Intensive Medical Therapy with Therapeutic Hypothermia for Malignant Middle Cerebral Artery Infarction

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Proximal MCA or ICA occlusion

Space occupying cerebral edema

Increased intracranial pressure (IICP)

Herniation of the Brain

Early neurological deterioration

Introduction

Decompressive surgery

Pooled analysis of three European randomized controlled trials (DECIMAL, DESTINY, HAMLET)

- Significantly fewer patients had an unfavorable outcome (mRS 5 or death) at 12 months, after decompressive surgery than after conservative management.
- The survival rate at 12 months was higher after decompressive surgery than after conservative treatment.
- Eligible age: 18 – 60 years

Modified Rankin Scale (mRS)

0 - No symptoms
1 - No significant disability
2 - Slight disability.
3 - Moderate disability
   (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
   (bedridden status)
6 - Dead

Circumstances limiting decompressive surgery

- Elderly patients
- Severely unstable medical status
- Refusal of the caregivers

Questionable favorable outcome (mRS 4) in 3 RCTs

- The probability of mRS 4 increases more than 10 times in surgery group
- Increased survival with moderate disability

Recent advance of intensive medical therapy

- Reduction in brain swelling effectively
- Coupled with hemodynamic systemic monitoring

Introduction of therapeutic hypothermia (or targeted temperature modulation, TTM)

- Neuroprotection: reduction in cerebral metabolism
- IICP control: reduction in vasogenic edema and inflammation
- Equivocal findings in previous clinical studies with malignant MCA infarction, but suggesting considerable anti-edema action

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**Intensive medical therapy**

Controled strategies for IICP

Mean ± standard deviation

Avg. dec. in ICP (mm Hg)

Hyperventilation  Mannitol  Barbiturates  Hypothermia  Hypertonic Saline  Lumbar CSF Drainage  Decompressive Craniectomy

Schreckinger M Neurocrit Care 2009;11:427-36
Controlled strategies for IICP

Stepwise management

A. Consideration of surgical decompression and/or drainage of cerebrospinal fluid.
B. General management
   a. Mechanical ventilation after rapid sequence intubation
   b. Head elevation to 30°
   c. Neutral neck position and avoidance of constricting tube ties
   d. Avoidance of hypoxia, hypercapnia, and hyponatremia
   e. Control of fever and hyperglycemia
   f. Treat seizures and use prophylactic anticonvulsants when appropriate
C. Sedation and analgesia
D. Hyperventilation: PaCO₂ 30-35 mmHg (or 25-30 mmHg)
E. Optimization of cerebral perfusion pressure: intracranial pressure ≤ 20 mmHg
   and cerebral perfusion pressure ≥ 60 mmHg (individualized)
F. Osmotherapy: mannitol or hypertonic saline
G. Therapeutic hypothermia
H. Barbiturate coma therapy

Systematized or protocolized intensive therapy is considered!

Modified from Stephan A. Mayer’s Concept

Jeon SB et al. J stroke 2014;16:146-60
To evaluate the specific characteristics between decompressive surgery and intensive medical therapy combined with therapeutic hypothermia.
• Retrospective single center study (2010.1 – 2015.3)

• Inclusion criteria

✓ Acute ischemic stroke involving MCA territory  

✓ Infarct volume > 82mL on baseline diffusion weighted image (DWI) within 6 hours from the onset  

✓ National Institutes of Health Stroke Scale (NIHSS)  
  ≥ 15 within 48 hours from the onset  
• Exclusion criteria

✓ Significant contralateral infarction

✓ Space occupying intra-infarct hemorrhage

✓ Refusal of further intensive care


63 patients with MCA infarct volume > 82mL on DWI within 6 hours screened

17 patients excluded
- 3 NIHSS < 15 within 48 hours from onset
- 5 concomitant contralateral infarction
- 2 space-occupying hemorrhagic transformation
- 7 Refusal of further critical care

45 patients enrolled and distributed

- 32 allocated to intensive medical therapy group
- 13 allocated to decompressive surgery group
• **Stepwise medical management**

  - **Therapeutic hypothermia**
    - Endovascular catheter or surface cooling device
    - Mechanical ventilation & Sedation
    - Targeting temperature to 34.5°C (Maintaining for 48 hours)
    - Rewarming for 48 hours

• **Decompressive surgery**
  - Removal of bone flap over the frontal, temporal, parietal, and occipital lobe at the site of the infarct
  - Expansion of swollen brain tissue extracranially

