Toward Individual Treatment in Cervical Artery Dissection: Subgroup Analysis of the TREAT-CAD Randomized Trial

Josefin E. Kaufmann, M Med [1,2] Henrik Gensicke, MD [1,2] Sabine Schaedelin, MSc,[3] Andreas R. Luft, MD,[4,5] Barbara Goeggel-Simonetti, MD,[6,7] Urs Fischer, MD,[1,6] Patrik Michel, MD,[8] Davide Strambo, MD,[8] Georg Kägi, MD,[6,9] Jochen Vehoff, MD,[9] Krassen Nedeltchev, MD,[10] Timo Kahles, MD,[10,11] Lars Kellert, MD,[12,13] Sverre Rosenbaum, MD,[14] Regina von Rennenberg, MD,[15] Christoph Riegler, MD,[15] David Seiffge, MD [6] Hakan Sarikaya, MD,[6] Annaelle Zietz, MMed,[1,2] Johannes Wischmann, MD,[12] Alexandros A. Polymeris, MD [1] Martin Hänsel, MD,[4] Christoph Globas, MD,[4] Leo H. Bonati, MD,[1,16] Alex Brehm, MD [17,18] Gian Marco De Marchis, MD, MSc,[1,9] Nils Peters, MD,[1,2] Christian H. Nolte, MD,[15,19] Hanne Christensen, MD,[14] Susanne Wegener, MD [4] Marios-Nikos Psychogios, MD,[17,18] Marcel Arnold, MD,[6] Philippe Lyrer, MD,[1] Christopher Traenka, MD [1,2#] and Stefan T. Engelter, MD, [1,2#] for the TREAT-CAD Trial

Objective: Uncertainty remains regarding antithrombotic treatment in cervical artery dissection. This analysis aimed to explore whether certain patient profiles influence the effects of different types of antithrombotic treatment.
Methods: This was a post hoc exploratory analysis based on the per-protocol dataset from TREAT-CAD (NCT02046460), a randomized controlled trial comparing aspirin to anticoagulation in patients with cervical artery dissection. We explored the

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.26886

Received Aug 2, 2023, and in revised form Dec 28, 2023. Accepted for publication Jan 23, 2024.

Address correspondence to Dr. Kaufmann, Department of Neurology and Stroke Center, University Hospital Basel and University of Basel, Petersgraben 4, 4051 Basel, Switzerland. E-mail: josefin.kaufmann@usb.ch

[#]C.T. and S.T.E. contributed equally.

From the [1]Department of Neurology and Stroke Center, University Hospital Basel and University of Basel, Basel, Switzerland; [2]Neurology and Neurorehabilitation, University Department of Geriatric Medicine FELIX PLATTER, University of Basel, Basel, Switzerland; [3]Department of Clinical Research, Clinical Trial Unit, University Hospital Basel and University of Basel, Basel, Switzerland; [4]Division of Vascular Neurology and Neurorehabilitation, Department of Neurology, University Hospital of Zurich and University of Zurich, Zurich, Switzerland; [5]Center for Neurology and Rehabilitation, Cereneo, Vitznau, Switzerland; [6]Department of Neurology, University Hospital Bern, University of Bern, Bern, Switzerland; [7]Department of Neuropediatrics, Institute of Pediatrics of Southern Switzerland, San Giovanni Hospital, Bellinzona, Switzerland; [8]Stroke Center and Neurology Service, Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland; [9]Department of Neurology and Stroke Center, Cantonal Hospital St Gallen, St Gallen, Switzerland; [10]Department of Neurology and Stroke Center, Cantonal Hospital Aarau, Aarau, Switzerland; [11]Medical Faculty, University of Basel, Basel, Switzerland; [12]Department of Neurology, Ludwig Maximilian University, Munich, Germany; [13]Institute for Stroke and Dementia Research, University Hospital, Ludwig Maximilian University, Munich, Germany; [14]Department of Neurology, Bispebjerg Hospital and University of Copenhagen, Copenhagen, Denmark; [15]Department of Neurology with Experimental Neurology, Center for Stroke Research Berlin, Charité–Universitätsmedizin Berlin, Berlin, Germany; [16]Research Department, Reha Rheinfelden, Rheinfelden, Switzerland; [17]Department of Neuroradiology, Clinic of Radiology and Nuclear Medicine, University Hospital Basel, Basel, Switzerland; [18]Department of Neuroradiology, University Hospital Zurich, Zurich, Switzerland; and [19]Berlin Institute of Healths at Charité, Charité–Universitätsmedizin Berlin, Berlin, Germany

Additional supporting information can be found in the online version of this article.

potential effects of distinct patient profiles on outcomes in participants treated with either aspirin or anticoagulation. Profiles included (1) presenting with ischemia (no/yes), (2) occlusion of the dissected artery (no/yes), (3) early versus delayed treatment start (</>median), and (4) intracranial extension of the dissection (no/yes). Outcomes included clinical (stroke, major hemorrhage, death) and magnetic resonance imaging outcomes (new ischemic or hemorrhagic brain lesions) and were assessed for each subgroup in separate logistic models without adjustment for multiple testing.

Results: All 173 (100%) per-protocol participants were eligible for the analyses. Participants without occlusion had decreased odds of events when treated with anticoagulation (odds ratio [OR] = 0.28, 95% confidence interval [CI] = 0.07–0.86). This effect was more pronounced in participants presenting with cerebral ischemia (n = 118; OR = 0.16, 95% CI = 0.04–0.55). In the latter, those with early treatment (OR = 0.26, 95% CI = 0.07–0.85) or without intracranial extension of the dissection (OR = 0.34, 95% CI = 0.11–0.97) had decreased odds of events when treated with anticoagulation.

Interpretation: Anticoagulation might be preferable in patients with cervical artery dissection presenting with ischemia and no occlusion or no intracranial extension of the dissection. These findings need confirmation.

ANN NEUROL 2024;00:1–12

Cervical artery dissection is a leading cause of stroke in young adults.[1] The question of optimal antithrombotic therapy for the prevention of stroke in patients with cervical artery dissection remains unresolved.[2,3] Currently, both anticoagulation and antiplatelets (aspirin or dual antiplatelets)[3] are used in cervical artery dissection patients.[4] Two randomized controlled trials—Cervical Artery Dissection in Stroke Study (CADISS)[5,6] and the biomarkers and antithrombotic treatment in cervical artery dissection trial (TREAT-CAD)[7,8]—compared these treatment regimens. However, neither of the trials nor a study-level meta-analysis of the aggregated study data—which was published within the 2021 European Stroke Organsation (ESO) guidelines[2]—was able to solve the clinically relevant question of whether to prefer antiplatelets or anticoagulants in cervical artery dissection patients.[2,3,5,6,8]

Thus far, the allocation of cervical artery dissection patients to antithrombotic treatment regimens has followed a universal approach in disregard of proven heterogeneity in patient-level baseline profiles.[4] From observational studies, we know that clinical and imaging baseline characteristics such as occlusion of the dissected artery or presentation with cerebral ischemia increase the risk of cervical artery dissection-related stroke.[9–16] However, it is unknown whether the effect of antithrombotic treatment depends on such patient profiles and which treatment regimen would be preferable for individual patients. Analyses based on observational data will not be able to answer this question, as treatment allocation in a nonrandomized setting is biased by the preferences of patients and treating physicians.[17] With these considerations in mind, we performed subgroup analyses on the dataset of the TREAT-CAD randomized trial to explore whether the treatment effect differs with the presence versus absence of specific patient profiles.

