Long-Term Results of Carotid Artery Stents to Manage Symptomatic Carotid Artery Stenosis and Factors That Affect Outcome

Marc S. Randall, MRCP; Fiona M. McKeivitt, MD, MRCP; Sanjeev Kumar, MRCP; Trevor J. Cleveland, FRCS, FRCR; Keith Endean, BMed Sci; Graham S. Venables, DM, FRCP; Peter A. Gaines, FRCP, FRCR

Background—Limited data are available about the long-term outcomes of the use of carotid artery stents in symptomatic patients and the impact of patient variables on the durability of endovascular carotid procedures. Outcome data previously reported from registry series mix symptomatic and asymptomatic patients. We present analysis of long-term follow-up, with independent neurological assessment, for patients with symptomatic high-grade carotid lesions undergoing stenting to identify patients at risk of recurrence.

Methods and Results—Prospectively collected data on 563 carotid stenting procedures in a single center were analyzed. Univariate and multivariate techniques were used to identify risk groups and beneficial technical adaptations. Ipsilateral stroke rates for all patients were 4.8%, 7.0%, and 9.5% at 30 days, 1 year, and 4 years, respectively. The rates improved to 2.7%, 4.1%, and 4.5% when patients were treated with optimal therapy. Retinal events had a lower risk of long-term recurrent ipsilateral stroke (hazard ratio = 0.228, CI = 0.082 to 0.632, P = 0.004) than cerebral events. A recurrent or residual stenosis of >50% had a statistically significant effect on long-term stroke recurrence in multivariate analysis (hazard ratio = 2.187, CI = 1.173 to 4.078, P = 0.014).

Conclusions—Patients with retinal presentations are a lower risk group to treat. Residual stenosis or restenosis >50% has a statistically significant trend to an increased risk of recurrence for ipsilateral stroke in the long term in this population. In our patients, a combination of procedural modifications and pharmacological changes seems to improve outcomes. (Circ Cardiovasc Interv. 2010;3:50-56.)

Key Words: carotid arteries • stents • registries • stroke

Cerebrovascular disease costs the economies of the European Union €34 billion per annum, with 62% of these costs directly related to healthcare expenditure.1 Carotid artery disease is implicated in ~25% of ischemic stroke cases.2 North American Symptomatic Carotid Endarterectomy and European Carotid Surgery Trials’ trialists demonstrated the benefits of surgery over best available medical therapy at the time to prevent recurrent carotid territory ischemic events.3,4 Carotid stenting, an alternative to carotid endarterectomy, is undergoing evaluation in 4 multinational randomized controlled trials.5–8 Analysis of the 30-day outcomes of EVA-3S and Stent-Protected Angioplasty versus Carotid Endarterectomy5,8,9 has been published, and follow-up analysis of both these trials is in press. The 30-day outcomes from the International Carotid Stenting Study have been presented at the European Stroke Conference.10,11 When combined with the meta-analysis of carotid angioplasty trials, our data on possible risks from the stenting procedure are reasonably robust.12 The Stenting and Angioplasty With Protection In Patients at High Risk for Endarterectomy (SAPPHIRE) and Carotid Revascularization Using Endarterectomy or Stenting Systems investigators suggest noninferiority of the stenting procedure in short- and long-term follow-up when investigating mixed cohorts of symptomatic and asymptomatic patients.13–15

Clinical Perspective on p 56

The clinical trial data suggest that carotid stenting is as durable as carotid endarterectomy in the long term, although it may have higher risks periprocedurally at 30 days. In addition to trial data, cohort studies allow outcomes to be analyzed from representative clinical practice. All previous cohort studies contained both symptomatic and asymptomatic patients, the majority being asymptomatic patients.16–20 To

Received October 21, 2008; accepted October 27, 2009.
From the Neurology Department (M.S.R., F.M.M., S.K., K.E., G.S.V.), Sheffield Teaching Hospitals National Health Service Foundation Trust, Royal Hallamshire Hospital; and Sheffield Vascular Institute (T.J.C., P.A.G.), Sheffield Teaching Hospitals National Health Service Foundation Trust, Northern General Hospital, Sheffield, UK.

The online-only Data Supplement is available at http://circinterventions.ahajournals.org/cgi/content/full/CIRCINTERVENTIONS.108.828335/DC1. Correspondence to Marc Randall, MRCP, Neurology Department, Royal Hallamshire Hospital, Glossop Rd, Sheffield, S10 2JF, United Kingdom. E-mail m.randall@tiscali.co.uk
© 2010 American Heart Association, Inc.

