IN-STENT RESTENOSIS AFTER CAROTID ARTERY STENTING: FROM DIAGNOSIS TO TREATMENT

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ABSTRACT

Although carotid artery stenting is a safe and effective treatment for preventing ischaemic stroke in significant carotid atherosclerotic disease, it can be complicated by in-stent restenosis (ISR). Factors involved in the ISR process are both mechanical and patient-related, but the most important is the neo-intimal thickening within stent struts, leading to lumen reduction. Overall incidence of carotid ISR is low and related embolic risk seems to be lower than native disease. Digital subtraction angiography is the gold standard for diagnosis. Nowadays, Doppler ultrasound should be considered the first-line investigation, due to its non-invasiveness and reproducibility. Computed tomography angiography remains useful when Doppler ultrasound is inconclusive. Indication and modality of treatment of ISR are still debated: both surgery (carotid endarterectomy with stent removal in most cases) or interventional procedures such as percutaneous transluminal angioplasty with simple balloon, cutting-balloon, drug-eluting balloon, and stenting, showed safety and efficacy in follow-up. Surgery is currently reserved for selected cases. Carotid ISR is an overall rare complication which can be easily identified at routine follow-up. This paper is a literature review and state-of-the-art assessment of ISR, clinical features, diagnosis, and treatment.

Keywords: Carotid artery stenting (CAS), carotid in-stent restenosis (ISR), Doppler ultrasound (DUS).

BACKGROUND

Ischaemic stroke represents a major health problem and is an important cause of long-term disability in developed countries. Mortality ranges between 10% and 30%[1] considering both myocardial infarction (MI) and recurrent stroke. Atherosclerosis from supra-aortic vessels and especially from the common carotid bifurcation is a major cause of recurrent ischaemic stroke, accounting for approximately 20% of all strokes,[2] nearly 80% of which may occur without warning. Carotid endarterectomy (CEA) is currently the established treatment for significant carotid stenosis. Randomised controlled trials show that CEA is safe and effective, reducing the risk of ischaemic stroke in both symptomatic and asymptomatic patients. Percutaneous carotid artery stenting (CAS) was initially proposed as an alternative treatment for high-risk patients, but accumulating data from a recent randomised controlled trial[3,4] suggest that CAS and CEA achieve similar long-term outcomes in terms of ischaemic stroke reduction. Compared with CEA, endovascular treatment is associated with significantly lower risks of MI (odds ratio [OR]: 0.44), cranial nerve palsy (OR: 0.08), and access site haematoma (OR: 0.37).[5] Restenosis after CAS is a poorly described phenomenon. Poor and discordant data are available on incidence, predictors, diagnostic approach, and therapeutic strategies.

IN-STENT RESTENOSIS: INCIDENCE AND PATHOPHYSIOLOGY

In-stent restenosis (ISR) likely results from vessel trauma causing physical irritation, endothelial dysfunction, and chronic inflammation leading to subsequent neo-intimal hyperplasia. It generally occurs <24 months after the first procedure or as *de novo* atherosclerosis.[6,7] The real incidence of ISR after CAS is unclear, with reports ranging from <5% to >21%.[8-11] Lal et al.[6] observed an incidence of 42.7% of patients with restenosis causing >40% diameter reduction and 16.4% with restenosis causing >60% diameter reduction at 5-year follow-up. Data from a retrospective investigation involving 3,179 CAS procedures, reporting the incidence of restenosis (defined as narrowing of ≥50% and peak systolic velocity [PSV] >175 cm/s), showed an acceptable rate of annual ISR >50% of 1.49% and a cumulative rate at 5 years of 6%.[12]

