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Periinterventional risk of angioplasty and stenting of intracranial atherosclerotic arterial stenosis in 35 patients with recent transitory ischemic attack or stroke

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Abbreviations

AACE	American Association of Clinical Endocrinologists
ACA	Anterior cerebral artery
ADA	American Diabetes Association
AHA	American Heart Association
AHA/ASA	American Heart Association / American Stroke Association
AICA	Anterior inferior cerebral artery
ASA	American Stroke Association
BA	Basilar artery
BES	Balloon-expandable stent
BMI	Body-Mass-Index
BVS	Bioresorbable vascular scaffolds
CCA	Common carotid artery
CT	Computed tomography
CHD	Coronary heart disease
CTA	Computed tomography angiography / CT angiography
FDA	Food and Drug Administration
HbA1c	Glycated hemoglobin
HDL	High density lipoprotein
ICA	Internal carotid artery
ICVA	Intracranial vertebral artery
i.v.	Intravenous
LDL	Low density lipoprotein
MCA	Middle cerebral artery
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
mRS	Modified Rankin Scale
NIHSS	National Institute of Health Stroke Scale
PCA	Posterior cerebral artery
PICA	Posterior inferior cerebral artery
PTA	Percutaneous transluminal angioplasty
PTAS	Percutaneous transluminal angioplasty with stenting

SAMMPRIS	Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis
SES	Self-expandable stent
TIA	Transient ischemic attack
TOAST	Trial of Org 10172 in Acute Stroke Treatment
UKT	Universitätsklinikum Tübingen, University Hospital of Tübingen
VA	Vertebral artery
WASID	Warfarin Aspirin Symptomatic Intracranial Disease
WHO	World Health Organisation

1. Introduction

1.1 Pathogenesis and epidemiology of atherosclerosis

Atherosclerosis is a chronic systemic disease with a metabolic and inflammatory base. Inflammation plays a key role in the formation, evolution and complication of atherosclerotic lesions[1]. Multiple stimuli, including homocysteine, oxidized LDL-cholesterol, toxins, such as components of cigarette smoke and others, lead to an injury of the vessel wall, causing an immunologically mediated reaction. After an injury of the vessel wall, monocytes and lymphocytes are attracted to the surface by injured endothelial cells and migrate beneath the surface to a subendothelial localization. Through the interiorization of lipids, macrophages evolve into foam cells. Cytokines and growth factors are released, with the consequent proliferation of smooth muscle cells leading to the formation of the "fibrous plaque", reducing the diameter of the vessel lumen[1].

Atherosclerotic lesions of the coronary arteries, extra- and intracranial arteries supplying the cerebral blood flow and the arteries of the lower extremities are of special clinical importance[2]. Intracranial atherosclerosis is a very common disease. As age increases so does the prevalence, as it is found in over 80-90% of the elderly population. Contrary to common believe, however, atherosclerosis, in its different states, is evident from early age and onwards, being found in up to 30% of individuals of 20 and 29 years of age[3]. The state of the present lesion advances with age, and while fatty streaks and fibrous plaques are already evident in the third decade of life, intimal necrosis and thickenings are found in individuals of increased age[4].

1.2 Risk factors

A variety of conditions and habits are known to be risk factors for atherosclerosis of the intracranial arteries. Commonly, we distinguish non-modifiable risk factors, such as advanced age, male gender, race and ethnicity, with a higher prevalence of intracranial atherosclerosis among the Hispanic, African American, Chinese, Korean and Japanese population, and modifiable risk factors, such as hypertension, diabetes, hyperlipidemia and, of minor

importance, tobacco and alcohol abuse[3,5,6,7,8,9,10,11,12,13]. Especially among young adults, diabetes, hypertension, smoking and heavy alcohol consumption are major risk factors for stroke[14,15]. Tobacco abuse and hypertension are two of the most modifiable of risk factors and are particularly strong risk factors among young African Americans[16]. Hypertensive subjects, regardless of smoking status and gender, have twice the incidence of stroke, and lowering blood pressure has been shown to significantly reduce the risk of stroke[17,18].

The male gender acts as an independent risk factor for atherosclerosis and subsequently stroke. This is partly explained by the absence of the hormonal protective factor found in women. The protective role of estrogen, through multiple mechanisms, is well established[19,20,21]. Its actions include, amongst others, the hepatic expression of genes responsible for coagulation and fibrinolytic proteins, the alteration of the serum lipid concentration, the antioxidant system and the production of other vasoactive molecules acting on the circulatory system, providing systemic protection from atherosclerosis and, subsequently, cardiovascular disease[19]. Another factor may be the difference in lifestyle between men and women. Modifiable lifestyle risk factors include nutrition, the habit of smoking, and regular physical exercise[22]. With higher proportions of individuals with a smoking habit, elevated alcohol consumption and higher BMI, the male gender has an elevated cardiovascular risk due to lifestyle determinants[22]. Women are known to be more likely to suffer from silent infarction[23]. This difference in the incidence of silent infarction may be explained by smaller infarction and subsequent absence or subtlety of symptoms, or the need for a better approach to diagnosing and treating stroke amongst women[24]. However, other authors describe a similar incidence of silent stroke for male and female individuals[23].

While it is well established that smoking significantly increases the risk of stroke in general and brain infarction specifically, it is nowadays often considered of minor importance[11,12,17]. The Framingham study, however, showed that taking into account other pertinent cardiovascular risk factors, smoking made a significant independent contribution to the risk of stroke in general, and brain infarction specifically[17]. The increase of risk was more pronounced in women

than men. With an overall relative risk of stroke associated with cigarette smoking of 1.5, the relative risk of cerebral infarction amounts to 1.9. As age increases, the importance of smoking as a risk factor for stroke decreases, with a relative risk for stroke of 2.9 among smokers of under 55 years of age and 1.1 for smokers over 75 years of age[15]. The risk of stroke increases as the number of cigarettes smoked a day increases; with the relative risk of stroke in heavy smokers (> 40 cigarettes / day) amounting to twice the relative risk of stroke in light smokers (< 10 cigarettes / day)[15,17]. However, it also showed a decreasing stroke risk after complete cessation of cigarette smoking, with a significantly reduced stroke risk after two years, and reaching the level of nonsmokers by five years after cessation[17].

1.3 Cerebral blood flow

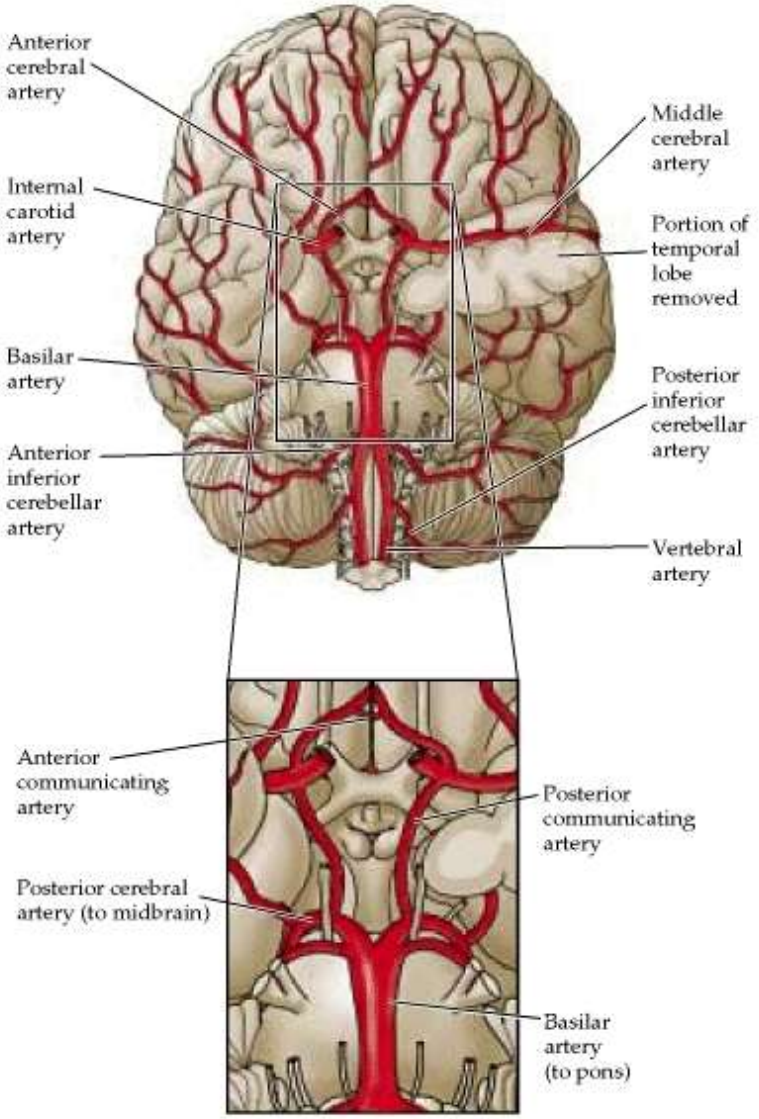
The brain is supplied with blood and nutrients from two sources; the internal carotid arteries (ICA), which arise by the bifurcation of the common carotid arteries (CCA), and the vertebral arteries (VA), which arise from the subclavian arteries and join on the ventral surface of the brainstem at the level of the pons, forming one singular basilar artery (BA)[25].

The BA and ICA join in an arterial formation at the base of the brain, called the "Circle of Willis"[25,26,27]. This connection of the anterior and posterior cerebral vessels aims to secure a continuous blood supply to any region of the brain even in the case of the occlusion of one of the major arteries[25,26]. Here, the ICA branches into two major cerebral arteries, the anterior cerebral artery (ACA) and middle cerebral artery (MCA), and the posterior cerebral arteries (PCA) and the anterior and posterior communicating arteries (ACA and PCA, respectively) arise[25].

Cerebral blood flow is further classified into the anterior and posterior circulation. By means of the ACA and MCA, the blood supplied by the ICA forms the anterior circulation of the brain, supplying the forebrain with blood. They give rise both to branches supplying the cortex, as well as branches penetrating the deeper parts of the brain, such as the basal ganglia and thalamus. The posterior circulation of the brain comprises the PCA, BA and VA

along with their respective branches, and supplies the posterior cortex, midbrain and brainstem with blood. In the brainstem, blood supply is established through midline, lateral and dorso-lateral arteries, which respectively supply medial structures, lateral structures and the dorso-lateral structures and cerebellum. Among the dorso-lateral arteries are the long circumferential arteries, responsible for the blood supply of distinct regions of the medulla and pons; the posterior inferior cerebral artery (PICA) and anterior inferior cerebral artery (AICA)[25].

The cerebral arteries and the Circle of Willis are shown in Graph 1.



Graph 1: The Circle of Willis and the cerebral blood supply
(Adapted graph, source: Purves et al. 2001, Neuroscience, 2nd edition.[25])

1.4 Stenosis of the intracranial arteries

The narrowing of the lumen of an artery by the described atherosclerotic lesion leads to stenosis. The grade of stenosis is commonly measured in transcranial duplex sonography, however CT angiography (CTA) and MR angiography (MRA) are widely used for measurement, too[28]. In Germany, the severity of stenosis used to be measured during transcranial duplex sonography applying the Doppler ultrasound ECST criteria, measuring the relation of the stenotic lumen to the proximal lumen before stenosis and differentiating between low grade (1-69%), moderate grade (70-79%), and high grade stenosis (80-99%)[29,30]. Now, however, the internationally accepted NASCET criteria are commonly applied, measuring the severity of stenosis in relation to the distal lumen of the artery and classifying it as low grade (1-49%), moderate grade (50-69%) and high grade (70-99%)[29,30].

Depending on the location of the affected artery supplying cerebral blood flow, atherosclerotic stenoses of these arteries are classified into intracranial, when located in the intracranial segments of the ICA, MCA, ACA, PCA, BA or intracranial vertebral artery (ICVA), and extracranial when located in the CCA or extracranial segments of the ICA or VA[25,31].

1.5 Transient ischemic attack and stroke

While atherosclerosis of the intracranial arteries is often asymptomatic, when significant stenosis forms, it can lead to severe damage[9,32,33]. Brain tissue in general, and neurons specifically, are very sensitive to oxygen deprivation due to their high metabolic rate, and consequently more sensitive than other types of cells of the human body with lower rates of metabolism[25]. Therefore, a compromised blood supply to the tissues of the brain is very likely to cause transient, or permanent damage due to cellular changes, and / or degeneration consecutive to the deprivation of oxygen and glucose, leading to severe neurologic deficits[9,25,32,33].

Intracranial atherosclerotic stenosis has long been known to cause transient ischemic attack (TIA) and stroke. In addition, plaque rupture, in-plaque

hemorrhage, thrombus formation and subsequent cerebral emboli are consequences of severe cerebral atherosclerotic disease[2].

Over the last few years, the definitions of the commonly used phrases of TIA and stroke have been debated. Stroke, a phrase used for centuries, was defined by the World Health Organization decades ago as “rapidly developing clinical signs of focal (or global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin"[34]. In the 1950s, the term TIA was first introduced, referring to "temporary vascular-related episodes of brain dysfunction that would not qualify as strokes", and was further defined by an Ad Hoc Committee on Cerebrovascular Disease in 1975 as “episodes of temporary and focal dysfunction of vascular origin, which are variable in duration, commonly lasting from 2 to 15 minutes, but occasionally lasting as long as a day (24 hours)", leaving "no persistent neurological deficit"[35,36]. However, with an improved understanding of ischemia due to advances in basic science, neuropathology and neuroimaging, the American Heart Association (AHA)/American Stroke Association (ASA) have considered the stated definitions as obsolete, considering especially the 24-hour inclusion criterion inaccurate and misleading[35]. In order to provide more accurate definitions which take into account modern scientific knowledge and imaging techniques, the AHA/ASA issued new definitions of TIA and ischemic stroke, defining TIA as "a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction" in 2009, and defining ischemic stroke as "an episode of neurologic dysfunction caused by focal cerebral, spinal, or retinal infarction" in 2013[35,37].

The TOAST classification denotes 5 subtypes of ischemic stroke[38]. Besides large-artery atherosclerosis, they include cardioembolism, small-vessel occlusion, stroke of other determined etiology and stroke of undetermined etiology[38]. Intracranial atherosclerotic disease leads to ischemic stroke through several of these mechanisms and accounts for up to 10-15% of all strokes[39]. It

causes stroke through perfusion failure posterior to the stenosis, and, in cases where the decreased blood supply caused by the stenosis by itself is not found sufficient to cause ischemia, through the formation of in-situ thrombosis on the stenotic site, as an embolic source or by occlusion of small branch vessels by the growing plaque[13,31,39].

Patients suffering from TIA or stroke are at great risk of suffering from recurrent stroke within a short period of time after, and stroke recurrence is a major threat to any patient with a history of prior stroke[40,41]. The state of the atherosclerotic lesion strongly influences the patient´s prognosis. In patients with ulcerated stenotic lesions, the rate of ipsilateral stroke recurrence is 11 times higher than with non-ulcerated lesions[42]. Overall, the risk of a recurrent stroke after suffering from a TIA or minor stroke is much higher than commonly stated, with a risk of recurrent stroke after TIA and minor stroke of 8.0% and 11.5% at 7 days, of 11.5% and 15.0% after one month and 17.3% and 18.5% at three months, respectively[43].

