Circulation

AHA SCIENTIFIC STATEMENT

Indications for the Performance of Intracranial Endovascular Neurointerventional Procedures

A Scientific Statement From the American Heart Association

ABSTRACT: Intracranial endovascular interventions provide effective and minimally invasive treatment of a broad spectrum of diseases. This area of expertise has continued to gain both wider application and greater depth as new and better techniques are developed and as landmark clinical studies are performed to guide their use. Some of the greatest advances since the last American Heart Association scientific statement on this topic have been made in the treatment of ischemic stroke from large intracranial vessel occlusion, with more effective devices and large randomized clinical trials showing striking therapeutic benefit. The treatment of cerebral aneurysms has also seen substantial evolution, increasing the number of aneurysms that can be treated successfully with minimally invasive therapy. Endovascular therapies for such other diseases as arteriovenous malformations, dural arteriovenous fistulas, idiopathic intracranial hypertension, venous thrombosis, and neoplasms continue to improve. The purpose of the present document is to review current information on the efficacy and safety of procedures used for intracranial endovascular interventional treatment of cerebrovascular diseases and to summarize key aspects of best practice.

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In 2009, the American Heart Association (AHA) published "Indications for the Performance of Intracranial Endovascular Neurointerventional Procedures,"[1] which reviewed outcomes data for the endovascular treatment of several cerebrovascular diseases and made recommendations for the indications for these procedures. Endovascular neurointervention has continued to be a rapidly evolving field, with new devices and techniques expanding the range of diseases that can be treated and improving the safety of the therapies. The volumes of these procedures appear to be increasing.[2] There has been a corresponding acceleration of outcomes research that establishes the efficacy of these treatments and clarifies their role relative to pharmacological or open surgical therapies. Since 2009, there have been substantial changes in the endovascular treatment of acute stroke, intracranial stenosis, cerebral aneurysms, and cerebral vascular malformations covered in the previous statement. This document updates the review of outcomes data for the efficacy and safety of these procedures and provides new recommendations for the use of these therapies. Furthermore, the document reviews and provides recommendations for 2 additional groups of endovascular therapies that are substantial components of many neuroendovascular programs: treatment of intracranial venous diseases and embolization of neoplasms.

Key Words: AHA Scientific Statements ■ cerebrovascular disorders ■ embolectomy ■ intracranial aneurysm ■ intracranial arteriovenous malformations ■ intracranial atherosclerosis ■ stroke ■ therapeutic embolization

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SCIENTIFIC STATEMENT VERSUS CLINICAL PRACTICE GUIDELINE

Since the publication of the original 2009 statement, the AHA and American College of Cardiology have codified the nature of and requirements for the clinical practice guideline and distinguished these statements from Suggestions for Clinical Practice. The clinical practice guidelines are the highest level of recommendations and are intended to inform the medical community of the clearly desired course of action in specific clinical circumstances. Because the treatments described in this document are changing rapidly and because reasonable practice varies widely nationally and internationally, this document continues to take the form of a scientific statement rather than clinical practice guidelines, and the products of the literature reviews and discussions of the expert group are to be considered suggestions for clinical practice. In this rubric, the AHA Classification of Recommendations and Levels of Evidence are not used. However, because quality of evidence for the different therapies discussed in this statement varies substantially, the quality of evidence on which each of the suggestions is based will be clearly described.

Computerized searches of the National Library of Medicine database of literature (PubMed) from July 2007 to January 2016 were conducted with 2 goals. The first goal was to identify published imaging and clinical outcomes data for intracranial endovascular cerebrovascular interventions that could be used as benchmarks for quality assessment. In addition, the process sought to identify those risk-adjustment variables that affect the likelihood of success and complications. The second goal was to identify data that can be used as the basis for monitoring the successful performance of endovascular cerebrovascular procedures. Key words and phrases for disease entities, including cerebral aneurysm, stroke, arteriovenous malformation (AVM), and cerebral stenosis, were used in conjunction with procedural terms, including coil, stent, thrombolysis, intervention, and endovascular treatment. Only English-language articles and articles with English-language translation were included. Abstracts were reviewed, and articles unrelated to the specific topic were excluded. Duplicate references and redundant publications were discarded.

WRITING GROUP COMPOSITION

The writing group was selected to represent a broad range of experience with, perspective of, and expertise in neurovascular disease and treatment. Participants were solicited from the AHA councils and interdisciplinary working groups by the AHA's chief scientific officer. The members of the writing group were identified on the basis of ≥1 of the following attributes: neurointerventionalists with a broad range of experience, clinical researchers who study the outcome of neurovascular procedures and stroke, directors of neuroendovascular training and treatment programs, and individuals knowledgeable about neurovascular diseases.

ENDOVASCULAR ACUTE ISCHEMIC STROKE INTERVENTION

Although there has been improvement in stroke-related mortality over the past decade, stroke remains the fifth leading cause of death (≈130 000 per year) and leading cause of disability in the United States with an incidence of nearly 800 000 cases annually, the majority resulting from acute ischemic stroke (AIS) from cerebrovascular occlusions.[3] Large vessel occlusion (LVO) disproportionally affects AIS-associated morbidity and mortality, with dependent disabilities contributing to its substantial economic costs (>$50–$60 billion annually).[4]

Intravenous Thrombolysis

Intravenous recombinant human tissue plasminogen activator (r-tPA) for thrombolysis of suspected cerebrovascular occlusions within 3 hours from symptom onset remains a US Food and Drug Administration (FDA)–approved, evidence-based treatment for AIS, proven to improve clinical outcomes since the landmark National Institute of Neurological Disorders and Stroke trial.[5] In 2009, a pooled analysis of multiple randomized trials, including ECASS III (European Cooperative Acute Stroke Study III), expanded the interventional window for intravenous r-tPA to 4.5 hours with specific exclusions (age >80 years, use of any anticoagulant, combination of both prior stroke and diabetes mellitus, and National Institutes of Health Stroke Scale [NIHSS] score ≥25).[6] However, patients presenting with AIS may be ineligible for intravenous r-tPA despite presenting within the 3- to 4.5-hour time window (with contraindications arising from systemic or intracranial hemorrhage risk) or harbor cerebrovascular occlusions refractory to intravenous r-tPA. Intracranial LVO is relatively resistant to intravenous r-tPA with low rates of early recanalization (distal internal carotid artery [ICA], 4.4%; M1 segment of the middle cerebral artery [MCA], 32.3%; M2 MCA, 30.8%; basilar, 4%),[7] probably as a result of clot composition (nonfibrin emboli) and volume (length >8 mm).[8] Because time to treatment and efficacy of reperfusion are paramount in stroke intervention, there should be no delays after administration of intravenous r-tPA to vascular imaging and endovascular therapy.[9]

Intra-Arterial Thrombolysis

Intra-arterial thrombolysis with prourokinase demonstrated early success in the PROACT (Prolyse in Acute

Cerebral Thromboembolism Trials) -1 and -2 with MCA occlusions.[10,11] The multicenter, controlled PROACT-2 trial randomized 180 patients (2:1) with M1-M2 MCA occlusions who were ineligible for intravenous r-tPA and presented <6 hours to receive intra-arterial prourokinase plus intravenous heparin versus intravenous heparin alone. PROACT-2 successfully demonstrated a 67% versus 18% immediate vessel recanalization rates (TIMI [Thrombolysis in Myocardial Infarction] grade 2–3) and absolute clinical benefit (40% versus 25% with modified Rankin Scale [mRS] score of 0–2) with intra-arterial thrombolysis regardless of higher symptomatic intracerebral hemorrhage (SICH) rates (12% versus 4%). A meta-analysis including MELT (Japanese Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial) reiterated excellent recanalization and clinical outcomes with intra-arterial prourokinase.[12,13] Although there may have been early Level I evidence for the efficacy and safety of endovascular treatment with intra-arterial thrombolytic therapy, prourokinase was not approved by the FDA and eventually became unavailable.

Because the intra-arterial prourokinase data were no longer clinically applicable and there was limited off-label experience with intra-arterial r-tPA, investigators were prompted to study bridging intravenous r-tPA (0.6 mg/kg) and adjunctive intra-arterial r-tPA (<20–22 mg) therapy in the EMS (Emergency Management of Stroke) and IMS (Interventional Management of Stroke) -1 and -2 trials.[14–16] Despite a pooled analysis of IMS studies that observed promising recanalization rates (53.3%–68.9%) and improved clinical outcomes (odds ratio [OR] >2) with reduced mortality (16% versus 24%) compared with the historical National Institute of Neurological Disorders and Stroke placebo control group, there was no significant benefit over the National Institute of Neurological Disorders and Stroke intravenous r-tPA cohort. Subsequently, the IMS investigators would pursue a randomized controlled trial (RCT) spanning 8 years to attempt FDA approval for intra-arterial r-tPA thrombolytic therapy.

After the publication of multiple RCTs demonstrating the more efficient revascularization of LVO with modern thrombectomy devices, the 2015 focused update of the AHA/American Stroke Association guidelines for endovascular AIS intervention reflected these changes in practice, further relegating intra-arterial fibrinolytic therapy to a role as an adjunct or second-line treatment.[17] A role remains for intra-arterial r-tPA thrombolysis in MCA occlusions that are not amenable to mechanical thrombectomy devices because of technical or anatomic challenges (vessel tortuosity or eloquent distal M2-M3 thromboemboli), but caution with respect to dose is advised in patients with contraindications to systemic intravenous r-tPA.

Mechanical Thrombectomy

As several mechanical thrombectomy devices evolved, industry-sponsored multicenter, single-arm treatment trials were performed to determine device safety and efficacy for FDA approval. The first-generation Merci retriever was initially assessed in the MERCI (Mechanical Embolus Removal in Cerebral Ischemia) and Multi-MERCI trials in patients who were ineligible or had failed intravenous r-tPA thrombolysis, resulting in independent clinical outcomes of 60.3% versus 69.4% TIMI grade 2 to 3 recanalization rates and 43.5% versus 34% with mRS scores of 0 to 2, respectively.[18,19] Second- and third-generation thrombectomy devices, including the Penumbra vacuum aspiration system and the Solitaire/Trevo stent retrievers, demonstrated progressively improving TICI (Thrombolysis in Cerebral Infarction) grade 2 to 3 recanalization rates in the Penumbra Pivotal (82%), SWIFT (Solitaire With the Intention for Thrombectomy), and TREVO2 (Thrombectomy Revascularization of Large Vessel Occlusions in Acute Ischemic Stroke) trials, independently of intra-arterial r-tPA thrombolysis.[20–22] In the SWIFT and TREVO2 trials, stent retrievers were randomized against first-generation Merci clot retrieval devices, demonstrating higher TICI grade 2 to 3 recanalization rates (Solitaire, 68% versus Merci, 30%; and Trevo, 86% versus Merci, 60%) and improved clinical outcomes at 90 days (Solitaire, 36% versus Merci 29%; and Trevo, 40% versus Merci, 22% with mRS scores of 0–2, respectively). Furthermore, SWIFT identified reduced mortality (17% versus 38%) and symptomatic hemorrhage rates (2% versus 11%) with the use of stent retrievers. It is important to note that neither of these mechanical thrombectomy device trials included a study arm with patients treated with intravenous r-tPA alone or a study arm of best medical therapy alone in patients ineligible for intravenous r-tPA.

