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Review

Disparities between guideline statements on acute and post-acute management of cervical artery dissection

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Abstract

Even though cervical artery dissection is one of the main reasons for ischemic stroke in young patients, acute management and post-acute primary or secondary prevention of cerebral ischemia differ significantly in different centers and countries. These discrepancies are reflected by the differences in guideline recommendations of major stroke societies. Our narrative review aims to shed light on the different recommendations in guideline-statements of stroke societies and to give an overview of the current literature concerning acute management and post-acute treatment of cervical artery dissection patients. In general, intravenous thrombolysis and mechanical thrombectomy are recommended, irrespective of stroke etiology, if administered within the label. Secondary prevention of cerebral ischemia can be achieved by antiplatelet intake or anticoagulation, with, to date, neither treatment establishing superiority over the other. Duration of antithrombotic treatment, statin use as well as optimal endovascular approach are still up for debate and need further evaluation. Additionally, it is still unknown, whether the recommendations given in any of the guideline statements are similarly relevant in spontaneous and traumatic cervical artery dissection, as none of the stroke societies differentiates between the two.

Keywords: Dissection; Treatment; Stroke; Guideline; Acute management

1. Introduction

The pathognomonic characteristic of a cervical artery dissection (CeAD) is a vessel wall hematoma in either supra-aortal extra-cranial carotid or vertebral artery [1]. They can occur spontaneously or with timely association to whiplash-type injuries or blunt head/neck trauma [2–4]. Diagnosis is established through neurovascular imaging with the intramural hematoma appearing as a semilunar hyper-intensity in fat-saturated T1 Magnetic resonance (MR)-imaging [5]. Literature to date has proposed different pathomechanisms. The first being the inside-out-model, an intimal tear with a consecutive outflow of blood from the true to the false lumen. Second, the outside-in-model, a primary vessel wall hematoma through rupture of vasa vasorum [6–9]. Indifferently, both instances result in the formation of an intramural hematoma with a high probability of generating a local mass effect on surrounding tissue through vessel dilatation (i.e., post-dissection aneurysm formation), or intraluminal propagation leading to vessel stenosis or occlusion [10]. The local distension of tissue through the vessel wall hematoma can cause local symptoms (headache, Horner's syndrome, cranial nerve palsies, pulsatile tinnitus) which are evident in nearly every CeAD patient hospitalized with CeAD [1,11–14]. Still, in hospital-based cohort studies almost 3 in 4 subjects with CeAD suffer cerebral ischemia [11,12,15,16]. Mechanistically, thrombus formation at the dissection site with consecutive distal embolization is believed to be the primary cause of ischemic stroke in these patients. Hemodynamic effects of CeAD-related occlusion are markedly less frequent [17–21]. Even though CeAD is established as one of the main reasons for ischemic stroke in young patients (<55 years old) [1,22], acute management and post-acute primary or secondary prevention of cerebral ischemia vary significantly. This is reflected by the discrepancies in guideline recommendations of major stroke societies [23–29]. Therefore, our narrative review aims to shed light on the differences in recommendations in guideline statements of stroke societies and to give an overview of the current literature concerning acute management and post-acute treatment of CeAD patients. Methodologically, we performed a thorough literature search through PubMed (MEDLINE 1966 to October 2021) including search terms "cervical artery dissection", "treatment", "endovascular stenting", "thrombolysis" and "thrombectomy" including all case reports, cohort studies and randomized controlled trials available.

2. Acute management

Acute stroke management has seen major improvements over the last decade, most importantly through the systematic application of endovascular treatment and the definition of wake-up stroke protocols [30–36]. Table 1

Table 1. Recommendations of stroke societies on the acute management of CeAD related ischemic stroke.

