THE LONG-TERM RESULTS OF STENT IMPLANTATION IN THE AORTOILIAC AND COMMON CAROTID ARTERIES

Ph.D. Thesis

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Table of Contents

List of Abbreviations

ABI: ankle-brachial index
AISOD: aortoiliac steno-occlusive disease
AUC: area under the curve
BMI: body mass index
BMT: best medical therapy
CCA: common carotid artery
CERAB: covered endovascular reconstruction of the aortic bifurcation
CI: confidence interval
CIA: common iliac artery
CREST: Carotid Revascularization Endarterectomy versus Stenting Trial
CTA: computed tomography angiography
DSA: digital subtraction angiography
DUS: duplex ultrasonography
EIA: external iliac artery
HR: hazard ratio
ICA: internal carotid artery
IQR: interquartile range
ISR: in-stent restenosis
LDL: low-density lipoprotein
LEAD: lower extremity artery disease
MRA: magnetic resonance angiography
MRI: magnetic resonance imaging
OR: odds ratio
PSV: peak systolic velocity
PTA: percutaneous transluminal angioplasty
SE: standard error
SF: stent fracture
TASC: TransAtlantic Inter-Society Consensus
TIA: transient ischemic attack

1. Introduction

1.1. Rise of Interventional Radiology

In recent decades, the appearance, admission, and quick progression of minimally invasive techniques has dramatically changed vascular surgery, marked as an "endovascular evolution" (1). It has to be stated that endovascular methods and therapies have now been administered to nearly all parts of conventional vascular surgery (1). This phenomenon can be explained by several factors, a few of which are listed. First, minimally invasive endovascular interventions are associated with reduced periprocedural morbidity (including cardiac, pulmonary, and infectious complications) and mortality compared to open surgery (2, 3). Second, a remarkable proportion of patients cannot be anaesthetized for a lack of vital indication due to comorbidities such as chronic heart failure or chronic obstructive pulmonary disease, which are related to higher rates of major cardiopulmonary complications and mortality following open surgical procedures (4). Third, patients experience far slighter pain postprocedurally in the case of endovascular therapies (5). Fourth, endovascular procedures are related to significantly decreased in-hospital stay, shorter recovery, and earlier return to preprocedural levels of activity (5–7). Fifth, aesthetic reasons might also play a role; as opposed to open surgery, radiological interventions avoid large incisions and do not cause scars (5).

1.2. Arterial Steno-Occlusive Disease

A wide array of vascular pathomorphological disorders can be treated in an endovascular manner, such as (re)stenosis/(re)occlusion, aneurysm, dissection, arteriovenous fistula, pseudoaneurysm, vascular malformation, etc. The most frequent arterial pathomorphological abnormalities are steno-occlusive diseases, caused mostly by atherosclerosis (8). However, other pathologies (like fibromuscular dysplasia, arteritis, endofibrosis, cystic adventitial disease, etc.) should also be taken into account, especially in patients who are younger, have no atherosclerotic manifestation in other vascular regions, or have a lack of risk factors for atherosclerosis (8, 9). In patients who

received radiation therapy, radiation-induced arteriopathy also has to be considered (10). Following coronary heart disease, lower extremity artery disease (LEAD) and ischemic stroke are the most common causes of atherosclerotic vascular morbidity (11).

1.3. Aortoiliac Steno-Occlusive Disease

Approximately 20% of people aged ≥65 years are affected by LEAD in the European Union (12). Following the superficial femoral artery, the aortoiliac segment (region) is the second leading location of LEAD (13).

1.3.1. Symptoms

Presentations of chronic aortoiliac steno-occlusive disease (AISOD) can be categorized according to the Fontaine classification (Table 1). The majority of patients are asymptomatic but even they have higher risk for cardiovascular events (14). The most frequent clinical presentation of AISOD is intermittent claudication, which is a pain localizing to the buttock, thigh, or calf, caused by exercise and resolved by rest (14, 15). In up to 25% of patients, intermittent claudication progresses to critical limb ischemia, which refers to the presence of ischemic rest pain and/or tissue loss (ulcerations, gangrene) (14, 16). The annual rate of major cardiovascular events (myocardial infarction, ischemic stroke, and vascular death) in patients with LEAD is 5%–7% (17). Additionally, the mortality rate of patients with claudication is 2.5-fold higher than that of nonclaudicants (17).

Table 1. Fontaine classification (14)

Stage	**Presentation**
I	Asymptomatic
IIa	Non-disabling intermittent claudication (>200 m)
IIb	Disabling intermittent claudication (<200 m)
III	Ischemic rest pain
IV	Ulceration or gangrene

1.3.2. Diagnosis

Following clinical examination (pulse palpation), the first diagnostic tool is the measurement of the ankle-brachial index (ABI), which is a noninvasive method to diagnose AISOD and to estimate generalized atherosclerosis and cardiovascular risk (14). An ABI ≤0.9 has high sensitivity and specificity in the diagnosis of LEAD and causes a 2- to 3-fold elevated risk for cardiovascular mortality (14).

Duplex ultrasonography (DUS) is usually the first imaging method to identify arterial stenoses and determine their severity. If revascularization is deliberated, the DUS suspicion of significant stenosis usually has to be confirmed by other imaging techniques (14). Computed tomography angiography (CTA) provides a "roadmap" of the entire vasculature and is widely used for noninvasive determination of vascular lesions (14). Magnetic resonance angiography (MRA) is an emerging alternative to CTA, especially in patients with mild-to-moderate chronic kidney disease. In the case of severe renal failure, non-contrast MRA techniques or superparamagnetic iron oxide nanoparticle–enhanced MRA can be applied (18, 19). However, magnetic resonance imaging (MRI) tends to overjudge the grade of stenosis, is not able to image calcifications, and has limited effectiveness in assessing in-stent lesions (14). Digital subtraction angiography (DSA) is used for the guidance of endovascular procedures; it enables the simultaneous completion of therapeutic interventions (14). In patients with chronic kidney disease, carbon-dioxide can be applied instead of iodinated contrast material (20, 21).

1.3.3. Treatment

Treatment of AISOD can be divided into best medical therapy (BMT) and invasive therapy. Revascularization should be considered when daily life activities are compromised (14).

1.3.3.1. Best Medical Therapy

Best medical therapy includes best pharmacological treatment, together with nonpharmacological methods like smoking cessation, physical activity, healthy diet, and weight loss (14). Several studies have evidenced that smoking cessation decreases cardiovascular events and mortality, and reduces the risk for limb loss (14). Medical treatment includes lipid-lowering, antihypertensive, and antithrombotic drugs. Keeping blood pressure under the target of 140/90 mmHg is proposed in order to lower the risk for cardiovascular events (14). Statin therapy has been proven to reduce cardiovascular events and all-cause mortality in all—including asymptomatic—patients (14). In isolated asymptomatic LEAD, antiplatelet therapy is not routinely indicated due to the lack of proven benefit, while in symptomatic patients, single antiplatelet therapy is recommended (14). Following percutaneous revascularization of AISOD, patients should be put on dual antiplatelet therapy for at least 1 month, followed by a lifelong monotherapy (14, 22).

1.3.3.2. Invasive Therapy – Kissing Stenting

Invasive therapy for AISOD includes open surgical (aortobiiliac bypass or aortobifemoral bypass), endovascular (kissing stenting), and hybrid (aortoiliac stenting plus iliofemoral/femorofemoral crossover bypass) methods (14, 23). For lesions involving the distal part of the infrarenal aorta and the origin of the common iliac arteries (CIAs), kissing stenting—due to its minimally invasive nature and because it can be performed even in high-risk surgery patients—has become the first treatment of choice in many institutes over the years. Kissing stenting can be carried out with bare metal or covered stents, which can be either balloon-expandable or self-expandable. Bare metal stents are made up of metals or metal alloys including stainless steel, cobalt-chromium, nitinol (an alloy of nickel and titanium), and Elgiloy (an alloy of cobalt, chromium, nickel, iron, molybdenum, and manganese) (24). Covered stents consist of a material, such as polytetrafluoroethylene, covering a metal stent (24).

Balloon-expandable stents are produced in a coiled status and the inflation of the balloon results in dilation of the stent to the vessel's diameter (25). Compared with self-expandable models, the radial force—which refers to the external pressure that a stent is able to resist—is higher in the case of balloon-expandable stents (25, 26). However,

they can collapse under critical external pressure, potentially causing severe clinical consequences (25). Stiffness describes the degree of reduction of the stent diameter under the application of external pressure. The radial stiffness of balloon-expandable stents is higher; thus, they significantly attenuate the compliance of an artery (25). Based on the above information, balloon-expandable stents are ideal for heavily calcified aortoiliac lesions (25).

Self-expandable stents are produced at the diameter of the vessel (or barely above it), then constrained within a delivery catheter until the planned delivery location is attained, where the constraint is extracted and the stent deployed (25). Compared with balloon-expandable models, self-expandable stents have a lower radial strength and radial stiffness but higher flexibility, which makes them able to accommodate the curves and bends in arteries (24, 25). As a consequence of lower radial and axial stiffness and higher compliance, self-expandable stents are more adaptable, and they suit their structure to that of the artery, rather than constrain the vessel to the form of the stent (25). In summary, the features of self-expandable stents make them highly suitable to less calcified lesions and/or elongated arteries (27). Generally, self-expandable nitinol stents should be favored for kissing stenting over balloon-expandable ones due to their lower mismatch area (28). Additionally, self-expandable stents minimize the chance of aortic rupture through their gradual expansion after balloon inflation (29). They might also decrease the risk for distal embolization by trapping more atherosclerotic material (29).

Because covered stents provided superior long-term patency and clinical outcomes than bare metal stents in complex AISOD, the covered endovascular reconstruction of the aortic bifurcation (CERAB) technique was introduced with the aim to overcome the drawbacks of kissing stenting, including mismatch area between the stent and arterial wall leading to flow disturbances, neointimal hyperplasia, and decreased patency (30–32). Recent results have shown that the CERAB technique can be performed with good mid-term (2- to 3-year) patency rates and clinical outcomes in patients with extensive AISOD (30, 32, 33).

1.3.3.3. Complications after Kissing Stenting

With the growing number of stent implantations, complications are to be expected with increasing frequency (34). Endovascular complications can be categorized generally as early (within 30 days) and late.

1.3.3.3.1. Early Complications

Early complications can be further classified as access site complications, complications related to passage of catheters and devices, and intervention-specific complications (34).

Access site hematomas, with or without pseudoaneurysms, are the most common complications of peripheral vascular interventions, occurring in 1%–11% of procedures (35). Their significance lies in the fact that they are associated with adverse clinical outcomes, including higher 30-day and 1-year mortality rates (35). Its most worrisome form is retroperitoneal hematoma, which is an uncommon but potentially fatal complication of the transfemoral approach (36). Pseudoaneurysms can be solved by reapplication of a compression bandage, ultrasound-guided compression, ultrasound-guided thrombin injection, endovascular intervention (e.g., covered stent implantation), or open surgical repair (37, 38). A randomized prospective study concluded that ultrasound-guided thrombin injection provides more favorable results than compression therapy and should be chosen as the first-line treatment (39). Indications for surgical management include rapid expansion, compressive symptoms, infection, and failure of other therapies (38). Arteriovenous fistula—caused mostly by inadvertent puncture—tends to close spontaneously within one year and symptoms rarely occur; therefore, nonoperative management and follow-up with DUS is recommended (40). Other complications include acute thrombosis or occlusion of the artery, arterial perforation, and nerve injury (34). Distal embolization is more frequently induced by passage of catheters and the intervention itself than by arterial puncture alone (34).

