

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

Exit Light-Enter Night*

*Phrase taken from
„Enter Sandman“ by *Metallica*
From the „Black Album“



Current Disclosures

Consultant	Boehringer Ingelheim, Daiichi-Sankyo, Neuravi
Honoraria	Boehringer Ingelheim, Medtronic, Neuravi
Scientific advisory board	Boehringer Ingelheim, Neuravi
Grants	Boehringer Ingelheim, German Research Foundation, German Ministry of Science, European Union
Stock and patents	None



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

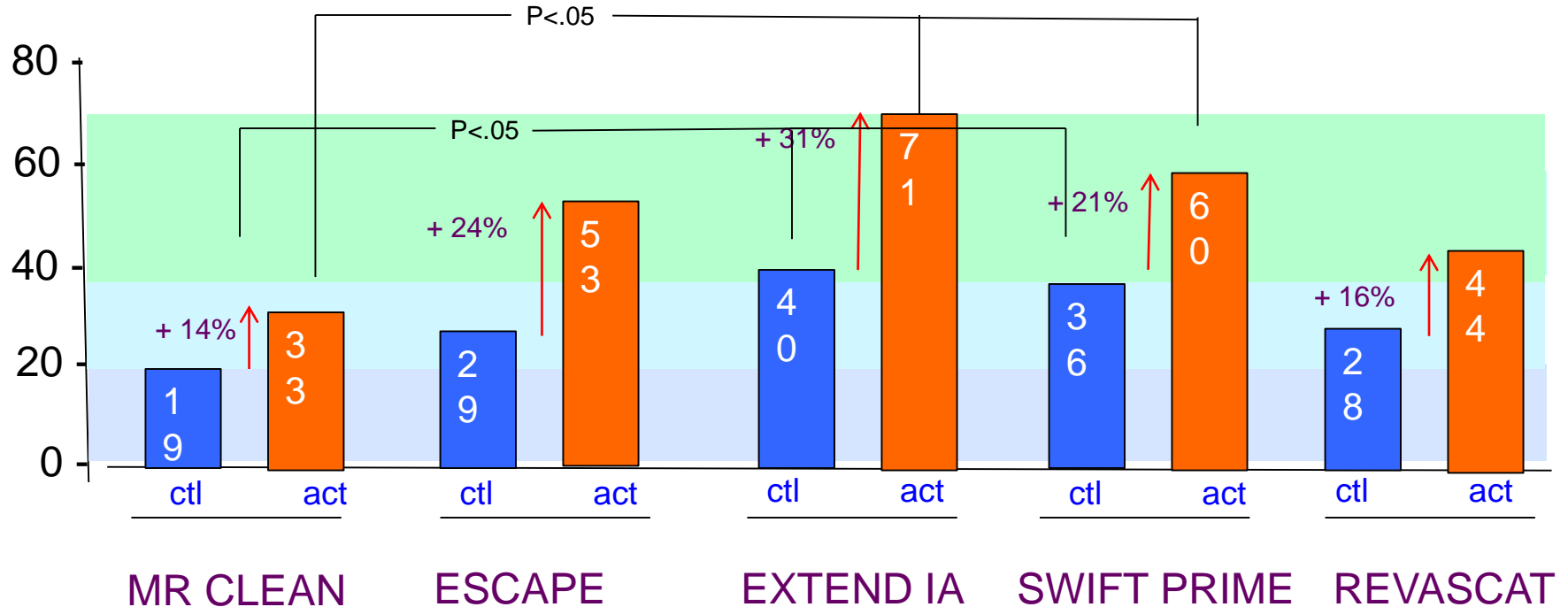
- ⇒ All studies clearly under 6h for recanalization or first pass (mdn around 4h) (except DAWN)
- ⇒ Results apply for rtPA co-treatment and Stent-Retrievers
- ⇒ However, major differences in response rates, even in control arms
- ⇒ When we ask whether we can replicate the outcome results of the clinical 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%

Berkhemer et al NEJM 2015, Goyank et al NEJM 2015, Campbell et al NEJM 2015, Saver et al NEJM 2015, Jovin et al NEJM 2015,

Let's summarize so far:

For which patients do the results currently apply?

