Update on Angioplasty and Stent Placement for Intracranial Atherosclerosis: Review of Evidence

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Professor of Neurology and Neurosciences

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Zeenat Qureshi Stroke Research Center
University of Medicine and Dentistry of New Jersey
**Intracranial Atherosclerosis**

- Wityk et al. Review of 274 consecutive patients evaluated at a community hospital for stroke or TIA. Intracranial disease (50% or greater atherosclerotic stenosis) in 8% of all patients in the study.
- Sacco et al. Review of 438 residents from northern Manhattan over age 39 years hospitalized for acute ischemic stroke Atherosclerotic infarction in 8% of the patients due to intracranial stenosis.
- An estimated 100,000 ischemic events in the United States are related to intracranial stenosis annually.
Is a New Treatment Modality for Intracranial Atherosclerotic Disease Really Required
Warfarin vs. Aspirin for Symptomatic Intracranial Disease (WASID)

An NIH / NINDS Funded Randomized, Double-Blind Multi-Center Clinical Trial

Warfarin vs. Aspirin for Symptomatic Intracranial Disease (WASID)

- Patients with symptomatic intracranial stenosis.
- Severity of stenosis 50% or greater confirmed by catheter angiography.
### Primary Endpoint: Stroke and Vascular Death

<table>
<thead>
<tr>
<th></th>
<th>Aspirin</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td># of Patients</td>
<td>280</td>
<td>289</td>
</tr>
<tr>
<td># Patients with Event</td>
<td>62 (22%)</td>
<td>63 (22%)</td>
</tr>
<tr>
<td>1yr / 2yr rates</td>
<td>15 / 21</td>
<td>17 / 22</td>
</tr>
<tr>
<td>Log-Rank p - value</td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>1.04 (0.73 – 1.48)</td>
<td></td>
</tr>
</tbody>
</table>
Warfarin versus aspirin for symptomatic intracranial disease

(Chimowitz M: International Conference on Stroke and Cerebral Circulation 2004)

Stroke and Vascular Death

Probability of Stroke / Vascular Death

Years after Enrollment

p = 0.83
## Major Hemorrhage

<table>
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<tr>
<td># of Patients</td>
<td>280</td>
<td>289</td>
</tr>
<tr>
<td># Patients with Event</td>
<td>9 (3%)</td>
<td>24 (8%)</td>
</tr>
<tr>
<td># Events / 100 pt-yrs</td>
<td>1.8</td>
<td>4.4</td>
</tr>
<tr>
<td>Log-Rank p – value</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio (95% CI)</td>
<td>0.39 (0.18 – 0.84)</td>
<td></td>
</tr>
</tbody>
</table>
Lessons learned

• The risk of stroke and vascular death associated with symptomatic intracranial atherosclerosis remains high even with best medical treatment.
• Warfarin does not reduce the risk of ischemic events and may increase the risk of major hemorrhages.
• HIGHLIGHTS THE NEED FOR DEVELOPING NEW TREATMENT MODALITIES.
Patients at High risk of Recurrent Ischemic Events
Stroke Free Survival and Its Determinants in Patients with Symptomatic Vertebrobasilar Stenosis. A Multicenter Study

- A total of 102 patients.
- The mean follow-up period was 15±15.9 months (range 1 to 60 months).
- Stroke-free survival by Kaplan Meier curve was 76% at 12 months and 48% at 5 years.
- The risk of recurrent stroke was 10.9 per 100 patient-years and the rate of recurrent stroke and/or death was 24.2 per 100 patient-years.

Low rate of 5 year stroke free survival by Kaplan Meier estimation

(Qureshi AI: Neurosurgery 2003; 52:1033-1044.)
Symptomatic Intracranial Atherosclerosis: Medication Failure

- Thijs et al. reported the prognosis of 52 patients with symptomatic intracranial stenosis who failed anti-thrombotic treatment. Primary or recurrent ischemic symptom while on anti-platelet or anti-coagulant therapy.
- Recurrent TIA, nonfatal or fatal stroke, or death occurred in 15 of 29 (52%) patients who failed antithrombotic treatment.
- The median time to recurrent TIA, stroke, or death was 36 days.

