The use of covered stents in the treatment of carotid artery stenosis

PH.D. THESIS

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List of Abbreviations

ADC  apparent diffusion coefficient
AHA  American Heart Association
BMS  bare metal stent
CABG  coronary artery bypass graft
CAD  carotid artery disease
CAS  carotid artery stenting
CCA  common carotid artery
CE  Conformité Européenne
CEA  carotid endarterectomy
CT  computed tomography
DSA  digital subtraction angiography
DWI  diffusion weighted imaging
ECA  external carotid artery
ECM  extracellular matrix
eNOS  nitric oxyde synthase enzyme
EPD  embolic protection device
ePTFE  enhanced poly-tetra-fluor-ethylene
ESS  endothelial shear stress
FFT  fast Furier transformation
Fr  French
HITS  high intensity transient signal
ICA  internal carotid artery
IU  international units
IVUS  intra vascular ultrasound
MES  microembolic signal
MI  myocardial infarction
MRI  magnetic resonance imaging
NINDS  National Institute of Neurological Disorders and Stroke
Nitinol  nickel-titanium naval ordnance laboratories
NO  nitric oxyde
NTS  nucleus tractus solitarius
NYHA  New York Heart Association
Pa  Pascal
PEO  proximal endovascular occlusion
PTA  percutaneous transluminal angioplasty
PTFE  poly-tetra-fluor-ethylene
RCT  randomized clinical trial
ROS  reactive oxygen species
SD  standard deviation
SDS  stent delivery system
<table>
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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>TCD</td>
<td>transcranial Doppler Ultrasound</td>
</tr>
<tr>
<td>TCFA</td>
<td>thin cap fibroatheroma</td>
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<td>TIC</td>
<td>thermal cranial index</td>
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1. Introduction

Ischemic cerebrovascular insults caused by embolization from internal carotid artery plaques (ACI) produces 25% of all strokes\(^1\). First major step in recognition of significance of carotid artery disease (CAD) was when C. Miller Fisher published clinicoanatomic correlations on occlusion of the carotid arteries in 1951\(^2\). The incidence of severe cerebrovascular disease rises with age. Doppler-ultrasound studies published in late eighties revealed that half of the male population over 75 years of age has atherosclerotic disease of the carotid arteries, but stenoses exceeding 50% only affect 4-5%.

A giant leap in prevention of stroke made in 1953 when M. DeBakey performs first carotid endarterectomy at the Methodist Hospital, Houston TX, USA\(^3\). In the same year Seldinger introduces his revolutionary technique of vascular access\(^4\). The first CEA case to be recorded in medical literature was performed by Felix Eastcott at St. Mary’s Hospital (London, UK) and published in the Lancet\(^5\). With these advancements made, prevention of ischemic stroke had risen to a new level. In 1977 a controlled study published favorable results using aspirin in cerebral ischemia\(^6\). Meanwhile CEA procedure numbers are rose exponentially all over the world. Only in the USA more than 100.000 procedures were done yearly in the beginning of 80s. At that time several authorities began to question the trend and the benefits of CEA over medical treatment, and the number of performed procedures dropped precipitously. The NINDS supported two major studies the NASCET and ACAS\(^7,8\) – meanwhile the European carotid surgery trialists collaborative group were also started the recruitment of patients for ECST trial\(^9\) - which were launched in the mid 80’s to identify the specific groups of people with CAD who would clearly benefit from the procedure. The studies confirmed that CEA is significantly reduces stroke rates in symptomatic patients with significant (>50% NASCET, >70% ECST) carotid stenosis when compared to aggressive medical therapy\(^10-12\). Treating asymptomatic carotid stenosis reduces the risk of ipsilateral and any stroke, by approximately 30% over three years, the absolute risk reduction is however small, but it gets higher with longer follow-up\(^13\). It should be emphasized that very few forms of treatment have undergone such a rigorous scrutiny to establish their role. The evidence collected from various studies is indisputable. This operation has been termed the „gold standard” against which other forms of treatment must be judged\(^14,13\).
In 1979 first successful percutaneous balloon angioplasty (PTA) was performed\textsuperscript{15}. Sporadic reports published in that time\textsuperscript{16-20} and the largest study published by Theron et al.\textsuperscript{21} failed to achieve comparable results to CEA, and had significantly higher complication rate. Significant embolization, elastic recoil and restenosis rendered discouraging results. Several groups including the International Society for Cardiovascular Surgery and Joint Council of the Society for Vascular Surgery voiced concerns regarding the safety of carotid PTA\textsuperscript{22,23}. However some studies reported promising results with PTA alone\textsuperscript{24}.

To mitigate the rates of post PTA restenosis stents were introduced with success in high flow arteries such as the iliac vessels and the aorta. Roughly 10 years passed before the first stent was implanted\textsuperscript{25}, the word was spread, and more and more carotid artery stenting (CAS) procedures were done. The continuous feedback from operators, innovative minds of the researchers and the race for the market, resulted in fast evolution of carotid stent design. But not only stents evolved, new guidewires for passing tortuous anatomy, new guiding catheters and low profile stent delivery systems appeared in the toolbox of interventional radiologists. The periprocedural complication rates were lowered with evolution of the tools and refinement of the technique.

1.2 Stents

It was proven that the concept of using stents in carotid artery stenosis is feasible, after that studies provided evidence on superiority of utilizing stents over PTA alone, the incidence of distal embolization, intimal dissection, elastic recoil and restenosis was significantly lower when using stents\textsuperscript{26-28}.

Nowadays only self-expandable stents are in use during extracranial CAS procedures. Stents can be made of stainless steel (e.g. Wallstent - Boston Scientific) or nitinol (e.g. Xact – Abbott Vascular, Precise - J&J Cordis). Research and development teams provided different stent designs, and every major company offers something for the toolbox of the endovascular surgeon.

It is well known that carotid stenoses are potentially dangerous not because of their hemodynamic effect but because significant distal embolization could originate from the atherosclerotic plaques, thus the primary goal would be the removal – which is done during CEA – or effective coverage of the plaque. Current carotid stents are literally lineal derivatives of peripheral stents, which were designed to reconstitute the
hemodynamically compromised vessels, and not to protect the brain from distal embolization. There is some evidence provided by M. Bosiers that smaller stent cell size actually reduces clinically significant embolization\textsuperscript{29}.

In 2002 a new peripheral stent was given the CE-mark\textsuperscript{30}. The novelty consisted of a porous polytetrafluorethylene membrane [ePTFE], which covered an open-cell nitinol stent. Stenoses of venous coronary grafts were the primary use of this stent, but in short time case studies were published and stated the feasibility of the device in carotid arteries\textsuperscript{31,32}. Atherosclerotic plaque could be covered completely with such a device, and from initiation of stent deployment it serves as a protection device in the rest of the procedure and also postprocedurally\textsuperscript{33,34}.

1.3 Anatomical review

The common carotid arteries differ in length and in their mode of origin. The right begins at the bifurcation of the innominate artery, the left originates from the highest point of the aortic arch. 70\% of the population has normal configuration of supraaortic vessels. Most common anatomic variation is the origin of the left CCA from the innominate artery is presented in 20\% of population\textsuperscript{35} (Fig. 1/C).

The bifurcation of the CCA in half of the cases is at the level of C4-5, in 38\% the bifurcation is one level above (C3-4) and in the lesser group it is below the intervertebral space of C4-5\textsuperscript{35}. In most adults the caliber of ICA equals that of ECA. External carotid artery has an extensive anastomotic network thus occlusion of ECA is usually not symptomatic.

Internal carotid artery lies postero-laterally to ECA. Considering the course and relations it can be divided into four segments namely: cervical, petrous, cavernous, and cerebral. At the beginning of the cervical portion the carotid sinus can be seen which – in adults - has a mean diameter of 7mms, at the cavernous part the vessel is 4mm in diameter. At the level of carotid sinus baroreceptors can be found in between the adventitial and medial layer of the vessel, these receptors relayed to nucleus tractus solitarius (NTS) increasing it’s activation resulting in inhibition of vasomotor nuclei and activation of vagal nuclei, resulting in peripheral vasodilatation, bradycardia and lowered cardiac contractility.
The arrangement of cerebral arteries into the circle of Willis creates collaterals in the brain circulation. In case of stenosis or occlusion of vessels below the level of communicating arteries flow from other vessels can often preserve the cerebral perfusion well enough to avoid symptomatic ischemia. A classic hemodynamically balanced circle is only seen in 34.5% of cases, rests of the cases are unbalanced. The propensity of the circle of Willis for anomalies and variations is of interest in that the hemodynamic stresses associated with these variations combined with defects in the media at vessel junctions predispose to aneurysm formation\textsuperscript{36,37}. The significance of ECA to ICA anastomotic pathways cannot be overemphasized. These interconnections are dynamic in nature and may present in various configurations depending on the underlying disease\textsuperscript{38,39}. As it is well known in case of severe ICA stenosis or occlusion of the vessel, the ipsilateral ECA contributes significantly to
intracranial blood flow\textsuperscript{40}. In such cases collaterals have to be visualized, and they importance should be noted, as they can determine the course of treatment\textsuperscript{41}.