With an increased life expectancy and a high mortality and disability rate due to stroke, it is of constantly growing importance in the medical world[44,45]. While in some Eastern European countries, stroke mortality is alarmingly high and keeps increasing, in Western countries it has decreased continually over the last decades[44]. Stroke has been one of the most common causes of death in Germany for several decades. In 1980, only acute myocardial infarction outnumbered cerebrovascular accidents as the most common cause of death[45]. The following decades experienced a descending death rate by stroke due to the advances in stroke management. As a result of a growing prevalence of cardiac conditions as well as conditions of the bronchus and lungs, stroke slowly decreased in rank on the list of the most common causes of death. From 86.6 deaths per 100.000 inhabitants in 1980, the number of deaths due to stroke decreased to 26.4 deaths per 100.000 inhabitants in 2010 and keeps further decreasing[45,46,47,48]. Despite its decreasing importance in mortality statistics, it was still the 6th most common cause of death in Germany in

2011[46,49]. These statistics, however, only account for fatal strokes. Although improved risk factor control and advances in stroke management have led to an important decrease in stroke mortality, the overall incidence of stroke has decreased in a disproportionately lower measure[50]. Internationally, with an ageing population and the successful reduction of stroke mortality, combined with an impossibility of equally reducing the overall stroke incidence, an increase in the prevalence of stroke survivors is observed[51]. In Germany, the average survival after stroke is more than 6 years for women and more than 8 years for men[51]. With lower death rates, the number of patients with disability and impairment due to stroke has increased and the consequences of stroke remain devastating on a personal and public level. Stroke related disabilities lead to a considerable decrease in quality of life[52]. The inability to work due to disability and diminished social activity are both direct consequences of stroke, which lead to an increase in depression among stroke survivors[52]. Female patients cope worse with post-stroke recuperation in the dimensions of mobility, physical function, independence, discomfort, and anxiety or depression[52,53,54,55]. Additionally, high incidences of stroke lead to important financial expenses for the public health system. In 2004, the total financial burden of first ischemic stroke to the German Health System was 7.1 billion Euro. The estimated undiscounted lifetime cost per case amounts to 54.552 Euro in men and 47.596 Euro in women[51]. However, the number of stroke patients and healthcare costs of strokes in Germany is expected to keep rising continuously, and the national projection of direct costs for the years 2006 to 2025 is of 108.6 billion Euro[51]. Hospital expenses and rehabilitation programs, the inability to work, the need for support due to dependencies on others for activities of daily living and the consequences of depression create a financial burden on society that calls for an improvement in stroke prevention, treatment and rehabilitation[51].

1.6 Treatment of intracranial stenosis

In recent years, the optimal treatment of symptomatic intracranial artery stenosis has been widely discussed. Since intracranial atherosclerotic disease is very common, clear recommendations are warranted. Several studies addressed this issue.

1.6.1 Medical treatment

The traditional approach to treat intracranial atherosclerosis consists of a combination of pharmacological treatment and the control of vascular risk factors.

Pharmacological management includes several key drugs, mainly antiplatelet drugs, including Aspirin and Clopidogrel, and oral anticoagulation, with Warfarin or Marcumar. Currently, Aspirin and Warfarin are used for stroke prevention in intracranial atherosclerotic stenosis in the United States[56]. However, patients treated with Warfarin have higher rates of adverse effects, such as death from vascular as well as non-vascular causes, major hemorrhage and myocardial infarction, than those treated with Aspirin[57,58]. With its easy administration, similar efficacy and superior safety profile, antiplatelet therapy is generally recommended over anticoagulation[4,59].

Risk factor control is of crucial importance in the treatment of patients with intracranial stenosis and includes the pharmacological and non-pharmacological control of modifiable risk factors, such as dyslipidemia, diabetes, and hypertension, as well as weight control and physical exercise. For instance, hypertension not only doubles the initial risk of stroke regardless of smoking habit and gender, it also leads to a worse outcome in stroke patients, acting as an independent prognostic factor for poor outcome due to higher rates of early recurrence and death, possibly because of the development of cerebral edema[17,60,61]. Correct medical treatment of the condition is essential, as an excessively low blood pressure secondary to antihypertensive medication also acts as an independent prognostic factor for poor outcome of stroke patients, presumably because of an increased rate of death due to coronary heart

disease (CHD)[61]. For individuals over 55 years of age, the systolic blood pressure is of higher importance than the diastolic blood pressure and the recommended target systolic blood pressure established by the World Health Organisation (WHO) is 140 mmHg or less for both genders[62,63]. For diabetic patients, due to a clear benefit of further lowering the blood pressure, the recommended target blood pressure is 130/80 mmHg[60,62,64]. While high levels of serum glucose or HbA1c are not generally acknowledged as a risk factor for intracranial atherosclerosis or stroke, the positive effects of successfully controlling serum glucose and HbA1c levels on the whole system are well established[65]. The levels of HbA1c recommended for disease control and prevention of long-term complications among diabetic patients by the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) are of less than 6.5% and less than 7.0% respectively[66,67].

In Germany, there is no specific program for a structured control of risk factors and the implementation of the opportune premises is left to the patient and treating doctor.

There is evidence for a particularly higher risk of recurrent stroke for patients with symptomatic intracranial arterial stenosis of 50-99% on medical therapy only[57,58]. In the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial, 1.8 years after a stroke, 22.1% of patients treated with aspirin exclusively had reached a primary endpoint, defined as ischemic stroke, brain hemorrhage or death from another vascular cause[57]. However, when a strict lifestyle modification program for intensive management of risk factors, such as overall cholesterol, LDL- and non-HDL-cholesterol blood levels as well as diabetes, smoking cessation, excess weight, and insufficient exercise, forms part of the treatment, the outcome proves to be much more favorable[68,69].

1.6.2 Interventional treatment

Aiming for a better outcome and lower complication rates, neuroradiologic procedures have been developed to treat symptomatic intracranial arterial stenosis. Currently, the two main pillars of interventional treatment are

percutaneous transluminal angioplasty (PTA) and percutaneous transluminal angioplasty with stenting (PTAS).

During PTA, balloon-angioplasty of the stenotic artery is performed with an angioplasty balloon generally slightly undersized to the original vessel diameter. PTA as primary treatment of intracranial stenosis of 50-99% has a favorable outcome with a 5-year stroke-free survival of up to 83%. However, due to restenosis, additional neurologic symptoms (TIA or stroke), or because the result of the original treatment is considered improvable, a high number of patients (19%) undergo treatment for the previously treated lesion during follow-up, repeating balloon-angioplasty or receiving a stent[70].

PTAS has been the object of medical investigation for several years. It consists of the performance of PTA of the stenotic site for predilatation and additional insertion of a stent. With intracranial PTA and PTAS evolving from procedures and devices originally designed for and used in coronary interventions, different stenting systems are available. Commonly used are balloon-expandable stent systems (BES), such as the Pharos Vitesse (Micrus Endovascular Corp.) and self-expandable stent systems (SES), such as the Wingspan Stent System (Stryker Neurovascular, Freemont, CA, USA, formerly Boston Scientific Neurovascular). Bare metal stents (BMS) and drug-eluting stents (DES) of the first and second generation are available for application. The great advantage of self-expandable devices is their high flexibility, allowing for non-traumatic expansion and non-traumatic adaption of the stent to the differences in diameter of the treated vessel[71].
The Wingspan Stent System with the Gateway PTA Balloon Catheter is currently the only FDA-approved intracranial stent device. The applied Gateway PTA-Balloon is available in various diameters and lengths, as well as the Wingspan Stent System, a 3.5-Fr nitinol over-the-wire, self-expanding stent, which is available in various diameters (from 2.5 to 4.5 mm) and lengths (from 9 to 20mm)[72]. It was initially approved by the FDA in 2005 for its use in patients with symptomatic intracranial stenosis refractory to antithrombotic therapy[73].

The Pharos Vitesse, while Conformité Européenne (CE) Mark-approved in Europe, is currently limited to investigational use in the US. It is a cobalt-chromium, open-cell, silicon carbide-coated balloon-expandable stent[74].
Multicenter, prospective and randomized controlled trials were conducted for both devices. The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial used the Wingspan Stent System, while the Vitesse Intracranial Stent Study for Ischemic stroke Therapie (VISSIT Study) used the Pharos Vitesse balloon-expandable stent, comparing PTAS with best medical therapy to medical therapy alone[68,74]. Both trials were stopped early due to interim analysis that demonstrated a significantly higher 30-day risk of stroke or death for patients in the endovascular treatment arm[68,74].

Studying its application in intra- and extracranial stenosis, PTAS has a very high overall delivery rate for stent placement (98%). Due to technical challenges caused by more difficult access and higher tortuousness, its delivery rate proved to be much lower in intracranial stenosis exclusively (89.7%). The periprocedural complication rate is also higher in procedures performed on an intracranial localization[75]. Studying the reasons of unsuccessful stent placement using the Wingspan stent system in PTAS of intracranial atherosclerotic stenosis, the authors distinguish delivery failure, where the system cannot be delivered into its proper position for the stenotic lesion, deployment failure of the stent, where in spite of the proper positioning of the Wingspan system the stent cannot be deployed, and retrieval failure, where the retrieval of the dual tapered tip after stent deployment cannot be performed, due to friction between stent and tip[76]. Among the possible reasons for these difficulties are the tortuousness of the cerebral arteries proximal and distal to the stenosis and the bulky profile of the tip of the stent system[76]. Consequently, depending on the location, one stenting system may present advantages or disadvantages over another. However, systematic research reviews have not found any significant difference in periprocedural complication rates between studies using a balloon-mounted stent system and those using a self-expanding stent[77].

As PTAS is of fairly recent introduction into general practice, the restenosis rate of intracranial stents has not been sufficiently studied. The occurrence of restenosis after inserting a self-expandable stent seems to be higher than when using a balloon-mounted stenting system, although restenosis is more likely to be symptomatic when using a balloon-mounted stent[77]. The rate of short-term restenosis is encouragingly low, but further studies will be necessary to determine the long-term outcome[75].

Initially, a considerable reduction to the degree of stenosis and a remarkably low stroke or death rate (4.5% at 30 days, 7.0% at 6 months) in international studies, such as the Wingspan Study, gave way to a broader use of PTAS in patients with high-grade intracranial atherosclerotic lesions refractory to medical treatment[78]. With a favorable outcome, and an apparently low complication rate compared to the complication risk of the same condition treated purely medically assessed in other trials, the procedure seemed to be a breakthrough in treating intracranial stenosis[57,78].

However, the SAMMPRIS trial, a large clinical trial which compared aggressive medical management alone to aggressive medical management in combination with PTAS to assess the superiority of an interventional treatment approach, resulted in important safety concerns[68]. The medical management of all patients consisted of dual antiaggregation and management of primary and secondary risk factors. The novelty of the aggressive medical treatment plan compared to the traditional approach was the inclusion of an individualized lifestyle modification program, focusing on exercise, correct nutrition, weight management and tobacco smoking cessation. With an otherwise identical treatment, a subgroup of patients additionally had PTAS performed on the qualifying lesion using the Wingspan stent system[68,69].
Against its investigators´ initial hypothesis that PTAS would result in a significant risk reduction for stroke recurrence in patients with symptomatic severe intracranial atherosclerotic stenosis, the results suggest a superiority of non-invasive medical treatment over PTAS in the short- and long-term. In the

initial 30 days after the procedure, 14.7% of PTAS patients and 5.8% of conservatively treated patients reached a primary endpoint. A large number of PTAS patients suffered from symptomatic brain hemorrhage after the procedure. Even after the critical periprocedural time span of 30 days, PTAS did not result in an improved outcome for patients with severe stenosis of the intracranial arteries. The proportion of patients with endpoints beyond 30 days of enrollment was of 10% in both groups. At 32.4 months, 23.9% of PTAS patients and 14.9% of medically treated patients had reached a primary endpoint[68,69].

In summary, the SAMMPRIS trial showed an unexpectedly high periprocedural complication rate for patients treated with PTAS and an unexpectedly low overall complication rate for those treated with aggressive medical treatment alone, who had a much lower short-term and consequently overall risk for any stroke and major hemorrhage. The investigators therefore conclude that, with equal complication rates beyond 30 days after the intervention, the evident superiority in short-term outcome makes aggressive medical therapy preferable to aggressive medical therapy plus PTAS in patients with symptomatic atherosclerotic intracranial stenosis[68,69].

In 2012, in response to the discouraging data on the outcome of patients treated with PTAS, the FDA limited the application of the Stryker Wingspan brain stent system to patients between 22 and 80 years that have had two or more strokes over 7 days prior to the planned treatment date due to severe stenosis (70-99%) of an intracranial artery despite medical treatment[79].

Improvements to the procedure´s safety profile assuring a lower risk of short-term complications would be necessary to make it a viable treatment strategy for intracranial stenosis. Thorough analysis of the available data might help identify high-risk patients and include only those patients in an interventional treatment approach, for whom a favorable outcome is expected.

1.7 Current scientific investigation

Intracranial PTA and PTAS have evolved from procedures and devices originally designed for and used in coronary interventions. Advances in coronary interventional technology have the promise for future developments to improve treatment of intracranial atherosclerotic stenosis, thus reducing periinterventional and long-term adverse events.

Literature on cardiologic interventions describes the use of the cutting balloon, which is designed with sharp blades to create regular longitudinal surgical cuts from the luminal surface and into the medial layer to limit irregular intimal injury and elastic recoil for treating in-stent restenosis as well as de-novo small vessel disease of coronary arteries[80]. Safety and durability in treatment of carotid artery restenosis with cutting balloons has been demonstrated[81,82].

Drug-eluting balloons, initially developed for coronary arteries, have already found applications in the treatment of in-stent restenosis of the carotid artery[83,84]. Covered with antiproliferative agents, such as paclitaxel, sirolimus or zotarolimus, these balloons are kept inflated for 30-60 seconds to allow for the adequate transfer of the antiproliferative agent during PTA[72]. Studies have shown the balloons to be successful in the treatment of in-stent restenosis, preventing restenosis in most patients and showing a significant increase in time to restenosis when recurrent in-stent restenosis does ultimately develop[85].

A new coating technology called "Shield Technology" (Medtronic), has been developed for flow-diverting stents and is currently used exclusively for the treatment of intracranial aneurysms[72]. It is now in early stages of clinical trials[72]. Shield Technology consists of the coating of the stenting material with phosphorylcholine, which is an integral component of the membrane in red blood cells and has demonstrated resistance to platelet adhesion and intimal hyperplasia[86,87]. Early studies have shown a reduced thrombogenicity of deployed stents[88]. This coating may potentially be used on existing stents for intracranial atherosclerotic disease[72].

With persisting concerns regarding the long-term adverse events after PTAS due to in-stent-stenosis and stent fracture, bioresorbable vascular scaffolds (BVS) have been developed[72]. BVS provide a mechanical support and drug

elution for a limited amount of time, after which they are completely reabsorbed[72]. However, a large meta-analysis of six randomized clinical trials, comprising data from 3738 patients with percutaneous coronary interventions, compared BVS to second-generation DES with the results indicating a higher risk of in-stent thrombosis in the BVS group[89]. This has been suspected to be due to the weaker structure of the polymer construction compared to the metal construction, thus requiring thicker bulky struts in BVS in order to improve tensile strength, which still remains inferior to DES[90].

In response to these results, biodegradable metallic stents, made of zinc or magnesium alloys for bioabsorbability, providing the tensile strength of metal, are being investigated. Currently used exclusively in coronary interventions, these biodegradable metallic stents may be incorporated into stents designed for the intracranial circulation[91].

Another approach to addressing late in-stent thrombosis has been to improve the endothelialization of the implant, avoiding the elution of drugs that may inhibit neointimal tissue growth and delay arterial healing in currently used DES[72].

Having recently received CE approval in Europe, the Combo stent (OrbusNeich) uses anti-CD34-antibody coating on the luminal surface with sirolimus drug elution on the abluminal surface, with the objective of combining the benefit of both types of therapy[72]. Other alternatives currently under investigation include (i) a combination of heparin and type IV collagen to enhance the endothelialization of a titanium surface[92], (ii) a combination of anti-CD34-antibodies and vascular endothelial growth factor in order to coat stainless-steel sheets to attract endothelial progenitor cells and promote differentiation[93], (iii) oligonucleotides to promote surface endothelialization[94], and (iv) gene-eluting stents, incorporating genes such as nitric oxide synthase, vascular endothelial growth factors and tissue inhibitor of metalloproteinases-3 to promote endothelialization and reduce neo-intima formation[95].

1.8 Objective of the study

At the University Hospital of Tübingen (Universitätsklinikum Tübingen, UKT), patients with symptomatic intracranial atherosclerotic stenosis are routinely treated by PTAS.

In light of the stated publications, the necessity of reviewing our own patients' data arose, to clarify uncertainties and help identify the best strategy for the clinical management of our patients with severe atherosclerotic stenosis of the intracranial arteries, focusing on maximizing the safety of the treatment and outcome.

To create comparable data under the conditions and treatment options at our center, along with the evaluation of the security profile and risks of the procedure, a retrospective study was designed to evaluate the short-term outcome of patients treated with PTAS for severe intracranial atherosclerotic stenosis at our center between 2007 and 2012.

Specifically, we addressed the following questions:

1. What is the short-term risk and what are the observed complications of PTAS of symptomatic intracranial arterial stenoses at UKT?
2. Does the collected data coincide with international literature on the subject, especially the SAMMPRIS trial results, and what are possible differences in the patient and treatment characteristics?
3. Should PTAS be the treatment of choice for our patients with severe atherosclerotic stenosis of the intracranial arteries?

2. Methods

In this chapter, after a brief outline of the research project and the performed study, the applied criteria and methods by which our study was conducted will be explained.

