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Carotid artery stenosis – Current evidence and treatment recommendations

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Abstract

Background: Carotid artery stenosis is an important cause for stroke. Carotid endarterectomy (CEA) reduces the risk of stroke in patients with symptomatic carotid stenosis and to some extent in patients with asymptomatic carotid stenosis. More than 20 years ago, carotid artery stenting (CAS) emerged as an endovascular treatment alternative to CEA. **Objective and Methods:** This review summarises the available evidence from randomised clinical trials in patients with symptomatic as well as in patients with asymptomatic carotid stenosis. **Results:** CAS is associated with a higher risk of death or any stroke between randomisation and 30 days after treatment than CEA (odds ratio (OR) = 1.74, 95% CI 1.3 to 2.33, $p < 0.0001$). In a pre-defined subgroup analysis, the OR for stroke or death within 30 days after treatment was 1.11 (95% CI 0.74 to 1.64) in patients <70 years old and 2.23 (95% CI 1.61 to 3.08) in patients ≥70 years old, resulting in a significant interaction between patient age and treatment modality (interaction $p = 0.007$). The combination of death or any stroke up to 30 days after treatment or ipsilateral stroke during follow-up also favoured CEA (OR = 1.51, 95% CI 1.24 to 1.85, $p < 0.0001$). In asymptomatic patients, there is a non-significant increase in death or stroke occurring within 30 days of treatment with CAS compared to CEA (OR = 1.72, 95% CI 1.00 to 2.97, $p = 0.05$). The risk of peri-procedural death or stroke or ipsilateral stroke during follow-up did not differ significantly between treatments (OR = 1.27, 95% CI 0.87 to 1.84, $p = 0.22$). **Discussion and Conclusion:** In symptomatic patients, randomised evidence has consistently shown CAS to be associated with a higher risk of stroke or death within 30 days of treatment than CEA. This extra risk is mostly attributed to an increase in strokes occurring on the day of the procedure in patients ≥70 years. In asymptomatic patients, there may be a small increase in the risk of stroke or death within 30 days of treatment with CAS compared to CEA, but the currently available evidence is insufficient and further data from ongoing randomised trials are needed.

Keywords

Carotid stenosis, carotid artery stenting, carotid endarterectomy

Introduction

Carotid artery stenosis is an important cause for stroke. Carotid disease becomes more prevalent with increasing age, affecting approximately 7.5% of all men and 5.0% of all women over 80 years of age.[1] The primary mechanism underlying cerebral ischaemia caused by carotid disease is plaque rupture and subsequent embolism to the brain. This has fostered the concept of the vulnerable or high-risk plaque, which is prone to rupture and cause cerebral ischaemia.[2] Carotid endarterectomy (CEA) reduces the risk for cerebral ischaemia in patients with symptomatic carotid stenosis and to some extent also in patients with asymptomatic carotid stenosis.[3,4] More than 20 years ago, carotid artery stenting (CAS) has emerged as a less invasive, endovascular treatment alternative to CEA.

Controversy remains over which patients require surgical or endovascular therapy and which patients can be safely treated with optimal medical management alone.

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This review summarises the available evidence from randomised clinical trials in patients with symptomatic carotid stenosis as well as in patients with asymptomatic carotid stenosis.

Risk factors for cerebral ischaemia caused by carotid stenosis

The risk for cerebrovascular events caused by carotid stenosis is determined by several factors. Overall, the risk for stroke in patients who recently experienced symptoms resulting from carotid stenosis (symptomatic carotid stenosis) is higher than in patients who have never experienced symptoms due to carotid stenosis (asymptomatic carotid stenosis). The risk for stroke is time dependent, being highest in the first weeks after the presenting event.[5] The type of presenting event is also of importance. The risk for recurrence is greater in patients who experienced a hemispheric stroke than in patients who presented with a transient ischaemic attack (TIA) or patients who suffered an ocular event (amaurosis fugax or retinal ischaemia).[5] Besides the presenting event and time since first symptoms, the degree of ipsilateral carotid stenosis is another important risk factor to determine future stroke risk.[5,6] Stroke risk is highest in patients with severe carotid stenosis.[7] Other known risk factors for future stroke include increasing age, an irregular and ulcerated plaque surface morphology (which is pathologically unstable), absence of angiographic collateral flow, impaired cerebral reactivity, high frequency of transcranial Doppler-detected emboli to the brain, hypertension and coronary heart disease.[5,7,8]

