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Title Page

Carotid Artery Stenting: Current State of Evidence and Future Directions

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Abstract

Both carotid endarterectomy (CEA) and carotid artery stenting (CAS) are common treatments for carotid artery stenosis. Several randomised controlled trials (RCTs) have compared CEA to CAS in the treatment of carotid artery stenosis. These studies have suggested that CAS is more strongly associated with periprocedural stroke, however CEA is more strongly associated with myocardial infarction. Published long-term outcomes report that CAS and CEA are similar. A reduction in complications associated with CAS has also been demonstrated over time. The symptomatic status of the patient and history of previous CEA or cervical radiotherapy are significant factors when deciding between CEA or CAS. Numerous carotid artery stents are available, varying in material, shape and design but with minimal evidence comparing stent types. The role of cerebral protection devices is unclear. Dual antiplatelet therapy is typically prescribed to prevent in-stent thrombosis, however evidence comparing periprocedural and postprocedural antiplatelet therapy is scarce, resulting in inconsistent guidelines. Several RCTs are underway that will aim to clarify some of these uncertainties. In this review, we summarise the development of varying techniques of CAS and studies comparing CAS to CEA as treatment options for carotid artery stenosis.

Key Words: carotid artery atherosclerosis, carotid artery stenosis, carotid artery stenting, carotid endarterectomy, stroke, stroke prevention

Introduction

Approximately 6.5 million strokes occur per year.¹ Stroke is the second-leading cause of death and is the leading cause of premature mortality and morbidity for both men and women.^{1,2} Atherosclerotic carotid artery stenosis is responsible for ~20% of strokes, typically occurring at the bifurcation of the internal and external carotid arteries.^{3,4} Unfortunately,

carotid atherosclerosis is often asymptomatic until a disabling or fatal stroke occurs. Patients with vascular disease and risk factors such as diabetes mellitus, hypertension, hyperlipidaemia and smoking are at significantly higher risk of developing carotid artery atherosclerosis. Not all patients with carotid atherosclerosis are at increased risk of stroke, however a strong association between severity of stenosis and stroke risk exists.²

Clinically important stenosis (the point at which the stroke risk is increased) varies between guidelines but is generally defined as stenosis >50% or >60%. The prevalence of clinically significant carotid artery stenosis is ~0-1% in the general population and ~1% in persons ≥65 years of age.⁵ The prevalence of severe asymptomatic carotid artery stenosis (>70%) is as high as 3.1%.⁶ Carotid artery stenosis can be treated medically or surgically to prevent stroke or stroke-related death. Treatment of carotid stenosis reduces stroke risk and stroke-related morbidity and mortality.³ Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are commonly used to treat carotid stenosis. CEA was first described by DeBakey in 1975 who reported successful use of this procedure in the 1950s. CEA has become conventional treatment for carotid artery stenosis.⁷

In this review, the history, techniques and trial data concerning the emergence and evolution of CAS as an alternative to CEA, are comprehensively examined.

Emergence of endovascular management of carotid artery stenosis

Endovascular treatment as an alternative to CEA emerged following trials demonstrating the benefit of angioplasty and stenting in patients with coronary artery disease. Since its first reported use for an intimal flap in 1989, a number of randomised controlled trials (RCTs) have demonstrated the long term safety and efficacy of CAS for carotid stenosis.⁸⁻²³ Cost effectiveness and its use in surgically inaccessible lesions made CAS an attractive prospect.²⁴ Since its inception, the technological aspects of endovascular treatment for carotid artery stenosis have evolved significantly, however this has come at the expense of its financial benefit.²⁵ Figure 2 outlines a case of high cervical internal carotid artery (ICA) stenosis successfully treated with CAS.

Complications such as plaque dislodgement, intimal dissection, elastic vessel recoil and late restenosis are thought to be more likely with angioplasty compared to CAS.²⁶ Although no

trials have evaluated stenting versus angioplasty alone, primary stenting is accepted as the endovascular technique of choice for carotid stenosis and has generally replaced balloon angioplasty.

CAS vs CEA in Carotid Artery Stenosis

Since the emergence of endovascular approaches, the preferred management of carotid artery stenosis has been widely debated. A large number of RCTs have attempted to evaluate which treatment is superior. Results of these studies show that periprocedural stroke is more common with CAS (particularly in symptomatic patients) while myocardial infarction (MI) is more common with CEA. The heterogeneous definitions of the MI endpoint in these studies has been a point of contention amongst the stroke community. Clinically silent ischaemic lesions are also more commonly associated with CAS despite being of uncertain clinical significance.^{27,28} Nevertheless, similar long-term outcomes with CAS and CEA have been reported in most RCTs and appears to be a statistically sound observation.²⁹

The WALLSTENT trial in 2001 was the first RCT to compare CAS with CEA, however this was prematurely terminated due to high complication rates in the stenting arm.³⁰ Though small, the first RCT to demonstrate that CAS produced outcomes comparable to CEA was published that same year.³¹ Since then, larger trials have demonstrated the safety and efficacy of CAS compared to CEA (Table 1).

Randomised Controlled Trials: Mixed Cohorts

The CAVATAS study (n=504) was the first multicentre RCT to suggest that endovascular management of carotid stenosis may be non-inferior to CEA, however wide confidence intervals make interpretation of some data difficult.⁹⁻¹¹ Similar periprocedural and long-term stroke, death and restenosis rates between groups were reported, however significantly more postoperative cranial nerve injuries (CNIs) and major groin/neck haematomas occurred with CEA. Patients in the endovascular arm who received a stent (n=50) had significantly lower risk of restenosis compared to those undergoing balloon angioplasty alone (n=145).

The CREST trial is the largest international RCT comparing CEA to CAS (n=2502) in a cohort of both symptomatic and asymptomatic patients.^{12,13} Periprocedurally, the stroke/death/MI rate did not differ significantly between groups although individual rates of periprocedural stroke, death and MI did differ. For example, significantly more

periprocedural strokes occurred with CAS but there were fewer periprocedural MIs. CNIs were more common with CEA.

Ten year follow up data reported no significant difference in the stroke/death/MI rates between the groups. Similar long-term results were seen with respect to postprocedural ipsilateral stroke, although periprocedural stroke/death and subsequent ipsilateral stroke numbers favoured CEA. This is attributable to periprocedural differences. No significant difference was seen between the two treatment groups with respect to restenosis or need for revascularization.

The SAPPHERE trial (n=334) is the only large multicentre RCT comparing CAS to CEA in 'high-risk' patients (defined as clinically significant cardiac disease, severe pulmonary disease, contralateral carotid occlusion or laryngeal-nerve palsy, previous radical neck surgery or cervical radiotherapy, recurrent stenosis after CEA and age >80).^{14,15} Over 70% of participants had asymptomatic stenosis. It reported non-inferiority of CAS with respect to periprocedural death/stroke/MI or postprocedural death/ipsilateral stroke, however these incidences were notably high. No significant differences in periprocedural death/stroke/MI or death/ipsilateral stroke between 31 days and 3 years and long-term restenosis was seen between groups. Whether patients who are 'high risk' according to SAPPHERE criteria have poorer outcomes with CEA has been disputed.³² Whether some of these patients required surgical or endovascular therapy has also been questioned.

