Predictors of carotid artery in-stent restenosis

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KEYWORDS
Carotid artery stenosis; Stent; Angioplasty; Restenosis; Stroke; Carotid ultrasound

Summary

\textbf{Background:} Carotid angioplasty and stenting (CAS) is increasingly being used as a treatment alternative to endarterectomy (CEA), especially in patients aged <70 years with significant carotid artery stenosis. However, an in-stent restenosis (ISR) might endangering the long-term efficacy of CAS. The aim of this article was to review the current literature regarding incidence and clinical significance as well as predictors of in-stent restenosis.

\textbf{Methods:} We conducted a systematic review of the literature to identify all studies on the abovementioned factors.

\textbf{Results:} 3 randomized-controlled trials comparing CAS and CEA and 13 single centre studies fulfilled our inclusion criteria. The occurrence of ISR after CAS ranged from 2.7 to 33% and was detected within the first year in most of the studies. The clinical impact as well as the therapeutic consequence of ISR remains unclear, but many baseline characteristics (age, prior CEA or radiation), procedural (insufficient stent deployment, stent dimensions, inflammatory marker) and follow-up factors (reduced HDL, diabetes mellitus) could be found to identify patients at special risk for ISR. A wide heterogeneity related to the definition and their corresponding ultrasound criteria for ISR was observed.

\textbf{Conclusions:} A close follow-up is suggested especially in those patients with predictors of an ISR. The wide range of ISR ultrasound definitions urges the need for an implementation of generally valid criteria in ISR diagnosis. Against the background of the unknown clinical significance of ISR and a lacking established treatment modality these findings should be taken into account when offering CAS as a treatment alternative to CEA.

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Introduction

Atherosclerotic stenosis of the internal carotid artery is known as a major risk factor for disabling stroke or death leading to enormous socioeconomic problems. The standard therapy for a symptomatic stenosis of the internal carotid artery has been a carotid endarterectomy (CEA) in combination with best medical treatment of concomitant cerebrovascular risk factors. In recent years, carotid angioplasty and stenting (CAS) has widely been used as a treatment of first choice in many patients, despite the fact that the randomized controlled trials and subsequent meta-analyses could not prove a general superiority of CAS over CEA [1–6]. However, the results of the aforementioned trials have been interpreted very controversially resulting in conflicting recommendations in various current guidelines.
In the American guidelines, for instance, the authors concluded that CAS could be used as an equivalent treatment modality to CEA in medium risk patients with a symptomatic carotid stenosis [7], whereas elsewhere, CEA still is advocated as the first treatment of choice [8]. Despite this ongoing current debate, there is accumulating evidence that a subgroup of patients aged <70 years may profit from a CAS intervention [3–5,9]. Because the clinical long-term outcome is of crucial importance especially in younger patients, the occurrence of an in-stent restenosis (ISR) could be one factor endangering the long-term efficacy and safety of CAS. Unfortunately, data concerning the rate and clinical impact of ISR during long-term follow-up are still sparse and show conflicting results [3,10,11] which may in part be attributable to different definitions of an ISR during ultrasound follow-up investigations [12,13].

This article briefly summarizes the currently available long-term data of randomized controlled trials comparing CAS and CEA and of several single centre studies regarding the incidence and clinical impact of ISR as well as clinical predictors for ISR.

Methods

A MEDLINE search was conducted by two independent reviewers (K.W. and J.W.) using the following keyword searches: ‘‘carotid artery’’, ‘‘stent’’, and ‘‘restenosis’’. As a key feature before retrieving a full text article after investigating a potentially beneficial abstract, the studies had to fulfill the following criteria: (1) studies had to be published between January 2000 and October 2011 in a journal which is indexed within the MEDLINE database, (2) the follow-up of the patients had to be performed for at least six months, (3) the occurrence of carotid in-stent restenosis had to be mentioned within the text, (4) articles had to be written in English and (5) at least 100 stented carotid arteries had to be investigated. If there was more than one publication about the same patient cohort, the most recent one or rather the publication with the longest follow-up time was used.

