Results of the Swiss AMI Study:

What can we achieve with stem cells?

ClinicalTrials.gov Identifier: NCT00355186

Davos; Cardiology update 2013 - 12th February 2013

Daniel Sürder, MD
Fondazione Cardiocentro Ticino
Lugano – Switzerland
daniel.suerder@cardiocentro.org
Background

Intracoronary BM-MNC infusion in the infarct related artery after AMI has been shown to be safe; however, its efficacy is still debated.

Optimal timing for cell delivery post-AMI is unknown. Previous studies indicated potential time dependent efficacy in subgroup analyses.

Study design & Methods

**BM-MNC**
- BM-Aspiration from the iliac crest (60ml)
- Centralized cell processing using density gradient centrifugation, without adding Heparin (UTC Lugano)

**CMR**
- Standardized protocol including cine and delayed enhancement
- Core-lab analysis (University Hospital Zurich)

Sürder et al. Am Heart J 2010
Endpoints & sample size

Primary endpoint:

→ Change in global LVEF at 4 mo. vs. baseline
  → Assumption: $\Delta LVEF = 3.5\%; \ SD \ of \ 6-7\%; \ drop \ out = 10\%$
  → For a independent sample $t$-test 58 paired CMR per group are needed - including drop out → $n = 64$ per group

Secondary endpoints:

→ Change in LV volumes, infarct size (DE CMR) and regional myocardial thickening
→ MACE (death, MI, coronary revascularization, stroke)
→ Predictors for efficacy (time to reperfusion, transmurality, microvascular obstruction)
Patient flow chart

STEMI  n = 200

- control group  n = 67
- BM-MNC therapy 5-7 days after STEMI  n = 66
- BM-MNC therapy 3-4 weeks after STEMI  n = 67

withdraw of PIC  n = 7
- death  n = 0
- no paired CMR examination available  n = 0

withdraw of PIC  n = 2
- death  n = 3
  - n = 1 before treatment
  - n = 2 after treatment
- no paired CMR examination available  n = 3

withdraw of PIC  n = 14
- n = 12: before treatment
- n = 2: after treatment
- death  n = 1
  - before treatment
- no paired CMR examination available  n = 3

Total 345 CMR analyses (24,430 slices)

- paired CMR evaluation available  n = 60
- paired CMR evaluation available  n = 58
- paired CMR evaluation available  n = 49
## Baseline characteristics of the patients

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 67)</th>
<th>Early (n = 65)</th>
<th>Late (n = 63)</th>
<th>p-value</th>
</tr>
</thead>
</table>
| Age – years (median; IQR) | 56 (14.5)        | 55 (15)        | 62 (15)       | 0.70 *  
                                      |                  |                |               | 0.06 ‡  |
| BMI - kg/m2 (median; IQR) | 26.7 (4.4)       | 27.0 (6.1)     | 27.0 (4.4)    | 0.92 *  
                                      |                  |                |               | 0.89 ‡  |
| Male gender - %         | 83.6             | 86.2           | 82.5          | 0.18 *  
                                      |                  |                |               | 1.00 ‡  |
| Hypertension - %        | 43.3             | 49.2           | 38.7          | 0.60 *  
                                      |                  |                |               | 0.72 ‡  |
| Hyperlipidemia - %      | 44.8             | 40.0           | 41.9          | 0.60 *  
                                      |                  |                |               | 0.86 ‡  |
| Diabetes - %            | 17.9             | 7.7            | 9.7           | 0.12 *  
                                      |                  |                |               | 0.21 ‡  |
| Smoking (active/previous) - % | 62.7       | 67.7           | 40.3          | 0.60 *  
                                      |                  |                |               | 0.01 ‡  |
| Familiary history of CAD - % | 35.8        | 26.1           | 24.2          | 0.26 *  
                                      |                  |                |               | 0.18 ‡  |
| 1 / 2 / 3 vessel disease % | 64/21/15    | 54/32/14       | 57/27/16      | 0.34 *  
                                      |                  |                |               | 0.73 ‡  |
| Previous PCI before AMI - % | 3.0           | 3.1            | 1.6           | 1.00 *  
                                      |                  |                |               | 1.00 ‡  |
## Characteristics of index AMI

