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REVIEW

Antithrombotic Treatment for Acute Extracranial Carotid Artery Dissections: A Meta-Analysis

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WHAT THIS PAPER ADDS

The article summarises a meta-analysis of antithrombotic treatment for extra cranial carotid artery dissections and concludes that there is no clear evidence for one type of treatment over another. In short, medical treatment lies at the discretion of the treating surgeon.

Introduction: Carotid artery dissection is a leading cause of stroke in younger patients, with an associated prevalence of 2.6–3.0 per 100,000 population. This meta-analysis aims to determine whether in patients managed medically, treatment with anticoagulants or antiplatelet agents was associated with a better outcome with respect to mortality, ischaemic stroke, and major bleeding episodes.

Patients and methods: A comprehensive search strategy was employed of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (January 1966 to March 2015), and EMBASE (January 1980 to March 2015) databases. Primary outcomes were death (all causes) or disability. Secondary outcomes were ischaemic stroke, symptomatic intracranial haemorrhage, and major extracranial haemorrhage during the reported follow-up period.

Results: No completed randomized trials were found. Comparing antiplatelets with anticoagulants across 38 studies (1,398 patients), there were no significant differences in the odds of death (effects size, ES, −0.007, $p = .871$), nor in the death and disability comparison or across any secondary outcomes.

Conclusion: There were no randomised trials comparing either anticoagulants or antiplatelets with control, thus there is no level 1 evidence to support their routine use for the treatment of carotid artery dissection. Also, there were no randomised trials that directly compared anticoagulants with antiplatelet drugs, and the reported non-randomised studies did not show any evidence of a significant difference between the two.

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INTRODUCTION

The incidence of carotid artery dissection (CAD) is quoted as 2.6–3.0 per 100,000 population,[1] although the true incidence may be higher as many remain undiagnosed.[2] CAD is the most common cause of stroke in males under 45 years of age,[3] and has an associated mortality of up to 5% with a full resolution occurring in excess of 90% of cases.[4] CAD is associated with trauma, aneurysm, hypertension, and atherosclerosis.[5] Presentation can vary from incidental findings of asymptomatic disease to cerebrovascular events, regional pain, and Horner's syndrome.

Although recent developments in noninvasive imaging have led to more frequent diagnoses, there is no consensus or high-level evidence on optimal management. Management strategies are aimed predominantly at limiting progression of dissection, preventing thromboembolic complications and maintaining cerebral perfusion.[1] The majority of patients are managed by antithrombotic treatment through anticoagulation or antiplatelet therapy,

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although endovascular intervention or surgery may be considered on an individualised basis.[1]

The aim of this study is to compare anticoagulation and antiplatelet treatment outcomes including death, ischaemic stroke, and intra- and extra-cranial haemorrhage in patients with extracranial carotid artery dissection using meta-analysis techniques.

METHODS

An electronic search was undertaken using the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (January 1966 to March 2015), and EMBASE (January 1980 to March 2015) databases. The search employed the term(s) "Carotid dissection," which was combined with each of the following Boolean operators: "antiplatelet," "anticoagulation," "extracranial." Abstracts of the citations identified by the search were then scrutinised by two authors to determine eligibility for inclusion in the analysis (MC, CS). The Cochrane Stroke Group Trials Register was also searched for relevant studies. Comprehensive searches were carried out and relevant papers were also interrogated for additional eligible studies including recent review papers. The search method adhered to the PRISMA statement for reporting systematic reviews (Fig. 1).[6] Outcome measures identified included death from all cause, death and disability, ischaemic strokes, symptomatic intracranial haemorrhage, and major extracranial haemorrhage.

All forms of trials and studies including at least 10 patients with carotid artery dissection that allowed comparisons between antiplatelet therapy and anticoagulation for the treatment of CAD were deemed eligible for inclusion. Any study analysing only one form of antithrombotic therapy was excluded. Further exclusion criteria included studies involving less than 10 patients, review articles, duplicate data (only the most recent series was included), and studies where no division was made between carotid and vertebral artery dissections. Patients with severe infarction (defined in line with the Modified Rankin Scale as severe disability, requiring constant nursing care and attention, bedridden, incontinent) or with significant co-morbidity that were not given any antithrombotic therapy were also excluded from the analysis. Data were collected by two authors (MC, CS) and the quality of the non-randomised studies was assessed using the Newcastle-Ottawa Scale (NOS) (Fig. 2). The NOS is primarily formulated by a point allocation system, assigning a maximum of nine points for the risk of bias in three areas: (i) selection of study groups (four points), (ii) comparability of groups (two points), and (iii) outcomes and/or exposure for cohort studies and case-control studies (two points). Studies looking at surgical intervention were not included in the analysis, because of a lack of substantial data.