Patients and Methods

We based our analyses on the complete per protocol dataset of the TREAT-CAD randomized trial (NCT02046460).[8,18] The trial was approved by all the responsible legal authorities and ethics committees of the participating centers, and the main results of the trial were published in 2021.[7,8]

In brief, TREAT-CAD was a multicenter, randomized, open-label, noninferiority trial with blinded assessment of endpoints. Participants aged ≥18 years with symptomatic carotid or vertebral artery dissection verified by magnetic resonance imaging (MRI) were randomly assigned to receive either aspirin 300mg daily or anticoagulation (vitamin K antagonists with lead-in heparin) for 90 days within 14 days of symptom onset. In patients randomized to anticoagulation therapy, bridging treatment with intravenous heparin or low-molecular-weight heparin was recommended until the target International Normalized Ratio (INR) (2, 3) was achieved. The type of vitamin k antagonist used as anticoagulation therapy or the decision to use bolus therapy was left to local practice.[8] The primary endpoint was a composite of clinical (ischemic stroke, major extracranial or intracranial hemorrhage, death assessed at 90 ± 30 days) and MRI outcomes (new ischemic or hemorrhagic brain lesions assessed at 14 ± 10 days after commencing treatment).[7,8] The per protocol population included participants who had a dissection verified by MRI criteria (centrally adjudicated), who received the allocated treatment and completed the assessment period.[8] Written informed consent from the patient or next of kin was required before enrollment.[8]

Among the 173 study participants included in the per protocol analyses, the primary endpoint occurred in 21 of 91 (23.1%) participants in the aspirin group and in 12 of 82 (14.6%) participants in the anticoagulation group. The absolute difference was 8.4% (95% confidence interval [CI] = −4.3 to 21.2%) in favor of anticoagulation, indicating that noninferiority of aspirin over anticoagulation was not shown. However, superiority of anticoagulation was also not shown (p for noninferiority = 0.55, noninferiority margin = 12%).[8]

Identification of Patient Profiles of Interest

Among the systematically ascertained baseline characteristics in TREAT-CAD,[8] we identified patient profiles with a putative impact on the occurrence of clinical or MRI outcomes according to the literature[6,9,11–14,19–25] and defined the following dichotomous subgroups:

presenting with cerebral ischemia—either clinical ischemic events (including transient ischemic attacks, amaurosis fugax, retinal infarction, and ischemic stroke), MRI lesions, or both—versus presenting with local symptoms only[6,11,13,14]; occlusion of the dissected artery at baseline defined as (1) flow or (2) no-flow in contrast-enhanced magnetic resonance angiography sequences, in line with prior research (no/yes)[9,11,14]; early versus delayed treatment start (divided by the median of the study population at 6 days)[13,22]; acute recanalization therapy including intravenous thrombolysis and/or endovascular therapy (no/yes)[20,23]; intracranial extension of the dissected artery (no/yes)[24,25]; site of dissection defined as internal carotid artery dissection versus vertebral artery dissection[11]; single versus multivessel dissection[11,12]; younger versus older age (divided by the median of the study population at 47 years)[19]; and male versus female[21] (Table S1, patient profile selection statement based on literature search).

Post hoc, we added the imaging feature of presence versus absence of a mural hematoma in the dissected artery.

Statistical Analysis

We based our analyses on the per protocol dataset, as we only wanted to include patients with a verified cervical artery dissection diagnosis and who had received the randomly allocated treatment according to the study protocol (Fig 1).

First, the aforementioned dichotomous subgroups were compared regarding the distribution of the type of antithrombotic treatment (ie, aspirin or anticoagulation) and the frequency of primary endpoints using chi-squared and Fisher exact tests.

Second, we performed exploratory post hoc subgroup analyses with logistic regression models. Outcomes were defined as a composite of clinical (ischemic stroke, severe extracranial or intracranial hemorrhage, death) and MRI outcomes (new ischemic or hemorrhagic brain lesions). Predictors were antithrombotic treatment (aspirin vs anticoagulation) and a dichotomized patient profile. A separate model was estimated for each subgroup, with marginal effects expressed by odds ratio (OR) with 95% CI.[26]

Third, we repeated the aforementioned subgroup analyses in participants who had presented with cerebral ischemia—that is, either clinical ischemic events, MRI lesions, or both—at baseline. All but one of the primary endpoints in TREAT-CAD occurred in such participants, indicating a higher risk for recurrent stroke and thus potentially differential treatment effects in such patients (see Fig 1).

We did not adjust for multiple testing. The results were summarized in forest plots. All analyses were performed using the statistical software R (v4.1.0; R Core Team 2021).

Post hoc, we assessed the frequencies of (1) clinical outcomes (ischemic stroke, major extracranial or intracranial hemorrhage, or death) and (2) functional outcomes (dichotomized into favorable (modified Rankin Scale [mRS] 0–2) versus unfavorable [mRS 3–6] outcome) across subgroups and stratified by type of antithrombotic treatment.

Results

Study Population

All 173 study participants (100%) of the TREAT-CAD per-protocol dataset were eligible for analyses. The median age was 47 years (interquartile range = 37–54), and 63 (36%) were women. The carotid artery was affected in

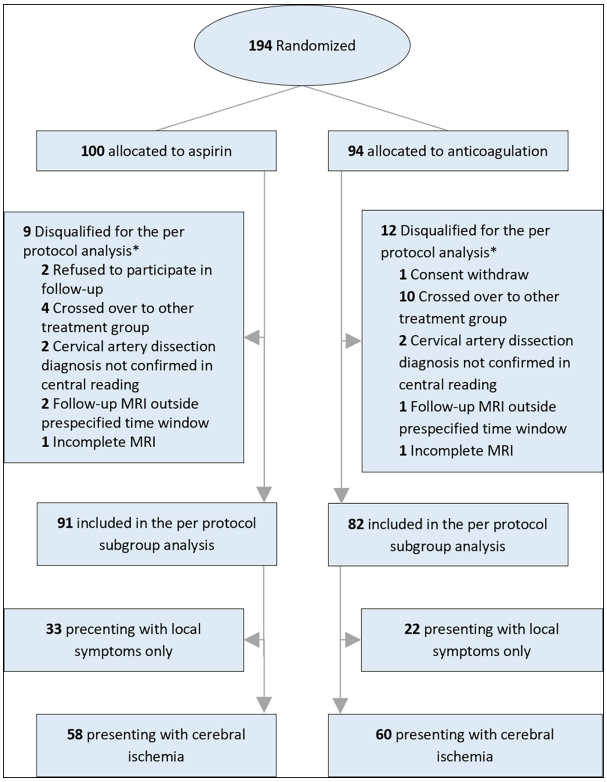

FIGURE 1: Consolidated Standards of Reporting Trials (CONSORT) flowchart. *Four participants (2 in each group) met more than one of these criteria. Of the 14 participants who had crossed over from one treatment arm to the other, none had experienced an outcome event (neither clinical nor magnetic resonance imaging [MRI] outcome) prior to or after the crossover had happened.

