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Authors	Gasior, Sara A.;O'Donnell, John P. M.;Davey, Matthew;Clarke, James;Jalali, Amirhossein;Ryan, Éanna;Aherne, Thomas M.;Walsh, Stewart R.
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Optimal Management of Asymptomatic Carotid Artery Stenosis: A Systematic Review and Network Meta-Analysis

Sara A. Gasior, John P.M. O'Donnell, Matthew Davey, James Clarke, Amirhossein Jalali, Éanna Ryan, Thomas M. Aherne, Stewart R. Walsh

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Short title: Systematic Review and Network Meta-Analysis of Optimal Management in Asymptomatic CAS

Optimal Management of Asymptomatic Carotid Artery Stenosis: A Systematic Review and Network Meta-Analysis

Sara A. Gasior [a,*], John P.M. O'Donnell [a,b], Matthew Davey [b,c], James Clarke,[b] Amirhossein Jalali [d], Éanna Ryan [b], Thomas M. Aherne [c] and Stewart R. Walsh[a,b]

[a]Department of Vascular Surgery, University Hospital Galway, Galway, Ireland
[b]Lambe Institute for Translational Discipline of Surgery, National University of Ireland, Galway, Ireland
[c]Department of Surgery, Royal College of Surgeons in Ireland, Dublin, Ireland
[d]School of Mathematical Sciences, University College Cork, Cork, Ireland

[*]Corresponding author. Department of Vascular Surgery, University Hospital Galway, Ireland. saragasior@gmail.com (Sara A. Gasior).

WHAT THIS PAPER ADDS

Optimal management of asymptomatic carotid stenosis remains challenging. Best medical treatment (BMT) has evolved such that it is no longer appropriate to combine different medical regimens under the broad heading of BMT. Therefore, a network meta-analysis was undertaking, which included traditional and modern BMT as separate arms. The results suggest that modern BMT may have comparable efficacy to carotid endarterectomy in reducing morbidity.

Objective: Management of asymptomatic carotid artery stenosis (ACAS), including carotid endarterectomy (CEA), carotid artery stenting (CAS), and best medical treatment (BMT), remains inconsistent in current practice. Early studies reported a benefit of CEA *vs.* BMT; however, the current risk–benefit profile of invasive therapy lacks consensus. By evaluating the effects of modern BMT *vs.* invasive intervention on patient outcomes, this study aimed to influence the future management of ACAS.

Methods: A systematic review and series of network meta-analyses were performed assessing peri-operative (within 30 days) and long term (30 days – 5 years) stroke and mortality risk between ACAS interventions. Total stroke, major, minor, ipsilateral, and contralateral stroke subtypes were assessed independently. Traditional (pre-2000) and modern (post-2000) BMT were compared to assess clinical improvements in medical therapy over the previous two decades. Risks of myocardial infarction (MI) and cranial nerve injury (CNI) were also assessed.

Results: Seventeen reports of 14 310 patients with > 50% ACAS were included. CEA reduced the odds of a peri-operative stroke event occurring *vs.* CAS (odds ratio [OR] 1.6, 95% confidence interval [CI] 1.1 – 2.2 [0 – 20 fewer/1 000]). CEA and CAS reduced the long term odds of minor strokes (OR 0.35, 95% CI 0.21 – 0.59 [20 fewer/1 000]) and ipsilateral strokes (OR 0.27, 95% CI 0.19 – 0.39 [30 fewer/1 000]) *vs.* all BMT. CEA reduced the odds of major strokes and combined stroke and mortality *vs.* traditional BMT; however, no difference was found between CEA and modern BMT. CAS reduced the odds of peri-operative MI (OR 0.49, 95% CI 0. 26 – 0.91) and CNI (OR 0.07, 95% CI 0.01 – 0.42) *vs.* CEA.

Conclusion: Modern BMT demonstrates similar reductions in major stroke, combined stroke, and mortality to CEA. The overall risk reductions are low and data were unavailable to assess subgroups which may benefit from intervention. However, BMT carries the potential to reduce the requirement for surgical intervention in patients with ACAS.

Keywords: Best medical treatment, Carotid artery disease, Carotid endarterectomy, Carotid stenting, Meta-analysis

<H1>INTRODUCTION

The optimal interventional strategy for asymptomatic carotid artery stenosis (ACAS) remains variable in current practice.[1] While a number of early randomised trials examining asymptomatic disease identified significant benefits associated with carotid endarterectomy (CEA) *vs.* best medical treatment (BMT),[2–4] a distinct lack of consensus remains regarding the potential risk to benefit profile of invasive intervention. This is largely related to improvements in the delivery and constitution of BMT in recent decades,[5] the evolution of treatment paradigms following the introduction of carotid artery stenting (CAS), and the relatively modest reductions in stroke risk associated with intervention.[2–4]

Indeed, since the conduct of the original trials of patients with ACAS,[2–4] stroke rates, for all degrees of ACAS, have reduced dramatically.[5] This potentially diminishes the benefits of asymptomatic CEA further and implies an improvement in BMT. Consequently, it has been hypothesised that up to 94% of interventions for ACAS may be unnecessary.[5] Additionally, randomised controlled trials RCTs; Asymptomatic Carotid Surgery Trial [ACST-1], Asymptomatic Carotid Atherosclerosis Study [ACAS]) have shown that men younger than 75–80 years with at least 60% ACAS have benefitted from CEA over BMT; however, other subgroups, including women, have not been shown to benefit from CEA *vs.* BMT.

CAS is a user dependent alternative that was introduced for patients deemed to be too high risk for CEA, with rates of periprocedural stroke following CAS consistently higher than those seen with CEA, despite ongoing developments in embolic protection devices.[6,7] Nevertheless, CAS is an economically attractive procedure for hospitals, being more prevalent in for profit hospital settings.[8] However, improved technologies, optimum patient selection, and a plateau in operator experience carries the possibility of diminished rates of periprocedural outcomes with further trials ongoing to evaluate this effect.