More recent research has focussed on the use of different imaging modalities to identify vulnerable or high-risk plaques and thus patients at particularly high risk for future stroke. MRI is able to visualise structural correlates of plaque instability with good histopathological correlation.[9,10] Intra-plaque haemorrhage (IPH) constitutes one of the most promising markers for plaque instability. Plaques with signs of IPH have a fundamentally altered biology, exhibiting rapid progression despite statin therapy and increasing the risk of cerebral ischaemia compared to plaques without IPH.[11–13] IPH is more prevalent in patients with symptomatic carotid stenosis and occurs in about 30–50%, while it is found in about 20–30% of patients with asymptomatic carotid stenosis.[14] A recent meta-analysis of individual patient data showed an increased risk of ipsilateral stroke in patients with IPH even when carotid stenosis was mild (<50% according to the criteria used in the North American Symptomatic Carotid Endarterectomy Trial (NASCET)).[15]

Symptomatic carotid stenosis

In patients with recently symptomatic carotid stenosis, the benefit of surgical removal of the carotid plaque (CEA) to prevent ipsilateral stroke was established in randomised controlled trials (RCTs) almost 30 years ago. In the 1980s and early 1990s, two large multicentre RCTs investigating the benefit of CEA versus medical therapy alone to prevent ipsilateral stroke in patients with symptomatic carotid stenosis were conducted: the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST). ECST showed a reduction in ipsilateral stroke with symptoms lasting longer than 7 days (including perioperative events) in the surgically treated participants from 20.6% to 6.8% at 3-year follow-up ($p < 0.0001$).[6] In NASCET, the risk of any ipsilateral stroke (again including perioperative events) was reduced from 26% to 9% after 2 years among participants with severe stenosis (70% or greater narrowing; $p < 0.001$) and from 22.2% to 15.7% after 5 years among participants with moderate stenosis (50–69% narrowing; $p = 0.045$).[16,17]

In both trials, the benefit of CEA was greatest in patients with severe carotid stenosis (>70%). In patients with moderate stenosis, the benefit of surgery was marginal and it remained unclear whether all patients benefitted from CEA.[5]

In the beginning of the 21st century, CAS was introduced as a less invasive treatment alternative for carotid stenosis. Initially, percutaneous transluminal balloon angioplasty without the insertion of stent devices was performed. Later, stent devices were specifically developed for the carotid arteries and primary stenting has since replaced balloon angioplasty alone as the endovascular treatment of choice.[18]

Today, various stent devices with different designs and configurations are in use. Previous studies demonstrated a higher risk of stroke during and/or immediately after the procedure in patients treated with open-cell stents due to incomplete coverage of the atherosclerotic lesion because of larger open areas between struts compared with closed-cell stents.[19–21] Closed-cell devices on the other hand are more rigid and therefore less flexible.[22] Consequently, mesh covered stents have been developed to combine the lower risk of peri-procedural stroke associated with closed-cell stents and the flexibility of open-cell stents.[23]

Potential advantages of CAS compared to CEA include the avoidance of a surgical incision in the neck and thus a lower risk of local complications such as cranial or cutaneous nerve injury and reduction in the rate of general surgical complications such as myocardial infarction.[24] However, CAS does not remove the atherosclerotic lesion at the carotid bifurcation and manipulation with the endovascular catheter in the vascular tree may dislodge emboli, which may cause distal embolisation and stroke. To prevent procedure-related stroke caused by dislodged emboli, cerebral protection systems have been introduced. The earliest of these devices were distal filters, which have to be advanced across the carotid stenosis first and deployed distally to capture any debris dislodged during the stenting procedure. However, whether these devices truly increase the safety of CAS remains controversial as they have to be

