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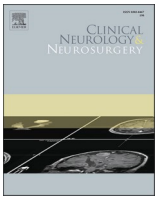

Individual participant data analysis comparing acute stroke patients with anterior *versus* posterior circulation dissections

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ABSTRACT

Background: Cervical artery dissection (CAD) is a relevant etiology of transient ischemic attacks and strokes. Several trials explored the significance of specific antithrombotic treatments, i.e. oral anticoagulation (OAC) versus antiplatelet treatment (APT), on recurrent ischemic complications and clinical outcomes. As overall incidence rates of complications were low there is still controversy which antithrombotic treatment should be used. However, up to now there has been no systematic investigation among CAD-patients with ischemic stroke specifically comparing clinical course and outcome of patients with anterior versus posterior CAD.

Methods: We performed an individual participant data analysis of patients with CAD and ischemic stroke. Over a five-year period we pooled data from three sites (i.e. West China Hospital, Chengdu, China as well as Erlangen and Giessen University Hospitals, Germany) and enrolled patients with CAD-associated ischemic stroke. Patient demographics, clinical and in-hospital measures as well as radiological data were retrieved from institutional databases. Clinical follow-up was over 6 months and included data on recurrent ischemic strokes and hemorrhages as well as clinical functional outcome assessed by the modified Rankin Scale dichotomized into favourable (mRS=0–2) and unfavourable.

Results: A total of 203 patients with CAD were included of which n=112 had anterior and n=91 had posterior CAD. Patients with posterior CAD were younger (46.0 vs. 41.0 y; $p<0.001$) than patients with anterior CAD and showed less often arterial hypertension. (42.0 % vs. 28.6 %; $p<0.048$). Antithrombotic treatment with APT and OAC was similarily distributed among patients with anterior and posterior CAD and not significantly differently related to ischemic or hemorrhagic complications during follow-up (all p=n.s.). Main difference between Chinese and German patients were mode of antithrombotic treatment consisting predominantly of APT in China compared to OAC in Germany. Functional outcome overall was good, yet worse in patients with anterior CAD compared to posterior CAD (80.2 % favorable in anterior CAD vs. 92.2 % in posterior CAD (p=0.014).

Conclusion: This study provides evidence that anterior and posterior CAD show baseline imbalances regarding age and comorbidity which may affect clinical outcome. There are no signals of superiority or harm of any specific mode of antithrombotic treatment nor relevant discrepancies in clinical outcome among Chinese and German CAD-associated stroke patients.

1. Introduction

Cervical artery dissection (CAD) is a relevant etiology of transient ischemic attacks and strokes [1–3]. The mean age of patients affected by dissection is 44–46 years and among this age population CAD represents the cause of stroke in 25 % [1, 4]. Randomized trials such as the CADISS

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trial, as well as meta-analyses, provided evidence for both, (i) an overall very low risk of recurrent stroke in patients with CAD, and (ii) a non-significant difference regarding an antithrombotic treatment either using platelet inhibitors (antiplatelet treatment, APT) or oral anticoagulation (OAC) [5–10].

Up to know, there has been no systematic analysis of ischemic stroke patients comparing CAD of the anterior *versus* posterior circulation. To address this issue – and to further shed light into potential ethnic differences among Caucasian and Asian patients – we performed an individual participant data analysis pooling acute stroke-patients with CAD from Germany and China. We sought to investigate possible differences in demographic and clinical parameters, specifically focusing on antithrombotic management and clinical outcomes, among stroke patients with CAD affecting anterior *versus* posterior circulation and among both countries.

2. Methods

2.1. Patient selection and study design

All consecutive patients with the diagnosis of ischemic stroke admitted to tertiary stroke centers (West China Hospital, Sichuan University, Chengdu, China; Department of Neurology, Friedrich-Alexander-Universität Erlangen, Germany; Department of Neurology, Justus-Liebig-Universität, Giessen) were included into institutional prospective databases which were approved by the local institutional ethics committees. Within a 5-year period we identified those patients with acute ischemic stroke and enrolled those into the present study with evidence of internal carotid or vertebral artery dissections as verified by CT angiography (CT-A), or magnetic resonance angiography (MR-A). Patients were followed-up at each participating center on a regularly basis 6 months after incident stroke.

