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Cerebrovascular Disease and Stroke (S Silverman, Section Editor)

Vertebral Artery Stenosis

Daniel C. Brooks, MD[1]
Joseph L. Schindler, MD[2,*]

Address
[1]Department of Internal Medicine, Division of Neurology, Stamford Health Medical Group and Stamford Hospital, Stamford, CT, USA
[*,2]Department of Neurology, Yale University School of Medicine, P.O. Box 208018, New Haven, CT, 06520-8018, USA
Email: Joseph.Schindler@yale.edu

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Abstract

Purpose of review Vertebral artery stenosis is a common condition associated with a very high risk of stroke. The goal of this review is to summarize the pathophysiology and natural history of vertebral artery stenosis and to evaluate the efficacy of medical and endovascular therapies.
Recent findings Early and aggressive initiation of medical care combined with advancements in antithrombotic and lipid-lowering therapies has substantially reduced the risk of stroke due to vertebral artery stenosis. Endovascular therapy does not appear to be beneficial with extracranial vertebral artery stenosis and appears harmful with intracranial vertebral artery stenosis.
Summary Risk of stroke due to symptomatic vertebral artery stenosis can be significantly reduced with implementation of standardized best medical therapy protocols focusing on ultra-early dual antiplatelet therapy, high-intensity statin therapy ± novel lipid-lowering agents, and aggressive risk factor control. Endovascular therapy with angioplasty and stenting is not likely to play a significant role in treatment.

Introduction

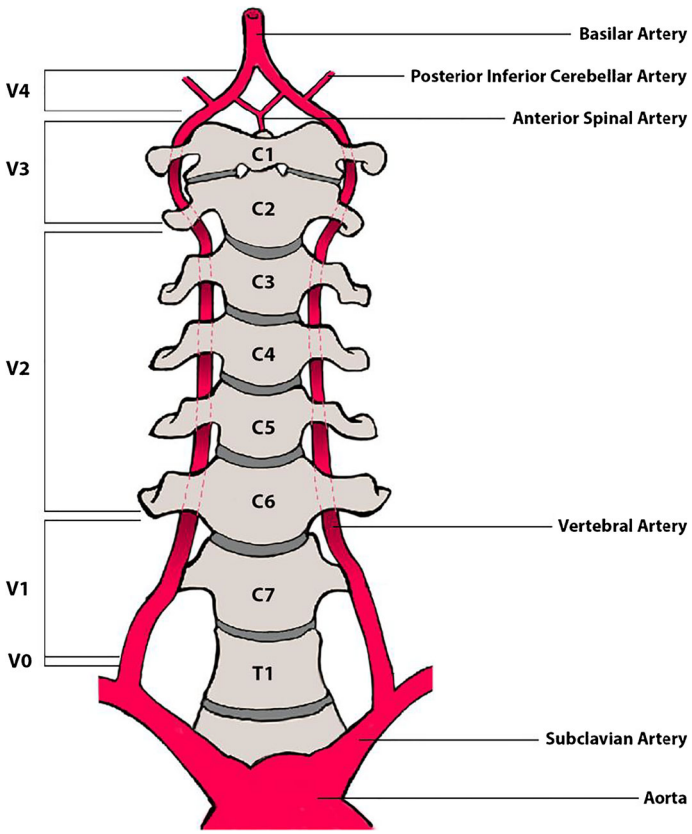
About 20% of ischemic strokes occur in the posterior circulation, a large cerebrovascular territory supplied by the vertebral arteries (VAs) which includes the brainstem, cerebellum, and inferior/posterior cerebral hemispheres [1]. Vertebrobasilar stenosis—of which atherosclerosis is by far the most common cause—is responsible for about 25–33% of ischemic strokes in the posterior circulation [2, 3]. Symptomatic VA stenosis is a high-risk condition compared with other ischemic stroke subtypes, associated with a perhaps threefold higher risk of recurrent stroke than small vessel disease or cardioembolism [4]. Multiple factors increase risk of stroke with VA stenosis. First, atherosclerosis appears to be a higher risk condition than other causes of VA stenosis such as dissection [4, 5]. Second, intracranial involvement of the disease process, whether atherosclerosis or dissection, is typically more

severe than extracranial involvement [4]. Third, the risk of ischemic stroke increases with the degree of VA stenosis. In patients with atherosclerosis, VA stenosis > 50% is associated with a much higher risk of ischemic stroke than stenosis < 50% or no stenosis at all [6]. Fourth, ischemic stroke risk is highest early after an initial ischemic event, whether atherosclerosis or dissection is the etiology [7, 8].

