Posterior Circulation Ischemia in the Endovascular Era

Roberta Novakovic-White, MD, Juan Mario Corona, MD, and Jonathan A. White, MD

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Correspondence
Dr. Novakovic-White
robin.novakovic@utsouthwestern.edu

Abstract

Background and Objectives
To perform literature review of clinical, radiographic, and anatomical features of posterior circulation ischemia (PCI) and systematic review of the literature on the management of basilar artery occlusion (BAO) and associated outcomes.

Methods
Review of literature was conducted to identify publications describing the risk factors, etiology, clinical presentation, and imaging for PCI. A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement. PubMed and Ovid MEDLINE were searched from 2009 to 2020 for articles relating to management of BAO. A synthesis was compiled summarizing current evidence on management of BAO.

Results
PCI accounts for 15%–20% of strokes. Risk factors are similar to anterior circulation strokes. Dizziness (47%), unilateral limb weakness (41%), and dysarthria (31%) are the most common presenting symptoms. A noncontrast head CT will identify PCI in 21% of cases; diffusion-weighted MRI or CT perfusion increase sensitivity to 85%. Recent trials have shown endovascular therapy can achieve >80% recanalization of BAO. In select patients, 30%–60% who receive endovascular treatment can achieve favorable outcome vs without. A total of 13% achieve good outcome and there is an 86% mortality rate.

Discussion
PCI can present with waxing and waning symptoms or clinical findings that overlap with stroke mimics and anterior circulation ischemia, making diagnosis more heavily dependent on imaging. Recanalization is an important predictor of improved functional outcome and survival. In this endovascular era, trials of BAO are fraught with deterrents to enrollment. Despite limitations, endovascular treatment has shown improved outcome in select patients.
Glossary

AC = anterior circulation; ACI = anterior circulation ischemia; AHA = American Heart Association; AICA = anterior inferior cerebellar artery; AIS = acute ischemic stroke; AT = antithrombotic treatment; BA = basilar artery; BAO = basilar artery occlusion; CI = confidence interval; CTA = CT angiography; CTP = CT perfusion; EVT = endovascular thrombectomy; IA-PT = intraarterial pharmaceutical thrombolysis; IAT = intra-arterial therapy; ICA = internal carotid artery; ICAD = intracranial atherosclerosis disease; ICH = intracerebral hemorrhage; IVT = IV thrombolysis; LVO = large vessel occlusion; mRS = modified Rankin Scale; MT = mechanical thrombectomy; NIHSS = National Institutes of Health Stroke Scale; OR = odds ratio; PC = posterior circulation; pc-ASPECTS = Alberta Stroke Program Early CT Score for the posterior circulation; PCA = posterior cerebral artery; PCI = posterior circulation ischemia; PICA = posterior inferior cerebellar artery; PPV = positive predictive value; RCT = randomized controlled trial; RR = risk ratio; SA = subclavian artery; SAH = subarachnoid hemorrhage; SCA = superior cerebellar artery; sICH = symptomatic intracerebral hemorrhage; SNIS = Society of Neurointerventional Surgery; VA = vertebral artery; VBD = vertebrobasilar dolichoectasia.

In the United States, the annual incidence of stroke is approximately 795,000, ranking as the fifth leading cause of death, with more than 146,000 deaths (1 in 19) per year.1,2 In the United States, 87% of strokes are ischemic, yet not all ischemic strokes are created equal.3 The presence of a large vessel occlusion (LVO) has been associated with significantly worse outcomes.3 Despite terminology variation, the most common definitions of LVO include the intracranial internal carotid artery (ICA), proximal middle cerebral artery (M1), second segment of the middle cerebral artery territory (M2), and basilar artery (BA). Additional arterial territory with variable acceptance as LVO include the vertebral artery (VA), proximal posterior cerebral artery (PCA), and proximal anterior cerebral artery.4 Depending on the classification used, angiographic studies have shown that LVO accounts for 31%–46% of acute ischemic strokes (AIS) and only 13% of TIA.5,6 Meanwhile, only 15%–20% of AIS are attributable to the vertebrobasilar circulation, which is associated with poor outcome in 68%–80% of patients.7,8

