Secondary Stroke Prevention

Hans-Christoph Diener
Department of Neurology and Stroke Center
Essen Germany
Secondary Stroke Prevention Outline

• Prevention of early stroke recurrence
• Combination antiplatelet therapy
• Anticoagulation in patients with atrial fibrillation (AF)
• Surgery versus stenting in symptomatic carotid stenosis
• Patients with cryptogenic stroke
• PFO closure in cryptogenic stroke
• Treatment of intracranial stenosis
Secondary Stroke Prevention Outline

- Prevention of early stroke recurrence
- Long-term combination antiplatelet therapy
- Anticoagulation in patients with atrial fibrillation
- Surgery versus stenting in symptomatic carotid stenosis
- PFO closure in cryptogenic stroke
- Treatment of intracranial stenosis
Cumulative risk of stroke after a transient ischaemic attack (TIA) or minor stroke

Log rank P=0.8
CHANCE Trial

• 5170 Chinese patients with TIA or minor stroke
• Randomised to aspirin monotherapy versus aspirin plus clopidogrel (300 mg + 75 mg) for 3 weeks, followed by clopidogrel mono-therapy
• Primary endpoint: recurrent stroke (ischemic or hemorrhagic)
Table 2. Efficacy and Safety Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aspirin (N=2586)</th>
<th>Clopidogrel and Aspirin (N=2584)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with Event no.</td>
<td>Event Rate %</td>
<td>Patients with Event no.</td>
<td>Event Rate %</td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>303</td>
<td>11.7</td>
<td>212</td>
<td>8.2</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke, myocardial infarction, or death from cardiovascular causes</td>
<td>307</td>
<td>11.9</td>
<td>216</td>
<td>8.4</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>295</td>
<td>11.4</td>
<td>204</td>
<td>7.9</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>8</td>
<td>0.3</td>
<td>8</td>
<td>0.3</td>
</tr>
</tbody>
</table>

![Survival Free of Stroke](image)

Hazard ratio, 0.68 (95% CI, 0.57–0.81)
P<0.001

<table>
<thead>
<tr>
<th>Days since Randomization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>No. at Risk</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Clopidogrel–aspirin</td>
</tr>
</tbody>
</table>
CHANCE Trial

• 303 events in mono-therapy
• 212 events in combination therapy
• HR = 0.68 sign. P< 0.001
• Any bleeding 41 versus 60 (HR 1.41, ns.)
POINT Trial

• High risk TIA (ABCD$_2$ >4) or minor stroke
• Randomised within 12 hours
  – Patients assigned to clopidogrel in addition to aspirin
  – Clopidogrel loading dose of 600mg followed by 75 mg, one tablet daily for 90 days
  – Controls assigned to placebo in addition to aspirin
• Primary endpoint at 90 days: combined vascular endpoint
• N = 4150
Conclusion

• Aspirin has very limited efficacy in the early prevention of recurrent stroke (3 months)
• Aspirin plus clopidogrel could be superior to aspirin monotherapy
Secondary Stroke Prevention
Outline

• Prevention of early stroke recurrence
• Long term combination antiplatelet therapy
• Surgery versus stenting in symptomatic carotid stenosis
• PFO closure in cryptogenic stroke
• Intracranial stenosis
Is combination therapy superior to mono-therapy?

- Aspirin plus clopidogrel
- Aspirin plus ER dipyridamole

**ER** = Extended Release
MATCH: Primary Endpoint (ITT)

IS, MI, VD, rehospitalization for acute ischemic event

Cumulative event rate

0.20

0.16

0.12

0.08

0.04

0.00

0

3

6

9

12

15

18

Months of follow-up

Placebo + Clopidogrel

ASA + Clopidogrel

RRR: 6.4%

(p=0.244)
CHARISMA

Cumulative Incidence of the Primary Composite End Point (%)