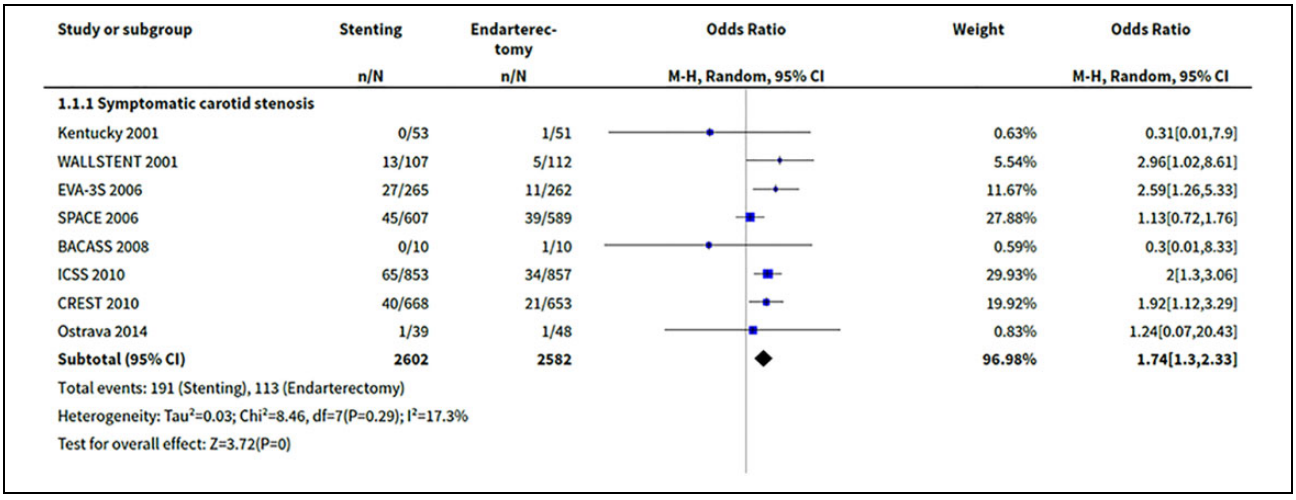

Figure 1. The combination of death or any stroke occurring between randomisation and 30 days after treatment could be extracted from 8 trials. The outcome occurred significantly more often among patients randomised to stenting than among those allocated to endarterectomy.

advanced across the lesion first, before they can be deployed and fulfil their intended purpose.[25,26] Moreover, distal filter devices cannot prevent emboli originating from the aortic arch occurring during catheter navigation in transfemoral CAS. Due to these issues, alternative protection systems, so-called proximal protection devices or flow reversal protection, have been developed. These devices introduce flow reversal across the carotid bifurcation to prevent any emboli dislodged during the procedure to cause ischaemic stroke. In addition, alternative access routes to avoid navigation of the aortic arch have been proposed. In recent years, direct catheterisation of the common carotid artery (T-CAR) has been increasingly implemented with promising results, especially in conjunction with flow-reversal protection systems.[27] However, high-quality evidence on the benefit of these novel protection systems is sparse and it remains to be shown whether these contemporary technologies improve procedural safety of CAS.

Following the introduction of CAS as an alternative to CEA, several large RCTs comparing both treatment options in patients with symptomatic or asymptomatic carotid stenosis were conducted.

The Endarterectomy versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) was a French multicentre trial, which started in November 2000 and randomised patients with $\geq$60% symptomatic carotid stenosis between CAS and CEA.[28,29]

The Stent-supported Percutaneous Angioplasty of the Carotid artery versus Endarterectomy trial (SPACE) trial randomised patients with symptomatic carotid stenosis of $\geq$50% or $\geq$70% (depending on the method of measurement) between CAS or CEA in Germany, Austria and Switzerland, from March 2001 until February 2006.[30,31]

The International Carotid Stenting Study (ICSS) randomised patients with symptomatic carotid stenosis of $\geq$50% to CAS or CEA between May 2001 and October 2008 in Europe, Australia, New Zealand and Canada. Short-term results up to 120 days after randomisation were published in 2010.[32] Long-term follow-up in this trial ended in 2011 and the results were published in 2014.[33]