Information was sought regarding diagnosis, clinical presentation, and diagnostic findings. All studies that

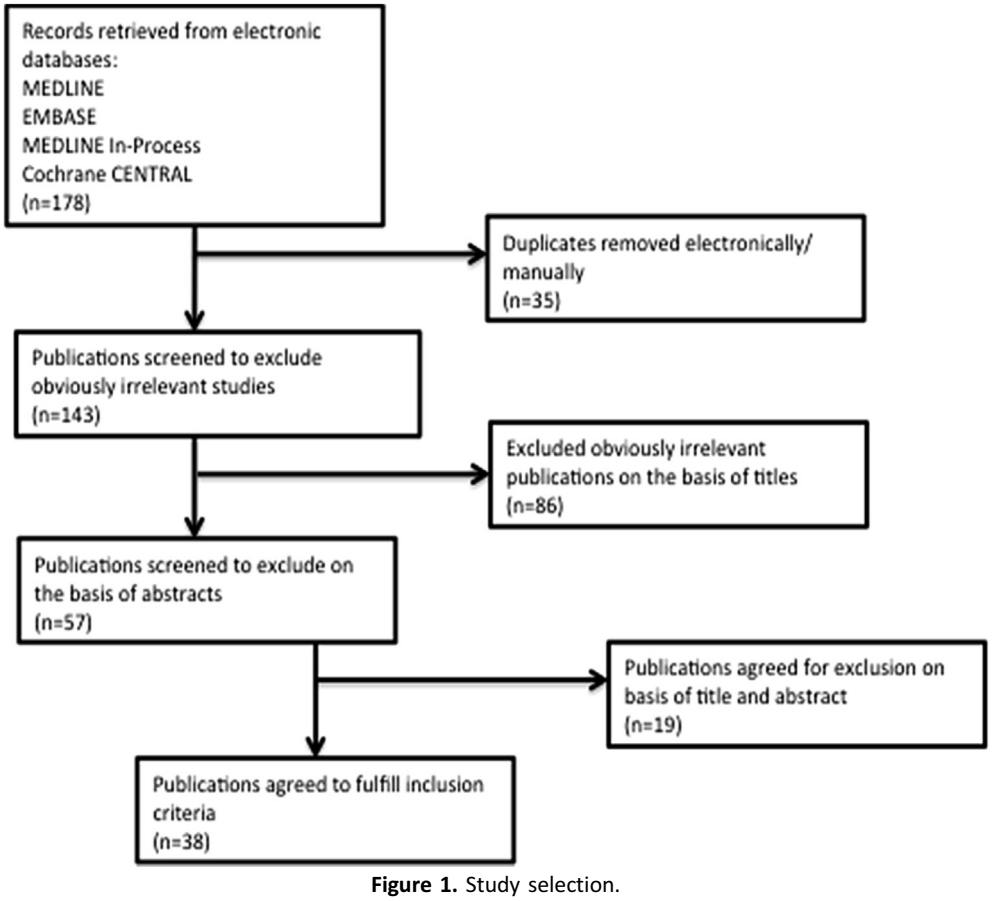

Figure 1. Study selection.

STUDY	SELECTION	COMPARABILITY	OUTCOME
Arauz 2006 (12)	★★★	★★	★★★
Ast 1993 (13)	★★	★★	★★
Biller 1986 (14)	★★	★★	★
Biousse 1998 (15)	★★	★	★★
Bogousslavsky 1987 (16)	★★	★★	★★★
Campos 2007 (17)	★★★	★★	★★
Caso 2004 (18)	★★★	★★	★★★
Chen 1984 (19)	★★★	★★	★★
Colella 1996 (20)	★★	★★	★★★
De Bray 1989 (21)	★★★	★★	★★
Dziewas 2003 (22)	★★★	★★	★
Eachempati 1998 (23)	★★★	★★	★★★
Eljamel 1990 (24)	★★	★★	★
Engelter 2000 (25)	★★★	★	★
Friedman 1980 (26)	★★	★★	★★
Georgiadis 2009 (27)	★★★★	★★	★★★
Gonzales-Portillo 2002 (28)	★★	★★	★
Kaps 1990 (29)	★★★	★★	★★
Kennedy 2012 (30)	★★**	★★	★★★
Landre 1987 (31)	★	★★	★
Lepojarvi 1988 (32)	★★★	★★	★
Li 1994 (33)	★★	★	★★
Luken 1979 (34)	★	★★	★★
Marx 1987 (35)	★★	★★	★★
Metso 2009 (36)	★★★	★★	★★★
Miller-Fisher 1978 (37)	★★	★★	★★
Mokri 1986 (38)	★★	★	★★★
Miller-Forell 1989 (39)	★★	★	★★★
Pieri 2007 (40)	★★★★	★★	★★
Rao 2011 (41)	★★★★	★★	★★
Richaud 1980 (42)	★★	★★	★
Schievink 1990 (43)	★★★	★★	★
Sellier 1983 (44)	★★	★	★★
Touze 2003 (45)	★★★	★★	★
Trieman 1996 (46)	★★★	★★	★★
Vanneste 1984(47)	★★	★	★★★
Wahl 2002 (48)	★★★	★★	★
Zelenock 1982 (49)	★	★★	★★