After retrieving the full-text article of abstracts which met the above mentioned criteria, the following data, if available, were extracted in a predefined data sheet: (1) number of arteries that were treated by CAS, (2) follow-up time, (3) baseline characteristics of patients (age, proportion of male patients), (4) amount and definition of ISR, (5) clinical complications of ISR, divided into stroke and death and (6) clinical factors which had been identified to predict the occurrence of an ISR during follow-up. After all relevant data had been extracted by the two reviewers, disagreements were resolved by consensus with the help of a third independent investigator (K.G.)

Results

We could identify 3 randomized, controlled studies (CAVATAS [14,15], SPACE [1,16] and EVA-3S [2,17]) and 13 [18–30] smaller single centre studies that fulfilled our inclusion criteria and reported incidence, clinical significance and predictors of recurrent in-stent stenosis after stent-protected angioplasty of significant internal carotid artery stenosis.

Detailed description of randomized trials of CAS versus CEA

Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) [14,15] was the first completed, prospective multicentre trial (24 centres in Europe, Australia and Canada) comparing endovascular versus surgical treatment of patients with symptomatic (96.4%) and asymptomatic carotid artery stenosis. CEA was performed in 253 patients, whereas 251 patients received endovascular treatment (mainly angioplasty alone). This study excluded high-risk patients, and stents were used selectively, when available, and in only 26% of cases (n = 55). During a median carotid ultrasound follow-up time of 4 years patients undergoing endovascular treatment were found to suffer significantly more often from severe restenosis (≥70%) or occlusion than patients after CEA [15]. When comparing balloon angioplasty alone to angioplasty and stenting, those patients who were treated with a stent (n = 50) had a significantly lower risk of developing restenosis of ≥70% (adjusted hazard ratio 0.43, 0.19–0.97; p = 0.04). Regarding the clinical complications in patients with a restenosis, the incidence of ipsilateral stroke or transient ischemic attack was significantly higher in patients with a restenosis ≥70% (cumulative 5-year incidence 22.7% vs. 10.9%, p = 0.04) compared to those with no ISR. Current or past smoking turned out to be independently associated with a higher incidence of restenosis [15].

The Stent-Supported Percutaneous Angioplasty of the Carotid Artery vs. Endarterectomy Trial (SPACE) assessed non-inferiority of CAS to CEA and randomized 1183 patients (CAS n = 605; CEA n = 595) with a symptomatic carotid artery stenosis as assessed with duplex ultrasound (≥50% according to NASCET criteria, or ≥70% according to ECST criteria) at 35 centres in Austria, Germany and Switzerland [1]. The type of stent and use of a protection system were chosen at the discretion of the interventionalist. Restenosis during follow-up were observed more frequently in those patients treated with CAS (4.6% vs. 10.7%, p < 0.001) compared to CEA [16]. The majority of the recurrent stenosis occurred within the first 6 months after the initial treatment (CAS n = 28 (51.9%), CEA n = 12 (52.2%)). Furthermore, additional new ISR were observed even after 24 months of follow-up after carotid stenting whereas no new recurrent restenosis was found after CEA beyond 2 years of follow-up. Because a predefined definition of ISR was not used during the study period and the definition of an ISR depends on the local criteria of each center, a slight overestimation of ISR might be possible [16].

Endarterectomy versus angioplasty in patients with symptomatic severe carotid stenosis (EVA-3S) trial [2] was carried out to demonstrate non-inferiority of CAS compared with CEA and enrolled 527 patients with ≥60% symptomatic carotid stenosis at 30 centres in France. In 507 patients (CAS n = 242, CEA n = 265) serial long-term carotid ultrasound follow-up was performed during a mean follow-up time of 2.1 years [17]. Although the development of a moderate stenosis (≥50–69%) within 3 years was found to differ significantly between the groups with a higher proportion after CAS compared to CEA (12.5% vs. 5.0%, p = 0.02), the incidence of a high-grade restenosis ≥70% showed no significant difference between the two groups (3.3% vs. 2.8%). A clinical impact of an ISR on ipsilateral stroke or death during...
follow-up could not be observed. Advanced age was a clinical risk factor, which could be identified to be predictive for developing carotid restenosis [17].

To date, to the best of our knowledge, no data about rates of restenosis have yet been published by the other commonly known large randomized controlled studies comparing CEA and CAS especially the International Carotid Stenting Study (ICSS) [31], the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) [4], and the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy study (SAPPHIRE) [11, 32].

