Vertebrobasilar Insufficiency

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Opinion statement

Vertebrobasilar insufficiency presents with characteristic symptoms and signs due to impaired perfusion of the cerebellum, the brain stem, and the occipital cortex. This may be due to reduced perfusion usually due to atherosclerosis or thromboembolism. Choice of treatment depends on understanding the different underlying pathophysiologic mechanisms. Antiplatelet therapy; reduction of risk factors such as diabetes, hypertension, hypercholesterolemia, and cigarette smoking; and a healthy lifestyle form the first line of management. Systemic anticoagulation in the short term also has a key role in selected cases. In patients with refractory symptoms on maximal medical therapy and underlying focal stenotic lesions, endovascular revascularization using stents and balloon angioplasty may be indicated. Bypass surgery is another option if there are factors that render endovascular therapy unsuitable.

Introduction

Approximately one quarter of ischemic strokes affect the posterior circulation [1,2]. Recent advances in noninvasive diagnostic imaging techniques, such as CT angiography (CTA) and magnetic resonance angiography (MRA), enable evaluation of the extra- and intracranial vertebral artery and the basilar trunk for stenotic lesions. Combined with diffusion/perfusion MRI or perfusion CT, the current stroke imaging protocols evaluate for acute or chronic infarcts with potentially salvageable tissue, together with any underlying arterial stenotic lesions. This enables choice of appropriate treatment strategies for individual patients.

The fundamental principle of treating anterior or posterior circulation stroke has relied on understanding the pathophysiology of different stroke mechanisms. Vertebrobasilar insufficiency (VBI) is due to a mismatch between blood supply and demand to the posterior circulation. The vertebrobasilar circulation is unique in that it is the only arterial system in the human body where two arteries join to form one main arterial trunk. There is also collateral supply through the posterior communicating arteries into the posterior cerebral circulation on many occasions. Atherosclerosis with its underlying risks of thromboembolism is a common cause of VBI followed by other mechanisms. Mechanisms of VBI include the following: atherosclerosis, emboli from artery to artery or from a central source (eg, heart); dissection; subclavian steal syndrome; extravascular compression from cervical spondylosis; arterial vasospasm; migraine; and inflammation (eg, vasculitis). It is important to remember that a proximal steno-occlusive lesion may lead to sluggish blood flow more distally. This predisposes to local thrombus formation that may subsequently embolize downstream. The anatomic and radiologic findings have to be interpreted in close correlation with the clinical presentation to determine the most likely underlying mechanism. Only this would enable an appropriate treatment strategy.

The fundamental principles of stroke management parallel risk reduction strategies advocated in cardiovascular medicine. This includes leading a healthy lifestyle, managing high serum cholesterol/hypertension/hyperglycemia, and cessation of smoking. In most cases antiplatelet agents are commenced, and in selected cases anticoagulation may be beneficial. In patients who have a demonstrable focal stenotic vertebrobasilar lesion with failed maximal medical therapy, consideration should be given to endovascular revascularization (Fig. 1) or bypass surgery. These procedures have their inherent risks and appropriate risk-benefit analyses have to be established. In this article, we present the various treatment options for VBI. We have attempted to outline the medical treatment of vertebrobasilar stroke in the acute, subacute, and chronic situations, followed by endovascular and emerging therapies.