Suggested predictors of ISR after CAS are advanced age, female sex, implantation of multiple stents, prior revascularisation treatment, suboptimal result with residual stenosis, elevated post-procedural serum levels of acute phase reactants, asymptomatic lesion, use of balloon-expandable stents,[11] and stent sub-expansion.[13] The clinical impact of significant ISR is uncertain, but neo-intimal hyperplasia seems to be associated with a reduced potential of embolisation compared with native lesions.[6,14] In most trials the higher incidence of ISR during follow-up was not found to have an impact on complication rates. It has therefore been postulated that restenosis might be a relatively benign disease.[7,15,16] In contrast, a study involving 215 patients and 12 reported cases of restenosis support showed that during the long-term follow-up period, the combined rate of ipsilateral stroke and death was significantly higher in the restenosis group (33.3% versus 10.8%).[17] In addition, de Donato et al.[12] demonstrated that stroke rate in the group of ISR patients was slightly superior to patients without ISR. Regarding stent technology, two types of stents have been mainly used until now: open-cell and close-cell stents. Open-cell stents are designed to keep some of the segments free from the adjacent rings, allowing greater adaptation to the vessel anatomy but less plaque coverage and higher risk of tissue prolapse. Closed-cell stent designs are characterised by a higher density of bridge interconnection, which reduces their conformability and increases the probability of malapposition but at the same time offers greater plaque coverage. Most registries show poor correlation between in-hospital and 30-day mortality, and stent design.[18,19] A study with intravascular optical coherence tomography after CAS confirmed that stent malapposition is more frequent with closed-cell stents, while plaque prolapse is more common with open-cell stents.[20] Long-term differences in terms of restenosis between open-cell and closed-cell stents have yet to be well evaluated. De Donato et al.[12] showed that post-procedural complication rates (stroke, transient ischaemic attack, death) are higher for the open-cell types and increase with larger free cell area. No difference in terms of restenosis was present in long-term follow-up; it has been suggested that after complete endothelisation of the stent, differences in stent type probably no longer play an important role.[21] A recent non-randomised, retrospective study comparing stent types by multidetector computed tomography angiography (CTA) showed that at follow-up, ISR was more common in the open-cell stent group (16 of 91 patients with open-cell stents and 3 of 84 patients with closed-cell stents had focal restenosis), without differences in clinical outcomes.[22]

A novel carotid stent design has recently been developed: the double layer mesh stent, which includes features of both stent types. It comprises an internal micromesh layer for plaque coverage and an external self-expanding nitinol layer for scaffolding, offering the flexibility that characterises open-cell design stents; in an initial experiment with seven patients this stent seemed to be safe and effective in the treatment of extracranial internal carotid artery (ICA) stenosis but further data are necessary.[23]

FROM DIAGNOSIS...

Digital subtraction angiography (DSA) is the gold standard for diagnosis of carotid ISR but it is associated with several complications such as access site haemorrhage, risk of thromboembolism, and iodinated contrast medium adverse reactions. It also carries a significant risk of morbidity and mortality, ranging from 1–4%.[24] Doppler ultrasound (DUS) is frequently used for routine follow-up after CAS because it is an easily used and non-invasive diagnostic tool. The degree of lumen diameter reduction, PSV, end-diastolic velocity (EDV), and the ratio of peak ICA to common carotid artery (CCA) velocity (ICA/CCA ratio)

are the most common parameters used for stenosis quantification. Accuracy of DUS compared with DSA has been evaluated in several studies. Keberle et al.[25] demonstrated a correlation between the two techniques of 97% (r=0.97; p<0.001). The sensitivity and specificity in the detection of high-degree stenosis were 100% and 93.3%, respectively. Cumbie et al.[26] found that a PSV ≥205 cm/s had a sensitivity and specificity of 100% and 96%, respectively, in detecting ISR ≥80%, whereas an ICA/CCA ratio ≥2.6 yielded sensitivity and specificity of 100% and 94%, respectively. They also found that EDV was not a good predictor of significant ISR, while the combination of PSV and ICA/CCA had 100% sensitivity and 97% specificity. When compared with CTA, DUS showed a specificity of 97.7%, sensitivity of 100%, a positive predictive value of 98.4%, and a negative predictive value of 100% for the detection of ICA restenosis.[27] A study involving 814 CAS procedures, 6,427 DUS examinations, and 1,123 angiographies found ISR ≥70% and ISR ≥50% in 22 patients and in 73 patients, respectively; DUS analysis using a combination of the three parameters (PSV, EDV, and ICA/CCA) achieved a specificity of 99% and a sensitivity of 98% for ISR ≥70% compared with angiography.[28]

Criteria for diagnosis of restenosis are not well established. Many studies have reported different parameters and cut-off values for ISR definition. Moreover, a stented artery has different biomechanical properties that make it comparable to a rigid tube, with the enhanced stiffness resulting in increased velocity. Lal et al.[29] showed that as the elastic modulus increases after stenting, the compliance of the vessel decreases. According to this evidence, they proposed adjusted criteria for the definition of stenosis in stented arteries, validated by angiography (Table 1).[30] A review[31] of 14 studies showed that, with computed tomography and angiographic control, DUS threshold values indicating a significant restenosis with a diameter reduction of 70%, 75%, or 80% were PSV threshold at 300–350 cm/s consistently, while EDV thresholds varied slightly more at 90–140 cm/s; the ICA/CCA ratio varied from 3.8–4.7. It was suggested to record the Doppler parameters of the stented vessel early after CAS and use them as a new starting point. This new baseline can help the subsequent follow-up, which should be as regular as possible since few data are available on the course of ISR. Lal et al.[6] also suggested a classification model for ISR based on morphology (Figure 1). The pattern of ISR together with the elevation in PSV and ICA/CCA ratios are indicative of the severity of ISR. According to this classification, Type III and IV lesions need treatment more frequently when associated with an 80% lumen stenosis. Regarding the clinical relevance of types of restenosis, they also showed that diffuse proliferative (Type IV) ISR lesions (and diabetes) were important determinants of long-term outcome after CAS.

