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Review Article

Cervical artery dissection: Pathology, epidemiology and management

Yang-Ki Kim [a,b], Sam Schulman [a,*]

[a] Department of Medicine, McMaster University, Hamilton ON, Canada
[b] Department of Medicine, Soonchunhyang University, Seoul, Korea

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ABSTRACT

Background: Cervical artery dissection is often treated with anticoagulants to prevent ischemic stroke. The risk-benefit ratio of anticoagulation versus antiplatelet therapy is unclear.
Objectives: To provide an educational review of current data on the disease to explain the rationale for the treatment options and to explore the results of management studies in order to determine if anticoagulation is justified.
Methods: We searched the databases MEDLINE and EMBASE as well as bibliographies for information on anticoagulants and antiplatelet agents in cervical, i.e. carotid and/or vertebral artery, dissection.
Results: There are no randomized controlled trials on the treatment. One systematic review from 2003 identified 20 case series or cohort studies. We identified 9 additional studies with a total of 1,033 patients. Of those, 731 received anticoagulation sometimes followed by platelet inhibition vs. 282 patients treated with antiplatelet agents alone. The rate of ischemic stroke was 2.3% vs. 6.9% and bleeding complications were reported in 0.7% vs. 0%.
Conclusion: It cannot be excluded that there is a net benefit from anticoagulant therapy in cervical dissection, but the studies are flawed by considerable bias. Very ill patients at a high risk of ischemic stroke may have been given aspirin due to fear of hemorrhagic complications. A randomized controlled trial is planned and will be crucial to resolve this issue.

Contents

Abbreviations: CAD, cervical artery dissection; ICAD, internal carotid artery dissection; VAD, vertebral artery dissection; TIA, transitory ischemic attack; hsCRP, high-sensitivity C-reactive protein; MTHFR, methylene-tetrahydrofolate reductase; AT, α1-antitrypsin; FMD, fibromuscular dysplasia; MRI, magnetic resonance imaging; CT, computed tomography; SAH, subarachnoid hemorrhage; MRA, magnetic resonance angiography; CTA, computed tomographic angiography; CDS, color duplex ultrasound; PPV, positive predictive value; NPV, negative predictive value; MES, microembolic signal; rtPA, recombinant tissue plasminogen activator; INR, international normalized ratio; IAD, intracranial arterial dissection; NIHSS, National Institutes of Health Stroke Scale; CADISP, Cervical Artery Dissection in Ischemic Stroke Patients; mRs, modified Rankin score; OR, odds ratio; CI, confidence interval.

* Corresponding author. Thrombosis Service, HHS-General Hospital, 237 Barton Street East, Hamilton ON, Canada L8L 2X2. Tel.: +1 905 5270271; fax: +1 905 5211551.
E-mail address: schulms@mcmaster.ca (S. Schulman).

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Introduction

Cervical artery dissection (CAD), i.e. internal carotid artery dissection (ICAD) and/or vertebral artery dissection (VAD), has an annual incidence of 2.6–3.0 per 100,000 [1,2]. The spontaneous dissection of the carotid or vertebral artery accounts for only about 2 percent of all ischemic strokes, but for 10 to 25 percent of such events in young and middle-aged patients [2–4].

The management consists of a combination of strategies including anticoagulants, platelet aggregation inhibitors, thrombolytic agents, endovascular stent angioplasty, or surgery. Although 70-86% of patients with ICAD and 90-96% of patients with VAD present with ischemic events, namely ischemic stroke and transitory ischemic attack (TIA), as initial clinical manifestation and the main mechanism is embolic rather than hemodynamic, a randomized trial of antithrombotic treatment has never been reported. This review focuses on etiology, pathogenesis, and comparisons between anticoagulants and platelet aggregation inhibitors in CAD [1,5,6]. A recent review by Redekop on the same topic focused on extracranial dissections and discussed more in depth the role of major blunt trauma [7]. That review also presented indirect evidence that early antithrombotic treatment in general appears to reduce the risk of stroke compared to no treatment. In our review the comparison of antiplatelet and anticoagulant therapy is further developed and we have also focused more on pathogenesis and risk factors to illustrate the mechanisms of disease that may provide a rationale for a specific treatment.

Method

Using the computerized search of MEDLINE database (1961 to April, 2008) and EMBASE (1980 to April, 2008) we retrieved articles published in English by using the following MeSH terms and text words: “internal carotid artery dissection”, “vertebral artery dissection”, “cervical artery dissection”, “anticoagulants”, “heparin”, “low-molecular-weight heparin”, “platelet aggregation inhibitors”, “aspirin”. In order to avoid duplication of data, we set criteria for inclusion of articles as those never used in meta-analysis and never reported as different topics in the same population. We reviewed the bibliographies of articles retrieved through the search for additional relevant articles. We retrieved 808 articles on the subject.

Definition and Classification

Cervical arterial dissection is defined as the splitting of the arterial wall of the carotid or vertebral artery. It is further classified as intracranial or extracranial artery dissection. The prevalence of extracranial artery dissection is more frequent than intracranial since the latter represents only 10-40% of CAD [6,8,9].

Pathogenesis

The extracranial portions of internal carotid and vertebral arteries are more vulnerable to dissection than their intracranial segments despite their similar size [10,11]. The vulnerability of the extracranial portion of the internal carotid artery has been explained by the fact that it is freely movable on the neck and its fixation at the entry into the carotid canal at the base of skull makes it susceptible to strain. In addition, the proximity of the carotid artery to the anterior surface of the upper cervical vertebrae contributes to its exposure for injury. The vulnerability of the extracranial portion of the vertebral artery to strain and sudden neck movement has been explained by the fact that it has high mobility when passing through the transverse foramina of cervical spines, as well as the change of direction from vertical to horizontal at the level of the first cervical vertebra, after which the artery becomes fixed [10].

Once a tear occurs in the wall of major arteries of the neck, blood is allowed to enter between the layers of the wall of the artery, forming an intramural hematoma. The splitting of the layers caused by an intramural hematoma results in either stenosis, when the intramural hematoma is formed between the intima and media, or aneurysmal dilatation, when the intramural hematoma is located between the media and adventitia [11]. As another suggested mechanism, intramural hemorrhage forms through ruptures of the vasa vasorum [12,13] without intimal tear, especially if the wall is arteriopathic [14].

It has repeatedly been suggested that underlying arteriopathy plays a role in the pathogenesis of spontaneous CAD. To study the connection between spontaneous CAD and connective tissue abnormalities, 25 patients diagnosed with the former without hereditary connective tissue disorder had dermal connective tissue analyzed with transmission electron microscopy. Abnormalities of collagen and elastic fibers within reticular dermis were identified in 17 (68%) of the patients with CAD, but were not present in any of the 10 controls ($p = 0.0003$), and the findings resembled those seen mainly in Ehlers-Danlos syndrome type III [15]. Based on the fact that skin plays the role of a window to hereditary diseases of the connective tissue [16], it was suggested that the systemic alterations in connective tissue components might be associated with weakness of the vessel wall causing spontaneous CAD [15,17]. This was supported by a study in which biopsy of the superficial temporal artery was obtained in 9 patients with spontaneous CAD [14]. A zone at the junction between the tunica media and the tunica adventitia had weakened with fissuring in 7 of 9 biopsy specimens, but not in any of the controls. Patients with spontaneous CAD may thus suffer from a generalized arteriopathy and reduced stability of the arterial wall [14].