105 participants (61%), whereas the vertebral artery was affected in 55 (32%) participants. Occlusion of the dissected artery at baseline was found in 55 participants (32%). A total of 118 participants (68%) presented with cerebral ischemia (either clinical ischemic events, MRI lesions, or both; Tables 1–4).

Distribution of the Type of Antithrombotic Treatment and Primary Outcomes

The distribution of the allocated treatment across all patient profiles was balanced within the predefined subgroups (see Tables 1–3).

Clinical or MRI outcomes occurred significantly more often (1) in participants with occlusion (16/55, 29%) than in those without (16/117, 14%; $p = 0.03$), (2) in participants presenting with baseline cerebral ischemia (32/118, 28%) than in those with local symptoms only (1/55, 2%; $p < 0.001$), and (3) in participants who had acute recanalization therapy (11/23, 48%) than in those without such a therapy (22/150, 15%; $p < 0.001$). For all other patient profiles—in particular early versus delayed treatment start and presence or absence of intracranial extension of dissected artery—there was no difference in frequency of outcome events across the predefined subgroups (see Tables 1–3; Table S2, baseline and outcome table with subgroups separated into allocated treatment).

Treatment Effect

A possible differential treatment effect between type of antithrombotic treatment and presence versus absence of dissected artery occlusion was observed. Specifically, participants without occlusion had decreased odds of clinical or MRI outcomes under anticoagulation treatment compared to under aspirin (OR = 0.28, 95% CI = 0.07–0.86), whereas among participants with occlusion such a treatment effect was not observed (OR = 1.6, 95% CI = 0.49–5.26).

For all other patient profiles and their subgroups, there were (1) no associations regarding the type of treatment and the odds of clinical or MRI outcomes and (2) no suspected differential treatment effect between antithrombotic treatment effect and the distinct patient baseline profiles (Fig 2).

Treatment Effects among Participants Presenting with Cerebral Ischemia

A total of 118 participants presented with cerebral ischemia, of whom 60 (51%) were treated with anticoagulation and 58 (49%) with aspirin. Of the overall 33 outcome events, 32 (97%) occurred in those participants presenting with cerebral ischemia. Among such participants, those without dissected artery occlusion had decreased odds of outcome events when treated with anticoagulation compared to with aspirin (OR = 0.16, 95% CI = 0.04–0.55). Furthermore, in participants presenting with cerebral ischemia, those with early treatment (OR = 0.26, 95% CI = 0.07–0.85) and those without intracranial extension of the dissection (OR = 0.34, 95% CI = 0.11–0.97) had decreased odds of outcome events when treated with anticoagulation as compared to aspirin (Fig 3).

The post hoc analyses of the distribution of (1) purely clinical outcomes and (2) dichotomized functional outcomes are displayed in Tables S3 and S4, respectively.

Discussion

Our post hoc analyses of the dataset of the TREAT-CAD randomized trial revealed the following key findings. (1) Participants without occlusion of the dissected artery had decreased odds of outcome events when treated with anticoagulation compared to with aspirin. (2) This effect was particularly notable in participants presenting with cerebral ischemia. (3) In participants presenting with cerebral ischemia, those with early treatment or those without intracranial extension of the dissection had decreased odds of outcome events when treated with anticoagulation as compared to aspirin.

Occlusion of the dissected artery was previously shown to be an important predictor of delayed ischemic events in cervical artery dissection patients.[9,11,14] Spontaneous recanalization of an occluded dissected artery can lead to thromboembolism from the arterial lesion.[27] Although stroke mechanisms in cervical artery dissection patients are not fully understood, prior analyses of infarct patterns in participants with cervical dissection showed that ischemic events are mostly of embolic origin.[28] One might assume that for the prevention of embolic events a more aggressive treatment regimen (ie, anticoagulation) would be beneficial. Counterintuitively, in our analyses, there was no differential treatment effect in participants with dissected artery occlusion, meaning that such participants did not benefit more from either treatment approach than from the other. Reasons for this remain elusive. We might infer that in the event of recanalization with subsequent embolism, neither treatment approach (vitamin K antagonists nor aspirin) is sufficiently effective and potent to prevent cerebral ischemia. This finding remains to be confirmed and might prompt for an intensified search for an alternative, more potent treatment approach in such patients—for example, specifically testing direct oral anticoagulants in such patients.

On the contrary, participants without dissected artery occlusion—indicating a lower risk of delayed

TABLE 1. Baseline Characteristics of the Patient Profiles

Characteristic	Patient Profile: Presenting Signs and Symptoms		Occlusion[a] Subgroup		Early versus Delayed Treatment Start	
	Local Symptoms Only	Cerebral Ischemia	No	Yes	Below the Median, <7 Days	Above the Median ≥7 Days
Patients, n	55	118	117	55	88	85
Age, yr, median (IQR)	47.00 (38.00–54.50)	47.00 (38.00–53.75)	47.00 (36.00–53.00)	49.00 (41.00–55.50)	46.50 (38.00–53.25)	48.00 (38.00–54.00)
Female, n (%)	21 (38.2)	42 (35.6)	44 (37.6)	18 (32.7)	37 (42.0)	26 (30.6)
Male, n (%)	34 (61.8)	76 (64.4)	73 (62.4)	37 (67.3)	51 (58.0)	59 (69.4)
Internal carotid artery dissection, n (%)[b]	43 (78.2)	62 (52.5)	71 (60.7)	33 (60.0)	57 (64.8)	48 (56.5)
Vertebral artery dissection, n (%)[b]	9 (16.4)	46 (39.0)	34 (29.1)	21 (38.2)	27 (30.7)	28 (32.9)
Multivessel dissection; no, n (%)	52 (94.5)	108 (91.5)	105 (89.7)	54 (98.2)	84 (95.5)	76 (89.4)
Multivessel dissection; yes, n (%)	3 (5.5)	10 (8.5)	12 (10.3)	1 (1.8)	4 (4.5)	9 (10.6)
Occlusion; no, n (%)	50 (90.9)	67 (57.3)	117 (100.0)	0 (0.0)	58 (66.7)	59 (69.4)
Occlusion; yes, n (%)	5 (9.1)	50 (42.7)	0 (0.0)	55 (100.0)	29 (33.3)	26 (30.6)
Cerebral ischemia; no, n (%)	55 (100.0)	0 (0.0)	50 (42.7)	5 (9.1)	28 (31.8)	27 (31.8)
Cerebral ischemia; yes, n (%)	0 (0.0)	118 (100.0)	67 (57.3)	50 (90.9)	60 (68.2)	58 (68.2)
Time from symptom onset to start of allocated treatment, days, mean (IQR)	7.02 (4.79)	6.82 (4.34)	6.88 (4.41)	6.91 (4.70)	3.60 (1.59)	10.28 (3.93)
Acute recanalization therapy; no, n (%)	55 (100.0)	95 (80.5)	102 (87.2)	47 (85.5)	78 (88.6)	72 (84.7)
Acute recanalization therapy; yes, n (%)	0 (0.0)	23 (19.5)	15 (12.8)	8 (14.5)	10 (11.4)	13 (15.3)
Intracranial extension; no, n (%)	43 (78.2)	83 (70.3)	95 (81.2)	30 (54.5)	61 (69.3)	65 (76.5)
Intracranial extension; yes, n (%)	12 (21.8)	35 (29.7)	22 (18.8)	25 (45.5)	27 (30.7)	20 (23.5)
Mural hematoma; no, n (%)	1 (1.8)	111 (94.1)	5 (4.3)	3 (5.5)	2 (2.3)	6 (7.1)
Mural hematoma; yes, n (%)	54 (98.2)	7 (5.9)	112 (95.7)	52 (94.5)	86 (97.7)	79 (92.9)
Aspirin, n (%)	33 (60.0)	58 (49.2)	58 (49.6)	32 (58.2)	43 (48.9)	48 (56.5)
Anticoagulants [VKA], n (%)	22 (40.0)	60 (50.8)	59 (50.4)	23 (41.8)	45 (51.1)	37 (43.5)
~*p*, chi-squared test	0.24		0.37		0.40	
Primary endpoint; no, n (%)	54 (98.2)	86 (72.9)	101 (86.3)	39 (70.9)	72 (81.8)	68 (80.0)
Primary endpoint; yes, n (%)	1 (1.8)	32 (27.1)	16 (13.7)	16 (29.1)	16 (18.2)	17 (20.0)
~*p*, chi-squared test	<0.001[c]		0.03[c]		0.91	

