Stroke

AHA SCIENTIFIC STATEMENT

Treatment and Outcomes of Cervical Artery Dissection in Adults: A Scientific Statement From the American Heart Association

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ABSTRACT: Cervical artery dissection is an important cause of stroke, particularly in young adults. Data conflict on the diagnostic evaluation and treatment of patients with suspected cervical artery dissection, leading to variability in practice. We aim to provide an overview of cervical artery dissection in the setting of minor or no reported mechanical trigger with a focus on summarizing the available evidence and providing suggestions on the diagnostic evaluation, treatment approaches, and outcomes. Writing group members drafted their sections using a literature search focused on publications between January 1, 1990, and December 31, 2022, and included randomized controlled trials, prospective and retrospective observational studies, meta-analyses, opinion papers, case series, and case reports. The writing group chair and vice chair compiled the manuscript and obtained writing group members' approval. Cervical artery dissection occurs as a result of the interplay among risk factors, minor trauma, anatomic and congenital abnormalities, and genetic predisposition. The diagnosis can be challenging both clinically and radiologically. In patients with acute ischemic stroke attributable to cervical artery dissection, acute treatment strategies such as thrombolysis and mechanical thrombectomy are reasonable in otherwise eligible patients. We suggest that the antithrombotic therapy choice be individualized and continued for at least 3 to 6 months. The risk of recurrent dissection is low, and preventive measures may be considered early after the diagnosis and continued in high-risk patients. Ongoing longitudinal and population-based observational studies are needed to close the present gaps on preferred antithrombotic regimens considering clinical and radiographic prognosticators of cervical artery dissection.

Key Words: carotid artery, internal, dissection ■ diagnosis ■ dissection ■ prevention and control ■ stroke ■ vertebral artery dissection

Cervical artery (internal carotid or vertebral artery) dissection can occur in the absence of major trauma.[1] It is usually attributable to an intimal tear or rupture of the vasa vasorum. This can lead to an intraluminal thrombus, vascular stenosis, occlusion, or dissecting aneurysm formation. Cervical artery dissections can present with local signs and symptoms (eg, pain or cranial nerve compression) or cerebral or spinal cord ischemia.[1]

Cervical artery dissection is an important cause of stroke and stroke-related disability in young adults.[2] Despite high-quality studies, data conflict on the diagnostic evaluation, treatment, and outcomes of patients with suspected non–major trauma–associated cervical artery dissection with or without cerebral ischemia.[2] Conflicting evidence has led to clinical equipoise and variability in practice across clinicians.[3]

In this scientific statement, we aim to provide an overview of non–major trauma–associated cervical artery dissection, hereafter referred to as cervical artery dissection, with a focus on summarizing the available evidence on the diagnostic evaluation, treatment approaches, and outcomes.

METHODS

A multidisciplinary team of 11 writing group members from neurology, neuroradiology, neurosurgery, emergency medicine, and interventional neurology were identified to

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cover the sections. Each writing group member wrote and reviewed at least 1 section. In this scoping review, authors performed a literature search using key words relevant to each section, and the search results were reviewed for relevant publications. The literature search focused on publications between January 1, 1990, and December 31, 2022, and included randomized controlled trials, prospective and retrospective observational studies, meta-analyses, opinion papers, case series, and case reports. Apart from meeting presentations for clinical trials, meeting abstracts were not included.

Using the information from relevant publications, the writing group members drafted their sections. Once the sections were complete, the writing group chair and vice chair compiled the manuscript and circulated it to the writing group members for review and feedback. Multiple drafts were circulated among writing group members until a consensus was achieved. A summary of suggestions to clinicians pertinent to each section is provided in the Table.

EPIDEMIOLOGY/RISK FACTORS

Cervical artery dissection contributes to 2% of all ischemic strokes[4] but up to 25% of ischemic stroke in adults <50 years of age.[5,6] Prior studies reported an incidence rate of 2.6 to 3.0 per 100 000 people[4,7,8] but the true incidence is likely higher,[9] partly because some patients with dissection may not seek medical attention because of self-limited or minor symptoms.

The mean age at diagnosis is 45 years.[7] Although the proportion of dissection-related stroke is higher in younger patients, the absolute prevalence of dissection-related ischemic strokes increases with age.[10] The incidence is slightly higher in men,[11] but the age at onset and the peak age prevalence of dissection-related stroke are lower in women (30–49 years) compared with men (50–89 years).[10,11]

The pathogenesis of cervical artery dissection is multifactorial and involves the interplay of comorbidities, environmental triggers, genetic or congenital factors, including connective tissue disorders, and anatomic factors such as elongated styloid process (>30 mm; Eagle syndrome) or increased vascular tortuosity (Figure S1).[1,12–14] Furthermore, risk factors may differ according to dissection location; recent systemic infection is more common in carotid artery dissection, and history of minor trauma is more common in vertebral artery dissection.[15]

CHALLENGES IN DIAGNOSIS

Clinical Diagnostic Challenges

Because of the often nonspecific nature of symptoms (eg, headache, neck pain, dizziness, and tinnitus), diagnosis of cervical artery dissection is challenging, especially in the absence of ischemic or localizing symptoms. In a statewide study of claims data, 3.1% of patients with cervical artery dissection were previously seen in the emergency department for possible related symptoms in the 14 days preceding diagnosis[16]; younger and female patients were more likely to have a probable missed diagnosis.[16]

Evaluation for suspected cervical artery dissection should include a detailed symptom history, questions about minor trauma, and a detailed neurological examination. Common initial symptoms of cervical artery dissection include facial pain, headache (≈65%), and neck pain (≈50%),[15] which tend to precede cerebrovascular ischemic symptoms[17,18]; thus, early diagnosis and treatment could reduce the risk of cerebrovascular ischemia. Isolated pain (without cerebral ischemia) occurs in 8% to 12% of diagnosed cases.[19,20] For internal carotid dissections, pain is often facial, frontal, or temporal, whereas vertebral artery dissections generally cause pain in the cervical or occipital area.[17,21] In carotid dissection, pain may also be associated with a (partial) Horner syndrome (≈25%[7]) and cranial nerve palsies (≈12%),[22] and both carotid and vertebral dissection can be associated with pulsatile tinnitus (≈8%).[17,23,24] In fact, a partial Horner syndrome in a patient with new or worsening headache may suggest a carotid dissection diagnosis. Headache characteristics are not specific but can rarely be acute and of thunderclap nature.