\textbf{Figure 2.} Diagram showing anastomotic connections between ECA, ICA and vertebral arteries\textsuperscript{41}.
1.4 Pathophysiology

Until recently the pathophysiology of atherosclerosis - after updating Virchow’s concept of atherosclerosis as a response to injury - was imagined as a bland arterial collection of cholesterol, complicated by smooth muscle cell accumulation. According to the cellular model, endothelial injury led to platelet aggregation and release of platelet-derived growth factor that would trigger the proliferation of smooth muscle in the intimal layer, forming the nidus of atherosclerotic plaque. The simplistic concept of the atheroma as a passive deposition of lipid debris in the artery wall, surpassed by advancements in cell biology and research on atherosclerosis.

Atherosclerosis begins in childhood and progresses silently through a long preclinical stage, and manifests clinically usually from middle age. Profound and dynamic changes in vascular biology has a significant effect on initiation and progression of the disease.

1.4.1 Effects of endothelial dysfunction

Although it is only a simple monolayer, the healthy endothelium is able to respond to physical and chemical signals by regulating vascular tone, thromboresistance, cellular adhesion, smooth muscle cell proliferation and immune response. Endothelium was first examined for its role in regulation of vascular tone. Nitric-Oxide (NO) plays a key role to maintain the vascular wall in quiescent state by inhibiting inflammation, thrombosis and cellular proliferation. In maintaining the quiescent, NO-dominated endothelial phenotype laminar shear stress is the major factor.

What is considered as endothelial dysfunction is in fact an activation process, which in certain circumstances can eventually contribute to arterial disease. Endothelial activation process is a switch from quiescent phenotype towards one that involves the host defense response. Most cardiovascular risk factors activate the molecular machinery which produces molecules intended to interact with leukocytes and platelets, and target inflammatory response to specific tissues to clear microorganisms. A fundamental change leading to activation is a switch from an NO-mediated silencing of cellular processes toward activation by redox signaling. Reactive oxygen species (ROS), in the presence of superoxide dismutase lead to generation of hydrogen-peroxide, which like NO diffuses rapidly, and alter protein functions, however the consequences are very different. It is intriguing that the enzyme nitric oxide synthase (eNOS) in appropriate circumstances can switch to generate ROS. The eNOS have a Janus face,
which allows the enzyme to both regulate the quiescent and active endothelium phenotype, this puts it in the center of endothelial homeostasis. Chronic production of ROS may exceed the capacity of cellular enzymatic and nonenzymatic anti-oxidants, and thus contribute to vascular disease by induction of sustained endothelial activation. Risk factors significantly contribute to chronic endothelial activation by increasing the availability of ROS\textsuperscript{48-51}. Regardless of the source of ROS, the interaction between ROS and NO sets up a vicious circle, which results in prolonged endothelial activation and further inflammation. Repeated or permanent exposure to cardiovascular risk factors exhaust the effect of endothelial cell’s anti-inflammatory mechanisms and consequently the endothelium cells becomes dysfunctional, the layer loses cell integrity and progresses to senescence and cells detach into the circulation\textsuperscript{52}. Integrity of the endothelium depends on the extent of the injury and on the endogenous capacity for repair. Two main endothelial repair mechanisms have been identified recently. During the process of local replication the damaged cells are replaced by duplicating adjacent mature endothelial cells, but if this would be the only repair mechanism then the integrity would decline rapidly as recent modeling study pointed out\textsuperscript{53}. An alternative maintenance and repair mechanism is the recruitment of circulating endothelium progenitor cells\textsuperscript{54}. Progenitor cells are mobilized from the bone marrow, and this process is partly NO-dependent, thus may be impaired in patients with vascular risk factors\textsuperscript{55}. Also risk factors inhibit the differentiation and function of the progenitor cells, moreover when progenitor cells are exposed to inflammatory cytokine profiles an altered differentiation may take place, and progenitor cells develop characteristics of other myeloid cells, like macrophages and dendritic cells\textsuperscript{56}. On the other hand, factors that have been proved to improve endothelial function and NO availability, such as exercise and statins, have been shown to have positive effect on progenitor cell mobilization\textsuperscript{57-59}. The importance of the balance between exposure to risk factors and the capacity for repair in the determination of the clinical endothelial phenotype has been highlighted by the demonstration that subjects with increased numbers of circulating endothelial progenitor cells have preserved endothelial function, despite exposure to high levels of risk factors\textsuperscript{60}. 
1.4.2 Effects of low endothelial shear stress

Although the entire vascular system is exposed to the atherogenic effects of atherosclerotic risk factors [Table 1], lesions form at specific regions of the arterial tree. Prevalent regions for plaque formation are in the vicinity of branch points, outer wall of bifurcations, and inner wall of curvatures, where disturbed flow occurs.

<table>
<thead>
<tr>
<th>MODIFIABLE RISK FACTORS</th>
<th>NONMODIFIABLE RISK FACTORS</th>
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<tbody>
<tr>
<td>Smoking</td>
<td>Age (Male &lt;75y, Female &gt;75y)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Omission of estrogen tx in case of early menopause</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>Male sex</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Genetic predisposition</td>
</tr>
<tr>
<td>Elevated CRP levels</td>
<td>Geometric variability of vessels</td>
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<tr>
<td>High blood pressure</td>
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<tr>
<td>Obesity</td>
<td></td>
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<tr>
<td><strong>EXACERBATING FACTORS</strong></td>
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<tr>
<td>Physical inactivity</td>
<td></td>
</tr>
<tr>
<td>Hyperhomocystinemia</td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
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Hemodynamic forces play significant role in regional localization of atherosclerotic lesions. Most fundamental of these forces is the endothelial shear stress (ESS), which is by definition the tangential stress derived from the friction of the flowing blood on the endothelial surface of the arterial wall, and is expressed in units of force / unit of area (N/m² or Pascal [Pa] or dyne/cm²; 1 Pa = 10 dyne/cm²). The force is proportional to the product of the blood viscosity (µ) and the spatial gradient of blood velocity at the wall (dv/dy) (figure 3).
First evidence implicating ESS in the localization of atherosclerosis was described by Caro et al. over 40 years ago. Later computational fluid dynamic simulations showed that areas with low ESS correlated to the localization of atherosclerotic lesions found during autopsy. In vivo animal experiments and human experiments with intravascular ultrasound (IVUS) or MRI and computational fluid dynamics studies also underlined the role of low ESS in atherosclerotic lesion formation and progression of the disease. Recent molecular and cellular studies have begun to clarify the detailed pathways by which low ESS leads to atherosclerosis as well as development of thin cap fibroatheromas, suspected “vulnerable plaques”.

Low ESS refers to ESS that is unidirectional at any given point but has a periodically fluctuating magnitude that results in a significantly low time-average (appr. <10 to 12 dyne/cm²) Fig 3. Low ESS typically observed at the inner areas of curvatures as well as upstream of stenoses.
Cellular effects of low ESS are listed in table 2. Pathophysiologic mechanisms involved in the remodeling of the atherosclerotic wall are not completely understood, but the dynamic interplay between local hemodynamic milieu and the biology of the wall is likely to be important. Reacting to low ESS an early fibroatheroma is formed. The vascular response to that fibroatheroma determines the nature of subsequent history of that plaque. If the ESS is normalized during remodeling, then the underlying hemodynamic stimulus for further plaque formation is resolved; a stable – quiescent plaque is formed. However, in the presence or exacerbation of certain local, systemic, and genetic factors there is a high chance that normal course of wall remodeling will be diverted. In this context low ESS persists and a self-perpetuating vicious cycle is established, between excessive expansive remodeling, plaque inflammation transforming the early fibroatheroma to a thin-cap fibroatheroma (TCFA). The stenotic

**Figure 4.** Definition and Example of Pulsatile, Low, and Oscillatory ESS. [adapted from Ku et al.]

Low and oscillatory ESS

(<10-12 dyne/cm²)

- Direction: Bidirectional (oscillatory)
- Magnitude: Low time-average

Pulsatile ESS

(15-70 dyne/cm²)

- Direction: Unidirectional
- Magnitude: Physiologic time-average

Cross-section

Blood flow
lesion either evolves with a phenotype promoting fibroproliferation consistently throughout its natural history course\textsuperscript{84} or in case of an inflamed TCFA a stenotic lesion represents the end-stage of cycles of microruptures and scaring\textsuperscript{85}. Low ESS does not play role in plaque erosion. At the neck of highly stenotic plaques high ESS might be responsible for the local endothelial erosion, and induction of thrombosis.

<table>
<thead>
<tr>
<th>Table 2. Effects of low ESS in atherosclerosis</th>
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<tr>
<td><strong>Attenuates</strong></td>
</tr>
<tr>
<td>NO dependent atheroprotection</td>
</tr>
<tr>
<td>ECM synthesis in vascular wall and fibrous cap</td>
</tr>
<tr>
<td><strong>Promotes</strong></td>
</tr>
<tr>
<td>LDL and cholesterol uptake, synthesis and permeability</td>
</tr>
<tr>
<td>oxidative stress</td>
</tr>
<tr>
<td>inflammation</td>
</tr>
<tr>
<td>vascular smooth muscle migration, differentiation and proliferation</td>
</tr>
<tr>
<td>ECM degradation in vascular wall and fibrous cap</td>
</tr>
<tr>
<td>plaque neovascularization</td>
</tr>
<tr>
<td>plaque calcification</td>
</tr>
<tr>
<td>plaque thrombogenicity</td>
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It can be concluded that low ESS is a powerful local stimulus for atherogenesis, formation and progression of quiescent plaque and differentiation to a high risk lesion. Temporary variations in the local intravascular hemodynamic environment lead to dynamic interactions with the arterial wall that might either exacerbate or ameliorate the progression of an early plaque.

