SYSTEMATIC REVIEW

Editor's Choice – Peri-Operative Outcomes of Carotid Endarterectomy are Not Improved on Dual Antiplatelet Therapy *vs.* Aspirin Monotherapy: A Systematic Review and Meta-Analysis

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WHAT THIS PAPER ADDS

This meta-analysis, with improved statistical methodology over previous meta-analyses of single *vs.* dual antiplatelet therapy (DAPT) for carotid endarterectomy (CEA), indicates that at the time of CEA in symptomatic or asymptomatic patients with carotid stenosis, peri-operative DAPT has no effect on the occurrence of the ischaemic CEA complications *vs.* peri-operative aspirin single antiplatelet therapy (SAPT). However, DAPT does result in an increase of haemorrhagic CEA complications. At the time of CEA, surgeons should consider SAPT rather than DAPT, but the overall quality of the evidence is poor.

Objective: A systematic review and meta-analysis of the peri-operative outcomes of carotid endarterectomy (CEA) on dual antiplatelet therapy (DAPT) *vs.* aspirin monotherapy was carried out, to determine optimal peri-operative management with these antiplatelet agents.

Data sources: The Web of Science, Pubmed, and Embase databases were searched from inception to July 2021. The corresponding authors of excluded articles were contacted to obtain additional data for possible inclusion.

Review methods: The main outcomes included ischaemic complications (stroke, transient ischaemic attack [TIA], and transcranial Doppler [TCD] measured micro-emboli), haemorrhagic complications (haemorrhagic stroke, neck haematoma, and re-operation for bleeding), and composite outcomes. Pooled estimates using odds ratios (ORs) were combined using a random or fixed effects model based on the results of the chi square test and calculation of I^2.

Results: In total, 47 411 patients were included in 11 studies, with 14 345 (30.2%) receiving DAPT and 33 066 (69.7%) receiving aspirin only. There was no significant difference in the rates of peri-operative stroke (OR 0.87, 95% confidence interval [CI] 0.72 — 1.05) and TIA (OR 0.78, 95% CI 0.52 — 1.17) despite a significant reduction in TCD measured micro-emboli (OR 0.19, 95% CI 0.10 — 0.35) in the DAPT compared with the aspirin monotherapy group. Subgroup analysis did not reveal any significant difference in ischaemic stroke risk between patients with asymptomatic and symptomatic carotid artery stenosis. DAPT was associated with an increased risk of neck haematoma (OR 2.79, 95% CI 1.87 — 4.18) and re-operation for bleeding (OR 1.98, 95% CI 1.77 — 2.23) *vs.* aspirin. Haemorrhagic stroke was an under reported outcome in the literature.

Conclusion: This meta-analysis found that CEA while on DAPT increased the risk of haemorrhagic complications, with similar rates of ischaemic complications, *vs.* aspirin monotherapy. This suggests that the risks of performing CEA on DAPT outweigh the benefits, even in patients with symptomatic carotid stenosis. The overall quality of studies was low, and improved reporting of CEA outcomes in the literature is necessary.

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INTRODUCTION

Carotid endarterectomy (CEA) is a proven and effective treatment for the prevention of ischaemic stroke secondary to carotid stenosis.[1–3] However, the risk of peri-procedural complications ranges from 3.6% to 8.1%, and includes ischaemic stroke, death, or haemorrhagic complications.[1–4]

Antiplatelet therapy has been shown to decrease the risk of ischaemic complications such as stroke or transient ischaemic attack (TIA), but this must be balanced against the possibility of increased haemorrhagic complications, such as haemorrhagic stroke, neck haematoma, or major bleeding.[5] The use of antiplatelet agents in the pre-carotid endarterectomy population has been increasing over time.[6] Often, surgeons are confronted with the decision about whether to continue or stop antiplatelet agents in patients undergoing CEA. Surveys of surgeons who perform CEA have shown significant variations in peri-operative antiplatelet prescribing patterns.[7,8] Although the vast majority would not stop aspirin prior to CEA, 43% and 55% of surgeons would stop clopidogrel prior to CEA for asymptomatic and symptomatic patients, respectively.[7]

There is currently still clinical equipoise regarding the optimal peri-operative antiplatelet regimen for patients undergoing CEA.[9–11] Previously, two meta-analyses of CEA outcomes on single (SAPT) *vs.* dual antiplatelet therapy (DAPT) have been performed. The first assessed DAPT *vs.* SAPT in patients undergoing carotid revascularisation, including both CEA and stenting, and found no difference in stroke or TIA but an increase in bleeding risk with DAPT in CEA.[12] Another study found no difference in stroke risk but an increase in the markers of bleeding complications with DAPT on CEA.[13] However, other large, retrospective comparative studies have previously found a statistically significant decrease in ischaemic stroke risk with DAPT, specifically with aspirin and clopidogrel.[9,11,14,15] Additionally, both meta-analyses used risk difference or rate difference for several outcomes, which may be less appropriate for rare events[16,17] and for retrospective data[18], compared to odds ratios (ORs).