2.2. Parameter acquisition and outcome measures

Clinical data were retrieved from the respective institutional databases and included the following parameters: patients´ demographics, medical history (hypertension, diabetes mellitus, history of smoking / migraine / trauma and other comorbidities) and National Institute of Health Stroke Scale (NIHSS) on admission, the use of single and dual APT (SAPT/DAPT) and OAC during hospital stay and thereafter until follow-up.

During follow-up visits data on recurrent ischemic strokes and hemorrhages were recorded and clinical outcome assessed by scale-trained physicians 6 months after stroke using the modified Rankin Scale (mRS) [11]. Endpoints of this study were (i) analysis of event rates (i.e. composite of ischemic and hemorrhagic complications as well as respective separate analyses) according to (a) site of dissection and (b) mode of antithrombotic treatment, and (ii) mRS-outcomes at 6 months, stratified into favorable outcome, defined as mRS 0–2, and unfavorable outcome (mRS 3–6). Ischemic lesions included ischemic stroke based on manifest imaging findings or persistent focal deficit of sudden onset lasting for >24 h, as described previously [12]; further, ischemic lesions also included TIA, defined as focal neurologic deficit of sudden onset lasting <24 h [13]. Hemorrhagic stroke was defined according to established criteria and included symptomatic, nontraumatic intracerebral hemorrhage [14].

2.3. Statistical analysis

Statistical analysis was performed using SPSS statistical software package 28.0 (SPSS Inc., USA). Categorial variables were presented as frequency and percentage, comparison between groups was done using Pearson chi square or Fisher's exact test. Distribution of data was established using Kolmogorov-Smirnov test. Data with normal distribution are presented as mean ± standard deviation (SD) and compared using Student's t-Test. Data without normal distribution are presented as median and range and compared using Mann-Whitney U-test. All statistical tests are two sided, the significance level was set at α=0.05.

3. Results

3.1. Baseline characteristics

Fig. 1 presents the study flowchart, Table 1 provides the baseline characteristics of all included patients. In total, 203 patients were analysed of which n=112 had with CAD of the anterior *versus* n=91 with posterior circulation ischemic strokes. Baseline characteristics revealed essentially no significant differences among patients with anterior *versus* posterior circulation CAD, except for (i) age and (ii) presence of arterial hypertension, i.e. patients posterior CAD were younger (46.0 (42.0–54.0) vs. 41.0 (36.0–48.0) years; p<0.001) and suffered less often from hypertension (47/112 (42.0 %) vs. 26/91 (28.6 %); p<0.048).

Comparing patients from China and Germany (supplementary Table 1) showed the following significant differences: patients from China tend to be younger (43.0 [37.0–48.0] vs. 47.0 [41.0–56.5]; p<0.001), less often female (21.6 % vs. 46.7 %; p<0.001) and had a worse neurological status on admission (NIHSS 2 [1–5] vs. 1 (0–5); p=0.041). Regarding comorbidities, patients from Germany showed a higher rate of hypertension (50.0 % vs. 24.3 %; p<0.001) and a higher rate of hyperlidipemia (32.6 % vs. 12.6 %; p<0.001). Regarding site of dissection there were no relevant significant differences. CAD was verified more often using CT-imaging in China compared to more MR-imaging in Germany (supplementary Table 1).

3.2. Antithrombotic management

Table 2 demonstrates antithrombotic treatment in patients with anterior *versus* posterior CAD-associated ischemic strokes. In the majority of all patients APT was used as secondary prevention without significant differences among patients with anterior *versus* posterior CAD (APT anterior CAD: 77/112 (68.8 %) vs. 65/91 (71.4 %); p=0.678). The rate of patients with DAPT and OAC was not significantly different. Comparing patients from China and Germany revealed that APT was used in nearly all CAD-patients from China (APT use in 91.9 %), thereby having relatively balanced patient-numbers on SAPT or DAPT (supplementary Table 1) and with low rates of subsequent chance in antithrombotic treatment. Contrary, in Germany the majority of patients received OAC (56.5 %) 32.6 % SAPT and only 10.9 % DAPT. Overall, the most frequent chance in antithrombotic treatment was replacing an initiated DAPT by a subsequent SAPT (supplementary Table 1).

