Endovascular stroke research after MRCLEAN

W. van Zwam

Maastricht UMC+

Layout

1. What do we know by now

2. Next research questions

    Anesthesia
    Aspiration

3. Ongoing and future research

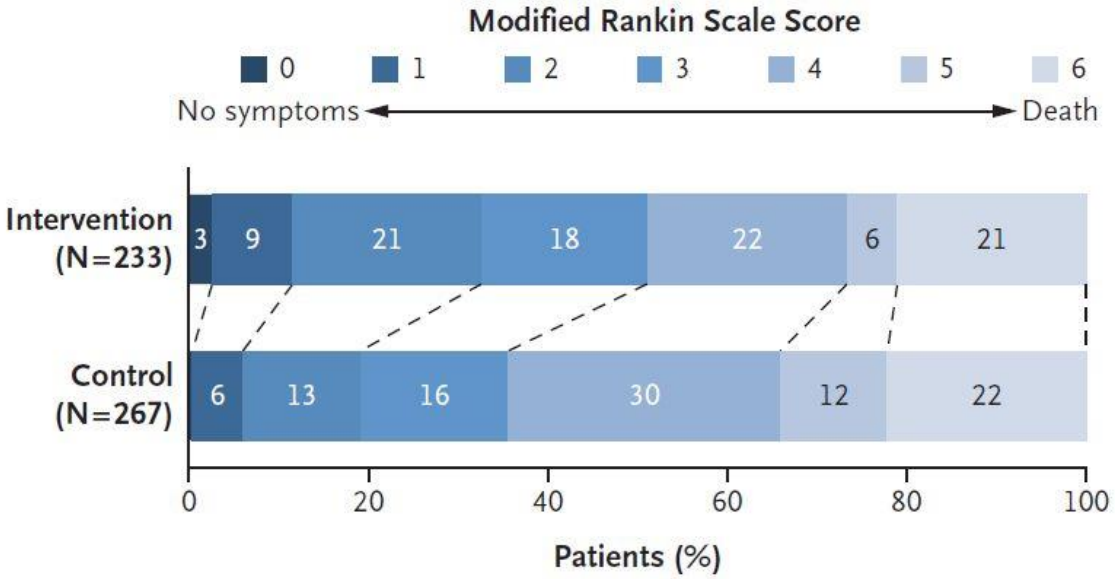
    Dutch initiatives

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 1, 2015 VOL. 372 NO. 1

A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

O.A. Berkhemer, P.S.S. Fransen, D. Beumer, L.A. van den Berg, H.F. Lingsma, A.J. Yoo, W.J. Schonewille, J.A. Vos, P.J. Nederkoorn, M.J.H. Wermer, M.A.A. van Walderveen, J. Staals, J. Hofmeijer, J.A. van Oostayen, G.J. Lycklama à Nijeholt, J. Boiten, P.A. Brouwer, B.J. Emmer, S.F. de Bruijn, L.C. van Dijk, L.J. Kappelle, R.H. Lo, E.J. van Dijk, J. de Vries, P.L.M. de Kort, W.J.J. van Rooij, J.S.P. van den Berg, B.A.A.M. van Hasselt, L.A.M. Aerden, R.J. Dallinga, M.C. Visser, J.C.J. Bot, P.C. Vroomen, O. Eshghi, T.H.C.M.L. Schreuder, R.J.J. Heijboer, K. Keizer, A.V. Tielbeek, H.M. den Hertog, D.G. Gerrits, R.M. van den Berg-Vos, G.B. Karas, E.W. Steyerberg, H.Z. Flach, H.A. Marquering, M.E.S. Sprengers, S.F.M. Jenniskens, L.F.M. Beenen, R. van den Berg, P.J. Koudstaal, W.H. van Zwam, Y.B.W.E.M. Roos, A. van der Lugt, R.J. van Oostenbrugge, C.B.L.M. Majoie, and D.W.J. Dippel, for the MR CLEAN Investigators*



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MR CLEAN
www.mrclean-trial.org
A Multicenter Randomized CLinical trial of Endovascular treatment for Acute Ischemic stroke in the Netherlands

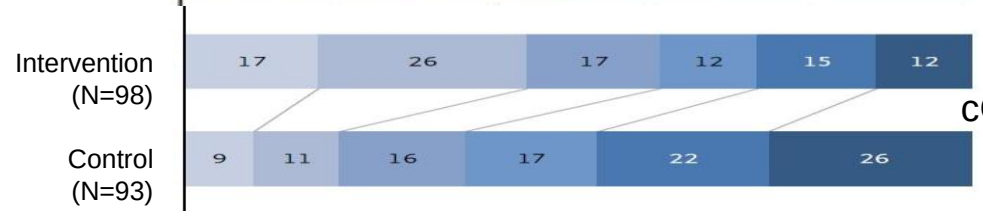
EXTEND-IA

N=70

acOR: **2.3**

SWIFT PRIME

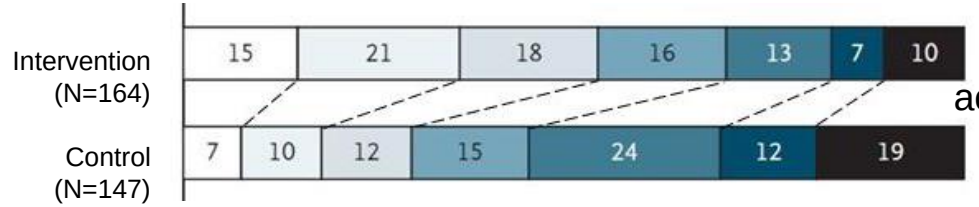
N=196



cOR: **2.63**

ESCAPE

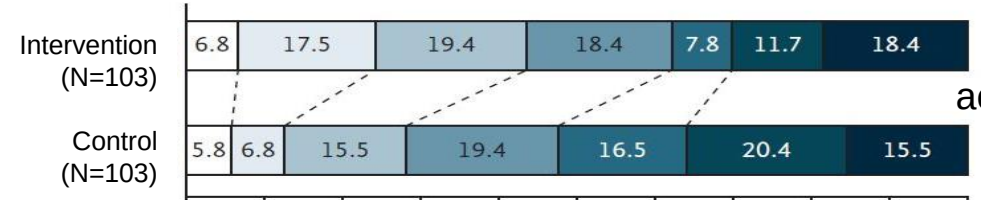
N=316



acOR: **3.1**

REVASCAT

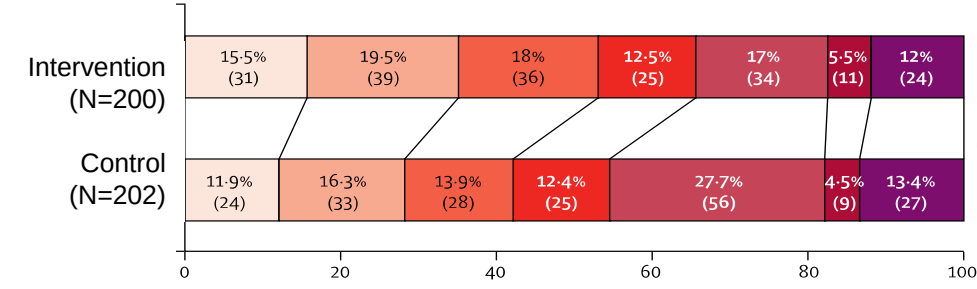
N=206



acOR: **1.7**

THRACE

N=402



OR: **1.55** *(mRS 0-2)*

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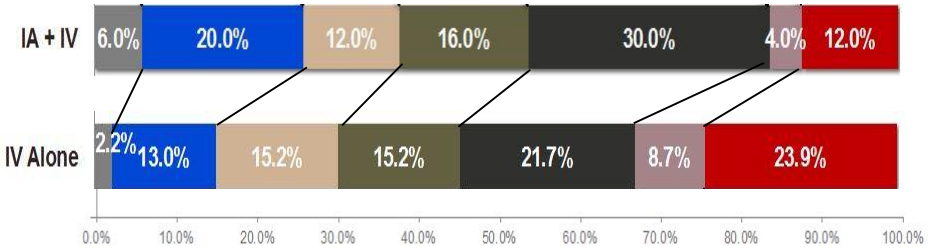
Stroke. 2016 Sep;47(9):2331-8

Therapy

N=96

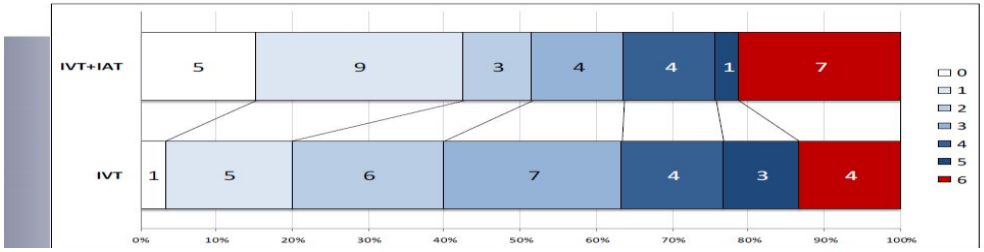


OR: **1.4**

P=0.44

J Neurol Neurosurg Psychiatry. 2017 Jan;88(1):38-44.