The subgroups of symptomatic *vs.* asymptomatic carotid stenosis also deserve special attention. Consensus medical management guidelines recommend aspirin monotherapy for asymptomatic atherosclerotic carotid artery disease and DAPT with aspirin and the addition of clopidogrel or dipyridamole for symptomatic carotid artery disease.[19,20] It remains unclear whether the second antiplatelet agent should be withheld pre-operatively and resumed after surgery to reduce bleeding risk or continued throughout the peri-operative period to reduce the ischaemic complication risk in patients with symptomatic carotid stenosis.[7]

As such, an updated systematic review and meta-analysis of the ischaemic, haemorrhagic, and overall outcomes of SAPT (aspirin) *vs.* DAPT was carried out, using improved statistical methodology. Ischaemic complications of interest included ischaemic stroke in all patients undergoing CEA and, in the asymptomatic *vs.* symptomatic subgroup, TIA and micro-emboli detected by transcranial Doppler (TCD). TCD has been shown to be predictive of ischaemic cerebral events when used peri-operatively.[21,22] Haemorrhagic complications assessed include haemorrhagic stroke, the formation of neck haematoma, major bleeding requiring re-operation, and total operating time. Other outcomes assessed included myocardial infarction (MI), mortality, and composite outcomes that aggregated some of the above outcomes.

MATERIALS AND METHODS

The search protocol, including research question and inclusion/exclusion criteria, was developed *a priori* according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[23]

The Web of Science, Pubmed, and Embase databases were searched from inception to July 2021. To identify studies of outcomes of CEA on aspirin *vs.* aspirin + clopidogrel, the following search terms were used in combination: "carotid", "endarterectomy", "Plavix", and "clopidogrel". The search was limited to studies in adult human patients aged ≥18 years and articles published in English. References of the included publications were searched manually for other relevant papers. The corresponding authors of articles excluded at the full text review stage of relevant papers were contacted; if they provided additional data that meant the study could then meet the inclusion criteria, the studies were also included in the meta-analysis.

Studies were included if they were randomised or had a prospective or retrospective study design that assessed peri-operative outcomes following CEA in patients on aspirin *vs.* aspirin + clopidogrel. To be included in the analysis, patients were required to have been started on the antiplatelet agents prior to surgery and be continued on the treatment to the time of surgery. Outcomes had to be reported as event rate in raw numbers, percentages, or ORs. The peri-operative period was defined as within the same hospitalisation or within 30 days of the procedure. The primary outcome was ischaemic stroke following CEA, and subgroup analysis of asymptomatic *vs.* symptomatic patients and for prospective *vs.* retrospective trials was performed. Other ischaemic outcomes were TIA and micro-emboli detected by TCD. As each institution had its own protocol, including length of monitoring and specific cutoff, the outcome of number of micro-emboli detected within that period of monitoring counted as excessive was dichotomised as excessive or not, to allow for pooling of event rates as ORs.

Secondary outcomes included measures of excessive peri-operative bleeding, namely hemorrhagic stroke, non-operative neck haematoma and re-operation rate for haemorrhage, which included uncontrolled bleeding from the incision or expanding neck haematoma. Neck haematomas were diagnosed based on physical examination, with or without ultrasound confirmation. The haemorrhagic stroke rate was also collected. Other outcomes were MI, death, operating time, and length of stay, as well as composite outcomes, which included stroke ± MI ± death following surgery.

If there were multiple studies from overlapping patient cohorts, such as those from the same centre, only studies that reported the largest patient cohort were included. Exclusion criteria included case reports, case series with fewer than 10 patients, single arm studies, review articles, conference abstracts, animal studies, and non-peer reviewed publications.

Two reviewers performed title and abstract screening from the search query results (J.C.K. and J.Z.). The full texts of eligible studies were obtained and reviewed for inclusion; any discrepancies were independently verified by another reviewer (S.T.). The quality of all eligible studies was evaluated independently and in duplicate by two reviewers (J.C.K. and C.R.P.), using the 2011 Oxford Centre for Evidence Based Medicine levels of evidence.[24]

The following data were extracted from each study: study design; country of origin; patient eligibility; inclusion/exclusion criteria; type of CEA performed; sex and age of patients; timing of antiplatelet treatment; and post-operative outcomes.

For statistical analysis, studies that reported peri-operative CEA outcomes for patients on aspirin *vs.* patients on aspirin and another antiplatelet agent were pooled for meta-analysis via OR. The chi square test and calculation of I^2 was used to assess heterogeneity between studies. Results with a p value $< .1$ and I^2 values $> 50\%$ were considered to denote significant heterogeneity between studies. Pooled estimates and 95% confidence intervals (CIs) were combined using a fixed effects model if there was no significant heterogeneity, or a random effects model if there was significant heterogeneity. A p value $< .05$ was set for statistical significance. A continuity correction was used when studies reported zero event rates in one arm. The meta-analysis was performed using Stata version 16 (StataCorp, College Station, TX, USA).

RESULTS

As seen in the PRISMA diagram (Fig. 1), the search strategy returned 2 018 results. Following abstract and full text screening, eight studies were included for analysis.[9,11,15,25–29] In addition, the authors of nine articles responded to the request for additional information,[6,30–37] and these were added if they met the inclusion criteria,[31,32,36] resulting in a total of 11 articles (Table 1). Across these studies, there were 47 411 patients, with 33 066 (69.7%) in the aspirin arm and 14 345 (30.3%) patients in the DAPT arm. Studies reported in hospital or peri-operative outcomes[9,25,28,31] or 30 day outcomes,[15,26,32] and these were pooled for statistical analysis. The overall level of evidence was low. There were only two randomised control trials (RCTs).[26,29] The remaining studies were retrospective[9,11,15,27,28,31,32] or prospective cohort studies.[25,36] All retrospective studies were graded as level 4, prospective studies with historical controls graded as level 3, and the RCTs were graded as level 2.[24]

