Drugs in R&D (2022) 22:187–203
https://doi.org/10.1007/s40268-022-00398-z

SYSTEMATIC REVIEW

Antiplatelets Versus Anticoagulation in Cervical Artery Dissection: A Systematic Review and Meta-analysis of 2064 Patients

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Accepted: 19 July 2022 / Published online: 3 August 2022

Abstract

Background and Objectives In young people aged < 50 years, cervical artery dissection (CeAD) is among the most common causes of stroke. Currently, there is no consensus regarding the safest and most effective antithrombotic treatment for CeAD. We aimed to synthesize concrete evidence from studies that compared the efficacy and safety of antiplatelet (AP) versus anticoagulant (AC) therapies for CeAD.

Methods We searched major electronic databases/search engines from inception till September 2021. Cohort studies and randomized controlled trials (RCTs) comparing anticoagulants with antiplatelets for CeAD were included. A meta-analysis was conducted using articles that were obtained and found to be relevant. Mean difference (MD) with 95% confidence interval (CI) was used for continuous data and odds ratio (OR) with 95% CI for dichotomous data.

Results Our analysis included 15 studies involving 2064 patients, 909 (44%) of whom received antiplatelets and 1155 (56%) received anticoagulants. Our analysis showed a non-significant difference in terms of the 3-month mortality (OR 0.47, 95% CI 0.03–7.58), > 3-month mortality (OR 1.63, 95% CI 0.40–6.56), recurrent stroke (OR 0.97, 95% CI 0.46–2.02), recurrent transient ischaemic attack (TIA) (OR 0.93, 95% CI 0.44–1.98), symptomatic intracranial haemorrhage (sICH) (OR 0.38, 95% CI 0.12–1.19), and complete recanalization (OR 0.70, 95% CI 0.46–1.06). Regarding primary ischaemic stroke, the results favoured AC over AP among RCTs (OR 6.97, 95% CI 1.25–38.83).

Conclusion Our study did not show a considerable difference between the two groups, as all outcomes showed non-significant differences between them, except for primary ischaemic stroke (RCTs) and complete recanalization (observational studies), which showed a significant favour of AC over AP. Even though primary ischaemic stroke is an important outcome, several crucial points that could affect these results should be paid attention to. These include the incomplete adjustment for the confounding effect of AP–AC doses, frequencies, administration compliance, and others. We recommend more well-designed studies to assess if unnecessary anticoagulation can be avoided in CeAD.

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Key Points

Both antiplatelet (AP) and anticoagulant (AC) drugs can be used in the management of cervical artery dissection due to similar rates of recurrent stroke, transient ischaemic attack, haemorrhage, mortality, and complete recanalization. Despite this similarity, it is possible that the statistically equal AC/AP profiles may be due to significant conflict zones among the AC–AP comparative studies.

We urge further well-designed clinical trials to determine whether or not unnecessary anticoagulation may be avoided in cervical artery dissection.

1 Introduction

Constituting 1–2% of all ischaemic stroke aetiologies [1], cervical artery dissection (CeAD) (i.e., extracranial internal carotid artery/vertebral artery dissection) is by far a significant contributor to almost one-fifth of ischaemic stroke cases in the younger age population [2–5]. For every 100,000 people, the incidence of CeAD is about 2.6 (95% confidence interval (CI) 1.86–3.33) per year in the general population [6]. Whether traumatic or spontaneous, CeAD carries a considerable risk of a recurrent ischaemic stroke (more common in the first 2 weeks of onset) [7, 8], intracranial haemorrhage (ICH), transient ischaemic attacks (TIAs) and, rarely, death [9–11]. Therefore, multiple studies were conducted over the last two decades aiming to minimize these potential risks via either medical or endovascular therapies [2, 9]. The choice of anticoagulation (AC) versus antiplatelet therapy (AP) has been the most demanding question to be addressed.

Unfortunately, current evidence substantially lacks proper conclusions as to CeAD acute and maintenance management with regard to AP/AC. The heterogenous nature of the previous CeAD studies poses a significant obstacle to their external validities [2–5, 7–13]. Specifically, the study design (retrospective or prospective, per-protocol/intention-to-treat analysis), time to randomization, the choice of AP or AC—based on the primary physician choice (either solely or months after randomization), the outcome definitions (symptomatic vs. major intracranial haemorrhage, possible vs. definite cause of ischaemic stroke, early vs. late stroke), time to follow-up and the follow-up methodology (whether ultrasonography (US)-based or angiographically based, subclinical vs. clinically oriented using magnetic resonance imaging (MRI) of the brain) constitute the most common areas of vast methodologic variations [8–14].

In addition, the wide CIs of many outcome findings in these studies stem from a limited sample size [9]. For example, an estimated number of 913 patients with an 80% power and a 5% significance level has been set since 2003 for addressing the AC/AP choice [15]. However, even the CADISS trial has failed to achieve this postulated count ($n = 250$) [10]. Moreover, the answer to the futility of AC/AP remains perplexing in the context of a low risk of recurrent stroke [10, 11, 14] . As a result, there is only a Class of Recommendation IIA and a Level of Evidence B for either therapy based on a single randomized controlled trial (RCT) carrying substantial limitations [10, 16]. Finally, the maximum estimated follow-up period for dissection patients was 28 months, which again adds temporal blurring in addition to the relatively low case load, as opposed to atherosclerotic aetiologies being studied, for instance [17]. In this regard, 58 months was the mean follow-up period in only one study [18]. As reported by Chowdhury et al. [19], clinical follow-up averaged 17.7 months, while Kennedy et al. [14] and Sarikaya et al. [20] only included 3-month follow-up results.

In view of the described methodologic heterogeneity, temporal limitations, and low sample sizes, we aimed, through this systemic review and meta-analysis, to mitigate these barriers in order to reach a possible consensus regarding the choice of AC versus AP strategy with an emphasis on the indications for both, the relative merit of either therapies, as well as the dose and duration of therapy.

2 Methods

2.1 Study Design

The current study is a systematic review and meta-analysis of the literature. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 standards were strictly followed in the course of conducting the study [21]. Our study's PROSPERO Registration number is CRD42022338493.

2.2 Eligibility Criteria and Study Selection

We included peer-reviewed RCTs and observational studies that compared AP therapy with AC in patients with CeAD. The main exclusion criteria were non-English studies, single-arm studies, conference abstracts, reviews and studies without separate data for the intervention and comparison groups.

2.3 Literature Search

We systematically searched the following electronic databases: PubMed, Web of Science, Cochrane, Scopus, Embase and OVID till September 2021. Across all databases, the most recent search was conducted on 30 September 2021. The search strategy used was (Aspirin OR Acetylsalicylic Acid OR 2 Acetyloxy benzoic Acid OR Acylpyrin OR Aloxiprimum OR Colfarit OR Dispril OR Easprin OR Ecotrin OR Endosprin OR Magnecyl OR Micristin OR Polopirin OR Polopiryna OR Solprin OR Solupsan OR Zorprin OR Acetysal OR Antiplatelet Therapy) AND (Anticoagulants OR Anticoagulant OR Anticoagulation Agent OR Indirect Thrombin Inhibitors) AND (cervical artery dissection). The search strategy was adjusted according to the database, for example, we used quotation marks for searching on Scopus. The selection process was carried out by two independent pairs of authors (B.K.A, M.A, M.T.H, A.A.A); another author (A.I.H) was consulted to resolve any conflicts, with an average disagreement of 4%.

2.4 Quality Assessment

To assess the quality of the included cohort studies, we used the Newcastle–Ottawa Scale (NOS) for assessing the quality of non-randomised studies [22]. The domains include selection, comparability and exposure. Each domain is assessed using stars, with a maximum of nine stars. Meanwhile, to assess the risk of bias of the included RCTs, we used the Cochrane risk of bias tool for RCTs [23]. The domains include random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. The assessment is based upon the judgment of low, high or unclear risk of bias. Two independent authors (M.A and B.K.A) assessed the quality of included studies; another author (A.I.H) was consulted to resolve any conflicts, with a disagreement of 3%.