Anatomy of the Posterior Circulation

To undertake a discussion on posterior circulation ischemia (PCI), it is prudent to first summarize the vascular anatomy. The cerebrovascular circulation is typically derived from 3 great vessels arising from the aortic arch in the superior mediastinum: brachiocephalic (also known as the innominate), left common carotid, and left subclavian arteries. Shortly after its origin, the brachiocephalic artery bifurcates into the right common carotid artery and the right subclavian artery (SA). In the most common configuration, the brain is supplied directly by 4 craniovertebral vessels: 2 ICAs (branches of the common carotid arteries) and 2 VAs. In the typical configuration, the right and left VAs arise from the ipsilateral SA. The vertebrobasilar system is composed of 2 VAs and an unpaired BA. The VAs are defined by 4 segments along their course (Figure 1). The preforaminal V1 segment arises as the first branch of the SA and courses posteriorly to enter the transverse foramen of the sixth cervical vertebrae and ascends as the V2 segment. As the VA ascends through the cervical vertebrae, small cervical muscular branches are given off to supply the surrounding musculature. After exiting the transverse foramen of the axis, the V3 segment courses laterally, then enters the transverse foramen of C1. This segment then courses over the posterior arch of the atlas and through the suboccipital triangle to the foramen magnum, entering the intracranial space as the V4 segment. Once intradural, the VA gives off an ipsilateral posterior inferior cerebellar artery...
(PICA) before joining the contralateral VA at the vertebrobasilar confluence to form the BA at the base of the pons.

The BA serves as the primary source of arterial supply to the brainstem, the remaining portion of the cerebellum, mesial temporal, and occipital lobes (Figure 2). The BA courses anteriosuperiorly within the basilar sulcus of the pons, giving off bilateral anterior inferior cerebellar arteries (AICAs), possibly the labyrinthine artery (alternatively an AICA branch), numerous pontine arteries (paramedian pontine and circumferential branches), and the paired superior cerebellar artery (SCA) (Figure 3). The BA divides to give rise to bilateral PCAs at the level of the proximal midbrain, just distal to the oculomotor nerves. The PCA joins the posterior communicating arteries, a limb of the circle of Willis, which serve as an important route for collateral circulation when needed.

Normal Anatomical Variation of the Posterior Circulation

There is significant anatomical variation of the vertebrobasilar circulation and its branches. Asymmetric VAs occur in over two-thirds of the population. Moreover, 50% of the population has some variation in the completeness of the circle of Willis. For example, the artery of Percheron is a rare anatomical variation in which a single arterial trunk arises from the PCA to supply bilateral thalami and midbrain. Other posterior anomalies include fenestration of the VA or BA, fetal origins to the PCAs, AICA–PICA variants, and even persistence of fetal carotid–basilar anastomoses, which typically regress as the posterior communicating artery develops (persistent trigeminal artery, persistent hypoglossal artery, proatlantal intersegmental artery, and persistent otic artery). Understanding the potential variant anatomy in the posterior circulation (PC) is imperative when defining etiology of a stroke and planning surgical or endovascular interventions.

Risk Factors for PCI

Clinicians often consider PCI as a separate entity from anterior circulation ischemia (ACI) regarding risk factors, clinical manifestations, etiology, and prognosis. An observation study compared etiology and risk factors of 2,245 consecutive

Figure 2 Basilar Artery as the Primary Source of Arterial Supply to the Brainstem, the Remaining Portion of the Cerebellum, and Mesial Temporal and Occipital Lobes

a = artery; br = branch; CN = cranial nerve; inf = inferior.
patients with MRI-confirmed PCI and ACI in a Chinese population.\textsuperscript{11} The authors concluded that the 2 stroke types are more similar than different pertaining to etiology and risk factors. Analysis of risk factor frequency in PCI and ACI revealed hypertension to be the most common in either group, occurring in 47.9\% of patients.\textsuperscript{11} Multivariate analysis identified 2 factors as conferring greater risk in PCI than ACI: male sex (odds ratio [OR], 1.392; 95\% confidence interval [CI], 1.085–1.786) and diabetes myelitis (OR, 1.667; 95\% CI, 1.275–2.180).\textsuperscript{11} Meanwhile, the frequency of other risk factors was similar between the 2 groups.