2.1 Research project and study design

The primary objective of our research project was to study the short-term outcome of all patients treated with PTAS for severe intracranial atherosclerotic stenosis and recent stroke or TIA at the Department for Diagnostic and Interventional Neuroradiology at the University of Tübingen.

Permission for a retrospective study was obtained by the institutional review board. A list of all patients who underwent PTAS at our institution from July 2007 through December 2012 (both included) was created. The hospital´s records on the clinical course of these possibly eligible patients was analyzed. For this, we reviewed all available documentation and clinical data on the conditions prior to treatment, during treatment and the short-term follow-up. For data collection, we applied previously defined parameters as listed below. For comparability, the criteria of data collection and analysis were based on those of the SAMMPRIS trial[98].

With the defined inclusion and exclusion criteria, I was able to identify and include 35 patients of the original list of 200 possibly eligible patients in this study, while in part simultaneously, another doctoral candidate, Toni Silber, was able to identify 46 patients for the conduction of his doctoral thesis[a,96]. The distribution of patients was regardless of individual characteristics of the patients or the intervention.

The respectively collected data form the basis for the development of the respective study subject of both doctoral theses. While he was not part of the elaboration of the study here presented with the specified sample of 35 patients, Toni Silber separately worked on his doctoral thesis on his patient collective of

[a] Silber reports a patient sample of n=34 evaluated by another doctoral candidate (Silber, 2015; p. 20), however n=34 only applies to the available information on applied stenting devices, while a total of 35 patients were included in the here presented study.

46 patients which has previously been published[96]. Raw data of the present study has been processed for a paper published on his study subject by Toni Silber in 2014[97].
Both doctoral theses and the published paper originate from the same study project with a joint systematic standardized data collection and the same therapeutic procedure - PTAS in intracranial atherosclerotic stenosis - as their subject of further study[96]. Therefore, although product of strictly separate statistical analysis, textual and content development and with a different study focus, both thesis share similarities, such as their conception, composition and parts of their respective structure.

For the here presented study, data analysis was performed using the previously specified evaluation. The subsequent further statistical and textual processing of the raw data of the 35 patients included in our study lead to the results presented later on.
The present study analyzes the short-term complication rate of PTAS in patients with recent stroke or TIA due to severe intracranial stenosis. It focuses in detail on the analysis of the comorbidities of the patient population and possible implications for the outcome of our patients. It will then continue with an analysis of the comparability and a detailed comparison of our results and the results of the SAMMPRIS trial[68,69,98]. In case of different complication rates between the two studies, we attempt to elaborate possible explanations by analysing the differences and similarities identified before.
New strategies to improve the established therapeutic approach, as well as possible alternatives are discussed in the context of the acquired information. Finally, a conclusion is made based on our own results and the available literature.

2.2 Treatment procedure at UKT

Patients were either admitted directly to our center or referred to our center by other hospitals. After admission, physical examination was performed and the severity of the neurological deficit was determined according to the National

Institute of Health Stroke Scale (NIHSS). If not provided on admission, neuroimaging was performed to quantify the severity of stenosis, using either CTA or MRA. Doppler ultrasound of the arteries supplying blood to the brain was performed in all cases.

As part of the standard treatment routine, prior to the intervention, the patients' responder statuses to Aspirin and Clopidogrel was tested. All patients were treated with 100mg per day of Aspirin on a continuous basis, and 75mg per day of Clopidogrel for a period of 90 days after the procedure. Patients with a non-responder status to Clopidogrel received a higher dosage of Clopidogrel, prescribing 150mg per day for 90 days. Patients without prior antithrombotic treatment with Clopidogrel received a loading dose of 600mg Clopidogrel prior to the intervention. All other pertinent pharmacological treatments, such as antihypertensive, antidiabetic or antihyperlipidemic agents were administered.

After the indication was confirmed by neuroimaging and written consent given, PTAS was performed under general anesthesia at the Department for Diagnostic and Interventional Neuroradiology, University of Tübingen.

For PTAS, the vascular system was accessed with a 5 to 6F guiding catheter most commonly in the femoral artery, although a radial or brachial artery approach is also possible[98]. To prevent clotting with the risk of subsequent thromboembolism during the procedure, intravenous heparin was given[96,98]. Depending on the territory of the suspected stenosis to be treated, the catheter was placed in the ACI or AV. The presence of severe stenosis was confirmed by arteriographic imaging. For PTA, the lesion was carefully crossed with a microwire and dilated with a balloon catheter[98]. Subsequent stenting was performed by delivering and deploying a SES or BES to the treated stenotic site. The BES, premounted on a slightly longer PTA balloon catheter, was deployed to the stenotic site by dilating the balloon, and thus expanding the stent[74]. The SES, preloaded on a delivery system, was introduced to the treatment site after predilatation of the stenotic lesion[99]. The puncture site was compressed for several hours to avoid local complications such as bleeding or the formation of pseudoaneurysm[100].

After the procedure, patients were transferred to our Intensive Care Unit or Stroke Unit for further monitoring and for periodical evaluation by trained neurologists. Procedural success was evaluated by a control CTA and after recovering consciousness, all patients were again evaluated by trained neurologists. Transcranial Doppler ultrasound was performed 24 hours after the procedure to assess the blood flow rate of the treated artery. Patients suffering from adverse events were evaluated by the corresponding neurologist and assessed by cranial MRI or CT. Patients presenting non-neurological symptoms were additionally evaluated by the corresponding specialist.

After stabilization, patients were transferred to the general neurologic ward and depending on their clinical course discharged into a rehabilitation facility later. Further follow-up was provided by the center as indicated by the clinical protocol and by the treating doctor´s judgment.

None of the treating specialists and other staff involved in patient care were aware of the conduction of this study.

2.3 Inclusion and exclusion criteria

Eligible patients were treated with PTAS for a symptomatic high-grade atherosclerotic stenosis of a major intracranial artery, which is defined as the narrowing of the lumen of the artery by 70%-99% according to the NASCET criteria due to atherosclerotic changes in the arterial wall[29,30]. Possible locations were the intracranial segments of the ICA, ICVA, MCA, ACA, BA and PCA. All patients had experienced a TIA or stroke secondary to the treated stenosis and underwent PTAS within 30 days after the qualifying event.

Patients were thus excluded if they had PTAS performed on a non-stenotic lesion, such as an aneurysm in an intracranial artery, or if a condition of non-atherosclerotic nature was defined as the cause of stenosis, such as the dissection of an intracranial artery or an inflammatory disease (for example cerebral angiitis).

Furthermore, we excluded patients with a complete obstruction of the artery, as well as patients with stenosis of less than 70%.

To avoid the uncertainty of possible sources of complication, patients with more than one stenosis in the same blood supply region were excluded, as well as those who received PTAS for more than one stenosis in different arteries within the 30 day observation period and all patients who had received thrombolytic therapy 24 hours prior to the procedure.

Due to the retrospective nature of our study and the creation of the list of possibly eligible patients by administration, only patients who successfully underwent PTAS were sure to be included in this list. Patients initially intended for PTAS but who did not undergo PTAS as planned or where the intervention was stopped before successful stenting were potentially not included in the list. We therefore decided to exclude these patients altogether to avoid faulty data and a selection bias.

In cases lacking information on the follow-up examinations, the hospital the patient was transferred to was contacted to investigate the patient´s progress. If it was impossible to obtain sufficient information on the established 30-day period, the patient was excluded to avoid incomplete or faulty data.

2.4 Studied items

In order to achieve maximum comparability with international studies such as the SAMMPRIS trial, we analyzed the same items and evaluated patient data by the same criteria[68]. All available hospital documentation and discharge reports, including those from referring hospitals, were analyzed to assess the following criteria for all eligible patients:

2.4.1 Patients' baseline characteristics

To characterize each patient, we registered gender, date of birth and age at procedure.

2.4.2 Risk factors

To accurately characterize the patient´s health status and cardiovascular risk, the presence of comorbidities and known risk factors for atherosclerosis and stroke at the time of the qualifying event were registered. A history of arterial

hypertension, diabetes, lipid disorders of the blood, CHD, congestive heart disease, atrial fibrillation, a smoking habit and a history of stroke other than the qualifying event were recorded.

The habit of smoking of the patient was documented. Patients were categorized into present smokers, past smokers and non-smokers. Known to be a strong risk factor for cardiovascular diseases and part of the determination of the vascular risk of a patient, the smoking habit was specifically documented at hospitalization. Patients with no information on their smoking history in the hospital documentation were therefore taken as non-smokers.

Patients previously not diagnosed with diabetes presenting a level of glycated hemoglobin (HbA1c) of 6.5% or higher were considered diabetic, as defined in the executive summary of the ADA[101].

A history of stroke other than the qualifying event was defined as any ischemic events not related to the stenosis subject to this study.

The intake of oral antithrombotic treatment with Aspirin and/or Clopidogrel, or oral anticoagulation with Marcumar, Dabigatran or Rivaroxaban at the time of the qualifying event was documented.

2.4.3 Biochemical and physical parameters

For further details on the patients' health status, a number of physical and biochemical parameters were registered. Using the documented height and weight at hospitalization, the Body-Mass-Index (BMI, body mass / body height in kg/m²) was calculated. We registered the last measured blood pressure (systolic/diastolic in mmHg) before the beginning of the procedure. From the patients´ laboratory record, we gathered the most recent blood levels, using levels measured at any point, preferably at the time of the qualifying event. Blood lipids analyzed were total cholesterol, LDL- and HDL-cholesterol (in mg/dL). The non-HDL-cholesterol was calculated by the provided total cholesterol and HDL-cholesterol levels. In case of an incomplete blood analysis not specifying all named parameters, in which case overall cholesterol and HDL-cholesterol were obtained from different blood analysis, non-HDL-cholesterol could not be calculated. As a biochemical marker for the level of

therapeutic control of diabetes, the most recent value of glycated hemoglobin (HbA1c in %) in blood was registered.

2.4.4 Stenotic artery

The localization of stenosis was analyzed, identifying the affected artery or points of confluence of several affected arteries and specifying the hemisphere. The stenosis was consequently listed as in the intracranial segment of the left or right ICA, the left or right ICVA, the left or right MCA, the left or right ACA, the left or right PCA, the BA, or any points of confluence between either of the stated. The degree of stenosis in percentage was registered applying the NASCET criteria[29,30].

2.4.5 Qualifying event

Any kind of neurologic deficit caused by the treated stenosis experienced during a period of 30 days prior to the procedure was considered a qualifying event. The definitions of TIA and stroke applied were those released by the AHA/ASA, as above stated, defining TIA as "a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarctation", and defining ischemic stroke as "an episode of neurologic dysfunction caused by focal cerebral, spinal, or retinal infarction"[35,37]. In patients who experienced more than one event of the same kind, solely the presence of the event was registered, not the duration.

In patients who experienced a stroke during the 30-day period prior to the procedure, the severity of stroke was quantified by the same criteria used by the SAMMPRIS trial investigators, accepting for evaluation the Modified Rankin Scale, the Barthel Index and the NIHSS[68,69,102]. The Modified Rankin Scale is a scale of 0 to 6, with higher scores indicating greater disability, while the Barthel Index is a scale of 100 to 0, with higher scores indicating less disability. The NIHSS is a scale of 0 to 42 points serving both for initial evaluation, as well as for follow-up reevaluation of a neurological deficit and has been proven to be a strong indicator for the outcome of stroke patients[103]. It evaluates eleven categories of possible deficits, with 0 points indicating no neurological deficit

measurable in the areas examined, and higher scores indicating stronger neurological impairment. The evaluated categories are the level of consciousness, the best gaze, the visual field, facial palsy, motor capacity, ataxia, sensory capacity, best language, dysarthria, and the presence of extinction and inattention (former neglect)[102]. Patients who directly attended our center were assessed by the treating neurologist at the moment of arrival, as part of the diagnostic protocol. In these cases, the score was retrieved from the hospital record. If the NIHSS score was not clearly indicated, the documentation on the physical examination at arrival was analyzed to calculate a comparable value. In the case of patients transferred to our center from other hospitals in the area, the documentation provided by the center first attended to was analyzed, either to obtain the documented NIHSS score at arrival or to establish a comparable value. In case of insufficient information about the clinical state of the patient, the NIHSS was not included. This was clearly specified in all cases.

2.4.6 Procedure

The date of the procedure was documented, and the time in days between the qualifying event and PTAS was calculated. In the case of patients with several events over the last 30 days prior to the procedure, the latest event was considered the qualifying event for the procedure. The procedural outcome was documented by registering any adverse event (as listed under "adverse events", page 35).

2.4.7 Devices

As stated above, although the only device specifically designed for this purpose is the Wingspan stent system, several types of stents are used during PTAS of intracranial stenosis. At our center, self-expanding stenting systems and balloon-mounted stenting systems were used according to the treating doctor’s choice. Some patients received a combination of stents, depending on the characteristics of the treated stenosis.

All stents are provided sterile and are articles of single use.

The type and number of stents were documented for each patient.

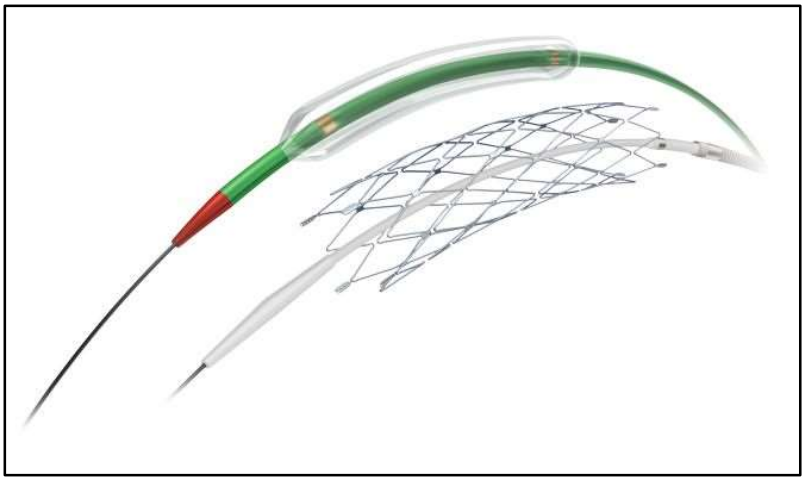
The commonly used stenting systems at our center include the below listed:

Self-expandable Stents (SES):

The Wingspan Stent System with the Gateway PTA Balloon Catheter (Stryker Neurovascular, Freemont, CA, USA, formerly Boston Scientific Neurovascular): The Wingspan Stent System with the Gateway PTA Balloon Catheter was initially approved by the FDA in 2005 for its use in patients with symptomatic intracranial stenosis refractory to antithrombotic therapy, although its use was further restricted in 2012[79]. It is a nitinol self-expandable stent and delivery system and consists of the Wingspan Stent, the Wingspan Delivery System and the Gateway PTA Balloon Catheter with an overall working length of 135 cm[99,104]. For its application, the stenotic lesion is first predilated with the Gateway PTA Balloon Catheter, which contains a proximal hub, polymer tubing, a Pebax balloon available in ten diameters (ranging from 1.5 to 4.0mm) and three lengths (ranging from 9.0 to 20.0mm) and two radiopaque marker bands at the distal end. After predilatation the preloaded Wingspan Stent is delivered to the treatment site with the Delivery System, which is a single lumen microcatheter with a changing material composition creating different regions of stiffness (proximal, middle, and distal). The Wingspan Stent has a tubular mesh design with several sections that self-expand individually as the Stent deploys and radiopaque markerbands on both ends. It is available in five diameters (2.5mm to 4.5mm) and three lengths (9.0mm, 15.0mm, and 20.0mm)[99,104]. The Wingspan Stent System with the Gateway PTA Balloon Catheter is shown in Graph 2.

The Solitaire Stent System (Medtronic, Inc.): The Solitaire stent system is a SES originally designed for neurovascular applications to support embolic detachable platinum coils in the interventional treatment of wide-necked cerebral aneurysms. It is available in various diameters (ranging from 4.0mm to 6.0mm) and lengths[105,106].

The Neuroform Stent System (Stryker Neurovascular): The Neuroform Stent System is a nitinol SES originally intended for the interventional treatment of wide neck intracranial saccular aneurysms in arteries with a diameter of 2.0 to 4.5mm[107,108].



