Can we repeat the thrombectomy clinical trial results in everyday clinical routine?

Exit Light-Enter Night*
<table>
<thead>
<tr>
<th>Category</th>
<th>Disclosures</th>
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<tbody>
<tr>
<td>Consultant</td>
<td>Boehringer Ingelheim, Daiichi-Sankyo, Neuravi</td>
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<tr>
<td>Honoraria</td>
<td>Boehringer Ingelheim, Medtronic, Neuravi</td>
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<td>Scientific advisory board</td>
<td>Boehringer Ingelheim, Neuravi</td>
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<tr>
<td>Grants</td>
<td>Boehringer Ingelheim, German Research Foundation, German Ministry of Science, European Union</td>
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<td>Stock and patents</td>
<td>None</td>
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Part I
Thrombectomy: The Evidence
- History
- Pooled analysis
- Differences between the trials
- To whom these results apply
The New Thrombectomy Trials

- February 2013: Three Thrombectomy RCTs are presented and published: all three show neutral results
- In consequence some health insurances do not pay for MT anymore
- October 2014: MR CLEAN is presented at the WSC 2014
- Thereafter several trials are put on hold, undergo interim analyses and are reported in 2014 and 2015
- Five clinical trial papers and two editorials are published in the NEJM within 4 months, and one followed in LANCET Neurology
- Only one trial using aspiration technology is neutral and not yet published
Overall Results

- All studies clearly under 6h for recanalization or first pass (mdn around 4h) (except DAWN)
- Results apply for rtPA co-treatment and Stent-Retriever

- However, major differences in response rates, even in control arms
- When we ask whether we can replicate the outcome results of the clinical trials in daily routine, we need to ask first:

  The results of which trial?
Favourable Outcome (mRS 0-2) in Comparison

mRS 0-2%

Range of Differences: 14-31%
Note the responses in the control arms: 19-40%

Let’s summarize so far:
For which patients do the results currently apply?

• Severe AIS with average NIH-SS 17
• CT-selection (the more advanced, the better the outcome)
• No age limit, but relatively young mdn age
• CTA proven Carotid-T or M1 occlusions
• Co-treatment with rtPA
• Early treatment with reperfusion or first thrombus pass clearly below 6h-the earlier the better
• Use of stentriever (Solitaire) devices
• Treatment in large volume endovascular centers
When the data are pooled, the overall outcome looks good, but not great

- mRS 0-1 26.9%; mRS 0-2 47%
- 53% remain dead or dependent
Part II
Factors influencing outcome

- Imaging requirements?
- Time to treatment?
- Recanalization rate?
- Experience and skills of the Interventionalist
What Explains the Differences in Outcome

Factors influencing patient outcomes in stroke trials are

- Age, Stroke Severity and Occlusion Site
  - These factors were not different between MT trials
- Patient Selection: Imaging requirements
  - Varied largely between the different MT trials
- Time to Groin/Recanalization
  - Fast in all MT trials (mdn under 4h), but still some differences
- Thrombus composition?
- TICI results (TICI IIb/III)
  - TICI results slightly varied between trials

The experience and the technical skills of the interventionalist (not tested!)
What Explains the Differences in Outcome

- Factors influencing patient outcomes in stroke trials are:
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- The experience and the technical skills of the interventionalist (not tested!)
Imaging-Requirements

- All studies CT based, no MRI
- Imaging Requirements should not delay treatment
- The more demanding the imaging requirements, the less patients did qualify for the study
- These patients may, however, have better chances to respond to tx
**Treatment Effects by Imaging Requirements**

**mRS 0-2%**

<table>
<thead>
<tr>
<th>Treatment Effects by Imaging Requirements</th>
<th>MR CLEAN</th>
<th>REVASCAT</th>
<th>ESCAPE</th>
<th>SWIFT PRIME</th>
<th>EXTEND IA</th>
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<tr>
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<td>3 act</td>
<td>2 ctl</td>
<td>2 act</td>
<td>3 ctl</td>
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<tr>
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<td>0 act</td>
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<tr>
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<td>6 act</td>
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<td>7 ctl</td>
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<tr>
<td>All RAPID</td>
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<td></td>
<td></td>
<td></td>
<td>1 act</td>
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Part III
Implementation

- Why are real life results different from the RCTs and meta-analyses?
- What is the Implementation status?
Whenever we deviate from clear indications, label or guidelines ("exit light") we will face poorer results and more complications ("enter night")

We have to accept that in real live we will treat patients not eligible for clinical trials
- “off label -aka- last chance”
- Only few of them will really benefit

Benchmarking should be done with patients reflecting the ideal study population
Results In Everyday Routine?