1.4.3 Inflammation in atherosclerosis

Multiple independent evidence now identifies inflammation being the key regulatory process that links multiple risk factors for atherosclerosis and its complications with altered arterial biology\textsuperscript{86}.

In general the inflammatory response provide host defenses against infection, also inflammatory mechanisms participate in the repair of injured tissues. Two arms of immune system are distinguishable. Innate immunity is the primitive arm it mounts
instantly and combats foreign invaders, often with preformed mediators. Thus innate immune response described as “fast and blunt”, it recognizes only a limited diversity of structures. The adaptive immune system in contrast, requires education, which requires time, and the response displays exquisite specificity. The inflammatory response in atherosclerosis, involves elements of both the innate and adaptive arms of immunity.

**Figure 5.** Cellular composition of atherosclerotic plaques. The atherosclerotic plaque features a core containing lipids (which include esterified cholesterol and cholesterol crystals) and debris from dead cells. A fibrous cap containing smooth muscle cells and collagen fibres stabilizes the plaque. Macrophages, T cells and mast cells populate the plaque, and are frequently in an activated state. They produce cytokines, proteases, prothrombotic molecules and vasoactive substances. Until complications occur, an intact endothelium covers the plaque (adapted directly from Hansson et al.: The Immune response in atherosclerosis).

In humans atherosclerotic plaques contain blood-borne inflammatory and immune cells, as well as vascular endothelial cells, smooth muscle cells, extracellular matrix, lipids and acellular lipid-rich debris. Atherosclerotic plaque in its clinically stable state has a fibrous cap, and an intact intimal layer covering it. (fig 5.). Plaques mature over time and gain new characteristics. A flow limiting stenosis may cause clinical symptoms, however most severe complication associated with the rupture of a plaque, which exposes prothrombotic material to the blood and causes acute occlusion at the site of disruption (fig. 6.). Innate immunity is involved early in atherosclerosis, represented by its most prominent cellular components the monocyte/macrophage system. The recruitment of monocytes starts early and it is continued even in established and clinically silent lesions. Hyperlipidemia is found to be the factor, which elicits a
profound enrichment of a proinflammatory subset of monocytes, other factors may also influence the activation of monocytes. Cells populating the plaque are frequently in active state responding to various risk factors, and producing substances promoting innate inflammatory response and thrombosis. Until recently thrombosis and inflammation have been considered as independent pathways in host defense response, however current advances in relation of innate immunity and atherosclerosis suggest an intimate interlacing of these convergent systems.

**Figure 6.** Plaque activation, rupture and thrombosis. When activated, immune cells release pro-inflammatory cytokines, which reduce collagen formation and induce the expression of tissue factor. Activated immune cells also release proteases weakening the collagenous cap. The destabilized plaque might rupture when exposed to the dynamic forces of arterial blood flow. Contact with subendothelial structures and procoagulants such as tissue factor promotes platelet aggregation and thrombosis. A thrombus forms finally leading to acute ischemia (adapted directly from Hansson et al.: The Immune response in atherosclerosis).

The key regulatory system in atherosclerosis and its complications is the highly specialized adaptive arm of immunity. The complexity of the signaling pathways
involved in atherogenesis appears at least daunting at first glance. Few human diseases have a longer “incubation period” than atherosclerosis. This disease can progress virtually unnoticed over many decades and present clinically later in life or even evade trespassing the clinical horizon at all. Despite the plethora of mediators and pathways that prevail during this prolonged period of lesion evolution, a unifying principle can simplify the fundamental concepts. The dynamism of plaque biology emerges as a major simplifying theory. Balances between positive and negative signals, between synthetic and degradative processes, between life and death, regulated by the alphabet soup of mediators ultimately determine the tempo of lesion evolution, complication, and clinical manifestations. By evoking elements of host defense reaction, atherosclerosis shares much with other inflammatory and/or fibrotic diseases.

The thorough description of regulatory mechanisms is well beyond the scope of current work, the delicate, interweaving immunological processes and responses illustrate the yin and yang of cellular immunity. Accordingly, the approach to the atherosclerotic lesion and to atherosclerosis generally should be done with extreme care, and with understanding of complicated, interlacing processes.

1.5 Distal Embolization during carotid stenting

The rationale for carotid revascularization is to reduce the risk of future strokes. As several studies showed distal embolization is the primary cause of peri and postprocedural complications, and it occurs during all phases of CAS. Currently the high risk of distal embolization is the Achilles heel for carotid stenting. Historically, stroke is a clinical diagnosis based upon the history and neurological examination. Most of the major studies to date used the clinical diagnosis for stroke as primary endpoint. Unlike myocardial infarction, adequate serum biochemical markers for central nervous system necrosis or injury are still not available. The lack of an easily measured surrogate haunting the neurologists for years, and now it is even a bigger problem as CAS and acute stroke treatment enters the mainstream. Technical development, introduction of highly dedicated CAS instruments and the accumulation of clinical expertise have been associated with a decrease in the rate of complications associated with carotid stenting. The most embologenic phases of the
CAS procedure include steps during which the plaque is being disturbed, such as predilatation, stent deployment and post-dilatation\textsuperscript{99,101}. It is interesting though that several reports suggest that a significant proportion of complications seems to occur in the post-procedural period\textsuperscript{102-104}, thought to result mainly from the plaque protrusion and embolization through the stent-struts\textsuperscript{29}. Evidence collected by M. Bosiers et al. on stent design differences influencing the clinical outcome, shows that using open cell stents – those having the largest free cell area – render higher post procedural complication rates\textsuperscript{29}. Focusing on the prevention of cerebral embolization during carotid stenting is the first and foremost priority. A variety of embolic protection devices were developed to address this issue Table 2. Distal occlusion balloon were the first protection device to use (PercuSurge Guardwire, Medtronic, Minneapolis, MN) but its use was hindered by inability to angiographically visualize the target lesion during stent deployment, the occasional patient intolerance to cessation of cerebral blood flow, and the fact that emboli could still reach the brain through external carotid artery collaterals, or at the completion of procedure due to incomplete aspiration\textsuperscript{99}. The appearance of filter-type distal protection devices swiftly replaced the distal occlusion balloon, because filters were much easier to use – even by less experienced operators, did not occlude cerebral blood flow – thus was well tolerated by patients, allowed visualization of the stenosis during stent deployment, and filters being small guidewire-like devices were compatible with the existing conventional CAS instruments. Filters are on the other hand, are only partially protective, allowing particles smaller than their pore size to pass, and by not conforming to the vessel shape accurately the emboli could pass by the filter. Furthermore these devices could cause severe spasms, occasionally are difficult to retrieve, and the filter can become so filled that spilling debris must be removed separately by aspiration before filter recovery\textsuperscript{105,106}. Furthermore the filters’ pore size is at minimum of 100µm, particles below that range would pass through with a greater probability. While distal filters’ performance in saphenous vein graft procedures was the base of their use in carotid artery stenting, interestingly there has never been any comparative demonstration of their effectiveness in cerebral circulation. In theory, proximal occlusion devices should be more effective than filters, as abovementioned shortcomings of filters are absent. A proximal endovascular occlusion (PEO) device is placed and functioning before the lesion, providing protection without the need of crossing the stenosis itself. PEOs are the only devices providing this type of safety. On
the other hand PEOs share the same drawbacks associated with flow occlusion as with distal carotid occlusion devices. Approximately 5-10% of patients would have some level of intolerance to occlusion, making it more difficult for the operator to manage the patient. The bulkiness of devices is another concern (8-10Fr tools have to be introduced). The increase in device complexity has discouraged interventionalists from widely implementing PEO technique.

Surprisingly, there have been no randomized trials available to demonstrate the safety and efficacy of any carotid EPD, however one early meta-analysis concluded that EPDs did reduce the stroke risk associated with CAS procedure. This was a collection of early heterogeneous data\textsuperscript{107}. Another more recent paper by Hellings et al. states that particularly filter-based devices increase the TCD-detected cerebral emboli\textsuperscript{108}. The lack of proven efficacy of carotid EPDs to reduce clinical events is problematic as there are complications related to their use\textsuperscript{109-111}.

<table>
<thead>
<tr>
<th>Carotid Embolic Protection Device</th>
<th>Manufacturer</th>
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<tbody>
<tr>
<td><strong>Distal occlusion balloon</strong></td>
<td></td>
</tr>
<tr>
<td>Percusurge Guardwire</td>
<td>Medtronic, Minneapolis, MN</td>
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<tr>
<td><strong>Distal filter devices</strong></td>
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<tr>
<td>AccuNet</td>
<td>Abbott Vascular, Abbott Park, IL</td>
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<td>AngioGuard</td>
<td>Cordis, Miami Lakes, FL</td>
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<td>FilterWire</td>
<td>Boston Scientific, Natick, MA</td>
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<td>Emboshield</td>
<td>Abbott Vascular, Abbott Park, IL</td>
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<tr>
<td>Spider</td>
<td>ev3, Plymouth, MN</td>
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<td>Interceptor</td>
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<td>Rubicon</td>
<td>Rubicon Medical, Salt Lake City, UT</td>
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<tr>
<td>FiberNet</td>
<td>Lumen Biomedical, Plymouth, MN</td>
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<tr>
<td><strong>Proximal endovascular occlusion</strong></td>
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<tr>
<td>Mo.Ma</td>
<td>Invatec, Roncadelle, Italy</td>
</tr>
<tr>
<td>Gore</td>
<td>W.L. Gore &amp; Associates, Flagstaff, AR</td>
</tr>
</tbody>
</table>
1.5.1 Measuring embolization

**Transcranial Doppler Ultrasonography (TCD)**

Transcranial Doppler ultrasound is capable of detecting solid and gaseous microembolic material within the intracranial cerebral arteries. The detection of microemboli is based on the measurement of the backscatter (not specular reflection) from the emboli, and at present no reliable conclusion as to the composition and the size of an embolus can be drawn from the echo of the embolus\(^{112}\). Microemboli traveling along an insonated vessel will appear as high intensity transient signals (HITS), which are of short duration as they rapidly pass through the sample volume. The backscatter of the ultrasound from normal flowing blood (including transient erythrocyte aggregates) is usually lower than the backscatter from solid emboli. The latter, however, is usually much lower than the backscatter from gaseous emboli of similar size.

