Cervical-artery dissections: predisposing factors, diagnosis, and outcome

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Cervical-artery dissection (CAD) is a major cause of cerebral ischaemia in young adults and can lead to various clinical symptoms, some of which are benign (eg, headache, neck pain, Horner's syndrome, and cranial-nerve palsy), but most patients have a stroke or transient ischaemic attack. In addition to trauma to the neck, other risk factors have been suggested, such as infection, migraine, hyperhomocysteinaemia, and the 677TT genotype of the 5,10-methylene-tetrahydrofolate reductase gene (*MTHFR* 677TT), although evidence is sparse. An underlying arteriopathy, which could in part be genetically determined, is believed to have a role in the development of CAD. Importantly, both research on and optimum management of CAD strongly rely on diagnostic accuracy. Although the functional outcome of CAD is good in most patients, socioprofessional effects can be important. Incidence of the disorder in the general population is underestimated. Mortality and short-term recurrence rates are low but possibly also underestimated. Further research is warranted to improve our understanding of the underlying pathophysiology, to assess the long-term outcome, and ultimately to provide treatment and prevention strategies.

Introduction

Cervical-artery dissections (CADs) are defined by the presence of a mural haematoma located in the arterial wall. Most have been reported to occur in the internal carotid artery, more than 2 cm after the bifurcation, although they can also occur in the vertebral artery. Although the clinical presentation of CAD can sometimes appear benign in cases of isolated pain or Horner's syndrome, dissections are a major cause of ischaemic stroke in young and middle-aged adults.[1] Early recognition and appropriate management of this disorder are therefore of great importance.

Although several comprehensive reviews have focused on different aspects of CAD such as risk factors[2] or treatment,[3] in this Review, we present a global overview of the epidemiology, suspected pathophysiology and predisposing factors, clinical and radiological characteristics, and therapeutic options. Additionally, we summarise published data on the outcome of CAD, including mortality rates and frequency of recurrent stroke and dissections. We deliberately focus on spontaneous (non-traumatic) CAD in adults because these cases are generally managed by neurologists or stroke physicians, whereas traumatic CAD and cases in children are more commonly handled by surgeons and paediatricians and can require different management strategies. Moreover, we do not discuss purely intracranial dissections or aortic dissections extending to the cervical arteries because the mechanisms, symptoms, and management of these disorders are different.

Epidemiology

The incidence of CAD in the general population is low, and is estimated to be about 2·6 (95% CI 1·9–3·3) per 100 000 inhabitants per year as reported in a recent North American population-based study.[4] This number is probably an underestimation as cases of CAD that have little or no clinical signs are likely to remain undiagnosed. Incidence is slightly higher in cities (eg, 3·0 per 100 000 per year in Rochester, MN, USA [for CAD],[4] and 2·9 per 100 000 per year in Dijon, France [for carotid-artery dissections only]),[5] possibly because individuals living in cities have better access to medical facilities. Vertebral-artery dissections are less common than carotid-artery dissections (1·0 per 100 000 per year [95% CI 0·5–1·4] *vs* 1·7 [1·1–2·3] in Olmsted County, MN, USA), although this difference has been reduced by the increased availability of MRI, which enables a non-invasive and accurate diagnosis of vertebral-artery dissection.[4] In 13–16% of cases, multiple CADs occur.[4,6,7]

In the North American study, CAD occurred in the community at a mean age of 45·8 years,[4] which is similar to reports from two large published multicentre series of CAD in European populations (44·0 years [459 patients][6] and 45·3 years [696 patients][7]).

In the North American population-based study[4] and in two large hospital-based CAD series, 50–52% of the patients were women,[8,9] whereas a slight predominance in men was reported in the European multicentre hospital-based series (53–57%).[6,7] Carotid-artery dissections seem to occur more frequently in men and at an older age (47·0 *vs* 43·4 years) than do vertebral-artery dissections, although data are scarce.[4,10]

Most published epidemiological data on CAD are from European and North American populations. The clinical and demographic patterns could be different in other populations. For example, in a consecutive series of 120 Mexican patients with CAD, the mean age was 35·5 years, 53·8% of patients were men, and the most common location was vertebral (55·4%). However, this study was hospital based and therefore subject to referral bias.[11]

Pathophysiology

The pathophysiology of CAD is poorly understood. Some researchers have postulated that patients with CAD could have a constitutional, at least in part, genetically determined weakness of the vessel wall and that

environmental factors such as acute infection or minor trauma could act as triggers.[12,13] The presence of an underlying vasculopathy is suggested by the fact that patients with CAD commonly present with concomitant arterial anomalies, such as fibromuscular dysplasia,[14] aortic-root dilation,[15] hyper-distensibility, and increased stiffness of the arterial wall,[16,17] as well as impaired spontaneous and endothelial-dependent vasodilation.[18–20] An association with intracranial aneurysms[21] and temporal artery histological changes[22] has also been suggested. About 50% of patients with CAD have connective tissue aberrations in their skin,[12,23–25] including composite collagen fibrils and fragmentation of elastic fibres. These anomalies seem to segregate in families in an autosomal-dominant pattern,[26,27] thus suggesting an underlying heritable connective tissue disorder that affects both vessels and skin. Another factor that also supports the presence of an underlying extracellular matrix defect is the high plasma concentrations of proteases, particularly matrix metalloproteinase 2, in patients with CAD.[28]

