# Peri-Procedural Stroke Risk: Carotid Artery Stenting versus Carotid Endarterectomy

By

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**STROKE** is the 5th leading cause of death in the United States, killing about 130,000 Americans a year[1]. The prevalence of stroke is roughly 3% of the population per year[1]. There are two types of stroke: hemorrhagic and ischemic. Hemorrhagic stroke is caused by bleeding into the cranial cavity while ischemic involves occlusion or restriction of blood flow to an area of the brain.[1] Potential pathophysiologic mechanisms of ischemic stroke include decreased perfusion due to a systemic cause or due to stenosis of a vessel that feeds the brain. Decreased perfusion due to a systemic cause, like persistent hypotension, causes global cerebral hypo perfusion. Vascular occlusion can occur due to plaque or embolization and causes decreased perfusion in the associated vascular bed. Cardioembolism is the most common cause representing about 37% of ischemic strokes[2]. Carotid artery atherosclerosis is a major risk factor and causes 10-15% of ischemic stroke[3]. Atherosclerosis can cause a gradual change in the vessel causing a narrowed area that restricts flow and can accumulate platelets which lead to an acute episode[4] . Risk of stroke from carotid artery stenosis depends on the severity of the stenosis among other risk factors including diabetes and hypertension.

Carotid endarterectomy (CEA) is an open surgical procedure was established in 1954 as a reliable treatment for carotid stenosis. In approximately 1990, a clinical trial supported the use of endarterectomy over aspirin alone[5]. Carotid artery stenting is a more recent procedure developed in the 1980s as a less invasive alternative treatment. It is important to compare and contrast each method of treatment to further identify the long-term outcomes associated with each option.

In Carotid endarterectomy a dissection of the carotid artery is made, plaque is removed, a patch is used to close the artery and the skin is closed. This procedure is completed with general anesthesia in an operating room. Risks include bleeding, myocardial infarction, stroke, and cranial nerve palsy.

Carotid artery stenting (CAS) is usually completed in the cardiac catheterization lab via percutaneous access of the right radial or femoral artery with a catheter. A wire is used to cross the lesion. A distal protection filter is usually deployed distally to catch any debris and prevent intraoperative stroke. A balloon is used to dilate the lesion and a stent is deployed. Following this the filter is removed. CAS is typically completed using conscious sedation. Risks include stroke, myocardial infarction, access site hematoma.

It is important to mention lifestyle modification, smoking cessation, diet, exercise and medical management of carotid artery stenosis. Many patients will not undergo carotid stenting or carotid endarterectomy. Medical therapy involves correcting or treatment for modifiable risk factors. The medical management typically includes antihypertensive medications, statin therapy, glucose control for diabetic patients, and antiplatelet therapy.

This paper serves to discuss presentation, diagnosis, and treatment options for carotid artery stenosis. The available evidence in systematic reviews will be examined comparing periprocedural risks of CEA versus CAS.

**Clinical Presentation**

Carotid Artery Stenosis can be symptomatic or asymptomatic which makes it difficult to identify. Asymptomatic carotid artery stenosis is when a patient is not aware that they have the disease, and they do not experience any symptoms. Symptomatic carotid artery stenosis is easier to identify. A patient is symptomatic if they have permanent or transient neurological symptoms related to the ipsilateral retina or hemisphere of their brain. Symptoms can include contralateral weakness, numbness of the extremities, loss of vision, dysarthria, aphasia, amaurosis fugax. Technically symptoms such as dizziness and syncope are not considered symptoms of carotid artery stenosis.

**Physical Exam**

Auscultation of the carotid arteries is a physical exam technique that can be utilized to identify potential plaque in the carotid arteries. There is a "whoosh" sound created as blood flow is more turbulent in arteries that have plaque. The presence of a carotid bruit is associated with increased risk of vascular disease, including stroke, myocardial infarction, and cardiovascular death[8]. Bruits can radiate from cardiac murmurs. Bruits that are louder above the clavicle more often to be a true carotid bruit, whereas bruits heard more intensely below the clavicle are likely to be cardiac murmurs. Bruits may not be present if there is a total occlusion of the vessel. It is important to listen to the heart sounds in all positions for multiple cardiac cycles to differentiate sounds heard.

**Diagnostic Testing**

Carotid Duplex Ultrasound is a non-invasive, cost effective test used as the first technique to identify potential plaque in the vessels. This technique uses doppler ultrasound to document flow in the vessel. This can be completed in the office or hospital setting in a little amount of time. It does not require contrast dye or radiation. On ultrasound, identifying carotid artery disease is based on flow velocities within the vessels. Increased velocity of flow may signify stenosis in a vessel. Completely occluded vessels will not have flow documented.