Although the exact clinical relevance of these findings remains uncertain, it may identify high-risk status for clinical stroke offering an opportunity to localize the source in patients with multiple potential sources and providing a possible monitoring tool for the efficacy of a chosen treatment. TCD can also be used as a quality control, training, and monitoring tool inside operation rooms for surgeries with risk of embolization\(^{113-115}\), evaluating their contribution to the postoperative neurobehavioral changes.

TCD has been used extensively to study embolization in patients with carotid and cardiac disease and a variety of procedures ranging from carotid stenting or endarterectomy to coronary artery bypass grafting. TCD is a very sensitive tool, and frequent HITS are noted in asymptomatic patients with carotid stenosis resting in bed, and those undergoing cardiac catheterization\(^{116-118}\). Bedside TCD monitoring revealed that spontaneous embolization to the brain is a fairly common and surprisingly well tolerated event, however “silent” ischemia was not evaluated. Animal studies showed that embolization with particle size \(<200 \text{ µm}\) in diameter are unexpectedly well tolerated without ischemic changes\(^{119}\). Albeit these findings might explain why carotid stenting in its current state has surprisingly good clinical results, but a later article published in 2003 by the same group exposes and explains the risks of embolization with sub \(100 \text{µm}\) particles\(^{120}\), which could not be filtered out with most currently available distal protection devices. Furthermore the authors outline that during atheroembolization other effects also should be taken into consideration, as plaque fragments causing cellular infiltration and fibrosis, which phenomenon is best described
for atheroemboli of the kidney, but it has been also observed in the brain\textsuperscript{121}. This effect might be one explanation of the late deterioration in intellectual function in patients after atheroembolization during coronary artery bypass\textsuperscript{122,123}.

**Diffusion Weighted Magnetic Resonance Imaging (DW-MRI)**

DWI is a magnetic resonance imaging method that produces in vivo images of biological tissues weighted with the local microstructural characteristics of water diffusion. In areas of lower\textsuperscript{65} the signal loss is less intense, such areas show higher signal intensity and the display from this areas is brighter. The use of a\textsuperscript{66-68} and suitable\textsuperscript{69-71} permits the acquisition of\textsuperscript{72-74} weighted images (images in which areas of rapid\textsuperscript{75-79} can be distinguished from areas with slow\textsuperscript{82}).

Reduction in apparent diffusion coefficient (ADC) of water happens within minutes of the onset of ischemia, due to a failure of high energy-metabolism, loss of ion homeostasis, and cytotoxic edema\textsuperscript{124,125}. Initially the changes in ADC were thought to represent an irreversible brain injury, and were a surrogate for clinical stroke. More recent studies complicated the situation and showed heterogeneity of DW-MRI findings in acute stroke, with many patients having complete resolution of the ADC abnormalities within a few days\textsuperscript{126-128}, Schlüter et al.\textsuperscript{129} found that in those patients who had ADC abnormalities after CAS procedure but did not develop neurological symptoms, follow-up MRI examinations were normal. Although it has to be pointed out that neuropsychological functions, which are at great risk during “silent” distal embolization were not evaluated, moreover it is well known from animal studies that normalization of the ADC values does not necessarily imply that the tissue is normal, the study by Ringer et al. showed that structural damage to the neurons could be found in spite of rapid and complete recovery of ADC values after temporary middle cerebral artery occlusion\textsuperscript{130}.

**1.5.2 Silent Ischemia**

Silent ischemia can be defined as an infarction of a non-eloquent cerebral region. Whereas non-eloquent means that infarction to such area yields no neurological symptoms during examination, contrary to apparent ischemia. But do we listen to the brain properly to perceive such eloquence? Neuropsychological deficit may not be
apparent to the clinician as neurological deficit but it can be similarly disruptive to the life of an individual.

Diffusion weighted MRI is the most efficient tool to identify post procedural embolic load. As for TCD, most studies searching for correlation between the HITS number and the extent of cognitive impairment are underpowered to show relationship – mostly because no reliable automatic method and software separating HITS emitted from gaseous and solid emboli were available to most investigators\textsuperscript{131}, however even TCDs without automatic HITS classification software are great tools for raising operator consciousness, acting as a real time feedback, urging more gentle manipulation, with chance of lowering both embolic burden and neurological complication rate.

Neuropsychological deficits can be detected after various procedures, e.g. percutaneous heart valve implantation, open-heart surgery, CABG, CEA, and endovascular diagnostic and therapeutic procedures. The embolic load can be periprocedurally measured by means of TCD, and complete postprocedural assessment of embolic load can be done by DW MRI. Arterial line filter used during CABG procedure has been showed to both reduce the embolic burden, and the neuropsychological deficit following it, suggesting that microemboli may contribute to such deficit\textsuperscript{132}. A study by Bokeria et al. found correlation between asymmetric cerebral embolic load during open heart surgery and the type and extent of postoperative cognitive impairment\textsuperscript{133}.

A systematic review of 32 DWI studies after CAS and/or CEA, by Schnaudigel et al.\textsuperscript{134} highlighted the fact that DWI lesions were significantly more frequent after carotid stenting (37% of CAS patients had new DWI lesions vs. 10% after CEA), underlining the well-known fact of higher embolic load during CAS. It is interesting that accumulated data (mostly from M. Bosiers et al.\textsuperscript{29}) suggests that stent design on its own, has a significant effect on occurrence of postprocedural DWI lesions.

During cerebral angiography and neurointerventional procedures, difficult to cannulate aortic arch vessels, more contrast usage and prolonged procedure times were also correlated with appearance of new DWI lesions\textsuperscript{135}. In clinical trials, 20% of novel DWI lesions appear in the contralateral hemisphere\textsuperscript{136,137}. Appearance of such DWI lesions after CAS in the contralateral hemisphere may correspond to catheter manipulation in the arch.
Numerous studies conducted by chest surgeons and cardiologists evaluating various surgical and endovascular procedures concluded that higher or repeated embolic load is not only a good predictor of stroke, MI and consequent prolonged in hospital stay, but can be associated with high prevalence and persistence of cognitive decline and or aggravation of vascular dementia\textsuperscript{123,138,139}.

It has to be emphasized that in most cases we have to get rid of the word “silent”. As during ischemia neurons suffer irreversible damage, we left our fingerprints after each potentially embologenic procedure. As Dr. Rockwood and Dr. Gubitz brilliantly state it in an editorial comment: “Eloquence implies that the speaker is deficient if the message does not get through, but what of the listener? How hard must we listen before we can conclude that nothing is being said? Just as recent generations of investigators and, later, practitioners have come to grips with molecular genetics and the magnetization of hydrogen molecules in radiofrequency fields, so a new crop of investigators is embracing the complexity of networks and systems approaches to brain function. If the

\textbf{Figure 7.} Comparison of 3 procedural variables on the incidence of new ipsilateral DWI lesions. (adapted from Schnaudigel et al\textsuperscript{134})
brain is speaking to us in mathematical terms, perhaps cerebral silence is less the problem than that of listener deafness”\textsuperscript{140}. 
Objectives

1. To measure the embolization rate during implantation of covered stents by means of transcranial Doppler ultrasound (TCD), and compare results with those obtained during implantation of conventional carotid stents.
2. To assess feasibility and efficacy of covered stents in internal carotid artery stenting
2. Defining baseline microembolization rate with TCD during conventional bare metal stent (BMS) implantation

2.1 Introduction

Transcranial Doppler ultrasound is a widely used technique in variety of settings to measure the rate of cerebral microembolization, both gaseous and solid. Its use is well established by several completed carotid stenting and endarterectomy studies\textsuperscript{111,114,141,142}. TCD data give us an invaluable real-time insight into procedure-related cerebral events, as well as giving important feedback to the operator. TCD embolus detection methods and techniques are intensely documented in the literature. Conventional Doppler instrumentations do not discriminate solid from gaseous emboli. In contrast multifrequency TCD allows differentiation by insonating the same sample volume with two different ultrasound frequencies. However solid and gaseous emboli could be differentiated using conventional devices too, but the results will be operator dependent, and interpretations of HITS include a significant learning curve. Thus record should be taken of every procedure, and the data have to be evaluated off line, after the procedure.

