CHAPTER 1
General introduction and outline of this thesis
ISCHEMIC STROKE: EPIDEMIOLOGY AND STROKE BURDEN

Stroke is a devastating condition. It has been ranked as the second most common cause of death accounting for roughly 10% of all deaths worldwide.\(^1\) In those who survive, stroke may be a major cause of long-term disability resulting in a reduced health-related quality of life. Many of these patients have to rely on health services and social services, relatives and friends to provide care and assistance. A large population-based cohort study showed that 70% of patients with stroke were either dead or disabled 5 years after the event.\(^2\) About one in five had been institutionalized in long-term nursing or residential care home settings during that period. Stroke recurrence has been shown a major predictor of disability.\(^3\) Prevention of stroke recurrence might therefore be a potential strategy to improve health-related quality of life in patients who have suffered a TIA or stroke.

Besides the huge impact on daily life for the individual patient, stroke imposes a significant economic burden on health care systems. In the Netherlands, there were 44,397 hospital admissions (without day care) for an acute cerebrovascular event in 2011, and care for stroke sufferers accounted for 2.5% of the total national health expenditure.\(^4\)

Of all strokes, 87% are of ischemic origin.\(^5^,\)\(^6\) Of those, approximately five to ten percent result from an unstable atherosclerotic plaque in the carotid artery.\(^7\) In patients with a so-called symptomatic carotid stenosis, the rate of stroke recurrence can be reduced by surgical treatment, thereby improving health-related quality of life.\(^8\)

TREATMENT OF SYMPTOMATIC CAROTID STENOSIS

The relationship between occlusive disease of the extracranial carotid artery and neurological symptoms was already suggested in the early nineteen-hundreds. In 1905, Chiari noted in a large consecutive series of autopsies that embolic material from the carotid artery could affect the brain, after finding thrombus superimposed on carotid artery plaques in some of the patients who had suffered cerebral embolism.\(^9\) Several years later, Hunt wrote a paper in which he described two patients who had suffered cerebral symptoms after traumatic lesion of the carotid artery. In both cases, thrombus was found in the carotid artery. In the same paper he also studied a series of twenty hemiplegic patients of which four had diminished pulsations of the carotid artery ipsilateral to the affected hemisphere. He therefore emphasized “the importance of obstructive lesions of the main arteries of the neck in the causation of softening of the brain...”.\(^10\)

At that time, however, these observations did not find their way into clinical practice. The technique of cerebral arteriography was not available yet. Moreover, after its introduction by Moniz in 1927, cerebral arteriography was initially only used to study cerebral tumours. It took another decade before Sjöqvist reported the first carotid thrombosis demonstrated by arteriography. A prolonged gap followed. In the early 1950s Fisher published two landmark articles reviving Chiari’s theory that ulcerative plaques of the carotid artery might cause cerebral embolism.\(^11,\)\(^12\) In these articles, he related transient hemispheric and retinal attacks to carotid artery disease and added the concept of (asymptomatic) “stenosis” as another possibility besides occlusion in the natural history of carotid artery disease. These articles laid the foundation for reconstructive surgery for occlusive carotid disease.

The field of vascular surgery was however just burgeoning those days. Vascular reconstructions of the carotid arteries were already performed, but mainly by surgical oncologists in radical neck dissections for malignancy.\(^13\) Moreover, the technique of endarterectomy, performed in the aortoiliac system, had just been described first several years earlier by Cid Dos Santos.\(^14\) The first carotid reconstructions for occlusive disease, which were performed shortly after Fisher’s publication in 1951, consisted therefore of excision of the occluded arterial segment followed by an end-to-end anastomosis. It was Debakey who claimed to have performed the first actual carotid endarterectomy in 1953, although published many years later.

