Antithrombotic therapy in patients with transient ischemic attack / stroke (acute phase <48h)

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Stroke Division, Hellenic Cardiovascular Research Society

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Stroke classification (based on etiology)

**Ischemic**
- Large vessel Atherosclerosis: 15-30%
- Cardioembolic: 18-33%
- Small vessel (lacunes): 17-25%
- Cryptogenic: 12-37%

**Hemorrhagic**
- Intracerebral hemorrhage: 15%
- Subarachnoid hemorrhage: 5-7%

*Images of brain scans corresponding to each category are shown.*
Transient ischemic attack (TIA)

- a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without evidence of acute infarction

Pathophysiology of TIAs

1. Large vessel atherosclerosis
   low-flow TIAs, true TIAs

2. Embolism
   - artery to artery embolism
   - cardioembolism

3. Small vessel diseases (Lacunes)
   Lipohyalinosis
   Microatheroma
Stroke risk after TIAs or Minor Stroke


8.0% (2.3–13.7)

11.5% (4.8–18.2)

3.0% Myocardial infarction

17.3% (9.3–25.3)

Risk of stroke (%) vs. Days

Log rank P=0.8

BMJ 2004;328;326-330
“Isn’t it funny, I went blind in the wrong eye? I am paralyzed on the left side, and I went blind in the right eye”

Montreal 1949
Craven LL. Acetylsalicylic acid, possible preventive of coronary Thrombosis
*Ann Western Med & Surg* 1950;4:95-99 (400 cases)

Craven LL. Prevention of coronary and cerebral thrombosis
*Mississippi Valley M J* 1956;78:213-215 (8000 cases)

Harrisson M, et al. Effect of aspirin on amaurosis fugax
*Lancet* 1971;2:743-744
Research data and recommendations

- Antiplatelets
- Anticoagulants (heparin)
“The stroke paradox”

• Few studies !!!
• Limited evidence based data
# Rates of acute vascular events in men and women in the OXVASC study

- **population** (91,106) between 2002 and 2005 -

<table>
<thead>
<tr>
<th>Event</th>
<th>Total, n</th>
<th>Men, rate</th>
<th>Women, rate</th>
<th>Total, rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cerebrovascular events combined</td>
<td>918</td>
<td>2.99</td>
<td>3.75</td>
<td>3.36</td>
</tr>
<tr>
<td>All coronary vascular events</td>
<td>856</td>
<td>3.89</td>
<td>2.33</td>
<td>3.13</td>
</tr>
<tr>
<td>All peripheral vascular events</td>
<td>188</td>
<td>0.79</td>
<td>0.57</td>
<td>0.69</td>
</tr>
</tbody>
</table>

Rates are per 1000 population per year

Rothwell PM et al. *Lancet* 2005
<table>
<thead>
<tr>
<th>Cause</th>
<th>Deaths</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>15,274</td>
<td>21.96</td>
</tr>
<tr>
<td>Coronary Heart Disease</td>
<td>13,075</td>
<td>18.80</td>
</tr>
<tr>
<td>Lung Cancers</td>
<td>6,497</td>
<td>9.34</td>
</tr>
<tr>
<td>Upper Respiratory</td>
<td>3,287</td>
<td>4.73</td>
</tr>
<tr>
<td>Colon-Rectum Cancers</td>
<td>2,568</td>
<td>3.69</td>
</tr>
<tr>
<td>Breast Cancer</td>
<td>2,196</td>
<td>3.16</td>
</tr>
<tr>
<td>Lung Disease</td>
<td>2,089</td>
<td>3.00</td>
</tr>
<tr>
<td>Kidney Disease</td>
<td>1,964</td>
<td>2.82</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>1,713</td>
<td>2.46</td>
</tr>
</tbody>
</table>

WORLD HEALTH RANKINGS 2010
http://www.worldlifeexpectancy.com/country-health-profile/greece
## Health and non Health Care Costs for Stroke in Greece, 2009