2.5 Data Extraction

We extracted data, in an excel sheet, on the following: (1) Summary of included studies: study ID (first author/year of publication), title, study design, country and date of implementation, participants and key inclusion/exclusion criteria, intervention group, control group, duration of follow-up, and conclusion. (2) Baseline characteristics of the included population: study ID (first author/year of publication), title, study groups and the total number on the group, age, gender, dissection type, admission mRs 0–2, and ≥3, hypertension, current smoking, alcohol use, stenosis, occlusion, aneurysmal, complete recanalization, partial recanalization, prior TIAs, prior treatment, and other relevant characteristics. (3) Study outcomes as described below. Data were extracted by two independent pairs of authors (B.K.A, M.A, M.T.H, A.A.A); another author (A.I.H) was consulted to resolve any conflicts, with an average disagreement of 4%.

2.6 Study Outcomes

The study outcomes included death, primary ischaemic stroke, primary TIA, recurrent stroke, recurrent TIA, symptomatic intracranial haemorrhage (sICH), major extracranial bleeding, excellent outcome at 6 months (modified Rankin scale (mRS) score = 0–2), poor outcome at 6 months (mRS score ≥ 3), complete recanalization, total adverse events, major haemorrhagic complications (bleeding), seizure, admission mRS score 0–2, admission mRS score ≥ 3, all haemorrhagic complications, time from baseline MRI to follow-up MRI (days), patients with new diffusion-weighted imaging (DWI) lesions, occlusion and stenosis.

2.7 Data Synthesis

We performed the analysis using Review Manager (RevMan) version 5.4. Data were pooled as odds ratio and 95% confidence Interval (CI) (dichotomous) or mean difference (MD) and 95% CI (continuous). Data were considered significant if $p < 0.05$. We measured heterogeneity using the I-square (I2) test and chi-square test. We considered the data heterogeneous with chi-square $P < 0.1$ and the I2-value was larger than 50%. When heterogeneity was found, we used the random-effect model, other than that we used the fixed-effect model. We performed subgroup analyses according to the study design (cohort or RCTs), or according to the follow-up duration (3 months, or more than 3 months) when available.

2.8 Publication Bias

Even though the total number of included studies was 15, the maximum number of included studies in an outcome was less than 10. Therefore, we did not assess the publication bias using funnel plots, following Cochrane handbook recommendation 10.4.3.1 [24].

2.9 Meta-regression Analysis

Meta-regression requires a minimum of ten studies to be included in each outcome analysis, as stated in the Cochrane Handbook for Systematic Reviews of Interventions [25], which did not exist in the context of our research. As a direct consequence of this, a meta-regression analysis cannot be constructed on the basis of the data that are currently available.

3 Results

3.1 Literature Search

Based on our systemic search, we initially had 1230 records, and 277 of them were removed as they were duplicates. We screened 953 records, of which 144 were suitable for full-text screening. Finally, we included 15 studies [8–11, 13–15, 17, 26–32] (Fig. 1).

3.2 Characteristics of the Included Studies and Population Baselines

The included studies were mainly observational (cohort) studies, but there were also two RCTs [9, 10]. The follow-up duration of the included studies ranged from 1 month to 12 months [8–11, 13–15, 17, 26–29, 31, 32]. Two studies reported data on carotid dissection only [17, 29], one reported data on vertebral dissection [13], one reported data on both [8], and the other studies did not specified the type. The mean age of patients in these studies [8–11, 13–15, 17, 26–32] ranged between 34.4 and 50.4 years (Tables 1, 2).

3.3 Risk of Bias

The included cohort studies had a score range of 8–9 stars out of 9, with the majority of studies scoring 8. Therefore, all studies were classified as high quality (Table 3). On the other hand, the included RCTs [9, 10] had a high risk of bias

