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Full Title: CURRENT EVIDENCE FOR ENDOVASCULAR THERAPY IN STROKE AND REMAINING UNCERTAINTIES (R1)

Short Title: Review of Evidence for Endovascular Therapy in Stroke

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Abstract

Class 1 level A evidence now supports endovascular thrombectomy as best practice in the management of large vessel occlusion acute ischemic stroke. However, significant questions pertaining to initial imaging, radiological assessment, patient selection and therapeutic limits remain unanswered. A specific cohort of patients who benefit from endovascular thrombectomy has been established, although current uncertainties regarding selection of those not meeting top-tier evidence criteria may potentially deny certain patients the benefit of intervention. This is of particular relevance in patients presenting in a delayed manner. While superior outcomes are achieved with reduced time to endovascular reperfusion, denying certain patients intervention based on symptom duration alone may not be appropriate. Advanced understanding of ischemic stroke pathophysiology supports an individualized approach to patient evaluation, given variance in the rate of ischemic core progression and the extent of salvageable penumbra. Physiological imaging techniques may therefore be utilized to better inform patient selection for endovascular thrombectomy and evidence suggests that a transition from time-based to tissue-based therapeutic thresholds may be of greater value. Multiple ongoing randomized controlled trials aim to further define the benefit of endovascular thrombectomy and it is hoped that these results will advance, and possibly broaden, patient selection criteria to ensure that maximum benefit from the intervention may be achieved.

Keywords: Stroke, Ischemia Reperfusion, Intervention, Thrombolysis, Radiology, Neurology, Interventional Neuroradiology, Thrombectomy, Endovascular

List of Abbreviations:

AIS: Acute Ischemic Stroke

ASPECTS: Alberta Stroke Programme Early CT Score

CI: Confidence Interval

CT: Computed Tomography

CTA: Computed Tomography Angiography

DWI: Diffusion Weighted Imaging

EVT: Endovascular Thrombectomy

ICA: Internal Carotid Artery

IV t-PA: Intravenous Tissue Plasminogen Activator

LVO: Large Vessel Occlusion

MCA: Middle Cerebral Artery

MIP: Maximal Intensity Projection

MRI: Magnetic Resonance Imaging

mRS: modified Rankin Scale

mTICI: modified Treatment In Cerebral Ischemia

OR: Odds Ratio

RAPID: Rapid Processing of Perfusion and Diffusion

RCT: Randomized controlled trial

sICH: Symptomatic Intracerebral Hemorrhage

WUS: Wake-Up Stroke

List of Study Names/Organizations:

AHA/ASA: American Heart Association/American Stroke Association

AXIS: AX200 for Ischemic Stroke

BASICS: Basilar Artery International Cooperation Study

DAWN: Diffusion Weighted Imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention

DEFUSE: Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study

ESCAPE: Endovascular treatment for Small Core and Proximal Occlusion Ischemic Stroke

ESO: European Stroke Organisation

EXTEND-IA: Extending the Time for Thrombolysis in Emergency Neurological Deficits – IntraArterial

HERMES: Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials

IMS: Interventional Management of Stroke

MR CLEAN: The Multicentre Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands

MR RESCUE: Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy

NIHSS: National Institutes of Health Stroke Scale

NINDS: National Institute of Neurological Disorders and Stroke

PISTE: Pragmatic Ischaemic Stroke Thrombectomy Evaluation

PROACT: Prolyse in Acute Cerebral Thromboembolism

RESILIENT: Randomization of Endovascular Treatment with Stent-Retriever and/or Thromboaspiration vs. Best Medical Therapy in Acute Ischemic Stroke Due to Large Vessel Occlusion Trial

REVASCAT: Endovascular Revascularization with Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours

SWIFT PRIME: Solitaire Flow Restoration versus the Merci Retriever for Acute Ischemic Stroke

SYNTHESIS: Intra-arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke

THERAPY: Assess the Penumbra System in the Treatment of Acute Stroke

THRACE: Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke

THRILL: Thrombectomy in Patients Ineligible for IV tPA

Introduction

Stroke is a cause of profound burden on individuals and economies worldwide, with current projections estimating exponential increase in its impact on society for many years to come.[1-3] Recent advancement in the understanding, assessment and treatment of large vessel occlusion (LVO) acute ischemic stroke (AIS) has shifted the management paradigm, particularly with the rapidly expanding use of endovascular thrombectomy (EVT) (Figure 1), although significant uncertainties remain as to best practice.[4, 5]

There is certainly a core group of patients, as specified by AHA/ASA guidelines, for whom the benefit of EVT is clear.[6] However, as the body of evidence pertaining to EVT continues to evolve, essential questions remain for patient sub-groups not meeting top-tier evidence criteria.[7] Occlusion location, ischemic core size or duration from symptom onset are some of the major variables that may exclude certain patients from EVT, and it is therefore of upmost importance that these factors be explored so as to minimize the numbers of patients denied potentially effective intervention.

Pathophysiology of Acute Ischemic Stroke

In cases of AIS, arterial occlusion leads to an interruption in cerebral perfusion and consequently a reduction in oxygen and glucose supply. Ultimately, this results in permanently infarcted tissue termed the ischemic core and it is the volume of this insult that has the most significant impact on patient outcome.[8-11] Collateral blood flow, such as that provided by the leptomeningeal vasculature, is a key factor in limiting the extent of perfusion deficit and slowing the rate of ischemic progression. This is a crucial point in the evolving management of AIS, as the extent of collateral flow appears unique to each individual, leading to variance in the rate of irreversible infarction and salvageable penumbra (Figure 2 & 3). While the ischemic core may be defined as cell death secondary to reduced cerebral blood flow, the penumbra may be considered a site of impaired cell function with failure to cross the threshold for cell

death, although this effect is transient. The goal of management is therefore to select patients with viable tissue and limit cell death by effective revascularization strategies, with clinical outcomes shown to be superior in those with better collateral flow.[12-23]

With this inconsistency in collateral flow, patient selection using time as a surrogate biomarker no longer seems logical nor appropriate. Time for one patient may mark rapid progression to a large ischemic core, whereas the same time for a slowly progressing patient may result in limited infarct and extensive penumbra, kept temporarily viable by superior collaterals. There is no reason to believe that collateral flow simply ceases to function in every patient at a arbitrary time limit thereby resulting in futile intervention, and so the focus must shift to individualized assessment.

Importantly, this is not to say that time should not be ignored. Early treatment improves outcome in AIS, with decreased time to reperfusion associated with reduced ischemic core expansion, improved functional status and lower mortality.[24-31] Therefore, time must remain a key focus, with emphasis on fast workflow and the development of efficient stroke management models, dictated by regional healthcare systems and populations.[32] However, when it comes to patient selection for revascularization, a shift towards tissue-windows places emphasis on individual pathophysiology and the use of time may well be destined to a practice of the past.[33]

Evolving Management Strategies

Best evidence for efficacy of IV t-PA was first published in 1995 by the NINDS rt-PA Stroke Study Group.[34] An initial 3-hour treatment window was extended to 4.5 hours, with efficacy confirmed through multiple meta-analyses.[35-39] However, in cases of LVO, the benefit of IV t-PA is limited due to the poor recanalization rates, reported to be as low as 15-25%.[40-43] This is of profound importance, as the degree of successful recanalization is the best predictor for good outcome.[40, 44] Given

these limitations, numerous intra-arterial interventions have been explored to date. The efficacy of targeted intra-arterial thrombolytic agents was first demonstrated in the PROACT II study in 1998, followed by, the IMS II study which established benefit in combined delivery of intravenous and intra-arterial t-PA.[45, 46]

In 2013, three separate RCTs - IMS III, SYNTHESIS Expansion and MR RESCUE - were published concurrently, with outcomes demonstrating no significant benefit in EVT compared to best medical management.[47-49] However, multiple issues with trial design, coupled with technological advancement during the trial periods, cast doubt over the validity of these results. There were limited requirements in evaluating the degree of cerebral ischemia in all three RCTs and there was no requirement to confirm LVO in IMS III and SYNTHESIS. Most notably, due to the prolonged inclusion period, second-generation thrombectomy devices were arriving on the market by the time the RCTs were in their concluding stages.[50-52] This is a profound limitation to these RCTs, given that second-generation devices have superior recanalization rates, better clinical outcomes and improved safety profiles when compared to the first-generation devices used predominantly throughout the original studies.[53-55] With this, the results were essentially outdated before their publication.