Negative RCTs: Importance of Patient and Imaging Selection, Thrombectomy Devices, and Stroke Processes

In 2013, enthusiasm for endovascular stroke intervention was tempered by publication of 3 prospective randomized open blinded end point (PROBE) superiority trials that failed to show benefit of intra-arterial therapies: SYNTHESIS (Local Versus Systemic Thrombolysis for Acute Ischemic Stroke), IMS-3, and MR RESCUE (Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy).[23–25] Although all 3 RCTs failed to prove the clinical efficacy of endovascular intra-arterial thrombolysis/thrombectomy compared with intravenous r-tPA or best medical therapy, these trials were instrumental in demonstrating the relative safety of endovascular treatment and in influencing patient

selection and trial methodologies for the successful RCTs to follow. Specifically, they identified the importance of criteria for vascular (computed tomographic angiography [CTA]/magnetic resonance [MR] angiography [MRA]) and adjunctive tissue (MR diffusion-weighted imaging [DWI]–perfusion-weighted imaging [PWI]/computed tomography [CT] perfusion CTP) imaging selection strategies, use of newer thrombectomy devices more likely to produce effective reperfusion (TICI grade 2b/3), and clinical process improvement to minimize treatment times.

SYNTHESIS randomized 362 patients to receive intravenous r-tPA within 4.5 hours versus intra-arterial r-tPA thrombolysis (≤0.9 mg/kg) within 6 hours of symptom onset.[24] Adjunctive thrombectomy was used in a minority of the endovascular arm (34% and only 14% with stent retrievers). There was no difference in disability-free survival at 90 days (34.8% versus 30.4% with mRS scores of 0–1), but the study was criticized because vascular imaging inclusion to confirm LVO was not required, recanalization rates were not reported, and the trial was confounded by an inherent discrepancy of intravenous versus intra-arterial r-tPA treatment delays (median onset to treatment time, 2.75 versus 3.75 hours).

IMS-3 randomized 656 patients (2:1) presenting with AIS (NIHSS score ≥10) to intravenous r-tPA (0.6 mg/kg) and endovascular treatment (intra-arterial r-tPA and thrombectomy device) versus intravenous r-tPA (0.9 mg/kg) alone within 3 hours from symptom onset.[23] The phase III trial was terminated prematurely for futility to show a clinical outcome benefit at 90 days in the endovascular arm (40.8% versus 38.7 % with mRS scores of 0–2), although a potential signal for endovascular efficacy was noted in patients with severe strokes presenting with an NIHSS score ≥20 (23.8% versus 16.8% with mRS scores of 0–2; *P*=0.06). Several factors may have played a role in this result, most notably the absence of a requirement for LVO diagnosis by CTA before randomization, leading to the absence of a treatable lesion (ICA or M1-M2 MCA thromboembolism) in 16% of those enrolled. Midtrial amendments corrected inequities to standardize the intravenous r-tPA dose and allowed the inclusion of patients with an NIHSS score ≥8 if LVO was confirmed with CTA vascular imaging. In a cohort with CTA-documented LVO, subgroup analysis was favorable for endovascular treatment (47.2% versus 38.5% with mRS scores of 0–2; *P*=0.0114).[26]

Significant time delays to endovascular treatment in the IMS-3 trial were observed, with mean±SD groin puncture times of 208±47 minutes after stroke onset and recanalization occurring nearly 2 hours later with a mean±SD of 325±52 minutes. In fact, the delay in the initiation of endovascular treatment was 32 minutes longer than in the earlier IMS-1 trial (>100 minutes from onset of intravenous r-tPA in IMS-3). The IMS investigators commented that this alone may have been responsible for their equivocal results because every 30-minute delay had been shown to be associated with >10% decrease in the probability of an independent functional outcome, and any reperfusion obtained after 347 minutes achieved no clinical benefit in quality-adjusted life-years.[9,27] Conversely, on subgroup analysis, patients who received intravenous r-tPA within 2 hours of symptom onset and underwent groin puncture at <90 minutes demonstrated a significant trend for endovascular treatment efficacy (OR, 1.77), reiterating the very important role of time to reperfusion (<4.5–6 hours).

Although IMS-3 introduced the newest thrombectomy devices into the trial, there was predominant use of intra-arterial thrombolysis (138 patients, 41.3%) and early-generation thrombectomy devices (Merci retriever, 95 patients [28.1%]; Penumbra aspiration, 51 cases [16.2%]), with few stent retrievers (5 patients, 1.5%). Hence, low TICI grade 2b/3 reperfusion rates (38% ICA/44% M1 MCA) may have contributed to the limited efficacy of endovascular treatment because successful revascularization (TICI grade 2b/3 versus 0–2a) was strongly associated with good functional outcomes (48.2% versus 13.9% with mRS scores of 0–2; *P*=0.001).

More complex, advanced imaging selection strategies based on MR DWI and PWI or CTP were postulated to select patients with AIS who would most benefit from endovascular reperfusion in the MR RESCUE trial.[23] The methodology evolved from the DIAS (Desmoteplase in Acute Ischemic Stroke Trial)/DEFUSE (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) studies and EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial), which sought to extend intravenous desmoteplase and r-tPA treatment windows with evolving perfusion postprocessing algorithms to define a significant mismatch ratio of salvageable ischemic tissue (penumbra) at risk for infarction to completed core infarct volume that would warrant intervention.[28–30] Promising DEFUSE-2 trial results were reported from a multicenter, prospective 99-patient cohort study in which all patients underwent intra-arterial endovascular therapy after MR DWI/PWI. Standardized postprocessing software (Rapid Processing of Perfusion and Diffusion [RAPID]) analysis was performed with the use of stricter definitions of DWI core (apparent diffusion coefficient <600 s/mm^2) and PWI penumbra (Tmax >6 seconds).[31] A "target mismatch" group was predefined as (1) a ratio between the volumes of critical ischemic tissue (penumbra) and infarct core ≥1.8 (mismatch ratio) with an absolute difference ≥15 mL, (2) infarct core volume <70 mL, and (3) volume of tissue with a severe delay in bolus arrival (Tmax >10 seconds) <100 mL. As in the DEFUSE and EPITHET intravenous r-tPA trials, patient

age and core DWI infarct volumes were significant predictors of favorable clinical response (decrease in NIHSS score of 8 points/NIHSS score of 0–1 at 30 days). Furthermore, early reperfusion (>50% volume reduction in baseline perfusion) with intra-arterial therapy was associated with a favorable clinical response (OR, 8.8; 95% confidence interval [CI], 2.7–29.0) and good 90-day functional outcomes (mRS score, 0–2) with an OR of 4.0 (95% CI, 1.3–12.2) in the target mismatch group (56% versus 31%), but no benefit was seen in the group with no mismatch (OR, 1.9; 95% CI, 0.2–18.7), suggesting efficacy of MR DWI-PWI–based patient selection for endovascular treatment.

The MR RESCUE results were discordant with the preliminary DEFUSE-2 findings. MR RESCUE was a phase IIb multicenter RCT that randomized 118 patients with LVO and anterior circulation stroke within 8 hours from symptom onset to endovascular versus standard medical therapy with analysis stratified by favorable penumbral (infarct core <90 mL and perfusion/core mismatch ratio of 1.4) or nonpenumbral patterns using pretreatment CT/MR perfusion imaging.[25] Although the trial demonstrated no significant difference in clinical outcomes with intra-arterial therapy in either the penumbral or nonpenumbral groups, it was prone to several limitations, including slow patient recruitment with small sample sizes subdivided into 4 study groups. MR/CTP–based imaging analysis used an earlier block permutation postprocessing algorithm, lower perfusion mismatch, and larger core infarct volume thresholds (median, 36 mL in MR RESCUE penumbral pattern versus 13 mL in DEFUSE-2 target mismatch group). In addition, patient randomization occurred at 5 to 6 hours after symptom onset, indicating substantial time delays to groin puncture with a mean±SD of 6.35±1.2 hours. It was postulated that the penumbral pattern in MR RESCUE may have represented oligemia in later time windows, not ischemia, as evidenced by the fact that the standard therapy group with a penumbral pattern exhibited very small volumes of infarct growth (6.7 versus 73 mL in the DEFUSE-2 nonreperfused target mismatch group). Suboptimal effective recanalization also resulted in only 25% of endovascularly treated patients achieving TICI grade 2b/3 reperfusion.

Critics of MR DWI-PWI– and CTP-based patient selection methodologies for AIS intervention cite the time versus tissue imaging delays, MR imaging accessibility and scan times resulting in endovascular treatment delays, lack of standardized postprocessing perfusion software, failure to quantitatively model the dynamic properties of in vivo cerebral perfusion (contrast delay-dispersion correction and retrograde pial collateral supply), and inability to differentiate a true penumbra (ischemic tissue destined to infarct without reperfusion) from a false penumbra (oligemic tissue that would survive regardless of reperfusion).[32] However, both vascular and advanced CT/MR perfusion imaging selection with standardized RAPID postprocessing software has played a prominent role in several of the successful RCTs to follow.

Positive RCTs: Evidence for Endovascular Stroke Intervention

In 2014 to 2015, 5 PROBE superiority trials provided Level 1A evidence for the benefit of endovascular treatment over intravenous r-tPA or best medical therapy. These phase III multicenter RCTs improved on the preceding trials by optimizing patient selection, vascular/advanced tissue imaging selection, endovascular reperfusion with third-generation thrombectomy devices, and treatment times.

MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke) was the first multicenter RCT to establish the superiority of adjunctive endovascular treatment over intravenous r-tPA/medical therapy alone.[33] MR CLEAN was conducted in 16 centers in Netherlands and randomized 500 patients presenting with AIS and inclusion criteria of NIHSS score ≥2 (median NIHSS score, 17), <6 hours from symptom onset, and an anterior circulation LVO (distal ICA, 27%; MCA M1-M2, 64%; anterior cerebral artery A1-A2, 9%) confirmed by CTA/MRA imaging. Although median Alberta Stroke Programme Early CT Score (ASPECTS) was 9, there were no specific tissue imaging- or time-based inclusion criteria. The majority of patients (87.1%–90.6%) received intravenous r-tPA with excellent symptom onset to intravenous r-tPA times (85–87 minutes), but there were marked delays to groin puncture of 260 minutes (interquartile range [IQR], 210–313 minutes) in the endovascular arm. Endovascular treatment with intra-arterial r-tPA or mechanical thrombectomy device was at the discretion of the neurointerventionalist, although a stent retriever was used in 81.5% of cases, resulting in 58.7% with TICI grade 2b/3 reperfusion in 332 minutes (IQR, 279–394 minutes) from symptom onset. Despite relatively modest endovascular recanalization rates and nearly 3-hour delays after intravenous r-tPA treatment, the primary outcome was reported in favor of interventional therapy with an adjusted OR of 1.67 (95% CI, 1.21–2.30) and 13.5% (95% CI, 5.9–21.2) absolute difference in functional independence (32.6% versus 19.1% with mRS scores of 0–2 at 90 days). Endovascular benefit extended to secondary outcomes and nearly all predefined subgroups (except pretreatment ASPECTS 0–4), including 24-hour CTA recanalization (75.4% versus 32.9%), final infarct volumes (49 versus 79 mL), age ≥80 years (OR, 3.24) and NIHSS score ≥20 (OR, 1.85). In addition to efficacy, endovascular treatment was noted to be safe with no significant differences in mortality at 30 days (18.9%

versus 18.4%) or SICH (6.4% versus 7.7%) and limited complications of new-territory emboli (5.6% versus 0.4%), vessel dissection (1.7%), or perforation/subarachnoid hemorrhage (SAH; 0.9%).

ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) was the second phase III multicenter RCT to demonstrate the benefit of endovascular treatment.[34] It was conducted in 22 centers throughout Canada, the United States, and Europe, but it was prematurely halted by the Data and Safety Monitoring Board (DSMB) for an unplanned interim analysis after the MR CLEAN results. ESCAPE enrolled 316 patients (1:1, 165 to endovascular treatment versus 150 to medical therapy) with a "disabling" AIS, no NIHSS inclusion criteria (median NIHSS score, 16–17), <12 hours from symptom onset, and anterior circulation LVO (ICA, 27%; MCA M1 or ≥2 M2, 70%; single M2, 3%) by CTA imaging. Furthermore, tissue imaging selection criteria required a small infarct core with CT ASPECTS >5 (median ASPECTS, 9) and CTA (preferably multiphase)/CTP imaging indicating at least moderate collaterals or penumbral tissue involving >50% of the MCA. The majority of patients (238 patients, 75%) received intravenous r-tPA with a median of 110 versus 125 minutes from symptom onset. Only 49 patients (15.5%) presented ≥6 to 12 hours after symptom onset to undergo randomization, an insufficient sample size to ascertain efficacy in delayed time windows. The trial also mandated strict endovascular time metrics with CT to groin puncture time <60 minutes (median, 51 minutes) and CT to revascularization time <90 minutes (median, 84 minutes to first reperfusion). Stent retriever thrombectomy was used in 72.7% of endovascular cases with first reperfusion within a median of 241 minutes (IQR, 176–359 minutes) from symptom onset, resulting in 72.4% higher TICI grade 2b/3 reperfusion rates. Primary end-point analysis identified an adjusted OR of 3.1 (95% CI, 2.0–4.7) favoring endovascular treatment to achieve functional independence (53% versus 29.3% with mRS scores of 0–2 at 90 days; $P<0.001$). Secondary end-point and subgroup analyses supported the benefit of endovascular treatment regardless of age >80 years, sex, NIHSS score ≥20, ASPECTS <8, intravenous r-tPA therapy, or ICA versus MCA occlusions. Endovascular treatment was found to be safe with reduced mortality (10.4% versus 19%; $P=0.04$) and no difference in serious adverse events with equivalent SICH rates (3.6% versus 2.7%) and very few vessel perforation/SAH complications (0.6%).

EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits With Intra-Arterial Therapy) was a phase II multicenter trial conducted in 10 centers in Australia and New Zealand.[35] After the reporting of the MR CLEAN results, this trial was also prematurely halted by the DSMB and terminated for efficacy with an interim analysis meeting the Haybittle-Peto stopping rule after randomizing only 70 patients with AIS (1:1, intravenous r-tPA plus endovascular treatment versus intravenous r-tPA thrombolysis alone). Inclusion criteria specified all patients to be eligible for intravenous r-tPA (0.9 mg/kg) <4.5 hours from symptom onset (median, 127 versus 145 minutes) with an anterior circulation LVO documented on CTA (ICA, 31%; M1-M2 MCA, 68%) but did not specify a minimum presenting NIHSS score (median, 17 versus 13). In addition, advanced tissue imaging selection with CTP or MR DWI-PWI using automated, standardized RAPID postprocessing software was required to identify patients with favorable ratios of ischemic penumbra (Tmax >6 seconds) to core infarct volumes (DWI or CTP regional cerebral blood flow <30%), excluding ≈25% of clinically eligible patients with an LVO. Perfusion imaging inclusion criteria defined a permissive mismatch ratio of 1.2, absolute mismatch or penumbra volumes >10 mL (median, 106 versus 115 mL), and core infarct volumes <70 mL (median, 12 versus 15 mL). Endovascular time–based metrics were limited to groin puncture <6 hours from symptom onset, but efficient stroke processes enabled median groin puncture times of only 210 minutes (IQR, 166-251 minutes), resulting in 86% with TICI grade 2b/3 recanalization (77% with stent retrievers) within 248 minutes (IQR, 204–277 minutes) from symptom onset. Primary outcomes of percentage of ischemic tissue to achieve reperfusion at 24 hours (median, 100% versus 37%; $P<0.001$) and early neurological improvement (80% versus 37% with ≥8-point reduction or NIHSS score of 0–1 at day 3; $P=0.002$) demonstrated a significant endovascular treatment benefit. Secondary outcomes confirmed the superiority of endovascular treatment over intravenous r-tPA with respect to functional independence (71% versus 40% with mRS scores of 0–2 at 90 days; $P=0.01$) and median infarct core growth at 24 hours (11 versus 35 mL; $P=0.007$). Endovascular treatment was safe with no significant differences in mortality (9% versus 20%) or SICH rates (0% versus 6%) and few complications limited to new-territory emboli (5.7%) and vessel perforation (2.9%).

SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment of Acute Ischemic Stroke) was a phase III multicenter RCT performed at 39 centers in the United States and Europe.[36] After the preliminary results of MR CLEAN and ESCAPE, the DSMB halted patient enrollment and then suspended the trial after an interim analysis in February 2015 confirmed prespecified criteria in favor of endovascular treatment. SWIFT PRIME randomized 196 patients with AIS (1:1, intravenous r-tPA plus endovascular treatment with the Solitaire stent retriever versus intravenous r-tPA thrombolysis alone) and inclusion criteria of age of 18 to 80 years, NIHSS score of 8 to 29 (median, 17), eligibility

for intravenous r-tPA <4.5 hours from symptom onset (median, 110.5 versus 117 minutes), and anterior circulation LVO (ICA, 17%; MCA M1, 72%; MCA M2, 10%) as per CTA/MRA imaging. Advanced tissue imaging selection with CTP or MR DWI-PWI using RAPID postprocessing software was required but with more stringent inclusion criteria than either EXTEND-IA or DEFUSE-2, including a mismatch ratio of 1.8, absolute penumbral or mismatch volume >15 mL, core infarct volume <50 mL, and malignant profile volume (Tmax >10 seconds) <100 mL. Subsequent to enrollment of 71 patients, the imaging enrollment criteria were amended to a "small to moderate core infarct strategy" with CT ASPECTS ≥6 to accommodate sites with limited perfusion imaging capabilities, although penumbral imaging was still performed in 81% of patients. As in ESCAPE, improved stroke process workflow was mandated with groin puncture goals <70 minutes (median, 57 minutes) from qualifying imaging and <6 hours from symptom onset, providing a median groin puncture time of 90 minutes (IQR, 69–120 minutes) from arrival and 224 minutes (IQR, 165–275 minutes) from symptom onset. Stent retriever thrombectomy was used in 88.8% of patients, resulting in 88% with TICI grade 2b/3 reperfusion. Primary outcomes satisfied the simultaneous success criteria of the overall distribution of mRS scores (shift analysis, $P<0.001$) and functional independence (60% versus 35% with mRS scores of 0–2) at 90 days in favor of endovascular treatment with a risk ratio of 1.70 (95% CI, 1.23–2.33). Secondary outcomes were nearly all consistent with an endovascular benefit, including change in NIHSS score at 27 hours (–8.5±7.1 versus –3.9±6.2; $P<0.001$) and successful reperfusion (>90%) at 27 hours with CTP/MR perfusion (83% versus 40%; $P<0.001$). In addition, endovascular benefit was maintained in high-risk subgroups of age ≥70 years, NIHSS score >17, ICA versus MCA occlusions, ASPECTS of 6 to 7, transfer status, and time delays from symptom onset to randomization ≥189 minutes. There was no significant difference in mortality at 90 days (9% versus 12%) or safety outcomes with respect to SICH (0% versus 3%) or SAH (4% versus 1%) complication rate.

REVASCAT (Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset) was a phase III multicenter RCT performed in 4 Spanish centers.[37] As a result of emerging evidence from the above RCTs, the DSMB halted further recruitment after the first interim analysis, despite not reaching the prespecified stopping boundary. REVASCAT randomized 206 patients (1:1 endovascular treatment with the Solitaire stent retriever versus medical therapy alone) presenting with AIS and inclusion criteria of age of 18 to 80 years (expanded midtrial to 85 years if ASPECTS >8), NIHSS score ≥6 (median, 17), and anterior circulation LVO (ICA, 26%; MCA M1, 65%; and MCA M2, 9%) as per CTA/MRA/digital subtraction angiography. Unless contraindicated, intravenous r-tPA was provided to the majority of patients (73%) presenting <4.5 hours with median intravenous thrombolysis times of 117.5 versus 105 minutes from symptom onset but with 30 minutes of observation for neurological improvement before the initiation of treatment in the endovascular arm. In addition, tissue imaging selection was used to exclude patients with large core infarcts with various CT/CTA/CTP modalities and required MR-DWI if >4.5 hours from symptom onset. Imaging inclusion criteria were mainly CT ASPECTS ≥7 or MR DWI ≥6 (median, 7 versus 8). Along with liberal time metrics for enrollment (groin puncture <8 hours from symptom onset), these factors may have contributed to slightly increased median groin puncture times of 269 minutes (IQR, 201–340 minutes) and median revascularization times of 355 minutes (IQR, 269–430 minutes) relative to ESCAPE, EXTEND-IA, and SWIFT PRIME. Endovascular thrombectomy was performed predominantly with stent retrievers (95%), resulting in 66% with TICI grade 2b/3 effective reperfusion rates. Primary outcome analysis favored endovascular thrombectomy with improvement in the distribution of mRS scores (shift analysis) and common OR of 1.7 (95% CI, 1.05–2.8). Secondary outcomes confirmed an endovascular benefit with increased functional independence (44% versus 28% with mRS scores of 0–2 at 90 days) with an OR of 2.1 (95% CI, 1.1–4.0), dramatic neurological improvement at 24 hours (59% versus 20% with a reduction of ≥8 points on the NIHSS or a score of 0–2) with 5.8 (3.0–11.1), and median infarct volume at 24 hours (16.3 versus 38.6 mL; $P=0.02$). Subgroup analysis maintained an endovascular benefit regardless of age ≥70 years, NIHSS score ≥17, ICA occlusions, time to randomization >4.5 hours, intravenous r-tPA treatment, or ASPECTS <8. Endovascular thrombectomy was safe with no significant differences in mortality at 90 days (18.4% versus 15.5%), SICH (1.9% versus 1.9%), or serious adverse events. Several procedural vascular complications were noted, including vessel perforation/SAH (4.9% versus 1.9%), new-territory emboli (4.9%), arterial dissections (3.9%), vasospasm requiring treatment (3.9%), and groin hematoma (10.7%)/pseudoaneurysms (1%).

The THRACE trial (Thrombectomie des Artères Cerebrales) was conducted in 26 French centers from 2010 to 2015.[38] After MR CLEAN, a second unplanned interim analysis precipitated the termination of the study after randomization of 414 patients (1:1, 204 intravenous r-tPA plus endovascular treatment versus 208 intravenous r-tPA alone) presenting with AIS and inclusion criteria of age of 18 to 80 years, NIHSS score of 10 to 25 (median, 18 versus 17), administration of intravenous r-tPA <3 to 4 hours from symptom onset

(median, 153 versus 150 minutes), and predominantly anterior circulation LVO (intracranial ICA, 15%; MCA M1, 84%; distal basilar artery, 1%) confirmed by CTA/MRA imaging. Similar to MR CLEAN, there were no tissue imaging- or time-based inclusion criteria except for the initiation of endovascular treatment <5 hours from symptom onset. However, initial MR imaging was available in >70% of enrolled patients with post hoc analysis demonstrating a CT/MR ASPECTS of 5 to 10 in the majority (89% versus 83%) of randomized patients. Because of early randomization and spontaneous clinical improvement in a significant proportion of the populations after intravenous r-tPA thrombolysis, mechanical thrombectomy was offered to only 141 of 204 patients (69%) in the endovascular arm and probably accounted for higher functional outcome status in both subgroups than in MR CLEAN. Furthermore, endovascular treatment was delayed because of mandated clinical assessments after the completion of intravenous r-tPA infusion (amended in late 2012 to just before the end of thrombolysis to improve revascularization times), resulting in relatively elevated treatment initiation times of 250 minutes (IQR, 210–290 minutes) from symptom onset. Neurointerventionalists used stent retrievers (83%) more than aspiration retrieval devices (16%) as the first-line system for mechanical thrombectomy with 11% crossover and were allowed to use intra-arterial r-tPA (mean dose, 8.8±6.4 mg in 11%) for persisting distal occlusions, resulting in a 69% with TICI grade 2b/3 reperfusion rate in a median of 303 minutes (IQR, 261–345 minutes) from symptom onset. Primary functional outcome analysis (mRS score of 0–2 at 3 months) confirmed the superiority of adjunctive mechanical thrombectomy to intravenous r-tPA alone (53% versus 42%) with an OR of 1.55 (95% CI, 1.05–2.30; *P*=0.028). Secondary outcome measures of NIHSS score at 24 hours (median, 9 versus 12 hours), 7 days (median, 4 versus 8 days), and 3 months (median, 2 versus 4 months) and Barthel Index of 95 to 100 at 3 months (61% versus 49%) also favored endovascular treatment. There were no significant differences in mortality at 3 months (12% versus 13%; *P*=0.70) or SICH at 24 hours (2% versus 2%; *P*=0.71). Procedural thrombectomy-related complications and adverse events were limited to vasospasm (23%), embolization in a new territory (6%), arterial dissection (3%), perforation (1%), and groin hematoma (2%) but without any clinical impact at 3 months.

