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Non-traumatic cervical artery dissection and ischemic stroke: A narrative review of recent research

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ABSTRACT

Cervical artery dissection (CAD) is a leading cause of ischaemic stroke (IS) in young and middle-aged adults. Despite well characterized clinical presentation, the diagnosis of CAD can be quite challenging due to a wide variety of symptoms ranging from minor neck pain to severe neurological symptoms. Invasive diagnostic procedures such as DSA are nowadays being replaced by the sensitive and CAD-specific sequences of MR. The most recent studies confirmed the overall efficacy of antiplatelet and anticoagulant therapies for CAD patients is equivalent, although patients should be qualified for concrete treatment on the basis of recently characterized clinical features. The use of NOAC in CAD-related IS prevention cannot yet be recommended due to the lack of evidences from randomized controlled trials. Endovascular therapies should be considered as the treatment of CAD, especially in the cases of large occlusion or antithrombotic treatment failure. Further research is needed to evaluate the efficacy of new imaging modalities and treatment options. This review summarize the last 5-year development of the diagnosis and treatment for CAD as a causative factor for IS.

1. Introduction

The incidence of stroke in young adults has been increasing over the last decades. This increase is essentially attributable to the incidence of ischaemic stroke (IS) as the rate of intracerebral and subarachnoid haemorrhage remain stable [1]. Spontaneous cervical artery dissection (CAD) represents a common cause of IS in young and middle-aged adults and should be considered if patient develops a new-onset head or neck pain with or without cerebral ischaemic symptoms [2]. An accurate diagnosis is essential for proper antithrombotic or endovascular treatment, however, may be challenging due to a large variety of symptoms [3]. This review summarizes the last five-year development of the imaging diagnosis, pharmacotherapy, and endovascular treatment for CAD with special regard to the management of IS.

2. Methods

2.1. Search strategy

Systematic literature search of NCBI/NLM PubMed and Cochrane databases was performed. A combination of the following terms was used: ("stroke" or "cerebral infarction" or "brain infarction" or "brain ischaemia") and ("cervical artery dissection" or "cervical dissection" or "carotid artery dissection" or "carotid dissection" or "vertebral artery dissection" or "vertebral dissection").

2.2. Inclusion and exclusion criteria

Evidence-based peer-reviewed articles, including randomized trials, case series, reports and reviews published within the last five years

Abbreviations: AC, anticoagulant (therapies); AP, antiplatelet (therapies); BB-MR black, blood magnetic resonance sequence; CaAD, carotid artery dissection; CAD, cervical artery dissection; CBCTA, cone-beam computed tomography angiography; CCA, common carotid artery; CEUS, contrast-enhanced ultrasound; CT, computed tomography; CTA, computed tomography angiography; DSA, digital subtraction angiography; EVT, endovascular treatment; FS-MR, fat saturation magnetic resonance sequence; HR-MR, high resolution magnetic resonance; ICA, internal carotid artery; IH, intramural hematoma; IS, ischaemic stroke; IVT, intravenous thrombolysis; MES, microemboli signals; MR, magnetic resonance; MRA, magnetic resonance angiography; mRS, modified Rankin Scale; MT, mechanical thrombectomy; NfL, neurofilament light chain level; NOACs, novel oral anticoagulants; PR, prevalence ratio; TO, tandem occlusion; US, ultrasound; VAD, vertebral artery dissection; VKAs, vitamin K antagonists

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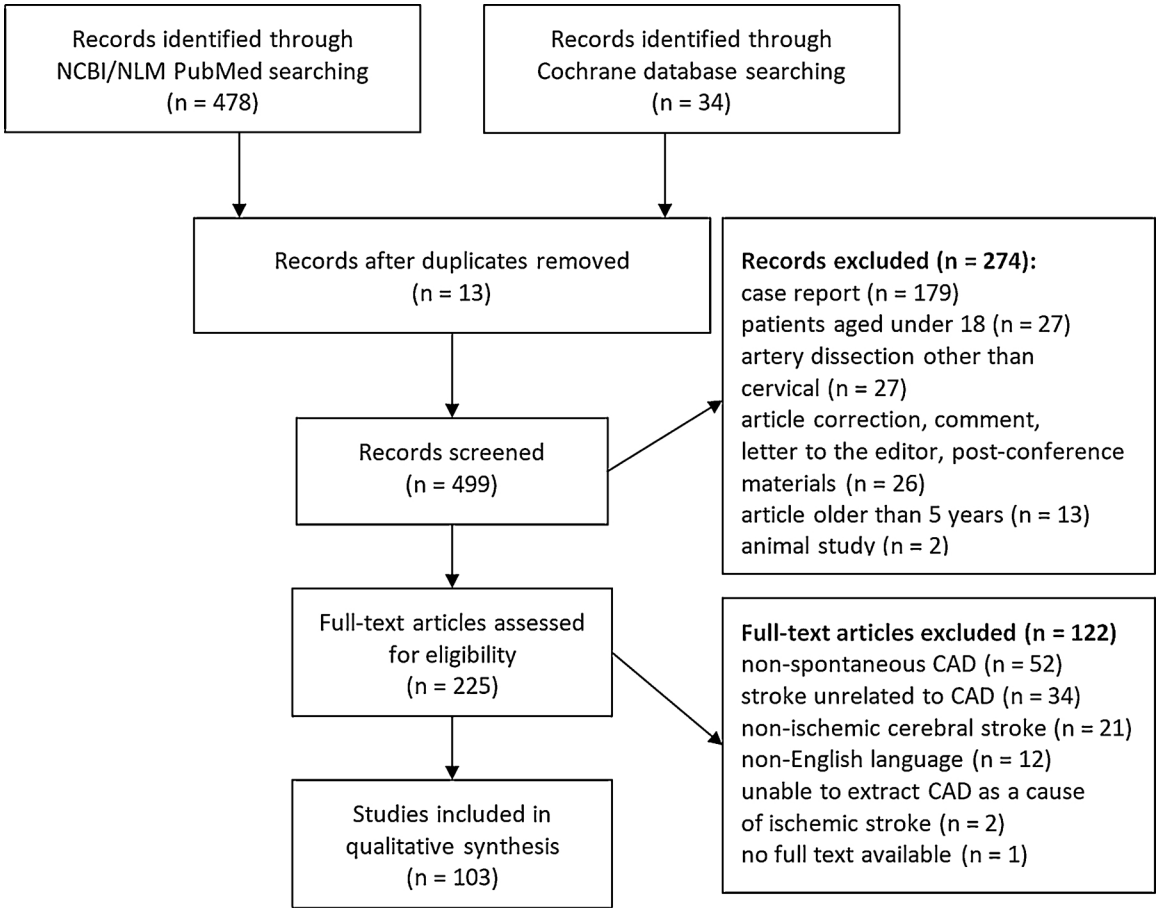