Stroke prevention can be considered in the context of urgency and medical versus interventional treatment. Emergently, acute VA occlusion is typically treated medically with thrombolysis, while mechanical thrombectomy is infrequently performed [9••]. Concerning urgent treatment, recent research on management of VA stenosis has evaluated both medical and endovascular therapies, similar to the approach taken with carotid artery stenosis. VA and carotid artery disease share certain features such as susceptibility to atherosclerosis and dissection and a similarly high risk of ischemic stroke which increases with degree of stenosis [5, 6]. But whereas early studies demonstrated benefit of carotid revascularization, no early trials were performed evaluating revascularization procedures for VA stenosis [4]. Over the past decade, multiple such trials have been conducted, with disappointing results for angioplasty and stenting. Medical therapy, on the other hand, has improved tremendously with emphasis on early initiation, standardization, and optimization of treatment along with antithrombotic and lipid-lowering therapeutic advances. This review article will assess both medical and endovascular management of VA stenosis and will also discuss VA anatomy, pathology, and imaging, as well as presenting symptoms and signs typical of vertebrobasilar ischemia.

Anatomy of the vertebral arteries

The VAs and their segments are shown in the figure.



The paired VAs supply blood to the upper part of the spinal cord, brainstem, cerebellum, occipital lobes, inferomedial temporal lobes, most of the thalami, the posterior part of the corpus callosum, and occasionally part of the posterior limbs of the internal capsules [1]. Traditionally, each VA is divided into 4 anatomical segments, labeled V1-V4. The ostium of the VA where it arises as the first branch off the subclavian artery (or rarely off the arch of the aorta) is sometimes labeled V0 [10, 11]. The first segment (V0/V1) extends from the ostium until it enters the sixth or fifth cervical vertebra (C6/C5) transverse foramen (TF) [1, 10, 11]. V2 courses through each subsequent TF including the TF of C2 [10, 11]. This alternating intraforaminal and interforaminal course exposes V2 to bony compression and dissection [10, 12]. V3 is the last extracranial segment and travels vertically through the TF of C1 and then loops posterormedially to penetrate the dura superior to C1 [10, 11]. This looping course renders V3 susceptible to dissection [1, 12]. The intracranial segment V4 extends alongside the anterolateral medulla and then joins the contralateral VA to form the basilar artery anterior to the pontomedullary junction [1, 10, 11]. Critical arterial branches arise from V4, including the anterior spinal artery, the posterior inferior cerebellar artery (PICA), and small medullary perforating arteries; posterior spinal arteries also may arise from V4 [10, 11].

Conditions causing vertebral artery stenosis

About 20% of ischemic strokes occur in the posterior circulation [1]. Large artery atherosclerosis is by far the most common etiology of vertebrobasilar stenosis and, varying with race and ethnicity, causes about 25–33% of all ischemic strokes [1–4, 13]. Small vessel disease and cardioembolism combine to cause another 50% of ischemic strokes, about 3% are of other determined etiology, and the remainder is of undetermined etiology after an initial diagnostic evaluation [2, 3]. Occult atherosclerosis and dissection frequently cause cryptogenic strokes [3]. Common conditions causing VA stenosis are discussed below.

- Atherosclerosis frequently affects the most proximal and most distal VA segments: V0/V1 more in white men and V4 more in white women and individuals of black and East Asian descent [1, 11, 14–16]. VA stenosis causes ischemia via multiple mechanisms, but atherosclerotic plaque rupture and distal embolization (thromboembolism) are the most common [1, 16, 17]. Plaque rupture and thrombosis can also occlude arterial branches off V4, while VA stenosis causing hemodynamic compromise (hypoperfusion) is thought to be responsible for only about 3% of posterior circulation ischemia cases [1, 16, 18].

Atherosclerotic VA stenosis carries a high risk of stroke relative to other ischemic stroke subtypes [4, 7]. If patients do not receive secondary prevention medications after a posterior circulation ischemic stroke or TIA, the estimated 90-day risk of stroke is 33.3% with intracranial vertebrobasilar stenosis > 50%, 16.2% with extracranial VA stenosis > 50%, and 7.2% without vertebrobasilar stenosis (such as patients with nonstenotic VA disease, small vessel disease, or cardioembolism) [4]. Initiation of basic secondary prevention medications

reduced the 90-day risk of stroke from 33.3 to 13.9% in patients with only intracranial vertebrobasilar stenosis, from 24.6 to 9.6% in patients with extracranial or intracranial vertebrobasilar stenosis, and from 7.2 to 2.8% in patients without any stenosis [4, 6, 15]. Other studies utilizing basic medical therapy reported similar results [19, 20].