Graph 2: The Wingspan Stent with the Gateway PTA Balloon Catheter
(Source: Stryker Neurovascular. 2020.[104])

Balloon-expandable Stents (BES):

The Pharos™ Vitesse™ Neurovascular Stent System (Biotronik AG): The Pharos™ Vitesse™ Neurovascular Stent System, specially designed for an intracranial application, is intended to be used in cerebral arteries with a reference diameter of 2.0 to 5.0mm[74]. It consists of a cobalt chromium BES coated with silicon carbide premounted on a rapid-exchange percutaneous transluminal angioplasty catheter with a semi-compliant balloon that is slightly longer than the stent and has two radiopaque markers. It is available in several lengths (ranging from 8.0 to 40.0mm) and diameters (ranging from 2.0 to 5.0mm)[74].

The Micro-Driver Stent (Medtronic, Inc.): The Micro-Driver Stent is a cobalt alloy balloon-mounted BMS with a rounded, modular design specifically intended for small vessels and tortuous anatomies[109]. It is available in three diameters (ranging from 2.25mm to 2.75mm) and 6 lengths (ranging from 8.0mm to 24.0mm)[109].

The Coroflex® Stent (B. Braun): The Coroflex® Stent is a cobalt-chrome alloy BMS with high flexibility designed for its application in small vessels[96].

2.4.8 Adverse events

Periprocedural complications were defined as complications that occurred within 30 days following PTAS. Complications occurring later than 30 days after the procedure were not taken into account in the present study and must be evaluated in future studies studying the long-term complication rate of the procedure.

The registered complications were further analyzed and divided into procedural complications and post-procedural complications and documented stating the time of appearance in days after the procedure. Procedural complications included iatrogenic dissection, the formation of a spurious aneurysm or other possible adverse events during the procedure, while post-procedural complications were further classified into ischemic stroke, symptomatic brain hemorrhage, non-symptomatic brain hemorrhage, death or myocardial infarction.

Ischemic stroke was defined as a new focal neurological deficit with a duration of a minimum of 24 hours not associated with brain hemorrhage on brain CT and MRI, and was further on divided into “disabling” and “non-disabling”, specifying if it occurred in the territory of the qualifying artery or not. Brain hemorrhage was defined as the presence of parenchymal, subarachnoid or intraventricular bleeding detected on the brain CT or MRI. It was considered symptomatic if associated with a seizure or a new focal neurological deficit lasting for at least 24 hours, in this case further distinguishing “disabling” and “non-disabling”, while it was considered non-symptomatic if no symptoms occurred or persisted for longer than 24 hours.

To differentiate between disabling and non-disabling, the Rankin score, Barthel Index and NIHSS were taken into account, applying the same criteria as the SAMMPRIS trial investigators[68,69]. The new neurologic deficit was considered disabling with a Rankin score of 4 or higher, a Barthel Index of 80 or less, or an overall score on the NIHSS of 7 or higher. The event was also considered disabling with an overall NIHSS of less than 7 in the case of a score on the NIHSS of 3 or more for motor examination of an arm or leg on a scale of 0 to 4, a score on the NIHSS of 2 or more for best language on a scale of 0 to 3, or a

score on the NIHSS of 3 for visual category on a scale of 0 to 3. All other events were considered non-disabling[68,69,98].

2.4.9 Endpoints

Possible endpoints were stroke, death or symptomatic brain hemorrhage within 30 days following PTAS for the qualifying lesion or after a revascularization procedure for the qualifying stenosis. Other registered adverse events, such as procedural complications and asymptomatic brain hemorrhage, though documented, did not qualify as endpoints.

2.5 Statistical analysis

We performed a primarily descriptive analysis of the collected data.

Our data was evaluated with Microsoft® Excel 2007 and IBM® SPSS® Statistics 24.

Percentages and arithmetic means were calculated, stating the corresponding standard deviation.

As another statistic measurement, we used Cramer´s V, a contingency coefficient based on Pearson´s chi-squared statistic, measuring the association between two variables, and indicating the relative strength of their relationship[110,111]. It may be applied to all levels of measurement, including nominal data, and its value varies from 0 (no association) to 1 (complete association of the studied variables). As the dependent variable of interest in our study, the adverse event, is of nominal measurement, and the independent variables, such as age by groups, comorbidities or devices applied during PTAS, are not of numeric or continuous measurement, statistics dictates the use of Cramer´s V[111].

2.6 Composition of the SAMMPRIS trial

The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis trial (SAMMPRIS) was a randomized, multicenter, two-arm clinical trial funded by the National Institute of Neurological Disorders and Stroke (NINDS)[68,69]. It compares aggressive medical

management with the performance of PTAS with aggressive medical management alone in patients with a recent stroke or TIA due to severe stenosis of a major intracranial artery. Its primary purpose was to determine whether the performance of PTAS results in a benefit in outcome by preventing the occurrence of a primary end point. The definition of primary endpoints included any stroke, death or symptomatic brain hemorrhage within the short-term follow up (30 days after enrollment or revascularization by PTAS) or stroke in the territory of the qualifying lesion during further follow-up (beyond 30 days)[68,69,98]. All other complications beyond the 30-day period after enrollment or PTAS (including for example non-stroke hemorrhage and myocardial infarction) were defined as secondary endpoints[98].

Eligible patients had an atherosclerotic stenosis of a major intracranial artery with a severity of 70-99% confirmed by catheter angiography and suffered from TIA or non-disabling ischemic stroke due to the qualifying lesion[98].

A summary of the defined inclusion and exclusion criteria is listed in Table 1 and Table 2.

	Inclusion Criteria
1	TIA or non-severe stroke within 30 days of enrolment attributed to 70-99% stenosis of a major intracranial artery (ICA, MCA stem (M1), VA, BA)
2	Modified Rankin score of ≤ 3
3	Stenosis length ≤14mm in an artery with an original diameter of 2.0-4.5 mm
4	Age ≥30 years and ≤80 years[b]
5	Negative pregnancy test in a female with menses in the last 18 months
6	Patient is available for inclusion and follow-up (by phone and for all follow-up visits) and understands purpose and requirements of the study, informed consent was given

Table 1: The SAMMPRIS trial: Summary of inclusion criteria
(Adapted table, source: Chimowitz et al. for the SAMMPRIS Investigators. Design of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Trial. 2011 J Stroke Cerebrovasc Dis.[98])

[b]Further detail on the criteria to be fulfilled in patients of an age of 30-49 years are specified in the original article on the study design of the SAMMPRIS trial[98]

Exclusion criteria	
1	Coexisting relevant stenosis of extra- or intracranial arteries (70-99%), occlusion, aneurysm or thrombus close to the target lesion
2	Recent (<30 days) stenting / angioplasty / endarterectomy of extracranial or intracranial arteries, previous treatment of the target lesion with stent / angioplasty or planned angioplasty / stenting of another lesion
3	Intracranial tumor, vascular malformation or untreated relevant chronic subdural hematoma
4	Thrombolytic therapy <24h
5	Progressive neurological signs <24h
6	Any cause of stenosis other than atherosclerotic disease, such as arterial dissection, Moya Moya disease, vasculitis, infections (herpes zoster or other viral vasculopathy, neurosyphilis), CSF pleocytosis, radiation induced vasculopathy, neurofibromatosis, fibromuscular dysplasia, sickle cell disease, post-partum angiopathy
7	Presence of unequivocal cardiac sources of embolism, such as chronic / paroxysmal atrial fibrillation, mitral stenosis, mechanical valve, endocarditis, dilated cardiomyopathy, EF<30%
8	Brain infarct of sufficient size (> 5 cms) to be at risk of hemorrhagic conversion or hemorrhagic infarct <30 days
9	Any history of primary parenchymal haemorrhage ever or other intracranial haemorrhage (subarachnoid, subdural, epidural) <30 days
10	High bleeding risk by peptic ulcer disease, major systemic haemorrhage <30days, platelets <100.000, haematocrit <30, INR >1.5, alcohol or substance abuse, uncontrolled severe hypertension, severe liver or renal impairment, indication for anticoagulation beyond the study, major surgery <30 days or in the next 90 days
11	Certain allergies (aspirin / clopidogrel / contrast dye / anesthesia / nitinol)
12	Severe discapacity or incapability of participating in follow-up, such as severe neurological deficit, dementia, psychiatric problems
13	Life expectancy <3 years
14	Pregnancy or unwillingness to use contraception at childbearing potential

Table 2: The SAMMPRIS trial: Summary of exclusion criteria
(Adapted table, source: Chimowitz et al. for the SAMMPRIS Investigators. Design of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Trial. 2011 J Stroke Cerebrovasc Dis.[98])

Patients were randomized (1:1) to the conservative study arm (aggressive medical treatment alone) or the interventional study arm (PTAS plus aggressive medical treatment)[98].

The medical management was identical in both groups, consisting of a continuous therapy of 325mg of aspirin per day and 75mg of clopidogrel per day for 90 days with a loading dose of Clopidogrel (600mg) in patients with no prior therapy with Clopidogrel. Additionally, all patients received intensive management of primary (systolic blood pressure and LDL-cholesterol levels)

and secondary risk factors (diabetes, non-HDL-cholesterol, smoking, excess weight, exercise) and a lifestyle modification program. This included the formulation of a personalized action plan focusing on exercise, correct nutrition, weight management and smoking cessation after a baseline assessment of the patient´s risk factors. Follow-up counseling sessions were performed and extensive support, as well as written health educational material, was given to help patients acquire the necessary skills, motivation and support to adhere to their personal plan[68,69,98].

In the interventional study arm, PTAS was performed under general anesthesia by experienced interventionalists at 50 sites in the United States. While a radial or brachial artery approach was permitted, PTAS was generally performed via a trans-femoral catheter (6F). The stenotic lesion was crossed with a microcatheter and angioplasty was performed after changing the catheter for an angioplasty balloon. After angioplasty, the catheter was changed for the Wingspan delivery system, deploying the Wingspan stent across the stenosis. In case of residual stenosis ≥50%, post-dilatation was performed with a new balloon catheter[98].

A close follow-up schedule was kept assuring the recording of all adverse events. Patients were contacted in personal visits at 4 days, 30 days, 4 months and then every 4 months with an interview, revision of medication and compliance and physical examination. Risk factor management of primary and secondary risk factors was closely monitored. A lifestyle coach initially contacted patients every 2 weeks, and if risk factor control was not optimal, control visits were scheduled more frequently. At the occurrence of a potential adverse events, patients were evaluated by a neurologist. Follow-up was finished 90 days after a primary end point, at death, at 3 years of follow-up, or at the end of the study (one year after enrollment of the last patient)[98].

2.7 Comparison of the SAMMPRIS trial and our study

For maximum comparability of the results of our study with the SAMMPRIS trial, the criteria of evaluation and the evaluated parameters for our study were

based on the SAMMPRIS trial[98]. Due to differences in research design and pre-existing conditions, however, variances could not be completely avoided.

We will perform an analysis to verify the comparability of our study and the SAMMPRIS trial by highlighting similarities and differences in study purpose, study design, methods, definition of concepts and studied items and parameters.

In continuation, we will conduct a comparison of the results of our study with the results of the SAMMPRIS trial, paying special attention to the patient collectives, highlighting differences in their baseline characteristics, comorbidities and clinical parameters, and the 30-day outcome of both studies. In the case of different short-term complication rates between the two studies, we will elaborate possible explanations by analysing the differences and similarities identified before.

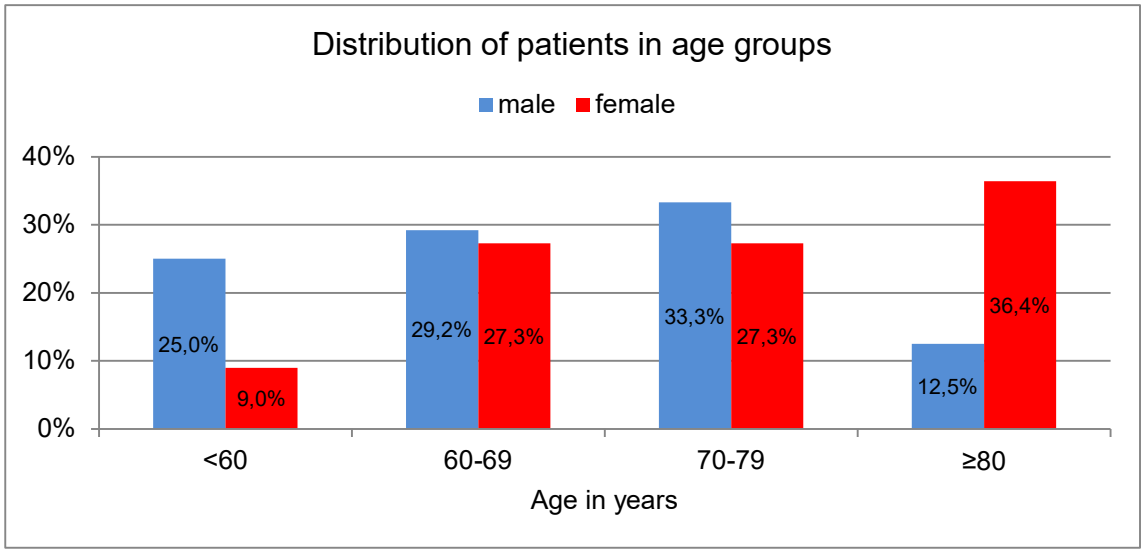
3. Results

After having explained the applied methods and inclusion and exclusion criteria, the results of the statistical analysis of the above stated parameters will be presented in this chapter.

3.1 Baseline characteristics

Of the 35 eligible patients, 24 (68.6%) were male and 11 (31.4%) were female. The average age at the moment of treatment was 69.2 years. Representing the age distribution by gender, remarkable differences were observed between male and female patients. With an average age of 68.3 years, male patients were notably younger than female patients, whose average age was of 71.3 years. On average, men were thus 3 years younger at the time of the procedure. Of all patients, 20.0% were under the age of 60 (n=7, 25.0% of men and 9.1% of women), 28.6% were between 60 and 69 years of age (n=10, 29.2% of men and 27.3% of women), 31.4% were between 70 and 79 years of age (n=11, 33.3% of all men and 27.3% of all women), and 20.0% were 80 years of age or older (n=7, 12.5% of men and 36.4% of women).

The distribution of patients in age groups is represented in Graph 3.

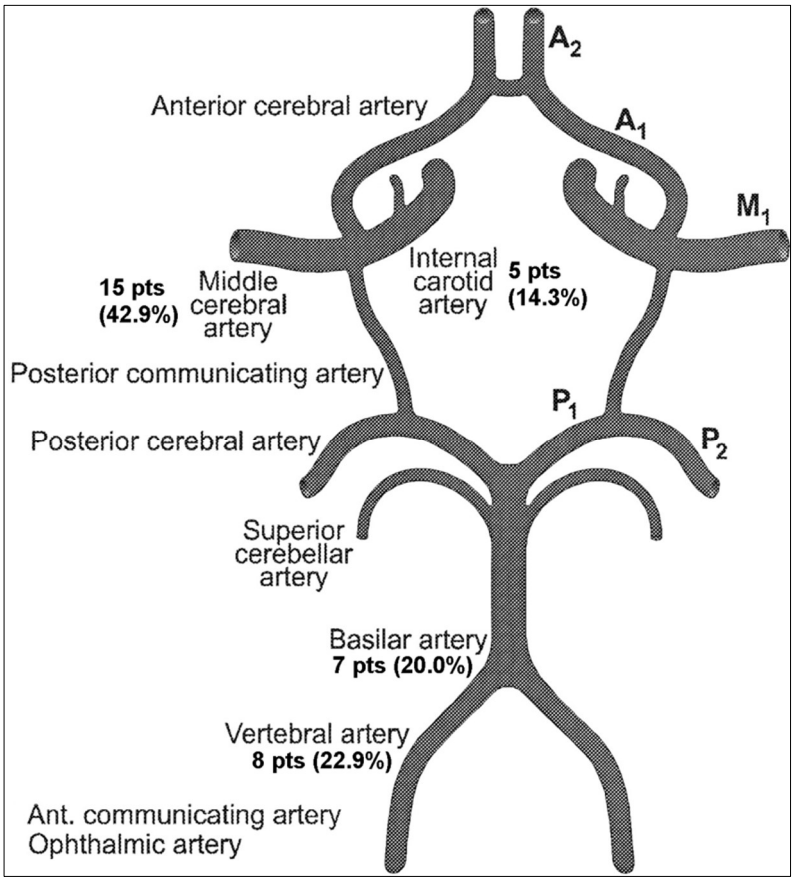


Graph 3: Distribution of patients in age groups
(Source: own data and analysis, n=35)

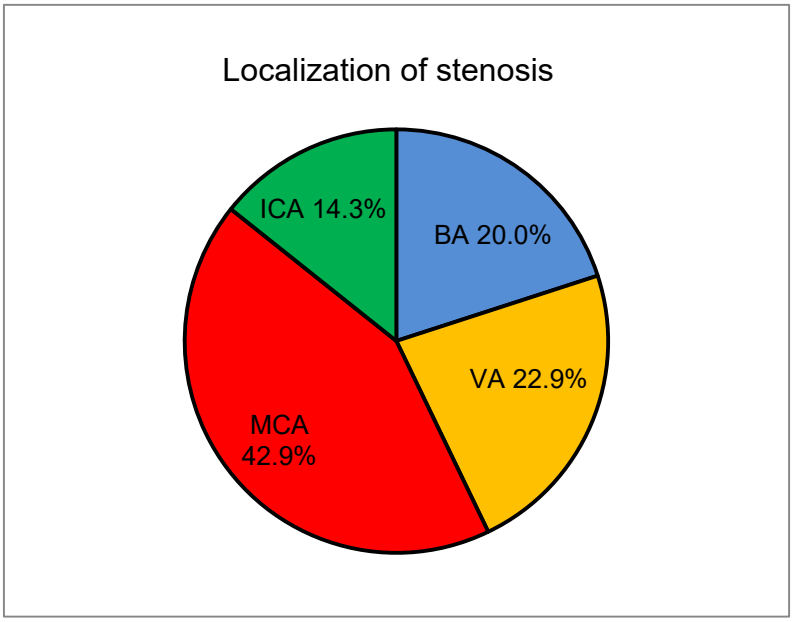
3.2 Stenotic lesion and qualifying event

All patients underwent PTAS for severe symptomatic intracranial arterial stenosis. The treated stenosis was located in the BA in 7 patients (20.0%), in the ICVA in 8 patients (22.9%, 6 on the left side, 2 on the right side), in the MCA in 15 patients (42.9%, 6 on the left side, 9 on the right side) and in the ICA in 5 patients (14.3%, 4 on the left side, 1 on the right side). In 16 cases (45.7%) the stenosis was located in the left cerebral hemisphere, and in 12 cases (34.3%) in the right cerebral hemisphere. There was no case of stenosis responsible for the qualifying event in the ACA or PCA.

