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Optimal Antiplatelet Therapy in Moderate to Severe Asymptomatic and Symptomatic Carotid Stenosis: A Comprehensive Review of the Literature

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WHAT THIS PAPER ADDS

This novel comprehensive review collates data on prescribed antiplatelet regimens and outcome events in patients with moderate–severe asymptomatic and symptomatic carotid stenosis who were included in the main randomised trials. The data have been critically appraised in patients randomised to "best medical therapy" alone or in combination with endarterectomy or stenting to provide clinicians with a practical, evidence based approach to antiplatelet therapy in this population. These comprehensive data and tables compliment and expand upon the recently published ESVS guidelines[1] on the management of atherosclerotic carotid and vertebral artery disease, and should promote future research to optimise peri-procedural and long-term preventive treatment in carotid stenosis patients.

Objectives: Carotid stenosis patients are at risk of vascular events despite antiplatelet therapy. Data on prescribed antiplatelet regimens have not been comprehensively collated from trials to guide optimal therapy in this population.

Methods: This review was conducted in line with the current Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Medline, Ovid, Embase, Web of Science, and Google Scholar from 1988 to 2018 were searched using the search terms "carotid stenosis", "asymptomatic", "symptomatic", "antiplatelet", and "anti-platelet" to identify randomised trials in patients with asymptomatic or symptomatic extracranial moderate–severe carotid stenosis on any form of antiplatelet therapy in which vascular events and pre specified composite outcome events were reported.

Results: Twenty-five studies were judged eligible for inclusion. Data from one randomised controlled trial showed no significant difference in benefit with aspirin versus placebo in asymptomatic carotid stenosis, but it is still reasonable to recommend aspirin (81–325 mg daily) for prevention of vascular events in these patients. Low to medium dose aspirin (81–325 mg daily) is superior to higher doses (>650 mg daily) at preventing recurrent vascular events in patients undergoing endarterectomy. Data from endovascular treatment (EVT) trials support peri-procedural treatment of asymptomatic and symptomatic patients with 81–325 mg of aspirin daily. The use of peri-procedural aspirin–clopidogrel in patients undergoing EVT is based on one pilot trial, but appears safe. Short-term aspirin–dipyridamole or aspirin–clopidogrel treatments are equally effective at reducing micro-embolic signals on transcranial Doppler ultrasound in patients with ≥50% symptomatic carotid stenosis. There is insufficient evidence to recommend routine aspirin–clopidogrel

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combination therapy to reduce the risk of recurrent clinical ischaemic events in patients with symptomatic moderate—severe carotid stenosis.

Conclusions: This comprehensive review outlines an evidence based approach to antiplatelet therapy in carotid stenosis patients. Future trials should randomise such patients to receive different antiplatelet regimens to assess their efficacy and safety and to optimise peri-procedural and long-term preventive treatment in this patient cohort.

Keywords: Asymptomatic carotid stenosis, Symptomatic carotid stenosis, Antiplatelet therapy, Literature review
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INTRODUCTION

The annual risk of ipsilateral ischaemic stroke varies from 0.34% to 2% in the territory of a 60—99% asymptomatic carotid stenosis in patients treated with "best medical therapy alone".[2—6] However, the ACES study showed that the annual risk of ipsilateral stroke distal to an asymptomatic ≥70% carotid stenosis increased from 0.7% in patients without micro-embolic signals (MES) to 3.6% in those with MES on transcranial Doppler ultrasound (TCD).[7] In contrast, the risk of recurrent ipsilateral stroke has been shown to be as high as 26% over 2 years in symptomatic severe (≥70%) carotid stenosis patients on "best medical therapy" alone.[8] Therefore, carotid stenosis patients were at risk of first or recurrent cerebrovascular events on what was considered to be the "optimal", contemporaneously available antiplatelet treatment regimens in these trials, especially those with recently symptomatic carotid stenosis. It must be noted that "best medical therapy" in some earlier trials preceded evidence on the efficacy of antiplatelet regimens other than aspirin monotherapy,[9,10] or of rigorous blood pressure control[11] and treatment with statins for secondary prevention following stroke.[12]

Aims

To guide physicians regarding the evidence base for, and the potential efficacy of, commonly prescribed antiplatelet regimens at preventing vascular events and pre-specified composite outcomes in patients with carotid stenosis, a comprehensive review of the literature was carried out to collate data from relevant randomised trials in patients with extracranial moderate to severe asymptomatic and symptomatic carotid stenosis who were treated with antiplatelet therapy.

METHODS

Search strategy

This comprehensive review was conducted in line with the main principles of the current Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Articles were identified through Medline, Ovid, Embase, Web of Science/Web of Knowledge, and Google scholar. The search was limited to studies published in English between January 1988 and July 2018, retrieved on the July 8, 2018. The following search terms were used: "carotid stenosis", "asymptomatic", "symptomatic", "antiplatelet", and "anti-platelet". The first author (S.J.X.M.) reviewed results from the electronic search and identified potentially relevant titles and abstracts. If the abstract suggested the article met the inclusion criteria, the full text article was obtained and reviewed by the first (S.J.X.M.) and independently by the supervising author (D.J.H.M.). Discrepancies were resolved by consensus between these authors, and submitted to all co-authors for final approval. The reference lists of selected studies and reviews were manually searched for additional relevant articles.

Articles were included if they met three key criteria:

1. Male or female patients ≥18 years;
2. Reasonably sized randomised trials (≥50 patients) in which a majority of patients had moderate (50—70%) or severe (70—100%) symptomatic or asymptomatic extracranial carotid stenosis according to NASCET[13] or ECST[14] criteria, with data on antiplatelet therapy use;
3. Reported short or long-term outcomes.

Data collection was performed in conjunction with data collection to prepare the latest European Society for Vascular Surgery guidelines on the management of atherosclerotic carotid and vertebral artery disease. Subsequent to the publication of these guidelines, the updated literature search identified data from three additional studies that have been included in this comprehensive review to enhance the original evidence base, as detailed below.[15—17]

RESULTS

Initially, 9107 articles were identified. After excluding 9,048, 25 originally identified articles reporting on 24,272 patients met the inclusion criteria (study sample size, 50—3024 participants; Fig. 1). Treatment regimens and outcomes following carotid endarterectomy (CEA) were compared with contemporaneously available best medical therapy (BMT) in three studies in symptomatic[13,14,18] and four in asymptomatic carotid stenosis patients.[5,19—21] Endovascular treatment (EVT) was compared with CEA in five studies in symptomatic,[14,22—25] four studies in asymptomatic patients,[2,26,27] and in one study in both symptomatic and asymptomatic patients.[28] Seven trials randomised symptomatic and asymptomatic patients to different treatment regimens,[29—34] and one had a three way design comparing