No. at Risk
Clopidogrel 7802 7653 7510 7363 5299 2770
Placebo 7801 7644 7482 7316 5212 2753
Effects of Clopidogrel Added to Aspirin in Patients with Recent Lacunar Stroke

The SPS3 Investigators*
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aspirin plus Placebo (N = 1503)</th>
<th>Aspirin plus Clopidogrel (N = 1517)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>rate (%/yr)</td>
<td>no.</td>
<td>rate (%/yr)</td>
</tr>
<tr>
<td>All major hemorrhages</td>
<td>56</td>
<td>1.1</td>
<td>105</td>
<td>2.1</td>
</tr>
<tr>
<td>Intracranial hemorrhages†</td>
<td>15*</td>
<td>0.28</td>
<td>22</td>
<td>0.42</td>
</tr>
<tr>
<td>Intracerebral</td>
<td>8</td>
<td>0.15</td>
<td>15</td>
<td>0.28</td>
</tr>
<tr>
<td>Subdural or epidural</td>
<td>6</td>
<td>0.11</td>
<td>7</td>
<td>0.13</td>
</tr>
<tr>
<td>Other</td>
<td>4</td>
<td>0.07</td>
<td>2</td>
<td>0.04</td>
</tr>
<tr>
<td>Extracranial bleeding</td>
<td>42</td>
<td>0.79</td>
<td>87</td>
<td>1.7</td>
</tr>
<tr>
<td>Gastrointestinal‡</td>
<td>28</td>
<td>0.52</td>
<td>58</td>
<td>1.1</td>
</tr>
<tr>
<td>Fatal hemorrhages</td>
<td>4</td>
<td>0.07</td>
<td>9</td>
<td>0.17</td>
</tr>
<tr>
<td>Intracranial</td>
<td>4</td>
<td>0.07</td>
<td>7</td>
<td>0.13</td>
</tr>
<tr>
<td>Extracranial</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Conclusions

Based on MATCH, CHARISMA and SPS3 in secondary stroke prevention the combination of clopidogrel plus aspirin is not more effective than clopidogrel or aspirin monotherapy

The combination of clopidogrel plus aspirin carries a higher bleeding risk than clopidogrel or aspirin monotherapy
European Stroke Prevention Study
ESPS 2
n = 6.602

- Placebo  
  (n = 1.649)

- Aspirin  
  2 x 25 mg  
  (n = 1.649)

- ER-DP  
  2 x 200 mg  
  (n = 1.654)

- Aspirin + ER-DP  
  2 x 25 mg ASA/200 mg ER-DP  
  (n = 1.650)

ESPS 2
Relative Risk Reduction for Stroke (pairwise comparisons)

DP ret = Dipyridamol retard
ESPS 2 Group, J Neurol Sci 1997;151(suppl):S1-S77.
Conclusion

The combination of aspirin plus modified-release dipyridamole is superior to aspirin monotherapy

The combination is more effective than aspirin in high risk patients

The combination has a higher bleeding risk
Secondary Stroke Prevention
Outline

• Prevention of early stroke recurrence
• Combination antiplatelet therapy
• **Anticoagulation in patients with atrial fibrillation (AF)**
• Surgery versus stenting in symptomatic carotid stenosis
• PFO closure in cryptogenic stroke
• Treatment of intracranial stenosis
OAC is more effective than ASA for secondary stroke prevention in AF

EAFT: European, multicentre RCT
1007 patients with non-rheumatic AF and recent TIA or minor ischaemic stroke (mean follow-up 2.3 years)

ASA = acetylsalicylic acid; EAFT = European atrial fibrillation trial; INR = international normalized ratio; OAC = oral anticoagulant; RCT = randomized controlled trial; TIA = transient ischaemic attack


![Stroke risk reduction vs placebo (%)](chart)

- OAC (INR 2.5-4.0)
- ASA (300 mg/day)

66% vs 14%
P < 0.001

n.s.
**RE-LY® prior stroke subgroup analysis: time to stroke or systemic embolism in patients with/without previous stroke or TIA**