Diagnostic Imaging Tools and Their Yield

The diagnostic modalities for cervical artery dissection are magnetic resonance imaging (MRI)/magnetic resonance angiography (MRA), computed tomography angiography (CTA), ultrasound, and conventional digital subtraction angiography (DSA). Historically, DSA has been considered the reference imaging technique to demonstrate the lumen content and can delineate the presence of an intimal flap, double lumen, and dissecting aneurysm.[25] DSA, however, provides limited information on the arterial wall (ie, intramural hematoma). Moreover, DSA carries periprocedural risks (≈0.5% iatrogenic dissection[26] and 0.15% stroke).[27]

CTA is an effective noninvasive alternative to DSA that can display luminal contour alterations with rapid acquisition time, ready availability, and high spatial resolution; disadvantages include the exposure to radiation and iodinated contrast, and for intramural hematoma, CTA may show an eccentric or crescent-shaped vessel wall thickening or the rind sign in vertebral dissection[28] (Figure 1), but these findings are neither sensitive nor specific to cervical artery dissection. A false-positive CTA can be due to streak artifact mimicking a double lumen and pulsation artifact mimicking an intramural hematoma. A false-negative CTA could be seen in the setting of a non–flow-limiting nondominant vertebral artery

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Table. Summary of Conclusions From Each Section

Section	Summary of suggestions
Epidemiology	Cervical artery dissection is a common cause of stroke in younger adults and caused by the interplay between comorbidities, genetic or congenital factors, anatomic factors, and environmental triggers.
Clinical diagnosis	It is reasonable to perform urgent cervical vascular imaging with CTA or MRI with MRA in patients with headache or neck pain associated with symptoms of ischemia or a partial Horner syndrome and considered in those with new or worsening headache or neck pain, especially when there is a history of minor cervical trauma or other risk factors for cervical artery dissection.
Imaging tools for diagnosis	In patients with suspected cervical artery dissection, an MRA or CTA is a reasonable test to consider. In patients with negative CTA and continued clinical concern for cervical artery dissection, MRA with fat-suppressed images may be considered, given the high sensitivity to visualize a mural hematoma. DSA should be avoided as a first-line diagnostic tool but may be considered in patients with clinical concern and negative MRA and CTA. Ultrasound might be useful for follow-up assessments of arterial remodeling.
Imaging diagnostic challenges	Imaging signs of dissection include a tapering stenosis or occlusion, intramural hematoma, dissecting aneurysm, double lumen, and dissection flap. It is crucial to carefully review the cervical vascular imaging studies of patients with ≥1 signs of dissection present and to recognize dissection mimics such as carotid artery web, fenestrated artery, pseudo-occlusion, and imaging artifacts.
Role of genetic testing	It is reasonable to screen patients with cervical artery dissection for clinical signs of monogenic connective tissue disorders (eg, recurrent dissection, family history, physical examination) and to perform appropriate genetic counseling and testing based on the previously discussed screening tools. Routine genetic testing in the absence of signs or symptoms of monogenic connective tissue disorder is not suggested because of its increased cost and low yield but may be considered in patients with recurrent dissection.
Diagnostic testing after dissection diagnosis	In patients with cervical artery dissection, it is reasonable to screen for cerebral aneurysm and aortic root dilation. In those with hypertension or evidence of fibromuscular dysplasia, screening for renal artery stenosis with a renovascular Doppler is reasonable.
Timing and predictors of ischemic stroke	The early ischemic stroke risk supports the timely recognition, diagnosis, and initiation of optimal antithrombotic treatment for cervical artery dissection. Clinicians can use demographics, clinical characteristics, and imaging findings to predict which patients are at higher risk of developing an ischemic stroke after cervical artery dissection.
IVT	In the absence of data suggesting safety concerns and given the proven efficacy of IVT in otherwise eligible patients with acute ischemic stroke, it is reasonable to consider IVT for patients with acute ischemic stroke with cervical artery dissection if they meet other standard criteria, as recommended by current guidelines. For patients with intracranial extension of the dissection, the risks and benefits of IVT are not well established.
Mechanical thrombectomy	It is reasonable to perform mechanical thrombectomy in otherwise eligible patients with a large-vessel occlusion in the setting of cervical artery dissection.
Antithrombotic treatment	Because most ischemic events occur within the first several days after diagnosis, optimizing antithrombotic treatment (when safe) early is of paramount importance. In addition, it is reasonable that clinicians start immediate antithrombotic treatment if deemed safe. Parenteral followed by oral anticoagulation may be considered in particular in patients at low risk of intracranial hemorrhage (small infarct size, no intradural extension, and no intracranial hemorrhage) but at high risk for ischemic stroke (eg, intraluminal thrombus, occlusive dissection). Although the evidence for use in cervical artery dissection is weak, a short course of dual antiplatelet therapy with a loading dose (followed by single antiplatelet agent) might be preferred over monotherapy when deemed safe, particularly in patients who would have qualified for the dual antiplatelet trials for early prevention after minor stroke/TIA. Otherwise, antiplatelet monotherapy could be used. In the absence of a general superiority of any antithrombotic regimen, it is reasonable that clinicians individualize treatment on the basis of the risk of ischemic stroke and ICH, as well as a shared decision-making process with their patients.
Antithrombotic treatment duration	It is reasonable that the duration of antithrombotic therapy in patients with cervical artery dissection be 3–6 mo. Decisions to extend antithrombotic therapy past the 6-mo mark may be considered in the context of an individual's overall vascular risk factor profile and in the context of neuroimaging features as remodeling occurs.
Subacute stenting	Patients with cervical artery dissection with significant stenosis causing distal hemodynamic compromise AND recurrent ischemic stroke despite optimal medical treatment AND who can withstand surgery may be considered for stenting as a measure for secondary stroke prevention.
Risk and predictors of recurrent dissection	The risk of recurrent cervical artery dissection is 1%–2% per y but is particularly increased in the first few months after the initial cervical artery dissection. Younger age and fibromuscular dysplasia are risk factors for dissection recurrence.
Precautions to reduce the risk of dissection recurrence	Because the risk of recurrent or worsening dissection is highest in the first few months after the initial dissection, it is reasonable that all patients with cervical artery dissection avoid activities that increase the risk of cervical injury for 1–6 mo from diagnosis and until healing of the index dissection. Furthermore, although there are no proven precautions to reduce the long-term risk of recurrent dissection, it is reasonable for health care clinicians to suggest that patients with cervical artery dissection who are at high risk for recurrent cervical dissection (eg, known connective disorder, recurrent dissection) avoid such activities lifelong.
Radiological recanalization of the dissection	Recanalization of cervical artery dissections occurs mostly in the first 12 mo after diagnosis. Cervical artery–dissecting aneurysms infrequently increase in size, become symptomatic, and require treatment. Recanalization and development or resolution of cervical artery–dissecting aneurysms do not seem to be affected by antithrombotic treatment regimens.

(*Continued*)

CTA indicates computed tomography angiography; DSA, digital subtraction angiography; ICH, intracranial hemorrhage; IVT, intravenous thrombolysis; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; and TIA, transient ischemic stroke.