Computed tomography angiography (CTA)/Magnetic Resonance Angiography (MRA) is another diagnostic tool used to image patients with suspected carotid artery stenosis. Both the CTA and MRA require IV contrast although the risk is less with MRA. CTA involves radiation and both require IV access.

Carotid angiogram is the definitive way to identify vessel features including tortuosity and degree of stenosis. This requires catheter placement into either the femoral or radial artery while the patient is under conscious sedation and involves contrast and radiation exposure. The potential risks include stroke, MI, bleeding, and infection.

**Treatment Options**

The cornerstone of treatment is lifestyle modification and medical management. Invasive treatment options include carotid artery stenting and carotid endarterectomy[9]. There are many risks and benefits to consider in the use of either method. The following systematic reviews pool data to show the efficacy of stenting versus carotid endarterectomy and the risk of peri procedural and long-term stroke.

**Methods:** The search databases utilized were the following: Cochrane Database of Systematic Reviews, PubMed, and TRIP database using keywords carotid artery stenosis, carotid artery stenting and carotid endarterectomy. My inclusion criteria consisted of: systematic reviews and meta analyses of randomized controlled trials. I excluded observational studies, clinical review papers, and abstracts. The quality evaluation will be completed through review of each systematic reviews use of the Cochrane risk of bias tool. Library **Search dates include:** June 2017 – November 2017

**Terms from PubMed**

Carotid artery stenting OR endarterectomy AND stroke

Carotid artery stenosis AND stroke

Carotid artery stenosis AND treatment options

**Mesh Terms:** Carotid stenosis, treatment, stroke, endarterectomy, stenting

**Results:** After searching Cochrane Database of Systematic Reviews, PubMed, and TRIP, I utilized four systematic reviews to compare the rates of periprocedural risks in CEA and CAS. I utilized systematic reviews published after 2015. Included in the four systematic reviews were a total of 17 different clinical trials.

**Zhang et al[10]** compared carotid artery stenting versus endarterectomy in a meta-analysis in 2015. This meta-analysis compared the effectiveness of stenting versus endarterectomy in studies between 2006 and 2015 to include primary endpoints of stroke and death in 30 days. The inclusion criteria included both randomized and non-randomized studies, with at least 20 patients in the study with at least 10 patients in each group for stenting versus endarterectomy. A total of 35 studies (27,525 patients) were used in the data analysis after excluding 734 studies. The article excluded systematic reviews, guidelines, case reports, and reviews. The average age of patients was 70 years old with 68% of the patients being men. They assessed the quality of the study utilizing the Cochrane risk bias tool with evaluation of publication bias using a funnel plot. Their results (RR 1.61 95% CI 1.29-2.01) revealed that CEA was superior to CAS in regards to stroke/death free rates in 30 days post intervention and that CEA was inferior to CAS for stroke/death at 1 year. The limitations include the inclusion of both RCTs and non RCTS and the lack of consideration of confounding factors such as age, anesthesia time, and symptomatic versus asymptomatic status. The results did suggest a difference in the results dependent on age, anesthesia, time, and symptoms. This can be due to recovery and difference in population. This review included all studies such as prospective, randomized, and retrospective trials which may weaken the data and limit the evidence significance. However, presented here in this paper are solely the RCT results. Among the included studies, heterogeneity was low but there are many

factors that are not able to be adjusted for in analyzing this data. Those factors include operator experience, antiplatelet therapy, symptomatic versus asymptomatic, stent types, and surgical technique of endarterectomy. These factors are important because they add variables that are hard to account for in the data analysis.