2.2 Subjects and methods

2.2.1 Carotid artery stenting with conventional bare metal stents

Between November 2005 and November 2007 we monitored 146 carotid artery stenting procedures in 134 patients. All carotid stentings performed by an experienced interventional radiologist (EV). All patients were premedicated with 75 mg clopidogrel and 100 mg aspirin at least 4 days before the procedure. Preoperative head CT and/or MRI scans were acquired and neurological examinations were done. The extent of the carotid artery stenosis was measured with the NASCET method\textsuperscript{143}, and the plaque morphology was noted (table 4.). Carotid technique was achieved by a standard technique, with gentle tool manipulation and low-profile devices\textsuperscript{144,145}. During intervention 5000 IU sodium heparine was administered intraarterially once or twice. 145 procedures were done via femoral route, in one case percutaneous access gained via brachial puncture. If necessary, predilatation was performed.
Table 4. Patient and lesion characteristics

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Patients</td>
<td>134</td>
</tr>
<tr>
<td>Mean Age</td>
<td>64.6 y ± 6.7 y SD</td>
</tr>
<tr>
<td>Procedures</td>
<td>146</td>
</tr>
<tr>
<td>Successful</td>
<td>145 (99.3%)</td>
</tr>
<tr>
<td>Plaque Morphology</td>
<td></td>
</tr>
<tr>
<td>Heavily calcified/irregular</td>
<td>67 (46%)</td>
</tr>
<tr>
<td>Ulcerated</td>
<td>48 (33%)</td>
</tr>
<tr>
<td>Smooth</td>
<td>28 (19%)</td>
</tr>
<tr>
<td>Fibrotic</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Plaque length</td>
<td>17.4 mm ± 4.3 mm SD</td>
</tr>
<tr>
<td>Mean stenosis</td>
<td>84.4% ± 6.7% SD</td>
</tr>
</tbody>
</table>

Five different conventional carotid stents were used (table 5.), 76 (52.4%) Carotid wallstent (Boston Scientific, Natick, MA, USA), 43 (29.7%) Xact (Abbott Vascular, Redwood, CA, USA), 16 (11%) Precise (Cordis Corp., Warren, NJ, USA), 6 (4.1%) Zilver (Cook Medical, Bloomington, IN, USA), 4 (2.8%) Cristallo Ideale (Invatec SPA, Roncadelle, Italy). Finally postdilatation was performed with balloon catheters ranging in diameter from 5 to 6 mms. Overdilation of implanted stents was avoided. The residual stenosis in all successfully treated vessels was <20%.

Table 5. Types of carotid stents used

<table>
<thead>
<tr>
<th>Stent Name</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carotid Wallstent (closed cell) [BSC]</td>
<td>76 (52.4%)</td>
</tr>
<tr>
<td>Xact (closed cell) [Abbott]</td>
<td>43 (29.7%)</td>
</tr>
<tr>
<td>Precise (open cell) [Cordis]</td>
<td>16 (11%)</td>
</tr>
<tr>
<td>Zilver (open cell) [Cook]</td>
<td>6 (4.1%)</td>
</tr>
<tr>
<td>Cristallo Ideale (open/closed design) [Invatec]</td>
<td>4 (2.8%)</td>
</tr>
</tbody>
</table>

The vital signs and cardiac rhythm were monitored by anesthesiologist, neurological assessment was frequent during intervention. Atropine up to 2 mg, was administered intravenously as necessary for bradycardia. On procedure completion control angiograms were done to evaluate recanalization and exclude intracranial vessel occlusion.

One procedure was technically unsuccessful, due to inability to pass the stent delivery system through a subtotal, heavily calcified stenosis; successful endarterectomy was
carried out later. One patient suffered a periprocedural minor stroke, after balloon dilatation. In another case we detected acute renal insufficiency, possibly due to cholesterol embolization.

### 2.2.2 Transcranial Doppler monitoring

Transcranial Doppler monitoring was carried out using conventional double gated TCD technique. A Multi-Dop® T (DWL, Compumedics Germany GmbH, Singen, Germany) TCD device was used. Procedure recording started before femoral artery puncture, and lasted for 10 minutes after wound closure. Assessment of postprocedural embolization was not done.

Ipsilateral medial cerebral artery was insonated through temporal window. A 2MHz probe was secured in a head ribbon. Two sample depth were used the distance between them was set at 5mm. The depth of distal gate was varying from 49 to 64mms (mean 55.6mm). The power and gain settings kept at minimum to prevent artifact development. Mean power was 98.5 mW, and the mean thermal index (TIC) was 1.01.

Microembolic signals were recorded, and then counted and attributed to each phase after procedure. We evaluated all major steps of CAS: (1) guiding manipulation, (2) microguidewire passage, (3) predilatation, (4) stent delivering system passage, (5) stent opening, (6) balloon catheter passage, (7) postdilatation. In our series protection devices were not used.

Conventional TCD methods are lacking temporal resolution for differentiating individual emboli during embolic showers occurring mostly during contrast media injections, stent opening and postdilatation. Embolic showers occurring during contrast media injection are considered less hazardous, as such showers composed mostly of gas bubbles (figure 8.146). For other cases (figure 9.) heartbeats/shower can be counted or standard rate of emboli/heartbeat during shower can be defined, which in our study was specified in 10 emboli per heartbeat according to guidelines104.
It is known from previous studies\textsuperscript{99,101,111,147} that all phases of CAS are potentially embologenic. As conventional TCD emboli detection is highly operator dependent, thus direct comparison between findings of different institutions would render highly inaccurate results. Our goal was to define the standard rate of embolization at each phase of CAS at our institution, for further investigation, and for future device comparison.

\textbf{Figure 8.} HITS “shower” detected during contrast media injection. Individual emboli could not be identified. Left: Doppler waves and the artifact caused by gas bubbles. Right: fast Fourier transformation of the data on the left.

\textbf{Figure 9.} Left: An embolic signal was detected at a depth of 58mm with a relative intensity increase of 32dB. The software also detected the velocity of the embolic signal (73.7cm/s). The time lag in occurrence of the two signals is also visible on a pre-FFT signal at the bottom. There is a lag of 7ms between the peaks of the two signals. This difference indicates that the embolus has traveled 5.16mm from the first to second sample volume \([6\text{ms} \times 737\text{mm}/1000\text{ms}=5.16\text{mm}]\). The expected preset difference was 5mm. On the right: emboli showing higher ultrasound scattering and frequency shift counted as gaseous emboli in the study.
2.2.3 Statistical analysis

Categorical variables were compared using $\chi^2$ test, and Student’s t test used for continuous variables.

2.3 Results

A total of 18796 microembolic signals were detected. MES were recorded in all major phases of carotid stenting procedures (figure 10.). 3 phases with significantly increased MES counts were identified, these were stent deployment (60.97 MES/patient), postdilatation (38.87 MES/patient), predilatation (20.1 MES/patient). There was no statistical difference in embolic counts measured during the use of different stent delivery systems and stent designs in our study.

![Figure 10. Mean MES count during various phases of unprotected carotid artery stenting.](image-url)
2.4 Conclusion

The above results are comparable to other published studies, where the same embolus detection method was used\textsuperscript{99,111}. The clinical significance of detected emboli was not evaluated. The embolic count refers to used CAS technique, and devices, and possibly plaque composition. Even though in our series there was statistical significance [with confidence interval of 95\%, p=7x10^{-4}] between plaque structure and embolic count, examination of plaque composition by means of US and DSA is not completely reliable and operator dependent, but could predict – in some cases higher risk of embolization during CAS. If needed, plaque structure should be examined with different more accurate, but widely available techniques – e.g. CT angiography\textsuperscript{147}. It seems logical to conclude that fewer manipulations render less emboli during CAS procedure, this was also hypothesized by other authors\textsuperscript{99,148}. CAS without the use of balloon dilatation and CPD is feasible, Baldi et al. published their favorable long-term results in 2011 of 236 patients treated using such technique\textsuperscript{149}.

It can be concluded that this trial was successfully evaluated the distribution of microembolic signals occurring during unprotected carotid artery stenting at our institution.
3. Measurement of embolization during covered stent implantation

3.1 Introduction

Idea of lowering the embolization during carotid stenting is not new, it was apparent early from beginning of the history of CAS that by not removing the plaque the operator is deemed to work in hazardous environment. To gain wide acceptance for CAS peri-, and postprocedural complications (caused mostly by embolization) should be lowered significantly. Various devices and methods evolved to protect the brain. Most of these are filters, designed with intention to retain embolic material in their basket, reversing the flow and redirecting the route of emboli is another viable option. Ever growing number of reports suggest the use of these devices by default, on the other hand some papers evaluating protected and unprotected CAS procedures found no significant difference in outcomes between two groups or a non-reduction of embolization rate during protected CAS, others advocate the routine nonuse of PDs. Outside the United States, usage of PDs is up to institutional or more likely a personal preference. As the reported rates of neurological complications are substantially decreasing, a shift from intra- to postprocedural complications is observed in high volume centers. Recently some investigators started to ask questions about postprocedural embolization. “Where do they come from?”.

Several groups – including ours – hypothesized that a device capable of covering the plaque in greater extent than the readily available bare metal stents would result a significantly lower embolization rate, both intra- and postprocedurally.

3.2 Subjects Methods

Five patients undergoing carotid artery stentgraft implantation (Symbiot, Boston Scientific) were monitored perioperatively with transcranial Doppler. The methods of monitoring are described above. Five patients were all males, mean age was 68 years ±7.04 SD. All of them had a symptomatic stenosis (mean 88.4% ± 5.36 SD, 3 involving left 2 right ICAs), one patient had contralateral ICA occlusion. Diagnostic US and preoperative angiography confirmed soft plaques in all patients complicated by ulceration in two cases, high rate of embolization was expected. Carotid stenting done using normal technique. Predilatation were not done, and no protection devices were
used. The stenoses were involving the ICA only, thus stentgraft implantation did not endanger the patency of ECA.