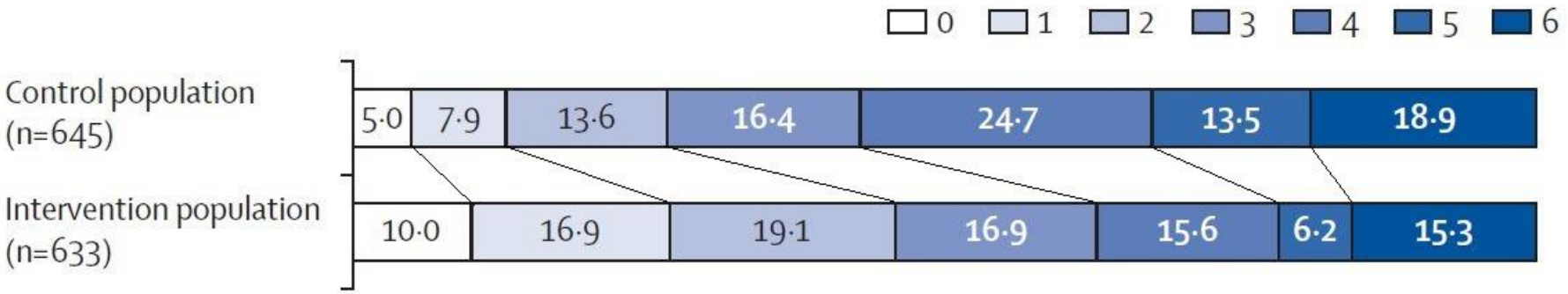
N=65



acOR: **2.59**

P=0.070

HERMES MR CLEAN ESCAPE EXTEND-IA REVASCAT SWIFT PRIME

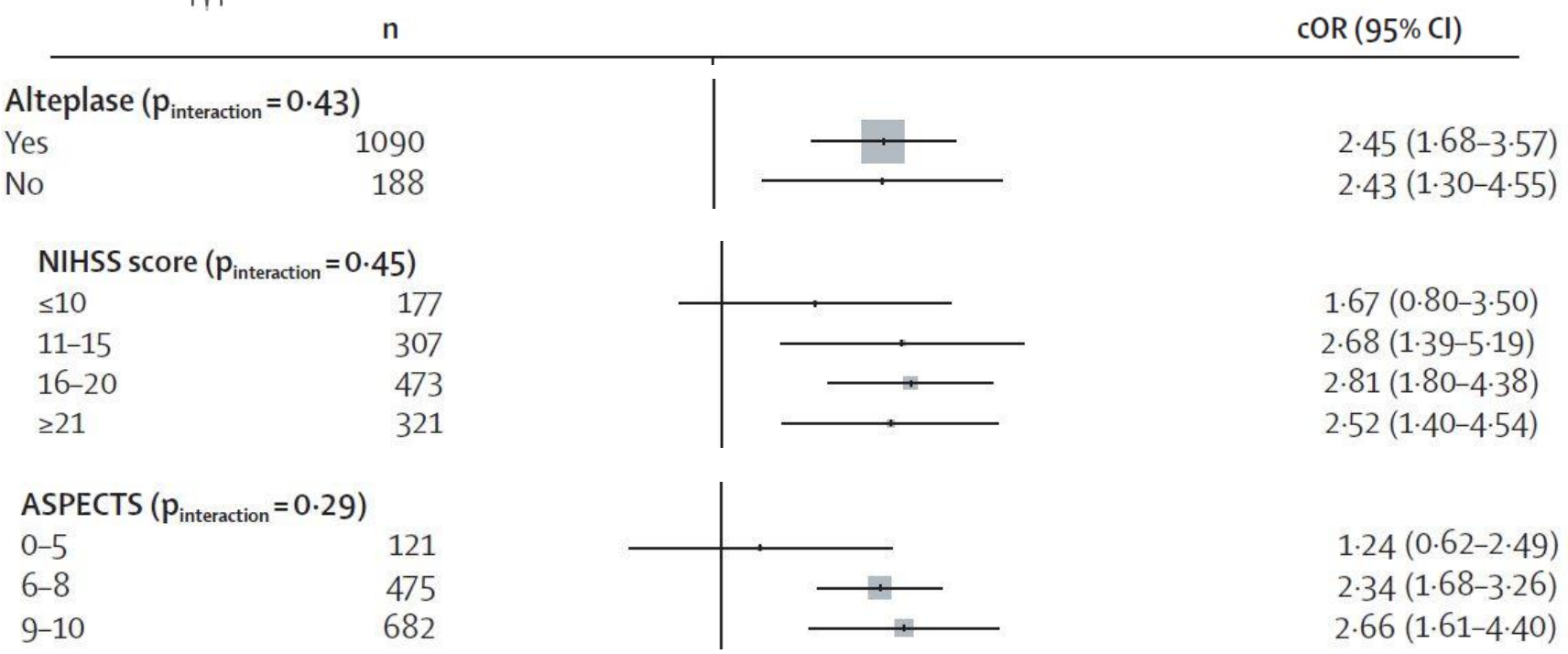


Adjusted cOR 2.49

NNT 2.6 !

Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. **Lancet**. 2016 Apr 23;387(10029):1723-31

HERMES MR CLEAN ESCAPE EXTEND-IA REVASCAT SWIFT PRIME



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Sustainable effect?

The NEW ENGLAND JOURNAL of MEDICINE

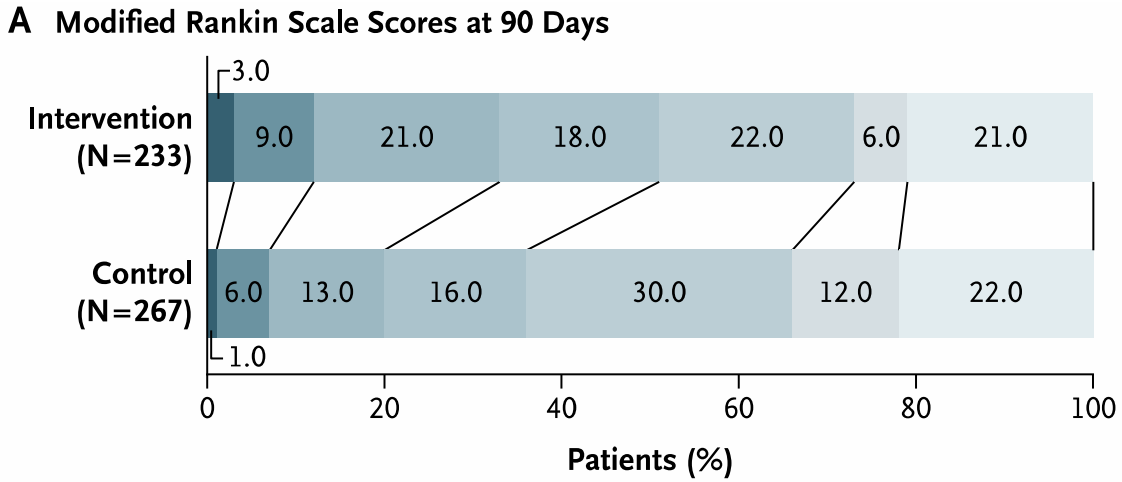
ORIGINAL ARTICLE

Two-Year Outcome after Endovascular Treatment for Acute Ischemic Stroke

Lucie A. van den Berg, M.D., Marcel G.W. Dijkgraaf, Ph.D., Olvert A. Berkhemer, M.D., Ph.D., Puck S.S. Fransen, M.D., Debbie Beumer, M.D., Hester F. Lingsma, Ph.D., Charles B.L.M. Majoie, M.D., Ph.D., Diederik W.J. Dippel, M.D., Ph.D., Aad van der Lugt, M.D., Ph.D., Robert J. van Oostenbrugge, M.D., Ph.D., Wim H. van Zwam, M.D., Ph.D., and Yvo B.W.E.M. Roos, M.D., Ph.D., for the MR CLEAN Investigators*

N Engl J Med 376;14: April 6, 2017. 1341-9

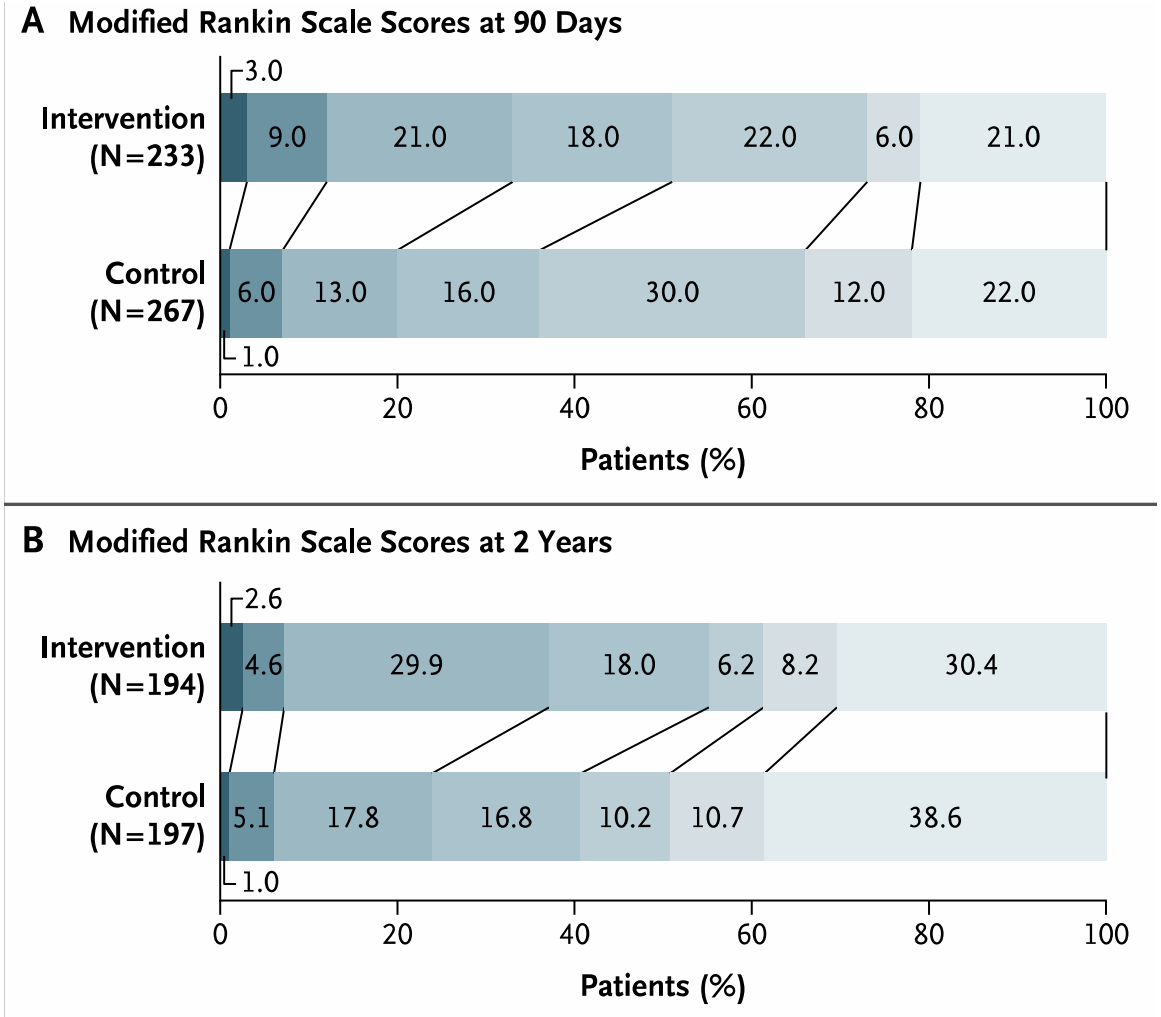
Sustainable effect?