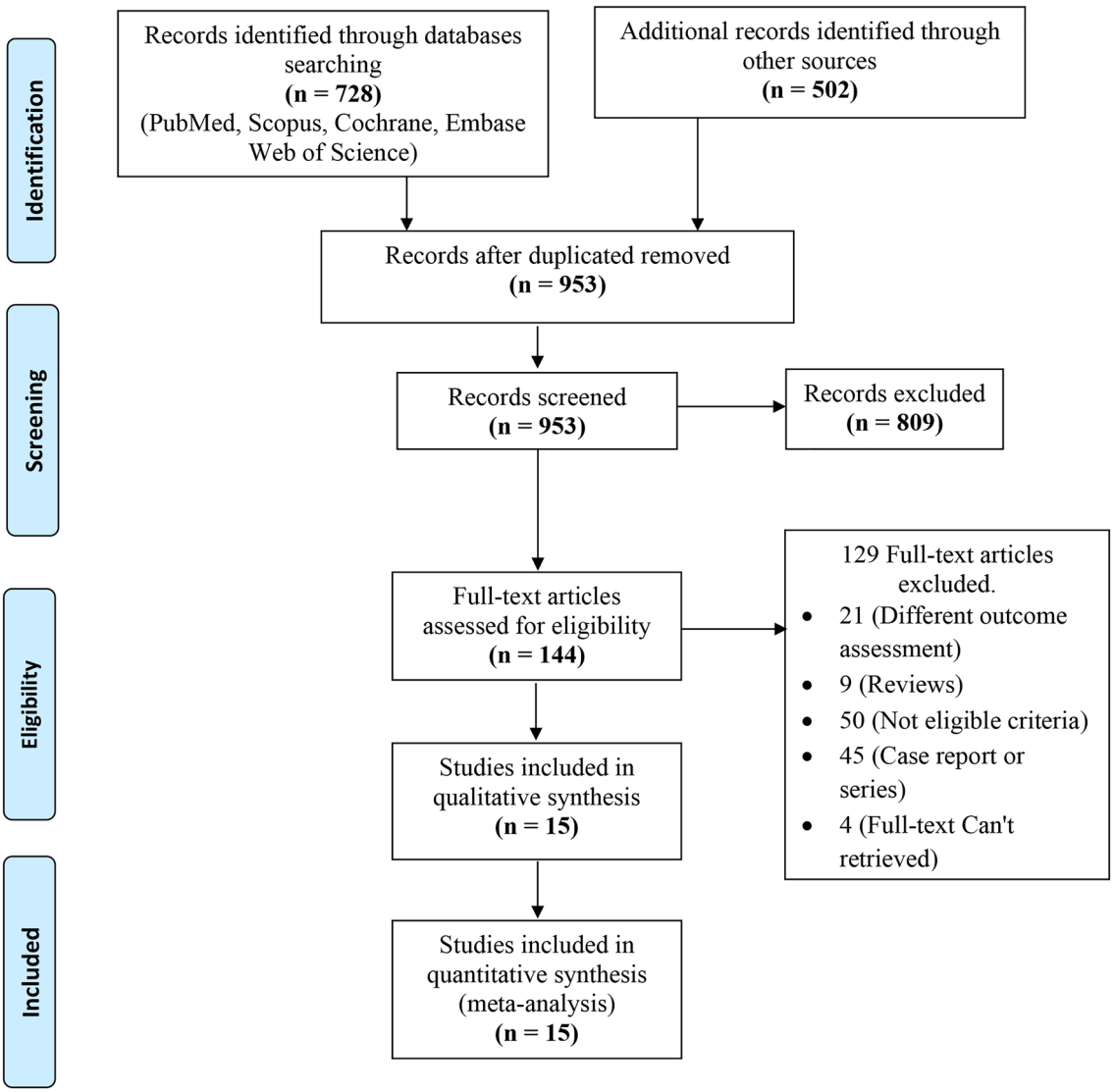

Fig. 1 PRISMA flow diagram

Table 1 Summary of included studies

Study ID	Design	Study arms		No.	Mean duration of follow up (months)
Arauz 2006	Cohort	Carotid dissection	Aspirin	44	6
			Anticoagulant	14	
		Vertebral dissection	Aspirin	38	
			Anticoagulant	34	
Arauz 2012	Cohort	Vertebral dissection	Antiplatelet	50	6
			Anticoagulant	49	
Caprio 2014	Cohort		Antiplatelet	40	7.5
			Anticoagulant	70	
			Anticoagulant	39	
Daou 2017	Cohort		Antiplatelet	70	24.3
			Anticoagulant	73	
Engelter 2000	Cohort	Carotid dissection	Antiplatelet	8	7.8
			Anticoagulant	25	
Gensicke 2015	Cohort		Antiplatelet	43	6
			Anticoagulant	25	
Georgiadis 2009	Cohort	Carotid dissection	Aspirin	96	3
			Anticoagulant	202	
Kennedy 2012	Cohort		Antiplatelet	59	12
			Anticoagulant	28	
Markus 2019	RCT		Antiplatelet	126	12
			Anticoagulant	124	
Weimar 2010	Cohort		Antiplatelet	32	31
			Anticoagulant	193	
Yaghi 2012	Cohort		Antiplatelet	31	6
			Anticoagulant	16	
Machet 2013	Cohort		Antiplatelet	13	
			Anticoagulant	31	
Engelter 2021	RCT		Aspirin	100	3
			Anticoagulant	94	
Vineetha 2019	Cohort		Antiplatelet	136	6
			Anticoagulant	64	
Beletsky 2003	Cohort		Anticoagulant	71	10
			Aspirin	23	

RCT randomized controlled trial

for allocation concealment and blinding of participants and personnel (Fig. 2).

3.4 Outcomes

3.4.1 Death During Short-Term Follow-Up (3 Months)

Five studies were included in the analysis with a total of 1,029 patients. The analysis showed insignificant statistical differences between the two groups (OR 0.47, 95% CI 0.03–7.58, $p = 0.59$). A subgroup analysis was performed. In cohort studies ($N = 585$ patients), the analysis also showed no significant differences between the two groups (OR 0.47, 95% CI 0.03–7.58, $p = 0.59$) (Fig. 3a).

3.4.2 Death During Long-Term Follow-Up (More Than 3 Months)

Five studies were included in the analysis with a total of 507 patients. The analysis showed no significant differences (OR 1.63, 95% CI 0.40–6.56, $p = 0.49$), and the results were homogenous ($p = 0.84$; $I^2 = 0\%$). A subgroup analysis

Table 2 Baseline for included studies

Study ID	Study arms		Age, y Mean (SD)	Gender, *n* (%)		Dissection type, *n* (%)		mRs 0–2, *n* (%)	mRs >= 3, n (%)	Hypertension, *n* (%)	Current smoking, *n* (%)	Admission NIHSS Mean (SD)	Follow-up in months Mean (SD)	Migraine, *n* (%)
				Male	Female	Spontaneous	Traumatic							
Arauz 2006	Carotid dissection	Aspirin	34.4 (12)	26 (45)	32 (55)			8 (18)	36 (82)					
		Anticoagulant						1 (8)	13 (92)					
	Vertebral dissection	Aspirin	36.3 (8)	44 (61)	28 (39)			22 (58)	16 (42)					
		Anticoagulant						15 (44)	19 (56)					
Arauz 2012	Vertebral dissection	Antiplatelet	39.2 (7.69)	32 (64)	18 (36)			43 (86)	7 (14)	6 (12)	15 (30)	5.28 (3.27)	48.98 (43)	
		Anticoagulant	36.49 (9.25)	30 (61.2)	19 (38.8)			39 (80)	10 (20)	9 (18.4)	16 (32.7)	7.66 (5.12)	44.86 (37.75)	
Caprio 2014		Antiplatelet	48.1 (13.2)	17 (42.5)	23 (57.5)					8 (20)				6 (15)
		Anticoagulant	41.4 (15)	21 (30)	49 (70)					13 (18.6)				13 (18.6)
		Anticoagulant	42.3 (12.1)	17 (43.6)	22 (56.4)					10 (25.6)				7 (17.9)
Daou 2017		Antiplatelet	49	31 (44)	39 (56)	49 (70)	21 (30)			25 (36)	18 (26)		23	
		Anticoagulant	44	31 (43)	42 (57)	53 (73)	20 (27)			28 (39)	19 (26)		30	
Engelter 2000	Carotid dissection	Antiplatelet	47.8 (12.6)	5 (63)	3 (37)	4 (50)				1 (13)	4 (50)			
		Anticoagulant	44.5 (9.26)	18 (72)	7 (28)	14 (56)				7 (28)	10 (40)			
Gensicke 2015		Antiplatelet	45 (11.5)	29 (67.4)	14 (32.6)									
		Anticoagulant	48.67 (12.58)	18 (72)	7 (28)									
Georgiadis 2009	Carotid dissection	Aspirin	46 (11)	53 (55)	43 (45)					25 (26)	37 (38.5)			
		Anticoagulant	46 (10)	115 (57)	87 (43)					56 (27.7)	53 (26.2)			
Kennedy 2012		Antiplatelet	45	34 (57.6)	25 (42.4)					12 (20.3)	10 (16.9)			13 (22)
		Anticoagulant	43	17 (60.7)	11 (39.3)					1 (3.6)	5 (17.9)			7 (25)
Markus 2019		Antiplatelet	49.3 (12)	87 (69)	39 (31)					29 (23)				20 (16)
		Anticoagulant	49.2 (12)	87 (70)	37 (30)					26 (21)				25 (20)

Table 2 (continued)

Study ID	Study arms	Age, y Mean (SD)	Gender, *n* (%)		Dissection type, *n* (%)		mRs 0–2, *n* (%)	mRs >= 3, n (%)	Hypertension, *n* (%)	Current smoking, *n* (%)	Admission NIHSS Mean (SD)	Follow-up in months Mean (SD)	Migraine, *n* (%)
			Male	Female	Spontaneous	Traumatic							
Weimar 2010	Antiplatelet	50.4	20 (72.5)	12 (27.5)					18 (56.3)	9 (29)	4.5		
	Anticoagulant	47.7	118 (60.2)	78 (39.8)					74 (37.8)	66 (34.7)	3		
Yaghi 2012	Antiplatelet	44 (12.3)	19 (61.3)	12 (38.7)					14 (45.1)	12 (38.7)			9 (29)
	Anticoagulant	46.7 (12.5)	10 (62.5)	6 (37.5)					8 (50)	8 (50)			5 (31.2)
Machet 2013	Antiplatelet	41.8 (9.6)									5.5 (6.3)		
	Anticoagulant	45.7 (8.5)									2.3 (4.1)		
Engelter 2021	Aspirin	46.6 (10.6)	62 (62)	38 (38)					32 (32)		2.1 (2.7)		
	Anticoagulant	45.5 (11.6)	61 (65)	33 (35)					28 (30)		2.5 (4.1)		
Vineetha 2019	Antiplatelet	43.44 (13.16)	103 (75.7)	33 (24.3)			67 (49.3)		60 (44.1)	48 (35.3)	8.18 (7.03_		11 (8.1)
	Anticoagulant	43.56 (12.98)	50 (78.1)	14 (21.9)			39 (60.9)		32 (50)	20 (31.3)	6.25 (5.7)		5 (7.8)
Beletsky 2003	Antico-agulant, Aspirin	44 (11)	56 (48)	60 (52)		68 (58.6)			21 (18)	23 (20)		10 (3.5)	15 (13)