Another question is whether an inflammatory mechanism is involved in the pathogenesis of arterial dissection. High-sensitivity C-reactive protein (hsCRP) is a pro-inflammatory marker and contributes to endothelial dysfunction through effects on vessel wall [18]. Sixty-two consecutive patients who suffered from ischemic stroke or TIA 9 to 24 months before study entry were classified as having large artery atherosclerosis (n = 21), non-traumatic CAD (n = 21), or cryptogenic embolism (n = 20), and were compared with a control group with age-matched volunteers without known vascular disease (n = 54). After adjustment for confounding variables, only CAD was associated with elevated hsCRP (odds ratio 7.9 [1.8 to 34]; $p = 0.004$). The authors assumed that the hsCRP level obtained so far from the event reflected the inflammatory response before the ischemic event and postulated that an inflammatory mechanism is involved in the development of CAD [18] since that response generally is considered to last for a maximum of 3 months after a stroke [19].

Causative and precipitating factors (Table 1)

Intrinsic factors

Hereditary underlying arteriopathy

In an observational study on CAD, 10 of 200 consecutive patients (5%) had a family history of spontaneous arterial dissection involving cervicocephalic arteries, aorta, or renal arteries in one or more of the members [20]. Familial prevalence specifically in CAD is not well documented although seven families with 15 patients have been reported [21]. Family histories of hereditary connective tissue diseases causing CAD were otherwise reported only in a minority of patients [22,23].

Underlying arteriopathy causing arterial dissection has been reported in patients with hereditary connective tissue diseases, such as Ehlers-Danlos syndrome type IV [24–26], Marfan's syndrome [27,28], osteogenesis imperfecta type I [22,29], autosomal dominant polycystic kidney disease [30,31], and pseudoxanthoma elasticum [32]. These are identified in 1 to 4% of patients with spontaneous CAD [33,34].

Beyond the proven hereditary connective tissue diseases, underlying arteriopathy has repeatedly been suggested. A study on the prevalence of connective tissue disease in patients with CAD reported that 3 of 15 (20%) seemed to suffer from inherited connective tissue disorders even though the exact type could not be identified despite extensive investigations [35]. This frequency was much higher than that of earlier published reports.

Genetic approaches to define the association between CAD and genetic factors have been attempted. One possibility is to search for mutations in genes coding for proteins in the connective tissue, e.g. collagen. No causative defects were identified in the candidate genes of COL3A1 [36], COL8A1 [37], COL8A2 [37], ABCC6 [38], and ELN (tropoelastin) [39]. COL5A1 [40] and COL5A2 [41] were investigated because the ultrastructural alterations of the dermal connective tissue in patients with CAD resembled those of Ehlers-Danlos syndrome. Among 19 patients with CAD missense mutations in COL5A1 were observed in 2 siblings, but the mother who carried the same mutant allele had neither an abnormal ultrasound study of the cervical arteries nor symptomatic dissection. Moreover, the majority of patients with CAD did not carry mutations in COL5A1. Similarly, COL5A2 missense mutations were found in 3 of 10 patients with CAD but also in healthy control subjects. Therefore, these mutations are unlikely to be causative for CAD.

The majority of genetic association studies that investigated the association between symptomatic CAD and a genetic polymorphism showed negative results except for ICAM-1 (intracellular adhesion molecule-1, CD54) and methylene-tetrahydrofolate reductase (MTHFR). Homocysteinemia is considered to be associated with CAD through induction of endothelial damage and the C677T polymorphism of the MTHFR gene is the most common defect associated with increased plasma level of homocysteine. In a study of the C677T polymorphism patients with CAD (n = 25), non-CAD ischemic stroke (n = 31) and controls without history of vascular disease (n = 36) were recruited. Median total plasma fasting homocysteine levels and the prevalence of TT genotype were significantly higher in patients with CAD than in control subjects (13.2 vs 8.9 μmol/L; $p = 0.006$, 36% vs 11.1%; $p = 0.045$), but there was no significant difference between patients with non-CAD ischemic stroke and control subjects or between patients with CAD and non-CAD ischemic stroke [42]. Another study with similar design found mean plasma fasting homocysteine levels of 9.81 μmol/L in patients with CAD vs 6.38 μmol/L in controls ($p = 0.001$) and a higher prevalence of the TT genotype in patients with CAD ($p = 0.034$) [43]. However, two subsequent reports failed to find any association between CAD and the TT genotype of MTHFR despite a greater number of patients [44,45].

Based on the suggestion that the plasma level of hsCRP is increased in the postacute phase after arterial dissection, indicating an inflammatory mechanism, the ICAM-1 gene that plays a role in the initial phase of inflammation was recently studied. The EE genotype of the E469K polymorphism of the ICAM-1 gene was more prevalent in 96 patients with spontaneous CAD than in 204 healthy volunteers without a history of vascular disease (27:96, 28.1% vs. 24:204, 11.8% ; $p = 0.002$) [46].

Some reports have suggested a possible etiologic role for α1-antitrypsin (AT) deficiency in patients with CAD [47–49]. α1-AT is an important plasma protease inhibitor for maintenance of arterial integrity. In a study of 22 patients with CAD, a low level of α1- AT was observed in 27% of the patients [50]. Conversely, in another study the frequency of mutations in the α1-AT gene in 74 patients with CAD was not significantly different from the normal control subjects [51]. Furthermore, in another study there was no significant difference in the serum level of α1-AT and in the frequency of mutations between 80 patients with CAD and same number of controls [52]. Considering these facts, α1-AT deficiency does not appear to play an important role in the cause of CAD.

Nonspecific underlying arteriopathy

Fibromuscular dysplasia (FMD) is a non-atherosclerotic, non-inflammatory disease that mainly involves the renal and carotid artery and presents with segmental stenosis of small and medium sized arteries [53,54]. FMD is an uncertain etiology and it is a nonspecific finding in various systemic disorders [11,54]. The reported prevalence of FMD in patients with CAD based on angiography is 12-18% in ICAD, 2-8% in VAD, and 8-16% in CAD [5,6,34,55,56].

Although embolism is usually considered the main mechanism of ischemic stroke in CAD, atherosclerosis does not appear to be contributing. In a study of 130 patients with ICAD investigated with magnetic resonance imaging (MRI) and computed tomography (CT), there was no or minimal evidence of atherosclerosis in craniocervical arteries and ascending aorta, and chronic asymptomatic cerebral infarcts were not observed [57].