The PISTE trial (Pragmatic Ischaemic Thrombectomy Evaluation) was conducted in 10 centers in the United Kingdom from 2010 to 2015.[39] The study was halted prematurely after randomization of only 65 patients (1:1, intravenous r-tPA plus endovascular treatment with any CE-marked device versus intravenous r-tPA thrombolysis alone) presenting with AIS with inclusion criteria of age >18 years, no minimum NIHSS score (median, 16), eligibility for intravenous r-tPA <4.5 hours (median, 120 minutes) from symptom onset, and anterior circulation LVO (ICA, 16%; MCA M1, 71%; or single M2, 13%) as per CTA imaging. Tissue imaging selection was limited to excluding patients with early hypoattenuation on noncontrast CT brain studies involving more than one third of the MCA distribution (median ASPECTS, 9). Ten experienced neurointerventional centers were mandated to uphold strict time metrics of <90 minutes (median, 82 minutes; IQR, 28–140 minutes) from starting intravenous r-tPA infusion to groin puncture and cannulating the target vessel <6 hours from symptom onset, resulting in expedient recanalization times of 251 minutes from symptom onset. Mechanical thrombectomy was performed in 81% of patients with a single device (primary stent retrieval, 68% versus aspiration retrieval, 32%) obtaining 87% effective TICI grade 2b/3 reperfusion. Although in the intention-to-treat analysis there was no significant difference in primary outcome of disability-free survival mRS score of 0 to 2 at 90 days (51% versus 40%) with an adjusted OR of 2.12 (95% CI, 0.65–6.94; *P*=0.204), there was a secondary outcome benefit of complete functional recovery (mRS score of 0–1 at 90 days) with adjunctive mechanical thrombectomy over intravenous r-tPA alone for an OR of 7.63 (95% CI, 1.56–37.22; *P*=0.010), probably because of the small sample size and early trial termination after the THRACE trial results. However, in the per-protocol primary outcome analysis, a significant benefit of mechanical thrombectomy was noted with an absolute difference of 22% (57% versus 35%) and OR of 4.92 (95% CI, 1.23–19.69; *P*=0.021) with an associated mRS distribution shift. There were no significant differences in other secondary outcomes, including early major neurological improvement (NIHSS score of 0–1 or improved ≥8 points), SICH (0%), or mortality (OR, 1.56; 95% CI, 0.29–8.40; *P*=0.599).

The HERMES collaboration (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials) performed a meta-analysis of 5 RCTs shown to study the efficacy of endovascular thrombectomy over medical therapy in AIS caused by LVO in the proximal anterior intracranial circulation (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT).[40] With the use of mixed-effects modeling with both fixed and random effects to account for intertrial variance, ordinal logistic regression analyses calculated common ORs for primary (mRS score improvement at 90 days on shift analysis) and secondary outcomes in the aggregated population (1287 patients: 634 with endovascular thrombectomy versus 653 with medical therapy) and in prespecified subgroups. Baseline demographics (median age, 68 years; 1 male:1 female), comorbidities, presentations (median NIHSS score, 17), LVO location (ICA, 21%;

MCA M1, 69%; and M2, 8%), and imaging ASPECTS (median, 9; IQR, 7–10) in the endovascular treatment population were balanced with control group parameters. Although there was less intravenous r-tPA treatment in the endovascular cohort (83% versus 87%; *P*=0.04), intravenous r-tPA treatment times from symptom onset (median, 100 minutes; IQR, 74–140 minutes) were equivalent. Stroke intervention processes across the trials yielded a median of 285 minutes (IQR, 210–362 minutes) from symptom onset to endovascular reperfusion with 71% obtaining successful revascularization (modified TICI grade 2b/3). In primary outcome analysis, endovascular thrombectomy was associated with a reduction in disability or mRS score shift at 90 days with an adjusted common OR of 2.49 (95% CI, 1.76–3.53; *P*<0.0001), determining a need to treat only 2.6 patients to derive benefit for a single patient. Secondary outcomes analyses confirmed a marked endovascular treatment benefit over medical therapy, including functional independence (mRS score of 0–2) at 90 days (46% versus 26.5%) with an OR of 2.71 (95% CI, 2.07–3.55; *P*<0.0001) and major early neurological recovery at 24 hours (50.2% versus 21.2%), defined as a reduction in NIHSS score from baseline of >8 points or a score of 0 to 1 with an OR of 4.36 (95% CI, 3.03–6.27; *P*<0.0001). There were no significant differences in mortality at 3 months (15.3% versus 18.9%; *P*=0.16), SICH (4.4% versus 4.3%; *P*=0.81), or parenchymal hematoma type 2 (5.1% versus 5.3%; *P*=0.88). In predefined subgroup analyses of the mRS distribution shift at 90 days, effects favored endovascular treatment over controls across all strata and included the power to address special-interest cohorts such as patients ≥80 years of age with an OR of 3.68 (95% CI, 1.95–6.92), randomization ≥300 minutes after symptom onset with an OR of 1.76 (95% CI, 1.05–2.97), patients ineligible for intravenous r-tPA with an OR of 2.43 (95% CI, 1.30–4.55), and presence of tandem cervical occlusions with an OR of 2.95 (95% CI, 1.38–6.32).

Extending the Time and Tissue Window for Endovascular Stroke Intervention

Advanced MR DWI-PWI and CTP imaging paradigms continued to be studied as selection criteria in populations who could benefit from endovascular treatment in the unknown (wake-up) or extended (>6 hour) time windows. Both the DAWN trial (DWI or CTP Assessment With Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) and DEFUSE-3 trial (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke) are PROBE multicenter RCTs to investigate the benefit of endovascular thrombectomy in patients presenting 6 to 24 or 6 to 16 hours from symptom onset or last seen normal, respectively, but with advanced CTP or MR DWI-PWI imaging selection strategies.[41,42] DAWN was halted by the DSMB after a planned interim analysis in early 2017 for significant endovascular treatment benefit; enrollment in the DEFUSE-3 trial has also halted by the DSMB with a pending interim data analysis.

Summary

This summary largely matches recent recommendations from the AHA guidelines for the early management of patients with AIS in terms of endovascular treatment.[17]

1. Observing patients after intravenous r-tPA to assess for clinical response before pursuing endovascular therapy is not required to achieve beneficial outcomes and is not recommended.
2. Endovascular therapy with stent retrievers is recommended over intra-arterial fibrinolysis as first-line therapy.
3. Intra-arterial fibrinolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of intravenous r-tPA might be considered, but the consequences are unknown.
4. Use of stent retrievers is preferred over other mechanical thrombectomy devices. The use of mechanical thrombectomy devices other than stent retrievers may be reasonable in some circumstances but is not yet supported by large RCTs.
5. In carefully selected patients with anterior circulation occlusion who have contraindications to intravenous r-tPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable. Inadequate data are available at this time to determine the clinical efficacy of endovascular therapy in such patients (eg, those with prior stroke, serious head trauma, hemorrhagic coagulopathy, or receiving anticoagulant medications).
6. If endovascular therapy is contemplated, a noninvasive intracranial vascular study is strongly recommended during the initial imaging evaluation of the patient with acute stroke but should not delay intravenous r-tPA if indicated. For patients who qualify for intravenous r-tPA according to guidelines from professional medical societies, initiating intravenous r-tPA before noninvasive vascular imaging is recommended for patients who have not had noninvasive vascular imaging as part of their initial imaging assessment for stroke. Noninvasive intracranial vascular imaging should then be obtained as quickly as possible.

7. The benefits of additional imaging beyond CT and CTA or MR and MRA such as CTP or DWI and PWI for selecting patients for endovascular therapy are unknown.
8. When treatment is initiated beyond 6 hours from symptom onset, the effectiveness of endovascular therapy is uncertain for patients with AIS who have causative occlusion of the ICA or proximal MCA (M1). New trial results addressing this topic will be available in the near future.
9. Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria: (1) prestroke mRS score of 0 to 1, (2) AIS receiving intravenous r-tPA within 4.5 hours of onset according to guidelines from professional medical societies, (3) causative occlusion of the ICA or proximal MCA (M1), (4) age ≥18 years, (5) NIHSS score of ≥6, (6) ASPECTS of ≥6, and (7) ability to initiate treatment (groin puncture) within 6 hours of symptom onset.
10. As with intravenous r-tPA, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. To ensure benefit, reperfusion to TICI grade 2b/3 should be achieved as early as possible and within 6 hours of stroke onset.
11. The technical goal of the thrombectomy procedure should be a TICI grade 2b/3 angiographic result to maximize the probability of a good functional clinical outcome. Use of salvage technical adjuncts, including intra-arterial fibrinolysis, may be reasonable to achieve these angiographic results if completed within 6 hours of symptom onset

ENDOVASCULAR TREATMENT OF INTRACRANIAL STENOSIS

Intracranial atherosclerotic disease is an important cause of ischemic stroke; its natural history associated with high recurrent stroke rates is estimated to be between 10% and 22% in the first year.[43] Hypertension, hyperlipidemia, type II diabetes mellitus, and metabolic syndrome are associated risk factors.[44] Mechanisms of stroke in patients with intracranial atherosclerotic disease include low-flow hemodynamic impairment, perforator-related strokes, in situ thromboembolism, and artery-to-artery embolism.

The management of patients with symptomatic intracranial atherosclerotic disease has made significant strides in the past decade, most notably from lessons learned by the WASID (Warfarin-Aspirin Symptomatic Intracranial Disease), SAMMPRIS (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis), and VISSIT (Vitesse Intracranial Stent Study for Ischemic Stroke Therapy) randomized clinical trials. Recent trials have demonstrated better-than-expected natural history with aggressive medical management, which now presides as first-line treatment of choice in patients with symptomatic disease.

The WASID trial was a multicenter randomized trial of patients with transient ischemic attack (TIA) or stroke related to 50% to 99% intracranial stenosis randomized to aspirin 1300 mg daily or warfarin.[43] The trial was stopped after enrollment of 569 patients because warfarin was found to be associated with higher rates of adverse events (major hemorrhage, death) and not superior to aspirin.

Patients at highest risk for recurrent ischemic events were those presenting early after their initial event (within 17 days of ischemic event) and patients with >70% stenosis (18% risk of recurrent stroke at 1 year versus 7%–8% in patients with 50%–69% stenosis), stratifying this patient subgroup as the target subgroup population in the subsequent intracranial stenting trials.[45]

Post hoc analysis in the WASID trial demonstrated that patients with higher blood pressure had increased risk of ischemic stroke in the territory of the stenotic vessel in subgroups of patients with both moderate (50%–69%) and severe (70%–99%) stenosis.[46] Elevated total cholesterol >200 mg/dL (hazard ratio, 2.06; *P*=0.0006) and elevated low-density lipoprotein >100 mg/dL (hazard ratio, 1.7; *P*=0.0326) were other predictors of recurrent ischemic stroke.[47] Patients with 70% to 99% stenosis with more collaterals as graded on baseline angiograms had diminished risk of recurrent territorial stroke.[48]

Intracranial Stenting Trials

The evidence gained from the WASID trial formed some of the tenets of medical management strategies and patient selection in the subsequent endovascular stenting trials. Two randomized clinical trials compared endovascular therapy with medical therapy in secondary stroke prevention of patients with symptomatic intracranial atherosclerotic disease >70% stenosis: the SAMMPRIS and VISSIT trials.