Atherosclerotic vertebral and carotid stenosis share many characteristics. First, risk of stroke is similarly high in both conditions [4, 21]. In one study of patients with symptomatic carotid stenosis who did not receive secondary prevention medications, the 90-day risk of ischemic stroke or TIA was 29% [22]. Second, stroke risk increases as the degree of stenosis increases [4]. VA stenosis > 50% is associated with a dramatic rise in stroke risk compared with patients who have stenosis < 50% or no stenosis at all [4, 6, 15]. Lastly, the risk of stroke is highest immediately after a stroke or TIA [4, 6, 15, 21].

- An arterial dissection is characterized by a mural hematoma in the arterial wall due to an intimal tear or to direct hematoma formation from rupture of the arterial wall vasa vasorum [8]. The hematoma can expand inward toward the intima or outward toward the adventitia, resulting in stenosis, pseudoaneurysm formation, or both [8]. Cervical artery dissections (CADs) occur at a rate of about 2.7 per 100,000 individuals per year and can arise spontaneously or due to trauma [8]. Twenty-seven to 53% of CADs occur in the VAs, with the V2 and V3 segments more commonly affected than V1 [1, 5, 8, 12, 23, 24]. In 13–16% of cases, multiple CADs occur [8]. CADs cause 1–2% of all ischemic strokes but 10–25% in young patients, with a mean age of dissection of about 45 years [5, 8, 24]. Approximately 2.5–7% of patients suffer an ischemic stroke during long-term follow-up after CAD, typically due to thromboembolism rather than hypoperfusion, with risk of stroke highest shortly after dissection occurs [1, 5, 8, 23, 24]. Ten percent of vertebral CADs extend intracranially, and roughly 1% of CADs cause subarachnoid hemorrhage [1, 8]. Long-term stability or resolution of arterial abnormalities is typically achieved within 3.5 months [8]. Upon follow-up imaging after 3–6 months, 25–40% of CADs are occluded, 33–46% have no obvious abnormalities, and the remainder have residual stenosis or pseudoaneurysm formation [5, 8, 24, 25]. Risk of recurrent CAD is about 1% overall, but in certain groups—such as patients with a connective tissue disorder or fibromuscular dysplasia—risk is higher [8, 24].
- Intracranial artery dissections (ICADs) constitute 11% of cervicocerebral dissection cases in patients of European descent, but in Asian patients, ICADs appear much more common [12, 26]. About 60–75% of spontaneous ICADs involve the VA V4 segment [27]. Distinguishing between V3 and V4 dissection can be challenging, as 10% of V3 dissections extend into the V4 segment [1]. ICAD carries a high risk of hemorrhage, as intracranial arteries have fewer elastic fibers in the media, a paucity of adventitial tissue, and no external elastic lamina compared with cervical arteries [26]. Fifty to 66% of patients with spontaneous V4 dissection present with intracranial hemorrhage [26, 27]. Endovascular therapy must be emergently pursued in these patients, as recurrent hemorrhage occurs in about 40–70% of

patients without therapy [26, 27]. In the one-third of patients presenting with V4 dissection without hemorrhage, lesions stabilize or heal in about 60% of patients within 3–6 months [27].

- The left VA's diameter is larger than the right's in 50% of cases [1, 10]. In 10–25% of individuals, one VA (usually the right VA) is markedly smaller than the other, a condition termed hypoplasia [1, 10]. When a VA is hypoplastic, it may terminate early (such as in PICA), and thus, the contralateral or dominant VA serves as a "functional basilar artery" and contributes all or nearly all blood flow to the basilar artery [10, 28]. Hypoplasia may increase risk of ischemic stroke [29].
- There are more than 200 known causes of ischemic stroke [3]. Most of these etiologies are quite rare and beyond the scope of this review. However, the following conditions can affect the extracranial and/or intracranial VAs and may warrant further investigation by the reader: dolichoectasia, autoimmune arteriopathies such as temporal arteritis and primary angiitis of the central nervous system (PACNS), fibromuscular dysplasia, reversible cerebral vasoconstriction syndrome (RCVS), posterior reversible encephalopathy syndrome (PRES), eclampsia, illicit drug-associated vasculopathy (which may overlap with RCVS), subclavian steal syndrome, and rotational VA occlusion (bow hunter's syndrome, often associated with cervical spondylosis).