IQR = interquartile range; VKA = vitamin K antagonists.
[a]Data missing for one participant.
[b]Multivessel dissections were excluded from this patient profile (n = 13).
[c]Statistically significant.

TABLE 2. Baseline Characteristics of the Patient Profiles

	Patient Profiles					
	Intracranial Extension of the Cervical Artery Dissection		Acute Recanalization Therapy		Site of Dissection[a]	
	Subgroups					
Characteristic	No	Yes	No	Yes	Internal Carotid Artery Dissection	Vertebral Artery Dissection
Patients, n	126	47	150	23	105	55
Age, yr, median (IQR)	46.50 (37.25–53.00)	50.00 (39.50–57.00)	47.00 (37.00–54.75)	48.00 (42.00–53.00)	50.00 (43.00–55.00)	38.00 (31.00–47.00)
Female, n (%)	46 (36.5)	17 (36.2)	55 (36.7)	8 (34.8)	33 (31.4)	25 (45.5)
Male, n (%)	80 (63.5)	30 (63.8)	95 (63.3)	15 (65.2)	72 (68.6)	30 (54.5)
Internal carotid artery dissection, n (%)[b]	76 (60.3)	29 (61.7)	91 (60.7)	14 (60.9)	105 (100.0)	0 (0.0)
Vertebral artery dissection, n (%)[b]	38 (30.2)	17 (36.2)	49 (32.7)	6 (26.1)	0 (0.0)	55 (100.0)
Multivessel dissection; no, n (%)	114 (90.5)	46 (97.9)	140 (93.3)	20 (87.0)	105 (100.0)	55 (100.0)
Multivessel dissection; yes, n (%)	12 (9.5)	1 (2.1)	10 (6.7)	3 (13.0)	0 (0.0)	0 (0.0)
Occlusion; no, n (%)	95 (76.0)	22 (46.8)	102 (68.5)	15 (65.2)	71 (68.3)	34 (61.8)
Occlusion; yes, n (%)	30 (24.0)	25 (53.2)	47 (31.5)	8 (34.8)	33 (31.7)	21 (38.2)
Cerebral ischemia; no, n (%)	43 (34.1)	12 (25.5)	55 (36.7)	0 (0.0)	43 (41.0)	9 (16.4)
Cerebral ischemia; yes, n (%)	83 (65.9)	35 (74.5)	95 (63.3)	23 (100.0)	62 (59.0)	46 (83.6)
Time from symptom onset to start of allocated treatment, days, mean (IQR)	6.85 (4.07)	6.98 (5.46)	6.87 (4.61)	6.96 (3.57)	6.59 (4.34)	7.36 (4.95)
Acute recanalization therapy; no, n (%)	109 (86.5)	41 (87.2)	150 (100.0)	0 (0.0)	91 (86.7)	49 (89.1)
Acute recanalization therapy; yes, n (%)	17 (13.5)	6 (12.8)	0 (0.0)	23 (100.0)	14 (13.3)	6 (10.9)
Intracranial extension; no, n (%)	126 (100.0)	0 (0.0)	109 (72.7)	17 (73.9)	76 (72.4)	38 (69.1)
Intracranial extension; yes, n (%)	0 (0.0)	47 (100.0)	41 (27.3)	6 (26.1)	29 (27.6)	17 (30.9)
Mural hematoma; no, n (%)	4 (3.2)	4 (8.5)	7 (4.7)	1 (4.3)	4 (3.8)	4 (7.3)
Mural hematoma; yes, n (%)	122 (96.8)	43 (91.5)	143 (95.3)	22 (95.7)	101 (96.2)	51 (92.7)
Aspirin, n (%)	66 (52.4)	25 (53.2)	76 (50.7)	15 (65.2)	59 (56.2)	24 (43.6)
Anticoagulants [VKA], n (%)	60 (47.6)	22 (46.8)	74 (49.3)	8 (34.8)	46 (43.8)	31 (56.4)
~*p*, chi-squared test	1		0.28		0.26	
Primary endpoint; no, n (%)	106 (84.1)	34 (72.3)	128 (85.3)	12 (52.2)	83 (79.0)	9 (69.2)
Primary endpoint; yes, n (%)	20 (15.9)	13 (27.7)	22 (14.7)	11 (47.8)	22 (21.0)	4 (30.8)
~*p*, chi-squared test	0.12		<0.001[c]		0.25	

IQR = interquartile range; VKA = vitamin K antagonists.
[a]Multivessel dissections were excluded from this patient profile (n = 13).
[b]Multivessel dissections were excluded from these two subgroups (n = 13).
[c]Statistically significant.