- Results in clinical routine will be best, if the patient selection is close to the “ideal” population.
- With very broad inclusion (e.g. long ttt, large core, pre-existing handicap) the treatment effects may shrink, disappear or may be outweighed by more risk.
- In everyday practice many patient deviate from the ideal group:
  - More distal occlusions\(\uparrow\), longer time windows\(\downarrow\), larger core\(\downarrow\), no collaterals\(\downarrow\), no rtPA possible\(\leftrightarrow\), older age\(\downarrow\), already disabled\(\downarrow\).
A Real Life Example (2016)

- Data from our university hospital service in Heidelberg
- 1200 ischemic strokes per year, 700 K catchment area
  - Total number recanalization therapies 411

<table>
<thead>
<tr>
<th>Modal.</th>
<th>n</th>
<th>NIH-SS</th>
<th>Age</th>
<th>DNT min</th>
<th>DTV min</th>
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<tr>
<td>All i.a.</td>
<td>256</td>
<td>17</td>
<td>76</td>
<td>35</td>
<td>79</td>
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An Example From a Small German Service

- How does our population look like, in comparison with RCTs and meta-analyses?
  - Comparable ttt and stroke severity
  - Imaging: CT, CTA and small core, but more ASPECTS <6, no advanced selection
  - less rtPA co-treatment (only 60%-I don´t know why)
  - up to 20% M1
  - more patients with unknown time window
  - almost 40% off label/off guideline (pre-morbid handicap, time window)
  - Age?
How do the 2016 results compare to MR CLEAN, the study with broadest inclusion and worst outcome?

NIH-SS mdn 17; onset to recan? (longest of all trials)

Age mdn 65 y

Age mdn 76 y

NIH-SS mdn 17, onset to groin 233 min
Comparison With Hermes Metaanalysis

- **HERMES**
  - NIH-SS mdn 17; onset to recan 285 min
  - Age mdn 67 y

- **HD**
  - NIH-SS mdn 17, onset to groin 233 min
  - Age mdn 76 y
My personal opinion

To use Thrombectomy in high quality and economically sound we need

- Large 24/7 centers with several teams
- High treatment numbers (>100 Pat/y)
- Training facilities
- Networks, Teleneurology, Transportation, Bridging
- If we adjust for differences in the patient characteristics, our results may come close to the overall thrombectomy results known from the metaanalyses of the large RCTs
Nationwide Thrombectomy Rates 2014-2016

Thrombectomy rates 2014
Place of treatment

- 0.1%-0.5%
- 0.5%-4.5%
- 4.5%-8.5%
- >8.5%

<table>
<thead>
<tr>
<th>Year</th>
<th>Place of treatment</th>
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<td>2014</td>
<td>0.1%-0.5% 0.5%-4.5% 4.5%-8.5% &gt;8.5%</td>
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<tr>
<td>2015</td>
<td>1.1% 3.6% 6.2% 38.6% 14.6%</td>
</tr>
</tbody>
</table>

3008 of a total of 7797 MT were performed in one of the 20 largest centers (<100 procedures/year)

5809 (75%) of all MT were performed in centers with >50 procedures/year

Total number in 2015:
- 7,790 MTs

Total number in 2016:
- 13,800 MTs

2014:
MT in 105 (25%) of reg
Thrombectomy works

It is a great addition to our acute stroke therapy for a selected group of patients.

About 10-15% of all stroke arrivals in a large center may be candidates for thrombectomy.

Results in daily practice will not mirror those of the best clinical trials.

Benchmarking should be performed using on-label/guideline patient results only.

Large centers with large patient numbers are key.

Conclusion