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Endovascular Treatment of Carotid In-Stent Restenosis

Ph.D. Thesis

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TARTALOM

ABBREVIATIONS

AI	Artificial intelligence
ARR	Absolute risk reduction
BA	Balloon angioplasty
BAT	Balloon-assisted tracking (technique)
BMS	Bare-metal stent
CAS	Carotid artery stenting
CCA	Common carotid artery
CT	Computed tomography
CTA	Computed tomography angiography
CAD	Coronary artery disease
CEA	Endarterectomy
CHD	Coronary heart disease
CKD	Chronic kidney disease
CRAO	Central retinal artery occlusion
DAPT	Dual antiplatelet therapy
DCB	Drug-coated balloon
DEB	Drug eluting balloon
DES	Drug-eluting stent
DM	Diabetes mellitus
DSA	Digital subtraction angiography
DUS	Doppler ultrasound
ECST	European Carotid Surgery Trial
EDV	End diastolic velocity
EESZT	National eHealth Infrastructure
ELA	Excimer laser atherectomy
ESVS	European Society for Vascular Surgery
FU	Follow-up
ICA	Internal carotid artery
ISR	In-stent restenosis
LDL	Low-density lipoprotein

LLL	Late lumen loss
LVO	Large vessel occlusion
MACE	Major adverse cardiovascular event
MDT	Multidisciplinary team
MMP	Matrix metalloproteinase
MPR	Multiplanar reformatting
MRA	Magnetic resonance angiography
NSTEMI	Non-ST-elevation myocardial infarction
PAD	Peripheral arterial disease
PSV	Peak systolic velocity
PTA	Percutan transluminal angioplasty
Re-PTA	Reangioplasty
SAPT	Single antiplatelet therapy
STEMI	ST-elevation myocardial infarction
SVD	Small vascular disease
TIA	Transient ischemic attack
TLR	Target lesion revascularisation
TO	Tandem occlusion
US	Ultrasound
VSMC	Vascular smooth vessel cell

PUBLICATIONS

This thesis is based on the following publications:

I. Marton A, Blényesi E, Török K, Balogh G, Gubucz I, Nardai S, Lenzsér G, Nagy C, Bajzik G, Tollár J, Repa I, Nagy F, Vajda Z. Treatment of In-stent Restenosis of the Internal Carotid Artery Using Drug-eluting Balloons. **Clin Neuroradiol**. 2023 Sep 7. doi: 10.1007/s00062-023-01343-6. Epub ahead of print. PMID: 37676281. **IF: 3,156**

II. Marton A, Blényesi E, Tollár J, Héger J, Nagy C, Szász K, Horváth G, Nagy F, Vajda Z. Az a. carotis interna in-stent restenosisának kezelésével szerzett tapasztalataink **IDEGGYÓGYÁSZATI SZEMLE PROCEEDINGS / CLINICAL NEUROSCIENCE PROCEEDINGS** 6: 1 pp. 29-29., 1 p. (2021)

III. Marton A, Nagy C, Lenzsér G, Nardai S, Gubucz I, Bajzik G, Nagy F, Vajda Z. Acut ischaemiás stroke neurointervenciós kezelése: kaposvári tapasztalatok. **IDEGGYÓGYÁSZATI SZEMLE PROCEEDINGS / CLINICAL NEUROSCIENCE PROCEEDINGS** 7: 3 pp. 156-157., 2 p. (2022)

Additional publications, not related to the thesis:

I. Szőts M, Marton A, Illés Z, Bajzik G, Nagy F. AZ LGI1--ENCEPHALITIS HAZÁNKBAN ELSŐKÉNT DIAGNOSZTIZÁLT ESETE [LGI1 ENCEPHALITIS: THE FIRST HUNGARIAN PATIENT]. **Ideggyogy Sz**. 2015 Jul 30;68(7-8):279-85. Hungarian. doi: 10.18071/isz.68.0279. PMID: 26380423. **IF: 0,8**

II. Szőts M, Marton A, Kövér F, Kiss T, Berki T, Nagy F, Illés Z. Natural course of LGI1 encephalitis: 3-5 years of follow-up without immunotherapy. **J Neurol Sci**. 2014 Aug 15;343(1-2):198-202. doi: 10.1016/j.jns.2014.05.048. PMID: 24928080. **IF: 4,553**

III. Blényesi E, Tollár J, Nagy C, Marton A, Héger J, Nagy F, Vajda Z. Az a. vertebralis intrakranialis szakasza tünetképző szűkületeinek **IDEGGYÓGYÁSZATI SZEMLE PROCEEDINGS / CLINICAL NEUROSCIENCE PROCEEDINGS** 6: 1 pp. 29-30., 2 p. (2021)

INTRODUCTION

BURDEN OF ICA ATHEROSCLEROTIC LESIONS

Ischemic stroke

Stroke is the most common significant manifestation of cerebrovascular disease and is the second greatest cause of disability and death globally, with low- and middle-income nations bearing the majority of the disease's burden. **[Vasu et al., 2021]** Globally, 13.7 million new incident strokes occurred in 2016; 87% of these were ischemic strokes, and a conservative estimate places 10%–20% of these as large vessel occlusion (LVO). It is the main reason for hospitalization for neurologic illness **[Steven et al., 2021]**. Since the late 1990s, there has been a decline in the incidence of stroke, which is correlated with better cardiovascular risk factor management, including better management of cardiac arrhythmias and decreased rates of smoking as well as hypertension, diabetes mellitus, and hyperlipidemia. **[Steven et al., 2021] [Virani et al., 2020]** The major lesion associated with ischemic stroke is brain infarction, which occurs as a result of artery stenosis or occlusion. Insufficient blood supply to brain tissue leads to an initial reversible impairment of tissue function, followed by a subsequent infarction event, ultimately leading to neuronal and supporting structure demise. Ischemia triggers a series of events that begin with the cessation of electrical activity, continue with the disruption of membrane function caused by the entry of calcium ions, result in calcium-dependent excitotoxicity, produce reactive oxygen species, and ultimately lead to cellular lysis. **[Steven et al., 2021]** The TOAST classification identifies five subtypes of ischemic stroke, including large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined origin, and stroke of unknown etiology. The level of agreement among physicians utilizing this rating approach was quite high. **[Adams et al., 1993**] Adequate treatment of ischaemic stroke reduces the mortality and disability of patients.

Tandem occlusion

A tandem lesion has been defined as the simultaneous presence of high-grade stenosis or occlusion of the cervical internal carotid artery and thromboembolic occlusion of the intracranial terminal internal carotid artery or its branches, typically the middle cerebral artery. It is present in 20–30% of patients with acute ischemic stroke caused by large intracranial vessel occlusion. Atherosclerosis or dissection were the primary cause, less commonly cardioembolism or undetermened etiology. Due to their poor responsiveness to fibrinolysis and/or large clot load, tandem occlusions (TOs) have poorer prognosis for reperfusion and clinical result after IV fibrinolysis. Since they can result in severe neurologic morbidity and mortality in as many as 70% and 55% of anterior circulation stroke patients, respectively, tandem occlusions are regarded as the worst-case situations. **[Di Donna et al., 2023]** Interventional cardiologists developed the balloon-assisted tracking technique (BAT), which involves exposing a partially deflated balloon out of the catheter tip to help the device pass through stenosed or spastic arterial segments. More recently, the application of the technique in the field of neurointervention has been used with encouraging results, the technique being feasible, safe and efficient. **[Nagy et al., 2022]**

A. centralis retinae occlusion

A form of an acute ischemic stroke is central retinal artery occlusion (CRAO), when the amaurosis fugax/transient monocular blindness lasts for more than a day. **[Cheng et al., 2019]** It is a serious disorder that frequently results in severe vision loss or blindness and may be an early sign of more cerebrovascular events. There are no effective evidence-based treatment options for this condition since the lack of scientific data. Summary statistics of patient data from relevant research show that, within 4.5 hours after the beginning of symptoms, 45% of patients receiving alteplase resulted a substantial improvement in visual acuity. **[Janska et al., 2022**] The causes are alike to those of ischemic stroke and are frequently categorized using the TOAST classification. **[Adams et al.,**

1993] Common cause is carotid artery stenosis, which is treatable surgically with endarterectomy (CEA) or with carotid artery stenting (CAS) as well. It should be considered similar urgent intervention as in other forms of stroke, since patients with carotid stenosis have a higher risk of stroke recurrence**. [Cheng et al., 2019]**

DEVELOPMENT AND PROGRESSION OF ATHEROSCLEROSIS

Atherosclerosis is a common chronic inflammatory condition affecting the artery wall. **[Poznyak et al., 2020]** The global mortality rate is significantly impacted by the prevalence of atherosclerosis. In contrast to previous decades, atherosclerosis now manifests in individuals at younger ages, exhibits a higher prevalence among women, and encompasses a broader range of ethnic backgrounds. **[Libby et al., 2021]** Atherosclerosis manifests in its advanced phases as the development of a lesion in the intimal layer of the arterial wall and the subsequent creation of plaque. The ensuing erosion or rupture of atherosclerotic plaques may lead to thrombotic events that have the potential to be deadly. It primarily involves the buildup of lipids and the presence of persistent inflammation inside the artery wall. **[Poznyak et al., 2020]** A heightened concentration of circulating altered low-density lipoprotein (LDL) has been shown as a significant factor contributing to the susceptibility of individuals to cardiovascular and cerebrovascular disorders **[Summerhill et al., 2019]**. Inflammation is the most prominent and intricate factor, beyond mere changes in lipid metabolism. **[Taleb et al., 2016]** The initial pathogenic event in the development of atherosclerosis is believed to be local endothelial dysfunction, which can be triggered by turbulent blood flow occurring at arterial bends or bifurcations. Upon exposure to mechanical stress, the endothelium of blood vessels undergoes activation, leading to the subsequent recruitment of circulating immune cells. Circulating monocytes adhere to the injured segment of the arterial wall and then infiltrate, differentiating into macrophages that actively absorb lipids by phagocytosis. These macrophages then transform into foam cells, which

are extensively dispersed inside atherosclerotic plaques. **[Poznyak et al., 2020]** Atherosclerotic lesions exhibit non-random distribution across the vasculature. Five primary classifications are known according to the distribution of arterial plaque. The coronary arteries, which are the primary branches originating from the aortic arch, together with the abdominal aorta and its visceral and main lower extremity branches, are locations that exhibit a heightened vulnerability to the atherosclerotic process. The clinical signs of the illness are mostly attributed to the location of plaque in these areas. The prognosis criteria and treatment choices for lesions in these arteries are determined by the patterns of arterial occlusive disease **[Frangos et al., 1999]**.

PREVENTIVE TREATMENT OF ICA LESIONS

Prevalence of ICA stenosis

Stenosis of the internal carotid artery presents a significant risk for stroke. Individuals who experience signs of cerebral ischemia, such as a transient ischemic attack or a minor disabling stroke, and have a carotid stenosis of 50% or more, have a significant risk of recurring events. Studies have shown that the risk of stroke was 21% within 2 weeks following the first TIA or stroke and increased to 32% after 12 weeks**. [Fairhead et al., 2005]** According to the research conducted by de Weerd et al, the prevalence of asymptomatic carotid artery stenosis in the general population was found to be 2% for moderate (50 %) stenosis and 0.5% for severe (70 %) stenosis. This analysis was based on the examination of 23,706 individuals using Doppler ultrasound (DUS). **[de Weerd et al., 2014].** Parallel with these data, it may be concluded that the number of cases of severe (70 %) ICA stenosis in Hungary is around 50,000.