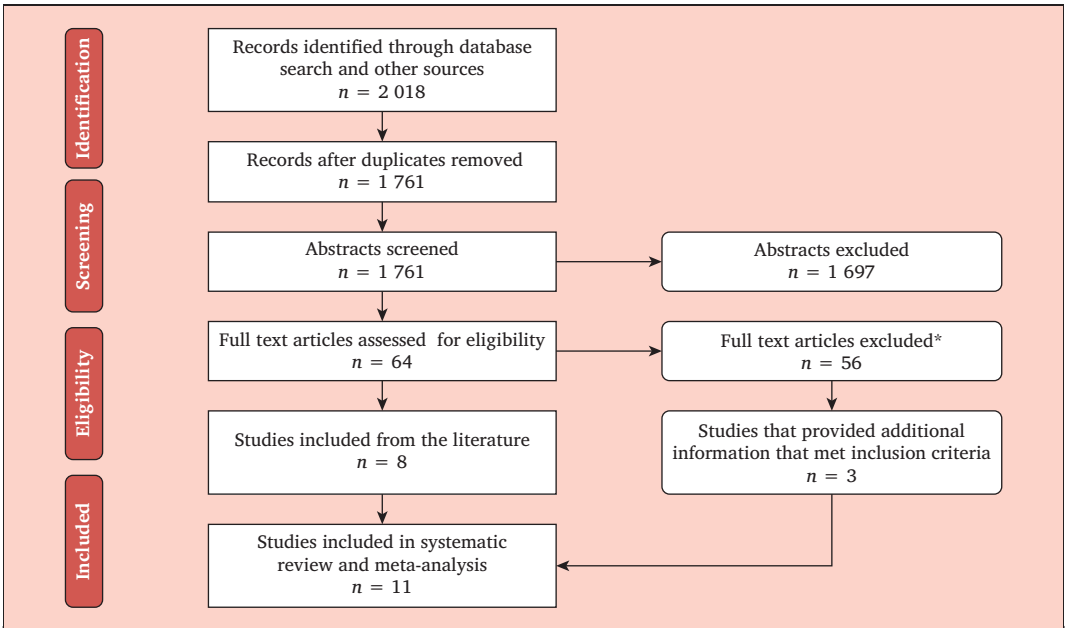

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for the literature search to identify studies of dual antiplatelet therapy *vs.* aspirin alone in carotid endarterectomy. *Reasons for exclusion included not reporting antiplatelet *vs.* anticoagulation outcomes separately; < 10 patients; larger cohort of the same population reported elsewhere; conference abstract; review article.

Table 1. Characteristics of the included studies for meta-analysis of dual antiplatelet therapy *vs.* aspirin alone in carotid endarterectomy (CEA)

Study, country	Type of study	Patients (DAPT/ total)	Symptomatic − %	Antiplatelet regimen	CEA procedure	Outcomes reported
Payne *et al.* (2004),[26] UK	RCT	46/100	84	150 mg ASA started 4 wk before surgery, single dose of 75 mg clopidogrel or placebo 12 h before surgery	Shunting (100%), TCD monitoring	Any stroke, micro-emboli, neck haematoma, re-operation for bleeding, MI, mortality, operating time
Vogten *et al.* (2008),[29] the Netherlands	RCT	9/27	NS	100 mg ASA with or without 75 mg clopidogrel started for at least 1 mo prior to surgery	Selective shunting (14.8%), standard patch, EEG and TCD monitoring	Micro-emboli, operating time
Nasr *et al.* (2010),[36] France	Prosp.*	34/112	35.7	75–300 mg ASA, with or without 75 mg clopidogrel started at least the night before surgery	NS	Any stroke, TIA, neck haematoma, re-operation for bleeding, MI, mortality, composite outcome
Sharpe *et al.* (2010),[27] UK	Retrosp.	270/1 091	85 (in DAPT cohort)	75 mg ASA daily and single 75 mg dose clopidogrel the night before surgery	Routine shunting, routine patching, TCD monitoring	Micro-emboli, any stroke (only in DAPT cohort)
Stone *et al.* (2011),[28] UK	Retrosp.	708/4 531	NS	ASA and clopidogrel started within 48 h of surgery	NS	Re-operation for bleeding
Chechik *et al.* (2012),[31] Israel	Retrosp.	16/91	53	75–325 mg ASA with or without 75 mg clopidogrel started prior to day of surgery	Selective shunting, routine patching	Any stroke, neck haematoma, re-operation for bleeding, MI, death, composite outcome, operating time, length of stay
Oldag *et al.* (2012),[25] Germany	Prosp.	112/522	54.8	100–300 mg ASA with or without 75 mg clopidogrel for at least five d, or for < five d but with a loading dose of 500 mg ASA or 300 mg clopidogrel, started at least 36 h before surgery	Selective shunting (39.5%), routine patching	Neck haematoma, re-operation for bleeding
Hale *et al.* (2013),[15] USA	Retrosp.	315/954	NS	Pre-operative ASA with or without clopidogrel at time of admission	Selective shunting, routine patching	Ischaemic stroke, TIA, neck haematoma, re-operation for bleeding, MI, mortality, composite outcome, LOS
Chisci *et al.* (2016),[32] Italy	Retrosp.*	79/959	27	ASA with or without clopidogrel started at least 24 h before surgery	Eversion (90%), selective shunting (7%)	Any stroke, TIA, neck haematoma, re-operation for bleeding, MI, mortality, composite outcome LOS
Jones *et al.* (2016),[9] USA	Retrosp.	7 059/2 8683	24.4	ASA with or without clopidogrel started within 48 h before surgery	Patching (88.9%), eversion (13.4%), shunting (52.5%)	Ischaemic stroke, TIA, re-operation for bleeding, MI, mortality, composite outcome
Zimmerman *et al.* (2018),[11] Germany	Retrosp.	5 697/10 3417	39.6	Peri-operative AP medication	Patching (51.6%), eversion (42.5%), shunting (42.8%)	Ischaemic stroke, re-operation for bleeding, MI, mortality

