THE EFFECTIVENESS OF INVASIVE THERAPY OF STENO-OCCLUSIVE LESIONS OF THE INTERNAL CAROTID ARTERY AND POPLITEAL ARTERY

Ph.D. thesis (short version)

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1. Introduction

Diseases resulting from arterial stenoses/occlusions continue to be associated with high rates of disability and are among the leading causes of death worldwide. This dissertation addresses the short- and mid- or long-term effectiveness of invasive treatment of steno-occlusive lesions of both the internal carotid artery (ICA) and popliteal artery (PA) and the factors influencing it.

2. Objectives

2.1. Restenosis rates in patients with ipsilateral carotid endarterectomy (CEA) and contralateral carotid artery stenting (CAS)

Because there are two ICAs, it is possible to evaluate the short- and long-term success of CEA and CAS in the same patient (ipsilateral CEA versus contralateral CAS). Since there are few such publications (we found a total of four), with a small sample size (up to 63 subjects), we considered it worthwhile to conduct an intra-patient comparison of restenosis on a larger sample size.

2.2. Short- and mid-term outcomes of stenting in patients with isolated distal ICA stenosis or post-surgical restenosis

Atherosclerosis and restenosis rarely affect the distal part of the ICA. Distal ICA lesions can only be approached with great difficulty through open surgery, either from the retromandibular fossa or in other ways. This makes stenting an invasive alternative to open surgery in these patients, even those who are symptomatic. Since there is no available literature data on the short- and mid-term efficacy of stenting in atherosclerotic or post-surgical restenotic distal ICA stenosis, we aimed to provide information on this topic.

2.3. Mid-term results and predictors of restenosis in patients undergoing endovascular therapy for isolated PA steno-occlusive disease

In the majority of studies, atherosclerotic PA stenosis was defined as isolated if the patient did not have ipsilateral femoral artery stenosis requiring invasive therapy. However, the publications are heterogeneous with respect to the arterial runoff and the type of radiological intervention used. Studies also seem to be inconsistent on the structure of the deployed stents. Therefore, we aimed to examine the mid-term results of PA endovascular techniques and to identify predictors of restenosis in a single-center, homogeneous population in terms of arterial runoff and type of stent implanted.

3. Methods

3.1. Restenosis rates in patients with ipsilateral CEA and contralateral CAS

In this single-center retrospective study, 117 consecutive patients who underwent CEA on one side and CAS on the other side between January 2001 and January 2019 were included.

Indications for CEA and CAS were based on international guidelines that were in force at the time of the intervention.

The type of open surgery was an eversion endarterectomy without routine shunt use, which was carried out under general anesthesia. Technical success was defined as the absence of visible plaque remnants and successful restoration of blood flow at the completion of the endarterectomy.

Stenting, which meant the deployment of a self-expanding stent, was executed in a standard manner. Embolic protection systems were routinely used, and postdilation of the stent was inevitable. Technical success was achieved if no extravasation, dissection, or >30% residual stenosis was seen on the final angiographic images.

The follow-up assessments consisted of interviewing the patient and ultrasound (US) examination of the cervical arteries. On the operated side, restenosis was considered 50–69% when the peak systolic velocity (PSV) was 210–270 cm/s and ≥70% when the PSV was >270 cm/s, while on the stented side, restenosis was considered 50–69% when the PSV was 225–350 cm/s and ≥70% when the PSV was >350 cm/s.

The following parameters were evaluated: pre- and post-procedural symptoms, presence and duration of atherosclerotic risk factors, type and duration of medications, grade of stenosis, length of the lesion, severity of plaque calcification, and plaque echogenicity.

Statistical analysis was performed with the software Stata 16.0 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

3.2. Short- and mid-term outcomes of stenting in patients with isolated distal ICA stenosis or post-surgical restenosis

This single-center retrospective study analyzed patients (N=66) who underwent stenting for atherosclerotic or post-surgical restenotic isolated distal ICA stenosis between January 2001 and January 2020.