Extrinsic factors

Various anamnestic details of hyperextension or sudden rotation of the neck frequently precede the development of CAD. Sudden neck movements may injure the arterial wall through mechanical stretching [11,58]. The minor injuries reported as a precipitating cause of CAD include coughing [59], vomiting [60], prolonged head tilting [61], roller coaster rides [62,63], diverse sports activities like golf [64], treadmill running [65], springboard and scuba diving [66], medical and surgical procedures like anesthesia [67], intravascular catheter placement [68], fine needle aspiration biopsy of the neck [69], and chiropractic manipulation [70,71].

These injuries may be distinguished from major traumatic causes characterized by direct injury, such as motor vehicle accident [72], direct hit to the neck [73], and strangulation [74,75]. Nevertheless it still remains uncertain which standard should be applied in the separation of traumatic from spontaneous causes [34]. Since each study has applied its own classification for definition of traumatic and spontaneous origins [5,6,56,76,77] and there is little evidence to prove their causal relationship due to low incidence rate, it is reasonable to classify spontaneous causes as including the presumed minor injuries mentioned above [6].

The proportion of dissections triggered by chiropractic manipulation in hospital based studies was 16-28% for CAD [5,6,58], and higher for VAD than ICAD, 72% and 28%, respectively [58]. The increased susceptibility of VAD in chiropractic manipulation is linked to the fact that the vertebral artery is exposed to torsion injury owing to the abrupt change in direction before entering skull [10,58]. In a case-control study of 51 patients with CAD, chiropractic manipulation done

within 30 days, occurred more often than among 100 controls (14% vs. 3%, $p=0.032$), and it was an independent risk factor for VAD [78]. However, it is still debated whether chiropractic manipulation should be considered as a true traumatic cause, and even though it might be presumed as such, and how long intervals from the chiropractic manipulation can be considered as relevant.

Acute infection was the suspected trigger for CAD in one case report [79]. In a case control study 43 patients with acute spontaneous CAD and 58 patients younger than 50 years with acute cerebral ischemia were questioned about the history of infection within 1 week before the event [80]. Recent infection, mainly respiratory, was more common in patients with CAD (25:43, 58.1%) than in controls (19:58, 32.8%) ($p=0.01$) and remained associated with CAD in the multivariate analysis (odds ratio [OR], 2.42; 95% confidence interval [CI] 1.01-5.80; $p=0.05$). There was, however, no association between serum antibodies against *Chlamydia pneumoniae* or heat shock protein 65 and CAD [80].

Clinical manifestations

Headache and neck pain are the most common symptoms in patients with CAD. Since headache may precede ischemic symptoms from the brain or eye by minutes or days, this localized warning sign should provide an important clue to the differential diagnosis against atherosclerotic disease with neurologic manifestations, which usually precede pain. This offers a chance to verify the diagnosis and treat the patient before cerebral ischemia develops [81,82]. A recent study reported that 20 of 245 patients (8%) with CAD presented with pain as the only symptom [83].

Internal carotid artery dissection

The presence of headache was reported in 44-69% in patients with ICAD [5,82,84]. Headache occurs in most cases ipsilateral to the dissection and mainly in the frontal or fronto-temporal area. Facial pain perceived between the mandible and zygomatic area including the ear, and ocular pain, which are considered clearly different from frontal headache, were observed in about half of patients with ICAD but not in VAD [82]. Neck pain confined to upper lateral cervical area develops in one quarter of patients with ICAD [82,85]. The headache may precede the first neurologic manifestation (43 of 92 [47%]) or occur approximately at the same time as the neurologic event (40 of 92, [43%]) [82]. The onset of headache is usually gradual, but some patients present with acute onset, or thunderclap onset resembling a subarachnoid hemorrhage. The quality is frequently described as constant, occasionally throbbing and the course is usually continuous. Although about one fourth of patients with ICAD had a history of migraine, about half of those perceived the headache as being unique. The median time to the appearance of other manifestations was 4 days [82].

Cerebral ischemia including stroke and TIA is the most common neurologic manifestation of ICAD reported in 49 to 84% of the patients. Like carotid stenosis of atherosclerotic cause, TIA or transient monocular blindness generally precedes the ischemic stroke in patients with ICAD [5,6,82,86]. Focal neurologic manifestations in patients with ICAD may present as ocular sympathetic palsy, cranial nerve palsy, transient monocular blindness, or pulsatile tinnitus. Oculosympathetic palsy without facial anhidrosis, referred to as partial Horner's syndrome, is a typical manifestation of ICAD observed in less than half of the patients, and it consists of miosis and ptosis ipsilateral to the dissection [5,6,82]. It is advisable to consider unilateral oculosympathetic palsy as a clinical manifestation of ICAD until proven to be of other origin [11]. Since innervation of sweat glands in the face is from the sympathetic plexus around the external carotid artery, facial anhidrosis is not present in ICAD [11]. Lower cranial nerve palsies from III to XII can be observed in less than one fifth of the patients. Thus distortion of the sense of taste due to involvement of the hypoglossal nerve is observed in about 10% of patients. Transient monocular blindness and pulsatile tinnitus are detected in one quarter of the patients [82]. Only less than one third of the patients present with the full set of typical manifestations, which include unilateral pain on the forehead, neck, or face accompanied by partial Horner's syndrome and followed by cerebral or retinal ischemia hours or days later [11,82].

Vertebral artery dissection

Headache was reported in 50-75% in patients with VAD [5,82,84,87], predominantly located to the occipital area and usually unilateral but not rarely bilateral. The characteristics of the headache are similar to that of ICAD, *i.e.* usually gradual onset, steady and pressure-like or throbbing pain in about half of the patients. About 50% of the patients with VAD consider the headache distinct. It frequently occurs simultaneously with the other manifestations of VAD, occasionally preceding them with a median interval of 14 hours [82]. The reported prevalence of neck pain ranges between 34% and 72%, which is slightly more frequent than ICAD (26-49%) [5,82,87]. Since posterior headache or neck pain as the first presenting symptom is commonly mistaken for muscle tension headache or musculoskeletal neck pain, the diagnosis of VAD is often not realized until focal ischemia develops [82]. Other important symptoms are vertigo, nausea and vomiting, unilateral facial numbness, and unsteadiness in about half of the patients [87].

Ischemic manifestations are ischemic stroke in 67-85% and TIA in 10-16% with at least one of them occurring in 77-96% of the patients [1,5,6,88]. Lateral medullary syndrome resulting in difficulty with swallowing or speaking or both is caused by the involvement of the brain stem, and occurs in less than one fifth of the patients with VAD. Other neurologic manifestations are cerebellar signs including gait ataxia, partial Horner's syndrome, and visual field abnormalities [6,87]. Subarachnoid hemorrhage (SAH) is detected in 3 to 8% of patients with CAD, but it is more common in intracranial artery dissection (20 to 23%) and then usually originating from dissection of the posterior circulation [6,8,9]. Intracranial arteries have fewer elastic fibers in the media, thinner adventitia, and no external elastic membrane, explaining the predisposition to bleed through the rupture of the adventitia [9].

Diagnosis

The diagnosis of CAD is based on direct visualization of the intramural hematoma and narrowing or occlusion of the arterial lumen.