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Control (n = 67)</th>
<th>Early (n = 65)</th>
<th>Late (n = 63)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary PCI – %</td>
<td>94.0</td>
<td>98.5</td>
<td>100.0</td>
<td>0.37 *</td>
</tr>
<tr>
<td>Concomitant PCI other than infarct related artery – %</td>
<td>18.2</td>
<td>12.3</td>
<td>11.1</td>
<td>0.47 *</td>
</tr>
<tr>
<td>Infarct vessel LAD/LCX/RCA -%</td>
<td>89/3/8</td>
<td>95/2/3</td>
<td>92/3/5</td>
<td>0.51 *</td>
</tr>
<tr>
<td>Pain to revascularization time (h)</td>
<td>4.5 (5)</td>
<td>4.8 (5.4)</td>
<td>4.0 (4.8)</td>
<td>0.57 *</td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>3.5 (0.5)</td>
<td>3.0 (0.5)</td>
<td>3.5 (0.5)</td>
<td>0.73 *</td>
</tr>
<tr>
<td>Drug eluting stent – %</td>
<td>71.6</td>
<td>80.0</td>
<td>81.0</td>
<td>0.31 *</td>
</tr>
<tr>
<td>TIMI flow before/after PCI</td>
<td>0/3 (0/0)</td>
<td>0/3 (0/0)</td>
<td>0/3 (0/0)</td>
<td>0.31/0.94 *</td>
</tr>
<tr>
<td>Use of Glycoprotein IIb/IIIa inhibitors / bivalirudin - %</td>
<td>71.7</td>
<td>78.5</td>
<td>78.1</td>
<td>0.88 *</td>
</tr>
<tr>
<td>Maximal creatin kinase - U/l (median;IQR)</td>
<td>3671 (3685)</td>
<td>4314 (3561)</td>
<td>3436 (3813)</td>
<td>0.22 *</td>
</tr>
<tr>
<td>Baseline nt-pro BNP - ng/l (median;IQR)</td>
<td>1103 (1848)</td>
<td>1450 (1442)</td>
<td>1581 (1912)</td>
<td>0.15 *</td>
</tr>
<tr>
<td>Baseline LVEF - % (median;IQR)</td>
<td>39.6 (11.2)</td>
<td>34.6 (16.1)</td>
<td>35.6 (11.2)</td>
<td>0.07 *</td>
</tr>
<tr>
<td>Baseline LVEDV – ml (median;IQR)</td>
<td>154 (44)</td>
<td>153 (49)</td>
<td>149 (47)</td>
<td>0.89 *</td>
</tr>
<tr>
<td>Baseline LVESV – ml (median;IQR)</td>
<td>94 (35)</td>
<td>94 (41)</td>
<td>97 (38)</td>
<td>0.54 *</td>
</tr>
</tbody>
</table>

* control vs. early  † control vs. late
# Characteristics of BM-MNC

<table>
<thead>
<tr>
<th>Cell characteristics (Median, IQR)</th>
<th>Early n = 62</th>
<th>Late n = 52</th>
<th>p-value (between group difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM aspiration volume (ml)</td>
<td>65 (15)</td>
<td>70 (15)</td>
<td>0.30</td>
</tr>
<tr>
<td>Total MNC ((10^6 \text{ cells}))</td>
<td>159.7 (125.8)</td>
<td>139.5 (120.5)</td>
<td>0.18</td>
</tr>
<tr>
<td>Viability - %</td>
<td>93.6 (5.55)</td>
<td>93.33 (6.60)</td>
<td>0.98</td>
</tr>
<tr>
<td>% CD 34+ cells</td>
<td>1.02 (0.72)</td>
<td>1.31 (0.97)</td>
<td>0.01 #</td>
</tr>
<tr>
<td>Total CD 34+ cells ((10^6 \text{ cells}))</td>
<td>1.6 (1.69)</td>
<td>1.45 (2.43)</td>
<td>0.68</td>
</tr>
<tr>
<td>% CD 133+ cells</td>
<td>82.65 (28.1)</td>
<td>78.45 (52.83)</td>
<td>0.34</td>
</tr>
<tr>
<td>Total CD 133+ cells ((10^6 \text{ cells}))</td>
<td>0.96 (1.46)</td>
<td>0.92 (2.06)</td>
<td>0.77</td>
</tr>
<tr>
<td>% Invasion</td>
<td>33 (18) *</td>
<td>26.5 (16.5) **</td>
<td>0.18</td>
</tr>
<tr>
<td>Invasion index</td>
<td>50.88 (24.38)*</td>
<td>45.64 (22.10) **</td>
<td>0.21</td>
</tr>
</tbody>
</table>