Study ID	Diabetes, *n* (%)	Hyperlipidaemia, *n* (%)	Prior stroke, *n* (%)	Atrial fibrillation, *n* (%)	Coronary artery disease, *n* (%)	Presentation, n(%)				Carotid artery dissection, *n* (%)	Vertebral artery dissection, *n* (%)	Carotid and vertebral artery dissection, *n* (%)	TIA, *n* (%)
						Headache	Neck pain	Ischaemic symptoms	Explicit trauma				
Arauz 2006													
Arauz 2012													
Caprio 2014	1 (2.5)	3 (7.5)	0 (0)	1 (2)	3 (7.5)	17 (42.5)	14 (35)	18 (45)	18 (45)	18 (45)	26 (65)		
	1 (1.4)	7 (10)	3 (4.3)	2 (2.9)	1 (1.4)	35 (50)	26 (37.1)	38 (54.3)	33 (47.1)	24 (34.3)	52 (74.3)		
	1 (2.6)	6 (15.4)	0 (0)	0 (0)	0 (0)	26 (66.7)	21 (34.4)	25 (64.1)	18 (46.2)	13 (33.3)	27 (69.2)		
Daou 2017	6 (8)	15 (22)	17 (24)							39 (55)	27 (39)	4 (6)	
	5 (7)	14 (19)	27 (37)							45 (62)	26 (36)	1 (2)	
Engelter 2000			5 (63)										0 (0)
			15 (60)										6 (24)

Table 2 (continued)

Study ID	Diabetes, *n* (%)	Hyperlipidaemia, *n* (%)	Prior stroke, *n* (%)	Atrial fibrillation, *n* (%)	Coronary artery disease, *n* (%)	Presentation, n(%)				Carotid artery dissection, *n* (%)	Vertebral artery dissection, *n* (%)	Carotid and vertebral artery dissection, *n* (%)	TIA, *n* (%)
						Headache	Neck pain	Ischaemic symptoms	Explicit trauma				
Gensicke 2015										20 (46.5)	20 (46.5)	3 (7)	
										17 (68.6)	6 (24)	2 (8)	
Georgiadis 2009	0 (0)	34 (35.4)			1 (1)								12 (12.5)
	2 (1)	61 (30.2)			1 (0.5)								25 (12.4)
Kennedy 2012	4 (6.8)	7 (11.9)	34 (57.6)			45 (76.3)	32 (54.2)						14 (23.7)
	0 (0)	1 (3.6)	23 (82.1)			18 (64.3)	15 (53.6)						7 (25)
Markus 2019	5 (4)	16 (13)				84 (67)	57 (54)			58 (46)	68 (54)		27 (21)
	5 (4)	19 (15)				83 (67)	63 (51)			60 (48)	64 (52)		20 (16)
Weimar 2010	6 (18.8)	6 (19.4)	3 (9.4)		3 (9.4)								1 (3.1)
	19 (9.7)	49 (25.8)	12 (6.1)		4 (2)								4 (2)
Yaghi 2012		9 (29)											
		4 (25)											
Machet 2013										10 (70)	4 (30)		
										25 (71)	10 (29)		
Engelter 2021	1 (1)	19 (19)				72 (72)				72 (72)	29 (29)	9 (9)	14 (14)
	3 (3)	20 (21)				64 (68)				58 (62)	38 (40)	5 (5)	10 (11)
Vineetha 2019	31 (22.8)	41 (30.1)	17 (12.5)		8 (5.9)		8 (5.9)			93 (68.4)	43 (31.6)		23 (16.9)
	20 (31.3)	22 (34.4)	4 (6.3)		3 (4.7)		4 (6.3)			39 (60.9)	25 (39.1)		14 (21.09)
Beletsky 2003	6 (5)		4 (3)			9 (7.8)				49 (42)	67 (58)	2 (1.7)	24 (20.7)

Table 3 Risk of bias for cohort studies

Study ID	1	2	3	4	5	6	7	8	Total	Quality
Arauz 2006	*	*	*	*	*	*	*	*	8	High
Arauz 2013	*	*	*	*	*	*	*	*	8	High
Caprio 2014	*	*	*	*	*	*	*	*	8	High
Daou 2017	*	*	*	*	*	*	*	*	8	High
Engelter 2000	*	*	*	*	*	*	*	*	8	High
Gensicke 2015	*	*	*	*	*	*	*	*	8	High
Georgiadis 2009	*	*	*	*	*	*	*	*	8	High
Kennedy 2012	*	*	*	*	*	*	*	*	8	High
Machet 2013	*	*	*	*	*	*	*	*	8	High
Weimar 2010	*	*	*	*		*	*	*	7	High
Yaghi 2012	*	*	*	*	*	*	*		7	High
Beletsky 2003	*	*	*	*		*	*	*	7	High
Vineetha 2019	*	*	*	*	*	*	*	*	8	High

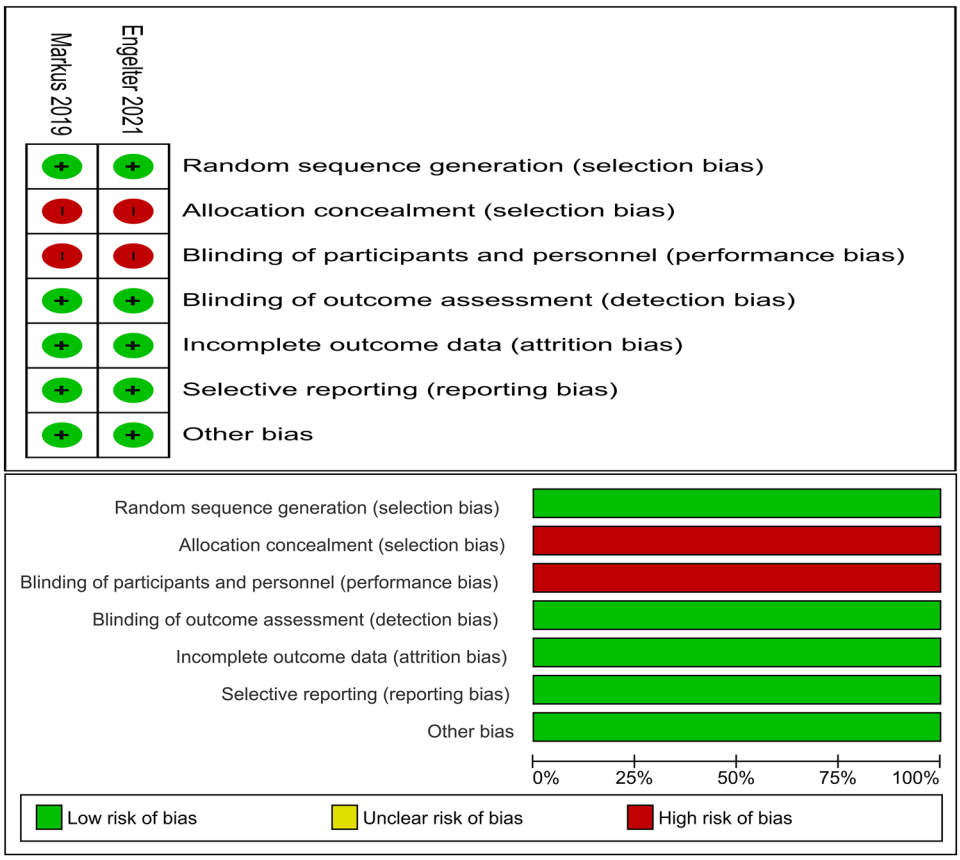

Fig. 2 Risk of bias graph and summary

was performed. In an RCT by Markus et al. [10] ($N = 250$ patients), the analysis also showed no significant differences between the two groups (OR 2.98, 95% CI 0.12–73.76, $p = 0.51$). In cohort studies ($N = 257$ patients), the analysis also showed no significant differences between the two groups (OR 1.37, 95% CI 0.28–6.64, $p = 0.7$), and the results were homogenous ($p = 0.72$; $I^2 = 0\%$) (Fig. 3b).