Conventional angiography demonstrates the arterial lumen and will show irregularities of the arterial wall. Double lumen and intimal flap on angiography are pathognomic findings of ICAD, but are only seen in less than 10% of cases [89]. Tapered narrowing of the internal carotid artery (referred to as “rat's tail” or “string sign”), a flame-shaped occlusion, and aneurysms are considered to be diagnostic, but are not considered to be specific [90]. The major angiographic patterns of CAD are radiologically classified into stenosis, occlusion, and aneurysm formation [12,89], constituting 41-75%, 18-49%, and 5-13%, respectively of CAD [5,6,55,89,91]. Irregular stenosis or occlusion usually starts in ICAD about 2 to 3 cm distal to the carotid bulb and in VAD in the distal segment of the artery at the level of the first and second cervical vertebrae [12,89]. Although conventional angiography has been a standard modality to diagnose CAD, magnetic resonance angiography (MRA) and computed tomographic angiography (CTA) have provided alternatives that are less invasive. Intramural hematoma can be directly identified with MRI [92–94]. Nevertheless, conventional angiography is preferable for patients receiving endovascular treatment as an assistant tool [90].

MRI has been used to detect intramural hematoma through T1-, T2- weighted imaging techniques and to demonstrate abnormalities within vascular lumen through MRA [93–95]. Intramural hematoma is characterized by an eccentric, crescent-shaped, hyperintense area adjacent to the arterial lumen with vascular expansion [93,96]. Since intramural hematoma in the acute stage of arterial dissection can be hypointense on T2- and T1-weigthed images, MRI may fail to detect intramural hematoma within the first 24 to 48 h after occurrence of arterial dissection. High signal intensity on T1-weighted images is obtained after a few days and can last up to 2 months. An increase of the external diameter of the artery may be the most valuable indicator of dissection at the very early stage [97,98]. Fat-suppression technique of MRI is useful in differentiating intramural hematoma from soft tissue since a small intramural hematoma is hard to distinguish from hyperintense fat around the vessel [98]. MRA demonstrating luminal change of the artery has shown good correlation with intra-arterial angiography [93]. The diagnosis of VAD through MRI is less sensitive and specific compared with that of ICAD because the diameter of vertebral artery is smaller with wide physiological variations [99].

Multisection CTA provides without invasiveness useful information about the arterial lumen and vessel wall using contrast and maximum intensity projection or multiplanar reformation technique. A recent case control study with 17 patients with VAD and 17 controls showed that sensitivity and specificity of multisection CTA compared to conventional angiography were 100% and 98%, respectively [100]. The expected advantages of CTA are suggested to be better information in the very acute phase when MRI may show hypointense intramural hematoma, accessibility after office hours, and minimal requirement for patient cooperation through quick examination [90,99]. Both MRA and CTA require good renal function.

Color duplex ultrasound (CDS) is commonly used as another noninvasive diagnostic method. The main findings are an echogenic intimal flap, known as the most specific sign, floating thrombus within vascular lumen, and an abrupt, smooth tapering of the arterial lumen. The hemodynamic information from Doppler is a bidirectional high resistance flow pattern (biphasic to and fro flow), markedly reduced blood flow velocity or absence of flow, and no flow in the false lumen on color flow Doppler imaging [101–103]. A recent study using CDS in patients with first carotid territory stroke, TIA or retinal ischemia was performed to examine the diagnostic accuracy [104]. Seventy-seven of 177 enrolled patients were diagnosed as ICAD before they underwent MRI and MRA. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for diagnosis with CDS were 96%, 94%, 92%, and 97%, respectively [104]. Given the high sensitivity and NPV, CDS should reliably exclude ICAD in patients with carotid territory ischemia [104].

However, in a retrospective study (ICAD 55, VAD 31) 11 of 86 patients (12.8%, ICAD 9, VAD 2) with confirmed CAD were initially negative on ultrasonography. The explanation was that ICAD was present in the distal arterial segments and that VAD was missed due to high variability [105]. This study suggested that when CAD is suspected but the result of ultrasonography is negative, repeat ultrasonography and further imaging with for example MRI should be performed [105]. In cases of VAD, the diagnosis using CDS is more difficult than in ICAD because the course of vertebral artery passing through between transverse process of cervical vertebrae is hard to fully examine [106].

Transcranial Doppler is not required for the diagnosis but may provide important information on the potential for development of stroke. Reduced blood flow velocity and microembolic signals (MES) may be the harbingers of a stroke. In a systematic review Ritter et al found that in a population with CAD (n = 82) MES was reported in 50% of those presenting with TIA or stroke but only in 13% of those with local symptoms [107].

The diagnosis of CAD requires a high level of suspicion. Fig. 1 illustrates the typical medical history and symptoms that should alert the physician and also suggests a diagnostic algorithm. It is difficult to recommend diagnostic imaging in every patient with unilateral headache without focal neurology, since the yield would be extremely low. The pathways suggested here are not necessarily the optimal ones in every medical care setting and the level of evidence is low in the absence of randomized studies.

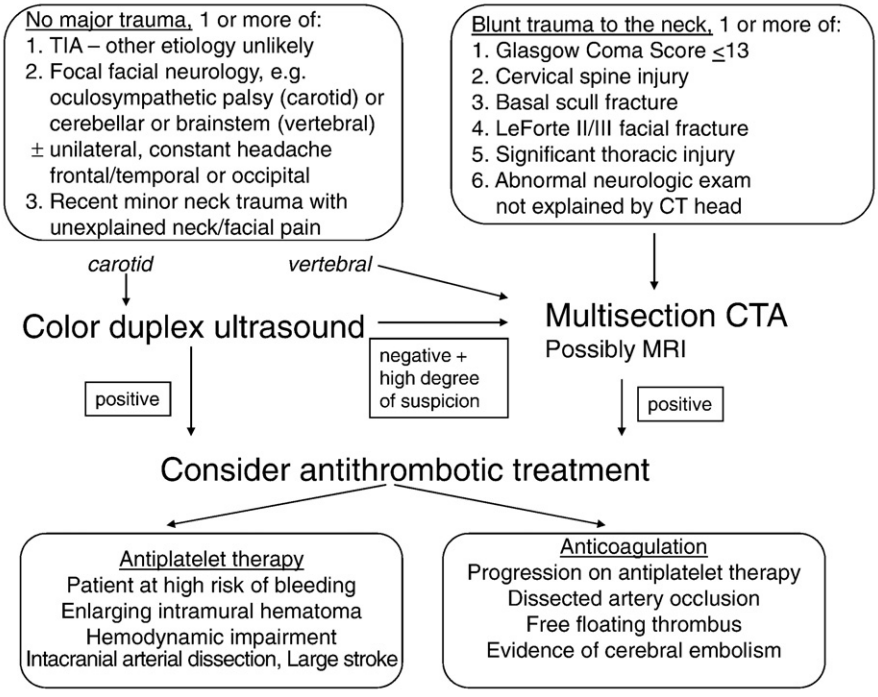

Fig. 1. Suggested diagnostic algorithm and choice of antithrombotic therapy. The criteria in case of blunt trauma are based on the study by Schneidereit et al [134].