With regard to BMT, initial guidelines were ambiguous about the medical management of ACAS and focused more on the degree of stenosis CEA. Medical interventions, specifically antiplatelet therapy, were seen more as a peri-operative adjunct rather than an independent strategy.[9] It was not until 1998 that other important risk factors such as blood pressure control, smoking cessation, lipid lowering drugs, moderate alcohol consumption, and antiplatelet therapy were also strongly advocated for.[10]

The ACST-1 trial was a randomised trial of early *vs.* deferred endarterectomy with BMT, and involved asymptomatic and recently asymptomatic patients with carotid stenosis.[11] This trial observed patients with ACAS managed with BMT alone from 1993 to 2003, and captured the developing trends toward modern BMT used today. It showed that BMT at the beginning of the trial (1993) included 91% antiplatelet drug use, 51% antihypertensive drug use, 5% anticoagulant use, and 11% lipid lowering drug use. By 2002, use of antihypertensives and lipid lowering therapies increased to 81% and 70% respectively.[11] By 2007, 88% antiplatelet drug use, 89% antihypertensive drug use, 11% anticoagulant use, and 80% lipid lowering drug use were reported.[12]

A systematic review of guidelines for the management of asymptomatic and symptomatic carotid stenosis documented a lack of clarity and underuse of evidence on medical treatment strategies alone to treat ACAS.[13] Furthermore, the review highlighted

concerns that guidelines are based on trials of CEA *vs.* medical treatments alone in which patients were randomised long before the modernisation of BMT, with no current literature highlighting the efficacy of modern BMT. A large amount of high quality data has been produced in the last four years, which may change the outcomes of previous meta-analyses.

Given this continued strategic uncertainty that exists in the asymptomatic patient cohort, this network meta-analysis (NMA) aimed systematically and definitively to appraise the current randomised trial literature to further inform treatment based decision making in those with significant asymptomatic stenosis. This NMA allowed for the comparison of three or more interventions simultaneously by combining both direct and indirect evidence across a network of studies, yielding more precise estimates than a single direct or indirect evaluation. Furthermore, it aimed to evaluate specifically the effects of modern BMT on patient outcomes *vs.* invasive intervention.

<H1>MATERIALS AND METHODS

<H2>*Statement of design*

This analysis was prospectively registered with PROSPERO on 29 December 2021 (CRD42021294015) and performed in accordance with guidelines outlined by the Preferred Items for Systematic Review and Meta-Analysis (PRISMA) extension statement for the reporting of systematic reviews incorporating NMAs of healthcare interventions.[14] Conduct was based upon the PRISMA guidelines, the PICO (population, intervention, comparator, outcome) framework,[15] and the protocol defined in PROSPERO. Ethical approval was not required as the outcome data have been published previously.

<H2>*Study eligibility*

Only published RCTs comparing at least two modalities of ACAS intervention (CEA, CAS, and BMT alone) were included. Patients allocated to CEA and CAS also received BMT. The minimum number of participants within a study was 50. All incorporated asymptomatic carotid disease was evaluated using duplex ultrasonography and/or computed tomography or magnetic resonance angiography (CTA and MRA, respectively). Any type of CEA including traditional, eversion, or modified eversion was included. CAS with and without an embolic protection device was included. BMT included antiplatelets, antihypertensives, lipid lowering agents (i.e., statins), and education to modify risk factors associated with increased stroke risk. Included articles were required to report at least one predefined study endpoint. English language reports alone were analysed, with no time limitation set for the date of publication.

Studies with insufficient data to permit statistical analysis were excluded. Primary authors were not contacted for missing data.

<H2>*Definitions*

Asymptomatic lesions were defined as image confirmed carotid stenosis ≥ 50% in the absence of preceding neurological symptoms, indicating a cerebrovascular event in the six months prior to study enrolment.

Stroke was defined as sudden onset of acute neurologic deficits with focal signs and symptoms lasting 24 hours or longer. Both ischaemic and haemorrhagic strokes were included. *Major stroke* was defined as one or more of the following: (1) on the basis of clinical data as at least moderate disability, with patients requiring help after the stroke; (2) a modified Rankin scale (mRS) score of 3 – 5 after one month; or (3) fatal (causing death directly or indirectly). These symptoms must have persisted for at least one month. *Minor stroke* was defined as one or more of the following: (1) on the basis of clinical data as slight or no residual disability, with patients able to perform most activities of daily living independently; or (2) an mRS score of 0 – 2 after at least one month. These symptoms must have persisted for at least one month. *Ipsilateral stroke* was defined as stroke in the vascular distribution of the study carotid artery. *Transient ischaemic attack* (TIA) was defined as a focal neurological deficit of abrupt onset lasting at least 30 seconds and resolving completely within 24 hours.

Myocardial infarction (MI) was defined as one or more of the following occurring within one month postprocedure: (1) elevated enzymes (creatine kinase, troponins); (2) electrocardiographic evidence of ischaemia; or (3) chest pain or symptoms consistent with ischaemia.

Cranial nerve injury (CNI) was defined as injury to the cranial nerve occurring within one month postprocedure.

Traditional BMT was defined as BMT that included only antiplatelet agents. Traditional BMT also included discussion of stroke risk factors and their modification, including hypertension, diabetes, abnormal lipid levels, excessive alcohol consumption, and tobacco use. This therapy was used in trials with recruitment dates prior to 2000. *Modern BMT* was defined as BMT including combinations of antiplatelet, antihypertensive, and lipid lowering agents. Modern BMT advocated for smoking cessation and moderate alcohol consumption, and glycaemic control. These therapies were used in trials with recruitment dates after 2000.

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The *peri-operative period* refers to events occurring within 30 days postprocedure (CEA or CAS). *Long term* refers to events occurring between 30 days to five years.

<H2>*Population, interventions, controls, and outcomes*

Patients with ACAS established with objective diagnostic measures (i.e., duplex ultrasonography, MRA, and CTA) were included in this study. Interventions assessed include CEA + BMT, CAS + BMT, and BMT alone. All interventions were administered in conjunction with BMT and will hereafter be referred to as CEA, CAS, or BMT. The control variable was any alternative, distinct ACAS treatment modality to that described in the intervention group. The primary goal was to determine which ACAS intervention demonstrates the lowest risk of stroke within a 30 day peri-operative period and in the long term (30 days – 5 years). Stroke subtypes included ipsilateral, contralateral, major, and minor stroke. Secondary goals included determining which intervention had the lowest risk of TIA and combined stroke and mortality between 30 days and five years, and the rate of adverse events (AEs). AEs assessed included MI and CNI within the 30 day peri-operative period.

<H2>*Search methodology and data extraction*

MEDLINE via PubMed, Embase, Scopus, and the Cochrane Central Register of Controlled Trials were systematically searched for relevant titles from 1990 until November 2021. Search medical subject headings (MeSH) in English included "asymptomatic carotid artery stenosis" [Mesh] AND "medical therapy" [Mesh] OR “asymptomatic carotid artery stenosis” [Mesh] AND “surgery” [Mesh] OR “asymptomatic carotid artery stenosis” [Mesh] AND “stent” [Mesh] for each database. Manual cross referencing of reference lists from previous reviews and included studies was also undertaken.