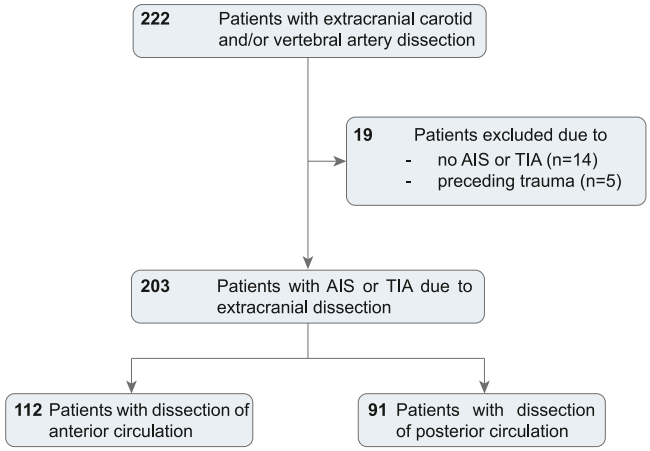

Fig. 1. Flowchart of included patients.

Table 1
Baseline Characteristics of patients with anterior versus posterior CAD.

Patients with dissection (n=203)	Anterior circulation (n=112)	Posterior circulation (n=91)	P Value (P<0.05)
Age, y ‡	46.0 (42.0–54.0)	41.0 (36.0–48.0)	**<0.001**
Female sex *	41 (36.6 %)	26 (28.6 %)	0.226
Asian (Chinese cohort)	54 (48.2 %)	57 (62.6 %)	**0.040**
Previous comorbidities			
Hypertension *	47 (42.0 %)	26 (28.6 %)	**<0.048**
Diabetes mellitus *	4 (3.6 %)	4 (4.4 %)	0.764
History of smoking *	32 (28.6 %)	23 (25.3 %)	0.599
History of hazardous alcohol use *	25 (22.3 %)	21 (23.1 %)	0.898
Hyperlipidemia *	22 (19.6 %)	22 (24.2 %)	0.436
History of Migraine *	7 (6.3 %)	5 (5.5 %)	0.820
Admission status			
NIHSS on admission ‡	2 (0–7)	1 (1–3)	0.171
pre-MRS ‡	0 (0–0)	0 (0–0)	0.465
Location of dissection			
Left ICA *	51 (45.5 %)	-	-
Right ICA *	50 (44.6 %)	-	-
Both ICA *	18 (19.8 %)-	-	-
Left VA *	-	39 (42.9 %)	-
Right VA *	-	34 (37.4 %)	-
Both VA *	-	-11 (9.8 %)	-
Diagnostic imaging			
CT + Angiography *	45 (40.2 %)	42 (46.2 %)	0.475
MRI + Angiography *	60 (53.6 %)	46 (50.5 %)	0.777
Digital subtraction angiography *	5 (4.5 %)	3 (3.3 %)	0.733

Baseline characteristics of the study population stratified by anterior vs. posterior CAD. Abbreviations: mRS: modified Rankin Scale; ICA: internal carotid artery; VA vertebral artery.

Table 2
Antithrombotic management of patients with anterior and posterior CAD.

Patients with dissection (n=203)	Anterior circulation (n=112)	Posterior circulation (n=91)	P Value (P<0.05)
Single Antiplatelet therapy (SAPT)	41 (36.6 %)	43 (47.3 %)	0.125
Dual Antiplatelet Therapy (DAPT)	36 (32.1 %)	22 (24.2 %)	0.211
Anticoagulant therapy (OAC)	35 (31.3 %)	26 (28.6 %)	0.680
Switch of therapy (n=30)			
OAC → DAPT	1/19 (5.3 %)	1/11 (9.1 %)	0.607
SAPT → OAC	1/19 (5.3 %)	0/11 (0.0 %)	0.633
DAPT → SAPT	17/19 (89.5 %)	9/11 (81.8 %)	0.611
OAC → SAPT	0/19 (0.0 %)	1/11 (9.1 %)	0.367