Less than two years later, the results of MR CLEAN, along with four other RCTs - ESCAPE, EXTEND-IA, REVASCAT and SWIFT PRIME - showed significant benefit for IV t-PA plus EVT (predominantly using second generation stent-retrievers (Figure 1c & 4), compared to IV t-PA alone, in cases of LVO AIS (Table 1).[56-60]

A meta-analysis was subsequently performed by the HERMES collaboration, with data pooled from these five RCTs. Outcomes from 1287 participants (634 intervention group vs. 653 control group) demonstrated significantly improved 90-day functional outcome with EVT, irrespective of patient group heterogeneity. A 90-day mRS of 0-2 was achieved in 46.0% in the intervention group, compared to 26.5% in the control, resulting in an adjusted OR of 2.71 and a number needed to treat to reduce disability by ≥1 on the mRS of 2.6. As seen with each individual study, there was no significant difference in 90-day mortality, parenchymal hematoma or sICH.[4] With this, HERMES confirmed EVT to be the accepted standard of care for patients with

proximal anterior circulation occlusions.[4, 5, 61] Furthermore, the REVASCAT investigators have since demonstrated persistent benefit, with superior functional independence in the intervention group at 1-year.[62]

Since the HERMES meta-analysis, two further RCTs, THRACE and PISTE, have added to the wealth of evidence supporting EVT. Patients in the EVT arm of THRACE had a higher rate of 90-day functional independence, defined as mRS of 0-2**,** with an OR of 1.55 and no significant difference in safety parameters.[63] PISTE recruited 65 patients prior to termination due to emerging evidence supporting EVT. While no significant difference was shown in 90-day functional independence between the intention-to-treat groups (may be explained by low sample size), there were significantly higher rates in the intervention group following per-protocol population analysis (mRS 0-2, 57% vs. 35%; OR, 4.92).[64]

The overwhelming evidence supporting EVT is reflected in latest international guidelines. The ESO now supports EVT within 6 hours of symptom onset in patients with LVO AIS, in addition to IV t-PA. However, specific criteria regarding patient selection remain largely undefined.[61] The AHA/ASA also recommend EVT to AIS patients who meet specific criteria, including a pre-stroke mRS score of 0-1, IV t-PA within 4.5 hours, internal carotid or proximal middle cerebral artery occlusion, age ≥18, NIHSS ≥6, ASPECTS ≥6 and initiation of treatment within 6 hours.[6] However, while benefit is clearly stated, both sets of guidelines state uncertainty as to effect of EVT >6 hours, suggesting the need for further research to define therapeutic limits.[6, 61] This is reflected in the contrasting guidelines from the Canadian Stroke Best Practice Recommendations, which support EVT up to 12 hours from symptom onset.[65]

Undoubtedly, this uncertainty within published guidelines is cause for concern, with specific exclusion criteria potentially denying benefit to certain patients. A recent study evaluated 1464 consecutive AIS patients, with just 8% of patients fulfilling MR CLEAN inclusion criteria and 6% for REVASCAT. Apart from absence of LVO (69%), the most common reason for exclusion was time from symptom onset exceeding the specified therapeutic window; with 38% of patients not meeting the MR CLEAN time limit of 6 hours and 35% not meeting the REVASCAT limit of 8

hours.[66] In an observational study evaluating EVT in 583 consecutive patients with LVO AIS, the same investigators found that a total of 234 (40%) patients were treated outside AHA/ASA guidelines, yet there was no significant difference in 90-day functional outcome, mortality or sICH between this group and those treated within the guidelines.[7]

The REVASCAT investigators have also demonstrated efficacy in EVT performed outside pre-specified selection criteria. Following publication, REVASCAT reviewed outcomes for every patient treated with EVT over a two-year period in Catalonia who was deemed ineligible for the original trial (n=340). Functional and safety outcomes were found to be, for the most part, similar to EVT patients within the trial, and superior to the controls receiving IV t-PA alone.[67]

The core group of patients who benefit from EVT has been identified. But this evidence suggests that with adherence to overly selective inclusion criteria (possibly reflected by the degree of success demonstrated by HERMES), a significant proportion of patients may be denied effective intervention.

The Impact of Time

In the knowledge that many patients may be excluded from EVT due to prolonged symptom duration, we must consider what it is that time actually reflects: evolving infarct and diminishing penumbra, at variable rates. Therefore, time may be better used as a crude predictor of EVT outcome, rather than an accurate measure for patient selection.

IMS III highlighted the time dependent effect on functional outcome, calculating reduced likelihood of functional independence at 90-days with increasing time to revascularization. The adjusted relative risk for good functional outcome (mRS 0-2)

was 0.88 for every 30-minute delay.[26] The MR CLEAN investigators demonstrated a 6% reduction in the absolute risk difference for good functional outcome with every hour of delayed reperfusion.[30, 56] Similarly, SWIFT PRIME demonstrated improved functional outcomes with early reperfusion, with an estimated 91% probability of achieving a mRS 0-2 when reperfusion occurred within 150 minutes of symptom onset. However, this probability decreased by 10% after the next 60 minutes and 20% for every 60 minutes thereafter.[31]

Most significantly, HERMES analysed the effect of time on patient outcome within their data pool. In patients who achieved successful revascularization, every 1-hour delay from symptom onset resulted in a less favourable outcome and each 9-minute delay resulted in 1 in every 100 patients scoring 1 level or greater on the mRS. Treatment effect was deemed insignificant at the 7 hour 18-minute mark from symptom onset to groin puncture.[29]

Duration from symptom onset is not the only factor predicting successful clinical outcome. Procedural time alone may influence effect, although there is insufficient evidence to draw conclusions. Spiotta et al. demonstrated that every 10-minute addition to procedure time reduced chances of good functional outcome by 0.87. Patients who achieved revascularization in procedures lasting less than 60 minutes had better functional outcome (53.6% vs. 30.8%; p=0.009), and fewer complications (3.4% vs. 11.0%; p=0.05). Specifically, there was no correlation between procedural time and sICH in this study.[68] However, conflicting evidence does exist regarding this impact.

Kass-Hout et al. evaluated the effect of procedural time and found that functional independence was associated with shorter mean procedural times, but only prior to adjusting for independent variables (mean procedural time, 73.1 minutes (mRS 0-2) vs. 86.7 minutes (mRS >2); p=0.0228). With multivariate analysis applied, the difference was no longer statistically significant. Furthermore, rates of sICH were significantly increased in patients with longer procedural times (mean procedural time, 79.67 minutes (no sICH) vs. 104.5 minutes (sICH); p=0.0319).[69]

From Time-Windows to Tissue-Windows

Evidence clearly supports fast workflow, measured by time. However, assessment of a patient's unique tissue insult may prove a more valuable selection tool. In addition to the duration of impaired cerebral perfusion, the degree of collateral blood flow is also vitally important and influences progression of infarct core on an individual basis. Hence, reconsidering how we view the stages of workflow and placing physiological neuroimaging central to individualized patient assessment is paramount.[33]

Analysis by ESCAPE revealed a significant predictor for positive outcome to be reduced time from imaging to EVT, with only a modest association between overall time from symptom onset to EVT. Therefore, duration from symptom onset to imaging may influence EVT eligibility, based on the extent of viable tissue present during assessment; while duration from imaging to EVT may dictate outcome, based on the extent of viable tissue salvaged.[33, 57, 70] This move from time-windows to tissue-windows is supported by a magnitude of evidence demonstrating EVT benefit in correctly selected patients, regardless of symptom duration.