acOR 1.67

N Engl J Med 376;14: April 6, 2017. 1341-9

Sustainable effect?



acOR 1.67

acOR 1.68

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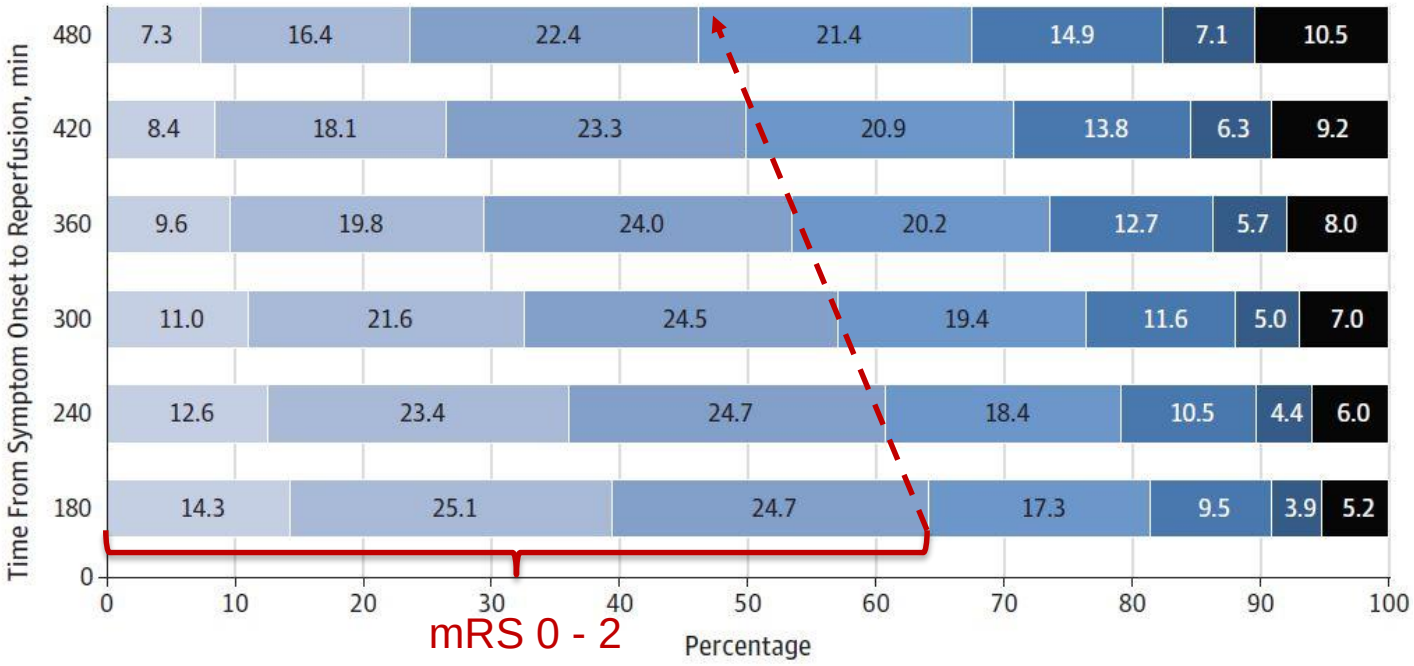
N Engl J Med 376;14: April 6, 2017. 1341-9

HERMES

MR CLEAN ESCAPE EXTEND-IA REVASCAT SWIFT PRIME

Stroke : Time lost is brain lost

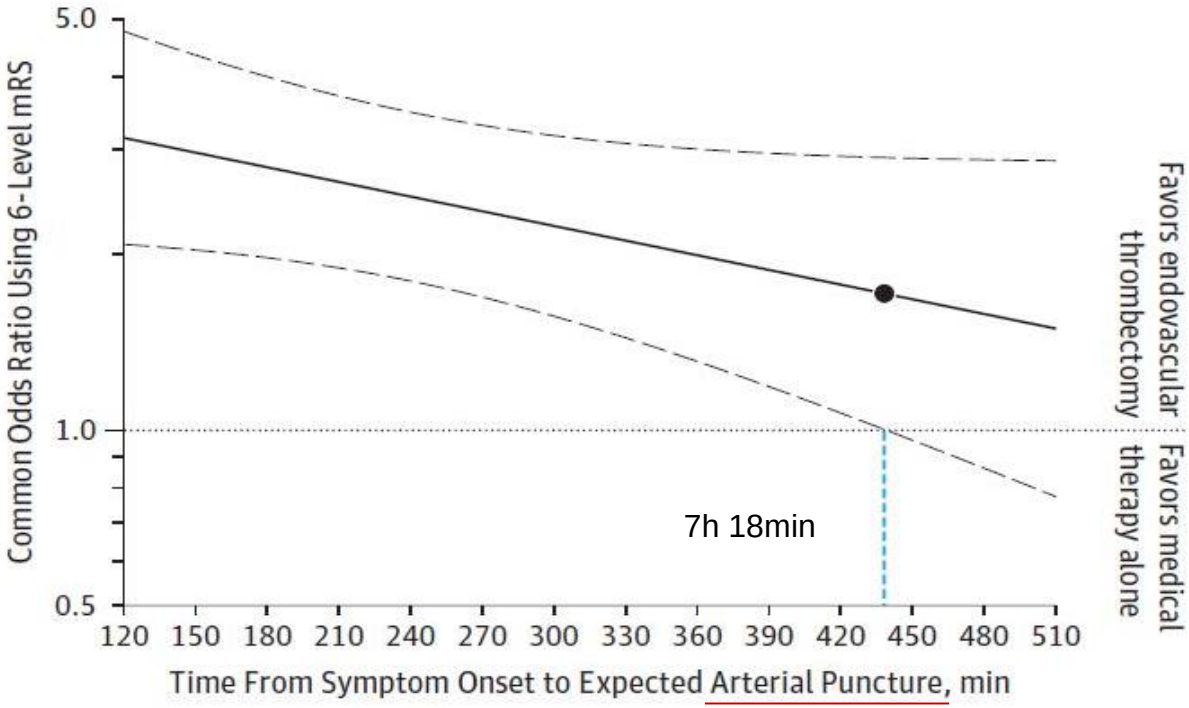


Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis. Jeffrey L. Saver, MD; Mayank Goyal, MD; Aad van der Lugt, et al. **JAMA**. 2016;316(12):1279-1288

P=0.001

HERMES

EXTEND-IA



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Research; the next question

Research; the next question

- Improve outcome
  - Basic: understanding clot, vessel wall, etc.
  - (Pre)clinical: farma, technique, anesthesia, etc

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- Improve outcome
  - Basic: understanding clot, vessel wall, etc.
  - (Pre)clinical: farma, technique, anesthesia, etc

- Patient selection
  - Expanding indication: >6hr, posterior circ., etc.
  - Limiting indication: Clinical (NIHSS, pre-mRS)
    Imaging (ASPECTS, Collat., Perfusion)

Research; the next question

- Improve outcome
  - Basic: understanding clot, vessel wall, etc.
  - (Pre)clinical: farma, technique, anesthesia, etc

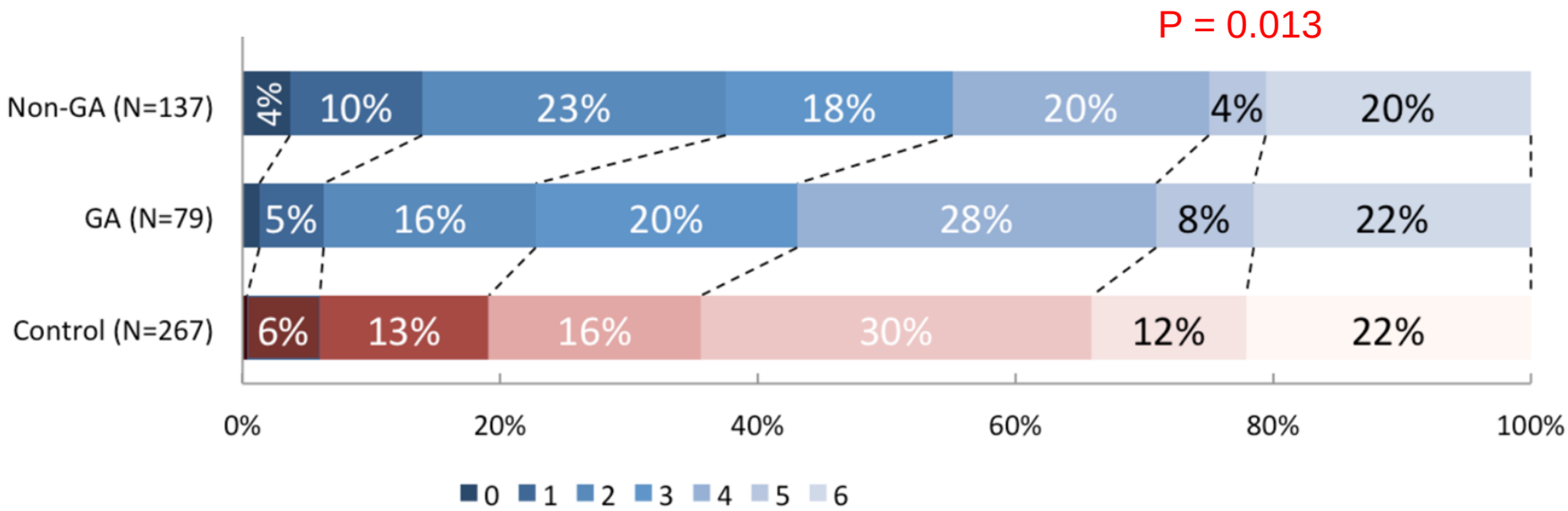
- Patient selection
  - Expanding indication: >6hr, hypertens, M2/M3, etc
  - Limiting indication: Clinical (NIHSS, pre-mRS)
    Imaging (ASPECTS, Collat., Perfusion)

- Logistics
  - In-hosp: Skip IV, Angio CT
  - Centralization, direct transfers, ship and drip, etc

