ORIGINAL ARTICLE

Carotid Artery Stenting with Distal Protection Using the Carotid Wallstent and FilterWire Neuroprotection: Single-Center Experience of 380 Cases with Midterm Outcomes

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Emerging data have supported the clinical efficacy of carotid artery stenting (CAS) in stroke prevention in high-risk surgical patients. This study was performed to evaluate the midterm clinical outcome of CAS using the Carotid Wallstent and FilterWire distal protection (both Boston Scientific, Natick, MA) at an academic institution. Risk factors for in-stent restenosis (ISR) were also analyzed. Clinical variables and treatment outcome of high-risk patients who underwent Carotid Wallstent placement with FilterWire EX/EZ neuroprotection were analyzed during a recent 54-month period. Three hundred eighty CAS procedures were performed in 354 patients. Technical success was achieved in 372 cases (98%), and symptomatic lesions existed in 85 (24%) patients. No patient experienced periprocedural mortality or neuroprotective device–related complication. The 30-day stroke and death rate was 2.7%, and the overall complication rate was 6.9%. The overall major or fatal stroke rates in symptomatic and asymptomatic patients were 4.6% and 1.3%, respectively (not significant). The overall stroke and death rates between the symptomatic and asymptomatic groups were 5.8% and 2.4%, respectively (not significant). The median follow-up period was 29 months (range 1–53 months). With Kaplan-Meier analysis, the rates of freedom from 60% or greater ISR after CAS procedures at 12, 24, 36, and 48 months were 97%, 94%, 92%, and 90%, respectively. The rates of freedom from all fatal and nonfatal strokes at 12, 24, 36, and 48 months were 97%, 91%, 89%, and 85%, respectively. Multivariable analysis of significant univariate predictors identified that postendarterectomy stenosis (odds ratio [OR] 3.98, $p = .02$) and multiple stent placement (OR 3.68, $p = .03$) were independent predictors of ISR. Our study yielded favorable short-term and midterm clinical results using Carotid Wallstent with FilterWire neuroprotection. Late follow-up results showed low rates of fatal and nonfatal stroke and favorable ISR rates compared with other carotid stent trials. Postendarterectomy and multiple stent placement were associated with subsequent ISR.

Key words: *carotid artery stenting, distal protection device, high-risk patients, restenosis*

Stroke is the most common cause of permanent disability and remains the third leading cause of death in industrialized countries.[1] It is estimated that the incidence of stroke-related death will double over the next 30 years in the Unites States. The economic impact of this condition is astonishing as the estimated costs for stroke patients in the United States for 2006 are estimated to reach $58 billion.[1] Atherosclerotic disease involving the extracranial carotid artery accounts for approximately 20% of all strokes or transient ischemic attacks. Although there is no controversy with regard to the efficacy of carotid endarterectomy (CEA) in stroke prevention in patients with high-grade carotid occlusive lesions,[2,3] carotid artery stenting (CAS) has become an acceptable treatment alternative for patients with severe carotid stenosis.[4]

The perceived benefits of CAS over CEA predominantly relate to its minimal invasiveness since a percutaneous stenting procedure can potentially reduce the patient anxiety that is commonly associated with a surgical procedure. However, a well-recognized pitfall of CAS that may have impeded the wide acceptance of this percutaneous intervention is distal cerebral embolization. This phenomenon can occur as a result of catheter manipulation in a plaque-laden carotid bifurcation owing to either

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balloon angioplasty or stent deployment.[5] The risk of cerebral embolization during CAS as a cause of procedure-related stroke has been highlighted in several clinical reports.[6–8]

Owing in part to the risk of procedure-related cerebral embolization, most physicians recognize the importance of performing CAS using embolic protection devices (EPDs). Several recent multi-institutional clinical studies have demonstrated the clinical efficacy of CAS using distal protection devices.[9–11] The purpose of this study is to report a single institutional experience of CAS using the Carotid Wallstent and the FilterWire neuroprotection system (both Boston Scientific, Natick, MA). Early and late clinical outcomes and risk factors contributing to restenosis were analyzed.