Guidelines	iv. thrombolysis	thrombectomy
AHA/ASA [23]	1. Reasonable safe and probably recommend, if: • Extracranial cervical artery dissection. • Administered within the label.	1. No CeAD specific recommendation given. Do not differentiate acute management from other etiologies. 2. If CeAD is suspected, vascular imaging of carotid and vertebral arteries may be reasonable to assess patient eligibility and endovascular procedural planning.
ESO [26,28]	1. Iv. tPA if: • Administered within the label.	1. EVT if Acute ischemic stroke with CeAD and large vessel occlusion of intracranial anterior circulation.
NICE [27]	1. No CeAD specific recommendation given.	1. No CeAD specific recommendation given.
DGN [29]	1. Possible and without elevated risk of complications if administered within the label.	1. Recommended if in accordance with criteria of inclusion of large EVT trials.

(Ref. [23,26–29]) holds acute management guideline recommendations of four of the largest stroke societies in the subset of patients suffering an ischemic stroke due to CeAD. In short, three of four stroke societies either recommend or describe the use of intravenous tissue-type plasminogen activator (iv. tPA) as reasonably safe, if administered within the label and if CeAD does not extend to intracranial vessel segments. The National Institute for Health and Care Excellence (NICE) guidelines however, do not differentiate between the acute management of CeAD-related stroke and an ischemic stroke of other etiology. Similarly, the American Heart Association/American Stroke Association (AHA/ASA), NICE and European Stroke Organization (ESO) guidelines do not alter their recommendations of endovascular thrombectomy in CeAD associated stroke compared to other causes of cerebral ischemia. Solely the German society of neurology (DGN) points out that their recommendation is based on a conclusion of analogy as subgroup analyses of CeAD patients in large-scale thrombectomy randomized controlled trials are missing.

Even though some of the guideline recommendations are amended regularly, it is to be expected that current evidence is not entirely depicted in the currently available statements as, for instance, the German society recommendations have been published as early as 2016.

2.1 Acute management — iv. tPA

The initial hesitancy on the use of iv. tPA did stem from case reports suggesting the possibility of further expansion of the vessel wall hematoma [37]. Four retrospective studies, a meta-analysis of 180 CeAD subjects with acute ischemic stroke within the Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombosis Register (SITS-ISTR) and a retrospective data analysis of 488 CeAD subjects with acute ischemic stroke, have invalidated this theory [38–41]. Each study emphasized that there was no increase in iv. tPA associated complications, including intracranial hemorrhages or extension of mural hematoma, when comparing CeAD to non-CeAD subjects with ischemic stroke. Concerning functional outcome, one retrospective single-center case-control study and a subanalysis of the Cervical Artery Dissection and Ischaemic Stroke Patients (CADISP) database did not find a significant difference concerning good 3-month functional outcome (modified Rankin Scale [mRS] 0–2) in CeAD subjects that did receive iv. tPA and those who did not (adjusted Odds Ratio [aOR] 0.95 [95 % confidence interval [CI] 0.45–2.00] [42]; OR 4.09 [95% CI 0.44–38.26] p = 0.377) [43]. Considering the low number of cases treated with iv. tPA (n = 74) in both studies combined and the non-randomized retrospective case-control design, one cannot conclude that iv. tPA is ineffective in patients with CeAD. As iv. tPA related complications were infrequent and subjects receiving iv. tPA had a significantly higher likelihood of being without neurological deficit (mRS 0), the use of iv. thrombolysis was either recommended or defined as reasonably safe in all three of the above-mentioned studies.

2.2 Acute management — endovascular thrombectomy

Evidence for endovascular thrombectomy (EVT) in acute stroke related to isolated CeAD is solely based on case reports and small case series [44–46]. However, if a tandem pathology (i.e., cervical internal carotid artery dissection and intracranial large vessel occlusion) is present, the level of evidence does improve. A literature review published in 2017 which encapsulated 16 studies concluded that EVT in CeAD patients with tandem pathology is associated with favorable outcome [47]. More recently, two separate cohort studies investigated EVT in subjects with intracranial large vessel occlusion secondary to CeAD. Both concluded that, even though CeAD increases the peri-procedural challenge (reflected by a longer median groin-puncture-to-flow restoration time [interquartile Range [IQR]: 98 [67–136] vs. 70 [45–100] minutes; $p < 0.001$]), EVT is both safe [48] and leads to a favorable functional outcome (if modified thrombolysis in cerebral infarction scale [mTICI] $\geq$ 2b achieved - favorable outcome at 3 months was signifi-

Table 2. Recommendations of stroke societies on post-acute management and prevention of cerebral ischemia in CeAD.