Anesthesia in MRCLEAN

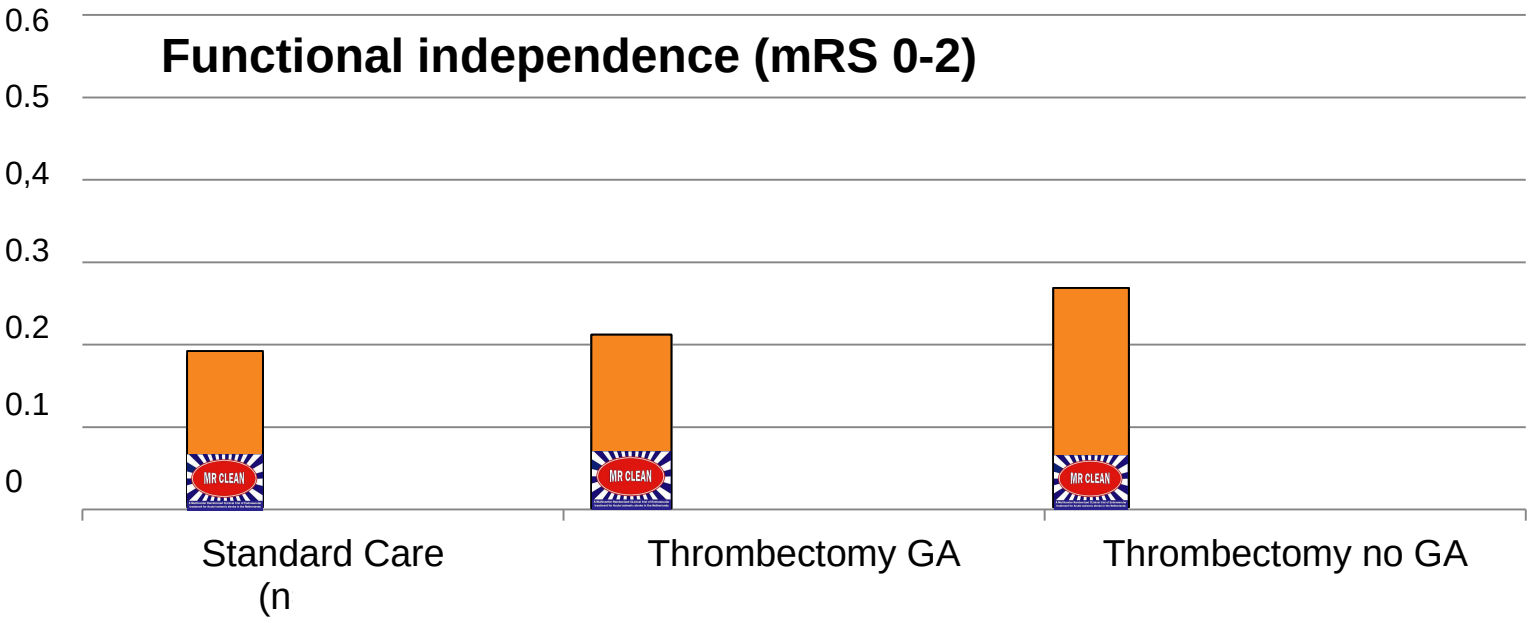
Common adjusted odds ratio Non-GA vs Control = 2.13 (95%CI 1.46 – 3.11)

Common adjusted odds ratio GA vs Control = 1.09 (95%CI 0.69 – 1.71)

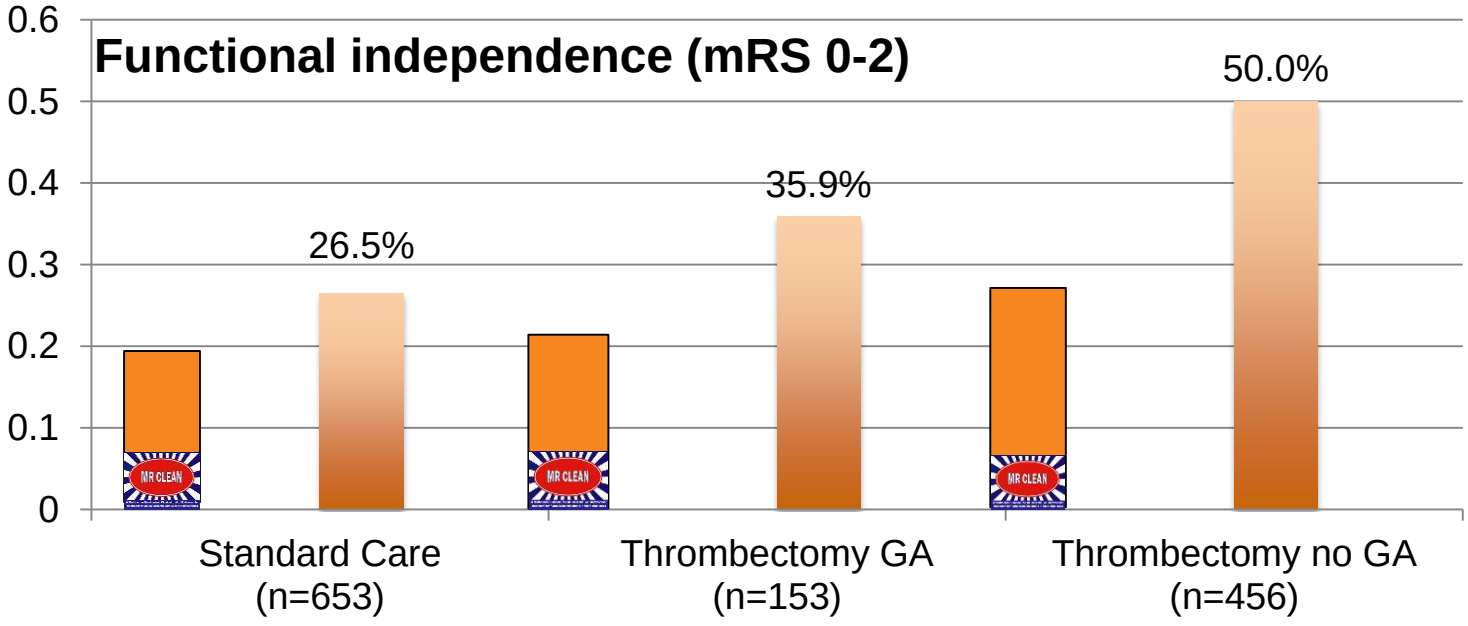


Neurology. 2016 Aug 16;87(7):656-64.

Anesthesia in MRCLEAN



Anesthesia in HERMES



GA vs Standard		no GA vs Standard		no GA vs GA	
OR (95%CI)	p	OR (95%CI)	p	OR (95%CI)	p
1.91 (1.25-2.91)	0.003	3.10 (2.33-4.12)	<0.001	1.79 (1.14-2.79)	0.01

Anesthesia in THRACE

	mRs 0-2
General Anesthesia (N= 67)	35 (52.2%)
Local Anesth or Sedation (N=74)	36 (48.6%)

P=0.67

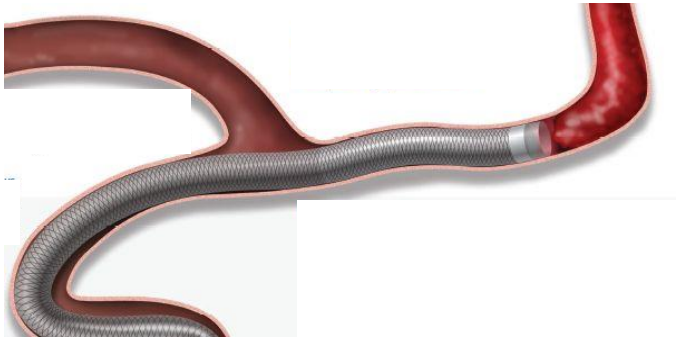
Sedation vs. Intubation for Endovascular Stroke TreAtment (SIESTA)

- No difference in primary outcome (Change in NIHSS at 24 hrs) and most secondary outcomes.

Effect of Conscious Sedation vs General Anesthesia on Early Neurological Improvement Among Patients With Ischemic Stroke Undergoing Endovascular Thrombectomy: A Randomized Clinical Trial. Schönenberger S. et al. **JAMA. 2016 Nov** 15;316(19):1986-1996