Risk reduction due to preventive treatment of ICA stenosis

Rothwell et al. analysed a pooled data from the European Carotid Surgery Trial (ECST), North American Symptomatic Carotid Endarterectomy Trial (NASCET), and Veterans Affairs trial (VA). They calculated the absolute

risk reductions with surgery at 3, 5, and 8 years for patients with different levels of stenosis (less than 30%, 30-49%, and 50% or greater by decile), as well as for near-occlusions. (Figure 1) Decile-based stenosis measurements were not accessible for VA. Consequently, the study was limited to ECST and NASCET. The surgical procedure resulted in a gradual improvement in the primary outcomes' benefits, ranging from 50-59% stenosis to 90% stenosis or higher (excluding near-occlusion). The effect shown at 3 years' follow-up in individuals with stenosis ranging from 50-59% and 60-69% was minimal, but increased over time. Individuals with stenosis ranging from 60% to 69% experienced a similar level of benefit compared to individuals with stenosis ranging from 70% to 79% after 8 years. Nevertheless, the advantages of surgery were observed solely in patients with stenosis levels of 80-89% and 90% or above (excluding near-occlusion), in terms of preventing disabling or fatal ipsilateral ischemic stroke, operational stroke, and operative mortality. **[Rothwell et al., 2003]**

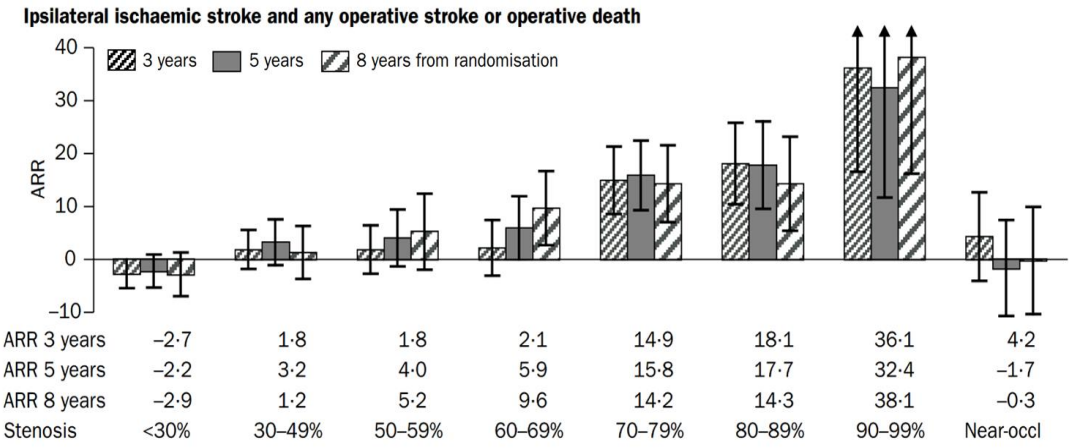

Figure 1. Effect of surgery on absolute risk of main trial outcomes at 3, 5, and 8 years' follow-up by degree of symptomatic carotid stenosis, in analysis of pooled data from ECST and NASCET.

Exact absolute risk reductions (ARR) with surgery are given below each graph. *Near-occl*=near-occlusion. **[Rothwell et al., 2003]**

Results of randomised trials

The endarterectomy procedure was first performed in 1954. The ACAS and ACST trials conducted in 1995 and 2004 respectively, provided evidence that endarterectomy significantly decreases the 5-year risk of a major stroke by 50% in individuals with asymptomatic ICA stenosis, as compared to medical treatment. **[Rosenfield et al., 2016]** Both the ACT-I trial conducted in 2016 and the CREST study conducted in 2021 have demonstrated that there is no detectable difference in the efficacy of carotid artery stenting (CAS) and endarterectomy for stroke prevention throughout the 5- and 10-year follow-up periods, respectively. **[Brott et al., 2016] [Halliday et al., 2021].** The ACST-2 trial revealed that major perioperative complications are similarly rare, and there is no difference in the long-term stroke prevention efficacy between carotid artery stenting (CAS) and carotid endarterectomy (CEA). **[Halliday et al., 2021]** The ongoing trials include the ECST-2 trial, which compares invasive therapy to conservative treatment for low risk ICA stenosis. The CREST-2 trial compares invasive therapy to conservative treatment for asymptomatic ICA stenosis. The CREST-H trial investigates the impact of asymptomatic ICA lesions on cognitive functions. Lal et al. have demonstrated a connection between asymptomatic carotid stenosis and cognitive impairment, which is not influenced by the established risk factors for vascular cognitive impairment. The impairment is mostly caused by a decrease in motor/processing speed and learning/memory abilities, and it is of mild to moderate intensity. The cause of impairment is most likely hemodynamic, as shown by a decrease in the ability of the brain's blood vessels to adapt and compensate for lower blood flow due to a decrease in pressure caused by the narrowing of the blood vessels, and insufficient development of alternative blood pathways. **[Lal et al., 2017]**

IN-STENT RESTENOSIS

Incidence

The occurrence of in-stent restenosis (ISR) following carotid artery stenting (CAS) has a significant impact on the long-term benefits and safety of CAS.

The reported incidence of ISR following CAS varies substantially, between 3% and 20%, explained in part by differing definitions of ISR, Doppler criteria used for identifying ISR, and the duration of follow-up time across operators. A meta-analysis conducted in 2017 examined the incidence of restenosis over 70% based on data obtained from randomized controlled trials that evaluated carotid endarterectomy (CEA) and carotid artery stenting (CAS). After CEA the rate of ISR > 70 % was 5,8 %, after CAS it was 10 %. The incidence of ipsilateral stroke following CEA at a follow-up period of 37 months was 5.0%, whereas the incidence following CAS at a follow-up period of 50 months was 0.8%. **[Kumar et al., 2017]** The TARGET-CAS prospective academic registry revealed an incidence of in-stent restenosis ranging from 4.6% to 6.3%. Notably, about half of the patients exhibited restenosis within a six-month timeframe. **[Tekieli et al., 2019]**

Comparison of other vascular territories (peripheral, coronary)

Several studies have demonstrated that there is cellular heterogeneity within the vascular system and vascular smooth muscle cells, which can vary based on the stage of development, state of damage, and specific location. Coronary arteries have distinct characteristics in terms of blood flow during the diastolic part of the cardiac cycle, in contrast to peripheral arteries which experience blood flow alterations during the systolic phase. **[Krueger et al., 2006]** It has been demonstrated a higher level of intimal hyperplasia in coronary arteries as compared with iliac arteries post-stenting, using a porcine model. The extent of restenosis was related to the extent of injury. **[Krueger et al., 2006] [Ward et al., 2002]**

Coronary arteries

The efficacy of conventional balloon angioplasty as a therapeutic option for bare-metal stent in-stent restenosis (BMS-ISR) is constrained by significant restenosis rates ranging from 40% to 60%. The utilization of drug-eluting stents (DES) for implantation in restenotic bare-metal stents

(BMS) has gained widespread acceptance among the medical community. The rates of restenosis following the implantation of a drug-eluting stent (DES) for the treatment of BMS-ISR range from 16% to 21%. Additionally, the rates of restenosis for the treatment of ISR in DES, regardless of the specific antiproliferative medication employed, are about 20%. Sheller et al. conducted a study over a period of more than five years to investigate the efficacy of paclitaxel-iopromide-coated balloons in the treatment of coronary bare-metal stent in-stent restenosis (BMS-ISR). The study found that the positive outcomes observed initially were maintained, and the coated balloon demonstrated similar results to an uncoated balloon. This is significant as it highlights the advantage of drug-coated balloons (DCB) over drug-eluting stents (DES) in enabling localized intravascular drug delivery without the requirement for stent implantation. **[Scheller et al., 2012]**

Moussa et al. reported the clinical significance of ISR. Those with ISR had a considerably higher prevalence of unstable angina than those without ISR (51.8% vs. 38.6%, p 0.001). 18.7% of people with ISR had a non-ST-elevation myocardial infarction (NSTEMI), and 8.5% of people with ISR had a STEMI. **[Moussa et al., 2020]**

Peripheral arteries

ISR has been recorded in 18-40% of patients following femoropopliteal stenting within the first year of therapy. One of the biggest issues in endovascular therapy for peripheral arterial disease (PAD) is the management of ISR. Standard balloon angioplasty with or without repeat stenting (with bare-metal stents, stent grafts, or drug-eluting stents), drugcoated or cutting balloon angioplasty, cryoplasty, and directed or laser atherectomy are also therapy possibilities for ISR. The best effective technique for treating ISR in the context of PAD is still controversial. A systematic review of the literature investigated the outcomes of different treatment strategies for ISR in PAD. Individual trial results indicated that drug-coated balloon angioplasty, treatment with the heparin-bonded

Viabahn endoprosthesis, and adjuvant excimer laser atherectomy (ELA) provide better outcomes than standard balloon angioplasty, as evidenced by lower rates of recurrent ISR, higher freedom from target lesion revascularization (TLR), technical success, primary patency rates, and clinical improvement. **[Hajibandeh et al., 2019]** Tan et al.'s study results clearly highlight the magnitude of the ISR problem in endovascular treatment of PAD. The researchers examined 260 femoropopliteal lesions treated in 250 patients with LifeStent self-expanding nitinol stents. The whole population's 3-year restenosis rate was predicted to be 72.9%, with 36.9% reporting significant limb adverse effects. **[Tan et al., 2021]**

Tsujimura et al. looked at the results of 453 individuals who had endovascular therapy for 481 femoropopliteal lesions with InnovaTM self-expanding nitinol stents. Restenosis occurred in 36% of patients after one year, and a significant adverse limb event occurred in 18%. The prevalence of diabetes in the studied population was 61%. **[Tsujimura et al., 2019]**

ISR pathogenesis

The processes of endothelialisation and neointimal development may be observed as reparative mechanisms following arterial damage resulting from balloon dilatation and stent insertion. Vascular wall damage triggers the activation of the inflammatory response due to mechanical stretching, denudation of the endothelium, and subintimal hemorrhage. The activation of the proliferative process is heavily influenced by both local and systemic inflammation. This process involves various activities such as the proliferation, migration, and differentiation of vascular smooth muscle cells (VSMCs), as well as the migration of matrix metalloproteinases (MMPs), DNA replication, and synthesis of extracellular matrix. The involvement of endothelial progenitor cells in the promotion of vascular smooth muscle cell proliferation and migration, resulting in enhanced neointimal accumulation after vascular wall damage, has been demonstrated. Neointimal hyperplasia is the outcome of these several processes. The subsequent expansion of neointima results in the recurrence of luminal

constriction in the blood artery, known as restenosis. This phenomenon is referred to as neoatherosclerosis. The primary mechanism that defines neoatherosclerosis is the buildup of macrophages with lipids, which then develop into foam cells within the neointima layer. Subsequently, it may be accompanied by the occurrence of necrotic core development, calcification, or thrombosis. **[Jakubiak et al., 2021]**