Circ Cardiovasc Interv is available at http://circinterventions.ahajournals.org

DOI: 10.1161/CIRCINTERVENTIONS.108.828335
address this, we devised our cohort analysis on prospectively collected, audit department approved, stenting data of recently symptomatic patients only. We attempted to assess whether procedural factors, patient factors, or restenosis had any impact on long-term outcomes from stenting procedures. We focused on those highlighted by previous work from the European Carotid Surgery Trial data set and mixed cohorts of symptomatic and asymptomatic patients undergoing stenting.26,27

Methods

Patients with recent carotid territory, cerebral or retinal ischemia, and carotid artery stenosis >70% (North American Symptomatic Carotid Endarterectomy Trial criteria) on angiogram have been considered for endovascular carotid intervention in our center since 1993. Treatment recommendations are made by a neurology/vascular surgery/vascular radiology multidisciplinary team. All patients are screened with carotid duplex and brain CT. Patients with carotid artery stenoses of >60% on duplex undergo arch aortography or magnetic resonance angiography (MRA) to confirm the stenosis and anatomy of the carotid vessel origins. Patients suitable for either endarterectomy or stenting are invited to participate in randomized intervention trials. Patients unsuitable or unwilling to undergo carotid endarterectomy are offered carotid stenting outside of these trials.

Prospective data collection, including a preoperative assessment, for each patient is performed by a neurologist (M.S.R., F.M.K., S.K., or G.S.V.). The database is maintained in accordance with the National Health Service and Sheffield Teaching Hospital Clinical Effectiveness Unit Service Evaluation Audit policies (database registration 2212). Stenting procedures are performed by interventional vascular radiologists (T.J.C., P.A.G.). The techniques have been described in previous publications from our center.26,27 From 1996 to 2006, our stenting technique has developed to include the use of cerebral protection devices whenever possible and the mandatory use of dual antiplatelet therapy.27 Dual therapy with clopidogrel and aspirin continues for 28 days after stenting, before reverting to aspirin or, since 2004, aspirin and dipyridamole. A small number of patients undergoing stenting before 2002 received only a 14-day course of dual therapy.

Poststenting neurological assessment was performed by a neurologist at 24 hours or after discharge if earlier. Neurological complications were classified as Amaurosis fugax, monocular visual loss <24 hours; transient ischemic attack, new neurological deficit <24 hours; minor stroke, new neurological deficits >24 hours but <7 days; and major stroke, new neurological deficit persisting >7 days. The Oxford modified handicap score was used to distinguish nondisabling (score 0 to 2) from disabling stroke (score >3).28

Thirty-day and yearly follow-up was performed in specialist clinics by a neurologist or stroke specialist nurse/radiologist with neurological support. All patients underwent duplex ultrasound at 30 days, at yearly follow-up visits, or at time of recurrent event when possible to assess for restenosis. Validated criteria for restenosis have been used.29 Patients missing or lost to follow-up were traced and contacted by telephone. Deaths were confirmed from medical records or death certificates obtained from the General Register Office (www.gro.gov.uk). Data collection was not routinely performed in all patients after 5 years follow-up and therefore was censored at this point for the purposes of analysis.

Statistical Analysis

Statistical analysis was performed using the SPSS version 15.0.1 software package. Event rates per thousand patient years of follow-up were calculated. Univariate analysis was performed using Kaplan–Meier and Cox survival analysis. A Cox proportional hazards model for multivariate analysis using a 0.10 cutoff after colinear variables had been screened, and the least significant variable discarded was then used. The analysis was repeated with year of procedure forced into the model to see whether the global effect of improved technique and experience affected the outcomes. Restenosis was entered as a time-dependent variable in the modeling after assessment of residuals; age and year of procedure were similarly assessed for effect of time, and they were not shown to have a significant time-dependent element after assessment. Analysis was performed for end points of ipsilateral stroke, ipsilateral stroke or vascular death, and all stroke and death.

Possible predictors of 30-day outcomes were examined using the \( \chi^2 \) test for discrete data and Student \( t \) test for continuous data before undertaking multivariate analysis with use of multiple logistic regression. This analysis has been tabulated and included as additional data for online publication only.

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=563</td>
</tr>
<tr>
<td>Mean age, [range], y</td>
</tr>
<tr>
<td>Patients aged &gt;80 years old, %</td>
</tr>
<tr>
<td>Male, %</td>
</tr>
<tr>
<td>Carotid treated, left/right</td>
</tr>
<tr>
<td>Mean time from event, [range], mo</td>
</tr>
<tr>
<td>Treated within 1 month of symptoms</td>
</tr>
<tr>
<td>Presenting event, retinal/cerebral</td>
</tr>
<tr>
<td>Hypertensive*</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>Hypercholesterolemia†</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>Type II diabetes</td>
</tr>
<tr>
<td>Smoking history</td>
</tr>
<tr>
<td>Current smoker</td>
</tr>
<tr>
<td>Medication use at time of stent</td>
</tr>
<tr>
<td>Clopidogrel</td>
</tr>
<tr>
<td>Statin</td>
</tr>
<tr>
<td>( \beta )-blocker</td>
</tr>
<tr>
<td>ACE inhibitor/( \beta ) blocker</td>
</tr>
<tr>
<td>Stent design</td>
</tr>
<tr>
<td>Open:closed</td>
</tr>
<tr>
<td>Carotid wall stent</td>
</tr>
<tr>
<td>Precise</td>
</tr>
<tr>
<td>Protection device used</td>
</tr>
<tr>
<td>Any device</td>
</tr>
<tr>
<td>Filter EZ devices</td>
</tr>
<tr>
<td>Total amount of follow-up, patient years</td>
</tr>
</tbody>
</table>

*British Hypertension society guidelines (grade 1)50 or on medication.†Total cholesterol >5 mmol/L.‡ACE indicates angiotensin-converting enzyme; All, angiotensin II receptor blocker.