The arterial wall can be injured by wires, catheters, or devices being passed through a blood vessel (34). Besides the typical morphological appearance of the intimal flap, dissection should be suspected if no blood can be drawn off the catheter (34). Patients with severe atheromatous disease are at higher risk for the development of

microembolization after passage of endovascular devices (34). Additionally, clots can form on wires and catheters in patients who do not receive anticoagulants (34).

Intervention-specific complications of aortoiliac stenting include subintimal passage of the guidewire, rupture of the CIA (particularly in small or calcified vessels), distal embolization (with higher risk when recanalizing total occlusions), and stent thrombosis (34).

1.3.3.3.2. Late Complication – In-Stent Restenosis

The most important late complication of kissing stent implantation potentially leading to recurrent symptoms is in-stent restenosis (ISR). ISR is defined as a decrease in luminal diameter due to ingrowing cells, extracellular matrix, and thrombus within the stented vessel or 5 mm to the proximal and/or distal edges of the stent (41).

1.3.3.3.2.1. Pathophysiology

The complex processes resulting in ISR can be partitioned into early (days to weeks) and late (weeks to months) phases (42) (Figure 1). The early phase starts with relocation of the axially transmitted plaque, reorganization of the thrombus, and an acute inflammatory response to the vessel wall injury (42). Reorganization of the thrombus is a process provoked by stent implantation due to endothelial damage, denudation of the endothelium, and medial dissection (43). Consequently, platelets are exposed to subintimal molecules, causing their adherence and aggregation, which contribute to the inflammatory reaction (42, 43). The increased migration of leukocytes (predominantly monocyte-derived macrophages) into the arterial wall followed by the continued secretion of cytokines, mitogens, adhesion molecules, and chemoattractants by platelets, monocytes, and smooth muscle cells promotes further leukocyte enrollment and infiltration (42). The key episode of the late phase is the phenotypic alteration of medial smooth muscle cells pursued by their recruitment and successive proliferation in the intimal layer (42). Subsequently, extracellular matrix and collagen are synthesized by smooth muscle cells, leading to neointima formation, which is the main cause of ISR

(43). The expansion of neointimal tissue is due to extracellular matrix synthesis by smooth muscle cells (42).

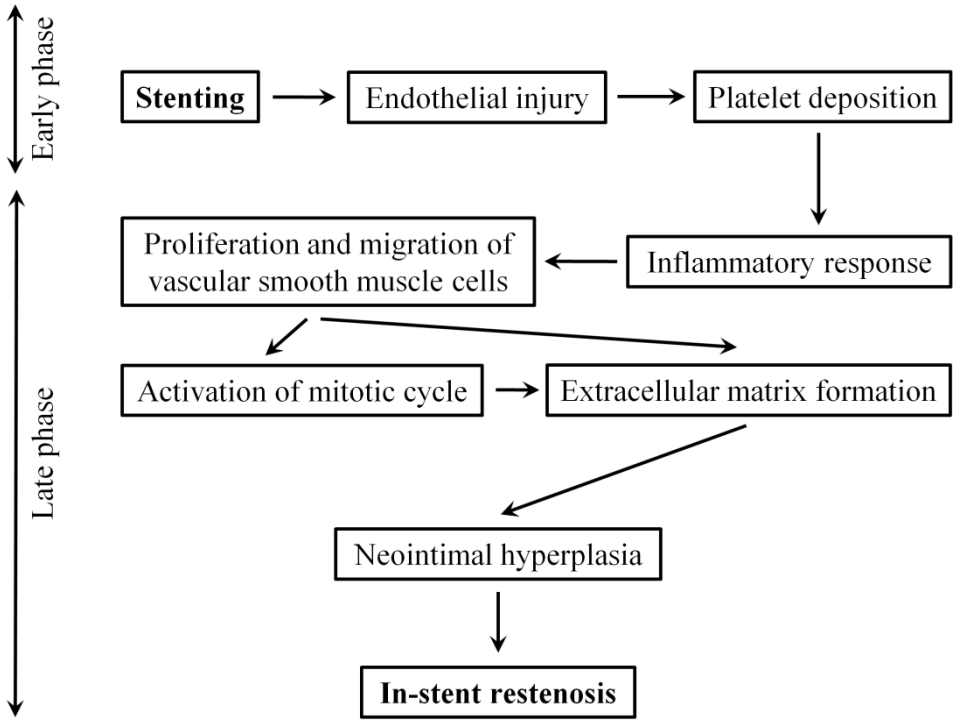


Figure 1. Pathophysiology of in-stent restenosis (42)

Neointimal hyperplasia can also be affected by the atherosclerotic process, resulting in a neointimal atherosclerotic change (neoatherosclerosis), which has been proven to contribute to late ISR, occurring usually beyond 5 years (44–46). Neoatherosclerotic lesions are marked by infiltration and aggregation of lipid-laden foamy macrophages within the neointimal hyperplasia following stent implantation, owing to the impossibility to sustain a completely functional endothelial surface within the stent (46, 47). Besides, insufficient recovery of the endothelium leads to an exaggerated infiltration of circulating lipids, which causes an increased atherosclerotic change in the nascent neointima (44). Neoatherosclerotic lesions may also contain calcification (46).

1.3.3.3.2.2. Prevalence and Predictors

The prevalence of ISR following aortoiliac kissing stenting was reported to be between 7% and 29%, but most studies have been limited due to a small sample size and a short follow-up duration (29, 48–51). There is limited data in the literature about the risk factors for ISR (29, 48, 50, 51). Houston et al. (48) found higher ISR rates in patients with bilateral CIA disease associated with distal aortic stenosis as seen in TransAtlantic Inter-Society Consensus (TASC) type D lesions. Age <50 years, the presence of iliac artery occlusion, and crossing of stents in the aorta were also shown as predictors for reduced primary patency (52).

1.4. Common Carotid Artery Stenosis

The annual incidence of stroke is approximately 0.2% in Europe, leading to 1.1 million deaths each year, which makes it the second most common cause of mortality (9). Of all strokes, about 10%–15% result from thromboembolism from a previously asymptomatic >50% internal carotid artery (ICA) stenosis (9). The proximal common carotid artery (CCA) is the second most frequent place for extracranial carotid artery stenosis; it is responsible for 1%–2% of all ischemic cerebral events (53). By contrast, atherosclerotic stenosis rarely occurs in the middle/distal CCA (54).

1.4.1. Symptoms

Carotid stenosis is considered symptomatic if associated with episodes of neurological dysfunction caused by focal carotid territory brain or retinal ischemia within the preceding 6 months, and asymptomatic in the case of no former symptoms or if symptoms arose more than 6 months ago (14). According to four population-based cohort studies including more than 23,000 participants with a mean age of 61 years, the prevalence of asymptomatic >70% ICA stenosis diagnosed on DUS was 0.5% (55). Carotid territory symptoms cover contralateral hemi-sensory deficit (e.g., numbness), contralateral hemi-motor impairment (e.g., weakness, clumsiness), cortical damage (e.g., aphasia, hemianopsia), and ipsilateral transient monocular blindness (amaurosis

fugax) (9). The significance of CCA stenoses lies in the fact that their neurological symptoms can be as severe as those of ICA stenosis, potentially leading to disability and socioeconomic burdens (56).

1.4.2. Diagnosis

Because of the potential of gaining anatomic as well as hemodynamic data and its high availability, DUS is generally the first-line imaging method if carotid artery stenosis is suspected (9). If percutaneous revascularization is planned, DUS needs to be complemented with CTA or MRA to depict the aortic arch, supraaortic trunks, carotid bifurcation, distal ICA, and the intracranial circulation (9). DSA is rarely needed for diagnostic aims, unless noninvasive imaging results are discordant (9).

1.4.3. Treatment

Therapeutic options for significant CCA stenosis include BMT and invasive therapy.

1.4.3.1. Best Medical Therapy

Risk factor control (smoking cessation, regular exercise, healthy diet, and weight loss) are essential for patients with carotid stenosis to reduce the risk for ischemic stroke (9). Hypertension and diabetes mellitus should be maintained to achieve a reduction in cardiovascular events and mortality (9). Statins seem to reduce the rate of myocardial infarction, stroke, and all-cause mortality in asymptomatic as well as symptomatic patients (9). The use of antiplatelet therapy is controversial in asymptomatic patients but low-dose aspirin can be recommended to prevent late cardiovascular events. In symptomatic cases, clopidogrel is favored (9).

1.4.3.2. Invasive Therapy – Percutaneous Antegrade Stenting

Invasive therapy for CCA stenosis includes surgical (e.g., carotid-subclavian bypass), endovascular (e.g., percutaneous antegrade stenting), and hybrid (e.g., open retrograde stenting) methods (9).

Because open surgery of an aortic arch branch origin stenosis, including proximal CCA lesions, is associated with significant morbidity and mortality rates, stenting (either antegrade or retrograde) is widely accepted as the primary therapy for proximal CCA stenoses (9, 57). Based on the fact that foreshortening is not expected, balloon-expandable stents can be deployed very precisely and are consequently ideal for ostial CCA lesions when accurate placement is required (25).

In contrast to the proximal CCA, none of the guidelines provide recommendations on the type of invasive therapy for middle/distal CCA lesions (9, 14, 58). In our institution, percutaneous antegrade intervention with self-expandable stents is the preferred method.

1.4.3.3. Complications after Common Carotid Artery Stenting

1.4.3.3.1. Early Complications

Besides general access site and passage-related complications detailed in chapter 1.3.3.3.1., carotid stenting also has specific complications.

Balloon-expandable stents can detach from the balloon, especially in the presence of calcified CCA origin. Although cerebral protection devices are frequently applied in patients with distal CCA stenosis, intraprocedural stroke might occur from embolization from the aortic arch or due to inappropriate filter implantation (9). According to data from the literature, minor stroke occurs in 0%–4.7%, while major stroke occurs in 0%–2% of patients following percutaneous antegrade proximal CCA stenting (59–64). Aortic arch atheroma, longer lesions, and diseased external carotid artery were identified as risk factors for procedural stroke and death after carotid artery stenting (9). Several problems can result from the use of distal cerebral protection devices, such as spasm of the ICA, filter obstruction, or separation of the filter from the delivery catheter (34).

1.4.3.3.2. Late Complications

1.4.3.3.2.1. In-Stent Restenosis

The prevalence of ISR in patients who underwent proximal CCA stenting was reported to be between 0% and 19% (59–64). No predictors for proximal CCA ISR have been identified so far (59–64). Additionally, we were unable to find publications on the long-term patency of middle/distal CCA stenting and the risk factors for ISR.

1.4.3.3.2.2. Stent Fracture

Stent fractures (SFs) can be categorized as type I, fracture of one strut; type II, fracture of multiple struts without stent deformity; type III, fracture of multiple struts with stent deformity; type IV, complete fracture of the stent without a gap; and type V, complete fracture of the stent with a gap (65) (Figure 2). There have been inconsistent data reported in the literature regarding whether SFs have a significant impact on the recurrence of stenosis (66–68). It seems that simple (type I and II) fractures have no clinical relevance, while complex (type III–V) fractures may lead to significant ISR (66). Except for one study including eight patients with proximal CCA stenting by Usman et al. (69), who reported one stent crush deformation, no detailed information is available about the incidence of CCA SFs.