![Graph](image)

### Cumulative hazard rates

<table>
<thead>
<tr>
<th>Group</th>
<th>Follow-up (years)</th>
<th>Number at risk (prior stroke)</th>
<th>Number at risk (no prior stroke)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dabigatran 110 mg</td>
<td>0</td>
<td>1195</td>
<td>4819</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>1159</td>
<td>4702</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1131</td>
<td>4578</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>908</td>
<td>3684</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>573</td>
<td>2371</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>289</td>
<td>1096</td>
</tr>
<tr>
<td>Dabigatran 150 mg</td>
<td>0</td>
<td>1233</td>
<td>4843</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>1200</td>
<td>4739</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1163</td>
<td>4616</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>938</td>
<td>3744</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>517</td>
<td>2427</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>321</td>
<td>1108</td>
</tr>
<tr>
<td>Warfarin</td>
<td>0</td>
<td>1195</td>
<td>4827</td>
</tr>
<tr>
<td></td>
<td>0.5</td>
<td>1159</td>
<td>4703</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1125</td>
<td>4593</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>895</td>
<td>3698</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>565</td>
<td>2325</td>
</tr>
<tr>
<td></td>
<td>2.5</td>
<td>251</td>
<td>1061</td>
</tr>
</tbody>
</table>

**BID = twice daily; TIA = transient ischaemic attack**

ROCKET AF Subanalysis: Secondary Prevention Results
Primary Efficacy Outcome

Kaplan–Meier survival curve showing time to the primary outcome (stroke or systemic embolism)

HR, 0.94; 95% CI, 0.77-1.16
Interaction
P = 0.23

HR, 0.77; 95% CI, 0.58-1.01

Intention-to-treat population.
HR, hazard ratio; TIA, transient ischemic attack.

ARISTOTLE: Apixaban reduced the risk of stroke vs. warfarin, whether or not patients had a previous stroke/TIA

Apixaban vs. warfarin:
- Previous stroke or TIA: HR: 0.76; 95% CI: 0.56 to 1.03
- No previous stroke or TIA: HR: 0.82; 95% CI: 0.65 to 1.03

This study was not designed to compare NOACs against one another. Comparison between NOACs is not valid because of population differences among the studies. No head to head data are available.

Ntaios G et al. Stroke 2012 Nov 13 [Epub ahead of print]
Effects of novel oral anticoagulants vs warfarin on stroke or systemic embolism in patients with AF and previous stroke or TIA (1)

<table>
<thead>
<tr>
<th>Stroke or Systemic Embolism</th>
<th>NOACs</th>
<th>Warfarin</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study or subgroup</strong></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>73</td>
<td>1694</td>
<td>98</td>
</tr>
<tr>
<td>RE-LY 110</td>
<td>55</td>
<td>1195</td>
<td>65</td>
</tr>
<tr>
<td>RE-LY 150</td>
<td>51</td>
<td>1233</td>
<td>65</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>179</td>
<td>3754</td>
<td>187</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>7876</td>
<td>7846</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>358</td>
<td>415</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=1.93$, df=3 (P=0.59); $I^2=0\%$

Test for overall effect: $Z=2.15$ (P=0.03)

This study was not designed to compare NOACs against one another. Comparison between NOACs is not valid because of population differences among the studies. No head-to-head data are available.

AF = atrial fibrillation; TIA = transient ischemic attack; NOAC = novel oral anticoagulant.