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*References*

- Jeon SB et al. J stroke 2014;16:146-60
- Hong JM et al. Stroke 2014;45:134-40
<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Decompressive surgery (N=13)</th>
<th>Intensive medical treatment (N=32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General demographics, n(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>58.2±15.1</td>
<td>67.6±12.9</td>
<td>0.043</td>
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<tr>
<td>Male gender</td>
<td>7 (53.8)</td>
<td>14 (46.7)</td>
<td>0.665</td>
</tr>
<tr>
<td><strong>Previous illnesses, n(%)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>10 (76.9)</td>
<td>17 (56.7)</td>
<td>0.207</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (30.8)</td>
<td>5 (16.7)</td>
<td>0.296</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>6 (46.2)</td>
<td>19 (63.3)</td>
<td>0.294</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>8 (61.5)</td>
<td>14 (46.7)</td>
<td>0.370</td>
</tr>
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<td>Smoking</td>
<td>5 (38.5)</td>
<td>5 (16.7)</td>
<td>0.120</td>
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<td>Prior stroke</td>
<td>2 (15.4)</td>
<td>10 (33.3)</td>
<td>0.228</td>
</tr>
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<td><strong>Cause of Stroke (TOAST), n(%)</strong></td>
<td></td>
<td></td>
<td>0.303</td>
</tr>
<tr>
<td>Large-vessel atherosclerosis</td>
<td>2 (15.4)</td>
<td>3 (10.0)</td>
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</tr>
<tr>
<td>Cardioembolism</td>
<td>7 (53.8)</td>
<td>23 (76.7)</td>
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<tr>
<td>Others or unknown</td>
<td>4 (30.8)</td>
<td>4 (13.3)</td>
<td></td>
</tr>
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<td><strong>Dominant hemisphere, n(%)</strong></td>
<td>3 (23.1)</td>
<td>14 (46.7)</td>
<td>0.146</td>
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<tr>
<td><strong>Territory of infarct, n(%)</strong></td>
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<tr>
<td>MCA only</td>
<td>8 (61.5)</td>
<td>21 (70.0)</td>
<td>0.587</td>
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<tr>
<td>MCA and ACA</td>
<td>3 (23.1)</td>
<td>9 (30.0)</td>
<td>0.642</td>
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<tr>
<td>MCA and PCA</td>
<td>2 (15.4)</td>
<td>0 (0.0)</td>
<td>0.028</td>
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<tr>
<td><strong>Mode of treatment</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Intravenous rt-PA</td>
<td>8 (61.5)</td>
<td>22 (73.3)</td>
<td>0.497</td>
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<td>Endovascular treatment</td>
<td>11 (84.6)</td>
<td>20 (66.7)</td>
<td>0.228</td>
</tr>
<tr>
<td>Osmotherapy</td>
<td>10 (76.9)</td>
<td>21 (70.0)</td>
<td>0.729</td>
</tr>
</tbody>
</table>
## Complications (during hospitalization)

<table>
<thead>
<tr>
<th>Complication, n(%)</th>
<th>Surgical decompression (N=13)</th>
<th>Intensive medical treatment (N=32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from brain herniation</td>
<td>4 (30.8)</td>
<td>3 (9.4)</td>
<td>0.073</td>
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<tr>
<td>Death from medical problems</td>
<td>0 (0.0)</td>
<td>3 (30.0)</td>
<td>0.237</td>
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<tr>
<td>Aspiration pneumonia</td>
<td>9 (69.2)</td>
<td>13 (43.3)</td>
<td>0.119</td>
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<tr>
<td>Pulmonary edema</td>
<td>5 (38.5)</td>
<td>6 (20.0)</td>
<td>0.203</td>
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<td>Venous thromboembolism</td>
<td>0 (0.0)</td>
<td>4 (13.3)</td>
<td>0.167</td>
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<td>Seizure</td>
<td>1 (7.7)</td>
<td>2 (6.7)</td>
<td>0.903</td>
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<td>Depression</td>
<td>0 (0.0)</td>
<td>7 (21.9)</td>
<td>0.066</td>
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<td>Tracheostomy</td>
<td>2 (15.4)</td>
<td>2 (6.7)</td>
<td>0.366</td>
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<tr>
<td>Urinary tract infection</td>
<td>2 (15.4)</td>
<td>2 (6.7)</td>
<td>0.366</td>
</tr>
<tr>
<td>Upper gastrointestinal bleeding</td>
<td>2 (15.4)</td>
<td>1 (3.3)</td>
<td>0.154</td>
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<tr>
<td>Sepsis</td>
<td>0 (0.0)</td>
<td>3 (10.0)</td>
<td>0.237</td>
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<tr>
<td>Electrolyte imbalance</td>
<td>5 (38.5)</td>
<td>2 (6.2)</td>
<td><strong>0.007</strong></td>
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<td>ARF</td>
<td>1 (7.7)</td>
<td>5 (16.7)</td>
<td>0.435</td>
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<td>Sore</td>
<td>1 (7.7)</td>
<td>3 (10.0)</td>
<td>0.811</td>
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<td>Arrhythmia</td>
<td>3 (23.1)</td>
<td>6 (20.0)</td>
<td>0.820</td>
</tr>
<tr>
<td>Myocardial infarction or other cardiomyopathy</td>
<td>2 (15.4)</td>
<td>1 (3.3)</td>
<td>0.154</td>
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### Functional outcome (3 months)