Factors that cause in stent restenosis

The precise risk factors contributing to the occurrence of restenosis following carotid artery stenting (CAS) have yet to be fully understood. Advanced age, hyperglycemia, smoking, and prior carotid endarterectomy (CEA) have been associated with an increased likelihood of restenosis. Residual stenosis **[Cosottini et al, 2010],** suboptimal technical outcomes **[Shillinger et al., 2003]**, smaller stent dimension **[Clark et al., 2006]** following CAS is associated with an increased likelihood of in-stent restenosis (ISR). Female gender, diabetes, dyslipidemia, hypertension, smoking, and chronic kidney disease (CKD) stage 4 or 5 may serve as possible risk factors for the occurrence of carotid restenosis. **[Texakilidis et al., 2019]** The findings of the CREST trial indicate that smoking is a distinct and autonomous risk factor for restenosis, but only in cases following carotid endarterectomy (CEA). **[Brott et al., 2010]** It was shown that hypertension serves as a risk factor for restenosis following CAS, but not following CEA. Hypercholesterolemia is well recognized as a significant risk factor for the development of atherosclerotic disease. Research findings have demonstrated a substantial correlation between hyperlipidemia and the occurrence of carotid restenosis following both CEA and CAS. **[Texakilidis et al., 2019]** Diabetes mellitus (DM) is a substantial risk factor in the pathogenesis of atherosclerotic cardiovascular illnesses, including coronary heart disease (CHD), cerebrovascular disease, and peripheral arterial disease (PAD). **[Glovaci et al., 2019]** Cardiovascular disease can be a predictor for >50% restenosis. **[Daou et al., 2016]** The rate of restenosis may be influenced by the characteristics

of the target lesion. There was a significant association seen between the presence of plaques measuring over 20 mm and calcifications with the occurrence of restenosis. Various anatomical, technical, and hemodynamic characteristics, including the presence of numerous stents, inadequate stent coverage in the common carotid artery (CCA), the persistence of stenosis after CAS, and the occurrence of contralateral carotid stenosis, may potentially contribute to the development **[Wasser et al., 2012].**

Classification of ISR

Restenosis may be classified as residual stenosis after unsuccessful revascularization or recurring stenosis after successful revascularization. Recurrent stenosis is the lack of residual stenosis at 1 month followed by >50% stenosis or occlusion. **[Arquizan et al., 2011]** Regarding the occurrence of restenosis following CAS) three distinct kinds of ISR have been identified and documented: 1. the "in-stent" restenosis produced by neointimal hyperplasia resulting from the narrowing of the lumen within the stent, either symmetrically or asymmetrically, subsequent to an initial favorable outcome. 2. "End-of-stent" restenosis refers to the recurrence of stenosis following carotid patch thromboendarterectomy, inflicted by either local causes or technical faults. 3. "Tandem" restenosis occurs less frequently and is potentially the most benign in terms of the durability of therapy. **[Ierardi et al., 2019]**

Diagnosis of ISR

The use of CAS for the treatment of carotid artery stenosis has gained acceptance currently as a safe alternative to CEA, particularly in patients at high surgical risk. CAS or CEA is followed by vascular imaging to detect thrombus or neointimal hyperplasia-induced restenosis. Duplex sonography, CTA, MRA, or selective digital subtraction angiography, which can assess carotid artery restenosis severity.

DUS

Doppler ultrasound (DUS) is advantageous in postprocedure monitoring following carotid intervention, since it aids in the identification of restenosis. It is a cost-effective and replicable technique that offers a noninvasive approach for diagnosing carotid artery atherosclerotic disease. Additionally, it may be utilized to evaluate restenosis during postoperative monitoring following carotid artery stenting (CAS). **[Ringer et al., 2002]**.

Multiple investigations were conducted to develop sonographic cut-off criteria for diagnosing various degrees of carotid in-stent restenosis (ISR). These studies utilized peak systolic velocity (PSV), end-diastolic velocity (EDV), and the internal to common carotid artery PSV ratio (I/C) as diagnostic parameters. The PSV criteria is often regarded as the most precise indicator of ISR. Indeed, it has a positive correlation with the degree of stenosis. The inclusion of EDV and I/C as criteria in the DUS evaluation has the potential to enhance its accuracy**. [Grant et al., 2003]**

A systematic analysis was conducted to assess twelve studies that presented sonographic criteria for grading at least 70% ISR. The selection of this threshold is mostly based on its prevalent utilization within vascular centers for the purpose of intervention. The researchers' conclusion is that a PSV value ranging from 300 to 350 cm/s can serve as a reasonably effective and responsive indicator for the presence of high grade ISR. **[Pizzolato et al., 2014]**

To assess restenosis, DUS examinations can be conducted at the intervals of 1 and 6 months initially, followed by yearly evaluations afterward**. [Brott et al., 2011**] Settaci et al determined in a study including a comprehensive follow-up protocol, which involved doing DUS examinations at regular intervals of 1, 3, 6, 9, and 12 months, followed by annual controls thereafter They defined a peak-systolic velocity (PSV) of greater than or equal to 300 cm/s, in conjunction with an end-diastolic velocity (EDV) of greater than or equal to 140 cm/s, a specificity of 99% and a sensitivity of 98% were attained for ISR values greater than or equal to 70%. **[Settaci et al., 2008]**

CTA

Computed tomography angiography (CTA) provides the capability to acquire three-dimensional reconstructions and centerline measurements for the segmentation of artery lumens. Moreover, CTA demonstrates high accuracy in the assessment of carotid stenosis. **[Samarzija et al., 2018]** It is a widely used noninvasive phenotyping technique for patients with suspected carotid stenosis. It offers a rapid and straightforward approach, enables the observation and objective evaluation of the extent of stenosis and characteristics of plaque morphology. **[Anzidei et al., 2012]** A potentially effective noninvasive alternative method that shows promise is the cone beam computed tomography (CT) technique, which involves the injection of intravenous contrast media. This procedure is often conducted in an angiographic suite that is equipped with a flat-detector. One problem of this technique is the absence of bolus tracking and limited accessibility, which may impede its use. **[M. N. Psychogios et al., 2010]** The precise visualization of the stent lumen and accurate quantification of in-stent restenosis are not achievable using MR imaging.

MRA

Magnetic resonance angiography (MRA) is a distinct method for assessing blood vessels that has several advantages. It is noninvasive, it does not expose the patient to ionizing radiation, it has the potential to be performed without the use of contrast agents, and it can provide three-dimensional representations that effectively display vascular abnormalities. There exist two primary methodologies for MR angiography. Contrast-enhanced magnetic resonance angiography (CE MRA) employs gadolinium as contrast, whereas time-of-flight (TOF) or phase contrast (PC) MRA relies on the natural circulation of physiological fluids. Standard magnetic resonance imaging (MRI) typically includes time-of-flight magnetic resonance angiography (MRA). Although this sequence does not require

a contrast medium, it has significant disadvantages. The spatial coverage of this technique is limited since it does not include the extracranial vasculature. Additionally, it is very susceptible to motion artifacts due to the fact that the magnetic resonance (MR) signal is produced by the motion of the blood. **[S. Bash et al., 2005**] Flow disturbances have a lesser impact on contrast-enhanced MR angiography. While time-of-flight MRA has a longer acquisition time, it is capable of imaging the entire supra-aortic area. However, it falls short in terms of spatial resolution compared to time-of-flight angiography. Contrast-enhanced MR angiography is a viable diagnostic alternative to CT angiography and DSA for the thorough assessment of neck and head arteries. It accurately identifies clinically important neurovascular disorders.

DSA

Despite the advancements in noninvasive diagnostic neuroimaging, digital subtraction angiography (DSA) continues to be widely regarded as the preferred method for imaging assessment of blood vessels and hemodynamics. This preference is mostly due to the exceptional spatial and temporal resolution capabilities offered by DSA. It is increasingly performed when considering interventions for extracranial and intracranial steno-occlusive disease. One of the disadvantages of this operation is its invasive character, which carries a stroke risk of 0.7% due to the requirement for intraarterial catheterization of the precerebral cervical arteries. In a neurointerventional practice characterized by a large volume of cases, it is expected that the incidence of significant complications related to diagnostic angiography should be minimized to a negligible level. The operator's level of expertise and procedural volume play a vital role in ensuring the safety of this intervention. **[R. Thiex et al., 2010]**

TREATMENT OF ISR

The indication for the invasive treatment of ISR is controversial. The current guidelines adopt a conservative approach, which is based on a single meta-analysis **[Kumar et al., 2017]** However, long term clinical effects of ISR regarding stroke prevention and cognitive disfunction are not fully understood at the present. Here we present a short overview of the currently used ISR treatment modalities and elaborate the pros and cons of ISR treatment in the Discussion.

The treatment approach most frequently utilized for in-stent restenosis (ISR) involves performing percutaneous transluminal angioplasty (PTA) with a conventional balloon, followed by subsequent repeat carotid artery stenting (CAS), and ultimately, carotid endarterectomy (CEA) with stent removal. Additional options include various endovascular procedures, such as repeated balloon angioplasty (CB-PTA), and more recent research indicates that repeated angioplasty with the application of drug-coated balloons (DCBs) is also a viable approach. Carotid artery bypass procedures, brachytherapy interventions, and deployment of drug-eluting stents (DESs) have been documented in a limited number of cases. **[Pourier et al., 2016].**

While traditional balloons are effective in temporarily restoring the lumen, they lack the ability to address the underlying pathophysiology of neointimal hyperplasia. **[Vajda et al., 2011]** Restenting is associated with the potential risk of developing intimal hyperplasia.

DEB re-PTA

Drug-eluting balloons (DEBs) provide several benefits compared to traditional balloons and drug-eluting stents. **[Vajda et al., 2011]** Drug-eluting stents have the ability to inhibit the excessive growth of neointimal tissue by gradually releasing an anti-inflammatory substance over an extended period. However, they are associated with an elevated likelihood of late in-stent restenosis (ISR), as well as other complications related to

stent placement, including the formation of blood clots within the stent (mural thrombus formation), incorrect positioning of the stent, stent compression, and a significant dependence on dual antiplatelet therapy. Drug-eluting balloons (DEBs) have the potential to overcome the constraints associated with stent implantation by simultaneously delivering an antiproliferative substance to reduce neointimal hyperplasia. **[Bhatia et al., 2020]**

Development of DEB technology

Andreas Grüntzig invented balloon angioplasty at the Medical Policlinic of the University of Zürich in the early 1970s. This was one of the most important technical and therapeutic improvements in medicine of the 20th century. It only took Grüntzig a few years to turn an idea into a working technical device. This was the first time that an artery could be opened up from the inside by pressing on a balloon at the tip of the catheter. Since it was first used in 1974 **[Grüntzig et al., 1974]**, balloon angioplasty has become the most common way to treat heart and peripheral circulation vascular problems. Braunwald described the treatment for acute myocardial infarction as "myocardial reperfusion," which began with Grüntzig's finding and is still going on today **[Braunwald et al., 2012]**. This phase has saved many patients from dying or becoming disabled. Significant advancements have been made in both the procedural approach and medical instruments utilized in coronary angioplasty since its inception. **[Grüntzig et al., 1978]**

Drug-coated balloons (DCBs) refer to angioplasty balloons that have been coated with a cytotoxic chemotherapeutic substance, thereby rendering them standard (semi-compliant) in nature. At now, the predominant choice of drug in commercially accessible drug-coated balloons (DCBs) is paclitaxel. The balloon in question employs iopromide, a contrast medium, as an excipient to keep the medicine on the balloon. Additionally, upon inflation of the balloon, iopromide's lipophilicity enables fast distribution to the vessel wall. The medication is uniformly administered to the vascular

wall during balloon inflation, in contrast to the non-uniform distribution observed with drug-eluting stents. The observed half-life of the final phase is about two months. **[Speck 2015**] Various paclitaxel-coated balloons are commercially available, employing diverse coating methods and excipients.

