Oral anticoagulation and new antiplatelet therapy in acute and chronic cerebral ischemia

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INSERM U1171
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Outline

- Background
- Acute stage of cerebral ischaemia
  - What is proven effective?
  - Antiplatelet agents
  - Heparin and heparinoids
- Secondary prevention after cerebral ischaemia
  - What is proven effective?
  - Antiplatelet agents
  - Oral anticoagulant
- Specific issues
  - Dissections
  - Prevention of DVT and PE
  - Cerebral haemorrhage under anticoagulants / antiplatelet therapy
  - Cerebral ischaemia under anticoagulants / antiplatelet therapy
- Conclusions
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Stroke: a public health issue

- 2400 / million inhabitants / year
- 80-85% ischaemic
- 50% preventable
- Treatable in case of hyperacute management

Life expectancy at birth in France

84.8
78.2
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- Conclusions
## Effective therapies in acute cerebral ischaemia

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Level of evidence</th>
<th>Death and handicap prevented for 1,000 patients treated</th>
<th>Target</th>
<th>Death and handicap prevented for 1,000,000 inhabitants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke unit</td>
<td>Several RCTs and meta-analysis</td>
<td>50 (mRS 0-1)</td>
<td>100%</td>
<td>120</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Several RCTs and meta-analysis</td>
<td>12 (mRS 0-1)</td>
<td>80%</td>
<td>23</td>
</tr>
<tr>
<td>rt-PA &lt; 3 h</td>
<td>Several RCTs and meta-analysis</td>
<td>143 (mRS 0-1)</td>
<td>20%</td>
<td>69</td>
</tr>
<tr>
<td>rt-PA 3-4.5h</td>
<td>Several RCTs and meta-analysis</td>
<td>71 (mRS 0-1)</td>
<td>10%</td>
<td>7</td>
</tr>
<tr>
<td>Interventional radiology</td>
<td>5** (+1) positive RCTs and meta-analysis of 8* trials</td>
<td>125* to 200** (mRS 0-2)</td>
<td>15%</td>
<td>19 to 30</td>
</tr>
<tr>
<td>Hemicraniectomy</td>
<td>Meta-analysis</td>
<td>250* (mRS 0-3)</td>
<td>1%</td>
<td>2 to 3</td>
</tr>
</tbody>
</table>
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- Conclusions
Aspirin

Day 14

<table>
<thead>
<tr>
<th>Event</th>
<th>Aspirin (300 mg)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>9</td>
<td>9,4</td>
</tr>
<tr>
<td>Ischaemic strokes</td>
<td>2,8</td>
<td>3,9</td>
</tr>
<tr>
<td>All strokes</td>
<td>3,7</td>
<td>4,6</td>
</tr>
<tr>
<td>Stroke death</td>
<td>11,3</td>
<td>12,4</td>
</tr>
<tr>
<td>Extracranial haemorrhage</td>
<td>1,1</td>
<td>0,6</td>
</tr>
</tbody>
</table>

IST group, Lancet 1997
## Aspirin vs control

N = 41,325 patients, 8 trials
Aspirin 160 to 300 mg, started < 48h
NEP: number of events prevented

<table>
<thead>
<tr>
<th></th>
<th>OR (IC 95%)</th>
<th>NEP / 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Under treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Recurrence of brain ischaemia</td>
<td>0.77 (0.69 – 0.87)</td>
<td>7</td>
</tr>
<tr>
<td>- Intracranial haemorrhage</td>
<td>1.23 (1.00 – 1.50)</td>
<td>-2</td>
</tr>
<tr>
<td>- Extracranial haemorrhage</td>
<td>1.68 (1.34 – 2.09)</td>
<td>4</td>
</tr>
<tr>
<td>- Deep venous thrombosis</td>
<td>0.78 (0.36 – 1.67)</td>
<td>-</td>
</tr>
<tr>
<td>- Pulmonary embolism</td>
<td>0.71 (0.53 – 0.96)</td>
<td>1</td>
</tr>
<tr>
<td><strong>End of follow-up (&gt;1 months)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Death or dependency</td>
<td>0.94 (0.91 – 0.98)</td>
<td>13</td>
</tr>
<tr>
<td>- Complete recovery</td>
<td>1.06 (1.01 – 1.11)</td>
<td>10</td>
</tr>
</tbody>
</table>