Fig. 1. PRISMA flow diagram of article selection process.

were included into this review. Major inclusion criteria were: age over 18, diagnosis of a spontaneous type of CAD, and the occurrence of ischaemic stroke symptoms. Studies were excluded if involved: post-traumatic lesions, diagnosis of haemorrhagic stroke, and dissections different from carotid or vertebral arteries.

3. Results

512 records were identified after applying above searching criteria. Articles were excluded for the following reasons: study older than 5 years, patients aged under 18, non-spontaneous CAD, non-ischaemic cerebral stroke, artery dissection other than cervical, stroke unrelated to CAD, inability to identify CAD among other IS causes, animal study. After applying exclusion criteria 103 articles were included into this review.

Fig. 1.

3.1. Epidemiology of CAD

CAD remains a leading cause of IS in the population of young adults. Stroke is preceded by CAD in 10–25% of patients aged under 45 and only in 1–2% of adults of all ages [2,4]. CAD is also the most frequent cause of stroke in the category of "other determined aetiology" in the TOAST (Trial of Org 10,172 in Acute Stroke Treatment) classification [5]. In general, the mean age of CAD occurrence ranges from 44 to 46 years [4,6–8]. The incidence of CAD decreases with age. Only 7,4% of CAD patients are older than 60 years [9].

The rate of carotid artery dissection (CaAD) is approximately 2.5–3 times higher than vertebral artery dissection (VAD) [8,10]. An annual overall incidence ranges from 2.6 to 5,0 per 100,000 young patients per year. In general population, incidence ranges from 1 to 1.5 to 2–3 per 100,000 for VAD and CaAD, respectively, although may be underestimated due to the possible presentation of mild or self-limited symptoms [6,11]. Asian patients develop VAD more frequently than CaAD as opposed to the other populations which may result from the partially different anatomical relations of the arteries [10]. In African patients CAD represents a less frequent cause of IS compared to the European patients [12]. Generally, there are no strong gender predisposition in the incidence of CAD [4,8].

3.2. Pathophysiology

A dissection is defined as a separation of the structural components of the arterial wall. CAD is considered as the second most frequent lesion observed in the cervical arteries after atherosclerosis [13]. A classification of CAD depends on the type of involved artery (vertebral or carotid), location (extracranial or intracranial), and pathophysiology (spontaneous or traumatic) [11]. The extracranial ICA (internal carotid artery) dissection is the most frequent type of CAD which typically occurs 2–3 centimetres above the bifurcation of CCA (common carotid artery) [7]. Multiple dissections are found in 15–20% of patients in the early stages of CAD [14]. It has to be noted that patients may not report a minor trauma, even if a dissection is described as "spontaneous" [10].

The appearance of intimal tear is essential for the pathophysiology of dissection. Blood from the arterial lumen penetrates the arterial wall leading to the creation of vessel wall hematoma [15]. Further significant lesion specific to CAD is the rupture of vasa vasorum causing pseudoaneurysm (lesion between adventitia and media) or arterial stenosis (lesion between intima and media) [8,15].

Ischaemic events originates from CAD are related to two major

mechanisms: thromboembolic or haemodynamic [16]. The formation of lesions with a high thrombogenic potential, such as endothelium damages, intimal flaps and wall irregularities, leads to the activation of blood clotting cascade. The occurrence of thrombus formation and artery-to-artery embolism (distal embolization) results in ischaemic events [8,17,18]. In addition, arterial lumen compression, as a result of mural hematoma enlargement, contributes to the hemodynamic ischaemia [8]. There is no consensus on which mechanism dominates in the pathophysiology of CAD-related ischaemia: artery-to-artery embolism or decreased blood flow through the compressed artery [2,19,20].

3.3. CAD symptoms

Clinical manifestation of CAD ranges from minor neck pain to severe neurological symptoms, including death [3]. The frequency of symptoms varies widely in the studies [17,21]. The most common symptom of either CaAD or VAD is a headache associated with 65–80% of cases [4,22]. A neck pain is likewise suggestive of CAD, especially when precedes the occurrence of cerebral ischaemia [21,23]. The localisation of headache may be instrumental in identifying dissected artery. Frontal or periorbital headache arguments for CaAD, while occipital one is specific to VAD [8]. Patients suffer from acute CAD-related IS are two times more likely to have a headache compared to stroke patients without CAD [24]. A headache is also a warning sign of subsequent IS [25,26]. Generally, IS and transient ischaemic attacks occur in 67–77% of CAD patients, although the stoke incidence may be overestimated (in some studies up to 95%) due to a bias of the recruitment from the stroke centres [7,22].

