The future of stroke treatment: A European perspective

Bart van der Worp
disclosures

speaker’s fees from
Boehringer Ingelheim
Bayer
The future of stroke treatment: A European perspective

Bart van der Worp
The future of stroke treatment: A dreamer’s perspective

Bart van der Worp
Do we need new or better stroke treatments?
dead or dependent with i.v. alteplase ≤ 3 h

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Thrombolysis n/N</th>
<th>Control n/N</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECASS 1995</td>
<td>28/49</td>
<td>25/38</td>
<td>0.70 [0.37, 1.30]</td>
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<tr>
<td>NINDS 1995</td>
<td>155/312</td>
<td>192/312</td>
<td>0.39 [0.10, 1.49]</td>
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<tr>
<td>ECASS II 1998</td>
<td>39/81</td>
<td>44/77</td>
<td>1.62 [0.29, 8.90]</td>
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</tr>
<tr>
<td>ATLANTIS B 1999</td>
<td>3/13</td>
<td>12/26</td>
<td>0.67 [0.49, 0.91]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATLANTIS A 2000</td>
<td>7/10</td>
<td>7/12</td>
<td></td>
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<tr>
<td>IST3 2012</td>
<td>299/431</td>
<td>323/418</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>896</strong></td>
<td><strong>883</strong></td>
<td>0.65 [0.54, 0.80]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 531 (Thrombolysis), 603 (Control)
Heterogeneity: Chi² = 1.87, df = 5 (P = 0.87); I² = 0.0%
Test for overall effect: Z = 4.23 (P = 0.000023)

Wardlaw 2014

59% vs 68% dead or dependent
intra-arterial treatment ≤ 6 h*

*: minority treated between 6 and 12 h

Goyal 2016
eligible for reperfusion therapy

- intravenous thrombolysis ± 20%
- intra-arterial treatment ± 10%
additional treatment options needed!

**neuroprotection**
- = protecting neurons from injury or degeneration
- = keeping neuronal and glial damage under the threshold of symptom manifestation

**can be aimed at different targets**
targets for neuroprotection
reperfusion
ischaemia

↓oxydative phosphorylation
↑anaerobic glycolysis

↓ATP

depolarisation

↑[Ca$^{2+}$]$_{i}$

opening VSCCs

↑glutamate

+glutamate receptors

↓Mg$^{2+}$ block

↑cAMP

+protein kinases

↑cytochrome c

↑adhesion molecules

↑cytokines

↑IEGs

↑target genes

↑inflammation

BBB damage

DNA damage

damage to cell membrane, proteins, cytoskeleton

lipid peroxidation

mitochondrial damage

•NO

↑arachidonic acid

+proteases

+endonucleases

+phospholipases

↑radicals

↑radicals

↑inflammation

DNA damage

target genes

cell death

↑lactate

↑H$^{+}$

acidosis

reversed Na$^{+}$/Ca$^{2+}$ exchange

↑Fe$^{2+}$/Fe$^{3+}$

+NO synthase

↑•NO

DNA damage

mitochondrial damage
1994
Tirilazad Efficacy Stroke Study (TESS)

- randomised
- double-blind
- international
- acute ischaemic stroke
- tirilazad mesylate vs. placebo
- n = 900
- Upjohn
tirilazad (Freedox®)

- 21-aminosteroid
- radical scavenger
- highly effective in animal models
- “lazaroid”
tirilazad meta-analysis 2000

<table>
<thead>
<tr>
<th>Daily dose &lt;= 6 mg/kg/day</th>
<th>STIPAS P/20 1994 24 / 84</th>
<th>3 / 26</th>
<th>3.9</th>
<th>2.49 [0.90, 6.88]</th>
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<tr>
<td></td>
<td>RANTTAS I P/35 19t</td>
<td>113 / 312</td>
<td>95 / 318</td>
<td>36.6</td>
</tr>
<tr>
<td></td>
<td>TESS I P/37 1996</td>
<td>112 / 229</td>
<td>96 / 215</td>
<td>29.0</td>
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<tr>
<td>Subtotal (95% CI)</td>
<td>249 / 625</td>
<td>194 / 559</td>
<td>69.5</td>
<td>1.31 [1.03, 1.67]</td>
</tr>
<tr>
<td>Chi-square 1.81 (df=2)</td>
<td>Z=2.22</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Daily dose &gt; 6 mg/kg/day</td>
<td>02</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>RANTTAS II M/81 1f</td>
<td>23 / 57</td>
<td>33 / 62</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>TESS II M/88 1997</td>
<td>86 / 176</td>
<td>73 / 172</td>
<td>22.7</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>109 / 233</td>
<td>106 / 234</td>
<td>30.5</td>
<td>1.06 [0.74, 1.53]</td>
</tr>
<tr>
<td>Chi-square 3.29 (df=1)</td>
<td>Z=0.33</td>
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<tr>
<td>Total (95% CI)</td>
<td>358 / 858</td>
<td>300 / 793</td>
<td>100.0</td>
<td>1.23 [1.01, 1.51]</td>
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<tr>
<td>Chi-square 6.02 (df=4)</td>
<td>Z=2.03</td>
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</table>

