Intracranial Stent Placement for Symptomatic Intracranial Stenosis as Part of a Clinical Trial Versus Outside a Clinical Trial

Farhan Siddiq, MD; Malik M. Adil, MD; Kiersten Norby, MD; Adnan I. Qureshi, MD

Background and Purpose—A high rate of postprocedure complications in the Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) trial has raised concerns whether such results are representative of intracranial stent placement in actual routine practice.

Methods—Using the Nationwide Inpatient Sample from 2008 to 2010, patients with cerebral ischemic events treated with intracranial stent as part of a clinical trial or outside the trial were identified. The composite end point (postoperative stroke, cardiac complications, and mortality) was reported.

Results—Of the 3447 patients who underwent intracranial stent placement, 223 patients (6.5%) were enrolled in a clinical trial. The rate of composite end point was higher in patients treated outside clinical trials compared with those treated within clinical trials (14.2% versus 4.5%; P=0.1). The proportion of patients discharged to home was higher in those treated in clinical trials (76.8% versus 49.6%; P=0.001).

Conclusions—Intracranial stent placement procedures outside a clinical trial have higher rates of postoperative stroke, cardiac complication, and mortality. (Stroke. 2013;44:3571-3572.)

Key Words: angioplasty ▪ stents ▪ stroke

A
fter the approval of the Gateway-Wingspan stent system, several prospective registries reported high rates of technical success, acceptable periprocedure complication rates, and 1-year ipsilateral stroke/death rates after intracranial stent (ICS) placement.1-3 The Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis (SAMMPRIS) trial4 was prematurely halted at the recommendation of the Safety Monitoring Board because of high 30-day stroke and death rate in the endovascular group (14.7%) compared with the medical group (5.8%).4

Several reports have raised concerns regarding the impact of operator experience, volume of the endovascular center, choice of the treatment device, and timing of the procedure.5,6 A recent study from 3 centers not participating in SAMMPRIS7 reported that the overall 30-day postprocedure stroke and death rate with angioplasty and ICS was 7.2% in the SAMMPRIS-eligible group and 3.3% in the SAMMPRIS-eligible, angioplasty-treated subgroup. Therefore, the question regarding generalization of the SAMMPRIS results is an essential component of medical decision making for patients with symptomatic intracranial stenosis. In our study, we compared the clinical outcomes of patients undergoing ICS placement enrolled in a trial with patients not enrolled in a trial. Because SAMMPRIS and Vitesse Intracranial Stent Study for Ischemic Therapy (VISSIT) were the only Investigational Device Exemption trials in the United States during the study time period, the results are effectively based on a comparison of the rates of postoperative complications between those treated in a trial and in general practice.

Methods

National Inpatient Sample (NIS) from 2008 to 2010 was used for our analysis. A comprehensive synopsis on NIS data is available at http://www.hcup-us.ahrq.gov.

We used the International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) primary diagnosis codes 433 to 437.1 to identify the patients admitted with ischemic stroke regardless of severity. ICD-9-CM procedure codes 00.62-00.65 were used to identify patients undergoing ICS placement excluding patients who received thrombolytic, endovascular treatment for stroke or intracranial aneurysm by using diagnosis-related group codes 543 and 39.71–39.79. We also used ICD-9-CM diagnostic codes V70.5 and V70.7 to identify patients enrolled in a clinical trial (CT) group. The remaining patients were placed in the outside clinical trial (OCT) group. V code identifies all patients who are enrolled in a trial and is used for Medicare reimbursements. Therefore, we expect a high level of accuracy and scrutiny for use of such code. Furthermore, among hospitals that identified themselves in the NIS database, ICS placement procedures with V code assignment were performed only in hospitals that were part of SAMMPRIS or VISSIT trials. Given the relationship between V code use and Medicare reimbursement, we performed an analysis including only Medicare patients for whom more consistent use is expected.

Study end points were neurological complication (ICD-9-CM code 997.00–997.09), cardiac complication (ICD-9-CM code 997.10),...
in-hospital mortality, and composite end point. Discharge status in NIS database was categorized into discharge to home and discharge to rehabilitation/nursing home.

Expanded materials and methods are provided in the online-only Data Supplement.

Results
Of the 3447 patients who underwent ICS placement during the study period, 223 were enrolled in a CT group, whereas 3224 patients underwent ICS placement outside the clinical trial. The CT group comprised older patients compared with the OCT group (68±10 versus 65±14 years; P<0.008). Sex and medical comorbidities (hypertension, diabetes mellitus, congestive heart failure, renal failure, dyslipidemia, and atrial fibrillation) were not different between the 2 groups.