Prospective Non-randomised Registries: Mixed Cohorts

The CaRESS study was a multicentre, prospective, nonrandomized trial (n=397) that supported the results of CREST and CAVATAS.^{33,34} There were no significant differences in death/stroke rates at 30 days, 1 year or 4 years between CEA and CAS groups. When analysed individually, rates of stroke and death at 4 years were similar. No significant difference in rates of death/MI/non-fatal stroke at 30 days, 1 year or 4 years was reported. In comparison to CREST, restenosis was more common with CAS, however revascularisation rates were similar between groups (p=0.263).

Randomised Controlled Trials: Symptomatic Carotid Artery Stenosis

Trials targeting symptomatic patients generally favour CEA over CAS.³⁵ ICSS is the largest RCT comparing CAS with CEA in patients with symptomatic carotid artery stenosis

(n=1713).^{21,22} The incidence of stroke/death/MI within 120 days of treatment was higher with CAS, as were 5-year stroke rates. Most strokes in this time period were non-disabling as 5-year rates of fatal/disabling strokes were similar. The combined outcome of procedure-related stroke/death or ipsilateral stroke during follow-up was also more frequent with CAS. Again, significantly more CNIs and haematomas occurred with CEA. Long-term rates of restenosis or occlusion did not differ between groups.

More unfavourable results were seen in the EVA-3S study, a multicentre non-inferiority RCT with a median follow up of 7.1 years (n=527).^{18–20} Exceptionally high rates of periprocedural stroke/death with CAS led to the trial being stopped prematurely. This also meant a statistical power of 80% was not achieved, making results difficult to interpret. Although 5-year rates of periprocedural stroke/death and non-procedural ipsilateral stroke were significantly higher with CAS, 10-year results were not significantly different. High rates of periprocedural stroke/death with CAS accounted for this, with similar postprocedural stroke numbers between groups. No significant difference was seen in restenosis rates.

Similar results arose from the SPACE study, another large multicentre international RCT (n=1200).^{16,17} Non-inferiority of CAS was not demonstrated with respect to periprocedural death/ipsilateral ischaemic stroke. Rates of ipsilateral ischaemic stroke at 2 years and periprocedural stroke/death were similar between groups. Recurrent stenosis was more frequent with CAS. Subgroup analysis of the CREST trial revealed no difference in periprocedural stroke/death/MI rates or long-term postprocedural ipsilateral stroke rates based on symptomatic status.^{12,13}

Randomised Controlled Trials: Asymptomatic Carotid Artery Stenosis

A lack of evidence makes the utility of CAS in asymptomatic patients uncertain. The Asymptomatic Carotid Trial (ACT-1) is the only multicentre RCT comparing CEA and CAS in asymptomatic patients (n=1453).²³ CAS was reported as non-inferior to CEA with respect to combined periprocedural death/stroke/MI or ipsilateral stroke within 1 year (3.8% vs 3.4% respectively). Some consider these rates somewhat high for what is thought to be a low-risk cohort, although these are the lowest reported complication rates to date. Both periprocedural stroke and death rates and postprocedure stroke rates up to 5 years were similar between groups, as were cumulative 5-year rates of stroke-free survival. This was also a sponsored study. As mentioned, no difference in periprocedural stroke/death/MI rates or long-term postprocedural ipsilateral stroke rates based on symptomatic status in the CREST trial.^{12,13}

Interim results from the ongoing ACST-2 trial report a 1% rate of periprocedural disabling stroke, fatal MI and death in all included participants.³⁶

RCTs performed in the 1990s showed that prophylactic CEA plus medical therapy provided better outcomes than medical therapy alone.³⁷ Several medications that are now considered best medical therapy (BMT), such as statins, were not available or in widespread use at the time of these trials and hence these results may no longer be applicable. Annual stroke rates in asymptomatic carotid artery stenosis have been reported as low as <1% with modern BMT.³⁸ BMT is now considered the gold standard for asymptomatic carotid artery stenosis in some guidelines. There is likely to be a small subset of patients with asymptomatic stenosis who are at high risk of stroke that would benefit from revascularisation, however the criteria to identify these patients have not been clearly established.

Complications Associated with CAS and CEA

Periprocedural stroke is more likely with CAS, however this difference has reduced with time (Figure 1a). In fact, CREST reported the fewest periprocedural complications compared to other RCTs. Overall, this trend may reflect the increasing skill of proceduralists, the need for credentialing and emerging endovascular techniques and technologies. Thus, results from earlier RCTs may be less applicable. Additionally, periprocedural stroke after carotid revascularisation is not always secondary to thromboembolism and often occurs due to haemodynamic disturbance.³⁹ MI is more common with CEA, likely due to the periprocedural anaesthetic risk, as are CNIs and haematomas (although many CNIs are non-permanent). Periprocedural death rates are similar between procedures and periprocedural stroke/death rates in favour of CEA are likely due to differences in stroke numbers (Figure 1b and 1d). MI rates have remained similar most likely reflecting factors other than proceduralist skill or experience (Figure 1c). The high rate of periprocedural MI during the SAPHIRE trial is likely due to patients being high risk.

Systematic Reviews

Several systematic reviews have strengthened the data surrounding CAS. A 2017 review of 6,526 patients from 5 RCTs and a mean follow up of 5.3 years demonstrated a higher risk of periprocedural stroke plus non-periprocedural ipsilateral stroke with CAS (OR 1.50; 95% CI

1.22-1.84), primarily due to increased minor stroke rates in the periprocedural period.³ CAS was associated with a lower risk of periprocedural MI and CNIs. No difference in periprocedural death/stroke/MI or non-periprocedural ipsilateral stroke was found and the composite outcome of periprocedural death, stroke, MI or CNI favoured CAS.

A 2012 Cochrane review of 7,572 patients from 16 trials reported similar rates of death or major/disabling stroke between treatments and found that endovascular treatment was associated with significantly lower risks of MI, CNI and haematomas.⁴ Rates of periprocedural death/stroke or ipsilateral stroke during follow-up significantly favoured endarterectomy, however post-procedural ipsilateral stroke rates were comparable. Restenosis was more common with endovascular therapy (OR 2.41; p=0.007).

Following reports that CEA may be advantageous in older patients, Howard et al. explored the association of age with treatment differences in a meta-analysis of symptomatic participants from four RCTs.⁴⁰ The periprocedural hazard ratio for stroke or death in the CAS group was noted to increase with age significantly, with no evidence of increased risk by age group with CEA. Compared to CEA, the HR for stroke or death in CAS was reported to be 1.61 in patients aged 65-69 and 2.09 for patients aged 70-74. This difference was almost entirely attributable to increased periprocedural stroke risk in the CAS group.

Stents

Factors that influence the choice of stent include device availability, clinical trial or post-marketing registry participation, stent cell structure, stent shape and specific embolic protection device (EPD) characteristics. Self-expanding stents have largely replaced the original balloon expandable stents of earlier trials. Modern stents can be classified as open/closed cell, bare metal or covered and tapered/non-tapered. The type of stent used depends on the indication and lesion characteristics.