Records were initially screened by abstract. Data searching and extraction were completed by two authors independently, with disagreements resolved in consultation with the senior author. All parts of the search and extraction were duplicated by two authors independently. Extracted data included study demographic and clinicopathological information, and described outcomes of interest. All data were tabulated in accordance with study protocols.

<H2>*Data management and analysis*

Descriptive statistics were used to report characteristics of included trials. Rates of stroke, mortality, and adverse events for each intervention were presented as odds ratios (ORs)

and/or risk difference (RD). ORs and RDs were calculated using crude event RCT data, to compare interventions using an intention to treat analysis, where applicable. The latest recorded data were analysed when multiple assessments were reported within any time frame.

NMAs were conducted using the netmeta and Shiny packages for R, with a frequentist statistical method, using a random effects model.[16] A random effects model was used to account for interstudy heterogeneity. Dichotomous meta-analyses were performed using Review Manager (RevMan Version 5.4; Nordic Cochrane Centre, Copenhagen, Denmark) following the Mantel–Haenszel method. Effect sizes were described with a 95% confidence interval (CI). Results were considered statistically significant at a *p* value of < .050 if the 95% CI did not include the value of 1. Rank probabilities were plotted against the possible ranks for all competing treatments. Quality of the network and indirect analyses was performed using *p* values associated with each comparison in the inconsistency tables generated from the analysis.

To assess whether advances in BMT make it as equally efficacious as its invasive counterparts, all available BMT data were analysed to identify a timepoint at which trials adopted modern BMT guidelines (antiplatelet, antihypertensive, lipid lowering agents, glycaemic control, and lifestyle/diet modifications) in their comparative arms. Studies after 2000 had all adopted modern BMT strategies and trials before 2000, unless otherwise stated, used traditional BMT strategies. Therefore, BMT was subcategorised into traditional BMT (pre-2000), modern BMT (post-2000), and combined BMT (all BMT data included).

The GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework was used to assess the quality of evidence presented in this NMA.[17] Methodological assessment of the included studies was undertaken using the Cochrane risk of bias assessment tool.[18]

<H1>RESULTS

<H2>*Search overview and characteristics of included studies*

The initial systematic search identified a total of 4 646 records, which provided 2 647 records for review after the removal of duplicates (Fig. 1). Forty-two full text articles were assessed, with 17 records eligible for inclusion, encompassing 13 RCTs and 14 310 patients.[2,4,6,19–30] Studies were primarily conducted in North America (*n* = 7) and Europe (*n* = 5), with publication dates ranging from 1990 to 2021 and reported follow up to five years. Outcome data were reported in the peri-operative period (*n* = 7/13) and follow up to five years, with

intervals ranging from one to five years. All randomised participants underwent intervention for ACAS. The pooled mean age of participants was 67.9 years (range 40 – 91 years);[9,22] the majority of patients in all reports were men. Further study characteristics are summarised in Table 1 and Supplementary Table S1. Peri-operative outcomes within 30 days included CAS and CEA only. BMT was added into the NMAs after the peri-operative period (beyond 30 days; Figs 2 and 3). Individuals allocated to the deferred CEA cohort in the ACST-1 trial were classified as receiving BMT alone. The definitions for each outcome were extracted directly from the included trials.

<H2>***Stroke***

<H3>Peri-operative stroke. Six RCTs (6 855 patients) provided data for peri-operative stroke within a 30 day period. This was a dichotomous comparison between CEA and CAS. Five studies reported data on all stroke events (Supplementary Figure S1). One study reported no events in either cohort and was excluded.[29] CEA reduced the odds of all stroke events occurring within 30 days peri-operatively *vs.* CAS (OR 1.6, 95% CI 1.1 – 2.2). CEA specifically reduced the odds of a minor peri-operative stroke (OR 1.7, 95% CI 1.1 – 2.6) (Supplementary Figure S2) but did not affect the odds of a major stroke event occurring (OR 0.89, 95% CI 0.33 – 2.3; Supplementary Figure S3). Neither intervention reduced the odds of contralateral peri-operative stroke (Supplementary Figure S4), or ipsilateral stroke event (OR 1.7, 95% CI 0.96 – 3.1; Supplementary Figure S5). GRADE assessment established a moderate degree of confidence to support these estimates (Table 2).

<H3>Long-term stroke. Thirteen RCTs (11 693 patients) comparing BMT alone, CAS + BMT, and/or CEA + BMT reported stroke events occurring between 30 days and five years (Table 2). There was a moderate to high degree of certainty that CEA significantly reduced the odds of all stroke events compared with BMT pre-2000 (OR 0.65, 95% CI 0.43 – 0.99) and BMT post-2000 (OR 0.53, 95% CI 0.30 – 0.94; Supplementary Table S2). However, no significant risk difference was established between CEA and both traditional or modern BMT (30 fewer per 1 000 cases [95% CI 30 fewer – 10 more and 95% CI 30 fewer – 20 more, respectively]).

When compared to combined BMT, both CEA (OR 0.35, 95% CI 0.21 – 0.59) and CAS (OR 0.51, 95% CI 0.26 – 0.98) significantly reduced the odds of a minor stroke occurring up to five years (Supplementary Table S3). GRADE assessment established a high degree of certainty that CEA resulted in 20 fewer minor stroke events per 1 000 patients (95% CI –0.03 – –0.01) than modern BMT (Table 2). CAS resulted in 10 fewer minor stroke

events per 1 000 patients (95% CI –0.02 – 0.0) than modern BMT (Table 2). CEA (OR 0.27, 95% CI 0.19 – 0.39) and CAS (OR 0.37, 95% CI 0.22 – 0.62) also reduced the odds of an ipsilateral stroke occurring up to five years *vs.* combined BMT alone, a finding consistent with the use of BMT before and after 2000 (Supplementary Table S4). When compared to CEA, there was a high level of certainty that traditional BMT resulted in 40 more events per 1 000 patients (95% CI –0.02 – –0.06) and modern BMT resulted in 30 more events per 1 000 patients (95% CI –0.01 – –0.04; Table 2). CEA reduced the odds of a major stroke *vs.* traditional BMT (OR 0.62, 95% CI 0.38 – 1.0); however, no difference was found between CEA and modern BMT (OR 0.59, 95% CI 0.32 – 1.1; Supplementary Table S5). With a low degree of confidence, the results demonstrated that CEA resulted in 10 fewer major stroke cases per 1 000 (95% CI 0 – –0.01) *vs.* modern BMT (Table 2).