The concept is not new - a study in 2010 reviewed outcomes from 55 patients presenting with AIS, selected by perfusion mismatch. A total of 34 patients treated with intra-arterial intervention <6 hours had no significant difference in functional independence compared to the 21 patients treated >6 hours.[71] A retrospective analysis by Jovin et al. on 237 patients with AIS who underwent intra-arterial intervention >8 hours of symptom onset with perfusion-based selection also showed similar results.[72] Turk et al. have demonstrated safety and efficacy for EVT in 247 AIS patients selected by perfusion-based imaging, regardless of time from symptom onset. Outcomes for patients undergoing intra-arterial treatment <8 and >8 hours were reviewed, with no significant difference in rate of functional independence.[73]

In the DEFUSE-2 prospective cohort study, patients were selected by MRI target mismatch and demonstrated similar rates of favourable outcome (30-day NIHSS of 0-1 or improvement of ≥ 8 from baseline) following EVT at 0-6 and 6-12 hours.[74] A further study has since compared patients in DEFUSE-2 to a control group from

AXIS II, demonstrating target mismatch patients in DEFUSE-2 who achieved successful revascularization had superior rates of good functional outcome when compared to the control, with efficacy maintained in the 6-12 hour EVT group.[75] Similarly, McTaggart et al. has shown the efficacy of late EVT following perfusion imaging. Rates of good functional outcome (mRS 0-2) in 41 patients undergoing EVT between 6-24 hours after symptom onset in LVO AIS were comparable to the HERMES EVT cohort.[76]

While much of the current evidence supporting late EVT used perfusion-based selection, ESCAPE (randomization up to 12 hours) and REVASCAT (randomization up to 8 hours) assessed patients using the ASPECTS quantitative evaluation tool [77], with additional evaluation by multiphase CTA in ESCAPE.[57, 59] ESCAPE included 49 patients treated >6 hours and while results in this group were not adequately powered, there was a direction of effect supporting EVT.[57] In REVASCAT, just 13 of the 103 patients randomized to the intervention arm underwent EVT >6 hours from symptom onset and sub-group analysis was not performed for this cohort.[59] However, in their subsequent analysis of EVT outside specified trial criteria, 75 patients underwent EVT >8 hours from symptom onset. In this sub-group, there were similar safety and functional outcomes as compared to the interventional arm of original study and superior outcomes compared to controls. Details regarding neuroimaging for the patients outside the REVASCAT trial are not given.[67]

Evaluating outcomes for those undergoing revascularisation following WUS may also help clarify the role of late intervention, although a scarcity of large-scale data pertaining to EVT limits our ability to draw conclusions.[78, 79] A retrospective review by Mokin et al. selected WUS patients for EVT by CT perfusion imaging. A total of 52 patients underwent EVT, with 48% of patients achieving a 90-day mRS of 0-2.[80] Konstas et al. also published their experience of EVT in WUS, using ASPECTS to evaluate the extent of infarct. A retrospective review of 12 EVT WUS patients was performed, with acceptable safety parameters, successful revascularization (mTICI 2b/3) and reduction of in-hospital NIHSS for all patients.[81]

The necessity for confirmation of LVO in selecting patients for EVT has been established. However, the best method for evaluating individual pathophysiology and appropriate inclusion thresholds remain undefined.[5, 27, 33, 82]

Calculation of ASPECTS, using CT or MRI, may objectively measure subtle parenchymal changes within the middle cerebral artery territory, thus assessing the extent of infarction.[77, 82] Both ESCAPE and REVASCAT used ASPECTS to inform patient selection, excluding patients with a CT score of <6 or <7 (or <6 on MRI), respectively.[57, 59] Patients with higher ASPECTS have increased benefit following EVT, conversely baseline scores of 0-4 are unlikely to have significant functional benefit and have increased complication rates.[83]

Consistent with this, MR CLEAN, which did not exclude patients based on low ASPECTS, had less favourable results compared to ESCAPE or REVASCAT, although it should be noted that the median ASPECTS in MR CLEAN was 9.[56, 57, 59] The MR CLEAN investigators have since performed sub-group analysis, concluding that patients with baseline ASPECTS of 5-7 still had benefit from intervention.[84] Also worth noting is the range of low ASPECTS included in the intervention arms of two of the most recent EVT RCTs, THRACE and PISTE. THRACE included 102 patients (52%) with ASPECTS 0-7 [22 patients (11%) with ASPECTS 0-4 and 80 patients (41%) with ASPECTS 5-7] [63], while PISTE included 7 patients (21%) with ASPECTS 0-7 [1 patient (3%) ASPECTS 0-4 and 6 patients (18%) with ASPECTS 5-7].[64] Furthermore, inter-observer variability in certain cases, especially in the hyperacute phase, has been reported.[85, 86] While ASPECTS is useful, given the uncertainty regarding treatment thresholds and reporting, it may not be the most reliable selection tool when used in isolation.

Assessment of collateral circulation with CTA has been used to indirectly assess tissue viability, thereby informing patient selection (Figure 2d & 3c). Multiple studies have shown that superior collateral blood flow on CTA correlates with improved

outcomes following EVT.[19-23] ESCAPE used multiphase CTA to determine the extent of collateral circulation and, when combined with ASPECTS, allowed for effective patient selection.[57] Analysis of data from the IMS III study also demonstrated the utility of evaluating collateral flow, with superior functional outcomes reported in patients with moderate to good collateral circulation and little benefit seen in patients without.[23]

An alternative method of physiological assessment is CT or MR perfusion imaging, with comparable accuracy reported for both.[82, 87-89] CT perfusion was used to screen infarct core volume in EXTEND-IA, with data analysed by RAPID software (iSchemaView, CA, USA).[58, 90, 91] Inclusion required an estimated infarct core <70ml, mismatch ratio >1.2 between estimated core and hypoperfused parenchyma or absolute mismatch volume >10ml, with these measures considered an indicator of sizable salvageable penumbra.[58] Similarly in SWIFT PRIME, 81% of patients were assessed for infarct core by CT perfusion, with analysis by RAPID.[60] Patients included in SWIFT PRIME with target mismatch profile, representing a small ischemic core and relatively larger penumbra, had highly favourable outcomes, including 27-hour infarct volume and functional independence, following EVT. Larger mismatch volumes at baseline were predictive of successful treatment effect.[11]

Significantly, EXTEND-IA and SWIFT PRIME yielded the best functional outcomes compared to the other 3 trials evaluated by HERMES.[56-60] However, a lack of standardization in perfusion data implies that its current role may be better directed towards identifying late presenting patients with viable penumbra, as opposed to an initial selection tool.[82] Concordant with this, the benefit of intra-arterial intervention without the need for perfusion assessment was clearly demonstrated by MR CLEAN, ESCAPE, REVASCAT and THRACE.[56, 57, 59, 63] Thus, caution must be exercised in the knowledge that strict criteria based on infarct core size and penumbra may exclude patients with potential benefit from intervention. Furthermore, the attainment of perfusion data should not significantly delay potential treatments. While there is value in obtaining such information, the best patient selection tools remain uncertain.[82, 92]

Ongoing Studies

There has been substantial progress in the management of AIS**,** but the need for further research is essential in order to address the remaining uncertainties regarding best practice. Multiple studies are currently investigating factors such as IV-tPA therapeutic time limits, thrombolytic substitutes, role of neuroprotectants and the efficacy of alternative treatment methods such as sonothrombolysis.[93] Specific to EVT, as outlined, research is essential in clarifying thresholds for patient selection, with particular focus now on treatment limits and appropriate tissue evaluation (Table 2).[94-98] Furthermore, although current evidence supports the use of stent-retrievers and bridging thrombolysis [4], alternative thrombectomy devices continue to be explored and the exact benefit of IV tPA in addition to EVT remains largely undefined.

