Management of cardiovascular disease

Acute coronary syndromes and intensive care

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Hyperglycemia and acute coronary syndromes

- Changing phenotype
GAMI
Study design

- **Patients**
  n = 181 MI, no diabetes
  B-glucose < 11.1 mmol/L

- **Controls**
  n = 185

- **OGTT**
  75 g glucose in 200 ml water
  Capillary blood glucose before and 120 min after glucose ingestion
OGTT at discharge
n = 168

Abnormal 67%

IGT 34%
DM 33%
NGT 33%

Controls
n = 185

Abnormal 35%

NGT 65%
IGT 24%
DM 11%

(Norhammar et al. Lancet. 2002;359:2140)

(Bartnik et al J Intern Med. 2004; 256: 288)
Metabolic variables in the GAMI trial
Patients with AMI without diabetes vs. age and sex matched controls

Patients n=145
Controls n=185

(Bartnik et al J Intern Med 2004; 256:288)
## The MI patient now and then
### Secular trends in the risk factor pattern

### 50 year old men in Gothenburg

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>1963</th>
<th>2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking (%)</td>
<td>56</td>
<td>22</td>
</tr>
<tr>
<td>Regular phys act (%)</td>
<td>32</td>
<td>24</td>
</tr>
<tr>
<td>Stress</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>24.8</td>
<td>26.8</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>87</td>
<td>95</td>
</tr>
<tr>
<td>S-Cholesterol (mmol/l)</td>
<td>6.4</td>
<td>5.5</td>
</tr>
<tr>
<td>S-Triglycerides (mmol/l)</td>
<td>1.3</td>
<td>1.7</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td>138/91</td>
<td>135/85</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>3.6</td>
<td>6.6</td>
</tr>
</tbody>
</table>

The patient with myocardial infarction now and then
Secular trends in risk factor pattern

Passed time
Lean, stressed, chain-smoking CEO

Present time
Sedentary, overweight labourer with the metabolic syndrome
Hyperglycemia and acute coronary syndromes

- Changing phenotype
- Influence on prognosis
The Swedish CCU registry 1995-2006
Time trends in 1-year mortality in AMI-patients with and without diabetes

(Norhammar et al Heart. 2007; 93:1577)
(Norhammar et al data on file 2003-2006)
Predictors of death in patients with diabetes and myocardial infarction

From DIGAMI 2
Independent risk predictors for mortality

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Updated FBG (+3 mmol/L)</td>
<td>1.20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (ten years)</td>
<td>2.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes duration (one year)</td>
<td>1.00</td>
<td>0.64</td>
</tr>
<tr>
<td>Gender (Male = 1)</td>
<td>0.89</td>
<td>0.40</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.14</td>
<td>0.48</td>
</tr>
<tr>
<td>Previous MI</td>
<td>1.18</td>
<td>0.26</td>
</tr>
<tr>
<td>Previous CHF</td>
<td>1.71</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>S-Creatinine (40 mmol/L)</td>
<td>1.13</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

(Malmberg et al. Eur Heart J 2005; 26:650)
Admission glucose predicts mortality in MI patients without known diabetes.

Event free survival (%)

- P-glucose < median 7.4 mmol/l
- P-glucose > median 7.4 mmol/l

2P = 0.0029 (Log-Rank test)

(Norhammar et al Diabetes Care 1999, 22: 1827)
Predictors of death in patients with acute coronary syndromes

Global Registry of Acute Coronary Events n= 57 406
Admission glucose n=22 001 Fasting glucose n=13 526

<table>
<thead>
<tr>
<th>F-glucose (mmol/l)</th>
<th>5.6</th>
<th>5.6-6.9</th>
<th>7-11</th>
<th>11-16.6</th>
<th>&gt;16.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion (%)</td>
<td>41</td>
<td>32</td>
<td>21</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65</td>
<td>67</td>
<td>68</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>Sex (female; %)</td>
<td>32</td>
<td>32</td>
<td>37</td>
<td>40</td>
<td>43</td>
</tr>
<tr>
<td>History of DM (%)</td>
<td>12</td>
<td>20</td>
<td>54</td>
<td>80</td>
<td>73</td>
</tr>
<tr>
<td>STEMI</td>
<td>35</td>
<td>43</td>
<td>44</td>
<td>42</td>
<td>39</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>33</td>
<td>34</td>
<td>35</td>
<td>33</td>
<td>37</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>32</td>
<td>24</td>
<td>22</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