If sedation is needed then GA is equal to Conscious Sedation

Aspiration



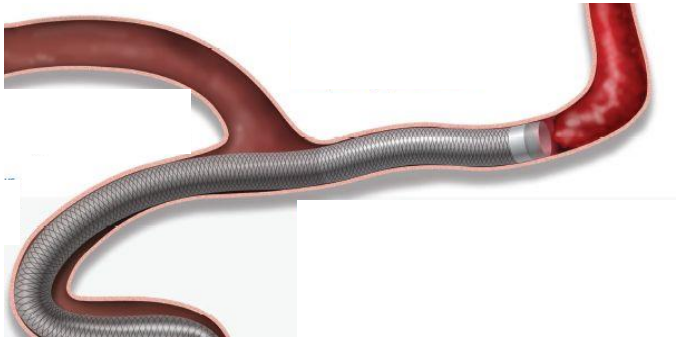
Aspiration

Therapy

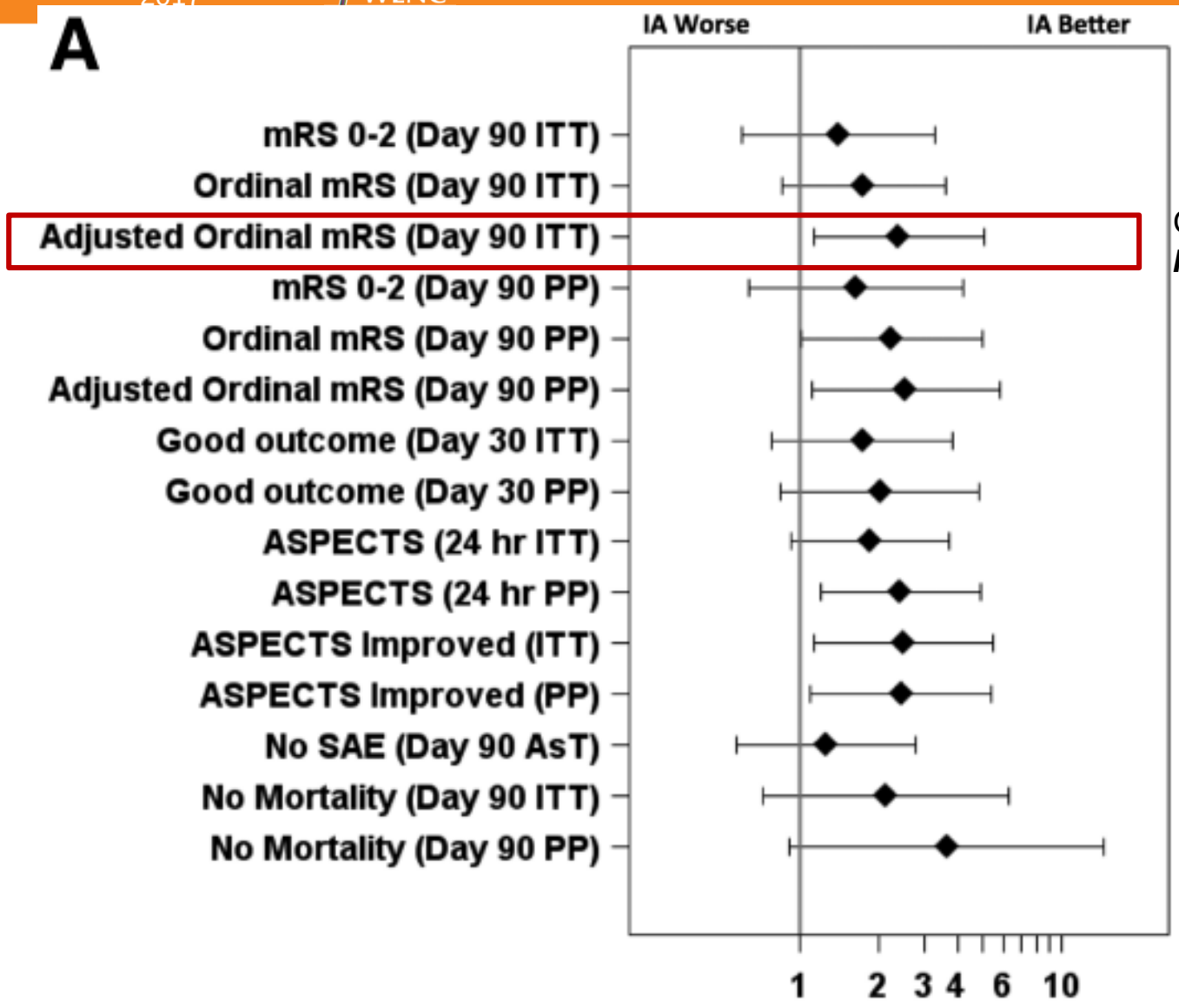
	mRs 0 – 2 (%)		
N	EVT	controls	OR
96	**38**	**30**	**1.4**

Primary outcome: mRS 0-2 P=0.44

In MRCLEAN and other trials: “shift on mRS”!



Stroke. 2016 Sep;47(9):2331-8



OR 2.4; 95% CI, 1.1–5.1
***P*=0.02**

*Unadjusted unless otherwise specified

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Aspiration

‘No evidence’ for effectiveness of aspiration.

- COMPASS and **ASTER** trials
  - Aspiration first vs stentretriever first

ISC Feb 22-24, 2017 Houston, Texas

Efficacy endpoints
(Core lab assessment)

n (%)	Aspiration First (n=192)	Stent Retriever First (n=189)	P value	Odds ratio
Successful reperfusion at the end of the endovascular procedure				
TICI 2b/3	164 (85.4)	157 (83.1%)	0.53	1.20 (0.68-2.10)
TICI 3	72 (37.5%)	73 (38.6%)	0.82	0.95 (0.63-1.45)
Use of Adjunctive Treatment (%)	63 (32.8%)	45 (23.8%)	0.053	1.56 (0.99-2.46)
Successful reperfusion after the frontline strategy alone				
TICI 2b/3	121 (63.0%)	128 (67.7%)	0.33	0.81 (0.53-1.24)
TICI 3	55 (28.6%)	67 (35.4%)	0.15	0.73 (0.47-1.13)

ASTER Trial Take Away

- First independent large RCT focusing on ADAPT technique with blinded assessment data

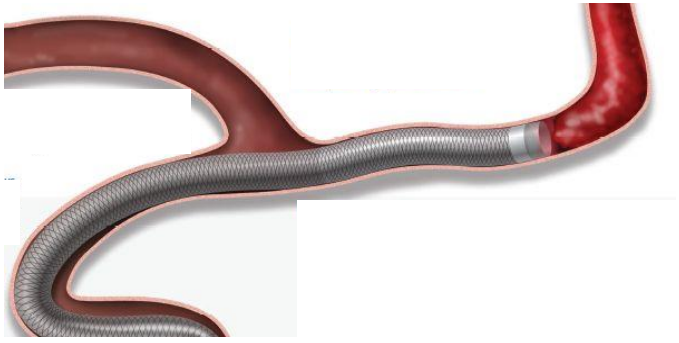
- ASTER trial shows **no statistical difference** between aspiration and stent retriever as a frontline thrombectomy approach
  - Similar efficacy and safety endpoints

- ASTER trial opens the door to add a new tool (ADAPT) to remove the clot.

- Subgroups analysis, Clinical outcomes, Cost-efficacy analysis will be presented at the ESOC, May, 2017

Aspiration

- Seems to be not inferior to stentretriever
- More / better data needed to show superiority or confirm non-inferiority



Dutch initiatives

- MRCLEAN Substudies

MRCLEAN ongoing substudies

THRAPS

THRombus **A**nalysis in intra arterial treated **P**atients with acute ischemic **S**troke

Study of hemostatic Markers and intra-ARterial Treatment in acute Ischemic Stroke

Dutch initiatives

- MRCLEAN Substudies
- Registry

Aims

Assess outcomes and safety after intra-arterial therapy (IAT) in everyday clinical practice

Investigate work-flow bottlenecks

Generate large dataset for further IAT research

- Patient selection
- Treatment optimization

Inclusion criteria

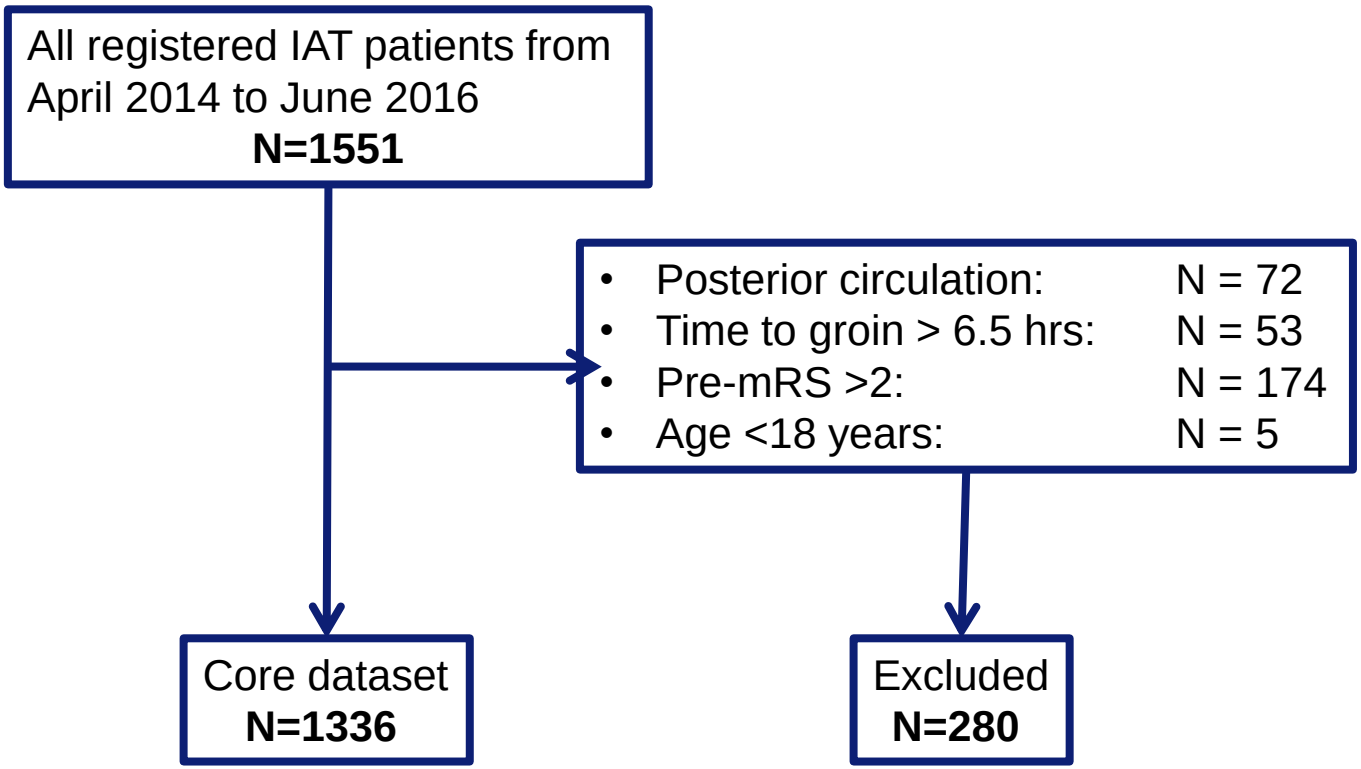
All consecutive patients treated with IAT for acute ischemic stroke in the Netherlands after completion of MR CLEAN (March 2014)

19 centers nationwide

Registry still ongoing (>2600 pt)