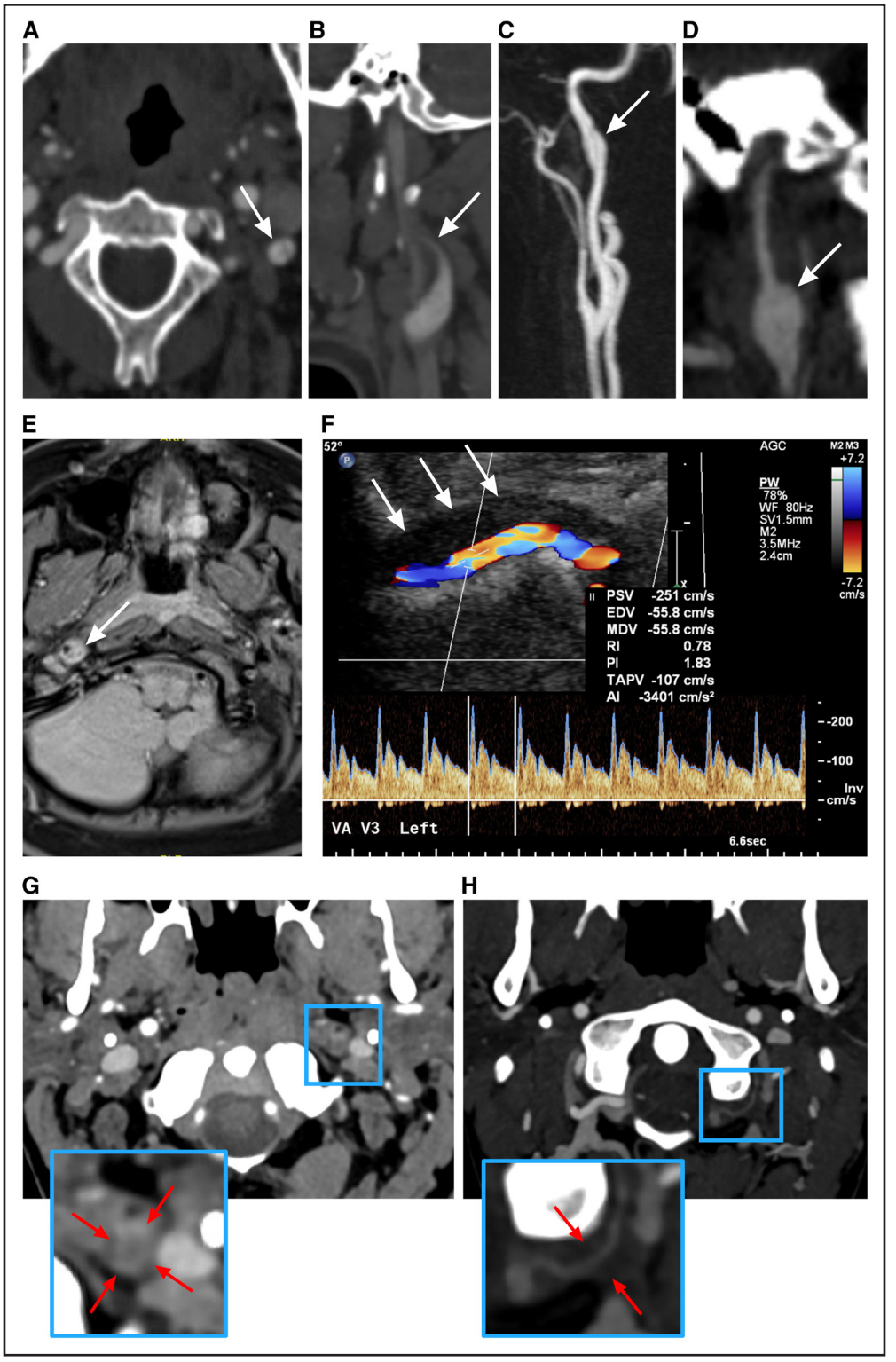

Figure 1. Imaging signs suggestive of dissection diagnosis.
A, Double lumen. **B**, Tapered or flame-shaped occlusion at typical dissection site. **C**, Intimal flap. **D**, Pseudoaneurysm. **E**, Intramural hematoma on fat-suppressed T1. **F**, Carotid imaging duplex mural hematoma (white arrows) as hypoechogenic structure compromising the arterial blood flow in the vertebral artery (V3 segment). **G**, Axial source image from computed tomography angiography (CTA) neck in a patient with complete occlusion of the left internal carotid artery (ICA) related to a dissection, showing the ring sign, with enhancement of the carotid wall and fresh nonenhancing thrombus within the carotid lumen. This sign is nonspecific for ICA dissection but points to a recent rather than a chronic occlusion. **H**, Axial source image from CTA neck in a patient with left vertebral artery dissection, with thrombus surrounding the hypoplastic but apparently normal lumen vertebral artery, known as the suboccipital rind sign, involving the atlanto-occipital (V3) segment.

dissection but most commonly is due to failure of attributing an abnormality to dissection.[29]

MRA may be superior to CTA for the identification of the intramural hematoma when the appropriate protocol including axial fat-suppressed T1-weighted images is used. Limitations of MRA include the cost, availability, patient-related restrictions (eg, pacemakers and claustrophobia), and diagnostic limitations of time-of-flight MRA of the neck (eg, signal loss due to turbulence or vessel turn, susceptibility to artifact, and flow reversal artifact). False-positive MRA can be due to a hyperintense signal in the setting of turbulent flow and adjacent structures simulating a periarterial double-lumen sign. False-negative MRA can be related to the absence of hyperintense signal of the intramural hematoma in the hyperacute setting.[29]

Overall, both MRA and CTA have good sensitivity and specificity for diagnosis of cervical arterial dissection. MRA has high sensitivity in diagnosing carotid dissection (95%), but its sensitivity is lower for vertebral artery dissection (60%) compared with DSA.[30] This is not the case with CTA, which has been shown to have similar sensitivity and specificity compared with DSA in diagnosing vertebral artery dissection.[25]

Ultrasound with color Doppler is noninvasive but is operator dependent and is of poor diagnostic utility,[31] especially when the dissection is high cervical. Ultrasound may be helpful in rare cases with hyperacute dissection where the intramural hematoma can be visualized on ultrasound but not MRA (Figure 1). Ultrasound generally requires confirmation by CTA or MRA. Ultrasound has been shown to be useful for follow-up assessments within the first 4 weeks, when arterial remodeling is most prevalent.[32]