Within the analysed non-randomised trials, there was a wide range concerning the amount of treated patients. The smallest study included 100 patients [33]; the largest number of CAS patients was enrolled in the study of Setacci et al. (n = 814) [25]. In the vast majority, patients aged 60 years or over with roughly two-thirds male sex were included in the reviewed studies. The relevant data which were extracted are delineated in Table 1. The diagnostic tool used to detect an ISR was serial duplex ultrasound in all studies (n = 13). A confirmatory diagnostic procedure such as CTA or conventional angiography had been carried out after ultrasound in ten studies [19, 21—27, 29, 25, 30]. Notably, there was a wide variation concerning the ultrasound criteria applied for the detection of an ISR between the studies. As one of the main key features for the detection of a restenosis, a cut-off peak systolic velocity is mentioned [19, 22, 24, 26, 28—30] sometimes in addition to other criteria such as end-diastolic velocity or the ICA/CCA index [18, 20, 21, 23, 25, 27].

Although the majority of the studies reported concise details about the exact time point of ISR occurrence, most ISR were found to occur within the first year (median: 8 months, IQR: 7—9) after CAS [16,18,20,21,26,29,30]. There was a wide range concerning the clinical complications for patients with ISR between 0% [21, 22, 24, 26, 29] and 25% [30] for stroke and from 0% [19, 21—23, 25, 26, 29] to 11.1% [18] for death, respectively.

Common baseline characteristics like advanced age [19], female gender [19], prior revascularization treatment, [23, 25, 27, 34, 35] the treatment of a radiogenic stenosis [23] or prior neck cancer [21] could be found to be predictive for ISR development. Furthermore, some cardiovascular risk factors such as smoking [17], lowered HDL cholesterol, [26] diabetes mellitus [22] or elevated HbA1c [18, 36] could be identified as predictors for ISR, too. In addition to traditional cardiovascular risk factors, periprocedural inflammatory markers were found to play a major role in ISR development [20, 30]. Finally, several procedure-related factors such as stent dimensions [30], implantation of multiple stents [19, 28], or an insufficient dilatation effect of CAS [19, 20, 28] could be identified to promote ISR.

Discussion

Recurrent stenosis after CEA was first described by Stoney and String in 1976 [37] and turned out to be associated with a higher rate of periprocedural complications during a secondary operation [9]. Soon after CAS had received broader acceptance as a potential alternative treatment option for patients with severe carotid artery stenosis, first reports about ISR were published in the late 1990s [38—40]. Since then, the awareness for detecting an ISR has increased further and was more frequently considered in published case series. Within one of the most recent meta-analyses, a 180% increase in the risk of intermediate to long-term carotid restenosis was observed after CAS as compared to CEA. [41] Since CAS is currently widely used as a treatment alternative to CEA, it is necessary to contribute to the ongoing controversial discussion regarding the incidence, clinical significance and appropriate therapeutic management of ISR in order to ameliorate long-term efficacy.

With regard to the etiology of ISR, there may be some similar mechanisms to recurrent stenosis after coronary artery stenting. First of all, an endothelial injury which is caused e.g. by balloon inflation and stent placement, seems to play a major role for the developing of ISR, both after CAS or coronary artery stenting. This damage could initiate a cascade of inflammatory processes, which finally leads to a neointimal proliferation and a concentric vessel lumen reduction. Like Schillinger et al. [20] we were recently able to support the notion of an inflammatory cascade as a main cause for ISR by showing that elevated periprocedural inflammation markers are significantly correlated with the development of an ISR [30]. The initial injury of the endothelial layer caused by balloon inflation, guide-wire manipulation or stent placement might explain why additional procedural factors could be identified within our literature review to influence the occurrence of ISR: the use of multiple stents during CAS [19, 28] or even wider and longer stent dimensions by their own [30] could be identified to be associated with a higher incidence of ISR. Potential endothelial injuries by either an amplified sheer force of the stent, a more pronounced abrasion or higher inflation pressure during the procedure are some of the discussed issues accountable for restenosis.

Despite the heterogeneity of the analysed studies, one of the most common findings was the time during which an ISR could be detected as it seems to develop most frequently within the first year after a CAS intervention [16, 18, 20, 21, 26, 29, 30]. This fact suggests the assumption that rather an intimal hyperplasia than an atherosclerotic burden is the main driven pathologic factor for an early restenosis.

