Citalopram In Patients With Acute Ischaemic Stroke (TALOS) - A Danish Randomised Controlled Trial on Functional Recovery and Cardiovascular Protection

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An investigator initiated trial

- Investigator driven
- 3 Danish inclusion sites
  - Stroke units
  - Aarhus, Aalborg & Glostrup
- No commercial funding

Funding
- The TRYG Foundation
- The Danish Council for Independent Research
- The Regional Medicine Fund
- The Aarhus University Research Foundation
Background - Potential Neuroprotection

**Improved recovery**
Clinical data from the FLAME\(^1\) gave rise to optimism
- Fluoxetine/placebo
- 118 moderate to severe ischaemic strokes
- Increased motor recovery (Fugl-Meyer motor scale)

**Vascular protection**
- No clinical trials
- Observational studies are inconsistent and confounded by depression
- Signal towards vascular prevention\(^2\)

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\(^1\) Chollet et al.: FLAME, Lancet Neurol 2011; 10: 123–30
\(^2\) Mortensen et al.: Stroke 2013; 44(82):420-6
Aim

There were two co-primary outcomes:

1. **Changes in functional disability** from one to six months measured by the modified Rankin Scale, and

2. **Composite vascular endpoint** of transient ischaemic attack/stroke, myocardial infarction or vascular mortality during the first six months
949 patients assessed for eligibility

307 excluded
92 not meeting inclusion criteria
126 declined to participate
89 other reasons

642 randomly assigned

323 allocated to placebo
323 included in intention-to-treat analysis
0 patients lost to follow-up primary, vascular endpoint
320 received placebo
3 did not receive placebo

36 discontinued intervention <31 days
13 consent withdrew
4 adverse event
12 indication for open-label
7 other reasons

284 included in per-protocol analysis (6 months or LOCF)

319 allocated to citalopram
319 included in intention-to-treat analysis
0 patients lost to follow-up for primary, vascular endpoint
318 received citalopram
1 did not receive allocated intervention

50 discontinued intervention <31 days
29 consent withdrew
6 adverse event
6 indication for open-label
9 other reasons

268 included in per-protocol analysis (6 months or LOCF)
Methods

• First-ever ischaemic stroke non-depressed patients
  • No upper limit in age or stroke severity
• Onset <7 days
• Double-blind, placebo controlled, randomised
• 1:1 allocation
• Standard dosage

1 Kraglund et al., International Journal of Stroke, 2015; 10(6), 985-87
# Trial Characteristics

- Sept 2013 to June 2016
- Total of 642 patients
- Early 6 months follow-up
  - Mean 146 days
- All patients had follow-up or registry information on vital status

<table>
<thead>
<tr>
<th>CHARACTERISTICS</th>
<th>Citalopram (n=319)</th>
<th>Placebo (n=323)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range; SD)</td>
<td>68·3 (24 to 97; 12·5)</td>
<td>68·4 (19 to 99; 12·8)</td>
<td>0·91</td>
</tr>
<tr>
<td>Male sex</td>
<td>199 (62%)</td>
<td>222 (69%)</td>
<td>0·09</td>
</tr>
<tr>
<td>NIHSS at admission (range; SD)</td>
<td>5·3 (0 to 27; 5·6)</td>
<td>4·8 (0 to 28; 4·8)</td>
<td>0·28</td>
</tr>
<tr>
<td>Onset to treatment, days (range; SD)</td>
<td>1·73 (0 to 6; 1·6)</td>
<td>1·55 (0 to 10; 1·5)</td>
<td>0·17</td>
</tr>
</tbody>
</table>

**PREMORBID MODIFIED RANKIN SCALE**

| Mean (range; SD)                          | 0·27 (0 to 3; 0·7) | 0·27 (0 to 3; 0·6) | 0·90 |

**REPERFUSION THERAPY**

<table>
<thead>
<tr>
<th>Any</th>
<th>109 (34%)</th>
<th>123 (41%)</th>
<th>0·056</th>
</tr>
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<tbody>
<tr>
<td>rt-PA</td>
<td>105 (33%)</td>
<td>129 (40%)</td>
<td>0·06</td>
</tr>
<tr>
<td>EVT</td>
<td>24 (8%)</td>
<td>22 (7%)</td>
<td>0·73</td>
</tr>
</tbody>
</table>

*rt-PA*: intravenous recombinant tissue plasminogen activator; *EVT*: Endovascular treatment
Results – Improvement on the modified Rankin Scale\(^1\)

Odds Ratio for mRS improvement: 1·27
(95\% CI: 0·92 to 1·74, p=0·14)

\(^1\) Taking the whole mRS range into account (ordinal, logistic regression)
Results – Cardiovascular Protection

Combined Vascular Outcome\(^1\)
- HR: \(0.89\) (95%CI: \(0.5\) to \(1.6\))

TIA/Stroke
- HR: \(1.07\) (95%CI: \(0.6\) to \(2.1\))

Myocardial Infarction
- HR: \(2.03\) (95%CI: \(0.2\) to 22)

Vascular Mortality
- HR: \(0.67\) (95%CI: \(0.2\) to \(1.9\))

\(^1\)TIA/stroke, myocardial infarction or vascular mortality
Conclusions

• Citalopram treatment after ischaemic stroke signals positive effect - though not statistical significant
  • improved functional recovery
  • vascular protection

• More placebo drop-outs due to depression may lead to confounding by depression

• Time is not yet to recommend SSRI as standard treatment in non-depressed after stroke

• TALOS confirms that SSRI is safe in ischaemic stroke patients