Atherosclerotic carotid disease, the vulnerable plaque in the vulnerable patient
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GENERAL INTRODUCTION
AND OUTLINE OF THIS THESIS
GENERAL INTRODUCTION

The burden of ischemic stroke
Stroke is the second leading cause of morbidity and mortality in industrialized countries.\textsuperscript{1-3} In 2015, stroke deaths accounted for 11.8\% of total deaths worldwide.\textsuperscript{3} The Global Burden of Disease Study showed that the absolute number of people affected by stroke substantially increased across all countries in spite of declines in age-standardized incidence, prevalence and mortality rates. Population growth and aging have played an important role in the observed increase in stroke.\textsuperscript{1,2} Surviving a stroke may lead to new undesired situations. About one in seven of the survivors had been institutionalized in long-term nursing or residential care home settings.\textsuperscript{4} In 2010, over 100 million disability-adjusted life-years (DALYs) were lost worldwide because of stroke.\textsuperscript{5,6} Of all strokes, 87\% are classified as ischemic.\textsuperscript{7} In about 10\% of the ischemic strokes, the carotid artery is the origin.\textsuperscript{8-10}

Surgery for carotid atherosclerotic disease
Atherosclerotic disease of the carotid bifurcation was first related to ischemic symptoms in the ipsilateral eye and cerebral hemisphere by Fisher in 1951.\textsuperscript{11} In that period, various surgical options for arterial diseases were developed and performed in humans for the first time.\textsuperscript{12} The first surgical intervention for carotid atherosclerotic disease was performed by a neurosurgeon, Raul Carrea, in Buenos Aires (Argentina) in 1951. He resected the diseased portion of the internal carotid artery, and reconstructed flow by using the external carotid artery to make an external carotid artery – distal internal carotid artery anastomosis. In 1954, Eastcott used a variant of this technique. The first carotid thromboendarterectomy was performed in 1953 by Michael DeBakey.\textsuperscript{13} In the following decades, carotidendarterectomy became one of the most performed procedures in vascular surgery.\textsuperscript{14} The landmark NASCET and ECST trials showed the benefit of carotid endarterectomy over medical therapy for patients with a symptomatic high grade stenosis of the internal carotid artery.\textsuperscript{15,16} The number needed to treat (NNT) was 6 in the NASCET and 9 in the ECST trial. However, carotid surgery comes at a price. In het NASCET and ECST trials, approximately 6\% of the patients suffered a perioperatively cerebrovascular event.\textsuperscript{15,16} Taking into account the risk of a cerebrovascular event after surgery, case selection becomes even harder in asymptomatic carotid stenosis. The ‘Asymptomatic Carotid Surgery Trial’ showed a NNT of 22 over a 10 year period, meaning that 22 asymptomatic patients have to undergo carotid surgery, to prevent 1 stroke after a 10 year period, as opposed to medical therapy.\textsuperscript{17,18}
Medical therapy for carotid atherosclerotic disease
The clear benefit of carotid surgery for a symptomatic high-grade carotid stenosis, and the smaller benefit for an asymptomatic stenosis, are under debate because of the progression made in medical therapy. Pooled data of nearly 16,000 patients (from 12 trials) showed a reduction in the 6 weeks risk of recurrent ischemic stroke of 60%, if acetylsalicylic acid was started as soon as possible after the index event.\textsuperscript{19} Statins are another group of drugs that have beneficial effect on carotid atherosclerosis, and the risk of stroke.\textsuperscript{20,21} If best medical treatment (BMT), consisting of acetylsalicylic acid, a statin and antihypertensive medication was started directly after a cerebrovascular event, the risk of a recurrent stroke within 90 days was even reduced by 80%.\textsuperscript{22} So the risk of a stroke diminishes by proper medical therapy, while the surgical risks have not reduced over the last years.

Factors regarding case selection for carotid surgery, the plaque
The discrepancy in absolute risk reduction after carotid endarterectomy in symptomatic and asymptomatic patients highlights the importance of factors other than plaque size and degree of luminal obstruction in determining risk.\textsuperscript{23} Muller et al. were the first to coin the concept of the vulnerable plaque. They stated that vulnerable atherosclerotic plaques are prone to triggers that produce acute risk factors, leading to acute ischemic cardiovascular events. This opposed to non-vulnerable atherosclerotic plaques, who are less susceptible for acute risk factors leading to plaque rupture and thrombotic events.\textsuperscript{24} Acute plaque rupture with subsequent thrombosis may occur in vulnerable plaques that do not physically appear threatening, whereas other lesions that are more flow-limiting may be dormant and not progress. The vulnerability is largely dictated by plaque morphology, which, in turn, is influenced by pathophysiologic mechanisms at the cellular and molecular level. Additionally, there is a growing notion that plaque instability is important in the etiology of acute cerebral ischemic events in patients with carotid disease.\textsuperscript{25,26} Therefore, it seems reasonable to select patients for intervention on the basis of plaque vulnerability assessed from morphologic characteristics, rather than on the degree of stenosis or the symptoms alone.