A triad of CAD symptoms includes pain (ipsilateral of the head, neck, and face), Horner's syndrome and ischaemic symptoms (cerebral or retinal), although the manifestation of all above symptoms is rare and may be observed only in less than one third of patients [4]. Compared to VAD, CaAD is associated with a higher frequency of Horner's syndrome, cranial nerve damage (XII, XI, X), tinnitus, ataxia, nausea and visual symptoms [7,8,17]. Posterior neck pain or occipital headache followed by posterior circulation ischaemia are usually considered as a suspicion of VAD [27]. Other specific VAD symptoms include vertigo and ipsilateral facial dysesthesia [21]. It should be mentioned that cervical pain and headache are less frequent in older patients making the diagnosis more challenging [9,28]. Overall estimated proportion of an asymptomatic course of CAD accounts for approximately 5% of all cases [4].

3.4. Risk factors

Risk factors for CAD include young age, current smoking status, increased leucocyte count and shortened aPTT [29,30]. CAD is also associated with distinct genetic variants, such as polymorphism of homocysteine metabolism enzymes and rare genetic imbalance affecting cardiovascular system [2,31,32]. Arterial tortuosity due to the weakened arterial wall is another risk factor for CAD [33–35]. Interestingly, hypertension, hyperlipidaemia, and diabetes mellitus may be inversely associated with CAD [29].

Patients developing CAD-related IS have higher serum neurofilament light chain (NfL) level compared to patients with TIA or local symptoms only. Increased NfL level correlates with both NIHSS and time from stroke onset [36]. Anaemia on hospital admission may aggravate the severity of CAD-related IS [37]. There are also not fully elucidated epidemiological observations of increased CAD incidence among patients graduating from university or practising medicine and higher CAD occurence during cooler months regardless of geographical location [38–41]. Interestingly, relatives of CAD patients may have fewer strokes at a young age than relatives of patients with IS attributable to other (non-CeAD) causes [42].

Migraine may accelerate vascular lesions observed in CAD. Altered response to nitric oxide and increased level of elastase in extracellular matrix are specific to both migraine and CAD [43]. Migraine without aura probably doubles the risk of CAD-related IS [44,45]. A pathogenic link between the two conditions is reinforced by the observation that the frequency and character of migraine attacks are modified after CAD-related IS more than after other stroke etiologic subtypes [46]. Marfan and Ehlers–Danlos syndromes are the connective tissue disorders with increased incidence of CAD [47,48]. Fibromuscular dysplasia is also correlated with CAD and may account for 5.6–21% of all cases with a high (15–20%) risk of stroke recurrence [49–52].

3.5. Prognosis

CAD prognosis is generally good – no further implications are observed in up to 90% of cases. Similarly, a mortality rate is low (2–5%) [8]. The vast majority of CAD patients achieve a functional independence at 3 months after symptoms onset [23]. CAD recurrence concerns less than 5–7% of CAD cases and usually develops within the first two months [8,53]. A radiological CAD subtype may also influence the prognosis – subtypes involving aneurysm and stenosis ale more likely to have a favourable outcome compared to subtype with occlusion [54]. A dissecting aneurysm and symptoms like Horner's syndrome or pulsatile tinnitus may indicate a more benign clinical course [55–58]. Even patients with transient increase of intramural hematoma (IH) volume and temporary progression of stenosis have an overall good prognosis due to spontaneous IH resorption [59].

A prevalence of new or recurrent IS varies widely and ranges from 1 to 3% even up to 60% of CAD cases [15,60] Recent large observational study revealed 1.25% risk of IS in the first 2 weeks following by 0.18% increase during weeks 3 to 4 and no significant risk increase within the 12-week post-dissection period [61]. Severe disability at hospital admission is the most clinically relevant predictor of death. Generally, patients developing IS as a result of CAD have greater rates of functional independence at 3 months compared to the other stroke causes [62,63].

3.6. CAD imaging

Technological advance of imaging techniques provided a constant increase in the rate of CAD diagnosis [8]. Imaging modalities described below include digital subtraction angiography (DSA), magnetic resonance (MR), MR angiography (MRA), computed tomography (CT), CT angiography (CTA), and neck ultrasound (US). Generally, CTA and MR/MRA are the most commonly applied non-invasive diagnostic imaging for patients with the suspicion of CAD. Visualization of IH is the most frequent sing of CAD [64,65].

4. DSA

DSA is treated by some authors as a decisive imaging technique verifying questionable findings due to the high spatial and temporal resolution of blood flow [16,66,67]. A "flame" sign is the most common finding in DSA as a result of tapered occlusion. "Double barrel" or "double lumen" signs originate from the subadventitial lesions separating "true" arterial lumen from the "false" one between intima and media. "True" lumen usually communicates with the "false" one at the distal end of stenosis. Unfortunately, intimal flap and "double lumen" signs can be observed in less than 10% of CAD cases [21]. The advantages of DSA include detection of wall irregularities and intimal tears. Two major limitations of DSA are the invasiveness of the procedure and the possible difficulties in the visibility of lesions within the arterial wall (IH and subadventitial dissections are not directly visible) [16,21]. Currently, DSA is performed mainly in the consideration of endovascular surgery. The cross-sectional techniques, such as CTA or MRA, are usually sufficiently effective compared to DSA [21,66].

Fig. 2.

