Results of the Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands

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for the MR CLEAN investigators
Disclosures

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• Covidien/EV3®
• MEDAC GmbH/LAMEPRO and
• Penumbra Inc.
• Top Medical/Concentric
Mr Clean this morning

- Some details on the design (vs Escape, Extend IA, Swift prime)
- Results, including pre-defined subgroup analyses results
- Draw attention to new results presented at ISC
Aim of MR CLEAN

To assess the effect of intra-arterial treatment on functional outcome after acute ischemic stroke caused by - a proven - intracranial arterial occlusion, against a background of best medical management *(with or without IV tPa)*.
Design – ‘probe design’

• Multicenter, prospective, randomized trial with open label treatment and
  • Blinded assessment of functional outcome at 90 days
  • Blinded assessment of neuro-imaging at baseline and follow-up

• Masked, web-based, random treatment allocation
Inclusion criteria

- Acute ischemic stroke

- Intracranial anterior circulation occlusion (confirmed by CTA)

- IA treatment within 6 hours from onset feasible

- Age ≥18

- NIHSS ≥ 2
Intervention

• Arterial catheterization with a microcatheter to the level of occlusion

• Mechanical treatment, delivery of a thrombolytic agent, or both

• Mechanical treatment:
  • use of a retrievable stent
  • thrombus retraction
  • aspiration
  • wire manipulation
Clinical outcomes

• Primary outcome: score on the modified Rankin scale at 90 days

• Secondary outcomes:
  • NIHSS at 24 hours and 1 week or discharge
  • Barthel index at 90 days
  • EuroQoL5D at 90 days
Neuro-imaging

- Post intervention DSA: mTICI score
  - 0: no perfusion
  - 2b: complete, but slow filling
  - 3: complete perfusion

- CTA at 24 hours: overall recanalization

- CT at 1 week: infarct size
  - Automated computer algorithm
  - All scans checked by human eye
Statistical analysis

Stratification for

- center
- NIHSS
- use of IV alteplase
- planned treatment modality (mechanical or not)

Primary effect parameter

- adjusted common odds ratio
- estimated with ordinal regression
- also called shift analysis

All effect estimates were adjusted for

- age
- NIHSS
- time since onset to randomization
- previous stroke
- atrial fibrillation
- diabetes mellitus
- carotid terminus occlusion on CTA
Patient accrual

N of patients


Expected

Observed
## Main clinical characteristics at baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention (N=233)</th>
<th>Control (N=267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>65 (55 to 76)</td>
<td>66 (56 to 76)</td>
</tr>
<tr>
<td>Male sex</td>
<td>135 (58%)</td>
<td>157 (59%)</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>17 (14 to 21)</td>
<td>18 (14 to 22)</td>
</tr>
<tr>
<td>Treatment with IV alteplase</td>
<td>203 (87%)</td>
<td>242 (91%)</td>
</tr>
</tbody>
</table>
Intervention details

- N=196
- Retrieval stent: N=190 (97%)
- Thrombolytics only: N=5 (2.6%)
- Other mechanical: N=1 (0.4%)

N=196
## Serious adverse events

<table>
<thead>
<tr>
<th>Serious Adverse Events</th>
<th>Intervention (N=233)</th>
<th>Control (N=267)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least one SAE</td>
<td>110 (47%)</td>
<td>113 (42%)</td>
</tr>
<tr>
<td>Parenchymal hemorrhage type 2 (PH2)</td>
<td>14 (6.0%)</td>
<td>14 (5.2%)</td>
</tr>
<tr>
<td>New ischemic stroke in different vascular territory</td>
<td>13 (5.6%)</td>
<td>1 (0.4%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>25 (11%)</td>
<td>41 (15%)</td>
</tr>
<tr>
<td>Hemicraniectomy</td>
<td>14 (6.0%)</td>
<td>13 (4.9%)</td>
</tr>
</tbody>
</table>
Recanalization on CTA

<table>
<thead>
<tr>
<th>aOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recanalization at 24 hrs</td>
</tr>
<tr>
<td>6.9 (4.3 to 10.9)</td>
</tr>
</tbody>
</table>

Bar chart showing the percentage of Categorie 1 for Control and Intervention groups.
Effect of intervention on primary outcome

**Common adjusted odds ratio: 1.67 (95% CI: 1.21 to 2.30)**
## Dichotomized mRS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>acOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0-1</td>
<td>2.1 (1.1 to 4.0)</td>
</tr>
<tr>
<td>mRS 0-2</td>
<td>2.2 (1.4 to 3.4)</td>
</tr>
<tr>
<td>mRS 0-3</td>
<td>2.0 (1.4 to 3.0)</td>
</tr>
<tr>
<td>mRS 0-4</td>
<td>1.5 (1.0 to 2.4)</td>
</tr>
<tr>
<td>mRS 0-5</td>
<td>1.1 (0.7 to 1.7)</td>
</tr>
</tbody>
</table>