TABLE 3. Baseline Characteristics of the Patient Profiles

	Patient profiles					
	Multivessel Dissection		Age Subgroups		Sex	
Characteristic	No	Yes	Younger than the Median, ≤47 Years	Older than the Median, >47 Years	Female	Male
Patients, n	160	13	88	85	63	110
Age, years, median (IQR)	47.00 (38.00–53.25)	51.00 (39.00–59.00)	38.00 (32.00–43.00)	54.00 (51.00–59.00)	41.00 (34.00–48.50)	50.50 (41.25–56.75)
Female, n (%)	58 (36.2)	5 (38.5)	43 (48.9)	20 (23.5)	63 (100.0)	0 (0.0)
Male, n (%)	102 (63.7)	8 (61.5)	45 (51.1)	65 (76.5)	0 (0.0)	110 (100.0)
Internal carotid artery dissection, n (%)[a]	105 (65.6)	0 (0.0)	42 (47.7)	63 (74.1)	33 (52.4)	72 (65.5)
Vertebral artery dissection, n (%)[a]	55 (34.4)	0 (0.0)	41 (46.6)	14 (16.5)	25 (39.7)	30 (27.3)
Multivessel dissection; no, n (%)	160 (100.0)	0 (0.0)	83 (94.3)	77 (90.6)	58 (92.1)	102 (92.7)
Multivessel dissection; yes, n (%)	0 (0.0)	13 (100.0)	5 (5.7)	8 (9.4)	5 (7.9)	8 (7.3)
Occlusion; no, n (%)	105 (66.0)	12 (92.3)	62 (70.5)	55 (65.5)	44 (71.0)	73 (66.4)
Occlusion; yes, n (%)	54 (34.0)	1 (7.7)	26 (29.5)	29 (34.5)	18 (29.0)	37 (33.6)
Cerebral ischemia; no, n (%)	52 (32.5)	3 (23.1)	28 (31.8)	27 (31.8)	21 (33.3)	34 (30.9)
Cerebral ischemia; yes, n (%)	108 (67.5)	10 (76.9)	60 (68.2)	58 (68.2)	42 (66.7)	76 (69.1)
Time from symptom onset to start of allocated treatment, days, mean (IQR)	6.86 (4.56)	7.23 (3.42)	6.69 (4.38)	7.08 (4.59)	6.52 (4.36)	7.09 (4.54)
Acute recanalization therapy; no, n (%)	140 (87.5)	10 (76.9)	78 (88.6)	72 (84.7)	55 (87.3)	95 (86.4)
Acute recanalization therapy; yes, n (%)	20 (12.5)	3 (23.1)	10 (11.4)	13 (15.3)	8 (12.7)	15 (13.6)
Intracranial extension; no, n (%)	114 (71.2)	12 (92.3)	67 (76.1)	59 (69.4)	46 (73.0)	80 (72.7)
Intracranial extension; yes, n (%)	46 (28.7)	1 (7.7)	21 (23.9)	26 (30.6)	17 (27.0)	30 (27.3)
Mural hematoma; no, n (%)	8 (5.0)	0 (0.0)	5 (5.7)	3 (3.5)	2 (3.2)	6 (5.5)
Mural hematoma; yes, n (%)	152 (95.0)	13 (100.0)	83 (94.3)	82 (96.5)	61 (96.8)	104 (94.5)
Aspirin, n (%)	83 (51.9)	8 (61.5)	44 (50.0)	47 (55.3)	35 (55.6)	56 (50.9)
Anticoagulants [VKA], n (%)	77 (48.1)	5 (38.5)	44 (50.0)	38 (44.7)	28 (44.4)	54 (49.1)
~*p*, chi-squared test	0.70		0.59		0.67	
Primary endpoint; no, n (%)	131 (81.9)	9 (69.2)	75 (85.2)	65 (76.5)	52 (82.5)	88 (80.0)
Primary endpoint; yes, n (%)	29 (18.1)	4 (30.8)	13 (14.8)	20 (23.5)	11 (17.5)	22 (20.0)
~*p*, chi-squared test	0.28		0.20		0.84	

IQR = interquartile range; VKA = vitamin K antagonists.

[a]Multivessel dissections were excluded from these two subgroups (n = 13).

TABLE 4. Baseline Characteristics of the Patient Profiles

Characteristic	Mural Hematoma		
	No		Yes
Patients, n	8		165
Age, years, median (IQR)	41.50 (34.75–51.00)		47.00 (38.00–54.00)
Female, n (%)	2 (25.0)		61 (37.0)
Male, n (%)	6 (75.0)		104 (63.0)
Internal carotid artery dissection, n (%)[a]	4 (50.0)		101 (61.2)
Vertebral artery dissection, n (%)[a]	4 (50.0)		51 (30.9)
Multivessel dissection; no, n (%)	8 (100.0)		152 (92.1)
Multivessel dissection; yes, n (%)	0 (0.0)		13 (7.9)
Occlusion; no, n (%)	5 (62.5)		112 (68.3)
Occlusion; yes, n (%)	3 (37.5)		52 (31.7)
Cerebral ischemia; no, n (%)	1 (12.5)		54 (32.7)
Cerebral ischemia; yes, n (%)	7 (87.5)		111 (67.3)
Time from symptom onset to start of allocated treatment, days, mean (IQR)	7.88 (3.56)		6.84 (4.52)
Acute recanalization therapy; no, n (%)	7 (87.5)		143 (86.7)
Acute recanalization therapy; yes, n (%)	1 (12.5)		22 (13.3)
Intracranial extension; no, n (%)	4 (50.0)		122 (73.9)
Intracranial extension; yes, n (%)	4 (50.0)		43 (26.1)
Mural hematoma; no, n (%)	8 (100.0)		0 (0.0)
Mural hematoma; yes, n (%)	0 (0.0)		165 (100.0)
Aspirin, n (%)	2 (25.0)		89 (53.9)
Anticoagulants [VKA], n (%)	6 (75.0)		76 (46.1)
~p, chi-squared test		0.15	
Primary endpoint; no, n (%)	4 (50.0)		136 (82.4)
Primary endpoint; yes, n (%)	4 (50.0)		29 (17.6)
~p, chi-squared test		0.04	

IQR = interquartile range; VKA = vitamin K antagonists.
[a]Multivessel dissections were excluded from these two subgroups (n = 13).

stroke—had decreased odds of clinical or MRI outcomes when treated with vitamin K antagonists (relative risk reduction of 67% albeit with a large CI of 4–89%) compared to those treated with aspirin. This differential treatment effect in favor of anticoagulation was more pronounced in presumably higher risk patients presenting with cerebral ischemia. Again, reasons for this finding remain to be determined. However, our results suggest that mechanisms of (thrombo-)embolism from the arterial lesion in patients with patent dissected artery[28] might resemble those in cardioembolic stroke, in which anticoagulation has been shown superior to aspirin.[29] These findings are particularly important, as both in our study and in prior large observational cohorts[9] roughly two thirds of cervical artery dissection patients had a patent artery. Thus, these findings potentially matter for the large majority of the affected population.

