endarterectomy. There was a higher risk of stroke with stenting and higher risk of myocardial infarction with endarterectomy during the periprocedural period.

Aneurysm:

ISUIA (2003): Assessed the natural history of unruptured intracranial aneurysms in patients who did not have surgery and evaluated morbidity and mortality associated with repair (either open surgery or endovascular procedures) across centers in the USA, Canada and Europe. Included 4060 patients (1692 did not have aneurysmal repair, 1917 had open surgery, and 451 had endovascular procedures). 5-year cumulative rupture rates for patients without history of SAH with aneurysms located in ICA, anterior communicating or ACA, or MCA were 0%, 2.6%, 14.5%, and 40% for aneurysms less than 7 mm, 7-12 mm, 13-24 mm, and 25 mm or greater respectively compared with rates of 2.5%, 14.5%, 18.4%, and 50% respectively for the same size categories involving posterior circulation and posterior communicating aneurysms. Age was a strong predictor of surgical outcome, and size and location of aneurysm predict both surgical and endovascular outcomes. Concluded that site, size, and group specific risks of natural history should be compared with site, size, and age-specific risks of repair for each patient.

ISAT (2005): Compared endovascular detachable-coil treatment or craniotomy and clipping in patients with ruptured intracranial aneurysms who were suitable for either treatment. Included 2143 patients with ruptured intracranial aneurysms admitted to 42 neurosurgical centers in UK and Europe with 1070 patients in the neurosurgical clipping group and 1073 patients in the endovascular coiling group. Found 250 (23.5%) of 1063 patients assigned to endovascular treatment were dead or dependent at 1 year compared to 326 (30.9%) of 1055 patients allocated to neurosurgery, with absolute risk reduction of 7.4% (95% CI, 3.6-11.2; P=0.0001). Concluded that endovascular coiling was more likely to result in independent survival at 1 year compared to neurosurgical

clipping with survival benefit for at least 7 years in patients with ruptured intracranial aneurysms. Risk of late rebleeding is low but was more common after endovascular coiling than after clipping.

PUFS (2013): Evaluated the safety and effectiveness of Pipeline Embolization Device (PED) in treatment of complex intracranial aneurysms. Enrolled 108 patients with recently unruptured large and giant wide-necked aneurysms which failed coiling or were considered uncoilable. Found that of 106 aneurysms, 78 met the study's primary effectiveness endpoint of complete aneurysm occlusion and absence of major stenosis at 180 days (73.6%; 95% posterior probability interval: 64.4%-81.0%). Six of 107 patients in the safety cohort had major ipsilateral stroke or neurologic death (5.6%; 95% posterior probability interval: 2.6%-11.7%). Concluded that PED is a safe and effective treatment of large or giant intracranial ICA aneurysms with high rates of complete aneurysm occlusion and low rates of adverse neurologic events, even in those failing previous alternative therapies.

PREMIER (2019): Assessed the safety and efficacy of the pipeline embolization device (PED) for treating wide necked small and medium intracranial unruptured aneurysms (measuring ≤12 mm along ICA or vertebral artery). 141 patients were treated with PEDs with mean aneurysm size of 5.0±1.92 mm, and 84.4% (119/141) measured <7 mm. 97.9% (138/141) patients had follow-up angiography at 1 year with 76.8% (106/138) of patients having met the primary effectiveness endpoint (complete Raymond grade 1 occlusion without major parent vessel stenosis (≤50%) or retreatment). The combined major morbidity and mortality rate was 2.1% (3/140). Concluded that treating wide necked small/medium aneurysms with PED yielded high rates of complete occlusion without significant parent vessel stenosis and low rates of permanent neurologic complications.