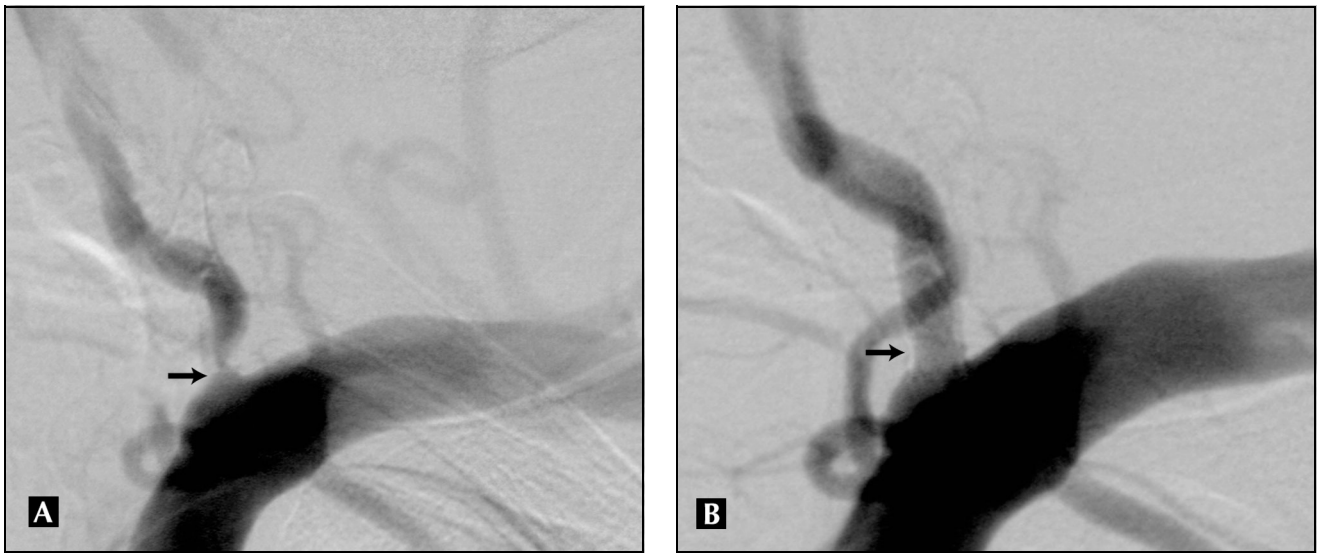

Figure 1. A left subclavian angiogram. **A,** Shows marked focal stenosis in the proximal left vertebral artery (*arrow*). **B,** This has been treated with a stent (*arrow*) followed by balloon angioplasty resulting in obliteration of the stenosis.

Therapy: acute phase

- When patients present with symptoms of posterior circulation transient ischemic attack (TIA) or stroke, an unenhanced cranial CT should be performed immediately or at the latest within the first 24 hours. Perfusion CT or MRI and noninvasive angiography (CTA or MRA of neck vessels and Circle of Willis) are performed depending on local availability. Detection of infarction of brain parenchyma with or without a steno-occlusive arterial lesion is the aim of the diagnostic studies. Clear cut-off in the clinically suspected arterial pedicle is in keeping with an embolus causing the stroke syndrome. If there is an occlusive lesion with potentially salvageable tissue with no hemorrhage, thrombolytic therapy is indicated (see Pharmacologic treatment section). Securing the airway in the presence of 9th or 10th nerve paresis, initiating intravenous (IV) fluid rehydration, and treatment of hypertension are key first-line therapies in the acute setting.
- If the diagnosis of TIA is made in the absence of hemorrhage, current practice is to initiate antiplatelet therapy with aspirin or clopidogrel, the latter being particularly used in patients with cardiovascular risk factors. When patients have recurrent TIA where the underlying cause is thought to be thrombo-embolism, due consideration should be given to anticoagulation. Endo-vascular therapy has to be considered in patients with underlying steno-occlusive lesions with symptoms that are refractory to maximal medical therapy (see Pharmacologic treatment section).

Pharmacologic treatment

Thrombolytics

IV alteplase (recombinant tissue plasminogen activator)

IV alteplase is licensed for use in acute stroke. IV administration in acute infarction of the brain stem is considered appropriate if the index event to treatment is within 3 hours (anterior and posterior cerebral circulation) and should always be administered under the supervision of a stroke neurologist. Any perceived benefit, although small, potentially outweighs the high risk of a catastrophic outcome without treatment [3].