**Etiology of PCI**

An observational study found the most frequent etiology for PCI and ACI was small-artery occlusion (37.6\% PCI vs 37.1\% ACI).\textsuperscript{11} However, a review of combined registries found the most common cause of PCI was large vessel atherosclerotic disease (35\%), while cardioembolism accounted for 18\%, small vessel disease 13\%, and 15\% remain undetermined.\textsuperscript{12} Meanwhile, individuals of Asian, African, and Hispanic ancestry are at higher risk for intracranial atherosclerosis disease (ICAD).\textsuperscript{13}

Large vessel atherosclerotic disease within the PC can lead to ischemia via hemodynamic failure (32\% of PCI) as well as in situ thrombosis or artery–artery thromboembolism.\textsuperscript{14} Chronic cerebral circulation insufficiency, from a hemodynamic flow-limiting stenosis, can be associated with acute events like AIS or TIA, as well as chronic complications such as vascular cognitive impairment and vascular dementia.\textsuperscript{15,16} Without addressing risk factors\textsuperscript{17} with aggressive medical therapy, symptomatic ICAD is at high risk of stroke recurrence, up to 25\%–30\% over 2 years after an index stroke.\textsuperscript{18,19} The most common location of atherosclerotic disease in the PC involves the proximal and distal segments of the VA (V1 and V4; Figure 1) and BA.\textsuperscript{14,20} Atherosclerotic disease rarely involves the cervical segments (V2 and V3). Thus, arterial dissection should be considered when the stenosis only involves atypical locations such as the V2 and V3 segments.\textsuperscript{21}

In the New England Medical Center PC registry, embolism was the most common mechanism, accounting for 40\% of PCIs (24\% cardiac origin, 14\% intraarterial, 2\% cardiac and arterial sources).\textsuperscript{14} However, the anterior circulation (AC) (ICAs bilaterally) receives 82\% of the brain’s blood supply and the remaining 18\% contributes to the VAs.\textsuperscript{22} Thus, the predominance of cardiac emboli should flow to the AC. A separate study confirmed cardioembolism occurred in a significantly smaller proportion of patients with PCI (5.4\%) compared to ACI (13.3\%; OR, 0.373; 95\% CI,
In PCI, the most frequent recipient sites of artery–artery embolism are the intracranial VA, PICA, distal BA, SCA, and PCA branches.

Vertebrobasilar Dolichoectasia
Vertebrobasilar dolichoectasia (VBD) is a term that refers to arterial elongation, dilatation, and tortuosity of the BA. Eighty percent of intracranial arterial dolichoectasia affect the BA. VBD is associated with wide range of proposed risk factors and etiologies: male sex, increasing age, hypertension, smoking, healed focal arterial dissections, prior radiation therapy, connective tissue disease, myxomatous emboli, infection, and diseases affecting elastic fibers (Marfan syndrome and tortuosity syndrome) as well as muscle cells in the tunica media (lysosomal storage diseases: Fabry disease and Pompeii disease). Dolichoectasia can remain an incidental finding or present with clinical manifestations. The estimated 5-year complication risk is 17.6% for AIS, 10.3% for brainstem compression, 10.1% for TIA, 4.7% for intracerebral hemorrhage (ICH), 3.3% for hydrocephalus, and 2.6% for subarachnoid hemorrhage (SAH); the estimated 5-year case mortality was 36.2%. Management depends on clinical presentation and disease severity. Treatment options include blood pressure control, antithrombotic treatments, endovascular procedures, or surgery. Endovascular treatment in patients with a presentation of compressive symptoms may not be beneficial.

Dissection of the Posterior Circulation
The mid portion of the VA, from its entry into the vertebral transverse foramen through its winding course over the ring of C1 and until its fixed entry point into the dura, is mobile and vulnerable to dissection. VA dissection may occur spontaneously or result from cervical trauma. VA dissections usually involve the distal portions of the extracranial VA as it winds around the upper cervical vertebral bodies (V3) and sometimes the V2 segment that enters the vertebral column (typically at C5 or C6). Although vertebral artery dissection can occur in any location along the vessel, the V2 and V3 segments are the most common locations. In young adults, cervical arterial dissections account for approximately 15% of strokes. A PCI with the clinical presentation of headache, neck pain, or history of trauma or neck manipulation should raise suspicion for a VA dissection. Approximately 10% of VA dissections will extend intracranially. Intracranial extension carries a higher risk of dissecting aneurysm formation, SAH, and mortality.