Figure 2. The Newcastle-Ottawa Scale (NOS) for study quality assessment.

reported at least one primary outcome comparing patients treated with anticoagulation versus those treated with antiplatelet therapy were included. Studies that did not have follow-up data or studies that had ambiguity surrounding treatment data were excluded from analysis. There was no stipulation on the type of imaging modality used to determine the diagnosis of CAD, which was derived from the visualisation of findings consistent with carotid artery dissection: irregularity of the vessel wall, angiographic string sign, pseudoaneurysm formation, and double barrel lumen.

Antithrombotic therapy (antiplatelet agent (AP) or anticoagulation (AC)) was defined as administration of any antiplatelet agent (AP, i.e. acetylsalicyclic acid, clopidogrel dipyridamole) or anticoagulation (AC, oral coumarin or therapeutic dose heparins). Patients were classified as being AP or AC based on their initial treatment modality. Regarding bleeding complications, a clear distinction was made to assess the first antithrombotic agent used, and not include patients who subsequently went on to receive thrombolysis as a treatment modality. Any form of surgery precluded the patient in the formal analysis.

Statistical analysis

To estimate treatment effects, data from non-randomised studies were analysed. The outcome measures of interest were obtained from studies that were deemed eligible. Studies that did not have follow-up data or studies that had ambiguity surrounding treatment data were excluded from analysis. An arcsine difference was used in the meta-analysis in conjunction with the Rucker conservative variance formula.[7] The attraction of this method is the

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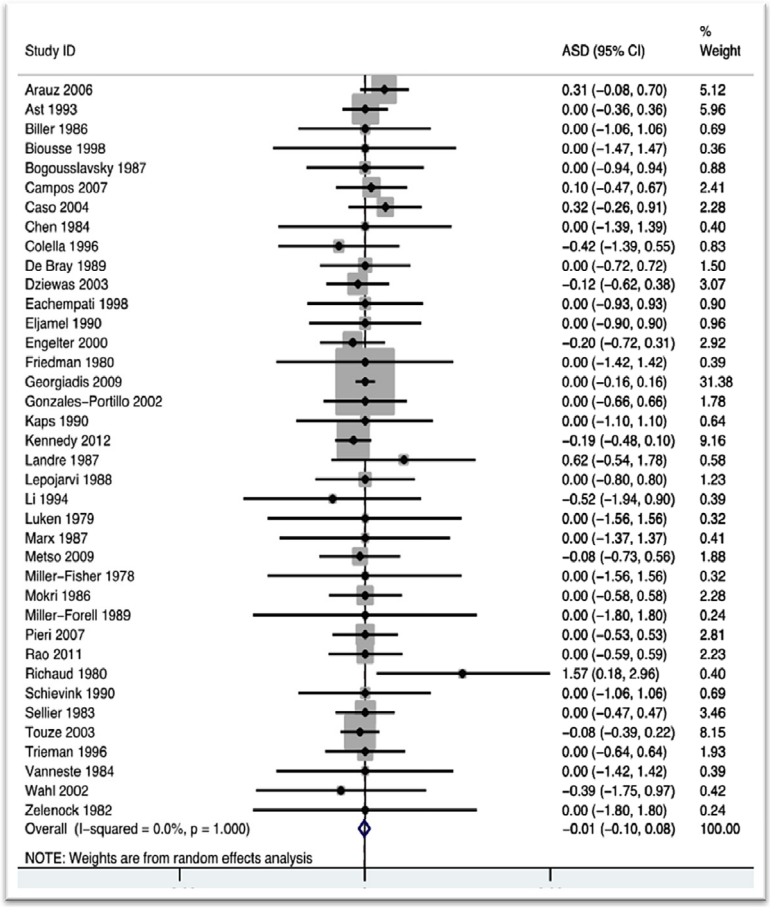