### 3.3 Results

All five monitored implantations were technically successful. All ECAs remained patent. There were no perioperative neurological complications. Obtained TCD data shows changes in embolization profile compared to findings during BMS implantation (fig.11.).

![Figure 11. Mean embolic signal counts obtained during BMS implantation (light blue columns) and Symbiot stentgraft (dark blue columns).](image-url)
3.4 Conclusion

Analysis of the obtained data showed a significant drop in MES counts during balloon delivery (10.3 MES vs 1 MES p=1.7x10^{-7} CI=99%) and postdilatation (38.9 MES vs. 7 MES p=1.3x10^{-5} CI=99%) compared to baseline embolization rates acquired during BMS implantation.

MES counts in the other two phases which include manipulation with the stentgraft – stent delivery system (SDS) passage and stent opening – were not significantly different from those obtained during BMS implantations.

A seemingly paradoxical elevation of MES count during stent delivery is noted. The possible explanation is that although the SDS of Symbiot is analogous to that of the Carotid Wallstent’s, the stent itself is considerably stiffer, due to its ePTFE covering. As it can be seen from the bar chart above (Fig. 11.) embolic counts more than doubled during stentgraft delivery (21.8 MES vs. 10.4 MES). Carefully evaluating the causes of this result, it was found that such difference can be attributed to one case where the covered stent had to be delivered through tortuous ICA anatomy, and during the passage of SDS an embolic count of 85 was registered. This one case exposes the risks of stiff stent and SDS usage in such environment. It have to be added at this point that stiff systems like Xact (Abbott Vascular) rendered slightly higher MES counts during passage in our series, but due to low sample rate in this trial the assumption that stiff SDSs are being more embologenic could not be proved statistically. The small number of TCD monitored stentgraft implantations prevented to show statistical difference in the phase of stent delivery (10.34 MES ±7.04 SD vs. 21.80 MES ± 25.28 SD p=0.42 NS CI=99%). Expecting higher force exertion of Symbiot SDS on vessel wall and plaque and adding the fact that due to patient selection protocol most stentgrafts were implanted in a highly embologenic environment, in such hostile milieu a more gentle device manipulation and greater experience in CAS is essential.

An opposite tendency is noticeable during stent opening, in this phase the stentgraft is hypothesized to act as a protecting device from the initiation of implantation (figure 12). Our findings might convey that impression, but again low number of patients involved could not consolidate this effect statistically (60.97 MES vs. 24.2 MES p=0.11 NS CI=99%).
The significant drop in MES counts in abovementioned postdilatation phases and possible embolization decrease during stent opening shows clear advantages of covered stent design, reducing the mean embolic count altogether by 44.6%.

Figure 12. Steps of stentgraft opening. From top to bottom.
1. SDS passage, delivery.
2. Initiation of opening, decrease of embolization rate expected from this phase.
4. Postdilatation, significant MES count reduction observed.
5. Stent fully opened, plaque maximally covered, graft acting as a protecting device.
4. Usage of covered stents in internal carotid artery stenosis
Study of feasibility and long term follow-up

4.1 Introduction

Most CAS-related complications occur as a result of embolization\textsuperscript{98}. Despite the decreasing neurological complication rate\textsuperscript{153}, microembolization remains a major concern. As it has been shown microembolic signals are detected by continuous transcranial Doppler monitoring in every phase of protected or unprotected CAS\textsuperscript{34,99,101,111,155} and in almost all patients, 22-36% of the patients exhibited new ischemic lesions detected by DW-MRI after CAS, clinical significance of these lesions is debated\textsuperscript{129,158,159}. As it is shown in our TCD monitoring study of 146 BMS implantation procedures, the most embolic phases of the CAS procedure include predilatation, stent deployment and post-dilatation\textsuperscript{99}. Furthermore, a significant proportion of complications seem to occur in the post-procedural period, thought to result mainly from embolization through the stent-struts\textsuperscript{29}. The application of protecting devices has been associated with a reduced rate of neurological complications\textsuperscript{107,160}. However, the use of protecting devices may actually increase the number of emboli\textsuperscript{111,161} and they are incapable of preventing post-procedural embolization.

A covered stent, in which the stent mesh is coated with a thin membrane, may prevent the passage of atherosclerotic material through the stent grid. Covered stents may efficiently reduce embolization during stent deployment, post-dilatation, and also post-procedurally. A randomized study conducted by Schillinger et al.\textsuperscript{156} has confirmed the superiority of covered stents compared with bare ones in terms of intra- and early procedural embolization, however, the rate of restenosis was higher among those who received stentgrafts. Our group has investigated early and long-term outcomes of CAS performed with the use of covered stents.

4.2 Subjects and Methods

From September 2002 to May 2007, 46 consecutive patients (63% symptomatic, 78.3% male, 67±8.6 yrs. of age) received covered stents in our center. Patients were included if they had symptomatic 60-99%, or asymptomatic 70-99% (according to the North American Symptomatic Carotid Endarterectomy Trial [NASCET] measurement
method\textsuperscript{7} stenosis of the internal carotid artery caused by embolic soft (echolucent) or mixed type (containing both soft and hard elements) plaques. Plaque characterization was performed using ultrasound and ulceration was noted on digital subtraction angiography (DSA). The covered stent was available in a maximum diameter of 5 mm and a maximum length of 45 mm; therefore the morphological inclusion criteria included a maximum 5 mm reference vessel diameter of the ipsilateral internal carotid artery and a maximum lesion length of 30 mm. In order not to obstruct flow into the external carotid artery, only patients with lesions allowing the selective stenting of the internal carotid artery without the need to cover the carotid bifurcation were enrolled. Exclusion criteria were the occurrence of a stroke within the previous 6 weeks, a previous major stroke within the territory of the stenotic artery with no useful recovery of function, a visible thrombus at the site of the lesion, carotid artery dissection, vessel narrowing caused by external compression by a tumor, a life expectancy of less than 2 years because of a known pre-existing condition, and the inability or unwillingness of the patient to provide informed consent. A team of radiologists, neurologists and neurosurgeons in accordance with a standardized protocol carried out patient evaluation, intervention and follow-up. The patients gave their written informed consent to the procedures, which followed institutional guidelines.

4.2.1 Patient Evaluation

The relevant medical history was taken and a thorough neurological examination was performed on all patients. Duplex ultrasound of the carotid arteries was used in all patients to discover hemodynamically significant stenosis, and to record plaque morphology. Computed tomography (CT) or magnetic resonance imaging (MRI) of the brain was performed in all patients before stent implantation. Criteria for patients at high risk included octogenarians, severe cardiac dysfunction (New York Heart Association class III/IV chronic heart failure, acute myocardial infarction within 4 weeks, unstable angina, or a coronary procedure within 4 weeks), and pulmonary disease causing significant functional limitation, contralateral carotid occlusion, and post-endarterectomy restenosis. Patient and lesion characteristics are shown below in Tables 6 and 7.
### Table 6.: Patient population characteristics

<table>
<thead>
<tr>
<th>Population</th>
<th>46 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>36 (78.3%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>50-90 years</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>67 ± 8.6 years</td>
</tr>
<tr>
<td>70-79 y</td>
<td>17 (36.9%)</td>
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<td>&gt;80y</td>
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</tr>
</tbody>
</table>

### Risk factor distribution

<table>
<thead>
<tr>
<th>Factor</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Mellitus</td>
<td>14 (30.4%)</td>
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<tr>
<td>Hypertension</td>
<td>36 (78.3%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>33 (71.7%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>22 (47.8%)</td>
</tr>
<tr>
<td>Severe cardiac dysfunction</td>
<td>1 (2.2%)</td>
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### Table 7.: Characteristics of treated lesions

<table>
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<tr>
<th>Count</th>
<th>46 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>29 (63%)</td>
</tr>
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### Degree of stenosis

<table>
<thead>
<tr>
<th>Mean ± SD</th>
<th>86% ± 7.2%</th>
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<tr>
<td>≥90%</td>
<td>26 (56.5%)</td>
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</table>

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
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</thead>
<tbody>
<tr>
<td>Contralateral ICA occlusion</td>
<td>5 (10.8%)</td>
</tr>
<tr>
<td>Postendarterectomy restenosis</td>
<td>2 (4.3%)</td>
</tr>
</tbody>
</table>

### Plaque morphology on angiogram

<table>
<thead>
<tr>
<th>Morphology</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smooth</td>
<td>15 (32%)</td>
</tr>
<tr>
<td>Ulcerated/Irregular/Unstable</td>
<td>31 (68%)</td>
</tr>
</tbody>
</table>

#### 4.2.2 Stenting protocol

Carotid artery stenting was performed according to a standard protocol as described previously\(^{144,145}\). Dual antiplatelet treatment (aspirin 100 mg plus clopidogrel 75mg daily) was started at least 4 days before the procedure and continued for a minimum of 4 weeks post-procedure. All stenting procedures were performed under local anesthesia.
by the same experienced interventional neuroradiologist (EV). Percutaneous access was acquired through the femoral artery. Brachiocephalic angiography with evaluation of the intracranial arteries and assessment of the collateral cerebral circulation always preceded the stenting. The degree of internal carotid artery stenosis was measured with the NASCET method\textsuperscript{143}, and morphology of the plaque surface was noted (table 6.). The final percentage stenosis was based on the angiographic findings. Carotid artery stenting was accomplished with gentle manipulation using low-profile devices. Protection devices were not applied. Heparin 5000 IU was administered intra-arterially once or twice during the intervention. Symbiot covered stents (Boston Scientific) were used in 5 different sizes: 4x31mm in 1 (2.2%), 4x45mm in 1 (2.2%), 5x20mm in 11 (23.9%), 5x31mm in 26 (56.5%), and 5x45mm in 7 (15.2%) cases. The Symbiot covered stent features a self-expanding nitinol stent encased in a thin porous polytetrafluoroethylene membrane. Predilatation was not necessary in any of the cases, whereas post-dilatation was used during every procedure. The residual stenosis in all successfully treated vessels was <30%. The vital signs were recorded regularly, the cardiac rhythm was monitored continuously, and neurological assessment was frequent during the intervention. Intravenous atropine, up to 2 mg, was administered as necessary for bradycardia. Control angiograms were recorded on procedure completion to evaluate recanalization and to assess the patency of intracranial vessels.