Imaging Diagnostic Challenges

The imaging hallmarks of dissection are the presence of intimal flap, intramural hematoma, double lumen, dissecting aneurysm, or in certain cases a tapering stenosis or occlusion (Figure 1). These findings are rarely present in conjunction, making the diagnosis often difficult. Furthermore, some of these findings are not specific to cervical artery dissection; for example, a pseudo-occlusion due to stagnant flow from a distal occlusion may mimic a dissection (Figure S2). Studies assessing the sensitivity of CTA to differentiate pseudo-occlusion from true occlusion of the extracranial internal carotid artery have found mixed results.[33–35] A duplication[36] or fenestration of the cervical internal carotid artery or vertebral artery may be mistaken for the double-lumen appearance seen in dissections (Figure S2). On the other hand, a chronic dissection with residual double lumen may be misinterpreted as a fenestration.[37] Furthermore, normal perivascular venous plexus or fat can appear bright on T2, mimicking an intramural hematoma. A crescentic (versus circumferential) appearance may favor dissection, particularly if the vessel lumen or wall is abnormal in the same location on postcontrast MRA or CTA. Last, multiple MRI or CTA artifacts can be a source of a false-positive study.[29]

Carotid artery dissections commonly originate in the distal portion of the cervical internal carotid artery (2–3 cm above the bifurcation), whereas in the vertebral artery, the majority are in the V2 or V3 segments. The location can be used to differentiate it from other arteriopathies such as atherosclerosis, which usually occurs at the internal carotid artery bifurcation or V1 and V4 segments and is often associated with calcification,[29,38] or carotid web, which is a variant of fibromuscular dysplasia characterized by a thin, linear membrane that extends from the posterior aspect of the internal carotid artery just beyond the carotid bifurcation[39] (Figure S2).

Differentiating an acute from a chronic dissection on imaging may be challenging and necessitates careful analysis of the CTA (carotid ring sign)[40] or MRI (acute to subacute intramural hematoma; Figure 1).

ADDITIONAL DIAGNOSTIC TESTING

Screening for Connective Tissue Disorders

Abnormalities of the connective tissue, a main component of the arterial wall, are considered a predisposing factor to developing cervical artery dissection. Cervical artery dissection is associated with well-defined monogenic connective tissue disorders, mainly vascular Ehlers-Danlos syndrome (*COL3A1* gene) and, to a lesser extent, Marfan syndrome (fibrillin 1 gene), osteogenesis imperfecta (*COL1A1* or *COL1A2* gene), and Loeys-Dietz syndrome (*TGFBR1*, *TGFBR2*, *TFFB2*, or *SMAD3* gene).[41] Large cervical artery dissection series have shown that clinical and molecular diagnosis of defined monogenic connective tissue disorders is extremely rare (<1%), and even family history is reported in only a minority (<5%).[42] On the other hand, cervical artery dissection risk is ≈10-fold higher in patients with monogenic connective tissue disorders such as Marfan syndrome[43]; thus, it is reasonable to educate them about signs/symptoms of cervical artery dissection.

Despite these data, genetic factors associated with connective tissue abnormalities play a role in cervical artery dissection pathogenesis. Clinical signs of connective tissue anomalies (ie, joint hypermobility, skin hyperextensibility, craniofacial dysmorphisms) in the absence of a defined connective tissue disorders are prevalent in cervical artery dissection.[44] Skin biopsy studies show that >50% of cervical artery dissection cases have ultrastructural connective tissue aberrations (ie, composite collagen fibrils and elastic fibers fragmentation), which are believed to have an autosomal-dominant inheritance.[45–47]

Other genetic conditions that have been shown to increase the risk of cervical artery dissection include methylene tetrahydrofolate reductase C677T polymorphism and mutations in the *PHACTR1* gene, which is also associated with fibromuscular dysplasia and migraine, thus supporting an overlap between these entities.[13] Last, whole-exome sequencing studies have shown enrichment of connective tissue disorder–related genetic variants among familial cervical artery dissection, which was characterized by high genetic heterogenicity.[48] Therefore, a referral to genetics for genetic counseling may be reasonable in patients with suspected connective tissue disorder and in those with multiple or recurrent dissection. In addition, genome-wide association studies are needed to help identify novel mutations. If a systemic vasculopathy is found, clinicians could consider referral to multidisciplinary clinics or vascular disease specialists who specialize in such disorders.

Utility of Intracranial Vascular Imaging, Aortic Imaging, and Renovascular Imaging

Aortic root dilation has been shown to be more frequent in patients with cervical artery dissections compared with healthy control subjects.[49,50] In fact, 1 study reported a 4-fold increased risk of aortic dissection in patients with cervical artery dissection.[51]

Fibromuscular dysplasia is a nonatherosclerotic, noninflammatory vasculopathy with 19% of fibromuscular dysplasia cases complicated by cervical artery dissection.[52] Cervicocephalic fibromuscular dysplasia is found in nearly 20% of cervical artery dissection cases.[52,53] In the ARCADIA-POL study (Assessment of Renal and Cervical Artery Dysplasia–Poland), fibromuscular dysplasia affecting at least 1 additional vascular bed was found in 39.5% of patients with cervical artery dissection.[54] Compared with patients with cervical artery dissection without fibromuscular dysplasia, fibromuscular dysplasia–related cervical artery dissection was associated with >3-fold increase risk of recurrent cervical artery dissection.[55] The diagnosis of fibromuscular dysplasia in patients with cervical artery dissection may lead to changes in clinical management,[56] especially with the presence of hemodynamically significant renal artery stenosis in patients with renovascular hypertension. Furthermore, in patients with cervical artery dissection and evidence of fibromuscular dysplasia, referral to a vascular specialist with expertise in fibromuscular dysplasia may be considered.

Furthermore, studies have shown an increased prevalence of cerebral saccular aneurysms unrelated to the dissection site in patients with cervical artery dissection, nearly 5.5% on cerebral angiography,[57] but the size was <5 mm in nearly two-thirds of these patients. There are limited data, if any, on whether saccular cerebral aneurysms in the setting of cervical artery dissection carry an increased risk of rupture.

A suggested diagnostic evaluation is provided in Figure 2.

PREDICTORS AND TIMING OF ISCHEMIC STROKE

In a small study of extracranial carotid artery dissections, the time interval between the first symptoms of dissection (local signs or transient ischemic attack [TIA]) and the onset of ischemic stroke ranged from a few minutes to 31 days; the majority of the patients (82%) experienced an ischemic stroke within the first week after symptom onset.[58] A large, retrospective crossover cohort study of patients with cervical artery dissection without ischemia found that the risk of stroke is limited to the first 2 weeks after dissection diagnosis (1.25% absolute increase in stroke risk compared with the corresponding period 1 year later) and that all strokes occurred within the first 4 weeks after an acute cervical artery dissection.[59] This may be an overestimate because some dissections, particularly those with minor self-limiting local symptoms, may go undiagnosed.