Standard dosage	Acute stroke (treatment must begin within 3 hours), by IV administration over 60 minutes, 900 mg/kg (maximum 90 mg); initial 10% of dose as a bolus dose by IV injection, remainder by IV infusion; please note that in basilar artery thrombosis the window for thrombolysis is prolonged up to 24 hours. IV alteplase is not recommended in patients over 80 years of age [4].
Contraindications	Acute hemorrhagic stroke, convulsion accompanying stroke, large stroke at risk of reperfusion hemorrhage, history of stroke in patients with diabetes, stroke in last 3 months, hypoglycemia, hyperglycemia.
Cautions	Monitor blood pressure (BP). If systolic BP greater than 180 mm Hg and if diastolic BP greater than 105 mm Hg, there is a need for antihypertensive therapy.
Special points	A systematic review of thrombolysis in acute stroke of 15 trials (5216 patients) concluded that there was an increase in symptomatic and fatal hemorrhage. However, the risks were offset by a reduction in disability in survivors, so that there is, overall, a significant net reduction in the proportion of patients dead or dependent in activities of daily living. Recombinant tissue-plasminogen activator (rt-PA) was used in more than 50% of cases [5]. In five case series totaling 150 patients who had thrombolysis for brain stem infarction, recanalization was achieved in 50% to 75% of cases. However, of those who reperfused, the mortality rate was 40% to 50% compared with 75% to 85% in historical control subjects [3].
Cost/cost-effectiveness	Expensive. Activase (Genentech, South San Francisco, CA), 50 mg, costs $1487 and 100 mg costs $2974.

Intra-arterial thrombolysis

This is discussed under the "Endovascular therapy" section later.

Anticoagulants

Heparin

	IV heparin may be considered in the treatment of recurrent acute TIA where the underlying cause is thought to be due to thromboembolism. Intracranial hemorrhage should be ruled out with a cranial CT scan. The role of heparin or its analogues in the setting of acute TIA is particularly important until anticoagulation with warfarin takes effect.
Standard dosage	After a standard loading dose of 70 U/kg of body weight intravenously, an hourly IV regimen to keep activated partial thromboplastin time (APTT) of 2.5 to 3 times the upper limits of the normal APTT is recommended.
Contraindications	Hemophilia and other hemorrhagic disorders, thrombocytopenia (including history of heparin-induced thrombocytopenia), peptic ulcer, recent cerebral hemorrhage, severe hypertension, severe liver disease (including esophageal varices) after major trauma or recent surgery to eye or nervous system; spinal or epidural anesthesia and hypersensitivity to heparin.
Main drug interactions	Digoxin, nicotine, tetracycline, and antihistamines may decrease effects; nonsteroidal anti-inflammatory drugs, aspirin, dextran, dipyridamole, and hydroxychloroquine may increase toxicity [3].
Main side effects	Hemorrhage, skin necrosis, thrombocytopenia, hyperkalemia, hypersensitivity reactions (including urticaria, angioedema, and anaphylaxis); osteoporosis after prolonged use (and rarely alopecia).
Cost/cost-effectiveness	Inexpensive. Heparin, 5000 U/mL in a 1-mL solution, 25 vials cost $22.50; 5000 U/100 mL of 0.45% sodium chloride, 250-mL solution, 24 packs cost $121.44.

Warfarin

	Warfarin is initiated with heparin in the treatment of recurrent TIA with documented source of emboli (eg, atrial fibrillation or dissection of the vertebral artery). Usually administered for a period of 3 months depending on clinical response to maintain an International Normalized Ratio (INR) of 2 to 3.
Standard dosage	Loading dose of 5 to 10 mg on day 1 to day 3 and titrate according to response.

Special points To date, there are no randomized controlled trials comparing IV heparin to placebo. A nonrandomized, concurrent, cohort study suggested that anticoagulation provided superior stroke protection for patients with vertebrobasilar TIA than for patients with carotid TIA [3]. A strong argument in favor of anticoagulation exists when a cardiac source of emboli is suspected (eg, atrial fibrillation). In patients with intracranial atherosclerosis, the recently published WASID (Warfarin-Aspirin Symptomatic Intracranial Disease) trial showed that the probability of ischemic stroke at 2 years did not differ between those treated with aspirin versus warfarin [6••]. This raises questions regarding the adequacy of monitoring the therapeutic dose once a month in the majority of patients in the trial and also in clinical practice. As Koroshetz [7] points out in his eloquent editorial, WASID does not preclude the use of warfarin in actual clinical practice. He suggests that future studies should be aimed at evaluating a combination of antiplatelets and warfarin with frequent monitoring of INR to ensure maximum efficiency.