<H2>***Mortality***

<H3>Peri-operative mortality. Six RCTs (6 855 patients) comparing CEA and CAS reported mortality occurring within the 30 day peri-operative period. Four trials were excluded from the analysis due to zero events in either arm.[6,7,26,29] Neither procedure was favoured to reduce the odds of 30 day peri-operative mortality (Supplementary Figure S6).

<H3>Long-term mortality. Nine RCTs (11 101 patients) comparing CEA + BMT, CAS + BMT, and BMT alone reported mortality from 30 days to five years. With a moderate level of certainty, the results demonstrated that no treatment was significantly superior in reducing the odds of mortality from 30 days to five years (Supplementary Table S6).

<H2>***Stroke and mortality***

Nine RCTs (4 690) reported the odds of stroke and mortality combined from 30 days to five years, in patients who received CEA + BMT, CAS + BMT, or BMT alone (Fig. 3G). One trial was excluded from the analysis due to zero events occurring in any treatment arm.[21] GRADE assessment established a moderate degree of confidence for all results in this cohort (Table 2). CEA significantly reduced the odds of stroke and mortality compared with BMT therapy pre-2000 (OR 0.72, 95% CI 0.58 – 0.89); however, no significant difference was found between modern BMT and CEA (OR 0.56, 95% CI 0.27 – 1.2; Supplementary Table S7). CEA resulted in 40 fewer events per 1 000 patients (95% CI –0.08 – 0.0) *vs.* traditional BMT but did not show a significant risk reduction *vs.* modern BMT (RD –0.04, 95% CI –0.1 – 0.02; Table 2).

<H2>***Trans-ischaemic attack***

Four RCTs (1 513 patients), reported TIA events occurring between 30 days and five years (Figure 3H). With a high degree of certainty, CEA ranked best in reducing the odds of a TIA within five years, significantly reducing the odds compared with combined BMT (OR 0.58, 95% CI 0.35 – 0.96; Supplementary Table S8).

<H2>***Adverse events***

<H3>**Myocardial infarction.** Six RCTs (855 patients) assessed MI events within a 30 day peri-operative period. Three RCTs were excluded from the analysis due to zero events.[7,26,29] There was moderate certainty that CAS reduced the odds of peri-operative MI *vs.* CEA (OR 0.49, 95% CI 0.26 – 0.91; Supplementary Figure S7). However, the risk difference was 0 fewer cases per 1 000 (95% CI 0 – –0.01; Table 2).

<H3>Cranial nerve injury. Five RCTs (5 360 patients) reported CNI within a 30 day peri-operative period. CAS reduced the odds of CNI *vs.* CEA (OR 0.07, 95% CI 0.01 – 0.42; Supplementary Figure S8). There was moderate certainty that the risk difference was 40 fewer per 1 000 (95% CI 0 – –0.07; Table 2). Only one RCT reported a CNI following CAS.[20]

Supplementary Tables S9 – S18 provide confirmation of the statistical accuracy of the analysis and can be viewed online.

<H1>**DISCUSSION**

ACAS remains a prevalent public health concern, potentially contributing to significant rates of disability and death.[31] Strokes, both major and minor, can have disabling consequences, with losses of function in performing activities of daily living. CEA + BMT, CAS + BMT, and BMT alone are interventions to manage ACAS that have been examined in the literature; however, in the context of ever improving medical therapy, the optimal therapeutic approach in this cohort remains a topic of contention. While previous trial data have continually highlighted the superiority of CEA or CAS over BMT with regard to stroke prevention,[2,4] later studies have suggested that the stroke risk in asymptomatic disease may be similar following the introduction of newer lipid-lowering and antiplatelet agents agents.[32–34]

The current study showed that modern BMT and CEA + BMT showed equivalent efficacy in reducing major strokes. This was a significant improvement compared with cohorts treated with traditional BMT. Furthermore, no significant difference in TIA risk or mortality risk was established between CEA + BMT and BMT. When comparing stroke subtypes, this study found that CEA + BMT reduced ipsilateral stroke events *vs.* modern BMT alone. Furthermore, CEA + BMT reduced the odds of a contralateral stroke event occurring; however, this result was relative, unsupported by a negligible clinical risk difference (0 – 20 fewer events per 1 000 patients).

The widespread use of lipid lowering drugs in the past two decades have promised improved outcomes and reduced stroke risks in patients using BMT alone.[32,35,36] In fact, in a meta-regression analysis of 26 studies, Raman *et al*. found that the rate of ipsilateral stroke was significantly lower in studies that closed recruitment between 2000 and 2010 (stroke risk 1.13% per annum) compared with those recruited before 2000 (stroke risk 2.38% per annum).[30] To account for differences in BMT prior to 2000, each outcome was assessed as combined (all studies from 1990 to 2021) traditional and modern BMT. In this NMA, when combined BMT (all studies from 1990 to 2021) was analysed, CEA + BMT was favoured to reduce long term stroke and most stroke subtypes and TIA *vs.* BMT. This is in agreement with studies that have compared BMT to CEA.[3,28,37] This may be attributed to a multitude of factors, perhaps increased use of medical therapy. For example, in the ACST-1 trial, the use of statins increased from 9% in 1993 to 81% in 2007.[24] Interestingly, CEA + BMT significantly reduced the odds of a major stroke compared with BMT before 2000; however, after 2000, this significance was lost, indicating no significant difference in treatment. This trend was also seen to reduce the odds of stroke and mortality.