3.3. Clinical outcomes

Any ischemic or hemorrhagic event during follow up occurred in 10/112 (8.9 %) patients with anterior vs 9/91 (9.9 %) in posterior CAD (0=0.815; Fig. 2*A*). Subanalysis did not show significant differences in the rate of ischemic or hemorrhagic complications among patients with anterior vs posterior CAD (Fig. 2*A*). Any ischemic or hemorrhagic event during follow up occurred in 6/61 (9.8 %) patients with OAC vs. 13/142 (9.15 %) in APT-patients (p=0.878; Fig. 2*B*). Subanalysis demonstrated that 5/61 (8.2 %) patients with OAC suffered from repeat ischemic stroke compared to 1/142 (0.7 %) in patients with APT (p=0.01), whereas hemorrhagic complications were not significantly different among patients with OAC (2/61; 3.3 %) and APT (12/142; 8.45 %) (p=0.236; Fig. 2*B*).

Functional outcome analysis at 6 months revealed that 87/111 (78,3 %) of patients with anterior CAD vs. 83/90 (92.2 %) with posterior CAD showed favourable clinical outcome (p=0.007; Fig. 3). Subanalysis of functional outcome among patients from China and Germany revealed no significant different outcomes with 82.9 % of all patients from China and 85.3 % of all German patients having mRS scores of 0–2 (supplementary Figure 1). Additionally, we performed a subanalysis on the topography of cerebral ischemia within the group of patients with anterior circulation dissections only, i.e. ischemia within the anterior *versus* middle cerebral artery (ACA/MCA). Of 37 patients available for this analysis, ischemia was present in ACA territory in 3 patients and in the MCA territory in 34 patients. Exploring functional outcomes of these patients revealed non significantly different mRS scores (ACA: mRS 0 (0−0); mean 0.333 ± 0.58 *versus* MCA: mRS 2 (0−3); mean 1.71 ± 1.45; p=0.118).

4. Discussion

The present study compared patients with ischemic stroke associated with anterior *versus* posterior circulation cervical artery dissections. Pooling individual participant data from China and Germany (i) revealed that baseline characteristics among anterior and posterior CAD patients were similar, with posterior CAD patients being significantly younger, (ii) provided evidence that antithrombotic management was not significantly different between anterior and posterior CAD, while Chinese patients were predominantly treated with antiplatelet treatment, whereas German patients were more often oral anticoagulated, (iii) established that ischemic and hemorrhagic complications were not statistically different among patients with anterior versus posterior CAD, and among OAC- and APT-patients respectively. Finally, (iv) clinical outcome was more often favourable in patients with posterior CAD, without differences when comparing Chinese to German patients. Some aspects emerge from the data.

First, regarding different baseline characteristics and clinical functional outcome of patients with anterior versus posterior circulation CAD, our findings are in line with previous reports on vertebral artery dissections and the relatively low age and few comorbidities of these patients [15]. This aspect may be one of the major drivers contributing to the overall better functional outcome observed in posterior CAD. Another aspect refers to the different clinical severity of lesions within the cerebellum compared to affection of the supratentorial middle cerebral artery territory; cerebellar lesions often appear clinically subtle with only minor or no measurable symptoms upon NIHSS assessment [16]. Further, in line with previous analyses, we found non-significant evidence that patients with cerebral infarcts in the territory of the anterior cerebral artery may have better prognosis than those patients with infarcts in the territory of the middle cerebral artery [17]. Additionally, this study adds value to the field as above findings were consistent when comparing Chinese and German patients. Hence, posterior CAD-patients in the setting of acute ischemic stroke and dissection may nonetheless be informed about the overall benign prognosis of the disease.