### Timing of BM-MNC treatment

<table>
<thead>
<tr>
<th>Days after AMI (Median, IQR)</th>
<th>Early n = 62</th>
<th>Late n = 52</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days after AMI (Median, IQR)</td>
<td>6 (2)</td>
<td>24 (7)</td>
<td>NA</td>
</tr>
</tbody>
</table>

* n = 29  
** n = 30
Results

Mean LVEF at baseline and 4 months

![Graph showing LVEF at baseline and 4 months, with p-values indicated for control, early, and late stages.]

- **Control**
  - Baseline: 40.0, n = 62
  - 4 months: 39.6, n = 60
  - p = 0.74

- **Early**
  - Baseline: 36.5, n = 59
  - 4 months: 37.9, n = 59
  - p = 0.12

- **Late**
  - Baseline: 36.3, n = 56
  - 4 months: 37.4, n = 49
  - p = 0.45

Note: The graph shows a comparison of left ventricular ejection fraction (LVEF) at baseline and 4 months across different stages (control, early, and late).
Primary Endpoint

Mean change in LVEF 4 months vs. baseline

Adjusting for baseline LVEF with ANCOVA testing:

<table>
<thead>
<tr>
<th>Estimate (95%CI)</th>
<th>p-value</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.25 (-1.83 to 4.32)</td>
<td>0.42</td>
<td>early vs. control</td>
</tr>
<tr>
<td>0.55 (-2.61 to 3.71)</td>
<td>0.73</td>
<td>late vs. control</td>
</tr>
</tbody>
</table>

- 0.4 % for control
+ 1.8 % for early
+ 0.8 % for late
Secondary Endpoints

Change in LV-volumes 4 months vs. baseline

LVEDV (ml)
P = 0.03 vs. control
P = 0.89 vs. control

LVESV (ml)
P = 0.07 vs. control
P = 0.79 vs. control
Secondary Endpoints

Change in scar size and regional LV function

Scar size (g)

P = 0.82 vs. control

Myocardial thickening in the infarct territory (mm)

P = 0.54 vs. control

P = 0.67 vs. control
Predictors for treatment efficacy

Change in LVEF

- **p = 0.0287**
- **p = 0.4274**
- **p for interaction = 0.028**

- **p = 0.0138**
- **p = 0.0567**
- **p for interaction = 0.003**

**Time pain to reperfusion (median 4.5 hours)**

- **< 4.5h**
- **> 4.5h**

- **n = 32**
- **n = 26**
- **n = 26**
- **n = 29**

- **n = 32**
- **n = 30**
- **n = 26**
- **n = 19**
## Clinical events during follow up

<table>
<thead>
<tr>
<th>Events</th>
<th>Control</th>
<th>Early</th>
<th>Late</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Events between randomization and therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0.24 *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(3.1%)</td>
<td>(1.7%)</td>
<td>0.48 ‡</td>
</tr>
<tr>
<td><strong>Events at 4 months follow up (cumulative)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>3</td>
<td>1</td>
<td>0.24 *</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(4.8%)</td>
<td>(1.7%)</td>
<td>0.48 ‡</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1.00 *</td>
</tr>
<tr>
<td></td>
<td>(1.6%)</td>
<td>(1.6%)</td>
<td></td>
<td>1.00 ‡</td>
</tr>
<tr>
<td>Rehospitalization for heart failure</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>0.50 *</td>
</tr>
<tr>
<td></td>
<td>(3.2%)</td>
<td>(3.6%)</td>
<td></td>
<td>1.00 ‡</td>
</tr>
<tr>
<td>Revascularization</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>1.00 *</td>
</tr>
<tr>
<td></td>
<td>(4.8%)</td>
<td>(4.9%)</td>
<td>(3.6%)</td>
<td>1.00 ‡</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1.00 *</td>
</tr>
<tr>
<td></td>
<td>(1.6%)</td>
<td>(1.7%)</td>
<td></td>
<td>1.00 ‡</td>
</tr>
<tr>
<td><strong>Combined events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death, myocardial infarction, revascularization,</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>1.00 *</td>
</tr>
<tr>
<td>rehospitalization for heart failure</td>
<td>(6.4%)</td>
<td>(7.9%)</td>
<td>(8.8%)</td>
<td>0.74 ‡</td>
</tr>
<tr>
<td>Death, myocardial infarction, revascularization,</td>
<td>4</td>
<td>6</td>
<td>5</td>
<td>0.74 *</td>
</tr>
<tr>
<td>rehospitalization for heart failure, stroke</td>
<td>(6.4%)</td>
<td>(9.5%)</td>
<td>(8.8%)</td>
<td>0.74 ‡</td>
</tr>
</tbody>
</table>