DAPT = dual antiplatelet therapy; RCT = randomised controlled trial; ASA = acetylsalicylic acid (aspirin); TCD = transcranial Doppler; MI = myocardial infarction; NS = not specified; EEG = electroencephalography; TIA = transient ischaemic attack; LOS = length of stay; AP = antiplatelet; Prosp. = prospective; Retrosp. = retrospective.
* Additional unpublished data provided.

Ischaemic outcomes

Seven studies reported the peri-operative ischaemic stroke rate comparing groups that received aspirin *vs.* aspirin + clopidogrel.[9,11,15,26,31,32,36] The pooled OR showed a non-significant trend towards decreased stroke risk with DAPT *vs.* aspirin alone (OR 0.87, 95% CI 0.72 — 1.05; Fig. 2). Three studies reported the peri-operative TIA rate;[9,15,36] again, this was not statistically significant (OR 0.78, 95% CI 0.52 — 1.17).

On subgroup analysis of four trials, no significant differences were found between the ischaemic stroke rate on DAPT *vs.* ASA for either asymptomatic (OR 0.66, 95% CI 0.42 — 1.02) or symptomatic carotid stenosis (OR 0.94, 95% CI 0.61 — 1.46), as seen in Fig. 3. There was no significant difference in ischaemic stroke risk on DAPT *vs.* ASA in prospective or retrospective trials (Fig. 3)

Three studies also assessed the number of micro-emboli seen on TCD in the post-operative period, as a corollary measure for ischaemic stroke risk.[26,27,29] The patients were dichotomised as high or low risk of stroke based on the cut off number of micro-emboli detected within the peri-operative time period, as defined by the study authors. There was a statistically significant decreased risk of having excessive micro-emboli when on aspirin and clopidogrel compared with aspirin alone (OR 0.19, 95% CI 0.10 — 0.35).

Bleeding risk

Six studies reported the rate of post-operative neck haematomas that did not require re-operation.[15,25,26,31,32,36] Aspirin and clopidogrel increased the neck haematoma risk *vs.* aspirin alone (OR 2.79, 95% CI 1.87 — 4.18).

Eight studies reported rate of re-operation for bleeding.[9,11,15,25,26,28,31,36] DAPT was associated with a greater risk of re-operation for bleeding *vs.* aspirin alone (OR 1.98, 95% CI 1.77 — 2.23; Fig. 4). One study reported blood transfusion rates, and found no difference between DAPT and aspirin alone.[26]

An indirect measure related to bleeding risk is the operating time, which may be increased if achieving haemostasis takes longer as a result of excessive platelet inhibition. Two studies reported total operating time,[29,31] and pooled analysis showed that total operating time was decreased in patients on aspirin alone *vs.* patients on DAPT (OR 0.78, 95% CI 0.31 — 1.24; Fig. 5). One study that assessed operating time reported that 30% of all patients on aspirin with clopidogrel undergoing CEA required ≥40 minutes from restoration of blood flow to closure of the neck wound *vs.* only 8% of patients on ASA alone ($p = .004$).[26]

Surprisingly, only two published studies reported on haemorrhagic stroke. One of the two RCTs included in the meta-analysis reported one "hyperperfusion stroke" in the DAPT cohort *vs.* none in the aspirin monotherapy cohort.[26] Another study reported one haemorrhagic stroke, which occurred following a hypertensive crisis, in 270 patients undergoing CEA on DAPT, but did not present ischaemic or haemorrhagic stroke outcomes in the aspirin monotherapy cohort.[27] From the additional patient information received from the study authors, no haemorrhagic strokes occurred following CEA in the DAPT cohort ($n = 129$) or the aspirin monotherapy cohort ($n = 1\,033$).

Other outcomes

Seven studies reported peri-operative MI,[9,11,15,26,31,32,36] and there was a statistically significant increased likelihood of peri-operative MI in patients on