Although different diagnostic tools and criteria were chosen to determine the presence of an ISR, the incidence is surprisingly constant throughout most of the publications under review. The rate of moderate (≥50%) and high-grade (≥70%) varies between 6.7—13.9% and 2.7—6.3%, respectively (see Table 1). Notably, this rate is higher as compared to those with a preceding CEA treatment within some of the randomised trials [16, 42], which has led to a keen discussion on the long-term durability of a CAS procedure [10]. Against the background that there is no established treatment standard for patients with an ISR, this should be considered before a CAS intervention is recommended as the preferred treatment modality. The surgical treatment of an ISR remains an exception since it is technically demanding and might be associated with peri-procedural complications [43]. In most of the cases, a redo-PTA or CAS is currently performed after ISR, which seems to be associated with an acceptable rate of periprocedural complications [29, 30, 35].

As a method of first choice to diagnose ISR, preferably a non-invasive technique should be chosen to avoid a potential
### Table 1  Main characteristics of all studies included.

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Mean follow-up time [mo], range</th>
<th>Number of treated arteries, male patients</th>
<th>Mean age (years) ± SD</th>
<th>Definition of ISR, DUS criteria (cm/s)</th>
<th>Proportion of ISR (%) during follow-up</th>
<th>Time to detection of ISR [months]</th>
<th>Complications of ISR-patients (%) during follow-up</th>
<th>Independent predictors of ISR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Willisfort-Ehringer (2002)</td>
<td>12b, 6—24a</td>
<td>303, 70%</td>
<td>70 ± 9</td>
<td>≥70% ICA/CCA &gt;4</td>
<td>3.0</td>
<td>&lt;12</td>
<td>Stroke 22.2 Death 11.1 Stroke 0.4 Death 0.0</td>
<td>Elevated HbA1c at baseline Age &gt;75 y Female gender Multiple stent deployment Suboptimal CAS result Prior CAS Suboptimal CAS result Elevated CRP after CAS Prior neck cancer</td>
</tr>
<tr>
<td>Khan (2003)</td>
<td>&lt;12, n.g.</td>
<td>209, 71%</td>
<td>72 &gt;75</td>
<td>≥50% PSV &gt; 140</td>
<td>6.7</td>
<td>n.g.</td>
<td>Stroke 0.4 Death 0.0</td>
<td>Prior neck cancer</td>
</tr>
<tr>
<td>Schillinger (2003)</td>
<td>6, n.g.</td>
<td>108, 68%</td>
<td>ISR 62, r60-76 +ICA/CCA &gt;2.5</td>
<td>≥50% PSV ≥ 150</td>
<td>13.9</td>
<td>≤6</td>
<td>Stroke 13.3 Death 6.7</td>
<td>Prior neck cancer</td>
</tr>
<tr>
<td>Skelly (2006)</td>
<td>5b, 0–30</td>
<td>109, 55%</td>
<td>70 ± 9</td>
<td>≥60% PSV ≥ 170</td>
<td>≥60% 11.0</td>
<td>≥60% 7</td>
<td>ISR &gt;60% Stroke 0.0 Death 0.0</td>
<td>Age &gt;75 y Female gender Multiple stent deployment Suboptimal CAS result</td>
</tr>
<tr>
<td>Lal (2007)</td>
<td>19.3, n.g.</td>
<td>255, n.g.</td>
<td>ISR 71.8</td>
<td>≥50% PSV ≥ 325 cm/s</td>
<td>≥50% 9.0</td>
<td>n.g.</td>
<td>Stroke 0.0 Death 0.0</td>
<td>Diabetes mellitus Worsening of suggested ISR pattern</td>
</tr>
<tr>
<td>Younis (2007)</td>
<td>24, 6–99</td>
<td>399, 67%</td>
<td>70 ± 3.5</td>
<td>≥80% EDV-ICA/CCA &gt;5,4</td>
<td>3.8</td>
<td>24.5 r 5–90</td>
<td>Stroke 20.0 Death 0.0</td>
<td>Prior CEA Radiogenic stenosis</td>
</tr>
<tr>
<td>AbuRahma (2008)</td>
<td>20, 1–78</td>
<td>144, 51%</td>
<td>70, r 40–88</td>
<td>≥50% PSV &gt; 224 cm/s</td>
<td>≥50% 7.6</td>
<td>n.g.</td>
<td>ISR &gt;50% Stroke 0.0 Death n.g.</td>
<td>CEA Radiogenic stenosis</td>
</tr>
<tr>
<td>Setacci (2008)</td>
<td>45, 0–73</td>
<td>814, 64%</td>
<td>73 ± 8</td>
<td>≥50% PSV ≥ 325 cm/s</td>
<td>≥50% 9.0</td>
<td>n.g.</td>
<td>ISR &gt;70% Stroke 0.0 Death 0.0</td>
<td>Prior CEA</td>
</tr>
<tr>
<td>Topakian (2008)</td>
<td>12, n.g.</td>
<td>102, 66%</td>
<td>66 ± 9</td>
<td>≥50% PSV ≥ 180 cm/s</td>
<td>9.8</td>
<td>≤12</td>
<td>Stroke 0.0 Death 0.0 Stroke 11.1 Death 0.0</td>
<td>Postprocedural low HDL cholesterol Prior CEA</td>
</tr>
<tr>
<td>Zhou (2008)</td>
<td>32, 6–48</td>
<td>282, n.g.</td>
<td>69, r 55–87</td>
<td>≥70% PSV ≥ 125, EDV &lt; 140</td>
<td>6.3</td>
<td>n.g.</td>
<td>Stroke 13.0 Death 8.7</td>
<td>Radiogenic stenosis</td>
</tr>
<tr>
<td>Cosottini (2010)</td>
<td>26b, 0–99</td>
<td>200, 74%</td>
<td>72 ± 8</td>
<td>≥50% PSV &gt; 220 cm/s</td>
<td>11.5</td>
<td>n.g.</td>
<td>Stroke 0.0 Death 0.0</td>
<td>Suboptimal CAS result Multiple stent deployment Cilostazol</td>
</tr>
<tr>
<td>Takigawa (2010)</td>
<td>28.8, 12–67</td>
<td>113, 86%</td>
<td>70 ± 7</td>
<td>≥50% PSV ≥ 150 cm/s</td>
<td>11.3</td>
<td>9 ± 3</td>
<td>Stroke 0 Death 0</td>
<td>CEA Radiogenic stenosis</td>
</tr>
<tr>
<td>Wasser (2011)</td>
<td>33.4b, 15–54a</td>
<td>210, 72%</td>
<td>68b ± 10</td>
<td>≥70% PSV ≥ 300 cm/s</td>
<td>5.7</td>
<td>9b, 3–17a</td>
<td>Stroke 25.0 Death 8.3</td>
<td>Leukocyte count after CAS Stent length Stent width</td>
</tr>
</tbody>
</table>