The SAMMPRIS trial compared aggressive medical therapy with aggressive medical therapy and percutaneous angioplasty plus stenting in patients with intracranial atherosclerotic 70% to 99% stenosis presenting within 30 days of a related stroke or TIA.[49] The antithrombotic regimen was identical in both arms and included aspirin 325 mg daily and clopidogrel for 90 days after enrollment. Aggressive medical therapy was modeled on risk factor control learned from the WASID trials, including target systolic blood pressure <140 mm Hg (<130 mm Hg if diabetic) and target treatment

low-density lipoprotein cholesterol <70 mg/dL (1.81 mmol/L). In addition, aggressive management of diabetes mellitus, smoking, weight, and insufficient exercise was undertaken with the help of a lifestyle modification program.

The trial was stopped after enrollment of 451 patients in April 2011, when a higher 30-day rate of stroke and death was present in the percutaneous angioplasty and stenting group compared with the aggressive medical therapy group (14.7% versus 5.8%; *P*=0.002).[49] Periprocedural stroke consisted of multiple pathogeneses, with perforator occlusion the most common subtype of the ischemic stroke complications, particularly in the basilar artery; SAH and reperfusion hemorrhage were the common subtypes of hemorrhagic events.[50] At long-term follow-up (median, 32.4 month), more patients in the stenting group had a primary end-point event compared with the medical group (52 of 224 [23%] versus 34 of 227 [15%]; *P*=0.025).[51]

The VISSIT trial was an international multicenter randomized clinical trial that compared balloon-expandable stents and medical therapy in patients with 70% to 99% symptomatic intracranial atherosclerotic disease.[52] The study enrolled patients from 27 sites (2009–2012). After the negative results of the SAMMPRIS trial in 2011, the study was halted, and analysis showed futility after 112 patients of a planned sample size of 250 were enrolled. The 30-day primary safety end point of stroke, death, or intracranial hemorrhage occurred in more patients in the stent compared with the medical group (24.1% versus 9.4%; *P*=0.05). Intracranial hemorrhage within 30 days occurred in more patients in the stent (8.6%) than in the medical (none; *P*=0.06) group. At 1 year, the primary outcome of stroke or hard TIA was higher in patients in the stenting group (36.2% versus 15.1%; *P*=0.02). Furthermore, worsening of baseline disability score (mRS score) occurred in more patients in the stent than in the medical group (24.1 versus 11.3%; *P*=0.09). The authors concluded that among patients with symptomatic intracranial arterial stenosis, treatment with a balloon-expandable stent resulted in an increased 30-day and 12-month risk of recurrent stroke or TIA compared with medical therapy. Table 1 summarizes the results of these 3 key trials.

With the publication of the SAMMPRIS trial results, the FDA issued a report narrowing the Humanitarian Device Exemption criteria for Wingspan and limiting its use to patients between 22 and 80 years of age who meet all of the following conditions: (1) The patient has had ≥2 strokes despite aggressive medical management; (2) the most recent stroke occurred >7 days before the planned treatment with Wingspan; (3) there is 70% to 99% stenosis caused by intracranial atherosclerosis related to the recurrent strokes; and (4) the patient made a good recovery from the previous stroke with an mRS score of ≤3 before Wingspan treatment. Furthermore, Wingspan should not be used for the treatment of stroke with onset of symptoms within ≤7 days of treatment or treatment of TIAs.[53] Given the historically high risk of recurrent infarction in this population, such patients may be reasonably considered for endovascular treatment.

Table 1. Summary of Stroke/Death Rate at 30 Days and 1 Year in the WASID, SAMMPRIS, and VISSIT Trials in Patients With >70% Symptomatic Intracranial Stenosis

	30-d Event Rate, Stroke/Death, %		1-y Event Rate, Stroke, %		2-y Event Rate, Stroke, %	
	Medical	Stent	Medical	Stent	Medical	Stent
WASID	10.7	NA	25	NA	NA	NA
SAMMPRIS (n=451; stroke/death)	5.8	14.7	12.2	19.7	14.1	20.6
VISSIT (n=112; stroke/death)	9.4	24.1	15.2	36.2	NA	NA

NA indicates not available; SAMMPRIS, Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis; VISSIT, Vitesse Intracranial Stent Study for Ischemic Stroke Therapy; and WASID, Warfarin-Aspirin Symptomatic Intracranial Disease.

Balloon Angioplasty

Balloon angioplasty is another potential modality that merits future study in patients with symptomatic intracranial stenosis compared with medical therapy. Periprocedural morbidity and mortality are estimated at 5% to 9%, and annual stroke rate is estimated at 2% to 3%.[54–56] However, this technique may be limited by risk of restenosis, need for bailout stenting, or rescue therapy.

New Trials

The China Angioplasty and Stenting for Symptomatic Intracranial Severe Stenosis is an ongoing randomized trial of patients with recent TIA or stroke and 70% to 99% intracranial stenosis comparing best medical therapy alone and best medical therapy with stenting. Patients with previous stroke related to perforator ischemia are excluded. In this trial, all patients would have stenting 3 weeks from the last ischemic event. The trial has recruited 380 patients and will be completed in 2019.

Summary

For patients with stroke or TIA resulting from stenosis of major intracranial artery, best practice includes the following (These statements parallel the AHA 2014 stroke guidelines)[57]:

1. For 50% to 69% intracranial stenosis, treatment with medical therapy (not angioplasty or stenting) is recommended.
2. For 70% to 99% stenosis, optimal medical therapy, which should include aspirin, clopidogrel for 90 days, maintenance of systolic BP <140 mm Hg, statin therapy, and aggressive risk factor modification, is recommended.
3. For 70% to 99% stenosis, intracranial stenting with the Wingspan or Pharos stent system should not be used as initial treatment, even in patients on antithrombotic medications at the time of stroke or TIA.
4. For patients with severe stenosis (70%–99%) of a major intracranial artery who have progressing symptoms, recurrent TIA, or stroke despite treatment with dual antiplatelet therapy, achievement of systolic BP <140 mm Hg and high-intensity statin therapy, angioplasty alone, or placement of a Wingspan stent may be warranted.
5. The utility of angioplasty alone or placement of stents other than Wingspan or Pharos is unknown and is considered investigational.

CEREBRAL ANEURYSMS

Although cerebral aneurysms affect a relatively small number of people each year, their importance is highlighted because of the severe morbidity and mortality associated with aneurysm rupture. In the past, cerebral aneurysms were commonly discovered only after rupture had produced SAH. Now, however, cerebral aneurysms are commonly detected as findings obtained from noninvasive imaging studies performed for other reasons. Treatment is indicated for ruptured and many nonruptured aneurysms, and there is substantial evidence from clinical trials supporting this practice.[58]

The prevalence of unruptured intracranial aneurysm is estimated to be up to 2% in an analysis of brain MR images,[59] and the prevalence of unruptured aneurysms is much more common than the event of SAH (up to 10 in 100 000 individuals). The estimated incidence of nontraumatic SAH in the United States is 7.2 to 9.0 per 100 000 per year, which has remained stable over the past 30 years.[60] Total deaths and in-hospital mortality after SAH have declined from 50% in the 1966 Cooperative Study to 30% (1979–1983) and 20% (2004–2008) in the National Hospital Discharge Survey.[60]

Several studies have evaluated the rupture risk of unruptured intracranial aneurysms, including ISUIA (International Study of Unruptured Intracranial Aneurysm), the UCAS (Unruptured Cerebral Aneurysm Study) Japan study, and the Finnish series by Juvela et al.[61] ISUIA demonstrated retrospective natural history data on 1449 patients with 1937 unruptured aneurysms selected for conservative management. Among patients with no history of SAH, the rupture risk was 0.05%/y for aneurysms <10 mm and ≈1%/y for larger aneurysms; larger aneurysm size and location in the posterior circulation were predictors of rupture risk. Among those with a history of SAH from a different aneurysm, the rupture risk was 0.5%/y for those <10 mm and ≈0.7%/y for larger aneurysms.

Phase 2 of the ISUIA included a prospective natural history study of 1692 patients with 2686 unruptured aneurysms with a mean follow-up of 4.1 years.[62] After the results were analyzed, aneurysm rupture rates were stratified by size (with a new cut point of <7 mm to define the smallest group of aneurysms), history of SAH from a different aneurysm, and location. Five-year cumulative rupture rates for patients without a history of SAH with aneurysms selected for conservative management in the anterior circulation (ICA, anterior communicating or anterior cerebral artery, or MCA) were 0%, 2.6%, 14.5%, and 40% for aneurysms <7, 7 to 12, 13 to 24, and ≥25 mm, 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 artery aneurysms. The structure of these modern studies is prone to selection bias because the group of aneurysms reserved for observation are probably less likely to hemorrhage than those for which intervention is performed; it is therefore likely that the observed hemorrhage rates in these studies are at the lower end of the rupture rates for the aneurysm population as a whole.

UCAS was a prospective cohort study of 5720 patients with 6697 unruptured cerebral aneurysms in the Japanese population.[63] The overall annual risk of rupture was found to be 0.95%/y. Size of the lesion, location, and presence of a daughter sac were risk factors for rupture. The 5-year risk of rupture for small aneurysms (<5 mm) of ≈1.7% was higher than in the ISUIA study but similar to that in the SUAVe study (Small Unruptured Intracranial Aneurysm Verification Study) of small aneurysms.[64] Compared with aneurysms that were 3 to 4 mm in the largest dimension, aneurysms that were 5 to 6 mm were not associated with a significantly increased risk of rupture, but the risk of rupture was significantly higher for all aneurysms that were ≥7 mm. Aneurysms located at the anterior communicating artery and posterior communicating artery junction with the ICA had a significantly greater risk of rupture. Unlike in ISUIA, the other posterior circulation aneurysms did not show a higher rupture risk. The modifiable risk factors of smoking and hypertension were also associated with higher rupture risks.

Juvela et al[61] performed long-term follow-up of 142 patients with unruptured aneurysms for a total of 3064 person-years. The majority of the patients being followed up originally presented with a ruptured aneu-

rysm for which the followed-up aneurysms were incidental. They found an annual rate of aneurysm rupture in the incidental aneurysms of 1.1%, and this rate was largely unchanged over the decades-long follow-up obtained. Given the presentation of prior SAH, multiplicity of aneurysms, and limitation to the Finnish population, these results may not be applicable to unruptured aneurysms generally.

Endovascular Therapy of Intracranial Aneurysms

The array of endovascular treatment options for intracranial aneurysms has evolved dramatically over the past 3 decades. From the introduction of the Guglielmi Detachable Coil in 1990[65] to balloon-assisted coil remodeling,[66] stent-assisted coiling, and flow diversion,[67] these technologies have increased the number of aneurysms that can be treated via endovascular methods with improved safety and efficacy and complete aneurysm closure.

The ATENA trial (Analysis of Treatment by Endovascular Approach of Nonruptured Aneurysms) was the first prospective multicenter study to evaluate clinical outcome and risks of endovascular coiling treatment (37% with balloon remodeling, 8% with stent assist) in 649 patients with 1100 aneurysms.[68] Morbidity and mortality were 1.7% and 1.4% at 1 month, respectively.

Three randomized trials evaluated the use of coated coils compared with bare platinum coils to reduce risk of aneurysm recurrence.[69–71] HELPS (Hydrogel-Coated Coils Versus Bare Platinum Coils for the Endovascular Treatment of Intracranial Aneurysms; 499 patients) was a randomized trial comparing patients with untreated aneurysms (ruptured or unruptured) and patients treated with hydrogel-coated coils or bare platinum coils (control). Fewer recurrences were seen in patients treated with hydrogel coils; however, increased numbers of patients treated with hydrogel coils developed hydrocephalus outside usual circumstances for its development. The Cerecyte Coil trial (500 patients) and the MAPS trial (Matrix and Platinum Science; 626 patients) did not show superiority of polymer-modified coils over bare platinum coils in the prevention of aneurysm recurrence.