Clinical presentation with vertebral artery disease

VA stenosis can lead to ischemic strokes throughout the posterior circulation, causing a wide array of symptoms and examination findings [30]. As a result, vertebrobasilar ischemia can be difficult to localize and challenging to diagnose [1, 31]. Misdiagnosis may occur in as many as 37% of patients [31]. It is therefore critical to employ a comprehensive approach to each patient, as symptoms, examination findings, and imaging when assessed in isolation have low sensitivity, low specificity, or both [1].

In a tertiary referral center registry of 407 consecutive patients with a posterior circulation stroke or TIA, the most common symptoms were dizziness (47%), unilateral limb weakness (41%), dysarthria (31%), headache (28%), and nausea or vomiting (27%) [30]. About 60–80% of patients with VA dissection (extracranial or intracranial) have headache, neck pain, or both [24, 26, 32]. The most common examination findings with vertebrobasilar ischemia are unilateral limb weakness (38%), gait ataxia (31%), unilateral limb ataxia (30%), dysarthria (28%), and nystagmus (24%) [30].

Imaging of the vertebral arteries

Brain imaging

Computed tomography (CT) reliably detects hemorrhage and frequently detects space-occupying lesions, but the sensitivity of CT for detecting acute posterior circulation ischemic stroke is only about 42% [33, 34]. Magnetic

resonance imaging (MRI) with diffusion-weighted imaging (DWI) is the gold standard for detecting ischemic strokes; MRI susceptibility sequences also reliably detect intracranial hemorrhage [34]. Importantly, MRI can be used to estimate if an ischemic stroke is hyperacute, acute, subacute, or chronic [35, 36]. However, issues with patient safety, tolerance, and contraindications may limit the use of MRI in up to 40% of patients [34, 37]. Additionally, the false-negative rate of MRI-DWI with acute ischemic stroke in the vertebrobasilar circulation is 12–30% [38, 39]. Strokes missed by MRI-DWI are typically acute (imaging obtained within 24 h of symptom onset), located in the brainstem, and small (less than 1 cc in volume) [38, 39]. False-negative MRI-DWI is rare when imaging is performed more than 24 h after symptom onset [39].

Arterial imaging

Cerebral catheter angiography (CCA) is the gold standard for evaluation of the VAs and permits therapeutic intervention, but CCA is invasive and carries an approximately 1% risk of stroke [13, 17, 40, 41]. Therefore, noninvasive arterial imaging is always first-line except in unusual circumstances [17].

Contrast-enhanced magnetic resonance angiography (CE-MRA) and computed tomography angiography (CTA) are noninvasive first-line imaging modalities to visualize the VAs, with time of flight MRA (TOF-MRA; i.e., MRA without contrast) second-line and duplex ultrasonography (DUS) third-line. The sensitivities of CTA, CE-MRA, and DUS for detecting VA stenosis are approximately 100%, 93.9%, and 70.2%, respectively, with specificities 95.2%, 94.8%, and 97.7%, respectively [42]. TOF-MRA has 100% sensitivity and 97.4% specificity for detecting intracranial VA stenosis, but only 53.8% sensitivity and 88% specificity for detecting extracranial VA stenosis due to anatomical impediments and motion artifact [42]. TOF-MRA can be helpful in patients for whom intravenous access is challenging as no contrast is needed [42].

MRI/MRA and CTA are first-line imaging modalities to diagnose dissection [8, 26]. Common angiographic findings of dissection are a long tapered stenosis, a tapered occlusion, a dissecting aneurysm, a luminal flap, a false lumen, or a mural hematoma [8, 26]. A specific sign for dissection is T1-weighted MRI with fat saturation showing an enlarged artery with a crescent-shaped rim of hyperintense or isointense signal (the hematoma) surrounding a small lumen [8, 26].

Perfusion imaging

Computed tomography perfusion (CTP) and magnetic resonance perfusion (MRP) accurately distinguish irreversibly damaged tissue (core infarct) from ischemic tissue which might be salvaged with reperfusion therapy (ischemic penumbra) [34]. CTP and MRP are integral in the evaluation of large vessel *anterior circulation* stroke [43–46]. CTP and MRP can accurately identify posterior circulation core infarct and penumbra but are not widely employed in the evaluation of vertebrobasilar stroke [9, 29, 47–50].

Treatment of symptomatic vertebral artery stenosis or occlusion

Table 1 summarizes the findings from trials and recommendations from guidelines and experts regarding treatment of symptomatic VA stenosis or occlusion. This is discussed in more detail below.