Second, with respect to the ongoing debate, and varying guideline recommendations, on whether CAD patients should receive APT or OAC, there have been numerous trials and meta-analyses [15]. Specifically, the CADISS trial did not reveal differences in outcome events and recanalization among APT and OAC-patients with CAD [6,18]. Of note, the majority of CAD-patients were either suffering from TIA or ischemic stroke, hence a comparable patient contingent as in the present study. Contrary, the TREAT-CAD trial, that also substantially enrolled patients with CAD but no intracerebral ischemic lesions, failed to document a noninferiority of APT compared to OAC [19], though overall event rates were low irrespective of treatment. Both studies however did not specifically focus on a comparison between anterior and posterior CAD, and did not exclusively include ischemic stroke patients, why the present study verifies comparable safety and efficacy profiles of APT and OAC in this specific patient population in both anterior as well as posterior CAD. These data fit well into the updated recent meta-analyses that overall argue in favour of APT, with preference of OAC in those CAD patients with vessel occlusion and ischemic stroke at CAD-onset [6–10, 18, 20–22].

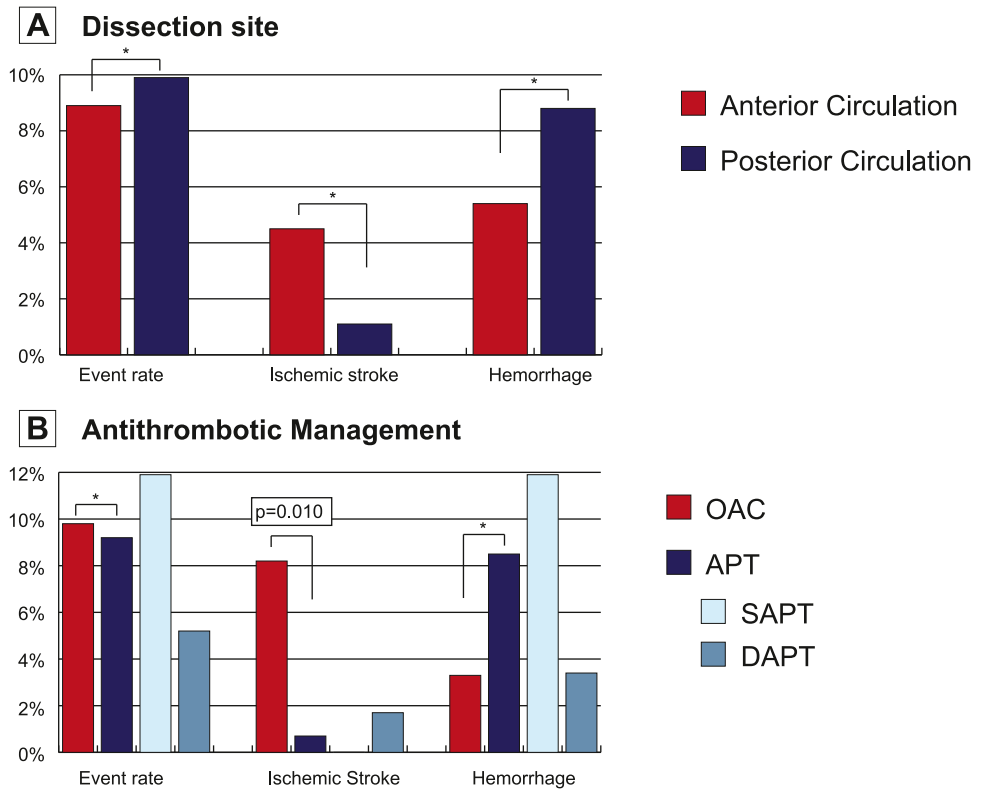

Fig. 2. Event rates of ischemic and hemorrhagic complications among follow-up period Percentages of ischemic and hemorrhagic complications as well as composite of both is presented for patients with anterior versus posterior CAD (A) and mode of antithrombotic treatment, i.e. OAC versus APT (B). (A) Composite endpoint of anterior vs. posterior complications: p=0.815, recurrent ischemic stroke (anterior 5/112 (4.5 %) vs. posterior 1/91 (1.1 %); p=0.227). Hemorrhagic complications: anterior 6/112 (5.4 %) vs. posterior 8/91 (8.8 %); p=0.337. (B) Numbers of events in patients with OAC vs. APT: composite: OAC 6/61 (9.8 %); SAPT 10/84 (11.9 %); DAPT 3/58 (5.2 %); recurrent ischemic stroke: OAC 5/61 (8.2 %); SAPT 0/84 (0 %); DAPT 1/58 (1.7 %); hemorrhagic complications: OAC 2/61 (3.3 %); SAPT 10/84 (11.9 %); DAPT 2/58 (3.4 %).