CT group patients had significantly shorter length of stay (5±4 versus 9±11 days; P<0.0001) compared with OCT group. Hospital teaching status was not different between the 2 groups (P=0.4).

The proportion of patients discharged to home was higher in the CT group (76.8% versus 49.6%; P<0.001). The proportion of patients discharged to rehabilitation/nursing home was higher in the OCT group (40.8% versus 18.7%; P<0.01). The adjusted odds ratio for discharge to rehabilitation/nursing home was 3.5 (95% confidence interval, 1.2 to 9.7; P=0.01) for the OCT group.

The rate of postoperative mortality was 9.6% in the OCT group and 4.5% in the CT group (P<0.4). The adjusted odds ratio of postoperative mortality was 2.0 (95% confidence interval, 0.2 to 14.4; P=0.5) for the OCT group. The rate of composite end point was 14.2% in the OCT group compared with 4.5% in the CT group (P<0.1). The adjusted odds ratio of composite end point was 3.4 (95% confidence interval, 0.5 to 21.5; P<0.1) for the OCT group.

In the subgroup analysis including only Medicare patients, the direction and magnitude of increased odds of the composite end point in the OCT group remained unchanged. The rate of composite end point was 14.7% in OCT group compared with 7.2% in the CT group (P<0.4). The adjusted odds ratio for composite end point for OCT group was 3.2 (95% confidence interval, 0.5 to 22.8; P=0.3).

Discussion
Our study demonstrated that the composite of postprocedure mortality, neurological, and cardiac complications was 14.2% in OCT patients compared with 4.5% in CT patients. Interestingly, there were no neurological complications reported in the CT group. There may be an ascertainment bias because the methods used for neurological assessment are usually more rigorous with independent neurologist ascertainment in a clinical trial as opposed to self-ascertainment in routine practice. Similarly, lower rates of in-hospital mortality and composite end point of stroke, cardiac events, and death are observed with cervical carotid artery stent placement in patients as part of a clinical trial compared with those in actual clinical practice. One explanation is that patients treated within clinical trials have more favorable characteristics than those treated as part of routine practice (cherry-picking phenomenon). The accuracy of the V code is not known; however, the code is essential for Medicare reimbursement for procedures that are not currently reimbursed as part of routine care. It is possible that some patients may have had ICS for other causes such as dissection or acute ischemic stroke treatment. Long-term outcomes cannot be assessed from the NIS database. We assume that discharge disposition has significant correlation with long-term outcome, but we do recognize that discharge to a short- or long-term care facility is not an ideal surrogate for postprocedure morbidity. Predictive value of discharge destination as a surrogate for evaluating unfavorable outcome at 3 and 12 months after stroke has been validated previously.

Conclusions
Periprocedure complication rate remains high in patients treated with the currently available ICS technology outside a clinical trial. There is no evidence to support that SAMMPRIS results are not a valid representation of intracranial angioplasty and stent placement in general practice at large.

Sources of Funding
This study was performed independently of any financial support.

Disclosures
This article has not been published previously and is not being considered for publication elsewhere in whole or in part in any language except as an abstract.

References
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The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/44/12/3571

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2013/10/17/STROKEAHA.113.002567.DC1

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SUPPLEMENTAL MATERIAL

Intracranial stent placement as part of a clinical trial versus those treated outside a clinical trial

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Supplemental materials and methods

Data collection: Study variables extracted were patient’s age; gender; race/ethnicity; co-morbidities (including hypertension, diabetes mellitus, congestive heart failure, renal failure, dyslipidemia, and atrial fibrillation); mean length of stay, hospital charges, hospital characteristics (teaching status).

Statistical analysis: The SAS 9.1 software (SAS Institute, Cary, NC) was used to convert NIS data into weighted counts to generate national estimates, following Healthcare Cost and Utilization Project (HCUP) recommendations. We performed univariate analysis, chi-square for categorical and t-test for continuous variables. A logistic regression analysis was used to identify the odds of patients discharge to rehabilitation/nursing home. Age, gender and atrial fibrillation variables were added as potential confounders (based on results of univariate analysis) to multivariate logistic regression model.
Supplemental Reference

1) Hcup databases. Healthcare cost and utilization project (hcup) rockville, md, 2011.//
Supplemental tables

Supplemental Table I: Patients’ demographic and clinical characteristics, hospital characteristics, and discharge outcomes of patients underwent intracranial stent placement inside and outside the clinical trial. Nationwide Inpatient Survey 2008-2010.