3.4.3 Primary Ischaemic Stroke

Five studies were included in the analysis with a total of 935 patients. The analysis showed insignificant statistical differences between the groups (OR 2.63, 95% CI 0.96–7.25, $p = 0.06$), and the results were homogenous ($p = 0.42$; $I^2 = 0\%$). For the subgroup analysis, in the RCTs ($N = 444$ patients), there was a significant favouring of

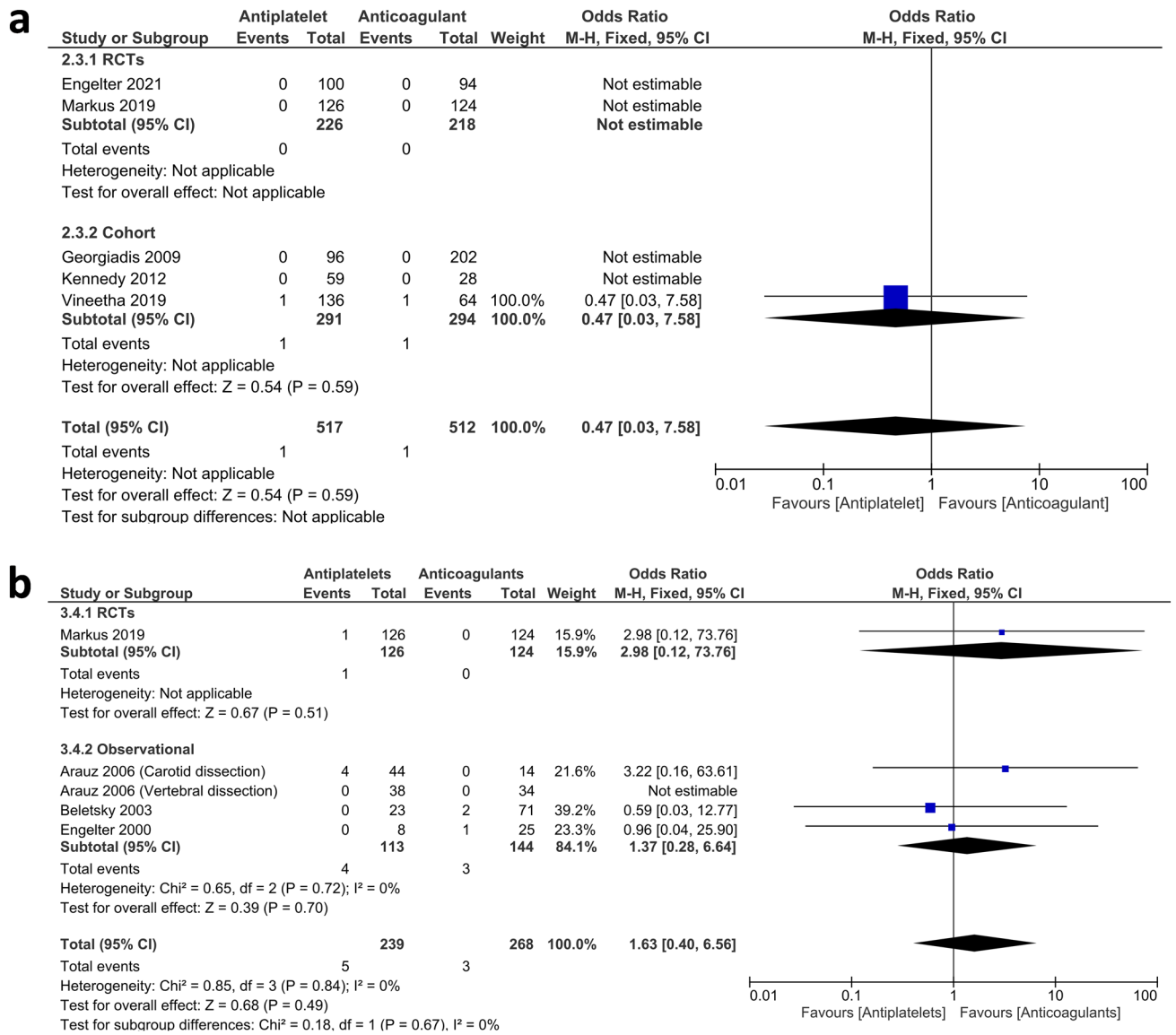

Fig. 3 **a** Death during short-term follow-up. **b** Death during long-term follow-up

AC over AP (OR 6.97, 95% CI 1.25–38.83, $p = 0.03$), and the results were homogenous ($p = 0.37$; $I^2 = 0\%$). For the cohort studies, there were no significant differences (OR 0.77, 95% CI 0.15–3.98, $p = 0.76$), and the results were homogenous ($p = 0.74$; $I^2 = 0\%$) (Fig. 4a).

3.4.4 Primary Transient Ischaemic Attack (TIA)

Four studies were included in the analysis ($N = 836$ patients). The analysis showed insignificant statistical differences between the groups (OR 0.54, 95% CI 0.20–1.44, $p = 0.22$), and the results were homogenous ($p = 0.57$; $I^2 = 0\%$). For the subgroup analysis in the RCTs ($N = 444$ patients), there were no statistically significant differences between the two groups (OR 0.37, 95% CI 0.08–1.59, $p = 0.18$), and the results were homogenous ($p = 0.59$; $I^2 = 0\%$). For the cohort studies, there still were no significant differences (OR 0.74, 95% CI 0.20–2.76, $p = 0.66$), and the results were homogenous ($p = 0.27$; $I^2 = 19\%$) (Fig. 4b).

3.4.5 Recurrent Stroke

Eight studies were included in the analysis ($N = 1{,}140$ patients). The analysis showed no significant statistical differences between the two groups (OR 0.97, 95% CI 0.46–2.02, $p = 0.93$), and the results were homogenous ($p = 0.91$; $I^2 = 0\%$) (Fig. 5a).

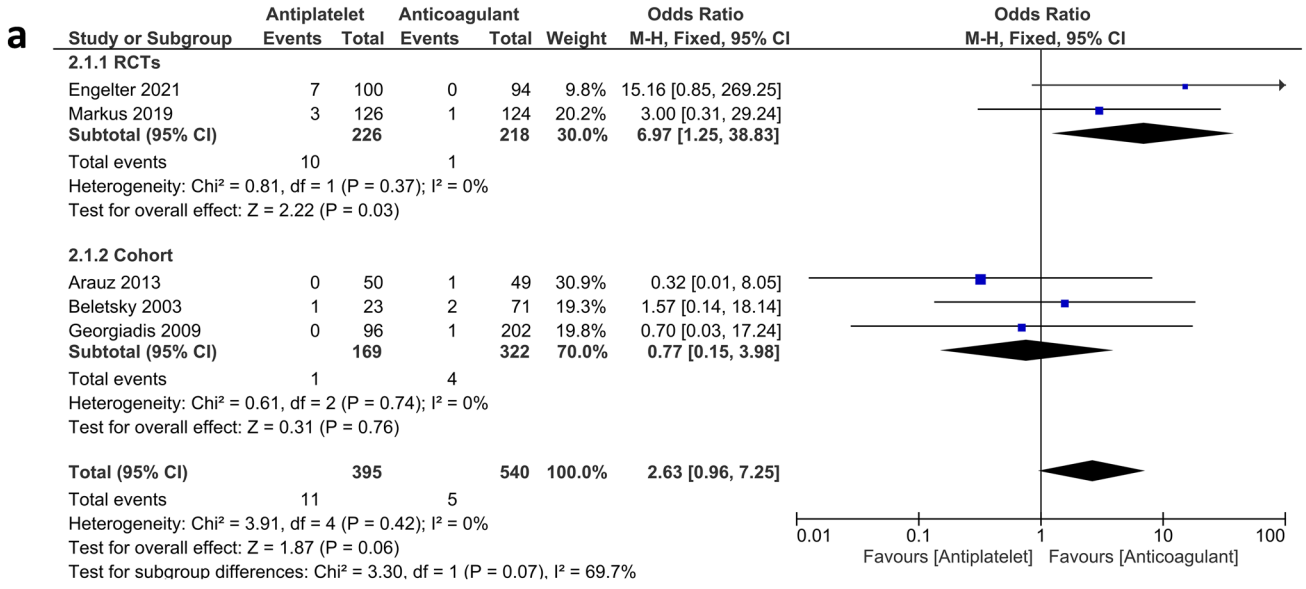

Fig. 4 **a** Forest plot of primary ischaemic stroke. **b** Forest plot of primary transient ischaemic attack (TIA)

3.4.6 Recurrent TIA

Five studies were included in the analysis ($N = 580$ patients). The analysis showed non-significant statistical differences between the groups (OR 0.93, 95% CI 0.44–1.98, $p = 0.85$), and the results were homogenous ($p = 0.78$; $I^2 = 0\%$) (Fig. 5b).