The first application of drug-coated balloons (DCBs) in the clinical setting was performed in lesions associated with peripheral artery disease and results were reported in Local Taxane with Short Exposure for Reduction of Restenosis in Distal Arteries (THUNDER) trial in 2008. The THUNDER study conducted a randomization of 154 patients who had femoropopliteal lesions. These patients were divided into two groups: one group had angioplasty with paclitaxel, while the other group did not receive paclitaxel. The study findings indicated that the use of drug-coated balloon (DCB) in angioplasty was linked with a statistically significant reduction in late lumen loss and a decreased risk of target lesion revascularization (TLR). Numerous following studies have demonstrated that drug-coated balloons (DCBs) exhibit more favorable results as compared to uncoated balloon angioplasty (BA) in the treatment of femoropopliteal lesions. In the context of managing obstructive coronary artery disease (CAD), drug-coated balloons (DCBs) were initially explored as a prospective intervention for in-stent restenosis (ISR) subsequent to the use of bare-metal stents (BMS) and drug-eluting stents (DES). This investigation was conducted through the Treatment of in-Stent Restenosis by Paclitaxel Coated PTCA Balloons (PACCOCATH–ISR I) study, which involved the enrollment of 52 patients in 2003. The study demonstrated a notable reduction in late lumen loss at the 6-month mark when comparing the use of coated balloon angioplasty with uncoated balloon angioplasty. Numerous following studies have provided further confirmation on the efficacy of drug-coated balloons (DCBs) in minimizing late lumen loss shown in angiographic assessments of in-stent restenosis (ISR) lesions. Further investigation was conducted on drug-coated balloons in the context of de novo coronary lesions, which

encompassed bifurcation lesions as well. **[Megaly et al., 2018]**

The outcomes of randomized trials investigating the efficacy of drug-coated balloons (DCB) in the treatment of small arteries exhibited considerable heterogeneity. The first generation of the Dior DCB device did not demonstrate angiographic noninferiority compared to the Taxus drug-eluting stent (DES) in the prematurely halted PICCOLETO research. In this investigation, the incidence of major adverse cardiac events (MACE) after 9 months was shown to be greater in the DCB arm. The results were attributed to the low efficacy of this initial drug-coated balloon (DCB). However, the newer-generation drug-coated balloons (DCB) has demonstrated the potential benefits of this technique in cases of sickness affecting the native blood vessels. The BELLO trial, also known as the Balloon Elution and Late Loss Optimization trial, demonstrated the angiographic superiority of the In-Pact Falcon Drug-Coated Balloon (DCB) compared to the Taxus stent. Additionally, the 3-year data from the study revealed a notable decrease in the incidence of Major Adverse Cardiovascular Events (MACE) in patients treated with the In-Pact Falcon DCB (14%) compared to those treated with the Taxus stent (30%), with a statistically significant p-value of 0.015. The RESTORE SVD study aimed to evaluate the effectiveness and safety of the RESTORE Paclitaxel Eluting Balloon (DCB) in comparison to the RESOLUTE Zotarolimus Eluting Stent (DES) for treating small coronary vessel disease. The study findings indicated that the DCB was not inferior to the DES in terms of percent diameter stenosis observed during angiographic follow-up. Additionally, there were no significant differences observed between the two treatments in terms of late lumen loss (LLL) and the occurrence of major adverse cardiac events (MACE) at the 12-month mark. The BASKET SMALL II research, which was adequately powered to evaluate clinical outcomes, examined the efficacy of drug-coated balloons (DCB) in the context of small vascular disease (SVD) with a reference vessel diameter of less than 3 mm. This study specifically focused on cases where lesion pre-dilatation had been successfully performed. The Sequent Please DCB

was compared to drug-eluting stents (DES) in this investigation. The primary outcome measure of major adverse cardiovascular events (MACE) at the 12-month mark was seen to be 7.3% in the drug-coated balloon (DCB) group and 7.5% in the drug-eluting stent (DES) group. The PICCOLETO II trial demonstrated the angiographic superiority of a new-generation drug-coated balloon (DCB) compared to one of the latest-generation drug-eluting stents (DES) in the treatment of native vascular disease. This advantage was shown in terms of the late lumen loss (LLL) endpoint. Furthermore, the study found that the clinical outcomes after one year were comparable between the two treatment approaches. The aforementioned discovery was validated across all pre-determined subcategories. **[Cortese et al., 2020]**

AIMS

The present examination is characterized as a retrospective study conducted at a single site, focusing on patients who experienced carotid in-stent restenosis. Multiple randomized trials have indicated a significant rise in the likelihood of ipsilateral stroke in individuals with in-stent restenosis **[Brott et al., 2010] [CAVATAS 2001] [International Carotid Stenting Study investigators 2010] [Bonati et al., 2022]** At the same time, the CREST-H study aims to evaluate cognitive outcomes in individuals diagnosed with cerebral hypoperfusion and cognitive impairment. Hemodynamically significant "asymptomatic" carotid disease may represent one of the few examples of treatable causes of cognitive impairment. If cognitive decline can be reversed in these patients, then it will be established a new indication for carotid revascularization independent of the risk of recurrent stroke. **[CREST-H]**
Therefore both symptomatic and asymptomatic carotid stenoses emphasizes the need of promptly diagnosing and treating ISR lesions, setting up the indication for neurointervention.

The primary objectives of this study were to determine:

1. The dynamics of the development of in-stent restenosis (ISR) following internal carotid artery (ICA) stenting.
2. The effectiveness and safety of angioplasty using drug-eluting balloons (DEB) in the management of ISR occurring in the ICA.
3. The incidence of secondary restenosis subsequent to the effective management of primary restenosis with DEB angioplasty.

Primary endpoints were death resulting from vascular disease, transient ischemic attack (TIA), and stroke related to the treated ICA. The secondary endpoint was a recurrent ISR lesion during follow-up.

METHODS

The present study is a retrospective cohort investigation conducted at Moritz Kaposi Teaching Hospital in Kaposvár, Hungary. The study utilized clinical and imaging data for analysis of the total of 950 stent-PTA procedures performed in our institution between March 2013 and March 2021. 45 patients developed internal carotid artery in-stent restenosis (ICA ISR). One patient had bilateral in-stent restenosis. The flow chart for patient (46 cases) inclusion is shown in Figure 2.

Our hospital has created a multidisciplinary team (MDT) to enhance interdisciplinary discourse and treatment decisions for patients diagnosed with cerebrovascular disease. The composition of this board is characterized by a heterogeneous assemblage of medical practitioners, encompassing specialists in neurology, neuroradiology, vascular surgery, and neurosurgery.

All patients undergoing the DEB re-PTA intervention were hospitalized in the Neurology Department and underwent appropriate preparation prior to the intervention. The preparation encompassed a comprehensive neurological examination that included a thorough assessment of the patient's neurological status by neurologists, along with the appropriate documentation of results. Additionally, laboratory investigations were conducted, and a cardiological examination was performed to ensure the patient's cardiovascular health. Furthermore, continuous monitoring was implemented to closely observe the patient's condition during the preparation process. The procedures were conducted by highly competent neurointerventionists at the Neurovascular and Interventional Unit of the Somogy County Moritz Kaposi Teaching Hospital. Following the DEB re-PTA, the patients had further monitoring in the Neurology Department.

The postprocedural follow-up after DEB re-PTA involved scheduling

outpatient appointments at intervals of 3 months during the first year, followed by intervals of 6 months thereafter, then yearly. During each session, a Carotid Doppler ultrasonography (DUS) examination was performed, incorporating Doppler velocity measurements with appropriate angle correction procedures, as well as B-mode imaging aided by color duplex. The cut-off values for substantial (>50%) in-stent restenotic lesions were determined by comparing the peak systolic velocity (PSV) ratios in the stented ICA segment and the common carotid artery (CCA) to a threshold of 2. Verification of a suspected in-stent restenosis (ISR) was conducted with the use of supra-aortic intracranial computed tomography angiography (CTA) done on a dual-source CT scanner (SOMATOM Definition Flash, Siemens, Erlangen, Germany). (Figure 5)

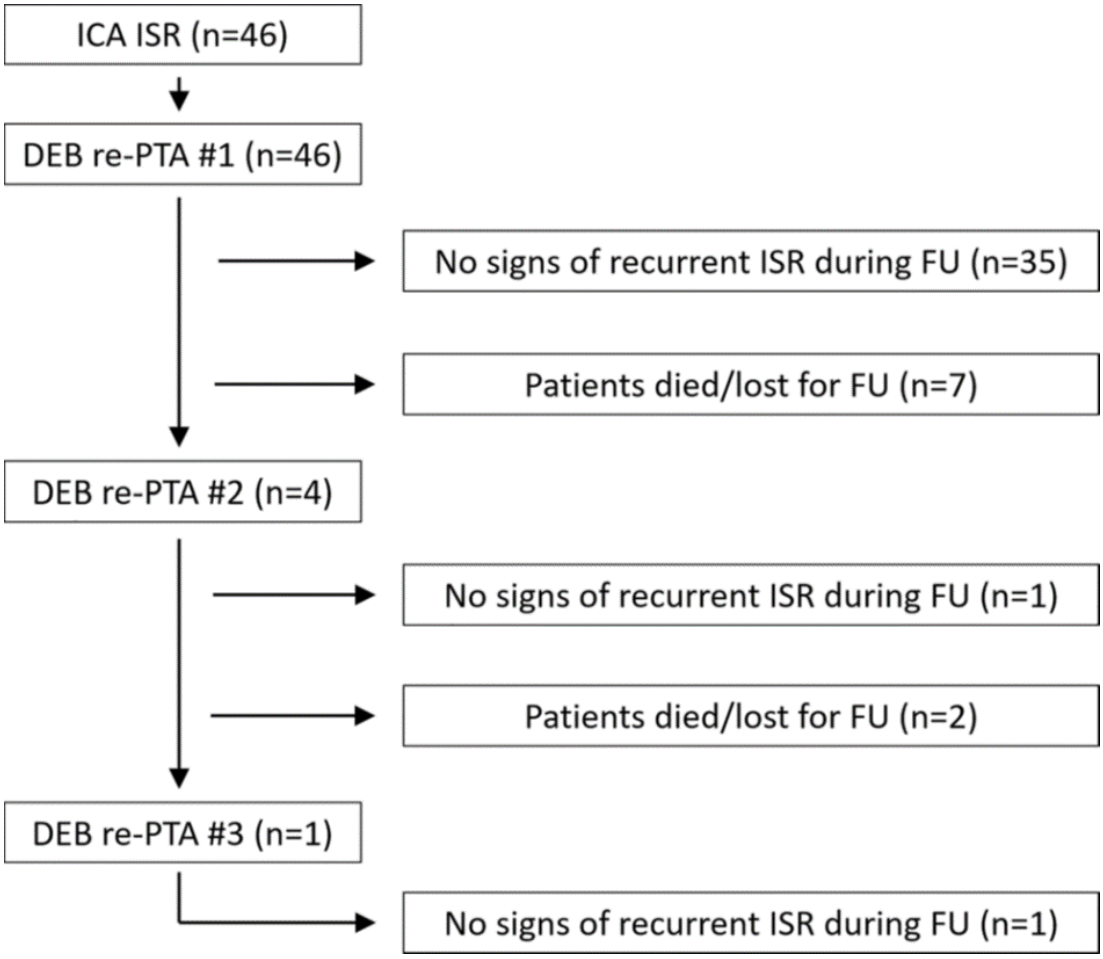

Figure 2. Schematic drawing illustrating the treatment and follow-up algorithm of recurrent stenotic lesions following carotid artery stenting. *ICA* internal carotid artery, *DEB* drug-eluting balloon, *ISR* in-stent restenosis, *PTA* percutaneous transluminal angioplasty, *FU* follow-up

Diagnosis of ISR

A comprehensive follow-up was conducted on all 950 patients who underwent carotid artery stenting (CAS), which involved regular outpatient visits every 3 months during the initial year and every 6 months afterward, serving as the primary diagnostic step. A Carotid Doppler ultrasonography (DUS) examination was conducted during each session.