Predictors of ischemic stroke in patients with cervical artery dissection are summarized in Table S1.[15,20,21,23,60–71] These predictors can be used to stratify which patients are at high risk of an ischemic stroke resulting from cervical artery dissection. Important predictors present in >1 study include male sex,[20,60,62,63] smoking,[60,61] vertebral artery involvement,[15,21,65] multiple dissections or early recurrent dissection,[64,65] high-grade stenosis or occlusion,[23,60,65] and intraluminal thrombus.[63,67,68,71] Although intraluminal thrombus can be diagnosed on CTA (donut or finger sign),[72] high-resolution MRI may be a better tool to visualize small and nonstenosing intraluminal thrombi.[71]

Transcranial Doppler is a noninvasive test that can identify patients with stroke-free cervical artery dissections who are at risk of a future stroke. Transcranial Doppler predictors of future ischemic stroke include presence of microembolic signals and abnormal cerebral vasoreactivity in carotid artery dissections and poststenotic flow in the basilar artery in vertebral artery dissections.[69,70] Serial transcranial Doppler may be used to examine response to antithrombotic treatment.[73]

HYPERACUTE TREATMENT

Intravenous Thrombolysis

Intravenous thrombolysis (IVT), with either alteplase or tenecteplase, is a highly efficacious acute ischemic stroke treatment and leads to improved functional outcome.[74] Theoretical safety concerns of IVT in patients with cervical artery dissection include not only intracranial hemorrhage (ICH) but also occurrence or enlargement

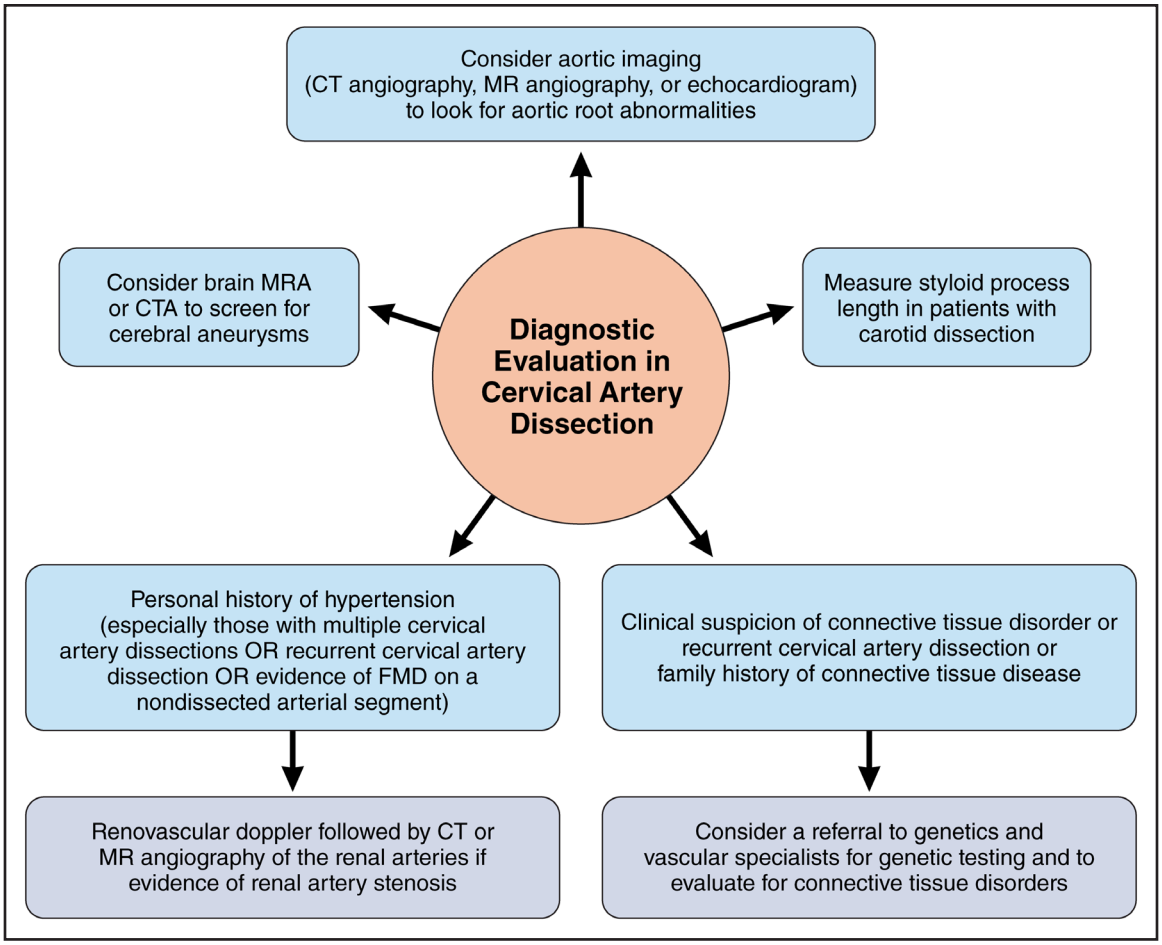

Figure 2. Suggested diagnostic evaluation of patients with cervical artery dissection.
CT indicates computed tomography; CTA, computed tomography angiography; FMD, fibromuscular dysplasia; MR, magnetic resonance; and MRA, magnetic resonance angiography.

of intramural hematoma. However, evidence for IVT in patients with acute ischemic stroke from cervical artery dissection remains limited and includes mostly observational studies. In these studies, patients with acute ischemic stroke from cervical artery dissection had similar ICH rates with IVT compared with those without cervical artery dissection; the rate of symptomatic ICH was 2% to 3%.[75–77] A meta-analysis of studies comparing IVT and no IVT in patients with ischemic stroke due to cervical artery dissection did not find an evidence of functional outcome or mortality benefit of thrombolysis,[78] but rates of symptomatic ICH were comparable between groups. These findings should be interpreted with caution because of the observational nature of the included studies. Small case series have not found increased pseudoaneurysm formation or rupture with IVT.[79]

In the absence of data suggesting safety concerns and given the proven efficacy of IVT in otherwise eligible patients with acute ischemic stroke, it is reasonable to consider IVT for patients with acute ischemic stroke with cervical artery dissection if they meet other standard criteria, as recommended by current guidelines.[2,80,81] For patients with intracranial extension of the dissection, the risks and benefits of IVT are not well established.[81]

Mechanical Thrombectomy

The need for emergent mechanical thrombectomy in patients with cervical artery dissection is based on existing criteria for thrombectomy in patients with acute large-vessel occlusion. A meta-analysis comparing patients with cervical artery dissection and concurrent acute ischemic stroke found that mechanical thrombectomy increased favorable functional outcomes (modified Rankin Scale score, 0–2 at 90 days) compared with medical management (62.9% versus 41.5%; P=0.006), with no difference in symptomatic ICH or mortality.[82]