Table 1. Findings and recommendations for the treatment of symptomatic VA stenosis or occlusion

Emergent treatment of acute VA occlusion	
Medical	• Acute VA occlusion is treated with thrombolysis up to 4.5 h from time last at neurological baseline [9••] • This time window may be expanded in carefully selected patients [9••, 36, 45]
Endovascular	• MT for acute VA occlusion has not been assessed in any large clinical trials • BEST trial included 12 patients with acute intracranial VA occlusion and did not utilize perfusion imaging [28•] • Among the 12 patients, BMT was associated with better outcomes than MT [28•] • Guidelines suggest MT for acute VA occlusion might be attempted in carefully selected patients within 6 h of symptom onset [9••]
Urgent endovascular treatment of symptomatic VA stenosis	
VIST trial [13•]	• Nonsignificant benefit of angioplasty and stenting over BMT for combined extracranial and intracranial atherosclerotic VA stenosis • These findings are questionable as the stent group received a more aggressive medication regimen than the BMT group
VAST trial [51]	• No evidence of benefit with stenting for either extracranial or intracranial atherosclerotic VA stenosis
VISSIT trial [52]	• Substantial harm was associated with intracranial arterial stenting for atherosclerotic stenosis • Number of patients with VA stenosis was not defined
SAMMPRIS trial [53–55]	• Substantial harm was associated with intracranial arterial stenting for atherosclerotic stenosis, including in the 60 patients enrolled with intracranial VA stenosis
CAVATAS trial [14]	• No evidence of benefit with angioplasty alone for extracranial atherosclerotic VA stenosis
Vertebral artery dissection	• For extracranial VA dissection, stenting should not be routinely considered, even with VA occlusion [8, 25] • For intracranial VA dissection, endovascular therapy is indicated if hemorrhage is present; medical therapy is indicated if hemorrhage is not present [26, 27]
Medical treatment of symptomatic VA stenosis	
Antithrombotic therapy	• Antiplatelet therapy should be utilized [9, 19] • 21 days of aspirin-clopidogrel initiated within 12–24 h after TIA or minor ischemic stroke reduces risk of ischemic stroke by 34% compared with aspirin [56, 57, 58•.] • Ticagrelor may soon replace clopidogrel in secondary stroke prevention [59], (ClinicalTrials.gov number, NCT03354429)
Lipid-lowering therapy	• Routinely monitor serum LDL [60, 61] • Highest-intensity statin therapy reduces LDL by 55–60% and reduces stroke risk by 30% in patients with large artery atherosclerosis [62, 63] • If serum LDL > 70 mg/dl despite statin therapy, adding a PCSK9 inhibitor or ezetimibe is estimated to reduce ischemic stroke risk by an additional 21–27% [64–67]
Hypertension	• In neurologically stable patients, long-term BP goal < 140/90 is indicated, with more aggressive BP goal < 130/80 possibly beneficial [9, 68, 69]
Long-term risk factor control	• Address smoking, diabetes, obesity, exercise, nutrition, illicit drug use, and excessive alcohol use [9, 53, 70]
Vertebral artery dissection	• For extracranial VA dissection, the CADISS trial found no difference in rates of ischemic stroke, arterial recanalization, or residual arterial abnormalities between antiplatelet therapy and anticoagulation [5••] • For intracranial VA dissection without hemorrhage, antiplatelet therapy is probably indicated over anticoagulation [26]

Chart summarizing treatment of symptomatic VA stenosis or occlusion. *BMT* best medical therapy, *BP* blood pressure *LDL* low-density lipoprotein, *MT* mechanical thrombectomy, *PCSK9* proprotein convertase subtilisin–kexin type 9, *TIA* transient ischemic attack, *VA* vertebral artery

Emergent treatment

Medical management of ischemic stroke caused by acute VA occlusion is centered on thrombolysis with recombinant tissue plasminogen activator (TPA), the use of which is strongly endorsed by guidelines up to 4.5 h from time last at neurological baseline, and in carefully selected patients this time, window may be expanded [9, 36, 45].

Unlike with acute anterior circulation large vessel occlusion, mechanical thrombectomy (MT) for acute VA occlusion has not been assessed in any large randomized controlled trials (RCTs) [9, 43, 44, 46]. The recently published BEST trial evaluated MT in patients with acute basilar artery occlusion and included 12 patients with intracranial VA occlusion resulting in no flow to the basilar artery (functional basilar artery occlusion) [28•]. Patients with actual basilar artery occlusion benefited from MT, but the patients with VA occlusion had worse outcomes with MT than with medical therapy alone. Guidelines suggest that MT might be attempted in carefully selected patients with VA occlusion in whom treatment can be initiated within 6 h of symptom onset, but there is little data to support this recommendation, and MT for acute VA occlusion is rarely performed [9, 70].

