Treatment issues in spontaneous cervicocephalic artery dissections

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The management of cervicocephalic arterial dissections raises many unsolved issues such as: how to best acutely treat patients who present with ischemic stroke or occasionally with sub-arachnoid hemorrhage? How to best prevent ischemic stroke in patients who present with purely local signs such as headache, painful Horner Syndrome or neck pain? How long and how should patients be treated after cervicocephalic arterial dissections? Can patients resume their sports activities and when? The consensus is that, given the well-established initial thromboembolic risk, an urgent antithrombotic treatment is required in patients with a recent nonhemorrhagic cervicocephalic arterial dissection, but the type of antithrombotic treatment – anticoagulants or aspirin – as well as the indication for a local arterial treatment such as angioplasty/stenting remain debated. Evidence from a randomized clinical trial would be welcome but such a trial raises major issues of methodology, feasibility and funding. Meanwhile, cervicocephalic arterial dissection remains a situation when a bedside clinician should use, on a case-by-case basis, best clinical judgment and adopt a stepped care approach in the minority of patients who deteriorate despite initial treatment.

Key words: carotid artery dissection, endovascular treatment, thrombolysis, treatment, vertebral artery dissection

Introduction

Spontaneous cervicocephalic artery dissections (CCAD) are increasingly recognized as a major cause of ischemic stroke, particularly in young subjects (1, 2), and CCAD treatment remains highly controversial. No randomized clinical trial (RCT) has so far been performed, and in the numerous published case series and reviews, treatment options range from no treatment – other than analgesics for head or neck pain – to a variety of treatments as different as anticoagulation, aspirin, thrombolysis, surgery and angioplasty with stenting. Such a diversity of treatment options merely reflects the huge heterogeneity of CCAD, linked to the association of several crucial factors:

- clinical presentation, which includes isolated pain, pain with local signs, ischemic events going from transient ischemic attacks (TIA) to massive cerebral infarction and sub-arachnoid hemorrhage (SAH)
- arterial involvement, which may be single or multiple, extracranial far more frequently than intracranial, and in the carotid territory more frequently than in the vertebrobasilar territory
- morphological status of the artery, which is highly variable, with a lumen that can be normal, stenosed, occluded, enlarged by a dissecting aneurysm or even ruptured, and
- delay from symptom onset to stroke, which is crucial in such a dynamic condition in which the dissected artery can rapidly reopen or remain occluded and in which patients with purely local symptoms experience an ischemic stroke a few days later.

Given this heterogeneity, there can be no uniform treatment in CCAD. The pros and cons of the various treatment options should be discussed on a case-by-case basis taking into account the four above-mentioned major factors. The bedside clinician dealing with CCAD patients mainly faces three situations, which themselves raise a number of treatment issues: first, issues of acute stroke treatment in patients presenting with stroke; second, issues of prevention of ischemic stroke in patients presenting with local symptoms or TIA; and third, issues of long-term postdissection treatment. Finally, the question arises as to what is the feasibility of a RCT in CCAD.

Treatment issues in acute stroke due to CCAD

By far, the most frequent variety of stroke in CCAD is ischemic stroke, which is the only type of stroke occurring in extracranial dissections, and the most frequent one in intracranial dissections. However, some patients with intracranial dissections present with SAH, either alone or with ischemic

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stroke, and obviously require a totally different therapeutic approach.

Ischemic stroke

In the largest series of CCAD to date, 410 of 696 patients (59%) presented with ischemic stroke (3). Two points should be emphasized before discussing treatment options: first, whereas the diagnosis of dissection can be sometimes easy when ischemic stroke occurs after trigger factors (e.g., cervical manipulation, roller coaster ride, blunt cervical trauma, etc.), followed by head or neck pain for a few days in a young stroke patient, it is far more difficult if ischemic signs occur without any preceding symptoms or local signs such as Horner's syndrome, so that in many cases, treatment has to be decided upon and performed without knowing that dissection is the cause. Second, brain imaging and transcranial Döppler (TCD) studies suggest that the most common mechanism leading to ischemic stroke in internal carotid artery dissection (ICAD) is artery-to-artery thromboembolism. However, hemodynamic impairment, alone or combined with thromboembolic events, is possible and should be looked for with TCD (4–7).