The highly anticipated results of DAWN were presented in Prague at the European Stroke Organization Conference in May 2017. Enrolment for DAWN was terminated by the data and safety monitoring board following the first interim analysis in Spring 2017, demonstrating efficacy in the intervention arm.[99] DAWN suggests that by using either DWI or CT perfusion imaging to carefully select patients, EVT may be safely performed up to 24 hours from symptom onset. DAWN demonstrated superior 90-day functional independence (mRS 0-2) when compared with best medical therapy (48.6% v 13.1%), with a number needed to treat of 2.8. As expected, patients undergoing earlier EVT continue to have better outcomes.[99]

The results of DAWN will of course need to be validated in other trials evaluating EVT benefit in 'late presenters'. Several of these trials are currently in the planning phase, such as MR CLEAN LATE, or actively recruiting, such as DEFUSE-3.[95]

While IV t-PA, in addition to EVT, is considered best practice in the management of LVO AIS, a debate is currently underway as to the degree of EVT augmentation with bridging thrombolysis.[100] IV tPA adds significantly to health care expenditure, increases time to groin puncture and presents potential risk to patients. On the other

hand, bridging thrombolysis may provide benefit due to effect on distal emboli, softening of thrombus resulting in fewer stent-retriever passes and shorter procedural times, and a degree of reperfusion in the event of failed EVT.[70, 101-104]

Multiple single-centre studies have analysed their EVT data, comparing outcomes of bridging thrombolysis with EVT alone. Comparable recanalization rates, functional outcomes, safety parameters and mortality rates have been reported.[102-107] Broeg-Morvay et al. additionally performed multivariate matching analysis and found lower rates of asymptomatic intracerebral hemorrhage and lower mortality rates in those treated with solely with EVT.[103]

Interestingly, this evidence is conflicted by a meta-analysis that included seven of the major RCTs: MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, THRACE and PISTE. Despite considerable heterogeneity, a significantly lower rate of severe disability or death (mRS 5-6) and a non-significant trend toward 90-day functional independence (mRS 0-2) was identified in patients receiving bridging thrombolysis. Worth noting however, is the low sample size in the EVT monotherapy group and confounding bias due to failure to randomize IV tPA, thus introducing variance in baseline characteristics and time to groin puncture. [108] The lack of patient randomization may also be considered a limitation in a number of the single-centre studies.[102, 105-107]

Ultimately, a RCT is required to define the role of bridging thrombolysis. Two RCTs, THRILL and RESILIENT, aim to evaluate EVT outcomes in patients in whom IV t-PA is ineffective or contraindicated, with 90-day functional independence the primary outcome parameter for both.[96, 97, 109] THRILL was originally scheduled for completion in 2018 but has since been terminated following results of MR CLEAN, ESCAPE, EXTEND-IA and SWIFT PRIME, with results yet to be published.[96] RESILIENT is currently ongoing, with target completion date in 2019.[97]

Current evidence supports EVT in the anterior circulation [4] but efficacy in the posterior circulation remains undefined. THRACE was originally designed to investigate EVT in both anterior and posterior circulation occlusions, however, only 2 basilar artery occlusions were included, thus, findings are only applicable to the

anterior circulation.[63] BASICS is an ongoing RCT evaluating EVT in basilar artery occlusions, with rate of 90-day functional independence as primary outcome and a target completion date in 2017.[98]

Regarding EVT methods, there is currently insufficient evidence to support alternatives to stent-retrievers. THERAPY evaluated the effect of aspiration thrombectomy in LVO AIS; however, the trial was halted prematurely due to emerging evidence for stent-retriever EVT. Consequently, the trial was deemed to be underpowered, with 105 patients recruited and no significant difference in functional independence between aspiration thrombectomy and control, although the direction of effect did support intervention.[110]

Conclusion

A wealth of high-quality evidence confirms EVT, in conjunction with IV t-PA, as the standard of treatment in suitable patients with LVO AIS. As our understanding regarding stroke pathophysiology evolves, it is now well recognised that not all patients will have the same outcomes, likely given variability in collateral arterial supply. Therefore, strict therapeutic time windows for intervention are likely to be surpassed by individualized patient selection. The evaluation of cerebral physiological status is of profound importance and emerging evidence within the literature would suggest that this holds the key to patient selection and ultimately improved patient outcome following EVT.

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List of Tables:

Table 1: Summary of key studies on endovascular intervention in acute ischemic stroke.

Study	IMS III	SYNTHESIS	MR RESCUE	MR CLEAN	ESCAPE	EXTEND-IA	REVASCAT	SWIFT PRIME	THRACE	PISTE
Patient Number (control)	434 (222)	181 (181)	64 (54)	233 (267)	165 (150)	35 (35)	103 (103)	98 (98)	204 (208)	33 (32)
Minimum Inclusion Imaging	CT	CT	CT, CTA, multimodal CT/MR	CT, CTA	CT, ASPECTS, mCTA	CT, CTA, CT Perfusion	CT, ASPECTS, CTA,	CT, CTA, CT/MR Perfusion	CT, CTA/MRA	CT, CTA/MRA
Therapeutic Window (hours)	5	6	8 (completion: 9)	6	12	6 (completion: 8)	8	6	5	6
Median Onset to Groin Puncture (min)	208	225	381	260	208	210	269	224	250	209
Median Onset to Revascularization (min)	325	n/a	n/a	332	241	248	355	252†	303	259
mTICI Grade 2b/3 Recanalization (%)	41	n/a	27	58.7	72.4*	86.2	65.6	88	69	87
90-day mRS 0-2 (%)	40.8 (38.7)	75.7 (84)	18.8 (20.4)	32.6 (19.1)	53 (29.3)	71.4 (40)	43.7 (28.2)	60.2 (35.3)	53 (42)	51 (40)

***** ESCAPE trial used original TICI Grade

† Onset to first deployment of stent-retriever

Table 2: Ongoing research on endovascular intervention in patients presenting with acute ischemic stroke.

Study	Original Target Completion Date	Intervention vs. Control	Primary Outcome	Therapeutic Window (hours)
DAWN	2017 (study terminated)	Trevo thrombectomy + best medical management vs. best medical management alone.	90-day mRS 90-day mortality	6-24
BASICS	2017	Thrombectomy + best medical management vs. best medical management alone	90-day mRS *	0-6
THRILL	2018 (study terminated)	Thrombectomy vs. best medical management in patients ineligible or refractory to IV tPA.	90-day mRS shift	0-7 + 1 †
RESILIENT	2019	Thrombectomy vs. best medical management in patients ineligible or refractory to IV tPA.	90-day mRS	0-6 + 1.5 ‡
DEFUSE-3	2020	Thrombectomy + best medical management vs. best medical management alone	90-day mRS	6-16

* BASICS uses a mRS 0-3 as measure of functional independence

† THRILL randomized patients up to 7 hours, intervention to be completed within 8 hours.

‡ RESILIENT randomizing patients from 0-6 hours from symptoms onset and intervention to be commenced within 90 minutes from randomization.

List of Figures:

Figure 1: Endovascular Thrombectomy in Acute Ischemic Stroke

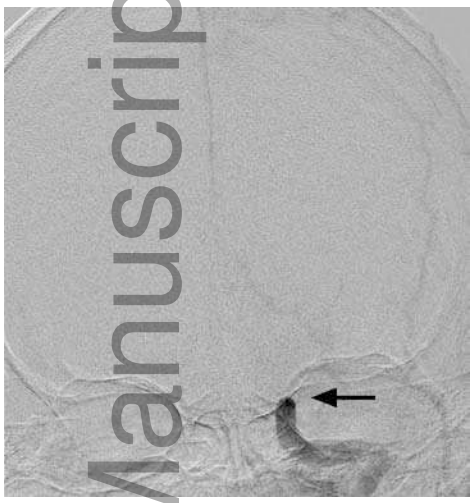


Fig. 1A

Fig. 1C

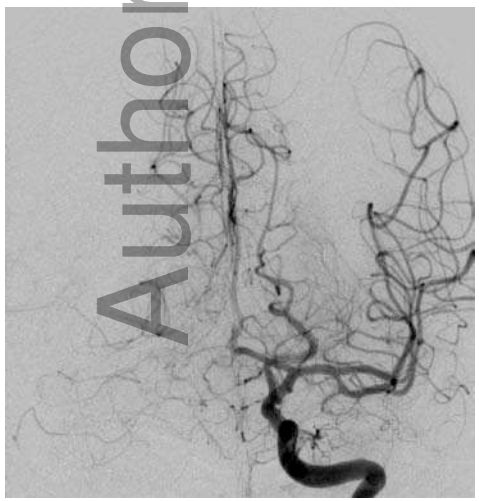


Fig. 1B

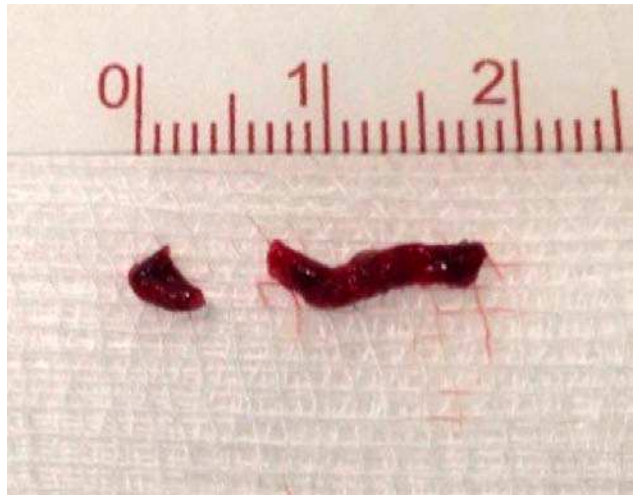


Fig. 1D

Figure 1:

A. Anterior-posterior selective left internal carotid artery (ICA) digital subtraction angiogram showing an acute occlusion of the left carotid terminus (black arrow) with no filling of blood vessels in the left cerebral hemisphere. Sluggish flow in the external carotid branches noted.