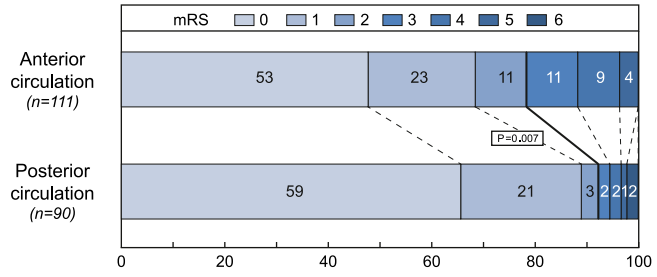

Fig. 3. Functional outcome after 6 months stratified for patients with anterior vs posterior CAD.

Third, regarding clinical long-term outcome, the data presented here corroborate that functional outcome is favourable in CAD, even in those patents with ischemic stroke [23]. Although we detected differences in outcome among patients with anterior and posterior CAD, we here wilfully avoid any overinterpretation given that we did not adjust for imbalanced baseline characteristics. Yet, we observed some interesting side findings when comparing Chinese and German patients. Specifically, antithrombotic management varied such that Chinese patients predominantly received APT, a management strategy that may have grown in clinical routine based on higher rates of hemorrhagic complications in Asian people under OAC [2, 24–27]. Larger studies including ethnicity aspects in choosing APT versus OAC in CAD appear warranted.

Our study has several limitations. Most importantly, it lacks a prospective design with intensive follow-up on every patient. Our data of recurrent strokes and hemorrhages is limited to hospital re-admissions and reporting of each patient on follow up. Furthermore, our data have been extracted from the hospital reporting system using the data of regularly visits to both centres and no systematic assessment of reperfusion of occluded vessels has been performed. Thus, these results have to be interpreted with caution. Of note, contrary to previous analyses on antithrombotic management in patients with CAD, this study for the first time solely focussed on ischemic stroke patients with dissections and did not enrol CAD patients without concomitant ischemic stroke. In light of this specific aspect, the event rates, notably ischemic stroke, appear higher than in previous reports, a finding most likely linked to above aspect and the fact that we also scored transient ischemic events as stroke [28,29].

5. Conclusion

In summary, our data verified similar rates of ischemic and hemorrhagic complications among patients with anterior versus posterior circulation cervical artery dissections. Moreover, there was no difference in patients treated with APT or OAC, while Chinese patients received more often APT compared to OAC in German patients. Clinical outcomes were slightly better in CAD-patients with posterior stroke, while outcomes were comparable when focusing on mode of antithrombotic treatment or an inter-country comparison.

Ethical guidelines

This study was performed according to ethical guidelines and was approved by the local institutional review boards and ethical committees of all sites.

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CRediT authorship contribution statement

Stefan Lang: Software, Resources, Methodology, Investigation. **Stefan Schwab:** Writing – review & editing, Validation, Supervision, Resources, Conceptualization. **Hagen B. Huttner:** Writing – review & editing, Validation, Supervision, Investigation, Conceptualization. **Stefan Gerner:** Software, Methodology, Investigation, Formal analysis, Data curation. **Sophie Lehmann:** Resources, Methodology, Investigation, Formal analysis, Data curation. **kilian froehlich:** Software, Investigation, Formal analysis, Data curation, Conceptualization. **Yang Zhang:** Software, Resources, Methodology, Formal analysis, Conceptualization. **Tobias Bobinger:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Yanan Zhang:** Writing – original draft, Project administration, Methodology, Conceptualization. **Li He:** Writing – original draft, Supervision, Data curation, Conceptualization. **Iris Muehlen:** Software, Resources, Methodology, Formal analysis. **Anne Mrochen:** Resources, Project administration, Methodology, Formal analysis.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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This manuscript contains essential parts of the medical thesis of Sophie Lehmann.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2024.108381.

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