Materials and Methods

Patient Cohort

Clinical data were reviewed from high-risk patients who underwent CAS from February 2002 to August 2006. Particular attention was paid to those patients undergoing Carotid Wallstent (Figure 1) placement with FilterWire (Figure 2) neuroprotection who formed the basis of this study patient cohort. All procedures were performed at the Michael E. DeBakey Veterans Administration Hospital, a Baylor College of Medicine–affiliated hospital. Carotid duplex ultrasonography was performed in all patients prior to the stenting procedure to document the high-grade carotid stenosis. Patients with symptomatic carotid stenosis 60% or greater and asymptomatic carotid stenosis 80% or greater were considered for this protocol.

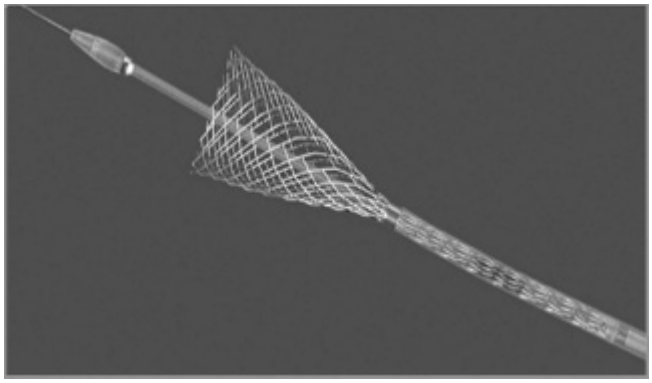

Figure 1. The Carotid Wallstent is a self-expanding stainless steel stent with a monorail delivery catheter system that contains a 5.0F to 5.9F shaft. The stent is available in diameters of 6, 8, and 10 mm and lengths of 20, 30, and 40 mm.

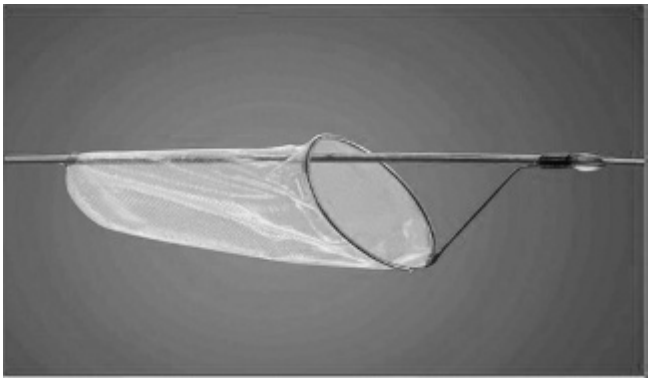

Figure 2. FilterWire EX/EZ emboli protection device with a suspended radiopaque nitinol loop, filter pore size 110 μm, sized for 3.5 to 5.5 mm–diameter vessels. The device is compatible with 0.014-inch guidewire.

Procedural indications, technique, and treatment outcome were examined.

Treatment indications were based on high-risk criteria adapted from a consensus report and our previous report.[12–14] Briefly, these criteria included various anatomic considerations, which included high carotid bifurcation (> C2 level), contralateral carotid occlusion, the presence of tracheostomy, a history of ipsilateral neck irradiation, previous radical neck dissection, or CEA. Moreover, the high-risk criteria included patients with one or more medical comorbidities, such as those with myocardial infarction or stroke in the previous 3 months. High-risk pulmonary dysfunction included patients with steroid-dependent chronic obstructive pulmonary disease or measured forced expiratory volume in 1 second less than 30% of predicted or less than 1 L/s. Lastly, high-risk cardiac dysfunction included those with a left ventricular ejection fraction less than 30%, as well as documented heart failure (stage III or IV of the New York Heart Association classification).

Antithrombotic Protocol

The patients were given clopidogrel (75 mg/d) and aspirin (81 mg/d) beginning 3 days prior to the intervention. Following the stenting procedure, clopidogrel was continued for 1 month, whereas aspirin was continued for life. Prior to June 2002, all patients undergoing CAS received an intravenous (IV) heparin bolus (100 U/kg) to achieve systemic anticoagulation during the carotid intervention. Following June 2002, the intraoperative anticoagulation regimen was changed to IV bivalirudin bolus (0.75 mg/kg) followed by an infusion rate of 1.75 mg/kg/h. At the

completion of the carotid stenting, IV bivalirudin was discontinued.