Predisposing factors
Environmental risk factors
Traumas are important predisposing factors for CAD. Traumatic CADs can occur as a result of major penetrating or non-penetrating traumas.[29] In published works, CAD has been shown to occur in about 1–2% of patients who have had blunt trauma, and the risk is also increased with trauma-associated injuries such as severe facial fractures, skull-base fractures, and traumatic brain injury. The risk of carotid-artery dissections is increased with major thoracic injuries, and that of vertebral-artery dissections is increased with cervical spine fractures or spinal cord injury.[30] In this Review, we focus on spontaneous CAD (ie, not associated with such severe trauma). Spontaneous CAD can be associated with minor traumas,[31,32] such as chiropractic manipulation,[33] various sporting activities,[34] whiplash injury, stretches and sudden neck movements, and severe coughing.[35] These minor traumas are usually characterised by hyper-extension, rotation, or lateroversion of the neck.[35] However, such traumas result in CAD in only a few individuals, and generally only once in any one person. Therefore, as the causal association between minor trauma and CAD is often difficult to establish, and as many cases of CAD occur without any trauma, other predisposing factors must play a part in the development of the disorder.

Several potential predisposing factors have been suggested, but most studies have had major methodological flaws, including a small sample size, selection bias, and confounding factors (described in detail elsewhere).[2] An association of CAD with history of recent infection has been reported,[36–38] potentially predisposing individuals to CAD via endothelial damage or prothrombotic mechanisms. Several studies have also reported a high frequency of hyperhomocysteinaemia[39–43] and migraine[44,45] in patients with the disorder. Low concentrations of α1 antitrypsin have been reported,[46] but this finding has not been confirmed.[47] In one study, significantly more patients with CAD were reported to be on oral contraceptives than those who did not have CAD.[48] A seasonal pattern in the incidence of CAD has also been suggested, with highest rates during autumn or winter. This pattern has been mainly attributed to an increased occurrence of infection and weather-related changes in blood pressure, coagulation parameters, and physical activity.[49,50]

A common assumption is that patients with CAD have few or no vascular risk factors. However, the association of CAD with vascular risk factors has been studied only rarely, usually in small samples,[8,17,18,37,51–57] and only two studies were specifically designed to assess this link.[55,58] In some studies, vascular risk factors were less common in patients with CAD than in young patients without CAD who had an ischaemic stroke,[37,51,52] whereas no association was seen in other publications.[8,17,18,53,54] Only a few studies have compared the prevalence of vascular risk factors between patients with CAD and healthy individuals.[55–58] One study found no association with vascular risk factors[56] and another found a reduced body-mass index in patients with CAD;[58] however, two others noted an increased prevalence of arterial hypertension in patients with the disorder,[55,57] although this association was significant only for patients with CAD with an ischaemic stroke in one of the two studies.[55]

Genetic risk factors
Genetic factors might also have a role in the pathophysiology of CAD, mainly as part of a multifactorial predisposition.[59,60] The prevailing theory is that CAD is a multifactorial disease caused by several genetic variants and environmental factors, each probably having a modest and potentially synergistic effect. Occasionally (<2% of cases), CAD has been associated with a known monogenic connective tissue disease, mainly vascular Ehlers-Danlos syndrome.[59–61] Even though this association is rare, screening patients with CAD for clinical signs that are suggestive of vascular Ehlers-Danlos syndrome is important and, if such signs are present, the patient should be referred to a geneticist. If the diagnosis is confirmed, preventive measures and genetic counselling can be proposed. The occurrence of CAD in patients with Marfan's syndrome or other known monogenic connective tissue disorders, such as osteogenesis imperfecta, seems even more rare than in patients with vascular Ehlers-Danlos syndrome.[59,60] Indeed, although there are a few case reports of CAD in patients with these connective tissue disorders,[59] and some observations of such patients in CAD series have been reported,[6,62,63] large studies of patients with Marfan's syndrome have not reported any cases of CAD and the prevalence of CAD in cohorts of patients with osteogenesis imperfecta is

unknown.[59] The association of monogenic connective tissue disorders with CAD has been reviewed in detail elsewhere.[59] Isolated reports of CAD in patients with other monogenic disorders, such as autosomal-dominant polycystic kidney disease,[64–66] α1 antitrypsin deficiency,[67–69] or hereditary haemochromatosis,[70] have been published. However, whether the concomitant occurrence of these disorders is higher than would be expected by chance is unclear, and these rare monogenic diseases cannot be deemed to be risk factors for CAD at the level of the general population. Similar comments apply to reports of CAD in patients with rare chromosomal disorders such as Turner's syndrome[71,72] or Williams syndrome.[73]