* control vs. early ‡ control vs. late
Intracoronary infusion of BM-MNC, either 5–7 d or 3–4 wks after primary PCI for STEMI, did not improve LV function as assessed by CMR at 4 months compared with control.

Subgroup analysis indicates potential benefit of i.c. BM-MNC in patients with early reperfusion (within 4.5 h from the onset of pain).

Adapted from Jeevanantham et al. Circulation 2012

<table>
<thead>
<tr>
<th></th>
<th>Difference in Mean</th>
<th>95% Confidence Interval</th>
<th>P for Z</th>
<th>P for Subgroup Differences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echo</td>
<td>3.61</td>
<td>2.18 to 5.04</td>
<td>&lt;0.00001</td>
<td>0.001</td>
</tr>
<tr>
<td>SPECT</td>
<td>2.60</td>
<td>−0.35 to 5.55</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>1.17</td>
<td>−0.60 to 2.95</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>LVG</td>
<td>7.08</td>
<td>4.77 to 9.38</td>
<td>0.0001</td>
<td></td>
</tr>
</tbody>
</table>

SWISS AMI: Δ LVEF early vs. control = 2.1%
Preliminary long term results
Kaplan-Meier estimate for Overall survival

Grouping variable: group / p-value logrank = 0.59

Time to Overall survival (days)
Kaplan-Meier estimate for coronary revascularization

Grouping variable: group / p-value logrank = 0.46

Time to coronary revascularization (days)
Combined EP:
Death, MI, revascularization, rehospitalization for HF
Biomarkers overall 3 groups

N = 175  
N = 169  
N = 156 (preliminary)
Biomarkers early treatment group

- N = 60
- N = 59
- N = 55 (preliminary)

[Graph showing nt-proBNP levels with values: 2082, 639, 435 with a decrease of 69%]

- BNPbase_early
- BNP4mo_early
- BNP12mo_early
Biomarkers late treatment group

N = 54
N = 50
N = 47 (preliminary)

2632

↓ of 72%

nt-proBNP ng/l
Biomarkers control group

N = 61  N = 60  N = 54 (preliminary)

- BNPbase_co: 1639
- BNP4mo_co: 686
- BNP12mo_co: 660

↓ of 58%
Acknowledgements

PI: Roberto Corti  
Co-PI: Daniel Sürder

CMR core lab:  
Robert Manka  
Juerg Schwitter  
Valentin Gisler  
Florian Mayer  
Christina Scheiben

USZ:  
Ines Bühler  
Simone Kaufmann

Sebastian Stoll  
Christoph Wyss  
Manuel Zipponi

CCT / UTC core lab:  
Tiziano Moccetti  
Lucia Turchetto  
Sabrina Soncin  
Viviana Lo Cicero  
Marina Radrizzani  
Giuseppe Astori  
Elena Pecchi

Inselspital:  
Aris Moschovitis  
Stephan Windecker  
Andreas Wahl  
Christa Schönenberger  

KS Luzern:  
Paul Erne  
Michel Zuber  
Christof Auf der Maur  
Peiman Jamshidi  
Doris Erne  
Brigitta Mehmann

UniversitätsSpital Zürich

Kantonsspital Luzern

Cardiocentricino

Inselspital