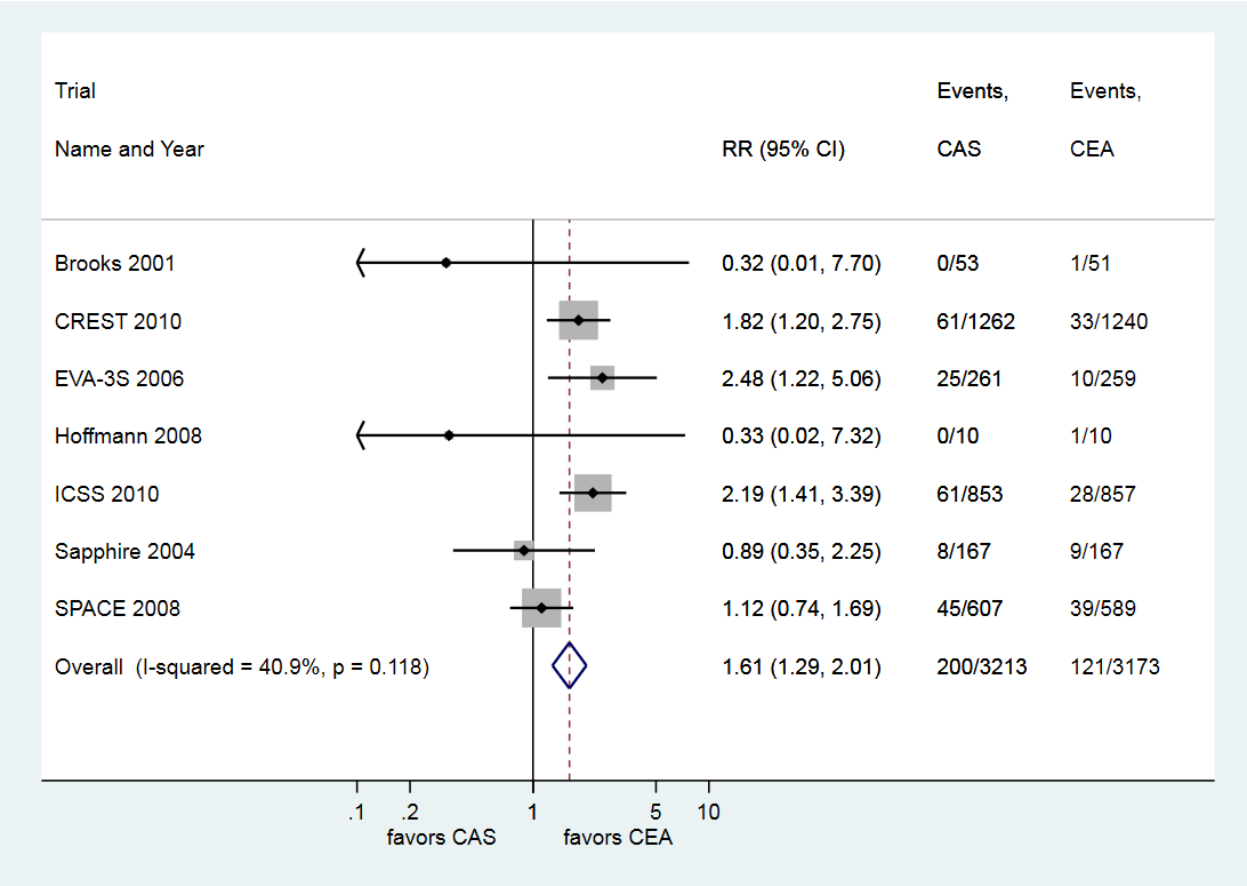


Figure 1. Forest plot utilizing raw data from RCTs from Zhang et al[10] showing stroke or death in thirty days