Results

Between March 1996 and August 2008, 562 carotid stenting procedures were performed on symptomatic carotid vessels, with follow-up until September 2008. The mean follow-up was 3.5 years, the median 4 years, and the range 30 days to 5 years. The presenting complaint was a retinal event in 144 (25.6%) cases. Baseline characteristics and rates of medication use at baseline of the patients treated are shown in Table 1. Hypertension was defined by internationally recognized criteria.50 Clopidogrel was used in addition to aspirin in 413 patients (73.6%).
At 4 years of follow-up, a total of 34 ipsilateral strokes had occurred. Of these events, 17 patients had a minor ipsilateral stroke and 12 patients had major ipsilateral strokes, and 5 stroke deaths had occurred. Applying Kaplan–Meier survival analysis to the entire data set allows for censored and missing data to be taken into account and predicts ipsilateral stroke rate percentages (±SE) of 4.8% (±0.9), 7.0% (±1.1), 8.0% (±1.2), 8.5% (±1.2), 9.5% (±1.3), and 10.7% (±1.5) at 30 days, 1, 2, 3, 4, and 5 years, respectively. Stroke rates were then recalculated for the “optimized” therapy of clopidogrel, statin, and embolic protection as well as for each of the elements individually. The rates for patients considered a high surgical risk by the SAPPHIRE trial criteria were also calculated, and no difference was seen between groups considered to be high and low risk (P=0.592). The results are tabulated in Table 2.

Table 2. Kaplan–Meier Calculated Ipsilateral Stroke-Free Survival Rates (Comparison With Mantel-Cox Log Rank Test)

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>30-Day Stroke-Free Survival, % (SE)</th>
<th>1-Year Stroke-Free Survival, % (SE)</th>
<th>4-Year Stroke-Free Survival, % (SE)</th>
<th>Log Rank P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>563</td>
<td>95.2 (0.9)</td>
<td>93.0 (1.1)</td>
<td>90.5 (1.3)</td>
</tr>
<tr>
<td>Optimal</td>
<td>296</td>
<td>97.3 (0.9)</td>
<td>95.9 (1.2)</td>
<td>95.2 (1.2)</td>
</tr>
<tr>
<td>Suboptimal</td>
<td>267</td>
<td>92.9 (1.4)</td>
<td>89.9 (1.9)</td>
<td>85.8 (2.2)</td>
</tr>
<tr>
<td>Protected</td>
<td>362</td>
<td>96.7 (0.9)</td>
<td>95.3 (1.1)</td>
<td>94.1 (1.3)</td>
</tr>
<tr>
<td>Unprotected</td>
<td>201</td>
<td>92.5 (1.9)</td>
<td>89.0 (2.2)</td>
<td>85.0 (2.6)</td>
</tr>
<tr>
<td>Statin</td>
<td>381</td>
<td>97.4 (0.8)</td>
<td>95.2 (1.1)</td>
<td>93.8 (1.3)</td>
</tr>
<tr>
<td>No statin</td>
<td>180</td>
<td>90.6 (2.2)</td>
<td>88.3 (2.4)</td>
<td>84.1 (2.6)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>413</td>
<td>97.3 (0.8)</td>
<td>95.6 (1.0)</td>
<td>94.1 (1.3)</td>
</tr>
<tr>
<td>No clopidogrel</td>
<td>148</td>
<td>89.2 (2.6)</td>
<td>85.2 (2.9)</td>
<td>81.3 (3.2)</td>
</tr>
<tr>
<td>High surgical risk</td>
<td>240</td>
<td>95.4 (1.4)</td>
<td>94.1 (1.5)</td>
<td>91.3 (2.0)</td>
</tr>
<tr>
<td>Low surgical risk</td>
<td>323</td>
<td>95.7 (1.1)</td>
<td>92.2 (1.5)</td>
<td>89.9 (1.7)</td>
</tr>
<tr>
<td>Trial patients</td>
<td>227</td>
<td>92.1 (1.8)</td>
<td>91.1 (1.1)</td>
<td>90.0 (2.0)</td>
</tr>
<tr>
<td>Non-trial patients</td>
<td>336</td>
<td>94.6 (1.2)</td>
<td>94.3 (1.3)</td>
<td>90.8 (1.8)</td>
</tr>
</tbody>
</table>