Urgent and "elective" endovascular therapy

Symptomatic VA and carotid artery stenosis are associated with a high risk of ischemic stroke [1, 4, 6, 15, 21, 22]. But whereas RCTs in the 1990s and 2000s demonstrated benefit of surgical and endovascular carotid revascularization, no such trials assessing VA revascularization were conducted during this period [4, 71]. Due to anatomical challenges, surgical intervention for VA stenosis is not typically considered [71]. Early case series suggested that angioplasty and stenting of proximal VA segments was safe and possibly beneficial, while endovascular therapy of distal VA segments (V3/V4) carried a 10% risk of periprocedural stroke [72–74]. RCTs assessing VA stenting soon followed and are reviewed below.

The VIST trial (Vertebral Artery Ischemia Stenting Trial) randomized 182 patients with a TIA or nondisabling stroke due to atherosclerotic VA stenosis 50–99% to best medical therapy (BMT) plus angioplasty and stenting versus BMT alone [13•]. Forty-eight patients with extracranial (nearly all in the V0/V1 segment) and 13 patients with intracranial VA stenosis underwent stenting. Within 30 days, 1/48 patients after extracranial stenting and 2/13 after intracranial stenting had a stroke [13, 75]. After 3.5 years, stenting was nonsignificantly favored over BMT (5 strokes in the stent group, 12 strokes in the BMT group; HR 0.40; 95% CI 0.14–1.13, $P = 0.08$). Unfortunately, medical therapy was not balanced between the groups: 1 month after enrollment, 57% of patients in the stent group were taking dual antiplatelet therapy (DAPT) with aspirin-clopidogrel compared with 33% in the medical group [13, 75]. Thus any (nonsignificant) benefit observed with stenting may have been due to more effective medical therapy than to stenting itself [75].

The VAST trial (Vertebral Artery Stenting Trial) randomized 115 patients with a TIA or nondisabling stroke in the previous 6 months due to atherosclerotic VA stenosis 50–99% to BMT plus angioplasty and stenting versus BMT alone [51]. Eighty-three percent of patients had extracranial VA stenosis, nearly all in the V0/V1 segment. The median time from qualifying event to randomization was 25 days; about one-third of patients were randomized within 2 weeks of their index event. Unlike in VIST, medical therapy was fairly well-balanced between the two groups. Within 30 days of treatment being initiated, 3/57 patients (1/48 with extracranial stenosis, 2/9 with intracranial stenosis) in the stent group and 1/58 patients (1/48 with extracranial stenosis, 0/10 with intracranial stenosis) in the medical group had a vertebrobasilar stroke. After 3 years 7/57 (12%),

patients in the stent group and 4/58 (7%) in the BMT group had a vertebrobasilar stroke. Post hoc analysis showed no suggestion of benefit in patients with either extracranial or intracranial VA stenosis.

The VISSIT trial (Vitesse Intracranial Stent Study for Ischemic Stroke Therapy) randomized 112 patients with a recent stroke or TIA attributable to intracranial arterial stenosis 70–99% to BMT plus balloon-expandable stent versus BMT alone [52]. The mean time from qualifying event to randomization was approximately 2 weeks in both groups. No information is currently available concerning the number of patients enrolled with VA stenosis. Medical management was well-balanced between the two groups and was much more aggressive than in VIST or VAST: 90 days of DAPT with aspirin-clopidogrel, antihypertensive therapy with systolic blood pressure (BP) goal < 140 mmHg, and statin therapy with low density lipoprotein (LDL) goal < 100 mg/dl. Within 30 days, 25.8% (17.2% ischemic stroke, 8.6% hemorrhage) of patients in the stent group and 5.7% (all ischemic strokes) of patients in the medical group had a stroke. After 1 year, 34.5% of patients in the stent group and 9.4% of patients in the medical group had a stroke in the territory supplied by the qualifying intracranial artery [52, 76].

The SAMMPRIS trial (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) randomized 451 patients with a recent stroke or TIA caused by intracranial arterial stenosis 70–99% to BMT plus Wingspan stent versus BMT alone [53–55]. Sixty of the 451 patients had VA stenosis [55•]. The median time from qualifying event to randomization was 7 days. Medical management was well-balanced between the two groups and was very aggressive: 90 days of DAPT with aspirin-clopidogrel, antihypertensive therapy with systolic BP goal < 140 mmHg, statin therapy with LDL goal < 70 mg/dl, and emphasis on smoking cessation, diabetes control, weight loss, and exercise. Within 30 days, 5.3% of patients in the medical group and 14.7% of patients in the stent group had an ischemic or hemorrhagic stroke [53]. After 2 years of follow-up for the 60/451 patients enrolled with VA stenosis, 9.5% of patients in the medical group and 21.1% of patients in the stent group suffered an event (a composite of ischemic events, hemorrhagic events, and death) [55•]. Subgroup analysis showed no benefit of stenting over medical therapy in any subgroup identified, including degree of stenosis, randomization before or after 7 days of the qualifying event, antithrombotic therapy when the qualifying event occurred, or symptoms of hypoperfusion [55•].