The vascular team of our center decided on the necessity of stenting for all patients based on the guidelines of the European Society for Vascular Surgery in force at the time. Stenting was performed in the standard manner with the implantation of self-expanding stents and embolic protection. Stenting was technically successful if there was no extravasation, dissection, or >30% residual stenosis on the final angiographic images.

Follow-up visits consisted of a patient interview and an US examination of the cervical arteries. Restenosis was defined as 50–69% if PSV was 225–350 cm/s inside the stent or at either end of the stent, and ≥70% if PSV was >350 cm/s. If the distal part of the stent was not visible by US, but indirect signs (ICA flow volume <159 mL/min, ICA PSV <33 cm/s, and/or common carotid artery PSV <42 cm/s) suggested ≥70% in-stent restenosis (ISR), the patient was submitted to computed tomography angiography.

The following parameters were assessed: cardiovascular risk factors and comorbidities, previous invasive vascular therapies, lesion- and intervention-related parameters, neurological events before and after stenting, ISR characteristics, and primary patency and mortality rates.

Statistical analyses were performed by using SPSS Statistics for Windows (Version 25.0.; IBM Corp., Armonk, NY, USA) and GraphPad Prism 7.01 (GraphPad Software Inc., La Jolla, CA, USA) software.

3.3. Mid-term results and predictors of restenosis in patients undergoing endovascular therapy for isolated PA steno-occlusive disease

Sixty-one patients from a single institution who had intervention between June 2011 and June 2018 for symptomatic isolated PA *de novo* steno-occlusive disease (no ipsilateral iliofemoral stenosis and at least two patent crural arteries) were retrospectively analyzed.

Endovascular interventions were executed through the femoral artery. Patients underwent percutaneous transluminal angioplasty (PTA) or stenting (selective or primary). Selective stenting was defined as the placement of a stent after PTA with suboptimal results (>30% residual stenosis or extensive intimal dissection). Primary stenting was defined as the placement of a stent after predilation of the lesion, irrespective of the PTA outcome. In general, PTA was favored for patients with non-occlusive short lesions, while primary stenting was chosen in patients with heavily calcified long lesions or total occlusions. Technical success was defined as <30% residual stenosis without extravasation or flow-limiting dissection. Clinical success was measured as patient-reported subjective betterment and/or improvement in at least one Rutherford category.

Follow-up examinations included evaluation of symptoms/complaints (Rutherford stage), palpation of peripheral pulses, measurement of ankle-brachial index (ABI), and US scanning. Significant restenosis was defined as PSV ≥250 cm/s in the treated PA segment.

Two groups of patients were distinguished according to the type of invasive therapy (PTA versus stenting). Both the PTA and stenting groups were divided into restenotic and non-restenotic subgroups and compared in terms of pre-procedural, imaging, procedural, and post-procedural data.

Statistical analyses were performed by using StatSoft Statistica 13.4 (Moonsoft Oy, Espoo, Finland) and GraphPad Prism 7.01 software.

4. Results

4.1. Restenosis rates in patients with ipsilateral CEA and contralateral CAS

The study group consisted of 39 women and 78 men (median age at CEA, 64.4 [IQR, 57.8–72.2] years; median age at CAS, 68.8 [IQR, 61–76] years). Neurological symptoms were significantly more frequent ($P<0.001$) before CEA than before CAS. Except for age ≥80 years ($P=0.033$), there was no significant difference in the presence of atherosclerotic risk factors at the time of CEA and CAS. The duration of smoking ($P<0.001$), hypertension ($P<0.001$), diabetes mellitus ($P<0.001$), and hyperlipidemia ($P=0.001$) was significantly shorter at the time of CEA than at the time of CAS.

With the exception of one stented stenosis (0.9%) presumably caused by radiotherapy, the other lesions (99.1%) were of atherosclerotic origin. There was no difference in the grade and length of stenosis, however, the majority of lesions (79.5%) in the CAS group were mildly or moderately calcified, compared with a balanced distribution of lesions in the CEA group according to the four categories of calcification. In terms of plaque echogenicity, most lesions in both groups were predominantly and uniformly echogenic; however, there were significantly more predominantly and uniformly echogenic lesions in the CAS group than in the CEA group. The majority of lesions in both groups were in the bulb; suprabulbar lesions were mostly treated with stenting.