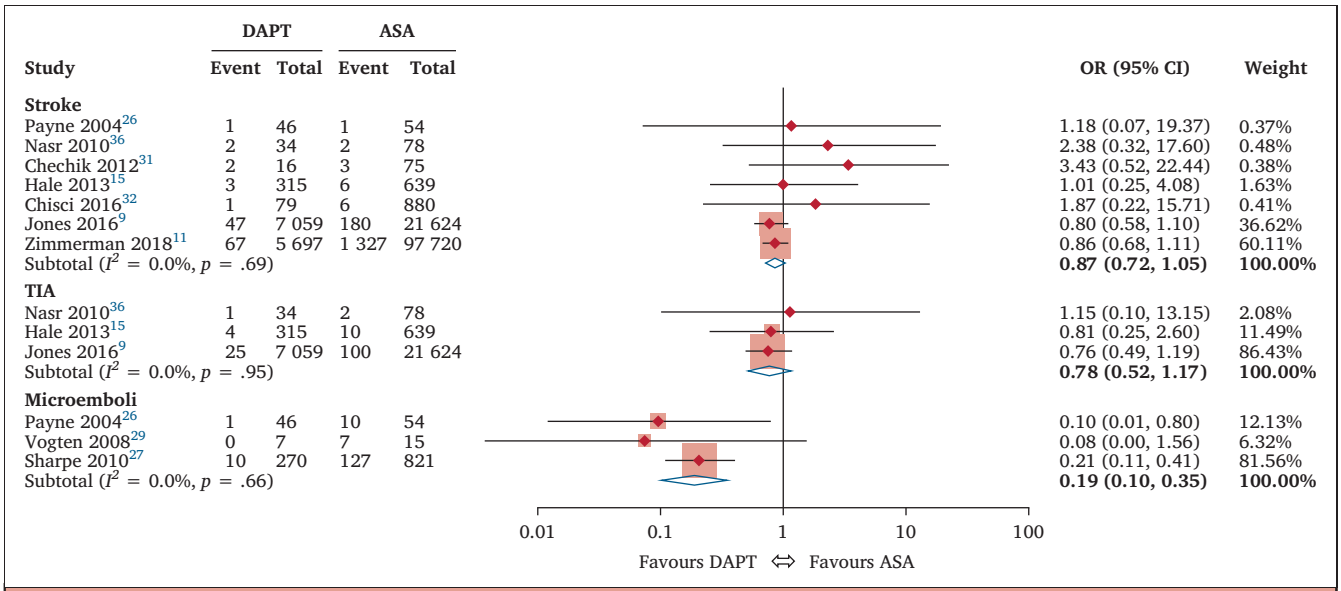

Figure 2. Forest plot of ischaemic stroke outcomes as stroke, transient ischaemic attack (TIA), and micro-emboli following carotid endarterectomy on dual antiplatelet therapy (DAPT) *vs.* aspirin (ASA) alone. OR = odds ratio; CI = confidence interval.