As in all ischemic strokes, the primary issue is to save the brain tissue at risk in order to allow the best possible recovery. The most effective way to save oligo-ischemic brain tissue is to re-open the occluded artery as early as possible, which can be achieved by several methods; the most widely used is intravenous (IV) thrombolysis with rt-PA, which is a very effective ultra early treatment for patients with acute ischemic stroke (8, 9). The CCAD was not an exclusion criterion in the large multicenter RCT showing the efficacy of rt-PA in acute ischemic stroke but the number of patients with CCAD included in these studies is not known because such patients were neither identified before thrombolysis nor analyzed retrospectively. The results of recent retrospective and uncontrolled observational studies of CCAD patients treated with IV thrombolysis suggest that safety, including the risk of intracerebral hemorrhage, and efficacy are similar to those in patients with other causes of ischemic stroke. Potential complications from longitudinal or transversal expansion of wall hematoma and vessel rupture causing cervical hemorrhage or SAH have not been reported (9–12).

Despite the lack of evidence, and although further data are needed, there is thus a strong case in favor of using IV rt-PA in patients with an acute ischemic stroke due to extracranial CCAD. Other options to reopen the artery include arterial thrombolysis (13), mechanical clot extraction, and acute stenting of a stenosed CCAD, followed by intra-arterial *in situ* thrombolysis or clot extraction, which have all been performed successfully in selected cases (14, 15).

This hyperacute IV or intra-arterial treatment only applies to a minority of patients with CCAD. In all other cases, as well as after the hyperacute treatment, all agree that an antithrombotic treatment is indicated but there are endless debates about which antithrombotic treatment should be given: heparin or aspirin? Heparin is the classically recommended treatment and is still used by a majority of stroke centers (16). However, both the available data from meta-analysis and observational studies and the classical arguments in favor of heparin strongly question this recommendation**.** Comparing antiplatelet drugs with anticoagulants, a Cochrane Database systematic review of 36 eligible observational studies including 1285 patients found no significant difference in the odds of death (OR 2·02, 95% CI 0·62–6·60) or the occurrence of ischemic stroke (OR 0·63, 95% CI 0·21–1·86) (17). There was, based on 36 studies including 463 patients, a nonsignificant trend in favor of anticoagulants (OR 1·77, 95% CI 0·98–3·22) but symptomatic intracranial hemorrhages (0·8%) and major extracranial hemorrhages (1·6%) occurred only in the anticoagulation group (17).

Another meta-analysis identified 34 nonrandomized case series including a total of 762 patients, of whom 494 received anticoagulants and 268 antiplatelet drugs (18). Only one of these studies was prospective (19). The risk of death was similar in the two groups (1·8%) and this was also the case for the risk of stroke: 1·9% in the antiplatelet group vs. 2% in the anticoagulant group. The combined endpoint of stroke or death occurred in nine of 268 (3·4%) patients in the antiplatelet group and 19 of 494 (3·8%) in the anticoagulant group ($P = 0{\cdot}43$). In a recent case series of 298 patients with internal carotid artery dissection, of whom 202 received anticoagulants and 96 received aspirin, the frequency of ischemic events (including TIAs) was 5·9% with anticoagulants vs. 2% with aspirin. Symptomatic intracerebral hemorrhage was observed in two anticoagulated patients and in none of the patients treated with aspirin (20). The results of these meta-analysis and observational data should be interpreted with extreme caution in the absence of randomization, but taken together, they nevertheless suggest that there is no superiority of anticoagulation over aspirin.