3.4.7 Symptomatic Intracranial Haemorrhage (sICH)

Three studies were included in the analysis ($N = 692$ patients). For the cohort studies ($N = 498$), there were no significant differences (OR 0.38, 95% CI 0.12–1.19, $p = 0.1$), and the results were homogenous ($p = 0.94$; $I^2 = 0\%$). In Engelter's RCT [9], there were no incidences of sICH (Fig. 6a).

3.4.8 Major Extra-Cranial Bleeding

Three studies were included in the analysis ($N = 539$ patients). There were no significant statistical differences between the groups (OR 0.45, 95% CI 0.09–2.30, $p = 0.34$), and the results were homogenous ($p = 0.64$; $I^2 = 0\%$). For the subgroup analysis, in the RCT by Engelter

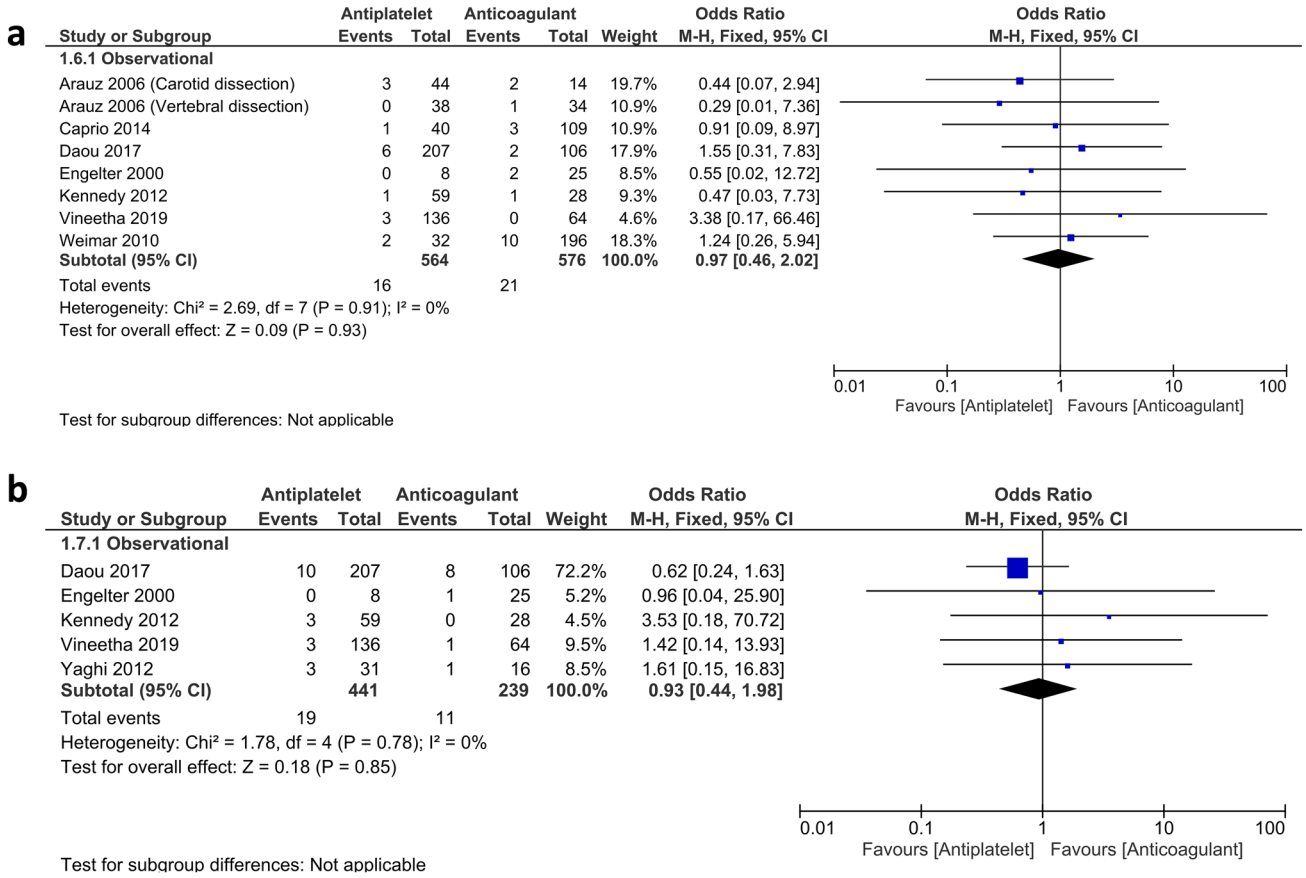

Fig. 5 **a** Forest plot of recurrent stroke. **b** Forest plot of recurrent transient ischaemic attack (TIA)

et al. [9] ($N = 194$ patients), there were no significant statistical differences between AP and AC (OR 0.31, 95% CI 0.01–7.71, $p = 0.48$). For the cohort studies, there were no significant statistical differences between AP and AC (OR 0.52, 95% CI 0.08–3.45, $p = 0.5$), and the results were homogenous ($p = 0.37$; $I^2 = 0\%$) (Fig. 6b).

3.4.9 Good Functional Outcome at 6 Months (mRS Score 0–2)

Six studies were included with a total of 803 patients. There were no significant statistical differences between the groups (OR 0.68, 95% CI 0.44–1.06, $p = 0.09$), and the results were homogenous ($p = 0.59$; $I^2 = 0\%$) (Fig. 7a).

3.4.10 Poor Outcome at 6 Months (mRS Score ≥ 3)

Six studies were included in the analysis with a total of 803 patients. The analysis showed marginally significant statistical differences between AC and AP (OR 1.56, 95% CI 1.00–2.42, $p = 0.05$), and the results were homogenous ($p = 0.49$; $I^2 = 0\%$) (Fig. 7b).

3.4.11 Total Adverse Events

Two studies were included in the analysis, accounting for 492 patients. The results showed no significant statistical differences between AP and AC (OR 0.60, 95% CI 0.32–1.15, $p = 0.12$), and the results were homogenous ($p = 0.89$; $I^2 = 0\%$). For the subgroup analysis, in the RCT by Engelter et al. [9], there were no significant statistical differences between AP and AC (OR 0.61, 95% CI 0.31–1.20, $p = 0.16$). For the cohort study by Georgiadis et al. [29], there were no significant differences (OR 0.52, 95% CI 0.06–4.73, $p = 0.56$). (see Online Supplementary Material (OSM) 1 and Fig. 8).

3.4.12 Complete Recanalization

Five studies were included with a total of 438 patients. There were no significant statistical differences between AP and AC (OR 0.70, 95% CI 0.46–1.06, $p = 0.09$), and the results were homogenous ($p = 0.23$; $I^2 = 29\%$). For the subgroup analysis, in the RCT by Markus et al. [10] ($N = 181$ patients), there were no significant statistical differences between AP and AC (OR 0.94, 95% CI 0.52–1.69, $p = 0.84$). For the cohort studies, there was a significant favouring of