4.2.3 Follow-up

Control neurological examination was performed routinely 24 hours, 1 month, 6 months and then yearly after stenting. Carotid duplex ultrasound was carried out 1 month, 6 months and then yearly after the procedure. The incidence of complications and any other medical events during the intervention and the subsequent follow-up period was recorded. The study endpoints were the occurrence of neurological events, and the development of in-stent restenosis (>50%, as measured by duplex ultrasound).
4.3 Results

Carotid artery stenting was technically successful in all 46 patients. Twenty-nine (63%) procedures were conducted in symptomatic cases. Sixteen (34.8%) patients belonged in the high-risk group, of whom 11 were symptomatic. The corresponding proportions of high-risk patients were 41.4% among the symptomatic, and 27.8% among the asymptomatic cases. The mean follow-up time was 34.3 months. The rate of patients lost to follow-up was 15.2%.

No new neurological symptoms or stroke were observed either periprocedurally or during the follow-up period. Three high-risk patients (6.5%) developed restenosis of the stented carotid artery. The first case was detected two years after the procedure; the second was noticed at the three-year and the third at the four-year follow-up. Patients underwent successful balloon angioplasty.

During the procedures, occlusion of the external carotid artery occurred in 3 (6.5%) cases, all of them remaining symptom-free. Our experience indicates that the occlusion of the external carotid artery is well tolerated, most probably because of its good collateral system. Although we are aware of the ECA’s importance in providing collateral pathways in case of carotid occlusion and incomplete Willis circle\textsuperscript{162}. In one patient a pseudoaneurysm was detected at the site of the femoral puncture, which was successfully treated with ultrasound-guided embolization.

Figures below show a stent removed 15 months after procedure. Histopathological examination found a normal intimal layer; giant cells were demarcating the foreign body with no signs of extended inflammation detected.
An ulcerated right ICA stenosis can be seen on Fig. 14/A, and immediately after implanting a covered stent (Fig. 14/B). 3.5 years later during carotid artery stenting of the contralateral ICA a control angiogram showed no restenosis and smooth contours of the previously stented right carotid artery (Fig. 14/C.).

Figure 13. Specimen acquired 15 months after stent implantation. A: Cross section of the ICA, arrows show the stent. (HE-56x) B: Cross section of the ICA, arrows show the stent. (HE-224x) C: CD68 immune staining, specific macrofage staining. Note the demarcation of the stent fragments (112x)
Figure 14. A: an ulcerated/irregular right ICA stenosis. B: control angiography after Symbiot stentgraft implantation. C: control angiography made during contralateral stent implantation 3,5 years after Symbiot implantation, shows no restenosis, and smooth contours of the treated vessel. The ECA is patent.
4.4 Conclusions

In hands of an experienced endovascular surgeon the use of covered stents in treatment of carotid artery disease is safe. During the long-term follow up of the patients the restenosis rate was low. The TCD findings prove the concept of covered stent acting as a protection device during and after stent deployment.
5. Discussion

The main cause of stroke in patients with carotid artery stenosis is embolization from the atherosclerotic plaque\textsuperscript{163,164}. Therefore main goals of the treatment of significant carotid stenosis are to prevent further distal embolization and to restore blood flow to the brain. It should be obvious that protecting the brain from future embolic attacks is the primary objective. Multicenter prospective randomized trials have demonstrated that the removal of the source of emboli during endarterectomy is beneficial in selected symptomatic or asymptomatic patients with significant carotid stenosis to significantly reduce the risk of stroke\textsuperscript{7-9,165-167}. Consequently, an endovascular approach should be able to cover and scaffold the stenosis sufficiently to prevent further embolization and to restore the patency of the treated vessel. Currently this is achieved in most cases with the application of stents, where the occurrence of neurological events after removal of the protection device depends largely on the character of the stent struts\textsuperscript{29,161,168}. As it is mentioned before stents used for carotid stenting are mostly unmodified derivatives of peripheral stents, which were designed to restore hemodynamics, therefore they are natively fall short completing the primary objective of the procedure.

To further improve carotid artery stenting, studies revealing the nature, risk and occurrence of embolization were conducted. TCD monitoring trials revealed the embolization profile of CAS procedures and this technique is now almost used as a quality control procedure. Our TCD monitoring results were comparable to those published in the literature. However direct comparison between the data acquired by different groups would render highly inaccurate results, as non-automated MES detection is greatly operator dependent. Although MES counts are not similar in TCD studies, the embolization profile is almost identical, showing the most dangerous phases of the procedure, which is a proof, that standard technique and devices yield to similar microembolization patterns. Authors advocating the omission of pre and postdilatation (steps with significantly higher risk of microembolization), and the use of EPDs report favorable outcomes with standard devices and altered technique\textsuperscript{148,149,169}. Several studies were successful to find correlation between plaque morphology and periprocedural adverse event rate\textsuperscript{170,171}. Evidence is accumulating that unstable, vulnerable plaques are associated with increased embolization during CAS\textsuperscript{108}. In our series we found significant correlation between the plaque morphology - as seen by means of US and DSA and embolic rate measured during CAS (p=7x10\textsuperscript{-4}, CI=95%). This information
provided a patient cohort with unstable plaques and elevated periprocedural embolization risk. This group then included into the covered stent study. Our group hypothesized that the most effective way to cover a plaque may be with the use of a device that combines the advantages of the arterial grafts and the self-expanding stents. The Symbiot stent-graft was originally developed for the treatment of the endoluminal lesions of saphenous vein grafts. As several reports and our trial indicates, such device may turn out to be useful not only for cardiac, but also for neurointerventional procedures. The Symbiot stent-graft might be well capable of serve as peri- and post-procedural protection device, efficiently reducing embolization right from the moment of stent opening until the development of the neoendothelium, therefore such device may be extremely useful in the treatment of carotid stenosis caused by highly embologenic plaques.

Results of the long-term follow-up do not seem to confirm the high rate (21.4%) of in-stent restenosis reported for such stents previously. Restenosis in our cohort was rare, occurring in only 3 patients (6.5%). Degree of in-stent restenosis was clinically irrelevant in all cases. All patients with restenosis were treated successfully with balloon angioplasty. The low rate of in-stent restenosis in our study may be related to the tissue friendly structure of the Symbiot stent-graft, which did not disturb the nourishing of the intimal layer via diffusion through the 80-micrometer pores of the polytetrafluoroethylene membrane. The odds of developing sterile inflammation are lower by using such microporous membranes than in the case of conventional peripheral polytetrafluoroethylene grafts.

TCD monitoring of some covered stent implantations rendered interesting data. Marked drop in MES counts during balloon delivery and postdilatation were shown. A paradoxical doubling in MES counts during SDS delivery lead us to conclusion, that the significantly stiffer SDS of the Symbiot stentgraft dislodged more emboli on its way through tortuous stenosis in highly embologenic environment, a similar but somewhat subtler effect have also been seen in the case of stiff BMS implantations (Xact, Abbott Vascular), but due to low sample rate could not rise to significant level. The greatest reduction in MES counts was awaited in stent deployment phase, where the stentgraft is hypothesized to act as a protection device. We found a marked reduction of embolization during that phase, but statistical significance could not be proved because of the low sample size. Altogether in our series the use of covered stents lowered the mean MES rate by 44.6%.
Until recently large randomized studies\textsuperscript{172-176} comparing CAS and CEA were unable to establish the noninferiority of CAS. Interpretation or misinterpretation of the results even led some to call for a moratorium on carotid stenting\textsuperscript{177,178}. What can we learn from these studies? Current results are suggesting that from a scientific point of view, CAS could not prove to be superior to surgery, in randomized trials in long-term results. Higher risks of restenosis in CAS arms were noted. And last but not least, very experienced interventionalists should only perform CAS. Perhaps we need better studies, and we might need better tools. However the recently published CREST study involving 2502 patients (1262 CAS and 1240 CEA) showed the contrary. There were no significant difference in the estimated 4-year rates of the primary end points between CAS and CEA groups\textsuperscript{179}. The table below shows the metaanalysis of the results of some randomized controlled trials to date (table 7.)\textsuperscript{180}.