Meta-analysis: The Cochrane Library 2004
FASTER

- N = 392, TIA or minor stroke, < 24h
- Clopidogrel (300 mg then 75mg) or Placebo on top of aspirin
- Prematurely stopped for low inclusion rate
- Stroke at 90 days
  - Clopidogrel 7.1% vs 10.8% RR = 0.7 (0.3 – 1.2)

Kennedy et al, Lancet Neurol 2007
Other antiplatelet agents

- **Ticagrelor tested in SOCRATES¹:**
  - evaluates whether ticagrelor, (antiplatelet agent that blocks the P2Y12 receptor) reduces the risk of major vascular events compared with aspirin when given within 24 h after symptom onset of a mild ischemic stroke or high-risk transient ischemic attack.

¹Johnston et al 2015.
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Heparin

- **Potential benefits**
  - Decreases risk of thrombus extension
  - Prevents recurrence of embolic events
  - Prevents DVT and PE

- **Potential risks**
  - Symptomatic intra-cranial haemorrhage
  - Severe extra-cranial haemorrhage
  - Thrombocytopenia
Haemorrhagic transformation

Predictors of HT

- Volume of infarct
- Clinical severity
- Brain oedema
- Early ischaemic signs
- Age
- High Blood pressure
- Cardio-embolic source
- On-going anticoagulant therapy
- Thrombolytic therapy
- Late recanalization
# Haemorrhagic transformation

**TABLE 1. Rates of HT Among Placebo Groups in Acute Stroke Trials of Intravenous Therapies**

<table>
<thead>
<tr>
<th></th>
<th>DIAS (Low+ High Dose)²²</th>
<th>AbESTT-I²⁴</th>
<th>CLOTBUST-II³³</th>
<th>NINDS²</th>
<th>ECASS-II²⁵</th>
<th>ECASS-I²⁶</th>
<th>Atlantis-B²⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>27</td>
<td>199</td>
<td>63</td>
<td>312</td>
<td>386</td>
<td>305</td>
<td>265</td>
</tr>
<tr>
<td>Baseline, median NIHSSS</td>
<td>12</td>
<td>9</td>
<td>17</td>
<td>15</td>
<td>11</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>0</td>
<td>1.0%</td>
<td>4.8%</td>
<td>0.6%</td>
<td>3.4%</td>
<td>6.8%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Criteria for symptomatic ICH</td>
<td>NIHSSS*</td>
<td>PI†</td>
<td>NIHSSS‡</td>
<td>PI§</td>
<td>PI or NIHSSS¶</td>
<td>N/A</td>
<td>PI</td>
</tr>
<tr>
<td>Timing of CT</td>
<td>72 hours</td>
<td>36–48 hours</td>
<td>N/A</td>
<td>24 hours</td>
<td>7 days</td>
<td>7 days</td>
<td>10 days</td>
</tr>
<tr>
<td>Asymptomatic ICH</td>
<td>18.5%</td>
<td>14.1%</td>
<td>N/A</td>
<td>2.9%</td>
<td>36.8%</td>
<td>29.9%</td>
<td>4.7%</td>
</tr>
</tbody>
</table>

*Any ICH associated with a worsening of 4 points or more on the NIHSS and confirmed by CT.
†Neurological deterioration was found and if hemorrhage was detected on brain imaging Causal link required.
‡Hemorrhage with clinical worsening (indicated by an NIHSS score of ≥4) within 72 hours of the onset of stroke.
§If not seen on a previous CT scan and there had subsequently been either a suspicion of hemorrhage or any decline in neurological status.
¶Documentation by the investigator of clinical deterioration, or adverse events indicating clinical worsening (e.g. drowsiness, increase in hemiparesis) or causing a decreased in the NIHSS score of 4 or more points.
||Determined by the local investigator.