The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) was a multicentre randomised trial conducted in the US and Canada between December 2000 and July 2008. The trial initially enrolled only patients with symptomatic carotid stenosis, but the eligibility criteria were changed in 2005 to include asymptomatic patients in addition to symptomatic patients. The final population consisted of 1321 patients with symptomatic and 1181 patients with asymptomatic stenosis. Results up to 4 years after randomisation were published in 2010.[34] Results over 10 years of follow-up were published in 2016.[35]

A meta-analysis of all available randomised trials showed CAS to be associated with a higher risk of death or any stroke between randomisation and 30 days after treatment than CEA (crude risks 7.2% vs. 4.4%; OR = 1.74, 95% CI 1.3 to 2.33, $p < 0.0001$; Figure 1). CAS was furthermore associated with a higher risk of the following outcome measures occurring between randomisation and 30 days after treatment than CEA: death or any stroke or myocardial infarction (crude risks 7.8% vs. 5.6%; OR = 1.43, 95% CI 1.14 to 1.80, $p = 0.002$), and any stroke (crude risks 6.9% vs. 4.0%; OR = 1.78, 95% CI 1.38 to 2.29, $p < 0.00001$). A pre-defined subgroup analysis revealed that the OR for stroke or death within 30 days after treatment was 1.11 (95% CI 0.74 to 1.64) in patients <70 years old and 2.23 (95% CI 1.61 to 3.08) in patients $\geq$70 years old, resulting in a significant interaction between patient age and treatment modality (interaction $p = 0.007$; Figure 2). The combination of death or any stroke up to 30 days after treatment or