A reduction of stroke risk with modern BMT has been demonstrated in the literature.[24,35,36,38] For example, the annual ipsilateral stroke risk of BMT with aspirin alone during the ACAS trial in 1995 was 2.2%,[2] improving to 1% in the ACST-1 trial in 2004,[3,24] when BMT included antiplatelet, antihypertensive, and lipid lowering therapies. In ACST-1,[3] lipid lowering treatment demonstrated lower rates of long term stroke in both groups, indicating that intensive medical therapy may decrease stroke risk by stabilising plaques and reducing microembolisation.[39,40] A decline in micro-emboli has coincided with better control of lipids and slower progression of carotid plaques, suggesting that the lesions themselves may be altered by the era of BMT.[39] Maintaining a healthy lifestyle and modifying risk factors, including hypertension, obesity, poorly controlled diabetes, increased alcohol intake, and smoking, have been associated with 90% of the risk of stroke.[41] Therefore, targeted

interventions aimed at modifying these risk factors can substantially reduce the burden of stroke.[41]

Therefore, this analysis supports the efficacy of modern BMT in reducing major stroke and combined stroke and mortality. The risk reduction of stroke between CEA + BMT and modern BMT are low, and current studies are reported in such a way that analysis of subgroups that may benefit from intervention cannot be performed (i.e., degree of stenosis and plaque morphology). Awareness that stroke risk in asymptomatic patients treated with BMT may be less than previously thought has led to calls for contemporary RCTs to include BMT as a separate intervention arm. Such studies should aim to document clearly the nature of the current BMT utilised. BMT should consist of the diagnosis and management risk factors, including hypertension, lipids, diabetes, tobacco smoking, atrial fibrillation, physical inactivity, sleep disorders, and excessive weight and alcohol consumption.[42] A blanket approach to CEA may not be the optimal treatment, and risk stratification to identify high-risk treatment groups may offer improvements in management as future studies continue to compare these modalities.

CAS has been reviewed in the literature in the management of severe ACAS. In this NMA, CEA reduced the odds of a stroke event *vs.* CAS within the peri-operative period, a finding consistent with previous trials.[6,7,20,25] Previous trials indicated that stroke risk was primarily increased due to peri-interventional ipsilateral strokes, decreasing considerably afterward.[6,20] Despite ongoing developments in embolic protection devices, the rates of periprocedural stroke following CAS remain consistently higher than those seen in CEA.[6,7]

CAS + BMT was found to reduce significantly the odds of a peri-operative MI and CNI compared with CEA + BMT. Although this finding is consistent with recent literature,[20,22,43] this NMA challenges the clinical relevance of these reductions in MI and CNIs as they are unsupported by a negligible risk difference (0 – 10 and 0 – 70 fewer events per 1 000 cases, respectively). There has been a changing environment for CAS over the last two decades with advances in distal protection and interventional devices, including balloon guiding catheters and more flexible catheters and wires.[44] While these ongoing advances may demonstrate success in reducing procedural strokes, further comparative analyses reflective of modern technology is required prior to CAS use in routine clinical practice.[45]

Despite the systematic search strategy, some treatment comparisons in the literature were limited. To date, one RCT directly compared BMT alone and CAS. Some interventions were under-represented in the number of available RCTs. Underpowering of specific

interventions may have resulted in the absence of statistically significant differences. Additionally, it is important to note that it was not possible perform sensitivity analyses assessing outcomes based on plaque morphology and degree of stenosis. These analyses carry the potential to identify patient cohorts more likely to benefit from intervention for ACAS and should have greater emphasis in future studies. In addition, some data could not be extracted due to study endpoints being combined with other outcomes. There was significant heterogeneity among the reported time intervals for each outcome, resulting in results being reported in wider rather than shorter time intervals. Thirdly, heterogeneity in follow up times resulted in reporting wider rather than specific time frames. Fourthly, data on exact BMT regimens, including resources and education, were not provided in some of the included RCTs, limiting the possibility of collecting data on other aspects of BMT offering additional correlations. Additionally, there was heterogeneity within the cohort treated with CAS with regard to the use of technology such as embolic protection devices. Finally, this analysis was limited to reports written in English and published in peer-reviewed journals; therefore, this review could be affected by language and publication bias (see Table 2).

<H2>*Conclusions*

Modern BMT demonstrates similar reductions in major stroke, combined stroke, and mortality to CEA + BMT. However, the overall risk reductions are low and current data are not available to assess subgroups that may still benefit from intervention. BMT has the potential to reduce the requirement for surgical intervention in patients with ACAS.

CONFLICT OF INTEREST

None.

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None.

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Characteristics.

Country (centres)	Sample dates	Sample size (patients)	Interventions	BMT	Embolic protection device, *n* (%)	Follow up duration	Degree of ICA stenosis
Austria, Germany, Switzerland (36)	2009–2014	513	CEA (203), CAS (197), BMT (113)	"As per current guidelines"	71 (36.0)	30 days–5 years	70–99%
USA and Canada (117)	2000–2008	2 502	CEA,CAS		1 213 (96.1)	4–10 years	50–69% US; ≥70 US, CTA MRA
USA and Canada (39)	1987–1993	1 662	CEA, BMT	Aspirin	–	2.7 years	≥60%
USA (65)	2005–2013	1 453	CEA (364), CAS (1 089)		1 089 (100%)	5 years	70–99% US or CT
USA (1)	1998–2002	85	CEA (42), CAS (43)		0 (0%)	4 years	>80%
USA (29)	2000–2002	237	CEA (120), CAS (117)		117 (100%)	1–3 years	≥80%
USA (11)	1983–1987	444	CEA (211), BMT (233)	Aspirin	–	3.9 years	≥50%
30 countries, 126 centres	1993–2003	3 120	CEA (1 560), BMT (1 560)	Antiplatelet, antihypertensive, lipid lowering therapies	–	5–10 years	≥60%

33 countries (130)	2008–2020	3 625	CEA (1 814), CAS (1 811)		1 344 (85% of per protocol sample)	5 years	≥60%
Israel (1)	Not reported	136	CEA (68), CAS (68)		68 (100%)	26 months	>70%
Germany (10)		410	CEA (206), BMT (204)	Aspirin and dipyridamole	–	3 years	50–90%
Russia (3)	2009–2013	55	CEA (31), BMT (24)	Antiplatelet (ASA), lipid lowering (atorvastatin), antihypertensive (amlodipine/losartan/hydrochlorothiazide) therapy	–	5 years	70–79%
USA (1)	2011–2013	60	CEA (31), CAS (29)		29 (100%)	6 months	>80%

RCT = randomised controlled trial; BMT, best medical treatment; ICA = internal carotid artery; SPACE-2 = Stent-Protected Angioplasty versus Carotid Endarterectomy at 2 years; CEA = carotid endarterectomy; CAS = carotid artery stenting; US = ultrasound; CREST = Carotid Revascularisation Endarterectomy Versus Stenting Trial; CTA = computed tomography angiography; MRA = magnetic resonance angiography; ACAS = Asymptomatic Carotid Atherosclerosis Study; ACT-1 = Asymptomatic Carotid Trial; ACST-1 = Asymptomatic Carotid Surgery Trial; ACST-2 = Asymptomatic Carotid Surgery Trial 2; AMTEC = aggressive medical treatment evaluation for asymptomatic carotid artery stenosis; ASA = acetylsalicylic acid.