The frequency of localization of each artery is represented in Graph 4 and Graph 5.



Graph 4: Localization of stenosis in the Circle of Willis
(Adapted graph, source: Hoksbergen et al. 2000. Stroke[27]. and own data and analysis, n=35)



Graph 5: Localization of stenosis
ICA: Intracranial carotid artery, BA: Basilary artery, MCA: Middle cerebral artery, VA: Vetebral artery
(Source: own data and analysis, n=35)

The severity of stenosis was analyzed by the evaluation of angiographic images. With an average reduction of the diameter of the stenotic artery of 85.3%, only one stenosis was 70-79%, 15 (42.9%) stenoses were 80-89%, and 19 (54.3%) displayed a 90% or higher reduction of the vessel diameter.
The qualifying event was a stroke in 20 patients (57.1%) and a TIA in 23 patients (65.7%) in the 30 days prior to the procedure. 12 patients (34.3%) suffered from one or several strokes exclusively, and 15 patients (42.9%) experienced TIAs exclusively. A total of 8 patients (22.9%) experienced a TIA and a stroke.

As part of the clinical routine at our center, complying with international guidelines for stroke management, and due to the retrospective character of the study, the severity of the stroke was assessed by the treating neurologist who determined the NIHSS[102,112]. The NIHSS was available for 90.0% of stroke patients (n=18). In three cases, we obtained the score from the hospital record as documented by the treating doctor. In 15 cases, we calculated the NIHSS score by evaluating the physical examination performed at initial admission to the hospital. In 2 cases, due to a lack of detailed information on the neurologic

deficit, we were not able to calculate the NIHSS score. Severity of stroke ranged from 0 to 6 points with an average of 2.7 points on the NIHSS. The NIHSS was of three or less points in 13 cases (72.2%), and of 4 to 6 points in 5 cases (27.8%).

3.3 Medical and interventional treatment

The vast majority of patients, 62.9% (n=22, 62.5% of men and 63.6% of women), were not currently undergoing treatment with antiplatelet agents or anticoagulation when they suffered from the qualifying event. 37.1% of patients (n=13, 37.5% of men and 36.4% of women) were under antiplatelet treatment at the time. 34.3% (n=12, 33.3% of men and 36.4% of women) were under antiplatelet monotherapy with 100mg of Aspirin per day and one patient was under treatment with 75mg of Clopidogrel per day (antithrombotic therapy) and Marcumar (oral anticoagulation, target INR of 2.0-3.0) due to a previously diagnosed condition of atrial fibrillation. None of the patients were under treatment with Clopidogrel or Marcumar in monotherapy, and none were treated with a combined therapy including Aspirin.

PTAS, first performed at our center in 2007, was performed on only one eligible patient in 2007, on 13 patients in 2009, on 9 in 2010, on 11 in 2011, and on only 1 in 2012. The procedure was performed within the first 30 days after the last qualifying event in all cases, with an average time of 8.2 days between the last qualifying event and the procedure. It was performed in the first 10 days after the qualifying event in 73.5% of cases (n=25), after 10 to 20 days in 20.6% of cases (n=7), and after more than 20 days in 5.9% of cases (n=2).

The patients´ characteristics, as well as data on the qualifying lesion, qualifying event and treatment are represented in Table 3.

Analyzed parameter	Result
Patients evaluated (n)	35
Male (%)	24 (68.6)
Female (%)	11 (31.4)
Age in years	69.2±10.3
Male patients	68.3
Female patients	71.3
Qualifying event	
Overall stroke (%)	20 (57.1)
Stroke exclusively (%)	12 (34.3)
Overall TIA (%)	23 (65.7)
TIA exclusively (%)	15 (42.9)
Stroke and TIA (%)	8 (22.9)
Severity of stroke (NIHSS)	2.7±1.7
Symptomatic artery	
Internal carotid (%)	5 (14.3)
Middle cerebral (%)	14 (42.9)
Vertebral (%)	8 (22.9)
Basilar (%)	7 (20.0)
Mean percentage of stenosis	85.3±5.3
70-79% stenosis (%)	1 (2.9)
80-89% stenosis (%)	15 (42.9)
90-99% stenosis (%)	19 (54.3)
time from qualifying event to procedure in days	8.2
Pharmacologic treatment at time of qualifying event (%)	
None	22 (62.9)
Antiplatelet therapy	13 (37.1)
Anticoagulation	1 (2.9)

Table 3: Patients, qualifying lesion, qualifying event and treatment
(Source: own data and analysis, n=35)

3.4 Devices

Information about the stent system used in the procedure was available for 34 patients. The stent system could not be identified in the analyzed documents in 1 case.

Most patients were treated with self-expanding stent systems exclusively, while only few patients were treated with balloon-mounted stent systems or received a combination of stent systems. Of the 29 patients (85.3%) treated with self-expanding stent systems, 27 (79.4%) were treated with the Wingspan Stent System exclusively while one patient (2.9%) received a Solitaire Stent. Of the 3 patients (8.8%) treated with a balloon-mounted stent system exclusively, two patients (5.9%) were treated with the Pharos Vitesse Neurovascular Stent System and one patient (2.9%) received a Coroflex Stent.
Only 2 patients (5.9%) received a combination of stent systems.

A summary of the used devices is shown in Table 4.

Stenting system	No. of patients (%)
Self-expandable Stents (SES)	29 (85.3)
The Wingspan Stent System	27 (79.4)
The Solitaire Stent System	1 (2.9)
The Neuroform Stent System	1 (2.9)
Balloon-expandable Stent (BES)	3 (8.8)
The Pharos™ Vitesse™ Neurovascular Stent System	2 (5.9)
The Coroflex® Stent	1 (2.9)
The Micro-Driver Stent	-
Combination of stents:	2 (5.9)
Wingspan Stent System / Micro-Driver Stent (SES + BES)	1 (2.9)
Wingspan Stent System / Solitaire Stent System (SES+SES)	1 (2.9)

Table 4: Applied devices
(Source: own data and analysis, n=34)

Information on the applied stenting system was available for all patients with adverse events. The registered adverse events were observed in patients treated with both types of stenting systems. Of the 6 patients with adverse events, 3 (50.0%) were treated with the self-expanding Wingspan stent system, one patient (16.7%) with a balloon-mounted stent system (Pharos Vitesse Neurovascular stent system), and 2 patients (33.3%) received a combination of systems.

3.5 Risk factors

The vast majority of patients, 94.3% (n=33, 100.0% of male patients and 91.0% of female patients) were under treatment for hypertension when they suffered from the qualifying event. Almost half of all patients were diabetic (n=15, 42.9% of all patients, 39.1% of male patients and 54.5% of female patients). While more male patients suffered from hypertension, the rate of diabetes was higher in women than men.

Of all patients, 51.4% (n=18, 45.8% of male patients and 63.6% of female patients) had previously been diagnosed with lipid disorders of the blood, again with a higher prevalence among women than men.

17.1% of all patients (n=6, 16.7% of male patients and 18.2% of female patients) had a history of coronary heart disease, and 8.6% (n=3, 8.3% of male patients, 9.1% of female patients) a history of congestive heart disease.

Three patients (8.6%), all men (12.5% of male patients), had previously been diagnosed with atrial fibrillation.

Of all patients, 17.1% (n=6, 16.7% of male patients and 18.2% of female patients) had a history of stroke other than the qualifying event. One of these patients suffered from TIA as a qualifying event, the other five patients from stroke. The rate of previous cerebrovascular events was notably higher in patients who suffered from stroke compared to patients with TIA exclusively.

While only one of the patients with TIA as a registered qualifying event (6.7%) had a history of stroke other than the qualifying event, 5 of 12 (41.7%) patients who suffered from stroke had experienced stroke before.

Overall, 31.4% of patients, all of which were male (n=11, 45.8% of male patients), had a history of smoking. 25.7% of all patients (n=9, 37.5% of male patients) stated they were currently smokers, and 5.7% (n=2, 8.3% of male patients) had formerly had a smoking habit. This means that 81.8% of patients with a history of smoking were current smokers, and 18.2% former smokers. 68.6% of patients (n=24, 54.2% of men and all women) had no history of prolonged tobacco abuse.

The analyzed risk factors are represented in Table 5.

Risk factors	No. of patients (%)
Hypertension (%)	33 (94.3)
Male (%)	*23 (100.0)*
Female (%)	*10 (90.9)*
Diabetes (%)	15 (42.9)
Male (%)	*9 (39.1)*
Female (%)	*6 (54.5)*
Lipid disorders (%)	18 (51.4)
Male (%)	*11 (45.8)*
Female (%)	*7 (63.6)*
Smoking history	11 (31.4)
male (%)	*11 (45.8)*
female (%)	*0 (0)*
Current (%)	9 (25.7)
male (%)	*9 (37.5)*
female (%)	*0 (0)*
Former (%)	2 (5.7)
male (%)	*2 (8.3)*
female (%)	*0 (0)*
Never (%)	24 (68.6)
male (%)	*13 (54.2)*
female (%)	*11 (100)*
History of coronary heart disease (%)	6 (17.1)
Male (%)	*4 (16.7)*
Female (%)	*2 (18.2)*
History of congestive heart disease (%)	3 (8.6)
Male (%)	*2 (8.3)*
Female (%)	*1 (9.1)*
Atrial fibrillation	3 (8.6)
Male (%)	*3 (12.5)*
Female (%)	-
History of stroke other than qualifying event (%)	6 (17.1)
Male (%)	*4 (16.7)*
Female (%)	*2 (18.2)*

Table 5: Risk factors overall and by gender
(Source: own data and analysis, n=35)

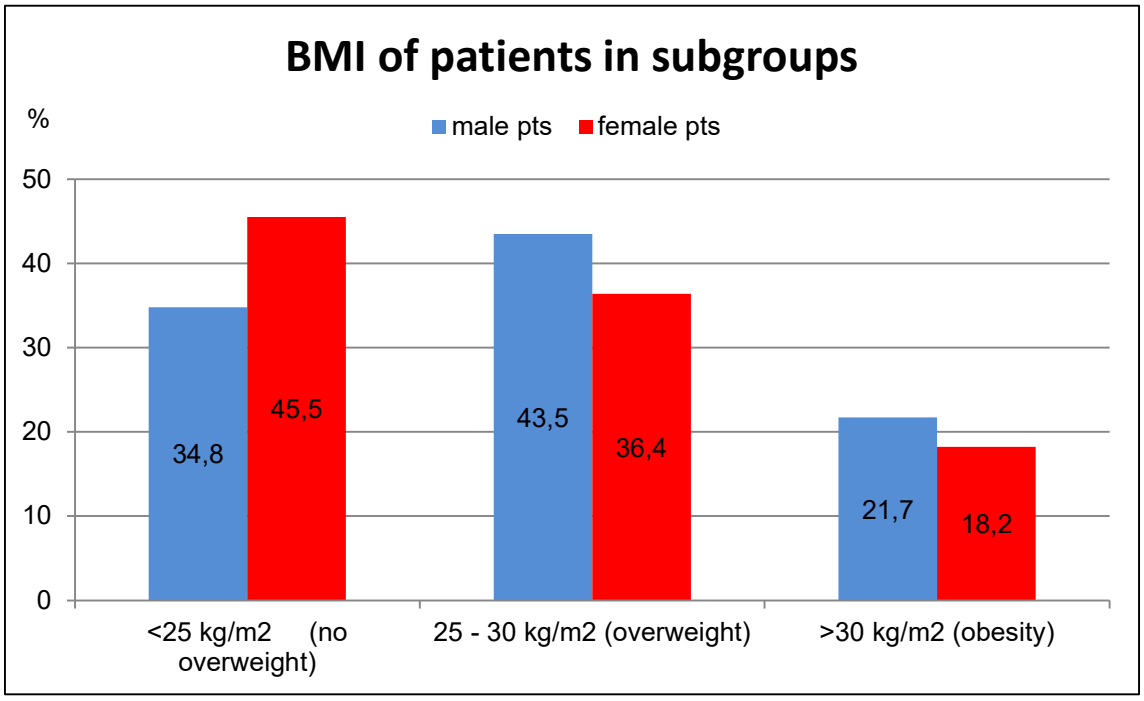
3.6 Biochemical and physical parameters

The average last blood pressure measured before the procedure was 148.6 mmHg systolic (1.4% lower in men and 3.0% higher in women) and 77.1 mmHg diastolic (0.6% higher in men and 1.3% lower in women), with an average blood pressure of 146.6/77.6 mmHg for men and of 153.1/76.1 mmHg for women. For diabetic patients, the average last blood pressure measured before the procedure was of 150.0/76.7 mmHg. It was higher in female diabetic patients (157.5/77.0 mmHg) than in male diabetic patients (145.0/76.6 mmHg).

The average lipid levels in blood were 137.1 mg/dL of LDL-cholesterol (1.0% higher in men and 2.2% lower in women), 46.3 mg/dL of HDL-cholesterol (6.1% lower in men and 14.3% higher in women), and 156.3 mg/dL of non-HDL-cholesterol (1.9% lower in men and 4.4% higher in women).

The average BMI amongst our patients was 26.9 kg/m^2, 27.4 kg/m^2 for men and 25.8 kg/m^2 for women. 38.2% of patients had a BMI below 25 kg/m^2 (n=13, 34.8% of male patients and 45.5% of female patients), 41.2% of 25-30 kg/m^2 (n=14, 43.5% of male patients and 36.4% of female patients), and 20.6% of 30 kg/m^2 or higher (n=7, 21.7% of male patients and 18.2% of female patients).

The BMI values are represented in Graph 6.



Graph 6: BMI of patients in subgroups
(Source: own data and analysis, n=35)

Of the 15 diabetic patients, glycated hemoglobin (HbA1c) was tested in 13 cases (86.7% of all diabetic patients, 88.9% of diabetic men and 83.3% of diabetic women). The average HbA1c for diabetic patients was 7.5%. For men it was higher (HbA1c of 7.9%; 6.1% higher than the overall average) and for women slightly lower (HbA1c of 6.7%; 9.8% lower than the overall average).
The analyzed risk factor parameters are represented in Table 6.