As regards the classical arguments in favor of heparin, the main one is the underlying prevailing thromboembolic mechanism of ischemic events in CCAD (distal emboli from a stenosis, embolization during recanalization of an occluded artery, and presence of a floating thrombus in some patients). However, there is no proof or scientific reason to think that antiplatelet drugs, which are used in other varieties of arterial stenosis or occlusion (21), would not be as effective to address this thromboembolic mechanism. The possibility of a hemodynamic mechanism underlying ischemic events in CCAD is often considered as an argument in favor of heparin because of the greater efficacy of anticoagulants over aspirin in low-flow situations, but it is not known whether this holds true for CCAD. Finally, the benefit/risk ratio of aspirin at the acute phase of ischemic stroke has been shown to be superior to that of heparin in randomized-controlled trials (22) so that heparin is nowadays rarely used in the acute treatment of cerebral infarction. Why heparin should be better than aspirin when the infarct is due to CCAD remains unclear, but even if heparin was indeed more effective, it may not be worth the risk and

inconvenience, considering the low risk of recurrent events in patients with ischemic stroke due to CCAD (20). Given these uncertainties, our first choice in patients with ischemic stroke due to CCAD is, as in other ischemic strokes, 300 mg of aspirin. Heparin is given – provided there are no contra-indications, such as a large infarct – in the rare cases with intraluminal thrombus, low middle cerebral artery (MCA) flow, or recurrence of ischemic events despite aspirin, if endovascular treatment is not feasible.

Symptomatic treatment of ischemic stroke due to CCAD is similar to that of other ischemic stroke; stroke unit care, which has a well-proven efficacy in reducing death, disability and need for long-term institutional care; bed rest if hemodynamic compromise is present; general medical management; hemicraniectomy in malignant MCA infarction; posterior brain surgery in large compressive cerebellar infarcts; and early rehabilitation (23, 24). Pain killers should be added for the headache, which may be extremely severe for several days and may last up to a month.

In summary, in ischemic stroke due to CCAD, as in all other varieties of ischemic stroke, the prognosis depends mainly on the amount and topography of brain cell damage. Treatment includes:

- reopening of the artery in the first few hours when feasible and by the most appropriate method on a case-by-case basis
- antithrombotic treatment: aspirin or heparin according to the best clinical judgment
- decompressive surgery in a few selected cases, and
- stroke unit care with the usual general medical treatment including bed rest if TCD shows signs of hemodynamic compromise.

SAH

SAH is rare and occurs only in intracranial artery dissections, mostly in the vertebrobasilar system (intracranial vertebral artery dissections (VAD) and basilar artery dissections) (25). Usually easily detected on CT scan, SAH may only be diagnosed at lumbar puncture, which should therefore be performed in case of clinical suspicion in patients with intracranial dissection before embarking on an antithrombotic treatment. If SAH is present, antithrombotic treatment is definitely contraindicated, even in patients who have both SAH and ischemic events. Symptomatic treatment of SAH is the same as in other varieties of SAH but the main issue is about the specific local arterial treatment, which is much more complicated and debated than for the classical aneurismal SAH. Surgery has been successfully used in patients with SAH due to intracranial VAD to prevent re-bleeding (26), but nowadays, surgery is more and more replaced by endovascular therapy such as stent-assisted coil embolization (27, 28). A rare therapeutic option of a large intracranial dissecting vertebral artery aneurysm is the proximal occlusion of the dissected artery, provided that the contralateral vertebral artery is patent (29).

Treatment issues in patients with CCAD presenting with local signs and/or TIA

The issue in patients presenting with local signs or TIA is no longer that of the acute stroke treatment but the prevention of cerebral infarction, the most feared complication.