![Bar graph showing the percentage of patients in each mRS category for control and intervention groups](image.png)

- mRS 0-1: 6% Control, 14% Intervention
- mRS 0-2: 15% Control, 17% Intervention
- mRS 0-3: 7% Control, 15% Intervention
- mRS 0-4: 1% Control, 7% Intervention
- mRS 0-5: 1% Control, 1% Intervention
Secondary neuro-imaging outcomes: Final infarct volume at 7 days

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final infarct volume</td>
<td>17 (0 to 33)</td>
</tr>
</tbody>
</table>
Subgroup analyses: age and NIHSS

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>acOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>500</td>
<td>1.67 (1.21 to 2.30)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;80</td>
<td>419</td>
<td>1.6 (1.13 to 2.27)</td>
</tr>
<tr>
<td>≥80</td>
<td>81</td>
<td>3.24 (1.21 to 8.62)</td>
</tr>
<tr>
<td>NIHSS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-15</td>
<td>164</td>
<td>1.71 (.96 to 3.02)</td>
</tr>
<tr>
<td>16-19</td>
<td>153</td>
<td>1.5 (.83 to 2.67)</td>
</tr>
<tr>
<td>≥20</td>
<td>183</td>
<td>1.85 (1.06 to 2.31)</td>
</tr>
</tbody>
</table>
Subgroup analyses: time from onset and IV alteplase

<table>
<thead>
<tr>
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<th>No. of patients</th>
<th>acOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>500</td>
<td>1.67 (1.21 to 2.30)</td>
</tr>
<tr>
<td>Onset to randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥120 min</td>
<td>449</td>
<td>1.69 (1.20 to 2.38)</td>
</tr>
<tr>
<td>&lt;120 min</td>
<td>51</td>
<td>1.57 (.50 to 4.85)</td>
</tr>
<tr>
<td>IV alteplase*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>55</td>
<td>2.06 (.69 to 6.13)</td>
</tr>
<tr>
<td>yes</td>
<td>445</td>
<td>1.71 (1.21 to 2.40)</td>
</tr>
</tbody>
</table>
### Subgroup analyses: neuro-imaging

<table>
<thead>
<tr>
<th></th>
<th>No. of patients</th>
<th>acOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>500</td>
<td>1.67 (1.21 to 2.30)</td>
</tr>
<tr>
<td><strong>ICA terminus occlusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>366</td>
<td>1.61 (1.10 to 2.33)</td>
</tr>
<tr>
<td>present</td>
<td>134</td>
<td>2.43 (1.24 to 4.77)</td>
</tr>
<tr>
<td><strong>ASPECTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-4</td>
<td>28</td>
<td>1.09 (.14 to 8.46)</td>
</tr>
<tr>
<td>5-7</td>
<td>92</td>
<td>1.97 (.89 to 4.35)</td>
</tr>
<tr>
<td>8-10</td>
<td>376</td>
<td>1.61 (1.11 to 2.33)</td>
</tr>
<tr>
<td><strong>Extracranial ICA occlusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent</td>
<td>354</td>
<td>1.85 (1.25 to 2.72)</td>
</tr>
<tr>
<td>present</td>
<td>146</td>
<td>1.43 (.77 to 2.64)</td>
</tr>
</tbody>
</table>
Conclusion

The Mr Clean trial is the first trial to show that intra-arterial treatment within 6 hours from stroke onset in patients with acute ischemic stroke caused by an intracranial arterial anterior circulation occlusion is safe and... clinical effective!

*Increase in good outcome (mRs 0-2) from 1 out of 5 to 1 out of 3 patients*
Upcoming new results

- ISC Nashville, Feb 2015
  - This afternoon: - 3:49 Room 207, Mr Clean, in depth and some additional analyses (Diederik Dippel)
  - Thursday: - 11:05 Hall B, Pooled analysis of the IMS III and MR CLEAN trials for patients with NIHSS of 20 or more (Joseph Broderick)
  - 11:53 Hall B, Time to treatment and time to reperfusion & Tx effect (Puck Fransen)
  - Friday: - 12:17 Hall B, General anesthesia or no General anesthesia & Tx effect (Olvert Berkhemer)

- ESOC Glasgow, April 2015
Executive committee: Wim H. van Zwam, Yvo B.W.E.M. Roos, Aad van der Lugt, Robert J. van Oostenbrugge, Charles B.L.M. Majoie, and Diederik W.J. Dippel

PhD Students: Olvert A. Berkhemer, Puck S.S. Fransen, Debbie Beumer, Lucie A. van den Berg


Outcome assessment: Yvo Roos, Jelis Boiten, Ewoud van Dijk, Peter J. Koudstaal.