Data analysis from April 2014 – June 2016

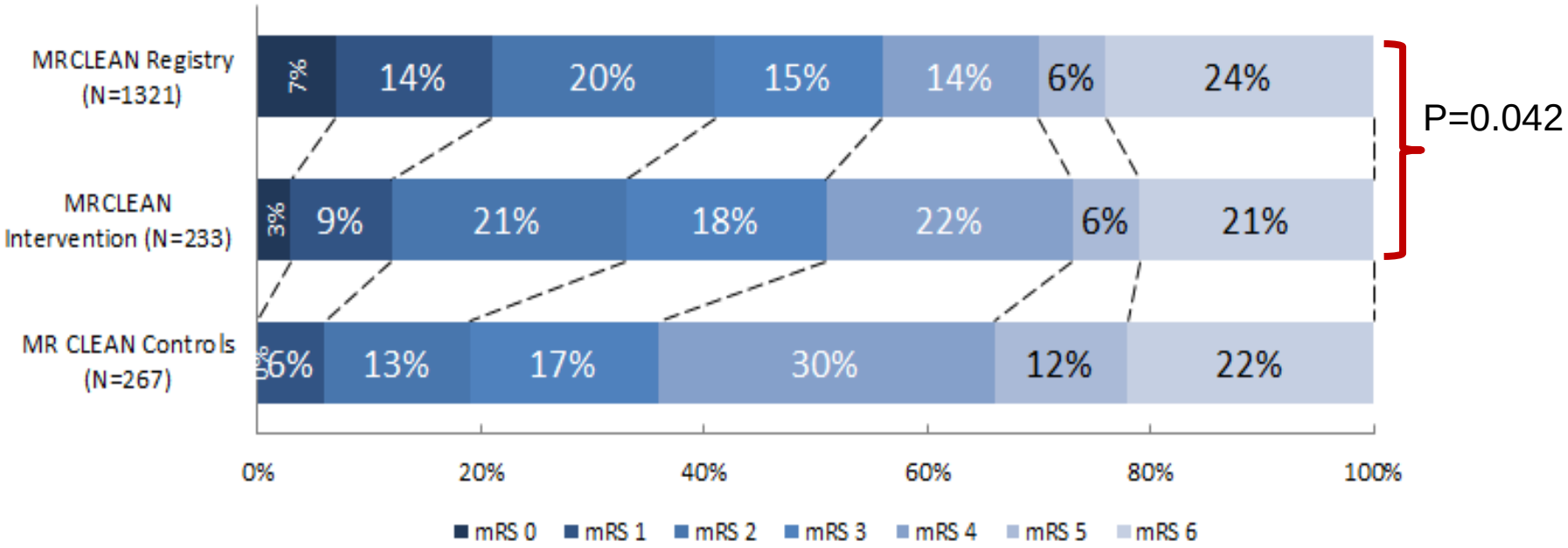
Core dataset flow chart



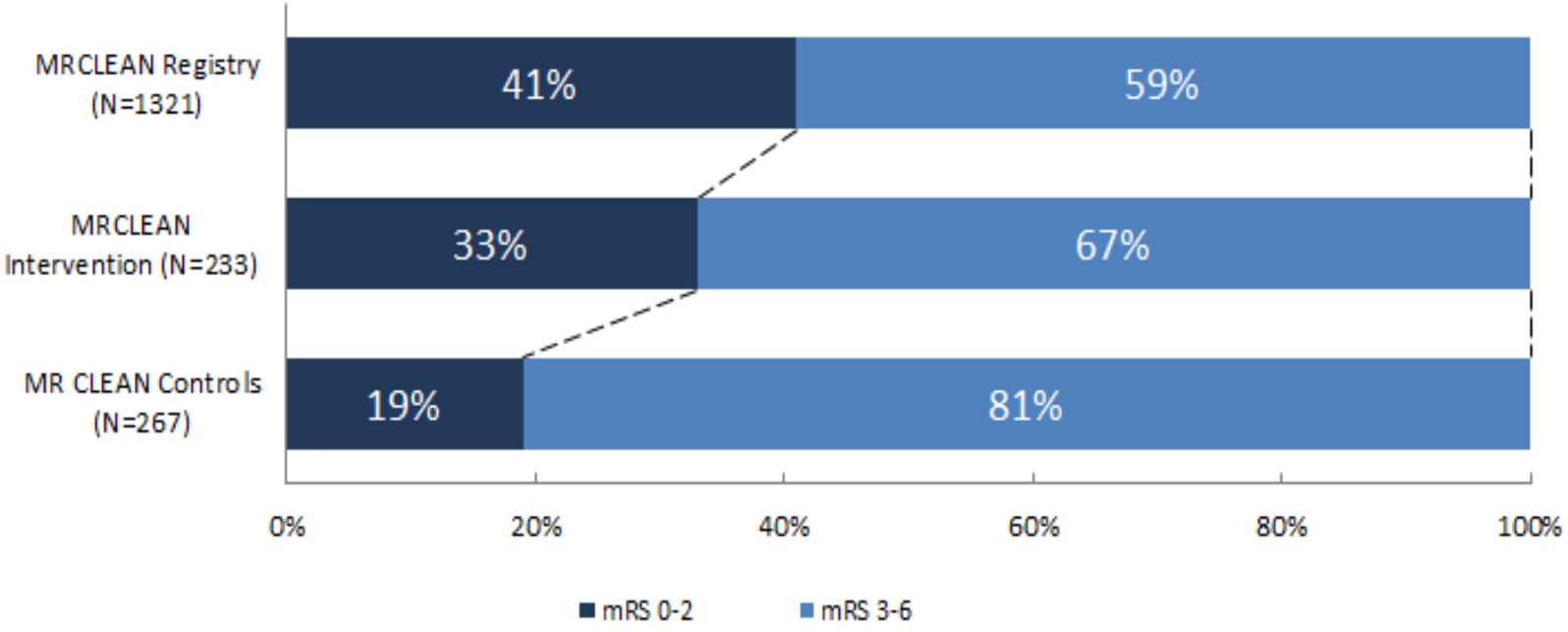
Important baseline characteristics

Baseline	MR CLEAN Registry (N = 1336)	MR CLEAN Intervention (N = 233)
Age - median (IQR)	70 (59-78)	66 (55-76)
Male sex	55%	58%
Baseline NIHSS - median (IQR)*	16 (11-20)	17 (14-21)
Intravenous thrombolysis	79%	87%
Onset to groin – median (IQR)	205 (160-265)	260 (210-313)
DSA / Catheterization only	13%	8%

Primary outcome: mRS at 90 days

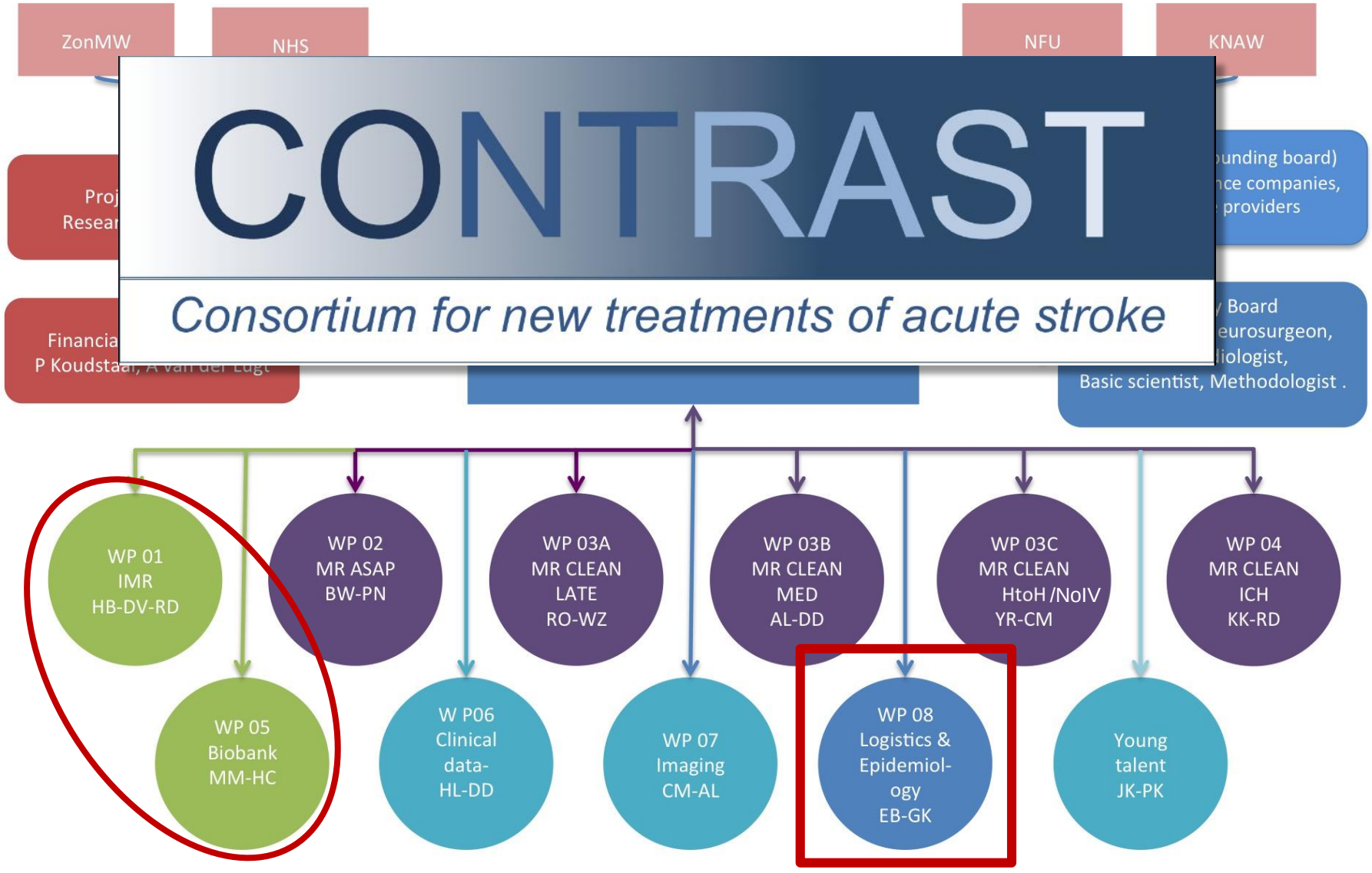


Dichotomized mRS (0-2 vs 3-6)



Dutch initiatives

- MRCLEAN Substudies
- Registry
- CONTRAST
  (CONsortium for new TReatments of Acute STroke)