<table>
<thead>
<tr>
<th>Functional outcome at 3 months</th>
<th>Surgical decompression (N=13)</th>
<th>Intensive medical treatment (N=32)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>mRS score, median*</td>
<td>5 (4.5-6)</td>
<td>4 (3-5)</td>
<td>0.036</td>
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<tr>
<td>Good outcome (mRS 0-3), n(%)</td>
<td>1 (7.7)</td>
<td>10 (31.2)</td>
<td>0.096</td>
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<td>Good outcome (mRS 0-2), n(%)</td>
<td>0 (0.0)</td>
<td>6 (18.8)</td>
<td>0.094</td>
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<td>Poor outcome (mRS 4-6), n(%)</td>
<td>11 (84.6)</td>
<td>22 (68.8)</td>
<td>0.275</td>
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<tr>
<td>Poor outcome (mRS 5-6), n(%)</td>
<td>10 (76.9)</td>
<td>13 (40.6)</td>
<td>0.027</td>
</tr>
<tr>
<td>Mortality</td>
<td>5 (38.5)</td>
<td>7 (21.9)</td>
<td>0.182</td>
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#### 3 Months

<table>
<thead>
<tr>
<th>Decompressive surgery (n=13)</th>
<th>mRS=0</th>
<th>mRS=1</th>
<th>mRS=2</th>
<th>mRS=3</th>
<th>mRS=4</th>
<th>mRS=5</th>
<th>Death</th>
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<tr>
<td>0</td>
<td>8</td>
<td>15</td>
<td>39</td>
<td>39</td>
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<table>
<thead>
<tr>
<th>Intensive medical therapy (n=32)</th>
<th>mRS=0</th>
<th>mRS=1</th>
<th>mRS=2</th>
<th>mRS=3</th>
<th>mRS=4</th>
<th>mRS=5</th>
<th>Death</th>
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<tbody>
<tr>
<td>3</td>
<td>9</td>
<td>6</td>
<td>13</td>
<td>28</td>
<td>19</td>
<td>22</td>
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# Surgery cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Onset to surgery (hr)</th>
<th>Herniation sign to surgery (hr)</th>
<th>Initial DWI volume (cc)</th>
<th>Baseline NIHSS</th>
<th>3m mRS</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>50.3</td>
<td>4.6</td>
<td>128.8</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>55.0</td>
<td>8.0</td>
<td>232.0</td>
<td>17</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>29.0</td>
<td>14.0</td>
<td>303.6</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>146.0</td>
<td>4.0</td>
<td>86.0</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>103.6</td>
<td>7.6</td>
<td>179.3</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>32.0</td>
<td>2.6</td>
<td>218.2</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>156.0</td>
<td>4.0</td>
<td>82.5</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>70.0</td>
<td>12.0</td>
<td>82.3</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>27.5</td>
<td>5.5</td>
<td>124.7</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>6.0</td>
<td>1.5</td>
<td>319.3</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>11</td>
<td>11.0</td>
<td>4.5</td>
<td>390.6</td>
<td>21</td>
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<tr>
<td>12</td>
<td>9.0</td>
<td>2.0</td>
<td>475.0</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>13</td>
<td>34.0</td>
<td>3.0</td>
<td>194.0</td>
<td>14</td>
<td>6</td>
</tr>
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</table>

## Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>3m mRS 3-4</th>
<th>3m MRS 5-6</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset to surgery time (hr)</td>
<td>83.8±53.9</td>
<td>47.8±48.4</td>
<td>0.293</td>
</tr>
<tr>
<td>Herniation sign to surgery time (hr)</td>
<td>5.5±2.2</td>
<td>5.7±4.3</td>
<td>0.959</td>
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<tr>
<td>Initial DWI volume (cc)</td>
<td>148.9±75.1</td>
<td>236.9±132.2</td>
<td>0.303</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>17 (16-17)</td>
<td>27 (14-21.5)</td>
<td>0.797</td>
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</table>
### Refusal of surgery