Measured risk indicating parameters	**Result**
Blood pressure (in mmHg)	
Systolic [patients evaluated]	148.6±20.7 [35]
Male	146.6
Female	153.1
Diastolic [patients evaluated]	77.1±12.3 [35]
Male	77.6
Female	76.1
Blood lipids levels (in mg/dL)	
LDL cholesterol [patients evaluated]	137.1±44.6 [29]
Male	138.5
Female	134.1
HDL cholesterol [patients evaluated]	46.3±12.3 [30]
Male	43.4
Female	52.9
Non-HDL cholesterol [patients evaluated]	156.3±59.9 [30]
Male	153.4
Female	163.2
Glycated hemoglobin in diabetic patients (in %) [patients evaluated]	7.5±2.2 [13]
Male	7.9
Female	6.7
Body-mass index (in kg/m^2) [patients evaluated]	26.9±3.9 [34]
Male	27.4
Female	25.8

Table 6: Measured risk indicating parameters
(Source: own data and analysis, n=35)

3.7 Adverse events

A total of 6 adverse events were registered in this study, consisting of 3 endpoints and 3 other adverse events. The overall probability of suffering from an adverse event within the first 30 days of the procedure was 17.1%, with a probability of reaching an endpoint of 8.6%.

All 3 endpoints registered in the 30-day period subject to this study and all 3 other adverse events were found in patients of more than 70 years of age.

The registered endpoints were one disabling ischemic stroke (2.9%), one symptomatic brain hemorrhage (2.9%) and one non-stroke related death (2.9%). An 84-year-old female patient had a disabling ischemic stroke in the territory of the treated artery. A 75-year-old female patient developed a fatal brain hemorrhage following the procedure. An 82-year-old male patient died of a non-stroke related death caused by heart failure after electrolyte imbalance and ventricular tachycardia 5 days after the procedure was performed.

The registered adverse events other than endpoints were one non-symptomatic brain hemorrhage (2.9%) and two iatrogenic arterial dissections (5.7%). In 2009, an 84-year-old female patient developed an asymptomatic brain hemorrhage after the intervention. In two patients, arterial dissection of the left VA was inflicted during the procedure, in both cases without any further complication after treating the dissected area with the insertion of a stent. In 2009, a Neuroform Stent had been used to treat the stenosis of the VA in the case of an 81-year-old female patient, and another stent of the same kind was used to treat the dissected area. In 2010, in the case of a 71-year-old male patient, the stenosis responsible for the qualifying event had been treated through the insertion of a self-expanding Wingspan stent and a Solitaire stent was used to treat the dissected area.

There is a very strong association between the independent variable “age”, analysed in four subgroups, and the dependent variable “complication rate” (V: 0,404[c])[113].

No adverse events were observed in the subgroup of patients of under 60 years of age and in the subgroup of patients of 60 to 69 years of age. However, in the subgroup of patients of 70 to 79 years of age, 18.2% of patients, and in the subgroup of patients of 80 years or older, 57.2% of patients suffered from an adverse event. Of these patients, the same percentage number suffered from an end point (28.6%) and from other adverse events (28.6%).

The cross table of the performed statistical analysis of association of variables is shown in Table 7.

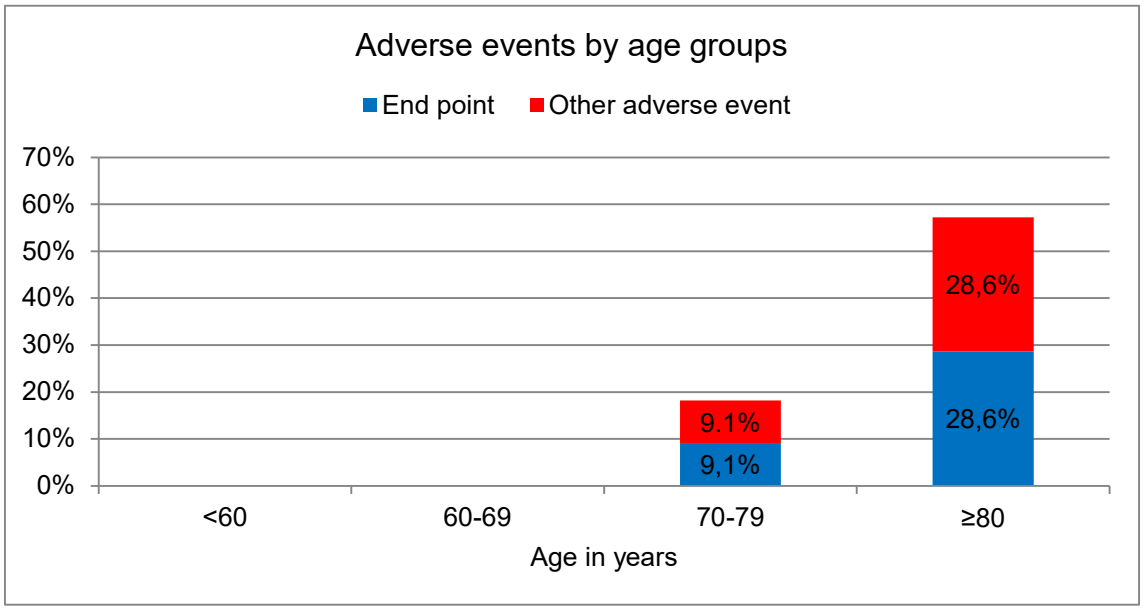
		Age group				**Gesamt**
		<60	60-69	70-79	≥80	
No event		7 *100%*	10 *100%*	9 *81.8%*	3 *42.9%*	29 *82.9%*
Adverse events	- any adverse event	0 *0%*	0 *0%*	2 *18.2%*	4 *57,1%*	6 *17,1%*
	- Other adverse event	0 *0%*	0 *0%*	1 *9.1%*	2 *28.6%*	3 *8.6%*
	- End point	0 *0%*	0 *0%*	1 *9.1%*	2 *28.6%*	3 *8.6%*
Overall patients		7 *100%*	10 *100%*	11 *100%*	7 *100%*	35 *100%*

Table 7: Patient age and adverse events
Cross table: Association between independent variable patient age and dependent variable of adverse events (V=0.404)
(Source: own data and analysis, n=35)

However, it is pertinent to stress the limited reliability of an exact interpretation of percentages and associations due to the limited number of included patients (n=35).

[c] Because of the nominal measurement scale of the dependent variable and the ordinal measurement scale of the independent variable, we opted against the use of a regression coefficient.

The occurrence of adverse events by age groups is shown in Graph 7.



Graph 7: Adverse events by age groups
(Source: own data and analysis, n=35)

All patients with adverse events had previously been diagnosed with hypertension, two of them suffered from hyperlipidemia.

None of the patients who experienced periprocedural complications suffered from diabetes or had a history of smoking.

Three of the patients with adverse events had a history of stroke other than the qualifying event, two of them were under medical treatment at the time of the qualifying event. One patient was under treatment with Aspirin in monotherapy, the other with Clopidogrel and Marcumar. One 75-year-old female patient, despite having experienced a stroke before the qualifying event, was not under antithrombotic treatment. The patient developed a symptomatic brain hemorrhage the day of the intervention and died one day later.

Of 3 patients with atrial fibrillation two had an adverse event, one of them died 5 days after the procedure due to ventricular tachycardia (non-stroke-related death), while the other had a procedural dissection of the VA.

A summary of the state of health and risk factors, as well as the applied stenting system of the patients with adverse events is displayed in Table 8.

Year	Sex	Age	Adverse event *(days after procedure)*	Stenting system	Risk factors / state of health
Endpoints					
2009	F	84	Ischemic stroke *(1)*	Wingspan, Micro Driver	HTN
2009	F	75	Symptomatic brain hemorrhage *(1)*, death *(2)*	Wingspan	History of stroke HTN UW
2011	M	82	Non-stroke related death *(5)*	Pharos Vitesse	AF (no treatment) CHD HTN OBS (class I)
Other adverse events					
2009	F	84	Asymptomatic brain hemorrhage	Wingspan	DLP HTN OW
2009	F	81	Procedural dissection	Neuroform	History of stroke (aspirin) HTN
2010	M	71	Procedural dissection	Wingspan, Solitaire	AF (Marcumar) DLP History of stroke (Clopidogrel) HTN OW

Table 8: Patients with adverse events and their state of health
AF: atrial fibrillation, CHD: congestive heart disease, DLP: dyslipidemia, F: female, HTN: arterial hypertension, M: male, OBS: obesity, OW: overweight, UW: underweight
(Source: own data and analysis, n=35)

No significant differences in the studied biochemical and physical parameters were found when comparing the patients who experienced periprocedural complications to the rest of the studied patient group.

4. Discussion

After having presented the results of the performed study, these results will be discussed critically in this chapter, putting them in context of literature on the subject.

4.1 Patients and their risk factors

The notably higher number of male patients compared to female patients, as well as the registered average age for men, 3.0 years lower than the average age for women, and the different distributions in age groups by gender is consistent with literature on the subject, with an earlier presence of symptomatic stenosis in men and an overall higher incidence of stroke in men. This phenomenon, which may be caused both by an earlier onset and/or a faster evolution of the atherosclerotic disease in men, as explained in the introduction, is possibly due to biological factors, such as the lack of hormonal protection, as well as behavioral factors, such as lifestyle differences[19,20,21,22].

The vast majority of patients, all male patients, and all patients with adverse events had previously been diagnosed with hypertension. The average last systolic blood pressure measured before the procedure (148.6 mmHg) exceeded the above stated recommended target established by the WHO[62]. While more male patients were known to be hypertensive, the higher average systolic blood pressure amongst female patients compared to male patients (153.1 mmHg vs. 146.6 mmHg) could reflect worse medical control of blood pressure among female patients. While even stricter target blood pressure measures have been defined for diabetic patients[62], in our patient group, the last systolic blood pressure measured before the procedure was higher in diabetic patients than the overall average. This was due to a remarkably high average systolic blood pressure in female diabetic patients. Nevertheless, being in a situation of high physical and psychological stress, the blood pressure measures taken shortly before the procedure should be handled with care, as they may not truthfully represent the patients' usual blood pressure.

The high number of diabetic patients in our patient sample correlates with diabetes being one of the main risk factors for intracranial atherosclerosis, subsequent stenosis and stroke[3,10,12]. The average HbA1c level of 7.45% observed amongst all diabetic patients and the even higher average HbA1c level of 7.90% for male diabetic patients exceeded the recommended levels by the AACE and the ADA[66,67]. The average HbA1c level of 6.72% amongst female diabetic patients was below the control level recommended by the ADA[67]. The exceeding levels of HbA1c found amongst the patient group reflect poor disease management and demand for better control through the treating specialists.

The registration of the smoking habit of our patients is the item most sensitive to being biased by the retrospective nature of the analysis. Knowing that the enquiry of the smoking habit of each patient was obligatory during anamnesis, in those few cases where no information was stated, the patient was assumed to be a non-smoker. Although the information was given in the majority of cases, this represents a possible source of error. In a minority of cases it may not have been enquired, and for this reason not documented, leading to incorrect data. Also, patients having abandoned their smoking habit many years ago might not have stated their former smoking habit or may not be marked by the treating neurologist as former smoker. However, as clearly stated in the Framingham Study, the stroke risk decreases significantly already two years after abandoning the smoking habit, equaling that of a nonsmoker after five years after smoking cessation[17]. Due to a lack of information on the intensity of smoking, we did not differentiate between heavy and light smokers. This is an important piece of information missing, as an increase in the number of cigarettes smoked per day strongly increases the relative risk of stroke, doubling the relative risk of stroke in heavy smokers (more than 40 cigarettes a day) compared to light smoker (less than 10 cigarettes a day)[17]. The value of information on the smoking status in our study is thus limited. Comparing our results to the national statistics on tobacco abuse for Germany, we observed much higher rates of smoking amongst the male patients of our study group

than the average German population[114]. The German population of 65 to 70 years of age, corresponding to the average age of our patients, had a remarkably lower rate of active smokers (13.9% in the German population versus 25.7% of active smokers in our patient group, n=9)[114]. Corresponding to the average age of female patients in our study, the rate of smokers amongst women of 65 to 70 years in the German population was 11%, opposed to no active smokers amongst the female patients in our study[114]. In the age group of 70 to 75 years, corresponding to the average age of male patients in our study, 12.5% of German men were registered as smokers, with a much higher rate of smokers amongst our male patients (n=9, 37.5%)[114].

4.2 Stenosis and devices

The location of the stenosis responsible for the qualifying event registered in our study varied from the pattern of location generally described in international literature. By far the most common location was in the MCA, followed by the ICVA, BA and ICA, while the in literature established order of frequency is BA, ICA, MCA, PCA and ACA[115]. While this variation of the established order may simply be the result of statistical deviation due to a low patient number, with the magnitude of the difference, other reasons must be considered. Depending on its location, stenosis may lead to ischemia in an earlier state, present symptoms of a more or less subtle kind, thus being more likely to be detected early, or show differently in imaging techniques, leading to difficulties in diagnosis. Secondly, once identified, difficulty accessing the location may vary between different locations, directly influencing the likelihood of successful interventional treatment depending on the location of the stenosis. Determined locations may have been more likely to be treated successfully by PTAS at our center, while other locations may have resulted in an alternative treatment method, either by failure of the intended interventional treatment, or by choice prior to the beginning of the treatment due to risk and feasibility assessment. This may ultimately have resulted in a selection bias in our study, where the performed interventional treatment of the qualifying lesion, rather than the presence of

stenosis by itself, was an inclusion criterion. We are, however, not aware of any such cases.

In our hospital, a variety of stent systems were used. The selection of the stenting system was at the discretion of the treating specialist. Silber describes a connection of the choice of stent with the periinterventional complication rate[96]. With the application of 6 different stenting systems in 35 patients, we refrained from statistically contrasting the different stenting systems in subgroup analyses. However, adverse events were observed in patients who received either type of system (BES/SES). This concurs with international research on the matter, where no difference in complication rate was found depending on the stenting systems utilized[77]. Due to the different characteristics of each device, it appears to be most sensible to leave the choice of the most suitable device based on the patient's characteristics to the treating doctor, as is common practice in our center.

The analyzed data of the present study did not suggest the occurrence of restenosis. However, the 30-day observational period set in this study was too short for restenosis to occur; due to the lack of a reasonable follow-up time range no conclusion as to the probability of restenosis could be made.

4.3 Complication rate and adverse events

We were able to answer our first proposed question with a short-term risk of reaching an endpoint of 8.6%, a probability of suffering from an adverse event of 17.1% and the registered complications listed under "3.7 Adverse events" on page 51.

The adverse events registered in this study took place over the years, with two other adverse events and two endpoints in 2009, one other adverse event in 2010 and one endpoint in 2011. In case of a learning effect over time, an accumulation of complications after the initiation of practicing the procedure at the center would be expected, with descending complication rates over time. This was not the case; there was no effect of learning observed.

PTAS was routinely performed in our department, which commonly promotes the acquisition of routine and expertise. Some clinics participating in international studies, where the procedure is performed at various centers and the results are combined, may treat a significantly smaller number of patients. This means they may not reach the level of expertise that is observed in our department, which may lead to a higher overall complication rate of PTAS. Therefore, only centers with high numbers of eligible patients should consider the performance of PTAS, always taking into account the necessity of practice and routine of the performing doctor.

Our statistical analysis shows a strong association between an advanced age and the occurrence of an adverse event. This translates into a much higher risk of periprocedural complications for patients of an age of 70 years or older, and even more so for patients of an age of 80 years or older. On the other hand, it showed a much lower risk of periprocedural complications for younger patients with a better safety profile for PTAS than expected.

The indication of PTAS with all its implications (anesthesia, medical treatment, physical and psychological stress) in elderly patients should therefore be review critically. Identifying high-risk patients and excluding them from the procedure may lead to an even lower complication rate for PTAS.

On the other hand, elderly patients generally have more comorbidities, a poor vascular status and a reduced state of health. They are naturally at a higher risk of complication of any disease or death than younger patients and could also have a worse prognosis if treated purely medically.

To confirm the suggested necessity of setting an age limit to the performance of PTAS, further studies analyzing the outcomes for both treatment options and differentiating patients by age groups must be conducted. A higher complication rate for this specific patient group through the interventional treatment compared to a purely medical treatment is still to be proven.

When aiming to compare the obtained data of our study to international literature and answer the second of our research questions, we face certain difficulties.

The events listed as "other adverse events" in our study were not registered in other studies or were not specifically marked in the corresponding publication. The percentage of asymptomatic brain hemorrhages, for example, though listed in the SAMMPRIS trial[68,69] and mentioned in publications on stent deployment failure[76] does not appear in most studies, and information on procedural events, such as iatrogenic dissection, is not generally given. In consequence, we did not dispose of comparable data on the incidence of other adverse events in international studies.