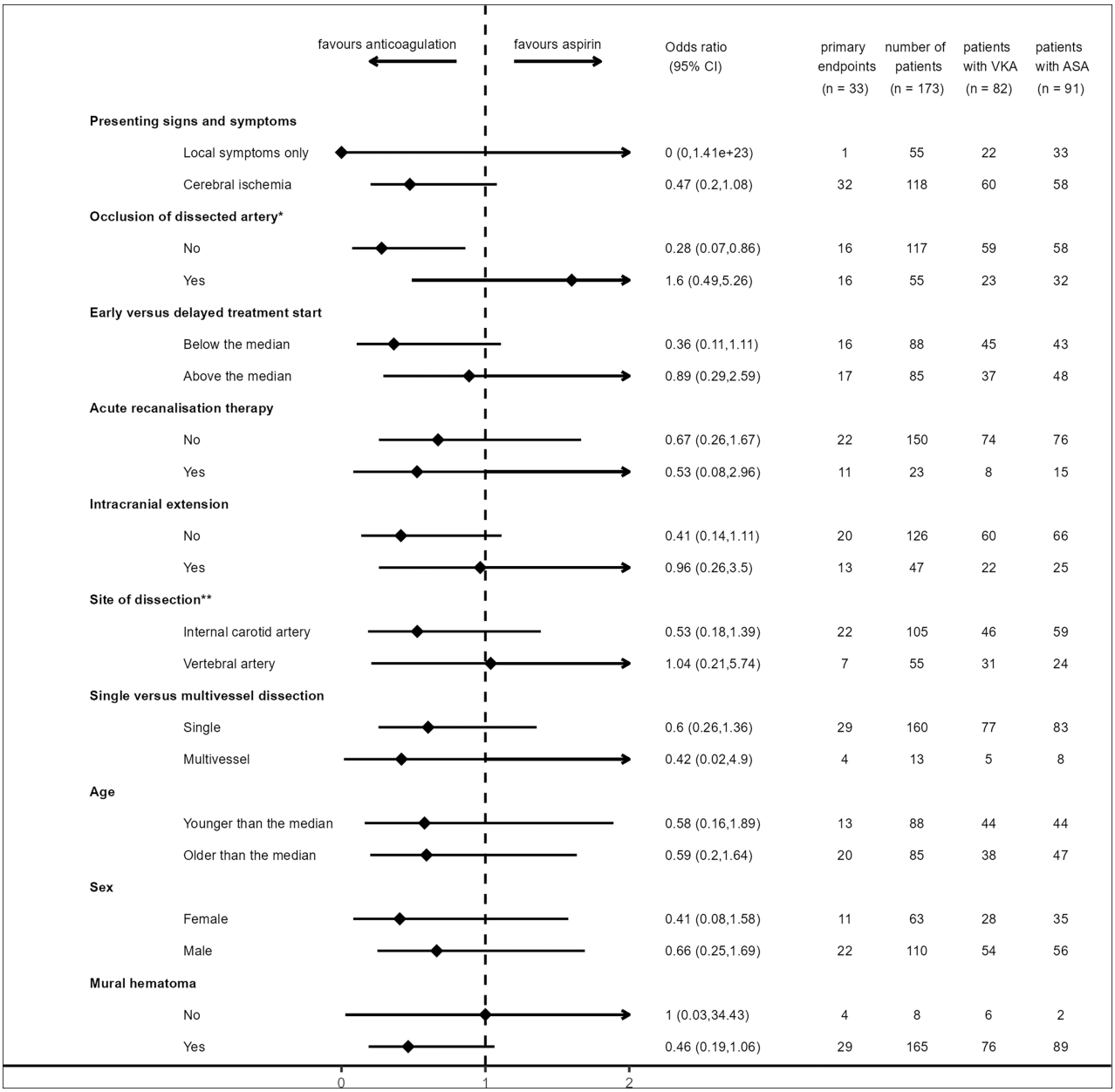

FIGURE 2: Subgroup analysis of the per protocol population. Results of the per protocol analysis are given as odds ratios (*black points*) with 95% confidence interval (CI; *black lines*) for the primary endpoint (the composite of clinical [ischemic stroke, major extracranial or intracranial hemorrhage, death] and magnetic resonance imaging outcomes [new ischemic or hemorrhagic brain lesions]). *Data missing for one participant. **Multivessel dissections excluded in this patient profile (n = 13). ASA = aspirin, VKA = vitamin K antagonists.

Reassuringly, prior concerns that anticoagulation might cause clinically relevant hemodynamic compromise of the dissected artery by enlargement of the mural hematoma[25] are not supported by our findings.

Interestingly, the aforementioned beneficial effect of anticoagulation was more pronounced if participants with a patent artery had presented with cerebral ischemia. These findings support the prognostic importance of cerebral ischemia at baseline. In CADISS, all outcome events—irrespectively of the treatment group—occurred in participants in whom the presenting symptom was stroke.[6] In TREAT-CAD, 32 of 33 participants with outcome events already presented with cerebral ischemia at baseline.[8] Although across all participants presenting with cerebral ischemia, the risk for outcomes did not differ considerably between those treated with aspirin and those treated with anticoagulation, anticoagulation might be beneficial for participants presenting with cerebral ischemia who had a patent dissected artery.

Observational studies[30] as well as both randomized controlled trials (TREAT-CAD and CADISS)[6,8] have shown that stroke preferentially occurs (or recurs) very

