Carotid artery stenting in asymptomatic and surgically high-risk patients: Single-centre, single-operator results

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BACKGROUND: Stroke represents the third leading cause of death in developed countries and the leading cause of disability in the elderly. Because asymptomatic, surgically high-risk patients have been systematically excluded from randomized trials of carotid endarterectomy and medical therapy, the management of this group of patients is still controversial. A single-centre, single-operator registry was analyzed to evaluate feasibility and safety of carotid artery stenting (CAS) with distal protection devices in consecutive, asymptomatic, surgically high-risk patients who were scheduled for endovascular treatment of significant carotid stenoses.

METHODS: A total of 122 consecutive, surgically high-risk, asymptomatic patients (150 carotid arteries, 59% men, mean [$\pm$ SD] age

69 $\pm$ 9 years) with severe carotid stenosis and one or more high-risk features for carotid endarterectomy were scheduled for CAS. All procedures were performed in a single centre by a single operator. All patients were prospectively asked to undergo a clinical 30-day follow-up.

RESULTS: A total of 154 stents were implanted in 150 carotid arteries. The primary success rate was 98.7%. The rates of stenosis before and after direct CAS were 81% $\pm$ 9% and 10% $\pm$ 13%, respectively. The median of fluoroscopic time of direct CAS was 6 min (range 2.5 min to 31.5 min). At 30 days, data were available in all patients. The combined 30-day mortality and stroke rate was 1.3%.

CONCLUSIONS: Short-term outcomes of CAS in asymptomatic, surgically high-risk patients treated by a single operator suggest a low periprocedural complication rate.

Key Words: Carotid artery stenosis; Stent; Stroke

Stroke represents the third leading cause of death in developed countries and the leading cause of disability in the elderly (1). Eighty per cent of strokes are ischemic, with the extracranial carotid artery contributing to 20% to 30% of cases. Among those patients, nearly one-half were previously asymptomatic (2,3). Surgical carotid endarterectomy (CEA) has been performed effectively for over 50 years as the primary treatment strategy for both symptomatic and asymptomatic patients with carotid artery disease. Substantial long-term hemodynamic and clinical benefits are attributable to this operation (4). However, several studies have shown that the clinical 'real-world' practice of carotid artery therapy involves many patients who would have been excluded from the major CEA studies and are at a high operative risk. Thus, there is still an ongoing debate on stroke prevention in surgically high-risk asymptomatic patients. The present discussion proceeds from the assumption that in the medical arms of the Asymptomatic Carotid Atherosclerosis Study (ACAS) and the Asymptomatic Carotid Surgery Trial (ACST), five-year rates of death or stroke were similar (12%) (5). Therefore, periprocedural rates of death or stroke in asymptomatic patients must not exceed 3% (2). However, an overview of published registries and observational studies demonstrated rates of death or stroke at 30 days of 0.8% to 3.8% in asymptomatic patients (6-8).

We retrospectively analyzed a single-centre, single-operator registry to evaluate feasibility and safety of carotid artery stenting (CAS) with distal protection devices in consecutive, asymptomatic, surgically high-risk patients who were scheduled

for endovascular treatment of significant carotid stenoses. The purpose of the present study was to answer the question of whether endovascular therapy is appropriate in this group of patients.

METHODS

Patients

From September 2005 until July 2008, 122 consecutive, surgically high-risk, asymptomatic patients (150 carotid arteries) with severe carotid stenosis and one or more high-risk features for CEA were scheduled for CAS. The patients were considered for revascularization in the presence of 70% or greater stenosis of the internal carotid artery. Stenoses were quantified according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria (9). Clinical criteria for high-risk patients were modified according to the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study (10), and are summarized in Table 1. Baseline demographic and clinical characteristics of percutaneously treated patients are presented in Tables 2 and 3. All patients provided their written informed consent before the procedure. Analysis was performed by intention to treat.

Stenting procedure and postprocedural protocol

Full details regarding the CAS procedure are described elsewhere (11). In brief, all procedures were performed via the femoral approach using a 6 Fr guiding sheath or 8 Fr guiding catheter. After performing the baseline angiography, a distal

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TABLE 1
Criteria for high-risk patients

Age ≥80 years
History of open heart surgery
Need for open heart surgery
History of myocardial infarction
Known multivessel disease
Left ventricular dysfunction with left ventricular ejection fraction ≤40%
Severe bronchopulmonary disease
Severe renal disease
Significant contralateral carotid disease
Previous endarterectomy