Open-cell stents have a free cell area of $>5\text{mm}^2$ and adapt well to the contour of the vessel making delivery easier but physically cover less of the target lesion, potentially posing a higher risk of embolisation as atherosclerotic material may prolapse through the stent struts. Closed-cell stents may kink the vessel if placed inappropriately. No published high quality RCTs compare open-cell to closed-cell stents and available evidence is conflicting. Published studies have shown a variety of results.⁴¹⁻⁴⁵ Conflicting results regarding procedural

microemboli and restenosis rates have also been reported.^{46–48} ‘Hybrid’ stents that combine characteristics of open-cell and closed-cell stents have been designed which possess a gradual change from open-cell to closed-cell design or have an abrupt point of change (shouldered).

Bare-metal stents (BMSs) are a metal scaffold that maintain patency of the vessel. BMSs covered with compounds such as polytetrafluoroethylene or polyethylene terephthalate which aim to prevent smooth muscle cell proliferation (and thus restenosis) and conceal strut openings are called covered stents. The only RCT comparing BMSs against covered stents in carotid artery stenosis demonstrated a lower risk of periprocedural and postprocedural microembolism with covered stents, however this trial was stopped early due to extremely high restenosis rates within the covered stent group and only 14 participants were recruited.⁴³

Tapered stents, characterized by a larger diameter proximally and narrow diameter distally, are designed to mimic the progressive narrowing of the ICA. Evidence on tapered versus non-tapered stents is poor, with only one published retrospective study in the literature.⁴⁹ This revealed no difference in the 30-day stroke rates between tapered and non-tapered groups, however restenosis at follow up was more common with non-tapered stents (2.6% vs 0%; $p=0.03$).

Stent Models

Several carotid artery stents have been approved by the FDA (Table 2). The first self-expanding stent was the Carotid Wallstent (Boston Scientific, Mountain View, CA, US). With the exception of the Carotid Wallstent, which is made from elgiloy, the majority of self-expanding carotid artery stents are made of nitinol. When exposed to the temperature of the human body, the thermal properties of nitinol stents allow them to achieve a predefined shape, whereas the expansion of the Carotid Wallstent relies on a spring-like action as its delivery sheath is withdrawn.

The Acculink nitinol stent was the first to be approved following the ARCHeR trial.⁵⁰ Following approval of the Guidant Acculink stent and Accunet EPD, the CAPTURE study commenced.⁵¹ This prospective, multicentre registry of 3,500 patients assessed outcomes of CAS using these devices in the same patients in the non-investigational setting. Following CREST, the FDA approved the use of the Acculink stent with the Accunet EPD in standard-risk patients with either symptomatic or asymptomatic carotid artery stenosis.¹³

Analysis of 12,135 carotid artery stent procedures in a large American registry indicated that stents were typically used with their respective EPD systems (78.2%).⁵² The most commonly used devices were the Acculink/Accunet, Xact/Emboshield (Abbott) and the Precise/Angioguard (Cordis, Milpitas, CAUSA) stents. Devices seldom used were the Protégé/SpiderFx (Medtronic, Plymouth, MN) (3.7%) and Carotid Wallstent/Filterwire (Boston Scientific, Natick, MA) (1.8%). Nonsignificant differences were seen with respect to rates of in-hospital stroke and death between the three most commonly used devices.

Techniques

Embolic Protection

Embolic complications of endovascular therapy have prompted the development of EPDs. Manipulation of sheaths and catheters in an atheromatous arch, wiring and delivery of devices across the lesion, balloon expansion, stent deployment and EPD removal may all lead to embolisation. Cerebral protection was first described in 1987 by Theron et al. using temporary distal balloon occlusion (TDBO).⁵³ In 1990, a triple co-axial catheter was developed.⁵⁴ Numerous EPDs have been designed using filters and guidewire-attached balloons. Distal filter embolic protection devices (f-EPDs) and proximal embolic protection devices (p-EPDs) are the two most commonly used EPDs.⁵² EPDs were used in most RCTs comparing CAS to CEA, however frequency of use and type of device varied considerably. Complications associated with EPDs include vasospasm and arterial dissection.⁴¹ Figure 3 demonstrates deployment of an f-EPD during CAS for a young patient with carotid stenosis secondary to fibromuscular dysplasia.

Embolic Protection vs No Protection

It is not clear whether cerebral protection is beneficial, with single centre RCTs using popular devices suggesting that EPDs provide no benefit.^{55,56} The SPACE trial drew similar conclusions.⁴¹ In comparison, a multicentre prospective registry of 1483 patients reported that patients treated with EPDs had lower rates of ipsilateral stroke (1.7% vs 4.1%; $p=0.007$) and non-fatal strokes/deaths (2.1% vs 4.9%; $p=0.004$).⁵⁷ An even larger registry of 11,243 patients supported this argument, reporting fewer periprocedural strokes and deaths with EPD use (2.23% vs 5.29%; $p<0.0001$).⁵⁸ A systematic review of 2,357 patients reported lower periprocedural stroke/death rates in patients who received cerebral protection, although death rates were almost identical.⁵⁹

EPD Techniques

P-EPDs achieve cerebral protection by occluding vessels proximal to the stenosis and stagnating flow while F-EPDs entrap embolic material that become dislodged during the procedure. P-EPDs establish protection prior to manipulation of the lesion but relies on collateral flow to maintain cerebral perfusion. P-EPDs require large introducer sheaths (8–9 Fr vs 6 Fr for f-EPD) which are more difficult to navigate and obscure the lesion during stent deployment. If flow through all ECA branches is not stagnated, the efficacy of the device may also be reduced. F-EPDs are inserted by traversing a wire through the lesion and placing the filter distally using a delivery sheath, where withdrawal of the sheath deploys the filter. Atherosclerotic plaques may embolise as instruments pass through and filters will only catch emboli larger than the pore size. F-EPDs can become obstructed with large emboli which may impair cerebral flow or spill out during retrieval. Concentric f-EPDs have a wire attached centrally and eccentric f-EPDs have it attached laterally, with neither consistently shown to be superior.^{44,60} F-EPDs are the most commonly used protection devices in the USA.⁶¹ Previously used distal balloons became obsolete after the safety of distal filters was demonstrated, although no head-to-head trials have compared the two.