Cost/cost-effectiveness Inexpensive. Warfarin, 2 mg per oral tablet, 100 tablets cost $60.89; in the 4-mg tablet, 100 tablets cost $63.25.

Antiplatelets

Aspirin

Standard dosage Standard loading dose of 300 mg immediately followed by 150 mg once a day.

Contraindications Allergy and active ulceration of the stomach or duodenum.

Cautions Monitor for gastric and hepatic intolerance. Caution when used in conjunction with anticoagulants and other antiplatelet agents because there is an increased risk of hemorrhage.

Special points Aspirin (160 or 325 mg/d) results in a small but statistically significant reduction in death and disability when given within 48 hours after ischemic stroke, as indicated by a combined analysis of available studies [8].

Cost/cost-effectiveness Aspirin in combination with dipyridamole is cost-effective compared with aspirin alone in patients with TIA and stroke [9]. Inexpensive. Enteric-coated aspirin per oral tablet of 975 mg, 100 tablets cost $3.19.

Clopidogrel

Clopidogrel, a potent antiplatelet agent, inhibits binding of adenosine diphosphate (ADP) to platelet receptor, thus preventing ADP-mediated activation of platelet aggregation. Used in secondary prophylaxis of stroke and also after arterial stent placements and/or angioplasty.

Standard dosage 300 mg immediately as a loading dose and 75 mg orally once a day.

Contraindications Active bleeding and breast-feeding.

Main side effects Dyspepsia, abdominal pain, diarrhea; bleeding disorders (including gastrointestinal and intracranial); less commonly nausea, vomiting, gastritis, flatulence, constipation, gastric and duodenal ulcers, headache, dizziness, paresthesia, vertigo, leukopenia, decreased platelets (very rarely severe thrombocytopenia), eosinophilia, rash, pruritus; very rarely colitis, pancreatitis, hepatitis, vasculitis, confusion, hallucinations, taste disturbance, blood disorders (including thrombocytopenic purpura, agranulocytosis, and pancytopenia), hypersensitivity-like reactions (including hypotension, bronchospasm, arthralgia, erythema multiforme, angioedema, fever, glomerulonephritis).

Special points The multicenter randomized MATCH (Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke) trial comparing clopidogrel alone versus clopidogrel with aspirin therapy in 7599 high-risk patients showed that there was a nonsignificant difference in reducing major vascular events [10••]. A randomized multicenter trial comparing aspirin (325 mg/d) versus clopidogrel (75 mg/d) showed that clopidogrel was more effective than aspirin in reducing the combined risk of myocardial infarction, stroke, or vascular death in patients with atherosclerotic vascular disease in the long term [11].

Cost/cost-effectiveness Relatively expensive. Per oral tablet of 75 mg, 30 tablets cost $126.49.

Ticlopidine

	This is a selective inhibitor of the ADP pathway of platelet activation. It is less frequently used these days due to its adverse effects of neutropenia and association with thrombotic thrombocytopenic purpura.
Standard dosage	250 mg per oral tablet twice a day with food.
Contraindications	Allergy, bleeding tendency, liver disorders.
Main side effects	Diarrhea, rash, nausea, vomiting, and neutropenia. Most adverse effects occur early in the course of treatment, but a new onset of adverse effects can occur after several months.
Special points	The TASS (Ticlopidine Aspirin Stroke Study) trial comparing ticlopidine and aspirin showed that there was a significant reduction of stroke in patients with TIA, particularly in the first year of ictus by 48%, and by 24% in the second year. It has also been shown to be effective in combination with aspirin in patients who have a coronary stent in the STARS (Stent Anticoagulation Restenosis Study) trial.
Cost/cost-effectiveness	Relatively expensive compared with aspirin but cheaper than clopidogrel. Per oral tablet of 250 mg, 30 tablets cost $81.71; film-coated per oral tablet of 250 mg, 30 tablets cost $59.89.