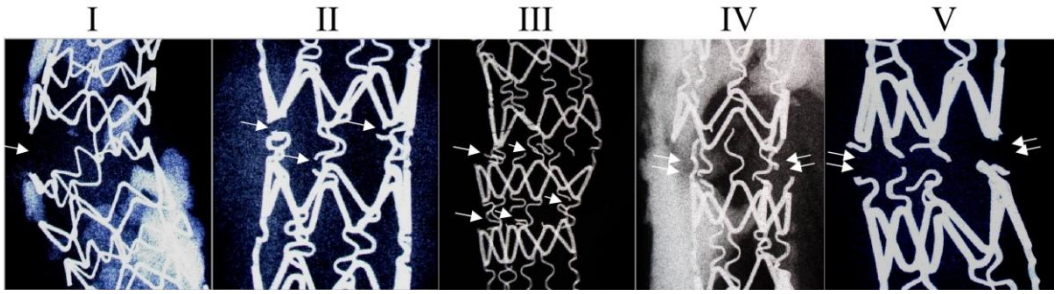


Figure 2. Stent fractures (from Nakazawa et al.) (65)

2. Objectives

2.1. Study I (Aortoiliac Kissing Stenting – Institutional Review Board Approval No. 245/2013)

Because large-scale studies are lacking with regard to the long-term success of aortoiliac kissing stenting, not every vascular specialist is convinced of the raison d'être of the kissing technique. Therefore, our first aim was to provide reliable information on the long-term primary, assisted primary, and secondary patency rates, and to shed light on the facilitators of ISR in patients who underwent reconstruction of the aortoiliac bifurcation with kissing stents at our department.

2.2. Study II (Proximal Common Carotid Artery Stenting – Institutional Review Board Approval No. 174/2018)

Even though SFs might affect patency rates, there is a paucity of data in the literature on the frequency of CCA SFs. Thus, the primary objective of our second study was to determine the prevalence of SFs following stent implantation in the proximal third of the CCA and to examine whether there is a correlation between SFs and ISR, reintervention, as well as long-term patency rates. We also aimed to evaluate the risk factors for CCA SFs.

2.3. Study III (Middle/Distal Common Carotid Artery Stenting – Institutional Review Board Approval No. 174/2018)

Middle/distal CCA stenosis rarely occurs; when it does, it is mostly treated with stent implantation. We did not find any publication on the incidence of and predictors for ISR following middle/distal CCA stenting. Therefore, our purpose was to determine the long-term patency rates and to investigate predisposing factors in the development of ISR in patients who underwent middle/distal CCA stenting. Our secondary goal was to identify the prevalence of middle/distal CCA SFs.

3. Results

3.1. Study I (Aortoiliac Kissing Stenting)

3.1.1. Patients

The total number of patients treated for AISOD with kissing stent reconstruction at the Heart and Vascular Center of the Semmelweis University between September 2001 and June 2015 was 108. One hundred and five cases used uncovered stents, while the remaining three cases used covered stents. Patients with covered stents were excluded from further analysis due to their small number. Thus, our retrospective study was based on the remaining 105 patients. An example of aortoiliac kissing stenting can be seen in Figure 3.

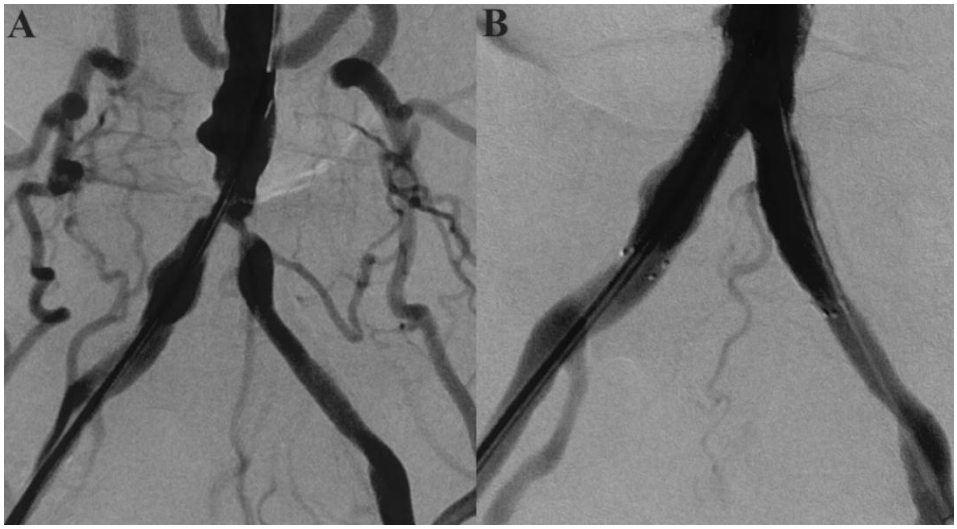


Figure 3. An example of aortoiliac kissing stenting (from the Heart and Vascular Center of the Semmelweis University). **A.** High-grade stenosis can be seen in the digital subtraction angiography image in the aortic bifurcation and the origin of the common iliac arteries. **B.** After kissing stent implantation, the completion angiogram showed a good morphological result.

Endovascular interventions were carried out through the common femoral arteries in 96 cases (91.4%), and through one brachial and one common femoral artery

in nine (8.6%). Kissing stents were positioned so that their crossing part in the aorta was at least 10 mm in length (Figure 4).

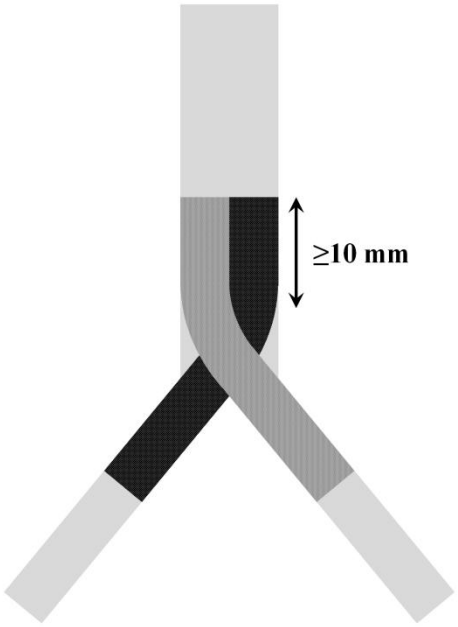


Figure 4. Kissing stent configuration in the aortic bifurcation

The median age of the 105 patients (64 women, 41 men) was 60.9 years (interquartile range [IQR], 56.3–69.2 years). The indication for kissing stenting was severe claudication (Fontaine IIb) in 91 patients (86.7%) and critical limb ischemia (Fontaine III–IV) in 14 (13.3%). Atherosclerotic risk factors included smoking in 91 patients (86.7%), hypertension in 99 (94.3%), hyperlipidemia in 63 (60%), diabetes mellitus in 39 (37.1%), obesity (body mass index [BMI] ≥30 kg/m^2) in 20 (19%), and chronic kidney disease in 13 (12.4%).

All patients were on antiplatelet therapy postprocedurally (acetylsalicylic acid, N=73; clopidogrel, N=10; dual antiplatelet therapy, N=22).

3.1.2. Vessel, Lesion, and Stent Characteristics

Anatomic variations of the aortic bifurcation were analyzed according to a classification created by our group. This classification takes into account the geometry of the abdominal aorta (straight versus elongated relative to the lumbar spine), the symmetry

of the aortic bifurcation (symmetrical versus asymmetrical relative to the infrarenal aorta), and the angle enclosed by the CIAs (acute versus obtuse) (Figure 5).

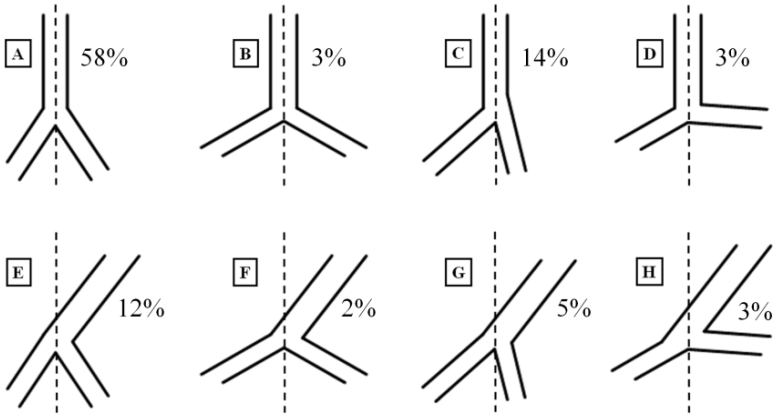


Figure 5. Anatomic variations of the aortic bifurcation

The underlying pathology was atherosclerosis in all patients. Lesions were categorized according to the TASC II classification (17): TASC A in 52 cases (49.5%), B in 29 (27.6%), C in four (3.8%), and D in 20 (19%). Two hundred and ten stents were deployed (self-expandable [12 different brands], N=180 [85.7%]; balloon-expandable [three different brands], N=30 [14.3%]). The median stent lengths were 60 mm (IQR, 60–80 mm) for self-expandable stents and 38 mm (IQR, 38–48 mm) for balloon-expandable models. The median length of the aortic segment of the stents was 19.5 mm (IQR, 14.7–24.7 mm). The median discrepancy between the diameter of the stent and the diameter of the CIA was 2 mm (IQR, 1–2.5 mm); the median stent-to-CIA diameter ratio was 1.25 (IQR, 1.1–1.3). The median discrepancy between the summed stent diameters and aortic diameter was 6.4 mm (IQR, 4.5–8 mm); the median summed stents-to-aorta diameter ratio was 1.5 (IQR, 1.3–1.7).

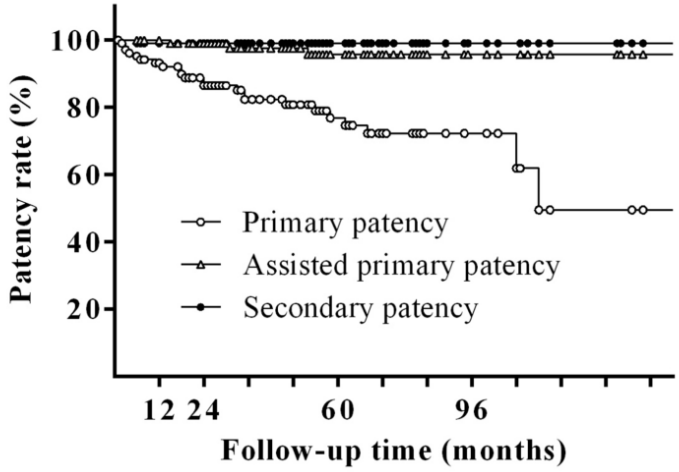
3.1.3. Early Postprocedural Period (within 30 Days)

The technical success rate, defined as ≤30% residual stenosis without dissection or extravasation, was 98.1% (>30% residual stenosis, N=2). Eight access site-related complications developed: two hematomas, five pseudoaneurysms, and in one case the closure device had to be removed surgically. One of the hematomas was treated

conservatively, while the other one was evacuated. Four out of five pseudoaneurysms were eliminated by ultrasound-guided injection of thrombin and one was managed surgically. The 30-day all-cause mortality rate was zero.