WEB-IT (2019): Woven EndoBridge Intrasaccular Therapy (WEB-IT) study evaluated the safety and effectiveness of WEB device for treatment of wide-neck bifurcation aneurysms. Enrolled 150 patients with wide-neck bifurcation aneurysms at 21 US and 6 international centers but 148 patients received with WEB implant. At the 12-month angiographic follow-up, 53.8% (77/143) of patients had complete aneurysm occlusion with adequate occlusion in 84.6% (121/143) of patients. One (0.7%) primary safety event of delayed ipsilateral parenchymal hemorrhage occurred on postop day 22. No primary safety events occurred after 30 days to 1 year. Concluded that WEB device provides an option for patients with wide-neck bifurcation aneurysms that is as effective as other available therapies and markedly safer.

AVM:

ARUBA (2014): Compared the risk of death and symptomatic stroke in unruptured brain arteriovenous malformation patients allocated to either medical management alone or medical management with interventional therapy. Enrolled patients at 39 clinical sites in 9 countries to medical management with interventional therapy (ex. Neurosurgery, embolization, or stereotactic radiotherapy, alone or in combination) or medical management alone (pharmacological therapy for neurological symptoms as needed). Outcome data was available for 223 patients with 114 assigned to interventional therapy and 109 to medical management. Study was stopped on April 15, 2013 when the DSM board recommended halting randomization because of the superiority of the medical management group. Found that the primary endpoint (time to composite endpoint of death or symptomatic stroke) was reached by 10.1% of patients in medical management group compared with 30.7% in the interventional therapy group. The risk of death or stroke was significantly lower in the medical management group than in the interventional group (hazard ratio 0.27; 95% CI, 0.14-0.54). Concluded that medical management alone is superior to medical management with interventional therapy for the prevention of death or stroke in patients with unruptured AVMs followed up for 33 months.

CVT/Venous sinus Stenting:

TO-ACT (2020): Evaluated the safety and efficacy of endovascular treatment in patients with severe form of cerebral venous thrombosis (CVT). Conducted in 8 hospitals in 3 countries (Netherlands, China, and Portugal) and inclusion criteria were adult patients aged ≥18 with radiologically confirmed CVT with at least 1 risk factor for poor outcome (mental status disorder, coma state, intracerebral hemorrhage, or thrombosis of deep venous system). Randomized 67 patients with 33 (49%) to the intervention group and 34 (51%) to the control group. Found that 22 intervention patients (67%) had mRS score of 0-1 compared with 23 control patients (68%) at 12 months. Mortality was not statistically significantly higher in the EVT group (12% vs 3%; P=0.20) and frequency of symptomatic ICH was not statistically significantly lower in the intervention group (3% vs 9%; P=0.61).

Intracranial Hemorrhage:

SCUBA (2018): Minimally invasive techniques do not permit clear visualization of residual clot burden in ICH hence a specific endoscopic technique called Stereotactic Intracerebral Hemorrhage Underwater Blood Aspiration (SCUBA) aimed to address shortcomings with use of a fluid-filled cavity. Retrospective case series including

patients who underwent endoscopic ICH evacuation with SCUBA technique from December 2015 to September 2017. Inclusion criteria were hematoma volume >20 cc, hematoma volume stability on two CT scans 6 hours apart, NIHSS ≥6, GCS ≥4, and baseline mRS <4. There were 47 patients who underwent ICH evacuation via SCUBA technique. Found that the mean preoperative ICH volume was 42.6 cc (SD 29.7) and mean postoperative ICH volume was 4.2 cc (SD 6.6) with average evacuation rate of 88.2% (SD 20.8). Active bleeding vessels were encountered in 23 cases (48.9%) of which 11 (23.4%) were from a single vessel and 12 (25.5%) were due to bleeding from multiple vessels. Concluded that the SCUBA technique provides a defined method for endoscopic hematoma evacuation while fluid-filled cavity in SCUBA Phase 2 has potential advantages of clear identification and cauterization of bleeding vessels with visualization of residual clot burden.

