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Original Article

Recanalization and Functional Outcome in Patients with Cervico-cephalic Arterial Dissections

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ABSTRACT: ***Background:*** Cervico-cephalic arterial dissections (CeAD) are an important cause of stroke in young patients. This study aimed to determine the frequency and predictors of recanalization in spontaneous CeAD and to study the effect of recanalization on functional outcomes. ***Methods:*** We identified patients presenting with acute ischemic stroke secondary to CeAD from the CT angiography (CTA) database of the Calgary Stroke Program. Dissections were diagnosed based on standard clinical and imaging findings. At the discretion of treating stroke Neurologists, the patients were either treated with single antiplatelet or dual antiplatelet or triple therapy. Follow-up imaging with CTA, magnetic resonance imaging, and DSA was completed, and a Modified Rankin scale (mRS) was performed to determine the outcome. ***Results:*** Fifty-six patients with CeAdD were studied. Thirty-four patients (18 VAD; vertebral artery dissection and 16 CAD; carotid artery dissection) were followed up for recanalization. Complete recanalization was observed in 27 subjects; 13 patients with VAD recanalized in comparison to 14 with CAD ($p = 0.40$). All non-recanalized patients had hypertension. A good clinical outcome ($mRS \leq 2$) was observed in 47 patients. Interestingly, the likelihood of a good neurological outcome was not influenced by recanalization status. There was no difference in clinical outcome for different sites in VAD, whereas patients with intracranial CAD had severe strokes ($NIHSS > 21$). ***Conclusions:*** CeAD has good recanalization rates and neurological outcomes, with recanalization seen even in vessels with initial complete occlusion. The presence of hypertension may influence recanalization. The efficacy of dual antiplatelets and heparin for early recanalization needs to be assessed in future clinical trials.

RÉSUMÉ : ***Recanalisation et résultat fonctionnel chez des patients présentant une dissection des artères cervicocéphaliques Contexte :*** Les dissections des artères cervicocéphaliques (DACC) sont une cause importante d'accidents vasculaires cérébraux (AVC) chez les jeunes patients. Cette étude visait à déterminer la fréquence et les facteurs prévisionnels de la recanalisation dans les DACC spontanées, et à évaluer les effets de la recanalisation sur les résultats fonctionnels. ***Méthodes :*** Des données concernant des patients présentant un AVC ischémique aigu secondaire à une DACC ont été tirées de la base de données CT Angiography du Calgary Stroke Program. Les dissections ont été diagnostiquées selon les résultats des examens cliniques et d'imagerie usuels. Les patients ont été traités par des antiplaquettaires en monothérapie ou en bithérapie, ou encore par de la trithérapie, à la discrétion du neurologue traitant. Des examens de suivi par imagerie, soit une angiographie par tomodensitométrie, une angiographie par résonance magnétique et angiographie numérique avec soustraction, ont été réalisés, et l'échelle de Rankin modifiée (ERm) a été utilisée pour déterminer les résultats. ***Résultats :*** Cinquante-six patients présentant une DACC ont été évalués. Trente-quatre patients (18 avec dissection de l'artère vertébrale [DAV] et 16 avec dissection de l'artère carotide [DAC]) ont fait l'objet de suivi aux fins d'évaluation de la recanalisation. Une recanalisation complète a été observée chez 27 patients, dont 13 atteints d'une DAV, et 14, d'une DAC ($p = 0{,}40$). Tous les patients chez qui il n'y a pas eu de recanalisation étaient atteints d'hypertension. Un bon résultat clinique (score ≤ 2 à l'ERm) a été observé chez 47 patients. Fait intéressant à noter, la probabilité d'un bon résultat neurologique n'était pas influencée par l'état de la recanalisation. Il n'y avait pas de différence en ce qui concerne les résultats cliniques associés aux divers sièges de DAV, tandis que les patients présentant une DAC intracrânienne ont subi de graves AVC (score > 21 à l'échelle NIHSS). ***Conclusions :*** La DACC est associée à un bon taux de recanalisation et à de bons résultats neurologiques, des recanalisations ayant été observées même dans les vaisseaux présentant une occlusion complète au départ. La présence d'hypertension pourrait influer sur la recanalisation. L'efficacité de la bithérapie antiplaquettaire et de l'héparine pour la recanalisation hâtive devra faire l'objet d'études cliniques.