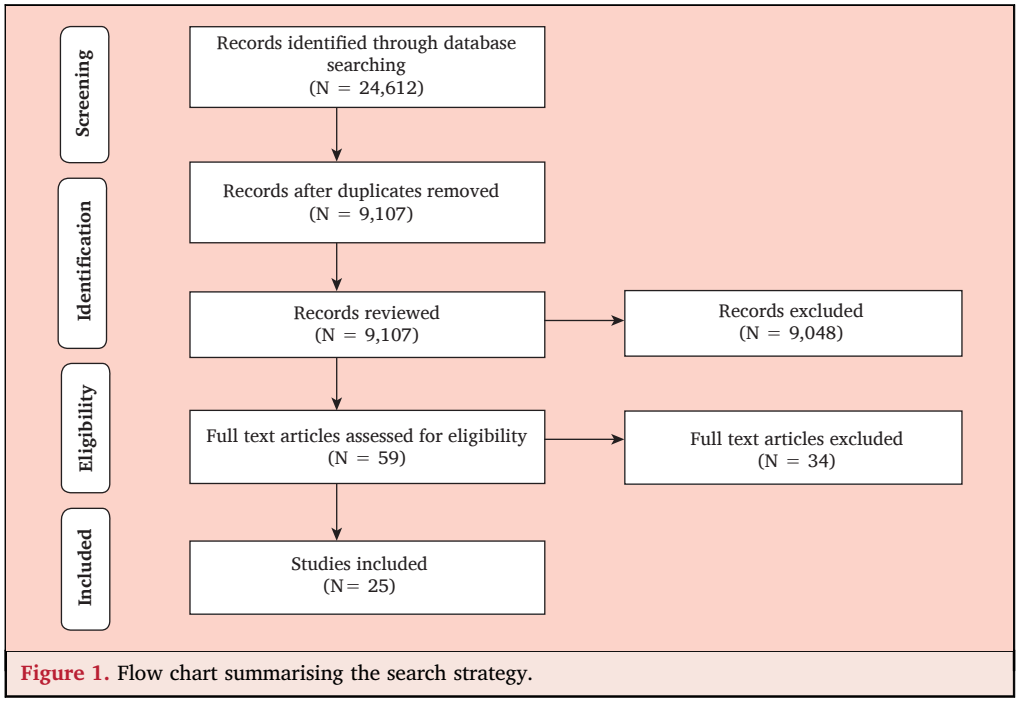

Figure 1. Flow chart summarising the search strategy.

BMT versus CEA versus EVT in asymptomatic patients.[35] All included trials met the criteria for level 1 evidence based trials.[36]

Asymptomatic carotid stenosis

Including data on asymptomatic patients from the Aspirin and Carotid Endarterectomy (ACE) trial[29] (see Table 5) and the Carotid Revascularisation Endarterectomy versus Stenting Trial (CREST),[28] which will be described in more detail in the "Symptomatic carotid stenosis" section, 13 randomised trials in asymptomatic patients (Tables 1 and 2) were eligible for inclusion in this review.

BMT. In total, four studies included asymptomatic patients who at least initially received BMT only. Two trials randomised patients between BMT and CEA,[6,21] one randomised between immediate CEA or deferral of CEA combined with BMT,[21] and SPACE-2 had a three way design comparing BMT versus CEA versus EVT.[35] In SPACE-2, aspirin or clopidogrel monotherapy (but not dual antiplatelet therapy) had to be administered for at least three days before CEA, but doses were not specified.[35] The Asymptomatic Cervical Bruit Study (ACB) was the only RCT to randomise asymptomatic carotid stenosis patients with ≥50% asymptomatic carotid stenosis of at least one artery to receive either 325 mg of enteric coated aspirin daily ($n = 188$) or placebo ($n = 184$).[20] After a median follow up of 2.3 years, there were no significant differences in the annual incidence of all ischaemic events (transient ischaemic attack [TIA], ischaemic stroke, unstable angina, MI, and death from any cause) in the aspirin versus placebo groups (11.0% vs. 12.3%, $p = .61$); however, the risk of ipsilateral stroke alone was not reported.

In this entire category, "trial primary outcomes" occurred in 0—20.6% of patients with asymptomatic >50% stenosis treated with BMT only, mainly with 81—1300 mg of aspirin daily, over a follow up period of between one and 120 months.[6,19—21,34]

CEA. Nine trials included asymptomatic patients randomised to CEA. In addition to SPACE-2 described above, two studies randomised patients between BMT[6,19] and CEA, and six randomised patients between CEA and EVT.[3,17,26—28,35] The majority of patients in these trials received aspirin monotherapy. The dose of aspirin was only specified in three trials (range 81—325 mg daily).[26,27] Interim data from the ACST-2 trial comparing CEA vs. EVT indicated that the majority of patients allocated to CEA received aspirin monotherapy ($n \simeq 300$), with approximately 60 patients on clopidogrel monotherapy and 40 patients on aspirin—clopidogrel combination therapy; however, the precise dose of each antiplatelet agent was not specified.[3] Overall, primary trial outcomes were observed in 1.5—20.1% of asymptomatic > 50% stenosis patients treated by CEA.[3,17,26—28,35]

EVT. In the six trials allocating asymptomatic patients to receive EVT, aspirin—clopidogrel combination therapy was recommended in the majority at least 24 hours[17,26] to three days before the procedure,[27,35] and continued for 2—4 weeks,[26,27] or 6 weeks[17,35] post-procedurally. In CREST, aspirin 325 mg twice daily and clopidogrel 75 mg twice daily was recommended for ≥48 hours before EVT, followed by aspirin 325 mg daily or twice daily for 30 days, combined with either clopidogrel 75 mg daily or ticlopidine 250 mg twice daily for ≥4 weeks.[28] Primary outcomes were

Table 1. Anti-thrombotic therapy data from randomised controlled trials in patients with Asymptomatic Moderate or Severe Carotid Stenosis (1993–1995)

Study/Year	Patients	Intervention	Antiplatelet/ Anticoagulant Therapy (AT)	Follow up	Primary & Secondary outcomes	Medical Group	CEA Group
VA[19] 1993 (Asymptomatic) [A]	Men with >50% Asymptomatic carotid stenosis (N = 444)	CEA (N = 211) *vs.* 'Optimal medical therapy alone' (N = 233)	A AT = N/A	Mean 4 years	1°: Combined incidence of ipsilateral neurological events	20.6%	8% ($p < 0.001$)
					2°: Ipsilateral stroke alone	9.4%	4.7% (p value N/A)
					All strokes	12.4%	8.6% (p non-significant)
ACAS[6] 1995 [B]	>60% Asymptomatic carotid stenosis (N = 1659)	CEA (N = 825) *vs.* Medical therapy alone (N = 834)	A AT = N/A	Median 2.7 years	1°: Ipsilateral stroke or any perioperative stroke or death	Estimated 5 year risk: 11%	Estimated 5 year risk: 5.1% ($p = 0.004$)
					2°: Ipsilateral TIA or stroke or any perioperative stroke or death	Estimated 5 year risk: 19.2%	Estimated 5 year risk: 8.2% ($p < 0.001$)
Asymptomatic Cervical Bruit Study[20] 1995 [C]	>50% Asymptomatic carotid stenosis	Enteric coated aspirin (325mg daily, N = 188) *vs.* Placebo (N = 184)	A AT = N/A	Median 2.3 years	1°: Annual rate of all ischaemic events and death from any cause	11% *vs.* 12.3 % ($p = 0.61$)	
					2°: Vascular events only	10.7%; vs. 11% ($p = 0.71$)	