MISTIE III (2019): Assessed whether minimally invasive catheter evacuation followed by thrombolysis, with the goal of decreasing clot size to 15 mL or less, would improve functional outcomes in intracerebral hemorrhage (ICH) patients. Randomized trial of image-guided, catheter-based removal of ICH of 30 mL or more (measured by ABC/2 method) conducted at 78 hospitals in the USA, Canada, Europe, Australia and Asia. 506 patients enrolled with 255 (50%) in the MISTIE group and 251 (50%) in the standard medical care group. Ultimately, 499 patients (n=250 in the MISTIE group; n=249 in standard medical care group) received treatment and were included in the analysis. The modified intention-to-treat primary adjusted efficacy analysis estimated that 45% of patients in the MISTIE group and 41% in the standard medical care group had an mRS of 0-3 at 365 days (adjusted risk difference 4% [95% CI –4 to 12]; p=0·33.Concluded that MISTIE did not improve the proportion of patients who achieved a good response 365 days after a moderate to large ICH.

ENRICH (2024): Although surgical evacuation trials of supratentorial ICH have not shown functional benefit, the benefit of minimally invasive surgical removal compared to medical management on outcomes was not known. Patients with lobar or anterior basal ganglia hemorrhage with hematoma volume of 30-80 mL were assigned in a 1:1 ratio within 24 hours of last known well to minimally invasive surgical removal of hematoma plus medical management (surgery group) or to medical management alone (control group). 300 patients were enrolled including 30.7% patients with anterior basal ganglia hemorrhages and 69.3% with lobar hemorrhages. After 175 patients were enrolled, adaption rule was triggered and only patients with lobar hemorrhages were enrolled. Mean score on utility-weighted mRS at 180 days was 0.458 in the surgery group and 0.374 in the control group (difference, 0.084; 95% Bayesian credible interval, 0.005 to 0.163; posterior probability of superiority of surgery, 0.981). Mortality by 30 days was 9.3% in the surgery group and 18.0% in the control group. 5 patients (3.3%) in the

surgery group had postoperative rebleeding and neurologic deterioration. Concluded that minimally invasive hematoma evacuation within 24 hours after an acute ICH resulted in better functional outcomes at 180 days than medical management. Death by 30 days occurred in fewer patients in the surgery group than in the control group.

Subdural Hematoma (MMA Embolization trials):

MAGIC MT (2024): Enrolled Chinese patients with symptomatic non acute subdural hematoma with mass effect to evaluate the effect of middle meningeal artery (MMA) embolization. Patients were assigned to undergo burr-hole drainage or nonsurgical treatment at surgeon's discretion, and patients in each group were randomly assigned in 1:1 ratio to undergo MMA embolization with liquid embolic material or to receive usual care. Randomized 722 patients with 360 to embolization group and 362 to usual-care group. Symptomatic recurrence or progression of subdural hematoma occurred within 90 days in 24 patients (6.7%) in the embolization group and 36 (9.9%) in the usual-care group. Incidence of serious adverse events was lower in the embolization group than in the usual-care group (6.7% vs. 11.6%, P=0.02). Concluded that MMA embolization resulted in 90-day incidence of symptomatic recurrence or progression similar to usual care but had lower incidence of serious adverse events in patients with symptomatic non acute subdural hematoma (of whom 78% underwent burr-hole drainage).

STEM (2024): Evaluated the effect of adjunctive middle meningeal artery embolization on the risk of treatment failure in patients with chronic subdural hematoma. Randomized patients with symptomatic chronic subdural hematoma to undergo MMA embolization as an adjunct to standard therapy (embolization group) or to standard treatment alone (control group). Enrolled 310 patients with 149 in the embolization group and 161 in the control group; 189 patients were to get surgical standard treatment and 121 nonsurgical standard treatment. The primary outcome event (composite of recurrent or residual chronic SDH measuring >10 mm at 180 days, reoperation or surgical rescue within 180 days, major disabling stroke, MI or death from neurologic causes within 180 days) occurred in 19 of 120 patients (16%) in embolization group in comparison to 47 of 129 patients (36%) in control group (odds ratio, 0.36; 95% CI, 0.20-0.66; P=0.001). 3% (4 of 144) patients in the embolization group and 3% (5 of 166) patients in the control group had either major disabling stroke or mortality within 30 days. Concluded that in patients with symptomatic chronic subdural hematoma, adjunctive MMA embolization resulted in lower risk of treatment failure than standard treatment alone without increasing incidence of disabling stroke or death in the short term.

