Intracranial Atherosclerosis
Life after SAMMPRIS

Hans Henkes
Klinikum Stuttgart, Germany
SAMMPRIS results find intracranial stents linked to more strokes and death
The goal was to show the superiority of intracranial stenting. The initial idea to use a coronary drug eluting stent was rejected by the FDA.

Against the advise of the inventors of the Wingspan System (a conventional old balloon and a self-expanding [aneurysm] stent with enhanced radial force) the „Stenting versus Aggressive Medical Management for Preventing Recurrent stroke in Intracranial arterial Stenosis“ (SAMMPRIS) study was initiated.
451 patients in the acute phase after TIA or cerebral ischemia due to a high grade stenosis of a large intracranial artery

50 US centers

aggressive medical treatment (AMT) vs. AMT + Stent-PTA (*Wingspan*)

(AMT = 325 mg ASA, 75 mg Clopidogrel for 90 days, Rusovastatin, blood pressure normalizing, life-style modification)

Chimowitz 2011
Primary endpoints

- stroke or death within the first 30 days after enrollment or after Stent-PTA during the follow-up period
- stroke in the territory of the target artery after 30 days
- for cross overs (from AMT to Stent-PTA): stroke or death within 30 days

N = 451

AMT = 227

AMT + Stent-PTA = 224

Chimowitz 2011
<table>
<thead>
<tr>
<th></th>
<th>AMT</th>
<th>Stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint 30 days</td>
<td>5.8%</td>
<td>14.7%</td>
</tr>
<tr>
<td>Primary endpoint 1 year</td>
<td>12.2%</td>
<td>20%</td>
</tr>
</tbody>
</table>

Chimowitz 2011
complications in Stent-PTA arm: 33 out of 224 (14.7%) patients

30 complications due to Stent-PTA
3 complications of diagnostic DSA

those 30 procedural complications included

19 ischemic (12 perforator strokes, 3 embolic, 2 perforator & embolic, 2 stent occlusions)

11 hemorrhagic (6 ICH, 5 SAH) !!!!!!!!!!!!

Chimowitz 2011
In SAMMPRIS the wrong physicians treated the wrong stenoses with the wrong device:

- many intracranial stenoses are not equally suitable for AMT and Stent-PTA
- the qualification criteria for the physicians performing the procedures in the stent arm were inadequate
- the enrollment rate per center was way too low
- the Wingspan system was already outdated
- the (high) in-stent re-stenosis rate after Wingspan was not addressed

However: SAMMPRIS confirms the high stroke rate under AMT (12% primary endpoint in 1 year under AMT)
Clinical trials concerning the treatment of intracranial atherosclerotic arterial stenoses, comparing one medical regime with one surgical or endovascular procedure can not properly reflect the clinical reality and the medical demands; the structure of these studies rather creates an „artefact“ than allowing a reasonable comparison of different treatment modalities.
The atherosclerotic stenoses of an intracranial artery is a progressive disease. Any known medical treatment (either antiaggregation or anticoagulation) will not remove an atherosclerotic stenosis. It may prevent distal emboli and may allow leptomeningeal collaterals to develop; the efficacy of this process is essentially unpredictable.

After a „maturation“ of several months or years, many stenoses will simply be untreatable by endovascular means, mainly due to an inability of microwire or balloon passage distal to the stenosis.
EXAMPLE STENOSSES NOT ACCESSIBLE
ARGUMENT #3

Arguments for a *medical* treatment

- less than 50% stenosis

- asymptomatic while under (dual) platelet function inhibition

- sufficient leptomeningeal collaterals

- „only“ perforator ischemia, no infarcts due to hemodynamic compromise
ARGUMENT #4