There are no large multicentre RCTs comparing p-EPDs and f-EPDs, however published studies generally support proximal protection. Data from three small RCTs and four observational studies were pooled in a recent meta-analysis, with the incidence of new ischemic lesions/patient on diffusion-weighted magnetic resonance imaging (dw-MRI) significantly lower in the proximal balloon occlusion group.⁶² Despite potentially being associated with subtle neurocognitive defects, the significance of these lesions is unclear as many are asymptomatic and disappear over time.⁶³ Castro-Afonso et al. reported fewer embolic events with f-EPDs.⁶⁴

A large retrospective analysis (n=10,264) reported no difference in the rates of stroke/death in-hospital or within 30 days between p-EPD and f-EPD cohorts, however p-EPD use was infrequent making this difficult to interpret.⁶¹ Another retrospective analysis of 3,160 patients also reported no significant difference in 30-day outcomes with a range of devices, although several limitations were present.⁶⁰ A technique combining the use of p-EPDs and f-EPDs (double protection) has also been described. A single-centre study (n=78) reported a

significantly lower incidence and number of postprocedure ischaemic lesions on dw-MRI with double protection compared to f-EPD.⁶⁵

Specific Patient Populations

Previous CEA

Restenosis rates following CEA range from 10-25%.⁶⁶ Redo CEA has an increased potential for CNIs and also carries an increased stroke risk compared with primary CEA.⁶⁶ There are no high quality data guiding management of these patients. A systematic review and meta-analysis of 4,399 patients from 50 studies reported no differences in 30-day rates of stroke/TIA/MI or long-term stroke rates between CAS and CEA groups for patients with restenosis.⁶⁷ CNIs were more common with CEA but recurrent restenosis was more common with CAS (both $p < 0.05$). Another review of 1,132 patients from 13 studies reported comparable results, with similar perioperative stroke/death rates between groups although restenosis rates were also similar.⁶⁸ A prospective non-randomised study of 91 revascularisation procedures (45 CAS, 46 redo-CEAs) reported similar restenosis rates between treatments.⁶⁹ Figure 4 demonstrates a case of CAS after previous CEA in a symptomatic patient. A chronically occluded contralateral ICA and previous surgery precluded surgical management.

Cervical Radiotherapy (C-XRT)

C-XRT accelerates the development of carotid artery stenosis, with the RR of TIA or ischemic stroke at least doubled.⁷⁰ The effects of radiotherapy can make surgery high risk however high quality trials comparing CAS to CEA are lacking. Restenosis is the primary concern of CAS. A prospective study of 150 high risk patients reported significantly higher rates of restenosis at 3 years with CAS in patients with previous c-XRT compared to those without (80% vs 26%; $p < 0.05$).⁷¹ Other studies have reported no difference in restenosis rates in patients who have received c-XRT.⁷² A systematic review and meta-analysis of 533 patients comparing CAS against CEA in patients with previous c-XRT reported similar rates of perioperative stroke/TIA between groups, however long-term stroke/TIA ($p = 0.014$) and restenosis ($p < 0.003$) were more likely with CAS. CNIs were more common with CEA however long-term rates of cerebrovascular events favoured CEA ($p = 0.014$).⁷³ No high quality trials have evaluated the utility of medical therapy in this cohort.

CAS in Other Settings

Acute Stroke and Tandem Lesions

Carotid artery stenosis is a major cause of stroke, usually due to unstable atheroma resulting in acute thrombosis or embolization.³ 10-20% of patients with acute ischemic stroke present with an additional ipsilateral high-grade ICA stenosis/occlusion.⁷⁴ This makes it difficult to separate single and tandem lesions in trials. Endovascular clot retrieval (ECR) and CAS are used to treat tandem lesions. Acute stroke classifies the extracranial carotid lesion as symptomatic, necessitating treatment. Stent deployment before or after ECR is controversial. Time lost deploying the stent or negotiating a tight stenosis may result in further ischaemic damage. Additionally, embolisation after stenting is less significant as emboli enter an occluded territory. Embolisation after ECR requires repeat thrombectomy. Stenting requires antiplatelet therapy (often in addition to intravenous (IV) thrombolysis), predisposing patients to intracranial haemorrhage. Pre-thrombectomy angioplasty is an alternative to stenting, however is associated with its own complications.²⁶

Evidence guiding management of tandem lesions is poor. Thrombolysis produces poorer outcomes with ICA and cerebral vessel tandem lesions compared to single-vessel occlusion.⁷⁵ Most large RCTs investigating ECR have excluded patients with tandem lesions. Subgroup analyses of the ESCAPE and REVASCAT trials reported more favourable neurological outcomes with tandem ICA and middle cerebral artery lesions treated with endovascular therapy over IV thrombolysis, whereas subgroup analysis of the MR CLEAN trial revealed no significant difference between groups.⁷⁶⁻⁷⁸ A multicentre retrospective analysis (n=170) reported an incidence of 9% for symptomatic intracranial haemorrhages (sICH) with CAS plus ECR for tandem occlusions.⁷⁹ In 77% of patients a Thrombolysis in Cerebral Infarction (TICI) score of $\geq 2b$ was achieved, however mortality was high (19%) and only 36% of patients had a modified Rankin score of ≤ 2 at follow-up.

A meta-analysis of 11 studies reported revascularisation and sICH rates of 83% and 4% respectively in emergency CAS.⁸⁰ At 3 months, favourable clinical outcomes were seen in 46% of cases and mortality was 13%. A 2017 review reported TICI $\geq 2b$ revascularisation was achieved in 79% of patients with tandem occlusions.⁸¹ Kappelhof et al. pooled the results of 7 studies, reporting significantly higher rates of recanalization with CAS compared to intra-arterial thrombolysis (IAT) (99% vs 61%; $p < 0.001$).⁸² Mortality rates favoured IAT (0% vs 34%; $p = 0.002$). Both meta-analyses are limited by difference in anti-platelet/thrombolysis regimens, endovascular techniques, definitions of 'revascularisation' and reporting of intracranial haemorrhages.

Treatment options for acute extracranial ICA occlusion include IV thrombolysis, CEA or endovascular therapy. There is no good evidence suggesting which of these is best. Acute ICA occlusion has a poor prognosis and mortality is as high as 73%.⁸³ IV thrombolysis is associated with poor outcomes in these patients.⁸⁴ A prospective study of 201 patients with acute ICA occlusion treated with IAT, endovascular mechanical therapy or a combination of both reported better recanalization rates with mechanical approaches compared with pharmacological thrombolysis alone (86%/82% with/without thrombolytics vs 47%; $p<0.001$).⁸⁵ These patients also achieved better neurological outcomes, although still poor. Mortality was 31% and favourable neurological outcomes at 3 months were achieved in only 28% of patients.

Studies evaluating CAS in acute ICA occlusion are lacking. Published retrospective studies are small and heterogeneous. Pooled data from 6 retrospective studies compared CAS to IAT. Stenting resulted in a higher recanalization rates (87% vs 48%; $p=0.001$), more favourable outcomes (68% vs 15%; $p<0.001$) and lower mortality (18% vs 41%; $p=0.048$).⁸² Other retrospective studies have reported recanalisation rates and sICH of 36.4-100% and 6-24.8% respectively. Neurological outcomes varied dramatically and were generally poor.^{86,87} Similar outcomes have been reported with emergent CEA.⁸⁸

There is currently a significant lack of data comparing expedited CEA to expedited CAS in patients who are recently symptomatic. Less than half of the RCTs comparing CAS to CEA reported on the timing of intervention. Of those that did, the overwhelming majority of interventions were performed more than 14 days after the symptomatic event. CREST reported the shorted median interval time at 22 days for CEA and 18 days for CAS. In fact, the mean delay in all RCTs was over 14 days and even over 1 month in all RCTs except two.⁸⁹ The lack of robust data investigating the safety and efficacy of CAS in the acute / peri-stroke period is particularly significant given the routine use of ECR for stroke.