Carotid Stent and Neuroprotection Device

The Carotid Wallstent and FilterWire EX/EZ neuroprotection system were used in patients in this study. The FilterWire EX/EZ is a 190 or 300 cm monorail, 0.014-inch, filter-type distal emboli protection guidewire. The filter pore size is 110 μm and when deployed fits 3.5 to 5.5 mm–diameter vessels. The Carotid Wallstent is a self-expanding stainless steel stent mounted on a monorail delivery catheter with a shaft size that ranges from 5F to 5.9F. The stent is a closed-cell design with nominal lengths of 20, 30, and 40 mm and nominal expanded diameters of 6, 8, and 10 mm.

Follow-Up Surveillance

A thorough neurologic evaluation was performed in the recovery room on all patients following the stenting procedure. Discharging patients home on postoperative day 1 was routine. A follow-up visit with routine carotid duplex ultrasonography was performed at 1, 6, and 12 months following the intervention and each year thereafter. Primary outcome measures included any major ipsilateral stroke, other major complication, or death during hospitalization for the stenting procedure. Secondary outcome measurements included minor ipsilateral stroke and in-stent restenosis (ISR). Minor stroke was defined as a transient neurologic deficit lasting longer than 24 hours but with no long-term residual deficit. If carotid duplex ultrasonography detected a high-grade in-stent stenosis, follow-up carotid angiography with possible balloon angioplasty was performed.

Data Analysis

Clinical variables that may be associated with ISR after CAS were analyzed. For the purposes of this analysis, we compared relevant clinical data in patients with no ISR versus those with a moderate degree of ISR ($\geq$ 60%). Statistical analysis was performed to determine the association between relevant risk factors and ISR with the Fisher exact test or Pearson's chi-square test in categorical variables. The Wilcoxon rank sum test was used to test for differences in continuous variables. Risk factors influencing the development of ISR were analyzed by univariate analysis, which was followed by multivariate stepwise logistic regression analyses. Kaplan-Meier methods were also used to analyze the patency data. All statistical analyses were performed using a statistical software program (*SAS*, SAS Institute, Cary, NC). All values were expressed as mean $\pm$ standard error of measurement. Statistical significance was accepted with a p value of less than .05.

Results

Patient Characteristics

Three hundred eighty CAS procedures were performed in 354 patients (339 male; overall mean age 71 years, range 54–88 years) during the study period. Detailed criteria of the high-risk eligibility of these patients are listed Table 1. Table 2 shows relevant demographic characteristics and treatment indications. Two hundred sixty-nine patients (76%) had asymptomatic stenosis, whereas 85 patients (24%) had symptomatic carotid artery disease.

Clinical Outcomes

Technical success was achieved in 372 (98%) of the 380 CAS procedures. Eight procedures were considered technical failures: six were due to the severe tortuosity of the aortic arch, which precluded safe advancement of the guiding catheter, and two remaining cases were due to failure in traversing the carotid stenosis. Among the 374 successful CAS procedures, the carotid artery stenosis decreased from 86 $\pm$ 14% (mean $\pm$ SD) before the stent placement to a post-stenting mean residual stenosis of 11 $\pm$ 7%. The 30-day stroke and death rate was 2.6% (n = 10), which included one hemispheric stroke owing to immediate carotid stent thrombosis, which was success-

Table 1. High-Risk Criteria for Patients Undergoing Carotid Stenting Procedure (n = 354)

High-Risk Category	*Patients,* n *(%)*
Cardiac dysfunction	89 (25)
Previous ipsilateral carotid endarterectomy	78 (22)
Pulmonary dysfunction	53 (15)
Recent myocardial infarction or stroke (within 3 mo)	42 (12)
Previous radical neck dissection	32 (9)
Contralateral carotid occlusion	28 (8)
Previous neck irradiation	21 (6)
High carotid bifurcation	18 (5)
Tracheostomy	10 (3)