[A] All patients received Aspirin 650 mg twice daily after randomisation or 325 mg daily if they were intolerant of this dose. By last follow-up, 57% were taking full dose, 27% were taking 325 mg of aspirin daily, and 16% had discontinued aspirin due to intolerance.
[B] All patients received 325 mg of aspirin daily. 'Estimated 5 year' absolute reduction in risk of stroke with CEA by approximately 1.2% per year during follow-up.
[C] Either enteric coated aspirin 325 mg daily or placebo.
In this and each subsequent table, **A** = Aspirin, **C** = Clopidogrel; **A** + **C** = Aspirin + Clopidogrel; **A** + **D** = Aspirin + Dipyridamole; **T** = Ticlopidine; AT = Anticoagulant Therapy. In the 4th column in each table, prescribed antiplatelet regimens are abbreviated in bold on the first line; anticoagulant therapy regimens, where appropriate, are specified below the antiplatelet regimens.

observed in 1.5–12% of EVT treated patients over 1–120 months.[3,17,26–28,35]

Symptomatic carotid stenosis

Including data from ACE and CREST, which also included asymptomatic patients, 14 RCTs in symptomatic patients were eligible for inclusion (Tables 3–5).

BMT only. To date, three randomised controlled trials (RCTs) included a BMT only cohort in symptomatic carotid stenosis patients with >50%,[18] 0–100%,[14] and <70% or 70–99% stenosis.[8] In the two trials in which aspirin doses were mentioned, patients were advised to take 325 mg daily, but long-term treatment adherence was not reported,[18] or the "most commonly prescribed" dose was 1300 mg daily (used in 85%).[8] Aspirin was prescribed in 79% of BMT versus 77% of CEA patients in ECST at three years follow up (doses not specified; $p = .25$).[37] In total, trial primary outcomes occurred in 19.4–26% of patients treated with BMT only (predominantly aspirin) over 12–36 months follow up.[8,18,37]

CEA. Nine RCTs in symptomatic patients included a CEA arm. Three RCTs compared CEA with BMT in symptomatic patients with >50%,[18] 0–100%,[14] and <70% or 70–99% stenosis;[8] six trials randomised ≥50–99% carotid stenosis patients to CEA or EVT.[15,22,23,25,28,38] CREST also included asymptomatic patients with >50% stenosis.[28]

Patients allocated to CEA, in whom the antiplatelet regimen was specified, received aspirin monotherapy (100–325 mg daily),[15,28,38] which was prescribed in 100% for ≥ one year after CEA in CREST[28] and in 79% at 24 months of follow up in SPACE.[38] Other long-term antiplatelet/antithrombotic regimens were prescribed in some patients over time in different trials,[23,25,38] including clopidogrel, aspirin–dipyridamole combination therapy, aspirin–clopidogrel combination therapy,[25,38] anticoagulants, or antiplatelet agents in combination with anticoagulants[23] (combination therapy not described in detail; Table 4).

Overall, various primary outcomes occurred in 1.96 – 14.2% of patients after CEA who were mainly treated with aspirin alone[22,23,28] or in combination with other antiplatelet regimens[15,25,38] over a 6–120 month follow up period.

EVT. In the six major trials included in this review in which symptomatic patients with ≥50–99% carotid stenosis were randomised to EVT,[15,22,23,25,28,38] four employed more modern stenting techniques.[23,25,28,38] EVT patients were predominantly prescribed dual antiplatelet therapy with

Table 2. Anti-thrombotic therapy data from randomised controlled trials in patients with Asymptomatic Moderate or Severe Carotid Stenosis (1995–2016)

Study/Year	Patients	Intervention	Antiplatelet/ Anticoagulant Therapy (AT)	Follow up	Primary & Secondary outcomes	Medical Group	CEA Group	EVT Group
SAPPHIRE [26] 2008 [D]	>80% Asymptomatic carotid stenosis (N = 334)	CEA (N = 167) *vs.* EVT with emboli-protection device (N = 167)	**A, A + C** AT = Both groups received peri-procedural heparin to maintain a therapeutic APTT: 250-300s	3 years	**1°:** Cumulative incidence of stroke, death or myocardial infarction within 30 days after the procedure, or death or ipsilateral stroke between 31 days and 1 year **2°:** Primary end-point plus ipsilateral stroke or death between 1 and 3 years	N/A	20.1% ($p = 0.048$) 26.9% ($p = 0.71$)	12.0% 24.6%
ACST [21] 2010 [E]	'Mainly' Asymptomatic >60% carotid stenosis (12% had symptoms ≤6 months) (N= 3120)	Immediate CEA (N = 1560) *vs.* Best Medical Treatment and deferral of CEA until required (N = 1560; 26% underwent CEA over 10 years)	**A** AT = N/A	10 years	**1°:** Perioperative mortality and morbidity (death or stroke within 30 days) and non-perioperative stroke	Any stroke = 16.9%	Any stroke = 10.8% RR = 0.54 (95% CI: 0.43 −0.68; $p <$ 0·0001)	N/A
ACST-2 [3] 2013 (Interim) [F]	70-99% Asymptomatic carotid stenosis (N = 986 ; 691 with one month follow-up	CEA (N = 348) *vs.* EVT (N = 343) with > 1 month follow-up	**A, C, A + C** AT = 6% (N = 65) of entire group on anticoagulants (not specified)	>1 month interim data	**1°:** Peri-procedural risks (stroke, MI, & death within the 1st month after allocation to CEA or EVT); Long-term prevention of stroke, particularly disabling or fatal stroke, in subsequent years (up to ≥ 5 years)	N/A	1% risk of disabling stroke; 3.5% risk of any stroke, MI or related death < 30 days (outcomes not reported separately)	As illustrated in CEA group
ACT-1 [27] 2016 [G]	N = 1453 Asymptomatic patients with 70-99% stenosis	CEA (N = 364) *vs.* EVT (N = 1089)	**A, C , A + C** AT = heparin or bivalirudin. EVT patients required activated clotting time of > 250 seconds	5 years	**1°:** Death, any stroke or MI during the 30 days after the procedure or ipsilateral stroke during the 365 days after the procedure. **2°:** Composite measure of complications, freedom from re-intervention or restenosis	N/A	3.4% ± 0.98 at 30 days (p value N/A) Ipsilateral 'major' stroke at 30 days = 0.27% ($p = 1.0$) Freedom from any stroke over 5 years = 94.7% ($p = 0.44$)	3.8% ± 0.59 at 30 days (p value not reported) Ipsilateral 'major' stroke at 30 days = 0.36% Freedom from any stroke over 5 years = 93.1%
SPACE-2 [35] 2016 [H]	N = 513 Asymptomatic patients with 70-99% stenosis	BMT alone (N = 113) *vs.* CEA + BMT (N = 203) *vs.* EVT + BMT (N = 197)	**A, C, A + C** AT = N/A	30 days	**1°:** Cumulative rate of death/any stroke within 30 days	0% 30 day stroke/death	1.97% (95% CI: 0.54 − 4.97%) 30 day stroke/ death (p value not reported)	2.54% (95% CI: 0.83 − 5.82%) 30 day stroke/ death