In sporadic CAD, several arguments suggest that genetic factors also have a role as part of a multifactorial predisposition.[60] First, there are several reports of familial cases of CAD in the absence of known connective tissue disorders.[74] Second, up to half of patients with CAD have abnormalities in skin connective tissue[12,23,24] that follow an autosomal-dominant inheritance pattern.[26,27] Third, patients with the disorder commonly present with concomitant arterial abnormalities, suggesting that there might be an underlying constitutional arteriopathy. Most studies that screened candidate genes for mutations and linkage analyses in familial CAD or inherited dermal connective tissue abnormalities yielded negative results,[59,60] and most genetic association studies were negative.[40,47,56,75,76,78–80] Five studies reported associations with variants in three different candidate genes: *ICAM1* (encodes intercellular adhesion molecule 1), *COL3A1* (encodes collagen, type III, alpha 1), and *MTHFR* (encodes 5,10-methylenetetrahydrofolate reductase).[41,42,57,77,81] The associations with the polymorphisms *ICAM1* Glu469Lys and the *COL3A1* 3′UTR two base-pair deletion have not been replicated as yet.[57,77] Three studies (of which two overlap[41,81]) reported an association with the 677TT genotype of *MTHFR*,[41,42,81] but three other studies did not replicate this finding[40,56,75] or did so only in subgroups of patients.[75] However, all published genetic association studies on CAD have been underpowered. More accurate data on genetic risk factors for CAD can be obtained only from much larger multicentre genetic association studies, such as the ongoing genome-wide association study within the Cervical Artery Dissections and Ischemic Stroke Patients (CADISP) consortium.[82] This consortium also aims to examine potential environmental risk factors and gene–environment interactions for CAD.

Clinical presentation
Ischaemic events
The clinical presentation of cerebral ischaemia caused by CAD (transient ischaemic attack or cerebral infarction) does not differ from that of cerebral ischaemia attributable to other factors. Accompanying symptoms and signs, such as Horner's syndrome and neck pain or headache that started shortly before the ischaemic event, can be suggestive of CAD (ischaemic strokes with preceding headache are rare, other causes being cerebral venous thrombosis, vasculitis, and reversible vasoconstriction syndrome). In rare instances, carotid-artery dissection can lead to retinal ischaemia (in 14 of 696 patients with CAD in the largest hospital-based series[7]), and rare cases of cervical spinal cord infarcts resulting from vertebral-artery dissections have been reported.[83]

Local symptoms and signs
The following symptoms and signs can occur separately or in combination: Horner's syndrome; unusual neck pain or headache; cranial-nerve palsy; tinnitus; and, rarely, cervical-root injury. Horner's syndrome and cranial-nerve palsy occur in carotid-artery dissections and cervical-root injury occurs in vertebral-artery dissections.

Sudden-onset Horner's syndrome, particularly if associated with headache or neck pain or with an ipsilateral ischaemic stroke in the carotid territory, can be considered to be specific to carotid-artery dissection and should lead to urgent investigation of the cervical arteries.

The characteristics of pain associated with CAD are not specific and can sometimes resemble migraine or even cluster headache.[84,85] CAD with isolated pain might be more common than expected[86] and is more often caused by extracranial vertebral-artery dissection, but can also be caused by carotid-artery dissections.[86] In a large series of CAD patients in whom pain was the only symptom, the pain was continuous in most cases, and headaches were mostly of a severe intensity and throbbing quality, whereas neck pain was more commonly constrictive and of moderate intensity.[86] The onset type ranged from thunderclap headache to progressive pain.

Cranial-nerve palsies are rare, representing less than 7% of CAD cases in large hospital-based series.[7] The hypoglossal nerve is the most commonly affected, followed by the IXth and Xth cranial nerves, which are topographically close to the carotid artery in its cervical trajectory.[87] The most likely mechanism is compression of the nerves by an enlarged carotid artery. Cranial-nerve ischaemia is another potential mechanism, particularly in very rare cases of upper cranial-nerve palsy.[88]

Other symptoms
Occasionally, CAD can lead to subarachnoid haemorrhage, usually when the dissection extends to the intracranial part of the vessel, with pseudoaneurysm formation and rupture (1% of CAD cases in the largest hospital-based series).[6,7] CAD can also be asymptomatic and discovered through routine examination (6% of CAD cases in the general population[4]). Several cases of asymptomatic or paucisymptomatic CAD probably remain undiagnosed.

Association and time course of symptoms and signs
Patients with CAD typically present with local symptoms and signs and subsequently develop an ischaemic event. The delay between onset of local symptoms and ischaemic manifestations can vary from a few minutes to several

weeks, and is usually less than a month.[8,89] Pain is the most common initial symptom.[4,90]

Patients who have only local signs or symptoms, without cerebral or retinal ischaemia, account for about 33% of all cases in the general population[4] and 23–24% in the largest hospital-based series.[6,7] In these hospital-based series, patients with CAD were identified through neurological departments and, therefore, were probably biased towards having a high frequency of cerebral ischaemic events. The proportion of patients who have CAD without cerebral ischaemia seems to be smaller in vertebral-artery dissections than carotid-artery dissections,[4] but this finding might be because of the low frequency of compression of adjacent structures in vertebral-artery dissections, and dissections with isolated pain are less likely to be diagnosed. Overall, the prevalence of CAD without cerebral ischaemia is probably underestimated because patients with sudden Horner's syndrome, isolated headache, neck pain, or who are asymptomatic might never seek medical attention. In some cases, cerebral ischaemia (or, more rarely, retinal or spinal cord ischaemia) can also occur without local signs.