Table 2. Patient Demographic Characteristics and Comorbidities

Patient Characteristics	*Patients,* n *(%)*
Total patients	354
Age (yr) (mean ± SD)	71 ± 8.4
Male gender	339 (96)
Asymptomatic carotid lesion	269 (76)
Symptomatic carotid lesion	
Stroke	21 (6)
Transient ischemic attack	28 (8)
Amaurosis fugax	35 (10)
Comorbidities	
Coronary artery disease	269 (76)
Smoking	278 (67)
Hypertension	315 (89)
Diabetes	202 (57)
Chronic obstructive pulmonary disease	78 (22)
Hypercholesterolemia	177 (50)
Renal insufficiency (creatinine > 1.5 mg/dL)	74 (21)

fully treated with rheolytic thrombectomy, as previously reported.[15] Additionally, six patients died of myocardial infarction within 1 month following hospital discharge. Two patients died of respiratory complications, and one patient suffered from a fatal pulmonary embolism. No difference was noted in the overall complication rate between symptomatic and asymptomatic patients (6.4% and 4.8%, respectively). The overall major or fatal stroke rates in symptomatic and asymptomatic patients were 4.6% and 1.3%, respectively. Moreover, no significant differences in overall stroke and death rates were noted between the symptomatic and asymptomatic groups (5.8% and 2.4%, respectively). No access-site complication or groin infection was noted in our series. The mean duration of hospital stay was 1.8 ± 1.5 days. The median follow-up period was 29 months (range 1–53 months). The rates of freedom from 60% or greater ISR after CAS procedures at 12, 24, 36, and 48 months were 97%, 94%, 92%, and 90%, respectively, based on the Kaplan-Meier analysis (Figure 3). The rates of freedom from all fatal and nonfatal strokes at 12, 24, 36, and 48 months were 97%, 91%, 89%, and 85%, respectively (Figure 4).

Risk Factor Analysis of ISR

Risk factor analysis of all demographic, preoperative, and intraoperative clinical data in relation to the development of ISR was performed. No significant differences were found with regard to etiology, gender distribution, and medical comorbidities (Table 3). Univariate analysis

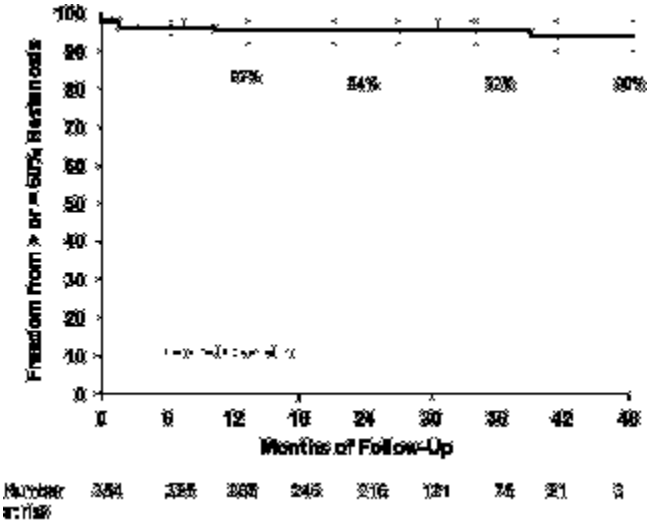

Figure 3. Kaplan-Meier analysis of freedom from ≥ 60% restenosis. The numbers at the bottom of the figure represent the number of patients at risk at the beginning of each time period.

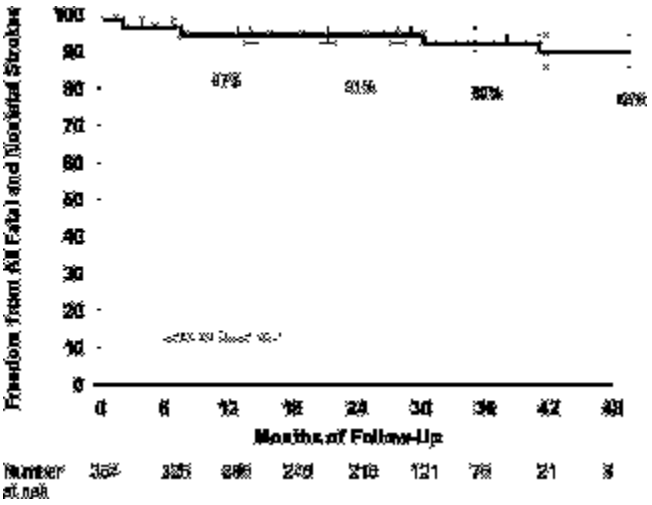

Figure 4. Kaplan-Meier analysis of freedom from all fatal and nonfatal strokes. The numbers at the bottom of the figure represent the number of patients at risk at the beginning of each time period.