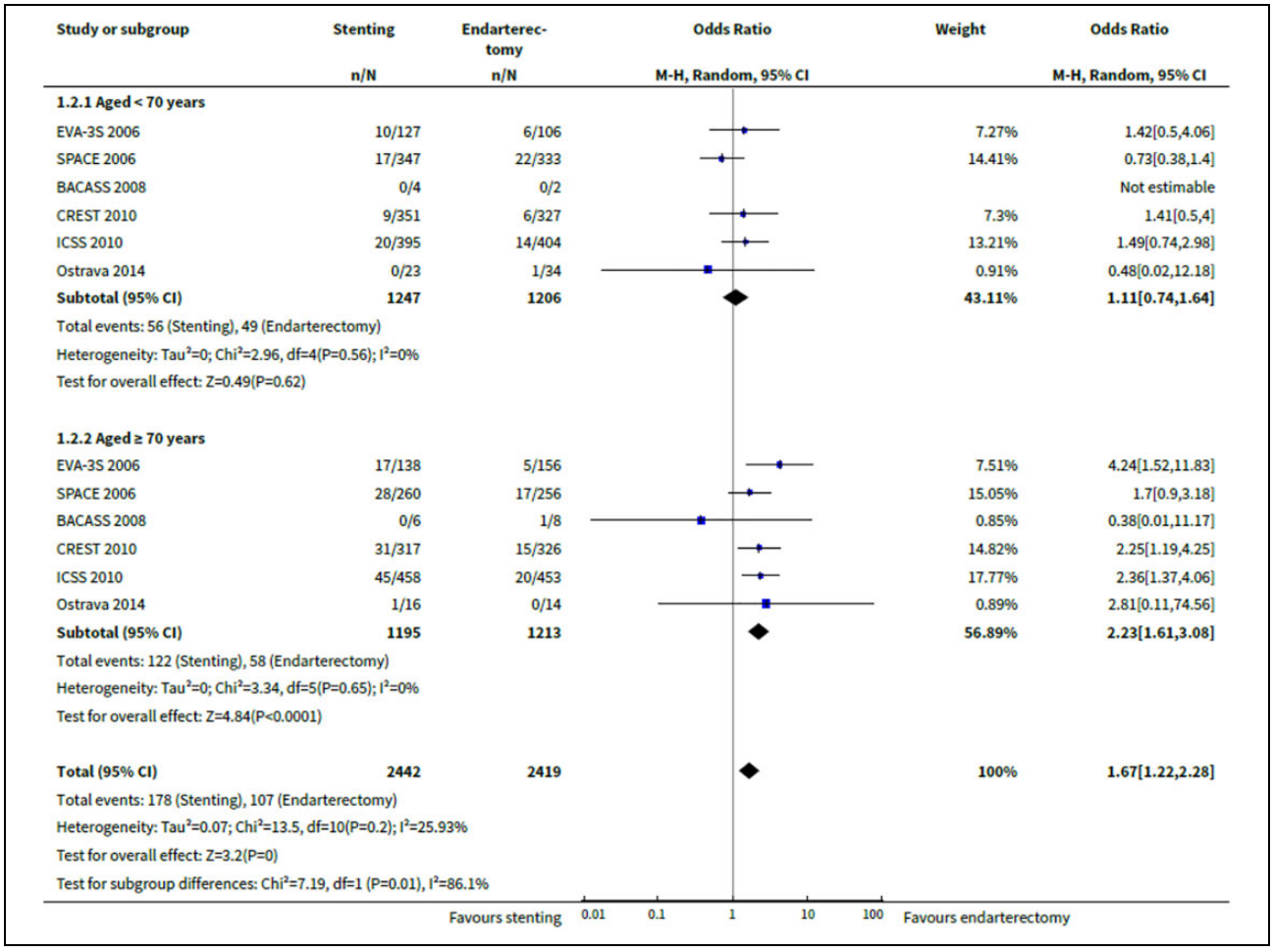

Figure 2. Subgroup analysis in patients with symptomatic carotid stenosis investigating the effect of age on the treatment effect. The risk of any stroke or death within 30 days after treatment was significantly higher in patients $\geq$70 years old treated with stenting than in patients treated with endarterectomy. Below the age of 70 years the rates of stroke or death did not differ significantly between treatments.

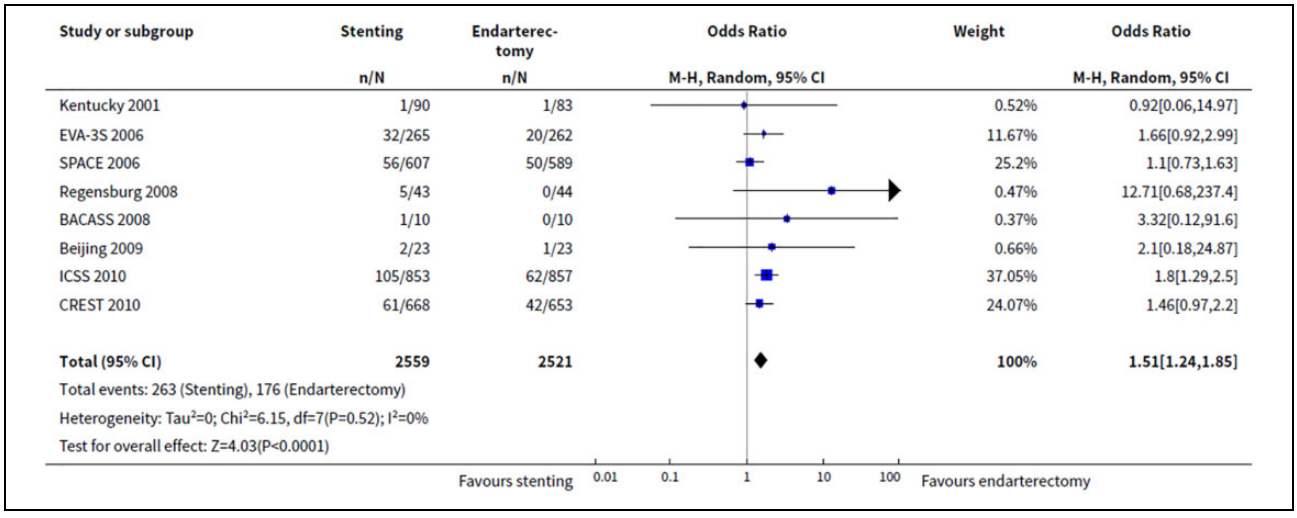

Figure 3. The combination of death or any stroke occurring between randomisation and 30 days after treatment or ipsilateral stroke until the end of follow-up could be extracted from 8 trials. The outcome occurred significantly more often among patients randomised to stenting than among those allocated to endarterectomy.