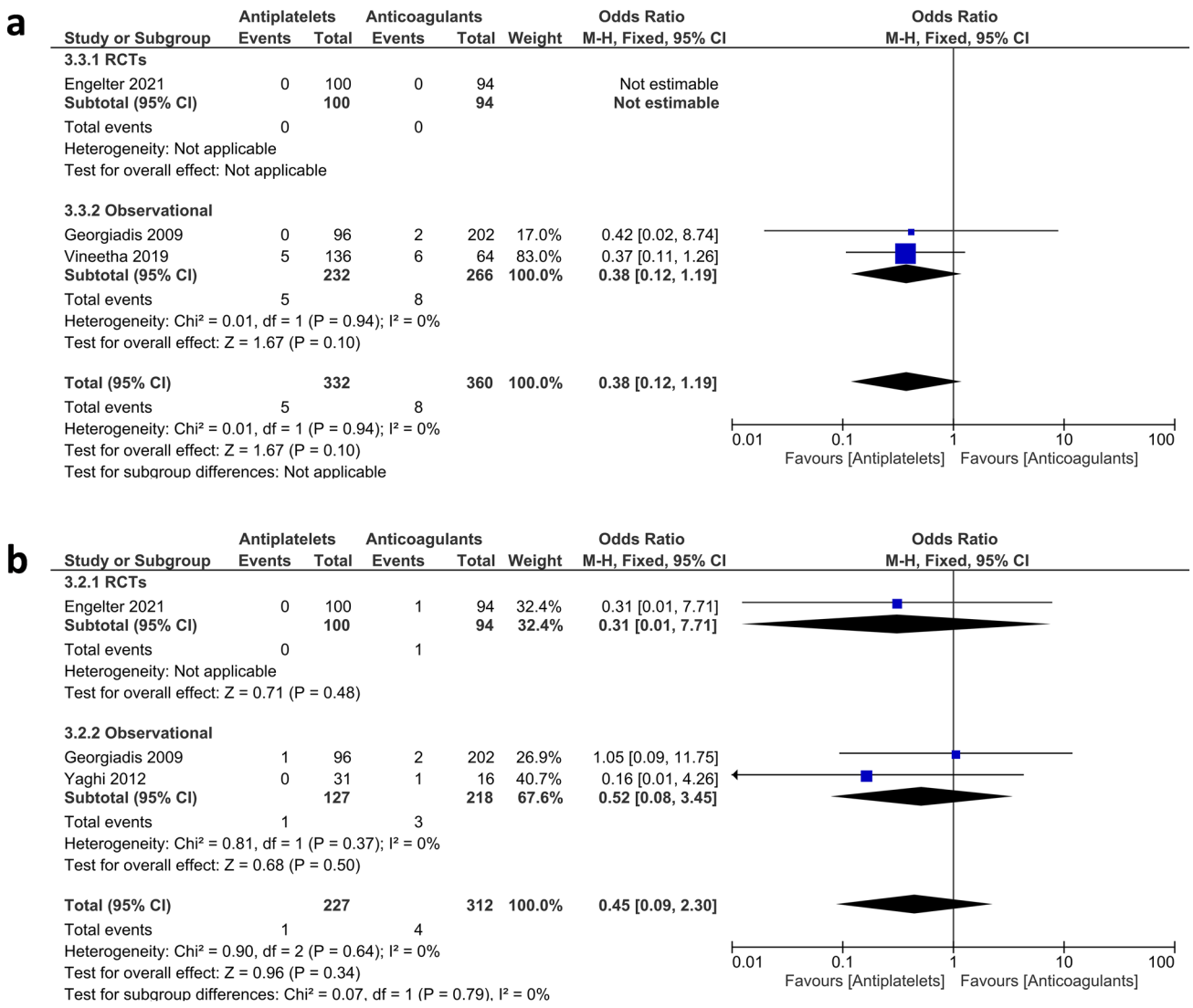

Fig. 6 **a** Forest plot of symptomatic Intracranial haemorrhage (ICH). **b** Forest plot of major extra-cranial bleeding

AC over AP (OR 0.52, 95% CI 0.29–0.94, $p = 0.03$), and the results were homogenous ($p = 0.35$; $I^2 = 8\%$) (OSM 1 and Fig. 9).

3.4.13 Other Outcomes

The analysis showed no significant statistical differences between the two groups in any of the major haemorrhagic complications (bleeding) ($p = 0.30$), all haemorrhagic complications ($p = 0.23$), admission mRS score 0–2 ($p = 0.97$), admission mRS score ≥ 3 ($p = 0.09$), seizures ($p = 1.00$), occlusion ($p = 0.30$), stenosis ($p = 0.60$), time from baseline MRI to follow-up MRI (days) ($p = 0.75$), and patients with new DWI lesions ($p = 0.66$). (OSM 1 and Figs. 10–14, respectively).

4 Discussion

CeAD is generally an uncommon cause of ischaemic stroke [8, 29], recurrent ischaemic events [15], and sICH [28], as compared with other aetiologies. However, it

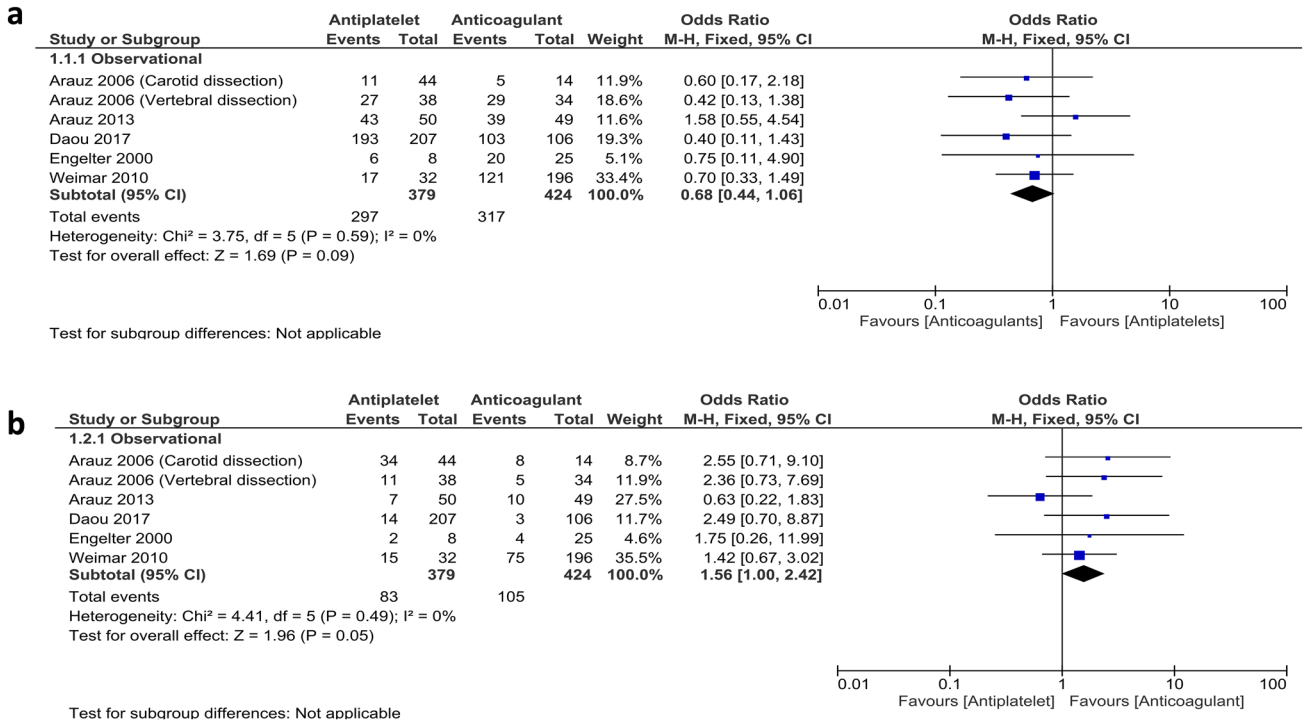

Fig. 7 **a** Forest plot of good functional outcome at 6 months (mRs = 0–2). **b** Forest plot of poor outcome at 6 months (mRs ≥ 3)

has been considered to be one of the common causes of cerebrovascular accidents in the younger population [10, 33]. Over the last two decades, advances in research have elucidated the natural history, pathophysiology and interventional management of CeAD [2, 14, 20, 34]. Nevertheless, clinical trials, reviews and metanalyses have failed to demonstrate the optimal medical management of CeAD [2, 14, 19, 20, 34, 35].