B

STUDY	Antiplatelet	Anticoagulation
Arauz 2006	4/44	0/14
Ast 1993	0/21	0/30
Biller 1986	0/5	0/1
Biousse 1998	0/1	0/3
Bogousslavsky 1987	0/2	0/21
Campos 2007	1/6	3/30
Caso 2004	1/10	0/9
Chen 1984	0/5	0/1
Colella 1996	0/2	2/12
De Bray 1989	0/4	0/14
Dziewas 2003	0/7	1/71
Eachempati 1998	0/3	0/5
Eljamel 1990	0/4	0/4
Engelter 2000	0/8	1/25
Friedman 1980	0/1	0/4
Georgiadis 2009	0/96	0/202
Gonzales-Portillo 2002	0/5	0/14
Kaps 1990	0/2	0/4
Kennedy 2012	0/66	1/30
Landre 1987	1/3	0/2
Lepojarvi 1988	0/4	0/7
Li 1994	0/1	1/4
Luken 1979	0/2	0/1
Marx 1987	0/1	0/6
Metso 2009	0/4	1/140
Miller-Fisher 1978	0/1	0/2
Mokri 1986	0/9	0/10
Miller-Forell 1989	0/1	0/1
Pieri 2007	0/10	0/14
Rao 2011	0/54	0/40
Richaud 1980	1/1	0/5
Schievink 1990	0/5	0/2
Sellier 1983	0/13	0/16
Touze 2003	0/18	2/279
Trieman 1996	0/6	0/12
Vanneste 1984	0/1	0/4
Wahl 2002	0/1	1/7
Zelenock 1982	0/1	0/1
TOTAL	**8**	**13**

Figure 3. (A) Comparison of AP and AC: Death from all cause. (B) Breakdown of comparison of AP and AC: Death from all cause.

asymptotically variance-stabilising transformation for the binomial distribution. Although not frequently used for meta-analyses, it is a validated analysis method for clinical data with binary endpoints and should in fact be used when the event in question is rare.[7]

RESULTS

A total of 178 papers were retrieved from electronic database searches, as outlined above. Thirty-five of the 178 papers were duplicates, so were removed from the end number. Eighty-six of the remaining 143 papers were obviously irrelevant publications — based primarily on the title (i.e. intra-cranial carotid, vertebral arteries). A further analysis of the abstracts meant that a further 19 papers were excluded. This left 38 papers that fulfilled the inclusion criteria (see Supplemental data).[12–49] All studies included in the analysis were observational case series. In the majority of studies, treatment decisions were made on an individualised basis and did not follow a prescribed protocol. There was an overall mean clinical follow-up of 17.7 months (range 1—72 months).

Primary outcomes

Death from all causes. Thirty-eight studies were analysed with 1,475 patients (428 antiplatelet (AP) and 1,047 anticoagulation (AC)) (Fig. 3A, B). A total of 21 (1.42%) patients had died by the end of the follow-up period. Patients with severe infarction or with significant comorbidity and therefore not treated with antithrombotic therapy, equating to 56, were not included in the analysis (separate from the 1,475 patients). Using the arcsine difference, the effects size was −0.007 with a 95% CI ranging from −0.095 to 0.081 ($p = .871$), indicating neither harm nor benefit of anticoagulation versus antiplatelet with respect to death during the follow-up period. There was no significant heterogeneity between the included series ($I^2 = 0\%$; $T^2 = 0\%$).

Death and disability. Twenty eight studies were analysed equating to 653 patients (254 AP and 399 AC) (Fig. 4A, B). Analysis showed there to be no benefit of antiplatelet therapy when compared to anticoagulation (ES −0.006, 95% CI −0.157 to 0.146; P = 0.940). There was no significant heterogeneity between the included series ($I^2 = 9.9\%$; $T^2 = 0.0155\%$).