Carotid endarterectomy was the first invasive therapeutic method in 95 patients. The median time interval between the two procedures was 50 (IQR, 8.5–102) months if the first procedure was CEA and 2.5 (IQR, 1–12.8) months if the first procedure was CAS. The technical success rate of the patients was 100%.

No one died during the early follow-up. The following complications occurred after CEA: four wound hematomas (3.4%), five cranial nerve injuries (4.3%), two cases of hemodynamic instability (1.7%), one myocardial infarction (0.9%), and five neurological ischemic events (4.3%). Two of the five neurological ischemic events were due to acute occlusion of the operated ICA; both patients underwent reoperation.

The following complications were observed after CAS: one post-puncture pseudoaneurysm (0.9%), four cases of hemodynamic instability (3.4%), and six ocular or neurological ischemic events (5.1%). One of the six neurological ischemic events was caused by acute stent occlusion; the patient had the stent surgically removed. There was no significant difference ($P=0.683$ and $P>0.999$, respectively) between CEA and CAS in either hemodynamic instability or early post-procedural neurological complications.

Median follow-up was 10 (IQR, 5.5–14) years after CEA and 6 (IQR, 3–10) years after CAS. One death occurred during the follow-up period. The cause of death was ventricular fibrillation. Ocular or neurological ischemic events corresponding to the operated side were reported in five patients (4.3%), and neurological symptoms corresponding to the stented side were reported in one patient (0.9%). The difference between the two sides was not statistically significant (P=0.213).

After CEA, there were eight cases of 50–69% restenosis (6.8%), 30 cases of 70–99% restenosis (25.6%), and two cases of occlusion (1.7%). After CAS, there were 12 cases of 50–69% restenosis (10.3%), five cases of 70–99% restenosis (4.3%), and one case of occlusion (0.9%). Nine patients developed bilateral restenosis and one of them had bilateral ICA occlusion.

The probability of restenosis is displayed in **Table 1**. The risk of restenosis was the same in the first year after the two procedures, followed by a lower risk throughout the follow-up in the CAS group. (**Figure 1**) There was a statistically significant difference between the two groups; the P-value of the log-rank test was 0.045. The crude incidence rate of restenosis was 2.5/100 person-years in the CAS group and 4.2/100 person-years in the CEA group, while the crude HR estimated by Cox regression was 1.80 (95% CI, 1.05–3.10; P=0.030). **Figure 2** shows the observed and predicted probabilities of being free from restenosis with treatment. The adjusted HR (1.85; 95% CI, 0.95–3.60; P=0.070) differed little from the crude HR. The final model included all important covariates (those that were either significant in the model or whose omission would have changed the effect size by more than 10% [smoking, hypertension, diabetes mellitus, level of calcification and echogenicity, location of lesions, and type of treatment]).

Table 1. Probability of restenosis

		1 year	2 years	3 years	5 years	11 years
CEA	*%*	10.4	16.6	18.4	22.3	33.7
	No. at risk	104	93	89	76	41
	95% CI	6.07–17.64	10.90–24.72	12.40–26.81	15.64–31.22	25.11–44.24
CAS	*%*	11.4	11.4	12.4	14.7	17.2
	No. at risk	101	94	80	62	15
	95% CI	6.79–18.84	6.79–18.84	7.54–20.07	15.64–31.22	25.11–44.24