Clinical Presentation of PCI
It can be difficult to recognize the clinical presentation of a PCI, as a majority will have a prorome of waxing-and-waning symptoms prior to the fixed deficits (most commonly vertigo, nausea, and headache up to 2 weeks before the stroke). This undermines the classic sudden onset of symptoms considered the sine qua non of AIS. Approximately one-fourth of PCI may be preceded by TIA. Adding to the ambiguity, symptoms can be nonspecific, such as dizziness, headache, alteration of consciousness, nausea, and ataxia. These symptoms are frequently dismissed as stroke mimics, leading to delays in diagnosis. Furthermore, there is significant overlap of symptoms between ACI and PCI, further befuddling localization.

Due to bilateral contribution of the VAs to the BA and the potential contribution of the posterior communicating artery (through the circle of Willis), occlusion of a single codominant VA frequently may be asymptomatic. Only in the presence of variant anatomy (VA ends in PICA) or occlusion/stenosis of the contralateral VA may the patient become symptomatic. Common symptoms related to PCI are taught as the “deadly Ds”: dizziness, dysphagia, diplopia, dysarthria, and dystaxia. Acute onset of neurologic deficits with crossed findings (e.g., ipsilateral cranial nerve symptoms and contralateral sensory or motor deficits) are classic for PCI. In one observational study of 407 patients, the most common symptoms of PCI were dizziness (47%), unilateral limb weakness (41%), dysarthria (31%), headache (28%), and nausea or vomiting (27%). A separate observational study of 1,174 consecutive patients with stroke found homolateral hemiparesis, central facial/lingual palsy, and hemisensory deficits were the 3 most common signs and symptoms in PCI and ACI. The signs with the highest predictive value favoring a diagnosis of PCI were Horner syndrome (positive predictive value [PPV] 100%; OR, 4.00), crossed sensory deficits (PPV 100%; OR, 3.98), quadranoponopia (PPV 100%; OR, 3.93), oculomotor nerve palsy (PPV 100%; OR, 4.00), and crossed motor deficits (PPV 92.3%; OR, 36.04), all with very low sensitivity (range 1.3%–4.0%).

Subclavian Steal
The VAs arise from the SAs bilaterally. Stenosis or occlusion of the proximal SA may be associated with a subclavian steal, which refers to a phenomenon of flow reversal through the ipsilateral VA steal flow from the PC. A classic presentation of this rare syndrome is unilateral arm pain with exertion and associated PC symptomatology (e.g., dizziness, vertigo, dysarthria, and even syncope with limb exertion). Physical examination findings suggestive of subclavian stenosis include discrepancy of 10 mm Hg or greater in systolic blood pressure between arms, delayed or decreased amplitude pulses in the affected side, and a supraclavicular fossa bruit. A significantly elevated arm pressure differential (>40–50 mm Hg) is more commonly associated with symptoms, complete steal, and the need for intervention.

Bow Hunter Syndrome
Bow hunter syndrome results from vertebrobasilar insufficiency secondary to dynamic mechanical occlusion or stenosis of a VA upon head rotation. The mechanical compression is most commonly due to cervical bony osteophytes at C1-2 or C5-7 in older patients or C1-C2 hypermobility. Symptoms vary widely depending on the amount of compensatory flow from the contralateral VA. Symptoms may be transient when blood flow is temporarily compromised, may persist with insufficient blood flow, or lead to stroke resulting from embolus or thrombus formation. Surgical decompression without fusion was found to
be safe and a reliable surgical option in patients with bow hunter’s syndrome.41

Imaging

Given the difficulty of an accurate clinical diagnosis, imaging becomes pivotal in the diagnosis of PCI.35 CT imaging can show hypodensity and loss of gray–white differentiation in ACI, but due to beam hardening from the dense skull base, identification of ischemic changes can be as low as 20% in the posterior fossa.43 Contrast-enhanced CT angiography (CTA) can detect LVO accurately and can aid in diagnosis. CT perfusion (CTP) has successfully predicted penumbra from ischemic core in the AC and shows promise in the PC (Figure 4).43-45 However, there remains a dearth of evidence regarding optimal perfusion appropriate thresholds to use in the PC.46 Furthermore, accurate calculations of both ischemic core and penumbral volumes in the posterior fossa are limited by skull base and orbit artifact.46 MRI remains the gold standard in the detection of PCI and should be considered in patients arriving in the late window.47,48