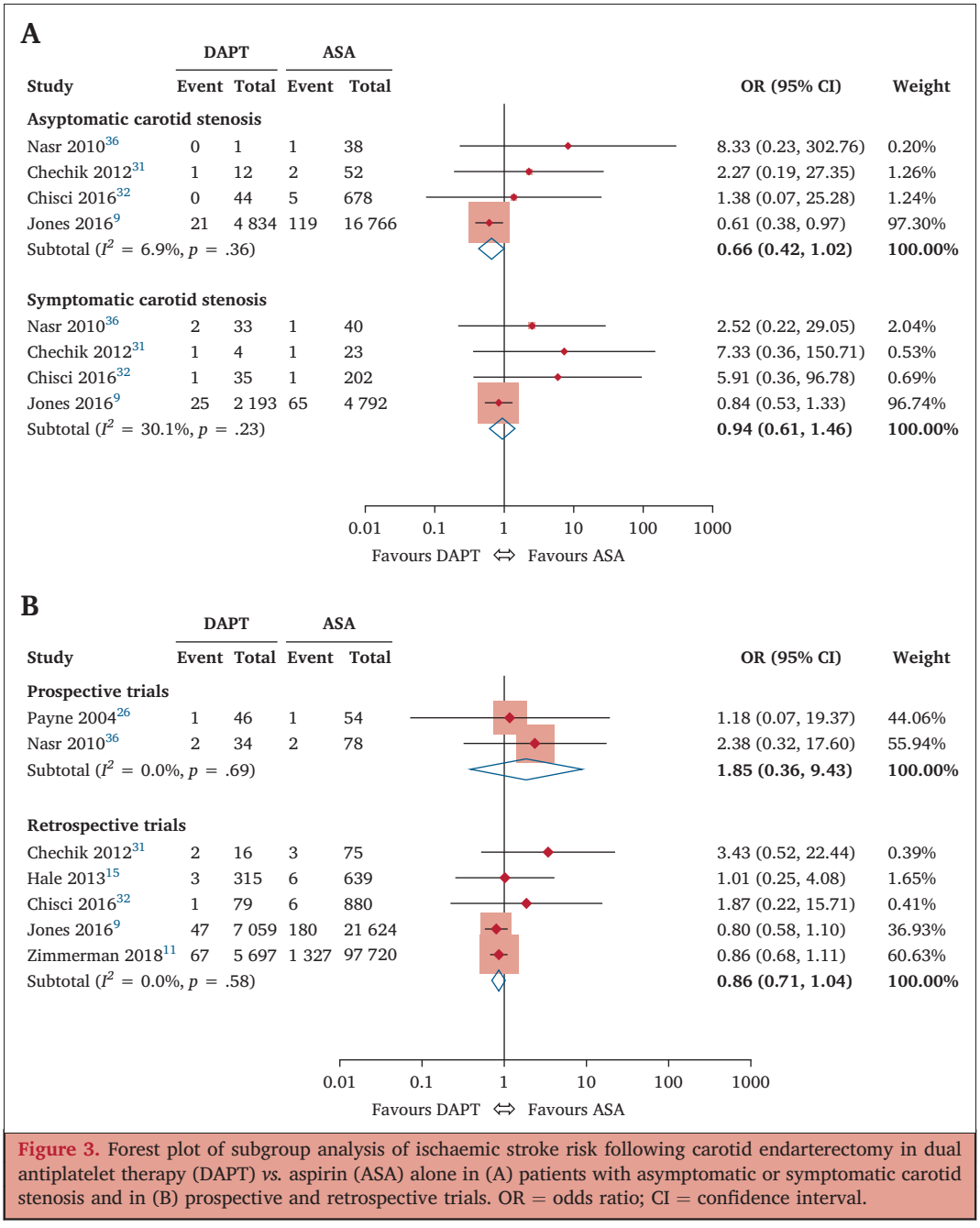

Figure 3. Forest plot of subgroup analysis of ischaemic stroke risk following carotid endarterectomy in dual antiplatelet therapy (DAPT) *vs.* aspirin (ASA) alone in (A) patients with asymptomatic or symptomatic carotid stenosis and in (B) prospective and retrospective trials. OR = odds ratio; CI = confidence interval.

DAPT *vs.* aspirin alone (OR 1.58, 95% CI 1.24 — 2.00; Fig. 4).

Seven studies reported peri-operative mortality, but four had zero events for both treatment arms.[9,11,15,26,31,32,36] In the remaining studies, it was found that patients on DAPT had a higher likelihood of peri-operative death (OR 1.46, 95% CI 1.13 — 1.89).

In terms of composite outcomes, five studies reported stroke or death,[9,11,31,32,36] and meta-analysis found no significant differences between the treatment groups (OR 1.03, 95% CI 0.88 — 1.21). A composite outcome of stroke/MI and stroke/MI/death from three studies was calculated (Supplementary Fig. S1).[31,32,36] There were no significant differences between the two groups. In addition, Hale *et al.* assessed the 30 day composite outcome of death, MI, stroke, renal failure, or respiratory failure, and found no significant difference between DAPT and aspirin alone.[15]

Three studies reported the post-operative stay in days; pooled analysis showed no significant differences between the treatment groups (Fig. 5).[15,31,32]

DISCUSSION

CEAs are commonly indicated for patients currently on SAPT or DAPT, prescribed to reduce their risk of stroke from carotid stenosis.[7,8] Surgeons are faced with the question of continuing or stopping these antiplatelet agents prior to CEA, and balancing the ischaemic *vs.* haemorrhagic risks involved.

Like the two previous studies, this meta-analysis did not find a statistically significantly decreased risk of peri-operative

