CHAPTER 8
Summary, general discussion and future perspectives
SUMMARY, DISCUSSION AND FUTURE PERSPECTIVES

Patients suffering a transient ischemic attack (TIA) or stroke due to a stenotic lesion in the carotid artery have a high risk of getting a recurrent ischemic event. Over two decades ago, the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the European Carotid Surgery Study (ECST) and the Veterans Affairs trial (VA309) showed a reduction in risk of recurrent disabling stroke or death by carotid endarterectomy (CEA) in certain groups of patients. The degree of stenosis appeared to be the primary risk factor for recurrent disabling events and death, and has therefore been used since as primary indicator for intervention. Moreover, further analyses of the pooled study data showed that risk of recurrence was affected by male sex, age and time between the primary ischemic event and CEA. All these factors are taken into account when assessing patients for CEA. Current guidelines are also still based on these studies.

There have however been many developments in treating patients with symptomatic carotid disease since. These have led to a reduction in 30-day stroke or death rate from 7.1% in the randomized trials in the early 1990s to 4.4% in symptomatic patients included in more recent trials (chapter 3). Important improvements have been made in the field of medical treatment and imaging. In addition, the endovascular approach to treat carotid disease has recently been introduced. These developments raise questions concerning the applicability of the results of the earlier landmark trials on contemporary patients. In the previous chapters we have tried to answer these questions to some extent. Here we will briefly summarize the former chapters and discuss the current issues regarding the treatment of patients with symptomatic carotid stenosis.

IMPROVEMENTS IN MEDICAL TREATMENT

In the landmark trials, medical treatment differed between centers and care providers. Patients were advised to quit smoking, received antiplatelet monotherapy (usually aspirin), got statins only when indicated (high-dose statins were not available at the time) and treatment goals for diabetes and hypertension differed widely from what we consider normal today. The medical management in symptomatic patients has improved tremendously since. Chapter 2 of this thesis summarizes trials conducted during the recent decades studying the separate components of best medical treatment (BMT) in patients with symptomatic carotid disease. The benefit in terms of stroke risk reduction due to improvements in medical therapy can be derived from several randomized studies. ACAS (Asymptomatic Carotid Atherosclerosis Study) and ACST (Asymptomatic Carotid Surgery Trial) showed a 60 to 70% reduction in the annual stroke risk in patients with asymptomatic stenosis over a time span of two decades. The 5-year risk of an ipsilateral event in medically treated patients was 11% in ACAS (published in 1995), 5.3% in the first period of the ACST study (published in 2004) and 3.6% in the second study of ACST (published in 2010). In accordance with these figures have several meta-regression analyses shown a decline in annual ipsilateral stroke risk over the past 25 years. The effect of intensive medical treatment has also been demonstrated in randomized studies including symptomatic patients, albeit in those having an intracranial stenosis. The SAMMPRIS trial (Stenting and Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis, published in 2014) showed that in patients with symptomatic high-grade intracranial stenosis intensive drug therapy even leads to a significantly lower risk of recurrence than intensive drug therapy combined with stenting. Moreover, not using a statin at the time of study entry appeared independently associated with an increased risk for a recurrent event or death within 30 days or a recurrent ipsilateral event after 30 days in the medical arm of the study. The key question remains in what extent current intensive medical therapy affects the risk of stroke recurrence in patients with a symptomatic carotid stenosis. The answer to this question may alter the indication for surgery. Perhaps the European Carotid Surgery Trial 2 (ECST-2) will answer this question in the nearby future. ECST-2 is an international randomized study comparing risks and benefits of BMT versus BMT combined with CEA or CAS in patients with symptomatic or asymptomatic, moderate to severe stenosis having a low or medium risk of future stroke. The study is currently recruiting patients. The medical arm of the study, in which patients are treated with optimal antiplatelet therapy, targeted cholesterol lowering therapy and, if required, targeted antihypertensive treatment, might provide us with the desired information about the effect of current BMT.

IMAGING

Improvements in medical therapy have narrowed the gap in absolute risk reduction between surgery and BMT. This undermines the applicability of the results of NASCET and ECST on currently treated patients with symptomatic carotid disease. Moreover, the absolute risk reductions found in NASCET and ECST indicate that, ultimately, CEA appears to be unnecessary in 92% of all patients with a 50-69% stenosis and in 84% of those with a 70-99% stenosis. Even if the perioperative risk of stroke or death would be reduced to 0%, these figures would only drop to 84% and 78% respectively. In other words, a reduction of perioperative morbidity and mortality due to improved techniques alone has only a small impact on the overall effectiveness of the treatment. Degree of stenosis as sole predictor for stroke recurrence and, with that, as indicator for intervention is thus not precise enough.

The most commonly used modality to assess stenosis severity, duplex ultrasound, also has its limitations. In chapter 4 of this thesis, we investigated the effect of an ipsilateral high-grade stenosis on the velocities measured in the contralateral carotid artery. After having performed a CEA of a symptomatic carotid artery in patients shown to have a bilateral significant stenosis by pre-operative duplex ultrasound, velocities measured at the site of the contralateral stenosis decreased such that 55% of the stenoses had to be reclassified to a lower degree of severity. In over one third of these patients, the contralateral stenosis appeared ultimately not to be significant.