Arguments for an endovascular treatment

- more than 70% stenosis

- TIA or cerebral ischemia despite dual antiaggregation or anticoagulation

- progressive stenosis with poor or missing collaterals

- hemodynamic compromise due to stenosis
HEMODYNAMIC COMPROMISE
HEMODYNAMIC COMPROMISE

pre  post
ARGUMENT #5

Treatment options for intracranial atherosclerotic stenoses

ASA
ASA + Clopidogrel or Prasugrel or Ticagrelor
DOAC + ASA, DOAC + Clopidogrel
Balloon angioplasty only
Balloon angioplasty + self-expanding stent
Self-expanding stent only
Balloon-expandible bare metal stent
Balloon-expandible drug eluting stent
Direct bypass
Indirect bypass
ARGUMENT #6

The endovascular treatment of intracranial stenoses
- can be a technically demanding procedure
- can be associated with significant risks
- is hardly ever a standardized treatment
- must be weight against treatment alternatives on an individual basis
- the documented rate of permanent morbidity and mortality related to intracranial stent PTA procedures in a given center and for a given operator has to be below 10%
ARGUMENT #7

Intracranial stent PTAs should only be performed in specialized neurovascular centers, including:

- vascular Neurology
- vascular Neurosurgery
- Neuroanesthesiology
- infrastructure (e.g., Multiplate, ICU, Stroke Unit, etc.)
- to be discussed: procedure frequency or case load, institutional experience, operator experience... (qualification issues)
<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Severe Complications</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kurre 2010</td>
<td>Intrastent</td>
<td></td>
<td>7%</td>
</tr>
<tr>
<td>Dorn 2012</td>
<td>Various</td>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>Vajda 2012</td>
<td>Enterprise</td>
<td></td>
<td>8%</td>
</tr>
<tr>
<td>Vajda 2012</td>
<td>DEB &amp; Enterprise</td>
<td></td>
<td>5%</td>
</tr>
<tr>
<td>Vajda 2012</td>
<td>Coroflex Please</td>
<td></td>
<td>4%</td>
</tr>
</tbody>
</table>
WHICH STENT?

Wingspan?
Wingspan has a higher radial force than Neuroform.
Gateway 2/15 8atm
WingSpan 2,5/15

post
5 Mo: recurrence
6 Mo: occlusion ➔ stroke

follow-up
AFTER THIS POINT: ALMOST EVERYTHING IS OFF LABEL
WHICH STENT?

Enterprise1
## Intracranial ISRS

<table>
<thead>
<tr>
<th>Autor</th>
<th>N=</th>
<th>Stent-Typ</th>
<th>restenosis occlusion</th>
<th>ipsilateral TIA stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jiang (2012)</td>
<td>454</td>
<td>balloon expandible</td>
<td>20%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>216</td>
<td>selfexpanding</td>
<td>28%</td>
<td></td>
</tr>
<tr>
<td>Vajda (2012)</td>
<td>209</td>
<td>Enterprise</td>
<td>25%</td>
<td>9.3%</td>
</tr>
<tr>
<td>Jiang (2012)</td>
<td>100</td>
<td>Wingspan</td>
<td>27%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(45 angio FU)</td>
<td></td>
</tr>
<tr>
<td>Costalat (2011)</td>
<td>60</td>
<td>Wingspan</td>
<td>17%</td>
<td>6%</td>
</tr>
<tr>
<td>Miao (2009)</td>
<td>79</td>
<td>balloon expandible</td>
<td>20%</td>
<td>25%</td>
</tr>
<tr>
<td>Levy (2007)</td>
<td>78</td>
<td>Wingspan</td>
<td>36%</td>
<td>27.6%</td>
</tr>
<tr>
<td>Jiang (2007)</td>
<td>94</td>
<td>balloon expandible</td>
<td>20%</td>
<td>26%</td>
</tr>
</tbody>
</table>
ISRS - over time