ZonMW
NHS
NFU
KNAW
CONTRAST
Consortium for new treatments of acute stroke
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providers
Financia
P Koudstaal, A van der Lugt
Board
eurosurgeon,
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Basic scientist, Methodologist .
WP 01
IMR
HB-DV-RD
WP 02
MR ASAP
BW-PN
WP 03A
MR CLEAN
LATE
RO-WZ
WP 03B
MR CLEAN
MED
AL-DD
WP 03C
MR CLEAN
HtoH /NoIV
YR-CM
WP 04
MR CLEAN
ICH
KK-RD
WP 05
Biobank
MM-HC
W P06
Clinical
data-
HL-DD
WP 07
Imaging
CM-AL
WP 08
Logistics &
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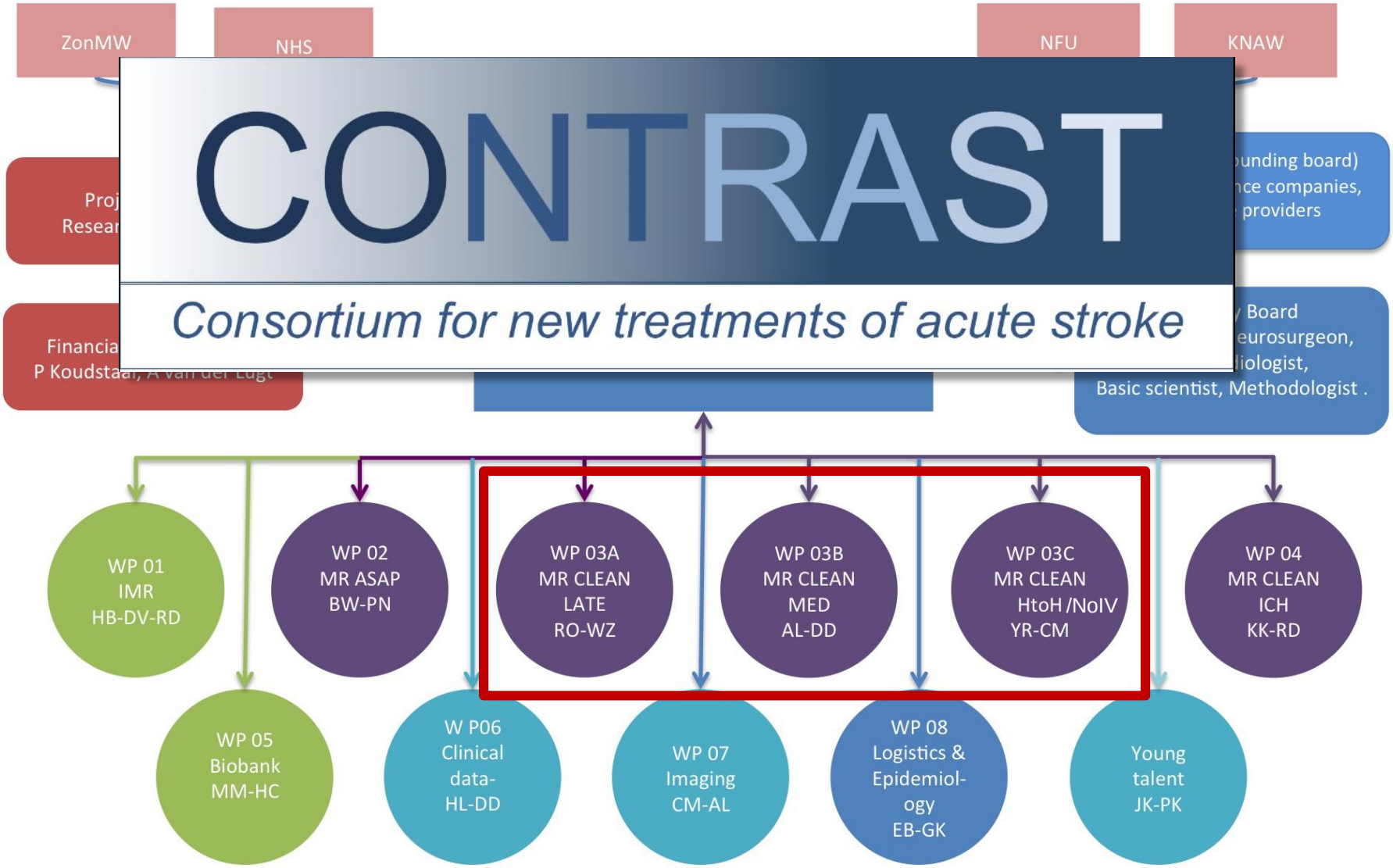
EB-GK
Young
talent
JK-PK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Basic scientist, Methodologist .
WP 01
IMR
HB-DV-RD
WP 02
MR ASAP
BW-PN
WP 03A
MR CLEAN
LATE
RO-WZ
WP 03B
MR CLEAN
MED
AL-DD
WP 03C
MR CLEAN
HtoH /NoIV
YR-CM
WP 04
MR CLEAN
ICH
KK-RD
WP 05
Biobank
MM-HC
W P06
Clinical
data-
HL-DD
WP 07
Imaging
CM-AL
WP 08
Logistics &
Epidemiol-
ogy
EB-GK
Young
talent
JK-PK

To assess the effect of intra-arterial treatment in patients with AIS who were last seen well **6 - 12 hours** before start of treatment, and who have (still) **collaterals** on CTA.

Inclusion criteria

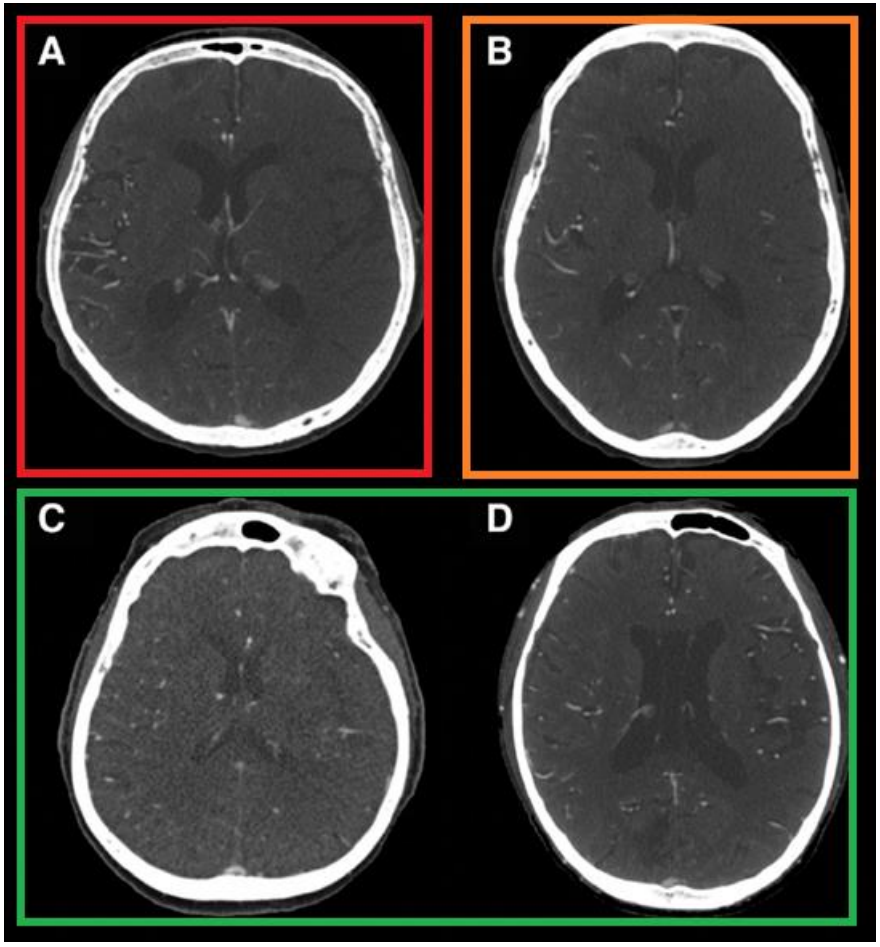
Same as MRCLEAN

Start of IAT possible between 6-12 hours or last seen well <12 hours

Presence of poor to good collateral flow (CTA)

- Maximum of 100 patients with poor collateral flow

Collateral grading 0 - 3



A: grade 0 = absent

B: grade 1 = >0% and ≤50%

C: grade 2 = >50% and <100%

D: grade 3 = 100%

Stroke. 2015 Dec;46(12):3375-82

Value of Computed Tomographic Perfusion–Based Patient Selection for Intra-Arterial Acute Ischemic Stroke Treatment

Jordi Borst, MD, MSc; Olvert A. Berkhemer, MD; Yvo B.W.E.M. Roos, MD, PhD; Ed van Bavel, PhD; Wim H. van Zwam, MD, PhD; Robert J. van Oostenbrugge, MD, PhD; on behalf of the MR CLEAN Investigators†

Stroke. 2016 Mar;47(3):768-76

Collateral Status on Baseline Computed Tomographic Angiography and Intra-Arterial Treatment Effect in Patients With Proximal Anterior Circulation Stroke

Olvert A. Berkhemer, MD*; Ivo G.H. Jansen, MD*; Debbie Beumer, MD; Puck S.S. Fransen, MD; Lucie A. van den Berg, MD; Albert J. Yoo, MD; Hester F. Lingsma, PhD; on behalf of the MR CLEAN Investigators†

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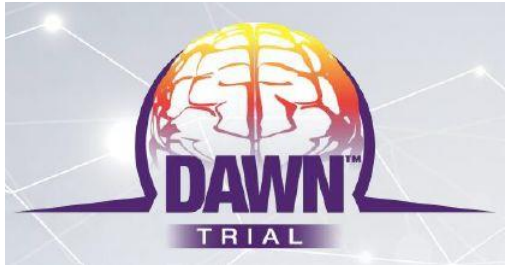
”Collateral score appears to better predict treatment effect than penumbral imaging”

Started: July 2014

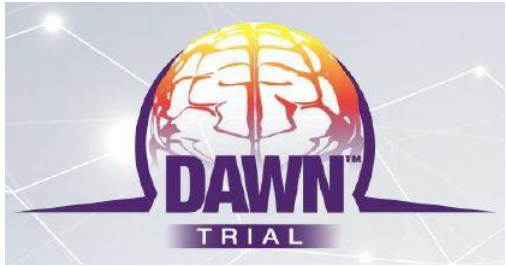
Multicenter RCT

Enrollment terminated: March 2017



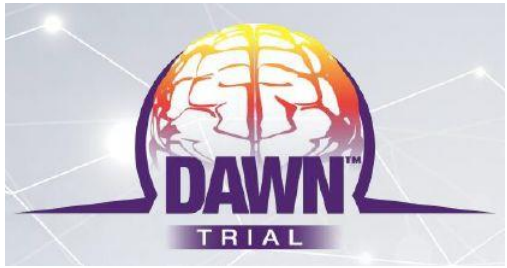
- Stryker; Trevo

- Independent; ‘all’ devices



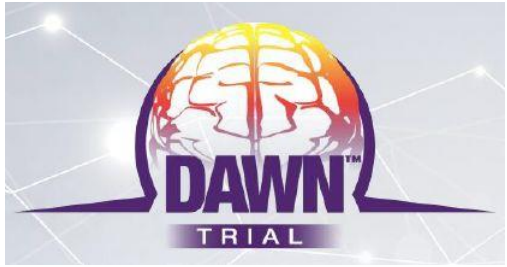
- Stryker; Trevo
- Selected neuro-intervention centers