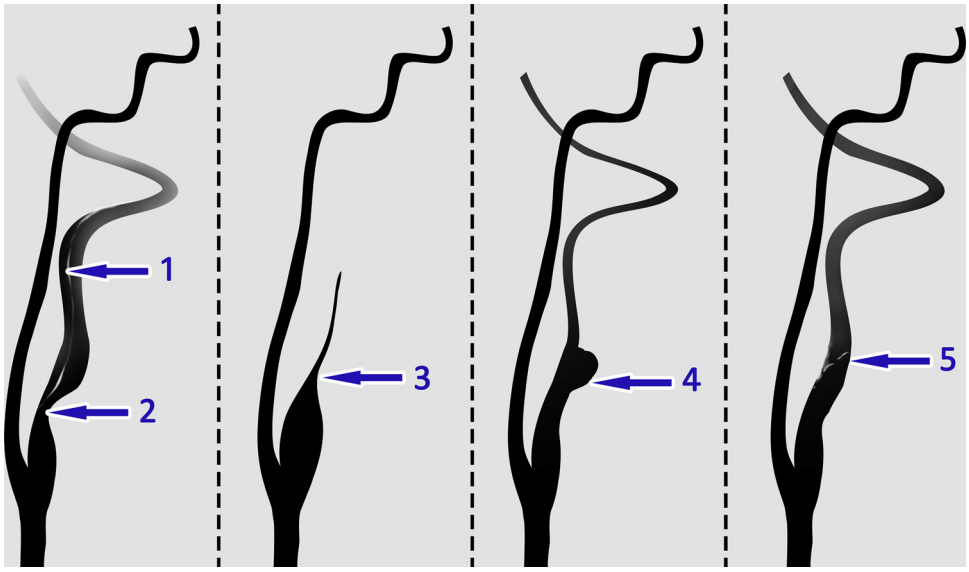

Fig. 2. Graphical representation of DSA imaging. Double-lumen sign and lifted intima (1), ICA stenosis (2), flame shaped occlusion (3), dissecting aneurysm (4) and intimal flap (5).

4.1. CT/CTA

CTA is the most commonly used imaging modality for CAD diagnosis [21]. Specific signs observed in CTA involve long stenosis of the arteries and increased wall thickness and diameter. Intimal flaps and multivessel lesions occur more commonly in traumatic type of CAD [68]. Intensified radiological attenuation and long segment of involved artery indicate on early suspicion of CAD as opposed to imaging findings observed in IS caused by the large-artery atherosclerosis or cardioembolism [69]. Notably, neither internal carotid bulb nor VA distal to V2/V3 segments junction are usually affected by dissection [3,8].

Cone-beam computed tomography angiography (CBCTA) provides a high spatial resolution in each plane. Compared with other image modalities, CBCTA can be a superior modality for the detection of intimal flap and "double lumen" signs, especially in VAD diagnosis [70]. In addition, the use of 128-slice CT scanners may confirm a suggestion of artery occlusion in MRA. A study comparing the effectiveness of 128-slice dual-source CTA and 1,5 T MRA in CD-related IS reported comparable effectiveness of both techniques in identifying intimal flaps, stenosis and lumen irregularity [67].

Disadvantages of CTA include slight specificity of the low-attenuation crescent sing of IH which may be mistaken for the presence of atheromatous plaque [21]. In addition, "flame" sign can be observed in case of pseudo-occlusion (a column of no distal blood flow blocks the proximal contrast penetration) [71]. Ionizing radiation is a certain disadvantage, although 128-slice CT, are able to scan faster and, thereby, use lower radiation doses compared to older scanners. Compared to MR/A, the advantages of CTA include faster acquisition (availability in emergency stroke assessment) and the absence of some contraindications such as metallic implants and pacemakers [67].

Fig. 3.

Fig. 3. Scheme of CT angiogram (CTA) of CAD; long narrowing of the left ICA (arrow 1).

4.2. MR/MRA

The visualisation of IH on FS-MR (fat saturation MR sequence) include a hyperintense signal ("crescent" sign) in T1-weighted imaging performed in the axial or oblique plane which corresponds to the methaemoglobin concentration [8,15]. Initially, IH can be indistinguishable from the surrounding tissue, as the time necessary for oxyhaemoglobin and deoxyhaemoglobin conversion to the methaemoglobin is prolonged to 72 h from symptoms onset. Thus, the sensitivity of T1-weighted MR in the first three days remains low [21]. A methaemoglobin "crescent" sign is observed in 837% of CAD cases, although the distinguishing from other sources of this sing or artefacts (such as epidural venous plexus, slow blood flow, failure of adequate fat saturation) can be difficult [67].

3D black blood (BB) T1 sequence can be more useful in CAD diagnosis than conventional imaging. The signal from blood flow is suppressed which enables a distinction between vessel wall and arterial lumen. Intraluminal contrast enhancement is usually a sign of thrombus formation [15]. Compared to the traditional imaging techniques, the advantages of 3D black blood T1 sequences include clearly, intense signal of IH, suitability for the assessment of arteries with tortuous course, and relatively short scan time [16]. Moreover, BB-MR is an useful tool to identify the enhanced risk for initial or recurrent CAD-related IS [15].

High resolution (HR) MR includes 3-dimensional FS-MR with a black-blood effect. HR-MR reveals hidden aetiologies of CAD lesions

invisible in DSA, including large IH in a false arterial lumen with complete occlusion [27,72]. HR-MR is currently treated as the optimal diagnostic technique particularly for subjects without clearly signs of dissection in conventional techniques. A confirmation of CAD supported by HR-MR reduces the necessity of the exclusion of steno-occlusive vascular lesions such as embolism or atherosclerosis. HR-MR is especially useful in examining VAD lesions localised in the closeness of bones and peri-arterial venous plexi. Arterial tortuosity, diameter variability, and arterial hypoplasia are another indications for the use of HR-MR [8,27]. A particular inconvenience of HR-MRI use is a necessity to target a potential lesion on previously performed MR scans [21].