DUS, duplex ultrasound; PSV, peak systolic velocity; EDV, end diastolic velocity; ICA/CCA, index of PSV of ICA and CCA; NISR, group of patients without ISR

r, range; n.g., not given.
a Interquartile range.
b Median.
harm for the patient during the essential long-term follow-up. In this context, serial duplex ultrasound investigations seem to best fulfill the requirements for long-term follow-up and have been used in all studies retrieved for the current review. As a secondary validation method, high-grade ISR could be confirmed by CT angiography in some selected cases. Since duplex ultrasound has turned out to lead to a reliable ISR diagnosis whereas conventional angiography is known to be an invasive procedure possibly linked with potentially dangerous complications such as stroke or bleedings, a conventional angiography should only be considered in those patients with a symptomatic or high-grade ISR, who are likely to be treated afterwards or within the same angiographic session.

A fact which could reduce the value of duplex ultrasound as a first choice method for serial follow-up investigations is the generally lacking agreement of exact ultrasound criteria to grade an ISR. Considering the peak systolic velocity (PSV) as the most commonly used duplex criterium, a considerable distribution of cut-off values could be observed. For example, the cut-off PSV for the diagnosis of an ISR of ≥50% varied from ≥140 cm/s in one study [19], over a PSV ≥175 cm/s in the publication of Setacci et al. [25] and a PSV ≥220 cm/s in the study by Cosottini et al. [28] up to a PSV ≥224 cm/s by AbuRahma et al. [24]. Despite the fact that ultrasound criteria have to be adapted to each local high quality ultrasound laboratory, the wide range of values between the studies urges the need for an implementation of generally valid ultrasound criteria in ISR diagnosis [12,13].