Keywords: Dissection; Stroke; Cervical artery; Vertebral artery

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Introduction

Cervico-cephalic arterial dissections (CeAD) are an important cause of ischemic stroke in young patients, accounting for 10–25% of cases in patients < 45 years of age.[1,2] The reported annual incidence of carotid artery dissections (CAD; 2.5–3 per 100,000) is twice that of vertebral artery dissection (VAD;1 to 1.5 per 100,000).[3,4,5] Various studies have looked at the clinical manifestation, risks, and treatment options in CeAD; however, there is still a dearth of literature regarding the factors associated and timing of recanalization post dissections.[6–8] The reported recanalization rates from the existing literature range between 42% and 85% within 3–6 months.[9–13] One of the recent studies analyzed 51 consecutive patients of confirmed CeAD and found that recanalization usually occurs within 6 months of symptom onset and the location or pattern of arterial dissection is not associated with vessel reopening.[14]

Stroke secondary to spontaneous dissections generally has a favorable outcome compared to strokes secondary to atherosclerotic disease. A few studies looked at the clinical outcome post-CeAD concerning recanalization status and infarction site and concluded that outcomes are less favorable after CAD.[15] Furthermore, dissected artery occlusions (DAO) are thought to carry a less favorable prognosis when compared to those without the occlusion.[16]

The aims of this study were (a) to determine the recanalization rates and factors influencing the same in spontaneous carotid and VADs; (b) to study the effect of recanalization, dissection site, locations of infarcts, and other vascular risk factors on the neurological outcomes post-CeAD.

Materials and Methods

We retrospectively identified records of a consecutive cohort of patients presenting with acute ischemic stroke secondary to carotid and VADs from the CTA database of the Calgary Stroke Program at the Foothills Medical Centre, University of Calgary, Canada. The Calgary CTA database is ethics board-approved retrospective study database. The imaging criteria for diagnosing dissections on CTA were (1) a narrowed centric or eccentric lumen surrounded by crescent-shaped, mural thickening and an associated increase in the external diameter; (2) an abrupt or tapered occlusive lumen and an associated increase in the external diameter; or (3) an aneurysmal-like dilated lumen or a dilated and narrowed lumen with or without crescent-shaped mural thickening or an intimal flap. The increased external diameter was determined by comparing it with the segment proximal to the dissections.[17,18] Magnetic resonance imaging (MRA) and time-of-flight sequences were obtained. Axial T1 fat-suppressed images were also analyzed. The criterion for a mural hematoma was an eccentric residual lumen surrounded by a semilunar signal alteration (crescent sign).[19] Digital angiographic findings of a double lumen (the presence of a false lumen or an intimal flap), stenosis involving an irregular long or short segment (the pearl and string sign), occlusion involving either the entire vertebral artery or only one segment of the artery, or a pseudoaneurysm associated with a narrowed arterial lumen were used as reliable angiographic findings indicative of cerebrovascular dissections.

The in-hospital and outpatient stroke clinic charts were reviewed and details of demographics, history, clinical features, and follow-up details were recorded. The following factors were noted in detail: age, sex, type of vessel involvement, side of involvement, history of hypertension, diabetes mellitus, hyperlipidemia, smoking, coronary artery disease, migraine with or without aura, chiropractic manipulation, NIHSS, and treatment received in the hospital. At the discretion of treating stroke Neurologists, the patients were either treated with single antiplatelet or dual antiplatelet or triple therapy comprising of dual antiplatelets and intravenous heparin. The decision to treat with intravenous heparin was based on thrombus location anticipating clinical worsening, also taking into consideration the size of infarcts seen on the brain scan. The off-label nature and the additional risk were explained to the patient's relatives or legally authorized decision-maker. The patients were followed for a period of 3 months to 2 years.

The carotid artery was divided into two segments for the current study; a proximal cervical segment and a distal segment that includes the petrous/cavernous/intracranial segment. The vertebral artery (VA) was divided into four segments: (V1 – the segment of artery from origin to the entry into transverse foramina of C7 vertebrae, V2 – course in the transverse foramina of cervical vertebrae from C7 to C2, V3 – from C2 foramen transversarium through vertebral canal intracranially, V4 – after piercing dura until it unites with contralateral VA to form the basilar artery. The area of involvement was confirmed by axial, coronal, and sagittal planes of CTA in all patients. Among patients with VADs, the topographical distribution of infarcts was divided into either supratentorial (involving, occipital lobe, and thalamus) or infratentorial involving brain stem and cerebellum.

