Nouveautés dans le traitement de l’Accident Vasculaire Cérébral Ischémique aigu

Joachim Schulz
Clinique de Neurologie
CHU Saint-Pierre Bruxelles
UMC Sint-Pieter Brussel
**Definition**

**Stroke**
Sudden loss of blood circulation to an area of the brain, resulting in a corresponding loss of neurologic function, associated with infarction.

**TIA**
Brief episode of neurological dysfunction resulting from focal brain, spinal cord or retinal ischemia, not associated with infarction.

**Pathophysiology**
Zone with cerebral blood flow of lower than 10 mL/100 g of tissue/min: **Ischemic core:**
Cells are presumed to die within minutes of stroke onset
1. Hypoxia>depletion of cellular ATP>Cellular sodium pumps disrupted> Influx of sodium and calcium ions
   >Passive inflow of water into the cell > cytotoxic edema
2. Dysfunction of the cerebral vasculature>breakdown of the blood-brain barrier within 4-6 hours
   >proteins and water flood into the extracellular space > **vasogenic edema**, brain swelling and mass effect peak at 3-5 days

Zones of decreased or marginal perfusion < 25 mL/100g of tissue/min: **Ischemic penumbra,**
Cells in the penumbra can remain viable for several hours

**Epidemiology**
Stroke is the fourth leading cause of adult death
Around 30.000 strokes in Belgium per year (=3000 in Brx/year, 8/day)
20% are hospitalized in the first 6h after onset
80% ischemic, 30% of which with an occlusion of a large artery

**Etiology**
1. Ischemic
   a. Thrombotic
      Large vessel (Atherosclerosis, Dissection, Arteritis)
   b. Cardio-Embolic
   c. Hemodynamic
   d. Venous
2. Hemorrhagic
Operational definitions of ischemic regions

- **Core**: irreversibly injured tissue
- **Penumbra**: at risk, but salvageable, if reperfusion occurs
- **Benign Oligemia**: decreased flow, but not at risk of infarction
Anatomy of the Human Cerebral Arteries

1 Aorta
2 Common Carotid Artery (CCA)
3 External Carotid Artery (ECA)
4 Internal Carotid Artery (ICA)
5 Middle Cerebral Artery (MCA)
6 Anterior Cerebral Artery (ACA)
7 Vertebral Artery (VA)
8 Basilar Artery (BA)
Carotid artery

- Aphasia
- Amaurosis fugax
- Facial paralysis
- Neglect
- Hemihypesthesia
- Hemiparesis

Basilary Artery

- Horner
- Abnormal eye movement
- Hemianopsia
- Motor/sensory facial loss
- Headache
- Vertigo
- Ataxia
- Vomiting
- Dysphonia
- Dysphagia
- Altered consciousness
Quantifying Stroke
NIH Stroke Scale (NIHSS)
The Modified Rankin Scale (mRS)

A scale for measuring the degree of disability or dependence in the daily activities. The scale runs from 0-6, running from perfect health without symptoms to death.

0 - No symptoms.
1 - No significant disability. Able to carry out all usual activities, despite some symptoms.
2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3 - Moderate disability. Requires some help, but able to walk unassisted.
4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6 - Dead.
Stroke Imaging

- Required to rule out hemorrhagic stroke
- Helps to predict treatment outcome:

CT findings in acute ischemic stroke
After 2 hours
- Focal parenchymal hypodensity
- Cortical swelling with sulcal effacement and loss of differentiation of basal ganglia and cortical gray-white matter and sulci
- Hyperdense MCA sign

MRI findings in acute ischemic stroke
- DWI changes after minutes
- FLAIR changes after >4.5 hours
• Alberta Stroke Program Early CT score (ASPECTS) is a 10-point quantitative topographic CT scan score.
• To compute the ASPECTS, 1 point is subtracted from 10 for any evidence of early ischemic change for each of the defined regions.
• Within the first 3 h of MCA stroke onset, baseline ASPECTS values correlate inversely with the severity of NIHSS and with functional outcome.
• Scores of 7 or less are correlated with both poor functional outcome and symptomatic intracerebral hemorrhage.
• Higher ASPECTS value (ASPECT 8-10) are associated with a greater extent of benefit from i.v. thrombolysis.
ASPECT Score Examples

Score 10

Score 3
Treating acute ischemic stroke
Evidence-based Acute Stroke Treatment in 2014

1. Early secondary prophylaxis
Reduce the risk for future stroke

2. Stroke unit treatment
Stroke patients who receive organised inpatient care in a stroke unit are more likely to be alive, independent, and living at home one year after the stroke.