At 4 years of follow-up, a total of 34 ipsilateral strokes had occurred. Of these events, 17 patients had a minor ipsilateral stroke and 12 patients had major ipsilateral strokes, and 5 stroke deaths had occurred. Applying Kaplan–Meier survival analysis to the entire data set allows for censored and missing data to be taken into account and predicts ipsilateral stroke rate percentages (±SE) of 4.8% (±0.9), 7.0% (±1.1), 8.0% (±1.2), 8.5% (±1.2), 9.5% (±1.3), and 10.7% (±1.5) at 30 days, 1, 2, 3, 4, and 5 years, respectively. Stroke rates were then recalculated for the “optimized” therapy of clopidogrel, statin, and embolic protection as well as for each of the elements individually. The rates for patients considered a high surgical risk by the SAPPHIRE trial criteria were also calculated, and no difference was seen between groups considered to be high and low risk (P=0.592). The results are tabulated in Table 2.

To compare with previous groups, univariate survival analysis for end points of stroke, or stroke and vascular death, was performed using Kaplan–Meier and Cox proportional hazards analysis (Table 3). Crossing hazards on the Kaplan–Meier plots were tested for chance by testing for an interaction with time; no interaction was seen. Statistically significant variables on the outcome of recurrent ipsilateral stroke included mode of presentation (P<0.001), presence of hypercholesterolemia (P=0.003), the use of clopidogrel (P=0.001), statins (P<0.001), and protection devices (P<0.001), the presence of a recurrent stenosis of >50% (P=0.008) analyzed as time-dependent, and the calendar year of treatment (P=0.004). The supplemental Figure shows the Kaplan–Meier curves for these outcomes. Analysis was repeated for recurrent ipsilateral stroke or vascular death, and ipsilateral stroke or any death as outcome measures (Table 3).

Multivariate analysis was then applied to all the variables included in Table 3; after screening for confounders, a P=0.10 was used as the cutoff for backward selection; the remaining significant variables that were reassessed are shown in (Table 4). Retinal presentations (hazard ratio [HR]=0.228, CI=0.082 to 0.632, P=0.004) had lower risk of recurrent stroke, and the presence of persistent or recurrent stenosis of >50% (HR=2.187, CI=1.173 to 4.078, P=0.014) was a risk factor for recurrent ipsilateral stroke. Clopidogrel use during the procedure has an impact on reducing the risk for recurrent ipsilateral stroke (HR=0.318, CI=0.185 to 0.545, P<0.001). A further analysis was undertaken with calendar year of the procedure forced into the model but made no difference in the outcome.

Inspecting the Kaplan–Meier curves suggests that 30-day outcomes have a significant impact on long-term outcomes in common with previous publications.9,22,23 Univariate and multivariate analysis of 30-day outcomes was performed to identify these variables. The results of the univariate analysis can be seen in the supplemental Table. Multivariate logistic regression analysis showed cerebral presentation to have a hazard ratio 6 times greater than retinal presentation (HR=6.668, CI=1.498 to 26.689, P=0.013). Clopidogrel use (HR=0.291, CI=0.100 to 0.841, P=0.023) was shown to be an independent variable lowering ipsilateral stroke recurrence at 30 days with diabetes increasing the risk of an adverse event (HR=2.361, CI=1.052 to 5.302, P=0.037; Table 5).

Discussion

Publications in press from the randomized controlled trials suggest that, in the long term, carotid stenting appears to be as durable as carotid endarterectomy in preventing future vascular events despite a higher 30-day risk.10,11 They highlight that 30-day perioperative event rates contribute to the majority of the excess recurrence in stenting.10 Our Kaplan–Meier stroke-free survival rates for the complete data set 4.8% (±0.9), 7.0% (±1.1), 8.0% (±1.2), 8.5% (±1.2), 9.5% (±1.3), and 11.3% (±1.5) at 30 days, 1, 2, 3, 4, and 5 years, respectively, compare favorably with the data from the randomized controlled trials of carotid stenting and surgery, suggesting that the durability of the procedure can be maintained when patients not conforming to randomized control trial entrance criteria are included in outcome analysis.3,10,11,20,31

Outside of a randomized controlled trial, patient selection is less rigorous and exclusive, and comparative cohort studies such as this one are useful to support data from randomized
controlled trials in real-life situations by including patients not eligible for trials. To date, one other cohort study stenting purely symptomatic patients, with a mean follow-up 25 months, has been published. The focus of this study was on the impact of stents in place of angioplasty to prevent restenosis, not on the identification of alternative risk factors undertaken in this analysis. Stent use did significantly reduce rates of restenosis of $\frac{70}{100}$% but did not affect long-term outcome measures. However, the role of restenosis on recurrent outcomes in patients with stents has yet to be proven, and the Stent-Protected Angioplasty versus Carotid Endarterectomy and SAPPHIRE groups disagree over its rate in comparison with endarterectomy.