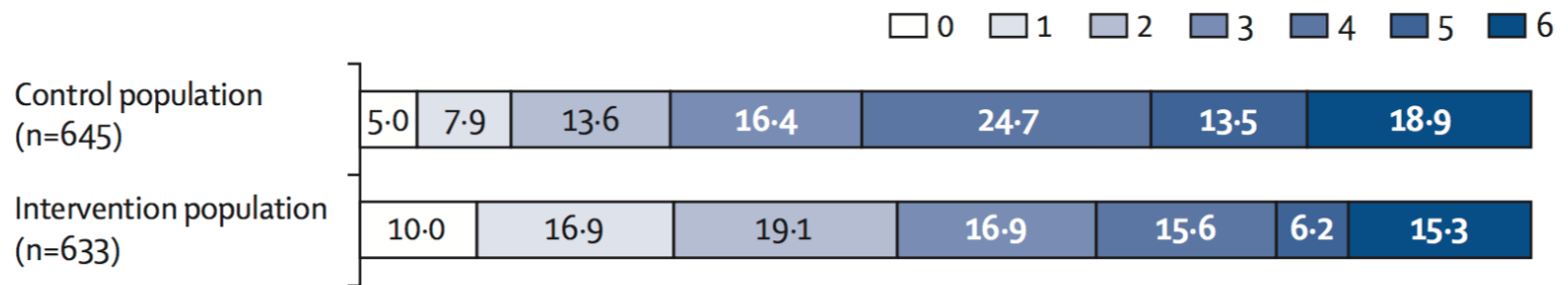
- Severe AIS with average NIH-SS 17
- CT-selection (the more advanced, the better the outcome)
- No age limit, but relatively young median age
- CTA proven Carotid-T or M1 occlusions
- Co-treatment with rtPA
- Early treatment with reperfusion or first thrombus pass clearly below 6h-the earlier the better
- Use of stentriever (Solitaire) devices
- Treatment in large volume endovascular centers



The HERMES Cooperation- Outcome Results

- ⇒ 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

A Overall



Goyal et al Lancet 2016

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?
 - TICl results (TICl Ib/III)
 - TICl results slightly varied between trials
- ⇒ The experience and the technical skills of the interventionalist (not tested!)