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Table 2. GRADE (Grading of Recommendations, Assessment, Development and Evaluations) analysis rank.		
Outcome	Effects and confidence in the estimate of effects	
	CAS	
Long Term Stroke: Total (Up to 5 Years)		No. Trials: 6
Follow Up: Range from	*26 - 120 Months*	No. Patients: 8
CEA	OR 0.76 [0.51; 1.15] Network estimate	10 fewer per 1 *more*)*
	Confidence of estimate: ⨁⨁⨁O	Moderate due to
Rank 1/5	Rank 2/5	
Long Term Stroke: Major (Up to 5 Years)		No. Trials: 3
Follow Up: Range from	*32 - 120 Months*	No. Patients: 4
CEA	OR 0.91 [0.54; 1.55] Network estimate	0 fewer per 1 *more*)*
	Confidence of estimate: ⨁⨁OO	Low due to impr
Rank 1/5	Rank 2/5	
Long Term Stroke: Ipsilateral (Up to 5 Years)		No. Trials: 6
Follow Up: Range from	*6 - 120 Months*	No. Patients: 6
CEA	OR 0.75 [0.50; 1.12] Network estimate	10 fewer per 1 *fewer*)*
	Confidence of estimate: ⨁⨁⨁O	Moderate due in
Rank 1/5	Rank 2/5	
Stroke & Mortality		No. Trials: 4
Follow Up: Range from	*26 - 120 Months*	No. Patients: 1

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CEA	OR 0.78 [0.57; 1.06] Network estimate	20 fewer per 1 *more)**
	Confidence of estimate: ⊕⊕⊕O	Moderate due to
Rank 1/5	Rank 2/5	
Mortality (30 days to 5 years)		No. Trials: 5
Follow Up: Range from	*26 - 120 Months*	No. Patients: 5
CEA	OR 0.93 [0.79; 1.08] Network estimate	0 fewer per 1 0 *more*)*
	Confidence of estimate: ⊕⊕⊕O	Moderate due to
Rank 1/5	Rank 5/5	
Long Term Stroke: Minor (Up to 5 Years)		No. Trials: 3
Follow Up: Range from	*48 - 120 Months*	No. Patients: 4
CEA	OR 0.70 [0.45; 1.07] Network estimate	10 fewer per 1 *fewer*)*
	Confidence of estimate: ⊕⊕OO	Low due to Indir
Rank 1/3	Rank 2/3	
Long Term Stroke: Contralateral (Up to 5 years)		No. Trials: 4
Follow Up: Range from	*48 - 120 Months*	No. Patients: 5
CEA	OR 0.79 [0.48; 1.29] Network estimate	10 fewer per 1 *more*)*
	Confidence of estimate: ⊕⊕OO	Low due to impr
Rank 1/3	Rank 2/3	
TIA (30 days to 5 years)		No. Trials: 2
Follow Up: Range from	*0 - 30 Days*	No. Patients: 5

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CEA	OR 0.91 [0.31; 2.65] Network estimate	10 fewer per 1 *more*)*
	Confidence of estimate: ⊕⊕⊕O	Moderate due to
Rank 1/5	Rank 2/5	
Minor Stroke (Within 30 days)		No. Trials: 3
Follow Up: Range from	*0 - 30 Days*	No. Patients: 5
CEA	OR 0.58 [0.38; 0.88] Network estimate	10 fewer per 1 *fewer*)*
	Confidence of estimate: ⊕⊕⊕O	Moderate due to
Rank 1/2	Rank 2/2	
Peri-Operative Stroke (Within 30 Days)		No. Trials: 5
Follow Up: Range from	*0 - 30 Days*	No. Patients: 6
CEA	OR 0.64 [0.46; 0.88] Network estimate	10 fewer per 1 *fewer*)*
	Confidence of estimate: ⊕⊕⊕O	Moderate due to
Rank 1/2	Rank 2/2	
Myocardial Infarction		
Follow Up: Range from	*0 - 30 Days*	No. Patients: 6
CAS	OR 0.49 [0.26; 0.91] Network estimate	0 fewer per 1 0 *fewer*)*
	Confidence of estimate: ⊕⊕⊕O	Moderate due to
Rank 2/2	Rank 1/2	
Cranial Nerve Injury		No. Trials: 5
Follow Up: Range from	*0 - 30 Days*	No. Patients: 5
CAS	OR 0.07 [0.01; 0.42] Network estimate	40 fewer per 1 *fewer*)*
	Confidence of estimate: ⊕⊕⊕O	Moderate due to
Rank 2/2	Rank 1/2	
Mortality (Within 30 days)		No. Trials: 6
Follow Up: Range from	*0 - 30 Days*	No. Patients: 6

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CEA	OR 0.75 [0.32; 1.75] Network estimate	0 fewer per 1 0 *fewer*)*
	Confidence of estimate: ⊕⊕⊕O	Moderate due to
Rank 2/2	Rank 1/2	

Red boxes indicate statistically insignificant findings; green boxes indicate statistically significant findings.

FIGURE LEGEND

Figure 1. Flowchart of the literature search according to the Preferred Items for Systematic Review and Meta-Analysis (PRISMA) statement. RCT = randomised controlled trial.

Figure 2. Forest plots comparing carotid endarterectomy (CEA) to all other interventions using combined direct and indirect evidence for all outcomes. Results are presented using odds ratios (ORs) and 95% confidence intervals (CIs) with a random effects model. Outcomes included (A) all stroke events, (B) minor stroke, (C) major stroke, (D) contralateral stroke, (E) ipsilateral stroke, (F) mortality, (G) stroke and mortality, and (H) transient ischaemic attack. BMT = best medical treatment; CAS = carotid artery stenting.

Figure 3. Network plots of all possible pairwise comparisons assessing outcomes. Outcomes included (A) all stroke events, (B) minor stroke, (C) major stroke, (D) contralateral stroke, € ipsilateral stroke, (F) mortality, (G) stroke and mortality, and (H) transient ischaemic attack. The size of the nodes and the thickness of edges depended on the number of people randomised and the number of trials conducted, respectively. BMT = best medical therapy; CAS = carotid artery stenting; CEA = carotid endarterectomy.

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Figure 1.