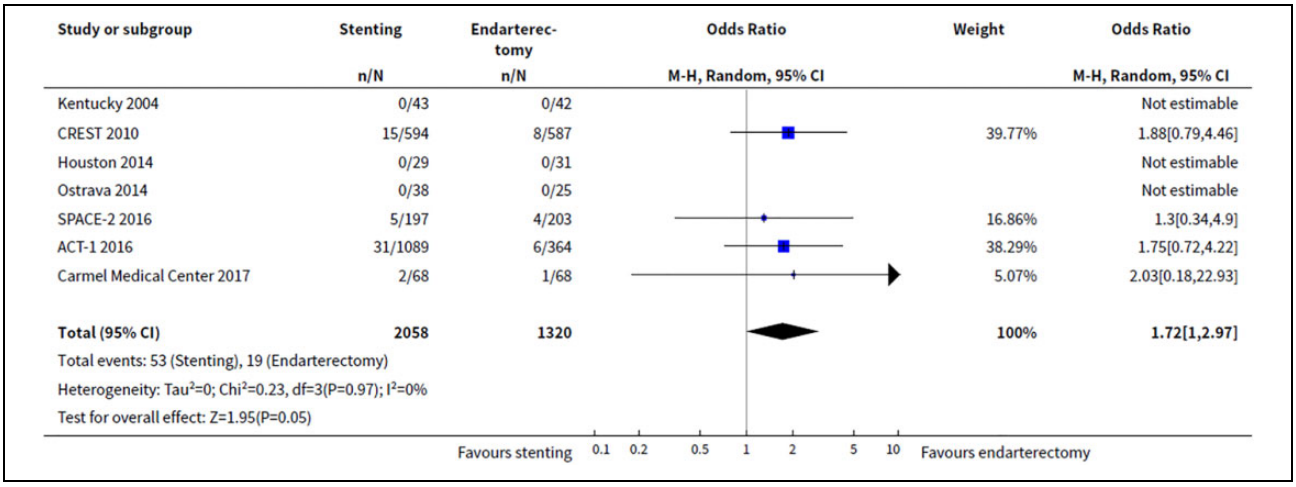

Figure 4. Comparison of death or any stroke between randomisation and 30 days after treatment in patients with asymptomatic carotid stenosis showing a non-significant increase of the outcome in patients treated with stenting compared to those treated with endarterectomy.

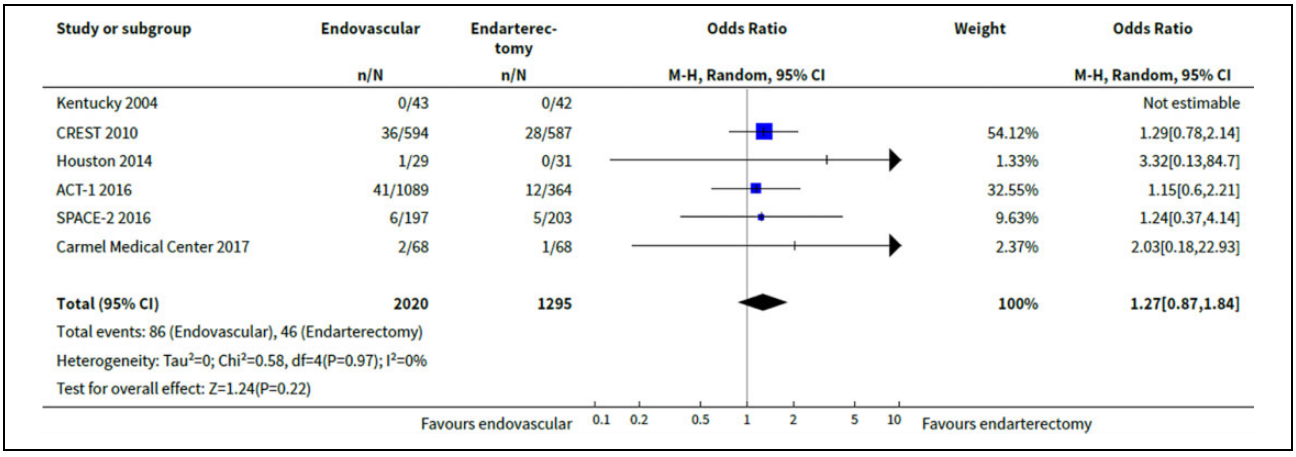

Figure 5. Comparison of death or any stroke between randomisation and 30 days after treatment or ipsilateral stroke until the end of follow-up in patients with asymptomatic carotid stenosis showing no significant difference between treatments.