Secondary outcomes

Ischaemic stroke. Thirty-six studies with 1,452 patients (420 AP and 1032 AC) reported on ischaemic strokes at the end of the follow-up period (Fig. 5A, B). Twenty-four patients (1.75%) suffered an ischaemic stroke. For 16 of the 24 patients, data on time of event was available. Ten of the 16

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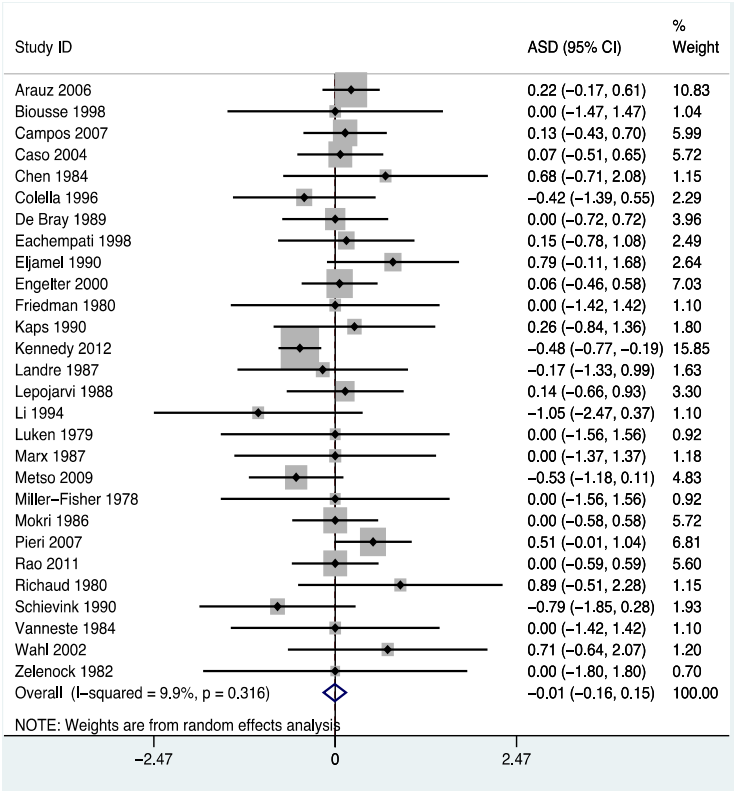

B

STUDY	Antiplatelet	Anticoagulation
Arauz 2006	34/44	8/14
Biousse 1998	0/1	0/3
Campos 2007	3/6	11/30
Caso 2004	4/10	3/9
Chen 1984	2/5	0/1
Colella 1996	0/2	2/12
De Bray 1989	0/4	0/14
Eachempati 1998	1/3	1/5
Eljamel 1990	2/4	0/4
Engelter 2000	2/8	5/25
Friedman 1980	0/1	0/4
Kaps 1990	1/2	1/4
Kennedy 2012	0/66	0/30
Landre 1987	1/3	1/2
Lepojarvi 1988	1/4	1/7
Li 1994	0/1	3/4
Luken 1979	0/2	0/1
Marx 1987	0/1	0/6
Metso 2009	0/4	36/140
Miller-Fisher 1978	0/1	0/2
Mokri 1986	0/9	0/10
Pieri 2007	5/10	1/14
Rao 2011	0/54	0/40
Richaud 1980	1/1	2/5
Schievink 1990	0/5	1/2
Vanneste 1984	0/1	0/4
Wahl 2002	1/1	4/7
Zelenock 1982	0/1	0/1
TOTAL	**58**	**80**

Figure 4. (A) Comparison of AP and AC: Death and disability. (B) Breakdown of comparison of AP and AC: Death and disability.

patients developed their stroke within 8 days of treatment being started. The stroke rate in the anticoagulation group was 1.74% (18/1,032) and 1.43% (6/420) in the AP group. The ES of −0.047 (95% CI −0.136 to 0.042, $p = .30$) indicated no significant difference between treatment options. There was no significant heterogeneity between the included series ($I^2 = 0\%$; $T^2 = 0\%$).

Symptomatic intracranial haemorrhage. Twenty-seven studies with 1,075 patients (378 AP and 697 AC) provided data about symptomatic intracranial haemorrhage stratified on the type of antithrombotic treatment (Fig. 6A, B). Symptomatic intracranial haemorrhages occurred only in the AC group and were present in five of 697 patients (0.72%). The ES of −0.045 with a 95% CI of −0.142 to 0.052 indicated no significant difference between the treatment options ($p = .364$). There was no significant heterogeneity between the included series ($I^2 = 0\%$; $T^2 = 0\%$).

Major extracranial haemorrhage. Analysis in respect of major extracranial haemorrhage was based on 14 studies involving 812 patients (317 AP and 495 AC) (Fig. 7A, B). Major extracranial haemorrhages occurred only in the AC group and were present in seven of 495 patients (1.42%). The ES of −0.058 with a 95% CI of −0.166 to 0.049 indicated no significant difference between the treatment options ($p = .289$). There was no significant heterogeneity between the included series ($I^2 = 0\%$; $T^2 = 0\%$).