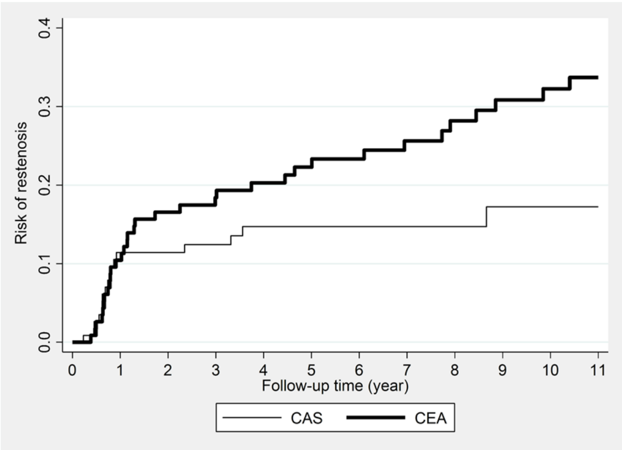

Figure 1. Risk of restenosis by the treatment group

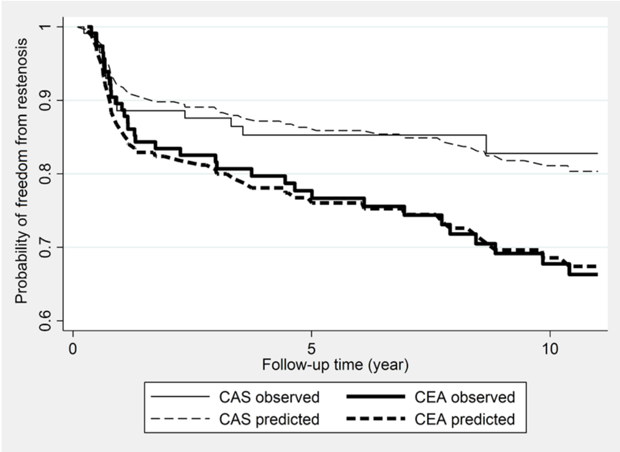

Figure 2. Observed and model-predicted probabilities of freedom from restenosis after treatment

4.2. Short- and mid-term outcomes of stenting in patients with isolated distal ICA stenosis or post-surgical restenosis

The 66 patients (women, N=13) had a median age of 66 (IQR, 61–73) years. Patients were divided into two etiological groups, atherosclerotic (AS, N=40 [60.6%]; median age, 67 [IQR, 61–74] years) and post-surgical restenotic (RES, N=26 [39.4%]; median age, 64.5 [IQR, 60.5–71] years). There was no significant difference (P=0.541) in median age between the AS and RES groups. Carotid surgery was eversion endarterectomy in all patients. The median time between CEA and CAS was 80 (IQR, 22–148) months. Nine patients were stented within 48 months of CEA. Of the 66 patients, 15 patients (22.7%) had some neurological symptoms before CAS. There was no significant difference (P>0.999) between the two groups in terms of pre-procedural neurological events. In the RES group, there were significantly more women (P=0.003) and significantly more patients with hypertension (P=0.010), patients who underwent contralateral carotid invasive treatment (P=0.015), and patients who had lower extremity arterial reconstruction (P=0.046).

The narrowest part of the ICA stenosis was at least 20 mm from the bifurcation in all patients. Among lesion-related parameters, only the length was significantly different between the two groups; AS lesions were significantly longer (P=0.002) than RES lesions.

Five different types of self-expanding stents were used. Technical success was achieved in 100% of the cases.

There were five intervention-related complications: one inguinal haematoma (1.5%) and four neurological events (6.1%; AS group, one TIA and one major stroke; RES group, two TIAs). The patient with major stroke lost consciousness 2 hours after an uneventful stenting procedure. Emergency CT scan showed extensive bleeding in the ipsilateral frontal and parietal lobes. The patient died on day 37 after stenting.

The median follow-up time was 34 (IQR, 15–87) months in the AS group and 41 (IQR, 28–74) months in the RES group. There was no significant difference (P=0.708) in the follow-up time between the two groups. Two cases (5%) of ISR 50–69% and one case (2.5%) of ISR ≥70% were detected in the AS group. All ISRs were located within the stent and were of focal type. No one in the RES group had ISR. The primary patency rate was 97.2% at 6 months, 94.4% at 12 and 24 months, and

89.7% at 36 and 48 months in the AS group, and 100% during the entire follow-up period in the RES group. The primary patency rates of the two groups were not significantly different (P=0.528). The survival proportion was 97.4% at 6, 12, and 24 months and 84.1% at 36 and 48 months in the AS group and 100% at 6, 12, and 24 months, 83.8% at 36 months, and 61.5% at 48 months in the RES group. The survival proportions of the two groups were not significantly different (P=0.289).