### Glucose level (mmol/l)

<table>
<thead>
<tr>
<th>Glucose Level (mmol/l)</th>
<th>Admission</th>
<th>Fasting</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6-6.9</td>
<td>Adm.</td>
<td>Fasting</td>
</tr>
<tr>
<td>7.0-10.9</td>
<td>Admission</td>
<td>Fasting</td>
</tr>
<tr>
<td>11.0-16.4</td>
<td>Admission</td>
<td>Fasting</td>
</tr>
<tr>
<td>≥16.5</td>
<td>Admission</td>
<td>Fasting</td>
</tr>
</tbody>
</table>

#### Adjusted OR for in-hospital death

Linking dysglycemia to cardiovascular disease

**Hyperglycemia**

**Oxidative stress**

↑ DAG*  
**PKC activation**

↑ TGFβ  
↑ cPLA₂  
↑ PG’s  
↓ Na⁺/K⁺ATP-ase  
↑ VEGF  
↑ PKC  
↑ ANP  
↑ BNP  
↑ TGFβ  
↑ PAI-1  
↑ ET-1  
(↑) eNOS

* = DAG = DiAcylGlycerol

(Brownlee Nature 2001;414:813)  
(Garcia Soriano et al Nature Medicine 2001;7:1)

<table>
<thead>
<tr>
<th>Basal membrane thickening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased membrane permeability</td>
</tr>
<tr>
<td>Cellular growth &amp; neovascularisation</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>↓ Fibrinolysis</td>
</tr>
<tr>
<td>Vascular occlusion</td>
</tr>
<tr>
<td>Decreased blood flow &amp; vascular reactivity</td>
</tr>
</tbody>
</table>
Hyperglycemia and acute coronary syndromes

- Changing fenotype
- Influence on prognosis
- Benefits with glucose lowering therapy
  In acute coronary syndromes
Rationale for insulin administration in ACS patients

Potential benefits with insulin in acute illness

- Antihrombotic: ↓ TF ↓ PAI-1
- Vasodilation: ↑ NO-release, ↑ eNOS, ↑ cAMP
- Glucose lowering
- Cardioprotective
- Neuroprotective
- Antiapoptotic
- Antioxidant: ↓ ROS
- Antiinflammatory: ↓ NF-κB, ↓ MCP-1, ↓ ICAM 1, ↓ CRP

Glucose-Insulin-Potassium for Acute Myocardial Infarction: Continuing Controversy Over Cardioprotection
Robert A Kloner and Richard W Nesto

Circulation 2008; 117: 2523 – 2533
Metabolic modulation with GIK in myocardial infarction
Metaanalysis of hospital mortality in placebo controlled trials

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>No</th>
<th>GIK</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>1977</td>
<td>Heng</td>
<td>27</td>
<td>8.3</td>
<td>0</td>
</tr>
<tr>
<td>1978</td>
<td>Stanley</td>
<td>110</td>
<td>7.3</td>
<td>16.4</td>
</tr>
<tr>
<td>1979</td>
<td>Rogers</td>
<td>134</td>
<td>6.5</td>
<td>12.3</td>
</tr>
<tr>
<td>1987</td>
<td>Satler</td>
<td>17</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1965</td>
<td>Mittra</td>
<td>170</td>
<td>11.6</td>
<td>28.2</td>
</tr>
<tr>
<td>1967</td>
<td>Pilcher</td>
<td>102</td>
<td>13.9</td>
<td>29.3</td>
</tr>
<tr>
<td>1968</td>
<td>Pentecost</td>
<td>200</td>
<td>15.0</td>
<td>16.0</td>
</tr>
<tr>
<td>1968</td>
<td>MRC</td>
<td>968</td>
<td>21.4</td>
<td>23.6</td>
</tr>
<tr>
<td>1971</td>
<td>Hjermann</td>
<td>204</td>
<td>10.6</td>
<td>20.0</td>
</tr>
<tr>
<td></td>
<td>All Patients</td>
<td>1932</td>
<td>16.1</td>
<td>21.0</td>
</tr>
</tbody>
</table>

Odds Ratio (99% CI) 0.72 (0.57 - 0.90)
One life saved for 20 treated

(Fath-Ordoubadi et al Circulation 1997; 96:1152)
Myocardial infarction

STEMI
$n = 20\ 201$

Infusion 24 hours
25% glucose
Insulin 50 IU/L
80 mEq/L potassium
Rate 1.5 ml/kg/h

HR = 1.03 (0.95-1.13) $p=0.45$

(CREATE-ECLA investigators JAMA 2005;293:437)c
Glucose-insulin-potassium in myocardial infarction
The CREATE-ECLA study