The most impactful technological innovation since the publication of the last intracranial aneurysm guidelines is flow diversion. A flow diverter is an endoluminal stent–like construct designed to reconstruct the diseased parent artery across from where the aneurysm lies. Several large series of flow diversion have shown remarkable results for the treatment of large or giant difficult-to-treat aneurysms that are prone to recurrence[72] with conventional endovascular coil technology.[67,73,74] The PUFS trial (Pipeline for Uncoilable or Failed Aneurysms) showed treatment success at the primary end point (complete occlusion at 6 months) in 74%. This cohort had a 5.6% rate of major ipsilateral stroke or death, promising results given the difficulty of treating these types of aneurysms.

FIAT (Flow Diversion in the Treatment of Intracranial Aneurysm Trial) was a recent randomized trial comparing angiographic and clinical outcomes with a flow diverter or with the best standard option (observation, coiling, stenting, or clipping) for patients with difficult-to-treat aneurysms. There was a concomitant registry of nonrandomized patients who received a flow diverter. The trial was stopped early because of safety concerns. Twelve of 75 patients (16%) who were allocated to or received flow diversion were dead (n = 8) or dependent (n = 4) at ≥3 months, crossing a predetermined safety boundary. Death or dependency occurred in 5 of 38 patients (13%) randomly allocated and treated by flow diversion and in 5 of 39 patients (12.8%) allocated to standard treatment. The primary efficacy outcome, defined as angiographic occlusion at 3 to 12 months combined with independent clinical outcome, was below expectations of the trial hypothesis: 16 of 38 patients (42%) randomly allocated to flow diversion failed to reach the primary outcome compared with 14 of 39 patients (36%) allocated to standard treatment. Of note, morbidity and mortality were lower for proximal carotid aneurysms (n=50, 8.0%) than for posterior circulation aneurysms (n=13, 46.2%). More randomized trials are necessary to determine the role of flow diversion in the management of patients with intracranial aneurysms.

Despite the widespread array of endovascular treatment options, the question of whether one should observe or treat an unruptured, asymptomatic aneurysm remains unanswered by clinical trials. TEAM (Trial on Endovascular Aneurysm Management) was a prospective randomized trial comparing coiling and conservative management in patients with unruptured aneurysm with the goal of studying safety and efficacy of endovascular treatment of intracranial aneurysm to prevent SAH. The trial was stopped in 2009 because of poor recruitment (80 patients).[75]

In the absence of prospective trials comparing treatment and conservative therapy for unruptured aneurysms, guides for patient selection such as the Unruptured Intracranial Aneurysm Treatment Score have been proposed, as have models such as the Population, Hypertension, Age, Size, Earlier Subarachnoid Haemorrhage, and Site scale to help predict the risk of future hemorrhage.[76,77]

Subarachnoid Hemorrhage

SAH from an intracranial aneurysm can carry significant morbidity and mortality for the patient. The risk of rerupture after SAH is highest in the first day (4%) and then is 1% to 2% each day in the first month.[78] The

risk of aneurysm rebleeding with conservative management is 20% to 30% in the first month after hemorrhage and then ≈3%/y.[79] Aneurysm rerupture is associated with a mortality of ≈67%. Ruptured aneurysms therefore need to be treated early to prevent rerupture. Comprehensive recommendations for the treatment of SAH and ruptured aneurysms have been published.[80]

Two trials demonstrated improved clinical outcomes from endovascular coiling compared with neurosurgical clipping. Coiling was shown to be associated with decreased death or dependence at 1 year compared with neurosurgical clipping in patients with SAH in both trials.[81]

ISAT (International Subarachnoid Aneurysm Trial) was a landmark international multicenter randomized clinical trial evaluating patients with ruptured aneurysms who the treating physician thought could be treated with either endovascular coiling or neurosurgical clipping. The trial intended to enroll 2500 patients; after an interim planned analysis of 2143 patients, the trial was stopped by the steering committee. Among the patients allocated to endovascular treatment, 24% were dependent or dead at 1 year compared with 31% allocated to neurosurgical treatment (190 of 801 [23.7%] versus 243 of 793 [30.6%]; *P*=0.0019).[81]

Long-term study of these patients was continued in all UK and some non-UK patients with a mean follow-up of 9 years. The risk of rebleeding from the treated aneurysm was increased with coiling compared with clipping, but the risks were very small (10 in the coiling group with 8447 person-years of follow-up versus 3 in the clipping group with 8177 person-years follow-up). This was equivalent to a rebleeding risk of 0.1%/y in the coiled patients and 0.03%/y in the clipped patients.[82]

At long-term follow-up, mortality was lower with coiling compared with clipping at 5 and 10 years in the ISAT study. A recent follow-up of ISAT patients reported that although rates of increased dependency alone did not differ between groups, the probability of death or dependency was greater in the neurosurgical group than in the endovascular group. Despite the small increased risk of recurrent SAH in the endovascular group, the probability of disability-free survival was greater in the endovascular than in the neurosurgical group at 10 years (OR, 1.34; 95% CI, 1.07–1.67).[83]

BRAT (Barrow Ruptured Aneurysm Trial) was a randomized trial of patients with SAH treated with alternating clip versus coil strategy. Of 725 screened patients, 500 eligible patients were enrolled prospectively in alternating method to clipping (n=238) or coiling (n=233). Crossover was permitted, but the primary outcome was based on the initial treatment assigned as an intention-to-treat analysis. At 1 year, poor outcome (mRS score >2) was higher in the clip versus the coil group (33.7% versus 23%; OR, 1.68; 95% CI, 1.08–2.61; *P*=0.02).

Table 2. Ongoing Cerebral Aneurysm Outcomes Trials

	Patient Population	Randomization	Primary Outcome	Enrollment, n
CURES	Unruptured aneurysm	Coil vs clip	Failure to close aneurysm, recurrent aneurysm, ICH at 1 y	Goal, 260; current, 136 (August 2016), projected completion in 2020
ISAT II	Ruptured aneurysm	Coil vs clip	Poor clinical outcome at 1 y	Goal, 1896; current, 89 (August 2016), projected completion in 2023

CURES indicates Canadian Unruptured Endovascular Versus Surgery; ICH, intracerebral hemorrhage; and ISAT, International Subarachnoid Aneurysm Trial.

Of treated patients assigned to the coil group, 124 of the 199 (62.3%) who were eligible for treatment received endovascular coil embolization. Patients who crossed over from coil to clip treatment did worse than patients assigned to coiling but no worse than patients assigned to clip occlusion.[84]

The 6-year results of the BRAT study showed no significant difference in poor outcome as defined by an mRS score >2 for coiled versus clipped patients (57 of 162 [35%] versus 72 of 174 [41%]; *P*=0.24). The outcomes for posterior circulation favored coiling. The retreatment rate was lower for clipping versus coiling (4.6% versus 16%; *P*<0.0001).[85] The drawbacks of the study were that it was underpowered to evaluate clinical outcome and that the assessment of anterior versus posterior circulation aneurysm outcomes was performed as a post hoc analysis.

Future

One of the most important and difficult decisions for aneurysm treatment in general, and unruptured aneurysms in particular, remains the choice between open surgical clip occlusion and endovascular aneurysm repair. In practice, the choice is driven not only by patient and aneurysm characteristics but also by local expertise and informed patient preference. Over the past 2 decades, there has been an increase in the proportion of aneurysms treated by endovascular means,[86] and in 2012, ≈60 % of ruptured aneurysms and 70% of unruptured aneurysm were treated with coil occlusion in the United States.[87] There are 2 important ongoing prospective trials comparing outcomes for these therapies (Table 2).

The CURES trial (Canadian Unruptured Endovascular Versus Surgery) is a randomized trial comparing the results of surgical clipping and endovascular treatment of unruptured aneurysms.[88] There is a composite primary end point of failure to accomplish aneurysm obliteration with the initial treatment modality, a major saccular

aneurysm remnant or recurrence, or intracranial hemorrhage at 1 year after treatment. The international study will address which strategy leads to the best overall clinical outcomes in terms of mortality, morbidity, and clinical efficacy.

ISAT II is a pragmatic multicenter randomized trial comparing clinical outcomes for non-ISAT patients with SAH allocated to coiling or clipping.[89] The primary end point is the incidence of poor clinical outcome (defined as an mRS score >2) at 1 year, similar to ISAT. The secondary end point is the presence of a major recurrence at 1 year. The goal recruitment is 1896 patients (862 in each arm plus 10% losses) to demonstrate a significant difference between coiling and clipping, hypothesizing 23% and 30% poor clinical outcome rates for coiling and clipping, respectively. The trial should involve at least 50 international centers and will take ≈12 years to complete.

New endovascular devices are in development, and preliminary results have been reported in small case series. These include endosaccular mesh devices[90–92] and modified stent devices designed for wide-necked bifurcation aneurysms.[93,94] Such devices are likely to improve safety and therapeutic efficacy for difficult-to-treat broad-necked aneurysms.

Summary

1. Endovascular treatment of unruptured cerebral aneurysms is reasonable to prevent SAH. Patients with unruptured cerebral aneurysms deemed amenable to endovascular treatment should be fully informed of the risks and benefits of endovascular and microsurgical treatments, as well as medical management and imaging surveillance.
2. Patients with nontraumatic SAH should undergo immediate vascular imaging to investigate the cause of the hemorrhage. CTA may be the first vascular imaging test and is often sufficient for treatment decisions. If CTA is inconclusive or is unable to show the cause of SAH, digital subtraction angiography remains the gold standard vascular imaging test.
3. Endovascular coil occlusion is appropriate for patients with ruptured cerebral artery aneurysms that are deemed treatable either by endovascular coiling or by surgical clipping.
4. Endoluminal flow diversion may be considered as an alternative to coil embolization in carefully selected cases, but there is insufficient evidence at this time to recommend this strategy as a treatment for most aneurysms. Strict adherence to the FDA's indications for use is probably indicated until additional trial data demonstrate an incremental improvement in safety and efficacy over existing technologies.

INTRACRANIAL AVMS

Intracranial AVMs are relatively uncommon vascular malformations but have substantial potential for causing intracranial hemorrhage and can produce devastating neurological injury or death. Brain AVMs have been thought to be congenital lesions, although recent evidence challenges this assertion.[95] They consist of abnormally formed blood vessels usually referred to as a nidus with low-resistance, high-flow connections between artery and vein, lacking a capillary bed.[96] The AVM detection rate is ≈1.3 per 100 000 person-years.[97–99] These lesions carry a substantial risk of intracranial hemorrhage, with hemorrhage present in approximately half of newly discovered AVMs[100] and with an estimated risk of rupture of 1%/y to 3%/y in patients with AVMs presenting without rupture.[101–103] Since the publication of the last AHA scientific statement on indications for the performance of intracranial endovascular neurointerventional procedures, advances have been made in our understanding of the natural history of cerebral AVMs and in knowledge of the risks and efficacy of treatment.

The treatment of AVMs is among the most controversial topics in endovascular neurointervention. The complexity of AVM treatment includes not only the technical aspects of the treatment modalities used but also the complex decision making needed to choose among various combinations of the available therapies. An AHA scientific statement on the management of brain AVMs has recently been published.[104] We focus here on the endovascular treatment of brain AVMs, remaining consistent with the recently published recommendations but expanding on material related to endovascular treatment. Transarterial embolization is 1 of the 3 primary treatment methods for intracranial AVMs, and it is often the first one attempted. It may be performed alone or before radiosurgery or surgical excision. The specific treatment strategy is generally determined by locally developed paradigms that incorporate specific structural features of the AVM and local experience and expertise of the treating multidisciplinary team members. There is a paucity of well-designed clinical trials to guide these decisions, and no multicenter or randomized clinical trial specifically evaluating multimodality therapy is available.