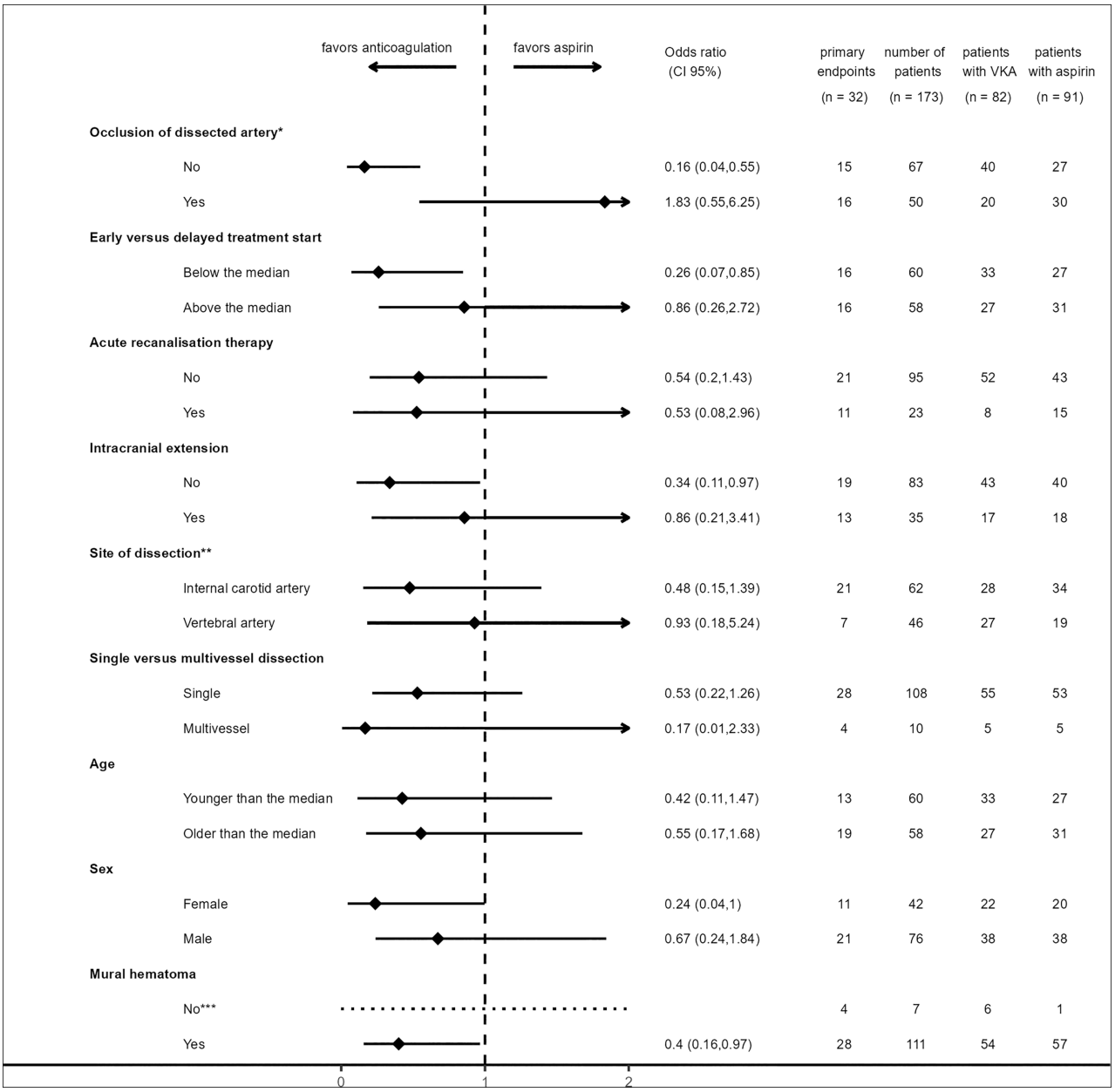

FIGURE 3: Subgroup analysis of the participants presenting with cerebral ischemia. Results of the per protocol analysis are given as odds ratios (*black points*) with 95% 95% confidence interval (CI; *black lines*) for the primary endpoint (the composite of clinical [ischemic stroke, major extracranial or intracranial hemorrhage, death] and magnetic resonance imaging outcomes [new ischemic or hemorrhagic brain lesions]). *Data missing for one participant. **Multivessel dissections excluded in this patient profile (n = 13). ***We provide descriptive figures for the subgroup without mural hematoma, as there are too few participants and endpoints in this subgroup for an informative odds ratio. VKA = vitamin K antagonists.

early after diagnosis (ie, hours to a few days), indicating the clinical importance of rapid antithrombotic protection for stroke prevention. In our study, among participants presenting with cerebral ischemia and early start of antithrombotic treatment, the use of anticoagulation seemed superior to the use of aspirin. This finding stresses the assumption of a notable benefit of anticoagulation over aspirin among patients presenting with cerebral ischemia in whom early anticoagulation is feasible.

Patients with stroke attributable to cervical artery dissection and intracranial extension might develop subarachnoid hemorrhage while under anticoagulation.[5] Thus, anticoagulation has not been recommended in such patients due to safety concerns.[25] Interestingly, our study did not support this concern, as participants treated with either aspirin or anticoagulation did not differ in the frequency of outcomes (neither ischemic nor hemorrhagic), which is also in line with a prior single-center observational study.[24] Of note, TREAT-CAD did not include

patients with purely intracranial dissections, for which our data do not provide any information. However, and clinically more importantly, our subgroup analysis indicated that participants presenting with cerebral ischemia who had no extension intracranially seemed to have an advantage with anticoagulation compared to aspirin.

Our analyses also indicated that significantly more outcomes occurred in participants who had received acute recanalization therapies than in those without (see Table 1). These findings must be interpreted cautiously. As only more severely affected patients with higher risk of recurrent events had acute recanalization therapies,[18] our findings are likely to be influenced by selection bias.

We are aware of several limitations. First, due to the limited number of participants, the TREAT-CAD trial was not powered for subgroup analyses, and we did not adjust for multiple statistical testing. This diminishes the validity of our results and leaves potentially important treatment effects undetected. Furthermore, interdependence between patient profiles is possible but could neither be confirmed nor excluded, because our sample size disallowed such analyses. In addition, the subgroups were not prespecified nor stratified for in the randomization process of the main trial. Furthermore, we did not include imaging features (including infarct pattern, degree of stenosis, recanalization) other than occlusion or mural hematoma at baseline in our analyses. Moreover, the clinical meaning of MRI outcomes without accompanying clinical symptoms is controversial,[31] although imaging outcomes had been used as surrogates for clinical outcomes in prior studies.[32–35] Therefore, we urge a cautious interpretation of our findings, which primarily should be considered hypothesis-generating. Moreover, we could test neither direct oral anticoagulants with their more attractive risk–benefit profile proven at least in cardioembolic stroke[36] nor dual antiplatelets. The latter had been reported to be superior to aspirin alone in (1) participants with transient ischemic attacks or mild strokes[37,38] and (2) reducing embolic signals at least in carotid stenosis of atherosclerotic origin,[39] and might increasingly also be used in dissection patients,[3] as also discussed in a recent guideline.[2]

The strengths of this subgroup analysis include the underlying dataset derived from a randomized controlled trial in which risk of bias in treatment allocation is significantly reduced compared to observational studies. Furthermore, including only the per protocol population of the TREAT-CAD trial ensures that our findings are based solely on participants with a verified diagnosis of cervical artery dissection. The blindly assessed, monitored, and centrally adjudicated outcomes increased the validity of our data. The baseline characteristics of our study population resemble those of large observational cohorts of patients with cervical artery dissections.[9,40] Thus, our results seem generalizable to patients with cervical artery dissection, including those outside a clinical trial population.

In conclusion, anticoagulation might be preferable in patients with cervical artery dissection presenting with ischemia and no occlusion or no intracranial extension of the dissection. Due to the explorative study design, these findings need confirmation.

Acknowledgments

We thank all TREAT-CAD study participants and their families, as well as all TREAT-CAD trial investigators, for their support. Open access funding provided by Universitat Basel.

Author Contributions

J.E.K., C.T., and S.T.E. contributed to the conception and design of the study. All authors contributed to the acquisition and analysis of data. J.E.K., H.G., A.R.L., B.G.-S., U.F., P.M., D.St., G.K., J.V., K.N., T.K., L.K., S.R., R.v.R., C.R., D.Se., H.S., A.Z., J.W., A.A.P., M.H., C.G., L.H.B., A.B., G.M.D.M., N.P., C.H.N., H.C., S.W., M.-N.P., M.A., P.L., C.T., and S.T.E. contributed to drafting the text or preparing the figures.

Potential Conflicts of Interest

Nothing to report.

Data Availability

There are still some research projects with these data planned at the University Hospital Basel. We will not publish the data until these projects are completed unless someone expresses interest in our data, in which case the data-sharing statement comes into effect. Data Sharing Statement: Study data may be provided upon reasonable request to the corresponding author. Such requests must consist of a detailed study proposal, a description of the study objectives, and a statistical analysis plan. Additional documents may be requested during study eligibility reviews for data sharing. The request must be approved by the corresponding author of this study and that of the main paper (i.e., the sponsor/investigator of the TREAT-CAD study), the study steering committee, and the principal investigators of each center. Each request will be assessed for its compliance with patient informed consent.