Diffusion-weighted imaging can show early ischemic changes even in the brainstem; however, MRI is not always easily available in the emergency setting. Meanwhile, catheter angiography is invasive and usually reserved for therapeutic rather than diagnostic purposes. However, newer protocols for direct transfer to angio-suite in patients suspected of LVO, where a cone beam CT can exclude ICH before invasive angiography, may be an effective strategy to reduce workflow time and increase odds of a favorable outcome.49

To predict functional outcome, a 10-point Alberta Stroke Program Early CT Score for the PC (pc-ASPECTS) has been introduced with vascular territories to tally in the midbrain, pons, bilateral thalami, bilateral cerebellar hemispheres, and bilateral cortical PCA territories (Figure 5).50 The score calculated from a noncontrast CT scan is relatively impoverished, however, a score calculated from the contrast-stained source images of the CTA or the CTP shows promise.50,51 A similar 10-point imaging score, the Basilar Artery on Computed Tomography Angiography (BATMAN) score, incorporates presence of collaterals and thrombus burden to predict clinical outcome in patients with basilar artery occlusion (BAO), where a lower BATMAN score is associated with poor outcome.52

Figure 4 CT Perfusion Has Successfully Predicted Penumbra From Ischemic Core in the Anterior Circulation (AC) and Shows Promise in the Posterior Circulation

(A) CT perfusion in patient with midbasilar thrombus extending to left posterior cerebral artery, based on automated perfusion analysis, region of core infarct is 0 mL (indicated by relative cerebral blood flow less than 30% of normal), Region of penumbra (mismatch volume = CBF volume - Tmax >6.0 s volume) involves the left superior cerebellar artery territory and the left PCA territory with a volume of 49 mL. (B) MRI post intervention DWI arrow demonstrates restricted diffusion in right anterior paramedian pons and (C) arrow demonstrates dark on ADC map in same territory as DWI, consistent with acute ischemia.

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Management of PCI

Early randomized controlled trials (RCTs) demonstrating the safety and efficacy of IV recombinant tissue plasminogen activator enrolled few patients with PCI (5% in the National Institute of Neurological Disorders and Stroke trial53 and 8.1% in the Third International Stroke Trial [IST-3]54). Intraarterial pharmacetical thrombolysis (IA-PT) began to be used in the treatment of acute BAO in the early 1980s.55 A systematic analysis focused on comparing IV thrombolysis (IVT) with IA-PT reported similar outcomes in both groups.56 Meanwhile, an RCT, halted early on account of slow recruitment and unavailability of urokinase, reported better outcomes for patients with BAO who received IA-PT compared to no thrombolysis.57 By the start of the new millennium, several observational studies of acute BAO examined intraarterial therapy (IAT) with early generation and less superior mechanical thrombectomy (MT) devices or IA-PT combined with or without bridging therapy. These studies demonstrated recanalization rates of 62.5%–92% with trends towards better outcomes and improved survival rates, despite rates of symptomatic ICH (sICH) between 0.9% and 18%.58-60

Methods

To elucidate best management of acute BAO in an endovascular era of newer generation MT devices, a systematic review was performed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Figure 6).1 PubMed and Ovid MEDLINE were searched from January 2009 to October 2020 for articles relating to management of BAO using search criteria BA, treatment, and stroke. Previous meta-analyses, RCTs, systematic reviews, and case series with more than 5 cases were included. Articles about pediatric population, isolated VA occlusion, VA stenosis treated with angioplasty and stenting for nonacute strokes, expert opinions, and study protocols (except for one RCT near completion) were not included. A synthesis was compiled summarizing the current evidence regarding management of acute BAO.

After removal of duplications, the initial search revealed 440 articles, of which 58 studies were related to acute BAO management. Thirty-seven publications58-94 and 1 RCT that reported results at an international meeting on May 13, 2020 (publication pending)95 met the final inclusion criteria. Data available from Dryad (references 61-103): doi.org/10.5061/dryad.wpzmbsbmm. Seven systematic reviews or meta-analyses and 2 reviews of the literature on the subject were included to identify articles that may have been missed during the literature review. Two studies were RCTs comparing IVT vs IVT plus endovascular thrombectomy (EVT). Twenty-one prospective or retrospective observational studies describing the recanalization rates and outcomes of BAO treated with EVT were identified. Five registries on PCI and 1 study protocol of an ongoing prospective RCT near completion were included. The articles were evaluated and the data are summarized below.