Local signs and TIAs

Local signs are extremely frequent and have a high diagnostic value in extracranial CCAD. The most frequent are headache; cervical or neck pain, which are present in 80–90% of cases; Horner syndrome, which is present in 30–40% of intracranial atherosclerotic disease (ICAD); and cranial nerve palsy, in 5–10% of ICAD (30–33). They may resume the presentation in up to one third of ICAD (34), probably far less in VAD (31). In the other cases, they precede the onset of ischemic stroke or, more rarely, in about 20% of cases (30), they occur together with the ischemic stroke. When this is the case, the issue is again at acute stroke treatment, whereas, when they are isolated, the crucial question is of the risk of ischemic stroke and how to prevent it. The same question applies even more urgently to patients presenting with TIAs, which occur in 15–29% of ICD (32) and 19% of VAD (31). For obvious reasons, there are no prospective data on the natural history of CCAD patients presenting with purely local signs and/or TIAs. Retrospective data indicate that ischemic stroke may occur up to one-month in ICAD, with 82% during the first week (30). The interval is much shorter in TIAs, from one-hour to 17 days in a recent series of VAD, with a median time interval of one-day (31), but only half of the patients with TIAs later had an ischemic stroke. Predictors of ischemic stroke in patients with isolated local signs are poorly identified but include TIAs (30, 31), silent microemboli at TCD (35), silent infarcts on MRI, TCD signs of hemodynamic compromise, stenosis $>80\%$ or occlusion of the dissected artery (33). These predictors, which have been established for ICAD, probably apply to VAD, although this has not been specifically studied.

Treatment of patients with local signs and/or TIAs

The issue is the choice of the best therapeutic options to prevent ischemic stroke, with the same dilemmas: which antithrombotic treatment: heparin or aspirin? Should bed rest be advised? Should the patient be hospitalized? Is a local arterial treatment needed and which one?

There are again no data on the comparison of anticoagulants and antiplatelet drugs in the prevention of cerebral infarction due to CCAD, but the present evidence from RCT favors the general use of antiplatelet drugs in arterial diseases (23). Why should it be different in stenosis or occlusion of dissected arteries? Theoretically, there is again a case in favor of anticoagulants in low-flow situations; however first, this happens in a minority of cases, and second, there are no data showing the superiority of anticoagulants over aspirin in very tight arterial

stenosis or occlusion of another origin. Cases have even been reported of intramural expansion with delayed occlusion of the dissected carotid in anticoagulated patients (36). In the absence of evidence, the choice of the antithrombotic treatment should thus remain at the discretion of the practicing physician, but there is clearly no scientific reason to stick to the classical recommendation to use anticoagulants to prevent cerebral infarction in CCAD.

With regard to other treatment options, their use depends on a case-by-case basis risk stratification and on a stepped care management according to the evolution of the patient.

For some patients, mainly those with isolated local symptoms and a normal arterial lumen or a stenosis $<50\%$, who seem to have a very low risk of ischemic stroke, aspirin on an outpatient basis may be sufficient (20, 33). This probably also applies to patients with ICAD seen after one-month, who also seem to have a very low risk, whatever the status of the artery (30), and possibly to patients with VAD although there are no similar studies.

For patients with local signs and/or TIA with a stenosis $>50\%$ or occlusion, who are known to have a higher risk of cerebral infarction (33), stroke unit care and antithrombotic treatment are required and bed rest may be added if there are TCD signs of hemodynamic risk. Initial stenting has been advocated (37), but the very low risk of ischemic stroke with the usual medical treatment, irrespective of the persistence of severe stenosis or occlusion, probably does not justify this approach (20, 38). In the few patients who have a new occurrence (if they had only local symptoms) or a recurrence of TIAs, a more aggressive treatment is required with reinforcement of the antithrombotic treatment using, for example, both heparin and aspirin, and/or, when feasible, performing angioplasty with stenting, which requires a previous high dose of clopidogrel (28, 37).

Treatment issues after CCAD

Type and duration of treatment

After the acute stage, the question arises of the type and duration of antithrombotic treatment, which, respectively, depends on the initial treatment and the arterial outcome. When heparin or low-molecular-weight heparin is initially used, it is usually replaced by oral anticoagulants as soon as the patient has stabilized, but replacement by antiplatelet drugs is another option. No change is usually needed when patients are initially treated with aspirin. The arterial outcome (as assessed by ultrasound CTA or MRA) is extremely variable and is best known for extracranial ICAD (38–43). Although recanalization may occur within a few days (38), most dissected arteries recanalize within three- to six-months, but the rate of recanalization depends on the initial dissection pattern: dissections with stenosis recanalize in over 90% of cases while occluded arteries remain occluded in about 60% of cases (40–43). Initial aneurysms persist in 60–70% of cases but an aneurysm may be seen later in 5–10% after an initial stenosis or occlusion (43). In a recent study of 61 patients with VAD, the rate of complete recanalization was 64% at 12 months, without any evidence of a relationship with the initial pattern, but only seven had an initial occlusion. Altogether, there are three long-term patterns of arterial outcome of dissected arteries: normalization, which is the most frequent; persisting occlusion; and aneurysm. In some cases, follow-up studies indicate permanent arterial changes, suggestive of an underlying fibromuscular dysplasia, which was not detectable at the acute stage of dissection (44, 45).