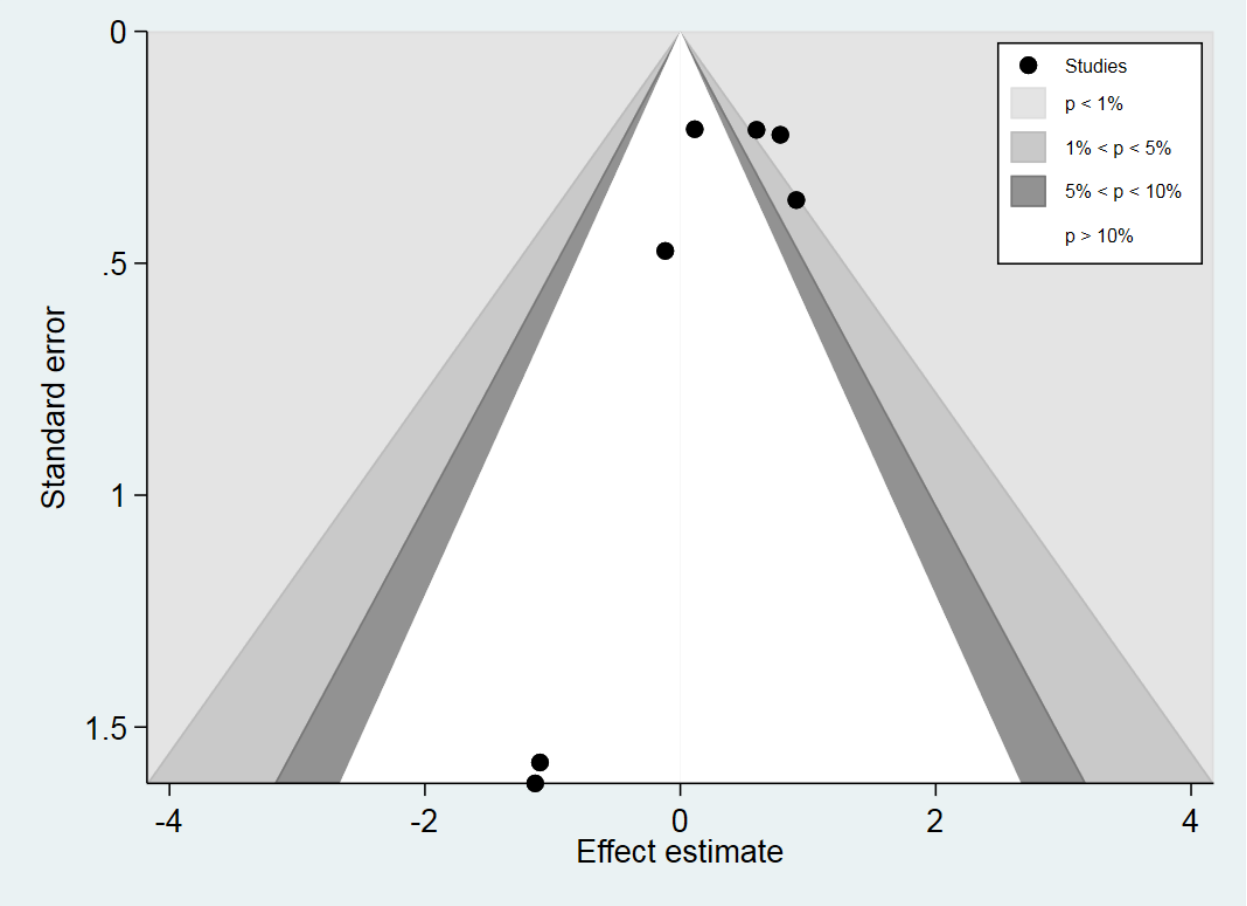


Figure 2. Funnel plot comparing RCTs that evaluated stroke or death in thirty days in stenting versus endarterectomy

**Yang et al**[11] included eight clinical trials with 7,005 patients to compare the efficacy and safety of CAS versus CEA. The studies that were included were randomized control trials, involved at least 20 patients, and were published and peer reviewed. They excluded all retrospective trials, observational studies, systematic reviews, and meta-analyses. The Cochrane risk bias tool was used to evaluate the quality of the studies included. There were not any high risk of bias domains. There was unclear risk of bias for the EVA-3s RCT in allocation concealment. The Kentucky and Markus trials were deemed unclear risk of bias in random sequence generation,

and blinding. The average age was 66-70 years old and the percentage of males was up to 80%. This data included primarily symptomatic patients. The results (RR 1.42 95% CI 1.20-1.67) reveled that CAS resulted in a significantly higher risk of stroke both in the long-term and periprocedural timeframe. They did not find heterogeneity that affected the results of the study. There were however, a small number of patients included in the meta-analysis. The limitations include an inability to do subgroup data analysis because of the lack of patients. There are important items to consider in the subgroups including age, symptoms, gender, use of distal protection devices that could shift the results and recommendations for treatment.

