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

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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
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,16,18,22–24

**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 aortography25 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.28 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.

Poststenotting 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 deficits ≤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).29

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.

**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.30 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.

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 recent 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 of 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 $\geq 70\%$ 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 3. 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)

<table>
<thead>
<tr>
<th>Variable</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>Event Rate/1000 Patient Years Follow-up</td>
<td>Event Rate/1000 Patient Years Follow-up</td>
<td>Event Rate/1000 Patient Years Follow-up</td>
</tr>
<tr>
<td>Sex, M:F</td>
<td>0.07:0.17</td>
<td>0.11:0.22</td>
<td>0.17:0.32</td>
</tr>
<tr>
<td>Side treated, L:R</td>
<td>0.10:0.10</td>
<td>0.14:0.15</td>
<td>0.24:0.20</td>
</tr>
<tr>
<td>Clinical trial, Y:N</td>
<td>0.13:0.08</td>
<td>0.19:0.12</td>
<td>0.26:0.19</td>
</tr>
<tr>
<td>SAPPHIRE risk, low:high</td>
<td>0.09:0.11</td>
<td>0.11:0.20</td>
<td>0.15:0.35</td>
</tr>
<tr>
<td>Age, &lt;80:&lt;80, y</td>
<td>0.06:0.36</td>
<td>0.08:0.90</td>
<td>0.11:0.91</td>
</tr>
<tr>
<td>Presentation, retinal:cerebral</td>
<td>0.05:0.08</td>
<td>0.10:0.12</td>
<td>0.22:0.18</td>
</tr>
<tr>
<td>Stent design, open:closed</td>
<td>0.27:0.06</td>
<td>0.46:0.09</td>
<td>0.53:0.14</td>
</tr>
<tr>
<td>Hypertension, Y:N</td>
<td>0.07:0.17</td>
<td>0.11:0.23</td>
<td>0.17:0.34</td>
</tr>
<tr>
<td>IHD, Y:N</td>
<td>0.15:0.08</td>
<td>0.24:10.0</td>
<td>0.42:0.14</td>
</tr>
<tr>
<td>Hypercholesterolemia, Y:N/U</td>
<td>0.05:0.68:1.73</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking history, Y:N</td>
<td>0.06:0.24</td>
<td>0.09:0.32</td>
<td>0.15:0.45</td>
</tr>
<tr>
<td>Diabetes, Y:N</td>
<td>0.46:0.05</td>
<td>0.73:0.08</td>
<td>1.03:0.12</td>
</tr>
<tr>
<td>Clopidogrel, Y:N</td>
<td>0.04:0.33</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin, Y:N</td>
<td>0.04:0.25</td>
<td>0.07:0.35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>β-blocker, Y:N</td>
<td>0.50:0.06</td>
<td>0.55:0.08</td>
<td>0.82:0.13</td>
</tr>
<tr>
<td>ACE/All inhibitors, Y:N</td>
<td>0.13:0.07</td>
<td>0.21:0.10</td>
<td>0.32:0.16</td>
</tr>
<tr>
<td>Protection device, Y:N</td>
<td>0.05:0.20</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### 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>Ipsilateral Stroke</th>
<th>Ipsilateral Stroke or Vascular Death</th>
<th>Ipsilateral Stroke or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>Age, y</td>
<td>1.019 (0.994 to 1.045)</td>
<td>0.129</td>
<td>1.031 (1.016 to 1.059)</td>
</tr>
<tr>
<td>Delay to treatment, mo</td>
<td>1.101 (0.980 to 1.237)</td>
<td>0.106</td>
<td>1.079 (0.976 to 1.194)</td>
</tr>
<tr>
<td>Restenosis &gt;50%</td>
<td>0.412 (0.215 to 0.789)</td>
<td>0.008</td>
<td>0.511 (0.270 to 0.965)</td>
</tr>
<tr>
<td>Year of treatment</td>
<td>0.843 (0.770 to 0.924)</td>
<td>&lt;0.001</td>
<td>0.860 (0.796 to 0.929)</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.
independent predictors of recurrent events.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.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 200233 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.27

Multivariate analysis in this case showed that only clopidogrel had clear independent benefit on the outcomes of ipsilateral stroke and vascular death in the long-term follow-up, despite statin and clopidogrel therapy appearing to be beneficial in univariate analysis. We have not, as we had hoped, been able to separate out individual effects of the other pharmacological therapies, and this may never be possible as most were introduced around the same time. The impact of