The CAVATAS trial (Carotid and Vertebral Artery Transluminal Angioplasty Study) randomized 16 patients (15 with V0/V1 stenosis) with a stroke or TIA within the previous 6 months caused by VA stenosis 50–99% to BMT plus angioplasty versus BMT alone [14]. After 4.7 years, there were no vertebrobasilar strokes in either treatment group.

A meta-analysis of RCTs evaluating stenting for VA stenosis was published recently [77]. Stenting for extracranial VA stenosis was found to be nonsignificantly favored over medical therapy, while stenting for intracranial VA stenosis had a hazard ratio of 1.06 (0.46–2.42) compared with medical therapy. These findings are surprising and seem to conflict with the results of the RCTs.

Our conclusions regarding stenting versus medical therapy for atherosclerotic VA stenosis: In our opinion, the RCTs showed no evidence of benefit with extracranial VA stenting when medical therapy was balanced

between stenting and medical groups, while intracranial VA stenting was associated with *substantial* harm compared with medical therapy. Multiple editorials reached similar conclusions [55, 75, 76, 78, 79]. Considering the reasonable safety profile of *extracranial* VA stenting, if patients with extracranial VA stenosis > 50% experience recurrent ischemic events despite optimal medical therapy then stenting could be considered. Based on the results above, however, it is not clear if *intracranial* VA stenting should be considered at all, even in the setting of symptoms related to hypoperfusion as these patients achieved no clear benefit from stenting in SAMMPRIS [55•].

VA stenting trials likely failed for multiple reasons. First, VA stenosis typically causes stroke via thromboembolism, not hypoperfusion [1, 16]. Therefore, antiplatelet therapy to prevent thrombosis and statin therapy to stabilize the atherosclerotic plaque would likely be more effective than stenting open the VA to increase blood flow [79]. But as discussed above, patients with intracranial VA stenosis causing hypoperfusion-related symptoms did not benefit from stenting either [55•]. Second, intracranial VA stenting likely caused periprocedural strokes by "snow-plowing" plaque into critical arterial branches off the V4 segment [76]. Third, the weak supportive tissue of intracranial arteries likely contributed to the high rates of hemorrhage observed with intracranial stenting [26, 52, 53]. Lastly, as will be discussed, medical therapy has improved significantly.

Medical therapy

"Best medical therapy" (BMT) protocols incorporating an ultra-early, standardized, and maximal medication approach have substantially lowered stroke risk over the past decade. SAMMPRIS instituted a very aggressive BMT protocol and reported that after 2 years, only 9.5% of patients enrolled with symptomatic intracranial VA stenosis had an ischemic event, a hemorrhagic event, or death [53, 55]. Similar historical cohorts had a 90-day stroke rate of 33.3% without medical therapy and 13.9% with basic medical therapy [4]. A BMT protocol for symptomatic extracranial carotid artery stenosis reduced the risk of stroke or TIA from 29 to 2.5% prior to patients undergoing endarterectomy [22]. Another BMT protocol reduced the 90-day risk of ischemic stroke for all ischemic stroke subtypes from 12 to 20% in historical cohorts to 3.7% [7]. Several components of a BMT regimen bear special mention.

- Because risk of stroke is highest in the first 10 days after an ischemic event, therapy should be initiated as early as possible, preferably within 12–24 h of symptom onset [7, 56, 57, 80]. Second, antiplatelet therapy rather than anticoagulation should be prescribed for large artery stenosis [9, 19]. In patients presenting within 12–24 h after a minor ischemic stroke or TIA, 21 days of DAPT with aspirin-clopidogrel were found to lead to a significantly lower rate of ischemic stroke than aspirin alone, 5.2% versus 7.8% (HR, 0.66; 95% CI, 0.56–0.77; $P < 0.001$) [56, 57, 80]. The benefit of DAPT accrues early after ischemic stroke or TIA, while the risk of hemorrhage increases after 21 days of DAPT without much benefit in reduction of ischemic stroke risk [56, 80, 81]. Guidelines now strongly recommend DAPT with aspirin-clopidogrel for

21 days in patients who present within 24 h of a minor ischemic stroke or TIA [9••].