The purpose of our analysis was to look at multiple factors affecting long-term stroke-free survival, using elements suggested previously to affect outcome, to see whether they are true

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate Assessment Causing Recurrent Ipsilateral Stroke, Stroke, and Vascular Death, and Stroke or any Death With Time Poststent Insertion (Kaplan–Meier Analysis for Nominal Variables and COX Analysis for Continuous and Time Dependent Variables)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, M:F</td>
<td>Sex, M:F</td>
</tr>
<tr>
<td>Side treated, L:R</td>
<td>Side treated, L:R</td>
</tr>
<tr>
<td>Clinical trial, Y:N</td>
<td>Clinical trial, Y:N</td>
</tr>
<tr>
<td>SAPPHIRE risk, low:high</td>
<td>SAPPHIRE risk, low:high</td>
</tr>
<tr>
<td>Age, &lt;80:≥80, y</td>
<td>Age, &lt;80:≥80, y</td>
</tr>
<tr>
<td>Presentation, retinal:cerebral</td>
<td>Presentation, retinal:cerebral</td>
</tr>
<tr>
<td>Stent design, open:closed</td>
<td>Stent design, open:closed</td>
</tr>
<tr>
<td>Hypertension, Y:N</td>
<td>Hypertension, Y:N</td>
</tr>
<tr>
<td>IHD, Y:N</td>
<td>IHD, Y:N</td>
</tr>
<tr>
<td>Smoking history, Y:N</td>
<td>Smoking history, Y:N</td>
</tr>
<tr>
<td>Diabetes, Y:N</td>
<td>Diabetes, Y:N</td>
</tr>
<tr>
<td>Clopidogrel, Y:N</td>
<td>Clopidogrel, Y:N</td>
</tr>
<tr>
<td>Statin, Y:N</td>
<td>Statin, Y:N</td>
</tr>
<tr>
<td>ACE/All inhibitors, Y:N</td>
<td>ACE/All inhibitors, Y:N</td>
</tr>
<tr>
<td>Protection device, Y:N</td>
<td>Protection device, Y:N</td>
</tr>
<tr>
<td>Age, y</td>
<td>Age, y</td>
</tr>
<tr>
<td>Delay to treatment, mo</td>
<td>Delay to treatment, mo</td>
</tr>
<tr>
<td>Restenosis &gt;50%</td>
<td>Restenosis &gt;50%</td>
</tr>
<tr>
<td>Year of treatment</td>
<td>Year of treatment</td>
</tr>
</tbody>
</table>
| ACE indicates angiotensin-converting enzyme; All, angiotensin II receptor blocker; IHD, ischemic heart disease; M, male; F, female; L, left; R, right; Y, yes; N, no; U, unknown.

Table 4. Multivariate Assessment Using Cox Proportional Hazards Assessment of Independent Contribution Toward Further Ipsilateral Stroke, Stroke or Vascular Death, and Stroke and any Death Poststent Insertion

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>1.019</td>
<td>(0.994 to 1.045)</td>
<td>0.129</td>
<td>1.037</td>
<td>(1.016 to 1.059)</td>
<td>0.001</td>
<td>1.043</td>
<td>(1.021 to 1.066)</td>
<td>0.001</td>
</tr>
<tr>
<td>Retinal presentation</td>
<td>0.228</td>
<td>(0.082 to 0.632)</td>
<td>0.004</td>
<td>0.278</td>
<td>(0.128 to 0.605)</td>
<td>0.001</td>
<td>0.460</td>
<td>(0.271 to 0.780)</td>
<td>0.004</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.693</td>
<td>(0.919 to 3.118)</td>
<td>0.091</td>
<td>2.091</td>
<td>(1.267 to 3.451)</td>
<td>0.004</td>
<td>1.921</td>
<td>(1.269 to 2.908)</td>
<td>0.002</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>0.318</td>
<td>(0.185 to 0.545)</td>
<td>&lt;0.001</td>
<td>0.427</td>
<td>(0.270 to 0.706)</td>
<td>0.002</td>
<td>0.928</td>
<td>(0.873 to 0.987)</td>
<td>0.017</td>
</tr>
<tr>
<td>Statin</td>
<td>1.655</td>
<td>(0.805 to 3.403)</td>
<td>0.170</td>
<td>2.187</td>
<td>(1.173 to 4.078)</td>
<td>0.014</td>
<td>1.148</td>
<td>(0.603 to 2.186)</td>
<td>0.674</td>
</tr>
<tr>
<td>β-blocker</td>
<td>0.424</td>
<td>(0.296 to 0.608)</td>
<td>&lt;0.001</td>
<td>0.370</td>
<td>(0.177 to 0.775)</td>
<td>0.008</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
independent predictors of recurrent events.\textsuperscript{21} Our long-term experience of stenting symptomatic carotid vessels presented here provides evidence for the combined benefits of the individual elements now making up the perceived minimum standard of care for a stenting procedure, but individual effects of pharmacological agents on recurrent events were of particular interest.\textsuperscript{27,32} Numerous modifications to the carotid stenting procedure have occurred in a short space of time, making determination of the individual changes difficult to detect any other way. It would now be impossible to reverse developments and assess each change individually. The heart protection study in 2002\textsuperscript{33} showed that all stroke or transient ischemic attack (TIA) patients, and therefore any patient requiring carotid stenting for a symptomatic carotid stenosis should be offered statin therapy. Therefore, the effects of statin therapy on the long-term outcomes from stenting can now only be assessed with this form of multivariate analysis and not a randomized controlled trial. Dual antiplatelet therapy with aspirin and clopidogrel is another example of what has become standard therapy at our institution since 2002 after clear benefit of the regimen on 30-day outcomes was shown in a randomized trial comparing this therapy with aspirin and heparin.\textsuperscript{27}