(CREATE-ECLA investigators JAMA 2005;293:437)
Metabolic modulation with GIK in myocardial infarction
GIK-OASIS 6 combined with CREATE-ECLA

- Both trials similarly designed
- Combined analyses
- 23,000 patients, 2,200 deaths, 2,800 heart failures & 4,000 deaths/heart failure events
- Aim clarifying mechanisms for neutral GIK effect in STEMI

(Diaz et al, ESC, Barcelona, 2006)
Metabolic modulation with GIK in myocardial infarction
GIK-OASIS 6 combined with CREATE-ECLA

Early (days 0-3) and late (days 4-30) outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>OR (fixed) 95% CI</th>
<th>Test for heterogeneity: p =</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death day 0-3</td>
<td>1.14 (1.02 - 1.27)</td>
<td>0.01</td>
</tr>
<tr>
<td>Death day 4-30</td>
<td>0.91 (0.79 - 1.04)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1.04 (0.96 - 1.14)</td>
<td></td>
</tr>
</tbody>
</table>

| Heart Failure          |                                   |                             |
| Heart Failure day 0-3  | 1.08 (0.99 - 1.18)                | 0.0009                      |
| Heart Failure days 4-30| 0.77 (0.64 - 0.92)                |                             |
| Total (95% CI)         | 1.02 (0.94 - 1.10)                |                             |

| Death/Heart Failure    |                                   |                             |
| Death/HF day 0-3       | 1.08 (1.01 - 1.17)                | 0.0005                      |
| Death/HF days 4-30     | 0.85 (0.75 - 0.95)                |                             |
| Total (95% CI)         | 1.01 (0.95 - 1.08)                |                             |

(Diaz et al, ESC, Barcelona, 2006)
Metabolic modulation with GIK in myocardial infarction
Interpretation and remaining question

- Early Hazard possible
- Late Benefit requires confirmation

Question
- Will lowering glucose levels without increased volume load reduce both early and late mortality?
- This hypothesis requires prospective testing
Rationale for insulin administration in ACS patients

Metabolic modulation
Glucose-Insulin-Potassium Infusion (GIK)

Metabolic control
Glucose lowering
Glucose lowering
Patients with myocardial infarction and type 2 diabetes

Long-term mortality in DIGAMI 1

Reduction in HbA1c ≤1%

Mean follow-up 3.4 år (1.6-5.6)

RR = 0.72 [0.92-0.55] p = 0.011
Absolute reduction 11%

Glucose lowering
Patients with myocardial infarction and type 2 diabetes

Long-term mortality in DIGAMI 1

All patients
Reduction in HbA1c ≈0.9%

![Graph showing death rates and long-term mortality](image)

RR = 0.72 [0.92-0.55] p = 0.011
Absolute reduction 11%

Mean follow-up 3.4 years (1.6-5.6)

Stratum 1
Reduction in HbA1c ≈1.4%

![Graph showing death rates and long-term mortality for Stratum 1](image)

RR = 0.49 [0.81-0.30] p = 0.0040
Absolute reduction 15%

Mean follow-up 3.4 years (1.6-5.6)

n = 272

Glucose lowering
Patients with myocardial infarction and type 2 diabetes

Long-term mortality by admission glucose in DIGAMI 1

(Malmberg et al Circulation 1999;99:2626)
Glucose lowering
Patients with myocardial infarction and type 2 diabetes

Long-term outcome in DIGAMI 2

Suspect MI + Type 2 diabetes or B-glucose >11 mmol/L

Group 1 (insulin+insulin)
Group 2 (insulin+conventional)
Group 3 (conventional)

(Malmberg et al Eur Heart J 2005;26:650)
Glucose lowering
Patients with myocardial infarction and type 2 diabetes

Long-term outcome in DIGAMI 2

Group 1 (insulin+insulin)
Group 2 (insulin+conventional)
Group 3 (conventional)

(Malmberg et al Eur Heart J 2005;26:650)
DIGAMI 2
Blood glucose over time by treatment group

(Malmberg et al Eur Heart J 2005;26:650)
Glucose lowering
Patients with myocardial infarction and type 2 diabetes

Early impact of insulin treatment on mortality for hyperglycaemic patients without known diabetes who present with an acute coronary syndrome

C Weston, L Walker, J Birkhead and National Audit of Myocardial Infarction Project, National Institute for Clinical Outcomes Research

Registry based (MINAP) 201 UK hospitals
Patients Trop positive ACS n=3835
No Diabetes glucose ≥11 mmol/l
Mortality 7 and 30 days