Continued

Table 2-*continued*

Study/Year	Patients	Intervention	Antiplatelet/ Anticoagulant Therapy (AT)	Follow up	Primary & Secondary outcomes	Medical Group	CEA Group	EVT Group
Mannheim [17] 2017 [I]	N = 136 Asymptomatic patients with 70-99% stenosis	CEA (N = 68) *vs.* EVT (N = 68)	**A, A + C** AT = N/A	Mean = 26 months	**1**: 30-day risk of TIA, stroke, MI, death (Outcome events not validated by an independent neurologist)	N/A	1.5% ipsilateral stroke at 30 days	1.5% ipsilateral stroke at 30 days (*p* not significant)
							No contralateral strokes	1.5% contralateral stroke (*p* not significant)
							Hyperperfusion syndrome 1.5%	Hyperperfusion syndrome 2.9% (*p* not significant)
							Composite outcome not reported	Composite outcome and *p* values not reported
					2: TIA, stroke, death or > 70% restenosis over 5 years (Outcome events not validated by an independent neurologist)		10.5%	9.2% (*p* not significant)

[D] Aspirin (81 or 325 mg/day) started at least 72 hours pre-procedurally and continued indefinitely. Patients in EVT arm also received Clopidogrel (75 mg daily) 24 hours before the procedure and continued for 2-4 weeks thereafter.
[E] 'Mainly' Aspirin: 91% in immediate group *vs.* 89% in deferral group (dose N/A). 26% of the deferral cohort subsequently underwent CEA.
[F] No symptoms for at least 6 months prior to randomisation; Aspirin (dose N/A); approximate N = 345 in EVT, 300 in CEA groups. Clopidogrel (dose N/A); approx N = 330 in EVT, 60 in CEA groups. Dual antiplatelet therapy approximate N = 320 in EVT, 40 in CEA groups.
[G] All patients received aspirin (325 mg daily) starting 3 days before the procedure and indefinitely after the procedure. Patients who underwent stenting also received clopidogrel daily (dose N/A) for 3 days before the procedure and for 30 days thereafter.
[H] BMT was implemented according to 'current evidence-based guidelines'. Aspirin or clopidogrel (but not dual antiplatelet therapy) had to be administered for at least 3 days before CEA. All patients in the EVT arm were treated with aspirin-clopidogrel dual antiplatelet therapy for at least 3 days before and for at least 6 weeks after CAS (doses not specified). The trial was terminated early after 513 patients were randomised due to slow recruitment.
[I] The authors reported that patients should have already been started on 'appropriate medical treatment' e.g. aspirin (dose or duration of aspirin not specified) and statins (74-82%) etc. EVT patients were prescribed clopidogrel 75 mg the day before and for 45 days after EVT. One assumes all EVT patients were on both aspirin and clopidogrel for this 46 day period only and possibly on aspirin monotherapy thereafter, but the precise proportion of patients in each treatment arm who were on aspirin-clopidogrel combination therapy or perhaps clopidogrel monotherapy was not reported.

aspirin—clopidogrel[15,23,25,28,38] or aspirin—ticlopidine[23,28] for 48[28] to 72 hours[23,38] before the procedure, and continued for ≥30 days afterwards (Table 4).[23,28,38] Aspirin doses varied from 100 mg daily to 325 mg twice daily,[15,22,23,25,28,38] combined with either 75 mg of clopidogrel daily,[15,23,25,28,38] or 250 mg twice daily[28] or 500 mg once daily[23] of ticlopidine. Long-term follow up for two years in SPACE and five years in ICSS revealed antiplatelet continuation rates of 89% and 87%, respectively, with aspirin monotherapy being most commonly prescribed.[25,38]

Primary outcomes occurred in 1.88 — 14.3% of patients after EVT who were mainly treated with initial aspirin—clopidogrel combination therapy, usually for one month after the procedure,[23,28,39] with longer term antiplatelet therapy left to the discretion of treating physicians.

Randomised trials of antiplatelet therapy in patients with carotid stenosis

Seven published studies specifically included symptomatic or asymptomatic patients randomised to receive different antiplatelet/antithrombotic regimens, three of these around the time of CEA and two around the time of EVT.

The CARESS study randomised patients with symptomatic ≥50% extracranial carotid stenosis with MESs on TCD to short-term treatment with aspirin alone (75 mg daily) or aspirin—clopidogrel combination therapy.[31] By Day 7, there was a significant reduction in MESs ($p = .0046$), with no significant increase in bleeding complications in patients on aspirin—clopidogrel compared with those on aspirin monotherapy. However, the study was not powered to show differences in clinical outcomes between groups during the short follow up period of the trial.

The AMBulatory Dual Antiplatelet (AMBDAP) study found that the relative reduction in MESs compared with baseline values was similar after randomisation to combination therapy with aspirin—dipyridamole ($n = 30$) versus aspirin-clopidogrel ($n = 30$) in patients with recently symptomatic ≥ 50% ICA stenosis (RR 75.5% vs. 77.5%; $p = .77$).[32]

Three studies specifically included symptomatic or asymptomatic carotid stenosis patients with information

Table 3. Data on antithrombotic therapy from randomised controlled trials of CEA *vs.* Best Medical Treatment in patients with Symptomatic Carotid Stenosis

Study/Year	Patients	Intervention	Antiplatelet/ Anticoagulant Therapy (AT)	Follow up	Primary & Secondary outcomes	Medical Treatment Arm	CEA Arm
VA Symptomatic [18] 1988 [J]	>50% Symptomatic stenosis (N =189)	CEA (N = 91) *vs.* Best Medical Treatment (N = 98)	**A** AT = N/A	12 months	Stroke or crescendo TIA	19.4%	7.7% ($p = 0.01$)
ECST [14] 1995 [K]	0-100% Symptomatic stenosis (N = 3024)	CEA (N = 1811) *vs.* Control (Surgery deferred for as long as possible; N =1213)	**A** AT = Similar' in both groups; names and doses N/A; 6% of CEA *vs.* 8 % of controls during F/U ($p = 0{\cdot}09$)	3 years	**1**: Death; major stroke or death within 30 days of treatment **2**: Major stroke not associated with trial surgery.	3 year ipsilateral 'major' stroke rate with 80 −100% stenosis = 20.6%	3 year ipsilateral 'major' stroke rate with 80−100% stenosis = 6.8% ($p < 0.001$)
NASCET[8] 1998 [L]	**Group 1:** Symptomatic <50% or 50-69% stenosis (N = 2226)	**Group 1:** CEA (N = 1108) *vs.* Best Medical Care (N = 1118)	**A** AT = N/A	**Group 1:** 5 years	**1**: Death, any stroke, ipsilateral stroke during peri-operative period and follow-up	**Group 1:** Ipsilateral stroke < 50% stenosis = 18.7% ($p = 0.16$) Ipsilateral stroke 50−69% stenosis = 22.2%	**Group 1:** Ipsilateral stroke <50% stenosis = 14.9% Ipsilateral stroke 50-69% stenosis = 15.7% ($p = 0.045$)
	Group 2: Symptomatic 70-99% stenosis (N = 659)	**Group 2:** CEA (N = 328) *vs.* Best Medical Care (N = 331)		**Group 2:** 2 years	**2**: Ipsilateral stroke	**Group2:** Ipsilateral stroke = 26%	**Group 2:** Ipsilateral stroke = 9% (p <0.001)