showed that post-CEA stenosis ($p < .02$), age > 75 years ($p < .01$) and multiple stent placement ($p < .02$) were associated with ISR. Multivariable analysis of significant univariate predictors revealed that post-CEA stenosis and multiple stent placement were independent predictors of ISR (Table 4).

Discussion

Since CAS was approved by the US Food and Drug Administration for clinical application in 2004, this percutaneous procedure has become a treatment

Table 3. Univariate Analysis of Risk Factors Associated with the Development of In-Stent Restenosis

Variable	*Without ISR,* n *(%)*	*Moderate ISR (≥ 60%),* n *(%)*	p *Value*
Total number of patients	291	62	
Age (yr) (mean ± SD)	73 ± 11	71 ± 16	NS
Male gender	280 (95)	59 (96)	NS
Age > 75 yr	61 (21)	32 (52)	.04
Multiple stent placement (> 1)	44 (15)	30 (48)	.03
Asymptomatic carotid lesion	39 (26)	9 (27)	NS
Symptomatic carotid lesion			
Stroke	28 (19)	8 (22)	NS
Transient ischemic attack	52 (35)	11 (34)	NS
Amaurosis fugax	36 (24)	5 (18)	NS
Comorbidities			
Coronary artery disease	212 (73)	44 (71)	NS
Congestive heart failure	61 (21)	12 (19)	NS
History of myocardial infarction	64 (22)	15 (24)	NS
Smoking	218 (75)	41 (66)	NS
Hypertension	215 (74)	49 (79)	NS
Diabetes	108 (37)	20 (32)	NS
Chronic obstructive pulmonary disease	76 (26)	150 (24)	NS
Hypercholesterolemia	102 (35)	20 (32)	NS
Renal insufficiency (creatinine > 1.5 mg/dL)	35 (12)	7 (11)	NS
CAS indications			
High-risk cardiac comorbidity	151 (52)	35 (57)	NS
High-risk pulmonary comorbidity	35 (12)	8 (13)	NS
History of neck irradiation	17 (6)	2 (3)	NS
Post-CEA stenosis	40 (14)	34 (55)	.02
High carotid bifurcation	9 (3)	2 (0.3)	NS
Prior radical neck dissection	6 (2)	2 (0.3)	NS
Cervical fusion	3 (1)	0 (0)	NS
Tracheostomy	3 (1)	0 (0)	NS

CAS = carotid artery stenting; CEA = carotid endarterectomy; ISR = in-stent restenosis; NS = not significant.

alternative in patients who are deemed high risk for endarterectomy. The short-term results reported from several large series are consistent with our findings in that this procedure can be performed with high technical success and low complication rates.[9,11,16,17] Although available data on long-term durability remain scarce, numerous reports, along with our findings, support good midterm clinical outcomes, with an incidence of ISR ranging from 2.7 to 6.4%.[11,18–21] Additionally, our study demonstrated that increased age and multiple stent placement are predictors of ISR following CAS.

Table 4. Multivariate Analysis of Risk Factors Predictive of Subsequent In-Stent Restenosis

Variable	p *Value*	*Odds Ratio (95% CI)*
Multiple carotid stent placement	.03	3.68 (1.4–5.36)
Post-CEA stenosis	.02	3.98 (1.2–4.93)

CEA = carotid endarterectomy; CI = confidence interval.