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></th>
<th>Ipsilateral Stroke or Vascular Death</th>
<th></th>
<th></th>
<th>Ipsilateral Stroke or Death</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
<td>P</td>
<td>HR</td>
<td>95% CI</td>
<td>P</td>
<td>HR</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>Sex</td>
<td>Female</td>
<td>0.599</td>
<td>0.257 to 1.397</td>
<td>0.236</td>
<td>0.641</td>
<td>0.285 to 1.437</td>
<td>0.280</td>
<td>0.768</td>
<td>0.359 to 1.640</td>
</tr>
<tr>
<td></td>
<td>Side treated</td>
<td>Left</td>
<td>1.066</td>
<td>0.512 to 2.219</td>
<td>0.865</td>
<td>1.089</td>
<td>0.539 to 2.201</td>
<td>0.811</td>
<td>1.279</td>
</tr>
<tr>
<td></td>
<td>Trial enrolment</td>
<td>Yes</td>
<td>1.781</td>
<td>0.844 to 3.761</td>
<td>0.130</td>
<td>1.756</td>
<td>0.855 to 1.437</td>
<td>0.125</td>
<td>1.526</td>
</tr>
<tr>
<td></td>
<td>SAPHIRE risk</td>
<td>High</td>
<td>2.792</td>
<td>0.205 to 38.073</td>
<td>0.441</td>
<td>1.305</td>
<td>0.148 to 11.548</td>
<td>0.811</td>
<td>0.730</td>
</tr>
<tr>
<td>Presenting event</td>
<td>Cerebral</td>
<td></td>
<td>6.668</td>
<td>1.498 to 26.689</td>
<td>0.013</td>
<td>7.169</td>
<td>1.624 to 31.641</td>
<td>0.009</td>
<td>3.135</td>
</tr>
<tr>
<td></td>
<td>Stent design</td>
<td>Open</td>
<td>1.289</td>
<td>0.460 to 3.610</td>
<td>0.629</td>
<td>1.193</td>
<td>0.437 to 3.258</td>
<td>0.731</td>
<td>1.147</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>No</td>
<td>0.739</td>
<td>0.324 to 1.683</td>
<td>0.471</td>
<td>0.637</td>
<td>0.286 to 1.418</td>
<td>0.270</td>
<td>0.689</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHD</td>
<td></td>
<td>Yes</td>
<td>0.207</td>
<td>0.017</td>
<td>2.438</td>
<td>0.208</td>
<td>0.488</td>
</tr>
<tr>
<td></td>
<td>Smoking history</td>
<td>Yes</td>
<td>0.498</td>
<td>0.227 to 1.093</td>
<td>0.082</td>
<td>0.452</td>
<td>0.214 to 0.951</td>
<td>0.036</td>
<td>0.589</td>
</tr>
<tr>
<td></td>
<td>Diabetic</td>
<td>Yes</td>
<td>2.361</td>
<td>1.052 to 5.302</td>
<td>0.037</td>
<td>1.958</td>
<td>0.887 to 4.323</td>
<td>0.097</td>
<td>1.439</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
<td>Yes</td>
<td>0.291</td>
<td>0.100 to 0.841</td>
<td>0.023</td>
<td>0.310</td>
<td>0.112 to 0.855</td>
<td>0.024</td>
<td>0.300</td>
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<tr>
<td></td>
<td>Statin</td>
<td>Yes</td>
<td>0.498</td>
<td>0.206 to 1.203</td>
<td>0.121</td>
<td>0.568</td>
<td>0.244 to 1.324</td>
<td>0.190</td>
<td>0.543</td>
</tr>
<tr>
<td></td>
<td>β-blocker</td>
<td>Yes</td>
<td>1.297</td>
<td>0.425 to 3.956</td>
<td>0.648</td>
<td>1.093</td>
<td>0.369 to 3.241</td>
<td>0.873</td>
<td>1.074</td>
</tr>
<tr>
<td></td>
<td>ACE/All blocker</td>
<td>Yes</td>
<td>0.809</td>
<td>0.281 to 2.280</td>
<td>0.689</td>
<td>0.668</td>
<td>0.245 to 1.824</td>
<td>0.431</td>
<td>0.821</td>
</tr>
<tr>
<td></td>
<td>Protection device</td>
<td>Yes</td>
<td>1.018</td>
<td>0.332 to 3.116</td>
<td>0.976</td>
<td>1.018</td>
<td>0.350 to 2.961</td>
<td>0.974</td>
<td>1.158</td>
</tr>
<tr>
<td>Age, y</td>
<td>&gt;80</td>
<td></td>
<td>0.494</td>
<td>0.054 to 4.534</td>
<td>0.533</td>
<td>0.934</td>
<td>0.170 to 5.114</td>
<td>0.937</td>
<td>0.942</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 poststensting clopidogrel ther-
rapy to see whether this benefit can be extended.34

In common with the endarterectomy trials, we have con-
firmed that retinal events have a significantly lower risk of
future recurrence than cortical events.21,38 A significant pro-
portion 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 sub-
jected to univariate analysis in other studies. The impact of
preexisting ischemic heart disease on any of the outcome
measures suggested by previous studies8 has not been dem-
onstrated. Increasing age has also been previously shown to be
a risk factor for 30-day adverse events,9,36 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 devel-
opments is considered when analysis of the randomized trials is
performed and may explain some of the differences demon-
strated 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 ca-
rotid 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 limi-
tations. Prospectively collected data in sequential patients over-
comes recall bias but missed patients introduce selection bias.
Our cohort also includes symptomatic patients felt to be unsuit-
able 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 neurolo-
gist, 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.