The first of several treatment decisions to be made with a patient who has a brain AVM is whether to pursue conservative management or intervention. For unruptured AVMs, the decision is controversial. The ARUBA trial (A Randomised Trial of Unruptured Brain Arteriovenous Malformations) was designed to study the benefits of conservative management versus intervention in unruptured AVMs,[101] and it is the only prospective randomized study to do so. This trial showed a lower incidence of stroke or death in the group receiving conservative management. However, features of

the study limit the conclusions that can be drawn from its results. ARUBA did not specify a treatment strategy; rather, local physicians decided which combination of embolization, surgery, and radiation therapy to use. This approach mimics current clinical practice, but it introduces variance that may mask the value of a particular therapeutic regimen, particularly with the small number of patients enrolled. This first published report from ARUBA includes only a few years of follow-up. Because AVM rupture risk does not appear to diminish over time after discovery, longer-term follow-up will be necessary for this study to properly inform clinical decision making. At present, an additional 5 years of follow-up is planned.

For patients with brain AVMs presenting with intracranial hemorrhage, it is common clinical practice to pursue either focused or definitive treatment of the AVM. Although there is no RCT showing better outcomes with intervention, this practice can be justified from the available natural history and treatment risk data. The risk of recurrent hemorrhage may be higher than it is for unruptured AVMs. A recent meta-analysis of the natural history in the absence of treatment showed an annual risk of recurrent hemorrhage of 4.8%,[103] and New York Islands data showed an even higher recurrent hemorrhage rate of 18%.[99] These data, combined with treatment risk data from ARUBA and other studies, suggest benefit for interventional treatment in one of its forms. The clinical effects of recurrent hemorrhage vary from mild to severe; therefore, outcomes after recurrent hemorrhage must be considered. Studies of outcomes after recurrent hemorrhage are limited, but results appear to depend on the method used to evaluate disability. In 1 large case series, repeat AVM hemorrhage produced little change in NIHSS score but produced a statistically significant worsening of mean mRS score from 2 to 2.7.[105] The relatively high risk of recurrent hemorrhage and the possibility of substantial clinical deterioration make it common clinical practice to pursue treatment for ruptured AVMs.

Endovascular embolization is used in many AVM treatment paradigms. For any of the treatment paradigms, complete obliteration is the goal. Partial treatment does not decrease the risk of AVM rupture[106] and may increase the risk of recurrent hemorrhage. Embolization may be used as a stand-alone treatment method. Although this strategy is less invasive than surgical resection, its ability to cure an AVM safely is limited to a small percentage of patients.[107] Rather, embolization is most commonly used preoperatively as a means of reducing the risks of surgical resection. Embolization may also be used to treat certain dangerous AVM features (eg, nidal aneurysms) or to reduce overall vital volume before or after stereotactic radiosurgery. In rare cases, partial embolization may be used to decrease high-flow arteriovenous shunting as a means of reducing symptoms that may be caused by the hypothesized vascular steal phenomenon.

Preoperative embolization is common clinical practice, particularly for larger AVMs or AVMs with higher Spetzler-Martin grade. For small AVMs in noneloquent locations, surgical resection or radiosurgery alone may be considered.[108] However, large AVMs that extend into areas of eloquent cerebral parenchyma carry substantial risk of intraoperative bleeding and postoperative neurological deficits. The practice of using preoperative embolization to reduce the size or complexity of larger AVMs is supported by older retrospective observational studies that have shown that preoperative embolization reduces operative time and surgical morbidity.[109,110] No multicenter or randomized prospective trial has been conducted to corroborate these conclusions with current treatment techniques. For successful incorporation of embolization into the treatment paradigm, the procedures must be relatively safe with low morbidity and mortality. In recent series, the morbidity and mortality related to embolization, primarily with liquid embolic materials, have varied from 2% to 12%.[111–115] Much of the variance in risk is likely the result of institution- or operator-specific patient selection and the treatment strategies used. The variability of procedural risks and the paucity of data with the most recent treatment paradigms limit the ability to make specific evidence-based statements about the role of preoperative embolization at this time.

Complete obliteration of AVMs with endovascular embolization may be achieved by original intent or during the course of embolization that was planned to be preoperative. The ability to eradicate AVMs with endovascular embolization alone has been improved with the introduction of the liquid embolic agent ethyl vinyl alcohol copolymer (Onyx, ethylene vinyl copolymer; Medtronic, Inc). With Onyx, curative treatment with embolization alone may exceed 50%.[116,117] Data on the safety and efficacy of endovascular embolization alone for AVM cure come from case series. For smaller, Spetzler-Martin grade 1 to 2 AVMs, surgery, embolization, or radiosurgery appears to show good results in small case series. In the few multicenter case series published, cure rates with embolization alone were more modest at 9% to 24%.[107,111,118] Newer transvenous embolization strategies may permit effective treatment of AVMs not amenable to transarterial embolization alone.[119] Stand-alone embolization versus preoperative embolization and surgical resection has not yet been studied in a prospective, randomized paradigm with a well-defined patient cohort and regimented techniques.

Embolization is also used before radiation therapy. It has been used most commonly in 2 scenarios. First, high-risk anatomic features for hemorrhage such as intranidal or feeding artery aneurysms can be eliminated

before the treatment of the larger AVM.[120,121] Treating these aneurysms with embolization, which can also be used for ruptured AVMs before surgery, is particularly important when radiation therapy is planned because of the several-year latency between the treatment and the nidal sclerosis that results in AVM cure. Second, reduction of the outer circumference of AVMs by embolization may reduce the volume of AVM tissue for radiation therapy sufficiently to permit radiation treatment of AVMs that would otherwise be too large. Small case series directly examining this approach show that AVM obliteration is feasible,[122,123] but there is concern that preoperative embolization may lead to decreased long-term AVM obliteration. Randomized controlled outcomes studies are lacking.

Evidence-based decision making for the treatment of cerebral AVMs requires further investigation into many facets of the treatment algorithm. The current levels of evidence for any of the aspects of AVM treatment are low. Trials of AVM treatment are challenging because of the relative rarity of these lesion and the many variations in therapeutic paradigms, techniques, and materials used by centers throughout the world. Furthermore, there is relatively rapid ongoing evolution of materials and technique. Some variables amenable to study include those discussed above but also the staging of embolization, time between embolization and other treatments, intraprocedural and postoperative blood pressure management, embolic agent (n-BCA, Onyx, or other newer agents in use outside the United States), use of balloon catheters and detachable-tip catheters, and treatment of large shunts. Long-term data from the ARUBA trial will be of interest, but the original cohort size remains small. Because there is little consensus on the best treatment algorithm for many AVMs, ARUBA is unlikely to be sufficient to inform the treatment of unruptured AVMs. Additional large randomized multicenter trials are difficult and expensive. TOBAS (Treatment of Brain AVM Study) is an ongoing multicenter RCT for patients with brain AVM comparing preventive interventions (surgery, radiation, embolization) and conservative medical management. There is a concurrent prospective registry to evaluate outcomes of consecutive patients who are not randomized. Registry data represent an important option for further study of this disease. However, because the data obtained to date show substantial variation in treatment risks, a major determinant in outcomes, any attempt to study endovascular AVM therapy will benefit from the regimentation of pretreatment decision making and treatment techniques.

Summary

1. Patients with newly discovered unruptured cerebral AVMs should be informed about natural history risks, which include a 1% to 3% annual risk of hemorrhage.
2. Patients with cerebral AVMs presenting with rupture should be informed about natural history risks, which include an annual cumulative rupture risk of up to 5%.
3. The discussion of treatment options with patients should include consideration of these risks weighed carefully against the relative risks of different intervention strategies (and their combination) and life expectancy.
4. When intervention is chosen, embolization alone is reasonable to consider as a strategy for select ruptured or unruptured AVMs.
5. When intervention is chosen, preoperative embolization is reasonable to consider for select ruptured or unruptured AVMs.
6. The relative rarity of cerebral AVMs and the paucity of outcomes data make it important to benchmark individual results and to promote both clinical trials and multi-institutional prospective registries.

DURAL ARTERIOVENOUS FISTULAS

Dural arteriovenous fistulas (DAVFs) are arteriovenous shunts partially or entirely within the dura mater. They are rare, acquired lesions, most often of uncertain origin, but can be associated with trauma, surgery, tumors, prior cerebral venous thrombosis (CVT), or infection in the vicinity of the fistula. The clinical presentation of DAVFs ranges from asymptomatic to potentially catastrophic with life-threatening intracranial hemorrhage. Their clinical presentation and natural history depend on the venous drainage pattern, which is the most important determinant of the patient's prognosis. In fistulas with a benign natural history, drainage does not involve the cerebral veins, and tinnitus or ocular symptoms are the most common forms of presentation. Fistulas with a high risk of hemorrhage are characterized by retrograde cortical venous drainage[124–126] and may present with intracranial hemorrhage, progressive neurological deficit, dementia, seizures, or intracranial hypertension.

Different classification schemes for DAVFs have been proposed (Table 3); 3 pivot on the principle of cortical venous reflux. With this type of classification, it has been demonstrated that DAVFs without cortical venous drainage have a very low likelihood of hemorrhage.[126,128,129] The natural history of aggressive DAVFs is variable and limited by data available in small case series. Type III and intravenous intracranial DAVFs have been reported to have hemorrhagic risk of ≈1.5%/y to 1.8%/y.[130,131] The estimated risk of mortality and morbidity with lesions with cortical venous reflux is 10% to 15%.[132]

Table 3. Classification Schemes for DAVFs

Djindjian and Merland[124]	Cognard et al[126]	Borden et al[125]	Geibprasert et al[127]
Type I: meningeal AVF draining into a sinus or meningeal vein	Type I: antegrade sinus drainage Type II: antegrade and reflux sinus drainage Type IIa: retrograde venous drainage into sinus only Type IIb: retrograde venous drainage into cortical vein only	Type I: drainage into sinus or meningeal vein	Ventral epidural, more often benign
Type II: meningeal AVF draining into a sinus with reflux into cortical veins	Type IIa+b: retrograde venous drainage into sinus and cortical vein	Type II: drainage into dural sinus or meningeal vein but also retrograde into subarachnoid veins	Dorsal epidural, multiplicity of fistula
Type III: meningeal AVF draining into cortical vein	Type III: drainage directly into cortical vein without venous ectasia	Type III: drainage into subarachnoid veins only	
Type IV: meningeal AVF with cortical venous drainage into a venous pouch	Type IV: drainage into cortical vein with venous ectasia >5 mm and 3 times larger than diameter of draining vein Type V: drainage into spinal perimedullary vein		Lateral epidural, more often with cortical or spinal venous reflux

AVF indicates arteriovenous fistula; and DAVF, dural arteriovenous fistula.