SAE committee: Robert van Oostenbrugge, Marieke J. Wermer, Zwenneke H. Flach

Imaging assessment: Charles B Majoie, Wim van Zwam, Geert J. Lycklama à Nijeholt, Marianne A.A. van Walderveen, Joost C. Bot, Henk A. Marquering, Marieke E.S. Sprengers, Sjoerd Jenniskens, Ludo F.M. Beenen, René van den Berg,

Independent DSA reader: Albert J. Yoo,

Trial methodologists: Hester F. Lingsma, Ewout W. Steyerberg,

Data monitoring committee: Martin Brown, Thomas Liebig, Theo Stijnen.
Thank you!

Questions?

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ADDITIONAL SLIDES
Why a new trial of intra-arterial treatment?

• Improved patient selection through widespread availability of CTA

• Fast access to treatment through good infrastructure

• Availability of promising new treatment modality: Retrievable stents
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- Availability of promising new treatment modalities: retrievable stents
Why a new trial of intra-arterial treatment?

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• Fast access to treatment through good infrastructure

• Availability of promising new treatment modality: Retrievable stents
Rationale

• IV alteplase, given within 4.5 hours leads to recanalization in about 1/3, and to recovery in 10% of patients (less in distal carotid or prox. middle cerebral artery occlusions)

• More than 1/3 of patients with acute ischemic stroke have a proximal intracranial arterial occlusion

• Up till the end of 2014 randomized controlled trials on intra-arterial treatment did not show a clinical beneficial effect
Patient flow in the study

Baseline CT, CTA N=502

2 pts refused participation

Allocation

Intervention N=233

17 did not reach angiosuite

20 DSA only

Received tx

IAT N= 196

mRS N=233

End of FU

Control N=267

1 pt IAT

Standard tx N=266

mRS N=267

Received tx

IAT N=196

mRS N=233
Timing

- Time from onset to start of IV alteplase:
  - Intervention: 85
  - Control: 87

- Time from onset to randomization:
  - Intervention: 204
  - Control: 196

- Time from onset to groin puncture:
  - Intervention: 260
Assessment of outcome at 90 days

- Single investigator not aware of allocated treatment
  - Telephone interview for mRS, Barthel and EQ5D
  - Masked structured report

- Central outcome assessment committee
  - Review of outcome report by 2 blinded assessors
  - 3rd blinded reviewer
Distribution of occlusive lesions at baseline

![Bar chart showing the distribution of occlusive lesions at baseline. The chart indicates the percentage of lesions at different locations (ICA terminus, M1, M2, A1/A2). The bars are color-coded: blue for control and red for intervention.](image)
Safety data: mortality

Days from randomization

Control

Intervention
Pre- and post intervention mTICI scores in treated patients

![Bar chart showing mTICI scores before and after intervention](chart.png)
## Secondary clinical outcomes: NIHSS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIHSS – 24 hrs</td>
<td>2.3 (1.0 to 3.5)</td>
</tr>
<tr>
<td>NIHSS – 1 week</td>
<td>2.9 (1.5 to 4.3)</td>
</tr>
</tbody>
</table>

![Bar chart showing NIHSS outcomes](chart.png)
Secondary clinical outcomes: Barthel Index

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI 19-20</td>
<td>2.1 (1.4 to 3.2)</td>
</tr>
</tbody>
</table>

Outcome Adjusted OR (95% CI)

Control

Intervention

BI 19-20 - 90 days
Secondary clinical outcomes: EQ 5D

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EQ 5D</td>
<td>0.06 (-0.01 to 0.13)</td>
</tr>
</tbody>
</table>
Active intervention center in MR CLEAN
Randomizing center in MR CLEAN
Intervention in close collaboration with other centers in MR CLEAN
Not active in MR CLEAN trial
High accrual rates in the Netherlands

This helped:
• Local PI’s were pairs of interventionist and neurologist
• 1-2 workshops with lots of interaction
• Pretrial registry of all IAT patients in NL

This made a big difference
• Everybody in NL has health insurance.
• Until 2012 no reimbursement for IAT
• IN 2012 conditional reimbursement was announced
• From 2013 until end of trial: reimbursement conditional on participation in MR CLEAN, by government decision.
• In 2012 after presentation of IMS 3 and MR RESCUE results all centers decided not to treat patients outside the trial.