3. Recanalizing therapy
Increase survival without disability (mRS 0-1)
a. i.v. thrombolysis max. 3h after onset (NINDS 1995)
b. i.v. thrombolysis max. 4.5h after onset (ECASS 2008)
i.v. Thrombolysis (IVT) for Ischemic Stroke

- Recombinant DNA-derived purified glycoprotein rtPA
- Serine protease with 527 amino acids
- Converts plasminogen in the presence of fibrin to plasmin
- High fibrin specificity (is activated where fibrin is at the clot)
- Administered systemically (i.v.) within 4.5 hrs after symptom onset
- Several contraindications (enhanced bleeding risk)
- 0.9mg/kg, max. 90mg, 10% as a bolus and 90% over 1 hr
- Short half-life <5min, cleared by the liver
IVT: Treatment delay, NIHSS and Age

Metaanalysis of 9 placebo-controlled trials, 6756 patients

Figure 2: Effect of alteplase on good stroke outcome (mRS 0–1), by treatment delay, age, and stroke severity

*For each of the three baseline characteristics, estimates were derived from a single logistic regression model stratified by trial, which enables separate estimation of the OR for each subgroup after adjustment for the other two baseline characteristics (but not for possible interactions with those characteristics). mRS=modified Rankin Scale.
IVT: Onset-to-treatment time and outcome

Metaanalysis of 9 placebo-controlled trials, 6756 patients

Figure 1: Effect of timing of alteplase treatment on good stroke outcome (mRS 0–1)
The solid line is the best linear fit between the log odds ratio for a good stroke outcome for patients given alteplase compared with those given control (vertical axis) and treatment delay (horizontal axis; $P_{\text{interaction}}=0.016$). Estimates are derived from a regression model in which alteplase, time to treatment, age, and stroke severity (handled in a quadratic manner) are included as main effects but the only treatment interaction included is with time to treatment. Only 198 patients (159 from IST–3) had a time from stroke onset to treatment of more than 6 h. The white box shows the point at which the estimated treatment effect crosses 1. The black box shows the point at which the lower 95% CI for the estimated treatment effect first crosses 1.0. mRS=modified Rankin Scale.

NNT for mRS of 0 or 1

- <1.5 hrs: 4.5
- 1.5 to 3 hrs: 9
- 3 to 4.5 hrs: 14.1

= Each additional 20 min: +1
# Time is Brain

Estimated Pace of Neural Circuitry Loss  
in Typical Large Vessel, Supratentorial Acute Ischemic Stroke (Duration ca. 10 hrs)

<table>
<thead>
<tr>
<th></th>
<th>Cells</th>
<th>Synapses</th>
<th>Fibers</th>
<th>Aging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neocortex</strong></td>
<td>20 billion</td>
<td>100 trillion</td>
<td>135,000 km</td>
<td>31 million/y</td>
</tr>
<tr>
<td><strong>Loss per stroke</strong></td>
<td>1.2 billion</td>
<td>8 trillion</td>
<td>7000 km</td>
<td>36 y</td>
</tr>
<tr>
<td><strong>per stroke hour</strong></td>
<td>120 million</td>
<td>800 billion</td>
<td>700 km</td>
<td>3.6 y</td>
</tr>
<tr>
<td><strong>per stroke min</strong></td>
<td>2 million</td>
<td>13 billion</td>
<td>12 km</td>
<td>3 wk</td>
</tr>
</tbody>
</table>
How to lower door-to-needle time

- Pre-notification of stroke team via phone
- Pre-aquisition of patient history
- CT kept empty
- Patient transfer directly to CT table
- Short distance to CT
- Point-of-care INR
- Prepare iv access and rtPA solution beforehand
- Neurological exam minimized
- Imaging minimized
- Rapid treatment decision
- Bolus administered on CT table

Modified from Meretoja, Neurology 2012
Limitations of IVT

- Risk of cerebral or systemic hemorrhage, no good prediction scales (2-8% vs. 0-3%)

- Several contraindications (CNS disorders, surgery, anticoagulation, etc.)