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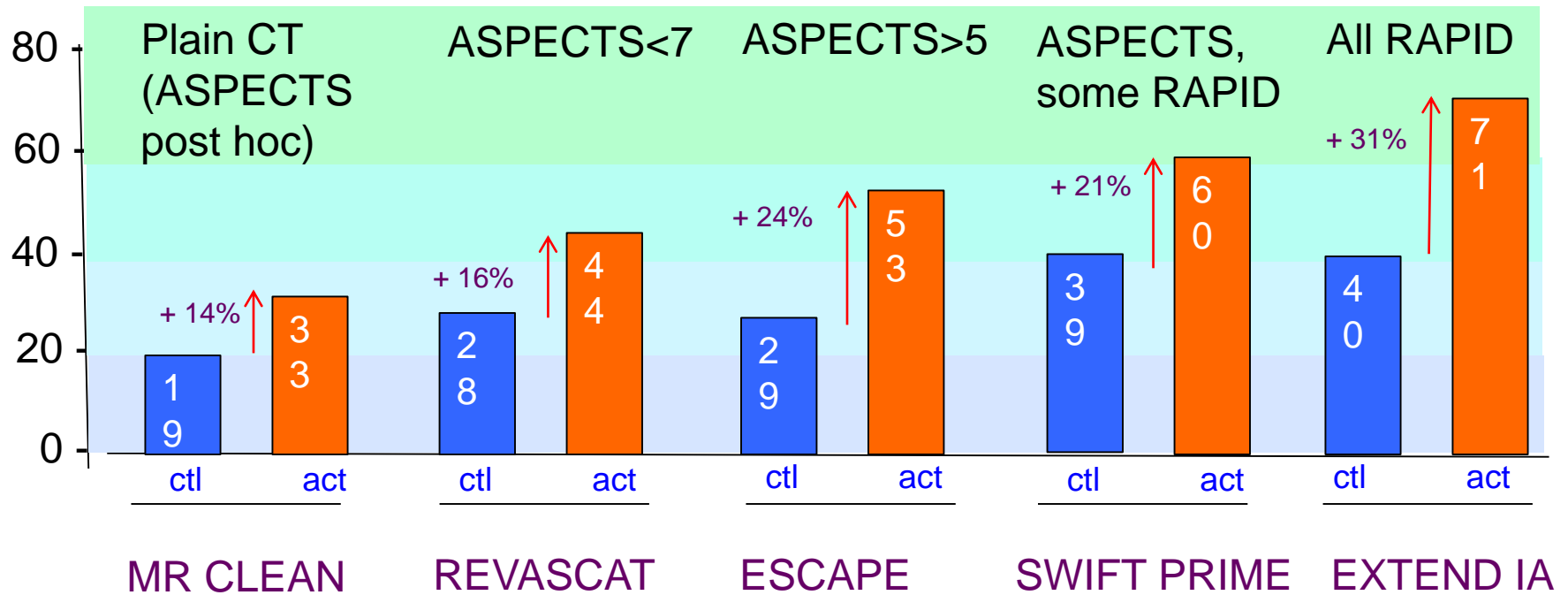
Imaging-Requirements

- ⇒ 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%



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Part III

Implementation

- Why are real life results different from the RCTs and meta-analyses?
- What is the Implementation status?



Exit Light-Enter Night

- ⇒ 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 life 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↑, longer time windows↓, larger core↓, no collaterals↓, no rtPA possible↔, older age↓, already disabled↓

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

Modal.	n	NIH-SS	Age	DNT min	DTV min
All	411	13	76	34	79
i.v.	155	5	75	34	-
i.v-i.a.	153	17	77	34	78
i.a.	103	17	75	35	79
All i.a.	256	17	76	35	79



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?