favours treatment  favours control

Tirilazad International Steering Committee 2000
tested in animal models of cerebral ischemia
tested in models of focal cerebral ischemia
- antioxidants
- calcium antagonists
- anti-inflammatory agents
- thrombolytics
- ...

- Polynesian ceremonial beverages
- aged garlic
- sea snail peptides
- Gingko biloba extracts
- ...

O’Collins 2006
effective in models of focal cerebral ischemia
tested in clinical trials of ischaemic stroke

O’Collins 2006
effective in clinical trials of ischaemic stroke
gap between laboratory and clinic

causes

- limitations clinical trials
- limitations animal studies
  - methodology (internal validity)
  - generalisability (external validity)
- publication bias
internal validity

- randomisation
- blinded outcome assessment
- sample size calculation
- ...
randomisation

- used in clinical trials since 1948
- main advantage
  - eliminates selection bias
Benjamin Franklin 1706 - 1790
Louis XVI
Mesmerism = animal magnetism
1784
blindfolding of patients

Antoine Lavoisier  Joseph-Ignace Guillotin  Jean-Sylvain Bailly
Mesmerism = animal magnetism
CAMARADES reviews of animal stroke studies

8 reviews
318 studies
11,417 animals

randomisation 34%
blinded outcome assessment 29%
sample size calculation 3%

Van der Worp 2010
generalisability
Does study quality matter?

- randomisation
- blinding
SR & meta-analysis NXY-059 for stroke

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

NXY-059 for the Treatment of Acute Ischemic Stroke

Ashfaq Shuaib, M.D., Kennedy R. Lees, M.D., Patrick Lyden, M.D., James Grotta, M.D., Antonio Davalos, M.D., Stephen M. Davis, M.D., Hans-Christoph Diener, M.D., Tim Ashwood, Ph.D., Warren W. Wasiewski, M.D., and Ugochi Emeribe, Ph.D., for the SAINT II Trial Investigators*
SR & meta-analysis NXY-059 for stroke

randomisation

blinded outcome assessment

$p < 0.001$

Macleod 2008
association ≠ causal relationship
<table>
<thead>
<tr>
<th>LIST</th>
<th>STATE</th>
<th>AVERAGE POPULATION IQ</th>
<th>PRESIDENT ELECT</th>
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<td>49</td>
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</tr>
<tr>
<td>50</td>
<td>Mississippi</td>
<td>85</td>
<td>George Bush</td>
</tr>
</tbody>
</table>
“The effect of experimenter bias on the performance of the albino rat”

- 12 students
- 60 rats
- students trained rats on T-maze task
- 10 trials / day for 5 days

Rosenthal & Fode 1963
students randomised
- “maze-bright” rats
- “maze-dull” rats

outcome measure: # correct responses
Figure 21.2  Average number of correct responses per rat per day

Rosenthal & Fode 1963
post-experimental questionnaire

maze-bright rats
- cleaner
- brighter
- more tame
- more pleasant

Rosenthal & Fode 1963
conclusion

- researchers too easily find what they are looking for
  - → detection bias

- solution: blinded outcome assessment
options for improvement

reporting guidelines

CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials

Kenneth F Schulz,¹ Douglas G Altman,² David Moher,³ for the CONSORT Group
options for improvement

reporting guidelines

Improving Bioscience Research Reporting: The ARRIVE Guidelines for Reporting Animal Research