Mechanisms underlying clinical presentation

Pathologically, CAD is associated with haematoma in the wall of a cervical artery (carotid or vertebral), secondary either to an intimal tear or to direct bleeding within the arterial wall caused by ruptured vasa vasorum. The intramural haematoma can expand towards the intima or the adventitia, resulting in a stenosis or in an aneurysmal dilation of the artery.[13]

The consequences of this haematoma are local symptoms and signs including headache and neck pain (supposedly attributable to a distension of the artery by the mural haematoma stimulating pain-sensitive receptors[86]), Horner's syndrome or cranial-nerve palsies resulting from stretching of sympathetic-nerve and cranial-nerve fibres by an enlarged carotid artery,[87] and, more rarely, cervical-root injury[63,91] caused by compression from an enlarged vertebral artery.

The mechanism by which CAD leads to cerebral or retinal ischaemia is thought to be usually embolic, from intra-luminal thrombi forming at the site of the intimal tear.[92] Haemodynamic infarcts are also possible. Occasionally, CAD can lead to subarachnoid haemorrhage when the dissection extends to the intracranial part of the vessel. Intracranial arteries have no external elastic limitans and have a thinner media and adventitia compared with cervical arteries, which is why intracranial arteries are more prone to rupture.[93]

Radiological diagnosis
Radiological hallmarks

CAD can present as a long tapered stenosis, a tapered occlusion, or a dissecting aneurysm.[94] Among 48 consecutive patients with CAD representative of the general population, stenotic CAD was the most common

form (48%), followed by occlusive (35%) and aneurysmal (17%) CAD.[4]

The most typical and specific sign for CAD is an enlarged artery with a crescent-shaped rim of hyperintense signal surrounding a lumen that is reduced in size. This sign can be seen on T1-weighted axial cervical MRI scans by use of a fat-saturation technique, and is indicative of a mural haematoma (figure 1). Within the first days of developing CAD, the mural haematoma can be isointense.[94] Other characteristics are a luminal flap, false lumen, long tapered stenosis, and dissecting aneurysm (figure 2). The presence of a long tapered stenosis is particularly suggestive of CAD when located at a common site of dissection (typically a few centimetres above the carotid bifurcation and in the V3 segment of the vertebral artery, after the artery exits the transverse foramina and before it enters the foramen magnum[94]), with visualisation of the healthy vessel calibre above and below, and when there is no evidence of atherosclerosis elsewhere. A carotid or vertebral occlusion without evidence of a mural haematoma cannot be diagnosed as a dissection unless it recanalises completely, subsequently revealing a dissecting aneurysm or a long tapered stenosis with the typical features described earlier. In this setting, follow-up imaging is crucial.

Negative imaging of the cervical arteries does not completely rule out the diagnosis of CAD, particularly if the procedure was undertaken at a late stage, as early recanalisations can occur.[13]

Imaging tools for diagnosis

At present, apart from the mural haematoma, which is best seen on axial cervical MRI, typical features of CAD can be visualised with magnetic resonance angiography, CT angiography, or conventional angiography. We prefer to use magnetic resonance angiography combined with T1-weighted axial cervical MRI scans with the fat-saturation technique because of its high sensitivity
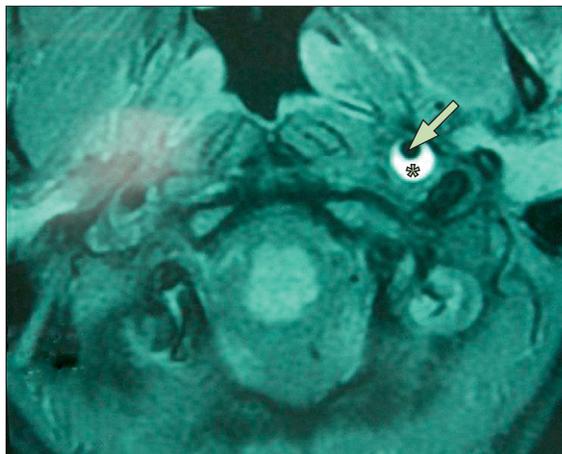