[J] Aspirin 325 mg daily 'recommended'. No further details available and continuation rates not described.
[K] Aspirin use in 58.7% of 'Medical Treatment Arm' *vs.* 54.7% of the CEA group at recruitment ($p < 0.05$); dose N/A. During follow up, aspirin prescribed in 79% of the Medical Treatment *vs.* 77% of the CEA group, but doses not specified ($p = 0.25$).
[L] **Group 1:** Percentages in Medical treatment & CEA groups, respectively: No Antithrombotics = 17% *vs.* 15%; Aspirin < 650mg daily = 45% *vs.* 48%. Aspirin > 650mg daily = 38% *vs.* 37%. **Group 2:** 85% were on anti-thrombotic therapy in each arm, and 'usually' aspirin 1300mg daily.

around the time of CEA. Lindblad et al.[33] randomised 232 patients (17 asymptomatic) undergoing CEA to placebo or aspirin 75 mg daily, starting the night before surgery and continuing for 6 months. Median stenosis severity on Duplex ultrasound was 80% in both groups. Intra-operative bleeding rates did not differ between the groups. Aspirin significantly reduced the incidence of disabling stroke in the first week vs. placebo (1.7% vs. 9.6%; $p = .01$). After 6 months follow up, there were no significant differences in the risk of recurrent TIA/stroke or death between groups.

The Aspirin and Carotid Endarterectomy (ACE) Trial randomised 2849 CEA patients to 81 mg, 325 mg, 650 mg, or 1300 mg of aspirin daily throughout the peri-operative period.[29] Aspirin doses of 81 mg and 325 mg were termed "low dose", whereas 650 mg or 1300 mg were termed "high dose". No significant differences in haemorrhagic stroke rates or "non-cerebral" bleeding complications were found between groups. The risk of stroke, MI or death at 30 days was not significantly lower in patients randomised to low dose vs. high dose aspirin (5.4% vs. 7.0%, $p = .07$). However, because the data could potentially have been biased by including patients taking >650 mg of aspirin daily before randomisation alongside patients who had only started taking aspirin the day before CEA, subsequent efficacy analysis excluding those patients taking >650 mg prior to randomisation revealed that the risk of stroke, MI, or death at 30 days was 3.7% on low dose versus 8.2% on high dose aspirin ($p = .002$).

Increasing embolisation on TCD in the early post-operative period after CEA increases the risk of post-operative thrombotic stroke. Payne et al.[30] randomised 100 patients (84% symptomatic) with a mean stenosis of 80−81% who were scheduled for CEA, and on 150 mg aspirin daily for ≥ 4 weeks, to receive a single dose of 75 mg of clopidogrel ($n = 46$) or placebo ($n = 54$) 12 hours pre-CEA. In comparison with placebo, clopidogrel reduced platelet fibrinogen binding in response to ADP on whole blood flow cytometry ($p < .05$) and conferred a tenfold reduction in the odds of patients having > 20 emboli on TCD in the first three hours post-operatively ($p = .01$). In clopidogrel treated patients, the time from flow restoration to skin closure (an indirect marker of haemostasis) was significantly increased ($p = .04$), although there was no increase in overall bleeding complications.

Table 4. Data on antithrombotic therapy from randomised controlled trials of CEA *vs.* EVT in patients with Symptomatic Carotid Stenosis

Study/Year	Patients	Intervention	Antiplatelet/ Anticoagulant Therapy (AT)	Follow up	Primary & Secondary outcomes	Medical Treatment Arm	CEA Arm	EVT Arm
KENTUCKY [15] 2001 [M]	Symptomatic >70% carotid stenosis (N = 104)	CEA (N = 51) vs. EVT (N = 53)	**A + C** AT = Peri-operative heparinisation with 100 U/kg in EVT patients	2 years	MI, All stroke, All TIA	N/A	1 fatal MI (1.96%; *p* value N/A) No strokes No TIAs	No MIs No strokes 1 TIA (1.88%; *p* value N/A)
CAVATAS [22] 2009 [N]	Carotid stenosis (mean severity = 86%) 97% Symptomatic ≤ 12 months (N = 504)	CEA (N = 253) *vs.* EVT. (N = 251)	**A** AT = IV heparin at the time of EVT and for ≥ 24 hrs afterwards, unless contra-indicated; CEA: N/A	3 years 8 years	**1**: Death or disabling stroke in any territory **2**: Ipsilateral non-peri-operative TIA or stroke	N/A	14.2% 17.2%	14.3% (HR: 1·03; 95% CI: 0·64−1·64; *p* = 0·9). 19.3 % (HR: 1·29; 95% CI: 0·78 −2·14)
EVA-3S [23] 2006 [O]	Symptomatic >60% carotid stenosis (N = 527)	CEA (N=259) *vs.* EVT (N = 261)	**A, C, A + C, A + T** AT = 12.3% of CEA group pre-operatively and 6.3% post-operatively; N/A for EVT group.	6 months; stopped earlier than planned	**1**: Composite of any stroke or death ≤ 30 days of treatment. **2**: Any stroke or death ≤ 6 months	N/A	3.9% 6.1% (*p* = 0.02)	9.6%; Relative risk: 2.5 (95% CI: 1.2 to 5.1). 11.7%
SPACE [38] 2006 [P]	Symptomatic >70% carotid stenosis (N= 1214)	CEA (N = 601) *vs.* EVT (N = 613)	**A, C, A + C, A + D** AT = 6% in CEA group *vs.* 5% in EVT group on Phenprocoumon at 24 months	2 years	Ipsilateral ischaemic stroke ≤ 2 years, including any peri-procedural stroke or death; Ipsilateral ischaemic stroke between 31 days and 2 years on an intention-to-treat (ITT) basis	N/A	8.8% 1.9%	9.5% (HR = 1·10; 95% CI: 0·75−1·61) 2.2% (HR = 1·17; 95% CI: 0·51−2·70)
ICSS [25] 2015 [Q]	Symptomatic ≥50% carotid stenosis (ITT population: N = 1710)	CEA (N = 857) *vs.* EVT (N = 853)	**A, C, A + C, A + D** AT = Vitamin K antagonists in 10% of CEA *vs.* 7%. of EVT group; Other anti-coagulants in 1% of CEA and 1% of EVT group; *p* values N/A	5 years	**1**: Fatal or disabling stroke in any territory between randomisation and last follow up **2**: Ipsilateral carotid territory stroke > 30 days after treatment Other **2**outcomes not displayed in this table		6.5% 3.4%	6.4% (HR: 1.06; 95% CI: 0.72 −1.57) 4.7% (HR = 1·29; 95% CI: 0·74−2·24; *p* = 0.36)
CREST [28] 2010 [R]	Total N = 1607: Symptomatic (N = 763) and Asymptomatic patients (N = 844) with >50% stenosis	CEA (N = 788) *vs.* EVT (N = 819)	**A, C, A + C, A + T** AT = N/A	10 years	**1**: Any stroke, MI, or death during the peri-procedural period or ipsilateral stroke up to 10 years after randomisation **2**: Risk of peri-procedural stroke or death and subsequent ipsilateral stroke up to 10 years after randomisation		9.9% (95% CI: 7.9 −12.2) (HR 1.1; *p* = 0.38) 7.9% (95% CI: 5.9−10) (HR 1.37; *p* = 0.04)	11.8% (95% CI: 9.1 −14.8) 11% (95% CI: 8.5 −13.9)