Ntaios G et al. Stroke 2012 Nov 13 [Epub ahead of print]
Effects of novel oral anticoagulants vs warfarin on haemorrhagic stroke in patients with AF and previous stroke or TIA (2)

<table>
<thead>
<tr>
<th>Haemorrhagic stroke</th>
<th>NOACs</th>
<th>Warfarin</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study or subgroup</td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>12</td>
<td>1694</td>
<td>31</td>
</tr>
<tr>
<td>RE-LY 110</td>
<td>2</td>
<td>1195</td>
<td>18</td>
</tr>
<tr>
<td>RE-LY 150</td>
<td>5</td>
<td>1233</td>
<td>18</td>
</tr>
<tr>
<td>ROCKET AF</td>
<td>22</td>
<td>3754</td>
<td>30</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>7876</td>
<td>7846</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>41</td>
<td>97</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2=7.07$, df=3 (P=0.07); $I^2=58$

Test for overall effect: $Z=4.79$ (P<0.00001)

This study was not designed to compare NOACs against one another. Comparison between NOACs is not valid because of population differences among the studies. No head-to-head data are available.

AF = atrial fibrillation; TIA = transient ischemic attack; NOAC = novel oral anticoagulant.

Ntaios G et al. Stroke 2012 Nov 13 [Epub ahead of print]
NOACs: special situations

- Patients >80 years
- CrCl 30–50 mL/min
- Prior GI bleed
- Prior intracerebral bleed
- Afib and carotid stenosis
- Start after TIA or stroke
- Cognitive impairment
- Gait apraxia and falls
- Afib and stable coronary heart disease
- Afib and DVT prevention
- Myocardial infarction
- Thrombolysis
Resumption of oral anticoagulation after ICH

A. Ischemic events

χ² P < .001

No OAC resumption

OAC resumption

B. Hemorrhagic events

χ² P = .48

No OAC resumption

OAC resumption

Kuramatsu et al. JAMA 2015
Suggestions for initiation or resumption of oral anticoagulation in AF patients after an intracranial haemorrhage

- **Patient has a history or suffered recently from intracranial haemorrhage**
  - **Contraindication for OAC**
  - **Cause of bleeding cannot be removed or treated**
  - **Intracerebral haemorrhage**
  - **Subdural hematoma (SDH)**
  - **Subarachnoidal haemorrhage (SAH)**

**Consider clinical factors favouring initiation OAC**

- **Older age**
  - Uncontrolled hypertension
  - Cortical bleed
  - Severe white matter lesions
  - Multiple microbleeds (>30)
  - Chronic alcoholism
  - Need for dual antiplatelet therapy after PCI

- **Younger age**
  - Well-controlled hypertension
  - Basal ganglia bleed
  - Nor or mild white matter lesions
  - SDH: surgical removal
  - SAH: aneurysm clipped or coiled
  - High risk of ischemic stroke

- **Consider LAA occlusion**
- **Consider LAA occlusion**
- **Initiate or resume OAC after 4-8 weeks**
NOACs: special situations

- Patients >80 years
- CrCl 30–50 mL/min
- Prior GI bleed
- Prior intracerebral bleed
- Afib and carotid stenosis
- Start after TIA or stroke
- Cognitive impairment
- Gait apraxia and falls
- Afib and stable coronary heart disease
- Afib and DVT prevention
- Myocardial infarction
- Thrombolysis
Initiation or resumption of anticoagulation depends on severity of stroke

**Time to re-initiation depends on infarct size:**
1 – 3 – 6 – 12 day rule (Diener’s Law)

- **TIA**
  - As soon as imaging has excluded a cerebral haemorrhage

- **Mild stroke**
  - 3–5 days after symptom onset

- **Moderate stroke**
  - 5–7 days after stroke onset

- **Severe stroke**
  - 2 weeks after stroke onset

*Mild = NIHSS score <8; moderate = NIHSS score 8–16; severe = NIHSS score >16
TIA, transient ischaemic attack
Huisman et al. Thromb Haemost 2012
Suggestions for initiation or resumption of oral anticoagulation in AF patients after an acute stroke or TIA

- **TIA or Ischemic Stroke**
  - Exclusion of intracerebral bleeding (ICB) by CT or MRI