Epidemiology

In population-based studies in the United States and France, the average annual incidence rate per 100,000 inhabitants was 2.6-3.0 for overall CAD, and separately for ICAD 1.7–1.9 and for VAD 1.0–1.1 [1,2]. Surprisingly, the incidence rate of VAD increased about 3 times after 1994, from 0.5 to 1.3 per 100,000 in Olmsted, MN, and from 0.5 to 1.5 per 100,000 in Rochester, MN [1]. It was surmised that the gradual increase of use of MRI led to increased recognition of VAD over time rather than a true surge of the incidence [1]. The spontaneous dissection of the carotid and vertebral artery accounts for only about 2 percent of all ischemic strokes [2–4].

All age groups can be affected by spontaneous dissections of the carotid and vertebral arteries, including children. The peak incidence is in the fifth decade of life, and women are about five years younger than men at the time of the dissection [11]. Recent reports on spontaneous dissections have shown similar demography with a mean age of 37-47 in men and 34-44 in women (Table 2).

The reports on sex differences in CAD are somewhat controversial [34,84]. We have summarized studies with data on sexual predilection, and there is a slight predominance of males (56%) (Table 2).

The annual incidence of ischemic stroke and TIA during a mean follow-up of 31 months was estimated to be 0.3% per year and 0.6% per year, respectively [91]. In a study with 161 consecutive patients with ICAD followed clinically and with ultrasound for 6.2 years the annual rate of stroke in the ipsilateral carotid territory was 0.3% in patients with transient severe stenosis or occlusion versus 0.7% among those with permanent pathology. The annual rate of stroke in any territory was 0.6% and 1.4%, respectively [108].

Relationship between CAD and thromboembolic disease

Arterial dissection disturbs the local blood flow and provides a chance to form a thrombus that blocks the circulation. The major underlying mechanism of ischemic stroke in arterial dissection is regarded as embolic rather than hemodynamic. To verify the cause of ischemic stroke in CAD, a retrospective study with 40 patients suffering from ischemic stroke and ICAD, based on the result of angiography and brain CT or MRI, used a classification according to maps of vascular territories and etiologies. Embolic origin resulting in territorial infarcts including cortical and subcortical ones accounted for 92.2% of all infarcts, whereas hemodynamic origin resulting in any infarct located between 2 arterial territories (referred to as "junctional" and "watershed" infarcts), was presumed in only 7.7% [109]. This study suggested that the hemodynamic mechanism could be important during the formation of the intramural hematoma, whereas the embolic one could be prominent after this phase, and ischemic stroke in patients with ICAD mainly occurred secondary to thrombus formation in the dissected artery. In another study in 130 patients with spontaneous ICAD similar diagnostic methods and classification for the stroke pattern were used as mentioned above. All patients with ischemic stroke and ICAD had territorial infarcts and 5% of these were accompanied by infarcts located between 2 arterial territories [57]. Transcranial Doppler monitoring was adopted to investigate the relationship between microemboli and early ischemic recurrence in 28 consecutive patients with ICAD. The MES in transcranial Doppler monitoring was detected in 46% of all patients. Early ischemic response, defined as a) a new ischemic event with involvement in the ipsilateral arterial territory as the previous stroke or as b) abrupt deterioration in the prior deficit within the first 7 days after index stroke, frequently occurred in 6 of 13 (46%) patients with MES compared with 1 of 15 (7.7%) patients without MES. In addition, MES disappeared in 70% of the patients within 24 hours once anticoagulant treatment started [110]. On the other hand, hemodynamic origin was suggested as an equally prevalent underlying mechanism as embolic origin in another study of 11 patients with stroke and ICAD [111].

Table 1
Causative or precipitating factors of cervical artery dissection.

Intrinsic factors
Hereditary underlying arteriopathy
Ehlers-Danlos syndrome type IV [24,25]
Marfan syndrome [27]
Osteogenesis imperfecta type I [22,29]
Autosomal dominant polycystic kidney disease [30,31]
Pseudoxanthoma elasticum [32]
Nonspecific underlying arteriopathy
Fibromuscular dysplasia [5,6,34,55,56]
Extrinsic factors
Trauma with obvious direct injury
Motor vehicle accident [72], direct hit on neck [73], strangulation [74,75]
Minor injury
Coughing [59], vomiting [60], prolonged head tilting [61], roller coaster rides [62,63]
Sport activities (golf [64], treadmill running [65], springboard and scuba diving [66])
Minor injury associated with medical and surgical procedures
Induction of anesthesia [67], intravascular catheter placement [68], fine needle aspiration biopsy of the neck [69]
Chiropractic manipulation [70,71]
Recent infection [79,80,135]

Table 2
Baseline characteristics of cervical artery dissection.

Author, Year, ref	Diagnosis (n)	Males, n (%)	Mean age
	ICAD : VAD : Both		Males : Females
Bassetti 1996 [131]	66 : 15: 0	49 (60)	46 : 44
Gonzales-Portillo 2002 [136]	17 : 8 : 2	15 (56)	38 : 43
Beletsky 2003 [6]	49 : 67 : 0	56 (48)	46 : 42
Kremer 2003 [108]	92 : 0 : 0	51 (55)	46
Dziewas 2003 [5]	78 :46 : 2	76 (60)	43.6 : 42.4
Pelkonen 2003 [55]	64 : 27 : 2	61 (66)	46.8 : 42.3
Bassi 2003 [56]	36 : 13 : 0	34 (71)	46.8
Guillon 2003 [135]	33 : 12 : 2	26 (55)	44.8
Touze 2003 [91]	289 : 75 : 95	243 (53)	44.0
Arnold 2006 [84]	501 : 163 : 32	399 (57)	47.5 : 42.5
Arauz 2006 [77]	58 : 72 : 0	70 (54)	36.5 : 34.3
Lee 2006 [1]	30 : 16 :2	24 (50)	45.8
Chandra 2007 [76]	11 : 9 : 0	10 (50)	44.8 : 39.6
Total	1,324 : 523 : 137	1,114 (56)	

ICAD : internal carotid artery dissection, VAD : vertebral artery dissection.

Treatment

Thrombolysis

Since thrombolytic therapy in CAD confers a risk of extension of the vessel wall hematoma, dislocation of intraluminal thrombus, SAH due to vascular leakage, and pseudoaneurysm formation, few studies have been performed [112]. There are two main regimens of thrombolysis in the treatment of acute stroke in patients with CAD. In intra-arterial thrombolysis recombinant tissue plasminogen activator (rtPA) or urokinase is directly administered into the occluded arteries distal to the dissection and the second regimen is intravenous administration of the same drugs. Urokinase (mean dose, 590,000 IU; range 400,000 to 1 million IU) was used intraarterially in 7 CAD patients within 6 hours of carotid territory stroke and 12 hours of basilar artery occlusion. The effect was evaluated by arteriography immediately after thrombolysis and the recanalization of the cervical artery was obtained in 3 of 7 patients (complete in 1 patient, partial in 2) whereas no change was observed in 4 of 7 [113]. In addition, intracerebral hemorrhage after thrombolysis was not observed in any patients, as evaluated with computed tomography or MRI within 24 hours of thrombolysis.