Guidelines	Medical treatment	Endovascular therapy (stenting)
AHA/ASA [53]	1. Acute ischemic stroke or TIA after CeAD • Antithrombotics for at least 3 months. 2. Ischemic stroke or TIA <3 months after CeAD • Reasonable to use either aspirin or warfarin. • No recommendation on duration.	1. Recurrent ischemic events after CeAD despite antithrombotic treatment EVT may be considered.
ESO [28]	1. In the acute phase, either anticoagulation or antiplatelet therapy can be prescribed • No recommendation on duration.	1. Uncertainty over the benefits and risks of endovascular management of CeAD associated stenosis/aneurysm in the post-acute phase.
NICE [27]	1. If ischemic stroke after CeAD, either anticoagulation or antiplatelet therapy can be prescribed • No recommendation on duration.	1. Not mentioned.
DGN [29]	1. Acute ischemic stroke or TIA or local symptoms due to CeAD • antiplatelets for at least 6 months or until vessel normalization. 2. If silent micro-embolism in transcranial sonography despite antiplatelet therapy • anticoagulation can be considered (escalation). • No recommendation on duration.	1. Recurrent ischemic events after CeAD • despite antithrombotic treatment EVT may be considered. 2. Extracranial dissecting aneurysms • Conservative management recommended.

cantly higher compared to mTICI 0/1/2a [64.7% vs. 22.2%, p = 0.030]) [49]. Also, in a randomized controlled trial performed by Gory *et al.* [50] comparing tandem stenoocclusive lesions due to CeAD or atherosclerosis, no difference in concerning functional outcome (OR 1.08 [95% CI, 0.50–2.30]) was found.

2.3 Acute management — discussion

In conclusion, the latest guideline statements of major stroke societies are in line with current literature on the acute management of CeAD-related stroke. Iv. tPA seems to be safe and increases the chance of life without neurological deficit (mRS 0) after CeAD-related stroke whereas EVT should be limited to those subjects with tandem pathologies. Still, randomized controlled trials on the acute management of CeAD-related stroke have hitherto not been performed, and some relevant questions, especially for iv. tPA use, remain unanswered. First, neither of the above-mentioned studies or guideline recommendations definitively differentiated between traumatic or spontaneous CeAD, which is understandable as the differentiation is often not easy to establish. If specifically asked, many patients report minor traumas in a loose temporal association with CeAD onset. It is unclear whether this reflects a recall bias or if minor traumas per se can induce CeAD on healthy blood vessels. It would be rewarding to find a discretion point between the two which secondarily would make it possible to assess, for instance, whether iv. tPA is safe or if mural hematoma progression is more likely in CeAD subjects with prior (minor) trauma. Secondly, it stands to reason if iv. tPA is safe in subjects with distal cervical artery segment involvement as several studies suggested a distal progression of the mural hematoma over time, possibly elevating the risk of subarachnoid haemorrhage in these subjects [51]. But it is important to point out that none of the four guideline statements recommends delaying the administration of iv. tPA or EVT to a priori exclude potential intracranial propagation of CeAD. Lastly, evidence of the optimal (acute) management of patients with isolated extracranial vessel occlusion, in general, is lacking. Still, also in this setting, iv. tPA should not be withheld when administered within the label. The above-mentioned stroke society guideline statements do not offer guidance for situations of severe hemodynamic compromise with fluctuating ischemic symptoms or progressive stroke. Therefore, endovascular approaches should be weighed on an individual patient basis against the risk of peri-procedural distal embolization [52].