Imaging findings associated with elevated risk of IS occurrence include a detection of artery stenosis, IH, pseudoaneurysm, and intraluminal thrombus [29]. Dissecting aneurysm, intimal flap and double lumen occur more commonly in IS patients with intracranial CAD compared to extracranial one [73]. It should be noticed that VAD imaging is more complicated than CaAD due to a small VA diameter (limited spatial resolution of cross-sectional imaging) and vertebral plexus mimicking intramural blood flow [21,70,74]. In addition, MR enables small infarction areas detection, having regard to those occurred in the posterior circulation cerebral region. The MR/A contraindications are different from CT/A ones and do not include pregnancy and impaired renal function due to the use of other than iodinated contrast agents [67].

Fig. 4.

4.3. Neck US

US is commonly used technique to confirm the diagnosis of emergency performed CTA or in order to monitoring affected arteries during the follow-up. CAD lesions observed in US include abnormalities in blood flow velocity, irregular artery stenosis, presence of IH (eccentric echogenic lesion), luminal thrombus, mobile flaps and “double lumen” sign [21,75]. The advantages of US include safety (almost no contraindications) and non-invasiveness of the procedure [18,75]. There are also certain limitations of US: operator-dependence, flow-related artefacts like Doppler angle dependence, aliasing artefact and difficulties in the examination of distal arterial segments [17,18,21]. The absence of US in the Canadian recommendations is explained by difficulties in the examination of VA and possible missing of changes above the angle of the jaw [65]. Moreover, the examination of elevated anatomical location of the carotid bifurcation in East Asian patients constitutes a technical US limitation in this population [10].

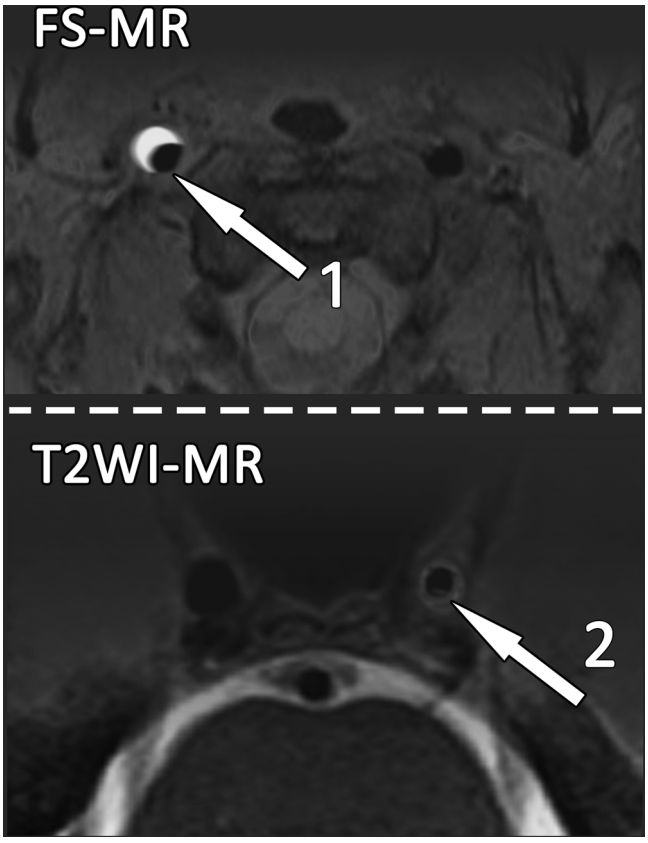

Fig. 4. Fat-saturation T1-weighted MR image (FS-MR); IH (intramural hematoma) as a “crescent” sign in the right ICA (arrow 1). T2 weighted image (T2WI-MR), IH and intimal flap (arrow 2) in the left ICA.

Contrast-enhanced ultrasound (CEUS) utilises the administration of microbubbles as an US contrast agent. Some studies support an evidence that CAD missed on conventional US can be diagnosed by CEUS due to the presence of intimal flaps or slow blood flow inside the false arterial lumen [18]. A detection of high intensity transient microemboli signals (MES) may be a decisive factor for the choice of appropriate antithrombotic therapy. MES, as a sign of arterial-arterial embolism, can be observed in up to 50% of CAD cases [76]. Patients with simultaneous existence of increased MES and abnormal breath hold index (a determinant of the cerebrovascular reactivity to hypercapnia) are at high risk of CAD-related IS [20,77].

Fig. 5.

4.4. CAD treatment

4.4.1. Antithrombotic treatment

The administration of alteplase in acute IS treatment (intravenous thrombolysis, IVT) is comparatively efficacious and safe in patients with CAD-related IS and those with miscellaneous causes of IS [78]. IVT does not adversely affect patients with CD-related IS more than patients with other cause IS, and thus the benefits of IVT treatment exceed the risk of harm. Similarly, a rate of favourable functional outcome does not differ between IS patients with and without history of CAD [3,4,79].

The use of antiplatelet (AP) or anticoagulant (AC) agents in CAD-related IS prevention is reasonable. The duration of pharmacotherapy should last from 3 to 6 months, although there are no official recommendations about treatment termination and a decision about the treatment duration ought to be based on the individual clinical factors [4,21,65]. AP therapy may be favoured when there are some contraindications to anticoagulation (systemic haemorrhage or recent surgery) or if the area of cerebral infarction is large. Moreover, AP agents should be administered when the dissection extends to intracranial or intradural regions and in case of spinal cord trauma. AC treatment is usually preferred in patients with severe stenosis, occlusion or multiple ischaemic lesions in single arterial territory, and if luminal thrombus or microembolism is detected [80,81]. However, despite proven efficiency of both AP and AC treatments, new ischaemic brain lesions may occur during the therapy [82].