We therefore urgently need another strategy to identify those patients who are at high risk for stroke in the nearby future. Over the past two decades, the concept of ‘vulnerable’ plaque has gained increasing attention: an unstable plaque with a high risk of rupture leading to thrombus formation and distal embolization. Histological studies of symptomatic and asymptomatic plaques have been able to identify morphological characteristics of vulnerable plaques. The challenge for current and future research is to identify those characteristics with imaging techniques in order to indicate those patients having plaques prone for rupture.

One of the techniques to visualize histological characteristics of vulnerable plaques is ultrasound. For instance, the grayscale of a plaque on a B-mode image can provide information about plaque...
INVASIVE TREATMENT OPTIONS: TIMING AND APPROACH

Timing

Pooled data from the NASCET, ECST and VA309 showed that patients who were randomized within two weeks of their ischemic event had a significant reduction in risk of recurrence during the first 5 years of follow up. However, the benefit of CEA declines steadily with time after the primary event.\textsuperscript{2} This fact is driven by the high recurrence rate during the first period shortly after the primary event.\textsuperscript{20} An optimal organization of the care chain of patients with a symptomatic carotid stenosis is therefore vital. A decade after the publication of the aforementioned pooled data in 2004 it still appears to be difficult to have surgery performed at all patients within two weeks after the index event.\textsuperscript{21,22} In order to optimize this care chain, we analyzed the clinical treatment course of these patients in a large general hospital (chapter 6). We mapped the course of care of all patients over a period of 10 years by splitting it into different components. Analysis showed a significant reduction in time between all separate components of the care chain since 2004. In 2011, however, a total median time of 19 days until surgery was still seen. Thirty-five percent underwent an intervention within 2 weeks after the index event, which is the timeframe within patients should have undergone surgery according to the current Dutch consensus. The duration of the clinical course in patients who had been externally referred was more than 3 times longer (median 67 vs. 21 days, $p < 0.01$). The total duration of the process did not affect the number of perioperative complications. A similar study in another large Dutch hospital showed similar results.\textsuperscript{23}

An optimal organization of the care chain can further shorten its duration.\textsuperscript{24,25} The importance is further underscored by recent studies showing a higher risk of recurrence than supposed immediately after the event, up to 17.2% within 72 hours.\textsuperscript{26,27,28} This rises the question what the true optimal timing to perform a CEA should be. Should we strive for an acute intervention instead of a semi-acute? Recent studies report varying 30-day morbidity and mortality rates (2.4% - 11.5%) in patients who have had surgery within 48 hours.\textsuperscript{24,25,26,28} A logical subsequent question is what perioperative outcome in terms of stroke or death is acceptable when performing a CEA in the hyperacute phase. The current guideline of 2 weeks results from the “old” landmark studies in which patients were hardly enrolled within the acute phase.\textsuperscript{11} Another issue is whether it is feasible at all to operate all patients within 48 hours, especially since a significant part of patients has not even been presented to a neurologist by that time. Further analysis of the study data presented in chapter 6 shows that particularly patients who present with amaurosis fugax have a substantial delay (median 9 days in the period 2009-2011). This group is also known to have a lower risk of recurrence and stable plaque characteristics by histological examination.\textsuperscript{11,22} Perhaps certain subgroups can be distinguished in the future, which do and do not benefit from a particularly early intervention.

Future studies will have to address these questions. First, however, it remains to be seen what the early risk of recurrence actually is being treated according to contemporary insights in best medical therapy. Perhaps the medical arm of ECST-2 will also provide clarity on this matter.

Approach

Chapter 3 describes the results of four major trials (EVA-3S, SPACE, and ICSS Crest) comparing CEA with carotid artery stenting (CAS). The chapter focuses on symptomatic patients and concludes that CEA should remain the gold standard and CAS may be offered as an alternative in patients in which surgery is not feasible. However, long-term results of both ICSS and CREST demonstrate no difference between both techniques in stroke or death rates beyond 30 days after the intervention. Thus the difference in outcome originates within these first 30 days. Improvement in the short-term results might therefore be a game changer in benefit of CAS. One third of the 30-day complications associated with CAS occur during the procedure itself.\textsuperscript{21} These procedural events may be due to technical failure. The transfemoral approach can lead to ligation of plaque debris by manipulation in the aortic arch and supra-aortic vessels. This has been demonstrated in the ICSS DW-MRI substudy, wherein more new ischemic lesions in the non-ipsilateral carotid circulation were seen after CAS than after CEA.\textsuperscript{22} The same problem may present when passing the vulnerable plaque with guide wires and catheters. In case embolic protection was considered in the aforementioned four trials, distal filter devices were used. This type of protection might lead to embolisation in the same manner. Furthermore, the filters have a pore size of at least 100 to 150 microns, allowing smaller particles to pass through. Fifty percent of the CAS patients in the ICSS DW-MRI substudy had of one or more new lesions on post-procedural MRI, compared with only 17% of patients who underwent CEA. The number was even the highest (73%) in the clinics where a protection device was used.\textsuperscript{22}
Although the clinical relevance of silent infarcts detected on post-procedural MRI is not yet entirely clear, they have associated with cognitive decline in the long term.28 The use of proximal embolic protection devices, in which a reverse in blood flow is established, might provide a possible solution to reduce the number of procedural events. However, its benefit over distal devices is still disputed in literature. Two recent meta-analyses show conflicting results. Moreover, the included studies in both publications show high heterogeneities.25,26