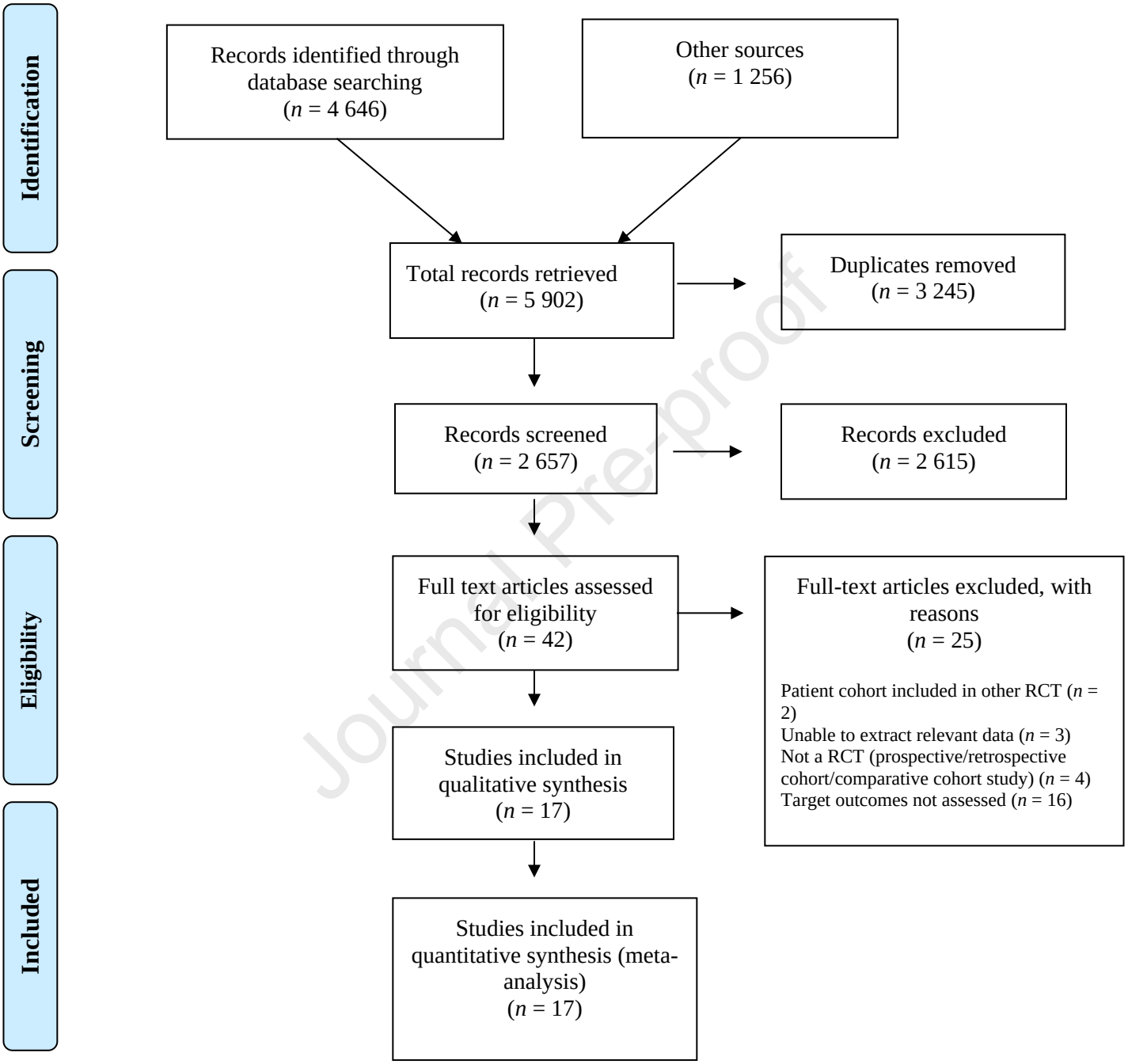

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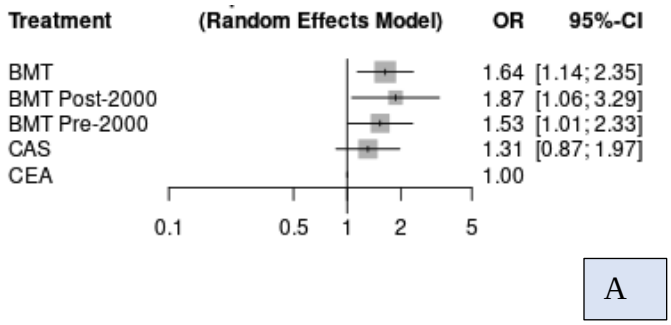
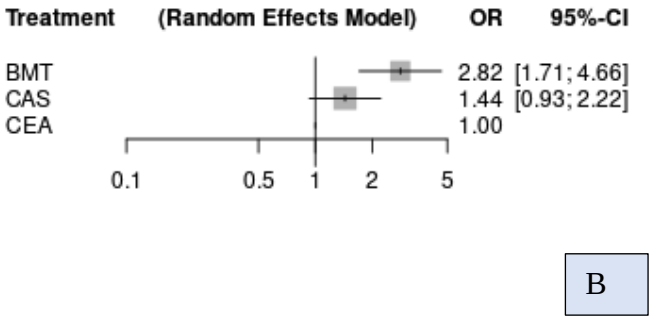
Figure 2.



A



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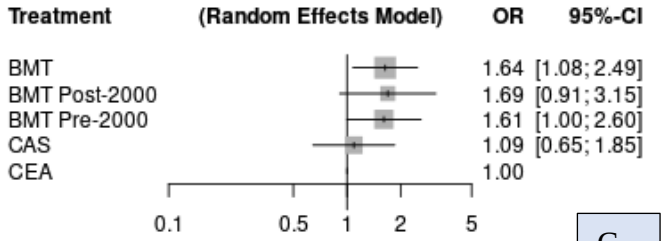

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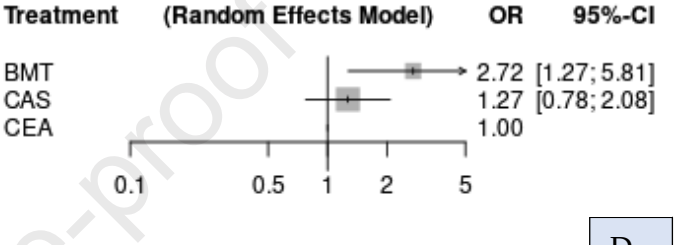