B. Anterior-posterior digital subtraction angiogram following thrombectomy showing successful recanalization of the left anterior circulation with good flow in the previously occluded vascular territory.

C. Fragments of retrieved thrombus from the left distal ICA within the walls of a Trevo 3 x 20 mm stent-retriever. Intra-arterial introduction of the stent-retriever is achieved via a transfermoral approach. The device is advanced to the occluded vascular territory and recanalization is achieved by stent deployment through a microcatheter at the site of occlusion. The thrombus is extracted following stent withdrawal.

D. Photograph of the retrieved thrombus fragments from left distal ICA.

Figure 2: Pathophysiological Variance: Slow Progressor

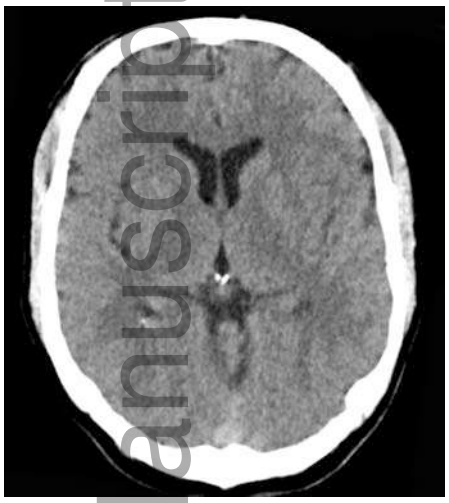


Fig. 2A

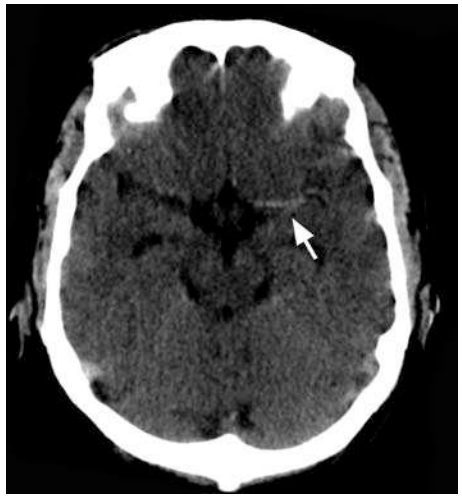


Fig. 2C

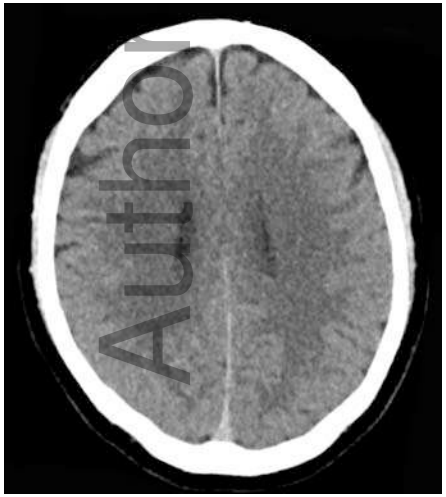


Fig. 2B

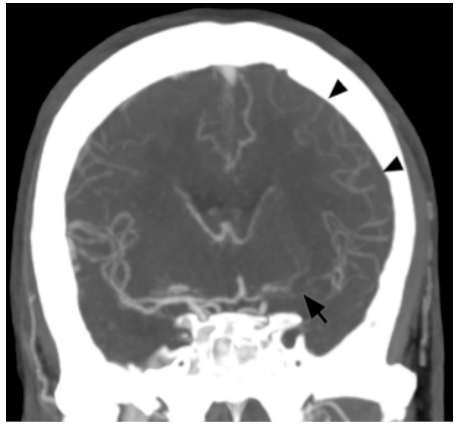


Fig. 2D

Figure 2:

Slow progressor: 49-year old male presented with sudden onset right-sided facial droop and neglect. NIHSS 17 on arrival.

A. Axial of non-contrast CT brain at ganglionic level performed at presentation, 5 hours from symptom onset. No evidence of established infarct or early ischemic change with an ASPECTS score of 10.

B. Additional axial CT brain at supraganglionic level showing no ischemic change and preserved grey-white matter differentiation.

C. Axial non-contrast CT brain in the same patient at a more inferior slice position showing a hyperdense left middle cerebral artery (MCA) sign, consistent with acute thrombus (white arrow).

D. Coronal MIP (maximal intensity projection) reconstruction from a CT angiogram performed at presentation showing an acute left M1 MCA occlusion (black arrow) with enhancement of the distal M3 cortical branches due to good leptomeningeal collateral supply to the left MCA territory (arrowheads).

The patient subsequently underwent endovascular thrombectomy, achieving successful recanalization (TICI 3). NIHSS was 2 at 24 hours post symptom onset and 0 at 30 days, with mRS of 0.

Figure 3: Pathophysiological Variance: Fast Progressor

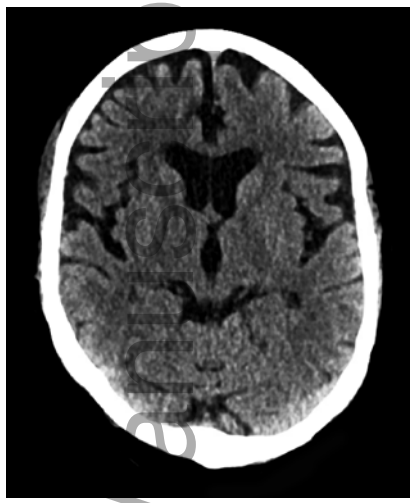


Fig. 3A

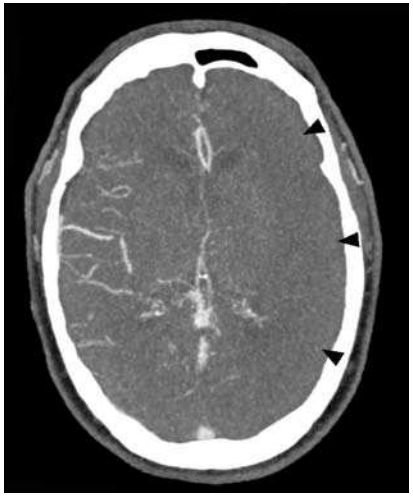


Fig. 3C

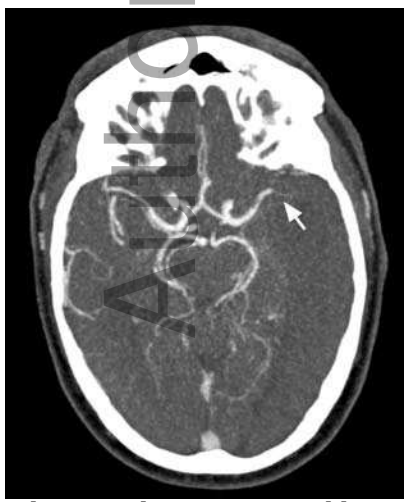


Fig. 3B

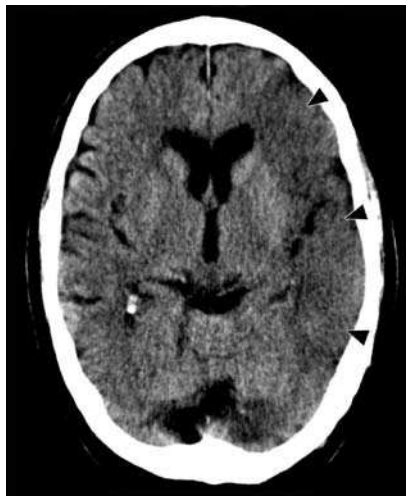


Fig. 3D

Figure 3:

Fast progressor: 73-year old male presented following sudden onset right-sided hemiparesis. NIHSS 23 on arrival.