Clopidogrel requires conversion to an active metabolite by cytochrome P450 isoenzymes to exert an antiplatelet effect, and in CHANCE, 58.8% of patients were carriers of *CYP2C19* loss-of-function alleles, which strongly predict clopidogrel nonresponsiveness [81]. In these carriers, clopidogrel demonstrated no benefit in stroke reduction [81]. A recent phase II trial found DAPT with ticagrelor-aspirin to be superior to clopidogrel-aspirin after a minor stroke or TIA, particularly in patients with *CYP2C19* loss-of-function alleles, with significantly reduced platelet activity and significantly lower risk of stroke in patients with large artery atherosclerosis [58•]. The combination of ticagrelor-aspirin versus aspirin alone after ischemic stroke or TIA is being evaluated in the recently completed THALES trial (ClinicalTrials.gov number, NCT03354429).

- Hyperlipidemia is associated with an overall 28% increased risk of ischemic stroke and is therefore a key target in BMT protocols [82]. Serum LDL should be routinely monitored, as ischemic stroke risk increases with LDL, while therapies which reduce LDL reduce stroke risk [59, 60]. Highest-intensity statin therapy reduces LDL by 55–60% and exerts a tremendous effect on patients with large artery atherosclerosis, reducing stroke risk by about 30% compared with placebo [61, 62]. In patients with symptomatic large artery atherosclerosis who have LDL > 70 mg/dl despite maximally tolerated statin therapy, addition of a proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitor or ezetimibe should be strongly considered [63•]. PCSK9 inhibitors reduce LDL by 50–60% and decrease risk of ischemic stroke by 25–27% when added to statin therapy [65, 66]. Ezetimibe was found to reduce ischemic stroke risk by 21% when added to statin therapy, but its effect on LDL is less than that of PCSK9 inhibitors [64]. Aggressive reduction of LDL is safe, well-tolerated, and extremely beneficial for patients of all ages, including the elderly [63, 83].
- In neurologically stable patients after an ischemic stroke or TIA, it is reasonable to initiate antihypertensive therapy if BP > 140/90 mmHg [9, 68]. Some patients may benefit from a long-term BP goal < 130/80 mmHg [68]. However, a subset of patients with vertebrobasilar stenosis might be susceptible to hypoperfusion with very aggressive BP intervention, so cautious medication adjustments and careful patient monitoring are warranted [67].

Therapy for extracranial and intracranial arterial dissection

Multiple studies evaluating antithrombotic therapy for cervical artery dissection (CAD), including the recently published RCT CADISS, have found no difference in rates of ischemic stroke, arterial recanalization, or residual arterial abnormalities between various regimens of antiplatelet therapy and anticoagulation [5, 24, 84–87]. If the V3 segment of the VA is dissected, antiplatelet therapy may be the safer choice due to the possibility of intracranial extension of the dissection [1, 8, 26]. Medical therapy alone tends to suffice for vertebral CAD, even in the setting of arterial occlusion; therefore, stenting should not be routinely considered [8, 25].

A majority of patients with intracranial VA dissection present with hemorrhage and are typically treated urgently with endovascular therapy [26, 27]. In patients presenting with V4 dissection without hemorrhage, antithrombotic therapy (usually antiplatelet therapy) is commonly utilized, with endovascular intervention pursued if recurrent ischemic events occur despite medical therapy [26, 27].

Emerging therapies and future directions

Compared with historical cohorts, BMT protocols have substantially reduced stroke risk in patients with VA stenosis. As we move forward, focus should be geared toward ultra-early medical intervention, standardization of care, and maximally tolerated therapy. Antithrombotic treatment continues to improve. But while aspirin-clopidogrel DAPT has proven successful, certain patients might not benefit from clopidogrel, and ticagrelor or another medication may replace it [58•]. The results of the THALES trial (ClinicalTrials.gov number, NCT03354429) will be published soon. Treatment of hyperlipidemia has rapidly evolved as well. High-intensity statin therapy remains first-line, but adjunctive therapy with a PCSK9 inhibitor or ezetimibe will likely become standard of care for high-risk patients [63•]. Stenting of extracranial VA stenosis failed to show benefit, while stenting of intracranial VA stenosis was harmful. As a result, future therapy of VA stenosis is likely to be primarily medical.

Compliance with Ethical Standards

Conflict of Interest
Daniel C. Brooks and Joseph L. Schindler declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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