Table 5. Multivariate Analysis of Variables Effect on 30-Day Outcome From Stroke, Stroke and Vascular Death, and Stroke and Death (Multiple Logistic Regression Analysis)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Ipsilateral Stroke</th>
<th></th>
<th>Ipsilateral Stroke or Vascular Death</th>
<th></th>
<th>Ipsilateral Stroke or Death</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>P</td>
<td>HR 95% CI</td>
<td>P</td>
<td>HR 95% CI</td>
<td>P</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.599 0.257 to 1.397 0.236</td>
<td></td>
<td>0.641 0.285 to 1.437 0.280</td>
<td></td>
<td>0.768 0.359 to 1.640 0.495</td>
<td></td>
</tr>
<tr>
<td>Side treated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>1.066 0.512 to 2.219 0.865</td>
<td></td>
<td>1.089 0.539 to 2.201 0.811</td>
<td></td>
<td>1.279 0.647 to 2.530 0.479</td>
<td></td>
</tr>
<tr>
<td>Trial enrolment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.781 0.844 to 3.761 0.130</td>
<td></td>
<td>1.756 0.855 to 1.437 0.125</td>
<td></td>
<td>1.526 0.763 to 3.052 0.232</td>
<td></td>
</tr>
<tr>
<td>SAPHIRE risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>2.792 0.205 to 38.073 0.441</td>
<td></td>
<td>1.305 0.148 to 11.548 0.811</td>
<td></td>
<td>0.730 0.075 to 7.112 0.786</td>
<td></td>
</tr>
<tr>
<td>Presenting event</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebral</td>
<td>6.668 1.498 to 26.689 0.013</td>
<td></td>
<td>7.169 1.624 to 31.641 0.009</td>
<td></td>
<td>3.135 1.059 to 9.282 0.039</td>
<td></td>
</tr>
<tr>
<td>Stent design</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>1.289 0.460 to 3.610 0.629</td>
<td></td>
<td>1.193 0.437 to 3.258 0.731</td>
<td></td>
<td>1.147 0.427 to 3.077 0.786</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>0.739 0.324 to 1.683 0.471</td>
<td></td>
<td>0.637 0.286 to 1.418 0.270</td>
<td></td>
<td>0.689 0.321 to 1.482 0.341</td>
<td></td>
</tr>
<tr>
<td>IHD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.207 0.017 to 2.438 0.208</td>
<td></td>
<td>0.488 0.063 to 3.782 0.492</td>
<td></td>
<td>0.930 0.107 to 8.077 0.947</td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.498 0.227 to 1.093 0.082</td>
<td></td>
<td>0.452 0.214 to 0.951 0.036</td>
<td></td>
<td>0.589 0.284 to 1.223 0.155</td>
<td></td>
</tr>
<tr>
<td>Diabetic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.361 1.052 to 5.302 0.037</td>
<td></td>
<td>1.958 0.887 to 4.323 0.097</td>
<td></td>
<td>1.439 0.652 to 3.178 0.368</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.291 0.100 to 0.841 0.023</td>
<td></td>
<td>0.310 0.112 to 0.855 0.024</td>
<td></td>
<td>0.300 0.112 to 0.807 0.017</td>
<td></td>
</tr>
<tr>
<td>Statin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.498 0.206 to 1.203 0.121</td>
<td></td>
<td>0.568 0.244 to 1.324 0.190</td>
<td></td>
<td>0.543 0.239 to 1.231 0.144</td>
<td></td>
</tr>
<tr>
<td>β-blocker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.297 0.425 to 3.956 0.648</td>
<td></td>
<td>1.093 0.369 to 3.241 0.873</td>
<td></td>
<td>1.074 0.373 to 3.092 0.895</td>
<td></td>
</tr>
<tr>
<td>ACE/All blocker</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.809 0.281 to 2.280 0.689</td>
<td></td>
<td>0.668 0.245 to 1.824 0.431</td>
<td></td>
<td>0.821 0.319 to 2.118 0.684</td>
<td></td>
</tr>
<tr>
<td>Protection device</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.018 0.332 to 3.116 0.976</td>
<td></td>
<td>1.018 0.350 to 2.961 0.974</td>
<td></td>
<td>1.158 0.414 to 3.235 0.780</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>0.494 0.054 to 4.534 0.533</td>
<td></td>
<td>0.934 0.170 to 5.114 0.937</td>
<td></td>
<td>0.942 0.179 to 4.969 0.944</td>
<td></td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme; All, angiotensin II receptor blocker; IHD, ischemic heart disease.
clopidogrel on long-term outcomes is likely to be due to its dramatic effects at 30 days. This raises questions about the possible benefits of prolonging poststenting clopidogrel therapy to see whether this benefit can be extended.