3.1.4. Follow-up Period

Follow-up examinations included evaluation of symptoms, if any, palpation of femoropopliteal and foot pulses, and measurement of ABI. Patients with relevant symptoms or those with decreased (≤0.9), borderline (0.9–1), or elevated ABI (>1.4) underwent DUS (14). Significant ISR (including total occlusion) was defined as an increase in peak systolic velocity (PSV) of >2.4 when compared to the proximal normal segment or no color flow (70). The presence of significant ISR was verified with CTA or DSA. The median follow-up time was 45 months (IQR, 21–69 months). Significant ISR (including total occlusion) was observed in 23 patients (21.9%; unilateral, N=12; bilateral, N=11). Stent occlusion was detected in 13 cases (Leriche syndrome, N=2). Endovascular reintervention was carried out in 14 patients (percutaneous transluminal angioplasty [PTA], one complemented with stenting), while open surgery was performed in six cases (aortobifemoral bypass, N=4; crossover bypass, N=2). Re-ISR developed in five patients (4.8%); three of them were treated endovascularly, while one of them underwent open surgical reconstruction. Patency was determined by the guideline of Rutherford et al. (71, 72) (primary patency: open stents without any reintervention; assisted primary patency: open stents after reintervention due to stenosis of the stents or adjacent vessel segments; secondary patency: open stents after reintervention due to stent occlusion) and was defined per patient and not per limb. Patency rates are shown in Figure 6. The median resting ABI improved from 0.53 (IQR, 0.48–0.57) before the procedure to 0.9 (IQR, 0.85–0.95) at the most recent follow-up.



Patency		6 months	12 months	24 months	60 months
Primary	%	95.2	93.2	86.5	76.9
	No. at risk	100	89	77	37
	SE	2.1	2.5	3.5	4.9
Assisted primary	%	100	100	98.9	95.8
	No. at risk	104	95	85	43
	SE	0	0	1.1	2.5
Secondary	%	99	99	99	99
	No. at risk	104	94	85	42
	SE	1	1	1	1

Figure 6. Primary, assisted primary, and secondary patency rates following aortoiliac kissing stenting. *SE*, standard error.

Kaplan-Meier analysis.

3.1.5. Predictors for In-Stent Restenosis

ISR occurred more frequently (P=.009) in younger patients (Table 2). The diameter of the aorta was significantly smaller (P=.009), while the length of the aortic part of the stents was significantly longer (P=.004) in the ISR compared with the non-ISR group (Tables 2 and 3). Other patient-, vessel-, lesion-, and stent-related parameters did not differ significantly between the two groups (Tables 2–4).

Table 2. Comparison of parameters of patients with and without in-stent restenosis following aortoiliac kissing stenting

Parameters	**All patients (N=105)**		**P value**
	ISR group (N=23)	**Non-ISR group (N=82)**	
Patient characteristics			
Age (years)	56.5 (50–65.7)	61.6 (57.5–70.5)	**.009**
Female sex	14 (60.9)	50 (61)	>.999
Smoking	21 (91.3)	70 (85.4)	.729
Hypertension	20 (87)	79 (96.3)	.117
Hyperlipidemia	15 (65.2)	48 (58.5)	.635
Diabetes mellitus	11 (47.8)	28 (34.1)	.328
BMI (kg/m^2)	25.3 (22.3–30.9)	25.4 (22.9–29)	.838
Obesity	6 (26.1)	14 (17.1)	.371
Chronic kidney disease	2 (8.7)	11 (13.4)	.728
Vessel characteristics			
Diameter of the left CIA (mm)	7.5 (6.9–8.9)	8 (7.2–9)	.714
Diameter of the right CIA (mm)	7.9 (7.3–8.5)	8 (7.1–9)	.209
Diameter of the aorta (mm)	12 (11–13)	13 (11.8–15.4)	**.009**
Lesion characteristics			
TASC II A	10 (43.5)	42 (51.2)	.638
TASC II B	6 (26.1)	23 (28)	>.999
TASC II C	2 (8.7)	2 (2.4)	.208
TASC II D	5 (21.7)	15 (18.3)	.765
Iliac and/or aortic heavy calcification	5 (21.7)	20 (24.4)	>.999

BMI, body mass index; *CIA*, common iliac artery; *ISR*, in-stent restenosis; *TASC*, TransAtlantic Inter-Society Consensus.

Continuous data are presented as the median and IQR (Q1–Q3) and group differences were compared using the Mann–Whitney *U* test. Discrete data are given as the counts (percentages) and group differences were compared using Fisher's exact test.

Table 3. Comparison of the 105 pairs of stents in patients with and without in-stent restenosis following aortoiliac kissing stenting

Stent characteristics I	**All pairs of stents (N=105)**		**P value**
	ISR group (N=23)	**Non-ISR group (N=82)**	
Aortic stent length (mm)	22.5 (20–27.3)	18 (14.3–24.1)	**.004**
Discrepancy between the sum of stent diameters and aortic diameter (mm)	7 (5.2–8.2)	6 (4–7.9)	.103

ISR, in-stent restenosis.

Data are presented as the median and IQR (Q1–Q3) and group differences were compared using the Mann–Whitney *U* test.

Table 4. Comparison of parameters of stents with and without in-stent restenosis following aortoiliac kissing stenting

Stent characteristics II	**All stents (N=210)**		**P value**
	ISR group (N=34)	**Non-ISR group (N=176)**	
Self-expandable	32 (94.3)	148 (84.2)	.180
Stent length			
Self-expandable (mm)	60 (60–80)	60 (60–80)	.336
Balloon-expandable (mm)	39 (39–39)	38 (38–52)	.372
Stent protrusion into the EIA	4 (11.8)	27 (15.3)	.792
Discrepancy between stent diameter and CIA diameter (mm)	2.1 (0.7–2.5)	1.9 (1–2.5)	.695

CIA, common iliac artery; *EIA*, external iliac artery; *ISR*, in-stent restenosis.

Continuous data are presented as the median and IQR (Q1–Q3) and group differences were compared using the Mann–Whitney *U* test. Discrete data are given as the counts (percentages) and group differences were compared using Fisher's exact test.

Univariate Cox regression analysis revealed older age, the presence of hypertension, and larger aortic diameter to be significant protective factors against ISR, while longer aortic part of the stents and larger discrepancy between the sum of stent diameters and aortic diameter were associated with worsened long-term patency (Table 5). Multivariable analysis showed longer aortic part of the stents to be the only significant determinant of ISR (Table 5).

Table 5. Predictors for in-stent restenosis after aortoiliac kissing stenting

Variables	HR (95% CI)	P value
Univariate analysis		
Age (years)	0.5 (0.31–0.81)	**.004**
Hypertension	0.15 (0.04–0.54)	**.003**
Diameter of the aorta (mm)	0.42 (0.25–0.7)	**<.001**
Aortic stent length (mm)	1.56 (1.16–2.09)	**.003**
Discrepancy between the sum of stent diameters and aortic diameter (mm)	1.64 (1.01–2.65)	**.043**
Multivariable analysis		
Age (years)	0.67 (0.39–1.16)	.152
Hypertension	0.27 (0.06–1.26)	.095
Diameter of the aorta (mm)	0.68 (0.34–1.38)	.288
Aortic stent length (mm)	1.44 (1.02–2.01)	**.035**
Discrepancy between the sum of stent diameters and aortic diameter (mm)	1.14 (0.57–2.28)	.702

CI, confidence interval; *HR*, hazard ratio.

Univariate and multivariable Cox regression analysis.

Regarding the length of the aortic part of the stents, 20 mm was identified by receiver operating characteristic analysis as the optimal cut-off value due to its highest sensitivity, specificity, and clinical relevance (Figure 7).

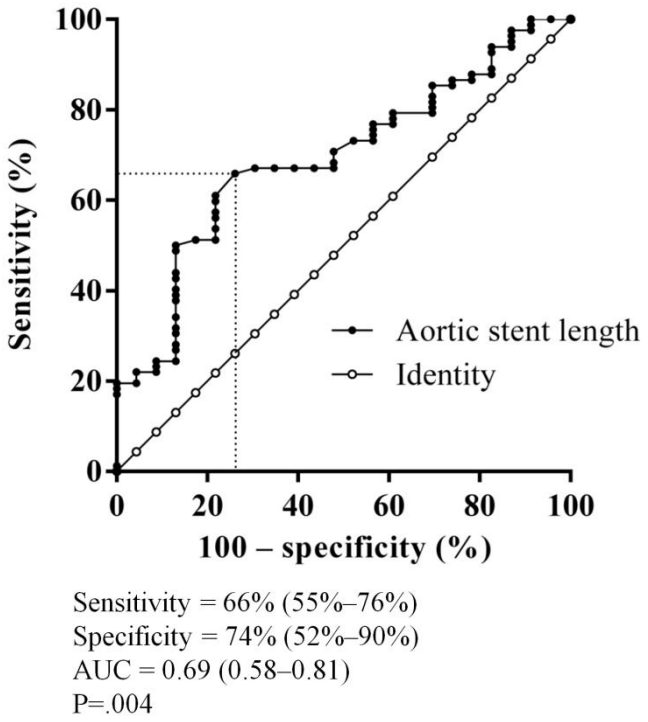
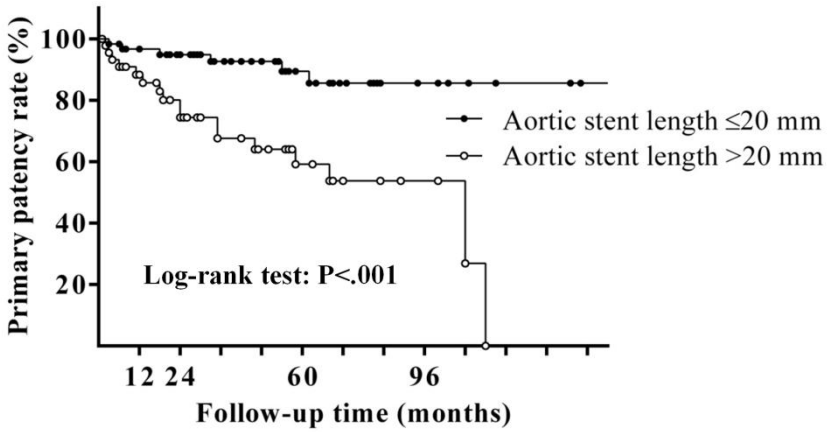


Figure 7. Receiver operating characteristic curve for the length of the aortic stent segment. *AUC*, area under the curve.

Dichotomization on the 20-mm cutpoint produced primary patency rates of 97%, 95%, and 89% at 12, 24, and 60 months, respectively, in patients whose aortic stent segment was ≤20 mm, versus 88%, 74%, and 59% at the same time points in patients whose aortic stent segment was >20 mm. The primary patency was significantly worse (P<.001) in patients with longer (>20 mm) aortic stent segments (Figure 8).