ipsilateral stroke during follow-up favoured CEA (OR = 1.51, 95% CI 1.24 to 1.85, $p < 0.0001$; Figure 3). However, the rate of ipsilateral stroke after the peri-procedural period did not differ between treatments (OR = 1.05, 95% CI 0.75 to 1.47, $p = 0.77$).[3]

Asymptomatic carotid stenosis

Compared to the wealth of data available for patients with symptomatic carotid stenosis, high-quality evidence for the best management of patients with asymptomatic carotid stenosis is sparse. Therefore, the optimal management of these patients remains controversial.[36] There has been some evidence from RCTs showing a significant reduction in stroke risk during long-term follow-up.[4,37,38] However, patient recruitment for these trials was performed more than 30 years ago and medical management of patients with carotid stenosis has evolved since then most notably with the introduction of statin therapy and better blood pressure control.

Concerning the best invasive treatment option for these patients, some evidence from RCTs comparing CAS to CEA is available. The two largest trials comparing CAS to CEA in patients with asymptomatic carotid stenosis were CREST, which also included patients with symptomatic carotid stenosis, and the Randomised Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis (ACT-1).[39] Another trial, the Stent-supported Percutaneous Angioplasty of the Carotid artery versus Endarterectomy trial 2 (SPACE 2), was stopped early due to slow recruitment.[40] A recent meta-analysis showed a non-significant increase in death or stroke occurring within 30 days of treatment with CAS compared with CEA (OR = 1.72, 95% CI 1.00 to 2.97, $p = 0.05$; Figure 4). The risk of peri-procedural death or stroke or ipsilateral stroke during follow-up did not

differ significantly between treatments (OR = 1.27, 95% CI 0.87 to 1.84, $p = 0.22$; Figure 5).[3]

Discussion and conclusions

In patients with symptomatic carotid stenosis, randomised evidence has consistently shown a higher risk of stroke or death within 30 days of treatment in patients treated with CAS compared to those treated with CEA. This extra risk is mostly attributed to an increase in strokes occurring on the day of the procedure or within 30 days thereafter in patients $\geq$70 years.[41,42] Beyond 30 days after treatment, CAS is as effective in preventing recurrent stroke as CEA. However, combining procedural safety and long-term efficacy in preventing recurrent stroke, CAS is still associated with higher risks than CEA.

In patients with asymptomatic carotid stenosis, there may be a small increase in the risk of stroke or death within 30 days of treatment with CAS compared to CEA, but the currently available evidence is insufficient to make firm recommendations. Further data from still ongoing randomised trials are needed.[43]

Most of the currently available evidence on medical therapy, endarterectomy and stenting in symptomatic and asymptomatic patients stems from trials conducted 10 to more than 20 years ago. Medical management of patients with carotid stenosis has advanced since then, most notably with a more widespread use of statins, more intensive antiplatelet regimens, better blood pressure control and increased awareness for vascular risk factors. Consequently, the stroke risk associated with carotid stenosis reported in TIA registries has decreased.[44,45] At the same time, the safety of carotid procedures has improved. A recent individual patient data meta-analysis investigating the procedural risk of both CEA and CAS over time showed a significant decrease in procedural risk over time in CEA but not in CAS.[46] However, the data used for this meta-analysis stem from trials conducted between 2000 and 2008. Some technological advances, especially in CAS, were only achieved after the completion of the trials included in this meta-analysis. More recent, mostly observational studies showed low procedural risks associated with CAS when performed with mesh-covered stent devices or proximal balloon occlusion protection devices.[47–49] However, randomised studies comparing CAS using state-of-the-art devices and protection systems with CEA are still lacking.

Therefore, identifying patients at high risk for stroke under contemporary medical therapy is of paramount importance and emphasises the need for individual treatment decisions. Considerable uncertainty remains, whether patients with asymptomatic carotid stenosis and also some patients with symptomatic carotid stenosis still benefit from carotid revascularisation. These patients should be included in currently ongoing randomised trials which address this question.[50]

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