- **TIA**
  - Start OAC
    - 1 day after acute event

- **Mild Stroke (NIHSS <8)**
  - 3 days after acute event

- **Moderate Stroke (NIHSS 8-15)**
  - 6 days after acute event
  - Exclude haemorrhagic transformation by CT or MRI at day 6

- **Severe Stroke (NIHSS >16)**
  - 12 days after acute event
  - Exclude haemorrhagic transformation by CT or MRI at day 12

**Consider additional clinical factors favouring early / delayed initiation**

- **Low NIHSS (<8)**
  - Small/no brain infarction on MRI
  - High recurrence risk e.g. cardiac thrombus on echo
  - No need for PEG
  - No need for carotid surgery
  - No haemorrhagic transformation
  - Clinically stable
  - Young patient
  - Blood pressure is controlled
  - Start OAC
    - 1 day after acute event

- **High NIHSS**
  - Large/moderate brain infarction
  - Needs PEG/major surgical intervention
  - Needs carotid surgery
  - Haemorrhagic transformation
  - Neurologically unstable
  - Elderly patient
  - Uncontrolled hypertension
  - Delayed initiation
    - After acute event

- **Needs PEG/major surgical intervention**
  - Delayed initiation
    - After acute event

- **Needs carotid surgery**
  - Delayed initiation
    - After acute event

- **Haemorrhagic transformation**
  - Delayed initiation
    - After acute event

- **Neurologically unstable**
  - Delayed initiation
    - After acute event

- **Elderly patient**
  - Delayed initiation
    - After acute event

- **Uncontrolled hypertension**
  - Delayed initiation
    - After acute event
Conclusion

• Oral anticoagulation is highly effective in secondary stroke prevention in patients with AF
• As a group the NOACs are superior to warfarin in preventing recurrent stroke, intracranial hemorrhage, major bleeding and death
• Time of initiation or resumption of OAC after stroke depends on the etiology (ischemic versus hemorrhagic) and other factors
Secondary Stroke Prevention Outline

• Prevention of early stroke recurrence
• Combination antiplatelet therapy
• Surgery versus stenting in symptomatic carotid stenosis
• PFO closure in cryptogenic stroke
Stenting or Angioplasty in Patients with Carotid Stenosis?
Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial

*International Carotid Stenting Study investigators*
Short term and intermediate term comparison of endarterectomy versus stenting for carotid artery stenosis: systematic review and meta-analysis of randomised controlled clinical trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naylor et al 1998</td>
<td>0.05 (0.00 to 0.99)</td>
</tr>
<tr>
<td>Wallstent 2001</td>
<td>0.34 (0.12 to 0.98)</td>
</tr>
<tr>
<td>CAVATAS 2001</td>
<td>0.99 (0.55 to 1.78)</td>
</tr>
<tr>
<td>Brooks et al 2001</td>
<td>3.18 (0.13 to 79.83)</td>
</tr>
<tr>
<td>Brooks et al 2004</td>
<td>1.15 (0.41 to 3.25)</td>
</tr>
<tr>
<td>SAPPHIRE 2004/8</td>
<td>0.38 (0.18 to 0.81)</td>
</tr>
<tr>
<td>EVA-3S 2006/8</td>
<td>0.84 (0.54 to 1.31)</td>
</tr>
<tr>
<td>SPACE 2006</td>
<td>3.32 (0.12 to 91.60)</td>
</tr>
<tr>
<td>BACASS 2007</td>
<td>0.57 (0.39 to 0.85)</td>
</tr>
<tr>
<td>ICSS 2009</td>
<td>0.67 (0.47 to 0.95)</td>
</tr>
<tr>
<td>Random effects model</td>
<td></td>
</tr>
</tbody>
</table>

Fig 2 | Forest plot of odds ratios of risk for composite of stroke or death within 30 days of carotid endarterectomy versus carotid artery stenting. ICSS also included myocardial infarctions (three for stenting, four for endarterectomy) in this endpoint. See footnote to table for full title of studies
CREST