DISCUSSION

CAD is the major cause of ischaemic stroke in young individuals, but currently there are no randomized trials available to assess the effects of anticoagulation versus antiplatelets for such patients. This meta-analysis showed no differences with regard to outcome or complication rates when comparing therapeutic anticoagulation with antiplatelet therapy. Specifically, there was no significant difference in observed mortality with low mortality rates observed when compared with more historical data.[8] When determining both ischaemic and haemorrhagic stroke rate, again no significant differences were seen although the point estimate of 1.04 when assessing ischaemic stroke suggests a potential trend towards a superiority of antiplatelet therapy. Bleeding-related complications were rare but did occur exclusively in the AC group of patients and it is likely the small sample size that prevents a statistical significance being seen. This is in keeping with results seen in other studies.[9]

The analysis excluded patients who presented with severe infarction or with significant comorbidity across the studies analysed, as no forms of antithrombotic medication were given and as such did not meet the inclusion criteria. Therefore, the estimated death rate of this review may not reflect not the entirety of CAD patients but only of patients who are well enough to receive any kind of antithrombotic treatment. A series of 55 dissection patients gives a mortality rate over a 3-month period to be 5.5%.[10] This is certainly higher than the calculated risk of 0.081%.

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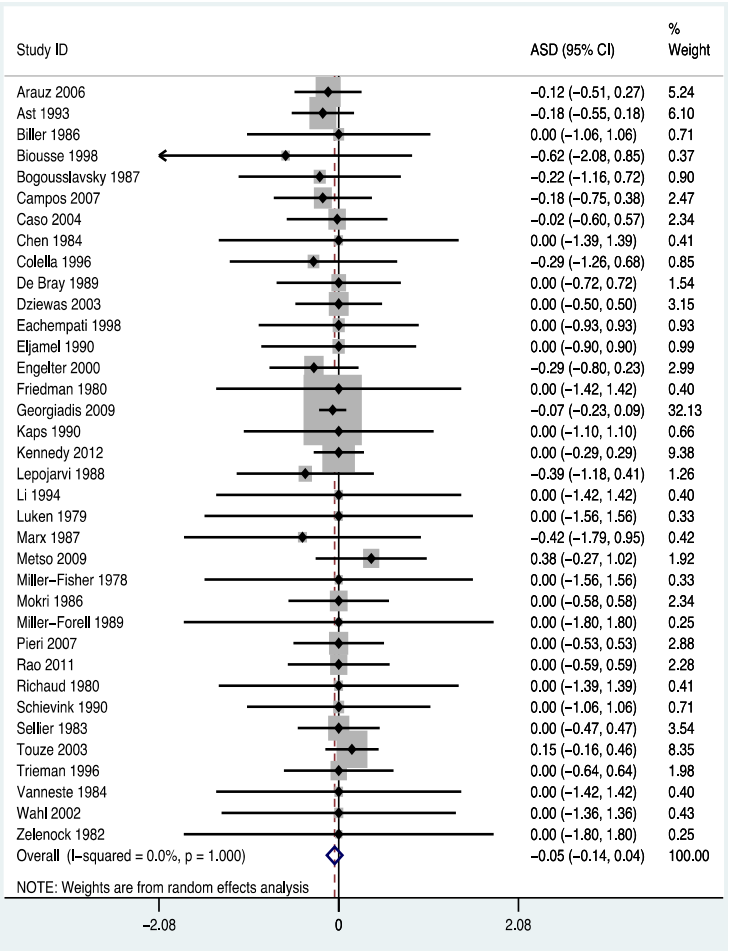

B

STUDY	Antiplatelet	Anticoagulation
Arauz 2006	3/44	2/14
Ast 1993	0/21	1/30
Biller 1986	0/5	0/1
Biousse 1998	0/1	1/3
Bogousslavsky 1987	0/2	1/21
Campos 2007	0/6	1/30
Caso 2004	1/10	1/9
Chen 1984	0/5	0/1
Colella 1996	0/2	1/12
De Bray 1989	0/4	0/14
Dziewas 2003	0/7	0/71
Eachempati 1998	0/3	0/5
Eljamel 1990	0/4	0/4
Engelter 2000	0/8	2/25
Friedman 1980	0/1	0/4
Georgiadis 2009	0/96	1/202
Kaps 1990	0/2	0/4
Kennedy 2012	0/66	0/30
Lepojarvi 1988	0/4	1/7
Li 1994	0/1	0/4
Luken 1979	0/2	0/1
Marx 1987	0/1	1/6
Metso 2009	1/4	3/140
Miller-Fisher 1978	0/1	0/2
Mokri 1986	0/9	0/10
Miller-Forell 1989	0/1	0/1
Pieri 2007	0/10	0/14
Rao 2011	0/54	0/40
Richaud 1980	0/1	0/5
Schievink 1990	0/5	0/2
Sellier 1983	0/13	0/16
Touze 2003	1/18	2/279
Trieman 1996	0/6	0/12
Vanneste 1984	0/1	0/4
Wahl 2002	0/1	0/7
Zelenock 1982	0/1	0/1
TOTAL	**6**	**18**