Warfarin versus aspirin for symptomatic intracranial disease
(Chimowitz M: International Conference on Stroke and Cerebral Circulation 2004)

No impact on risk of stroke in the territory:
- Age
- Race
- All other vascular risk factors
  (smoking, MI, angina, CAD, CABG, CHF, PVD, DVT, prior stroke or TIA, CEA, hypertension, lipid disorder, family history)
- Location of stenosis
- Length of stenosis
- Antithrombotic med at time of qualifying event
- Treatment assignment
Warfarin versus aspirin for symptomatic intracranial disease

Multivariate Analysis

(Kasner S: International Conference on Stroke and Cerebral Circulation 2005)

- Female gender: HR=1.68 (1.07-2.65)
- Stenosis 70-99%: HR=2.46 (1.55-3.91)
Time from Qualifying Event

- Median=17 days (max 90 days)

- **Time from Qualifying Event and early enrollment (≤17 days)** associated with greater risk: HR=1.6 (95% CI: 1.1-2.9)
Selection of Candidates for Endovascular Treatment

- Patients with intracranial stenosis who have ischemic symptoms while on antiplatelet or anticoagulant therapy
- Patients with symptomatic vertebrobasilar stenosis
- Patients with ischemic symptoms related to hypoperfusion
- Patients who are being considered for coronary artery bypass grafting
- Patients with severe stenosis (greater than 70%)

(From. Qureshi AI. Lancet 2004; 363:804-813)
Intracranial stent placement: The procedure
Mechanism of ischemic events

Distal embolization
Superimposed thrombus
Hypoperfusion

Mechanism of beneficial effect of stent

- Distal embolization
- Superimposed thrombus
- Hypoperfusion

Remodeling reduces thrombogenecity

Restore diameter of vessel to improve perfusion

Stent placement for middle cerebral artery stenosis
Symptomatic Intracranial Vertebral Artery Stenosis
Primary stent placement
Post-treatment Result

0 °L
19 °CRA
2 °LAO

NORMAL

46:19

INJECT

DSA

...READY
Intracranial angioplasty and stent placement can restore vessel lumen and cerebral blood flow.
Intracranial angioplasty and stent placement can restore vessel lumen and cerebral blood flow.
Histopathology of intracranial stent
Intracranial Stent Placement
Results of Clinical Studies
Clinical and Angiographic Results of Angioplasty and/or Stent Placement for Intracranial Atherosclerotic Disease

(Qureshi AI: J Neuroimaging 2005;15:240-9)

• Twenty-four patients (mean age 61.0±13.5 years; 15 were men) underwent 29 procedures for treatment of 55 to 99% stenosis.

• The procedures included PTA (n=16), primary stent placement (stent placement without angioplasty) (n=9), and PTA after unsuccessful stent placement (n=3).
Short-term Results

- There was immediate reduction of stenosis (mean ± SD) from 85±13% to 24±26%.
- Overall 1 month stroke rate per procedure was 6%.
Stroke-free survival after intracranial angioplasty and stent placement

Endovascular

Medical treated
Qureshi et al.
Neurosurgery 2003;
52:1033-1044.
Ipsilateral stroke prevention rate

Time (months)

Endovascular

Medical failures
Thijs et al. Neurology
2000;55:465-466
A comparison of the outcome of patients with 70% to 99% stenosis and TIA or stroke within 30 days prior to stenting in this registry (n = 86) vs patients in WASID with 70% to 99% stenosis and TIA or stroke within 30 days prior to enrollment (n = 122)
Medically treated

Stent treated

Months after recruitment or stent treatment
Stenting of SYmptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA)
(The SSYLVIA Study Investigators Stroke 2004 35: 1388 – 1392)

- **Study Design:** Selective, non-randomized, multi-center, prospective feasibility study
- **Inclusion Criteria:** Patients with symptomatic cerebral atherosclerosis >50% were eligible for this study
- **Secondary Outcome(s):** Angiographic evaluation of stented area at 6 months, and target lesion-related stroke at 1 year.
The SSYLVIA Study Investigators
Stroke 2004; 35: 1388 – 1392

61 patients
43 intracranial arteries
18 extracranial vertebral arteries

Technical success
58/61 (95%)

One month stroke
rate 6.6%

Late stroke
rate 7.3%

6 month angiographic restenosis (32%)
Symptomatic in one-third
Stent placement as first line treatment for symptomatic intracranial stenosis

- High technical success
- Acceptable rates of peri-operative complications
- Low restenosis rates
- Efficacy demonstrated in clinical trial
Stent placement as first line treatment for symptomatic intracranial stenosis

- High technical success
- Acceptable rates of peri-operative complications
- Low restenosis rates
- Efficacy demonstrated in clinical trial
Intracranial angioplasty and stent placement

- Ready for a randomized comparison between best medical treatment and endovascular treatment.
- An option for high-risk patients with recurrent symptoms.
- Approved by Food and Drug Administration for symptomatic intracranial stenosis $\geq 50\%$ AND recurrent ischemic symptoms (HUMANATARIAN USE APPROVAL ONLY).