- Carotid surgery versus angioplasty plus stenting
- 2502 patients
- 47% asymptomatic, 53% symptomatic
- Mean age 69 Jahre
- 35% females
- Degree of stenosis for inclusion
  60% (asymptomatic), 50% (symptomatic)
## CREST

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stenting</th>
<th>Surgery</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1262</td>
<td>1240</td>
<td></td>
</tr>
<tr>
<td>Primary*</td>
<td>7.2%</td>
<td>6.8%</td>
<td>n. s.</td>
</tr>
<tr>
<td>30 days</td>
<td>5.2%</td>
<td>4.5%</td>
<td>n. s.</td>
</tr>
<tr>
<td>Stroke</td>
<td>4.1%</td>
<td>2.3%</td>
<td>Sign.</td>
</tr>
<tr>
<td>MI</td>
<td>1.1%</td>
<td>2.3%</td>
<td>Sign.</td>
</tr>
<tr>
<td>Cranial Nerve</td>
<td>0.3%</td>
<td>4.8%</td>
<td>Sign.</td>
</tr>
<tr>
<td>Ipsilat. Stroke</td>
<td>2.0%</td>
<td>2.4%</td>
<td>n. s.</td>
</tr>
</tbody>
</table>

*Primary: Stroke, MI, Death, Ipsilateral Stroke, 4 years
Age dependency in CREST
Influence of sex on outcomes of stenting versus endarterectomy: a subgroup analysis of the Carotid Revascularization Endarterectomy versus Stenting Trial (CREST)

Virginia J Howard, Helmi L Lutsep, Ariane Mackey, Bart M Demaerschalk, Albert D Sam II, Nicole R Gonzales, Alice J Sheffet, Jenifer H Voeks, James F Meschia, Thomas G Brott, for the CREST investigators

Figure: Kaplan-Meier curves of the primary endpoint
CAS=carotid artery stenting. CEA=carotid endarterectomy.
Conclusions

- Endarterectomy has a lower complication rate than stenting
- Re-stenosis is higher after stenting
- Endarterectomy is preferred in females and patients >70 years
- Protection devices are not protecting
- Complication rate needs to be <6%
Secondary Stroke Prevention
Outline

• Prevention of early stroke recurrence
• Combination antiplatelet therapy
• Surgery versus stenting in symptomatic carotid stenosis
• Treatment of symptomatic intracranial stenosis
• PFO closure in cryptogenic stroke
Stenting versus Aggressive Medical Therapy for Intracranial Arterial Stenosis

Marc I. Chimowitz, M.B., Ch.B., Michael J. Lynn, M.S., Colin P. Derdeyn, M.D., Tanya N. Turan, M.D., David Fiorella, M.D., Ph.D., Bethany F. Lane, R.N., L. Scott Janis, Ph.D., Helmi L. Lutsep, M.D., Stanley L. Barnwell, M.D., Ph.D., Michael F. Waters, M.D., Ph.D., Brian L. Hoh, M.D., J. Maurice Hourihane, M.D., Elad I. Levy, M.D., Andrei V. Alexandrov, M.D., Mark R. Harrigan, M.D., David Chiu, M.D., Richard P. Klucznik, M.D., Joni M. Clark, M.D., Cameron G. McDougall, M.D., Mark D. Johnson, M.D., G. Lee Pride, Jr., M.D., Michel T. Torbey, M.D., M.P.H., Osama O. Zaidat, M.D., Zoran Rumboldt, M.D., and Harry J. Cloft, M.D., Ph.D., for the SAMMPRIS Trial Investigators*
Conclusion

Best medical therapy is more effective in patients with symptomatic intracranial stenosis compared to stenting.
Secondary Stroke Prevention Outline

• Prevention of early stroke recurrence
• Combination antiplatelet therapy
• Anticoagulation in patients with atrial fibrillation (AF)
• Surgery versus stenting in symptomatic carotid stenosis
• **Patients with cryptogenic stroke**
• PFO closure in cryptogenic stroke
• Treatment of intracranial stenosis
Patients with Embolic Stroke of Undetermined Source are a subset of patients with cryptogenic stroke.