<table>
<thead>
<tr>
<th>Patients undergoing Intracranial stent placement</th>
<th>Within clinical trials</th>
<th>Outside clinical trials</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Number (%)</td>
<td>223</td>
<td>3224</td>
<td></td>
</tr>
<tr>
<td>Age (mean±SD)</td>
<td>68±10</td>
<td>65±14</td>
<td>0.008</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>108(48.4)</td>
<td>1290(40)</td>
<td>0.4</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>144(67.7)</td>
<td>1855(69)</td>
<td></td>
</tr>
<tr>
<td>African Americans</td>
<td>21(10)</td>
<td>420(15.6)</td>
<td>0.2</td>
</tr>
<tr>
<td>Hispanic</td>
<td>32(15)</td>
<td>188(7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>15(7.3)</td>
<td>222(8.2)</td>
<td></td>
</tr>
<tr>
<td>Co-morbid conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>186(83.6)</td>
<td>2556(79.2)</td>
<td>0.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>72(32.4)</td>
<td>938(29.1)</td>
<td>0.7</td>
</tr>
<tr>
<td>Condition</td>
<td>Category 1</td>
<td>Category 2</td>
<td>P-value</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>10(4.5)</td>
<td>328(10.1)</td>
<td>0.1</td>
</tr>
<tr>
<td>Renal failure</td>
<td>31(13.7)</td>
<td>292(9)</td>
<td>0.5</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>5(2.3)</td>
<td>212(6.6)</td>
<td>0.1</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>15(6.8)</td>
<td>515(16)</td>
<td>0.1</td>
</tr>
<tr>
<td>Length of stay (Mean ±SD)</td>
<td>5±4</td>
<td>9±11</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hospital teaching status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Teaching</td>
<td>208(93.3)</td>
<td>2857(89.2)</td>
<td>0.4</td>
</tr>
<tr>
<td>Non teaching</td>
<td>15(6.7)</td>
<td>347(10.8)</td>
<td></td>
</tr>
<tr>
<td>Discharge disposition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>171(76.8)</td>
<td>1599(49.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Rehabilitation/nursing home</td>
<td>42(18.7)</td>
<td>1316(40.8)</td>
<td>0.01</td>
</tr>
<tr>
<td>In hospital complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-operative mortality</td>
<td>10(4.5)</td>
<td>309(9.6)</td>
<td>0.4</td>
</tr>
<tr>
<td>Neurologic complications</td>
<td>0(0)</td>
<td>147(4.6)</td>
<td>NA</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>0(0)</td>
<td>34(1.0)</td>
<td>NA</td>
</tr>
<tr>
<td>Neurologic and/or cardiac</td>
<td>0(0)</td>
<td>177(5.6)</td>
<td>NA</td>
</tr>
<tr>
<td>complication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite endpoint</td>
<td>10(4.5)</td>
<td>460(14.2)</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Abbreviation: SD= standard deviation
Supplemental Table II: Effect of outcomes of patients underwent intracranial stent placement outside clinical trial.

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Un-adjusted</th>
<th>Adjusted for age and gender</th>
<th>Adjusted for age, gender, and atrial fibrillation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rehabilitation/nursing home</td>
<td>OR (95% C.I.)</td>
<td>P value</td>
<td>OR (95% C.I.)</td>
</tr>
<tr>
<td></td>
<td>3.3(1.2-9.4)</td>
<td>0.01</td>
<td>3.6(1.2-10.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.5(1.2-9.7)</td>
</tr>
<tr>
<td>Composite endpoint</td>
<td>OR (95% C.I.)</td>
<td>P value</td>
<td>OR (95% C.I.)</td>
</tr>
<tr>
<td></td>
<td>3.4(0.5-23.5)</td>
<td>0.1</td>
<td>3.5(0.5-25.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.4(0.5-21.5)</td>
</tr>
<tr>
<td>Post-operative mortality</td>
<td>OR (95% C.I.)</td>
<td>P value</td>
<td>OR (95% C.I.)</td>
</tr>
<tr>
<td></td>
<td>2.2(0.3-15.5)</td>
<td>0.4</td>
<td>2.3(0.3-17.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.0(0.2-14.4)</td>
</tr>
</tbody>
</table>

Abbreviation: OR = odds ratio; CI= confidence interval
Table III: Patients’ demographic and clinical characteristics, hospital characteristics, and discharge outcomes of patients underwent intracranial stent placement inside and outside the clinical trial. Nationwide Inpatient Survey 2008-2010 (Medicare patients).