Basilar Artery Occlusion: Observational Studies

The Basilar Artery International Cooperation Study (BAICS) registry was a prospective multicenter observational study that enrolled 592 patients with BAO from 2002 until 2007, comparing the efficacy of antithrombotic treatment (AT; n = 183), IVT (n = 121), and IAT (n = 288).94 Overall, 68% of patients had a poor outcome, a 36% mortality rate was noted, and no statistically significant superiority was seen for either treatment strategy. In the IAT group, 62% of patients received only IA-PT; of those who received MT, the modern superior devices were not available during the recruitment period of the study. Patients in the IVT group were more commonly treated within 3 hours of BAO than patients in the IAT group (risk ratio [RR], 2.38; 95% CI, 1.83–3.10). Meanwhile, severe deficits were more often found in patients treated with IAT. In a direct comparison, the authors concluded after adjustment, patients with mild to moderate deficits (mean National Institutes of Health Stroke Scale [NIHSS] score 10.7) more often had a poor outcome if treated with IAT rather than IVT (RR, 1.49; 95% CI, 1.00–2.23); meanwhile, patients with a severe deficit (mean NIHSS 28) had similar outcomes when treated with either IVT or IAT (RR, 1.06; 95% CI, 0.91–1.22). Alternatively, patients with severe deficit seemed to benefit from combination of IVT followed by IAT (absolute risk of death or...
dependency was 19% with IVT and 10% with IAT, lower than the risk with AT). The overall rate of dependency or death in the group treated with AT was 93%.94

Multiple case series and observational studies have tried to shed light on the benefit of EVT in BAO (Figure 7), especially after the discouraging results of the BASICS registry published in 2009.94 In 2015, an investigator-initiated multicenter registry for 148 patients with BAO who received EVT was published.62 In this ENDOSTROKE study, good outcome (modified Rankin Scale [mRS] score 0–2) was seen in 34% of patients and mortality rate was 35%.62 A systematic review of the literature between 1970 and 2015 reported on a combined total of 1,942 patients with BAO treated with IA-PT (n = 642) or IA-MT (n = 1,300).63 The mortality rate was significantly lower in the IA-MT group (36.0%) compared to the IA-PT group (50.3%) and at 3 months favorable outcome was more likely to occur in the IA-MT group (OR, 1.24; 95% CI,
1.004–1.53). IA-PT with MT was more likely to achieve partial or complete recanalization (OR, 1.4; 95% CI, 1.13–1.73). Meanwhile, there was no difference in the rate of sICH after intervention (OR, 1.05; 95% CI, 0.76–1.45).63

In 2019, a meta-analysis on the current data up to 2018, with emphasis on the latest treatment modalities for BAO, was published.64 The weighted pooled rate of mortality was 43.16% (95% CI, 38.35%–48.03%) in the IVT group, 45.56% (95% CI, 39.88–51.28) in the IA-PT group, and 31.40% (95% CI, 28.31%–34.56%) in the EVT group. The weighted pooled rate of good outcome (mRS 0–2) at 3 months was 31.40% (95% CI, 28.31%–34.56%) in the IA-PT group, and 31.40% (95% CI, 28.31%–34.56%) in the EVT group. On subgroup analysis, no difference was seen between stent retriever and thrombo-aspiration thrombectomy in regards to clinical outcome and safety profile.64 Similarly, a prospective observational study on 48 patients with BAO treated with a stent retriever was published in 2019.65 Good outcome was achieved in 60.4% of patients. Meanwhile, the BASILAR group conducted a nonrandomized prospective cohort study, enrolling 829 consecutive patients in China from 2014 to 2019 with symptomatic acute BAO within 24 hours from estimated occlusion.66 Medical treatment plus EVT (n = 647) was associated with better outcomes compared to standard medical treatment alone (n = 182). EVT was associated with a significantly higher rate of 90-day mRS 0–3 (adjusted OR, 4.70; 95% CI, 2.53–8.75) and a lower mortality rate at 90 days (adjusted OR, 2.93; 95% CI, 1.95–4.40) despite an increase in sICH (7.1% vs 0.5%).66