The probability of reaching an endpoint was the figure used to compare the presented data with other studies. The probability of reaching an endpoint in the analyzed 30-day observation period in our study (8.6%) was similar to previous study results, and remarkably lower than the observed 30-day complication rate for patients treated with PTAS described in the SAMMPRIS trial (14.7%)[68]. However, the published periprocedural rates of stroke and death after stenting for intracranial atherosclerosis vary greatly (ranging from 0% to 50%, with a median of 7.7%)[77]. Silber describes a probability of reaching an end point of 6.5% in his patient collective of 46 patients, which is similar to the complication rate found in our study[96]. He attributes the lower, and thus reasonable, complication rate of PTAS amongst his patient sample to the choice of stent, individual vascular status of the patient and the performance of PTAS in a hospital of maximum care with a well-established Department of neuroradiology[96]. Due to the limited patient number and lack of data on a control group, we were not able to verify these findings in our study.

A detailed comparison of our data with the SAMMPRIS trial will be performed in chapter 5.

No 30-day recurrence rate for a traditional conservative treatment approach was available for an accurate comparison with our results. The 30-day complication rate in our study was higher than in the conservative treatment

arm of the SAMMPRIS trial (5.8%). However, as will be discussed in more detail in chapter 5, there are important differences in treatment which limit the comparability of the medical management group of the SAMMPRIS trial and the traditional medical treatment consisting of antiplatelet therapy[68,69]. While a 1-year recurrence rate of 23% in patients with severe atherosclerotic stenosis of the intracranial arteries and a traditional treatment approach have been described previously, the 1-year rate of primary endpoints was as low as 12.2% in the SAMMPRIS trial, thus suggesting differences in outcome due to the new conservative treatment applied[57,58,68,69].

To compare the outcome of patients after PTAS to international data on PTAS and medical management and come to a clear consent on the superiority of this treatment, long-term complication rates for PTAS at our center must be evaluated.

The possibility of additionally lowering the stroke recurrence rate without adding the risk of periprocedural complications of an intervention when treating patients with severe intracranial atherosclerotic stenosis with medical treatment and a lifestyle modification program, as has been suggested in international literature, must be considered and studied in the future[68,69].

4.4 Limitations

This study provides data on the short-term outcome of patients treated with PTAS at the University Hospital of Tübingen and assists in trying to evaluate the risk of the procedure and prognosis of these patients. However, it has several limitations that need to be considered while evaluating the results.

It is a monocentric study, and therefore its results must thus be interpreted and are not to be extrapolated to other hospitals.

As a hospital of maximum care, patients from a large geographical area are treated at our center and could therefore be included in this study. We evaluated the highest possible number of patients available, taking into account all patients treated with PTAS in our institution since the initiation of the procedure and excluding only those strictly not eligible by the above stated

criteria. Still, due to the relatively low incidence of the disease, treatment restrictions and the recent instauration of the studied treatment approach, the number of patients included was limited and may not be representative of the general patient population. Studies with larger patient numbers and meta-analysis on the topic should be carried out to counterproof the presented results.

Besides the limited patient count, the present study is clearly characterized by its retrospective nature. Although this has well-known advantages, as requiring less time, funding and involved professionals than other study models, it also comes with universally known disadvantages. Its primary disadvantage lies in the limitation of the amount and accuracy of its data. The most important and almost exclusive source of information was the patient's hospital record, up to several years old, in some cases originally on paper with posterior digitalization, and written and documented by professionals with no knowledge of the posterior performance of this study. Naturally, their primary objective in the documentation of the data lay in the well-directed patient care rather than the collection of supplementary data, such as may be the Rankin Score and Barthel Index, not routinely determined in our institution. In many cases, we experienced difficulties and at times it was impossible to collect information. This showed in the varying number of patients evaluated in several items and was marked in all cases. Also, as the University Hospital of Tübingen is a center of reference of the region, many patients were referred to the hospital by other centers and some information was either not available or only partially available, as it was not originally collected and documented at our center. In general, the center is provided with a medical discharge report from the referring center, which, though digitalized and introduced in the hospital's database, may not contain all items evaluated in our study. Being a retrospective study undertaken by a team not involved in primary patient care, the information found in the hospital records was interpreted as best possible and its flawlessness and accuracy had to be relied on.

Ultimately, the inclusion and exclusion criteria may present a selection bias. Unintended selection may have occurred before data evaluation, as only

patients treated successfully with PTAS were evaluated. Hypothetically, patients with planned PTAS but unsuccessful stent placement due to a variety of possible reasons would not be included in the initial list of possibly eligible patient. This could theoretically influence the analysis of comorbidities and outcome in general and by subgroups. As it would also represent a clear selection bias when trying to evaluate the feasibility or success of PTAS, as stated above, patients with unsuccessful PTAS were excluded altogether. We can therefore not draw any conclusion as to the success rate of PTAS or possible reasons for failure of an attempted intervention.

We studied the outcome of patients with intracranial stenosis treated with PTAS exclusively. Unfortunately, no data is available on a corresponding patient group treated conservatively. Therefore, a comparison in outcome of both treatment options at our center was not possible. Our results can merely be compared to the data published in the recent scientific literature. Different criteria and treatment standards may apply limiting accurate comparability.

5. Comparability and comparison to the SAMMPRIS trial

One of the principal reasons of conducting this study was the alarmingly high short-term complication rate amongst patients with severe atherosclerotic stenosis in intracranial arteries treated with PTAS reported in the SAMMPRIS trial. The consecutive questioning of the interventional therapy as the treatment of choice for patients with severe intracranial stenosis makes the following comparison of both studies and patient samples of special importance[68,68].

5.1 Comparability of the SAMMPRIS trial and our study

In order to be able to compare our results with those of the SAMMPRIS trial, we made it our goal to evaluate a maximum number of parameters by the same criteria. However, there were clear limitations to this initiative, limiting the comparability of the two studies.

The greatest difference lies in the different study designs and in the case of this present study with the above stated limitations, as well as the number of patients included.

The inclusion criteria were similar with several exceptions (listed in Table 1, page 37). While the SAMMPRIS trial enrolled only patients of 30 to 80 years of age, our patient group contained one 80-year old and six patients with more than 80 years of age. Also, the SAMMPRIS trial excluded all patients with progressive neurological signs within 24h before enrolment, while 4 of our patients (3 with stroke and one patient with TIA) received treatment the same day of the qualifying event. Patients with certain comorbidities (listed in Table 2, page 38) were excluded, as well[98].

The SAMMPRIS trial investigators classified endpoints into primary and secondary endpoints. In this study, only events occurring in the 30-day period after the procedure were analyzed to study the short-term complication rate; all registered endpoints would therefore be classified as primary endpoints under the SAMMPRIS trial criteria[98].

While the SAMMPRIS trial made use of the Wingspan stenting system exclusively, a variety of devices were used at our center[98]. Though there is no evidence that the use of several types of stents, self-expandable and balloon-

mounted, should be responsible for the difference in periprocedural complications, the possibility of an effect of the used devices on differences in number and type of complications as well as the outcome must be considered[77]. Different characteristics of each stenting system may influence the applicability and harmfulness of the stent, with certain systems having advantages over others depending on the conditions of each case. The localization of the stenosis, the characteristics of the patients' circulatory system and tortuousness and morphology of the arteries may be a possible influence[76].

Due to differences in standard treatment procedures and legal policies, there were differences in the applied treatment regimens. In accordance to current treatment guidelines in Germany[59], the dose of aspirin given in intracranial atherosclerotic disease was 100mg per day, whereas the SAMMPRIS investigators administered a dose of 325mg daily[68,98].

In addition to the medical therapy, patients in the SAMMPRIS trial were enrolled in a lifestyle modification program for the management of primary and secondary risk factors, which provided them with a personalized action plan adjusted to each patient individually, focusing on exercise, correct nutrition, weight management and tobacco smoking cessation, and regularly seen in follow-up counseling sessions to help them acquire the necessary skills, motivation and support to adhere to the plan[68].

In Germany, while patients are advised to make changes in their lifestyle, including smoking cessation, weight loss, doing physical exercise and maintaining a healthy diet, there is neither a specific program to raise awareness amongst future doctors, and transmitting, promoting and supporting these measurements with patients, nor a steady control of risk factors. Patients are left to the application of these measures by themselves and in many cases do not succeed in applying these changes. Therefore it was and remains to this moment impossible to apply the aggressive medical treatment that was proposed by the SAMMPRIS investigators and proved highly favorable in outcome[68,69].

An overview of differences of the two studies is shown in Table 9.

	UKT	SAMMPRIS PTAS group
Study purpose	Study the short-term outcome of PTAS in patients with severe intracranial stenosis and try to optimize the safety profile of PTAS	Compare aggressive medical management alone with aggressive medical management plus PTAS with the use of the Wingspan stent system in high-risk patients with intracranial arterial stenosis
Research design	Longitudinal: retrospective (analysis of records)	Longitudinal: prospective (randomized clinical trial)
Investigation period	July 2007 - December 2012	November 2008 - April 2011
Inclusion criteria	Successful PTAS within 30 days after TIA or stroke attributed to 70-99% atherosclerotic stenosis of ICA / ICVA / MCA / ACA / BA / PCA - - - - - Available information on 30-day follow-up -	Recent TIA or non-severe stroke (within 30 days of enrolment) due to 70-99% stenosis of ICA / MCA stem (M1) / VA / BA Modified Rankin score ≤ 3 Stenosis length ≤ 14mm Diameter of vessel 2.0-4.5mm Age 30-80 years Negative pregnancy test Patient available for follow-up (telephonic and personal visits) Informed consent given
Exclusion criteria	Other etiology of stenosis or non-stenotic lesion (such as aneurysm, dissection, cerebral angiitis), stenosis <70% or >99%, additional stenosis in the same blood supply region, PTAS for another lesion within 30 days, thrombolytic therapy <24 hours, unsuccessful PTAS, incomplete information on the 30-day outcome	Additional severe stenosis of intracranial arteries, previous treatment of the site ever or another site <30days or planned, in-lesion thrombosis, close-by aneurysm, intracranial tumor, thrombolytic therapy <24h, progressive neurologic signs <24h, recent infarction, cerebral hemorrhage <30days, other etiology of stenosis, sources of cardioembolism, systemic hemorrhage <30days, certain allergies, major surgery <30 days or planned, psychiatric diseases, limited life expectancy (<3 years)
Studied objects	Patient collective Comorbidities Devices Short-term complication rate - Comparison of outcome with the SAMMPRIS trial	Patient collective Comorbidities - Short-term complication rate Long-term complication rate Comparison of outcome: medical treatment vs. PTAS
Treatment	PTAS Dual antiaggregation Pharmacologic risk factor management	PTAS Aggressive medical treatment (dual antiaggregation, intensive risk factor management, lifestyle modification program)
Applied medical devices	Various stenting systems, including SES (Wingspan, Solitaire, Neuroform) and BES (Pharos Vitesse, Coroflex, Micro-Driver)	The Wingspan Stent System exclusively

Definition: Adverse events	**End point:** stroke, death or symptomatic brain hemorrhage within 30 days following PTAS for the qualifying lesion **Other adverse event:** iatrogenic dissection, spurious aneurysm, asymptomatic brain hemorrhage, any other event in the 30-day period	**Primary end point:** stroke, death or symptomatic brain hemorrhage <30 days, ischemic stroke (territory of the qualifying artery) >30 days **Secondary end point:** stroke, death, myocardial infarction, major non-stroke hemorrhage >30 days
Duration of follow-up	30 days after PTAS	3 years or until 90 days after a primary end point, death, the end of the study (one year after enrollment of the last patient)
Patients evaluated	35	224 [SAMMPRIS trial interventional arm]

Table 9: Comparison of the SAMMPRIS trial and our study
(Adapted table, source: Chimowitz et al. for the SAMMPRIS Investigators. Design of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Trial. 2011 J Stroke Cerebrovasc Dis.[98])

5.2 Comparison of the results of the SAMMPRIS trial and our study

Comparing the results of our study to those of the SAMMPRIS trial, we observe several differences. Even with a much higher percentage of male patients at our center, who in our patient group were shown to lower the average patient age, the average age of patients was much higher than in the SAMMPRIS trial patient group[69].

The distribution in location of the affected artery was similar in both trials[69].

The mean percentage of the reduction of the diameter of the stenotic artery was remarkably higher among UKT patients, with more patients presenting high-grade stenosis than among the SAMMPRIS trial patients. While amongst the SAMPPRIS trial patients, most suffered from stenosis with a reduction of diameter of the affected artery by 70 to 79% and the smallest subgroup of patients had stenosis with a reduction of diameter by over 90%, the majority of UKT patients (54.3%) suffered from stenosis with a reduction of diameter of the affected artery by over 90%, while only one subject presented with a stenosis with a reduction of diameter by 70 to 79%[68].

While a large majority of patients in the SAMMPRIS trial were under antithrombotic therapy at the time of the qualifying event, this was the case in a minority of the UKT patients only (64.7% vs. 37.1%)[68].

A comparison of the included patients and their qualifying lesions are represented in Table 10.

Patients and qualifying lesion	**UKT**	**SAMMPRIS PTAS group**
Patients evaluated	35	224
Age in years	69.2±3.4	61.0±10.7
Male sex (%)	24 (68.6)	127 (56.7)
Female sex (%)	11 (31.4)	97 (43.3)
Qualifying event		
Overall stroke (%)	20 (57.1)	142 (63.4)
Overall TIA (%)	23 (65.7)	82 (36.6)
Stroke exclusively (%)	12 (34.3)	no data available
TIA exclusively (%)	15 (42.9)	no data available
Both (%)	8 (22.9)	no data available
Symptomatic qualifying artery		
Internal carotid artery (%)	5 (14.3)	45 (20.1)
Middle cerebral artery (%)	14 (42.9)	92 (41.1)
Vertebral artery (%)	8 (22.9)	38 (17.0)
Basilar artery (%)	7 (20.0)	49 (21.9)
Stenosis of symptomatic qualifying artery		
Mean percentage of stenosis	90±5.3	80±7
70-79% stenosis (%)	1 (2.9)	107 (48.0)
80-89% stenosis (%)	15 (42.9)	92 (41.3)
90-99% stenosis (%)	19 (54.3)	24 (10.8)
[patients evaluated]	[34]	[224]
Time from qualifying event to randomization in days	8	7
Interquartile range	5-10	4-16
Antithrombotic therapy at time of qualifying event (%)	13 (37.1)	145 (64.7)

Table 10: Comparison of patients and their qualifying lesion: UKT and SAMMPRIS patients
(Source: Chimowitz et al. Stenting versus Aggressive Medical Therapy for Intracranial Stenosis. 2011. NEJM[68]. and own data and analysis, n=35)

In both studies, a high prevalence of hypertension and diabetes was observed[69]. Both CHD as well as a history of stroke had a slightly higher prevalence amongst SAMMPRIS patients[69].

Taking into account the previously stated possible sources of error in the UKT patients´ data, the differences in smoking history, with a much higher percentage of patients with a current or former history of smoking among SAMMPRIS patients, are to be treated with reservation[69].

Lipid disorders previously diagnosed in a majority of SAMMPRIS patients (86.6%), were diagnosed in only 51.4% of patients included in our study.

The presented risk factors are represented in Table 11.

Risk factors	**UKT**	**SAMMPRIS PTAS group**
Hypertension (%)	33 (94.3)	201 (89.7)
Diabetes (%)	15 (42.9)	106 (47.3)
Lipid disorders (%)	18 (51.4)	194 (86.6)
Smoking history	[35]	[223]
Never (%)	24 (68.6)	90 (40.4)
Former (%)	2 (5.7)	79 (35.4)
Current (%)	9 (25.7)	54 (24.2)
History of coronary heart disease (%)	6 (17.1)	47 (21.0)
History of congestive heart disease (%)	3 (8.6)	no data available
Atrial fibrillation	3 (8.6)	no data available
History of stroke other than qualifying event (%)	6 (17.1)	60 (26.8)

Table 11: Comparison of risk factors: UKT and SAMMPRIS patients
(Source: Chimowitz et al. Stenting versus Aggressive Medical Therapy for Intracranial Stenosis. 2011. NEJM. [68] and own data and analysis, n=35)

The blood LDL- and non-HDL-cholesterol levels were remarkably higher among the UKT patients[69]. It is impossible to tell with certainty whether this reflects a true difference in the state of health, possibly due to a lack of pharmacologic

treatment of the higher number of previously undiagnosed lipid disorders amongst the UKT patients, or is simply explained by the timing of the drawing of blood samples.