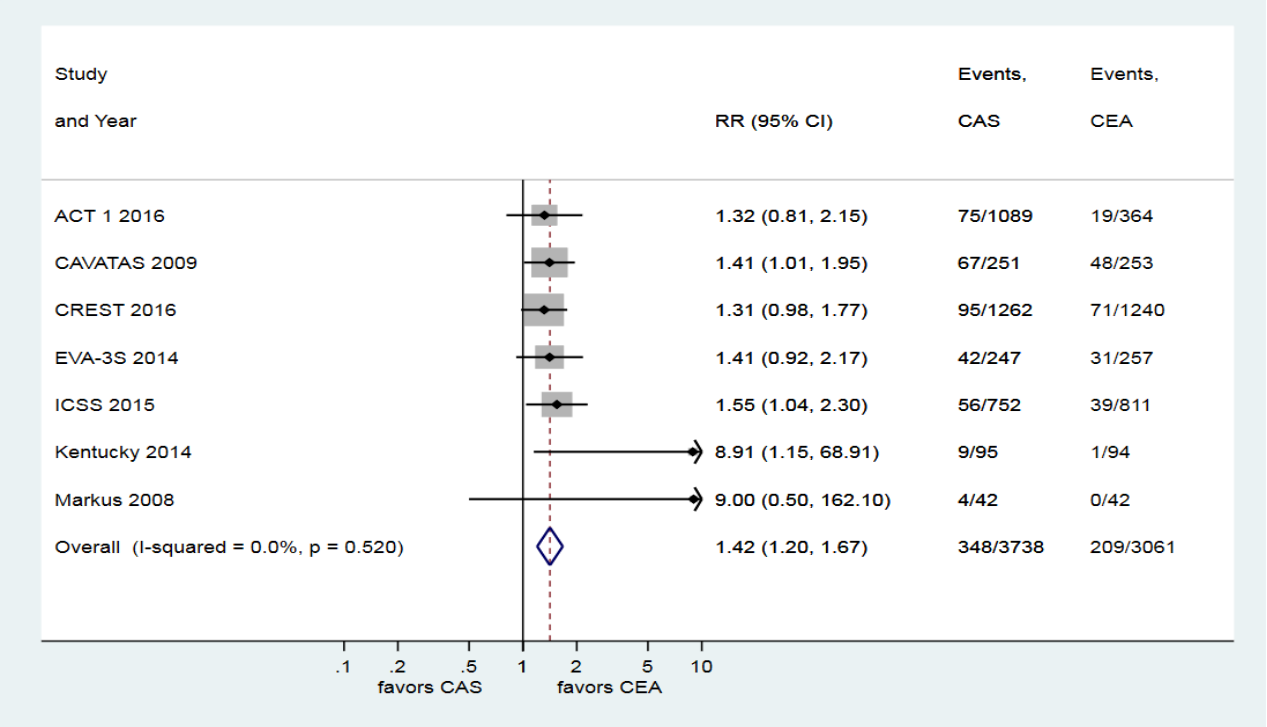


Figure 3. Forest plot utilizing raw data from Yang et al illustrating odds ratios for the cumulative incidence of stroke.

**Sardar et al**[12] utilized five clinical trials and 6,526 patients to compare the effectiveness of CAS versus CEA for the prevention of stroke in patients with carotid artery stenosis. Inclusion criteria included randomized clinic trials with at least 50 patients that used embolic protection. Studies that were excluded were isolated balloon angioplasty and abstracts only. These studies were evaluated using the Cochrane risk bias tool. Most of the included RCTs were determined to be low risk of bias in all categories. There were no designations for high risk of bias. EVA-3S 2006, did receive unclear bias in the allocation concealment domain. The Sapphire trials from 2008 and 2004 received unclear bias in the selective reporting domain. From review of the funnel plots, there did not seem to be evidence of publication bias. Of the five trials, two of them included only symptomatic patients. In this set of studies, the average age was 67-72 years old with 56-78% of participants being male. The results suggested an increased risk of any kind of stroke from the date of procedure through long term follow up with CAS versus CEA, however they were mostly non-disabling periprocedural strokes. The limitations of this study include the inability to adjust for different protocols, characteristics of patients, and definitions of outcomes. There continues to be a wide variety of lesion, types of stents, and operator experience, which cannot be accounted for in this research. Operator experience is key because most of the major clinical trials have been conducted at centers of excellence in these procedures which may not truly reflect the outcomes at smaller institutions where experience is less and risk may be more.