Dipyridamole

Standard dosage	By mouth, 300 to 600 mg/d in three to four divided doses before food.
Contraindications	Hypersensitivity to the drug.
Main side effects	Gastrointestinal effects, dizziness, myalgia, throbbing headache, hypotension, hot flushes, and tachycardia; worsening symptoms of coronary heart disease; hypersensitivity reactions such as rash, urticaria, severe bronchospasm, and angioedema; increased bleeding during or after surgery; thrombocytopenia reported.
Special points	Enhances the action of anticoagulants. Also, there is an increased risk of bleeding when given in conjunction with other antiplatelets.
Cost/cost-effectiveness	Expensive IV solution and inexpensive per oral preparation. IV solution of 5 mg/mL, 2 mL of 10 vials cost $73.40. Per oral 25-mg tablet, 100 tablets cost $4.75.

Therapy: subacute and chronic phases

- Secondary prevention with antiplatelet agents for stroke after TIA is indicated because the risk of a stroke after a TIA in the first year is in the order of 10% to 15%. This is particularly high in the initial period following the index event. In patients without a cardiac source of emboli, the relative risk reduction is 18% and the absolute risk reduction is 13% for stroke following treatment with aspirin [12]. Clopidogrel is superior to aspirin in patients with a high risk for stroke with concomitant vascular, cardiac, and other risk factors.

Pharmacologic treatment

Aspirin

The treatment regimen in the subacute and long-term phases is similar to that in the acute setting as outlined earlier.

Clopidogrel

Long-term use of clopidogrel is recommended in patients with TIA and coexistent cardiovascular risk factors.

Heparin

Unfractionated IV heparin is discontinued after the INR is therapeutic with warfarin. Subcutaneous low molecular weight heparin over a few months has not shown any benefit in clinical trials. This is not commonly used in clinical practice.

Warfarin

Anticoagulation initiated in acute TIA/infarction is continued for at least 3 months in patients who have a central source of thromboembolism. The key is to ensure maximum length of therapeutic range that may require frequent monitoring of the INR once in less than a week in the majority of cases.

Atorvastatin

For the purposes of this article, we have described the role of atorvastatin. Other statins are in use and the description of each is beyond the scope of this article. A trial comparing placebo with atorvastatin in patients with type 2 diabetes, with no history of heart disease, and low cholesterol showed that 48% fewer statin-treated patients experienced strokes compared with those who received placebo; the overall mortality rate for patients taking atorvastatin was 27% lower than for those on placebo [13].

Standard dosage Initiate with 10 mg once a day to a maximum of 40 mg [4].

Contraindications Allergy, pregnancy (causes birth defects), and breast-feeding.

Cautions Interaction with cyclosporine, gemfibrozil, niacin, clarithromycin, erythromycin, ketoconazole, fluconazole, itraconazole causing muscle damage. Avoid alcohol intake because the combination with statins may adversely affect the liver.

Cost/cost-effectiveness Relatively inexpensive. Per oral tablet of 10 mg, 30 tablets cost $74.14; at 20 mg, 30 tablets cost $109.31.

Antihypertensives

We outline the use of perindopril in this section but this is not exclusive. Several antihypertensives may be considered in the treatment of hypertension. The PROGRESS (Perindopril Protection Against Recurrent Stroke Study) multicenter, randomized, placebo-controlled trial showed that perindopril alone or in combination with indapamide in hypertensive or nonhypertensive patients with a recent history of TIA or stroke reduced the risks of stroke [14]. A range of antihypertensive medications may be required either alone or in combination.

Standard dosage 2 to 4 mg once a day to a maximum of 8 mg/d.

Contraindications Angiotensin-converting enzyme (ACE) inhibitors are contraindicated in patients with hypersensitivity to ACE inhibitors (including angioedema) and in known or suspected renovascular disease. ACE inhibitors should not be used in pregnancy.