In patients with cervical artery dissection and acute ischemic stroke presenting with tandem occlusion, debate exists about the optimal approach. Approaches include opening the extracranial dissection first and then addressing the intracranial large-vessel occlusion (antegrade) or opening the intracranial large-vessel occlusion and then securing the extracranial dissection

(retrograde). The majority of multicenter analyses show similar rates of recanalization and symptomatic ICH between the 2 approaches.[83,84] Most studies also report similar 90-day functional outcomes, but 1 retrospective study found better functional outcome with the retrograde approach.[85] Aspiration, angioplasty, and stenting have proved to be successful with equivalent outcomes in retrospective series.[83]

Acute Stenting

Cervical artery dissections may cause stenosis or occlusion of the lumen but more often do not lead to hypoperfusion of the distal territory,[86] and stenting of cervical artery dissection as an acute treatment modality remains controversial. Although many studies report safety with stenting and even higher rates of vessel patency the day after mechanical thrombectomy, an improvement in functional outcome has not been found.[83–85,87,88] In randomized, multicenter studies of extracranial stenting, subgroup analysis of patients with cervical artery dissection failed to show a functional benefit after stent placement.[87,88] However, stenting of a stenotic or occluded dissected segment of the vessel can be considered to improve distal perfusion in patients with neurological deficits due to hypoperfusion.[89,90] During a 9-year period, a study of 73 patients undergoing acute stenting for carotid dissection and associated hypoperfusion or intracranial thrombosis found a clinically relevant thrombosis and thromboembolism rate of 8% and a symptomatic hemorrhage rate of 5% with no recurrence of ischemic symptoms. In this study, however, 38% of patients (25/66) had abnormalities of the stented artery, leading to additional follow-up and retreatment in 17% (11/66).[91] Therefore, given the observational and retrospective nature of these studies and their small sample size and limited generalizability, acute stenting of the dissected artery in the absence of hypoperfusion remains controversial. The ongoing TITAN trial (Thrombectomy in Tandem Occlusion) will shed more light on further safety and efficacy of emergency stenting in tandem occlusion.

SECONDARY STROKE PREVENTION AND OTHER TREATMENT INDICATIONS

Antithrombotic Treatment

The majority (≈85%) of ischemic strokes in the setting of cervical artery dissection occur as a result of artery-to-artery embolization.[86] Thus, early antithrombotic therapy is essential to reduce the risk of further embolization or thrombus formation. Antiplatelets and anticoagulation are commonly used for stroke prevention in cervical artery dissection. Meta-analyses of observational data have yielded conflicting results about the effectiveness and safety of either treatment.[92–98] A treatment algorithm is suggested in Figure 3.

Two randomized trials, CADISS (Cervical Artery Dissection in Stroke Study) and TREAT-CAD (Biomarkers and Antithrombotic Treatment in Cervical Artery Dissection), have examined anticoagulation versus antiplatelet therapy for cervical artery dissection. CADISS was a UK-based, multicenter, randomized, controlled, open-label trial designed to show feasibility of a randomized controlled trial in patients with cervical artery dissection. CADISS had 250 participants, 118 with carotid dissection and 132 with vertebral artery dissection. Participants were recruited 3.7±1.9 (mean±SD) days after symptom onset, which was cerebral ischemia in 224 and local symptoms in 26 participants. Participants were randomly allocated to either anticoagulation (124 patients, vitamin K antagonist [VKA] with lead-in heparin in 112/124 and 12/124 without bridging) or antiplatelet in 126 patients for 3 months (intention-to-treat population). Antiplatelet treatment was heterogeneous, with 22% of patients receiving aspirin alone, 33% receiving clopidogrel alone, 28% receiving aspirin plus clopidogrel, 16% receiving aspirin plus dipyridamole, and 1% receiving dipyridamole alone. The treatment effect was calculated by logistic regression analyses with odds ratios and CIs in the intention-to-treat-population for the primary study end point (ipsilateral stroke or death) assessed by blinded investigators. Within the 3-month study period, ischemic stroke occurred in 3 of 126 patients in the antiplatelet group and in 1 of 124 patients in the anticoagulation group (odds ratio, 0.34 [95% CI, 0.01–4.23]). No major hemorrhage was observed in the antiplatelet group, whereas in the anticoagulant group, 1 subarachnoid hemorrhage occurred in a patient with intracranial extension of an extracranial vertebral artery dissection. In 20% of the participants, the diagnosis of dissection was not confirmed by central adjudication. When such cases were excluded, the per-protocol analysis across 197 participants again showed no statistically significant difference between treatment groups for the primary outcome.[99] Two additional ischemic strokes (1 in each treatment arm) occurred during the subsequent 3- to 12-month observational follow-up period.[100]

TREAT-CAD was a multicenter, open-label, randomized, controlled, noninferiority trial comparing aspirin with VKA in the treatment of cervical artery dissection. Noninferiority of aspirin would be shown if the upper limit of the 2-sided 95% CI of the absolute difference between groups was <12%. If noninferiority were shown, aspirin would be preferable because of its ease of use and lower cost. TREAT-CAD enrolled 194 participants, of whom 100 were assigned to aspirin and 94 to VKA for 90 days. The per-protocol population comprised 173 participants (89% study participants) who had a symptomatic, MRI-verified dissection of the carotid artery (in 115, 66%), the vertebral artery (in 61, 35%), or both arteries (in 3, 2%). Overall, 123 of 173 participants (71%) presented with clinical signs of cerebral ischemia, whereas 50 of 123