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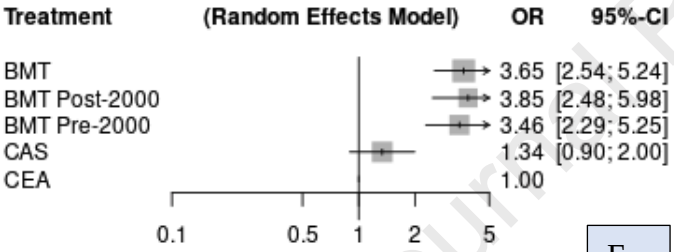

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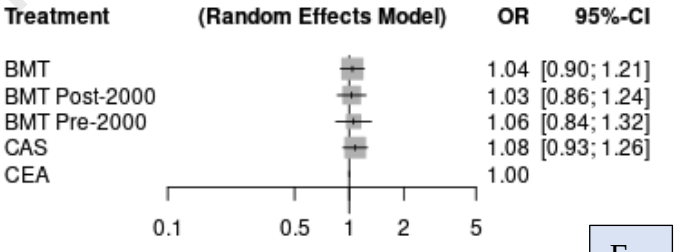

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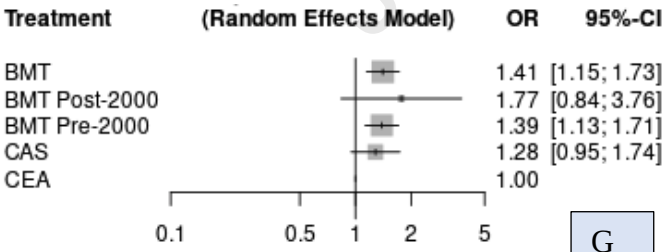

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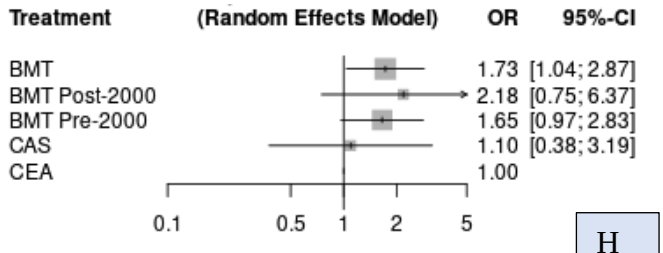

H

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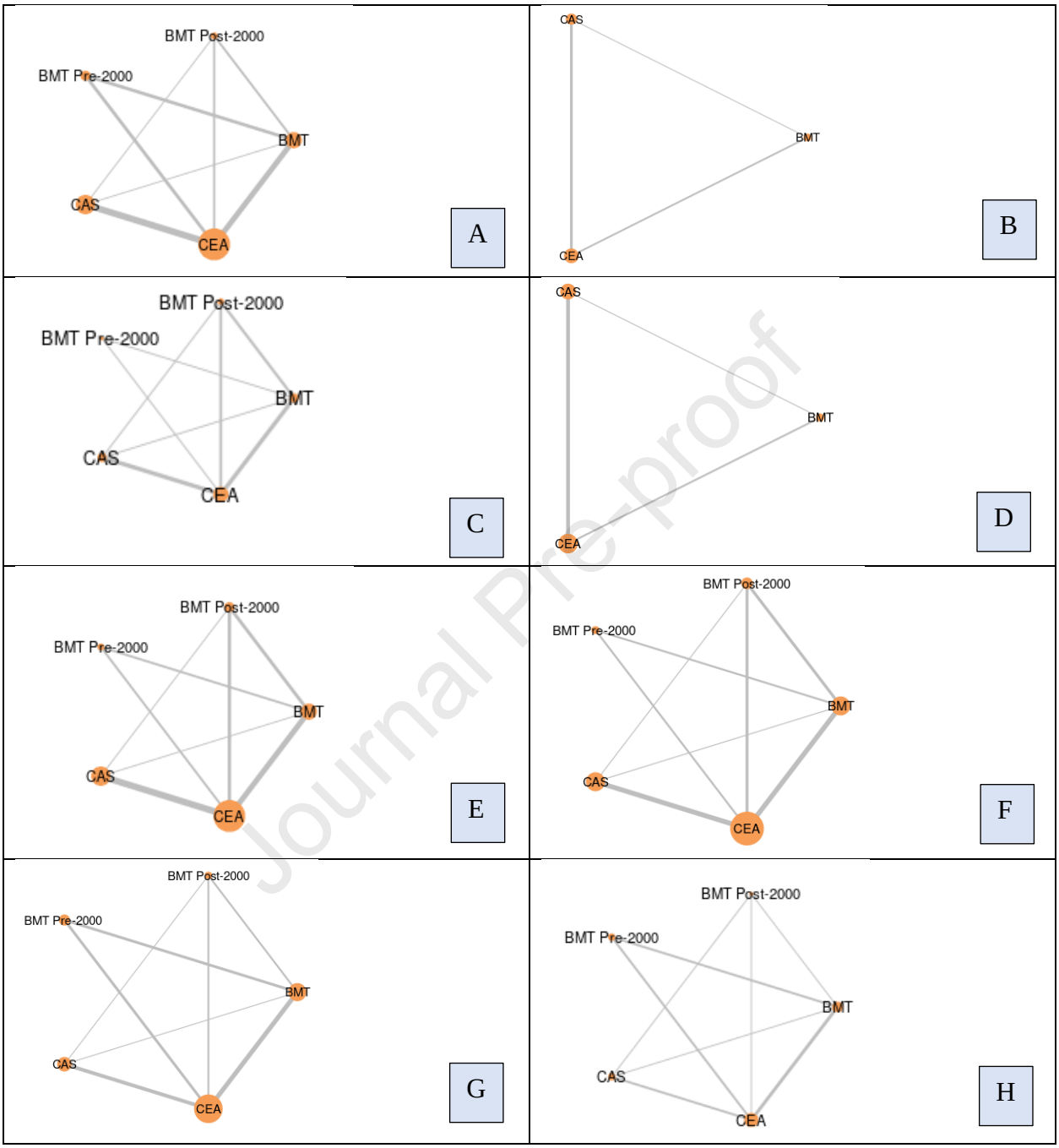
Figure 3. Network Plots of Each Comparison.



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Short title

Systematic Review and Network Meta-Analysis of Optimal Management in Asymptomatic CAS

Supplementary Material

Supplementary Tables S1 – S18

Supplementary Figures S1 – S8

Figures

Figure 1 – please follow instructions on page D of guide for a PRISMA flowchart.

Figure 2 – Forest plots, please follow the instructions on page G1 onwards.

Figure 3 – other type of plot.

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