- Independent; ‘all’ devices
- All hospitals performing thrombectomy in the Netherlands



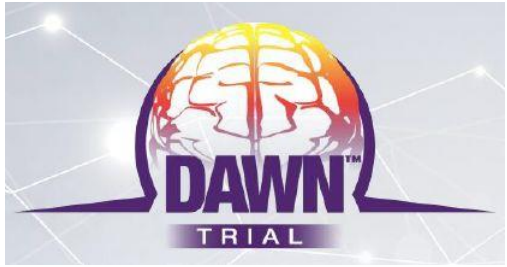
- Stryker; Trevo
- Selected neuro-intervention centers
- Onset – Rand. time 6-**24** hrs

- Independent; 'all' devices
- All hospitals performing thrombectomy in the Netherlands
- Onset – Rand. time 6-**12** hrs



- Stryker; Trevo
- Selected neuro-intervention centers
- Onset – Rand. time 6-**24** hrs
- NIHSS ≥ 10

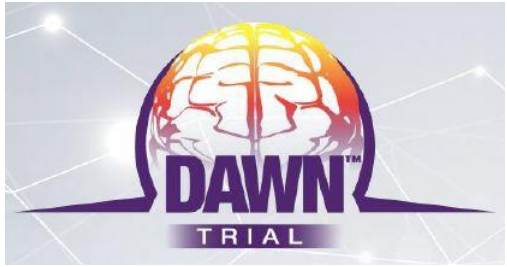
- Independent; 'all' devices
- All hospitals performing thrombectomy in the Netherlands
- Onset – Rand. time 6-**12** hrs
- NIHSS ≥ 2



- Stryker; Trevo
- Selected neuro-intervention centers
- Onset – Rand. time 6-**24** hrs
- NIHSS ≥ 10
- DWI or CTP mismatch
- - 0-<21 cc core infarct and NIHSS ≥ 10 (and age ≥ 80 years old)
- - 0-<31 cc core infarct and NIHSS ≥ 10 (and age < 80 years old)
- - 31 cc to <51 cc core infarct and NIHSS ≥ 20 (and age < 80 years old)

- Independent; 'all' devices
- All hospitals performing thrombectomy in the Netherlands
- Onset – Rand. time 6-**12** hrs
- NIHSS ≥ 2
- Moderate or good collaterals (CTA)

Maastricht UMC+



- Stryker; Trevo
- Selected neuro-intervention centers
- Onset – Rand. time 6-**24** hrs
- NIHSS ≥ 10
- DWI or CTP mismatch

mRS	0	1	2	3	4	5	6
Weight	10	9.1	7.6	6.5	3.3	0	0

- Independent; ‘all’ devices
- All hospitals performing thrombectomy in the Netherlands
- Onset – Rand. time 6-**12** hrs
- NIHSS ≥ 2
- Moderate or good collaterals (CTA)
- Prim. Outcome: mRS

To assess the effect of **unfractionated heparin or acetyl salicylic acid**, alone or in combination, in patients with acute ischemic stroke, who undergo intra-arterial treatment for a confirmed anterior circulation occlusion.

Design

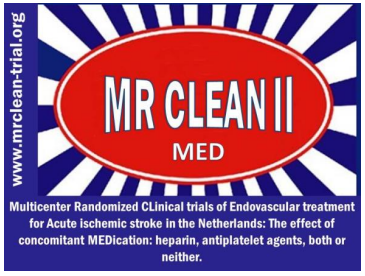
Design: 2x3 factorial and PROBE design

Study size: 1500 patients

Primary outcome: mRS after 90 days

Secondary outcomes: NIHSS at 24 h and 5-7 days, mTIC, infarct size at 5-7 days.

Safety parameters: death, any neurological deterioration >4 points on the NIHSS and SICH.

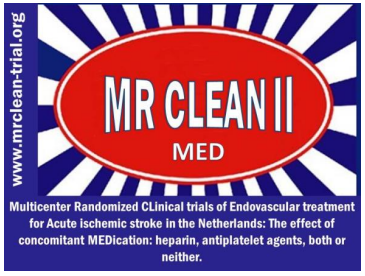


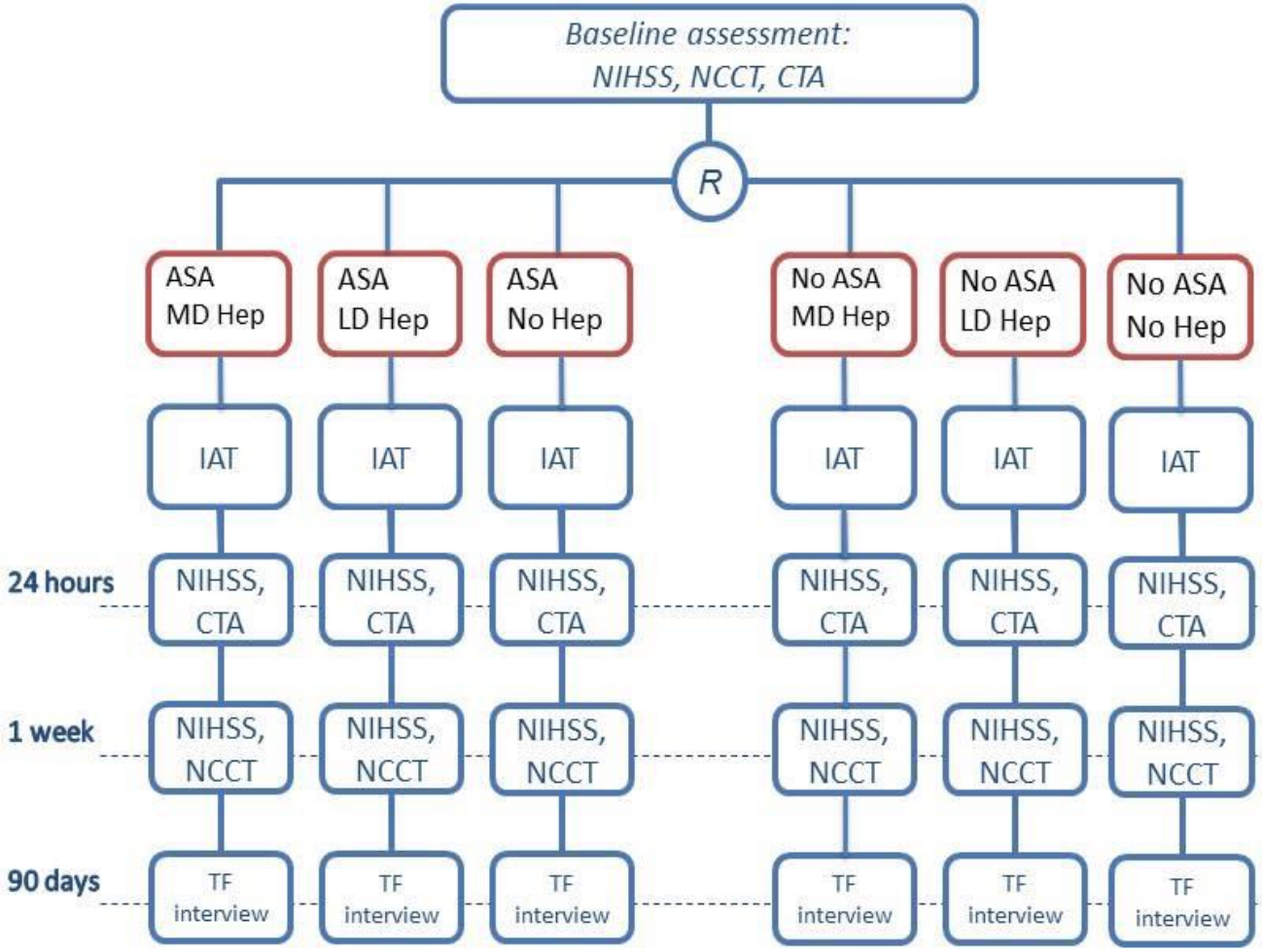
Medication

A: Unfractionated heparin, either
- 0: No heparin
- 1: Low dose (loading dose of 5000 IU followed by 5000 IU in 12 hours)
- 2: Moderate dose (loading dose of 5000 IU followed by 10,000 IU in 12 hours)

B: Acetylsalcylic acid, either:
- 0: No acetylsalicylic acid
- 1: Intravenous acetylsalicylic acid (300 mgs)

All followed by regular antiplatelet treatment 24 hours post intervention.





www.mrclean-trial.org

MR CLEAN II
MED

Multicenter Randomized CLinical trials of Endovascular treatment for Acute ischemic stroke in the Netherlands: The effect of concomitant MEDication: heparin, antiplatelet agents, both or neither.

Maastricht UMC+

MR CLEAN NO IV

Aim

To determine whether **direct** mechanical thrombectomy (MT) for acute ischemic stroke caused by a proximal large vessel occlusion is more effective than MT preceded by IV alteplase

MR CLEAN NO IV

Hypotheses

We expect a 10% absolute increase in good outcome after omission of IV alteplase before MT through

- Fewer symptomatic hemorrhages
- Fewer adverse events related to tPA
  - Toxicity, fragmentation, blood brain barrier disruption

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Design

Primary aim

- Superiority

Secondary aim

- Test for non-inferiority
- Allows for a clinically relevant outcome assessment

MR CLEAN NO IV

Design

PROBE design

Sample size: 500

Primary outcome: mRS after 90 days

Secondary outcomes: NIHSS at 24 h and 5-7 days, mTIC, infarct size at 5-7 days.

Safety parameters: death, any neurological deterioration >4 points on the NIHSS and SICH.

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Thank you