Imaging

DUS

In the present investigation, we utilized peak systolic velocity (PSV) values of 220cm/s and 300cm/s as thresholds to classify luminal narrowing rates above 50% and 70% as moderate and severe in-stent restenosis (ISR), respectively. Follow-up assessments were conducted at the Neurology Department of our hospital, wherein the ISR ultrasonography results were evaluated by a minimum of two or more neurologists during the course of the follow-up period. It is important to highlight that all Duplex ultrasound (DUS) evaluations were consistently performed inside the confines of a singular neurological center, utilizing identical ultrasound equipment. The utilization of angiography was limited to patients exhibiting a peak systolic velocity (PSV) equal to or more than 220 cm/s, or those experiencing compromised vision due to artefacts.

CTA

During the process of performing Doppler ultrasound (DUS) in cases where there was suspicion of an in-stent restenosis (ISR), confirmation was obtained through the utilization of computed tomography angiography (CTA). The precise evaluation of supra-aortic stenosis and restenosis is of utmost importance in order to effectively prepare for stenting procedures or subsequent treatments. The utilization of 64-multi-slice dual energy CT angiography is considered a beneficial imaging technique in the post-procedural monitoring of patients who have had supra-aortic stenting, including intracranial procedures, despite its inherent limitations. The test

exhibits a substantial negative predictive value; nonetheless, in instances where ambiguity arises or reintervention is indicated, it is advisable to pursue further follow-up measures, including invasive procedures. By doing CT angiography with appropriate technique and sufficient post-processing, it is possible to produce high-quality pictures in a noninvasive manner, hence enhancing patient comfort and satisfaction.

TREATMENT WITH DEB

Procedure

Patients with high-grade (>50%) ISR lesions were scheduled for DEB re-PTA in our study. The drug-coated balloon (DEB) is directly coated with the drug, eliminating the requirement for a polymer. This characteristic facilitates expedited vascular repair. DEBs are composed of three main components: a balloon catheter, a lipophilic antiproliferative agent, and a drug carrier (known as an excipient) that enhances the solubility of the medication. Paclitaxel is the most common utilized pharmaceutical agent that efficiently hinders the migration of smooth muscle cells by irreversibly inhibiting the normal functioning of microtubules. This results in the halt of cell replication specifically during the anaphase and metaphase stages of mitosis. The compound has a pronounced lipophilic nature, which imparts a distinctive characteristic of extended retention in vascular smooth muscle. Consequently, this property enables a prolonged antiproliferative effect while minimizing systemic toxicity, rendering it a highly suitable pharmaceutical agent for deployment in drug-eluting balloons (DEBs). (Figure 3, 4) Results of a mere 33 DEB re-PTA procedures of ICA ISR have been published in case series in the literature altogether. **[Bhatia et al., 2020]**

Figure 3. Paclitaxel elluting balloon **[Scheller et al., 2006]**

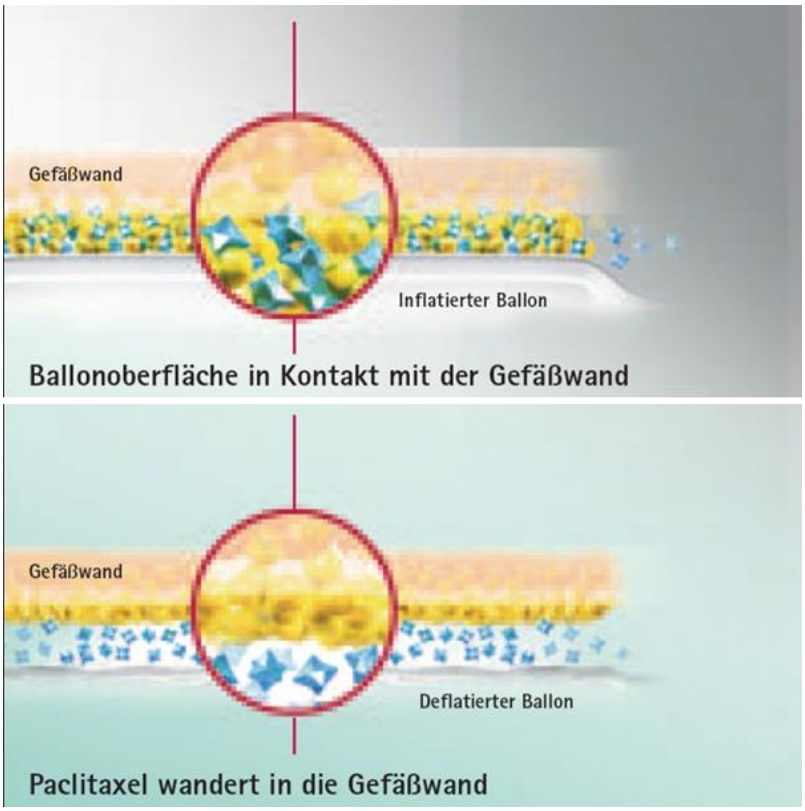

Figure 4. Paclitaxel is administered to the vessel wall by the process of mechanical balloon expansion, typically lasting for a duration of 30 to 60 seconds, following appropriate vessel preparation. **[Scheller et al., 2006]**

The benefits and drawbacks, along with the potential hazards, of utilizing conventional or drug-eluting balloons were extensively deliberated with the patients prior to the procedure (DEB re-PTA), and signed informed consent was obtained from each individual. The procedures were conducted on the patient while they were under the influence of local anesthetic. An anesthesia team was present and ready to assist if needed. The procedures utilized a 6 French femoral or radial access. Following the establishment of access, all patients were administered an intravenous dosage of 5000 international units of sodium heparin. The extent of ISR lesions was initially confirmed with the targeted administration of contrast agent into the common carotid artery on the afflicted side, thereafter accompanied by the placement of a 6F guide catheter into the same artery. The application of a filter device was not implemented. A microwire with a diameter of 0.014 inches was inserted into the lesion of the internal carotid artery (ICA) using intravascular ultrasound (ISR) guidance. Prior to dilating the ICA bulbus, 0.5mg of atropine was administered intravenously as a premedication to prevent severe bradycardia or asystole. The dilatation of the ICA bulbus was performed using a paclitaxel-eluting balloon measuring 6×30mm (Elutax, Aachen Resonance, Aachen, Germany). The balloon was inflated to a pressure of 6 atmospheres for a duration of 30 seconds, with pressure control monitored using a manometer. The duration of inflation was reduced, and prompt deflation of the balloon occurred in instances where the patients' heart rate dropped below 50 beats per minute. After the occurrence of deflation, the balloon was subsequently extracted, and a series of control angiographic procedures were conducted to ascertain the impact of re-percutaneous transluminal angioplasty (re-PTA) and to rule out the presence of cerebral emboli. Following the conclusion of the surgery, the femoral access sites were sealed using a closure device (Angio-Seal, Terumo, Tokyo, Japan). Meanwhile, the radial access sites were closed with the application of manual compression.

Figure 5. illustrates the method of drug-eluting balloon (DEB) re-percutaneous transluminal angioplasty (PTA) for the treatment of an in-stent restenosis (ISR) lesion located in the right internal carotid artery (ICA) of a 63-year-old female patient. A stenotic lesion of significant severity located in the proximal segment of the right internal carotid artery (ICA) was effectively managed with the implementation of a stent, followed by angioplasty, resulting in a favorable outcome. After a period of 6 months, the ultrasound (DUS) detected a high-grade ISR in the precise area of the first abnormality. This detection was subsequently confirmed by the utilization of dual-source computed tomography angiography (CTA) and catheter angiography. A procedure including the utilization of a paclitaxel eluting balloon was conducted to accomplish angioplasty, with favorable morphological outcomes. The patient underwent a follow-up Doppler ultrasound (DUS) examination 52 months following the drug-eluting balloon (DEB) re-percutaneous transluminal angioplasty (re-PTA) surgery. The results of the DUS revealed no evidence of recurrent in-stent restenosis (ISR).

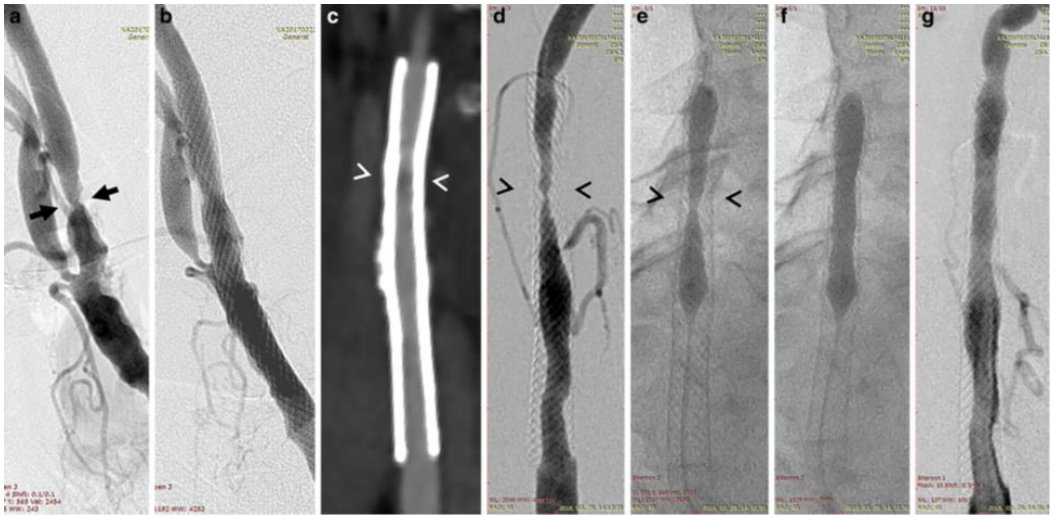

Figure 5. Illustrative case demonstrating the DEB re-PTA procedure of an ISR lesion of the right-sided ICA in a 63-year-old female patient. A highgrade stenotic lesion in the proximal portion of the right ICA (*arrows* in **a**) was treated with stent implantation, followed by angioplasty with good result (**b**). The DUS after 6 months suggested a high-grade ISR in the location of the original lesion, which was verified by dual-source CTA (**c**) and catheter angiography (**d**, *arrowheads* in **c**–**e** point to the stenotic lesion). **e**, **f** Angioplasty using a paclitaxel eluting balloon was performed with good morphological results (**g**). The patient had the last follow-up DUS 52 months after the DEB re-PTA procedure, showing no signs of a recurrent ISR.

ICA internal carotid artery, *DEB* drug-eluting balloon, *ISR* in-stent restenosis, *DUS* Doppler ultrasound, *PTA* percutaneous transluminal angioplasty, *CTA* computed tomography angiography

Medication

At the beginning of the procedure (DEB re-PTA), all patients were administered an intravenous dose of 5000IU of sodium heparin. A regimen of oral dual antiplatelet medication consisting of 100mg of acetylsalicylic acid and 75mg of clopidogrel was administered for a duration of 6 months, followed by the continuation of clopidogrel monotherapy. Patients receiving

long-term single or dual antiplatelet therapy (SAPT or DAPT) were consistently assessed using the Multiplate test (Roche Deutschland Holding GmbH, Grenzach-Wyhlen, Germany) to assess the effectiveness of SAPT/DAPT and, if needed, to administer alternative antiplatelet medication.