[M] All patients received 325 mg of aspirin and 75 mg of clopidogrel before EVT or CEA for an unspecified period. Continuation rates post-intervention not specified. The Activated Clotting Time was maintained at > 300 during the procedure in EVT patients.

[N] CEA group: detailed data N/A, but the authors stated that 'antiplatelet therapy' was continued throughout follow-up in both groups. Aspirin (minimum dose 150 mg daily) or an alternative antiplatelet agent, for at least 24 hours before EVT.

[O] Daily aspirin (100 to 300 mg daily) and clopidogrel (75 mg daily) or ticlopidine (500 mg daily) were recommended for 3 days before and 30 days after stenting. 38.2% of the post-op CEA group were on antiplatelet therapy alone, 6.3% were on anticoagulants, and 55.5% were on antiplatelet agents in combination with anticoagulants (combination therapy not described in detail). 100% of the EVT group were on antiplatelet therapy after an unspecified duration of follow-up, of whom 85.4% were on 'dual anti-platelet therapy' with aspirin and either clopidogrel (75 mg) or ticlopidine (500 mg).

[P] CEA patients received 100 mg of Aspirin daily whereas EVT patients received 100 mg aspirin plus 75 mg clopidogrel daily for at least 3 days before and 30 days after the intervention. By 24 months: In the CEA group: 79% were on aspirin, 11% on clopidogrel, 2% on aspirin + dipyridamole, and 2% on aspirin + clopidogrel; In the EVT group: 69% were on aspirin, 11% on clopidogrel, 1% on aspirin + dipyridamole, and 8% on aspirin + clopidogrel.

[Q] For stenting procedures, a combination of aspirin and clopidogrel was recommended (dose and duration not specified). At 5 years, in the CEA group: 51% were on aspirin, 14% on clopidogrel, 15% on aspirin + dipyridamole, and 5% on aspirin + clopidogrel; in the EVT group: 57% were on aspirin, 12% on clopidogrel, 14% on aspirin + dipyridamole and 4% on aspirin + clopidogrel; *p* values N/A.

[R] CEA: Aspirin 325 mg daily before procedure and for at least a year thereafter. EVT: Aspirin 325 mg twice daily and clopidogrel 75 mg twice daily for at least 48 hours before stenting; after EVT, patients received 325mg of aspirin daily or twice daily for 30 days, combined with either clopidogrel 75 mg daily or Ticlopidine 250 mg twice daily for at least 4 weeks; longer-term anti-thrombotic therapy was not specified in the EVT group. Of note, there were no significant differences in peri-procedural stroke and death rates after CEA (2.5%) *vs.* (1.4%) EVT in asymptomatic patients (HR: 1.88; *p* value N/A).

Table 5. Symptomatic and asymptomatic patients randomised to different medication regimens

Study/Year	Patients	Study	Antiplatelet/ Anticoagulant Therapy (AT)	Follow up	Primary & Secondary outcomes	Outcome
Lindblad [33] 1993 [S]	232 patients; median stenosis of 80% (17 Asymptomatic)	Randomised to Aspirin 75mg/day (N = 117) or Placebo (N = 115)	**A** AT = N/A	6 months	Early disabling stroke in 1st week All recurrent neurological events All deaths	1.7% vs. 9.6% ($p = 0.01$) 21% placebo *vs.* 12.8% aspirin ($p = 0.12$) 8.7% placebo *vs.* 3.4% aspirin ($p = 0.11$)
ACE [29] 1999 [T]	2849 patients (70% had >70% stenosis) scheduled for endarterectomy. 54% Asymptomatic (N = 1539) and 46% Symptomatic (N = 1310)	Randomised to low dose (N = 1935) or high dose (N = 1409) Aspirin	**A** AT = N/A	3 months	**1°:** Combined rate of stroke, myocardial infarction, and death **2°:** Ipsilateral stroke or death	6.7% [low dose] *vs.* 8.4% [high dose]; ($p = 0.03$) 4.9% [low dose] *vs.* 6.5% [high dose]; ($p = 0.07$)
Payne *et al* [30] 2004 [U]	100 patients scheduled for endarterectomy (average stenosis = 80-81%) 16% Asymptomatic and 84% Symptomatic	Randomised to Aspirin + Clopidogrel (N = 46) or Aspirin + Placebo (N = 54)	**A, A + C** AT = N/A	3 hours post-operatively	Post-operative >20 MES detected on TCD	2.2% on Aspirin + Clopidogrel vs. 18.2% on Aspirin + Placebo ($p = 0.01$)
CARESS [31] 2005 [V]	≥50% Symptomatic carotid stenosis with micro-emboli on TCD (N = 107)	Dual Aspirin & Clopidogrel (N = 51) *vs.* Aspirin monotherapy (N = 56)	**A, A + C** AT = None as this was an exclusion criterion	7 days	**1°:** Proportion of patients MES + on day 7 **2°:** Proportion of patients MES + on day 2 and 7 as well as embolisation rate	MES positivity lower with dual therapy than aspirin monotherapy on day 7 (43.8% *vs.* 72.7%; $p = 0.0046$)
McKevitt *et al* [34] 2005 [W]	> 70% stenosis undergoing EVT (N = 50, 38 Symptomatic, 9 Asymptomatic, 3 excluded from analysis)	75 mg Aspirin daily + IV Heparin (N = 24) *vs.* Dual Aspirin & Clopidogrel (N = 23)	**A, A + C** AT = IV Heparin 1 mg/Kg	30 days	**1°:** 'Neurological complication rate' including amaurosis fugax, TIA and all stroke	Aspirin + Heparin 25% vs. Aspirin + Clopidogrel 0% ($p = 0.02$)
Dalainas [16] 2006 [X]	70-90% stenosis (88% Asymptomatic) undergoing EVT (N = 100)	Group A: Aspirin + 24 hours of IV Heparin (N= 50) *vs.* Group B: Aspirin + Ticloplodine (N= 50)	**A, A + T** AT = 24 hour post-op heparin infusion (dose N/A)	30 days	**1°:** Ipsilateral Neurological complications (Cerebrovascular events) **2°:** Cerebral haemorrhagic complications or gastrointestinal bleeding **2°:** Groin / Retroperitoneal haematoma	1°: Aspirin + Heparin 16% *vs.* Aspirin + Ticlopidine 2% ($p < 0.05$) 2°: No cerebral haemorrhage or gastrointestinal bleeding 2°: Aspirin + Heparin 4% *vs.* Aspirin + Ticlopidine 2% ($p > 0.05$)