3 Post-acute and long-term medical treatment

Post-acute and long-term medical treatment, as well as indication for endovascular intervention after CeAD with or without cerebral ischemia, have been debated for years. Still, randomized controlled trials delivering definitive answers on both medical and endovascular treatment are scarce. The lack of evidence is reflected by the varia-

tion in recommendations given by stroke societies in their guideline statements (Table 2, Ref. [27–29,53]).

3.1 Medical treatment — antiplatelet agents and anticoagulation

To date, no randomized controlled trial compared antithrombotic therapy after CeAD to placebo. The current evidence almost solitarily stems from comparisons concerning the safety and effectiveness of antiplatelet agents versus anticoagulation. A retrospective analysis of 298 prospectively recruited subjects with spontaneous CeAD concluded that after a follow-up of 3 months the risk of ischemic stroke, transient ischemic attack (TIA), or retinal ischemia is low and probably does not depend on the type of antithrombotic agent used (cumulative risk in anticoagulation vs. antiplatelet: 5.9% vs. 2.1%) [54]. Further, Georgiadis *et al*. [54] reported no difference in hemorrhagic adverse events in those taking anticoagulants (2%) and those taking aspirin (1%). These results were mirrored by two independent meta-analyses performed in 2008 and 2012 [21,55]. Menon *et al*. [55] recorded similar rates of death (1.8% vs. 1.8%) and ischemic stroke (1.9% vs. 2.0%) in 762 spontaneous CeAD patients receiving antiplatelet or anticoagulation treatment respectively. Kennedy *et al*. [21] emphasized that there was no significant difference between antiplatelet use or anticoagulation in CeAD subjects concerning recurrent stroke risk (antiplatelet 13/499 [2.6%], anticoagulant 20/1137 [1.8%], OR 1.49) or mortality (antiplatelet 5/499 [1.0%], anticoagulant 9/1137 [0.8%], OR 1.27) at 3-month follow-up. In 2013 though, a meta-analysis by Sarikaya *et al*. [56], incorporating 37 studies of CeAD subjects, concluded that due to safety advantages, more patient-friendly usage, and lower treatment costs, antiplatelet agents should be favored after CeAD. They based their argument on the finding that the treatment effect preventing cerebral ischemia/hemorrhage or death within 3-months ultimately favors antiplatelet use (relative risk 0.32). Still, the authors pointed out that none of the included studies were randomized controlled trials. After restricting the included studies to those with higher methodological quality, the advantage of antiplatelet agents over anticoagulants was less obvious (relative risk 0.73). In light of these in-homogenous results, the first randomized open-label trial of antiplatelet use vs. anticoagulation in CeAD was performed and published in 2015 [57]. Within the so-called Cervical Artery Dissection In Stroke Study (CADISS) multicenter trial, 250 patients with CeAD receiving either antiplatelet agents or anticoagulation were recruited and evaluated concerning 3-month outcomes of all-cause mortality or ipsilateral stroke. The consortium concluded that there was no significant difference between the treatment groups with the authors acknowledging several limitations. First, randomization of patients occurred after the hyper-acute phase following CeAD (mean 3.65 days). Additionally, as there was no a priori centralized radiological confirmation of CeAD, in 52 randomized patients CeAD could not be confirmed at a retrospective review of imaging data. Further, the type (aspirin, clopidogrel, dipyridamole) and dosage of antiplatelet treatment were not standardized. Lastly, the event rate was low with stroke or death in 3% in the antiplatelet group (n = 110) and 1% in the anticoagulant group (n = 96) (OR 0.346, 95% CI 0.006–4.390; $p = 0.66$). More recently, Engelter *et al*. [58] published another multicenter randomized controlled trial (TREAT-CAD) of 194 subjects with CeAD. Two of the most pronounced differences between the TREAT-CAD and the CADISS trial were the standardized antiplatelet group (aspirin 300 mg once daily) and the composite primary endpoint encapsulating clinically evident stroke and silent MRI lesions [58]. Overall, as the endpoint occurred in about one in four patients receiving an antiplatelet agent and only one in seven under anticoagulation (absolute difference 8% [95% CI –4–21], non-inferiority $p = 0.55$) the authors concluded that non-inferiority of aspirin compared to vitamin K-antagonists could not be established. As these data also do not incorporate the hyper-acute phase of CeAD, stroke guideline statements could not define specific treatment recommendations, which is unfortunate as most ischemic events post-CeAD occur during the first couple of days [11,59,60]. Solely the German society argues that similarly to subjects with multiple recurrent ischemic attacks or strokes or low flow-situations with a high risk of intraluminal thrombus formation, anticoagulation can be considered with an initial bridging using unfractionated or low-molecular-weight heparin.