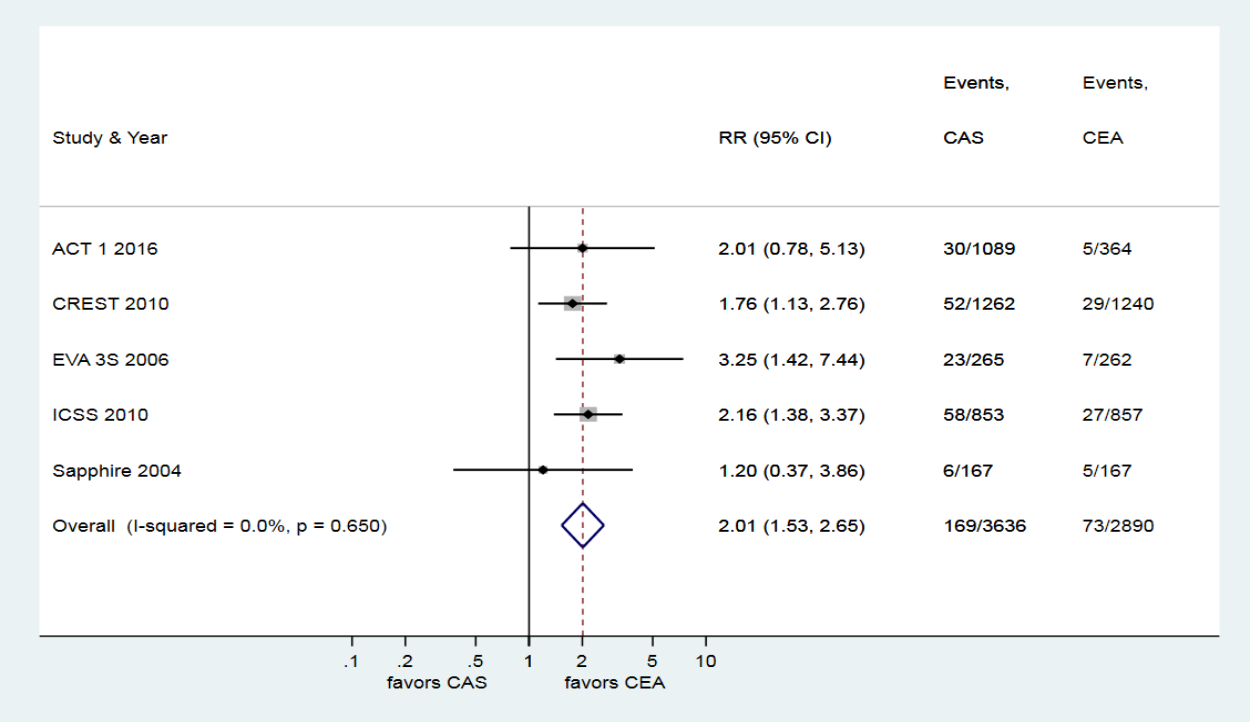


Figure 4. Forest plot from Sardar et al showing the increased risk of any periprocedural stroke in comparison of CAS and CEA.

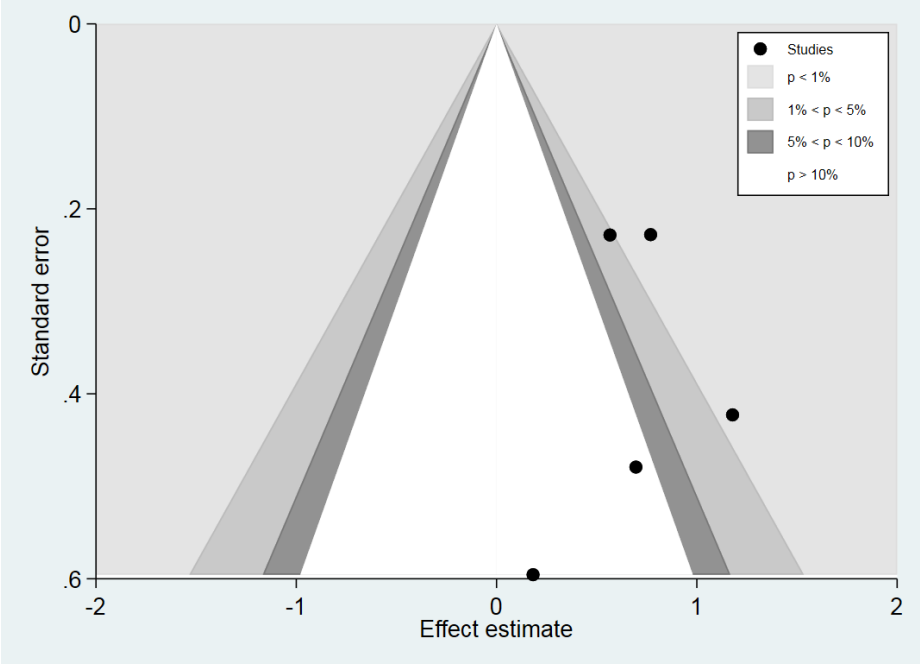


Figure 5. Funnel plot utilizing raw data from Sardar et al regarding periprocedural stroke rates.

**Moresoli et al**[13] reviewed five randomized control trials for a total of 4,534 patients who were randomized between CEA and CAS. This systematic review was specifically interested in the rates of events in asymptomatic patients, which consisted of 3,019 patients in those five randomized control trials. This review included studies only if they had greater than or equal to 50 asymptomatic patients. They did not include trials with differences in anticoagulation/antiplatelet pre-and post procedure. However, they did not make exclusion decisions based on embolic protection device use. Evaluation of the quality of the study was completed using the Cochrane risk bias tool. In their evaluation of bias, the risk was low or unclear in all categories except for the Sapphire trial in which it was a high risk due to incomplete outcome data due to the difference in lost to follow up in each arm: 14.4% in the CAS arm and 29.9% in the CEA arm. The unclear categories were noted in sequence generation and funding. In this collection of patients that were asymptomatic, the average age was 67-69 years old, with the majority of patients being male. The results suggested an increased rate of stroke peri procedurally in asymptomatic patients that underwent CAS (RR of 1.90 and a 95% CI 1.01-3.56). There is heterogeneity in the studies including length of follow up and patient characteristics, types of devices used, and types of embolic filters used, as well as technical skill of the operator. Another large limitation includes the few number of RCTs included in this meta-analysis.