In common with the endarterectomy trials, we have confirmed that retinal events have a significantly lower risk of future recurrence than cortical events.21,35 A significant proportion of this is due to the effect on 30-day outcomes shown here and by other authors.23 Our analysis has also highlighted that recurrent stenosis of >50% is likely to contribute as an independent risk factor for an event. This effect appears to date from the time of the procedure in some cases and therefore must represent residual stenosis from the procedure because restenosis could not have developed in this time. If this can be confirmed in analysis of another cohort, it suggests very strongly to all carotid stenting practitioners that they should not leave a high-grade residual stenosis. It is also noted that statistical analysis of our patients is suggesting that restenosis may be protective against the combined end point of recurrent stroke and all death. However, this is most likely a statistical anomaly and probably reflects the fact that death from other cause is affecting a greater proportion of these patients at 4-year follow-up, diluting the impact of the restenosis on the outcome of stroke.

This analysis has investigated variables only previously subjected to univariate analysis in other studies. The impact of preexisting ischemic heart disease on any of the outcome measures suggested by previous studies17 has not been demonstrated. Increasing age has also been previously shown to be a risk factor for 30-day adverse events9,36 but this was not confirmed in our series analyzed as either a continuous or nominal (age >80) variable for short- and long-term outcomes in common with another recently published series.24 It is clear from this analysis that detection of effects from individual changes in procedural technique is not likely to be possible with data available to us. However, when the therapies are analyzed as a combination, the impact on outcome is dramatic in the long term. Before all patients received dual antiplatelet therapy, statin therapy, and the routine use of a protection device, 7.2% of patients experienced recurrent ipsilateral stroke at 30 days; when these therapies became standard, the rates reduced to 2.6%. The benefits are then continued into long-term follow-up and impact on the Kaplan–Meier calculated outcomes at 1, 2, and 3 years. It is therefore important that the effect of these procedural developments is considered when analysis of the randomized trials is performed and may explain some of the differences demonstrated between endarterectomy and stenting at 30 days in Stent-Protected Angioplasty versus Carotid Endarterectomy, EVA-3S, and the International Carotid Stenting Study recently presented at the European Stroke Conference.

Previous cohort studies had limitations that we attempted to minimize in our analysis by using larger numbers, purely symptomatic patients, and longer follow-up. Our study analyzes symptomatic patients in a center performing endovascular carotid intervention since 1993 and carotid stenting since 1995. This minimizes the “learning curve effect” on the outcomes in most of the patients described here.37,38 The year the procedure was undertaken was forced into the multivariate analysis to account for learning and changing technique and was not shown to be independently significant. Our study is not without limitations. Prospectively collected data in sequential patients overcomes recall bias but missed patients introduce selection bias. Our cohort also includes symptomatic patients felt to be unsuitable for carotid endarterectomy due to high surgical risk and anatomic or morphological reasons, but this did not seem to affect outcomes when analyzed by inclusion in a trial or by SAPPHIRE risk.9–11 Our patients were evaluated by a neurologist, not the interventionalist, after the procedure to reduce underreporting of outcomes and may have led to a higher detection rate of minor neurological events.

This study is presently the most extensive multivariate cohort analysis of purely symptomatic patients under follow-up and has attempted to assess the impact of restenosis and time to restenosis. The effects of individual procedural changes are too small to detect, but it suggests that optimal patient selection and combination therapy has the most significant impact on long-term outcome and complications at 30 days. The issue of residual stenosis or restenosis of >50% has been highlighted as a possible risk factor for recurrent stroke events and needs more investigation, but in the first instance practitioners should ensure that they leave as little residual stenosis as possible.

Sources of Funding
Dr Randall received wage payments from 2002 to 2004 from a central research fund to which Boston Scientific, who manufacture stents and protection devices used in some of the patients in this study, previously contributed.

Disclosures
None.