Follow-up imaging with CTA, MRA, and DSA done within 3 weeks – 24 months of the stroke onset was used to document vessel status on follow-up. This was scored as showing either complete recanalization (if the blood flow was completely restored), partial recanalization (reduction in the degree of stenosis or a change from occlusion to stenosis), or non-recanalized (absent flow observed in the vessel). Patients with complete recanalization on follow-up imaging were termed as recanalized and those with partial and no recanalization were termed as non-recanalizers. A Modified Rankin scale (mRS) was performed at admission and then on follow-up visits which varied between 3 and 24 months. Good neurological outcome was defined as mRS ≤ 2.

Statistical analysis was performed using SPSS version 18. Univariate analysis was performed using the independent t-test and Fischer exact test to study factors governing recanalization and good outcome.

Results

Recanalization

Among the total of 1341 patients in the CTA database, 78 patients with dissections were screened. Of these, 22 patients were excluded from the study due to the presence of artifacts and poor quality of images. After exclusions, 56 patients with carotid (n = 26) and VADs (n = 30) were analyzed. Thirty-four patients (18 patients with vertebral artery and 16 patients with CADs) with follow-up imaging were analyzed to look for recanalization. There were 21 males (62%) and 13 females (38%) with a mean age of 41.5 ± 7.5 years. A history of suspected neck trauma (like sudden movements during exercise, skiing) was observed in ten patients including six patients with a history of manipulative neck treatment. Neck pain and headache as presenting symptoms were observed in 12 patients (35.3%). Twenty-six patients were treated with antiplatelets and/or intravenous heparin and eight patients received anticoagulation (warfarin) at discharge.

One patient with CAD was treated with acute stenting. Complete recanalization was observed in 27 (79.4%) patients, 13/18 patients (72.2%) with VADs recanalized in comparison to

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14/16 patients (87.2%) with CADs (p = 0.40). Recanalization was documented between 3 and 6 months of the index event. There was no significant change in recanalization rates in females (11/13, 84.6%) versus males (16/21, 79.1%), (p = 0.56). The recanalization rate among patients who received anticoagulation along with dual antiplatelet therapy in the acute phase was high (90 %, 21/24), in comparison to patients receiving single antiplatelet therapy alone (60%, 6/10), (p = 0.056). There was no evidence of symptomatic or intracranial hemorrhage among patients who were treated with dual antiplatelets or triple therapy. The area of involvement of the vessel (V1, V2 vs V3, V4 in the vertebral artery, and proximal vs distal carotid artery involvement) did not influence recanalization rates (p = 0.279). Intracranial carotid dissections were all partial rather than complete. Among vascular risk factors, all non-recanalized had a history of hypertension (7/7, 100%) (p = 0.01). The presenting symptoms and the vascular risk factors in patients with and without recanalization are outlined in Table 1. 79% (n = 19/24) of patients with irregular narrowing or incomplete occlusions at baseline recanalized when compared to 60% (n = 6/10) vessels with complete occlusion (P = 0.09); Table 2.

Outcomes

The likelihood of good neurological outcome was not influenced by recanalization status; 22/27 (81.4%) patients with recanalization and 5/7 (71%) patients without recanalization had good outcomes (p = 0.061).

Among 56 patients (carotid artery involvement = 26, vertebral artery involvement = 30) with CeAD analyzed, a good clinical outcome was seen in 47 (84%) patients. Given different clinical presentations and varied anatomical involvement among patients with carotid and vertebral arteries, they were analyzed separately to determine individual variables affecting the outcomes. In patients with CAD, those with petrous and intracranial involvement had severe strokes when compared to cervical segment ($p \leq 0.05$), whereas in patients with VAD, there was no difference in clinical outcomes for patients with V3, V4 (23/26) segment involvement in comparison to patients with involvement of V1, V2 (3/26) segment (p = 0.082), although the number of patients with V1 and V2 involvement was quite small. About 88% (15/17) of patients with CAD and 95% (21/22) of patients with VAD and NIHSS < 10 had good neurological outcomes. There was no difference in clinical outcome for baseline stenotic carotid dissections in comparison to occlusive carotid dissections (p = 0.09). Also, there was no difference in clinical outcomes in patients who were treated with a single antiplatelet (11/26, 42%), in comparison to those who were treated with dual antiplatelet and heparin (15/26, 58%) (p = 0.27) for CAD. Among 24 patients with VAD treated with dual antiplatelets or triple therapy (dual antiplatelets + intravenous heparin), 22 (91%) had good neurological clinical outcomes in comparison to 3/6 (50%) of those treated with a single antiplatelet (p = 0.04). In patients with VAD, those with thalamic and occipital infarcts (n = 9/30, 30%) had poor neurological outcomes as compared to the small infratentorial, brainstem, and cerebellar infarcts (n = 21/30, 70%), ($p \leq 0.01$). Neck manipulations and trauma were observed in 9 (30%) patients with VAD. Recurrence of neurological events was not observed in this cohort of patients during the study follow-up time. Baseline characteristics and different variables with clinical outcomes in CAD and VAD are outlined in Tables 3 and 4.