The potential for transformation of a benign fistula to an aggressive type is low. One series showed an absence of transformation in 84 type I DAVFs (47 followed up for 6 months–23 years) other than 1 type I DAVF that progressed to type IIa as a result of increased flow.[126] Factors that may lead to worsening DAVF grade or progression include younger age at presentation, angioarchitecture suggestive of venous hypertension such as venous sinus dilatation, pseudophlebitic cortical venous pattern,[133] stenosis or thrombosis of the draining veins, increased arterial flow, and appearance of a new fistula site or extension of the initial shunt into 2 shunts.[134]

The treatment of DAVF should be tailored to its anatomy, clinical presentation, and consideration of its natural history. In general, treatment should be conservative for asymptomatic benign lesions, whereas more aggressive approaches can be considered with fistulas with cortical venous reflux, hemorrhagic presentations, or debilitating tinnitus. As with any arteriovenous shunt, the most effective and durable treatment consists of occlusion of the venous recipient of the fistula.[135] Venous occlusion should be targeted at the fistulous point. If occlusion downstream to the fistulous site is achieved, persistent arterial flow may lead to rupture of pial veins for type III fistulas or rerouting of flow in type I or II fistulas. One should also avoid occlusion of normal venous pathways because this may result in venous infarction or life-threatening intracranial hemorrhage.[136]

Most dural fistulas can be managed by endovascular transarterial or transvenous approach, but some may be more appropriately approached by surgery. Generally, cavernous and transverse-sigmoid DAVFs are treated with transvenous approach with coils; type III fistulas are more commonly treated with transarterial liquid embolic agents.[137]

Radiosurgery is an alternative option for patients with high-risk medical comorbidities, for fistulas that are not amenable to endovascular or surgical treatment, or as salvage therapy in cases refractory to embolization or surgery. Radiosurgery offers delayed latency cure of 1 to 3 years, and obliteration rates range from 52% to 74%.[138] Radiosurgery may not be recommended if more urgent treatment is indicated as in fistulas with cortical venous reflux or hemorrhagic presentation.

Summary

For patients with DAVF, best practice includes the following:

1. For patients with neurological symptoms or hemorrhage referable to the dural fistula, treatment with the goal of complete fistula occlusion is recommended. Endovascular therapy alone may be curative, or endovascular therapy may be used with other therapies such as surgery or radiosurgery.
2. For patients with asymptomatic dural fistula with aggressive angiographic features (ie, cortical venous reflux), treatment is recommended. Endovascular therapy alone may be curative, or it may be used with other therapies such as surgery or radiosurgery.
3. For patients with asymptomatic dural fistulas without aggressive angiographic features, conservative management is recommended.

CEREBRAL VENOUS THROMBOSIS

CVT is an uncommon form of stroke, accounting for ≈1% of all stroke.[139] Risk factors are usually related to an underlying prothrombotic state, venous stasis, trauma, infection, or hypovolemia. Both congenital and acquired prothrombotic states have been implicated. Among the acquired states, pregnancy and oral contraceptive use are among the most commonly seen.

The mainstay of therapy for CVT is anticoagulation, a practice based on 2 randomized studies with a total of 79 patients enrolled and supported by many observational studies.[139] For most patients, the prognosis with such treatment is good. However, for patients who have a markedly diminished level of consciousness on arrival, including those who are comatose or have a poor natural history, mortality rates are as high as 53%.[140] Endovascular therapy is reserved primarily for those who have failed anticoagulation, typically those with either new or increasing ICH despite therapeutic anticoagulation or those who have a markedly diminished level of consciousness or worsening focal neurological deficits.

A variety of endovascular techniques have been described for the treatment of CVT. These include prolonged direct thrombolytic infusion,[141] rheolytic thrombectomy devices,[142] and newer large-bore aspiration thrombectomy systems[143–145] and stent retrievers.[146] The additional benefit of direct thrombolysis used with mechanical thrombectomy and the degree of recanalization needed are unknown.[147] Most procedures are performed with the patient under general anesthesia, and concomitant anticoagulation is used. Both femoral and jugular venous accesses have been described.

Outcomes data are largely limited to small case series. In aggregate, these show positive results with a good safety profile for both thrombolytic infusion and mechanical thrombectomy devices.[148] A retrospective study comparing intrasinus thrombolytic infusion with mechanical thrombectomy (with or without thrombolytic) in 63 patients revealed that patients with more severe deficits were more likely to be treated with mechanical thrombectomy but that no difference in clinical response could be demonstrated.[149] Full recanalization was achieved in 50% of patients, and full or partial recanalization was achieved in 91%.

There is an ongoing PROBE comparing anticoagulation alone with anticoagulation plus endovascular therapy in CVT.[150] Included are patients with proven CVT who are considered high risk for deterioration such as depressed mental status, coma, intracranial hemorrhage, or straight sinus thrombosis. Endovascular therapies include local administration of thrombolytic medication with or without additional mechanical thrombectomy.

Summary

1. Patients with CVT should be treated with systemic anticoagulation as first-line therapy.
2. In patients with CVT who are at high risk for deterioration (severely depressed mental status, coma, straight sinus thrombosis at presentation; those with neurological deterioration or increasing intracranial hemorrhage despite systemic anticoagulation), the use of endovascular techniques, including direct intrasinus thrombolysis or mechanical thrombectomy, may be considered.

IDIOPATHIC INTRACRANIAL HYPERTENSION

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri or benign intracranial hypertension, is a disorder with elevated intracranial pressure in the absence of a structural lesion.[151] Long-term risk of IIH is related to visual deterioration and disabling symptoms such as severe headache and pulsatile tinnitus. Studies have shown that transverse sinus stenosis is almost universally seen in patients with IIH.[152] Intracranial pressure is in dynamic equilibrium with pressure in the intracranial veins and dural venous sinuses. Although the venous outflow from the head is complex and variable, the transverse sinuses form the major conduit for venous outflow. If there is high resistance to outflow in the bilateral transverse sinuses, intracranial hypertension is likely.

The primary medical treatments for IIH include weight loss, acetazolamide (thought to reduce cerebrospinal fluid production), diuretics, and high-volume lumbar punctures. However, a proportion of patients fail medical therapy with either progressive visual deterioration or severe lifestyle-disabling headaches. In these cases, a variety of more aggressive interventional therapies are available, including optic nerve sheath fenestration, surgical cerebrospinal fluid diversion procedures, and transverse sinus stenting.

Endovascular approaches are based on the creation of a lower-resistance pathway in at least 1 of the transverse and sigmoid sinuses. Because imaging assessment of stenosis is difficult and correlates poorly with symptoms,[152] inclusion criteria generally include assessment of intraluminal pressure gradients. Most patients treated have had measured gradients of >10 mm Hg.[151] Stenting has usually been performed with self-expanding stents.[153–159] Angioplasty of the sinus has also been described in conjunction with stent placement alone,[160] but angioplasty without stenting has not been described in the literature. The periprocedural management with respect to anticoagulation or antiplatelet medication is not standardized. A recent meta-analysis of the outcomes of venous sinus stenting

showed that the procedure had produced self-reported improvements in headache, vision, and papilledema of 83%, 78%, and 97%, respectively.[151] These outcomes compared favorably with sheath fenestration and surgical cerebrospinal fluid diversion procedures. The major and minor complication rates for venous sinus stenting were 2.2% and 4.4%, respectively.

No randomized clinical trials have been reported that allow assessment of the procedure relative to medical management or the other interventional techniques. There are 3 trials currently registered with ClinicalTrials.gov. Two of these are single-arm trials of stenting in patients with medically refractory pseudotumor,[161,162] and the third is a randomized trial of traditional surgical cerebrospinal fluid diversion with stenting.[163]

Summary

1. In patients with medically refractory IIH and progressive visual deterioration or lifestyle-disabling symptoms of headache or pulsatile tinnitus, it is reasonable to offer endovascular stenting of transverse sinus stenosis.

EMBOLIZATION OF INTRACRANIAL AND HEAD AND NECK NEOPLASMS

Management of intracranial and head and neck neoplasms generally involves a multidisciplinary team of medical and surgical specialists organized to address organ-specific symptomatology or systemic manifestations of metastasis. Embolization or occlusion of the vascular supply to a tumor is usually part of a broader clinical plan such as surgical resection but may be palliative when performed alone to control hemorrhage or disability from inoperable tumors. Perioperative embolization of vascular tumors may help to reduce risks of major blood loss, stroke, or cranial nerve injury during surgery. Thus, tumor embolization has become an integral part in the management of some brain, spine, head, and neck tumors. The Society of Neurointerventional Surgery has published a set of guidelines for physicians involved in the care of patients with neurovascular neoplastic diseases.[164]

Originally described in 1975, endovascular embolization evolved to palliate or aid in the resection of vascular malformations, vascular tumors such as meningiomas, and nasopharyngeal carcinomas.[165,166] Advancements in fluoroscopic vascular imaging and catheter technology allowed more precise delivery of embolic materials to tumor vessels without injury to surrounding normal tissues. Specific training and organ- and disease-specific knowledge and skills to accomplish favorable results with minimal morbidity subsequently developed in the field of neurointerventional surgery.

Indications for preoperative tumor embolization vary and have not been subjected to rigorous scientific inquiry. Size and location of the tumor and surgical expertise can affect the decision to pursue vascular embolization. In general terms, the indications for embolization include the following: (1) decreased surgical morbidity through reduction of blood loss, (2) decreased surgical morbidity through reduction of operative time, (3) control of surgically inaccessible arteries supplying the tumor to reduce damage to surrounding normal tissues, (4) improved tumor visibility and resulting increased incidence of complete surgical resection, (5) prevention of hemorrhage from unresectable tumors, and (6) relief of intractable pain. Highly vascular cranial tumors for which preoperative embolization is commonly performed include meningioma, hemangiopericytoma, hemangioblastoma, paraganglioma, juvenile angiofibroma, neurogenic tumors, esthesioneuroblastoma, and benign and malignant bone tumors of the skull and spine.[165–175]

For meningiomas, studies of preoperative embolization are limited to nonrandomized series. Studies have demonstrated decreased blood loss and transfusion requirement,[176] but the degree of reduction varies[175,177] and the effect on overall postoperative outcomes is unclear. A recent meta-analysis reports a complication rate of 4.6% for this procedure.[178] The uncertainty of the value of this procedure is reflected in the widely varying use of preoperative embolization of meningiomas among institutions.

For hemangioblastomas, embolization may reduce operative blood loss and surgical difficulty.[179] Studies of preoperative embolization for these tumors consist of small case series. Reports of the safety of the procedure vary markedly, with some studies showing low complication rates and high efficacy[180] and others showing a substantial risk of tumor hemorrhage around the time of embolization.[181]

Among the varied vascular tumors of the face, skull base, and neck, paragangliomas are the most studied. Preoperative embolization is considered necessary when these tumors involve the skull base (eg, glomus jugulare) and may still have value in those tumors lower in the neck (eg, carotid body tumor).[182,183] For the latter, embolization decreases intraoperative blood loss and operative time in retrospective case series,[184] but its effect on outcomes has been questioned.[185,186]

For many tumors of the skull base, face, or neck, percutaneous embolization is also feasible, and interest in this approach has been increasing.[187–189] Studies of this alternative technique, generally with liquid embolic agents, are limited to small case series. In accessible tumors, this approach may have lower risks of distal arterial embolization and can be used when such risks limit transarterial embolization.[190] Nevertheless, retrograde

passage of material into feeding arteries is commonly present and can produce nontarget embolization.[186]

Intra-arterial chemotherapy, particularly for malignant neoplasms, with or without combination radiation therapy or surgery has been used experimentally and in practice around the world for the treatment of nonresectable head and neck squamous cell carcinoma and other neoplasms.[191–200] In the United States, intra-arterial chemotherapy has most recently been successfully applied to the treatment of retinoblastoma.[201,202] Despite its use on an experimental or a palliative basis, the role of intra-arterial chemotherapy remains unproven in large-scale randomized trials.[203]

Safety and efficacy are defined by the successful conclusion of the arteriographic procedure, substantial devascularization of the target neoplasm, palliation or resolution of the patient's symptoms, or improved surgical outcomes without complications. The head, neck, and brain are highly vascularized with an extensive network of extracranial-to-intracranial collateral arterial anastomoses. Errant embolization can lead to disabling cranial nerve injury or stroke.[204,205] For this reason, specific training in dedicated neurointerventional programs has been advised.[206]

Summary

1. Preoperative embolization is a commonly performed adjunct to surgical removal of select vascular tumors of the brain, skull base, face, and neck.
2. Retrospective case series show intraoperative advantages of preoperative embolization.
3. Complications, which are site and tumor specific, must be considered when preoperative embolization is considered.
4. Randomized studies of overall outcomes for preoperative embolization in any of its varied forms have yet to be performed.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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