Khatri et am, Stroke 2007
Heparin

Day 14

- Death: 9 Heparin, 9.3 Placebo
- Ischaemic stroke: 2.9 Heparin, 3.8 Placebo
- All strokes: 4.1 Heparin, 4.2 Placebo
- Stroke death: 11.7 Heparin, 12 Placebo
- Extracranial haemorrhages: 1.3 Heparin, 0.4 Placebo

IST group, Lancet 1997
## Anticoagulants vs controls

N = 23,547 patients, 22 trials
Unfractionated heparin, LMWH, heparinoids, VKA, antithrombin.
Started within 14 days
NEP: number of events prevented

<table>
<thead>
<tr>
<th>Event</th>
<th>OR (IC 95%)</th>
<th>NEP/ 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Under treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Recurrence brain ischaemia</td>
<td>0.76 (0.65 – 0.88)</td>
<td>9</td>
</tr>
<tr>
<td>- Intracranial haemorrhage</td>
<td>2.52 (1.92 – 3.30)</td>
<td>9</td>
</tr>
<tr>
<td>- Extracranial haemorrhage</td>
<td>2.99 (2.24 – 3.99)</td>
<td>9</td>
</tr>
<tr>
<td>- Deep venous thrombosis</td>
<td>0.21 (0.15 – 0.29)</td>
<td>281</td>
</tr>
<tr>
<td>- Pulmonary embolism</td>
<td>0.60 (0.44 – 0.81)</td>
<td>4</td>
</tr>
<tr>
<td><strong>End of follow-up (&gt; 1 month)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Death</td>
<td>1.05 (0.98 – 1.12)</td>
<td>-</td>
</tr>
<tr>
<td>- Death or dependency</td>
<td>0.99 (0.93 – 1.04)</td>
<td>-</td>
</tr>
</tbody>
</table>

Meta-analysis: The Cochrane Library 2004
Anticoagulants vs controls

Meta-analysis: The Cochrane Library 2004
## Anticoagulants vs. antiplatelets

### Comparison: 01 Anticoagulants vs. antiplatelet agents
#### Outcome: 01 Death or dependence at end of follow-up

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>OR (95% CI Fixed)</th>
<th>Weight %</th>
<th>OR (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Unfractionated heparin, high dose</td>
<td>IST 1997</td>
<td>1526 / 2411</td>
<td>1489 / 2408</td>
<td>42.8</td>
<td>1.05 [0.93, 1.18]</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>1526 / 2411</td>
<td>1489 / 2408</td>
<td>42.8</td>
<td>1.05 [0.93, 1.18]</td>
</tr>
<tr>
<td></td>
<td>Test for heterogeneity chi-square=0.00 df=0 p=0.00001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect z=0.75 p=0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 Unfractionated heparin, low dose</td>
<td>IST 1997</td>
<td>1535 / 2407</td>
<td>1499 / 2408</td>
<td>42.2</td>
<td>1.07 [0.95, 1.20]</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>1535 / 2407</td>
<td>1499 / 2408</td>
<td>42.2</td>
<td>1.07 [0.95, 1.20]</td>
</tr>
<tr>
<td></td>
<td>Test for heterogeneity chi-square=0.0 df=0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect z=0.09 p=0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>03 Low molecular-weight heparin, high dose</td>
<td>HAFST 2000</td>
<td>146 / 224</td>
<td>146 / 225</td>
<td>3.9</td>
<td>1.25 [0.71, 1.96]</td>
</tr>
<tr>
<td></td>
<td>TAIST 2001</td>
<td>292 / 488</td>
<td>143 / 245</td>
<td>5.5</td>
<td>1.18 [0.66, 1.62]</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>440 / 652</td>
<td>269 / 470</td>
<td>9.3</td>
<td>1.13 [0.88, 1.44]</td>
</tr>
<tr>
<td></td>
<td>Test for heterogeneity chi-square=0.21 df=1 p=0.65</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Test for overall effect z=0.88 p=0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>04 Low molecular-weight heparin, low dose</td>
<td>TAIST 2001</td>
<td>301 / 486</td>
<td>143 / 245</td>
<td>5.5</td>
<td>1.16 [0.65, 1.59]</td>
</tr>
<tr>
<td></td>
<td>Subtotal (95% CI)</td>
<td>301 / 486</td>
<td>143 / 245</td>
<td>5.5</td>
<td>1.16 [0.65, 1.59]</td>
</tr>
</tbody>
</table>