Nevertheless, pooled data from SPACE, EVA-3S and ICSS ($n=2839$) suggested that the timing of intervention following symptomatic events may be clinically important.⁹⁰ The highest rates of stroke/death for CAS occurred when intervention was performed within 7 days of the qualifying symptomatic event. Stroke/death rates for CEA during this time were at their lowest. Alternatively, performing CAS >14 days after the qualifying event produced

the lowest stroke/death rates in this group. Stroke/death rates for CEA during this time were at their highest. However, as this study did not include patients presenting acutely with tandem lesions or internal carotid artery occlusion, it cannot be extrapolated to patients presenting with acute stroke.

Medical Therapy

Medical Therapy with CAS

Stent thrombosis is a feared complication of CAS. Stent insertion may cause intimal injury leading to platelet adhesion and thrombus formation. Bare metal may incite thrombosis. Guidelines suggest administration of dual antiplatelet therapy (DAPT) pre and postprocedure along with antihypertensives, beta-blockers and lipid-lowering agents. However, guidelines regarding periprocedural and postprocedural DAPT therapy are inconsistent (Table 3). Evidence guiding the recommendations is poor and largely based on coronary artery stenting trials. No large RCTs evaluating antiplatelet therapy in CAS have been performed, in particular on DAPT versus aspirin alone.

Two RCTs comparing DAPT to single antiplatelet therapy in CAS have been published.^{91,92} The first compared aspirin and clopidogrel to aspirin and heparin (n=47). Neurological complications were more common in the heparin group (25% vs 0%; p=0.02). The other compared acetylsalicylic acid (ASA) and heparin with ASA and ticlopidine (n=100). Neurological complications were more common with heparin and ASA (16% vs 2%; p<0.05). No significant difference in bleeding and 30-day stent thrombosis/occlusion occurred in either study. A meta-analysis combining these studies reported no differences in bleeding complications between DAPT and single-agent groups, however DAPT did reduce TIA risk (p=0.003).⁹³ Statins have been shown to lower periprocedural stroke, death and MI risk. Reiff et al. reported an ischaemic stroke, MI or death OR of 0.31 (p=0.006) with statins (specific statin not described).⁹⁴ Groschel et al. reported similar results using several different statins (4% vs 15%; p<0.05).⁹⁵ Statin use has not been evaluated in RCTs.

Few studies have evaluated the role of newer antiplatelets. One retrospective study comparing aspirin and clopidogrel to aspirin and prasugrel in neurointervention suggested that aspirin/prasugrel posed a higher risk of haemorrhage (3.6% vs 19.4%, p=0.02).⁹⁶ No haemorrhagic complications were seen with aspirin/clopidogrel in patients who underwent CAS or angioplasty. Two were seen in the aspirin/prasugrel group (33.3%). Two similar retrospective studies reported no adverse events in 18 non-responders to clopidogrel who

underwent neurointervention using ticagrelor and in 18 patients who underwent CAS using ticagrelor.^{97,98}

Current Guidelines

CAS guidelines are not uniform and have not been updated with the most recent data (Table 4). The American Stroke Association's recommendations differ depending on the severity of stenosis and vascular risk factors.⁹⁹ Citing a lack of evidence, the 2011 NICE guidelines argue that CAS for asymptomatic stenosis should only be used in specific circumstances however CAS for symptomatic stenosis is supported.¹⁰⁰ The Society for Vascular Surgery generally recommends CEA over CAS in patients who are not surgically high-risk.¹⁰¹ The European Society for Vascular Surgery advocate for the use of CAS as an alternative to CEA in patients who are high-risk and/or provided that the documented procedural stroke/death risk is <6%.¹⁰²

Uncertainties and Future Directions

Despite multiple RCTs, the CEA versus CAS debate continues. Trials suggest that periprocedural strokes are more likely with CAS however MI is more likely with CEA, as are CNIs and haematomas. Medium and long-term results favour neither CAS or CEA. Results from the CREST trial are the most robust when it comes to long-term efficacy of CAS, however this study is over a decade old and it is conceivable that outcomes have changed with increased proceduralist experience and advancing endovascular technology. CAS may have a role in specific patient populations, however this is yet to be shown in trials.

Several RCTs are underway to evaluate the role of CAS in asymptomatic carotid stenosis and will help build upon results from the ACT-1 study. No high quality RCTs have compared CEA to CAS in complicated patients such as those with previous ipsilateral CEA or c-XRT, however this is unrealistic recruiting sufficient patient numbers would be difficult. These are required to govern evidence-based management in these cohorts. There is a lack of good evidence regarding specific stent or EPD superiority. Given the global variety in device use, RCTs comparing common stents and EPDs would be of significant use.

The area most lacking in evidence is the role of medical therapy in CAS. No large RCTs have compared periprocedural or postprocedural DAPT therapies or DAPT versus aspirin alone in CAS. Additionally, no RCTs have compared BMT to either CEA or CAS in carotid artery

stenosis since the introduction of many modern medications. SPACE-2, CREST-2, ACST-2 and ECST-2 will provide crucial evidence to address these gaps in the literature (Table 5).

Conclusion

Stroke is a major contributor to the global health burden. Many strokes occur secondary to carotid artery stenosis. CAS has become an alternative treatment for carotid artery stenosis and multiple trials have compared CAS to CEA. Periprocedural stroke is more commonly associated with CAS, however MI is more commonly associated with CEA. Long-term outcomes are comparable. The role of CAS to treat carotid artery stenosis is widely debated and guidelines are heterogenous. CAS can be performed using different techniques, equipment and medications and it has not yet been established which combination of these produces the best outcomes for specific indications. Further high quality RCTs are required to address these shortcomings and controversies, in order to provide a stronger basis for evidence-based management and consistent practice guidelines.

Conflict of interest

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Table 1: Summary of RCTs comparing CEA to CAS for carotid artery stenosis (EPD = embolic protection device, CNI = cranial nerve injury, MI = myocardial infarction)

Trial	Proceduralist Inclusion Criteria	Symptomatic/ Asymptomatic (% symptomatic)	EPDs used in CAS arm (Y/N, % of patients)	Devices Used	Results	Other
CAVATAS 2002 (n=504) 9-11 Recruitment period: March 1 st 1992 until July 31 st 1997	Nil specified	Both (90%)	Not mentioned	Stents: Wallstent Streker Palmaz EPD: N/A	Similar rates of periprocedural disabling stroke/death (6.4% vs 5.9%; p=0.8) and death/any stroke (10.0% vs 9.9%, p=0.98) 8-year rates of ipsilateral non-perioperative stroke were 11.3% vs 8.6% (HR 1.22) and for any non-perioperative stroke were 21.1% vs 15.4% (HR 1.66) Significantly more postoperative CNIs (0% vs 8.6%; p<0.0001) and major groin/neck haematomas (1.2% vs 6.7%; p<0.0015) with CEA Long-term restenosis more common in endovascular arm (adjusted HR 3.17; p<0.0001), lower rates of restenosis with angioplasty plus stenting vs angioplasty alone (HR 0.43)	Strict inclusion and exclusion criteria Median follow up 5 years CAS arm was angioplasty +/- CAS. 26% of CAS arm received a stent Wide confidence intervals make interpretation of some data difficult
SAPPHIRE 2004 (n=334) 14,15 Recruitment period: August 2000 until July 2002	CEA arm: median 30 procedures/year (range 15-100). Complication rates that met the criteria of the American Heart Association CAS arm: median 64 total procedures (range 20-700). Incidence of periprocedural stroke or death	Both (29%)	Y, 96%	Stents: Smart Precise EPDs: Angioguard Angioguard XP	CAS non-inferior with respect to death/stroke/MI within 30 days or death/ipsilateral stroke between 31 days and 1 year (12.2% vs 20.1%; p=0.004) No significant difference in rates of periprocedural death/stroke/MI or death/ipsilateral stroke between 31 days and 3 years (24.6% vs 26.9%; p=0.71) Rates of restenosis requiring intervention at 3 years were also similar (2.4% vs 5.4%; p=0.26)	Surgically high-risk patients only