Figure 1: **Axial MRI scan showing a mural haematoma and residual lumen**
Axial MRI scan showing a semilunar hyperintense signal caused by a mural haematoma (black star), and an eccentric hypointense signal attributable to the residual lumen (arrow).
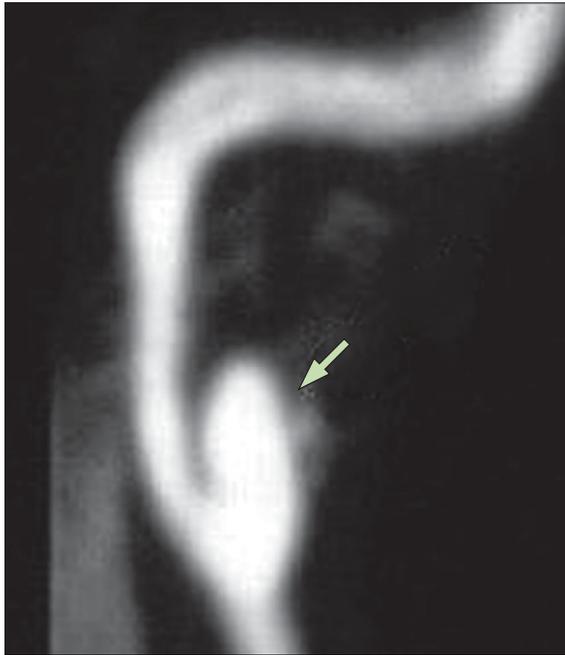
Figure 2: Magnetic resonance angiography showing a pseudoaneurysm of the internal carotid artery
The arrow indicates the pseudoaneurysm of the internal carotid artery.
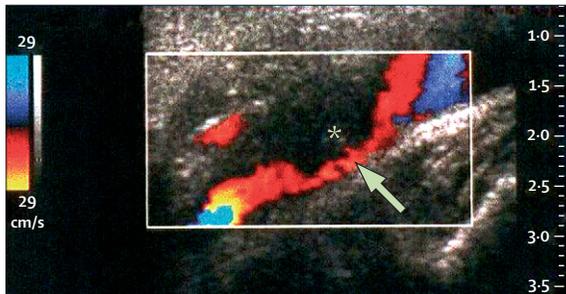
Figure 3: Colour Doppler-coded ultrasonography showing a stenosis of the internal carotid artery caused by the dissection
Stenosis of the internal carotid artery is indicated by the arrow. The white star denotes a dissection.

and specificity and the absence of irradiation. However, CT angiography is useful for the diagnosis of CAD, provided that technical requirements, such as appropriate timing of the bolus of contrast material, are met.[94,95] Owing to concerns about radiation exposure, CT angiography is usually done only when there is a contraindication or difficult access to MRI;[95] however, this technique might reveal more features of CAD than MRI, particularly for vertebral-artery dissections.[96] Conventional angiography, which was the reference method for diagnosis before the advent of MRI, is no longer recommended for the diagnosis of CAD, not only because it is invasive,[97] but also because it does not enable visualisation of the mural haematoma.

Combined colour duplex and Doppler sonography is another non-invasive technique for the diagnosis of CAD

(figure 3), but this should be considered only as a screening tool as it is highly operator dependent and has a poor diagnostic yield for CAD located near the skull base and within the transverse foramina.[94] Furthermore, although the sensitivity of ultrasound was reported to be high (in the setting of a specialist stroke centre) for the diagnosis of carotid-artery dissection causing ischaemia,[98] this technique is poor for the diagnosis of carotid-artery dissection with isolated Horner's syndrome.[99] This finding might be explained by the fact that, in patients with only local symptoms, the dissection rarely causes stenosis with subsequent haemodynamic impairment, and is, therefore, less likely to be detected by ultrasound.[100] Thus, when CAD is suspected, positive or negative findings on colour duplex ultrasound of the cervical arteries require confirmation by magnetic resonance or CT angiography. In the near future, high-resolution magnetic resonance images at 3·0 Tesla,[101] or that use a dedicated surface coil,[102] could improve the ability to differentiate an intramural haematoma from an intraluminal thrombus in occlusive dissections in the acute phase.

In summary, in any ischaemic stroke, transient ischaemic attack, or transient monocular blindness in a young or middle-aged adult with no other confirmed cause, CAD must be ruled out by arterial imaging, including at least one imaging technique other than colour duplex ultrasound. Urgent imaging of the cervical arteries should also be done in cases of Horner's syndrome (or, more rarely, lower cranial-nerve palsy) with headache or neck pain. Magnetic resonance angiography with axial cervical MRI is strongly recommended in this setting, as the dissection is often subadventitial and identification of the mural haematoma is, therefore, essential for a diagnosis of CAD. An appropriate investigation of cervical arteries (including magnetic resonance or CT angiography) should also be done in cases of recent unusual headache or neck pain of unknown cause, particularly if the pain is continuous and of moderate to severe intensity, as pain can be the only clinical symptom of CAD.[86]

Treatment
Anticoagulants or antiplatelets are usually recommended in the acute phase of CAD to prevent primary or recurrent ischaemic events. However, no randomised trial has been done to assess and compare the efficacy of these treatments. A study assessing the feasibility of a randomised trial comparing anticoagulants with antiplatelets is underway.[103] If the incidence of cerebral ischaemia after diagnosis of CAD is in the low range of what has been reported in published work, any clinical trial will be unlikely to have sufficient statistical power to establish the efficacy of either treatment. In the absence of randomised data, the best evidence at present is from a Cochrane systematic meta-analysis of non-randomised studies that reported on outcomes with antiplatelets versus anticoagulants.[104] There was no significant