EMBOLISE (2024): Assigned patients with symptomatic subacute or chronic subdural hematoma with indication for surgical evacuation to MMA embolization plus surgery

(treatment group) or surgery alone (control group). Randomized 197 patients to the treatment group and 203 patients to the control group. Surgery occurred before randomization in 136 of 400 patients (34%). Found that hematoma recurrence or progression leading to repeat surgery occurred in 8 patients (4.1%) in the treatment group compared to 23 patients (11.3%) in the control group (relative risk, 0.36; 95% CI, 0.11-0.80; P=0.008). Functional deterioration happened in 11.9% of patients in the treatment group and 9.8% of patients in the control group while 90-day mortality was 5.1% in the treatment group and 3.0% in the control group. Concluded that in patients with symptomatic subacute or chronic subdural hematoma with indication for surgical evacuation, MMA embolization plus surgery had lower risk of hematoma recurrence or progression leading to reoperation than surgery alone.

DAVF/CSF Venous Fistula

Dural arteriovenous fistula:

Cerebral Dural Arteriovenous Fistulas: Clinical and Angiographic Correlation with a Revised Classification of Venous Drainage (1995): Reviewed the symptoms and progression of dural arteriovenous fistulas (AVFs) and correlated findings with various angiographic patterns. Facilitated classification into 5 types: type I (located in main sinus with antegrade flow), type II (in main sinus with reflux into sinus (IIa), cortical veins (IIb), or both (IIa + b), type III (with direct cortical venous drainage without venous ectasia), type IV (with direct cortical venous drainage with venous ectasia), and type V (with spinal venous drainage). Found that Type I DAVFs had a benign course and in type II, reflux into sinus induced intracranial hypertension in 20% and reflux into cortical veins induced hemorrhage in 10%. Hemorrhage occurred in 40% of type III dural AVF cases and 65% of type IV cases. Type V had progressive myelopathy in 50% of cases. Concluded that this classification is useful for determining risk of each dural AVF to guide therapeutic decision-making.

CSF venous fistula:

Clinical and imaging outcomes of cerebrospinal fluid-venous fistula embolization (2022): Evaluated the outcomes of patients with spontaneous intracranial hypotension (SIH) who underwent transvenous embolization of cerebrospinal fluid-venous fistulas (CSFVFs) confirmed on digital subtraction myelography (DSM) in a single center retrospective analysis. Included 40 patients with mean Bern score improvement from 5.7 ±3.0 at baseline to 1.3±2.0 at follow-up ($p<0.0001$). Mean HIT-6 (Headache Impact Test) score at baseline was 67.2±11.1 and 41.5±10.1at follow up ($p<0.0001$). Median PGIC (Patient Global Impression of Change) was 1, with 36 patients (90%) reporting at least minimal improvement and 32 patients (82.5%) reporting much or very much improvement. Complications were persistent local site pain in 12 patients (30%),

suspected rebound intracranial hypertension needing medical intervention in 7 patients (17.5%) and asymptomatic tiny Onyx emboli to lungs in 3 patients (7.5%). Concluded that transvenous embolization of CSF venous fistulas using Onyx was safe and effective with significant improvement in headache and overall clinical outcomes in nearly 90% of patients as well as improvement in MRI brain abnormalities.

Anatomy of Spinal Venous Drainage for the Neurointerventionalist: From Puncture Site to Intervertebral Foramen (2022): Comprehensive review summarizing the organization of spinal venous drainage and provides a practical roadmap from puncture site to foramen for transvenous spinal procedures.