4.3. Mid-term results and predictors of restenosis in patients undergoing endovascular therapy for isolated PA steno-occlusive disease

Twenty-six patients (42.6%) were in the PTA group, while 35 patients (57.4%) were in the stenting group. The median age in the PTA group was 65.1 (IQR, 60.7–71.9) years. The indication for radiological intervention was severe claudication (Rutherford grade 3) in 12 cases (46.2%) and critical limb ischemia (Rutherford grade 4–6) in 14 cases (53.8%).

The median age in the stenting group was 63.5 (IQR, 56.9–71) years. The indication for radiological intervention was severe claudication in 21 cases (60%) and critical limb ischemia in 14 cases (40%).

The pathological background in all cases was atherosclerosis. In the PTA group, the steno-occlusive disease affected the P1 segment in 13 cases (50%) and so did the P2 segment in eight cases (30.8%). Multi-segment disease within the PA was observed in five cases (19.2%). The median degree of stenosis was 95 (IQR, 90–100) %, the median lesion length was 26.7 (IQR, 11.6–72.9) mm, and calcification was observed in 13 patients (50%).

In the stenting group, the steno-occlusive disease affected the P1 segment in 14 cases (40%) and so did the P2 segment in 12 cases (34.3%). Multi-segment disease within the PA was present in nine cases (25.7%). The median degree of stenosis was 100 (IQR, 90–100) %, the median lesion length was 52.8 (IQR, 23.4–80.6) mm, and calcification was observed in 22 patients (62.9%). In all cases, a self-expanding Astron Pulsar stent (Biotronik AG, Bülach, Switzerland) was deployed. Primary stenting was performed in 15 patients (42.9%) and selective stenting in 20 patients (57.1%).

Technical success was achieved in 100% of patients. In one stented patient, a retroperitoneal hematoma was observed. The 30-day all-cause mortality rate was zero.

At 6 weeks, the clinical success rate was 92% in the PTA group and 89% in the stenting group. The median resting ABI in the PTA group improved significantly ($P<0.001$) from 0.40 (IQR, 0.28–0.52) before the procedure to 0.90 (IQR, 0.84–1.02) at 6-week follow-up. For the stenting group, the ABI also improved significantly ($P<0.001$) from 0.37 (IQR, 0.24–0.51) to 0.89 (IQR, 0.80–1.0).

The median follow-up time was 29 (IQR, 16–47) months in the PTA group and 26.5 (IQR, 6–47) months in the stenting group. Follow-up time was not significantly different ($P=0.435$) between groups. Nine patients (34.6%) in the PTA group (stenosis, N=7; occlusion, N=2) and 12 patients (34.3%) in the stenting group developed restenosis (stenosis, N=5; occlusion, N=7).

The primary patency rate was 85.7% at 6 months, and 71.4% at 12 and 24 months in the PTA group, while in the stenting group it was 91.2% at 6 months, 88.2% at 12 months, and 68.9% at 24 months. There was no significant difference (P=0.629) in primary patency rates between groups.

Re-restenosis was observed in three patients (3/9; 33.3%) in the PTA group and in six patients (6/8; 75%) in the stenting group. In the PTA group, two out of three patients underwent invasive therapy, whereas in the stenting group, four out of six patients underwent repeated revascularization.

The secondary patency rate was 100% at 6 months, and 90% at 12 and 24 months in the PTA group, while in the stenting group it was 100% at 6 months, 97.1% at 12 months, and 90.6% at 24months. There was no significant difference (P=0.603) in secondary patency rates between groups.

In the PTA group, neither atherosclerotic risk factors nor lesion and balloon parameters were significantly different between the RES and non-RES subgroups. In the stenting group, stents implanted in the P1 segment were significantly less likely (P=0.010) to develop restenosis compared with P2 plus multi-segment stents.