	Sample size*	CAD type	Mean follow-up (years)	Recurrence rate (%)†	Type of event (n)
Guillon et al[113]	16	ICAD (aneurysmal)	3·1	0	..
Touzé et al[109]	35	VAD and ICAD (aneurysmal)	3·5	0	..
Touzé et al[6]	457	VAD and ICAD	2·6	2·7	Stroke (4), TIA (8)
Bogousslavsky et al[114]	23	ICAD (with stroke)	3·2	4·2	Stroke (1)
Arauz et al[11]	130	VAD and ICAD	1·6	4·6	Stroke (6)‡
Leys et al[115]	105	VAD and ICAD	3·0	4·8	Stroke (2), TIA (3)
Gonzales-Portillo et al[116]	27	VAD and ICAD	4·8	7·4	Stroke (2)§
Benninger et al[117]	38	ICAD (aneurysmal)	6·5	7·9	Stroke (3)
Treiman et al[118]	24	ICAD	9·3	8·3	TIA (2)
Engelter et al[119]	33	ICAD	2·3	9·1	Stroke (2), TIA (1)
Kremer et al[120]	92	ICAD	6·7	11·9	Stroke (5), TIA (6)¶
Beletsky et al[8]	105	VAD and ICAD	1·0	13·3	Stroke (9), TIA (5)‖

Studies describing recurrent events without details on the type of event were not included in this table.[121] de Bray and co-workers[14] reported a rate of stroke recurrence of 0·4% per year, but did not mention the exact number of events and the type of stroke. Wessels and co-workers[122] reported a rate of stroke recurrence of 6%, but the population included both extracranial and intracranial vertebral-artery dissections. CAD=carotid-artery dissection. ICAD=internal carotid-artery dissection. TIA=transient ischaemic attack. VAD=vertebral artery-dissection. *With follow-up data available. †Absolute rate. ‡In the first 2 weeks after the diagnosis. §One ischaemic stroke occurred after percutaneous balloon angioplasty for treatment of a persistent vertebral-artery pseudoaneurysm. ¶One patient also had a subdural haematoma during follow-up. ‖Of these events, five stroke and three TIA recurrences occurred before enrolment in the study (the rate of recurrence was 5·7% after enrolment).

Table 1: Risk of recurrence of ischaemic stroke or TIA in patients with CAD

difference in the rates of death or disability between both treatment groups. Thus, at present, empirical arguments are used to choose between anticoagulants or antiplatelet drugs, and the decision should be made on a case-by-case basis; an algorithm to help with this decision has been published.[3] In a recent UK-based survey,[105] 50% of the physicians who responded always treated CAD patients with anticoagulants, 30% always used antiplatelets, and 15% used either anticoagulants or antiplatelets.

Anticoagulation is sometimes preferred over antiplatelet drugs when there is a severe stenosis, an occlusion (with a risk of embolisation before recanalisation), or a pseudo-aneurysm, provided that the infarct is not too large. Anticoagulants might also be prescribed when a thrombus is seen in the arterial lumen or when the presence of multiple ischaemic lesions in the same arterial territory or high-intensity transient signals on transcranial Doppler suggest an embolic mechanism.[3]

Conversely, antiplatelet drugs are commonly favoured when there is a general contraindication to anticoagulants or when CAD is associated with a large infarct, exposing the individual to a high risk of haemorrhagic trans-formation.[3] Whether antiplatelets should be preferred in cases of local symptoms only is still a matter of debate. Antiplatelet drugs might also be preferred to anticoagulants when there is an intracranial dissection that could lead to a subarachnoid haemorrhage (some centres systematically do a lumbar puncture when an intracranial dissection is involved[63]). However, in the setting of a large single-centre registry, patients with CAD with an intracranial extension of the dissection, presenting without subarachnoid haemorrhage, had a favourable outcome with anticoagulants.[106]

The optimum duration of antithrombotic treatment is unclear; follow-up imaging is important to guide the duration of treatment. Anticoagulants are usually

	Sample size*	CAD type	Mean follow-up (years)	Recurrence rate (%)†
Mokri et al[90]	36	ICAD	4·9	0 (0)
Guillon et al[113]	16	ICAD (aneurysmal)	3·1	0 (0)
Engelter et al[119]	33	ICAD	2·3	0 (0)
Touzé et al[109]	35	VAD and ICAD (aneurysmal)	3·5	0 (0)
Gonzales-Portillo et al[116]	27	VAD and ICAD	4·8	0 (0)
Beletsky et al[8]	105	VAD and ICAD	1·0	0 (0)
Arauz et al[11]	130	VAD and ICAD	1·6	0 (0)
Lee et al[4]	48	VAD and ICAD	7·8	0 (0)
Nedeltchev et al[107]	154	ICAD	1·0	1 (0·6)
Touzé et al[6]	457	VAD and ICAD	2·6	4 (0·9)
Kremer et al[120]	92	ICAD	6·7	1 (1·1)
Desfontaines et al[125]	60	ICAD	3·1	1 (1·7)
Leys et al[115]	105	VAD and ICAD	3·0	3 (2·9)
d'Anglejan Chatillon et al[126]	62	ICAD	3·4	2 (3·2)
Bassetti et al[127]	81	VAD and ICAD	2·8	3 (3·7)
Bogousslavsky et al[114]	23	ICAD (with stroke)	3·2	1 (4·3)
Dziewas et al[10]	126	VAD and ICAD	0·5	6 (4·8)‡
de Bray et al[14]	103	VAD and ICAD	4·0	5 (4·9)§
Schievink et al[9]	200	VAD and ICAD	7·4	14 (7·0)¶
Treiman et al[118]	24	ICAD	9·3	2 (8·3)
Dittrich et al[128]	36	VAD and ICAD	0·6	9 (25·0)‖