Factors regarding case selection for carotid surgery, the patient
Atherosclerosis is a systemic disease, rather than just a local problem in a single arterial segment.\textsuperscript{27,28} In the 1950s, several epidemiological studies were set in motion with the aim of clarifying the cause of cardiovascular disease. Soon after the Framingham Heart Study started, researchers had identified cigarette smoking, high cholesterol and high blood pressure levels as important
factors in the development of cardiovascular disease. In subsequent years, the Framingham study and other epidemiological studies have helped to identify other risk factors, which are now considered classical risk factors.\textsuperscript{29,30} Among these risk factors are body mass index, blood cholesterol, blood pressure and glucose/diabetes mellitus.\textsuperscript{30} It was Haller who in 1977 used the term metabolic syndrome (MetS) for a combination of factors (obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia, steatosis hepatitis) describing the additive effects of these risk factors on atherosclerosis\textsuperscript{31}, but at that time there was no clear consensus on which factors should be included. In 2009 consensus had been reached about the term MetS, consisting of a cluster of risk factors for cardiovascular disease and type 2 diabetes mellitus, which occur together more often than by chance alone. These risk factors include raised blood pressure, dyslipidemia (raised triglycerides and lowered high-density lipoprotein cholesterol), raised fasting glucose, and central obesity.\textsuperscript{32} Patients with MetS have a 2-fold risk of developing cardiovascular disease (CVD) and a 1.5-fold increased risk of all-cause mortality compared to patients without MetS.\textsuperscript{33} Various studies have shown a positive association between MetS and the development of atherosclerosis, resulting in an increased incidence and more rapid progression of carotid atherosclerotic plaque formation in patients with MetS.\textsuperscript{34-36} In carotid surgery, patients with MetS are at a greater risk for perioperative morbidity as well as stroke, myocardial infarction and death. There seems to be a greater risk for the development of restenosis after surgery in patients with MetS, compared to patients without MetS.\textsuperscript{37-39}

OUTLINE OF THIS THESIS

Part I - The vulnerable plaque
The indication for carotid surgery on the basis of luminal stenosis and symptoms alone, refrain patients with a vulnerable plaque (but a low-grade stenosis, or no symptoms of cerebrovascular disease yet) from the benefits of surgery. On the other hand, patients with a stable plaque can be exposed to the risks of carotid surgery, only on the basis of a high-grade luminal stenosis. The holy grail in patient selection for carotid surgery, would be to identify the patients with a vulnerable plaque, prone to rupture. Those are the patients likely to most benefit from a carotid intervention. In chapter 2 the current imaging modalities are judged on their ability to visualize vulnerability within the atherosclerotic carotid plaque. In chapter 3 we used a specific novel molecular imaging technique to identify levels of matrix metalloproteinases (MMPs) across the entire plaque. Areas with high-levels of MMPs were declared hot spots. With this novel imaging modality
of multispectral near-infrared fluorescence imaging using a smart activatable fluorescent probe, these hot spots (of plaque vulnerability) would be detected in the atherosclerotic carotid plaque (ex-vivo). The aim was to detect components of plaque vulnerability, within the atherosclerotic plaque. In chapter 4, the hot spots detected with the multispectral near-infrared fluorescence molecular imaging were analyzed for their components, and related to the composition of the areas with low levels of MMPs (so called cold spots).

Part II - The vulnerable patient
This part addresses the clinical outcome of carotid surgery in patients with multiple high-risk factors of cardiovascular disease. Chapter 5 evaluates the influence of metabolic syndrome on the outcome after carotid endarterectomy, with a focus on cerebrovascular events, myocardial infarction and death. In chapter 6, we used a combined cohort of two tertiary referral centers to investigate the role of metabolic syndrome on the occurrence of carotid restenosis after carotid endarterectomy.

This thesis is concluded by a summary, general discussion and future perspectives (chapter 7), in English and Dutch, respectively.
REFERENCES