References


---

**CLINICAL PERSPECTIVE**

This article reviews routine carotid stenting practice in a cohort of purely symptomatic patients focusing on patient and procedural factors that influence long-term outcome. This sort of analysis has never previously been published to our knowledge and compliments the new data available from the recently published carotid stenting studies. It has highlighted the possible importance of residual stenosis at the time of stenting or restenosis of >50% as a possible risk factor for future stroke recurrence. This important finding needs further validation in another cohort of patients. We have also shown that some factors previously felt to affect long-term outcomes in univariate analysis have a more limited impact than previously thought. Clinicians and patients should also be aware that stenting in patients with cerebral events seems to have up to 6 times the risk of retinal events. It has not been possible with our cohort to determine the individual benefits of each of the procedural changes in the carotid stenting process, but we have shown that the modern therapies applied during stenting have significant benefits.
Long-Term Results of Carotid Artery Stents to Manage Symptomatic Carotid Artery Stenosis and Factors That Affect Outcome
Marc S. Randall, Fiona M. McKevitt, Sanjeev Kumar, Trevor J. Cleveland, Keith Endean, Graham S. Venables and Peter A. Gaines

Circ Cardiovasc Inter. published online January 26, 2010;
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/early/2010/01/26/CIRCINTERVENTIONS.108.828335

Data Supplement (unedited) at:
http://circinterventions.ahajournals.org/content/suppl/2010/02/16/CIRCINTERVENTIONS.108.828335.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Interventions can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Interventions is online at:
http://circinterventions.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL

Supplemental Tables and figures

Table A

Figure 1
Table A  Univariable assessment of variables influence on 30 day outcomes from stroke and stroke and vascular death.

(Chi square, Fishers and Student T test) (online only)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of patients</th>
<th>Ipsilateral Stroke</th>
<th>Ipsilateral Stroke or Vascular Death</th>
<th>Ipsilateral Stroke or any Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>% stroke rate</td>
<td>p</td>
<td>% stroke rate</td>
</tr>
<tr>
<td>Sex</td>
<td>M : F 380 : 182</td>
<td>6.8 : 5.5</td>
<td>0.587</td>
<td>7.4 : 6.0</td>
</tr>
<tr>
<td>Side treated</td>
<td>L : R 282 : 281</td>
<td>7.1 : 5.7</td>
<td>0.606</td>
<td>7.8 : 6.1</td>
</tr>
<tr>
<td>Clinical trial</td>
<td>Y : N 227 : 363</td>
<td>7.9 : 5.4</td>
<td>0.226</td>
<td>8.4 : 6.0</td>
</tr>
<tr>
<td>SAPPHIRE risk</td>
<td>Low : High 324 : 239</td>
<td>7.1 : 5.5</td>
<td>0.489</td>
<td>7.4 : 6.3</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;80 : &gt;80 497 : 65</td>
<td>6.5 : 6.2</td>
<td>0.927</td>
<td>6.9 : 7.7</td>
</tr>
<tr>
<td>Presentation</td>
<td>Retinal : Cerebral 144 : 419</td>
<td>1.4 : 8.1</td>
<td>0.003</td>
<td>1.4 : 8.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Y : N 376 : 185</td>
<td>6.7 : 5.9</td>
<td>0.855</td>
<td>7.5 : 5.9</td>
</tr>
<tr>
<td>IHD</td>
<td>Y : N 199 : 362</td>
<td>5.1 : 7.2</td>
<td>0.372</td>
<td>6.1 : 7.5</td>
</tr>
<tr>
<td>Hypercholesteri &lt; Y : N : DK 442 : 86 :</td>
<td>4.5 : 11.6 : 18.2</td>
<td>0.001</td>
<td>5.0 : 11.6 : 21.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Smoking Hx</td>
<td>Y : N 427 : 134</td>
<td>5.4 : 9.7</td>
<td>0.104</td>
<td>5.6 : 11.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Y : N 99 : 462</td>
<td>11.1 : 5.4</td>
<td>0.043</td>
<td>11.1 : 6.1</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Y : N 413 : 148</td>
<td>3.6 : 14.2</td>
<td>&lt; 0.001</td>
<td>4.1 : 14.9</td>
</tr>
<tr>
<td>Statin</td>
<td>Y : N 381 : 180</td>
<td>3.9 : 11.7</td>
<td>0.001</td>
<td>4.5 : 12.2</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>Y : N 77 : 484</td>
<td>6.6 : 6.4</td>
<td>0.954</td>
<td>7.0 : 6.6</td>
</tr>
<tr>
<td>ACE / AII block</td>
<td>Y : N 145 : 416</td>
<td>4.1 : 7.2</td>
<td>0.239</td>
<td>4.1 : 8.0</td>
</tr>
<tr>
<td>Protection device</td>
<td>Y : N 362 : 208</td>
<td>4.2 : 10.4</td>
<td>0.006</td>
<td>4.7 : 10.9</td>
</tr>
<tr>
<td>Age</td>
<td>years 0.243</td>
<td></td>
<td></td>
<td>0.243</td>
</tr>
<tr>
<td>Delay to Tx</td>
<td>months 0.301</td>
<td></td>
<td></td>
<td>0.245</td>
</tr>
<tr>
<td>Year of treatment</td>
<td></td>
<td>0.010</td>
<td></td>
<td>0.017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
</tbody>
</table>
Figure 1 Kaplan Meier Curves of variables assessed in Univariable analysis for the outcome of recurrent ipsilateral stroke. Comparison between variables with Log Rank statistic. (online only)
Statin use at time of Stent

Beta blocker use at time of stent

ACE inhibitor / A2 blocker use at stent insertion

Protection device used during stenting procedure