A retrospective review described 33 patients with spontaneous ICAD and vascular occlusion treated with intravenous rtPA (0.9 mg.kg

body weight) within 3 hours after stroke onset, followed by anticoagulants or platelet aggregation inhibitors [112]. The degree of stenosis was evaluated with digital subtraction angiography performed within 50 hours after thrombolysis. No stenosis, at least 50% stenosis, or occlusions were observed in 8 (24%), 8 (24%), and 17 patients (52%), respectively. On repeated computed tomography within 52 hours of thrombolysis, 4 hemorrhagic transformations, no parenchymal hematoma, and no subarachnoid hemorrhage were observed [112].

Through combining the study mentioned above with a literature review, it was suggested that intravenous thrombolysis is not associated with a high risk of new or progressive local signs (0:50 patients), pseudoaneurysm formation (1:44), SAH (0:50), asymptomatic hemorrhagic transformation (4:50), or symptomatic intracranial hemorrhage (1:50) [112,113].

Anticoagulation

Although there is no randomized trial evaluating antithrombotic treatment, the conventional treatment for CAD is anticoagulation based on the presumed embolic mechanism. The duration of the treatment is generally 3 to 6 months and the therapeutic range with vitamin K antagonists is international normalized ratio (INR) 2.0 to 3.0 [114]. This approach is based on the observations that recanalization occurs in a large proportion of the patients within the first 2 to 3 months following the dissection, and recurrence of symptoms may occasionally occur between 3 and 6 months after the dissection following discontinuation of anticoagulation, but only very rarely after 6 months [114].

The majority of the patients with CAD in many case series received antithrombotic treatment. As summarized by us in Table 3, 651 of 933 patients (70%) received anticoagulants and 282 (30%) received a platelet aggregation inhibitor. Although anticoagulant treatment is widely used to manage patients with CAD, this routine is still under debate [115–117]. Lyrer [116] pointed out four reasons against routine anticoagulation for the extracranial arterial dissection: 1) anticoagulant treatment may provoke enlargement of the intramural hematoma, leading to worsening of the hemodynamic condition, 2) recurrence of ischemic stroke in CAD is rare, and the therapeutic benefit in terms of reduced occurrence of ischemic strokes is very limited, but the risk of bleeding complication remains during the entire period of anticoagulation, 3) hemodynamic changes may contribute to ischemic stroke, and occurrence or recurrence of stroke has been reported in spite of anticoagulant treatment or platelet aggregation inhibitor therapy, 4) in a Cochrane systematic review of the effect of antithrombotic drugs, anticoagulant treatment was not superior to platelet aggregation inhibition regarding primary outcomes, such as death or dependency (Table 4).

Based on the finding that intracranial arterial dissection (IAD) carries a higher risk of SAH leading to a life-threatening condition, anticoagulant treatment is considered contraindicated for these patients [114,118]. Conversely, a recent retrospective study of IAD concluded with a different view [8]. In this report 81 consecutive patients presented with IAD without SAH or aneurysm. They were all managed with immediate heparin or low-molecular-weight heparin for 5-7 days followed by oral vitamin K antagonist for 3 months, and none of the patients developed intracranial bleeding such as SAH or recurrence of stroke at 3 months. On the other hand, 21 of 22 patients who had IAD and SAH at the time of presentation had a fusiform aneurysm caused by arterial dissection and 7 of the 22 patients died within 3 months in spite of surgical intervention without anticoagulant treatment. This study suggested that for IAD patients presenting without aneurysm and SAH anticoagulation treatment is safe [8]. Immediate anticoagulant treatment is not indicated for patients with CAD and severe stroke. This is based on the observation that the rate of symptomatic hemorrhagic transformation increased in patients with severe stroke with National Institutes of Health Stroke Scale (NIHSS) score of 15 or more as reported in a trial comparing the heparinoid danaparoid with placebo [119,120].

Recently, the Cervical Artery Dissection in Ischemic Stroke Patients (CADISP) Study Group suggested criteria for immediate anticoagulation. These consisted of 1) high intensity transient signals detected by transcranial Doppler monitoring despite dual platelet aggregation inhibition, 2) occlusion or pseudo-occlusion, 3) multiple TIAs or strokes affecting multiple regions (same circulation), and 4) free-floating thrombus [121].

Platelet aggregation inhibitors

The platelet aggregation inhibitors were in many studies primarily used in patients with contraindications to anticoagulation, CAD in the absence of any ischemic symptom, and following 3 to 6 months of anticoagulant treatment because of residual luminal irregularity [6,77,108,110,114]. Aspirin alone has mainly been used at a dose of 100 to 325 mg or occasionally clopidogrel at a dose of 75 mg daily.

The CADISP Study Group suggested criteria for platelet aggregation inhibitors, namely 1) severe stroke with NIHSS score $\geq$15, 2) no brain imaging available, 3) accompanying intracranial dissection, 4) local compression syndromes without stroke or TIA, 5) concomitant diseases with increased bleeding risk (extra- or intracranial), and 6) insufficient intracranial collaterals [121].

Comparisons between anticoagulants and platelet aggregation inhibitors

We have summarized the number of patients with CAD from studies providing separate analysis of outcomes according to treatment methods (Table 3). In addition to the Cochrane systematic review of 26 studies from 2003 [122], we identified 7 more studies fulfilling our criteria.

The systematic review by Lyrer and Engelter included all studies with at least 4 patients suffering from extracranial internal carotid artery dissection [122]. They retrieved initially 87 case series, but only 26 studies with 327 patients contained a comparison between the two treatments. Results on deaths (Table 3) or deaths and disability were presented based on this number. Results were also provided on stroke and major hemorrhage based on 571 patients, but the details of those studies were not provided.

In our analysis, all cause mortality was 1.8% (6 of 336, 95% CI 0.7-3.9) with anticoagulants and 2.8% (6 of 215, 95% CI 0.6-6.0) with platelet aggregation inhibitors. The overall mortality without consideration of the type of treatment was 2.1% (22 of 933, 95% CI 1.0-6.0) (Table 3). The difference in the number of patients and the sum of those with antithrombotic treatment is due to the fact that mortality was reported according to the type of treatment in 3 of the 8 studies [6,77,122]. In the systematic review the proportion of dead or disabled patients treated with platelet aggregation inhibitors or anticoagulants was 23.7% (14 of 59) and 14.3% (17 of 119), respectively, but the difference was not statistically significant (Peto OR 1.94, 95% CI 0.76-4.91), although the result appeared to favor platelet aggregation inhibitors [122].