	<6%					
EVA-3S 2006 (n=527) 18-20 Recruitment period: November 2000 until September 2005	CEA arm: ≥ 25 CEAs in the year before enrolment CAS arm: ≥ 12 CAS procedures or ≥ 35 stenting procedures of the supraaortic trunks, of which at ≥ 5 were CAS. If not, proceduralists were supervised until criteria fulfilled	Symptomatic	Y, 92%	Not mentioned	Significantly higher incidence of periprocedural stroke/death with CAS (3.9% vs 9.6%; RR 2.5) 5- year risk of periprocedural stroke/death and non- procedural ipsilateral stroke significantly higher with CAS (11.0% vs 6.3%; p=0.04), although non-significant 10 years (11.5% vs 7.6%; p=0.07) Similar postprocedural stroke numbers (6 vs 8; p=0.67). No significant difference in restenosis rates (7 vs 12; p=0.26)	Trial stopped prematurely due to high incidence of periprocedural stroke/death with CAS, hence underpowered Median follow up of 7.1 years
SPACE 2006 (n=1200) 16,17 Recruitment period: March 2001 until February 2006	CAS arm: ≥ 25 successful consecutive percutaneous transluminal angioplasty or stent procedures CEA arm: 25 consecutive CEAs and provision of mortality and morbidity rates	Symptomatic	Y, 27%	Stents: Carotid Wallstent Precise Acculink EPDs: PercuSurge GuardWire FilterWire EX AngioGuard NeuroShield Carotid Trap	Non-inferiority of CAS not demonstrated with respect to periprocedural death/ipsilateral ischaemic stroke (6.84% vs 6.34%; p=0.09) Similar rates of ipsilateral ischaemic strokes at 2 years and any periprocedural stroke/death (9.4% vs 7.8%; log-rank p=0.31) Recurrent stenosis more frequent with CAS (11.1% vs 4.6%; p=0.0007)	
ICSS 2010 (n=1713) 21,22 Recruitment period: May 2001 until October 2008	CEA arm: 50 previous carotid operations (≥ 10/year) CAS arm: >50 stenting procedures, with ≥ 10 cases in the carotid artery If not,	Symptomatic	Y, 72%	Not mentioned	Incidence of stroke/death/MI within 120 days higher with CAS (8.5% vs 5.2%; p=0.006) Significantly more CNIs (1 vs 45) and haematomas (31 vs 50; p=0.0197) with CEA 5-year stroke rates higher with CAS (8.9% vs 5.8%; p=0.04) 5-year risk of fatal/disabling strokes similar (6.4% vs 6.5%; p=0.77)	

	procedures were proctored by an outside proceduralist until satisfied that the centre could perform the procedure				Procedure-related stroke/death or ipsilateral stroke during follow-up more frequent with CAS (p=0.001) Long-term rates of restenosis/occlusion similar between groups (HR 1.25)	
CREST 2010 (n=2502)^{12,13} Recruitment period: December 2000 until July 2008	CEA arm: >12 procedures/year with complication and death rates <3% if asymptomatic and < 5% if symptomatic CAS arm: endovascular experience and CAS result evaluation, participation in training and a lead-in phase of training	Both (53%)	Y, 96%	Stent: RX Acculink EPD: RX Accunet	Similar rates of periprocedural stroke/death/MI between groups (5.2% vs 4.5%; p=0.38) Significantly more periprocedural strokes with CAS (4.1% vs. 2.3%; p=0.01) Significantly more periprocedural MIs with CEA (1.1% vs. 2.3%; p=0.03) No significant difference in stroke/death/MI rates between groups at 10 years (11.8% vs 9.9%; p=0.51) Higher rates of stroke/death and ipsilateral stroke in the CAS group at 10 years (HR 1.37) Similar long-term postprocedural ipsilateral stroke rates between groups (HR 0.99) Similar rates of restenosis/revascularization between groups (HR 1.24)	
ACT-1 2016 (n=1453)²³ Recruitment period: March 30th 2005 until January 18th 2013	Both arms: >25 recently performed procedures. Approval of these outcomes by committee. Participation in a lead-in phase whereby sites performed ≥2	Asymptomatic	Y, 100%	Stent: Xact EPDs: Emboshield Emboshield Pro Emboshield NAV6	CAS non-inferior with respect to combined periprocedural death/stroke/MI or ipsilateral stroke within 1 year (3.8% vs 3.4%, p=0.01) Periprocedural stroke and death rates (2.9% vs 1.7%; p=0.33) and postprocedure stroke rates up to 5 years (2.2% vs 2.7%; p=0.51) similar between groups	Participants relatively healthy (<79 years of age and not high-risk for surgery)

	cases				Cumulative 5-year rates of stroke-free survival similar between groups (93.1% vs 94.7%; p=0.44).	
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Table 2: Names and characteristics of commonly used carotid artery stents

Stent	Manufacturer	Material	Closed/Open	Free cell area (mm ²)	Tapered/Non-tapered
Casper	Microvention-Terumo (Tustin, CA, USA)	Nitinol	Closed	0.375/0.600 (double layer)	Tapered
Wallstent	Boston Scientific (Natick, MA, USA)	Elgiloy (non-magnetic Cobalt-Chromium-Nickel-Molybdenum alloy)	Closed	1.08	Non-tapered
Xact	Abbott Vascular (Abbott Park, IL, USA)	Nitinol	Closed	2.74	Either
NexStent	Boston Scientific	Nitinol	Closed	4.70	Tapered
Precise	Cordis (Bridgewater, NJ, USA)	Nitinol	Open	5.89	Non-tapered
Exponent	Medtronic (Minneapolis, MN, USA)	Nitinol	Open	6.51	Either
Protégé	Covidien (Irvine, CA, USA)	Nitinol	Open	10.71	Either
Acculink	Abbott Vascular	Nitinol	Open	11.48	Either
Zilver 518® RX	Cook Medical (Bloomington, IN, USA)	Nitinol	Open	12.76	Non-tapered
Cristallo Ideale	Medtronic	Nitinol	Hybrid: closed-cell center; open-cell ends	NA	Either
Sinus-Carotid-Rx	Optimed (Ettlingen, Germany)	Nitinol	Hybrid: open-cell center; closed-cell ends	NA	Either