Meta-analysis: The Cochrane Library 2004
Association anticoagulant + antiplatelets

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Brain ischaemia</th>
<th>Pulmonary embolism</th>
<th>Haemorrhagic stroke</th>
<th>Severe haemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin 25000 + aspirin</td>
<td></td>
<td></td>
<td></td>
<td>7.5%</td>
</tr>
<tr>
<td>Heparin 25000</td>
<td></td>
<td></td>
<td></td>
<td>7.2%</td>
</tr>
<tr>
<td>Heparin 10000 + aspirin</td>
<td></td>
<td></td>
<td></td>
<td>4.2%</td>
</tr>
<tr>
<td>SC heparin</td>
<td></td>
<td></td>
<td></td>
<td>4.9%</td>
</tr>
<tr>
<td>Aspirin</td>
<td></td>
<td></td>
<td></td>
<td>5.1%</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td>5.9%</td>
</tr>
</tbody>
</table>

IST group, Lancet 1997
Cardio-embolic ischaemic stroke

7 trials, n = 4624 patients

Recurrent ischaemic stroke: 3% vs 4.9%, OR 0.68 (0.44 – 1.06), p = 0.09, NNT 53

Symptomatic intracranial haem : 2.5% vs 0.7%, OR 2.89 (1.19 – 7.01), p=0.02, NNH 55

Paciaroni et al, Stroke 2007
- It is recommended that aspirin (160–325 mg loading dose) be given within 48 h after ischaemic stroke (Class I, Level A)
- It is recommended that if thrombolytic therapy is planned or given, aspirin or other antithrombotic therapy should not be initiated within 24 h (Class IV, GCP)
- The use of other antiplatelet agents (single or combined) is not recommended in the setting of acute ischaemic stroke (Class III, Level C)
- The administration of glycoprotein-IIb-IIIa inhibitors is not recommended (Class I, Level A)
- Early administration of unfractionated heparin (UFH), low molecular weight heparin or heparinoids is not recommended for the treatment of patients with acute ischaemic stroke (Class I, Level A)
When to start OAC in cerebral ischaemia + atrial fibrillation?

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>ESO 2008(^1)</th>
<th>AHA/ASA 2006(^2), ACCP 2008(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA or minor IS</td>
<td>Immediately</td>
<td>&lt; 2 weeks</td>
</tr>
<tr>
<td>Large infarct</td>
<td>Wait 4 weeks</td>
<td>Extra delay (not detailed)</td>
</tr>
</tbody>
</table>

\(^1\)Cerebrovasc Dis 2008;25:457–507;  \(^2\)Stroke 2006;37;577–617;  \(^3\)Chest 2008
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- Specific issues
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  - Cerebral ischaemia under anticoagulants / antiplatelet therapy
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## Areas of certainty