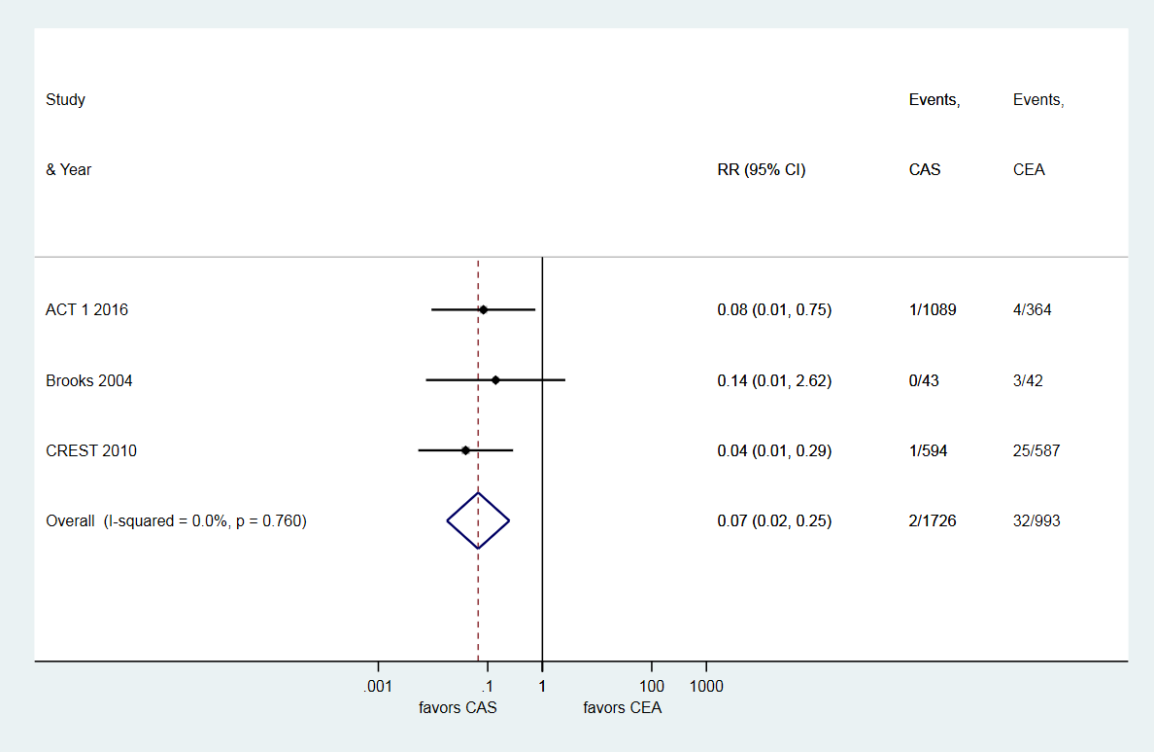


Figure 6. Forest plot from Moresoli et al showing increased risk of cranial nerve palsy in endarterectomy versus stenting

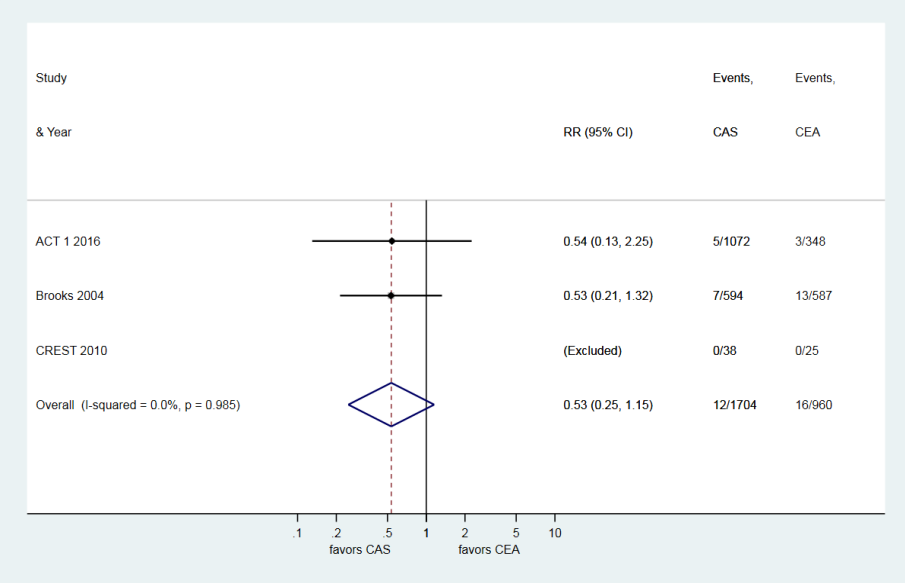


Figure 7. Forest plot from Moresoli et al showing increased risk of myocardial infarction in endarterectomy versus stenting

