Time to reperfusion and effect of intra-arterial treatment in the MR CLEAN trial

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for the MR CLEAN investigators
Disclosures

Funded by the Dutch Heart Foundation

Nominal, unrestricted grants from

- AngioCare BV
- Covidien/EV3®
- MEDAC Gmbh/LAMEPRO and
- Penumbra Inc.
Rationale

• Until recently intra-arterial treatment (IAT) for acute ischemic stroke was not proven effective in RCT’s

• MR CLEAN showed a significant favorable effect for IAT that was consistent in almost all subgroups.

• Time is an important predictor for clinical outcome and treatment effect in all ischemic diseases
Rationale 2

- In MR CLEAN, treatment had to be started within 6 hours from stroke onset

- Time from onset to treatment (TOT) is relevant for clinical decision making

- Time from onset to reperfusion (TOR) is important to assess the impact of treatment duration, knowing when to stop the intervention

- TOT and TOR combined give valuable information for clinical practice
Aim

• To assess the interaction of TOT and TOR with treatment on outcome in the MR CLEAN trial

• To assess if treatment was effective in the full 6 hour time window of our trial
Methods

• Primary outcome measure is the score on the mRS at 90 days
• Primary effect parameter: acOR for shift on the mRS, estimated with ordinal logistic regression (aka shift analysis)

• All analyses based on intention to treat principle

• TOT: time from stroke onset to the moment the micro catheter was in the groin
• TOR: time from stroke onset to time TICI 2b/3 was reached, or end of procedure in case reperfusion was not reached
Statistical analysis

• Baseline characteristics are reported by tertiles (early-medium-late) of TOT

• Interaction of TOT and TOR with treatment effect was tested by including interaction terms in the regression model

• All estimates were adjusted for:
  • Age
  • Baseline NIHSS
  • Diabetes
  • History of previous stroke
  • Atrial fibrillation
  • ICA terminus occlusion
### Main characteristics at baseline (by tertile of TOT)

<table>
<thead>
<tr>
<th>Clinical characteristic</th>
<th>Early tertile (n=167)</th>
<th>Medium tertile (n=168)</th>
<th>Late tertile (n=165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years – median (IQR)</td>
<td>67 (57-77)</td>
<td>66 (53-75)</td>
<td>64 (55-75)</td>
</tr>
<tr>
<td>Male sex – n (%)</td>
<td>94 (56%)</td>
<td>99 (59%)</td>
<td>99 (60 %)</td>
</tr>
<tr>
<td>NIHSS score - median (IQR)</td>
<td>17 (13-22)</td>
<td>17 (14-22)</td>
<td>18 (15-22)</td>
</tr>
</tbody>
</table>
Distribution of time from onset to treatment

Median: 256 minutes (IQR 210-314 minutes)

< 3 hours: 11.5%

3 - 4.5 hours: 45%

4.5 - 6 hours: 44%

(8.8 % > 6 hours)
Distribution of time from onset to reperfusion

Median: 332 minutes (IQR 279-394 minutes)

< 3 hours 1.5%

3 - 4.5 hours: 22%

4.5 - 6 hours: 40%

> 6 hours: 37%
Interaction between time from onset to treatment (TOT) and treatment effect

5:13, CI through unity

acOR 1.3 at 6 hours
Absolute difference in chances of good outcome between treated and not treated, by TOT

- 2 hours: ARD 19%
- 6 hours: ARD 3%

4% decrease per hour treatment delay

\( p = 0.26 \)
Interaction between time from onset to reperfusion (TOR) and treatment effect

6:19 hrs, CI through unity
Absolute difference in chances of good outcome between treated and not treated, by TOR

- 2 hours: ARD 33%
- 6 hours: ARD 6.5%
- Almost 7% decrease per hour treatment delay
- $p=0.038$

### Graph
- **Absolute risk difference on mRS 0-2**
- **Time from onset to reperfusion (hours)**
- **acOR**
- **ub 95% CI**
- **lb 95% CI**
- **unity**
Conclusions

- We found a strong interaction of *Time from Onset to Reperfusion* with the effect of treatment

- Interaction of *Time from Onset to Treatment* and treatment effect was not statistically significant, but biologically plausible

- When reperfusion is reached within 2 hours, absolute risk difference is 33%. After 6 hours, absolute risk difference is 6.5%

- Chances of good outcome decrease rapidly with every hour of treatment delay.

- There is no reason to withhold treatment within the 6 hour time window
Implication

Patients with acute ischemic stroke should have vessel imaging and appropriate treatment as soon as possible.
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Conclusions

• We found a strong interaction of TOR with the effect of treatment

• Interaction for TOT and treatment effect was not statistically significant, but biologically plausible

• When reperfusion is reached within 2 hours, absolute risk difference is 33%. After 6 hours, absolute risk difference is 6.5%

• Chances of good outcome decrease rapidly with every hour treatment delay.

• There is no reason to withhold treatment within the 6 hour time window

• Implication: patients with acute ischemic stroke should have vessel imaging and appropriate treatment as soon as possible
Statistical analysis (more)

- TOT and TOR in controls were imputed based on time to randomization.
- Interaction of TOT and TOR was tested by including interaction terms in the model.
- Shape of relation between treatment effect and time was tested with restricted cubic splines with 3 knots.
- Final model was selected based on chi2 of the model with spline interactions compared to the model with a linear interaction term.
- acOR and 95% CI of time was plotted, based on the estimated parameters in the model with the adjusted interaction terms.
- The absolute risk of an mRS 0-2 over time was calculated from the model, seperately for the intervention and control group) >> plotted absolute risk differences and corresponding 95% confidence intervals.