If the dissected artery has normalized or if there is a persisting stable occlusion, there is no reason to maintain antithrombotic treatment. In case of persisting aneurysm or fibromuscular dysplasia, the arterial flow may no longer be laminar and may thus favor platelet emboli. Although this theoretical risk has not been properly documented, it argues in favor of long-term aspirin treatment. Several studies have shown that persisting aneurysms after extracranial dissections have a benign long-term prognosis and do not require surgical or endovascular treatment (42, 43), except in the very rare cases of aneurysm enlargement leading to local compressive symptoms, or of recurrent ischemic events distal to the aneurysm. Overall, the long-term risk of ischemic events is very low, ranging from 0·3% to 1·4% per year in the first few years including events related to recurrent dissections (39, 42, 46).

Recurrences of dissection

The CCAD involve more than two arteries simultaneously or in a short time frame in 25% of cases and may occasionally be associated with dissections of other arteries, such as renal, hepatic or celiac arteries (47, 48). Such cases have indistinctly been reported as multiple dissections or as early recurrences so that the exact frequency of early recurrences is not known. The risk of late recurrences is also poorly known but seems very low: 0·3% per year in a retrospective of 432 patients with a mean follow-up of 31 months and none in the only prospective series, of 48 patients, followed for a mean of 7·8 years (49). Late recurrences seem to be more frequent in patients with an underlying connective tissue disorder, while early recurrences suggest a unique transient triggering phenomenon (50). There is no known treatment for the prevention of recurrences, whether early or late.

Sport activities

Many dissections occur after sports activities of all types or after activities involving usual or unusual neck movements. The issue of sport activities in young patients with dissections is therefore a very frequent one. It is also one of the most difficult, particularly when dealing with young patients who want to resume their sports activities as early as possible. Given the risk of ischemic stroke during at least the first month (30) and the possibility of early recurrences of dissections (47, 48), it

seems appropriate to avoid sports and other activities implying forced or brisk head movements until normalization or stabilization of the dissected artery. There are, however, very difficult situations in which there is a tension between a patient's clinical best interest and their overall best interest, particularly for professional sportsmen who need to resume their sport activity rapidly. Later on, the low long-term risk of recurrence suggests that many sports activities can be resumed depending, on a case-by-case basis, on the status of the artery, the presence of an underlying arteriopathy, the type of sports activity and the psychology of the patient.

Issue of RCT in CCAD

The absence of any evidence in the treatment of CCAD points to the need for an RCT in this condition (51). For a study comparing anticoagulants and antiplatelet drugs, analyses have suggested a large sample size of approximately 2800 patients. This would provide sufficient clinical end-points to detect a 5% difference in the proportion of patients dependent or dead from 20% to 15% (a 25% relative odds reduction). A UK-based feasibility study, Cervical Artery Dissection in Stroke Study (52), started in 2006 and has recruited 80 patients up to August 2010. It is likely that an international collaboration will be needed to recruit such a number of patients and to obtain sufficient funding. Moreover, several methodological issues still arise. First, is it appropriate to mix patients with local signs only, in whom the primary aim is the prevention of stroke, and patients with established ischemic stroke, in whom the main focus is on improving stroke outcome? Second, would it be feasible to perform an RCT devoted only to prevention in patients with purely local signs or TIAs? And what should be compared on top of antithrombotic treatment: anticoagulants vs. aspirin or stenting vs. no stenting? Third, should only extracranial dissections be included or also intracranial (excluding those with SAH)? And what about VAD involving the V3 segment that often extends intracranially with an unknown risk of bleeding? Fourth, what would be the best endpoint? The combination of death and disability was used by the Cervical Artery Dissection and Ischemic Stroke Patients group to calculate the number of 2800 patients required in an RCT (51), by contrast to nearly all recent RCT of acute stroke treatment, which used total or partial recovery (8) as the primary endpoint. Furthermore, it is likely that in an RCT, the event rate would be lower than the 20% death and disability rate obtained from meta-analysis of historical series. It might be further lowered if a huge number of patients with purely local signs were included.