Conclusions

• Endovascular procedures have revolutionized the treatment of patients with cerebrovascular diseases.

• Anticipated developments in technology will continue to increase the success rate of these procedures.

• As physicians and nurses, we must be familiar with the emerging indications of these procedures to provide the best treatment options for our patients.
Primary Angioplasty versus Stent Placement for Intracranial Atherosclerotic Disease: Is there an equipoise?

Adnan I. Qureshi MD
Professor and Executive Director, Minnesota Stroke Initiative
Vice Chairman, Department of Neurology

Farhan Siddiq MD, M. Fareed K. Suri MD, Gustavo J. Rodriguez MD, Ramachandra P. Tummala MD, Jill Novitzke RN, Gabriela Vasquez PhD, Robert A. Taylor MD,

Zeenat Qureshi Stroke Research Center
University of Minnesota, Minneapolis, MN
Evolution of endovascular treatment for intracranial atherosclerotic disease

Primary angioplasty

Balloon expandable stents

Angioplasty + self-expanding stent


Evolution of endovascular treatment for intracranial atherosclerotic disease

- **Primary angioplasty**
- **Balloon expandable stents**
- **Angioplasty + self-expanding stent**

- Some lesions cannot be treated by stent placement!!
- Most interventionalist think that stent is superior!!

|------|------|------|------|

Evolution of endovascular treatment for intracranial atherosclerotic disease

- Balloon expandable stents
- Most interventionalist think that stent is superior!!
- Some lesions cannot be treated by stent placement!!
- Vessel diameter <2mm
- Tortuous vessels
- Lower residual stenosis
- Lower dissection
- Lower restenosis


Primary angioplasty

Stent placement
Better angiographic results!!!
But better clinical outcomes
Comparison of outcomes of primary angioplasty and of stent placement in patients with coronary artery disease

# Meta-analyses of trials comparing primary angioplasty versus stent

<table>
<thead>
<tr>
<th>Studies</th>
<th>Population</th>
<th>Death or MI</th>
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<tr>
<td><strong>Dundar Y (Scand Cardiovasc J</strong></td>
<td><strong>50 trials (n=16500)</strong></td>
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<td>Stent better</td>
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<td><strong>Brophy et al.</strong></td>
<td><strong>29 trials (n=9918)</strong></td>
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<td><strong>Al Suwaidi J et al.</strong></td>
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### Comparing primary angioplasty versus stent patients treated in practice settings outside clinical trials

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<td>Veterans (n=27,224)</td>
<td>Stent better</td>
<td>NA</td>
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Comparing primary angioplasty versus stent patients treated in practice settings outside clinical trials

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Recognize the strengths and weaknesses of data derived from percutaneous coronary intervention PRIOR to extrapolation!!!!
Concurrent comparison of outcomes of primary angioplasty and of stent placement in high-risk patients with symptomatic intracranial stenosis

Concurrent comparison of outcomes of primary angioplasty and of stent placement

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Angioplasty-treated (n=22)</th>
<th>Stent-treated (n=22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate post-procedure severity</td>
<td>28±18</td>
<td>17±13</td>
<td>0.02</td>
</tr>
<tr>
<td>Immediate residual stenosis &lt;30%</td>
<td>12 (55%)</td>
<td>20 (91%)</td>
<td>0.011</td>
</tr>
<tr>
<td>Immediate residual stenosis &lt;50%</td>
<td>18 (82%)</td>
<td>21 (95%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Multiple angioplasties performed</td>
<td>16 (73%)</td>
<td>9 (41%)</td>
<td>0.032</td>
</tr>
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Concurrent comparison of outcomes of primary angioplasty and of stent placement at 1 year post-procedure

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<tr>
<td>Major stroke free survival</td>
<td>95%±5%</td>
<td>93%±7%</td>
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<tr>
<td>Major stroke free and second procedure free survival</td>
<td>89%±8%</td>
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Concurrent comparison of outcomes of primary angioplasty and of stent placement at 1 year post-procedure

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Great angiographic benefit does not appear to translate into incremental clinical benefit.