Primary patency		6 months	12 months	24 months	60 months
Aortic stent length ≤20 mm	%	98.3	96.6	94.8	89.4
	No. at risk	59	55	49	24
	SE	1.7	2.3	2.9	4.7
Aortic stent length >20 mm	%	90.9	88.3	74.4	59.1
	No. at risk	41	34	28	13
	SE	4.3	4.9	7.1	9

Figure 8. Primary patency rates for patients with short versus long aortic stent segments after aortoiliac kissing stenting. *SE*, standard error.

Kaplan-Meier analysis.

3.2. Study II (Proximal Common Carotid Artery Stenting)

3.2.1. Patients

A total of 93 patients were treated for stenosis of the proximal third of the CCA at the Heart and Vascular Center of the Semmelweis University during the study period of 2006–2016. In 2018, patients were asked to return for a fluoroscopic examination of the implanted stents. Excluded patients were those who had only PTA (N=10), deceased during the follow-up (malignancy, N=4; acute myocardial infarction, N=3; car accident, N=1), or had not responded for the invitation for the fluoroscopic examination (N=5). Among those who were excluded, none had any postprocedural complication. The remaining 70 patients with 70 CCA stents were included in the final analysis.

The suspicion of significant CCA stenosis by DUS was verified with CTA or MRA in all cases. The indication for intervention was the presence of either

asymptomatic, but ≥70% stenosis (N=62 [88.6%]) or symptomatic, ≥60% stenosis (N=8 [11.4%]). Asymptomatic patients underwent stenting because they had multivessel supraaortic steno-occlusive disease and/or were awaiting coronary artery bypass grafting or valve replacement. In addition, all asymptomatic patients were thought to have an increased risk of stroke on BMT due to a history of contralateral transient ischemic attack (TIA)/stroke or the presence of ipsilateral silent infarction, large CCA lesion, and/or vulnerable CCA plaque on the computed tomography/magnetic resonance images (73). As a neurological symptom, amaurosis fugax was seen in four patients, TIA in three, and minor ischemic stroke ipsilateral to the lesion in one.

The median age of the 70 patients (37 women, 33 men) was 60.9 years (IQR, 54.8–63.8 years). Risk factors for atherosclerosis included smoking in 56 patients (80%), hypertension in 66 (94.3%), hyperlipidemia in 37 (52.9%), diabetes mellitus in nine (12.9%), and obesity (BMI ≥30 kg/m^2) in 16 (22.9%).

All patients had antiplatelet therapy (acetylsalicylic acid, N=28; clopidogrel, N=22; ticlopidine, N=1; dual antiplatelet therapy, N=19) and 70% of them had statins postprocedurally.

3.2.2. Lesion-, Procedure-, and Stent-Related Parameters

The etiology was presumably atherosclerosis in 67 patients (95.7%), arteritis in one (1.4%), and fibromuscular dysplasia in two (2.9%). The median stenosis grade was 80% (IQR, 75%–90%) and the median stenosis length was 9 mm (IQR, 7–13 mm). Mild calcification was observed in 20 cases (28.6%), moderate in six (8.6%), and heavy in six (8.6%). The presence and grade of calcification were assessed on the fluoroscopic images: Lesions were defined as mildly calcified if single or multiple punctate calcifications were seen, as moderately calcified if single or multiple linear areas of calcification were present, and as heavily calcified if continuous calcification with no visible breaks was observed within the lesion (74). Lesions were identified on the left side in 57 patients (81.4%). The origin of the CCA was involved in 59 cases (84.3%).

An example of proximal CCA stenting can be seen in Figure 9. All interventions were executed through the right or left common femoral artery. Primary stenting (stent implantation after predilation of the lesion regardless of the outcome of PTA) was

performed in 22 patients (31.4%), while direct stenting (stent deployment without predilation of the lesion) was performed in 48 (68.6%). Seventy stents were deployed (balloon-expandable [six different brands], N=61 [87.1%]; self-expandable [five different brands], N=9 [12.9%]). The median diameter of the balloon-expandable stents was 8 mm (IQR, 8–8 mm), while it was 9 mm (IQR, 8–10 mm) in the case of the self-expandable stents. The balloon-expandable stents were 19 mm (IQR, 18–29 mm), while the self-expandable stents were 40 mm (IQR, 40–50 mm) in median length.

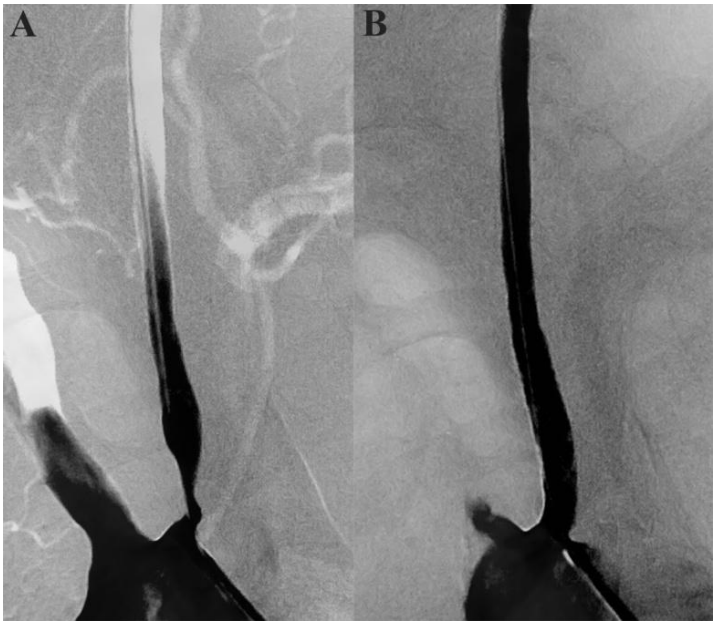


Figure 9. An example of proximal common carotid artery stenting (from the Heart and Vascular Center of the Semmelweis University). **A.** A digital subtraction angiography image showing high-grade stenosis in the proximal part of the left common carotid artery. **B.** After stent implantation, a good morphological result can be seen on the completion angiogram.

3.2.3. Early Postprocedural Period (within 30 Days)

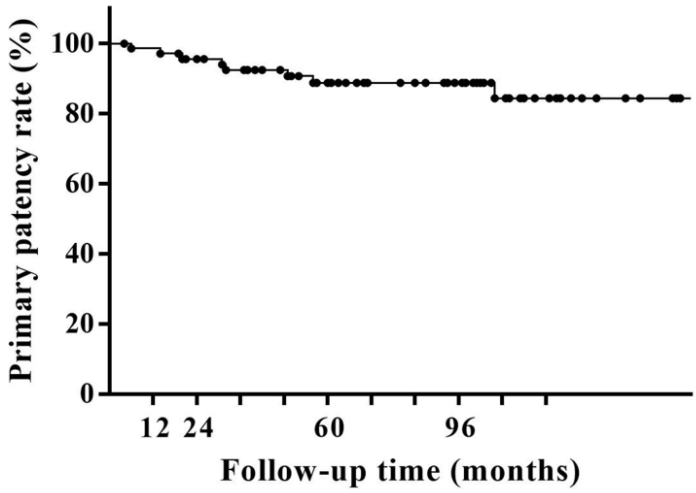
Technical success meant ≤30% residual stenosis without dissection or extravasation, and was achieved in all cases. There were four complications: two puncture site (2.9%), one stent-related (1.4%), and one neurological (1.4%). The following puncture site complications were noted: one inguinal hematoma, which was evacuated surgically, and one common femoral artery occlusion, which was solved by surgical thrombectomy.

The stent-related complication meant that the stent could not be passed through the high-grade, heavily calcified CCA stenosis and could not be pulled back to the sheath, because its caudal end had partially opened. The stent was drawn down and implanted into the right CIA. Thereafter, the CCA stenosis was extensively predilated and it was successfully stented with a new balloon-expandable stent. The neurological complication in another patient was a middle cerebral artery stroke caused by embolism most likely when the stent was pushed through the tight stenosis. Clinical findings included aphasia, ipsilateral facial weakness, and contralateral hemiparesis. Intracranial angiogram showed proximal M1 segment occlusion on the left. Immediately after the stent placement, intravenous thrombolysis was started with recombinant tissue plasminogen activator (0.9 mg/kg) and the patient was transferred to the National Institute of Clinical Neurosciences, where an atheromatous fragment was removed from the middle cerebral artery with a stent retriever device. The length of time between the onset of stroke and the attempted rescue was 4 hours. The patient left the hospital with mild dysarthria 7 days after the treatment. None of the patients died within 30 days after the intervention. The clinical success rate, defined as the absence of death, emergency open surgery, stroke, or acute myocardial infarction through hospital discharge, was 98.6%.

3.2.4. Follow-up Period

Follow-up examinations included symptom assessment and bilateral carotid DUS. In patients with recurrent symptoms and/or abnormal DUS, significant (≥70%) ISR was suspected. In the case of the left CCA indirect (≥20% lower distal CCA PSV value compared with the untreated side or tardus-parvus waveform in the distal part of the treated CCA and/or ICA) (60), while in the case of the right CCA either direct (≥240 cm/s PSV) or indirect DUS signs were used. The presence of significant ISR was verified with CTA or DSA. The median follow-up time was 75.5 months (IQR, 47–109 months). Significant (≥70%) CCA ISR was found in eight patients (11.4%; stenosis, N=5; total CCA occlusion, N=3). Lesions were significantly longer (P=.010) in patients with CCA ISR (14 mm [IQR, 10–21.5 mm] versus 8 mm [IQR, 6–11 mm]). Other patient-, lesion-, procedure-, and stent-related factors had no significant impact on CCA

ISR development (data not shown). Reintervention (PTA with plain balloon, N=3; PTA with drug-coated balloon, N=1) was performed in four patients (5.7%) with nonocclusive ISR (symptomatic, N=1). The primary patency rates were 99%, 99%, 96%, 89%, and 89% at 6, 12, 24, 60, and 96 months, respectively (Figure 10).

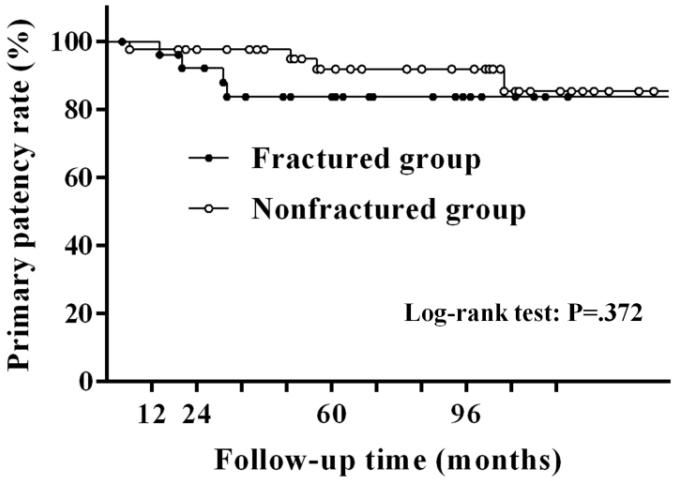


Primary patency	6 months	12 months	24 months	60 months	96 months
%	98.6	98.6	95.6	88.8	88.8
No. at risk	69	69	63	44	29
SE	1.4	1.4	2.5	4	4

Figure 10. Primary patency rates after proximal common carotid artery stenting. *SE*, standard error.

Kaplan-Meier analysis.