Conclusion

The CCAD is an extremely heterogeneous condition that raises many unsolved treatment issues. The only consensus is that patients with recent extracranial CCAD should urgently receive an antithrombotic treatment. Although evidence from an RCT would be optimal, present data suggest that the difference in the benefit/risk ratio between anticoagulants and antiplatelet drugs – if it exists – is very small. Given the expected difficulties in recruitment, the risks are huge of a type II error or of a premature cessation of the trial, as in the Rapid Anticoagulation Prevents Ischemic Damage study, which aimed at comparing heparin and aspirin in the far more frequent nonlacunar ischemic strokes (53). Meanwhile, CCAD remains a situation when a bedside clinician should use, on a case-by-case basis, the best clinical judgment, and adopt a stepped care approach in the minority of patients who deteriorate despite initial treatment.

References

1 Leys D, Bandu L, Hénon H *et al.* Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke. *Neurology* 2002; **59:**26–33.

2 Arnold M, Halpern M, Meier N *et al.* Age dependent differences in demographics, risk factors, co-morbidity, etiology, management, and clinical outcome of acute ischemic stroke. *J Neurol* 2008; **255:** 1503–7.

3 Arnold M, Kappeler L, Georgiadis D *et al.* Gender differences in spontaneous cervical artery dissection. *Neurology* 2006; **67:**1050–2.

4 Lucas C, Moulin T, Deplanque D, Tatu L, Chavot D. Stroke patterns of internal carotid artery dissection in 40 patients. *Stroke* 1998; **29:** 2646–8.

5 Benninger DH, Georgiadis D, Kremer C, Studer A, Nedeltchev K, Baumgartner RW. Mechanism of ischemic infarct in spontaneous carotid dissection. *Stroke* 2004; **35:**482–5.

6 Srinivasan J, Newell DW, Sturzenegger M, Mayberg MR, Winn HR. Transcranial Doppler in the evaluation of internal carotid artery dissection. *Stroke* 1996; **27:**1226–30.

7 Koch S, Amir M, Rabinstein AA, Reyes-Iglesias Y, Romano JG, Forteza A. Diffusion-weighted magnetic resonance imaging in symptomatic vertebrobasilar atherosclerosis and dissection. *Arch Neurol* 2005; **62:**1228–31.

8 The National Institute of Neurological Disorders and Stroke rt-PA Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995; **333:**1581–7.

9 Engelter ST, Rutgers MP, Hatz F *et al.* Intravenous thrombolysis in stroke attributable to cervical artery dissection. *Stroke* 2009; **40:**3772–6.

10 Derex L, Tomsick TA, Brott TG *et al.* Outcome of stroke patients without angiographically revealed arterial occlusion within four hours of symptom onset. *Am J Neuroradiol* 2001; **22:**685–90.

11 Arnold M, Nedeltchev K, Sturzenegger M *et al.* Thrombolysis in patients with acute stroke caused by cervical artery dissection: analysis of 9 patients and review of the literature. *Arch Neurol* 2002; **59:**549–53.

12 Georgiadis D, Lanczik O, Schwab S *et al.* IV thrombolysis in patients with acute stroke due to spontaneous carotid dissection. *Neurology* 2005; **64:**1612–4.

13 Furlan A, Higashida R, Wechsler L *et al.* Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. prolyse in acute cerebral thromboembolism. *JAMA* 1999; **282:**2003–11.