There is currently a very controversial discussion on the clinical impact of ISR. Amongst others, the results from the SPACE study have encouraged those claiming that restenosis might be a relatively benign pathology [16,44]. On the other hand, especially long-term follow-up data raise concern that patients with ISR could be suffering from a higher complication rate in comparison to patients without ISR [30]. Since CAS is often recommended the treatment of choice in younger patients (<70a) [3—5,9] it is of greatest interest to evaluate the complication rates of ISR in the long run. By now, the results regarding the incidence and clinical complications of ISR in the randomized controlled trials comparing CAS and CEA [4,6,11] are eagerly awaited.

The unresolved clinical impact of ISR further highlights the importance to identify independent risk factors which are predictive for an ISR. These would be helpful to detect those patients in which a tight follow up is necessary. Advanced age [17,19] has been found to be predictive for an ISR, which would further contribute to the recommendation of choosing a CEA as the first treatment of choice especially in elderly patients [3,5]. CAS is frequently recommended in patients with a restenosis after CEA because a redo-CEA sometimes appears to be technically difficult and might bear a higher periprocedural risk than the initial operation [7] or in patients with a radiogenic stenosis [45]. When considering the optimal treatment option for those patient subgroups, one should take into account though that a CAS procedure because of a CEA-restenosis or radiation-induced stenosis is also associated with a higher rate of ISR [20,23,34,35]. An insufficient result after a CAS procedure, e.g. due to insufficient stent adaptation, could be shown to be associated with a higher risk of ISR occurrence [19,20,28]. Therefore, to ameliorate the long-term benefit of a CAS, it is a worthwhile aim to pursue a perfect stent adaptation to the vessel lumen. The fact that an aggressive postdilation bears the risk of distal embolization and microvascular injury, which may itself initiate neointimal hyperplasia complicates the procedure. Furthermore, the characteristics of the stent deployed are of special interest regarding the incidence of ISR. Usually, the selection of the stent length and width are based on angiographic findings in order to appropriately cover the stenosis. However, narrower and longer stents were correlated with a higher ISR risk [28,30]. It is conceivable that a stent with a larger diameter results in a reduced flow-velocity, less turbulences and thus in less frequent ISR. A longer stent, which is used to cover longer lesions, probably represents the presence of a high plaque burden and has repeatedly been identified as an independent predictor for periprocedural complications [46,47].

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Although it is clear that mainly anatomical conditions lead to the selection of a specific stent, it is recommendable to choose the shortest but widest stent as possible in order to minimize the risk of ISR development and to closely follow-up those patients in whom a longer, narrower stent has been used.

After a successful CAS, a stringent monitoring of cardiovascular risk factors seems to be essential. Not only with regard to primary and secondary stroke prevention, but also especially in the context of ISR development, several publications show a correlation between the presence of cardiovascular risk factors, such as tobacco use [17,42], diabetes mellitus [18,22], e.g. represented by an elevated HbA1c [36], low HDL cholesterol [26], and the occurrence of an ISR.

**Conclusions**

ISR after CAS is frequently observed within the first year of follow-up and might be associated with a higher risk for clinical complications. Against the light that a CAS intervention is frequently recommended as an alternative treatment strategy to CEA especially in patients aged <70 years, a tight and long-lasting follow-up is warranted. Particularly patients who are of advanced age, treated for a radiogenic stenosis or a recurrent stenosis after CEA, or with the presence of cardiovascular risk factors such as tobacco use, diabetes mellitus or a dyslipoproteinemia or certain procedure-related factors (a narrow or long stent, insufficient stent adaptation after CAS or the use of multiple stents) are prone to develop an ISR. A significant heterogeneity especially regarding the exact duplex criteria to identify an ISR has been observed between the reviewed studies thus supporting the need to establish commonly accepted criteria for ISR-grading. With respect to the possible clinical relevance of an ISR and a lacking commonly accepted treatment strategy, all efforts should be made to carefully follow-up especially those patient subgroups at risk for ISR in order to further develop an optimized treatment strategy.

**References**