Twenty-seven SFs (38.6%) were detected on fluoroscopic images taken in three directions (posteroanterior and right/left anterior oblique): type I in eight, type II in ten, type III in four, type IV in two, and type V in three cases. There was no significant difference between the fractured and the nonfractured group regarding the number of patients with ISR (developing at any time during the follow-up) and reintervention (P=.701 and P=.636, respectively). The primary patency rates also did not differ significantly (P=.372) in patients with and without SF (Figure 11).



Primary patency		6 months	12 months	24 months	60 months	96 months
Fractured group	%	100	100	92.1	83.8	83.8
	No. at risk	27	27	24	16	9
	SE	0	0	5.3	7.4	7.4
Nonfractured group	%	97.7	97.7	97.7	91.9	91.9
	No. at risk	43	43	40	31	21
	SE	2.3	2.3	2.3	4.5	4.5

Figure 11. Primary patency rates for patients with and without stent fracture after proximal common carotid artery stenting. *SE*, standard error.
Kaplan-Meier analysis.

3.2.5. Predictors for Stent Fracture

Calcification was more common (P<.001) in the fractured than in the nonfractured group (Table 6). Other patient-, lesion-, and stent-related parameters showed no association with SF (Table 6). Univariate logistic regression analysis revealed calcification to be a significant predictor for SF (unit change odds ratio [OR], 13.2; 95% confidence interval [CI], 3.9–45.1; P<.001). Gamma statistics demonstrated a significant positive correlation between the SF type and the degree of calcification (gamma=0.632, P<.001).

Table 6. Comparison of parameters of patients with and without stent fracture following proximal common carotid artery stenting

Parameters	**All patients (N=70)**		**P value**
	Fractured group (N=27)	**Nonfractured group (N=43)**	
Patient characteristics			
Age (year)	61.4 (57.2–66.9)	60.4 (53.5–63.5)	.248
Female sex	13 (48.1)	24 (55.8)	.625
Smoking (current or former)	23 (85.2)	33 (76.7)	.542
Hypertension	25 (92.6)	41 (95.3)	.636
Hyperlipidemia	14 (51.9)	23 (53.5)	>.999
Diabetes mellitus	5 (18.5)	4 (9.3)	.292
BMI (kg/m^2)	27.3 (24.4–30.1)	26.4 (21.4–29)	.336
Obesity	7 (25.9)	9 (20.9)	.771
Lesion characteristics			
Stenosis grade (%)	80 (70–90)	80 (75–90)	.692
Length (mm)	10 (7–13)	8 (6–14)	.517
Calcification	24 (88.9)	8 (18.6)	**<.001**
Heavy calcification	6 (22.2)	0 (0)	**.002**
Left side	23 (85.2)	34 (79.1)	.753
CCA origin involvement	25 (92.6)	34 (79.1)	.183
Stent characteristics			
Balloon-expandable	26 (96.3)	35 (81.4)	.138
Balloon-expandable stent diameter (mm)	8 (7–8)	8 (8–8)	.396
Self-expandable stent diameter (mm)	10 (10–10)	8.5 (7.5–10)	>.999

Balloon-expandable stent length (mm)	25 (18–29)	19 (18–29)	.320
Self-expandable stent length (mm)	60 (60–60)	40 (34.5–47)	>.999

BMI, body mass index; *CCA*, common carotid artery.

Continuous data are presented as the median and IQR (Q1–Q3) and group differences were compared using the Mann–Whitney *U* test. Discrete data are given as the counts (percentages) and group differences were compared using Fisher's exact test.

With regard to the analyzed patient-, lesion-, and stent-related parameters, the group of patients with complex (type III–V) fracture did not differ significantly from those with simple (type I–II) fracture.

3.3. Study III (Middle/Distal Common Carotid Artery Stenting)

3.3.1. Patients

A total of 68 patients were treated for stenosis of the middle/distal CCA at the Heart and Vascular Center of the Semmelweis University between 2000 and 2018. In 2018, patients were asked to return for a fluoroscopic examination of the implanted stents. The middle/distal CCA was defined as the segment from 30 mm cranial on the left side and 15 mm cranial on the right side to the CCA origin to 10 mm caudal to the carotid bifurcation. Patients who had anamnestic history of prior ipsilateral carotid surgery (N=7), irradiation in the neck region (N=7), or in whom the angiographic or DUS morphology was highly suspicious of carotid fibromuscular dysplasia (N=2) or arteritis (N=1) were excluded from the study. Our study was based on the remaining 51 patients, who underwent radiological intervention with 51 self-expandable stents.

Diagnosis of the middle/distal CCA stenosis was established with DUS, CTA, or MRA, and it was verified with DSA during the procedure. The indication for intervention was the presence of either asymptomatic, but ≥70% luminal narrowing (N=23 [45.1%]) or symptomatic, ≥60% stenosis (N=28 [54.9%]). Asymptomatic patients underwent stenting if they showed multivessel supraaortic steno-occlusive

disease. In addition, all asymptomatic patients were thought to have an increased risk for stroke even while on BMT (73).

The median age of the 51 patients (21 women, 30 men) was 63.5 years (IQR, 55.2–68.3 years). Risk factors for atherosclerosis included smoking in 46 patients (90.2%), hypertension in 50 (98%), hyperlipidemia in 33 (64.7%), diabetes mellitus in 17 (33.3%), and obesity (BMI $\geq$30 kg/m^2) in 11 (21.6%).

All patients were on antiplatelet therapy (acetylsalicylic acid, N=15; clopidogrel, N=12; dual antiplatelet therapy, N=24) and 74.5% of them had statins postprocedurally.

3.3.2. Vessel, Lesion, and Stent Data

Elongation of the CCA was noted in four patients (7.8%). Atherosclerosis was the putative etiology of the stenosis in all patients. The median stenosis degree was 80% (IQR, 75%–90%) and the median stenosis length was 13 mm (IQR, 10–20 mm). Calcification was seen in 11 cases (21.6%); heavy calcification was observed in six patients (11.8%). (The presence and grade of calcification were defined in the same way as for proximal CCA lesions.) Lesions were identified on the left side in 37 patients (72.5%). The location of the stenosis was isolated middle CCA in 26 cases (51%), isolated distal CCA in 22 (43.1%), and middle and distal CCA in three (5.9%).

Interventions were executed through the common femoral, radial, or brachial arteries. Self-expandable stents were implanted in all cases; predilation was carried out only in two patients, but postdilation was routinely performed (Figure 12). The use of a cerebral protection device (FilterWire EZ, Boston Scientific Corp., Marlborough, MA, USA) was left to the discretion of the interventional radiologist and was applied in 40 cases (78.4%). Stents were made of Elgiloy in 39 patients (76.5%) and nitinol in 12 (23.5%). The median diameter of the stents was 8 mm (IQR, 7–9 mm), while their median length was 30 mm (IQR, 30–40 mm).

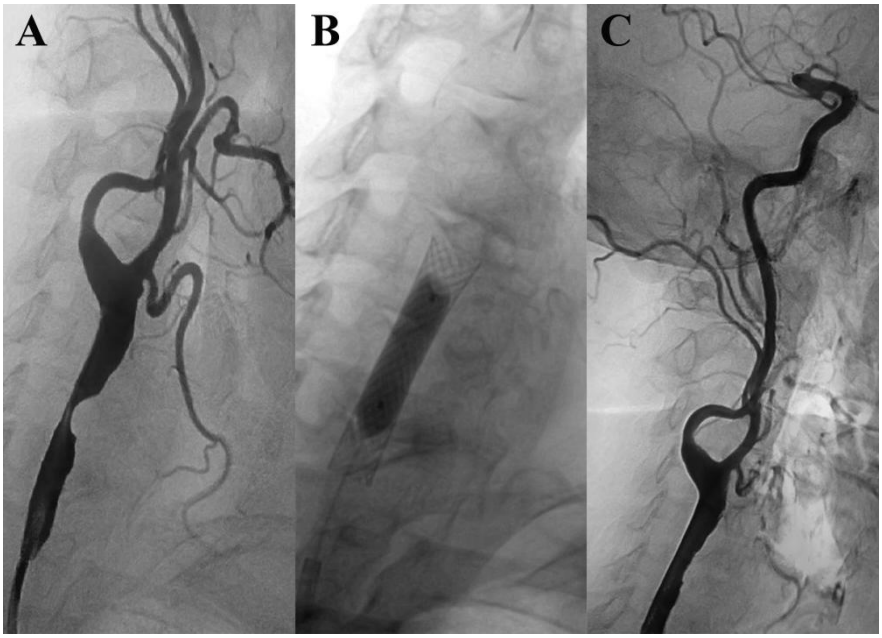


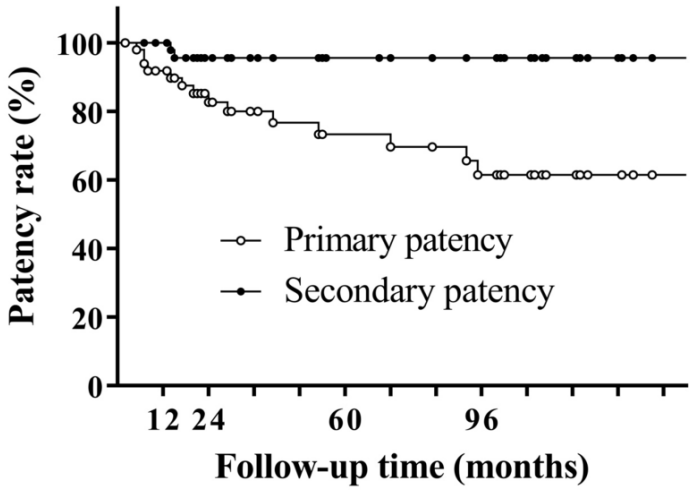
Figure 12. An example of distal common carotid artery stenting (from the Heart and Vascular Center of the Semmelweis University). **A.** A digital subtraction angiography image showing high-grade stenosis in the distal part of the right common carotid artery. **B.** After implantation of a Wallstent (7 × 30 mm), postdilation was performed with a Sterling balloon (6 × 20 mm). **C.** Minimal residual stenosis can be seen on the completion angiogram.

3.3.3. Early Postprocedural Period (within 30 Days)

Technical success, defined as ≤30% residual stenosis, was achieved in all patients. The following four complications (7.8%) were observed: one femoral pseudoaneurysm, which was eliminated by ultrasound-guided injection of thrombin, and one allergic reaction to contrast material causing perioral edema and urticaria, which was treated with chloropyramine and methylprednisolone. Two neurological complications developed: one contralateral hemiparesis plus aphasia that lasted for 5 minutes after balloon inflation, and one transient contralateral upper extremity numbness. A cerebral protection device was utilized in both these patients, with debris found in the filter of the latter. All neurological symptoms disappeared spontaneously. CT examination performed within 2 hours of the onset of symptoms revealed no evidence of acute brain ischemia or intracranial arterial obstruction in either patient. The 30-day all-cause mortality rate was zero.