- Incomplete recanalisation (1% if Thrombus length >8mm)

- Time window of 4.5 hrs
The main risk of IVT is early symptomatic Intracranial Hemorrhage (ICH)

Metaanalysis of 7012 patients, day 1-7
IVT recanalisation rate correlates inversely with Thrombus length.
Male patient, 54 years old with ICA occlusion.
Complete recanalisation after thrombus aspiration

Courtesy of C. Möller-Hartmann, Essen
History of intraarterial stroke treatment

1981 First Intraarterial thrombolysis
1999 Intraarterial thrombolysis study (PROACT II)
2004 Loop/ corcscrew for thrombus retrieval (MERCI)
2009 Thrombus fragmentation via microwire (Penumbra device)
2009 Bypassing and fragmentation of thrombus by stent expansion (SARIS)

Adapted from Möhlenbruch and Bendszus 2015
Risks and shortcomings of Intraarterial Thrombectomy

- Catheter-induced emboli
- Thrombus-derived emboli
- Vascular dissection/perforation

- Incomplete recanalisation rate
- Few patients eligible
- Long preparation time
- Experienced interventionalist required
- Elongated vessels may not be reachable
- Posterior territory cannot be occluded
- Emboli in small vessels cannot be targeted

> Studies until 2014 with neutral results
(older devices, angio not obligatory, no rtPA)
IAT 2015

5 independent randomized controlled multicenter trials published in NEJM

Design:
- IVT vs. IVT+ IAT with stent retriever
- Primary outcome mRS 0-2
- Inclusion time up to 12hrs
- Angiography controlled
Solitaire™ FR Revascularization Device
A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke

Figure 1. Modified Rankin Scale Scores at 90 Days in the Intention-to-Treat Population.
ESCAPE

Modified Rankin Scale Score

A Overall

Control (N=147)

Intervention (N=164)

Patients (%)
Figure 2. Scores on the Modified Rankin Scale at 90 Days in the Intention-to-Treat Population.
**Figure 1.** Functional Outcomes at 90 Days, According to the Score on the Modified Rankin Scale.
Figure 1. Distribution of Functional Scores at 90 Days (Intention-to-Treat Population).
## Overview IAT Studies with Stent Retriever

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Occlusion</th>
<th>max OTT (h)</th>
<th>IVT treated (%)</th>
<th>Imaging criteria</th>
<th>90d mortality (%)</th>
<th>Bleeding rate (%)</th>
<th>Recanalisation (%)</th>
<th>90d outcome (%)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>iv/iv+ia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>267/233</td>
<td>CarT, M1, M2</td>
<td>6</td>
<td>90</td>
<td></td>
<td>22/21</td>
<td>6/8</td>
<td>59</td>
<td>19/32</td>
<td>7</td>
</tr>
<tr>
<td>ESCAPE</td>
<td>118/120</td>
<td>CarT, M1, M2</td>
<td>12</td>
<td>76</td>
<td>ASPECTS 6-10</td>
<td>19/10</td>
<td>4/3</td>
<td>72</td>
<td>29/53</td>
<td>4</td>
</tr>
<tr>
<td>EXTEND IA</td>
<td>35/35</td>
<td>CarT, M1, M2</td>
<td>6</td>
<td>100</td>
<td>Perfusion</td>
<td>20/9</td>
<td>6/0</td>
<td>86</td>
<td>40/71</td>
<td>3</td>
</tr>
<tr>
<td>SWIFT-PRIME</td>
<td>98/98</td>
<td>CarT, M1</td>
<td>6</td>
<td>98</td>
<td>ASPECTS 6-10</td>
<td>12/9</td>
<td>3/0</td>
<td>88</td>
<td>35/60</td>
<td>4</td>
</tr>
<tr>
<td>REVASCAT</td>
<td>103/103</td>
<td>no better post IVT</td>
<td>8</td>
<td>73</td>
<td></td>
<td>16/18</td>
<td>2/2</td>
<td>66</td>
<td>28/44</td>
<td>6</td>
</tr>
</tbody>
</table>
## Meta-Analysis of 8 randomized trials