A. Axial of non-contrast CT brain performed at presentation, 2 hours from symptom onset. No evidence of established infarct or early ischemic change with an ASPECTS score of 10.

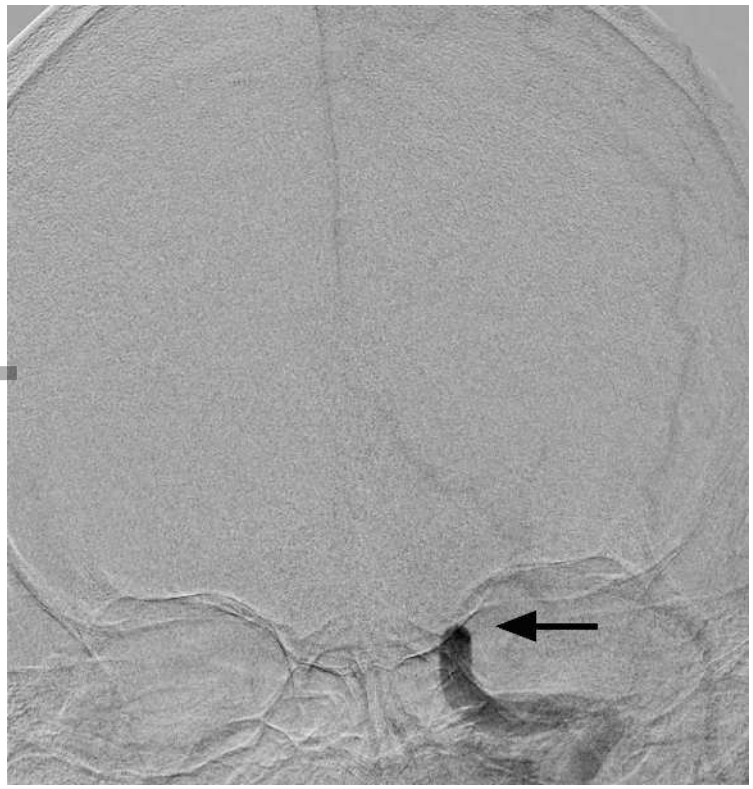
B. Axial MIP (maximal intensity projection) image from CT angiogram on the same patient showing left distal M1 segment MCA occlusion (white arrow).

C. Axial MIP (maximal intensity projection) image from CT angiogram on same patient showing poor leptomeningeal collateral supply in the left MCA territory, as shown by absence of M3 cortical branches (arrow heads).

D. Patient referred to tertiary centre. Repeat imaging performed at 2 hours 45 minutes after initial imaging, 4 hours 45 minutes from symptom onset. Axial non-contrast CT brain showing large established infarct in the left MCA territory (arrow heads) with an ASPECTS score of 3.

This patient showed significant interval deterioration clinically and radiologically as a result of poor leptomeningeal collateral supply to the infarct territory. Deemed unsuitable for intervention after repeat imaging demonstrating large established infarct. Patient ultimately had poor functional outcome.

Figure 4: Second Generation Stent-Retriever



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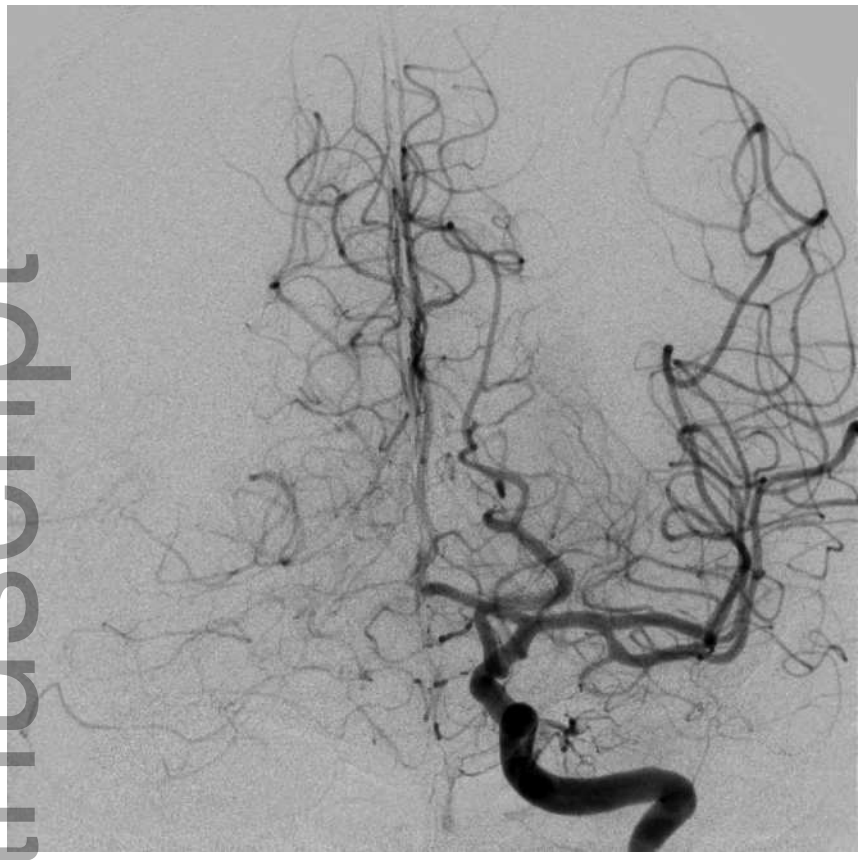

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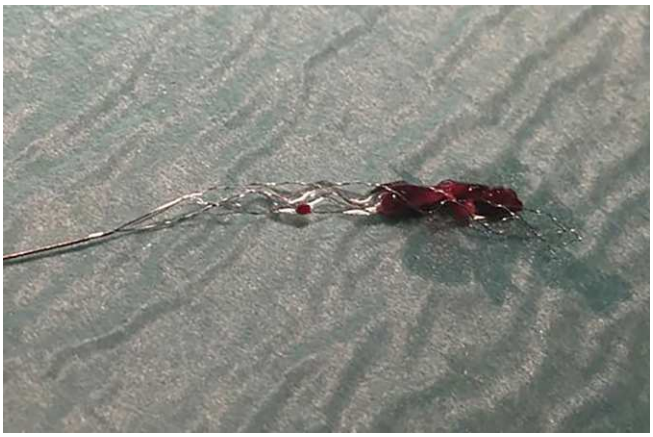

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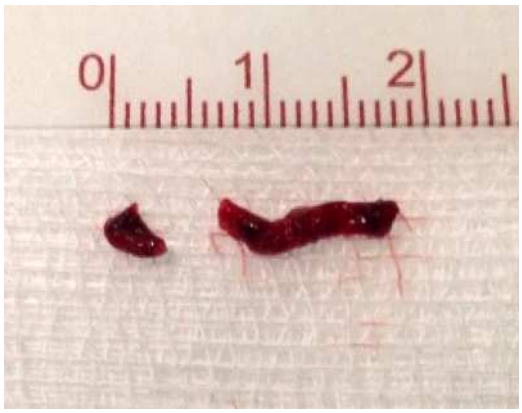