Concurrent comparison of outcomes of primary angioplasty and of stent placement

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<tr>
<th>Characteristics</th>
<th>Angioplasty-treated (n=11)</th>
<th>Stent-treated (n=11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from procedure to F/U angiogram</td>
<td>10.5±9.4</td>
<td>11.6±10</td>
<td>0.9</td>
</tr>
<tr>
<td>Angiographic restenosis</td>
<td>5 (44%)</td>
<td>3 (27%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Repeat procedure</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Comparison of Primary Angioplasty with Stent Placement for Treating Symptomatic Intracranial Atherosclerotic Disease: A Multi-center Study

## Comparison of Primary Angioplasty with Stent Placement

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Angioplasty (n=98)</th>
<th>Stent treated (n=92)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual stenosis (≥ 50%)</td>
<td>14 (15%)</td>
<td>4 (4%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Peri-procedural complications</td>
<td>8 (8%)</td>
<td>9 (9%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Stroke</td>
<td>7 (7%)</td>
<td>7 (7%)</td>
<td>0.95</td>
</tr>
<tr>
<td>Death</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
<td>0.58</td>
</tr>
</tbody>
</table>
Binary restenosis survival function excluding the patients with significant immediate postprocedural residual
Stroke and/or-death survival function excluding the stroke or death events occurring in the peri-procedural period.
Stroke and/or-death survival function excluding the stroke or death events occurring in the peri-procedural period.

No clear difference between procedures..
Comparing apples and oranges...
Comparison between Primary Angioplasty and Stent Placement for Symptomatic Intracranial Atherosclerotic Disease: Meta-analysis of case series

### Meta-analysis of case series

<table>
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<tr>
<th>Primary angioplasty</th>
<th>Versus</th>
<th>Stent placement</th>
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<tbody>
<tr>
<td>33 studies</td>
<td>36 studies</td>
<td>36 studies</td>
</tr>
<tr>
<td>1027 pts</td>
<td></td>
<td>1291 pts</td>
</tr>
</tbody>
</table>
## Meta-analysis of case series

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Angioplasty treated Events (%)</th>
<th>Stent treated Events (%)</th>
<th>Relative Risk (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month stroke and death</td>
<td>91 (8.9%)</td>
<td>104 (8.1%)</td>
<td>1.1 (0.84-1.4)</td>
</tr>
<tr>
<td>1-year stroke and death</td>
<td>125 (17.1%)</td>
<td>123 (11.1%)</td>
<td>1.54 (1.2-1.9)</td>
</tr>
<tr>
<td>Restenosis rates</td>
<td>115 (14.2%)</td>
<td>119 (11.1%)</td>
<td>1.28 (1.0-1.6)</td>
</tr>
<tr>
<td>Technical Success rates</td>
<td>197 (79.8%)</td>
<td>680 (95%)</td>
<td>0.84 (0.8-0.9)</td>
</tr>
</tbody>
</table>
Worse than comparing apples and oranges.....
Evolution of endovascular treatment for intracranial atherosclerotic disease

Interventional neuroimaging. [Review]
Khatri R. Gomez CR. Qureshi Al.

- Primary angioplasty
- Balloon expandable stents
- Angioplasty + self-expanding stent

Timeline:
- 1990
- 1995
- 2000
- 2005
Evolution of endovascular treatment for intracranial atherosclerotic disease

Interventional neuroimaging. [Review]
Khatri R. Gomez CR. Qureshi AI.

Primary angioplasty

Time effect NOT
Treatment effect……


self-expanding stent
Evolution of endovascular treatment for intracranial atherosclerotic disease

Interventional neuroimaging. [Review]
Khatri R. Gomez CR. Qureshi Al.

Primary angioplasty

Time effect NOT
Treatment effect......
No association between the year of publication and 1-year incidence of stroke-and/or-death for all studies (beta coefficient = 0.003, SE 0.026, p = 0.90)


self-expanding stent
Time to grab the bull by the horns!!
A Randomized Comparison of Primary Angioplasty versus Stent Placement for Symptomatic Intracranial Stenosis

Qureshi AI; Neurosurgery. 2004 Feb;54(2):248-64.
Angioplasty versus Stent: Inclusion Criteria

- Intracranial stenosis that results in angiographically visible reduction of lumen of the affected artery. Stenosis of the subject artery is greater than 70%; OR the patient has previously failed antithrombotic or anticoagulant therapy with stenosis of 50% or greater.

- Stenosis involving the arteries within the cranium or those encased by the cranial bones. These include petrous and cavernous segments of the internal carotid artery and the intradural segment of the vertebral artery.

- Ischemic events referable to the artery with the stenosis in the last 3 months.
Angioplasty versus Stent: Inclusion Criteria

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- Ischemic events referable to the artery with the stenosis in the last 3 months.

Greater or equal to 70%
OR
Greater or equal to 50%
(if medication failure)
----by angiography
Angioplasty versus Stent: Exclusion Criteria

- Proximal occlusive disease greater than 50%, either in the proximal carotid artery, common carotid artery, cervical internal carotid artery, or the cervical vertebral artery that would preclude safe introduction of a guiding catheter or guiding sheath.