Within the last five years five studies comparing AP and AC therapies in CAD treatment and secondary stroke prevention were published (Table 1). In the first study performed in 2015 AP therapy was variable with aspirin, clopidogrel, and dipyridamole; AC group was treated with heparin or warfarin only. No differences in the IS prevention and death rate were found. Two more cases of recurrent IS were observed in the AP group, however, the difference was statistically insignificant and counterbalanced by a one case of major subarachnoid haemorrhage in the AC group [74]. In further study, a similar rates of IS and haemorrhagic events were observed during 26 months of AP or AC therapies. The worst overall outcome was reported in patients who received both AP and AC treatment [60]. Accordingly, there are no benefits from adding a second antiplatelet agent when previous CAD-related IS occurred during taking aspirin in monotherapy [83]. A recanalization rate was another clinically important endpoint investigated in the studies. The “recanalization” term was defined as ≥50% relative improvement

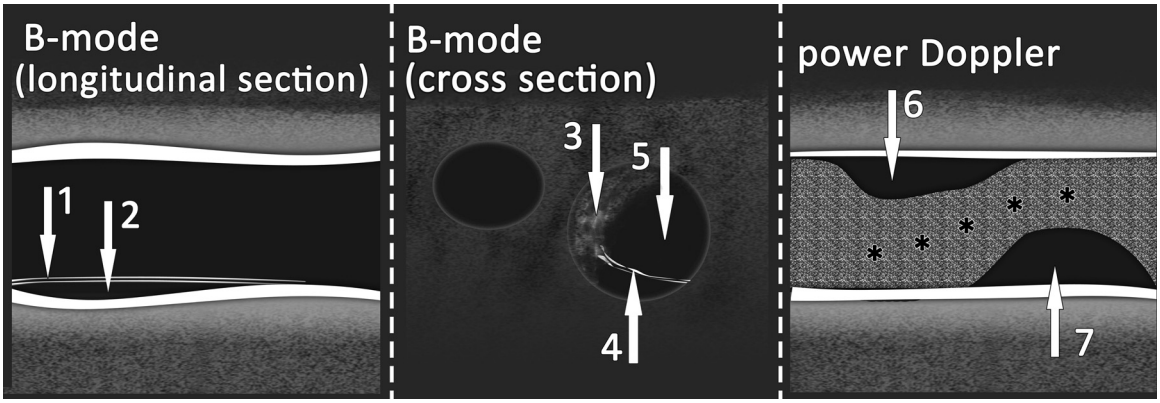

Fig. 5. Gray-scale US graphical representation of CAD. B-mode ultrasound longitudinal section shows intima-media complex (1) and intramural hematoma (IH) (2). Cross section image reveals echogenic intraluminal thrombus formation (3), intimal flap (4), and residual arterial lumen (5). Black asterisks in the power Doppler image indicate impaired blood flow due to IH (6,7).

in stenosis during the treatment. After 1 month of pharmacotherapy, no differences were found between AC and AP therapy, even despite higher rate of stenosis at baseline in AC group compared to AP (99% versus 50%) [26]. Interestingly, according to the power calculations, a large total sample size (of almost 10 000 participants) is required to perform a definitive study on the risk of stroke, death or major bleeding, due to the low occurrence of above endpoints in CAD patients [74] Table 2.

Only two small studies compared the effectiveness of NOACs (novel oral anticoagulants) therapy to standard antithrombotic treatment in the prevention of CAD-related IS. First study revealed that the NOACs therapy is characterised by similar rates of recurrent IS and fewer haemorrhagic complications, although higher rate of radiographic worsening compared to traditional AP or AC therapies was observed. Notably, especially young patients receiving NOACs had a better tolerance of the medicine compared to warfarin (less interactions with diet and lifestyle, no need to frequent laboratory monitoring) [80]. In the second study, no statistical differences were found between NOACs and VKAs (vitamin K antagonists) in the assessment of IS severity and recanalization rates. The clinical effectiveness of two compared groups was similar, however, all patients treated with NOACs had favourable outcome (modified Rankin scale ≤ 1), no bleeding complications or recurrent dissections. In the VKAs group 1 death and 1 case of serious intracerebral haemorrhage was reported, although there were large disparity in the group sizes (6 patients in NOACs group and 62 in VKAs) [84]. In summary, current data on NOAC in CAD treatment should be interpreted with caution due to the insufficient clinical experience, small number of study participants and non-random treatment allocation [2,85,86].

5. Interventional treatment

The effectiveness of mechanical thrombectomy (MT) in IS caused by CAD is similar to IS resulted from atherosclerotic lesions. No significant differences were found in the rates of favourable outcome at 90 days (mRS 0–2), successful reperfusion, symptomatic intracerebral haemorrhage and 90-day mortality [88]. MT in CAD patients is relatively safe and does not significantly increase the risk of symptomatic intracranial haemorrhage and 90-day mortality [89].

Indications for endovascular treatment (EVT) include recurrent cerebral ischaemic events despite pharmacotherapy, contraindications to antithrombotic therapy, pharmacological treatment failure, significant flow limitation as a result of IH, the occurrence of pseudoaneurysm or in case of coexistence of both embolism and hypoperfusion [4,8,21]. Considering hemodynamic and embolic causes of ischaemia, EVT is especially beneficial for patients with not only, but mainly hemodynamic CAD causes [90]. To date, no randomized controlled trials comparing interventional treatment and pharmacotherapy were performed. One study provided class III evidence of similar rate of functional independence (mRS 0–2 at 90 days) of intra-arterial treatment

Table 1
Advantages and disadvantages of imaging techniques used in CAD diagnosis.