**IVT (n=1110) vs. IAT+IVT (n=1313)**

<table>
<thead>
<tr>
<th>90d mortality (%)</th>
<th>Bleeding rate (%)</th>
<th>Recanal. &gt;=2b (%)</th>
<th>90d outcome (% mRS 0-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.8/15.8</td>
<td>5.1/5.7</td>
<td>34/76</td>
<td>32/45</td>
</tr>
</tbody>
</table>

*p=0.27  p=0.56  p<0.001  p<0.005*
### Subgroup Analysis SWIFT-PRIME

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>97</td>
<td>1.75 (1.11–2.78)</td>
<td>0.78</td>
</tr>
<tr>
<td>Female</td>
<td>93</td>
<td>1.61 (1.03–2.50)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥70 yr</td>
<td>83</td>
<td>1.78 (1.03–3.09)</td>
<td>0.88</td>
</tr>
<tr>
<td>&lt;70 yr</td>
<td>106</td>
<td>1.67 (1.13–2.47)</td>
<td></td>
</tr>
<tr>
<td>NIHSS score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤17</td>
<td>110</td>
<td>1.49 (1.05–2.11)</td>
<td>0.55</td>
</tr>
<tr>
<td>&gt;17</td>
<td>80</td>
<td>2.21 (1.17–4.19)</td>
<td></td>
</tr>
<tr>
<td>Occlusion location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>30</td>
<td>2.04 (0.67–6.21)</td>
<td>0.87</td>
</tr>
<tr>
<td>M1</td>
<td>133</td>
<td>1.74 (1.23–2.46)</td>
<td></td>
</tr>
<tr>
<td>M2</td>
<td>18</td>
<td>1.35 (0.41–4.41)</td>
<td></td>
</tr>
<tr>
<td>Geographic location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United States</td>
<td>129</td>
<td>1.63 (1.11–2.39)</td>
<td>0.66</td>
</tr>
<tr>
<td>Europe</td>
<td>62</td>
<td>1.85 (1.05–3.24)</td>
<td></td>
</tr>
<tr>
<td>ASPECTS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 or 7</td>
<td>43</td>
<td>1.98 (0.73–5.33)</td>
<td>0.94</td>
</tr>
<tr>
<td>8–10</td>
<td>142</td>
<td>1.62 (1.17–2.24)</td>
<td></td>
</tr>
<tr>
<td>Site of initial administration of t-PA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study hospital</td>
<td>126</td>
<td>1.61 (1.13–2.30)</td>
<td>0.87</td>
</tr>
<tr>
<td>Outside hospital</td>
<td>64</td>
<td>1.77 (0.91–3.45)</td>
<td></td>
</tr>
<tr>
<td>Time from onset to randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;189 min</td>
<td>96</td>
<td>1.62 (1.08–2.42)</td>
<td>0.97</td>
</tr>
<tr>
<td>≥189 min</td>
<td>94</td>
<td>1.77 (1.07–2.93)</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>191</td>
<td>1.70 (1.23–2.33)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 2. Analysis of Functional Independence at 90 Days in Prespecified Subgroups.

Saver JL, NEJM 2015
Female patient A.R. mRS 0, 60 years. VKA-treated for mechanical valve, INR 2.1 on admission. Hemiplegia, global aphasia, gaze palsy since 3.5 hrs., in CTA left M1 occlusion.

No IVT but IAT (alone).