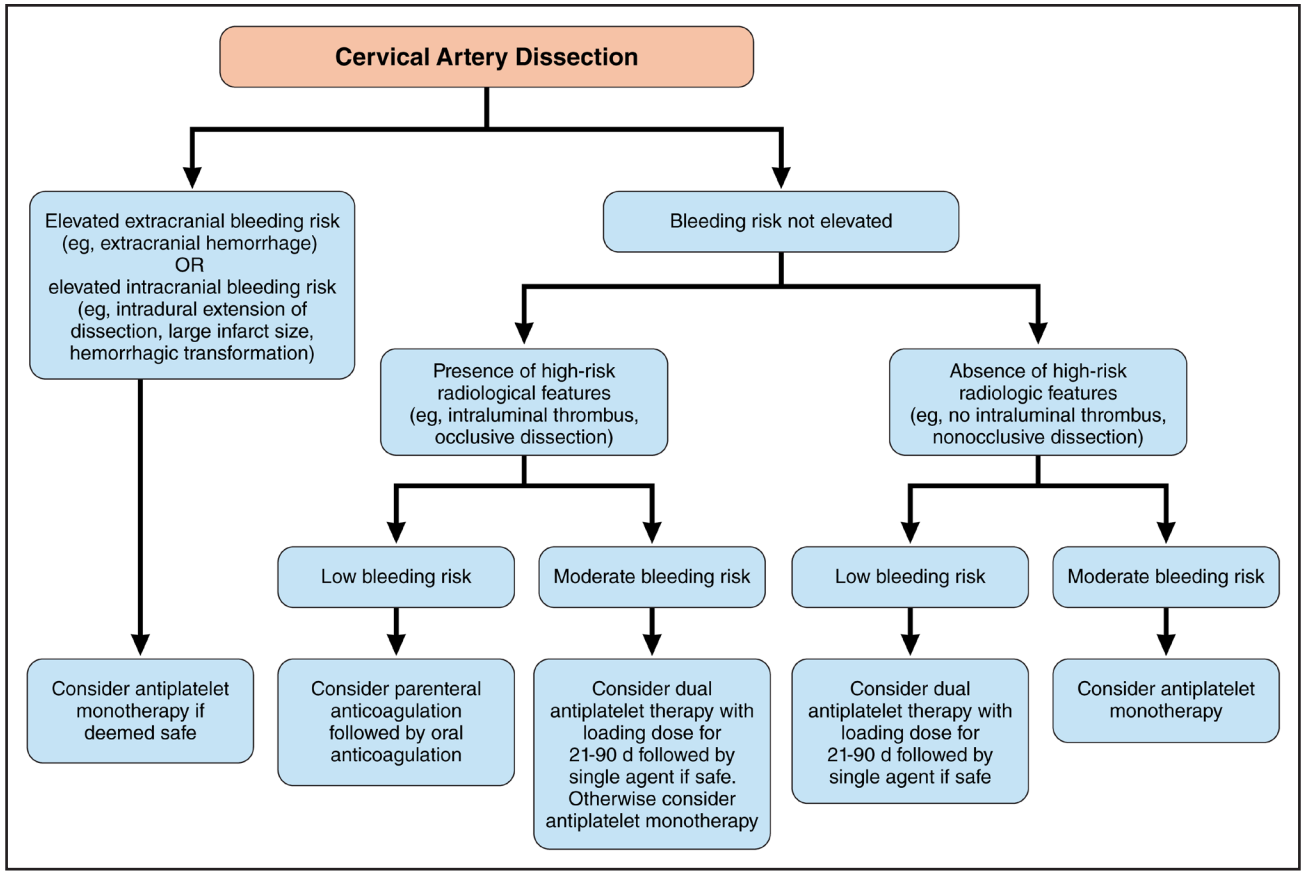

Figure 3. Suggested algorithm for antithrombotic treatment selection in patients with cervical artery dissection.
Patients are stratified according to radiological risk factors for intracranial hemorrhage (eg, large infarct, hemorrhagic transformation, and intracranial extension of the dissection) and important radiological risk factors for ischemic stroke (eg, presence of intraluminal thrombus and high-grade stenosis or occlusion).

(29%) had local symptoms only. Study treatment was aspirin (300 mg/d) in 91 participants (53%) and VKA in 82 participants (47%; of whom 51 had lead-in heparin) and was started a median of 3 days after hospital admission or 7 days after the first symptom (mostly pain). The primary end point in TREAT-CAD was a composite of clinical outcomes (stroke, major hemorrhage, death) and MRI outcomes (new ischemic or hemorrhagic brain lesions) in the per-protocol population assessed at 14 days (clinical and MRI outcomes) and 90 days (clinical outcomes only) after treatment onset. The primary composite end point occurred in 21 patients (23%) in the aspirin group and in 12 patients (15%) in the VKA group (absolute difference, 8% [95% CI, −4 to 21]; noninferiority P=0.55). Accordingly, noninferiority of aspirin was not shown. All ischemic strokes (n=7) occurred in the aspirin group, whereas the only major, albeit extracranial (gastrointestinal bleeding), hemorrhage occurred in the VKA group. There were no deaths in either group. Five of the 7 ischemic strokes in the aspirin group occurred (or recurred) on day 1 after treatment onset, suggesting the importance of early initiation of antithrombotic treatment, whichever the clinician might choose.[101]

A meta-analysis combining the per-protocol results from CADISS and TREAT-CAD at 3 months for the composite outcome of ischemic stroke, major bleeding, or death demonstrated a pooled odds ratio of 0.35 (95% CI, 0.08–1.63) for VKA compared with antiplatelet.[2]

Direct oral anticoagulants, which were not tested in CADISS or TREAT-CAD, have been compared with VKA in a meta-analysis of observational data. The rates of stroke/TIA in the VKA (n=699) and direct oral anticoagulant (n=53) groups were 12.3% (95% CI, 0%–28.6%) and 5.7% (95% CI, 0%–12.2%), respectively. The rates for intracranial, minor, and major extracranial bleedings among VKA- and direct oral anticoagulant–treated patients were 1.2%, 3.7%, and 1.2% compared with 0%, 6.5%, and 0%, respectively. Major limitations include the nonrandomized treatment allocation and the differently sized groups, in particular the limited number of patients in the direct oral anticoagulant group (n=53).[102]

Given the equipoise, a tailored approach for decision-making between anticoagulation and antiplatelet use after an acute cervical artery dissection considering individual patient bleeding risk and the presence or absence of high-risk features is reasonable. The presence of

radiographic high-risk features that are known predictors of ischemic stroke after dissection (such as severe stenosis or occlusion, intraluminal thrombus) in patients with low risk of bleeding may warrant anticoagulation therapy. Patients without radiographic high-risk features or those with an elevated risk of extracranial hemorrhage or ICH (eg, large infarct size, hemorrhagic transformation, intradural extension of extracranial dissection) may be better suited for antiplatelet therapy, with either antiplatelet monotherapy or a short course of dual antiplatelet therapy for 21 to 90 days (in line with minor stroke/TIA and CADISS) if considered safe, followed by single antiplatelet therapy.

Last, although the risk of bleeding with antithrombotic treatment is low, if it occurs, it is reasonable to hold antithrombotic treatment and to weigh the risks and benefits of anticoagulation reversal, considering the risk of recurrent stroke and the risk of worsening hemorrhage.