CTA is a non-invasive technique with high resolution and quick acquisition times. In native lesions, it is the imaging technique of choice in the case of tortuous carotid, severe calcification, short neck, and high bifurcation.[32] Sensitivity of this technique is 100% for severe native stenosis (≥70%), with a specificity of 63%; the negative predictive value of CTA demonstrating <70% carotid artery stenosis was 100%.[33] For ISR detection CTA has some limitations such as beam hardening from the metallic stent, which may make evaluation of the residual lumen difficult. Furthermore, the need for external beam radiation and injection of intravenous iodinated contrast medium limit the use of CTA for selected cases. New evidence is needed from selected studies involving patients with carotid ISR to assess the real diagnostic value of computed tomography in this setting.

Magnetic resonance angiography (MRA) is a safe, non-invasive, and high resolution imaging technique for carotid artery stenosis, with no need for radiation. MRA in native carotid lesions has a pooled sensitivity and specificity of 95% and 90%, compared with DSA in detecting stenosis ≥70% versus <70%, whereas in the same study DUS showed a sensitivity and specificity of 96% and 100%, respectively.[34] For detecting occlusion, both DUS and MRA are very accurate. Contrast enhanced MRA appears to overcome the limitations seen with unenhanced MRA; however, it does not offer significant advantages over two dimensional time of flight MRA.[35] Metallic related artefacts can hamper the use of MRA for evaluation of ISR. Thus, CTA is preferred to MRA for surveillance of carotid ISR,[36] and we can assert that DUS is the first test for imaging follow-up in patients treated with carotid stents.

In selected cases, when results of DUS are inconclusive, CTA is required. Discrepancies in results with either of these techniques should be confirmed using DSA.

Table 1: Comparison of parameters for defining stenosis between native and stented carotid artery as criteria for diagnosis.

Reduction in vessel diameter from stenosis (%)	Native carotid artery	Stented carotid artery
0–19	PSV <130 cm/sec	PSV <150 cm/sec ICA/CCA ratio <2.15
20–49	PSV 130–189 cm/sec	PSV 150–219 cm/sec
50–79	PSV 190–249 cm/sec EDV <120 cm/sec	PSV 220–339 cm/sec ICA/CCA ratio ≥2.7
80–99	PSV ≥250 cm/sec EDV ≥120 cm/sec ICA/CCA ratio ≥3.2	PSV ≥340 cm/sec ICA/CCA ratio ≥4.5

CCA: common carotid artery; EDV: end-diastolic velocity; ICA: internal carotid artery; PSV: peak systolic velocity.
PSV and EDV measurements for stented carotid arteries are performed within the stented segments.
Adapted from Lal BK et al.[30]