ESUS = embolic stroke of undetermined source

Embolic Stroke of Undetermined Source (ESUS)

Panel 2: Criteria for diagnosis of embolic stroke of undetermined source*

- Stroke detected by CT or MRI that is not lacunar†
- Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischaemia
- No major-risk cardioembolic source of embolism‡
- No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, drug misuse)

*Requires minimum diagnostic assessment (panel 3). †Lacunar defined as a subcortical infarct smaller than or equal to 1.5 cm (≤2.0 cm on MRI diffusion images) in largest dimension, including on MRI diffusion-weighted images, and in the distribution of the small, penetrating cerebral arteries; visualisation by CT usually needs delayed imaging greater than 24-48 h after stroke onset. ‡Permanent or paroxysmal atrial fibrillation, sustained atrial flutter, intracardiac thrombus, prosthetic cardiac valve, atrial myxoma or other cardiac tumours, mitral stenosis, recent (<4 weeks) myocardial infarction, left ventricular ejection fraction less than 30%, valvular vegetations, or infective endocarditis.

Panel 3: Proposed diagnostic assessment for embolic stroke of undetermined source*

- Brain CT or MRI
- 12-lead ECG
- Precordial echocardiography
- Cardiac monitoring for ≥24 h with automated rhythm detection†
- Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography)

*Imaging of the proximal aortic arch is not needed; special blood tests for prothrombotic states only if the patient has a personal or family history of unusual thrombosis or associated systematic signs or disorder. †Cardiac telemetry is not sufficient.
Indexschlaganfall (ESUS)*

"Diagnoseweg": MRT-/CT-Untersuchung zum Ausschluss von Lakunen; Carotis-US und ≥ 24-stündige Rhythmusaufzeichnung zum Ausschluss von VHF

Dabigatran (150 oder 110 mg 2 x tgl.)†
Placebo (für ASS)

ASS (100 mg 1 x tgl.)

Placebo (für Dabigatran)

Primärer Endpunkt: Schlaganfall

Therapieende
n = 3000

n = 3000

30-tägiger Follow-Up

0 Tage - 3 Monate‡

0,5 - 3 Jahre

* mRS ≤ 3, Alter ≥ 60 oder 50-59 Jahre mit zusätzlichen Risikofaktoren; † Alle Patienten erhielten Dabigatran 150 mg 2 x tgl., ausgenommen Patienten ≥ 75 Jahre oder mit einer CrCl von 30-50 ml/min. Diese Patienten erhielten Dabigatran 110 mg 2 x tgl.; ‡ 0 Tage - 6 Monate bei Patienten > 60 Jahre mit zusätzlichen Risikofaktoren.

CrCl = Kreatinin-Clearance; mRS = modifizierte Rankin-Skala; R = Randomisierung; US = Ultraschall


Secondary Stroke Prevention Outline

• Prevention of early stroke recurrence
• Combination antiplatelet therapy
• Surgery versus stenting in symptomatic carotid stenosis
• Treatment of intracranial stenosis
• PFO closure in cryptogenic stroke
PFO Closure in Cryptogenic Stroke

At present 3 negative randomised trials (with a trend for efficacy for PFO closure)
For which patients is PFO closure recommended?

- Clinical circumstances indicating paradoxical emboli
- Recurrent stroke in patient <65 years on aspirin or warfarin
Secondary Stroke Prevention Summary

- Prevention of early stroke recurrence
- Combination antiplatelet therapy
- Anticoagulation in AF
- Surgery versus stenting in symptomatic carotid stenosis
- Stroke prevention in ESUS
- PFO closure in cryptogenic stroke
- Treatment of intracranial stenosis