Over the past 5 years, we have reported our experience and repeatedly analyzed the outcome of patients undergoing CAS.[13,14,22,23] This study represents a subset analysis of patients who received the Carotid Wallstent with the FilterWire protection device. Consistent with our previous finding, we noted a temporal decline in procedure-related adverse events, including all strokes and deaths.[14] Although the Wallstent system remained unchanged throughout the study duration, we switched the neuroprotection device from the FilterWire EX system, which was used in the first 65 patients, to the FilterWire EZ system in all remaining patients. This shift of EPD use was

made due to the availability of the FilterWire EZ device in 2004, which was a concentrically designed filter system that facilitates the complete vessel wall apposition following the filter basket deployment. We do not believe that the decline in CAS-related adverse events was a function of the change in the FilterWire device. Rather, it reflects a multifactorial phenomenon. As CAS becomes a widely performed intervention, catheters and guiding sheaths that were specifically designed for this treatment modality became available. These products were smaller in profile and more flexible, facilitating the catheterization in tortuous carotid vessels. As we gained experience, we became keenly aware of the importance of patient selection to ensure treatment success. We learned along with others' experiences that, for instance, heavily calcified plaques with a long segment or ulcerated stenosis represent an unfavorable lesion for CAS, and such a lesion is best treated with endarterectomy. Another factor that might be responsible for our treatment success relates to the modification of our anticoagulation regiment. Our present practice uses intravenous bivalirudin, which is a direct thrombin inhibitor, instead of weight-based heparin infusion during the procedure. As noted in our previous report, we observed a significant reduction in hemorrhagic complications following the modification of this anticoagulation regimen.[13] Lastly, the temporal decline in procedure-related complications underscores a learning curve associated with CAS procedures, as we had previously reported.[14]

The findings from our study showed an overall incidence of stroke and death of 2.6% at 30 days, which compares favorably with the 30-day outcome of several other high-risk CAS studies.[17,24–26] When analyzing the overall major or fatal stroke rate in symptomatic and asymptomatic patients, our study revealed a difference that was not statistically significant between the two patient cohorts (4.6% symptomatic versus 1.3% asymptomatic). These outcomes were comparable to the recently reported ARCHeR trial (ACCULINK for Revascularization of Carotids in High-Risk patients). In this multicenter nonrandomized prospective study that enrolled 581 high-risk patients who underwent an ACCULINK (Guidant, Santa Clara, CA) carotid stent placement, the study reported major or fatal stroke rates in symptomatic and asymptomatic patients of 4.3% and 0.7%, respectively.[9] The overall stroke rates noted in our patient cohorts were similar to the stroke rate of 2.1% in the surgical arm of the NASCET (North American Symptomatic Carotid Endarterectomy Trial), which included normal–surgical risk patients.[27] Likewise, the 30-day risk of disabling or fatal stroke in the normal-risk ACAS (Asymptomatic Carotid Surgery Trial) was 1.4%, which remained similar to that of our asymptomatic cohorts.[28] Comparison of our results underscored the procedural safety of CAS using the Wallstent and FilterWire EPD as they yielded similar efficacy profiles with other highly regarded endarterectomy trials.

In one of the earlier investigations that evaluated the efficacy of CAS using the Wallstent, Alberts and colleagues randomized 219 patients with high-grade symptomatic carotid artery stenosis to either CEA or CAS treatment groups.[29] All patients in the CAS group received the Wallstent. The 30-day periprocedural stroke and death rate was 12.1% for CAS and 4.5% for CEA ($p = .049$). The 1-year ipsilateral stroke rate was 3.6% in the surgical group, in contrast to 12.2% in the stent group ($p = .022$). This trial was halted prematurely by the researchers owing in part to the high complication rate in the CAS patient cohorts. Subsequent data analysis showed numerous methodologic flaws in the study, which included heterogeneous antiplatelet regimens and potential patient selection bias. More importantly, the study found that the majority of CAS-related complications were clustered around physician investigators with minimal or no previous CAS experience.[29,30] The findings of this study were in sharp contrast to a recent multicenter prospective study known as the BEACH trial (The Boston Scientific EPI: A Carotid Stenting Trial for High-Risk Surgical Patients), which evaluated the clinical efficacy of the Carotid Wallstent and FilterWire protection device.[16] The study enrolled 747 patients at high surgical risk for endarterectomy who underwent Carotid Wallstent placement with FilterWire distal protection. The authors reported remarkable early outcomes, with an overall procedure success rate of 98%. The 30-day composite major adverse event was 5.8%, which was comparable to other large CAS series.[9–11] Specifically, the 30-day incidence of death, stroke, and myocardial infarction was 1.5%, 4.4%, and 1.0%, respectively.[16]