Carol Kilkenny¹*, William J. Browne², Innes C. Cuthill³, Michael Emerson⁴, Douglas G. Altman⁵
a message from the President to those who continue to perform animal stroke studies of poor quality:
requirements for testing in clinical trial

animal studies

- good quality of evidence
- broad range of evidence
  - multi-centre phase III animal trial?
- no relevant impact of publication bias
- benefit under conditions of clinical trial
- safe & feasible
hypothermia
ischaemia

↓ oxydative phosphorylation
↑ anaerobic glycolysis

↓ ATP

depolarisation
opening VSCCs

↑ [Ca\textsuperscript{2+}]_i

↑ radicals
damage to cell membrane, proteins, cytoskeleton

↑ lactate
↑ H\textsuperscript{+}

acidosis

reversed Na\textsuperscript{+}/Ca\textsuperscript{2+} exchange

↑ Fe\textsuperscript{2+}/Fe\textsuperscript{3+}

+ NO synthase

↑ arachidonic acid

+ proteases
+ endonucleases

↑ cytochrome c

↑ cAMP

↑ glutamate
+ glutamate receptors

↓ Mg\textsuperscript{2+} block

↑ glutamate

↑ adhesion molecules

↑ prokineses

↑ cytokines

↑ inflammation

↑ IEGs

↑ inflammation

DNA damage

damage to cell membrane, proteins, cytoskeleton

nimodipine

↑ target genes

↑ inflammation

DNA damage

BBB damage

↑ cytochrome c

↑ endonucleases

↑ proteases

↑ arachidonic acid

lipid peroxidation

mitochondrial damage

cell death
ischaemia

↓ oxydative phosphorylation
↑ anaerobic glycolysis

↑ [Ca^{2+}]_i

↓ Mg^{2+} block
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↑ cytochrome c

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↑ cytoskeleton

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↑ inflammation
UP target genes
DNA damage

↑ glutamate
+ glutamate receptors

↑ cAMP

↑ [Ca^{2+}]_i

↑ [Ca^{2+}]_i

↑ cytochrome c
+ endonucleases
+ phospholipases

↑ arachidonic acid

↑ NO synthase

↑ Fe^{2+}/Fe^{3+}

↑ lactate
↑ H^+

acidosis

reversed Na^+/Ca^{2+} exchange

↑ Fe^{2+}/Fe^{3+}
+ NO synthase

↑ •NO

lipid peroxidation

DNA damage
proteins, cytoskeleton
mitochondrial damage

BBB damage

↑ cytokines
+ proteases

↑ inflammation

↑ IEGs

↑ target genes
DNA damage

cell death
ischaemia
↓ oxydative phosphorylation
↑ anaerobic glycolysis
↓ ATP
depolarisation
opening VSCCs
↑ [Ca$^{2+}$]$_i$
↑ radicals
DNA damage
proteins, cytoskeleton
mitochondrial damage
lipid peroxidation
mitochondrial damage

hypothermia
↓ Mg$^{2+}$ block
+ glutamate receptors
+ glutamate
+ protein kinases
+ cAMP
+ cytochrome c
+ endonucleases
+ phospholipases
+ proteases
+ cytokines
+ adhesion molecules
+ IEGs
 ↑ inflammation

cell death
systematic reviews of animal stroke models

Sena 2010
cooling to 32 – 34°C in clinical trials

effective in:
- postanoxic encephalopathy
- neonatal hypoxic-ischaemic brain damage

not effective in:
- traumatic brain injury
- bacterial meningitis

HCASG 2002
Bernard 2002
Shankaran 2005
Andrews 2015
Mourvillier 2013
methods to cool stroke patients
surface cooling

34 - 35°C

ice-cold saline
intravascular cooling

Mack 2003
Can be done by neurologist!
## Clinical Trials in Acute Ischaemic Stroke

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>n</th>
<th>Cooled</th>
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<tbody>
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<td>COOL-AID</td>
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<td>NOCSS</td>
<td>2006</td>
<td>22</td>
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<td>ICTuS-L</td>
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<td>MHAIS</td>
<td>2013</td>
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<td>COOLIST</td>
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<td>ICTUS 2</td>
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<td>165</td>
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</table>