### Table 1. Strategies of Proven Benefit for Secondary Prevention of Stroke

<table>
<thead>
<tr>
<th>Indication and Strategy</th>
<th>Key Trial or Meta-Analysis</th>
<th>Results†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Routine‡</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood-pressure lowering</td>
<td>PROGRESS(^{11}): ACE inhibitor plus diuretic vs. placebo; primary end point: total strokes</td>
<td>RRR, 28.0%; ARR, 4.00 percentage points; NNT, 97</td>
</tr>
<tr>
<td>Cholesterol lowering (statin)</td>
<td>SPARCL(^{12}): statin vs. placebo; primary end point: first stroke</td>
<td>RRR, 16.0%; ARR, 2.20 percentage points; NNT, 218</td>
</tr>
<tr>
<td>Antiplatelet therapy (unless anticoagulation indicated)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin (first-line therapy)</td>
<td>ATTC(^{13,14}): aspirin vs. placebo; primary end points: nonfatal stroke, nonfatal MI, and death from vascular causes</td>
<td>RRR, 13.0%; ARR, 1.00 percentage points; NNT, 100†</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>CAPRIE(^{15}): clopidogrel vs. aspirin; primary end points: ischemic stroke, MI, and death from vascular causes</td>
<td>RRR, 8.7%; ARR, 0.51 percentage points; NNT, 196</td>
</tr>
<tr>
<td>Aspirin plus dipyridamole</td>
<td>ESPS2(^{16}): aspirin plus dipyridamole vs. aspirin; primary end point: stroke</td>
<td>RRR, 23.8%; ARR, 2.97 percentage points; NNT, 74</td>
</tr>
<tr>
<td>Symptomatic high-grade stenosis: carotid endarterectomy</td>
<td>NASCET(^{17}): carotid endarterectomy plus medical treatment vs. medical treatment alone; primary end point: any ipsilateral ischemic stroke</td>
<td>RRR, 65.0%; ARR, 5.30 percentage points; NNT, 9</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>EAFT(^{18}): warfarin vs. placebo; primary end point: all strokes</td>
<td>RRR, 36.0%; ARR, 8.0 percentage points; NNT, 12</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>RE-LY(^{19}): dabigatran vs. warfarin; primary end points: stroke and systemic embolism</td>
<td>RRR, 34.0%; ARR, 0.58 percentage points; NNT, 172intel</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>ROCKET AF(^{20}): rivaroxaban vs. warfarin; primary end points: stroke and systemic embolism</td>
<td>RRR, 13.0%; ARR, 0.30 percentage points; NNT, 333</td>
</tr>
<tr>
<td>Apixaban</td>
<td>ARISTOTLE(^{21}): apixaban vs. warfarin; primary end points: stroke and systemic embolism</td>
<td>RRR, 21.0%; ARR, 0.33 percentage points; NNT, 303</td>
</tr>
</tbody>
</table>

From Davis and Donnan, NEJM 2012
## Areas of uncertainty

**Table 2. Controversial or Investigational Secondary-Prevention Strategies.**

<table>
<thead>
<tr>
<th>Target</th>
<th>Possible Strategy</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early recurrent stroke</td>
<td>Combined aspirin and clopidogrel for 90 days from stroke onset</td>
<td>Increased risk with combination therapy vs. aspirin or clopidogrel alone, but meta-analysis suggests possible benefit of combination therapy after TIA or minor stroke; POINT (NCT00991029): combination therapy vs. aspirin, ongoing</td>
</tr>
<tr>
<td>Carotid stenosis</td>
<td>Carotid-artery stenting</td>
<td>Higher risks of periprocedural stroke and death with stenting than with endarterectomy, although risks similar with the two treatments among patients 70 years of age or younger</td>
</tr>
<tr>
<td>Acute-arch atheroma</td>
<td>Antiplatelet therapy vs. anticoagulation</td>
<td>Common cause of stroke; most effective treatment unknown; ARCH (NCT00235248): aspirin plus clopidogrel vs. warfarin, ongoing</td>
</tr>
<tr>
<td>Intracranial arterial stenosis</td>
<td>Intracranial stenting</td>
<td>Higher rate of stroke and death with intracranial stenting than with aggressive medical therapy in one trial (SAMMPRIS), but other trials ongoing</td>
</tr>
<tr>
<td>Carotid dissection</td>
<td>Antiplatelet therapy vs. anticoagulation</td>
<td>Optimal treatment unclear; CADISS (NCT00238667): aspirin vs. warfarin, ongoing</td>
</tr>
<tr>
<td>Patent foramen ovale</td>
<td>Percutaneous closure device vs. medical therapy</td>
<td>No benefit observed with percutaneous closure in CLOSURE I; other trials ongoing</td>
</tr>
</tbody>
</table>