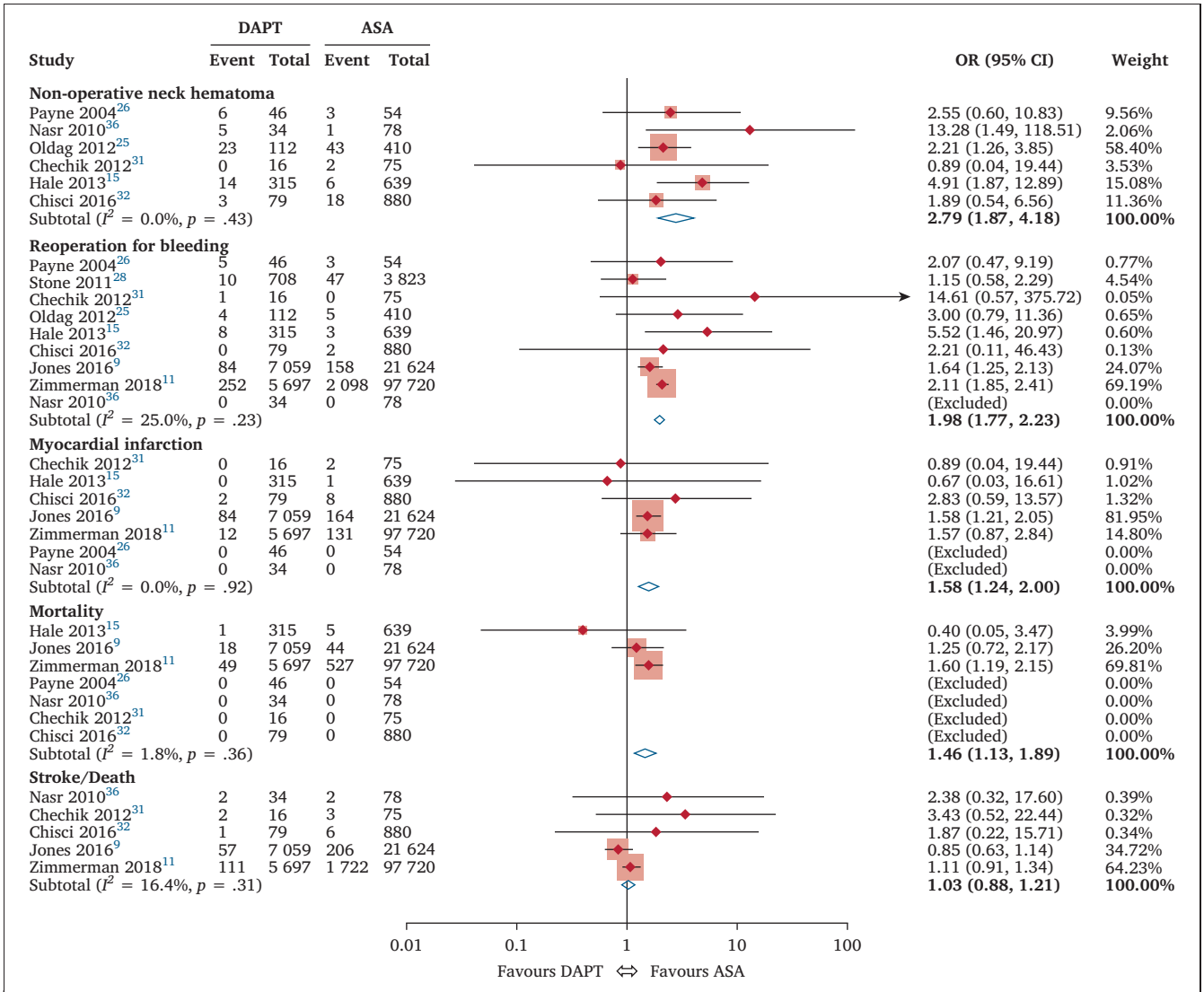

Figure 4. Forest plot of haemorrhagic outcomes, myocardial infarction, mortality, and stroke or death following carotid endarterectomy on dual antiplatelet therapy (DAPT) *vs.* aspirin (ASA) alone. OR = odds ratio; CI = confidence interval.

ischaemic cerebrovascular events with DAPT.[12,13] Several studies that were included in these previous meta-analyses were excluded, owing to grouped outcomes for CEA and carotid stenting, starting DAPT after the procedure, and not specifying aspirin as the SAPT (see Table 2).[10,37–39] In addition, pooled ORs rather than risk difference or rate difference were used, for improved statistical methodology.[16–18]

Additionally, in a subgroup analysis of symptomatic *vs.* asymptomatic carotid stenosis, it was found that DAPT did not decrease stroke risk *vs.* aspirin in either subgroup. DAPT is commonly recommended for patients with symptomatic carotid artery stenosis to prevent ischaemic events, and it is also recommended that CEA be performed within two weeks of the index event.[19,20] Emerging evidence may also suggest that even earlier carotid surgery, specifically targeted within 48 hours if the index event is a TIA, and within seven days if the index event is stroke, may lead to improved outcomes.[40]

Based on this meta-analysis, the risks of performing CEA on DAPT seem to outweigh the benefits in symptomatic patients. However, the risk of pre-operative ischaemic events may not be adequately captured in this analysis, as these events were not reported in the studies included and neither was the timing of CEA in symptomatic patients. The incidence of recurrent stroke after an index cerebrovascular event in patients with symptomatic carotid stenosis ranges from 5% to 8% at 48 hours, from 4% to 17% at 72 hours, from 8% to 22% at 7 days, and from 11% to 25% at 14 days.[20] Taking this into consideration, it may be suggested that unless patients undergo CEA shortly (within 48 hours) after the index event, DAPT may be started to reduce the risk of recurrent ischaemic events. Then, the second antiplatelet agent should be withheld peri-operatively to reduce the risk of haemorrhagic complications. Additional prospective studies are required to further assess this recommendation. For patients with

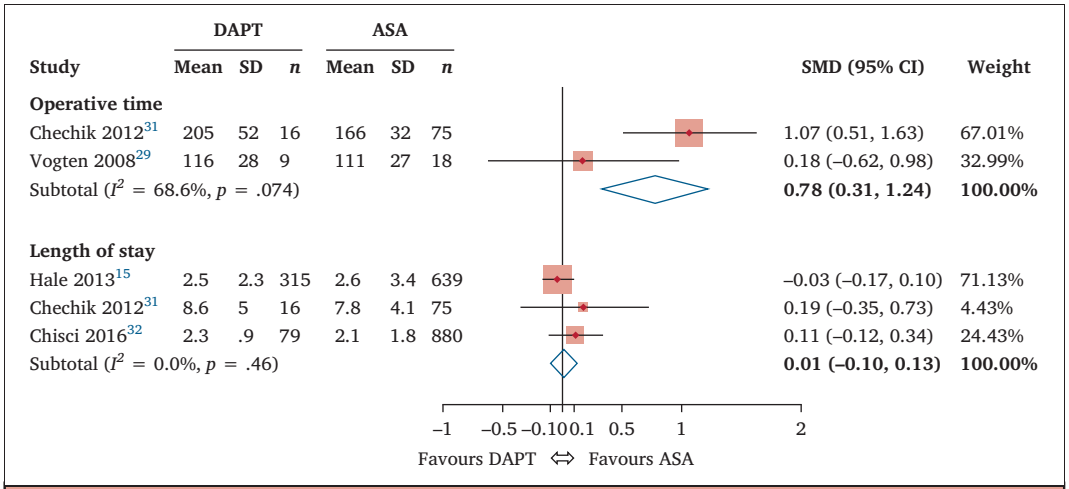

Figure 5. Forest plot of continuous outcomes of operating time and length of stay following carotid endarterectomy on dual antiplatelet therapy (DAPT) vs. aspirin (ASA) alone. OR = odds ratio; CI = confidence interval.

asymptomatic carotid stenosis, this analysis suggests that starting these patients on DAPT peri-operatively would not be recommended.

Micro-emboli detected on TCD have previously been found to be predictive of stroke risk, which has been validated in post-operative patients with a threshold of positivity of 10 micro-emboli per hour.[21] In the three studies that assessed micro-emboli, which included two RCTs, cerebral micro-embolisation was decreased with aspirin and clopidogrel *vs.* aspirin alone.[26,27,29] Although each study had varying monitoring protocols and cutoff thresholds, all three also found that DAPT with clopidogrel significantly decreased the number of micro-emboli post-operatively.[26,27,29] However, this was not reflected in the actual ischaemic event rates found.