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Initial DWI volume (cc)</th>
<th>Baseline NIHSS</th>
<th>3m mRS</th>
<th>Medical problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>51</td>
<td>244.3</td>
<td>18</td>
<td>6</td>
<td>A.fib, Rheumatic heart disease</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>86</td>
<td>267.2</td>
<td>14</td>
<td>6</td>
<td>Lung cancer, cardiac tamponade</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>67</td>
<td>303.6</td>
<td>22</td>
<td>6</td>
<td>none</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>84</td>
<td>363.8</td>
<td>16</td>
<td>6</td>
<td>NSTEMI, aspiration pneumonia</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>85</td>
<td>95.9</td>
<td>19</td>
<td>6</td>
<td>none</td>
</tr>
<tr>
<td>6</td>
<td>F</td>
<td>89</td>
<td>116.5</td>
<td>16</td>
<td>6</td>
<td>ARF</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>80</td>
<td>154.0</td>
<td>17</td>
<td>6</td>
<td>Heart failure</td>
</tr>
</tbody>
</table>

NSTEMI = non ST-segment elevation myocardial infarction

### Medical illness

- **Cardiac dz**
- **Cancer**
- **Pneumonia**
- **Renal failure**
- **none**
<table>
<thead>
<tr>
<th>Status</th>
<th>MR (day 0)</th>
<th>MR (day 4)</th>
<th>CT (day 7)</th>
</tr>
</thead>
</table>
| NIHSS: 22  
Initial DWI: 87.5cc  
3m MRS: 4 | ![MR Image](image1.png) | ![MR Image](image2.png) | ![CT Image](image3.png) |
| NIHSS: 18  
Initial DWI: 139.7cc  
3m MRS: 2 | ![MR Image](image4.png) | ![MR Image](image5.png) | ![CT Image](image6.png) |
| NIHSS: 22  
Initial DWI: 177.2cc  
3m MRS: 3 | ![MR Image](image7.png) | ![MR Image](image8.png) | ![CT Image](image9.png) |
| NIHSS: 15  
Initial DWI: 183.5cc  
3m MRS: 0 | ![MR Image](image10.png) | ![MR Image](image11.png) | ![CT Image](image12.png) |
Discussion

- Relatively higher mortality in decompressive surgery group in the present study
  - Possible variability of the surgery process among the operators
  - Difficult to be managed by intensivists after surgery
  - Higher mean age (58 years) comparing to the other studies (mean 43.2 to 51.6 years at the previous RCTs)
    - Majority of stroke occur in people over age 65 in real practice
    - Despite successful result in DESTINY 2014 with older patients (>60 years), still controversial findings in the studies
  - Probable restriction of further intensive medical therapy due to unstable patient’s status in peri-operative period
Discussion

- Higher prevalence of mRS 0-3 in intensive medical therapy group
  - Systematized intensive medical protocol
  - Rapid & proper thrombolytic management within optimal time window
    - Onset to door time (mean): 73.4 minutes
    - IV t-PA: 73.3%
    - Endovascular treatment: 66.7%
  - Advance in modulation of targeted temperature, particularly in rewarming stage
    - Most complications occur in rewarming stage
    - Prevention of infection / antishivering management
**Discussion**

**HeADDFIRST** (Pilot clinical trial)

**Standardized Medical Management Protocol**

- Airway management
- Ventilator Settings
- Blood pressure control and Agents
- Management of fluid and electrolytes
- Gastrointestinal and nutritional management
- Hematological monitoring and management
- Intracranial pressure monitoring
- Sedation
- Mannitol
- Anticonvulsants
- Deep vein thrombosis prophylaxis
- Secondary stroke prevention with antithrombotics
- Rehabilitation

**Hemicranieotomy and Durotomy Upon Deterioration From Infarction-Related Swelling Trial (HeaDDFIRST)**

- Possible benefit from standardizing medical management
- Lower mortality in medical management group than in other published trials

Jeffrey I et al. Stroke 2014;45:781-7
Discussion

• **Remained question for mRS 4**
  - Increased proportion of patients with mRS 4 at follow up in intensive medical therapy group
    - Combined with decreased mortality
  - Further investigate the points capable of switching mRS4 to mRS3
  - Consider psychological and social aspects integrally

• **Distinct role of decompressive surgery for lowering IICP**
  - Potent decompressive effect
  - Sort the candidates of decompressive surgery urgently
  - Concomitant intensive medical therapy within the limits of the possible
Limitation

- Retrospective study design
  - Selection bias
  - Bias from withdrawal of further critical care

- Lack of other tools checking psychological and social aspects

- Small sample volume
Conclusions

**Proper & Rapid acute stroke management**

IV thrombolysis / Endovascular therapy

**Standardized intensive medical therapy**

**Very old & severe medical illness**

- Good response to medical therapy

**Intensive medical therapy**

**Not good response to medical therapy**

- Suitable vital condition for surgery

**Decompressive surgery**

**Malignant MCA infarction**

- **Hyperthermia**
- **Pentobarbital**
- **Hyper ventilation**
- **Osmotherapy**
- **CPP optimization**
- **Light Sedation**
- **Surgical decompression (parenchymal debulking, CSF)**
- **Easy Venous Drainage: position, intrathoracic pressure, fluid management**
Thank you for your attention!