### Hypothermia and Pneumonia Rates

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypothermia Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>de Georgia 2004</td>
<td>2</td>
<td>18</td>
<td>1</td>
<td>21</td>
<td>14.2%</td>
<td>2.33 [0.23, 23.66]</td>
<td>2004</td>
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<tr>
<td>Hemmen 2010</td>
<td>14</td>
<td>28</td>
<td>3</td>
<td>30</td>
<td>44.5%</td>
<td>5.00 [1.61, 15.57]</td>
<td>2010</td>
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<tr>
<td>Piironen 2014</td>
<td>7</td>
<td>18</td>
<td>2</td>
<td>18</td>
<td>30.7%</td>
<td>3.50 [0.84, 14.61]</td>
<td>2014</td>
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<tr>
<td>Geurts 2015</td>
<td>8</td>
<td>15</td>
<td>0</td>
<td>6</td>
<td>10.7%</td>
<td>7.44 [0.49, 111.82]</td>
<td>2015</td>
</tr>
</tbody>
</table>

**Total (95% CI):**
- **Hypothermia Events:** 79
- **Control Events:** 75
- **Total Weight:** 100.0%
- **Risk Ratio:** 4.42 [1.99, 9.83]

**Heterogeneity:** Chi² = 0.58, df = 3 (P = 0.90); I² = 0%

**Test for overall effect:** Z = 3.65 (P = 0.0003)

---

**Geurts 2016**

**hypothermia:** 39%

**controls:** 8%
a multi-centre, randomised, controlled, clinical trial of hypothermia for acute ischaemic stroke

EuroHYP-1
trial design

- randomised, multicentre, international
- open, blinded outcome assessment
- 800 awake patients with ischaemic stroke
- cooling to 34 - 35°C for 12 h
- start ≤ 6 h of onset
  - AND < 2.5 h of thrombolysis
- 1st inclusion November 2013
pethidine
(= meperidine)
buspirone
something more simple?
effect of fever in animal models

→ 43% increase infarct size
temperatures > 37.5°C after stroke:

- 1/3 of patients on day 1
- associated with poor outcome

- guidelines recommend(ed) treatment of fever
- → may be too late
- prevention of fever better??

Jauch 2013; Steiner 2014; Hemphill 2015; Ntaios 2015
paracetamol trial - PAIS

- 1400 patients with acute stroke
- paracetamol 6 x 1 g for 3 days vs. placebo
- start ≤ 12 h from symptom onset

Den Hertog 2009
results PAIS trial

treatment with paracetamol →

- body temperature ↓ 0.3°C
- temperature > 37.5°C at 24 h: 30% → 15%
improvement with paracetamol at 3 months

aOR: 1.21 (0.97 – 1.51)

if true:

- extremely safe, simple, and cheap treatment

Den Hertog, Lancet Neurol 2009
PRECIOUS: PREvention of Complications to Improve Outcomes in elderly patients with acute Stroke

- PROBE, 2*2*2 factorial
- n = 3800 (ischaemic stroke and ICH)
- open treatment, start ≤ 24 h, for 4 days
  - ceftriaxone – 2 g daily
  - paracetamol – 4 g daily
  - metoclopramide – 30 mg daily
- primary endpoint: mRS @ 90 days
Funding: EU Horizon 2020 programme – grant agreement 634809
nitroglycerine

= glycercyl trinitrate (GTN)
- NO donor
- systemic and cerebral vasodilator

NO donors in animal studies
-↑ cerebral blood flow
-↓ infarct size
**Table: ENOS 2015**

<table>
<thead>
<tr>
<th>Category</th>
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**Diagram: Bias Assessment**

- Favours glyceryl trinitrate
- Favours no glyceryl trinitrate

**ENOS 2015**
GTN – ambulance trial

RIGHT
- n = 41
- start GTN ≤ 4 h
- ambulance setting
GTN – ambulance trial

- feasible & safe
- $\text{RR}_{\text{sys}} @ 15 \text{ min: } 180 \rightarrow 153 \text{ mm Hg}$
mRS vs. time to start of treatment
GTN trials

- PROBE, phase III
- adult patients with suspected stroke
- transdermal GTN in a dose of 5 mg/day vs. standard care
- start in the ambulance, ≤ 4 or 3 h
conclusions

- neuroprotection is not dead
- translation from bench to bedside may improve with better interaction between the laboratory and the clinic
- promising treatments are currently tested in clinical trials
4th European Stroke Organisation Conference
16-18 May 2018 | Gothenburg, Sweden
ESO - The Voice of Stroke in Europe