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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.

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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

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SUPPLEMENTAL MATERIAL

Supplemental Tables and figures

Table A

Figure 1
<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 p</td>
<td>% stroke rate p</td>
<td>% stroke rate p</td>
</tr>
<tr>
<td>Sex</td>
<td>M : F 380 : 182</td>
<td>6.8 : 5.5 0.587</td>
<td>7.4 : 6.0 0.723</td>
<td>7.6 : 6.6 0.731</td>
</tr>
<tr>
<td>Side treated</td>
<td>L : R 282 : 281</td>
<td>7.1 : 5.7 0.606</td>
<td>7.8 : 6.1 0.507</td>
<td>8.5 : 6.1 0.331</td>
</tr>
<tr>
<td>Clinical trial</td>
<td>Y : N 227 : 363</td>
<td>7.9 : 5.4 0.226</td>
<td>8.4 : 6.0 0.311</td>
<td>8.4 : 6.6 0.415</td>
</tr>
<tr>
<td>SAPPHIRE risk</td>
<td>Low : High 324 : 239</td>
<td>7.1 : 5.5 0.489</td>
<td>7.4 : 6.3 0.737</td>
<td>8.0 : 6.3 0.513</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;80 : &gt;80 497 : 65</td>
<td>6.5 : 6.2 0.927</td>
<td>6.9 : 7.7 0.795</td>
<td>7.5 : 6.2 0.704</td>
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<tr>
<td>Presentation</td>
<td>Retinal : Cerebral 144 : 419</td>
<td>1.4 : 8.1 0.003</td>
<td>1.4 : 8.8 &lt;0.001</td>
<td>2.8 : 8.8 0.015</td>
</tr>
<tr>
<td>Stent design</td>
<td>Open : Closed 91 : 470</td>
<td>6.7 : 6.4 0.891</td>
<td>7.0 : 6.7 0.904</td>
<td>6.7 : 7.4 0.795</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Y : N 376 : 185</td>
<td>6.7 : 5.9 0.855</td>
<td>7.5 : 5.9 0.598</td>
<td>7.7 : 6.5 0.731</td>
</tr>
<tr>
<td>IHD</td>
<td>Y : N 199 : 362</td>
<td>5.1 : 7.2 0.372</td>
<td>6.1 : 7.5 0.605</td>
<td>6.6 : 7.7 0.735</td>
</tr>
<tr>
<td>Hypercholesterole</td>
<td>Y : N : DK 442 : 86 : 33</td>
<td>4.5 : 11.6 : 18.2 0.001</td>
<td>5.0 : 11.6 : 21.2 &lt;0.001</td>
<td>5.2 : 12.8 : 21.2 &lt;0.001</td>
</tr>
<tr>
<td>Smoking Hx</td>
<td>Y : N 427 : 134</td>
<td>5.4 : 9.7 0.104</td>
<td>5.6 : 11.2 &lt;0.001</td>
<td>6.3 : 10.4 0.128</td>
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<tr>
<td>Diabetes</td>
<td>Y : N 99 : 462</td>
<td>11.1 : 5.4 0.043</td>
<td>11.1 : 6.1 0.083</td>
<td>10.1 : 6.7 0.285</td>
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<tr>
<td>Clopidogrel</td>
<td>Y : N 413 : 148</td>
<td>3.6 : 14.2 &lt;0.001</td>
<td>4.1 : 14.9 &lt;0.001</td>
<td>4.4 : 15.5 &lt;0.001</td>
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<tr>
<td>Statin</td>
<td>Y : N 381 : 180</td>
<td>3.9 : 11.7 0.001</td>
<td>4.5 : 12.2 0.001</td>
<td>4.7 : 12.8 &lt;0.001</td>
</tr>
<tr>
<td>Beta Blocker</td>
<td>Y : N 77 : 484</td>
<td>6.6 : 6.4 0.954</td>
<td>7.0 : 6.6 0.887</td>
<td>6.6 : 7.4 0.789</td>
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<tr>
<td>ACE / AII block</td>
<td>Y : N 145 : 416</td>
<td>4.1 : 7.2 0.239</td>
<td>4.1 : 8.0 0.133</td>
<td>4.8 : 8.2 0.200</td>
</tr>
<tr>
<td>Protection device</td>
<td>Y : N 362 : 208</td>
<td>4.2 : 10.4 0.006</td>
<td>4.7 : 10.9 0.009</td>
<td>5.0 : 11.4 0.006</td>
</tr>
<tr>
<td>Age</td>
<td>years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delay to Tx</td>
<td>months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year of treatment</td>
<td></td>
<td></td>
<td></td>
<td>0.010 0.017 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)