Table 3: Periprocedural and postprocedural medical therapy guidelines for CAS

Guideline	Regimen
American Stroke Association 2011 ⁹⁶	81-325mg aspirin and 75mg clopidogrel (or 250mg BD ticlopidine if intolerant of clopidogrel) 3 days pre-procedure, continued for 'at least 30 days', after which aspirin is to continue
European Society for Vascular Surgery 2017 ⁹⁸	Start DAPT with aspirin (300 mg initially for up to 14 days followed by 75 mg daily if not already taking aspirin) and clopidogrel (75 mg daily) 3 days prior to CAS. Aspirin and clopidogrel should be continued for at least 1 month, followed by clopidogrel thereafter, unless the treating physician opts for an alternative long-term antiplatelet regimen
Society for Vascular Surgery 2011 ⁹⁹	325mg aspirin and 75mg clopidogrel or 250mg ticlopidine for 'at least 3 days' pre-procedure and post-procedure for 30 days

	exactly, after which aspirin alone should continue
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Table 4: Carotid artery stenosis guidelines

Guideline and Year	Recommendation
American Stroke Association's 2014 ⁹⁶	CEA is advised for patients with recent stroke/TIA and >50% stenosis if patients are of low perioperative risk and patient factors have been considered CAS may be used in symptomatic patients at average/low risk of periprocedural complications with stenosis of >70% on non-invasive imaging or >50% by catheter-based imaging or non-invasive angiogram and perioperative risk is low Patient age and surgical risk should also be considered when considering CAS vs CEA
Nice 2011 ⁹⁷	All patient selection should be carried out by a multidisciplinary team and the interventionalists should have specific training and expertise in the technique Asymptomatic carotid artery stenosis: CAS should only be used with special arrangements for clinical governance, consent and audit or research Patients must understand the uncertainty about the procedure's

	efficacy, the risk of stroke and other complications Symptomatic carotid artery stenosis: CAS for symptomatic carotid stenosis is supported provided that arrangements are in place for clinical governance and audit or research During the consent process, clinicians should ensure that patients understand the risk of stroke and other complications associated with this procedure
Society for Vascular Surgery 2011 ⁹⁸	In most patients with carotid stenosis for intervention, CEA is preferred to CAS Asymptomatic patients with $\geq 60\%$ stenosis should be considered for CEA provided the patient has a 3- to 5-year life expectancy and perioperative stroke/death rates are $\leq 3\%$ CEA is preferred over CAS in patients >70 years of age, with long ($>15\text{mm}$) lesions, pre-occlusive stenosis, or lipid-rich plaques who are not surgically high-risk CAS is preferred in symptomatic patients with $>50\%$ stenosis who are surgically high-risk There are insufficient data to recommend CAS for asymptomatic patients with 70%-99% stenosis
European Society for Vascular Surgery 2017 ⁹⁹	In recently symptomatic patients with a 50-99% stenosis who present with adverse anatomical features or medical comorbidities that are considered to make them 'high risk for CEA', CAS should be considered, provided the documented procedural death/stroke rate is $<6\%$ When revascularization is indicated in 'average surgical risk' patients with symptomatic carotid disease, CAS may be considered as an alternative to surgery, provided the documented procedural death/stroke rate is $<6\%$. When decided, it is recommended to perform revascularization of symptomatic 50-99% carotid stenoses as soon as possible, preferably within 14 days of symptom onset.

Table 5: Active carotid artery stenting trials

Trial name	Comparison	Anticipated completion
SPACE 2: Stent-protected angioplasty in asymptomatic	Two 2-arm clinical trials comparing CAS, CEA, and best	July 2020

carotid artery stenosis versus endarterectomy (ISRCTN78592017)	medical therapy in asymptomatic patients with carotid stenosis	
ACST-2: Asymptomatic Carotid Surgery Trial (NCT00883402)	An international randomised trial to compare CEA with CAS to prevent stroke in asymptomatic patients with carotid stenosis	December 2019
CREST-2 (NCT02089217)	2 parallel multicentre randomized, observer-blinded end point clinical trials evaluating intensive medical management alone, intensive medical management plus CEA and intensive medical management with CAS in asymptomatic patients with carotid stenosis	December 2020
ECST-2: European Carotid Surgery Trial (ISRCTN97744893)	Multicentre, randomised, controlled, open, prospective clinical trial comparing medical therapy with medical therapy and revascularisation in patients with carotid artery stenosis	March 2022

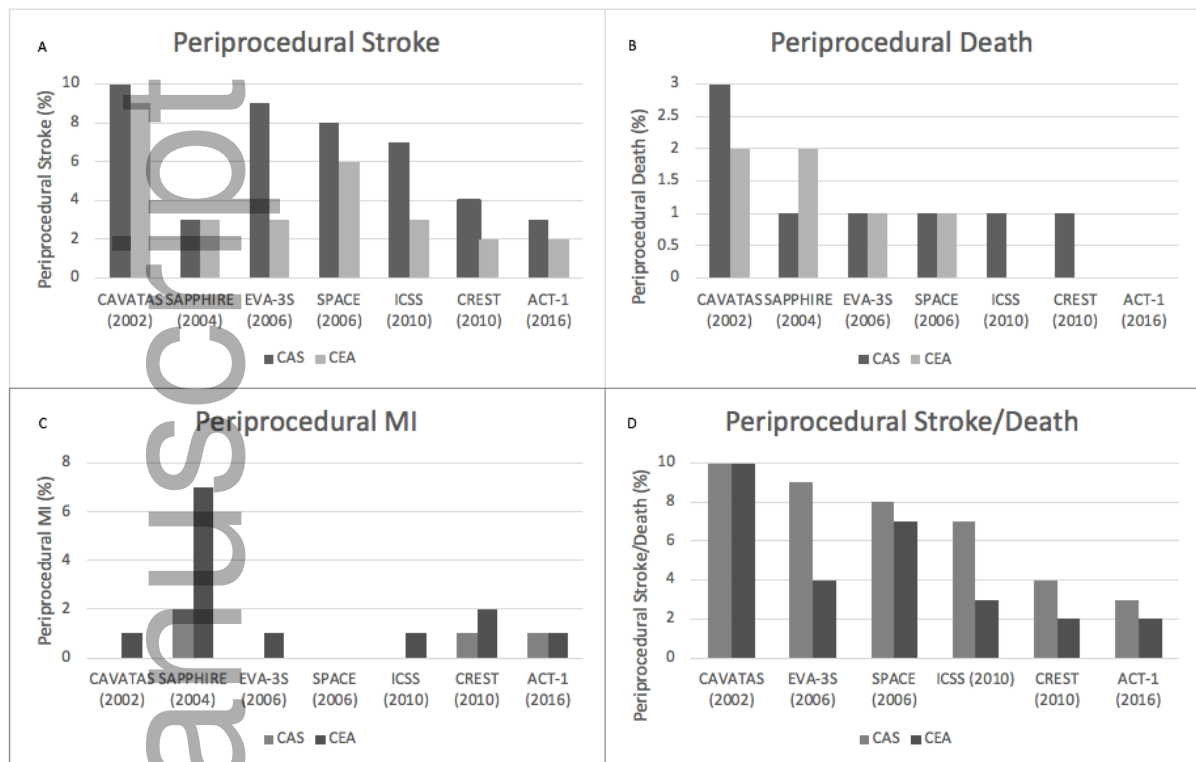
Figure 1

Fig 1. Complication rates (rounded to the nearest percentage) from CEA vs CAS RCTs over time. RCTs are listed in chronological order. **A.** Periprocedural stroke rates. **B.** Periprocedural death rates. **C.** Periprocedural MI rates. **D.** Periprocedural stroke/death rates.