### Health Care Costs

<table>
<thead>
<tr>
<th>Health Care Costs</th>
<th>€ (thousands)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary care</td>
<td>17.943</td>
<td>1.8</td>
</tr>
<tr>
<td>Outpatient care</td>
<td>39.985</td>
<td>4.0</td>
</tr>
<tr>
<td>Accident &amp; Emergency</td>
<td>7.982</td>
<td>0.8</td>
</tr>
<tr>
<td>Inpatient Care</td>
<td>429.643</td>
<td>42.3</td>
</tr>
<tr>
<td>Medications</td>
<td>67.606</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>Total Health Care Costs</strong></td>
<td><strong>563.158</strong></td>
<td><strong>56.1</strong></td>
</tr>
</tbody>
</table>

### Non Health Care Cost

<table>
<thead>
<tr>
<th>Non Health Care Cost</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Production loses due to mortality</td>
<td>148.642</td>
<td>14.8</td>
</tr>
<tr>
<td>Production loses due to morbidity</td>
<td>177.057</td>
<td>17.6</td>
</tr>
<tr>
<td>Informal Care</td>
<td>115.323</td>
<td>11.5</td>
</tr>
<tr>
<td><strong>Total Non Health Care Costs</strong></td>
<td><strong>441.022</strong></td>
<td><strong>43.9</strong></td>
</tr>
</tbody>
</table>

### Total Care Costs

| Total Care Costs                      | 1.004.180      |     |

*European Cardiovascular disease statistics, 2012 edition*
Antiplatelet therapy in acute stroke (<48h)

**Aspirin** (160-325 mg)

(IST και CAST trials, 40 000 ασθενείς)

- death and dependency (NNT 70)
- recurrence of stroke (NNT 140)

_Lancet 1997;349:1569-1581_

Acute Ischemic Stroke

Antithrombotic Trialists’ Collaboration

(therapy < 3 weeks)

Antithrombotic Trialists’ Collaboration, BMJ 2002
Recommendations

- **Aspirin** (160–325 mg loading dose) should be given within 48 hours after ischaemic stroke *(Class I, Level A)*

- If thrombolytic therapy is planned or given, aspirin or other antithrombotic therapy should not be initiated within 24 hours *(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)*
Class I Recommendation
The oral administration of aspirin (initial dose is 325 mg) within 24 to 48 hours after stroke onset is recommended for treatment of most patients (Class I, Level of Evidence A)

Class III Recommendations
1. as European

The panel supports research testing the usefulness of emergency administration of clopidogrel in the treatment of patients with acute stroke.

Stroke. 2011 Jan;42:227-276
Dual or mono antiplatelet therapy for patients with acute ischemic stroke or transient ischemic attack: systematic review and meta-analysis of randomized controlled trials

- aspirin+dipyridamole or aspirin+clopidogrel
- 3766 patients with acute (≤3 days) ischemic stroke/TIAs
- Dual therapy significantly reduced
  - 23% stroke recurrence (RR, 0.67; 95% CI, 0.49-0.93)
  - 25% composite vascular event (stroke, myocardial infarction, vascular death), (RR, 0.75; 95% CI, 0.56-0.99)
- Dual therapy was also associated with a non-significant trend to increase major bleeding, dual 15 (0.9%) versus mono 6 (0.4%; risk ratio, 2.09; 95% CI, 0.86-5.06).