Continued

Table 5-*continued*

Study/Year	Patients	Study	Antiplatelet/ Anticoagulant Therapy (AT)	Follow up	Primary & Secondary outcomes	Outcome
King *et al* [32] 2011 [Y]	Recently symptomatic ≥50% carotid stenosis on Aspirin. Ambulatory TCD x 12 hours performed at baseline and after 48 hours (N = 60)	Aspirin + Dipyridamole (N=30) *vs.* Aspirin + Clopidogrel (N = 30)	**A, A + C, A + D** AT = None as this was an exclusion criterion	48 hours	MES frequency on TCD	Similar reduction in MES frequency with Aspirin + Dipyridamole *vs.* Aspirin + Clopidogrel (75.5% *vs.* 77.5%; $p = 0.77$)

[S] Randomised to aspirin 75 mg (N = 117) or placebo (N = 115) from the night prior to surgery to at least 6 months thereafter.
[T] Randomised to receive aspirin 81 mg daily (N = 709) or 325 mg daily (N = 708) [combined into 'low dose group'] *vs.* 650 mg daily (N = 715) or 1300 mg daily (N = 717) [combined into 'high dose group'].
[U] All patients received 150 mg of aspirin for 4 weeks prior to procedure. Patients randomised to also receive one dose of clopidogrel 75 mg or placebo 12 hours prior to surgery.
[V] All patients received 75 mg of aspirin daily. Patients randomised to also receive clopidogrel were given a loading dose of 300 mg of clopidogrel on day 1, followed by 75 mg of clopidogrel daily until day 7; Matching placebo was administered to the placebo group.
[W] Randomised to 75 mg aspirin daily + IV Heparin (APTT R: 1.5-2.5 x 24 hours) versus 75 mg aspirin daily plus clopidogrel (300 mg stat 6-12 hours pre-op, 75 mg 2 hours pre-op + 75 mg daily for days 1-28).
[X] Group A: Aspirin 325 mg daily at least 7 days before the procedure combined with a heparin infusion for 24 hours post-operatively (dose of heparin not specified) and aspirin 325mg monotherapy daily thereafter. Group B: Aspirin 325mg daily and ticlopidine 250mg twice daily for at least 7 days before the procedure and for 30 days thereafter, followed by 325 mg daily of long-term aspirin monotherapy. All patients also received 100 IU/Kg of heparin during the EVT procedure.
[Y] All patients were on aspirin at the start of the study: 300 mg loading dose and then 75 mg daily. After randomisation, patients were also allocated to receive dipyridamole MR 200 mg twice daily or clopidogrel (300 mg loading dose, and then 75 mg daily) for 30 days.

McKevitt et al.[34] randomised 50 patients undergoing EVT for ≥70% carotid stenosis to 75 mg of aspirin daily and intravenous heparin for 24 hours (target APTT ratio 1.5—2.5) or dual antiplatelet therapy with aspirin 75 mg daily and "loading doses" of clopidogrel followed by 75 mg of clopidogrel daily for 28 days. In total, 47 patients with data available for analysis underwent stenting, 38 of whom were symptomatic and nine asymptomatic. The combined risk of ipsilateral amaurosis fugax, TIA, and all stroke was 25% in the aspirin—heparin group versus 0% in the aspirin—clopidogrel group after 30 days follow up ($p = .02$). Bleeding complications (groin haematoma or "excessive bleeding" at the groin site) occurred in 17% of the aspirin—heparin and 9% of the aspirin—clopidogrel group ($p = .35$).

Dalainas et al.[16] randomised predominately asymptomatic patients with ≥70% carotid stenosis who were undergoing EVT to receive aspirin 325 mg daily and 24 hours of post-operative IV heparin versus aspirin 325 mg daily combined with ticlopidine 250 mg twice daily for 30 days following EVT (Table 5).There was a significant excess of ipsilateral ischaemic stroke or TIAs ($p < .05$), but no significant excess of haemorrhagic complications in the aspirin—heparin compared with the aspirin-ticlopidine combination groups. Although the authors clearly explained their rationale for using ticlopidine rather than clopidogrel in this trial, ticlopidine is no longer routinely used in TIA or stroke patients due to its less favourable adverse effect profile than clopidogrel.

DISCUSSION

This novel, detailed review has revealed that 325 mg of aspirin monotherapy daily has not been shown to significantly reduce the incidence of all ischaemic events and death from any cause compared with placebo in a randomised trial in patients with >50% asymptomatic carotid stenosis.[20] However, data from a meta-analysis of primary prevention trials showed that aspirin therapy was associated with a 12% reduction in "serious vascular events", predominately fatal myocardial infarction (MI).[40] Observational data from the ACES study showed that treatment with "antiplatelet therapy" significantly reduced the two year risk of ipsilateral TIA or stroke, or stroke or any cardiovascular death compared with "no antiplatelet therapy" during follow up.[1,41] As such, it is recommended that asymptomatic patients receive aspirin (75—325 mg daily) or another antiplatelet regimen to reduce the risk of cardiac and other vascular events in this patient population.

Data from interventional trials in asymptomatic patients support the use of 81—325 mg of aspirin daily peri-procedurally.[19,26,27,42] There are no data from RCTs regarding the efficacy of clopidogrel monotherapy or aspirin—dipyridamole combination therapy in asymptomatic patients,[2] but if intolerant of aspirin, it is reasonable to empirically use clopidogrel monotherapy for protection of vascular events pending data from future RCTs.[1]

Low to medium dose aspirin (81—325 mg daily) is superior to higher dose aspirin (650—1300 mg daily) at preventing recurrent vascular events in patients with predominantly moderate to severe asymptomatic or symptomatic stenosis undergoing CEA.[29] Data from modern intervention trials in symptomatic patients also support the use of 100—325 mg of aspirin daily if aspirin is prescribed in the peri-procedural period around CEA or EVT.[22,23,25,38,43]