Vajda et al. Neurosurgery 2012
## Drug Eluting Stents

<table>
<thead>
<tr>
<th>Stentsystem/ Stentfamilie</th>
<th>Hersteller</th>
<th>Wirkstoff</th>
<th>Trägerbeschichtung</th>
<th>Stentgerüst</th>
<th>Endpunkt klinisch</th>
<th>Endpunkt angiographisch</th>
<th>Literatur</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biostabile Polymerbeschichtung</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cypher-Familie</strong></td>
<td>Cordis</td>
<td>Sirolimus</td>
<td>Polyethylenglykol (PVA)</td>
<td>Stainless steel</td>
<td>++</td>
<td>++</td>
<td>[2, 16, 17, 31, 32, 200, 201]</td>
</tr>
<tr>
<td><strong>Toxus-Familie</strong></td>
<td>Boston Scientific</td>
<td>Paclitaxel</td>
<td>Poly-Steren-bisobutyl-b-styren (SiS)</td>
<td>Stainless steel</td>
<td>++</td>
<td>++</td>
<td>[15, 20, 21, 25, 33, 202]</td>
</tr>
<tr>
<td><strong>BioElement</strong></td>
<td>Abbott</td>
<td>Everolimus</td>
<td>Poly-Vinylidenfluorid-Hexfluoro-Propylen (PVDF-HFP)</td>
<td>CoCr</td>
<td>++</td>
<td>++</td>
<td>[16, 20, 21, 201]</td>
</tr>
<tr>
<td><strong>Promus Element</strong></td>
<td>Boston Scientific</td>
<td>Zotarolimus</td>
<td>Phosphorylcholin (ABT 578)</td>
<td>CoCr</td>
<td>++</td>
<td>++</td>
<td>[14, 16, 20, 21, 201]</td>
</tr>
<tr>
<td><strong>EndoV-Familie</strong></td>
<td>Boston Scientific</td>
<td>Zotarolimus</td>
<td>Phosphorylcholin (ABT 578)</td>
<td>CoCr</td>
<td>++</td>
<td>++</td>
<td>[17, 25, 28]</td>
</tr>
<tr>
<td><strong>EndoV Sprint</strong></td>
<td>Medtronic</td>
<td>Zotarolimus</td>
<td>Phosphorylcholin (ABT 578)</td>
<td>CoCr</td>
<td>++</td>
<td>++</td>
<td>[14, 16, 20, 21, 201]</td>
</tr>
<tr>
<td><strong>Resolute-Familie</strong></td>
<td>Medtronic</td>
<td>3 Komponenten Biolinx</td>
<td></td>
<td>CoCr</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Resolute</strong></td>
<td>Medtronic</td>
<td>3 Komponenten Biolinx</td>
<td></td>
<td>CoCr</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Coroflex Please</strong></td>
<td>B. Braun</td>
<td>Paclitaxel</td>
<td>Stainless steel</td>
<td>--</td>
<td>(++)</td>
<td></td>
<td>[35, 36]</td>
</tr>
<tr>
<td><strong>Biodegradierbares Polymer</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Biomatrix-Familie</strong></td>
<td>Biosensors</td>
<td>Biolimus A9</td>
<td>PLA</td>
<td>Stainless steel</td>
<td>+</td>
<td>–</td>
<td>[31, 32]</td>
</tr>
<tr>
<td><strong>Biomatrix Flex</strong></td>
<td>Terumo</td>
<td>Biolimus A9</td>
<td>PLA</td>
<td>Stainless steel</td>
<td>–</td>
<td>+</td>
<td>[33]</td>
</tr>
<tr>
<td><strong>Neo</strong></td>
<td>Cordis</td>
<td>Sirolimus</td>
<td>Resorbierbarer Polymer</td>
<td>CoCr</td>
<td>–</td>
<td>+</td>
<td>[203]</td>
</tr>
<tr>
<td><strong>Nobori</strong></td>
<td>Terumo</td>
<td>Biolimus A9</td>
<td>PLA</td>
<td>Stainless steel</td>
<td>–</td>
<td>+</td>
<td>[33]</td>
</tr>
<tr>
<td><strong>Polymerfreie Beschichtung</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Yukon (ISAR)</strong></td>
<td>Translumina</td>
<td>Sirolimus</td>
<td>Kein Polymer</td>
<td>Stainless steel</td>
<td>–</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Bioabsorbierbare Stents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Absorb</strong></td>
<td>Abbott</td>
<td>Everolimus</td>
<td>PLDA</td>
<td>PLLA (bioabsorbierbarer Stent)</td>
<td>–</td>
<td>(+)</td>
<td>[39]</td>
</tr>
</tbody>
</table>