Two-thirds of the 30-day events occur after the intervention itself has been performed.31,32 Most of these events do happen on the day of the intervention itself, but a symptom-free interval after the procedure separates them from intraprocedural events. The post-procedural events are attributed to protrusion of plaque material through the meshes of the stent, thereby providing a mechanism that can lead to cerebral embolization, either directly, or by additional thrombus formation. Depending on the density of struts, stents can be classified into stents with a closed-cell or an open-cell configuration. Closed-cell stents are characterized by small free cell areas between struts, whereas open-cell stents have larger gaps uncovered. Research in symptomatic patients demonstrates that post-procedural events are more common after using stents with larger meshes and stents with an open cell design.31,32,33,34 Moreover, the increased 30-day risk associated with open cell stents might extend beyond the perioperative period. Follow up of patients included in the ICSS DW-MRI substudy demonstrated a possible increased risk of recurrent clinical cerebrovascular events in patients treated with an open-cell design stent (HR 3.09; 95% CI: 0.89 - 7.10; p = 0.075).35 Using optical coherence tomography, plaque protrusion and rupture of the fibrous cap of the plaque have actually shown to occur more frequently with the use of an open-cell design stent (up 61.5%).41

In order to obviate plaque protrusion, a new generation of stents is being developed. These stents are double-layered and consist of an open cell stent, allowing flexibility, coated with a fine-meshed membrane for proper scaffolding the vulnerable plaque. In a small study in 30 patients (33.3% symptomatic) the feasibility of the double-layered C-Guard ™ (InspireMD, Boston, MA, USA) was evaluated. No cerebral events were observed during 30 days after placement. In only 37% of patients symptomatic) the feasibility of the double-layered C-Guard ™ (InspireMD, Boston, MA, USA) was confirmed these results in a larger cohort (101 patients, 55% symptomatic).42 A subsequent study confirmed these results in a larger cohort (101 patients, 55% symptomatic).42 A comparable study on another double-layered stent, the RoadsaverTM (Terumo Corp., Tokyo, Japan), demonstrated only one periprocedural cerebrovascular event.43 These initial data are promising but need to be confirmed in larger, multicenter studies. Perhaps the combination of a membrane covered stent iand procedural protection by a proximal flow reversal device will change the odds in favor of CAS in the nearby future.

COST REDUCTION AND OPTIMIZATION OF CARE

The ultimate goal of CEA is to reduce the chance of developing a disabling stroke or death. Pooled data from NASCET, ECST and VA309 show a 5-year absolute risk reduction of 7% in developing a disabling ipsilateral recurrence, perioperative stroke or perioperative death. Although this is a significant reduction in outcome, still 34 patients have to undergo surgery to prevent one event. Again, these studies are outdated. Best medical treatment, better patient selection and good integrated care for patients with symptomatic carotid stenosis will decrease primary intervention and recurrence-rate. This might result in substantial savings in costs. In an era where health care costs rise uncontrollably while resources are constrained by budget cuts, cost reduction is important to re-allocate available resources to those patients who need them most. Cost reduction can thus result in optimization of care.

There are many ways to monitor the cerebral perfusion during CEA. Every modality has its own advantages and disadvantages and none of them has been proven better with regard to the number of intraoperative stroke.44 However, these modalities may differ in labor intensity and thus in costs. The purpose of Chapter 7 was to assess the cost-effectiveness of two different intraoperative neuromonitoring modalities, namely stump pressure measurement (SPM) and EEG combined with TCD. The study provides a clear insight into the structure of costs made during admission for CEA and demonstrates that costs are significantly lower using SPM during CEA compared to EEG/TCD. There was no significant difference in the number of perioperative stroke or death rates, but given the relatively small number of patients studied and the retrospective design of the study, we should be careful to draw conclusions about the true cost-effectiveness of both strategies relative to each other.

CONCLUSIONS

The treatment of patients with a symptomatic carotid stenosis has evolved tremendously since the publication of the landmark trials on which the current guidelines are still based. Medical therapy has greatly improved, narrowing the gap between medical and invasive treatment. However, there are no actual evidence based data in symptomatic patients to support this assumption. There is also an increasing insight into the histological characteristics of symptomatic plaques. Multiple imaging techniques can already visualize one or more of these characteristics. However, to date, none of these techniques has been validated externally. As soon as the medical arms in current trials have demonstrated the effect of the contemporary medical therapy in symptomatic patients, and imaging techniques are externally validated for the detection of high-risk plaques, better patient selection will be possible. Then, further studies might determine how and when to treat those patients who still benefit an intervention in spite of contemporary medical management. Although current developments in CAS appear very promising, at the moment CEA remains the gold standard for patients with a symptomatic carotid stenosis.
REFERENCES