Postprocedural Follow-up

The postprocedural follow-up protocol resembled that which occurred after the original stent-PTA procedure. This entailed scheduling outpatient appointments at three-month intervals during the first year, followed by visits every six months thereafter. A Carotid Doppler ultrasonography (DUS) examination was conducted during each session. Cut-off values of 220cm/s and 300cm/s were employed to determine the peak systolic velocity (PSV) for luminal narrowing rates above 50% (moderate) and 70% (severe) in the case of in-stent restenosis (ISR). In instances where there was suspicion of a recurrent intracranial stenosis and occlusion, confirmation was obtained by the utilization of computed tomography angiography (CTA). The series of thin slices, measuring 0.6 mm in thickness, were examined using the technique of multiplanar reformatting (MPR). The axis of the stented segment was determined by examining two planes that were perpendicular to each other. Axial pictures, which were perpendicular to this axis, were thoroughly examined over the whole stented section. The precise quantification of luminal narrowing in the internal carotid artery (ICA) was hindered by its relatively small diameter. As a result, a binary approach was employed, classifying cases as either confirmed or rejected for the presence of intraluminal stenosis. Once a computed tomography angiography (CTA) verified the presence of a recurring intracranial stenosis and restenosis (ISR) lesion, a multidisciplinary team (MDT) including neurologists, vascular surgeons, and interventional neuroradiologists examined the clinical and imaging data to make informed decisions on treatment options. As per the choice made by the multidisciplinary team (MDT), a supplementary re-

percutaneous transluminal angioplasty (re-PTA) procedure was conducted utilizing the same method and drug-eluting balloon (DEB) as before outlined. The primary outcomes assessed in this study were mortality caused by vascular disease, transient ischemic attack (TIA), and stroke specifically associated with the treated internal carotid artery (ICA). The secondary endpoint of the study was the occurrence of a recurrent in-stent restenosis (ISR) lesion throughout the follow-up period.

Data Collection and Statistical Analysis

The collected initial data included demographic information such as age and sex, as well as medical history including hypertension, atrial fibrillation, diabetes, dyslipidemia, smoking history, and presence of a neoplastic condition prior to and after the re-PTA intervention. The preprocedural parameters that were gathered encompassed the stent type, as well as the dates of the original stent-PTA, identification of ISR, and the subsequent re-PTA treatment. The quantification of luminal narrowing resulting from intimal hyperplasia was determined on non-subtracted DSA images using the methodology employed in the ECST trial **[ECST 1998]**. This approach relies on the accurate assessment of in-stent intimal hyperplasia by referencing the stent wall, which aligns with the stenosis calculation method utilized in the ECST study. The location of vascular access and the specific type of anti-aggregation medicine were also documented. The parameters used to assess technical success and outcomes in this study included the rate of successful re-PTA, which was defined as achieving less than 50% residual stenosis. Other parameters assessed were procedural complications, specifically ischemic stroke resulting from distal emboli, as well as postprocedural adverse events such as access site complications. The length of the follow-up period was also considered, along with the modified Rankin scale (mRS) score at the last follow-up. Additionally, the occurrence of any stroke during the follow-up period was recorded. As a result of the COVID-19 epidemic, the majority of the subsequent follow-up appointments were conducted via telephone

interviews. In the event of a patient's passing during the follow-up period, efforts were made to document the reason of death, if ascertainable.

RESULTS

During the period from March 2013 to March 2021, our institution conducted endovascular treatment on 46 high-grade (>50%) in-stent restenosis (ISR) lesions located at the origin of the internal carotid artery (ICA). This treatment involved the use of angioplasty with a drug-eluting balloon (DEB). A total of 45 patients, with a median age of 64.9 years (ranging from 46.9 to 75.8 years) and a male-to-female ratio of 3.2:1, underwent this procedure. Among these patients, only one developed bilateral ISR. During the aforementioned time frame, a total of 950 intracranial artery (ICA) stent-percutaneous transluminal angioplasty (PTA) procedures were conducted at the same medical facility. This resulted in an estimated incidence of in-stent restenosis (ISR) of around 5%. However, it should be noted that the precise rate of ISR could not be determined due to the lack of extensive examination of the cases without ISR. Table 1 presents the patient demographics, features of ISR lesions, and associated risk factors. In all, 16 lesions (35%) were observed in the Roadsaver group, whereas 30 lesions (65%) were observed in the Wallstent group. Out of the initial 46 lesions in the internal carotid artery (ICA), 52% (24/46) were symptomatic when the stent was implanted. However, only 2% (1/46) of the lesions that developed in-stent restenosis (ISR) exhibited symptoms, specifically mild hemiparesis, homonymous hemianopsia, and central facial palsy. The remaining lesions that developed in-stent restenosis ISR were asymptomatic and were identified during routine follow-up using duplex ultrasound (DUS). The imaging work-up in cases of a suspected in-stent restenosis (ISR) on DUS always included a computed tomographic angiography (CTA) in order to exclude false positive DUS readings, before performing invasive imaging (DSA). A CTA positive for ISR could be confirmed by the DSA series in all the cases. The study found that the median duration between the stent-PTA and the identification of ISR lesions was 8.2 months, with a range of 1.4 to 186.2 months. Additionally, it was observed that 24% (11 out of 46) of the ISR

lesions appeared more than 1 year after the CAS treatment. The frequency of ISR lesion development is seen in Figure 6.

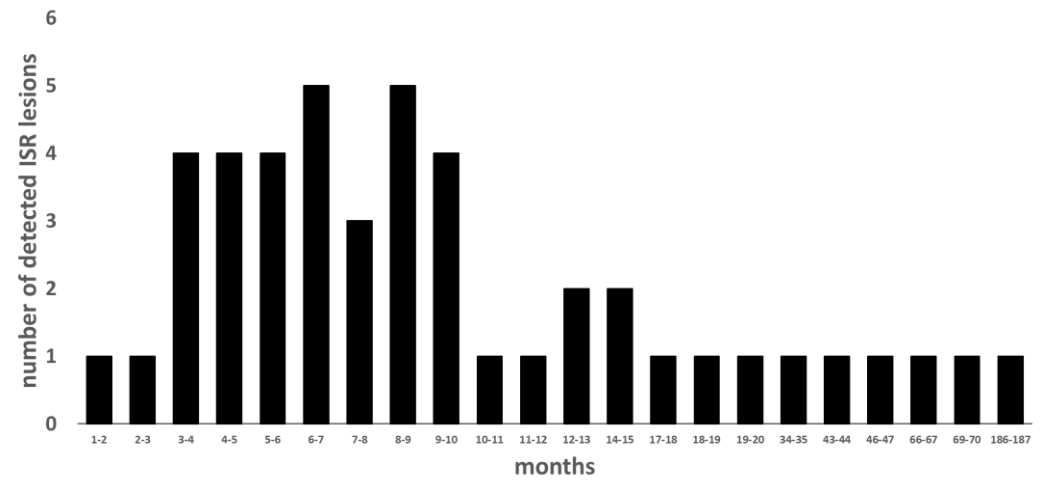

Figure 6. Diagram showing the frequency of newly detected ISR lesions in the follow-up period following CAS. *ISR* in-stent restenosis

Nr.	Age	Gender	Time of ISR detection after CAS (month)	ISR ECST (%)	Risc factors
1	62,8	m	4,1	80-90%	HT, DM, hBMI
2	63,4	m	69,1	50-70%	HT, smoking
3	47	m	8,2	70-80%	HT, DM, smoking
4	73	m	43,8	50-70%	HT, hBMI, HL
5	71,4	m	9,7	60-70 %	HT, smoking, hBMI
6	70,1	f	186,2	80-90%	HT, DM, HL
7	67,9	m	14	70-80%	HT, smoking, hBMI, HL
8	66,1	m	34,3	60-70%	HT, DM, smoking, hBMI, HL
9	69,2	m	8,5	80-90%	HT, smoking
10	66,6	f	7,4	80-90%	HT, smoking, HL
11	73,9	m	3,4	70-80%	HT, smoking, HL
12	67,4	f	3,7	60-70%	HT, DM
13	63,2	m	3,9	70-80%	HT, smoking, HL
14	68,5	m	7,4	50-60%	HT, smoking
15	62,1	f	4,8	60-70%	HT, smoking, hBMI
16	57,3	m	19,8	50-60%	HT, smoking, HL
17	71	m	3	70-80%	smoking, hBMI
18	62,2	m	9,7	50-60%	HT, smoking, hBMI
19	60,6	m	14,3	80-90%	HT, smoking, hBMI
20	75,9	m	12,1	80-90%	HT, Smoking
21	67,7	m	1,4	70-80%	HT, DM, smoking, hBMI, HL
22	71,2	f	8,9	60-70%	HT, smoking, hBMI, HL
23	59,2	m	10	80-90%	HT, smoking, hBMI
24	60,7	m	66,4	50-60%	HT, smoking, hBMI
25	62	m	17,1	60-70%	HT, DM, smoking, hBMI, HL
26	69,1	m	6,2	70-80%	HT, smoking
27	64,6	m	6,3	60-70%	HT, DM, smoking, hBMI, HL
28	56,5	m	5,9	60-70%	HT, DM, hBMI, HL
29	55,8	m	5,4	60-70%	HT, DM, smoking, hBMI
30	67,3	m	9,3	50-60%	HT, smoking, HL
31	51,2	m	8,6	60-70%	HT, DM, hBMI, HL
32	61,4	m	5,5	50-60%	HT, smoking, hBMI, HL
33	67,9	m	6,5	80-90%	hBMI
34	52	m	5,3	60-70%	HT, DM, HL
35	65,1	m	8,4	70-80%	HT, DM, hBMI, HL
36	58,3	f	13	60-70%	HT, HL
37	65,7	f	4,2	50-60%	HT, smoking, hBMI, HL
38	67,8	m	6,3	60-70%	HT, smoking, hBMI, HL
39	69,9	m	7,7	60-70%	HT, DM, hBMI, HL
40	63,3	f	6,2	80-90%	HT, smoking, hBMI
41	68,6	m	9,5	70-80%	HT, smoking, hBMI, HL
42	64,9	m	46,6	50-60%	HT, smoking, hBMI, HL
43	61,1	f	18,6	50-60%	HT, smoking, hBMI
44	59,9	f	11,6	70-80%	HT, DM, hBMI, HL
45	65,4	f	4,9	90-99%	HT, smoking, hBMI, HL
46	52,3	m	3,7	70-90%	smoking, hBMI

Table 1. Patient data, lesion characteristics and risk factors of the cohort. ISR: in stent restenosis, CAS: carotid artery stenting, ECST: European Carotid Surgery Trial, HT: hypertension, DM: diabetes mellitus, hBMI: high body mass index, HL: hyperlipidemia

The luminal narrowing induced by in-stent restenosis (ISR), as evaluated on the digital subtraction angiography (DSA) images, had an average value of 70±2% (standard error of mean). The observed range of luminal narrowing varied from 50% to 90%. In all instances, technical success was achieved, as shown by the presence of a residual stenosis that was less than 50%. The average rate of residual stenosis was found to be 27±2%, with a range spanning from 5% to 49%. No intraprocedural or postprocedural complications were observed. Figure 5 displays an illustrative example. Clinical follow-up data was collected from all 45 patients (100%) through various methods. These methods included direct communication during personal or telemedical follow-up visits, telemedicine interviews with relatives or the general practitioner, and accessing follow-up data from the National eHealth Infrastructure (EESZT) database. The average follow-up time was 31.7 months, ranging from 1 to 96 months. None of the patients experienced any recurring strokes within the region of the treated internal carotid artery (ICA). Out of the total sample size of 45 patients, a proportion of 9 individuals (20%) experienced mortality during the designated follow-up time. The reason for passing away in six cases was attributed to neoplasms, with four cases involving pulmonary neoplasms, one case involving renal neoplasm, and one case involving head and neck cancer. Additionally, one case was attributed to the consequences of anterior spinal artery syndrome, while the cause of death in the remaining two cases remains unknown. Out of the six fatal neoplasms, three (50%) had already been diagnosed before to the DEB re-PTA procedure. Two patients, whose cause of death was unclear, were no longer being monitored 3 and 24 months following the re-PTA surgery. Relatives verified their deaths through telephone interviews, but the specific reason could not be determined in both cases.