Glycated hemoglobin levels amongst diabetic patients were clearly lower in the UKT patient group, possibly indicating better control of blood sugar in diabetic patients[69].

The BMI was remarkably lower among UKT patients, too. While the average BMI for UKT patients was 26.9 kg/m2, classifying as overweight, the average BMI of SAMMPRIS patients was 30.3 kg/m2, classifying as obesity I[69].

The measured indicating parameters are represented in Table 12.

Measured risk indicating parameters	UKT	SAMMPRIS PTAS group
Blood pressure in mmHg		
Systolic [patients evaluated]	148.6±20.7 [35]	143.9±20.6 [220]
Diastolic [patients evaluated]	77.1±12.3 [35]	77.9±10.7 [220]
Lipids in mg/dL		
LDL cholesterol [patients evaluated]	137.1±44.6 [29]	96.3±38.5 [219]
HDL cholesterol [patients evaluated]	46.3±12.3 [30]	37.8±10.6 [219]
Non-HDL cholesterol [patients evaluated]	156.3±59.9 [30]	116.6±43.9 [219]
HbA1c in diabetic patients in % [patients evaluated]	7.5±2.2 [13]	7.9±2.1 [102]
Body-mass Index [patients evaluated]	26.9±3.9 [34]	30.3±6.2 [224]

Table 12: Comparison of measured risk indicating parameters: UKT and SAMMPRIS patients
(Source: Chimowitz et al. Stenting versus Aggressive Medical Therapy for Intracranial Stenosis. 2011. NEJM. [68] and own data and analysis, n=35)

While PTAS has been shown to have high short-term complication rates in international trials such as the SAMMPRIS trial, we registered a comparatively low number of complications in the present study[68,69]. Despite the above stated differences in patient selection, both the inclusion of patients of over 80 years of age, with their correspondingly higher probability of comorbidities, as well as the inclusion of patients with acute neurologic symptoms suggest the inclusion of patients in a less stable state of health and thus with a higher tendency of

reaching an endpoint in our study. Our statistical analysis showed a strong association of advanced age and the occurrence of adverse events. Therefore, if influenced by these differences, our results would be suspected to lead to a worse outcome than those of the SAMMPRIS trial. The contrary was the case. While 17.1% of patients suffered from adverse events, only 8.6% of patients reached an endpoint. Although higher than the percentage of patients reaching an endpoint in the medical group of the SAMMPRIS trial (5.8%), the rate of reaching an endpoint among UKT patients was remarkably lower than among patients of the PTAS group in the SAMMPRIS trial (14.7%)[68,69].

A comparison of the adverse events is represented in Table 13.

Adverse events	**UKT**	**SAMMPRIS PTAS group**
	no. of patients (%)	
Endpoints (within 30 days after procedure)		
Any endpoint	3 (8.6)	33 (14.7)
Ischemic stroke in territory of qualifying artery	1 (2.9)	23 (10.3); 1 fatal (0.4)
Ischemic stroke in other territory	0	0
Symptomatic brain hemorrhage	1 (2.9); 1 fatal (2.9)	10 (4.5); 4 fatal (1.8)
Non-stroke-related death	1 (2.9)	0
Other adverse events		
Asymptomatic brain hemorrhage	1 (2.9)	2 (0.9%)
Procedural arterial dissection	2 (5.7)	No data available

Table 13: Comparison of endpoints: UKT and SAMMPRIS patients
(Source: Chimowitz et al. Stenting versus Aggressive Medical Therapy for Intracranial Stenosis. 2011. NEJM. [68] and own data and analysis, n=35)

Two of the three patients with an endpoint and two of the three patients with other adverse events were over 80 years of age (84 and 82 years and 84 and 81 years, respectively), and would not have been included in the SAMMPRIS

trial[98]. Excluding all patients of more than 80 years of age, as was done in the SAMMPRIS trial, the complication rate in the present study would be lowered considerably, with 3.6% of patients experiencing an endpoint and 7.1% of patients experiencing any adverse event.

PTAS was performed the day of the qualifying event on 4 patients. One of them reached an endpoint. Excluding all patients who would not have been enrolled in the SAMMPRIS trial due to their age or the early procedure, no primary endpoint and only one other adverse event occurred (4.0%).

6. Conclusion

We must aim for the best treatment for our patients with intracranial atherosclerotic stenosis currently available.

This study suggests a favorable short-term outcome for most patients with intracranial atherosclerotic stenosis treated by PTAS at the University Hospital of Tübingen.

A number of adaptations and regulations may be opportune to further improve the safety profile of PTAS such as the exclusion of patients with very recent ischemic events, as indicated in the latest international guidelines[79]. The introduction of a personalized lifestyle modification program, with strict control of modifiable risk factors, and intensive patient counseling seems vital to improving patient care, as it has been shown to have a great effect on the patient's short-term and long-term outcome[68]. An individualized treatment approach that takes risk factors, comorbidity and anatomical characteristics of the stenotic artery into consideration may further improve patient outcome.

We found a much higher risk of periinterventional complications in elderly patients and recommend the consideration of setting an age limit to exclude high-risk patients from PTAS and improve the safety profile of the intervention. For our patients under the age of 70 years, PTAS was considerably safer than described.

Long-term complication rates for PTAS at our center must be evaluated in further studies with higher patient numbers for reliable results, to be able to compare the outcome to international data on PTAS and medical management and perform subgroup analysis to further optimize the outcome.

Answering the third and last of the proposed research questions, with the described premises of excluding elderly patients, PTAS at our institution seems considerably safer than described in the literature and appears to be a reasonably safe treatment method for our patients with symptomatic severe intracranial atherosclerotic stenosis.

Summary

This retrospective study was performed to analyse the periinterventional risk of PTAS (percutaneous transluminal angioplasty with stenting) in 35 patients with recent transitory ischemic attack (TIA) or stroke due to severe intracranial atherosclerotic arterial stenosis treated at the University Hospital of Tübingen (UKT, Universitätsklinikum Tübingen) between 2007 and 2012.

The inclusion criteria were adapted to those of the SAMMPRIS trial. In 2011, this multicenter trial compared PTAS to an intensified conservative treatment of intracranial stenosis and showed a much higher complication rate in the interventional treatment arm.

To improve the safety profile of the intervention and the outcome, the results of our study were analyzed and compared to international literature, highlighting and analyzing differences in patient selection, procedure and outcome.

The majority of patients were male (68.6% vs. 31.4%) and the average age was 69.2±3.4 years. The stenosis showed an average of 85.3±5.3% in reduction of diameter of the arterial lumen, and stenosis was located in the middle cerebral artery (42.9%), intracranial vertebral artery (22.9%), basilar artery (20.0%) and intracranial carotid artery (14.3%). The qualifying event was a stroke in 34.3% of patients, a TIA in 42.9% of patients, and both in 22.9% of patients. The included patients had relevant previously known comorbidities leading to a high cardiovascular risk; 94.3% had hypertension, 42.9% were diabetic, 51.4% had lipid disorders of the blood, 17.1% a history of coronary heart disease, 8.6% a history of congestive heart disease and 8.6% atrial fibrillation. 17.1% of patients had already suffered from a stroke previously and 31.4% had a history of smoking.

For PTAS, both self-expanding and balloon-mounted stent systems were used, and adverse events were observed in both groups. In three cases, a primary end point was reached (ischemic stroke, lethal brain hemorrhage, death by a non-neurologic cause) and in three cases other adverse events were observed (asymptomatic brain hemorrhage, procedural dissections). The overall probability of suffering from any adverse event within the first 30 days of the procedure was 17.1%, with a probability of reaching an endpoint of 8.6%. A decrease of the complication rate over the years could not be observed.

We found a strong association of an advanced age and the occurrence of periinterventional complications.

Despite the inclusion of patients of a higher age, with a higher degree of stenosis and more acute symptoms, the observed complication rate was considerably lower than in the SAMMPRIS trial (8.6% vs. 14.7%). When strictly applying the inclusion criteria of the SAMMPRIS trial, no primary endpoint (0.0%) and only one other adverse event was observed (4.0%). The SAMMPRIS trial, besides medical and interventional therapy, included a lifestyle modification program focusing on the intensive management of risk factors, smoking cessation, nutrition and physical exercise that proved highly favorable for the outcome of patients.

In this study, the interventional treatment of severe intracranial atherosclerotic stenosis with PTAS at the UKT was shown to be considerably safer than described in international literature.

According to our results, further lowering the complication rate by adaptations, such as the exclusion of high-risk patients (for example patients over a certain age by setting an age limit or with very recent events as described in literature) would be possible. To improve patient care, the introduction of a personalized lifestyle modification program with strict control of modifiable risk factors and intensive patient counseling should be considered.

Zusammenfassung

Diese retrospektive Studie untersucht das periinterventionelle Risiko der Behandlung hochgradiger intrakranieller Stenosen mittels perkutaner transluminaler Angioplastie mit Stentimplantation (PTAS) bei 35 Patienten mit transitorischer ischämischer Attacke (TIA) oder Schlaganfall am Universitätsklinikum Tübingen im Zeitraum von 2007 bis 2012.

Die Einschlusskriterien wurden an die der SAMMPRIS-Studie angelehnt. Diese Studie zum Vergleich des Therapieerfolges von PTAS und konservativer Behandlung intrakranieller Stenosen kam 2011 zu dem Ergebnis einer deutlich erhöhten Komplikationsrate bei interventioneller Behandlung mittels PTAS.

Es erfolgt eine Analyse der Ergebnisse unserer Studie und der Vergleich mit der internationalen Literatur, insbesondere im Hinblick auf Unterschiede bei den eingeschlossenen Patienten, Eingriffen und den Ergebnissen.

Von den 35 Patienten waren 68,6% männlich und 31,4% weiblich, das Durchschnittsalter betrug 69,2±3,4 Jahre. Das Gefäßlumen wurde durch die Stenose im Schnitt um 85±5,3% reduziert. Die Lokalisation war zu 42,9% in der A. cerebri media, zu 22,9% im intrakraniellen Abschnitt der A. vertebralis, zu 20,0% in der A. basilaris und zu 14,3% in der A. carotis interna. Die Stenose hatte bei 34,3% der Patienten zum Schlaganfall, bei 42,9% der Patienten zur TIA und bei 22,9% der Patienten zum Auftreten beider Ereignisse geführt.

Die in die Studie eingeschlossenen Patienten waren bereits im Vorfeld an relevanten Komorbiditäten erkrankt, die zu einem entsprechend hohen kardiovaskulären Risiko führten. So litten 94,3% an arterieller Hypertonie, 42,9% an Diabetes mellitus, 51,4% an Dyslipidämie, 17,1% an koronarer Herzkrankheit, 8,6% an Herzinsuffizienz und 8,6% an Vorhofflimmern. Bereits einen Schlaganfall erlitten hatten 17,1% der Patienten, bei 31,4% bestand eine Raucheranamnese.

Es wurden sowohl selbstexpandierende als auch ballonexpandierende Stents implantiert, Komplikationen traten in beiden Gruppen auf. In drei Fällen kam es zum primären Endpunkt (ischämischer Schlaganfall, letale intrakranielle Blutung, Tod ohne neurologische Ursache), in drei weiteren zu einem anderen unerwünschten Ereignis (asymptomatische intrakranielle Blutung, zwei Dissektionen). Somit ergab sich bei einem Risiko von 17,1%, innerhalb der ersten 30 Tage nach dem Eingriff eine Komplikation zu erleiden, ein Risiko von

8,6%, für einen primären Endpunkt. Eine Abnahme der Komplikationsrate über die Jahre war nicht zu beobachten. Unsere Ergebnisse zeigten einen ziemlich starken Zusammenhang zwischen dem Auftreten periinterventioneller Komplikationen und steigendem Alter mit entsprechend höherem Komplikationsrisiko für ältere Patienten.

Trotz des Einschlusses von Patienten höheren Alters, mit höhergradigeren Stenosen und akuteren Symptomen war die Komplikationsrate deutlich geringer als in der SAMMPRIS-Studie (8,6% vs. 14,7%). Unter strikter Einhaltung der Einschlusskriterien der SAMMPRIS-Studie würde sich kein primärer Endpunkt (0,0%) und lediglich ein anderes unerwünschtes Ereignis (4,0%) ergeben. Die in der SAMMPRIS-Studie durchgeführte Behandlung umfasste zudem neben der medikamentösen und interventionellen Therapie ein Programm zur Umstellung des Lebensstils mit Fokus auf Ernährung, körperliche Aktivität, Therapie möglicher Begleiterkrankungen und Raucherentwöhnung, welches sich als deutlich prognoseverbessernd erwies.

Die interventionelle Behandlung hochgradiger intrakranieller Stenosen am Universitätsklinikum Tübingen mittels PTAS erwies sich im Rahmen dieser Arbeit als deutlich sicherer als in der internationalen Literatur beschrieben. Unter Ausschluss der Hochrisikogruppe älterer Patienten scheint sie für den Großteil unserer Patienten als eine Therapiemethode mit vertretbarer Komplikationsrate.

Eine weitere Senkung der Komplikationsrate mittels Modifikationen der Indikationsstellung, wie dem Ausschluss von Hochrisikopatienten, beispielsweise mittels der Einführung einer oberen Altersgrenze, wäre nach unseren Ergebnissen möglich. Die Ergänzung um ein personalisiertes Programm zur Umstellung des Lebensstils analog zur SAMMPRIS-Studie sollte zur Verbesserung der Patientenversorgung erwogen werden.

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Erklärung zum Eigenanteil der Dissertationsschrift

Die vorliegende Arbeit wurde am Universitätsklinikum Tübingen unter Betreuung durch PD Dr. med. Felix Bischof durchgeführt.

Die Konzeption der vorliegenden Arbeit, einschließlich der Festlegung der Auswahlkriterien für das Patientenkollektiv, sowie die zu untersuchenden Fragen, erfolgte in Zusammenarbeit mit PD Dr. med. Felix Bischof.

Ich konnte entsprechend den festgelegten Auswahlkriterien unter Betreuung durch PD Dr. med. Felix Bischof 35 Patienten erfassen. Teilweise parallel erfasste ein weiterer Doktorand von Herrn PD Dr. med. Felix Bischof nach den gleichen Kriterien 46 Patienten für seine Doktorarbeit. Die jeweils separat erfassten Daten sind Grundlage der jeweiligen Dissertationsschriften beider Doktoranden.

Mögliche Ähnlichkeiten der Dissertationsschriften, insbesondere in Konzeption, Aufbau und Inhalt, rühren von der gemeinsamen Ausrichtung und Leitung des Forschungsprojektes durch PD Dr. med. Bischof, sowie der identischen Methodik des Eingriffes und der Datenerfassung, die nach einem vorgegebenen System erfolgte.

Die für die vorliegende Dissertationsarbeit durchgeführte statistische Datenanalyse der Daten von 35 Patienten und gesamte weitere Arbeit an der Abhandlung erfolgte in eigenständiger Arbeit und unabhängig von Dr. med. Toni Silber unter Betreuung durch Herrn PD Dr. med. Bischof durch mich.

Die statistische Analyse und Verarbeitung der durch mich erfassten Rohdaten und die Ausarbeitung der in dieser Arbeit veröffentlichten Daten erfolgte in Rücksprache mit PD Dr. med. Felix Bischof durch mich.

Die textuelle Verarbeitung der Ergebnisse, sowie die Ausarbeitung von Inhalt und Form der Dissertationsschrift einschließlich der Entwicklung der Forschungsfragen und hier veröffentlichten Ergebnisse und getroffenen Aussagen, einschließlich der Analyse und des Vergleichs mit der SAMMPRIS Studie, erfolgte unter Betreuung durch Herrn PD Dr. med. Bischof durch mich.

Die Rohdaten des von mir untersuchten Patientenkollektivs wurden von Herrn Dr. med. Silber zu einem späteren Zeitpunkt in einer Publikation weiterverwendet, jedoch nicht die in dieser Dissertationsarbeit durchgeführte statistische, inhaltliche und textuelle Verarbeitung, die bisher nicht publiziert wurden (Silber et al, Eur. J Radiol. 2014).

Ich versichere, das Manuskript selbständig nach Anleitung von PD Dr. med. Felix Bischof verfasst zu haben und keine weiteren als die von mir angegebenen Quellen verwendet zu haben.

Stuttgart, den 25.02.2020,

Julia Lucia Glatzner

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