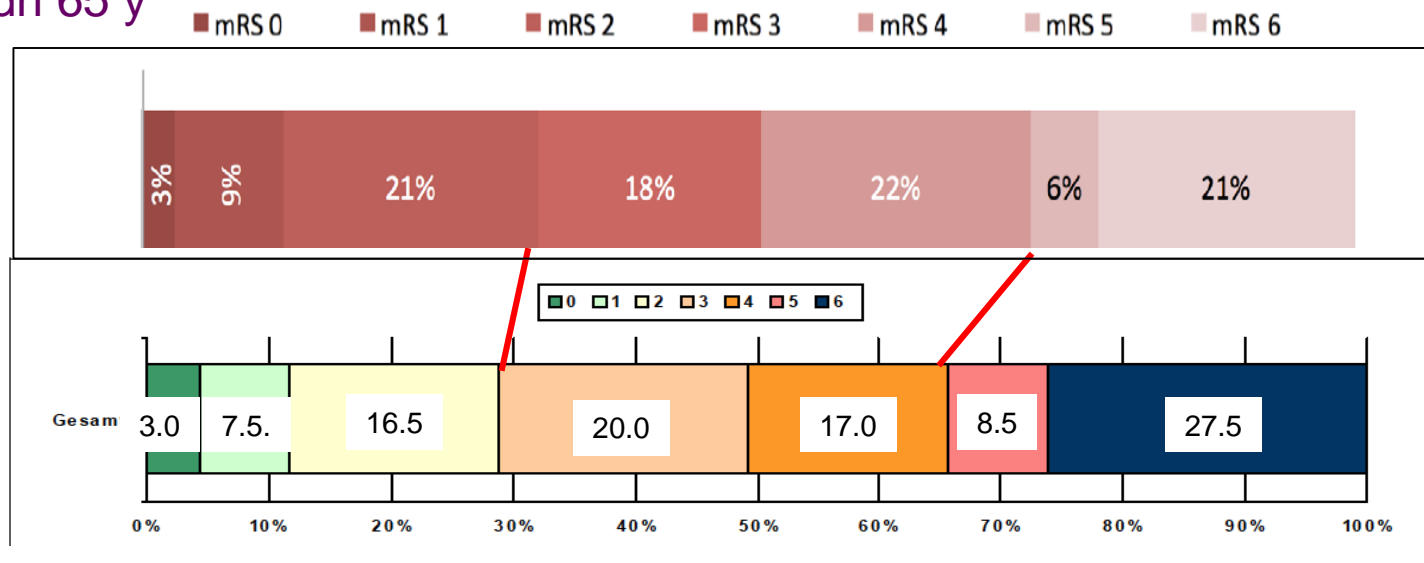


An Example From a Small German Service

⇒ 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



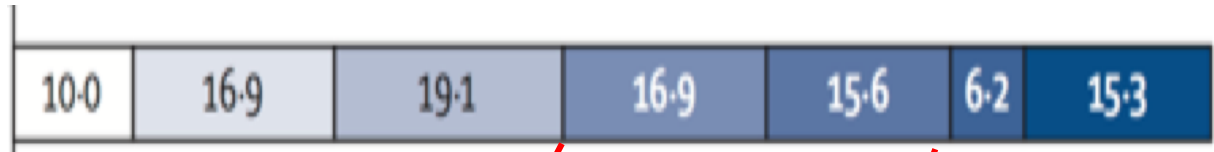
Age mdn 76 y

NIH-SS mdn 17, onset to groin 233 min

Comparison With Hermes Metaanalysis

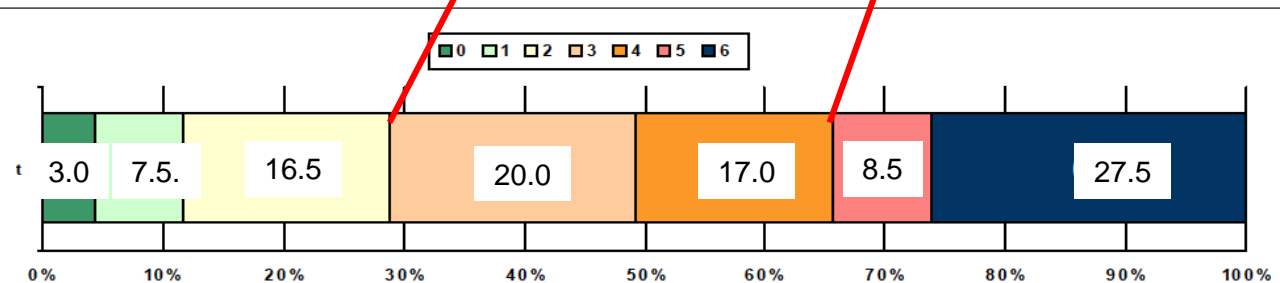
- **HERMES** NIH-SS mdn 17; onset to recan 285 min