**Basilar Artery Occlusion: RCTs**

In AIS secondary to LVO, modern EVT approaches have demonstrated superiority in reducing disability and mortality in the anterior circulation.96 However, of the RCT establishing efficacy of MT, only THRACE enrolled patients with LVO in the posterior circulation (1% of study population).97 No RCT has demonstrated benefit of EVT with MT in acute BAO and only 2 RCTs, hindered by excessive crossover between treatment arms and poor recruitment, have reported results.67,95 A third RCT, the BAOCHE Trial, is a multicenter Chinese randomized trial of revascularization with retrievable stents vs best medical therapy in patients presenting from 6 to 24 hours from symptom onset with a BAO is estimated to reach study completion in December 2021.98

The BEST trial is a multicenter, randomized, open-label trial, with blinded outcome assessment of thrombectomy in...
patients presenting within 8 hours of vertebrobasilar occlusion at 28 centers in China.67 Patients were randomly assigned (1:1) to EVT plus standard medical therapy or standard medical therapy alone. After 131 patients were randomized, the study was terminated prematurely because of excessive crossovers and progressive drop in recruitment. The study’s primary endpoint analysis failed to show a difference in the proportion of patients with favorable neurologic outcomes (mRS 0–3 at 90 days 42% [28 of 66 patients] in the intervention group vs 32% [21 of 65 patients] in the control group; adjusted OR, 1.74; 95% CI, 0.81–3.74) despite 71% achieving successful reperfusion (modified Thrombolysis in Cerebral Infarction 2b or 3) in the intervention group (stent retriever utilized in 83% of thrombectomies). In the medical treatment arm, 22% of the patients ended up receiving EVT for various reasons. When the data were analyzed, to assess the effects of crossover, there were higher rates of good outcome in patients who received the intervention compared to those who received standard medical therapy alone in the as-treated population (47% in the intervention group vs 24% in the standard therapy group; adjusted OR, 3.02; 95% CI, 1.31–7.00). Patients with VA occlusion tended to do better with medical treatment whereas patients with BAO tended to do better with intervention. Mortality at 90 days was similar between groups (33% in the intervention vs 38% in the control group) despite a higher incidence of sICH in the intervention group.67

The second trial to report results is the BASICS trial, a multicenter, open-label, phase III intervention RCT with blinded outcome assessment, investigating the efficacy and safety of additional IAT after IVT in patients with BAO within 6 hours from last known well.93 From 2011 until December 2019, 300 patients were enrolled; however, recruitment was hampered by the reluctance of many physicians, already convinced of EVT superiority, to randomize patients with BAO to receive IVT alone. The final results of the trial similarly demonstrated that EVT failed to outperform best medical management (absolute risk reduction 6.5%), largely due to a better than expected outcome in the control group. However, EVT tended to be more effective in patients over 70 years old and in patients with NIHSS ≥10, concluding best medical management might be the better treatment option in patients with a mild deficit (NIHSS <10). EVT seemed to be safe, with only 3.9% of patients in the interventional arm having sICH within 3 days of the procedure.95

Outcome

Predictors of outcome in PCI are less clearly defined than in ACI. Observational studies, systematic reviews, and meta-analysis of the literature61,77,79,81,89,91 as well as 2 RCTs67,95 have shown EVT can improve outcomes in select patients with acute BAO. Multiple variables have been investigated to predict good outcome in patients with BAO. Analysis of the BASIC registry found patients ≥75 years with BAO had an increased risk of poor outcome, yet 22% did achieve good outcome.69 A multivariate analyses of a retrospective case series demonstrated that time to reperfusion beyond 6 hours reduced the chances of a good outcome by half (OR, 0.47; 95% CI, 0.23–0.95) and risk for death was reduced by >80% if collaterals were present (OR, 0.16; 95% CI, 0.03–0.87) and if recanalization was successful (Thrombolysis in Cerebral Infarction 2b–3) (OR, 0.19; 95% CI, 0.05–0.78).71