Studies describing recurrent events without details on the type of event were not included in this table.[121] Wessels and co-workers[122] reported a rate of CAD recurrence of 3%, but the population included both extracranial and intracranial vertebral-artery dissections. CAD=cervical-artery dissection. ICAD=internal carotid-artery dissection. VAD=vertebral-artery dissection. *With follow-up data available. †Absolute rate. ‡Within 1 month in four patients, and within 1 year for two patients. §Two recurrences occurred 1 year after the first dissection and the remaining recurrences occurred 4, 9, and 10 years later.[14] ¶Two patients also had a renal-artery dissection during follow-up. ‖The recurrence occurred within 1 to 4 weeks after the initial CAD in seven patients.[128]

Table 2: Risk of recurrence of CAD

maintained for no longer than 6 months, but long-term prevention of cerebral ischaemia with antiplatelets can be proposed on the basis of empirical arguments in cases

	Sample size*	Dissection type	Mean follow-up (years)	Mortality rate (%)†
Touzé et al[109]	35	VAD and ICAD (aneurysmal)	3·5	0 (0)
Touzé et al[6]	459	VAD and ICAD	2·6	0 (0)‡
Kremer et al[120]	92	ICAD	6·7	0 (0)
Mokri et al[90]	36	ICAD	4·9	0 (0)
Mokri et al[130]	25	VAD	3·8	0 (0)
Schievink et al[9]	200	VAD and ICAD	7·4	1 (0·5)
Ast et al[131]	68	ICAD	1·0	1 (1·5)
d'Anglejan Chatillon et al[126]	62	ICAD	3·4	1 (1·6)
de Bray et al[14]	103	VAD and ICAD	4·0	2 (1·9)
Lee et al[4]	48	VAD and ICAD	7·8	1 (2·1)
Engelter et al[119]	33	ICAD	2·3	1 (3·0)
Arauz et al[11]	130	VAD and ICAD	1·6	4 (3·1)
Bassetti et al[127]	81	VAD and ICAD	2·8	3 (3·7)
Treiman et al[118]	24	ICAD	9·3	3 (12·5)
Pozzati et al[121]	19	ICAD (occlusive)	8·2	3 (15·8)
Bogousslavsky et al[114]	30	ICAD (with stroke)	3·2	7 (23·3)

CAD=cervical-artery dissection. ICAD=internal carotid-artery dissection. VAD=vertebral-artery dissection. *Studies not included in this table were those that included only patients with follow-up data available,[113] as they are biased towards patients who survived the acute stage; those that reported mortality rates after CAD, but that did not mention the delay between CAD occurrence and death; and those that did not report the duration of follow-up.[132] †Within the first month or during the initial hospitalisation. ‡Two patients died after the acute phase (at 2·4 and 23·7 months).

Table 3: Mortality during the acute stage of CAD

of residual stenosis, occlusion, or aneurysm, even though these patients have not been proven to have an increased risk of ischaemic recurrences. A longer and closer follow-up is recommended for patients with an underlying connective tissue disorder, a family history of CAD, or fibromuscular dysplasia, because of the heightened risk of CAD recurrence.

The currently available observational studies suggest that thrombolytic therapy should not be withheld in patients in whom CAD is associated with an acute ischaemic stroke.[110] In the rare cases in which there is an underlying monogenic connective tissue disease, such as vascular Ehlers-Danlos syndrome, specific treatments and preventive measures might apply.[111] Surgical or endovascular treatments are usually not recommended for spontaneous CAD, as the risk of recurrent ischaemic events seems to be low and correlates poorly with the presence of residual stenosis or dissecting aneurysms. Because of the invasive character of these treatments, they should be restricted to exceptional cases of ischaemic events that are recurrent despite optimum medical treatment[112] until randomised data are available. Different rules might apply for intracranial dissections or CAD caused by penetrating trauma, but this is beyond the scope of this article.