	Advantages	Disadvantages
DSA	- high spatial and temporal resolution	- adverse reactions to contrast media
	- time-resolved blood flow dynamics	- exposure to ionizing radiation
	- sensitive detection of wall irregularities and intimal tears	- low detection sensitivity of the lesions within the arterial wall
CT/A	- commonly available technique	- adverse reactions to contrast media
	- short duration of scanning	- exposure to ionizing radiation
	- high sensitivity and specificity of CBCTA	- potential resemblance between dissection and atherosclerotic stenosis/ occlusion
MR/A	- the most detailed assessment of tissues	- contraindications such as metallic implants and pacemakers
	- availability of high resolution modalities enhancing the sensitivity and specificity (e.g. FS-MR, BB-MR)	- low sensitivity of T1-weighted images within 3 initial days
	- detailed imaging of the arterial wall useful in differential diagnosis of the steno-occlusive vascular lesions	- relatively long duration of scanning
US	- commonly available	- severe operator-dependence quality of examination
	- short implementation time (emergency)	- hindered imaging of distal arterial segments
	- almost no contraindications to apply	
	- may affect a choice of proper pharmacotherapy if MES detected	- flow-related artefacts

BB-MR – black blood magnetic resonance sequence, CAD – cervical artery dissection, CBCTA – cone-beam computed tomography angiography, CTA – computed tomography / angiography, DSA – digital subtraction angiography, FS-MR – fat saturation magnetic resonance sequence, HR-MR – high resolution magnetic resonance, MES – microemboli signals, MR/A – magnetic resonance/ angiography.

Table 2
Studies on antiplatelet versus anticoagulant CAD therapies in the primary or secondary ischaemic stroke prevention (published within the last 5 years).

N	Study design	Duration (months)	Baseline characteristic	Outcomes	R
75	retrospective, single-centre cohort study	1	CAD symptoms onset < 2 weeks, 48% patients with IS/TIA	AP v. AC: no difference in RS prevention, no difference in the rate of ≥ 50% relative stenosis improvement	2018 [87]
233	Retrospective single-centre	26	32 % patients with IS/TIA	AP v. AC: similar rate of RIS and SH + IH, AP: 3 RIS, AC: 2 RIS, AP + AC: 1 RIS, unfavorable clinical outcome (mRS 3-6): 5% AP, 3% AC, 10% combined treatment	2017 [60]
250	prospective, multi-centre, randomised, controlled	3	CAD symptoms onset < 7 days, 96% patients with IS/TIA	AP v. AC: no significant difference in RS and death prevention, AP: 3 RIS, 0 SH, AC: 1 RIS, 1 SH	2015 [74]
68	retrospective single-centre	6	100 % patients with IS	complete recanalization: 83% NOAC, 55% VKAs favorable clinical outcome (mRS ≤ 1) 100 % NOACs, 77% VKAs	2015 [84]
149	Retrospective single-centre	7.5	54.4% patients with IS/TIA	NOAC: 2 RIS, AP: 1 RIS, AC: 1 RIS, IH + SH: 0% NOAC, 2.5%AP, 11.4% AC worsened stenosis on follow-up imaging: 3 in NOAC, 0 in AC, 0 in AP	2014 [80]

AP – antiplatelet therapy (acetylsalicylic acid, clopidogrel and others), AC – anticoagulant therapy (mainly heparin or warfarin), CAD – cervical artery dissection, IH – intracranial haemorrhage, mRS – modified Rankin scale, N – number of participants, NOACs – novel oral anticoagulants, non-vitamin K oral anticoagulants, R –references and year of publication, RIS – recurrent ischaemic stroke, SH – subarachnoid haemorrhage, TIA – transient ischaemic attack, **v.** – versus, VKAs – vitamin K antagonists.

methods (MT, intra-arterial thrombolysis, stenting and angioplasty) [91]. Many studies demonstrated acceptable long-term clinical and radiographic outcomes of EVT [92,93]. EVT in CAD-related IS is considered as relatively feasible and safe [94,95].

No clear recommendations on EVT in tandem occlusion (TO) caused by CAD were published. TO occurs when the obstruction of extracranial ICA coexists with the intracranial ICA or MCA occlusion [96]. Low efficacy of IVT, large infarct areas and high rates of disability and death are observed in patients with TO. So far, the most common method of endovascular TO treatment include “proximal-to-distal” strategy (called “anterograde”), in which revascularization begins from the extracranial arteries and ends in intracranial ones. However, anterograde approach may not be the optimal management, as the procedure of ICA stent placement delays intracranial revascularization and enhances necrotic core volume. Second strategy, “distal-to-proximal”, consists of prior treatment of intracranial occlusion and restoring cerebral blood flow through the circle of Willis [97]. The rate of successful recanalization is substantial and favourable clinical outcome (mRS < 2) can be achieved in up to 70% of patients. Currently, there is a growing evidence that “distal-to-proximal” approach is more effective due to the reduced duration of cerebral ischaemia [96,97].

The main advantages of EVT include high revascularisation rate and an opportunity for restoring vessel lumen integrity [98,99]. Stent thrombosis, peripheral thromboembolism, and arterial spasm are the most common complications of the procedure [4]. Moreover, most extracranial CaAD is localised above the carotid bulb (at the skull base), thus surgical reconstruction methods may result in perioperative stroke and cranial nerve injury [90]. Generally, patients with CaAD tends to have more successful stent placements compared to VAD patients [100]. The main technical difficulty remains the navigation within the dissected artery and catheterizing false lumen which may aggravate the dissection [97,101,102]. However, the novel retriever wires have no need to utilize a long microwire to hold the position inside the “true” lumen of dissected artery and the anterograde reperfusion is achieved faster (usually during extracranial artery stenting) [101]. Other inconvenience of EVT concerns arterial tortuosity which adds complexity to the revascularization procedure [103]. Unfortunately, time to TO treatment may be prolonged due to the initial clinical presentation other than dissection and no suspected need for an experienced endovascular therapist [94]. Considering the most frequent adverse events of EVT, the improvement of devices and techniques should comprises reduction of the risk of thromboembolism and thrombus formation [102]. Novel flow-diverter stents used in the treatment of CaAD are more flexible, provide a better deployment in the dissected artery and cause less discomfort at the placing site during neck movements compared to stiffer, steel stents [90].