In our review the incidence of intracranial bleeding complications following anticoagulant treatment (Tables 3) was 0.6% (4 of 667, 95% CI 0.2-1.5) versus none following antiplatelet treatment (0 of 288), and the overall incidence was 0.4% (4 of 955, 95% CI 0.1-1.1). The studies quoted in this review except for those of Lyrer [122] and Pelkonen [55] included intracranial CAD [6,56,76] or did not specify whether this subset was included (Table 3). The intracranial bleeding complications are more frequent in intracranial CAD, and still the incidence of bleeding complications is very low. Ischemic stroke in anticoagulant treatment occurred in 2.3% (16 of 703, 95% CI 1.3-3.7) and in antiplatelet treatment in 6.9% (21 of 304, 95% CI 4.3-10.4). The overall incidence of ischemic stroke was 3.7% (37 of 1,007, 95% CI 2.6-5.0). Compared to the results of the meta-analysis on extracranial ICAD where the incidence of ischemic stroke was 1.2% (5 of 414) with anticoagulant treatment and 3.8% (6 of 157) with antiplatelet

Table 3
Clinical outcomes in cervical artery dissection according to antithrombotic treatment.

Author, Year, ref	Therapy	N	Follow-up, months	Ischemic stroke complications, n	Intracranial bleeding complications, n	Recurrence of dissection, n	Death, n
Lyrer 2003 [122]	anticoagulation	218	NA	5*	2*	NA	4
	antiplatelet	109		6*	0*		2
Beletsky 2003 [6]	anticoagulation	71	10	3	NA	9†	2
	antiplatelet	23		2	NA		0
Kremer 2003 [108]	anticoagulation	58	74 - 86	4	1	NA	4†
	antiplatelet	32		4	0		
Dziewas 2003 [5]	anticoagulation	113	NA	1	1	6†	1†
	antiplatelet	9		6	0		
Pelkonen 2003 [55]	anticoagulation	78	NA	NA	NA	3†	2†
	antiplatelet	4		NA	NA		
Bassi 2003 [56]	anticoagulation	35	NA	NA	0	NA	2†
	antiplatelet	7		NA	0		
Arauz 2006 [77]	anticoagulation	47	19	3	0	0	0
	antiplatelet	83		3	0	0	4
Lee 2006 [1]	anticoagulation	31	93.6	NA	NA	0	1†
	antiplatelet	15		NA	NA	0	
Total	anticoagulation	651		2.3% (16/703) (95% CI 1.3-3.7)	0.6% (4/667) (95% CI 0.2-1.5)		1.8% (6/336**) (95% CI 0.7-3.9)
	antiplatelet	282		6.9% (21/304) (95% CI 4.3-10.4)	0% (0/288)		2.8% (6/215) ** (95% CI 1.0-6.0)
	Total	933	10 - 93.6	3.7% (37/1007) (95% CI 2.6-5.0)	0.4% (4/955) (95% CI 0.1-1.1)	3.8% (18/474) (95% CI 2.3-5.9)	2.8% (22/933) (95% CI 1.0-6.0)

NA : not available. *These numbers are based on a different population with 414 with ICAD and 157 with VAD. **Numbers are based on the studies where death rates were separated for treatment (refs 6,76,120). †Numbers are total for the study, not specified per treatment.

treatment, and the incidence of intracranial hemorrhage was 0.5% (2 of 414) with anticoagulant treatment and 0% with antiplatelet treatment [122], the results in our review show slightly higher rates of ischemic stroke but similar rate of intracranial bleeding complications. Since there was no randomized study in this review or in the meta-analysis, outcome events might be subject to bias and also underrepresented. The higher incidence of ischemic stroke with antiplatelet therapy may be explained by the possibility that these patients had more serious conditions.

In a randomized controlled trial for the secondary prevention of non-cardioembolic stroke, Warfarin versus Aspirin in Secondary Stroke Prevention (WARSS) study, there was no difference between warfarin and aspirin to prevent further ischemic events [123]. The only way a fair comparison of anticoagulants with platelet aggregation inhibitors can be made to justify any antithrombotic treatment as the first line of therapy is with a large randomized controlled trial. Based on the results of the meta-analysis performed by Lyrer et al, the sample size needs to be at least 1400 in each treatment arm to detect with a power of 90% a 5% difference in the proportion of patients dead or disabled from 24% to 19% (a 25% relative odds reduction). The study design should contain a strict definition of ICAD or VAD, a standardized diagnostic protocol, random allocation to each type of antithrombotic treatment, and accurate assessment of outcome with no bias [122]. A feasibility study of Cervical Artery Dissection of Stroke Study (CADISS) is actually ongoing in United Kingdom.

Fig. 1 contains a suggestion for choice of antithrombotic therapy.

Table 4
Arguments for and against anticoagulant therapy in patients with cervical artery dissection.

For anticoagulation	Against anticoagulation
Major cause of ischemic stroke in CAD was considered as embolic through the analysis of stroke pattern and observation of microembolic signals	Not superior to antiplatelet therapy regarding the incidence of "death or disabilitiy"
Relatively high incidence of ischemic complications compared to that of bleeding complications	Enlargement of the intramural hematoma
Relatively short term requirement for anticoagulation about 3 months	Increased risk of symptomatic hemorrhagic transformation, mainly in severe strokes (NIHSS score 15) Continuing bleeding risk during anticoagulation Possibility of hemodynamic cause for ischemic stroke in patients with CAD

Surgical and Interventional treatment

Symptomatic CAD requires mainly medical management initially to prevent further thrombus formation or embolization. When medical management is insufficient, endovascular therapy or surgical treatment should be considered [124]. These conditions include recurrent symptoms despite anticoagulation [125–127], contraindication to anticoagulation [126,127], expanding or symptomatic pseudoaneurysm [126,128], and significantly compromised cerebral blood flow [125].

A recent study reported treatment using endovascular stent angioplasty in 7 patients with carotid artery dissection [124]. The indications for this treatment were ongoing ischemia despite anticoagulation in three patients, expanding pseudoaneurysms in three, and significantly reduced cerebral blood flow in one. All lesions with luminal narrowing were dilated with a small (2.5 to 4 mm) coronary balloon before stent manipulation, and self-expanding or balloon-expandible stents were used in each vessel treated according to the vessel size and location. There were no immediate clinical complications, no significant residual stenosis as evaluated by ultrasonography, CTA, or repeat digital subtraction angiography, immediate improvement or resolution of neurologic deficits, and no recurrent ischemia during follow-up (mean duration, 14 months) except for an asymptomatic intraprocedural dissection and a hemorrhagic conversion of a large infarct after endovascular therapy [124]. In a larger cohort of 26 consecutive patients and 29 stenting procedures the average 71% dissection-induced stenosis was eliminated [129]. There were 3 peri-procedural TIAs but no stroke, 2 late re-occlusions with one stroke and 2 patients with late recurrent TIAs. In both studies intravenous heparin was given during the procedure, aiming at activated clotting time of 250-300 s, together with clopidogrel (continued for 4-6 weeks) and aspirin indefinitely.