Cox regression analysis identified lesion location as a predictor of ISR (HR, 2.54; 95% CI, 1.16–5.54; P=0.019).

5. Conclusions

5.1. Restenosis rates in patients with ipsilateral CEA and contralateral CAS

The intra-patient comparison of CEA and CAS tilts the balance towards CAS with respect to restenosis (especially ≥70% restenosis).

5.2. Short- and mid-term outcomes of stenting in patients with isolated distal ICA stenosis or post-surgical restenosis

Early complications and ISR rates of distal ICA stenting are acceptable and are not influenced by the etiology of the lesion. However, the mid-term mortality rate of the RES group is high. The lower survival is probably not due to the stenting procedure but to the more complex comorbidity profile of the RES population.

5.3. Mid-term results and predictors of restenosis in patients undergoing endovascular therapy for isolated PA steno-occlusive disease

Mid-term patency of PA interventions is good. Stenting is not superior to PTA (if selective stenting is not considered a loss of patency). Lesions located in the P2 segment or in multiple segments are more prone to restenosis, therefore, patients undergoing stenting in these segments or undergoing PTA should be followed more closely.

6. Bibliography of the candidate's publications

6.1. Peer-reviewed articles with relevance to the current work

1. Nguyen DT, Bérczi Á, Nyárády BB, Szőnyi Á, Philippovich M, Dósa E. (2022) Short- and Mid-Term Outcomes of Stenting in Patients with Isolated Distal Internal Carotid Artery Stenosis or Post-Surgical Restenosis. J Clin Med, 11: 5640. **IF: 3.9**

2. Nguyen DT, Vokó B, Nyárádi BB, Munkácsi T, Bérczi Á, Vokó Z, Dósa E. (2022) Restenosis rates in patients with ipsilateral carotid endarterectomy and contralateral carotid artery stenting. PLoS One, 17: e0262735. **IF: 3.7**

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6.2. Other peer-reviewed articles

1. Mihály Z, Booth S, **Nguyen DT**, Vecsey-Nagy M, Vértes M, Czinege Z, Péter C, Sótonyi P, Varga A. (2023) A Propensity-Matched Comparison of Ischemic Brain Lesions on Postprocedural MRI in Endovascular versus Open Carotid Artery Reconstruction. J Cardiovasc Dev Dis, 10: 257. **IF: 2.4**

2. Zhubi Bakija F, Bagyura Z, Fábián A, Ferencz A, Kiss L, Szenczi O, Vadas R, Dósa E, **Nguyen DT**, Csobay-Novák C, Jermendy ÁL, Szelid Z, Soós P, Kovács A, Merkely B. (2023) Long-term prognostic value of left atrial longitudinal strain in an elderly community-based cohort. Geroscience, 45: 613–625. **IF: 5.6**

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5. Bagyura Z, Takács A, Kiss L, Dósa E, Vadas R, **Nguyen DT**, Dinya E, Soós P, Szelid Z, Láng O, Pállinger É, Kőhidai L, Merkely B. (2022) Level of advanced oxidation protein products is associated with subclinical atherosclerosis. BMC Cardiovasc Disord, 22: 5. **IF: 2.1**

6. Bérczi Á, Vértes M, **Nguyen DT**, 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.e2. **IF: 4.860**

7. Pomozi E, Lengyel B, Osztrogonácz P, **Nguyen DT**, Szeberin Z. (2021) Az aortobiiliacalis occlusiv érbetegség miatt végzett aortobifemoralis bypass műtétek

hosszú távú eredményeinek elemzése [Long-term analysis of the results of aorto-bifemoral bypass surgery for diffuse aorto-biiliac occlusive disease]. Orv Hetil, 162: 99–105. **IF:0.707**

8. Vértes M, **Nguyen DT**, 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**

9. Vértes M, **Nguyen DT**, 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.e1. **IF: 4.268**

10. Hüttl AB, Hüttl A, Vértes M, **Nguyen DT**, 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.e1. **IF: 3.405**

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