3.3.4. Follow-up Period

Follow-up examinations included evaluation of symptoms and DUS assessment of the neck arteries on both sides. In patients with abnormal DUS (direct sign: ≥300 cm/s PSV within or at the ends of the CCA stent (9); indirect sign: tardus-parvus waveform in the ICA) (60), significant (≥70%) ISR was suspected. Stent occlusion was diagnosed when neither color nor Doppler signal was detected in the stent. The presence of significant ISR/stent occlusion was confirmed by CTA or DSA. The median follow-up time was 35 months (IQR, 20–102 months). Significant (≥70%) ISR developed in 14 patients (27.5%; stenosis, N=10; entire CCA occlusion, N=4). Nonocclusive ISRs were symptomatic in two patients; both patients had ipsilateral TIA. Entire CCA occlusions were asymptomatic. Reintervention (PTA with a plain balloon, N=5; restenting, N=1) was conducted in six patients (11.8%) with nonocclusive ISR. The indication for reintervention was symptomatic ISR in two patients and rapid ISR progression on BMT in four. The remaining patients with nonocclusive ISR or entire CCA occlusion received BMT. Recurrent ISR was noted in two cases: one was treated with PTA with a drug-eluting balloon (Ranger, 7 × 40 mm, Boston Scientific Corp., Marlborough, MA, USA), while the other continued on BMT. Primary and secondary patency rates can be seen in Figure 13.



Patency		6 months	12 months	24 months	60 months	96 months
Primary	%	98	91.8	82.6	73.3	61.4
	No. at risk	49	45	33	21	16
	SE	2	3.9	5.6	7.1	8.7
Secondary	%	100	100	95.6	95.6	95.6
	No. at risk	51	48	36	23	18
	SE	0	0	3	3	3

Figure 13. Primary and secondary patency rates after middle/distal common carotid artery stenting. *SE*, standard error.

Kaplan-Meier analysis.

Ischemic neurological symptoms unrelated to the treated CCA were observed in five patients (9.8%; contralateral TIA, N=2; contralateral minor stroke, N=1; vertebrobasilar events, N=2).

Of 51 patients, 47 (92.2%) returned for a fluoroscopic examination of the implanted stents. Two SFs (4.3%; one class I and one class III) were detected.

3.3.5. Predictors for In-Stent Restenosis

ISR developed significantly more frequently (P<.001) in patients with hyperlipidemia, which was assumed to be present if noted in the medical reports of the patient and/or if the patient was taking drugs for it (Table 7). All patients with ISR had hyperlipidemia. Other patient-, vessel-, lesion-, and stent-related parameters, including SF, did not differ significantly between the two groups (Table 7).

Table 7. Comparison of parameters of patients with and without in-stent restenosis following middle/distal common carotid artery stenting

Parameters	All patients (N=51)		P value
	ISR group (N=14)	Non-ISR group (N=37)	
Patient characteristics			
Age (year)	64.2 (58.3–66.7)	62.7 (55.2–68.7)	.908
Female sex	8 (57.1)	13 (35.1)	.206
Smoking (current or former)	12 (85.7)	34 (91.9)	.606
Hypertension	14 (100)	36 (97.3)	>.999
Hyperlipidemia	14 (100)	19 (51.4)	**<.001**
Diabetes mellitus	6 (42.9)	11 (29.7)	.507
BMI (kg/m^2)	23.5 (22–27.9)	26.7 (24.2–29.4)	.351
Obesity	3 (21.4)	8 (21.6)	>.999
Lesion characteristics			
Stenosis grade (%)	80 (75–90)	80 (75–90)	.319
Length (mm)	14 (10–18)	12 (9–20)	.668
Calcification	3 (21.4)	8 (21.6)	>.999
Stent characteristics			
Diameter (mm)	7 (7–9)	8 (7–9)	.227
Length (mm)	30 (30–40)	40 (30–40)	.280
Fracture[a]	0 (0)	2 (5.9)	>.999

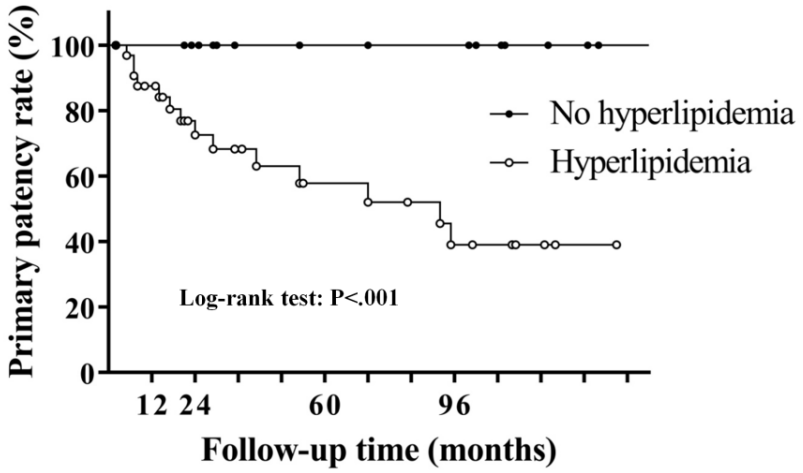
BMI, body mass index; *ISR*, in-stent restenosis.

Continuous data are presented as the median and IQR (Q1–Q3) and group differences were compared using the Mann–Whitney *U* test. Discrete data are given as the counts (percentages) and group differences were compared using Fisher's exact test.

[a]Stent fracture was examined in 47 patients (ISR group, N=13; non-ISR group, N=34).

The primary patency rate was 100% at 6, 12, 24, and 60 months, respectively, in patients without hyperlipidemia, while it was 97%, 88%, 73%, and 58% at 6, 12, 24,

and 60 months, respectively, in patients with hyperlipidemia. The primary patency rates were significantly worse (chi-square, 11.08; degrees of freedom, 1; P<.001) in patients with hyperlipidemia compared with those without hyperlipidemia (Figure 14).



Primary patency		6 months	12 months	24 months	60 months
No hyperlipidemia	%	100	100	100	100
	No. at risk	18	18	16	11
	SE	0	0	0	0
Hyperlipidemia	%	96.9	87.5	72.6	57.8
	No. at risk	32	28	18	11
	SE	3.1	5.8	8.4	10.2

Figure 14. Primary patency rates for patients with and without hyperlipidemia after middle/distal common carotid artery stenting. *SE*, standard error.

Kaplan-Meier analysis.

4. Discussion

4.1. Study I (Aortoiliac Kissing Stenting)

The most important findings of our first study are the 77% primary, 96% assisted primary, and 99% secondary patency rates at 60 months following kissing stent implantation and that a longer aortic part of the stents is a significant predictor for ISR.

The first results on the long-term patency of the aortoiliac kissing stents were reported by Haulon et al. (75) in 2002; they mentioned a 79.4% primary patency rate at 36 months. This publication was soon followed by some others in which the primary patency rates were 87%–97%, 65%–96%, and 64%–82%; the assisted primary patency rates were 95%–100%, 93%–100%, and 73%–93%; and the secondary patency rates were 94%–100%, 91%–100%, and 69%–91% at 12, 24, and 60 months, respectively (29, 48, 49, 71, 76, 77). Our patency rates are similar to the data found in the literature. Most of the above-mentioned studies examined only the short- and long-term patency rates of the aortoiliac kissing stents and they did not provide sufficient information on the risk factors for the development of ISR. Our observation that ISR occurs more frequently in younger patients is in line with previously published data. Yilmaz et al. (52) identified age <50 years as a predisposing factor for reduced primary patency. Davies et al. (78) showed that patients requiring reintervention of the iliac arteries were more commonly of a younger age. The reason for these findings might be that the course of atherosclerosis is even more aggressive in younger patients, which leads to earlier and more severe development of vascular disease (79).

The result that patients with hypertension have a lower risk for ISR might be surprising. However, carvedilol, which is a beta blocker drug, is known to have anti-free-radical and smooth muscle cell proliferation–inhibitory effects that can have a favorable influence on the prevention of ISR (80). Despite the peripheral vasoconstrictor side effect of beta blockers, more than 50% of our hypertensive patients were treated with carvedilol-containing drugs, which might lead to their decreased risk for ISR.

Self-expandable stents are usually oversized in order to assure optimal wall apposition and to avoid stent migration (81, 82). Generally, 1-mm oversizing is

recommended (82). However, severe oversizing (nominal stent diameter-to-artery ratio >1.4:1) results in injury of the media due to overstretching of the arterial wall, which leads to a long-term inflammatory response and, consequently, exuberant neointimal proliferation, as reported in a recent porcine study (81). Our higher ISR rate in patients with smaller aortic diameters and larger discrepancy between the sum of stent diameters and the aortic diameter is consistent with these findings.

In our study, a longer aortic part of the stents was noted to be a significant determinant of ISR. About 10 mm of the stent should protrude into the aorta on both sides to ensure adequate coverage of the bifurcation lesions and to obtain optimal geometry of the kissing stents (83). If the bifurcation as well as the distal third of the infrarenal aorta is diseased, the length of the stent protrusion can be even longer. We assume that in the case of long-segment contact of the stents with each other and the aortic wall, the fracture rate of the stents is higher and an overstretching effect occurs on a larger surface of the aorta; therefore, the chance for the development of ISR is increased.

The limitations of this study may have impacted our results. First, patients were retrospectively enrolled and the results represent experience at a single institution. Second, the combination of extensive lesions in the aorta and iliac arteries should currently be treated with other techniques like CERAB. We had limited access to covered stents until 2014. Third, several different uncovered stents were used for the treatment of AISOD in our study population.

4.2. Study II (Proximal Common Carotid Artery Stenting)

In the present study, proximal CCA SFs were identified in 39% of patients and calcification was a significant predictor for SF. The primary patency rates did not differ significantly in patients with and without SF.

There are few studies on the SF frequency of the aortic arch vessels. We have previously reported a 34% SF rate in subjects treated for innominate artery stenoses/occlusions (84). The incidence of fracture was found to be 35% in patients who had stenting of the prevertebral subclavian artery either with balloon-expandable or self-expandable models (66). The 39% SF rate revealed by the current study is consistent

with these experiences. The relatively high prevalence of fractures in patients with innominate, subclavian, and proximal CCA stents can be explained by the fact that the impact of vessel movement on metal fatigue and fracture through the transmission of mechanical forces—such as flexion, torsion, and tension/compression during the cardiac cycle—is quite pronounced in these vascular regions (85). However, in a retrospective review of 27 ostial supraaortic trunk lesions managed with balloon-expandable or self-expandable stents, only three type IV SFs in the innominate artery were detected in addition to two mid-body stent crush deformities (one innominate artery and one CCA) (69). No definite explanation can be given for the lower SF rate mentioned in this study, but differences in patient and lesion characteristics, as well as procedure-related factors among the studies, can be assumed.

Patient-related (e.g., hypertension, chronic kidney disease), vessel-related (e.g., tortuosity), lesion-related (e.g., site, etiology, stenosis grade, length), balloon/stent-related (e.g., material, type, design, conformity, diameter, length), and procedure-related (e.g., malposition, distortion, residual stenosis) parameters were shown to influence SF (85, 86). In this study, the presence of calcification was identified to be the only factor that affects SF. The predictive value of calcification for SF was also demonstrated in other parts of the vascular system (86, 87). The alteration of regional wall rigidity and the creation of excessive focal pressure on certain struts of the stents are thought to be the mechanisms through which calcification is associated with SF (84).