<table>
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<th>STUDY</th>
<th>CAS</th>
<th>CEA</th>
<th>OR (95% CI)</th>
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</thead>
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<tr>
<td>Leicester</td>
<td>5/11</td>
<td>0/12</td>
<td>12.88 (1.85 to 89.61)</td>
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<td>Wallsten</td>
<td>13/107</td>
<td>5/112</td>
<td>2.76 (1.05 to 7.22)</td>
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<td>Kentucky - Sympt</td>
<td>0/53</td>
<td>1/51</td>
<td>0.13 (0 to 6.56)</td>
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<tr>
<td>Kentucky - Asympt</td>
<td>0/43</td>
<td>0/42</td>
<td></td>
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<td>25/251</td>
<td>25/253</td>
<td>1.01 (0.56 to 1.81)</td>
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<td>SAPPHIRE</td>
<td>8/167</td>
<td>9/167</td>
<td>0.88 (0.33 to 2.34)</td>
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<tr>
<td>EVA – 3S</td>
<td>25/265</td>
<td>10/262</td>
<td>2.47 (1.24 to 4.90)</td>
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<tr>
<td>SPACE</td>
<td>46/599</td>
<td>38/584</td>
<td>1.19 (0.77 to 1.86)</td>
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<td>1/10</td>
<td>0.14 (0 to 6.82)</td>
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<td>28/821</td>
<td>2.17 (1.42 to 3.33)</td>
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<td>CREST</td>
<td>66/1262</td>
<td>56/1240</td>
<td>1.18 (0.82 to 1.68)</td>
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<td>POOLED</td>
<td>249/3596</td>
<td>173/3554</td>
<td>1.4 (1.14 to 1.89)</td>
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|              | 6.9%      | 4.9%      |        |

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<th>OR (log scale)</th>
<th>CEA better</th>
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<td>1</td>
<td>10</td>
<td>100</td>
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Table 7. Meta-analysis of the randomized trials comparing carotid artery stenting with carotid endarterectomy. Numbers showing periprocedural adverse event rates. (adapted from Roffi M et al. Carotid artery stenting vs. endarterectomy\textsuperscript{177})

When applying the abovementioned results, one should be aware of limitations of these clinical studies. The most striking detail is the minimal endovascular experience required per protocol, which was incredibly low, and this should raise important ethical questions and more importantly cast doubts on the applicability of the results. The
operator experience issue must have been ignored by the trial designers despite the fact that operator inexperience caused catastrophic results during the first randomized single center study comparing CAS and CEA. When the role of CEA was established, the new procedure had to show that therapy is efficacious in the hands of the most skilled operators on selected (favorable) patients. In NASCET a rate of less than 6% for stroke and death occurring within 30 days of operation for at least 50 consecutive carotid endarterectomies performed within the previous 24 months. ACAS is another example where patients at high risk for surgery were excluded, and both centers and individual surgeons had to demonstrate a 30-day death or stroke rate of <3% to be able to enroll. In addition, during the study the surgeons were audited in the presence of more than one complication and were allowed to continue enrollment only if no operator-related problem was observed. No sign of the above requirements were to found in endovascular arms of randomized CAS vs. CEA trials. In CAVATAS training in neuroradiology and angioplasty – but not necessarily in the carotid artery – was mandatory, proctored procedures were allowed for investigators with little skill in cerebrovascular angioplasty. EVA-3S a French trial perhaps is the most notorious for its low requirements. Study demanded only 12 previous CAS procedures, alternatively for those who failed to meet this already soft requisite, enrollment was still possible if the operator had performed 5 CAS procedures and at least 35 stenting procedures of the supra-aortic trunks in his lifetime, finally who failed to meet even these requirements performing the procedure and joining the study was still possible if the procedure was conducted under supervision of an experienced tutor – defined as someone with experience of at least 12 CAS procedures. Even with these low requirements in expertise EVA-3S investigators found that CAS is as effective as CEA in midterm ipsilateral stroke prevention. It has to be added that CAS in France was never reimbursed. More demanding studies in terms of expertise were the SAPPHIRE and SPACE trials. In SAPPHIRE investigators had to submit their procedures to an executive review committee, and the CAS periprocedural stroke and death rate should be <6%, no proctor assisted procedures were allowed. Main publication of the SPACE trial described a minimum of 25 successful consecutive PTA or stenting procedures, however a second publication reveals that during the trial, a modification of the study protocol allowed tutored participation for interventionalists who had a total experience of 10 CAS procedures. In ICSS a total experience of 50 stenting procedures were sufficient if 10 of these involved the carotid artery, tutor assisted
procedures were allowed for operators with insufficient experience. The CREST trial stands out in terms of required endovascular expertise. Investigators with experience in more than 15 CAS were allowed to enter the lead in phase of the study if the interventional management committee, to whom each interventionalist had to submit the documentation of their previous cases, approved them. Candidates who were approved for participation in the lead-in phase underwent training in the use of the CREST study devices, after completion of the training those with more experience ($\geq 30$ cases) performed 5-10 procedures, and those with less experience ($< 30$ cases) performed 10 to 20 procedures in the lead-in phase. These strict requirements were the basis of the favorable results reported by CREST investigators$^{186}$. As for pre-CREST RCTs it still remains unanswered why low requirements regarding endovascular expertise were proposed by trial leaderships and accepted by Ethical Committees. At this point a wide spectrum of speculations might arise, but it is very probable that for enrolling sufficient number of patients to empower these trials in short time, requirements had to be significantly lowered for endovascular arm. In the light of CREST results it is now clearly seen how damaging these decisions were. It has to be emphasized again that the main purpose of randomized testing is to show that the new therapy is efficient in the hands of most skilled operators. The majority of the randomized controlled trials miss this very point, and CAS procedure is now judged upon these biased results. As of December 2010 eight large-scale prospective non-randomized CAS trials involving more than 1000 patients were published, for a total of 22700 patients (Table 8.). Current complication rates for CEA are used as benchmarks to estimate the interventional risk. Perioperative stroke and death rate should be $<3\%$ for asymptomatic and $<6\%$ for symptomatic patients$^{187,188}$. As procedural safety is increasing these figures cannot be considered as a reliable central estimate of risk but rather the upper acceptable limit$^{189}$. CAPTURE 2 which is a North American trial involving 180 hospitals and 459 operators$^{136}$, found an inverse relationship between adverse event rate and hospital patient volume as well as between individual experience and complication rate. A threshold of 72 cases was found to be necessary for consistently achieving stroke and death rates within the limits of current recommendations. Pooled results from recent EXACT and CAPTURE 2 studies show an adverse event rate comparable to CEA standards in population analogous with AHA guidelines (non octogenarians), namely 5.3\% for symptomatic and 2.9\% for asymptomatic patients. In octogenarians the death and stroke rate in symptomatic and
asymptomatic cases were 10.5 and 4.4%, respectively. A large single center trial conducted in Mercogliano, Italy including 1300 CAS patients using proximal endovascular occlusion during procedure report 30 day death and stroke rate of 1.4%, with independent neurological assessment. As C.J. White stated - If the results of Stabile et al. are reproducible, the strategy of adopting PEO devices for CAS will be a true game changer.

Table 8. 30-day event rates in CAS studies involving more than 1000 patients

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<tr>
<th>Name</th>
<th>Publ Year</th>
<th>n</th>
<th>Industry sponsored</th>
<th>Surgical high risk</th>
<th>EPD</th>
<th>Sympt Pat</th>
<th>D/S</th>
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<td>PEO CAS</td>
<td>2010</td>
<td>1300</td>
<td>No</td>
<td>Yes</td>
<td>Mand</td>
<td>49.8%</td>
<td>1.38%</td>
<td>3%</td>
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<td>2009</td>
<td>5297</td>
<td>Yes</td>
<td>Yes</td>
<td>Mand</td>
<td>13%</td>
<td>3.3%</td>
<td>6.2%</td>
<td>2.9%</td>
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<tr>
<td>EXACT</td>
<td>2009</td>
<td>2145</td>
<td>Yes</td>
<td>Yes</td>
<td>Mand</td>
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<td>7.0%</td>
<td>3.7%</td>
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<td>SVS</td>
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<td>1623</td>
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<td>45%</td>
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<td>2001</td>
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<td>5341</td>
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<td>3.6%</td>
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<td>CAPTURE 2</td>
<td>2007</td>
<td>3500</td>
<td>Yes</td>
<td>Yes</td>
<td>Mand</td>
<td>14%</td>
<td>5.7%</td>
<td>10.6%</td>
<td>4.9%</td>
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CAS consensus documents, on both sides of the Atlantic started to focus more on highlighting and credentialing the “turf war” that have plagued the advancement and technological development of this intervention since it’s inception. These documents are concentrating more on obtainable skills for an endovascular specialist in the field. Training which is not only relies upon catheter expertise but includes global comprehension of carotid disease management is highly desirable.

6. Conclusions

The results of our studies indicate that the use of covered stents for atherosclerotic carotid artery stenosis is feasible and is associated with a significantly lower intraprocedural embolization rate and low frequency of neurological complications in the periprocedural period and during long-term follow-up. The rate of restenosis in our trial was low.

We propose that manufacturers and users of carotid stenting devices should pay more attention to creating devices that manage to cover the embolicogenic plaque sufficiently,
pass safely even through subtotal stenoses, and nevertheless spare the external carotid artery.
Acknowledgements

Hereby I wish to express my deepest gratitude to everyone who has helped to complete this work.

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Last but not least I am deeply grateful to my father Dr. Miklós Szólics to keeping a critical eye on this work and tirelessly reviewing the thesis, and the rest of my family for continuous support and encouragement during the preparation of this dissertation.
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93. Davenport, P. & Tipping, P. G. The role of interleukin-4 and interleukin-12 in


APPENDIX