<table>
<thead>
<tr>
<th>Patients undergoing Intracranial stenting</th>
<th>Clinical trial patients</th>
<th>Outside trial patients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Number (%)</td>
<td>141</td>
<td>1707</td>
<td></td>
</tr>
<tr>
<td>Age (mean)</td>
<td>72±15</td>
<td>73±20</td>
<td>0.1</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>46(32.8)</td>
<td>729(42.7)</td>
<td>0.5</td>
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<tr>
<td>Race/ethnicity</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>109(77.4)</td>
<td>983(71.0)</td>
<td></td>
</tr>
<tr>
<td>Blacks</td>
<td>10(7.4)</td>
<td>204(14.7)</td>
<td>0.2</td>
</tr>
<tr>
<td>Hispanic</td>
<td>22(15.2)</td>
<td>92(6.6)</td>
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<tr>
<td>Other</td>
<td>0(0)</td>
<td>107(7.7)</td>
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<tr>
<td>Co-morbid conditions</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>119(84.7)</td>
<td>1403(82.1)</td>
<td>0.7</td>
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<tr>
<td>Diabetes mellitus</td>
<td>41(29.3)</td>
<td>497(29.1)</td>
<td>0.9</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>10(7.2)</td>
<td>183(10.7)</td>
<td>0.6</td>
</tr>
<tr>
<td>Renal failure</td>
<td>31(21.8)</td>
<td>181(10.6)</td>
<td>0.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>--------------------------------</td>
<td>----------</td>
<td>----------</td>
<td>-------</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0(0)</td>
<td>101(6.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>5(3.6)</td>
<td>350(20.3)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Length of stay (Mean ±SD)</td>
<td>4±8</td>
<td>8±21</td>
<td>&lt;.0001</td>
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<td>Hospital teaching status</td>
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<td></td>
<td>0.5</td>
</tr>
<tr>
<td>Teaching</td>
<td>131(93.0)</td>
<td>1524(89.3)</td>
<td></td>
</tr>
<tr>
<td>Non-teaching</td>
<td>10(7.0)</td>
<td>183(10.7)</td>
<td></td>
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<tr>
<td>Discharge disposition</td>
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<td>0.03</td>
</tr>
<tr>
<td>Home</td>
<td>104(74.0)</td>
<td>770(45.1)</td>
<td></td>
</tr>
<tr>
<td>Rehabilitation/nursing home</td>
<td>27(18.8)</td>
<td>774(45.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>In hospital complications</td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Post-operative mortality</td>
<td>10(7.2)</td>
<td>10(9.5)</td>
<td>0.7</td>
</tr>
<tr>
<td>Neurologic complications</td>
<td>0(0)</td>
<td>94(5.5)</td>
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</tr>
<tr>
<td>Cardiac complications</td>
<td>0(0)</td>
<td>20(1.1)</td>
<td></td>
</tr>
<tr>
<td>Neurologic and/or cardiac</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>complication</td>
<td>0(0)</td>
<td>109(6.4)</td>
<td></td>
</tr>
<tr>
<td>Composite endpoint</td>
<td>10(7.2)</td>
<td>251(14.7)</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Abbreviation: SD = standard deviation
Table IV: Effect of outcomes of patients underwent intracranial stent placement outside clinical trial. (Medicare patients)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Un-adjusted OR (95% C.I.)</th>
<th>P value</th>
<th>Adjusted for age and gender OR (95% C.I.)</th>
<th>P value</th>
<th>Adjusted for age, gender, risk factors OR (95% C.I.)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rehabilitation/nursing home</td>
<td>3.5(1.0-11.4)</td>
<td>0.04</td>
<td>3.4(1.0-11.3)</td>
<td>0.04</td>
<td>3.4(1.2-9.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>Composite endpoint</td>
<td>2.2(0.3-17.3)</td>
<td>0.4</td>
<td>2.3(0.3-20.6)</td>
<td>0.4</td>
<td>3.2(0.5-22.8)</td>
<td>0.3</td>
</tr>
<tr>
<td>Postoperative mortality</td>
<td>1.3(0.2-10.9)</td>
<td>0.7</td>
<td>1.4(0.1-11.8)</td>
<td>0.7</td>
<td>1.9(0.3-13.8)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Abbreviation: OR = odds ratio; CI= confidence interval