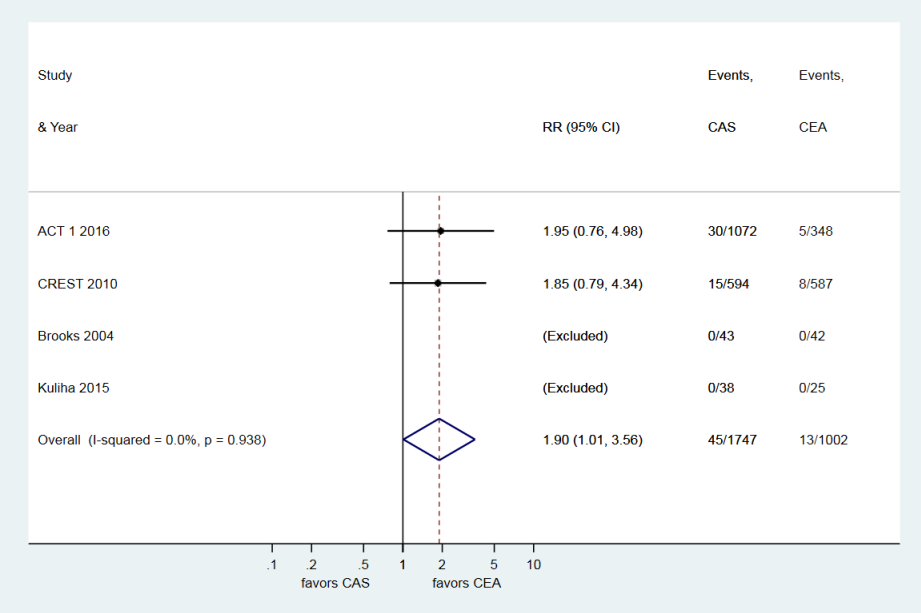


Figure 8. Forest plot from Moresoli et al showing increased risk of periprocedural stroke in carotid artery stenting versus endarterectomy.

## Discussion

Based on these systematic reviews, there is evidence to suggest the reduced risk of stroke following CEA compared to CAS.

Carotid artery stenosis can be asymptomatic or symptomatic which makes it difficult to diagnose. Currently, no screening recommendations exist for asymptomatic disease. While diagnosis includes an ultrasound and carotid angiogram, different treatment modalities exist and may vary depending on the individual patient. The mainstay treatment is lifestyle modification and medical therapy including risk factor modification with statin therapy, blood pressure management, glucose control and antiplatelet therapy. All patients with carotid artery stenosis should be receiving medical therapy at minimum in addition to any intervention to reduce the risk of stroke. Carotid endarterectomy could be considered for any patient without high surgical risk. High risk surgical features include: severe coronary artery disease, congestive heart failure, myocardial infarction in past 6 weeks, severe pulmonary disease, renal failure, age >80 and anatomical difficulties. Carotid artery stenting is an alternative to CEA for selected patients who need revascularization and are high surgical risk. There are risks and benefits associated with each procedure and choosing the best treatment option for your patient is largely individualized. Patient preferences for treatment must be considered as an integral part of the decision. While there have been an increasing number of studies comparing stenting and endarterectomy, these studies do not address medical management alone. The CREST 2 randomized control trial is looking to address this variable. The CREST 2 trial consists of two multicenter RCTs of carotid revascularization and intensive medical management versus medical management alone in patients with asymptomatic carotid stenosis[14]. One trial will randomize patients 1:1 to endarterectomy versus no endarterectomy and another will randomize patients 1:1 to carotid

stenting with embolic protection versus no stenting. In all of the treatment arms, the medical management will be identical. This trial is currently enrolling and will address an integral component of intensive medical management. Intensive medical management should be implemented regardless of invasive treatment modality. Dividing and investigating treatment options in asymptomatic versus symptomatic patients must be thoroughly evaluated. Overall, it is hard to use data from meta analyses because these have limitations including study heterogeneity and experience of the operators. There is continued need to evaluate the risk and benefits associated with treatment for carotid artery stenosis. As technology and medical management excel, there may be more ways to integrate treatment for individual patients that decreases the risk of periprocedural stroke and associated risks of the procedures.

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