Key results are summarized in Figure 1.

Table 1: Comparison of symptoms and the vascular risk factors in patients with and without recanalization

	Total number of patients N = 34	With recanalization N = 27	Without recanalization N = 7	P value
Age, mean (range)	39.5 (22 - 75)	38 (22 - 68)	44 (34 - 75)	0.954
Sex (M)	21	16	5	0.561
Signs and symptoms				
Neck pain	12	9	3	0.524
Vertigo	8	5	3	0.386
Hemiparesis	9	8	1	0.419
Horner's syndrome	3	3	–	0.363
Trauma	10	7	3	0.468
Hypertension	11	4	7	0.015
Diabetes	4	2	2	0.451
Smoking	4	3	1	0.561
Migraine	2	2	–	0.465
Types				
Stenotic (n = 24)		20	4	0.09
Occlusions (n = 10)		6	4	
Single antiplatelet drug	10	6	4	0.06
Dual antiplatelet and	24	21	3	
Heparin				
Good outcomes (MRS = <2)	27	22	5	0.06

Table 2: Showing percentage of imaging abnormalities detected on baseline CTA in patients with cervicocephalic dissections (34 patients) with recanalization data

Description of baseline imaging finding	N	Recanalization N (%)
Abrupt or tapered occlusive lumen	3	2/3 (66)
A narrowed centric or eccentric lumen	11	9/11 (82)
Filling defect with thrombus	7	7/7 (100)
Alternate dilated or narrow lumen with flap	3	3/3 (100)
Complete occlusion	10	6/10 (60)

Discussion

In this study, we evaluated the predictors of recanalization and functional outcomes in patients presenting with CeAD. A good clinical outcome was observed in around 81% of our patients which is similar to that reported in the existing literature. The clinical outcome was not affected by the site of dissection in patients with VAD in contrast to CAD where patients with intracranial dissections suffered severe strokes. Although NIHSS might underestimate the clinical severity in posterior circulation stroke, most of the patients with dissections who were mild to moderately

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Table 3: Comparison of factors in patients with carotid artery dissections having good and poor neurological outcomes

Carotid artery dissections (n = 26)	MRS 0–2 (n = 20)	MRS 3–6 (n = 6)	P-value
Age	40.2+−7.1	43.1+−7.2	0.61
Sex(male) (n = 18)	14	4	0.75
Hypertension (n = 7)	5	2	0.35
Diabetes (n = 3)	3	–	0.43
Baseline NIHSS <= 10 (n = 17)	15	2	0.02
=>10 (n = 9)	4	5	
Trauma (n = 8)	5	3	0.19
Type			
Stenotic (n = 17)	14	3	0.24
Occlusive (n = 9)	6	3	
Site			
Proximal cervical carotid (n = 18)	16	2	0.05
Petrous and intracranial (n = 8)	4	4	
Clot burden < 6 (n = 16)	10	5	0.16
Treatment			0.27
Single antiplatelet	11	4	
Dual antiplatelet or triple therapy	10	1	

Table 4: Comparison of factors in patients with vertebral artery dissections having good and poor neurological outcomes

Vertebral artery dissections (n = 30)	MRS 0–2 (n = 25)	MRS 3–6 (n = 5)	P-value
Age	38.4 (+/−) 6.4	40.2(+/−) 6.7	0.61
Sex (male) (n = 21)	19	3	0.14
Hypertension (n = 10)	8	2	0.80
Diabetes	3	1	0.88
Baseline NIHSS <= 10 (n = 22)	21	1	0.01
Trauma (n = 10)	8	2	0.8
Type			
Stenotic (n = 19)	17	2	0.08
Occlusive (n = 11)	8	3	
Brainstem and cerebellum	20	1	0.01
supratentorial	5	4	
Site			
V1 and V2 (n = 5)	3	2	0.08
V3 and V4 (n = 25)	23	2	
Treatment			0.04
Single antiplatelet (n = 6)	3	3	
Dual antiplatelet or triple therapy n = 24	22	2	
Long term anticoagulation (3 months)	5	1	0.74

affected (NIHSS < 10) had a good neurological outcome. Also, for the first time in literature, our study highlighted the role of triple therapy (dual antiplatelets and heparin) in the management of these patients.