Several studies examining the coronary and lower limb arteries have revealed a rise in adverse clinical events in tandem with SF (86–88). However, not much is known about the relationship between SF and ISR after stent placement in vessels of the aortic arch. In a study by Usman et al. (69), all supraaortic trunk ISRs occurred in fractured stents. We previously found that subclavian artery SFs are associated with worsened long-term patency rates (66). In contrast to these findings, we did not observe any association between either ISR or postprocedural symptoms and SF in patients who underwent innominate artery stenting (84). Moreover, we found no impact of SF on ISR, reintervention, and patency rates. The reason behind the controversial findings in the published studies regarding the importance of SF on adverse clinical outcomes might be the differences in the type of stent used, the follow-up duration, and the SF classification systems.

There are several limitations in this study. First, different stents were utilized for the endovascular therapy of the proximal CCA stenoses. Second, the exact date of SF is unknown because fluoroscopic screening was performed only once. Third, only 79% of patients had CTA preprocedurally; therefore, fluoroscopic images were used to assess the presence and grade of calcification. Fourth, lesions with different etiologies resulted in a nonhomogeneous cohort.

4.3. Study III (Middle/Distal Common Carotid Artery Stenting)

To summarize our results, the primary patency rate was 73% at 60 months following middle/distal CCA stenting and ISR developed more frequently in patients with hyperlipidemia.

Similarly to ICA stenosis, invasive therapy for CCA stenosis is recommended only in symptomatic and those asymptomatic patients with at least one clinical and/or imaging characteristic (history of contralateral TIA/minor stroke, the presence of silent brain infarction, detection of stenosis progression and/or large/vulnerable carotid plaque, evidence of spontaneous embolization on transcranial Doppler monitoring, coexistence of intracranial disease, etc.) that makes them at "higher risk for stroke" on BMT (9, 14, 73). The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST-2) is designed to further refine the treatment of asymptomatic patients with high-grade carotid artery stenosis (89), but its final results are still several years away. Currently, in the case of proximal CCA stenosis, open retrograde stenting is increasingly frequently applied because it minimizes the chance of intraoperative complications and embolic events during and after the procedure (9, 90). In contrast to ostial CCA lesions, open retrograde stenting is often technically not feasible in patients with middle/distal CCA stenosis, and the rates of periprocedural stroke and mortality of the open surgical reconstructions are not negligible (1%–8% and 0.4%–8%, respectively) (91–95); therefore, in our Center, percutaneous antegrade stenting has become the first treatment of choice for middle/distal CCA stenosis.

The technical success rate of percutaneous antegrade stenting of proximal CCA ranges between 95% and 100% (59–64, 96). Access site complications were observed in less than 6% of patients (59–64, 96). So far, only one procedure-related death has been

reported; this was due to retroperitoneal bleeding (59–64, 96). TIA occurred in 0%–5.9% (ipsilateral, 0%–2%), ipsilateral minor stroke in 0%–4.7%, ipsilateral major stroke in 0%–2%, and myocardial infarction in 0%–1.5% within 30 days following antegrade stenting of the proximal CCA (59–64, 96). Tang et al. (64) reported that 66.7% of symptomatic patients were relieved of initial symptoms, and the rest showed improvement. In the current work, the technical success and complication rates were similar to those mentioned above.

The prevalence of proximal CCA ISR is 0%–19% (59–64, 96). Paukovits et al. (62) examined the patency and showed a primary patency rate of 58% at 60 months in patients who underwent percutaneous antegrade proximal CCA stenting. Our study revealed significant ISR in 27.5% of patients and a 73% primary patency rate at 60 months. Our 27.5% ISR rate is worse than those noted in proximal CCA (59–64, 96). No definite explanation can be given for our higher ISR rate, but differences in patient, lesion, and stent characteristics among studies can be presumed.

No predictors for CCA ISR have been identified to date. Corresponding to other studies (97, 98), we also evaluated several possible risk factors and found hyperlipidemia to be significantly more common among patients with ISR. The role of hyperlipidemia in the formation of neointimal hyperplasia has also been demonstrated by other research groups (99–103). Hyperlipidemia increases the entry of low-density lipoprotein (LDL) into the intima and its progressive oxidative alteration in the subendothelial space. Oxidized LDL results in further lipid infiltration across the intact endothelium, where it aggregates and activates the release of mitogens from platelets, macrophages, and endothelial cells; this, in turn, stimulates smooth muscle cell proliferation, thereby leading to neointima formation (99, 100).

The middle/distal CCA has not been examined before in the context of SF. The SF rate was reported to be 39% in patients treated for proximal CCA stenosis (96). In the present study, the SF rate was much lower (4.3%). SFs have several known predictors (stent design and length, grade of residual stenosis, etc.), but the two most important ones are location of the stent and calcification of the lesion (85–87, 96). On the one hand (in general), the low SF rate in this patient population can be explained by the less significant effect of the beating heart and shear forces from the curvature of the

aortic arch compared with the proximal CCA. On the other hand (in the current study), the number of heavily calcified lesions was not deemed to be considerable.

Our results should be regarded in light of several limitations. First, the study was retrospective in nature. Second, the sample size was small and inhomogeneous, factors that did not permit detailed regression analyses in terms of risk factors for ISR or stent occlusion. Third, not all patients had CTA preprocedurally; therefore, fluoroscopic images were used to judge the presence and grade of calcification. Fourth, different stents were implanted in the middle/distal CCA.

5. Conclusions

5.1. Study I (Aortoiliac Kissing Stenting)

The kissing stent technique can be performed with good long-term patency rates for the minimally invasive treatment of AISOD. Patients whose iliac stents protrude too far into the aorta need closer follow-up care.

5.2. Study II (Proximal Common Carotid Artery Stenting)

Fractures frequently occur in a wide variety of stent devices deployed in the proximal third of the CCA. The presence of calcification predisposes a patient for SF, but SFs seem to have no effect on ISR, reintervention, and long-term patency rates.

5.3. Study III (Middle/Distal Common Carotid Artery Stenting)

Stenting of the middle/distal CCA can be performed with acceptable patency rates. If intervention is unequivocally needed, patients with hyperlipidemia would require closer follow-up care.

6. Summary

Cardiovascular diseases are the leading cause of mortality worldwide. Following coronary heart disease, LEAD and stroke are the most common causes of atherosclerotic vascular morbidity. One of the most frequent manifestations of LEAD is AISOD, which can be treated with kissing stenting. The CCA is the second leading place for extracranial carotid artery stenosis and is responsible for 1%–2% of all cerebral ischemic events. Because open surgery of CCA lesions is associated with notable morbidity and mortality rates, stenting has become the primary therapy for CCA stenoses. However, insufficient data are available on the long-term patency rates of aortoiliac kissing and CCA stenting and the risk factors for ISR.

We found primary patency rates of 95%, 93%, 87%, and 77% at 6, 12, 24, and 60 months, respectively, following aortoiliac kissing stenting of 105 patients. A longer aortic part of the stents was found to be the only significant independent predictor for ISR (hazard ratio, 1.44; 95% CI, 1.02–2.01; P=.035). The primary patency was significantly worse (P<.001) in patients with longer (>20 mm) aortic stent segments.

During a median follow-up time of 76 months, significant ISR was observed in 11.4% of the 70 patients who underwent proximal CCA stenting. SFs were detected in 38.6% of cases but the primary patency rates did not differ significantly (P=.372) in patients with and without SF. Logistic regression analysis revealed calcification to be a significant predictor for SF (OR, 13.2; 95% CI, 3.9–45.1; P<.001).

Following middle/distal CCA stenting of 51 patients, the primary patency rates were 92%, 83%, 73%, and 61% at 12, 24, 60, and 96 months, respectively. ISR developed more frequently (P<.001) and the patency rates were significantly worse (P<.001) in patients with hyperlipidemia compared with those without hyperlipidemia.

Our findings indicate that the aortoiliac kissing stent technique can be performed with good long-term patency rates. Patients whose iliac stents protrude too far into the aorta need closer follow-up care. In the proximal third of the CCA, SFs frequently occur. The presence of calcification predisposes for SF, but SFs seem to have no effect on long-term patency rates. Middle/distal CCA stenting can be performed with acceptable patency rates. If intervention is unequivocally needed, patients with hyperlipidemia would require closer follow-up care.

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8. Bibliography of the Candidate's Publications

8.1. Peer-Reviewed Articles with Relevance to the Current Work

I. Vértes M, Juhász IZ, Nguyen TD, Veres DS, Hüttl A, Nemes B, Hüttl K, Dósa E. (2018) Stent protrusion >20 mm into the aorta: A new predictor for restenosis after kissing stent reconstruction of the aortoiliac bifurcation. J Endovasc Ther, 25: 632-639. **IF: 2.986**

II. Vértes M, Nguyen TD, Székely G, Bérczi Á, Dósa E. (2020) The incidence and risk factors of stent fracture in patients treated for proximal common carotid artery stenosis. J Vasc Surg, 71: 824-831. **IF: 4.268**

III. Vértes M, Nguyen TD, Székely G, Bérczi Á, Dósa E. (2020) Middle and distal common carotid artery stenting: Long-term patency rates and risk factors for in-stent restenosis. Cardiovasc Intervent Radiol, 43: 1134-1142. **IF: 2.740**

8.2. Other Peer-Reviewed Articles

1. Hüttl AB, Hüttl A, **Vértes M**, Nguyen TD, Bérczi Á, Hüttl K, Dósa E. (2019) The presence of long and heavily calcified lesions predisposes for fracture in patients undergoing stenting of the first part of the subclavian artery. J Vasc Surg, 70: 1146-1154. **IF: 3.405**

2. Bérczi Á, **Vértes M**, Nguyen TD, Bérczi V, Nemes B, Hüttl K, Dósa E. (2021) Early and long-term results of the endovascular treatment of patients with isolated infrarenal aortic stenosis. J Vasc Surg, 73: 510-515. **IF: 4.268**

3. Mihály Z, **Vértes M**, Entz L, Dósa E. (2021) Treatment and predictors of recurrent internal carotid artery in-stent restenosis. Vasc Endovasc Surg, 55: 374-381. **IF: 1.089**

4. Nguyen TD, Bayerle P, **Vértes M**, Bérczi Á, Dósa E. (2021) Mid-term results and predictors of restenosis in patients undergoing endovascular therapy for isolated popliteal artery steno-occlusive disease. Imaging, 13: 69-75. **IF: -**

5. Daches S, **Vértes M**, Matthews K, Dósa E, Kiss E, Baji I, Kapornai K, George CJ, Kovacs M. (2021) Metabolic Syndrome among Young Adults at High and Low Familial Risk for Depression. Psychol Med, pending publication. **IF: 7.723**

8.3. Published Abstracts

1. Juhász I, **Vértes M**, Nguyen TD, Nemes B, Hüttl K, Dósa E. (2017) Az iliaca kissing in-stent restenosisok (ISR-ek) lehetséges rizikófaktorai (in Hungarian). Érbetegségek, Suppl. 2: 14.

2. Nguyen TD, **Vértes M**, Juhász I, Heltai K, Merkely B, Hüttl K, Dósa E. (2017) Az N-acetil-cisztein (NAC) parenterálisan, mellékhatás nélkül alkalmazható dózis maximumának meghatározása – fázis I. tanulmány (in Hungarian). Érbetegségek, Suppl. 2: 38.

3. Vértes M, Juhász IZ, Nguyen TD, Nemes B, Hüttl K, Dósa E. (2018) Az iliaca kissing in-stent restenosisok új, eddig nem ismert rizikófaktora (in Hungarian). Magyar Radiológia, 92: 156.

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