14 Nedeltchev K, Remonda L, Do DD *et al.* Acute stenting and thromboaspiration in basilar artery occlusions due to embolism from the dominating vertebral artery. *Neuroradiology* 2004; **46:**686–91.

15 Lavallée PC, Mazighi M, Saint-Maurice JP *et al.* Stent-assisted endovascular thrombolysis versus intravenous thrombolysis in internal carotid artery dissection with tandem internal carotid and middle cerebral artery occlusion. *Stroke* 2007; **38:**2270–4.

16 Menon RK, Markus HS, Norris JW. Results of a UK questionnaire of diagnosis and treatment in cervical artery dissection. *J Neurol Neurosurg Psychiatry* 2008; **79:**612.
17 Lyrer P, Engelter S. Antithrombotic drugs for carotid artery dissection. *Cochrane Database Syst Rev* 2010 :CD000255.
18 Menon R, Kerry S, Norris JW, Markus HS. Treatment of cervical artery dissection: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2008; **79:**1122–7.
19 Beletsky V, Nadareishvili Z, Lynch J, Shuaib A, Woolfencen A, Norris JW. Cervical artery dissection. Time for a therapeutic trial? *Stroke* 2003; **34:**2856–60.
20 Georgiadis D, Arnold M, von Buedingen HC *et al.* Aspirin vs anticoagulation in carotid artery dissection: a study of 298 patients. *Neurology* 2009; **72:**1810–5.
21 Markus HS, Droste DW, Kaps M *et al.* Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) Trial. *Circulation* 2005; **111:**2233–40.
22 International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomized trial of aspirin, subcutaneous heparin, both, or neither among 19 435 patients with acute ischaemic stroke. *Lancet* 1997; **349:**1569–81.
23 European Stroke Organisation (ESO) Executive Committee, ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis* 2008; **25:**457–507.
24 Vahedi K, Hofmeijer J, Juettler E *et al.* Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol* 2007; **6:** 215–22.
25 Hosoya T, Adachi M, Yamaguchi K, Haku T, Kayama T, Kato T. Clinical and neuroradiological features of intracranial vertebrobasilar artery dissection. *Stroke* 1999; **30:**1083–90.
26 Otawara Y, Ogasawara K, Ogawa A, Kogure T. Dissecting aneurysms of the bilateral vertebral arteries with subarachnoid hemorrhage: report of three cases. *Neurosurgery* 2002; **50:**1372–5.
27 Peluso JP, van Rooij WJ, Sluzewski M, Beute GN, Majoie CB. Endovascular treatment of symptomatic intradural vertebral dissecting aneurysms. *Am J Neuroradiol* 2008; **29:**102–6.
28 Wakhloo AK, Mandell J, Gounis MJ *et al.* Stent-assisted reconstructive endovascular repair of cranial fusiform atherosclerotic and dissecting aneurysms. Long-term clinical and angiographic follow-up. *Stroke* 2008; **39:**3288–96.
29 Iihara K, Sakai N, Murao K *et al.* Dissecting aneurysms of the vertebral artery: a management strategy. *J Neurosurg* 2002; **97:**259–67.
30 Biousse V, D'Anglejan-Chatillon J, Touboul PJ, Amarenco P, Bousser MG. Time course of symptoms in extracranial carotid artery dissections. A series of 80 patients. *Stroke* 1995; **26:**235–9.
31 Arnold M, Bousser MG, Fahrni G *et al.* Vertebral artery dissection: presenting findings and predictors of outcome. *Stroke* 2006; **37:** 2499–503.
32 Treiman GS, Treiman RL, Foran RF *et al.* Spontaneous dissection of the internal carotid artery: a nineteen-year clinical experience. *J Vasc Surg* 1996; **24:**597–605.
33 Baumgartner RW, Arnold M, Baumgartner I *et al.* Carotid dissection with and without ischemic events: local symptoms and cerebral artery findings. *Neurology* 2001; **57:**827–32.