The subsequent imaging findings of DUS following the initial drug-eluting balloon (DEB) re-PTA were obtained for all 46 lesions. The median follow-up duration was 24 months, ranging from 1 to 96 months. These results

showed the presence of an asymptomatic, high-grade (>50%) recurrent in-stent restenosis (ISR) lesion in 4 cases (8.7%). The recurrence was further confirmed by computed tomography angiography (CTA). All of the recurring lesions manifested in male individuals and were subjected to a second drug-eluting balloon (DEB) percutaneous transluminal angioplasty (PTA), as previously detailed, followed by continued monitoring of clinical and imaging outcomes. Throughout the follow-up period, there were no observable signs of ischemia in the hemisphere that was impacted. One instance of a third occurrence of neointimal hyperplasia, which was of high grade and asymptomatic, was identified in a single patient, accounting for 2% of the total cases, occurring 12 months after the second drug-eluting balloon re-percutaneous transluminal angioplasty (DEB re-PTA). The aforementioned lesion had a third DEB re-PTA, and a subsequent follow-up after a period of 36 months revealed no evidence of a fourth occurrence of in-stent restenosis (ISR).

DISCUSSION

Carotid stenosis is a pathological state distinguished by the narrowing of the carotid arteries. The main goal of treatment is to decrease the stroke incidence by the efficient management or elimination of plaque buildup and the prevention of blood clot formation. The majority of people afflicted with carotid stenosis often do not exhibit any symptoms until the arterial passage experiences significant constriction or the formation of a clot occurs. The initial manifestation of symptoms is commonly observed in the form of a transient ischemic attack (TIA). The symptoms have a brief duration lasting only a few minutes, followed by complete dissipation, resulting in the individual's return to their baseline condition. It is essential to not overlook TIAs due to their potential significance as a precursor to an oncoming ischemic stroke. The symptoms of (TIA) or an ischemic stroke can be limb weakness, difficulties in speech, facial palsy, visual disturbances, and hemiparesis or -plegia.

TREATMENT OF ICA STENOSIS

The recent large randomized trials that have compared the safety and efficacy of carotid stenting (CAS) and endarterectomy (CEA) have demonstrated similar outcomes in terms of stroke prevention. These findings have led to a change in the treatment approach, shifting from a preference for endarterectomy to a more balanced acceptance of both methods. **[Meschia et al., 2022]** Both CEA and CAS have a disadvantage in the form of the emergence of neointimal hyperplasia, which leads to the gradual and substantial recurrence of stenotic lesions within the stent, known as in-stent restenosis (ISR). The etiology and nature of the substance responsible for luminal constriction differ significantly from those of the primary atherosclerotic plaque. The presence of endothelium on the neointimal tissue and the absence of debris material within the plaque indicate a low risk of heightened thrombogenicity and embolization **[Buccheri et al., 2016]**. However, if the luminal narrowing progresses

rapidly, it can cause a reduction in blood flow velocity and potentially lead to a thrombotic occlusion of the internal carotid artery (ICA).

TREATMENT OF ICA IN-STENT RESTENOSIS

According to the most recent guidelines from the European Society for Vascular Surgery (ESVS), it is recommended to utilize the identical treatment criteria employed for the selection of symptomatic patients with primary atherosclerotic stenosis. Therefore, it is suggested to treat symptomatic restenosis (50-99%) with carotid endarterectomy (CEA) or carotid artery stenting (CAS) within 14 days after the onset of symptoms. However, the topic of asymptomatic restenosis remains a source of significant controversy in academic discourse. Although there is a common perception that asymptomatic restenosis is often benign, the aforementioned recommendations propose that in cases with post-CEA 70-99% asymptomatic restenosis, reintervention might be contemplated after a thorough evaluation by a multidisciplinary team. It has been observed that a severe asymptomatic restenosis above 70% following carotid endarterectomy (CEA) is indeed linked to a notably elevated likelihood of experiencing a late ipsilateral stroke. When faced with the need for revascularization in patients with restenosis, the selection between redo carotid endarterectomy (CEA) or carotid artery stenting (CAS) should be determined through a comprehensive evaluation by a multidisciplinary team, taking into account the expertise of local surgeons and interventionists, as well as the preferences expressed by the patient. **[Naylor et al., 2023] [Stilo et al., 2020]**

Regarding the indication of treatment of asymptomatic ICA ISR lesions, the situation is more controversial. According to the European Vascular Surgery recommendation **[Naylor et al., 2023]**, there is IA evidence supporting the use of medical therapy instead of intervention for the treatment of asymptomatic high-grade carotid in-stent restenosis (ISR). This recommendation is supported by the meta-analysis conducted by

Kumar **[Kumar et al., 2017]**, which revealed a significant reduction in the risk of stroke on the same side as the restenosis, with a reduction of only 0.8%. In-stent restenosis was present, and the adverse clinic does not appear to be tightly associated, which raises doubts about the purpose of re-PTA according to their research**.**

In our opinion, the meta-analysis by Kumar et al. has its limitations. For example, the validation of the in-stent restenosis (ISR) in their study was only conducted using DUS. The PSV cut-off values applied in the studies analyzed by Kumar et al. exhibited a significant degree of variability. The meta-analysis included data from 11 prospective studies, in six of those a PSV of 210 cm/s was used as cut-off criteria for >70 % restenosis, no relevant information on PSV cut-off was given in two studies and only in the remaining three used PSV values that can be found as standards in the literature and are also applied routinely in our clinical practice (220 cm/s >50 %, 300 cm/s > 70 % ISR) **[Settaci et al., 2008] [Pizzolato et al., 2014]** In our opinion, this resulted in the inclusion of patients with minor degree of ISR into this meta-analysis, substantially diluting the specificity of the study.

On the other hand the median follow-up duration of patients was 4 years and the study does not provide any insights into the probable progression of the ISR beyond this time period. ISR is a late complication of the stenting procedure and even late progression of the condition can lead to complete occlusion of the treated ICA. To our knowledge, there is no solid evidence in the literature showing that occlusion of a stented ICA would always be asymptomatic. Therefore, we believe that an effective and safe treatment modality for ICA ISR (DEB re-PTA) is non-inferior to no treatment. The rationale for the work presented in this thesis was assessment of first of all the safety and the efficacy of DEB re-PTA in ICA ISR.

An additional point is the effect of ICA luminal narrowing on cognitive function. A number of recent studies (e.g. **[Lazar et al., 2021] [Marshall**

et al., 2020] [Marshall et al., 2023] [Schröder et al., 2019] [Norling et al., 2019]) documented a positive correlation between “asymptomatic” narrowing of the ICA lumen and cognitive impairment. The phenomenon is similar to angina pectoris resulting from coronary artery stenosis or claudication resulting from atherosclerotic stenotic lesions of the lower limb arteries. Based on these results, the CREST-H randomized trial was initiated and is still recruiting patients to investigate the clinical significance of the hemodynamic effects caused by ICA stenosis. In this regard, the hemodynamic effect of luminal narrowing caused by an atherosclerotic plaque or intimal hyperplasia does not seem to differ. As stated in the previous paragraph, we believe that a safe and effective treatment option for ICA ISR might play an important role in the prevention of cognitive impairment as a result of ICA ISR.”

Further exploring the power of luminal narrowing in the indication of the invasive treatment of ISR, the most recent ESVS Guideline (2023) defines the threshold for preventive invasive treatment for asymptomatic ICA stenotic lesions caused by atherosclerosis by a luminal narrowing of 60% **[Naylor et al., 2023, Recommendation 20, IIbB**], regardless of the biological and imaging properties of the plaque, the recommendation is based solely on the degree of the luminal narrowing. The same guideline does not indicate an invasive treatment for ICA stenotic lesions caused by ISR even at more than 70% luminal narrowing **[Naylor et al., 2023, Recommendation 105, IA**]. We see a slight inconsistency when looking at these two recommendations, both considering solely the luminal narrowing for the indications.

As a sidenote, we cautiously express our reservation for a IA recommendation in a clinical guideline, which based on a single meta-analysis. For instance, the case of the meta-analysis of Katsanos et al. can be mentioned here, showing a rise in mortality following the utilization of DEB balloons in peripheral atherosclerotic disease **[Katsanos et al., 2018]**. The study initiated a heated discussion pro and contra, as well as regulatory decisions from the FDA and the EU, until in 2021, a second

meta-analysis employing comparable technique **[Dinh et al., 2021]** confirmed the opposite of the aforementioned results, revealing the methodological deficiencies and inaccuracies present in the Katsanos study. We are not aware of any confirming or refuting meta-analysis regarding the article by Kumar et al., however we believe, it might be advisable to exercise caution when evaluating an IA evidence based on a single research.

TREATMENT OF ICA IN-STENT RESTENOSIS WITH DEB RE-PTA

In the management of in-stent restenosis of the carotid artery (ICA ISR) the therapeutic options that can be considered include repeated carotid artery stenting (CAS), endarterectomy, or reangioplasty (percutaneous transluminal angioplasty) (rePTA) utilizing either a conventional balloon or a drug-eluting balloon (DEB) **[Huang et al., 2021]**. While the use of paclitaxel-eluting drug-eluting balloons (DEBs) for the treatment of in-stent restenosis (ISR) in various vascular territories such as the coronary **[Scheller et al., 2012]**, peripheral **[Gerardi: et al., 2018]**, and intracranial **[Vajda et al., 2011]** arteries has been extensively studied and proven to be safe and effective, there is a limited amount of published data on the application of DEBs specifically for the treatment of internal carotid artery (ICA) ISR. Only 33 cases of DEB re-PTA procedures for ICA ISR have been reported in the literature as part of case series. **[Bhatia et al., 2020]**

The present study examines the safety and effectiveness of a paclitaxel-eluting balloon for treating in-stent restenosis of the extracranial carotid artery by a retrospective cohort analysis of 45 patients (46 cases). There were no cases of vascular mortality, transient ischemic attack (TIA), or stroke in the treated internal carotid artery (ICA) area, which were the key endpoint events. A reoccurrence of an in-stent restenosis (ISR) lesion after a drug-eluting balloon (DEB) re-percutaneous transluminal angioplasty (PTA) operation was observed as a secondary endpoint in 8.7% of the lesions. These recurrent ISR lesions were effectively managed with a

subsequent re-PTA procedure, with one case requiring a third re-PTA procedure. Notably, no additional cases of recurrent ISR lesions were observed throughout the follow-up period.