TABLE 2
Baseline demographic and clinical characteristics

Age, years, mean ± SD (range)	69±9 (46–86)
Male sex, %	59
History of myocardial infarction, %	34
History of open heart surgery, %	20
Previous coronary artery intervention, n	42
Known multivessel coronary artery disease, n	57
Left ventricular dysfunction, %	12
Severe renal disease, %	21
Severe bronchopulmonary disease, %	16
Current smoker, n	44
Hypertension, n	94
Hypercholesterolemia (>5 mmol/L), %	29
Hypertriglyceridemia (>2 mmol/L), n	34
Diabetes mellitus, %	46

protection filter device was used. One of two filter devices was used at the operator's (JV) discretion; Filter Wire EZ (Boston Scientific Corporation, USA; 137 procedures) or Angioguard (Cordis, Johnson and Johnson, USA; 13 procedures). CAS was performed using the following self-expanding stents: Precise RX (Cordis, Johnson and Johnson, USA; 57 stents), Xact (Abbott Laboratories, Ireland; 37 stents), Carotid Wallstent Monorail (Boston Scientific Corporation, Ireland; 32 stents), sinus-Carotid-RX (Optimed, Germany; 20 stents), NexStent (EndoTex Interventional Systems Inc, USA; four stents) and VascuFlex SEC (B Braun, Germany; four stents). Stents were implanted with or without previous lesion dilation. After stent deployment, postdilation (8 atm to 12 atm) was performed with a balloon (4 mm to 6 mm × 20 mm) matched to the distal reference vessel diameter to achieve optimal stenting results. Residual stenosis less than 30%, absence of an uncovered intimal dissection and nonlimited flow were considered to constitute a satisfactory result. The anticoagulant and antithrombotic protocol comprised administration of 200 mg to 500 mg of acetylsalicylic acid and 300 mg of clopidogrel at least 24 h before the procedure. Intra-arterial administration of a heparin bolus at the beginning of the procedure (50 IU to 100 IU per kg body weight) maintained an activation clotting time of 250 s to 300 s. Atropine 0.5 mg to 1 mg intravenously was used before postdilation in patients with a heart rate of less than 60 beats/min. The patients were discharged on dual antiplatelet therapy (acetylsalicylic acid 100 mg/day and clopidogrel 75 mg/day) and acetylsalicylic acid was continued indefinitely.

TABLE 3
Medication before coronary artery stenting

Medication	Frequency (%)
Acetylsalicylic acid	88
Acetylsalicylic acid + clopidogrel	86
Statin	83
Angiotensin-converting enzyme inhibitor	68
Beta-blocker	71

The patients were monitored continuously during the intervention and the whole in-hospital period. All patients were repeatedly examined by nursing staff and physicians (including a neurological examination); all symptomatic patients were examined by board-certified neurologists. Postprocedural intracranial evaluation with magnetic resonance imaging or computed tomography was performed when the neurological status of the patient changed. Electrocardiography was recorded in all patients after CAS and on the following day. Asymptomatic patients who underwent uncomplicated procedures were discharged on the following day. All patients were prospectively asked to undergo 30-day clinical follow-up. Major clinical events (neurological death and/or stroke) were recorded.

Definitions

The patients were considered asymptomatic if they had no symptoms in the previous six months. The patients underwent a complete clinical (including neurological) examination before and after the procedure and at a 30-day follow-up. Stroke was defined as a neurological deficit that persisted for more than 24 h, minor stroke was defined as a new neurological deficit that resolved completely or returned to baseline within 30 days. Myocardial infarction was defined as the appearance of new pathological Q waves on a standard electrocardiogram in two or more leads. Major adverse events (primary end point) were death from neurological reasons and/or stroke.

Statistical analysis

Microsoft Excel with Analyse-it (Analyse-it Software Ltd, United Kingdom) was used for the study database and its analysis. Continuous variables are expressed as the mean ± SD, and categorical variables are expressed as counts and percentages. Fluoroscopic time is presented as the median and range.

RESULTS

A total of 122 asymptomatic, surgically high-risk patients underwent 150 CAS procedures. There were no complications associated with diagnostic angiography. Procedural success was achieved in all procedures except two (1.3%). These two failures were due to tortuous calcified carotid arteries associated with type III aortic arch. Subsequently, these patients were sent for surgery. The mean stenosis before stenting was 81%±9% and mean stenosis after stenting was 10%±13%. Table 4 summarizes interventional and angiographic characteristics.