3.2 Medical treatment — DOACs

It is unknown whether the favorable risk-benefit ratio of direct oral anticoagulants (DOACs) compared to vitamin K-antagonists in the setting of primary and secondary prevention of stroke in patients with atrial fibrillation similarly applies to the post-acute phase after CeAD. Three small single-center analyses of CeAD subjects, however, independently concluded that DOACs are similarly effective compared to vitamin K-antagonists. But the number of patients involved (in total 49 receiving DOAC) was too small to draw firm conclusions [61–63]. Concerning safety, the risk of hemorrhagic complications was either similar to or less likely in DOACs compared to vitamin K-antagonists. Only Caprio *et al*. [63] could describe a higher likelihood of radiographic worsening of CeAD-related stenosis due to intramural hematoma extension under DOAC treatment.

3.3 Medical treatment — duration

The duration of medical treatment post-CeAD is debated. Most guideline statements do not definitively state the recommended time of either antithrombotic treatment, with only the German stroke society recommending antiplatelet agents for at least 6 months after CeAD and onwards until vessel status normalization [29]. The lack of

guidance from stroke societies stems from the hitherto inconsistent evidence on the matter, with further pitfalls being two-fold. First, one has to differentiate the low risk of recurrent CeAD from the non-negligible risk of early recurrent cerebral ischemia, as is reported to be evident in up to 13% of cases [1,64–66]. These studies would definitively support thorough medical treatment but, as most data on recurrent ischemia are based on hospital-based short-term follow-up analyses encapsulating the first few months after CeAD, the best long-term treatment approach remains unknown. Only 7 studies to date reported a follow-up of more than 2.5 years with per-year recurrence rates of cerebral ischemia ranging from 0.9%–1.7%. But, as cohort details (solely carotid artery CeAD or both carotid and vertebral artery CeAD recruitment) and treatment strategies varied significantly, definitive arguments for solid recommendations remain elusive [67–72]. Second, CeAD-related vessel pathologies represent a changing entity over time (i.e., with recanalization of occlusions, flow normalization of prior stenosis or post-CeAD aneurysm formation) making treatment decisions even more complex. Studies suggest that vessel remodeling is typically finished after about 6 months [1,73]. Even if extradural post-dissection aneurysms or residual stenosis are evident, the thromboembolic/bleeding risk seems to be low in the long-run, especially under antiplatelet treatment [1,70,73].