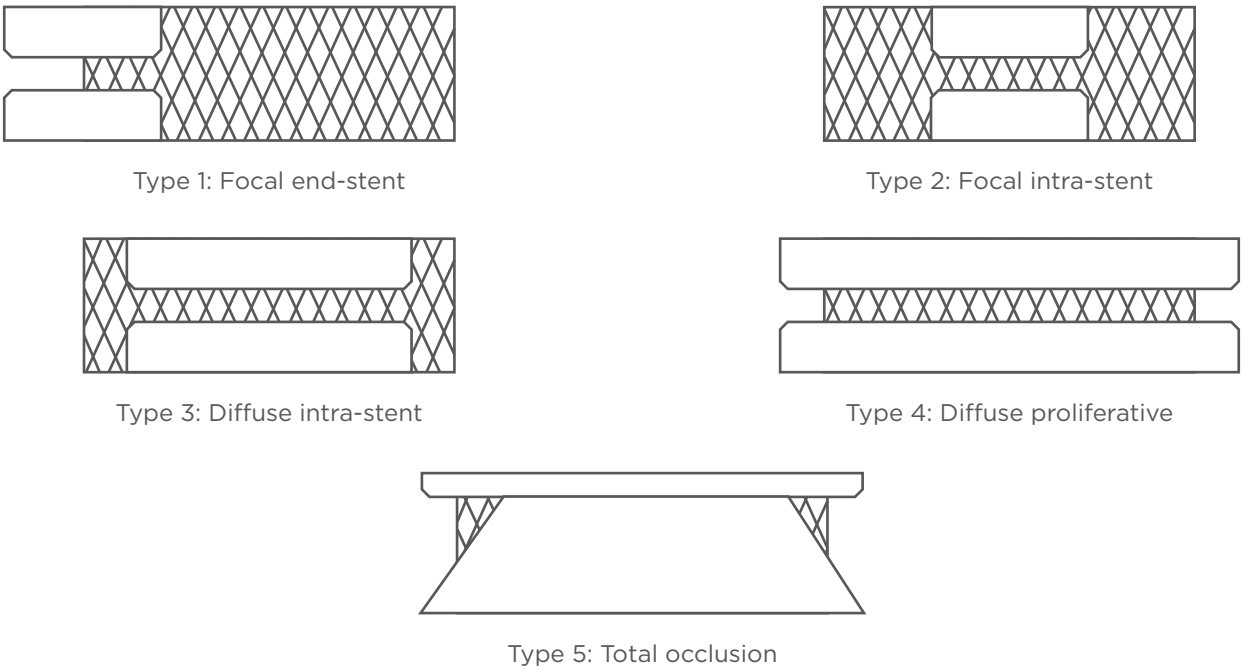

Figure 1: Morphologic description and classification of in-stent restenosis.
Adapted from Lal BK et al.[30]

...TO TREATMENT

The treatment of choice for ISR is still largely debated and no indications have been clearly established, due to the lack of sufficient data. Surgeons currently base their choice on the angiographic appearance of the lesions and the operators' experience. Surgical treatment options include CEA with stent removal or artery bypass. Percutaneous interventional approaches include balloon angioplasty alone (percutaneous transluminal angioplasty [PTA]), cutting balloon angioplasty (CB-PTA), stenting, brachytherapy, and more recently drug-eluting balloon (DEB) angioplasty.

The first step in preventing ISR is to reduce modifiable clinical risk factors. Diabetes, dyslipidaemia, and smoking are independent predictors of restenosis or occlusion after CAS procedures.[37] For this reason it is reasonable to think that a good glycaemic control and low levels

of HbA1c should be a strong recommendation to these patients; in fact in coronary ISR, low levels of HbA1c are related to reduced major adverse cardiac events at long-term follow-up, mainly for reduction in target vessel revascularisation.[38] Topakian et al.[39] showed that high post-procedural high density lipoprotein cholesterol level, measured 1 month after CAS, is a weak, but independent, predictor of carotid stent patency at 1 year; they also showed that ISR was significantly associated with continuous smoking. The authors of this study therefore suggest a strict control of cholesterol levels and cessation of smoking. Use of statins is associated with decreased peri-operative and late ischaemic stroke risk and reduced mortality rates in patients undergoing CAS, but lacks a significant benefit in terms of reduction of restenosis rate.[40]

Although there is no specific pharmacological therapy to reduce incidence of carotid ISR, cilostazol seems to have a positive impact. A recent meta-analysis including seven studies and 1,297 patients treated with CAS showed a significantly lower ISR rate with cilostazol treatment after a mean follow-up of 20 months, without affecting MI/stroke/death events, both in the early and late settings.[41]