Short-term treatment with aspirin (75—160 mg) and clopidogrel (300 mg loading dose, followed by 75 mg daily for 7 days) is effective at reducing MES on TCD in patients with ≥50% symptomatic extracranial carotid stenosis from CARESS.[31] However, there is insufficient evidence to recommend short-term aspirin and clopidogrel combination therapy to significantly reduce the risk of "clinical outcomes of recurrent TIA or stroke" in patients with extracranial carotid

stenosis, because this study was not designed or powered to detect differences in clinical outcomes.[31] The use of a single 75 mg dose of clopidogrel 12 hours pre-operatively in patients already established on 150 mg of aspirin daily significantly reduced the incidence of having > 20 MES on TCD within three hours of CEA, but increased the time to securing haemostasis peri-operatively.[30]

Pre-operative aspirin—dipyridamole therapy appears to be as effective at reducing MES as aspirin—clopidogrel combination therapy in patients with ≥50% recently symptomatic extracranial carotid stenosis with MES on TCD.[32] These data are interesting because vascular surgeons who might be concerned about peri-operative bleeding risks on aspirin—clopidogrel combination therapy during CEA also have the option of operating on aspirin—dipyridamole; this regimen did not increase the risk of bleeding compared with aspirin monotherapy in an overall TIA and ischaemic stroke patient population in the ESPS-2 trial.[9]

Virtually every guideline recommends that EVT patients should receive dual antiplatelet therapy throughout the peri-procedural period.[3,22,23,26—28,35,38,39] However, this is largely based on the coronary disease literature, with data from only one small pilot RCT in EVT patients on aspirin and clopidogrel.[34] No RCT has randomised EVT patients to aspirin—clopidogrel versus aspirin—dipyridamole. Notwithstanding this, most investigators now advise at least four weeks of aspirin—clopidogrel treatment after EVT[15,17—19,33,38] which appears to be safe.[3,17,23,25—27,38,43] This is based on the fact that patients typically continued aspirin—clopidogrel combination therapy for 4—6 weeks after EVT[23,25—28,35,38] and then typically reverted to antiplatelet monotherapy, predominantly with aspirin thereafter. In practice, physicians may opt to continue clopidogrel instead of aspirin monotherapy after 4 weeks to optimise long-term protection against vascular events.[1,10] Secondary analysis of the CREST[44] and EVA-3S trials[45] found no significant association between antiplatelet use and restenosis rates in the CEA or EVT cohorts. However, to our knowledge, no randomised trial has specifically compared the effects of different antiplatelet regimens on carotid restenosis rates; this issue warrants further study.

In patients not undergoing intervention due to patient or physician choice, it is reasonable to extrapolate data from trials in TIA/stroke patients overall to recommend treatment with either clopidogrel 75 mg daily or aspirin 75 mg daily in combination with dipyridamole MR 200 mg twice daily.[1] Aspirin monotherapy (75—325 mg daily) should be considered in patients with dipyridamole or clopidogrel intolerance, and dipyridamole MR 200 mg twice daily monotherapy if intolerant of aspirin and clopidogrel.[1]

This review had some limitations. The studies included in this review varied in their approach to antiplatelet therapy. Because surgical or endovascular intervention was the primary focus of these interventional trials, reporting of antiplatelet regimens, dosing and duration was sometimes incomplete or not reported. Data were included from all randomised trials in patients with moderate to severe carotid stenosis because of the robustness of event reporting in these trials to assess outcomes on contemporaneously prescribed antiplatelet regimens, but the majority of trials did not actually randomise patients to receive different antiplatelet regimens. Therefore, direct comparisons of efficacy and safety of different regimens in the arms of many of these trials was impossible. However, the available data do allow one to inform patients of the risk of recurrent events on specific named antiplatelet treatment regimens at least. Published studies did not always provide detailed data on the proportions of patients with different degrees of stenosis or occlusion, and sometimes combined symptomatic and asymptomatic patients in the analyses, thus making clinical interpretation difficult. Furthermore, because of the heterogeneity of trial design, inclusion criteria, outcome measures, and duration of follow up, a systematic assessment of bias of all of the included trials was not conducted as part of this comprehensive review process, and a meta-analysis of published data was not performed. Furthermore, a meta-analysis of all published and non-published individual patient data was beyond the scope of this review.

Among the interventional trials, only one study in asymptomatic patients reported "extra-cerebral" bleeding events[27] and two studies independently described the risk of haemorrhagic stroke.[20,21] In symptomatic patients, only three studies reported on the risk of haemorrhagic stroke,[22,25,38] and none reported on any other bleeding events aside from post-operative haematomas. The risk of bleeding on these antiplatelet regimens warrants further investigation in future studies.

Overall, symptomatic patients treated with "optimal medical therapy alone" had a numerically higher risk of recurrent vascular events (19.4—26% over 1—3 years)[13,14,18] compared with their asymptomatic counterparts (11—20.6% over 2.7—4 years).[5,18] However, the risk of recurrent vascular events in asymptomatic carotid stenosis patients has markedly decreased over time on more modern secondary preventive therapy, for example, with rates of "non-peri-operative stroke" of only 1.3—1.8% annually in the under 75 year old "deferred intervention group" in the last five years of recruitment to ACST.[21] Potential explanations for this observed decline in non-peri-operative stroke risk in ACST include the increasing use of statins over time, and potential differences in plaque morphology, with higher risk plaques more likely to become symptomatic earlier during follow up.

Symptomatic ≥50% carotid stenosis patients were at risk of recurrent vascular events in the peri-operative (3.9—9.6%) and post-operative period (6.1—14.3% over 6—96 months) despite contemporary antiplatelet regimens. Significant peri-operative (1.97—3.5%) and longer-term post-operative risks of recurrent vascular events of 5.1—26.9% over 2.7—3 years[26] have been observed in asymptomatic patients, with the risk of outcomes mainly determined by other comorbidities, thus emphasising the importance of optimising future antiplatelet therapy regimens in this patient population also.

High on treatment platelet reactivity (HTPR) on *ex vivo* platelet function/reactivity testing is a potential risk factor for vascular events on antiplatelet therapy.[46] To date, no

studies have been adequately powered to definitively comment on whether *ex vivo* HTPR status predicts the risk of vascular events in asymptomatic or symptomatic carotid stenosis patients.[47,48] Furthermore, the use of short-term[31,49] or ambulatory[32] TCD monitoring for MES may act as a surrogate marker of the efficacy of antiplatelet regimens in vivo, and the inclusion of *nested* platelet function/reactivity and TCD studies within future trials has the potential to enhance trial design and facilitate personalised medicine in individual carotid stenosis patients.

In conclusion, there is a relatively limited evidence base to guide the choice of optimal antiplatelet therapy in patients with carotid stenosis. However, the available data collated in this review do allow clinicians to inform patients of the risk of recurrent events on specific, named antiplatelet treatment regimens used in randomised trials. Detailed reporting of antiplatelet regimens, combined with intra-group randomisation of patients should also be performed, where feasible, in future randomised trials, with comprehensive reporting of recurrent cerebrovascular events, to assess the relative efficacy and safety of different antiplatelet regimens to optimise peri-procedural and long-term preventive treatment in asymptomatic and symptomatic carotid stenosis patients.

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