Our study provides the most extensive case series to date on the treatment of internal carotid artery in-stent restenosis (ICA ISR) utilizing a drug-eluting balloon (DEB) device. The findings provide significantly superior outcomes in terms of preventing the recurrence of stenotic lesions compared to other approaches documented in existing literature.
The incidence rates of in-stent restenosis (ISR) after carotid artery stenting (CAS) exhibit significant variation, ranging from 3% to 31%. This variability may be attributed to several factors, including the specific threshold used to define luminal constriction, the Doppler criteria employed throughout the follow-up process, and the duration of the follow-up period. These findings have been published in several studies **[Bhatia et al., 2020] [Nahler et al., 2017] [Chen et al., 2021] [Mihály et al., 2021]**.
The current study refrains from analyzing the factors contributing to the development of in-stent restenosis (ISR) in the patient cohort under investigation. However, we can provide an approximate estimation of the primary ISR rate in our center, which is approximately 5%. This estimation is based on the total number of carotid artery stenting (CAS) procedures conducted and the identification of ISR lesions during the follow-up period within the same timeframe. Although a comprehensive examination of the follow-up data from all patients with carotid artery stenosis (CAS) has not been conducted, it can be approximated that our findings align with the 5.7% incidence of in-stent restenosis (ISR) (>50%) published in a recent meta-analysis encompassing over 16,000 cases of carotid artery stenting **[Clavel et al., 2019**].

In the current study cohort, the mean luminal narrowing was determined to be 70%, indicating a significant level of stenosis. However, it is noteworthy that just one lesion, accounting for a mere 2% of the cases, exhibited

symptoms. This finding prompts further consideration of the appropriateness of employing preventative invasive treatments in such cases. The issue of in-stent restenosis (ISR) was initially recognized as a significant concern in the context of coronary arteries, leading to the advancement of drug-eluting coronary stents (DES) **[Kastrati et al., 1993].** Based on existing understanding, there is now a lack of medicinal interventions that can effectively halt or reverse the progression of neointimal hyperplasia. The secondary analysis of the International Carotid Stenting Study (ICSS) evaluated the potential risk of stroke related with ISR. The study's analysis revealed a cumulative 5-year risk of at least moderate (50%) in-stent restenosis (ISR) of 40.7%. Furthermore, it was shown that patients with ISR had a substantially greater likelihood of experiencing an ipsilateral stroke in comparison to persons who did not have ISR. According to the study of Bonati **[Bonati et al., 2018]**, the incidence of stroke caused by ISR may be higher (7,8 % over 6 years) as seen in the meta-analysis of Kumar (0,8 % over 4 years). Although it is not statistically significant (p=0.15), but to some extent is higher than in patients without ISR (3,8%). According to these findings, an intervention such as DEB-PTA or re-PTA may be effectively performed by skilled physicians without complications, consequently preventing the occurrence of a stroke.

The personal experience we have seen supports the aforementioned fact that ISR is a progressive disorder that carries the potential danger of stent blockage if left untreated. In such cases, DEB angioplasty emerges as a reliable and low-risk therapy choice. It is important to acknowledge, however, that in order to establish the appropriate use of a preventative invasive therapy, randomized trials must be done.

The current literature on the management of internal carotid artery in-stent restenosis (ICA ISR) highlights the insufficiency of evidence and randomized controlled trials (RCTs) in providing recommendations for

determining appropriate indications and selecting treatment modalities **[Huang et al., 2021] [Stilo et al., 2020]** A comprehensive analysis was conducted on 35 studies pertaining to the treatment of carotid in-stent restenosis (ISR), including a total of 1374 interventions **[Huang et al., 2021]**. The findings of this review indicated that the most often preferred treatment options for carotid ISR were repeat carotid artery stenting (CAS) at a rate of 66.3%, percutaneous transluminal angioplasty (PTA) using conventional balloons at a rate of 17.5%, and carotid endarterectomy (CEA) at a rate of 14.3%. The findings of the three techniques exhibited comparable rates of stroke and transient ischemic attack (TIA) throughout the postoperative period. Specifically, the rates were 1.1% for percutaneous transluminal angioplasty (PTA), 1.1% for revascularization with carotid artery stenting (rCAS), and 1.5% for carotid endarterectomy (CEA). The study found that carotid endarterectomy (CEA) was correlated with a postoperative mortality rate of 2.5%, whereas the risk of long-term stroke and transient ischemic attack (TIA) in the percutaneous transluminal angioplasty (PTA) group was 5.7%. Following percutaneous transluminal angioplasty (PTA), the incidence of in-stent restenosis (ISR) recurrence was found to be 27.8%. Similarly, following repeat carotid artery stenting (CAS), the rate of ISR recurrence was 8.2%. Conversely, after carotid endarterectomy (CEA), the rate of ISR recurrence was significantly lower at 1.6%.

A new publication by Mihály et al. presents the biggest cohort study to date on the use of conventional balloons for the treatment of in-stent restenosis (ISR) in the internal carotid artery (ICA). The study included 46 lesions that were treated with re-PTA using conventional balloons, and in 3 instances, a paclitaxel-eluting balloon was utilized **[Mihály et al, 2021]**. The researchers documented a recurrence rate of 21.7% for in-stent restenosis (ISR) and a stent occlusion rate of 6.5% during a median follow-up period of 29.5 months. This results in a total recurrence rate of 28.2%, which closely aligns with the recurrence rate of 27.8% reported in the evaluation conducted by Huang et al. **[Huang et al., 2021]**.

Bhatia et al. recently conducted an analysis on the existing literature on the treatment of carotid in-stent restenosis (ISR) using drug-eluting balloons (DEB) and percutaneous transluminal angioplasty (PTA). A total of 33 ICA ISR lesions were examined in the DEB therapy study, which included two cases from the researchers themselves. Out of these lesions, 11 (33%) were determined to be symptomatic. The study demonstrated positive outcomes in terms of technical success rates, procedural safety, and follow-up results. During the follow-up period, there were four instances of recurrent ISR lesions, with three being asymptomatic and one being symptomatic. These cases accounted for 12% of the total sample size (4 out of 33). **[Bhatia et al., 2020]**

In the current investigation, all internal carotid artery in-stent restenosis lesions were solely treated with drug-eluting balloon (DEB) angioplasty. This study was conducted based on the promising outcomes of a previous research, in which the authors examined the effectiveness of drug-eluting balloons (DEB) compared to conventional balloons in the re-percutaneous transluminal angioplasty (re-PTA) of 63 intracranial in-stent restenosis (ISR) lesions. The earlier study revealed a significant decrease in the recurrence rate of ISR, with DEB demonstrating a rate of 9% compared to the 50% recurrence rate observed with conventional balloons **[Vajda et al., 2011]**. The recurrence rate of ICA ISR in our study is 8.7%, which closely aligns with the recurrence rate of 9% published in other studies on intracranial drug-eluting balloon (DEB) re-percutaneous transluminal angioplasty (PTA) **[Vajda et al., 2011]**. Additionally, our findings indicate that our recurrence rate is approximately one third of the recurrence rate (27-28%) reported in other studies that utilized traditional balloons **[Huang et al., 2021] [Mihály et al., 2021]**. The incidence of in-stent restenosis (ISR) recurrence after drug-eluting balloon (DEB) percutaneous transluminal angioplasty (PTA) is comparable to the reported rate of 8.2% observed in a subsequent carotid artery stenting (CAS) procedure **[Huang et al., 2021]**. It is important to acknowledge that the management of

sequential recurrent lesions can be effectively addressed through repeated drug-eluting balloon (DEB) percutaneous transluminal angioplasty (PTA) procedures. However, it should be recognized that the same level of ease may not be achieved with repeat carotid artery stenting (CAS) interventions, as the implantation of a third or even a fourth co-axial stent in the same vessel segment can present challenges.

The present study has several limitations. Firstly, its design is observational and nonrandomized, which introduces methodological and selection biases that are typical to this type of study. The imaging data were not validated by a central laboratory. The retrospective dataset may contain bias as a result of patients lost to follow-up and missing data. A comprehensive examination of the main stent-PTA procedures was not conducted. The present cohort only utilized a single kind of drug-eluting balloon (DEB). It is reasonable to hypothesize that variations in drug type, concentration, and the technique employed to secure the drug to the balloon may have a substantial impact on the effectiveness of different DEBs **[Joner 2011].**

CONCLUSION

The use of a paclitaxel-eluting balloon in the treatment of extracranial carotid in-stent restenosis (ISR) has been found to be a safe and successful alternative to other available therapeutic methods. The primary rates of recurrence are approximately one third of the rates described in the existing literature for re-PTA using traditional balloons. The recurring lesions might be effectively treated by performing further drug-eluting balloon (DEB) percutaneous transluminal angioplasty (PTA) operations, ultimately leading to the successful prevention of in-stent restenosis (ISR). While there is an expanding amount of evidence about the efficacy of drug-eluting balloon (DEB) technology in the therapy of carotid in-stent restenosis (ISR) based on retrospective case series, there is a significant need for larger-scale prospective, controlled studies to firmly establish the role of this technology in the toolbox of neurovascular interventionists.

THESES

The main results of the present thesis are the following:

1. The overall incidence of in-stent restenosis (ISR) in the internal carotid artery (ICA) in our investigated cohort is 5%, with a peak development time of 6-8 months.

2. Based on our analysis of the largest ICA ISR patient cohort known to date, the treatment of ISR of the extracranial ICA using angioplasty with paclitaxel-eluting balloon (DEB) is effective and safe.

3. The incidence of a recurring (ISR) lesion following DEB angioplasty was 8,7% identified as a secondary outcome following DEB angioplasty. The recurring ISR lesions were successfully re-treated with a follow-up re-PTA procedure, and in one case, a third re-PTA treatment was necessary. No further occurrences of recurring ISR lesions were detected over the whole follow-up duration, emphasizing the efficacy of the procedure.

4. The primary endpoints, including vascular death, transient ischemic attack (TIA), and stroke were not reached in any of the cases, underlining the safety of the procedure.

5. The results provide markedly superior outcomes in preventing the reoccurrence of stenotic lesions compared to alternative methods described in current literature.

DISCLOSURE

The AI-powered writing assistant (Quillbot, Learneo Inc., Redwood City, CA, USA) was used during the preparation of this thesis for assistance with medical writing and content editing, in accordance with the recent editorial guidelines reported in Radiology **[Moy et al., 2023]**.

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7. sz. melléklet

DOKTORI ÉRTEKEZÉS BENYÚJTÁSA ÉS NYILATKOZAT A DOLGOZAT EREDETISÉGÉRŐL

Alulírott

név: ..... dr. Marton Annamária.....

születési név: .....Marton Annamária.....

anyja neve: ..... Darvas Ildikó.....

születési hely, idő: .....Csíkszereda, 1981.02.09.....

.....

Endovascular treatment of carotid in-stent restenosis című doktori értekezésemet a mai napon benyújtom a(z) Pécsi Tudományegyetem Doktori Iskola

PR2-K21 Endovaszkuláris intervenciók szerepe az érbetegek életminőségének javításában Programjához/témacsoportjához

Témavezető(k) neve: .....Dr. Vajda Zsolt c. egyetemi tanár.....

Egyúttal nyilatkozom, hogy jelen eljárás során benyújtott doktori értekezésemet
- korábban más doktori iskolába (sem hazai, sem külföldi egyetemen) nem nyújtottam be,
- fokozatszerzési eljárásra jelentkezésemet két éven belül nem utasították el,
- az elmúlt két esztendőben nem volt sikertelen doktori eljárásom,
- öt éven belül doktori fokozatom visszavonására nem került sor,
- értekezésem önálló munka, más szellemi alkotását sajátomként nem mutattam be, az irodalmi hivatkozások egyértelműek és teljesek, az értekezés elkészítésénél hamis vagy hamisított adatokat nem használtam.

Továbbá nyilatkozom, hogy hozzájárulok a doktori értekezésem DOI azonosító igényléséhez.

Dátum: 2024.04.24

.....
doktorváromanyos aláírása

....
témavezető aláírása társtémavezető aláírása