From Davis and Donnan, NEJM 2012
Outline

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Aspirin

- 13% RRR for major ischemic events after non-selected TIA or ischemic stroke\(^1\)
- Incidence of GI-bleedings: dose-dependent
- No difference of efficacy with the daily dose
  - \(< 160 \text{ mg} / 160 – 325 / >500 \text{ mg}\)

\(^1\)ATT collaboration, 2002; \(^2\)Algra et al, 1996.
Other antiplatelet agents

- Clopidogrel\(^1\) and combination of aspirin plus dipyridamole\(^2\) are superior to aspirin, but with very small absolute benefits.
- Comparison of aspirin plus dipyridamole with clopidogrel: similar outcomes in the two treatment groups.\(^3\)
- No benefit, and increased hemorrhagic risks, with the combined use of clopidogrel and aspirin as compared with clopidogrel alone\(^4\) or aspirin alone\(^5\) for long-term secondary prevention after stroke.

\(^1\)CAPRIE, 1996; \(^2\)Algra et al, 2006; \(^3\)Sacco et al, 2008; \(^4\)Diener et al, 2004; \(^5\)Bhatt et al, 2006.
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Oral anticoagulation

Vitamin K antagonists for secondary prevention in atrial fibrillation.

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Target INR</th>
<th>Strokes/patients (anticoagulation vs placebo or no treatment)</th>
<th>RRR (%)</th>
<th>ARR (% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFASAK</td>
<td>671</td>
<td>2.8-4.2</td>
<td>9/335 vs 19/336</td>
<td>54</td>
<td>2.6</td>
</tr>
<tr>
<td>SPAF-I</td>
<td>421</td>
<td>2.0-4.5</td>
<td>8/210 vs 19/211</td>
<td>60</td>
<td>4.7</td>
</tr>
<tr>
<td>BAATAF</td>
<td>430</td>
<td>1.5-2.7</td>
<td>3/212 vs 13/208</td>
<td>78</td>
<td>2.4</td>
</tr>
<tr>
<td>CAFA</td>
<td>878</td>
<td>2.0-3.0</td>
<td>6/187 vs 9/191</td>
<td>33</td>
<td>1.2</td>
</tr>
<tr>
<td>SPINAF</td>
<td>571</td>
<td>1.4-2.8</td>
<td>7/281 vs 23/290</td>
<td>70</td>
<td>3.3</td>
</tr>
<tr>
<td><strong>EAFT</strong></td>
<td>439</td>
<td>2.5-4.0</td>
<td>20/225 vs 50/214</td>
<td>68</td>
<td>8.3</td>
</tr>
<tr>
<td>Total</td>
<td>2900</td>
<td></td>
<td>53/1450 vs 133/1450</td>
<td>64 (95% CI 49-74)</td>
<td>8.4</td>
</tr>
</tbody>
</table>


Table 1: Adjusted-dose anticoagulation compared with placebo or no treatment

1EAF, 1993
Oral anticoagulation

- Vitamin K antagonists for cardio-embolic stroke.
  - VKAs are also more effective than aspirin alone or combination aspirin plus clopidogrel
  - Aspirin on top of VKAs does not provide any additional benefit and increases the bleeding risk
Antithrombotic agents

- **Vitamin K antagonists for non cardio-embolic stroke.**

  - VKAs are not more effective than aspirin to reduce the risk of recurrent stroke after non cardioembolic strokes and are associated with an increased bleeding risk. \(^1,2\)

1Mohr et al, 2001; 2SPIRIT, 1997
New oral anticoagulant

Figure 1: Stroke or systemic embolic events
Data are n/N, unless otherwise indicated. Heterogeneity: I²=47%; p=0.13. NOAC=new oral anticoagulant. RR=risk ratio. dabigatran 150 mg twice daily. †Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.
New oral anticoagulant