Age mdn 67 y



- **HD**

Age mdn 76 y



NIH-SS mdn 17, onset to groin 233 min

My personal opinion

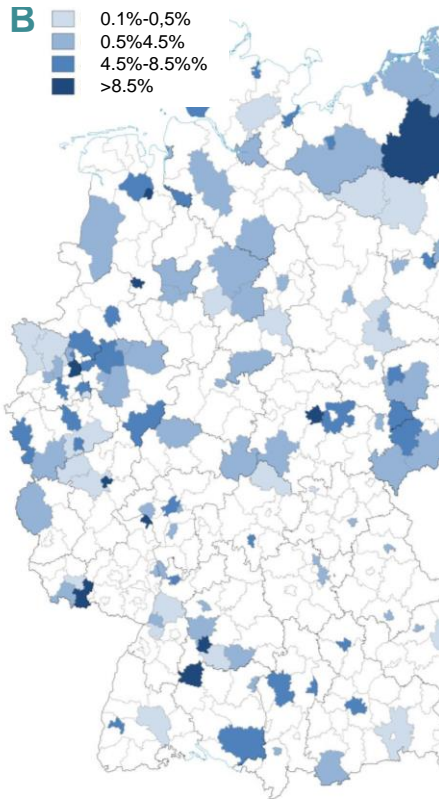
- ⇒ To use Thrombectomy in high quality and economically sound we need
- Large 24/7 centers with several teams
 - High treatment numbers (>100 Pat/y)
 - Training facilities
 - Networks, Teleneurology, Transportation, Bridging
 - If we adjust for differences in the patient characteristics, our results may come close to the overall thrombectomy results known from the metaanalyses of the large RCTs



Nationwide Thrombectomy Rates 2014-2016

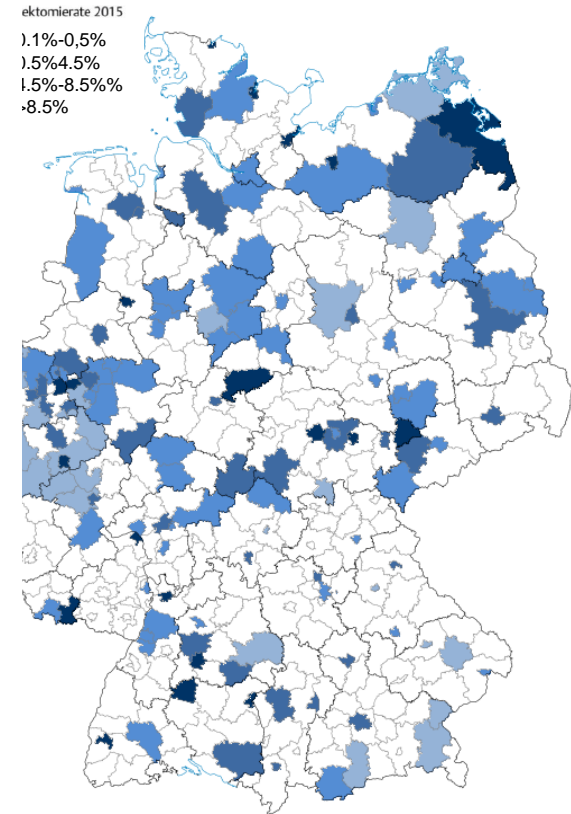
Thrombectomy rates 2014

Place of treatment



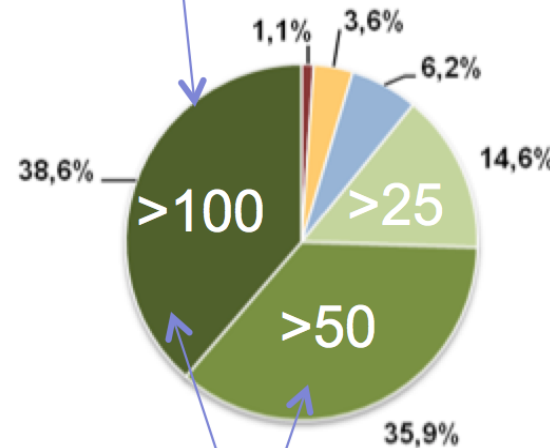
Thrombectomy rates 2015

Place of treatment



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

2015



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

Total number in 2016:
13,800 MTs

2014:
MT in 105 (25%) of reg

Conclusion

- ⇒ Thrombectomy works
- ⇒ It is 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