Datenlage: ++ mehrere positive randomisierte Studien, + eine positive randomisierte Studie, (+) Registerdaten, – keine klinischen Daten; Publikation jeweils in „peer-reviewed journals“. Literaturzitate relevanter klinischer Studien seit der letzten Aktualisierung des Positionspapiers.
Drug Eluting Stents

SeQuent ISAR (Sirolimus)
Indications and Results

Efficacy
- All DES reduce the likelihood of re-intervention at the target vessel compared to BMS
- **EVEROLIMUS, SIROLIMUS, ZOTAROLIMUS** - Resolute are the most efficacious

Safety
- **No** difference in procedural mortality compared to BMS
- All DES (but not Paclitaxel DES) reduced the risk of MI
- **EVEROLIMUS** has the best safety profile concerning stent thrombosis
## Drug Eluting Balloons

<table>
<thead>
<tr>
<th>Ballonsystem</th>
<th>Hersteller</th>
<th>Zusatz zur Beschichtung</th>
<th>Wirksubstanz</th>
<th>Angiographische Endpunktstudien</th>
<th>Literatur</th>
</tr>
</thead>
<tbody>
<tr>
<td>SeQuent Please</td>
<td>B. Braun</td>
<td>Kontrastmittel (Iopromid)</td>
<td>Paclitaxel 3 μg/mm²</td>
<td>++ (ISR, de novo mit Stent)</td>
<td>[41, 43, 44, 45, 46, 96, 118]</td>
</tr>
<tr>
<td>Dior II</td>
<td>Eurocor</td>
<td>Schellack</td>
<td>Paclitaxel 3 μg/mm²</td>
<td>–</td>
<td>[47]</td>
</tr>
<tr>
<td>Pantera Lux</td>
<td>Biotronik</td>
<td>Butyryl-triheyl Zitrat</td>
<td>Paclitaxel 3 μg/mm²</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Elutax</td>
<td>AachenResonance</td>
<td></td>
<td>Paclitaxel 2 μg/mm²</td>
<td>–</td>
<td>[204]</td>
</tr>
<tr>
<td>In.Pact Falcon</td>
<td>Medtronic Invatec</td>
<td>Harnstoff</td>
<td>Paclitaxel 3 μg/mm²</td>
<td>(+)</td>
<td></td>
</tr>
</tbody>
</table>

**ISR** Therapie der Instentstenose.

*Studienlage (publiziert in „peer-reviewed journals“): ++ mehrere positive randomisierte Studien, + eine positive randomisierte Studie, (+) Registerdaten, – keine klinischen Daten.*
Drug Eluting Balloons

SeQuent Please, Sequent Please NEO
Results and Indications

### ISRS

**DEB vs. uncoated PTA**

Event free survival at 2 years
(Stent thrombosis, TLR, MI, Stroke, death)
Scheller 2008

### DEB vs. DES (Paclicatxel)

Event free survival at 2 years
(Stent thrombosis, TLR, MI, death)
Unverdorben 2009

---

![Graph showing event-free survival between coated and uncoated balloons.](image)
3 months f/u

12 months f/u
ISRS treatment with DEB

Vajda et al. AJNR 2011
20 conventional balloons - 43 SeQuent Please DEBs
6 % „failed attempts“ with SeQuent Please!
DEB and Enterprise
DEB and Enterprise
DEB and Enterprise
DEB and Enterprise

3 month FU
54 stenoses (52 patients)
technical failure 19 %
30 d Stroke, death 8.8 %
8.9 months FU 0%
restenoses 3 %