After Thrombectomy NIHSS=4 with mild deficits.
Summary IAT

IAT(+IVT) vs. IVT (alone) in ischemic stroke of the anterior circulation:

- higher vessel recanalisation rate
- better 90d clinical outcome (mRS0-2)
- for least up to 6 hours onset-to-puncture time
- without increase in mortality or ICH
- reduced onset-to-reperfusion time with better clinical outcome
# Open questions IAT

## Which occlusion should be treated?
- Superior for Carotis T and M1
- Unclear if benefit for M2 (OR = 1.35 in SWIFT-PRIME subgroup analysis)
- No evidence that IAT superior in posterior circulation (No ballon occlusion possible)

## Max. time window (to groin puncture)
- Benefit at least up to 6h after symptom onset
- Unclear if 6-12h is indicated

## Which NIHSS range?
- Rule of thumb: NIHSS > 11 = proximal occlusion
- IAT benefit independent from NIHSS in subgroup analysis
- IVT benefit decreases with increasing NIHSS

## Wait for IVT success?
- No: „drip and ship“

## IVT necessary before IAT?
- No extra benefit in ESCAPE subgroup analysis

## Age limit?
- No limit, no decrease in ther. benefit in higher age

## Imaging requirements?
- No benefit wenn ASPECT < 5 (CT, DWI)
- Perfusion not obligatory but estimation of core-penumbra

## Importance of collaterals?
- No data

## Anesthesia? Sedation?
- Worse outcome with intubation anesthesia in subgroup
**Recommendations: Endovascular Interventions**

1. Patients eligible for intravenous r-tPA should receive intravenous r-tPA even if endovascular treatment is being considered.

2. Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria
   a. Prestroke mRS score 0 to 1
   b. Acute ischemic stroke receiving intravenous r-tPA within 4.5 hours of onset
   c. Causative occlusion of the ICA or proximal MCA (M1)
   d. Age ≥18 years
   e. NIHSS score of ≥6
   f. ASPECTS of ≥6
   g. Groin puncture within 6 hours of symptom onset.

3. When treatment is initiated beyond 6 hours from symptom onset, the effectiveness of endovascular therapy is uncertain.

4. In patients with anterior circulation occlusion who have contraindications to intravenous r-tPA; causative occlusion of the M2 or M3 portion of the MCA, the ACA, VA, BA or PCA; patients <18 years; prestroke mRS score >1, ASPECTS <6, or NIHSS score <6, endovascular therapy may be reasonable.

5. Observing patients after intravenous r-tPA to assess for clinical response before pursuing endovascular therapy is not required.

6. Use of stent retrievers is indicated in preference to the MERCI device.

7. The technical goal of the thrombectomy procedure should be a TICI grade 2b/3 angiographic result, achieved as early as possible and within 6 hours after stroke onset.

**Recommendations: Imaging**

1. Emergency imaging of the brain is recommended before any specific treatment for acute stroke is initiated.

2. For patients who qualify for intravenous r-tPA, initiating intravenous r-tPA before noninvasive vascular imaging is recommended. Noninvasive intracranial vascular imaging should then be obtained as quickly as possible if endovascular therapy is contemplated.

3. The benefits of additional imaging beyond CT/CTA or MRI/MRA such as CT perfusion or diffusion-and perfusion-weighted imaging for selecting patients for endovascular therapy are unknown.
And if Thrombectomy fails
Hemicraniectomy within 48h after Malignant MCA Occlusion

Figure 1. Functional Outcome after Hemicraniectomy and after Conservative Treatment Alone According to the Modified Rankin Score.
Hemicraniectomy within 48h after Malignant MCA Occlusion

![Graph showing survival rates for Hemicraniectomy and Control groups over months.](image-url)
Hemicraniectomy increases survival without severe disability among patients with a malignant middle-cerebral-artery infarction.
Evidence-based acute Stroke Treatment in 2015

1. Stroke unit treatment increases likelihood to be alive, independent, and living at home one year after the stroke.
2. Early secondary prophylaxis reduces risk for future stroke.
3. i.v. thrombolysis increases survival without disability (mRS 0-1).
4. i.a. thrombectomy increases survival without requiring assistance (mRS 0-2).
5. Hemicraniectomy increases survival without severe disability (mRS 0-4).
**Suspicion AVC aigu**

**Sur place**
1. Garantir ABC
   Examen: NIHSS, GCS
2. A quelle heure le patient était la dernière fois en état neuro normal?
3. HM (maladies de sang/cerveau, OP/AVC/trauma/hémorragies récent, anticoagulation actuelle, grossesse, démence)
4. Info Neurologue, Radiologie
5. 2x voies i.v.+ prise de sang: INR, Quick, TT (bleu), formule (mauve), Na, K, Crea, GOT, GPT, CK, CRP (vert)
   