The incidence of hemodynamically significant ISR in our study was 8% at 3 years, which remained consistent with other clinical series.[9,21,23,31–33] The true incidence of ISR in our series is likely to be higher because of a small percentage of patients lost to follow-up, particularly patients who were referred from outside facilities. A recent study encompassing 372 patients treated with a Carotid Wallstent noted a 3.6% incidence of high-grade ISR ($> 80\%$) during a follow-up period of 12 months.[19] Similarly, Chakhtoura and colleagues reported an 8% high-grade ISR rate during their 18-month follow-up of 50

CAS procedures.[33] Their slightly higher ISR rate is likely reflected by the high percentage of patients whose CAS was performed for postendarterectomy restenosis. The authors also reported a restenosis rate of 5% and predicted a 5-year clinically significant ISR rate of 6.4% by using life table analysis and Kaplan-Meier survival curves.[32] Willfort-Ehringer and colleagues similarly reported a favorable outcome of a 3% high-grade ISR rate during their mean of 12 months' follow-up of 303 Wallstents.[31] Furthermore, they prospectively evaluated 125 CAS procedures by using ultrasonography and demonstrated that the diameters of the self-expanding stents steadily increased over 2 years and that the neointimal thickness increased up to 12 months and then stabilized thereafter. They thus postulated that the complex interaction between neointimal proliferation and stent expansion might contribute to the good midterm outcome of CAS.[34]

Using univariate risk factor analysis, we identified three variables that are associated with the development of ISR, which included increased age ($\geq$ 75 years), multiple stent placement, and post-CEA stenosis (see Table 3). With multivariate analysis, we further identified post-CEA stenosis and multiple stent placement as predictors of ISR (see Table 4). Similar findings were also reported by Setacci and colleagues, who noted a 3.6% ISR rate after 407 CAS procedures.[19] These authors reported that post-CEA restenosis was an independent predictive factor for the development of ISR. They further postulated that this phenomenon might be related to the aggressive intimal hyperplastic reaction in this patient cohort, whether the method of carotid intervention was endarterectomy or stent placement.[19] Although our study did not show gender as a risk factor for post-CAS restenosis, it was previously postulated that female patients are more likely to develop post-CAS restenosis owing in part to their smaller carotid artery caliber, in which flow compromise is more likely to occur with recurrent disease.[35] This observation was further validated by Khan and colleagues, who confirmed that female gender was a risk factor for ISR.[36] In this same report, researchers also noted that increased age and multiple stent insertion were predictors for the development of ISR, findings that were consistent with our results. It is noteworthy that several large clinical studies have previously identified various risk factors for postendarterectomy restenosis, which included hypertension, hyperlipidemia, and smoking.[37–39] These factors, as noted in our study as well as others, did not appear to influence the development of post-stenting restenosis.[21,35,36]

Admittedly, there are several limitations in our study, which were related to the retrospective nature of the study and their potential patient selection and treatment bias. Additionally, patients analyzed in this study were not randomized with regard to their treatment strategy, which obviously does not allow for a comparative analysis with endarterectomy. Because all patients received the Wallstent and FilterWire distal protection, this study design does not allow patient subgroup analysis in the absence of FilterWire protection. Lastly, because this study took place at a Veterans Administration hospital, nearly all patients were male, which precluded an impartial assessment regarding the role of gender in the outcome of the CAS procedure.

In conclusion, the results of our series demonstrated that Carotid Wallstent placement with FilterWire distal protection provides excellent 30-day clinical outcomes and a low incidence of late stroke and ISR rate in high–surgical risk patients. The findings of our study are consistent with other series that support CAS as a safe and effective treatment modality for stroke prevention in high-risk patients. Further studies are needed to validate the efficacy of this percutaneous intervention in patients with low or moderate surgical risk for endarterectomy.

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