Does Cyclosporine ImpRove Clinical outcome in ST-elevation myocardial infarction patients? (the CIRCUS study)

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DECLARATION OF INTEREST

Neurovive Pharmaceuticals, AB:
- Research contracts
- Consulting/Royalties/Owner/ Stockholder of a healthcare company
Reperfusion injury contributes to myocardial infarction

Onset of chest pain → First medical care → Cath lab admission → PCI Reperfusion

30 minutes to 12 hours

Ischemia injury

WINDOW TO START TREATMENT OF REPERFUSION INJURY

Reperfusion injury

Ischemia / Reperfusion

- ATP
- Pi
- Ca²⁺
- ROS

Transition pore → Cyclosporine

Mitochondria
Phase II trial: cyclosporine reduces infarct size in STEMI

STEMI < 12 hrs
PCI treatment
TIMI flow grade 0-1
No visible collateral

Cyclosporine (or saline)
(2.5 mg/kg, IV bolus)

Day 1-3
CK / TnI release
Infarct size

Day 5 MRI

CMR infarct size

Figure: MRI infarct size
Short axis view of the left ventricle showing an area of hyper-enhancement within the anterior wall (arrows), indicative of myocardial infarction.

Piot et al. NEJM 2008
OBJECTIVE
To determine whether cyclosporine might improve clinical outcome in STEMI patients

PRIMARY ENDPOINT
Combined incidence within 1 year after STEMI of:
all-cause mortality; worsening of heart failure during initial hospitalization or re-hospitalisation for heart failure; LV remodeling

(LV remodeling (echo): increase > 15% of LVEDV at 1 year versus initial discharge)
Study population and recruitment

- 18 years
- symptom onset < 12 hrs
- ST shift ≥ 0.2 mV in two contiguous anterior leads
- LAD as culprit artery with TIMI flow grade 0 – 1

### Anterior STEMIs

#### Randomized (n=970)

- Cyclosporine (n = 475)
  - No informed content (n=1)
  - Imprisoned and therefore ineligible (n=1)
  - Did not receive any treatment (n=4)
  - Missing or poor echographic data (n=74)

- Control (n=495)
  - Did not receive any treatment (n=4)
  - Missing or poor echographic data (n=95)

#### Cyclosporine (n = 395)

#### ITT Analysis

#### Primary endpoint Analysis

#### Control (n=396)

- First patient included: 2011 April, 19
- Last patient included: 2014 February, 16
- Last visit last patient: 2015 April 2nd

42 investigation centres in 3 countries
## Primary and secondary outcomes at 1 year

<table>
<thead>
<tr>
<th>(Death / HF / LV remodeling)</th>
<th>Cyclosporine (n=395)</th>
<th>Control (n=396)</th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>233 (59.0%)</td>
<td>230 (58.1%)</td>
<td>1.04 [0.78; 1.39]</td>
<td>0.77</td>
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| Death: all-cause             | 7.1 %                | 6.6 %            | 1.09 [0.63 ; 1.90]  | 0.76    |
| Death: cardiovascular        | 6.1 %                | 6.1 %            | 1.01 [0.56 ; 1.81]  | 0.98    |
| HF worsening or re-hospitalization for HF | 22.8 % | 22.7 % | 1.01 [0.72 ; 1.41]  | 0.97    |
| HF worsening                 | 15.7 %               | 16.9 %           | 0.92 [0.63 ; 1.34]  | 0.65    |
| Re-hospitalization for HF    | 10.6 %               | 10.4 %           | 1.03 [0.65 ; 1.63]  | 0.89    |
| LV remodeling                | 42.8 %               | 40.7 %           | 1.09 [0.82 ; 1.46]  | 0.53    |
| Cardiogenic shock            | 6.6 %                | 6.1 %            | 1.09 [0.61 ; 1.94]  | 0.77    |
| Recurrent Myocardial infarction | 2.3 % | 3.8 % | 0.59 [0.26 ; 1.37]  | 0.22    |
| Stroke                       | 1.8 %                | 3.0 %            | 0.58 [0.22 ; 1.48]  | 0.25    |
| Major bleeding               | 1.8 %                | 2.3 %            | 0.73 [0.27 ; 2.00]  | 0.54    |
In anterior STEMI, cyclosporine did not reduce the risk of the composite outcome

- One out of four patients died or was hospitalized for heart failure despite receiving state-of-the-art medical care.

- Despite the results of CIRCUS, the concept that reperfusion injury is clinically important. The impact on clinical outcome of recent encouraging phase II trials remains however to be determined.