In terms of haemorrhagic outcomes, DAPT significantly increased the post-operative neck haematoma and re-operation rates for expanding neck haematoma or significant bleeding from the incision. Post-operative neck haematoma has been shown to be associated with increased operative mortality, neurological complications, adverse cardiac events, and cranial nerve injury.[41] Surgical time and closure time, markers of increased bleeding, were also increased on DAPT, whereas blood transfusion rate and wound drainage volume were not.[26] Some studies have postulated that the increased bleeding complication risk remains at an acceptably low level, justifying the use of DAPT in decreasing the ischaemic event risk peri-operatively, especially in patients with important indications for clopidogrel use, such as symptomatic carotid artery stenosis or cardiovascular indications.[9,25,28] Literature from non-CEA populations has also shown an increased cardiac or cerebrovascular event risk with the premature withdrawal of antiplatelet agents.[42–44]

Table 2. Excluded studies that were included in the two previous meta-analyses of dual antiplatelet therapy *vs.* aspirin alone in carotid endarterectomy

Study	Reason for exclusion
Saadeh *et al.* (2013)[37]	Reported grouped outcomes for patients who were receiving neither aspirin nor clopidogrel (20%), or were taking aspirin alone (80%)
Alcocer *et al.* (2014)[38]	Reported grouped outcomes for patients undergoing CAS and CEA
Barboza *et al.* (2016)[39]	Started dual antiplatelet therapy one day after procedure
Illuminati *et al.* (2017)[10]	Did not specify aspirin as the single antiplatelet agent

CAS = carotid artery stenting; CEA = carotid endarterectomy.

Only two studies reported on the haemorrhagic strokes that occurred in their DAPT cohort.[26,27] Whether this represents a very low rate of haemorrhagic strokes or under reporting is uncertain. Several large studies did not include haemorrhagic stroke or intracerebral haemorrhage as an outcome measure.[9,11,15] There were no reported cases of haemorrhagic stroke reported following CEA on DAPT or on aspirin monotherapy in the additional data received from the study authors. In the literature, rates of haemorrhagic stroke following CEA range from 0.20% to 0.80%.[45–47] Improved reporting of this rare but feared complication is required to determine fully the safety of DAPT in CEA.

There was an increased post-operative MI and death rate in the DAPT cohort in this meta-analysis. This has been suggested to be secondary to a worse cardiovascular risk profile in this group of patients.[12] Patients on DAPT are likely to have symptomatic carotid artery disease, coronary artery disease, or to have undergone prior coronary artery bypass grafting or another coronary intervention.[9] Additionally, operating time has been found to be longer on DAPT, which places an additional strain on the patient. These factors may explain the increased MI and death rate in the DAPT cohort.

In the current literature, composite outcomes following CEA often comprise stroke and mortality, with or without MI,[1–3] which may neglect the risks of haemorrhagic complications. In this review, which includes additional unpublished data obtained from certain study authors, five studies were found to have used stroke and death as the composite outcome; three studies used stroke, death, and MI; and one

study used stroke, death, MI, renal failure, and respiratory failure.[9,11,15,31] There were no significant differences between the DAPT and the aspirin monotherapy groups in any of these composite outcomes. An overall measure of the rate of all peri-operative complications, including ischaemic and haemorrhagic outcomes (both intracranially and at the operation site), and their effect on functional outcome might be the best way to capture outcomes after CEA, specifically outcomes that may be the most relevant to the patient. This could take the form of 30 day modified Rankin Scale or some other measurement of function that best captures the effect of a complication on the patient's overall clinical outcome.

As with most meta-analyses, this review was limited by the studies available in the literature. Most were retrospective reviews and other observational trials, with only two RCTs. Additional subgroup analyses could not be performed as a result of the heterogeneity in reporting. Reporting of ischaemic stroke outcomes for asymptomatic *vs.* symptomatic carotid artery stenosis was lacking in many studies, limiting the number of studies available for this subgroup analysis. Information on the timing of CEA in symptomatic patients and ischaemic events that occurred while waiting for surgery was also lacking. Similarly, haemorrhagic stroke rates were under reported. Owing to the low number of studies reporting 30 day outcomes, studies that reported in hospital complication rates were pooled with studies that reported 30 day complication rates; however, it is recognised that assessment at 30 days may capture events that might be missed if only in hospital assessments were performed. There was also variability in the antiplatelet regimen used, which may have introduced potential bias. In addition, although several studies reported composite outcomes, no overall outcome that captures all types of complications and their effects on morbidity/mortality was reported in the literature. It is recommended that future studies report ischaemic and haemorrhagic stroke rates, and functional outcomes at 30 days for patients with asymptomatic and symptomatic carotid stenoses separately when reporting CEA outcomes.

In conclusion, within the largest meta-analysis conducted to date, it was found that CEA while on DAPT increased the risk of haemorrhagic complications without decreasing ischaemic stroke rates, compared with aspirin monotherapy. This suggests that the risks of performing CEA in patients on DAPT outweighs the benefits, even in patients with symptomatic carotid stenosis. However, the overall quality of studies was low, and improved reporting of CEA outcomes in the literature is necessary.

CONFLICT OF INTEREST STATEMENT AND FUNDING

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2021.12.037.

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