   2-3 l O2/min
   Monitoring $S_{O2}$, RR, ECG, f, glucose, température, RR
   Correction: Glucose <50 ou >200; Temp > 37.5°C, electrolytes, RR <90
   RR>220sys: Urapidil 10-50mg iv, après 4-8mg/h i.v.
   RR>120dia: Clonidin 0.15-0.3mg i.v., $S_{O2}<$95%
6. Transfert rapide à St Pierre

**St Pierre**
1. Transfert directe et rapide au CT
2. CT à blanc (wake-up, grossesse: IRM)
3. Examen clinique par Neurologue de garde et révision des images avec radiologue de garde
4. Décision +/- i.v. thrombolyse
   RR<185/110
5. Décision +/- Angio CT, Perfusion
6. Décision +/- Thrombectomie
7. Info et Transfer Centre Interventionnel
8. Ponction femorale
9. Thrombectomie

**Onset-to-IVT time**
Ant: max. 4,5h
Post: max. 12h (Si coma< 4h)

**Onset-to-groin time**
max. 6-12h

**Door-to-needle time**
max. 30 min

**Image-to-groin time**
max. 90 min
Disability-adjusted life year for cerebral vascular disease per 100,000 inhabitants in 2004 [157]

1650-1825
1825-2000
>2000
Intracerebral Hemorrhage after IVT and INR Registry with 23437 patients

Figure 2. Relationship Between International Normalized Ratio and Risk of Symptomatic Intracranial Hemorrhage in Warfarin-Treated Patients (Baseline INR ≤ 2.0)

Solid line indicates risk of symptomatic intracranial hemorrhage (sICH); dashed lines, 95% confidence intervals. Logistic regression modeling was conducted to examine the relationship between international normalized ratio (INR) and binary outcome of sICH. The Stone and Koo additive spline method was fitted to generate the plot; adequacy of linearity was tested using likelihood ratio statistic by comparing the linear and nonlinear logistic models.
Overall IVT Outcome is favourable

Metaanalysis of 12 trials, 7012 patients

Figure 2: Effects of rt-PA on outcomes at final follow-up
Data are numbers, unless otherwise indicated. Treatment was administered up to 6 h after the stroke. rt-PA = recombinant tissue plasminogen activator. IST-3 = Third International Stroke Trial. mRS = modified Rankin Scale.
IVT Onset-to-treatment Time and Intracerebral Hemorrhage

Metaanalysis on 2775 patients from 8 trials
Should people aged over 80 receive thrombolysis?

Metaanalysis of 12 trials with 7012 patients

<table>
<thead>
<tr>
<th>Trials</th>
<th>Events/patients</th>
<th>Odds ratio (95% CI)</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rt-PA</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>Treated up to 6 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤80 years</td>
<td>10</td>
<td>1372/2612</td>
<td>1.16 (1.04–1.29)</td>
</tr>
<tr>
<td>&gt;80 years</td>
<td>3</td>
<td>237/870</td>
<td>1.22 (0.98–1.53)</td>
</tr>
<tr>
<td>All trials</td>
<td>10</td>
<td>1609/3482</td>
<td>1.18 (1.07–1.30)</td>
</tr>
<tr>
<td>Treated up to 3 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤80 years</td>
<td>6</td>
<td>254/512</td>
<td>1.51 (1.18–1.93)</td>
</tr>
<tr>
<td>&gt;80 years</td>
<td>2</td>
<td>111/384</td>
<td>1.68 (1.20–2.34)</td>
</tr>
<tr>
<td>All trials</td>
<td>6</td>
<td>365/896</td>
<td>1.56 (1.28–1.90)</td>
</tr>
<tr>
<td>Treated between 3–6 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤80 years</td>
<td>7</td>
<td>1054/2004</td>
<td>1.09 (0.96–1.24)</td>
</tr>
<tr>
<td>&gt;80 years</td>
<td>2</td>
<td>126/486</td>
<td>0.97 (0.73–1.30)</td>
</tr>
<tr>
<td>All trials</td>
<td>7</td>
<td>1180/2490</td>
<td>1.07 (0.96–1.21)</td>
</tr>
</tbody>
</table>