Several studies indicate that endovascular treatment, including balloon angioplasty and CB-PTA alone or in conjunction with additional stenting, is the preferred strategy to treat carotid ISR.[42] A review[43] of several studies involving patients with carotid ISR treated with percutaneous approach revealed that after ISR intervention, recurrent restenosis occurred in 12 of 84 cases (14%): 8 after repeat PTA and 4 after repeat CAS placement. One study enrolled 16 cases of ISR (on 482 primary CAS procedure); 13 (81.3%) patients were treated with balloon angioplasty and 3 (18.7%) had the stent removed: patency rates were 68.8% and 81.3%, respectively. These data show that ISR is an ongoing process that requires frequent repeated interventions due to recurrence after primary treatment by balloon angioplasty alone.[44] Recently, a balloon-expandable zotarolimus-eluting stent (ZES) was used by Tekieli et al.[45] to treat significant ISR after CAS in seven patients; at long-term follow-up (mean 17 months) five patients revealed no evidence of restenosis or stent fracture/deformation. In the other two patients the ZES was implanted at the distal edge and protruded beyond the original carotid stent, causing deformation/kinking of the segment and leading to symptomatic stent occlusion over time. This suggests that ZES treatment is feasible and effective if it is placed within the original stent. Evidence is accumulating to support the efficacy of DEBs as a new endovascular strategy for ISR treatment.[46] Montorsi et al.[47] treated seven carotid ISR patients with DEB and there was no ISR recurrence, as measured by DUS, at a mean follow-up of 13.7 months. Vajda et al.[48] recently reported DEB treatment of intracranial stent restenosis in 51 patients. Compared to conventional balloons, the ISR recurrence rate was significantly lower with DEB (9% versus 50%) at 8-month follow-up. Limited data exist on the use of DEB as a treatment of ISR in extracranial CAS. Gandini et al.[49] analysed seven patients treated with DEB for recurrent ISR after a previous endovascular treatment for carotid ISR; over a mean follow-up of 36.6±2.7 months, ultrasound imaging identified recurrent ISR in only three patients at 32 months after DEB angioplasty. The target vessel revascularisation rate was 33.3% at 36 months, concluding that DEB may have a potential role in improving outcomes of those patients treated for early recurrent carotid ISR. Few cases have been treated with brachytherapy.[50]

Regarding surgical treatment, CEA with stent removal is the most frequently used technique: it is reserved for heavily calcified lesions with suboptimal primary stenting results, pre-occlusive lesions no longer approachable by PTA, stent technical failure, and primary stent thrombosis. Endovascular treatment is usually preferred when surgical limitations on stented carotid artery are present, mainly: 1) carotid artery dissection may be difficult or even impossible owing to an intense peri-arterial inflammatory process that may envelop the vessels after CAS; 2) the inflammatory reaction within the stented artery causes tight stent adherence to the arterial wall, making identification of the endarterectomy plane very difficult; 3) the use of a long stent makes it difficult to dissect out the entire stent and sometimes it is impossible to safely gain proximal and/or distal control of the CCA and ICA; 4) the difficulty involved in cutting the artery caused by the metallic stent; and 5) the care required during removal of the stent to avoid vessel wall penetration because of the vessel wall thinning from the stent coils. A recent review[51] collected 41 cases of ISR in the literature treated with CEA

and stent removal; primary closure of the arteriotomy was performed in 5 patients; 3 patients (7.3%) needed graft interposition; and 33 (80.5%) were closed with a venous or prosthetic patch. A good postoperative outcome was achieved in 85.4% of cases (without ischaemic events or neck haematoma); 7.3% of patients presented transient ischaemic stroke in the early period after surgery; neck haematoma requiring surgical revision was present in 7.3% of patients. In long-term follow-up (mean 15.3 months) no adverse neurological events or recurrent restenosis were reported.

A consensus on the best treatment modality in different cases of carotid ISR is not currently available. New DUS criteria enables the selection of patients with a particularly high-risk lesion; in these cases, medical therapy should be chosen only when invasive treatment is high-risk, based mainly on clinical status and comorbidities. Invasive treatment should be planned by a multidisciplinary team, involving interventional cardiologists, vascular surgeons, DUS experts, radiologists, and anaesthesiologists to discuss both patient and plaque features, along with local resources. In general, endovascular treatment is recommended as the first choice wherever possible, mainly because it is the less invasive option and has good results. The choice should be made on a case-by-case basis with a careful analysis of the lesion features mentioned previously, along with a patient-specific consideration of the advantages and disadvantages of both endovascular and surgical treatment.

CONCLUSION

Restenosis after CAS is a developing and complex process which occurs in 5% to >20% of patients. We suggest a careful selection of patients with native atherosclerotic carotid lesions suitable for endovascular treatment, in order to avoid high-risk procedures for mechanical complication and subsequently ISR. Several diagnostic techniques are available to accurately diagnose ISR; DUS is frequently used as a baseline diagnostic tool because it is non-invasive, easy to perform, and reproducible at follow-up. Using the new ISR patterns classification we are able to recognise patients who need invasive therapy, or determine the correct timing of the next follow-up investigation. ISR is a phenomenon under investigation, and the treatment of choice is still largely debated. Lack of sufficient data implies that no clear indications have been established, although non-invasive strategies show encouraging results when used after an appropriate selection of cases. A multidisciplinary expert team is the best way to choose the optimal treatment modality. ISR after CAS represents a challenge for the application of new techniques in the field.

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