3.4 Endovascular management — stenting

Only the German stroke society- and the most recently published AHA/ASA guidelines comment on endovascular management in CeAD after the first few hours of symptom onset. Both state that stenting can be considered in subjects with recurrent cerebral ischemia despite sufficient antithrombotic treatment. The ESO guidelines emphasize the uncertainty concerning the risk/benefit ratio of endovascular management of CeAD-associated stenosis/aneurysm in the post-acute phase. In general, stenting in CeAD is considered safe and reliable, but the evidence to date is primarily based on case reports and case series, entailing major selection and reporting bias [74–82]. Similarly, the sole systematic review encapsulating 140 subjects with vessel stenosis due to either spontaneous, traumatic or iatrogenic CeAD in internal carotid or vertebral arteries, could not incorporate studies with high methodological quality as no randomized controlled - or controlled clinical trials exist [81]. Regardless, the authors reported a combined success rate of reperfusion and/or vessel normalization of 99% for internal carotid artery and 100% for vertebral artery CeAD with low rates of intervention-related complications (<2% for each internal carotid artery or vertebral artery). Interestingly though, within the initial 3 months after endovascular therapy, stent occlusions occurred in 2% of internal carotid artery and 14% of vertebral artery stents (mean 17.7 months). To date still, most recent studies are limited due to the small sample size but Marnat *et al*. presented one of the largest cohorts of CeAD subjects with acute stenting of internal carotid arteries in tandem occlusion of the anterior circulation [83–85]. The authors performed a retrospective analysis of 136 CeAD subjects within the TITAN and ETIS registries, 65 of which received emergency stenting. Even though successful reperfusion was more likely in stented subjects, neither 3-month favorable outcome, nor symptomatic intracerebral hemorrhage or 90-day mortality differed between the groups. In the case of post-dissection aneurysms, recent reports have presented cases in which stent-graft repair was able to reliably manage these vascular pathologies [86]. Still, conservative (medical) treatment is recommended by the German guidelines, which is supported by the current evidence in literature [59,70,87].

3.5 Secondary prevention of ischemic stroke

The AHA/ASA guideline statement is the only one commenting on the management of common vascular risk factors after CeAD-related ischemic stroke. They recommend that hypertension should be managed according to existing guidelines and oral contraceptive pills or hormone replacement therapy should be discontinued. Further, the AHA/ASA concludes that there is no evidence for the use of statins in CeAD subjects, as they rarely are high-risk cardiovascular patients [88]. It is commonly known that vascular risk factors in general are infrequent in CeAD patients. Risk profiles differ compared to patients with ischemic stroke of other etiology, especially with hypercholesterolemia being less frequent in CeAD [89–93]. But as statin use is recommended in all subjects after suffering ischemic stroke, it is a valid question whether long-term lipid lowering therapy is beneficial after CeAD. Recently, Yang *et al*. [94] performed a quantitative proteomics analysis of serum samples in CeAD- and non-CeAD-related stroke patients, which resulted in differential expressions of proteins, among others, involved in lipid metabolism. Therefore, the authors hypothesized these disturbances may be involved in the pathophysiology of CeAD. Though the pathophysiological aspect may be interesting, one could adhere to current literature recommending a “the lower, the better” approach concerning blood cholesterol, especially in subjects with an elevated cardiovascular risk profile [95].

3.6 Post-acute management — discussion

In conclusion, the current evidence suggests that anticoagulation in CeAD should be considered for at least 3 months after the initial event [58]. Afterwards, or if anticoagulation is contraindicated (e.g., large infarct volume, recent surgery or gastrointestinal bleeding), antiplatelet agents are a valuable second option [1,57]. Gaps in knowledge on medical treatment include whether (1) initially non-stenotic CeAD or those without cerebral ischemia (i.e., no or local symptoms only) benefit from treatment, (2) differences in management strategies should be considered between traumatic or spontaneous CeAD, as most of the afore-

mentioned studies did not differentiate between the two, (3) dual anti-platelet or DOAC treatment would be a viable option in CeAD subjects [96,97]. The optimal duration of treatment is unclear but, since vessel remodeling takes about 6 months, duration should be decided on an individual patient basis according to follow-up examinations and evaluation of vessel status (e.g., residual vessel pathology vs. complete normalization of vessel lumen). Further, studies on factors associated with early clinical worsening in CeAD subjects, especially those with hemodynamic compromise, can be rewarding, as these unique patients might benefit from early flow restoration by stenting. Yet, periprocedural risks have to be weighed against potential benefits.

Author contributions

LM-S, SKi and MK chose the topic of the work, performed the literature review and drafted the manuscript. TP, SKo, BD and KM assisted in the literature review, drafting of tables and critically revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

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