Figure 2: Secondary efficacy and safety outcomes
Data are n/N, unless otherwise indicated. Heterogeneity: ischaemic stroke I²=32%, p=0.22; haemorrhagic stroke I²=34%, p=0.21; myocardial infarction I²=48%, p=0.13; all-cause mortality I²=0%, p=0.81; intracranial haemorrhage I²=32%, p=0.22; gastrointestinal bleeding I²=74%, p=0.009. NOAC=new oral anticoagulant. RR=risk ratio.
New oral anticoagulant

![Graph showing comparison between NOAC and Warfarin](image)

**Figure 3: Major bleeding**
Data are n/N, unless otherwise indicated. Heterogeneity: I²=83%; p=0.001. NOAC=new oral anticoagulant. RR=risk ratio. Dabigatran 150 mg twice daily.
†Rivaroxaban 20 mg once daily. ‡Apixaban 5 mg twice daily. §Edoxaban 60 mg once daily.
Atrial fibrillation

- High-risk:
  - Oral anticoagulation (Vitamin K antagonist with target INR 2-3, or new OAC)

- Medium-risk:
  - Oral anticoagulation (Vitamin K antagonist with target INR 2-3, or new OAC)
  - Or aspirin 325 mg / day

- Low-risk:
  - Aspirin 325 mg / day
  - Or no treatment
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Only 1 trial (CADISS) stopped for low recruitment rate.

**Dissection**

The Cochrane Library 2003
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Prevention of DVT and PE

- N = 740 patients, 6 trials
- Les DVT OR = 0.52 (0.56 – 0.79)
- No effect on death
Outline

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Cerebral haemorrhage under anticoagulant therapy

- Incidence
  - 0.3% - 0.6% / year
- Often leads to death
- Restart AC?

Predictors
- Age > 75 years
- High BP
- INR > 4-5
- Previous stroke
- Combination with aspirin
- Lobar ICH
- White matter changes
- Microbleeds
Cerebral haemorrhage under anticoagulant therapy

- AHA / ASA recommendations (Stroke 2011)
- For patients who develop ICH, SAH, or SDH, it is reasonable to discontinue all anticoagulants and antiplatelets during the acute period for at least 1 to 2 weeks and reverse any warfarin effect with fresh frozen plasma or prothrombin complex concentrate and vitamin K immediately (Class IIa; Level of Evidence B).
- Protamine sulfate should be used to reverse heparin-associated ICH, with the dose depending on the time from cessation of heparin (Class I; Level of Evidence B). (New recommendation)
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## Cerebral ischaemia under anticoagulant therapy

<table>
<thead>
<tr>
<th></th>
<th>Proximal occlusion</th>
<th>No Proximal occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>INR &lt; 1.7</strong></td>
<td>i.v. rtPA +</td>
<td>i.v. rtPA alone</td>
</tr>
<tr>
<td></td>
<td>thrombectomy</td>
<td></td>
</tr>
<tr>
<td><strong>INR ≥ 1.7</strong></td>
<td>Thrombectomy alone</td>
<td>Conservative management</td>
</tr>
</tbody>
</table>
For patients who have an ischemic stroke while taking aspirin, there is no evidence that increasing the dose of aspirin provides additional benefit. Although alternative antiplatelet agents are often considered, no single agent or combination has been studied in patients who have had an event while receiving aspirin (Class IIb; Level of Evidence C).
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Take home message

- At the acute stage of cerebral ischaemia
  - aspirin alone, or combined with clopidogrel for a short period of time, should be given, immediately or after 24 hours in case of thrombolytic therapy
  - Heparin provides no benefit

In secondary stroke prevention

- Aspirin, or clopidogrel, or the association aspirin plus dipyridamole in indicated except in AF
- In AF patients should receive OAC, with a new one when possible, otherwise with a VKA and a target INR 2-3