- Severe peripheral vascular disease which precludes successful insertion and catheterization.

- Stroke in the last 7 days of sufficient size (on CT or MRI) that places him/her at risk of hemorrhagic conversion during the procedure.

- Severe vascular tortuosity or anatomy that would preclude the safe introduction of a stent delivery device or balloon catheter or microwire.
Angioplasty versus Stent: Exclusion Criteria

- Proximal occlusive disease greater than 50%, either in the proximal carotid artery, common carotid artery, cervical internal carotid artery, or the cervical vertebral artery that would preclude safe introduction of a guiding catheter or guiding sheath.
- Severe peripheral vascular disease which precludes successful insertion.
- Stroke in the last 7 days of sufficient size (on CT or MRI) that places him/her at risk of hemorrhagic conversion during the procedure.
- Severe vascular tortuosity or anatomy that would preclude the safe introduction of a stent delivery device or balloon catheter or microwire.

Both procedures are possible AND Can be performed with reasonable safety (interventionalist’s judgment)
Eligible subjects are randomized 1:1 to either the primary angioplasty or stent placement group using randomly mixed permutations of different size.

Once the subject consents and meets enrollment criteria, the subject ID and randomization assignment are obtained by opening a randomization envelope.
### Current status-Ongoing

17 patients screened; 14 randomized

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<tr>
<th>Primary angioplasty</th>
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<tr>
<td>6 patients</td>
<td></td>
<td>7 patients</td>
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Interested in participating..
quireshi@umn.edu
Conclusions

• Caution needs to be exercised prior to assuming superiority of stent placement over primary angioplasty for treatment of intracranial atherosclerotic disease based on case series and data from percutaneous coronary intervention.

• Differential angiographic results between the two procedures may not necessarily translate into incremental clinical benefit.

• The current evidence emphasizes the need for a randomized controlled trial to compare the clinical outcome of angioplasty alone and angioplasty with stent placement for intracranial atherosclerotic disease.
Thank you

Minnesota Stroke Initiative and Zeenat Qureshi
Stroke Research Center
Initial experience with drug eluting stents for intracranial atherosclerosis
(Qureshi AI: Cerebrovascular section meeting 2005, New Orleans, LA)

17 patients with symptomatic intracranial atherosclerosis ≥ 50%

Technical success 15 of 17 (88%)

One month outcomes
Major stroke 0 of 15
Death 0 of 15
Minor neurological events 3 of 15
High Time for Multicenter Randomized Clinical Trial !!!
Preventing Restenosis of Arteries Intracranially with a Sirolimus-Eluting stent (PRAISE) Study: A Phase I Clinical Trial

**Primary Hypothesis**
The 30-day rate of stroke or death will not be significantly higher with the Cypher drug-eluting stent than it was with the Neurolink bare metal stent in the SSYLVIA trial.

**Secondary Hypotheses**
The frequency of technical success (deployment of the stent at the target lesion with full coverage of the lesion and less than 50% residual stenosis) with the Cypher stent will not be significantly lower than it was with the Neurolink stent in SSYLVIA.

The 6-month restenosis rate in this pilot clinical trial will suggest potential superiority of the Cypher stent over the Neurolink stent for preventing restenosis.
Conclusions

• The feasibility of angioplasty and stent placement for treatment of intracranial atherosclerotic disease has been demonstrated.
• Early reports suggest encouraging results for long-term stroke prevention.
• Anticipated developments in stent designs will continue to increase the success rate of these procedures.
# Ischemic Stroke In Territory of Symptomatic Artery

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</table>
Technical success rates

- **High technical success (95% or greater)**
- **Moderate technical success (≥50%)**
  - Inability to place guide catheter up to base of skull OR
  - Segment of severe proximal tortuosity (defined as a angle of less than 90 degrees in any axis) OR
  - Segment of proximal intracranial atherosclerotic disease (defined as segment greater than 5 mm in length) OR
  - Required stent length for adequate lesion coverage >10 mm
- **Low technical success (<50%)**
  - Combination of above mentioned factors or multiple segments of proximal severe tortuosity or proximal intracranial atherosclerotic disease.
Intracranial Atherosclerosis

• Wityk et al. Review of 274 consecutive patients evaluated at a community hospital for stroke or TIA. Intracranial disease (50% or greater atherosclerotic stenosis) in 8% of all patients in the study.

• Sacco et al. Review of 438 residents from northern Manhattan over age 39 years hospitalized for acute ischemic stroke Atherosclerotic infarction in 8% of the patients due to intracranial stenosis.

• An estimated 100,000 ischemic events in the United States are related to intracranial stenosis annually.