Figure 5. (A) Comparison of AP and AC: Ischaemic stroke. (B) Breakdown of comparison of AP and AC: Ischaemic stroke.

Furthermore, when assessing the outcome of death or disability, no obvious superiority between anticoagulation and antiplatelet therapy was observed. although the narrow confidence interval (−0.157 to 0.146) indicates that any effect could be smaller.

A further limitation to this analysis was the inadequacy of the papers to comment on the severity of cerebrovascular events. This is important as it may have influenced the type of antithrombotic used and combination, such as dual antiplatelet therapy, which is predominantly related to local policies and individual patient factors. The focus of the included studies varied widely and general outcome analysis was not uniformly applicable, and a number of potential biases warrant consideration. The data from non-randomised studies are recognised to be exposed to biases and the outcome parameters may be inadequately represented.[11] Furthermore, selection biases must be considered across the studies as doses of medication and methodology of blood pressure control were not homogenous. Treatment was largely decided by the treating physician rather than from defined treatment protocols. In addition, the sample size of the only outcome with a result close to significance (i.e. death or disability, $p = 0.06$) was much smaller than that of other outcomes, as several studies did not provide data about disability. A further limitation, with utilisation of the NOS, is the challenging point of an under-appreciation of confounding factors, presenting measurement challenges (e.g. the risk profile of patients, including blood pressure, family history).

This study has provided higher quality data using robust statistical analysis on this patient group. Ideally, the development of an international registry to log all the diagnostic approaches, therapeutic treatments, and pre-defined outcomes will allow for a higher quality data to be collated on this disease process and prognostic indicators. The Cervical Artery Dissection and Ischaemic Stroke Patients (CADISP) Group (CADISP, 2009) has initiated such a registry, preliminary results of which have been included in this analysis. Furthermore, a large randomised control trial comparing anticoagulants with antiplatelets in CAD is important and could solve the debate of whether to use immediate anticoagulation or not. A UK-based study is ongoing (CADISS, 2009) and preliminary results have been published.

Conclusion

Until large registry or level 1 evidence is available, the present data suggest that patients with CAD have equal

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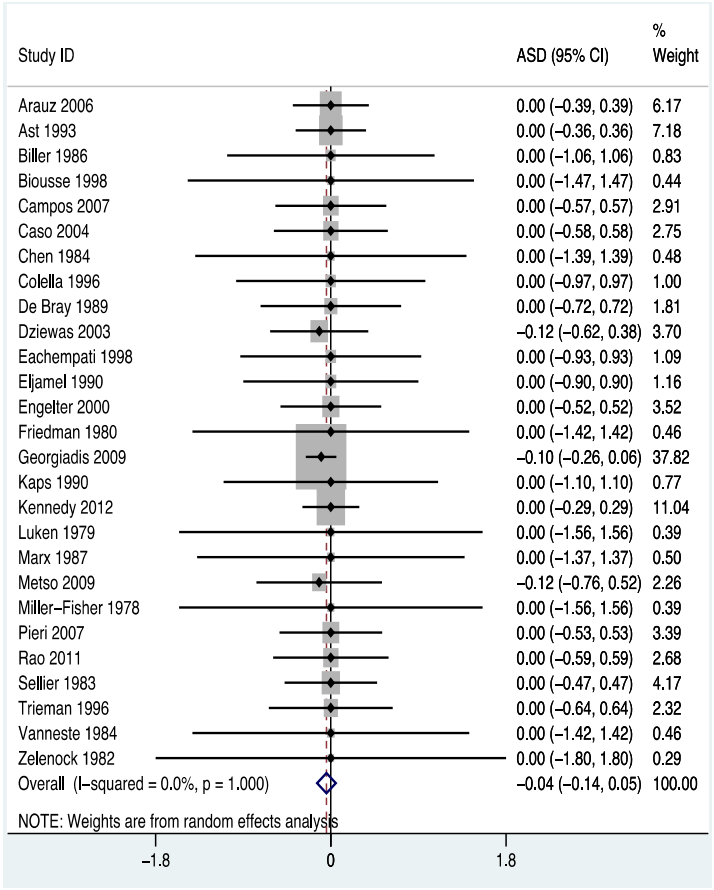