Cautions Renovascular disease, risks for hypotension, receiving concomitant antihypertensive therapy with other agents.

Cost/cost-effectiveness Inexpensive. Per oral tablet of 2 mg, 100 tablets cost $132.49; at 4 mg, 100 tablets cost $145.73.

Endovascular therapy

- Angiographic studies in 4748 patients with ischemic stroke showed proximal extracranial vertebral artery stenosis from 18% to 22% [15]. In the past few years, endovascular stenting and balloon angioplasty has emerged as a relatively safe and effective therapy in patients with subclavian and extracranial vertebral artery stenosis with a high level of success [16–18]. Endovascular stenting of intracranial stenosis is recommended for patients with TIA despite maximum medical therapy because the risk of stroke in these patients can be as high as 52% [19]. This is particularly relevant in high-risk patients for stroke who do not have collateral blood supply [18]. The SSYLVIA (Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries) study (n =43 intracranial and 18 extracranial vertebral artery stenosis) showed that the postprocedural stroke rate at 30 days was 7% and the recurrent stenosis greater than 50% at 6 months was 30% in the intracranial arteries. Four more patients had a stroke after the 30-day postoperative period [20•]. Further developments in intracranial

stent technology may improve the long-term benefits of this procedure [21]. There have been varying reports on long-term patency after stenting and angioplasty, ranging from 10% in one study [22] to 43% in another [23]. In one of the studies, all four patients who had only angioplasty had restenosis of more than 70% at 1-year follow-up. The SSYLVIA study showed that restenosis occurred in 35% of patients stented and 61% of these were asymptomatic [20•]. Current practice is to deploy a stent across the stenosis ideally with a distal cerebral protection device and perform balloon angioplasty to achieve near normal luminal diameter.

Intra-arterial thrombolysis with rt-PA

Intra-arterial thrombolysis with rt-PA has been promoted because high concentrations of thrombolytic agent can be administered locally and it also facilitates mechanical clot retrieval [24]. This is advocated in patients who are outside the window of 3 to 6 hours from ictus and are not suitable for IV thrombolysis. This is particularly relevant in basilar artery thrombosis, which has a poor inherent prognosis.

Standard procedure A microcatheter is placed in close relation to the thrombus and rt-PA is injected.

Contraindications All contraindications that apply to IV thrombolysis.

Standard dosage 5 to 10 megaunits. See above for more information.

Stent and angioplasty

Current practice involves stenting and angioplasty of the vertebrobasilar arteries as a single procedure in carefully selected patients who are enrolled in a registry and are then closely monitored and followed up. The reader is referred to the paper by Phatouros *et al.* [25] for a detailed review on endovascular therapy of noncarotid extracranial cerebrovascular disease.

Emerging therapies

Abciximab

Abciximab is a monoclonal antibody fragment that binds to the platelet glycoprotein IIb/IIIa receptor and inhibits platelet aggregation. Early reports from ongoing trials in treatment of acute stroke presenting up to 6 hours show promise. It is also used in acute thromboembolism secondary to endovascular intervention. Several phase 1 studies are underway investigating its adjuvant use with intra-arterial thrombolysis.

Standard dosage 0.25-μg/kg bolus followed by a 0.125-μg/kg/min IV infusion for 12 hours.

Contraindications Bleeding tendency, hypersensitivity.

Adverse events Bleeding.

Cost/cost-effectiveness Relatively inexpensive compared with thrombolytics. IV solution, 2 mg/mL, 5 mL costs $584.02.

Mechanical devices

These can be divided into those that either disrupt or retrieve thrombus. Phase 1 studies of clot disruption using ultrasound-emitting catheters and photoacoustic energy emitting system have shown adequate safety and feasibility [26,27].

Eluting stents

Studies in dogs using sirolimus-eluting stents showed reduction in smooth muscle proliferation and did not impair endothelialization. These features suggest that sirolimus-coated stents may inhibit in-stent stenosis. Additional studies with long-term follow-up are needed for further evaluation [28].

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