Since then, many advances have been made. It soon became clear that endarterectomy was most effective for stenotic lesions rather than for total occlusions, in which restoration of flow was possible in only 40% of cases. Moreover, it was also gradually realized that the principal role was one of stroke prevention, instead of treatment for complete or profound strokes, as operative mortality rates in these patients had been reported between 20 and 60%.\(^15\) Improvements were also made in the medical management of carotid artery disease. The role of anticoagulant therapy was established by proving that platelet inhibition with aspirin reduced further stroke risk by 19%.\(^16\)

With the publication of the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Study (ECST) in the 1990s the benefit of CEA over medical treatment in symptomatic patients was established definitely. Subgroup analyses of these studies further defined patient selection criteria for surgical treatment and emphasized the importance of urgent intervention, which had been advised otherwise until then.\(^17,\)\(^18\)\(^,\)\(^19\) Moreover, the Asymptomatic Carotid Arteriosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST) showed a benefit for CEA in certain groups of asymptomatic patients as well, though in a lesser extent.\(^20,\)\(^21\)

These and many other studies since then have greatly contributed to our understanding of carotid artery disease and the way we treat our patients today. Although much has been changed over the last 60 years, the technique of CEA itself did not evolve significantly, except the introduction of several variations like patch closure and evasion CEA. In the present endovascular era, however, the fate of CEA is no longer certain with the rapidly evolving technique of carotid artery stenting (CAS).

OUTLINE OF THE PRESENT THESIS

The treatment of carotid artery stenosis is thus constantly subject to changing perceptions and new developments. Much has been published about this topic and there is undoubtedly even more to come. However, despite all advancements made in the last decades, we are still not able to precisely identify those patients most likely to benefit from an intervention, and with that, to improve the outcome of treatment. Moreover, due to the advancements made, important questions arise concerning how to treat the symptomatic patient today. In this thesis, we have tried to address, to a certain extent, some of these questions.

In the first part of this thesis, we will address two questions regarding the current, multifaceted, treatment of symptomatic carotid disease, with medical therapy and surgical intervention as a...
mainstays. First, what is the current status regarding medical treatment? Trials are being described which have led to guidelines concerning what we consider to be the best medical therapy (BMT) today. Both secondary prevention and perioperative medical management are discussed. In chapter 3 we provide an overview of current interventions in carotid artery disease. Trials and registries focusing on the role of carotid stenting as an alternative to CEA are discussed and we will answer the question whether CAS has taken over the role of CEA.

In the second part of this thesis, we will focus on duplex ultrasound imaging in order to study a potential role of this modality in improving patient selection. Although angiography was used to assess the degree of stenosis in NASCET and ECST, duplex imaging has been the method of choice nowadays due to both its non-invasive character and its accessibility. But is duplex good enough to accurately select those patients at high risk for stroke recurrence? Duplex measures peak systolic and end diastolic velocities which can be used to classify the degree of stenosis. Changes in peak systolic velocity are however influenced by changes in volume flow. In case of bilateral carotid disease, shunting of blood flow through the least stenotic artery might lead to higher velocities measured by duplex and an erroneously overestimation of the degree of stenosis. In chapter 4, we investigated the possible overestimation of a contralateral stenosis and its clinical impact.

Since we have gained more insight into the histological changes in the symptomatic plaque, another question regarding optimal patient selection is if duplex can adequately characterize the ‘vulnerable’ plaque, that is, the high-risk plaque prone for rupture with subsequent thrombus formation and distal embolisation. In chapter 5 we studied the potential role of computer-assisted quantification of echogenicity of the carotid plaque in identifying high risk patients by trying to validate the Gray-Scale Median as a predictor for carotid plaque vulnerability.

The last part of this thesis deals with non-clinical aspects relating the care for patients with carotid stenosis. Historically, surgeons were advised to defer CEA for 6 weeks in patient strokes so as to minimise the risk for haemorrhagic transformation.\textsuperscript{21,22} Data from NASCET and ECVT showed however a greater reduction in recurrent event if patients were treated shortly after the index event.\textsuperscript{23} Although these data were published over a decade ago, recent studies still show delay between index event and surgery.\textsuperscript{24,25} So how can we decrease the delay to surgery in order to improve patient outcome? To answer this question, we performed a retrospective cohort study to gain insight into the duration and the various components of the clinical treatment course for patients with symptomatic carotid artery stenosis (chapter 6).

The last study (chapter 7) of this thesis is related to the ongoing debate whether or not to use intraoperative cerebral monitoring and if so, which modality to use. None of the currently used modalities has been proved superior with regard to intraoperative stroke risk reduction.\textsuperscript{26} They do however differ in labour intensity and might consequently be associated with different costs. Increasing costs of healthcare and decreasing health resources force to re-allocate these resources to optimise the delivery of care to the highest risk patients. We therefore aimed to study the cost-effectiveness of two of these shunting strategies during CEA.

We conclude this thesis with a summarizing general discussion.

REFERENCES