B

STUDY	Antiplatelet	Anticoagulation
Arauz 2006	0/44	0/14
Ast 1993	0/21	0/30
Biller 1986	0/5	0/1
Biousse 1998	0/1	0/3
Campos 2007	0/6	0/30
Caso 2004	0/10	0/9
Chen 1984	0/5	0/1
Colella 1996	0/2	0/12
De Bray 1989	0/4	0/14
Dziewas 2003	0/7	1/71
Eachempati 1998	0/3	0/5
Eljamel 1990	0/4	0/4
Engelter 2000	0/8	0/25
Friedman 1980	0/1	0/4
Georgiadis 2009	0/96	2/202
Kaps 1990	0/2	0/4
Kennedy 2012	0/66	0/30
Luken 1979	0/2	0/1
Marx 1987	0/1	0/6
Metso 2009	0/4	2/140
Miller-Fisher 1978	0/1	0/2
Pieri 2007	0/10	0/14
Rao 2011	0/54	0/40
Sellier 1983	0/13	0/16
Trieman 1996	0/6	0/12
Vanneste 1984	0/1	0/4
Zelenock 1982	0/1	0/1
TOTAL	**0**	**5**

Figure 6. (A) Comparison of AP and AC: Symptomatic intracranial haemorrhage. (B) Breakdown of comparison of AP and AC: Symptomatic intracranial haemorrhage.

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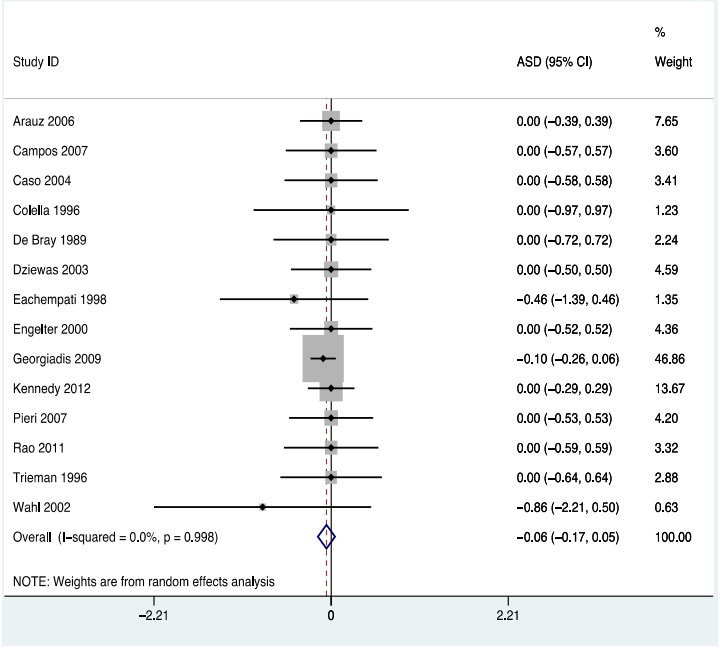

B

STUDY	Antiplatelet	Anticoagulation
Arauz 2006	0/44	0/14
Campos 2007	0/6	0/30
Caso 2004	0/10	0/9
Colella 1996	0/2	0/12
De Bray 1989	0/4	0/14
Dziewas 2003	0/7	0/71
Eachempati 1998	0/3	1/5
Engelter 2000	0/8	0/25
Georgiadis 2009	0/96	2/202
Kennedy 2012	0/66	0/30
Pieri 2007	0/10	0/14
Rao 2011	0/54	0/40
Trieman 1996	0/6	0/12
Wahl 2002	0/1	4/7
TOTAL	**0**	**7**

Figure 7. (A) Comparison of AP and AC: Major extracranial haemorrhage. (B) Breakdown of comparison of AP and AC: Major extracranial haemorrhage.

outcomes whether treated with antiplatelet agents or anticoagulation, and, as such, treatment lies at the discretion of the treating physician and on a case-by-case basis. Evidence suggests that patients derive no greater benefit from one treatment over the other. The main limitation of this analysis is the gap in the literature for randomised controlled trials and, therefore, the completion of such trials is warranted.

CONFLICT OF INTEREST

None.

FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this chapter can be found at http://dx.doi.org/10.1016/j.ejvs.2015.04.034.

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