Figure 2

Fig 2. Procedural and post-procedural images of carotid artery stenting for left-sided base of skull ICA stenosis. **A.** Anterior view of ICA stenosis (black arrow). **B.** Lateral view of ICA stenosis (arrow). **C.** Stent position pre-deployment (BeGraft coronary stent graft (Bentley Innomed GmbH, Hechingen, Germany), arrow). **D.** Achievement of ICA patency post-deployment of stent (arrow). **E.** Anterior view of intracranial circulation post-deployment of stent (arrow). **F.** Postprocedural magnetic resonance angiography depicting stent artefact and contrast follow through patent ICA (arrow)

Figure 3

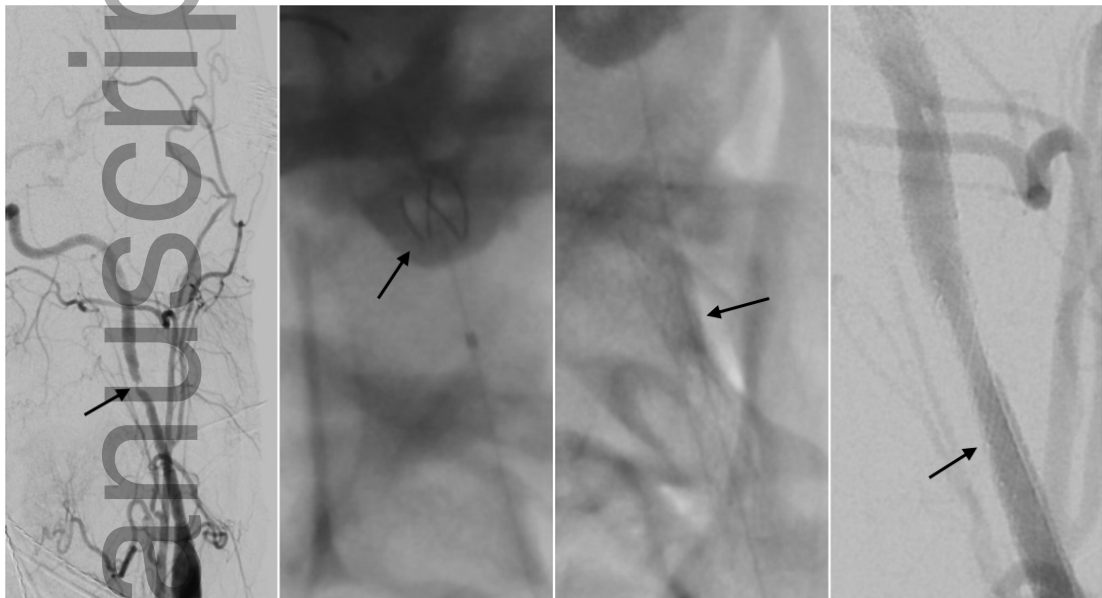


Fig 3.

Procedural images of carotid artery stenting for left-sided high cervical ICA stenosis in a young female with likely fibromuscular dysplasia. **A.** Anterior view of ICA stenosis (arrow). **B.** Deployment of Emboshield f-EPD (arrow). **C.** Positioning of Casper stent pre-deployment (arrow). **D.** Achievement of ICA patency post-deployment of stent (arrow).

Figure 4

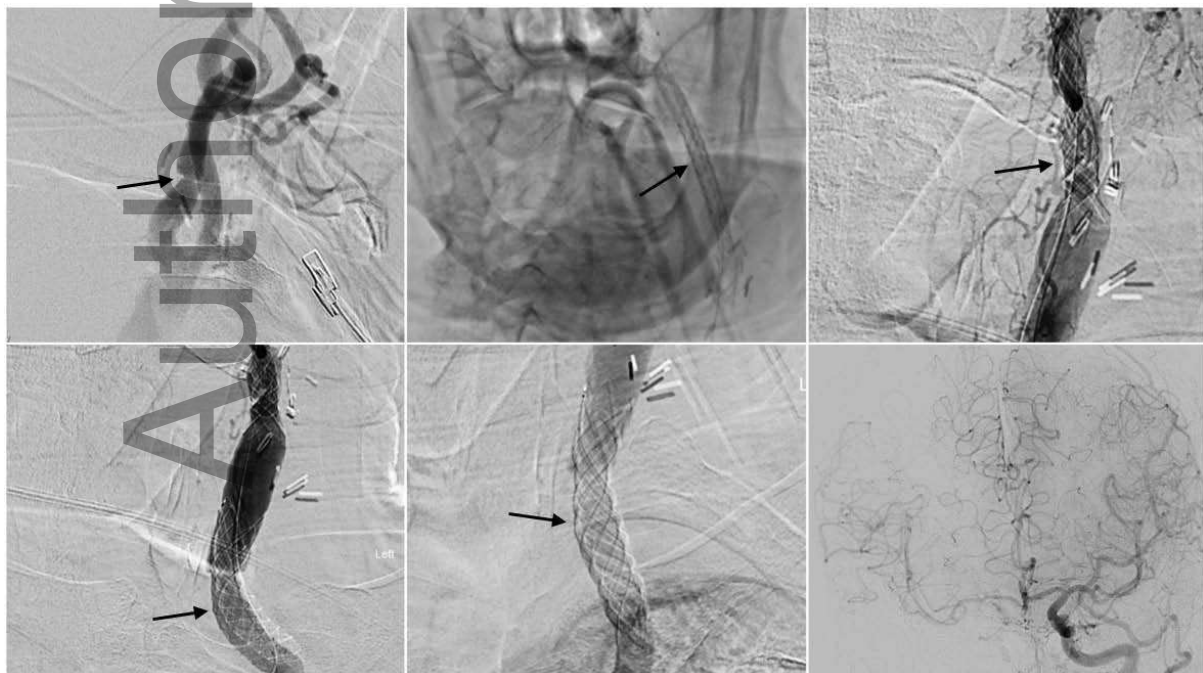


Fig 4. Procedural images of carotid artery stenting for left-sided cervical ICA stenosis and common carotid artery (CCA) ‘kink’ in a patient with previous CEA and complete occlusion of right-sided CCA. **A.** Anterior view of ICA stenosis (arrow). **B.** Positioning of Casper stent pre-deployment (arrow). **C.** Achievement of ICA patency post-deployment of stent (arrow). **D.** Position of CCA stent relative to ICA stent (arrow). **E.** CCA stent (green arrow). **F.** Anterior view of intracranial circulation post-deployment of stent with known right CCA occlusion

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