Duration of Antithrombotic Therapy

The risk of recurrent ischemia attributable to cervical artery dissection appears to be the highest in the first 2 to 4 weeks after diagnosis. In a prospective multicenter observational study of 1390 patients, 68 patients had a recurrent stroke or TIA (7.53/100 person-years); this was ipsilateral to the dissected artery in 80.8% and associated with a recurrent cervical artery dissection in 19.1%.[103] Risk of stroke/TIA up to 6 months was 1.4% overall. All events occurred while the individual was on antithrombotic therapy and were ipsilateral to the dissected vessel. Beyond 6 months, 48 additional ischemic events occurred (3.4%; 23 TIAs and 25 ischemic strokes). There were no significant differences in the proportion of events in those who had continued compared with those who had discontinued antithrombotics (3.3% of 985 taking antiplatelets, 2.0% of 204 on anticoagulation, 4.5% of 201 on no antithrombotic treatment). Of 25 recurrent strokes occurring beyond 6 months, only 1 stroke was related to recurrent cervical artery dissection; all others were not cervical artery dissection related.

Subacute Endovascular Treatment of Dissection

Endovascular therapy increasingly serves as a secondary stroke prevention strategy in a minority of patients with cervical artery dissection, relieving stenoses, improving blood flow and low perfusion, and preventing emboli formation. Angioplasty and stenting may be fairly safe and beneficial in a limited population of patients with flow-limiting stenosis who fail medical treatment.[104,105] A 140-subject retrospective study with a mean follow-up of 1 year suggests that stenting is effective and the rate of ischemic stroke recurrence is low (1.4%).[106] Furthermore, endovascular treatment can be considered in patients refractory to maximal medical treatment. When angioplasty and stenting are not feasible, vessel sacrifice may be considered in patients with recurrent ischemic stroke but adequate compensatory circulation. Thus, overall, endovascular intervention could be considered in the rare case of clinically symptomatic disruption of cerebral perfusion despite best medical management, including hemodynamic optimization and antithrombotic use.

RISK AND PREDICTORS OF RECURRENT DISSECTION

The literature reporting risks of recurrence after incident cervical artery dissection is limited by heterogeneous duration of follow-up and variable use of routine follow-up vascular neuroimaging, which may detect asymptomatic recurrences. Reported rates of recurrence range from 0.7% to 1.9% per patient-year (Table S2).[55,64,107–109] One prospective multicenter study (n=1194) reported a recurrence rate of 3.3% over a mean of 34 months. Median time to recurrence was 3 months. Fibromuscular dysplasia (adjusted hazard ratio, 2.36 [95% CI, 1.13–4.90]) and history of migraine (adjusted hazard ratio, 2.86 [95% CI, 1.24–6.62]) were both independently associated with recurrence.[55] Other studies showed that younger age[108,109] and fibromuscular dysplasia[110] are predictors of recurrent dissection. Another large study examining recurrence within the first 6 months combined prospective and retrospective cohorts. Of 1958 patients, 1.5% with single artery involvement at baseline and 2% of those with multiple arterial dissections had a recurrent ischemic stroke or TIA. Median time to recurrence was 1.45±1.09 months; 48.6% were within the first month.[64]

Some studies report biphasic risks of recurrence: early, within the first month of the initial event, and late, on the order of months to years.[108,109] A prospective study of 238 participants receiving routine follow-up ultrasound found that 9.2% went on to have recurrent cervical artery dissection within the first month of the index event.[109] Later recurrences occurred in 7.1% (n=17) and were associated with younger age, and >40% of recurrent events were asymptomatic.

One series specifically examining risk of recurrence in 91 women who experienced cervical arterial dissection during pregnancy or puerperium found a recurrence rate of 4.4%, none associated with subsequent pregnancies.[111]

LIFESTYLE MODIFICATIONS TO AVOID RECURRENT/WORSENING DISSECTION

Trivial or minor head/neck trauma and manipulation within the preceding month are important risk factors for dissection seen in up to 40% of cases and are more common in patients with dissection compared with

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individuals with non–dissection-related ischemic stroke or healthy control subjects.[112] These minor traumas include neck manipulation (eg, massage, chiropractic manipulation, yoga), extreme head and neck movements or posture (hyperextension or overbending), heavy lifting, and sport activities such as golfing, contact sports, and skiing.[112] It remains uncertain whether avoiding activities associated with cervical trauma risk lowers the risk of worsening or recurrent dissection.

FOLLOW-UP IMAGING AND RECANALIZATION OF THE DISSECTION

One-third of patients with cervical artery dissection who presented with occlusion (25% of total patients with cervical dissection) have resolution at follow-up, with a median time to healing of 4 months.[7] Healing can continue up to 12 months after the initial dissection, beyond which further recanalization is rare.[113] Regardless, in patients with severe stenosis or occlusion, there is no correlation between chronic residual arterial disease and stroke rate beyond the first 6 months from diagnosis.[114] However, data are limited because of the low event rates and limited follow-up periods.

Another common consequence of a dissection is a cervical artery–dissecting aneurysm, which can resolve or decrease in size in half of patients but can increase in size or develop de novo later on. In the CADISS study, 9.1% of patients with cervical dissection at baseline had a dissecting aneurysm, and the incidence at 3 months was 14.5 %.[115] Continuous follow-up shows increased incidence up to 19.4% at a median of 6 months after presentation.[116] The risk of developing a cervical artery–dissecting aneurysm is higher in patients with multiple dissections.[116]

Cervical artery–dissecting aneurysms in patients with cervical artery dissection have a benign prognosis[115,117] and are not associated with an increased risk of recurrent stroke or rupture.[118] Treatment with antiplatelets or anticoagulants did not seem to affect the persistence or resolution of the dissecting aneurysm or the development of new dissecting aneurysm.[115] Cervical artery–dissecting aneurysms can enlarge and rarely cause compressive symptoms,[115,119] (eg, dysphagia, hoarseness, and even stridor secondary to mass effect on local structures such as the vocal cords and oropharynx or recurrent laryngeal nerve). Cervical artery–dissecting aneurysms causing significant mass effect often require treatment with stent-assisted coiling or flow diversion or complete sacrifice to cure the aneurysm and reduce associated mass effect.[120–122] Coiling may be favored if there is concern for aneurysm rupture or rerupture, but dense coil packing may exacerbate mass effect, in which case flow diversion alone without coiling may be more effective in achieving vessel reconstruction.

CONCLUSIONS

Cervical artery dissection occurs as a result of the interplay among risk factors, minor trauma, anatomic and congenital abnormalities, and genetic predisposition. The diagnosis can be challenging both clinically and radiologically. In patients with acute ischemic stroke due to cervical artery dissection, acute treatment strategies such as thrombolysis and mechanical thrombectomy are reasonable in otherwise eligible patients. We suggest that the antithrombotic therapy choice be individualized and continued for at least 3 to 6 months. The risk of recurrent dissection is low, and preventive measures may be considered early after the diagnosis and continued in high-risk patients. Ongoing longitudinal and population-based observational studies are needed to close the present gaps in preferred antithrombotic regimens considering clinical and radiographic prognosticators of cervical artery dissection.

ARTICLE INFORMATION

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

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*Modest.

†Significant.

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