References

1. Debette S, Leys D. Cervical-artery dissections: predisposing factors, diagnosis, and outcome. Lancet Neurol 2009;8:668–678.

2. Debette S, Mazighi M, Bijlenga P, et al. ESO guideline for the management of extracranial and intracranial artery dissection. Eur Stroke J 2021;6:XXXIX–LXXXVIII.
3. Kasner SE. Antithrombotic therapy for cervical arterial dissection. Lancet Neurol 2021;20:328–329.
4. Engelter ST, Lyrer P, Traenka C. Cervical and intracranial artery dissections. Ther Adv Neurol Disord 2021;14:17562864211037238.
5. Markus HS, Hayter E, Levi C, et al. Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): a randomised trial. Lancet Neurol 2015;14:361–367.
6. Markus HS, Levi C, King A, et al. Antiplatelet therapy vs anticoagulation therapy in cervical artery dissection: the cervical artery dissection in stroke study (CADISS) randomized clinical trial final results. JAMA Neurol 2019;76:657–664.
7. Traenka C, Gensicke H, Schaedelin S, et al. Biomarkers and antithrombotic treatment in cervical artery dissection—design of the TREAT-CAD randomised trial. Eur Stroke J 2020;5:309–319.
8. Engelter ST, Traenka C, Gensicke H, et al. Aspirin versus anticoagulation in cervical artery dissection (TREAT-CAD): an open-label, randomised, non-inferiority trial. Lancet Neurol 2021;20:341–350.
9. Traenka C, Grond-Ginsbach C, Goeggel Simonetti B, et al. Artery occlusion independently predicts unfavorable outcome in cervical artery dissection. Neurology 2020;94:e170–e180.
10. Lyrer PA, Brandt T, Metso TM, et al. Clinical import of Horner syndrome in internal carotid and vertebral artery dissection. Neurology 2014;82:1653–1659.
11. Lichy C, Metso A, Pezzini A, et al. Predictors of delayed stroke in patients with cervical artery dissection. Int J Stroke 2015;10: 360–363.
12. Compter A, Schilling S, Vaineau CJ, et al. Determinants and outcome of multiple and early recurrent cervical artery dissections. Neurology 2018;91:e769–e780.
13. Weimar C, Kraywinkel K, Hagemeister C, et al. Recurrent stroke after cervical artery dissection. J Neurol Neurosurg Psychiatry 2010;81: 869–873.
14. Gensicke H, Ahlhelm F, Jung S, et al. New ischaemic brain lesions in cervical artery dissection stratified to antiplatelets or anticoagulants. Eur J Neurol 2015;22:859–861.
15. Wu Y, Wu F, Liu Y, et al. High-resolution magnetic resonance imaging of Cervicocranial artery dissection: imaging features associated with stroke. Stroke 2019;50:3101–3107.
16. Dziewas R, Konrad C, Drager B, et al. Cervical artery dissection?Clinical features, risk factors, therapy and outcome in 126 patients. J Neurol 2003;250:1179–1184.
17. Grimes DA, Schulz KF. Bias and causal associations in observational research. Lancet 2002;359:248–252.
18. Engelter ST, Dallongeville J, Kloss M, et al. Thrombolysis in cervical artery dissection—data from the cervical artery dissection and Ischaemic stroke patients (CADISP) database. Eur J Neurol 2012;19: 1199–1206.
19. Traenka C, Dougoud D, Simonetti BG, et al. Cervical artery dissection in patients ≥60 years: often painless, few mechanical triggers. Neurology 2017;88:1313–1320.
20. Traenka C, Jung S, Gralla J, et al. Endovascular therapy versus intravenous thrombolysis in cervical artery dissection ischemic stroke—results from the SWISS registry. Eur Stroke J 2018;3:47–56.
21. Metso AJ, Metso TM, Debette S, et al. Gender and cervical artery dissection. Eur J Neurol 2012;19:594–602.
22. Morris NA, Merkler AE, Gialdini G, Kamel H. Timing of incident stroke risk after cervical artery dissection presenting without ischemia. Stroke 2017;48:551–555.
23. Engelter ST, Rutgers MP, Hatz F, et al. Intravenous thrombolysis in stroke attributable to cervical artery dissection. Stroke 2009;40: 3772–3776.
24. Metso TM, Metso AJ, Helenius J, et al. Prognosis and safety of anticoagulation in intracranial artery dissections in adults. Stroke 2007; 38:1837–1842.
25. Engelter ST, Brandt T, Debette S, et al. Antiplatelets versus anticoagulation in cervical artery dissection. Stroke 2007;38:2605–2611.
26. Sun X, Briel M, Walter SD, Guyatt GH. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. BMJ 2010;340:c117.
27. Traenka C, Streifler J, Lyrer P, Engelter ST. Clinical usefulness of serial duplex ultrasound in cervical artery dissection patients. Cerebrovasc Dis 2020;49:206–215.
28. Koennecke HC, Trocio SH Jr, Mast H, Mohr JP. Microemboli on transcranial Doppler in patients with spontaneous carotid artery dissection. J Neuroimaging 1997;7:217–220.
29. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857–867.
30. Biousse V, D'Anglejan-Chatillon J, Touboul PJ, et al. Time course of symptoms in extracranial carotid artery dissections. A series of 80 patients. Stroke 1995;26:235–239.
31. Bae HJ, Debette S. Commentary on the cervical artery dissection in stroke study trial. Stroke 2016;47:1413–1415.
32. Bonati LH, Jongen LM, Haller S, et al. New ischaemic brain lesions on MRI after stenting or endarterectomy for symptomatic carotid stenosis: a substudy of the international carotid stenting study (ICSS). Lancet Neurol 2010;9:353–362.
33. O'Donnell MJ, Eikelboom JW, Yusuf S, et al. Effect of apixaban on brain infarction and microbleeds: AVERROES-MRI assessment study. Am Heart J 2016;178:145–150.
34. Sharma M, Hart RG, Smith EE, et al. Rivaroxaban for prevention of covert brain infarcts and cognitive decline: the COMPASS MRI substudy. Stroke 2020;51:2901–2909.
35. Sondergaard L, Kasner SE, Rhodes JF, et al. Patent foramen Ovale closure or antiplatelet therapy for cryptogenic stroke. N Engl J Med 2017;377:1033–1042.
36. Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet 2014; 383:955–962.
37. Johnston SC, Easton JD, Farrant M, et al. Platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trial: rationale and design. Int J Stroke 2013;8:479–483.
38. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 2013;369: 11–19.
39. Markus HS, Droste DW, Kaps M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: the Clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis (CARESS) trial. Circulation 2005;111:2233–2240.
40. Debette S. Pathophysiology and risk factors of cervical artery dissection: what have we learnt from large hospital-based cohorts? Curr Opin Neurol 2014;27:20–28.