Current data on surgical therapy are limited [3]. A progressive clinical course despite pharmacotherapy, contraindications for stenting and anatomically accessible lesions are considered as arguments in favour of currently rarely performed surgical treatment [64].

Fig. 6.

6. Conclusions

The suspicion for of CAD should be considered in young adults with ischaemic symptoms reporting headache, neck pain or Horner’s syndrome, although the diagnosis may be challenging due to wide symptoms diversity. A development of high-resolution and 3-dimensional imaging increased the diagnostic potential of MR/MRA which enables safer and more specific CAD diagnosis compared to DSA. Despite similar overall efficacy of antiplatelet and anticoagulant treatment, choosing an appropriate therapy should be based on the considering of patient-specific indications for treatment. Current encouraging data on the use of NOAC are insufficient to recommend their use in CAD-related IS prevention. Endovascular therapies may be considered as the acute treatment for CAD in case of large occlusion or antithrombotic therapy

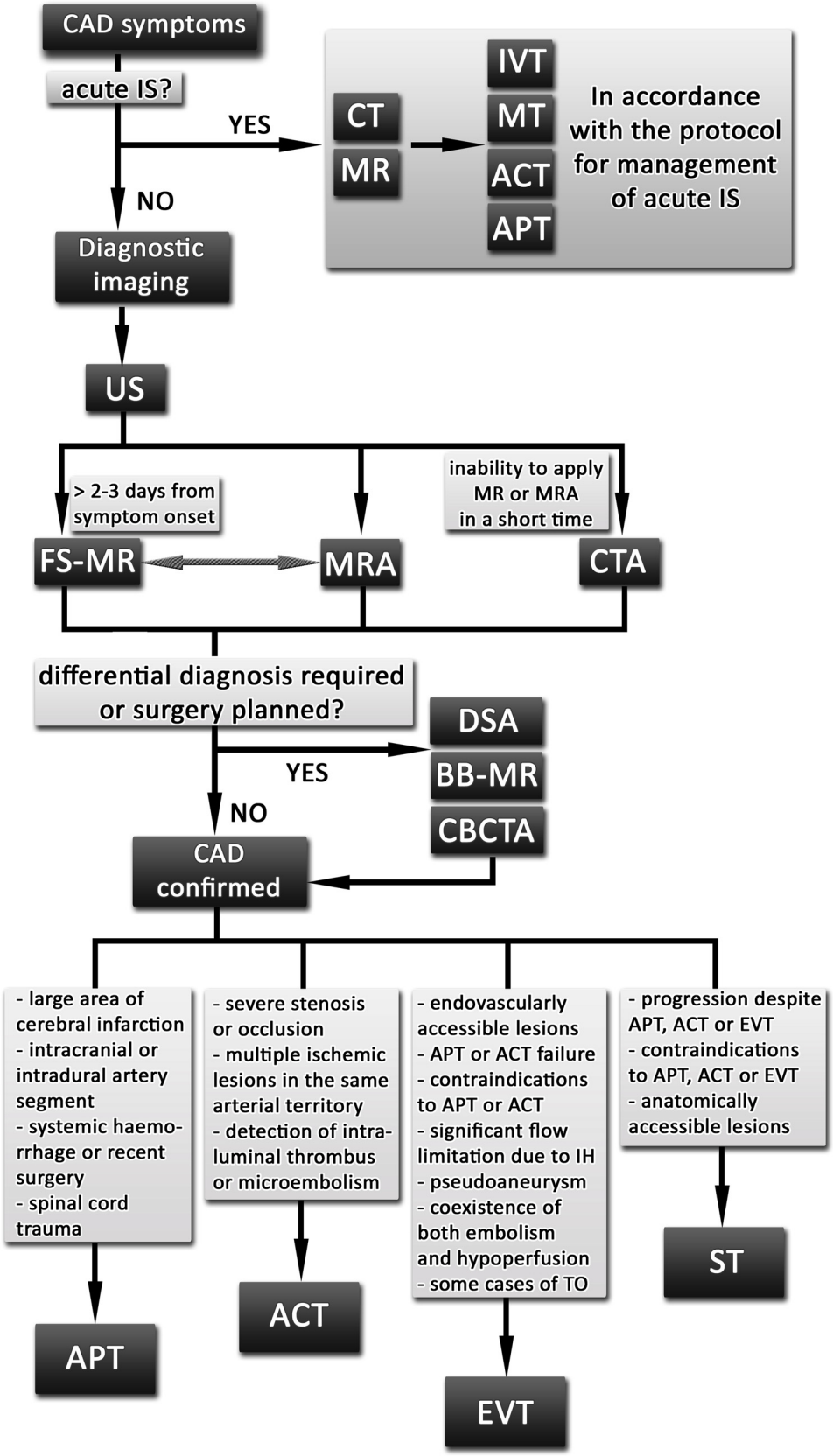

Fig. 6. Management of patients with CAD. ACT – anticoagulant therapies, AP – antiplatelet therapies, BB-MR – black blood magnetic resonance sequence, CAD – cervical artery dissection, CBCTA – cone-beam computed tomography angiography, CTA – computed tomography angiography, DSA – digital subtraction angiography, EVT – endovascular treatment, FS-MR – fat saturation magnetic resonance sequence, ICA – internal carotid artery, IH – intramural hematoma, IS – ischaemic stroke, IVT – intravenous thrombolysis, MRA – magnetic resonance angiography, MT – mechanical thrombectomy, TO – tandem occlusion, US – ultrasound.

failure. Due to the lack of randomized controlled trials, further research is needed to investigate which patients benefit most from each imaging and treatment modality.

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Declaration of Competing Interest

None.

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