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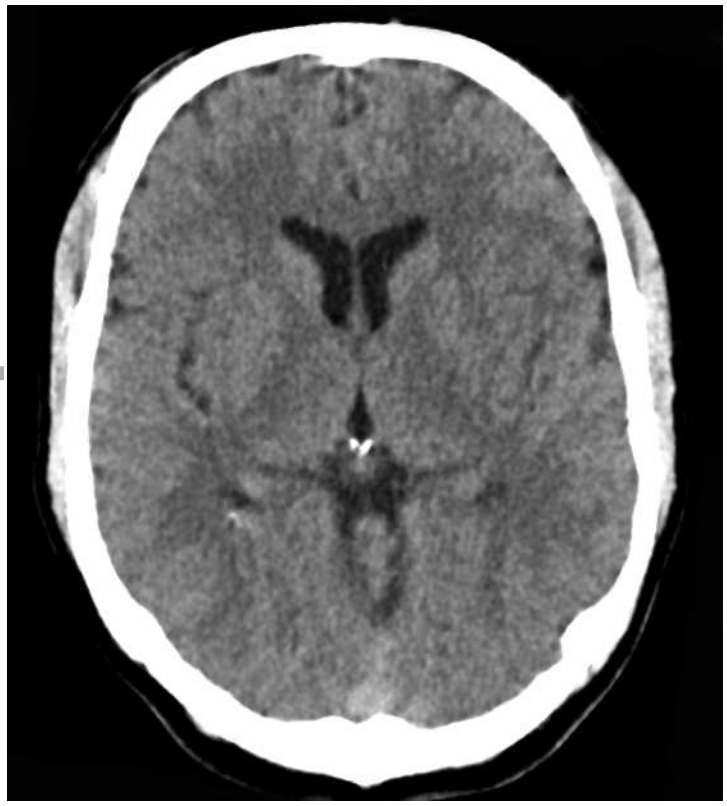

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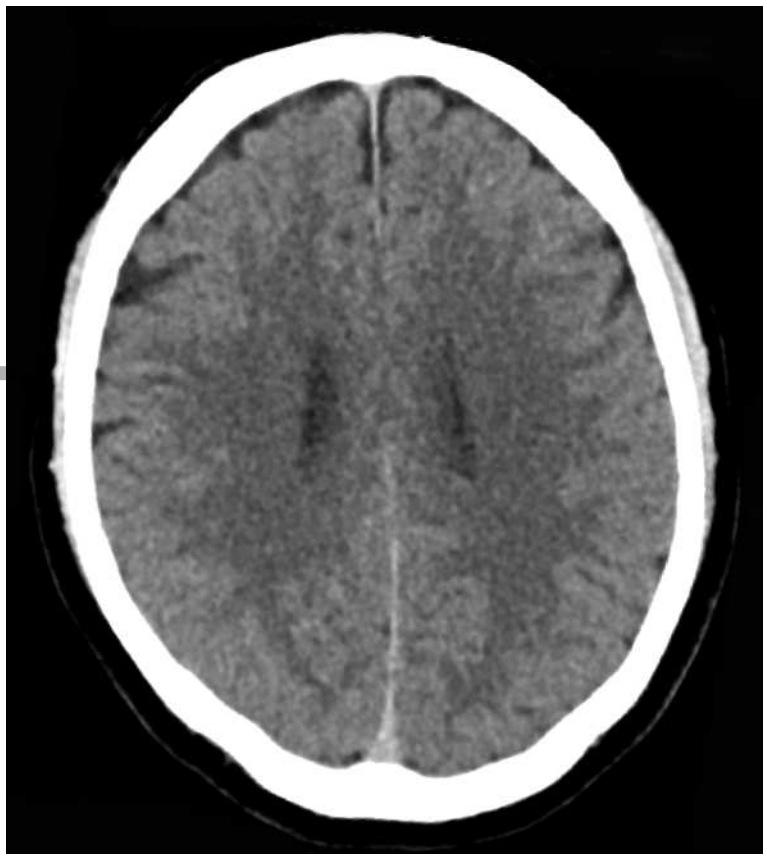

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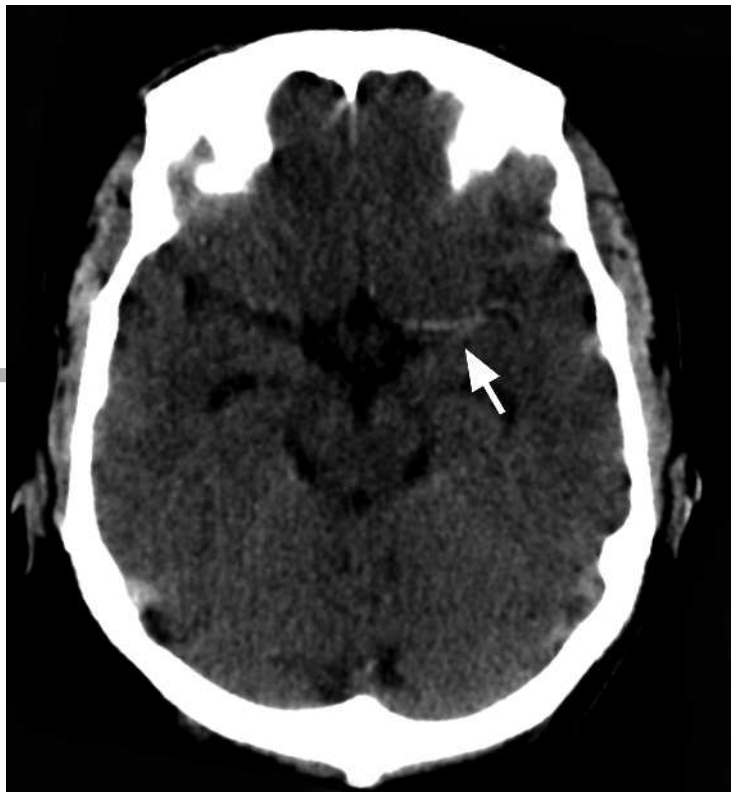

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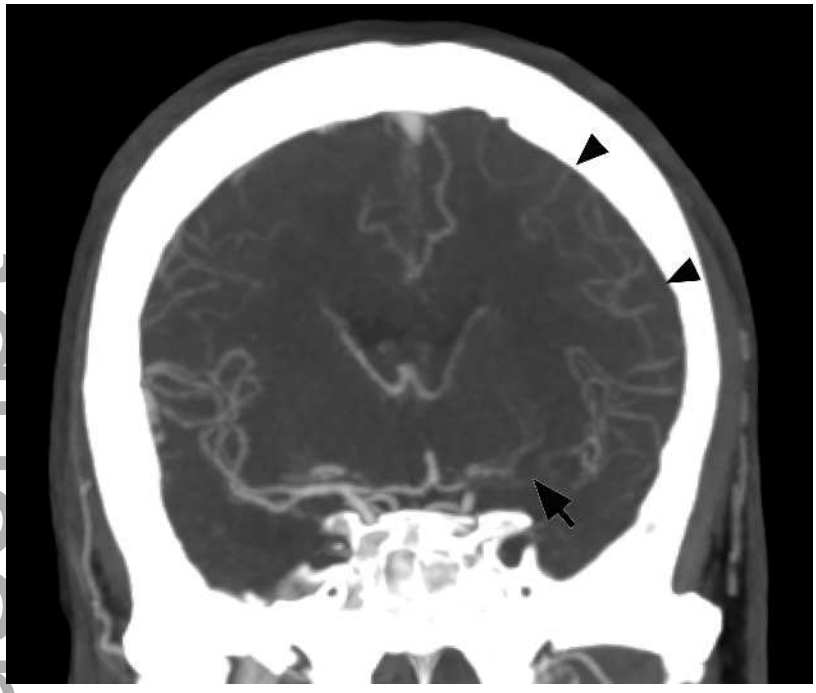