Unfavorable outcome was reported in 100% of patients with sICH postintervention.71 In a separate retrospective case series, multivariate logistic regression indicated that only smoking (OR, 2.61; 95% CI, 1.23–5.56), low baseline NIHSS (OR, 1.09; 95% CI, 1.04–1.13), and successful reperfusion status (OR, 10.80; 95% CI, 1.36–85.96) were associated with good outcome in patients with PCI who received EVT.72 Meanwhile, a multivariate analysis of a retrospective study of consecutive patients with BAO confirmed that PC collateral score (OR, 1.69; 95% CI, 1.10–2.60) and NIHSS (OR, 0.84; 95% CI, 0.77–0.93) remained the only independent predictors of favorable outcomes.73 Similarly, high pc-ASPECTS and BATMAN scores on pretreatment CT scan have been shown to be predictors of good outcome in some studies but not in others.65,70,74 However, using the BASILAR prospective registry, it was demonstrated that patients with BAO and pc-ASPECTS ≥5 benefited from EVT.99

Discussion

Despite the paucity of evidence, societal guidelines have outlined recommendations for the use of EVT in PCI.48,96 The American Heart Association (AHA) guidelines report EVT for select patients with acute BAO may be reasonable (AHA class IIb, level C–LD).96 Although the AHA recommends EVT within 24 hours in select patients with LVO in the AC, the recommendation is limited to patients treated within 6 hours from symptom onset for PCI.96 One may wonder if this is appropriate given the devastating outcomes in patients with BAO in the absence of treatment. Supporting AHA recommendations, poor outcome was reported in patients with severe stroke treated beyond 9 hours in the BASICS study.69 Meanwhile, in the ENDO-STROKE study, no association was seen between time to treat and clinical outcome; however, there was a trend towards worse outcome after 9 hours from onset of symptoms.25 However, the BASILAR registry concluded that EVT administered within 24 hours of estimated occlusion was associated with better functional outcomes and reduced mortality.46 The Society of Neurinterventional Surgery (SNIS) guidelines did not include the same time limitation and instead recommended use of perfusion imaging to select appropriate candidates.88,70 In addition, given that patients with PCI often have a waxing and waning pro-drome, the SNIS guidelines further recommend labeling time of stroke onset to the most recent cluster of symptoms.48

In the absence of EVT, BAO has a mortality rate of 86%63,76 and a 13% rate of good outcome.100 While the evidence demonstrates clear benefit of MT for LVO in ACI, similar high-level evidence is lacking for PCI. Nonetheless, given the potential for such debilitating outcomes, recent guidelines outline similar treatment strategies with IVT and EVT in both circulations. Extrapolating from the high level of evidence for
EVT in the AC, there seems to be a presumption of benefit for thrombectomy in BAO, leading to a loss of equipoise when physicians are presented with the opportunity to enroll patients into an RCT investigating MT in acute BAO.

Further constraints to enrolling patients with BAO into clinical trials are inherent in the low incidence of the disease (196–4% of all ischemic strokes) and the ambitious clinical presentations, which can lead to delays in diagnosis. Patients with PCI generally arrive later to the hospital and case presentations, which can lead to delays in diagnosis. Patients with PCI. Despite these limitations, this review of the literature suggests recalibration of the BA is an important predictor of improved functional outcome and survival. 56,79,89,91,103 Although mortality remains high and similar to patients who do not receive endovascular treatment, outcomes can be favorable in approximately 30%–60% of patients who receive EVT. In this endovascular era, RCT assessing the best management for BAO are fraught with deterrents to enrollment; perhaps the loss of equipoise embodies the critical position of these patients.

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Appendix Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberta R. Novakovic-White, MD</td>
<td>The University of Texas Southwestern Medical Center</td>
<td>Designed and conceptualized article; analyzed data; drafted manuscript for intellectual content</td>
</tr>
<tr>
<td>Juan Marie Corona, MD</td>
<td>The University of Texas Southwestern Medical Center</td>
<td>Literature review; major role in acquisition and analysis of data from review of literature</td>
</tr>
<tr>
<td>Jonathan A. White, MD</td>
<td>The University of Texas Southwestern Medical Center</td>
<td>Interpreted the data; revised manuscript for intellectual content</td>
</tr>
</tbody>
</table>

References

Data available from Dryad (references 61-103): doi.org/10.5061/dryad.wp8s9bmm
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