Vajda et al. Cardiovasc Intervent Radiol 2012
## DES in Neuroradiology

<table>
<thead>
<tr>
<th>author</th>
<th>n=</th>
<th>type of stent</th>
<th>failure</th>
<th>restenosis</th>
<th>occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vajda (2012)</td>
<td>106</td>
<td>Coroflex Please</td>
<td>7%</td>
<td>3.8%</td>
<td>0.9%</td>
</tr>
<tr>
<td>Lu (2012)</td>
<td>24</td>
<td>Taxus Express Excell</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Firebird</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steinfort (2007)</td>
<td>13</td>
<td>Taxus</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Qureshi (2006)</td>
<td>21</td>
<td>Cypher Taxus express</td>
<td>14%</td>
<td>14%</td>
<td>0%</td>
</tr>
<tr>
<td>Gupta (2006)</td>
<td>29</td>
<td>Cypher</td>
<td>10%</td>
<td>5%</td>
<td>0%</td>
</tr>
<tr>
<td>Abou-Chebl (2005)</td>
<td>8</td>
<td>Cypher Taxus</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
TAXUS™ Element™ Stent
Recoil - flexibility - wall apposition
Results with Taxus Element

N = 78 stenoses

Length of stenoses
Median 6.4 mm (4-14 mm)

Stent dimensions
Diameter:
slightly undersized
Length:
as short as possible (8 mm)
(6x Taxus > 8 mm)
Results with Taxus Element

Technical success

In 68 / 78 stenoses successful (87%)

10 failures (13%)

- 3 conventional PTA
- 1 DEB
- 1 DEB & Enterprise
- 3 PTA & Enterprise
- 1 treated with a smaller Taxus Element
- 1 transbrachial approach, success with Taxus Element
Results with Taxus Element

Taxus Element - technical failure
Results with Taxus Element

Taxus Element - technical failure

1.5 mm
2 mm
Attempt 2.25 / 8 Taxus Element
- 6F Envoy
- 6 F Vista brite Tip
Post PTA and Enterprise
Results with Taxus Element

Robust access required
Robust access required

Anterior circulation
- 8 F Vista Brite Tip
- 0.57 DAC or
- 0.58 NavienA+
  - 115 cm!
- Traxcess EX

Posterior circulation
- 6 F Vista Brite Tip
Results with Taxus Element

57 stenoses with F/U DSA

ISRS
Results with Taxus Element

Clinical results

1 (1.8%) ipsilateral stroke
- Clopidogrel was stopped after 9 months
1 (1.8%) stroke in another vascular territory
Acute stroke

n = 8

Loading with 600 mg Clopidogrel and 500 mg ASA
prior to transport
or via gastric tube prior to the procedure

1 intraprocedural thrombus formation
treated with an IV Integrilin bolus
Results with Taxus Element

Acute stroke
Results with Taxus Element

Acute stroke

mTE pREset 4 / 20
1 passage

1.5 mm

Taxus Element 2.25 / 8

Early stent occlusion

2 mm
Results with Taxus Element

Acute stroke

Pre Integrilin

Post 8 mg Integrilin IV
Results with Taxus Element

Acute stroke
Our current concept

Primary treatment

Most stenosis: PTA with a conventional balloon (pITA)

Increased recurrence risk: PTA with a DEB (SeQuent Neo Please)

Dissection, recoiling: PTA + selfexpanding stent (pITA, SeQuent Neo Please, Enterprise2)

Short stenosis, straight vessels...: DES (Coroflex ISAR)

Avoid snow plow effect: no PTA, just SE stent (Solitaire)
Our current concept

In stent re-stenosis

DEB or DES
(SeQuent Neo Please or Coroflex ISAR)

PTA
(pITA)

Adjacent de novo stenosis

like primary treatment
PTA (pITA)
PTA (pITA)
PTA (pITA)

Synchro2 0.014”, pITA 1.5 mm, 8 atm
PTA (pITA)
PTA (pITA)

Lumen at least double
THE MANAGEMENT OF INTRACRANIAL STENOSES IS NOT MASS SPORTS