There were no periprocedural intracranial hemorrhages or periprocedural myocardial infarctions; there was one minor stroke resulting in an in-hospital event rate (0.7%). Transient hypotension and/or bradycardia were observed in 63 procedures (42%), and were all reversed rapidly within several hours by treatment with intravenous fluids. Two patients expired during

TABLE 4
Interventional and angiographic characteristics of the study population

Lesion located in LICA/RICA, %	45/55
Restenosis after stenting, %	5
Restenosis after CEA, %	4
Stenosis of treated lesions, %, mean $\pm$ SD	81 $\pm$ 9
Residual stenosis, %, mean $\pm$ SD	10 $\pm$ 13
Stent length, mm, median (range)	40 (20–70)
Atropine during procedure, % of cases	52
Contralateral ICA occlusion, %	9
External carotid artery stenosis >50%, % of cases	21
Vertebral artery disease, % of cases	10
Fluoroscopic time, min, median (range)	6 (2.5–31.5)
Contrast medium, mL, median (range)	130 (50–250)

CEA Carotid endarterectomy; ICA Internal carotid artery; L Left; R Right

the in-hospital stay from non-neurological reasons – one died from pneumonia two weeks after stenting and the second patient died from heart failure three weeks after the procedure. Both fatal events were unrelated to the procedure.

All patients participated in 30-day follow-up. One patient (0.7%) had a new minor stroke. The remaining patients were asymptomatic. There have been no deaths, myocardial infarctions, repeat procedures or access site complications. The outcomes of short-term follow-up are summarized in Table 5.

DISCUSSION

In the present study, we demonstrated that CAS with an embolic protective device can be performed with low periprocedural morbidity in asymptomatic patients at high risk for adverse events with endarterectomy. The primary technical success rate of the CAS procedure was 98.7%. Clinical follow-up data at 30 days were available for all patients and the major adverse event rate (neurological death and/or stroke) was 1.3%.

Surgical studies with asymptomatic patients have shown only mild annual absolute risk reductions of approximately 1% for asymptomatic patients (2,5). Thus, current American Heart Association guidelines recommend CEA in asymptomatic patients with 60% to 99% internal carotid artery stenosis, if the risk of perioperative stroke or death is less than 3% (12). Furthermore, the 2005 guidelines from the American Academy of Neurology recommended that eligible patients be 40 to 75 years of age and have a life expectancy of at least five years (13).

Because asymptomatic, surgically high-risk patients have been systematically excluded from randomized trials of CEA and medical therapy, the management of this group of patients is still controversial. Unfortunately, there are important controversial issues relating to even asymptomatic, surgically low-risk patients (14). Proponents of the conservative approach suggest that ACAS and ACST (2,5) are outdated and the current best medical therapy was not available in these trials. The other controversial issue is the that stenosis threshold for recommending revascularization ranges from 60% to 80%. Thus, there is a real need for additional randomized studies in this field; in the meantime, we should collect additional data in nonrandomized registries. In the Global Carotid Artery Stent Registry, which provides an insight into 'real-world' clinical practice around the world, the 30-day complication rate was

TABLE 5
Incidence of major adverse events within a 30-day follow-up (150 procedures)

Adverse event	Total
Number of procedures	150
Death from neurological reasons, %	0
Major stroke, %	0
Minor stroke, %	1.3
Primary end point, %	1.3

2.95% (15). However, several 'centres of excellence' have recently reported even better results, with death or stroke rates ranging from 0% to 2.6% (6,8,16,17).

Unlike our study, the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial (18) demonstrated very poor outcomes of patients treated with CAS. The strikingly different results may be due to a number of potential factors. In particular, the EVA-3S study included symptomatic patients treated by physicians with little experience; stents were implanted by physicians who had performed as few as five previous CAS procedures. Thus, we believe that the treatment of high-risk symptomatic patients and the individual investigator experience may have influenced the poor final results in this study by incorporating the individual learning curve. Thus, we strongly emphasize the crucial importance of long training (and a long learning curve). As has been stated repeatedly (14,19–21), the incidence of periprocedural events decreases with increasing operator experience. Therefore, it was recommended to perform a minimum of 30 supervised diagnostic cervicocerebral angiograms and 25 supervised CAS procedures before performing CAS independently (14). However, as has been shown recently (19), a much longer learning phase is expected for achieving competence in performing carotid interventions.

The present single-centre, single-operator study must be understood in the context of its limitations. First, all these procedures were performed by a single operator with personal experience of more than 500 procedures performed as a primary operator. Thus, this characteristic does not reflect the 'real-world' clinical practice of carotid interventions. On the other hand, this fact underlines the essential role of appropriate physician training and credentialing (20,21). Second, the number of included patients does not allow a reasonable subgroup analysis and identification of characteristics of the patients or lesions that may be associated with a different risk of complication.

CONCLUSIONS

Short-term outcomes of CAS in asymptomatic, surgically high-risk patients treated by a single operator suggest the low periprocedural complication rate is within the accepted ranges proposed for the treatment of carotid artery disease.

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