Our study showed that 79.4% of patients with CeAD recanalized within 6 months, with no significant differences among the type of vessels involved. These findings are as per the results of previous studies reporting 92 to 100% vessel recanalization occurring within the first 6 months after dissections.[9,20,21] Vessels with irregular narrowing and incomplete occlusion at presentation had marginally higher recanalization rates as compared to the ones with initial complete occlusion (79% vs 60%). Traenka et al recently analyzed the data from three multicentre cohorts (CADAISP-Plus) and also concluded that DAO predicts a poorer outcome and recanalization in patients with CeAD.[16] Lee et al have reported, complete recanalization on follow-up in 46% of patients with stenosis, 33% with occlusions, and 12% with dissecting aneurysms at baseline in the general population.[22]

One of the previous studies specifically looked at the association of vascular risk factors with CeAD and ischemic stroke in young. It revealed that although hypertension in CeAD is less common than in non-CeAD ischemic stroke it can still be a risk factor for CeAD.[23]

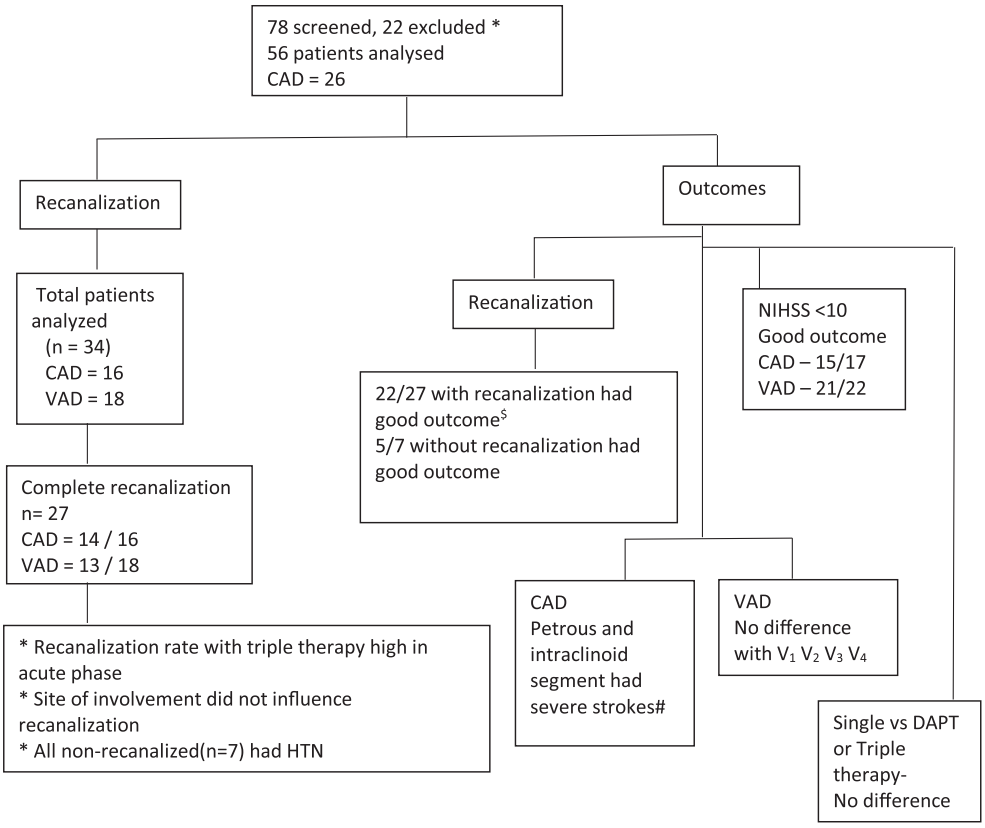
We found that the absence of hypertension was the only vascular risk factor that influenced recanalization. This observation has earlier been reported by Caso et al and can be explained by the fact that hypertension can cause a direct effect on the elasticity and permeability of the arterial wall making it prone for atherosclerosis with increased clot burden and these vessels are less likely to completely recanalize.[9] One potential confounder for such a finding could be old age as hypertensive patients are likely to be older. Other than receiving blood pressure lower agents, hypertensive patients were not treated differently from normotensive patients in our study.