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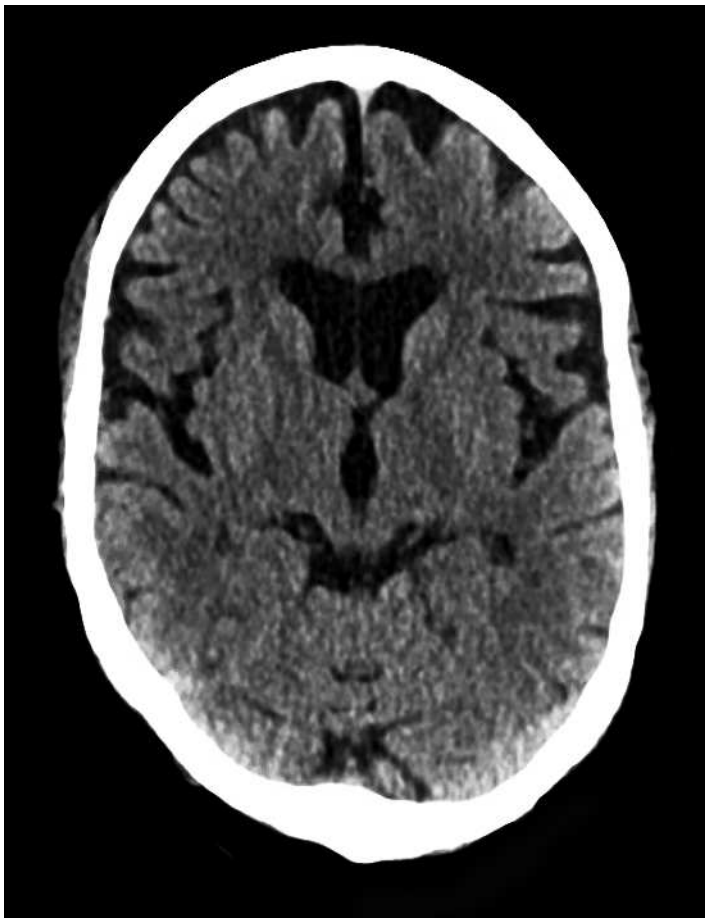

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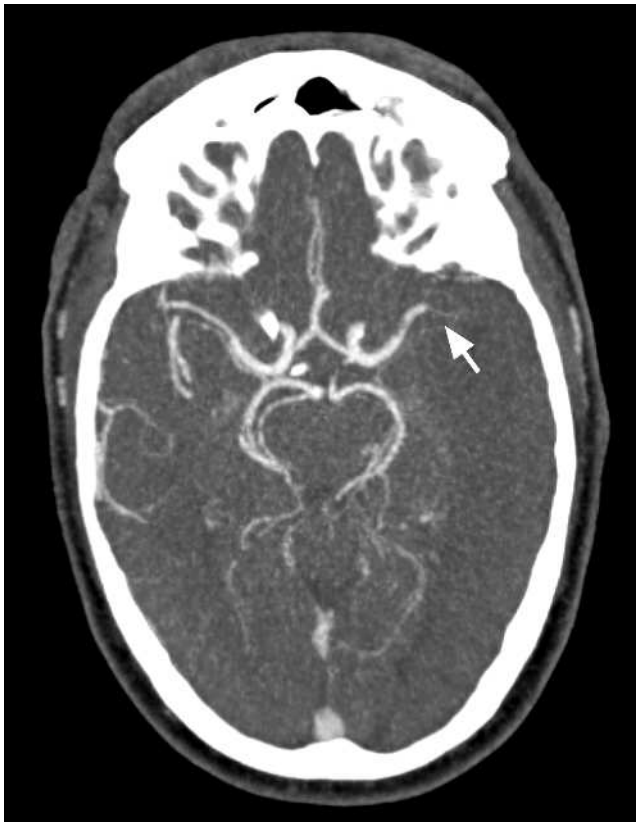

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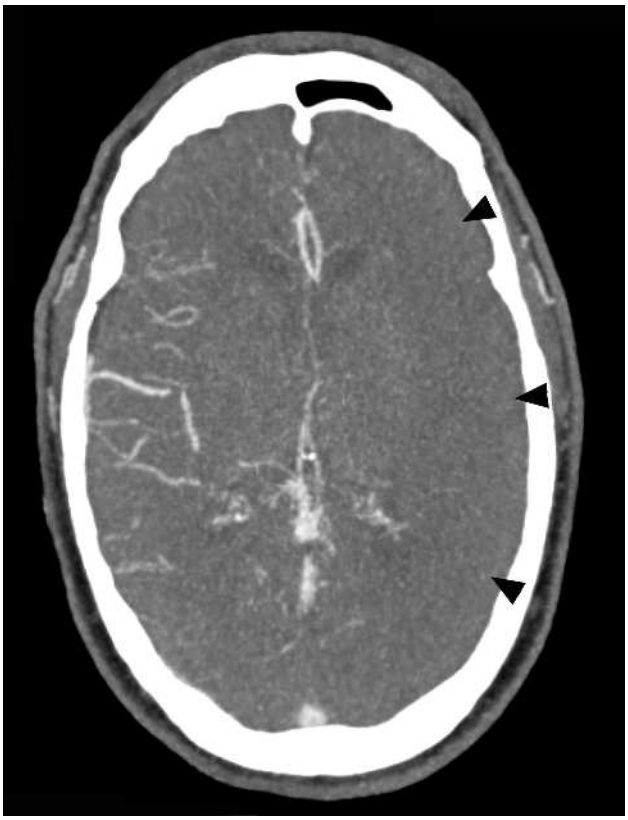

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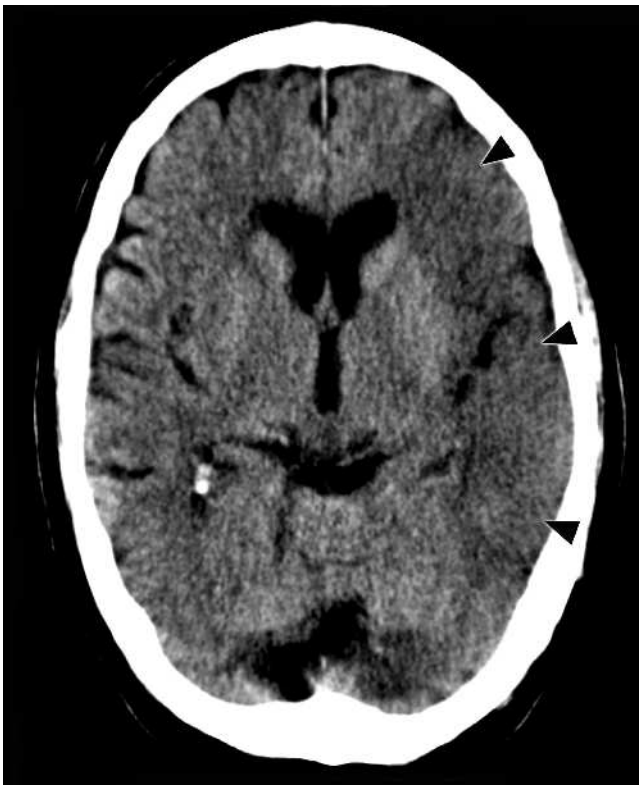

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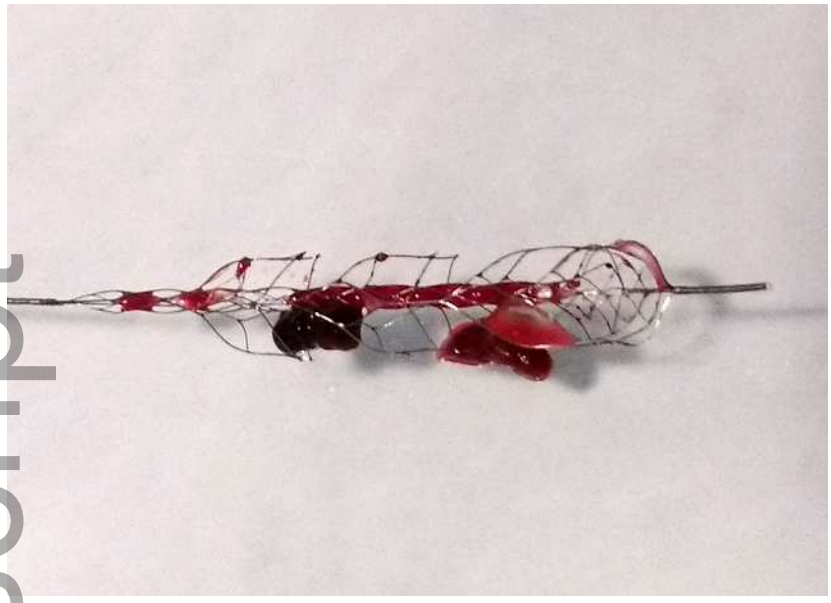

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Date:
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