Figure 4: Effect of rt-PA on alive and independent at the end of follow-up, subgrouped by age and time to treatment
Data are numbers, unless otherwise indicated. rt-PA=recombinant tissue plasminogen activator. IST-3=Third International Stroke Trial.
Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke


![Graph showing Rankin Distribution](image-url)
## Subgroup Analysis ESCAPE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Common Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>&gt;80 yr</td>
<td>3.0 (1.3–6.8)</td>
</tr>
<tr>
<td>≤80 yr</td>
<td>2.7 (1.7–4.3)</td>
</tr>
<tr>
<td><strong>ASPECTS</strong></td>
<td></td>
</tr>
<tr>
<td>8–10</td>
<td>2.6 (1.7–4.1)</td>
</tr>
<tr>
<td>&lt;8</td>
<td>2.7 (1.0–7.2)</td>
</tr>
<tr>
<td><strong>Cervical carotid occlusion</strong></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9.6 (2.6–35.5)</td>
</tr>
<tr>
<td>No</td>
<td>2.2 (1.4–3.3)</td>
</tr>
<tr>
<td><strong>IV alteplase</strong></td>
<td></td>
</tr>
<tr>
<td>Received</td>
<td>2.5 (1.6–4.0)</td>
</tr>
<tr>
<td>Not received</td>
<td>2.6 (1.1–5.9)</td>
</tr>
<tr>
<td><strong>NIHSS score at baseline</strong></td>
<td></td>
</tr>
<tr>
<td>6–19</td>
<td>2.6 (1.6–4.2)</td>
</tr>
<tr>
<td>&gt;19</td>
<td>2.4 (1.1–5.3)</td>
</tr>
<tr>
<td><strong>Location of occlusion</strong></td>
<td></td>
</tr>
<tr>
<td>ICA with involvement of the M1 MCA segment</td>
<td>2.6 (1.2–5.9)</td>
</tr>
<tr>
<td>M1 MCA segment or all M2 MCA segments</td>
<td>2.7 (1.7–4.4)</td>
</tr>
<tr>
<td><strong>Time from stroke onset to randomization</strong></td>
<td></td>
</tr>
<tr>
<td>≤180 min</td>
<td>2.6 (1.5–4.5)</td>
</tr>
<tr>
<td>&gt;180 min</td>
<td>2.5 (1.4–4.5)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.5 (1.4–4.5)</td>
</tr>
<tr>
<td>Female</td>
<td>2.6 (1.5–4.4)</td>
</tr>
</tbody>
</table>
2015 Thrombektomy via stent retriever
(MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, REVASCAT studies)
Collaterals

<table>
<thead>
<tr>
<th>Category</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good collaterals</td>
<td>5</td>
<td>Compared to asymptomatic contralateral hemisphere, there is no delay and normal or increased prominence of peripheral vessels; normal extent within the occluded arteries territory within the symptomatic hemisphere.</td>
</tr>
<tr>
<td>Intermediate collaterals</td>
<td>4</td>
<td>Compared to asymptomatic contralateral hemisphere there is a delay of one phase in filling in of peripheral vessels but prominence and extent is the same.</td>
</tr>
<tr>
<td>Poor collaterals</td>
<td>3</td>
<td>Compared to asymptomatic contralateral hemisphere there is a delay of two phases in filling in of peripheral vessels but prominence and extent is the same except for a one-phase delay and decreased prominence (thinner vessels) / reduced number of vessels in some part of the territory occluded.</td>
</tr>
<tr>
<td>Poor</td>
<td>2</td>
<td>Compared to asymptomatic contralateral hemisphere there is a delay of two phases in filling in of peripheral vessels and decreased prominence and extent or a one-phase delay and some regions with no vessels in some part of the territory occluded.</td>
</tr>
<tr>
<td>Poor</td>
<td>1</td>
<td>Compared to asymptomatic contralateral hemisphere there are just a few vessels visible in any phase within the occluded vascular territory.</td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
<td>Compared to asymptomatic contralateral hemisphere there are no vessels visible in any phase within the occluded vascular territory.</td>
</tr>
</tbody>
</table>