Evolving rationales in medical treatment of CeAD have varied from the expert-based trend of discouraging AP in preference for AC (based on the assumption that stroke occurs via thromboembolic phenomena) [36], to metanalysis and observational study-based favouring of AP (due to the observed haemorrhagic events induced by the AC and hypothesized mural wall haematoma progression because of the AC) [20, 37], versus fairly treating AP/AC on a neutral basis due to lack of any superior evidence for either therapy [14, 34]. A paradigm shift in AC/AP practice has taken place following the first randomized controlled and multicentre CADISS trial [2].

To date, there has been no change in clinical evidence from the CADISS trial, which concluded that AC and AP were not statistically different in terms of adverse effects and clinical outcomes, namely death, ischaemic stroke, TIA or haemorrhage [2, 10, 35].

In our study, we concluded that—at 6 months—there was no statistically significant difference between AC and AP in terms of morbidity (TIA, recurrent strokes, recurrent TIAs, new strokes, sICH, major intracranial bleeding), total adverse events, complete recanalization and mortality, apart from the significant favouring of AC for cases of ischaemic stroke, which is considered a relatively different finding from other trials and was in agreement with findings from Vineetha et al. [11].

Although the consistently negative results may carry an apparent reproducibility among the AC–AP comparative studies, it is very important to recall similar consistently negative trials that later revealed superiority outcomes, such as the WASID trial (Warfarin-Aspirin Symptomatic Intracranial Disease) [38]. Although the scope of the WASID trial is not related to the context of dissection, we speculate that some analogy could be learnt in terms of the research methodology. Prior to the WASID trial, studies testing AC versus AP for intracranial artery stenosis had initial spurious non-significant results due to multiple flaws not initially taken into consideration [39, 40]. The global versus restricted definition of ICH as well as the lack of specification for the exact dosage and scheduling of both AC/AP were among the most striking issues that the WASID investigators utilized to turn the management from a negative trial to supportive evidence for AP in patients suffering from intracranial arterial stenosis (besides increasing the sample size) [38].

Similarly, there are noteworthy areas of conflict that could possibly contribute to the 'statistically' comparable AC/AP profiles in CeAD patients, regardless of the inadequate sample size. As mentioned earlier, the included RCTs had a high risk of bias for allocation concealment, and blinding of both participants and personnel, in addition to high risk of bias for outcome assessment blinding and high risk of other bias [9, 10].

We assume that the following two potential domains for bias need to be addressed more precisely in future trials:

1) *The definition of true dissection-related stroke (DRS):*
   In most of the studies, the definition of DRS was vague, and in some of the cases they were diagnosed merely on the basis of clinical evaluation or telephone surveys [10], in addition to the fact that many of the participants had co-morbidities that could also have caused the stroke, so this may have masked the real picture of genuine dissection-caused strokes [10, 29]. In a few studies, for example in the study of Geniscke et al. [28], the DRS was clearly defined, yet the sample size was low, giving a spuriously elevated percentage of stroke in the 74 patients in addition to the widened confidence intervals [11]. Added to that is the fact that the short-term 5-day MRI-based follow-up and the sole clinical follow up at 6 months have contributed to the vague nature of the stroke (whether ischaemic or haemorrhagic) [28], raising the need for larger population studies with a combined clinical-radiologic definition of ischaemic stroke spectra (territory, size and angiographic data) along the whole follow-up duration [9].
2) *The AP/AC scheduling:*
   Though there was a statistically significant AC–AP difference in terms of ischaemic stroke occurrence in our study, this finding should be interpreted with caution, as it is very important to recall the myriad of medication-related biases in terms of incomplete adjustment for the confounding effect of AP–AC doses, frequencies and compliance with administration, which should be taken into consideration as they may greatly influence the outcome difference. There are few studies that clearly stated these exact AC/AP full details, including the dose, duration of therapy, use of dual versus single AP therapy, and the compliance profile [9, 34]. Engelter et al. [9] were among the few investigators who clearly revealed the baseline medication data, including doses of 100–300 mg for the APs and the 2–3 INR-guided ACs.

   Moreover, there were methodologic variations with regard to the inclusion criteria for AP/AC selective administration. In some studies, APs were prescribed for sizable stroke cases mainly, in contrast to the TIA-presenting patients who were prescribed ACs [34]. In other trials, most patients with severe carotid stenosis were enrolled in the non-vitamin K-dependent new oral anticoagulants (NOACs) group [26]. To complicate the situation more, some studies, including the CADISS trial itself, had a final treatment design based on the treating physician's discretion [8, 10]. To sum up, fully detailed medication scheduling data are of utmost importance in future randomized studies, being as important as the consideration of a statistically powerful sample size.

   Other areas of conflict that need to be considered in future trials include: (1) the homogenization and prolongation of follow-up duration for AC/AP arms [15, 17, 27], as a relatively short and variable follow-up duration could act as a possible cause of conflicting results [10, 15, 17, 27]; (2) a more structured inclusion of relevant study subsets, such as paediatric populations [27], patients presenting with non-stroke-related local symptoms, and cases suffering from dissection-related retinal ischaemia [29]; and (3) suggesting more individualized AP/AC management paradigms for traumatic versus spontaneous aetiologies [27], patients presenting with vascular occlusion [28], patients with aspirin intolerance [10], and intracranial versus extracranial dissection locations [10, 27].

4.1 Strengths

Despite the existence of published meta-analyses across observational studies that yielded inconclusive results, our findings appeared to be more conclusive. We aimed to perform a high-quality study to avoid previous limitations. These include, and are not limited to, our inclusion of RCTs as subgroup analysis. Others include: (1) Our inclusion of high-quality observational studies, as low quality or variation in quality appeared to affect the results of previous studies. This is supported by what Sarikaya et al. [20] stated, "Results of our overall analysis suggest an advantage of antiplatelets over anticoagulants on nearly all outcomes,… Stratified analyses according to methodological quality showed less pronounced advantages of antiplatelets in studies of higher methodological quality, with point estimates nearer the line of no difference at 1 and credibility intervals compatible with both relevant advantages and disadvantages of antiplatelets over anticoagulants". (2) The previous studies had small sample sizes and were subjected to selection bias, which is also stated in one of those studies. (3) Some of the previous meta-analyses [41, 42] included studies that had different main aims, therefore, their results and conclusions were not as focused and conclusive as ours.

A meta-analysis across both RCTs and observational studies has recently been published [43]. Their results were consistent with ours, therefore, supporting our methodology and data. However, what differs and adds more value to our study is that we analysed new outcomes, which included the

intervention's influence on imaging-based outcomes (such as new ischaemic lesions on DWI sequences). Moreover, we analysed death in a long-term follow-up, which was previously reported as a limitation in some studies.

To recapitulate, our study did not show a considerable difference between the two groups. However, some important variables were reported in a few studies; for example, death and primary ischaemic stroke were only reported in five studies. Also, primary TIA was reported in only four studies. However, all of them exceeded the minimal sample size needed to meet the required statistical constraints. Still, we recommend more well-designed clinical trials to assess if unnecessary anticoagulation can be avoided in CeAD.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40268-022-00398-z.

Declarations

Funding No external funding was used in the preparation of this article.

Conflicts of interest/competing interests Abdulrahman Ibrahim Hagrass, Bashar Khaled Almaghary, Mohamed Abdelhady Mostafa, Mohamed Elfil, Sarah Makram Elsayed, Amira A. Aboali, Aboalmagd Hamdallah, Mohammed Tarek Hasan, Mohammed Al-kafarna, Khaled Mohamed Ragab and Mohamed Fahmy Doheim declare that they have no potential conflicts of interest that might be relevant to the content of this article.

Ethical approval Not applicable.

Availability of data and material The data that support the findings of this study are available on request from the corresponding author.

Registration and protocol Our study's PROSPERO Registration number is CRD42022338493.

Code availability Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Author contributions Conception and design of the work by KMR, and MFD. Selection process and data collection by BKA, MA, MTH, AAA and AIH. Data analysis and interpretation by AH and KMR. Drafting the article by MAM and SME. Critical revision and editing of the article by AIH, MFD and ME.

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