Outcome
Resolution of arterial abnormalities
The proportion of patients with complete resolution of arterial abnormalities varies between studies and was estimated at about 46% for stenoses, 33% for occlusions,

and 12% for dissecting aneurysms in the general population.[4] The likelihood of complete recanalisation seems highest in patients with CAD who present with only local symptoms and signs.[107] Occlusions can lead to residual stenoses, and residual aneurysms can appear after the acute phase in initially stenotic or occluded arteries.[108,109] In CAD cases representative of the general population, complete resolution or stable residual luminal irregularity was documented after a median duration of 0·29 years and in 82% of cases within the first year.[4]

Recurrences
Recurrent ischaemic events seem to be rare, although early recurrences (before the patient is discharged from the acute stroke unit) are not always accounted for in published series. The rate of ischaemic recurrences has been estimated to be between 0%[4] and 13·3%[8] at 1 year (table 1), with the largest recurrence rates observed when recurrent events that occurred before the diagnosis of CAD are taken into account.[8] Recurrent ischaemic events usually occur during the first weeks after the dissection.[6,8] Factors associated with an increased risk of recurrent ischaemic events are multiple dissections[6] and a history of hypertension.[8] Although isolated cases of ischaemic strokes caused by chronic dissecting aneurysms of the carotid artery have been reported,[123,124] two prospective series of aneurysmal CAD found no ischaemic events after about 3 years of follow-up.[109,113] Similar rates of ischaemic recurrences have been reported in 46 patients with CAD with a transient stenosis or occlusion and in 46 patients with CAD with a permanent stenosis or occlusion.[120] However, in another series of 130 consecutive patients with CAD, ischaemic recurrences were attributed to a worsening carotid stenosis in five of six cases.[11]

Recurrences of dissections are rare (table 2); they seem to be most frequent within the first 2 months after the initial event,[128] and some dissections that were diagnosed as multiple might have occurred sequentially within a short time frame. Late recurrences are possibly underestimated as studies with long-term follow-up are scarce. Recurrent dissections were not reported in the only population-based series with follow-up data of 48 patients with CAD (mean duration of follow-up: 7·8 years).[4] In hospital-based series, the rate of recurrent dissections was estimated to be between 0%[6] and 25·0%[128] (table 2). The recurrence rate is probably overestimated in tertiary referral series, which can tend to emphasise unusual cases.[9] Risk factors for recurrent CAD are younger age,[9] a family history of CAD,[74] vascular Ehlers-Danlos syndrome,[1] and fibromuscular dys-plasia.[1,10,14] Early recurrences of dissection in the weeks after the initial event could be a manifestation of a unique transient disorder, whereas late recurrences occurring several months or years later could indicate an underlying connective tissue weakness.[13,129] The prognosis of recurrent CAD has been described as benign.[128]

Mortality and functional outcome

Mortality rates in the acute phase of CAD are generally low in published series (<5%),[4,6,11] although higher rates of up to 23% have been reported in previous series of subsets of patients with more severe CAD, such as CAD with arterial occlusion or ischaemic stroke (table 3).[114,121] In general, mortality after CAD might be underestimated, as patients with severe forms of CAD sometimes die before arterial imaging can be done. In support of this possibility, data from studies on patients with acute complete middle cerebral artery infarction have suggested that CAD could be a major cause of malignant cerebral infarction.[133]

Functional outcome is described as good in about three-quarters of patients with CAD,[13,108] but the effect in terms of quality of life and socioprofessional integration can be important.[1,134] The functional outcome after CAD does not seem to be better than in other types of ischaemic strokes in young individuals.[1] Factors associated with a poor functional outcome are presence of cerebral ischaemia,[10] arterial occlusion,[10,135] carotid location,[11] older age, and a high National Institutes of Health stroke scale score at onset.[63] In addition to sequelae related to cerebral ischaemia, residual headache or neck pain has been described in some patients,[115,136] but published data are scarce.

Conclusions

As one of the major causes of ischaemic stroke in young adults, early identification and management of CAD is important. As well as trauma, several environmental and genetic risk factors have been suggested to underlie CAD, but the current evidence is limited to small series, which do not always use the most appropriate controls and are commonly not replicated. The clinical presentation can include one or several of various symptoms such as headache, neck pain, Horner's syndrome, cranial-nerve palsy, and cerebral (and, more rarely, retinal or spinal cord) ischaemia. Although ultrasound is a practical screening tool, magnetic resonance angiography with cervical MRI and CT angiography are required to confirm (or rule out) the diagnosis.

Medical treatments and prevention strategies are currently based on empirical data only. Antiplatelets or anticoagulants are usually prescribed to prevent recurrent ischaemic events. Mortality rates are low but are probably underestimated as patients with malignant infarcts often die before a diagnosis is made. As in other causes of stroke in young adults, the functional outcome is generally good, but the socioprofessional effects can be detrimental. Recurrence of cerebral ischaemia and CAD seem to be rare, although some data suggest that early ischaemic and late CAD recurrences could be underestimated.

Research that aims to improve our understanding of the environmental and genetic factors predisposing to CAD and that assesses the long-term outcomes of this disease is needed. Whether a randomised trial is feasible

in view of the low incidence of the disease is currently being assessed. A better understanding of the underlying pathophysiology and the natural history of the disease through large prospective multicentre cohorts could also be helpful to improve therapeutic and preventive strategies. Several multicentre efforts are already underway to meet these needs.

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