Stroke. 2012 Apr;43(4):1058-66
Antiplatelets in Acute Ischemic Stroke
(Greece 23 hospitals)

Hellas Stroke Registry (2009-2010)
\( n=2700 \)

- rt-PA: 2%
- Aspirin: 45%
- Clopidogrel: 33%
- Other antiplatelets: 2%
- All antiplatelets: 74%

Unpublished data
## Anticoagulants in Acute Ischemic Stroke


<table>
<thead>
<tr>
<th>Event</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep venous thrombosis</td>
<td>0.27</td>
<td>0.08-0.96</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.34</td>
<td>0.17-0.69</td>
</tr>
<tr>
<td>Extracranial hemorrhage</td>
<td>2.17</td>
<td>1.10-4.28</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>1.77</td>
<td>0.95-3.31</td>
</tr>
<tr>
<td>Mortality</td>
<td>1.05</td>
<td>0.83-1.32</td>
</tr>
<tr>
<td>Mortality + disability</td>
<td>0.87</td>
<td>0.72-1.06</td>
</tr>
</tbody>
</table>

**Conclusion:** no clear benefit

*Bath P, Stroke 2000;31:1770-1778*
Anticoagulants in Acute Ischemic Stroke
Cochrane Database Syst Rev 2004: Meta-analysis

- Subcutaneous UFH at low or moderate doses
- Nadroparin
- Certoparin
- Tinzaparin
- Dalteparin
- Danaparoid IV
  - 22 trials, anticoagulant therapy was associated:
    - Nine fewer recurrent ischemic strokes per 1,000 patients treated (OR 0.76; 95% CI 0.65–0.88)
    - Nine more symptomatic intracranial hemorrhages per 1,000 (OR 2.52; 95% CI 1.92–3.30)
Anticoagulants in Acute Ischemic Stroke
Guidelines Ischaemic Stroke 2008

**Recommendation**

- Early administration of unfractionated heparin, low molecular weight heparin or heparinoids is not recommended for the treatment of patients with ischaemic stroke (Class I, Level A)

- Not preventing early recurrent stroke,
- Not halting neurological worsening,
- Not improving outcomes after acute ischemic
Experts opinion «full-dose» in selected cases (IV level)

- High risk recurrent cardioembolism (minor lesions)
  - prosthetic heart valves, AF, ventricular or left atrial thrombus
- Extracranial dissection of cervical arteries
- High-grade arterial stenosis prior to surgery
- Crescendo TIA's
- Cerebral venous thrombosis

- Contraindications for heparin treatment:
  - Large infarcts (e.g. more than 50% of MCA territory)
  - Uncontrollable arterial hypertension
  - Advanced microvascular changes in the brain

European Stroke Organization 2008
Low dose heparins

Recommendations

- Low-dose s.c. heparin or low molecular weight heparins should be considered for patients at high risk of DVT or pulmonary embolism (Class I, Level A) ESO 2008

In patients with acute ischemic stroke and restricted mobility, we suggest prophylactic-dose subcutaneous heparin (unfractionated heparin [UFH] or low-molecular-weight heparin [LMWH]) or intermittent pneumatic compression devices over no prophylaxis (Grade 2B). (CHEST 2012)
HOW DO TRIAL DATA RELATE TO TREATING INDIVIDUAL PATIENTS?

..this approach can be characterized as “personalized medicine” because it emphasizes the medical and personal details of each individual.

The most appropriate treatment:
- for a particular patient,
- with a particular stage of disease,
- with particular coexisting conditions,
- at a particular age.

The 2009 H. Houston Merritt Lecture

Louis R Caplan, Arch Neurol 2011
Basilar Artery Occlusion

(Bilateral Pontine infarction)

- 67 yo men
- HTN, Cholesterol, past MI
- 4 crescendo TIAs in 1 week
- On aspirin

- Aspirin 100mg+
- Clopidogrel 75+
- IV heparin
- BP: 180-200 mmHg
What if the stroke or TIAs occur despite antiplatelet treatment?

- Is the patient taking the tablets?
- Are the doses optimal?
- Is the diagnosis correct?
- Review the history again – are the attacks really typical of stroke/TIA?
- What is the mechanism?
- Repeat imaging or cardiac evaluation may be helpful
Conclusions

- Aspirin for acute ischemic stroke
- No any other antiplatelet is recommended
- Low-dose sc or LMWH for patients at high risk of DVT and pulmonary embolism