There was no recurrence of ischemic events seen in our cohort although a recurrence rate of around 2.5 % has been reported in the CADISS trial.[7] Recurrence is frequently associated with multiple dissections and is more commonly seen in patients with a history of hypertension.[24,25] In the present study, favorable rates of complete recanalization were observed irrespective of baseline occlusive status of the vessel, associated vascular risk factors, or treatment received. Furthermore, complete recanalization did not influence the functional outcome in patients with acute stroke, which is in keeping with the findings of acute stroke treatment trials.[26–28]

In our study, the use of long-term antiplatelet agents (> 6 months) or anticoagulation did not affect recanalization status which has also been shown in a Cochrane meta-analysis.[29] Results from the CADISS trial also showed no difference in the prevention of strokes in patients treated with antiplatelets or anticoagulants.[7] There was an improvement in recanalization status of stenotic dissections on dual antiplatelets alone and with IV heparin (triple therapy) documented within 3 weeks of the onset of symptoms, although not statistically significant. There has been no data to support this treatment modality. We hypothesize that patients with stenotic dissections causing incomplete occlusion due to thrombus are the target patients for this therapy. No adverse events from this treatment were noted in our study. The safety and clinical efficacy of this therapy need to be proven in a randomized trial before accepting as one of the standard treatments in acute stroke with dissections.

The present study showed that good neurological outcomes were observed in the majority of patients irrespective of recanalization

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*Excluded due to image artifacts
$ good outcome was defined as mRS≤2
# severe strokes-NIHSS>21

Figure 1: Summary of results.

status in either vessel. This is in agreement with the literature where good functional outcomes are described in 75–80 % of patients with CeAD.[4,24] Mortality rates in the acute phase of CeAD are generally low (< 5%), although higher rates of up to 23% have been reported in patients with CADs with malignant cerebral infarcts. Also, poor neurological outcomes have been observed in patients with carotid dissections and large territorial strokes.[20,28,30] In the present study, there were more disabling strokes in distal carotid artery occlusions (petrous and the intracranial segments of ICA) as compared to proximal occlusions, which has also been shown in a large follow-up study by Arauz et al.[28] Previous data suggests that small infratentorial and lateral medullary infarcts caused by VADs have good neurological outcomes as compared to large supratentorial and hemispheric infarcts, the same was reflected in our results.[9] In patients with carotid and VADs, low baseline NIHSS (<=10) at presentation was associated with good neurological outcomes, and this observation is in agreement with the findings shown in a study on VADs by Arnold et al.[31]

Patients receiving dual antiplatelets or triple therapy, through early recanalization did influence the outcomes in VADs ($p = 0.03$), but not in patients with CADs ($p = 0.27$), especially for those with and intracranial dissections.

Our study has limitations. It is retrospectively analyzed data, that originates from a tertiary care center, hence severe cases might have been over represented. We did not adjust for multiple comparisons. The interobserver reliability of our proposed grading system for dissection is not known. However, available grading systems are derived for patients with dissection following blunt neck trauma which does not apply to most of our cohort. There is no uniformity in the type of imaging used at baseline and follow-up for comparison which may have affected our conclusion. Most of the patients with CAD had mild to moderate strokes, NIHSS < 10 (65%) and did not undergo any intervention, including thrombectomy. However, the rates of recanalization and good outcomes are similar to that seen in recent studies. This study is unique in the way that it gives us an indication for the use of dual antiplatelets or triple therapy in this cohort of patients, showing it to be safe and with some effect on recanalization. This may have clinical implications in changing the management of these patients in the future.

Conclusions

Our study suggests that CeAD has good recanalization rates and neurological outcomes, irrespective of the status of the vessel at presentation, with good recanalization rates seen even in vessels with initial complete occlusion. The absence of hypertension may influence recanalization rates to some extent, with no other clinical and vascular factors positively affecting it. The efficacy of dual antiplatelets and IV heparin in early recanalization needs to be further studied through prospective studies and randomized trials. Low baseline NIHSS at the presentation in patients with both carotid and VADs are associated with good

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neurological outcomes. Distal CADs and supratentorial infarcts are associated with poor outcomes.

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Statement of Authorship. AW: Collection of data,analysis and interpretation of data, drafting the manuscript and design of study.

MA: analysis and interpretation of data, drafting the manuscript and design of study.

BM: interpretation of data and drafting the manuscript.

SB: Concept and design of study, interpretation and analysis.

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