34 Arnold M, Baumgartner RW, Stapf C *et al.* Ultrasound diagnosis of spontaneous carotid dissection with isolated Horner syndrome. *Stroke* 2008; **39:**82–6.
35 King AS, Osman A, Willson M *et al.* Embolic signal detection at baseline in the cervical artery dissection in stroke study (CADISS). *Int J Stroke* 2009; **4**(Suppl. 2)**:** 3.
36 Dreier JP, Lurtzing F, Kappmeier M *et al.* Delayed occlusion after internal carotid artery dissection under heparin. *Cerebrovasc Dis* 2004; **18:**296–303.
37 Cohen JE, Gomori JM, Umansky F. Endovascular management of symptomatic vertebral artery dissection achieved using stent angioplasty and emboli protection device. *Neurol Res* 2003; **25:**418–22.
38 Nagasawa H, Tomii Y, Yokota C *et al.* Images in cardiovascular medicine. Acute morphological change in an extracranial carotid artery dissection on transoral carotid ultrasonography. *Circulation* 2008; **118:**1064–5.
39 Kremer C, Mosso M, Georgiadis D *et al.* Carotid dissection with permanent and transient occlusion or severe stenosis: long-term outcome. *Neurology* 2003; **60:**271–5.
40 Sturzenegger M, Mattle HP, Rivoir A, Rihs F, Schmid C. Ultrasound findings in spontaneous extracranial vertebral artery dissection. *Stroke* 1993; **24:**1910–21.
41 Nedeltchev K, Bickel S, Arnold M *et al.* R2-recanalization of spontaneous carotid artery dissection. *Stroke* 2009; **40:**499–504.
42 Benninger DH, Gandjour J, Georgiadis D, Stöckli E, Arnold M, Baumgartner RW. Benign long-term outcome of conservatively treated cervical aneurysms due to carotid dissection. *Neurology* 2007; **69:**486–7.
43 Guillon B, Brunereau L, Biousse V, Djouhri H, Lévy C, Bousser MG. Long-term follow-up of aneurysms developed during extracranial internal carotid artery dissection. *Neurology* 1999; **53:**117–22.
44 Arauz A, Márquez JM, Artigas C, Balderrama J, Orrego H. Recanalization of vertebral artery dissection. *Stroke* 2010; **41:**717–21.
45 de Bray JM, Marc G, Pautot V *et al.* Fibromuscular dysplasia may herald symptomatic recurrence of cervical artery dissection. *Cerebrovas. Dis* 2007; **23:**448–52.
46 Touzé E, Randoux B, Méary E, Arquizan C, Meder JF, Mas JL. Aneurysmal forms of cervical artery dissection: associated factors and outcome. *Stroke* 2001; **32:**418–23.
47 Dittrich R, Nassenstein J, Bachmann R *et al.* Polyarterial clustered recurrence of cervical artery dissection seems to be the rule. *Neurology* 2007; **69:**180–6.
48 Arnold M, Stapf C, Baumgartner RW *et al.* Triple and quadruple spontaneous cervical artery dissection: presenting characteristics and long-term outcome. *J Neurol Neurosurg Psychiatry* 2009; **80:**171–4.
49 Lee VH, Brown RD, Mandrekar JN, Mokri B. Incidence and outcome of cervical artery dissection: a population-based study. *Neurology* 2006; **67:**1809–12.
50 Debette S, Leys D. Cervical-artery dissections: predisposing factors, diagnosis, and outcome. *Lancet Neurol* 2009; **8:**668–78.
51 Engelter ST, Brandt T, Debette S *et al.* Antiplatelets versus anticoagulation in cervical artery dissection. *Stroke* 2007; **38:**2605–11.
52 Cervical artery dissection in stroke study trial investigators. Antiplatelet therapy vs anticoagulation in cervical artery dissection: rationale and design of the Cervical Artery Dissection n Stroke Study (CADISS). *Int J Stroke* 2007; **2:**292–6.
53 Chamorro A, Busse O, Obach V *et al.* The rapid anticoagulation prevents ischemic damage study in acute stroke – final results from the writing committee. *Cerebrovasc Dis* 2005; **19:**402–4.