Surgical treatment includes resection with vein interposition graft, arterial ligation or clipping, thrombendarterectomy with patch angioplasty, extracranial to intracranial bypass surgery [130]. Surgical repair was in a case series of 50 patients associated with a 12%

incidence of death or minor stroke and a 55% incidence of cranial nerve damage, which usually was transient [124,130]. Therefore surgery should be reserved for cases with intractable persistent ischemic symptoms in spite of medical treatment in patients who would not be candidates for endovascular therapy [114].

Prognosis

The rate of the recurrent dissection was reported as 2% per month during the first month after the first episode and then 1% per year during a mean follow-up of 7.4 years in a study performed in 200 patients with CAD [34]. The cumulative rate of recurrent dissection was 3.7%, 5.0%, and 11.9% at 2, 5, and 10 years, respectively [34]. The delayed recurrence of the dissection was observed more frequently in other studies [55,91,131]. The high risk of recurrence during the first month is believed to be related to transient arteriopathy whereas late recurrence may be due to a chronic underlying arteriopathy [34]. Recurrent dissections mainly occurred in arteries not affected by the initial dissection [34,131]. Increasing age was in one study inversely associated with the risk of recurrence ($p=0.03$) and the cumulative rate of recurrent dissection during 10 years after the initial event was 16.8% in patients younger than 45 years versus 6.1% in older patients [34]. In the same cohort the rate of recurrent arterial dissection in patients with a positive family history was higher than those without (5 of 10 [50%] vs 11 of 190 [5.8%], relative risk of 6.3, [95% CI, 2.2 to 18.3; $p=0.0007$]) [20]. In our review, the incidence of recurrent dissection is 3.8% (18 of 474, 95% CI, 2.3-5.9) after a mean follow-up of 47 months but data was only available from 5 studies (Table 3).

The functional recovery determined by modified Rankin score (mRs) during follow-up is summarized in Table 5. The clinical outcome was classified as favorable (mRs of 0 to 2) or unfavorable (mRs of 3 to 5). After a median follow-up of 6 months, 75% of the patients had a favorable outcome (805 of 1070, 95% CI, 73-78). Prognostic factors related to poor functional outcome are arterial occlusion and the occurrence of stroke ($p<0.05$) [5].

In a study with follow-up angiography in 23 patients with ICAD, recanalization rate was 85% within 3 months [132] (Table 6). In another study, recanalization was seen in 82% of the stenoses but in only 30% of the occlusions [55]. There are several reports on the neurological impact of the vascular outcome or recanalization of arterial stenosis or occlusion. In a sonographic assessment of recanalization in 48 patient with ICAD, the recanalization occurred in 68% of the dissections during the first 2 months after the onset of symptoms, without any influence on neurologic outcomes, such as ischemic stroke or TIA [101]. In a long-term follow-up of patients with ICAD and persistent (46 patients, 6.2 years) or transient (46 patients, 7.2 years) severe stenosis or occlusion, there was no relation between residual arterial pathology and stroke rate [108]. There are two reports that neurologic outcomes are influenced by the presence of good collaterals rather than recanalization or type of antithrombotic treatment [101,133]. Therefore, in cases with residual severe stenosis or occlusion without recurrent ischemic stroke after treatment, it is still uncertain whether surgical treatment would be beneficial for prevention of stroke. In addition, since in two long-term studies annual rates of ischemic stroke were as low as 1.4% in permanent and 0.6% in transient severe stenosis or occlusion [108], and 0.7% after treatment [91], invasive interventions like surgery or endovascular therapy would be beneficial only in highly selected patients. The high rate of complication in surgical treatment also needs to be considered.

CAD has a benign long-term prognosis in terms of low rate of recurrent dissection, high proportion of favorable functional outcome, and low rate of ischemic and bleeding complications.

Table 5
Functional recovery using modified Rankin disability score (mRs) during follow-up.

Author, year, ref	Diagnosis	n	Time of evaluation, months	Favorable outcome*, n (%)
Gonzales-Portillo 2002 [136]	ICAD + VAD	27	58	23 (85)**
Beletsky 2003 [6]	ICAD + VAD	105	12	93 (89)
Kremer 2003	ICAD	73	3	56 (77)
Lyrer 2003 [122]	ICAD	178		147 (83)
Deziwas 2003 [5]	ICAD + CAD	126	6	88 (70)**
Auraz 2006 [77]	ICAD + VAD	130	6	72 (55)
Lee 2006 [1]	ICAD + VAD	48		44 (92)
Arnold 2006 [84]	ICAD + VAD	383	3	282 (74)
Total	ICAD + VAD	1,070	6	805 (75) (95% CI 73-78)

* Defined as mRs 0-2.
** Favorable outcome was 0-1 in this study.

Table 6
Comparisons of the recanalization at the time of diagnosis and during follow-up.

	Steinke 1994 [101], n (%)	Nakagawa 2000 [137], n (%)	Pelkonen et al : 2003 [55], n (%)
No of dissection	50, all ICAD	17, all VAD	111 ; ICAD 76, VAD 35
Method of evaluation	Doppler ultrasonography	Conventional angiography	Conventional angiography
Time of follow-up evaluation	~24 months	~340 days	3-6 months
Radiologic findings			
Stenosis			
Initial, n (%)	39 (78)	8 (47)	56 (50)
Follow up, n (%)			
Recanalization	26 (67)*	3 (38)**	41 (84)**
Occlusion	6 (15)	4 (50)	3 (6)
No change	7 (18)		3 (6)
Other		1 (12)§	2 (4)§§
Occlusion			
Initial, n (%)	11 (22)	3 (18)	38 (34),
Follow up, n(%)			
Recanalization	8 (73)	2 (67)	9 (30)
No change	3 (27)	1 (33)	20 (67)
Other			1 (3)§§§

* Recanalization of the dissection was defined as the reappearance or increase of diastolic blood flow in the Doppler spectrum.
** There was no definition of recanalization.
§ Aneurysm formation.
§§ Two patients had slight improvement.
§§§ Progression of thrombosis of artery.

Conclusion

Our conclusions are hampered by several limitations in this literature review. Firstly, there is no randomized study of the treatment and therefore all the reported results may be subject to bias. Secondly, conclusions regarding optimal treatment for CAD according to etiology are impossible since the studies differ on the definition of and presentation of results according to spontaneous CAD or traumatic CAD. Thirdly, most available data do not separate extracranial from intracranial CAD. The location of CAD is important for the evaluation of safety. If the population includes a large proportion of intracranial CAD, it may lead to overestimation of the risk of hemorrhagic complication and mortality.

CAD is of great importance in stroke in the young and middle-aged patients. Hereditary or nonspecific underlying arteriopathy, injury due to stretching of the arterial wall, and inflammation in the arterial wall may cause CAD, however, the etiology of CAD often remains uncertain. With embolic origin as the presumed pathogenic mechanism for stroke, anticoagulant or antiplatelet treatment strategies have been tried. The overall prognosis of CAD is excellent with good functional recovery and a low rate of recurrent dissection, ischemic and bleeding complications. A direct comparison of anticoagulant with antiplatelet treatment in a large randomized controlled trial is required to determine the best treatment strategy.

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