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Day 7</th>
<th>Day 30</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin 36%</td>
<td>11.6</td>
<td>15.8</td>
<td>1.51</td>
<td>1.22 – 1.86</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No insulin 64%</td>
<td>16.5</td>
<td>22.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(Weston et al. Heart 2007; 93: 1542)
Glucose lowering
Patients with myocardial infarction and type 2 diabetes

The Hyperglycemia: Intensive Insulin Infusion In Infarction (HI-5) Study
A randomized controlled trial of insulin infusion therapy for myocardial infarction

- Acute study, 24 h with DIGAMI inclusion criteria
- Target glucose level <10 mmol/l
- Power calculation: Estim 1-year mortality 25%, 850 pat.
- Stopped prematurely n=240, 6-months mortality ≈ 7%

- As in DIGAMI 2 no difference in glucose control
- As in DIGAMI 2 no difference in mortality

(Cheung et al. Diabetes Care 2006; 29:765)
Glucose lowering
Patients with myocardial infarction and type 2 diabetes

The Hyperglycemia: Intensive Insulin Infusion In Infarction (HI-5) Study
A randomized controlled trial of insulin infusion therapy for myocardial infarction

Glucose levels during 24 h predicted mortality

<table>
<thead>
<tr>
<th></th>
<th>24-h mean blood glucose level ≤8 mmol/l</th>
<th>24-h mean blood glucose level ≥8.1 mmol/l</th>
<th>Significance</th>
<th>Adjusted odds ratio (95% CI)*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inpatient mortality</td>
<td>0%</td>
<td>7%</td>
<td>0.05</td>
<td>7.2 (0.9–58.9)</td>
<td>0.07</td>
</tr>
<tr>
<td>3-month mortality</td>
<td>2%</td>
<td>9%</td>
<td>0.05</td>
<td>4.7 (1.0–22.4)</td>
<td>0.05</td>
</tr>
<tr>
<td>6-month mortality</td>
<td>2%</td>
<td>11%</td>
<td>0.02</td>
<td>5.6 (1.2–26.1)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, and cardiac intervention (PTCA or thrombolysis).

(Cheung et al. Diabetes Care 2006; 29:765)
Hypoglycemia and acute coronary syndromes

Lowest blood glucose during hospitalisation for MI
713 patients with diabetes
Adjusted 2-year mortality

≤3.0 mmol/L/ ≤55 mg/dl
(n=44; 20 deaths)

1.93 (1.18-1.3.17)

3.1-6.5 mmol/L/ 56-119 mg/dl
(n=364; 101 deaths)

Reference

≥6.6 mmol/L/ ≥120 mg/dl
(n=276; 107 deaths)

1.48 (1.09-1.99)

(Svensson et al Eur Heart J 2005;26:1255)
Symptomatic hypoglycemia during hospitalisation in DIGAMI 2

(Mellbin et al. Heart 2009; 95:721)
Symptomatic hypoglycemia during hospitalisation in DIGAMI 2

Symptomatic hypoglycemia n=45

Adjusted for age, sex, smoking, diabetes duration, previous MI, CHF, renal function, PCI and CABG and updated mean fasting glucose

Total mortality

Unadjusted: Adjusted

Hypoglycaemic events identifies patients at high risk by other reasons e.g. low body weight and long diabetes duration

Death/Stroke/Reinfarction

Unadjusted Adjusted

(Mellbin et al. Heart 2009; 95:721)
### Summary of studies in patients with ACS and hyperglycemia

**Hyperglycemia and Acute coronary Syndrome. A Scientific Statement from the American Heart Association Diabetes Committee**

**Table: Study Results**

<table>
<thead>
<tr>
<th>Study</th>
<th>Glucose difference (intensive vs. control)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIGAMI I</td>
<td>9.6 vs 11.7 mmol/l (24-h)</td>
<td>1-year mortality 19 vs 26%</td>
</tr>
<tr>
<td>DIGAMI II</td>
<td>No significant difference</td>
<td>2-year mortality no difference</td>
</tr>
<tr>
<td>CREATE-ECLA</td>
<td>Higher 24 h-glucose in GIK-group (8.6 vs. 7.5 mmol/l)</td>
<td>30-day mortality no difference</td>
</tr>
</tbody>
</table>

"Control of hyperglycemia may be more critical than the dose of insulin administered"
Glycemic control and acute coronary syndromes
Summary of studies in patients with ACS and hyperglycemia

\[\text{(Deedwania et al. Circulation 2008;17:1610)}\]

**Summary of studies in patients with ACS and hyperglycemia**

**Hyperglycemia and Acute coronary Syndrome. A Scientific Statement from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity and Metabolism**

**P Deewania, Kosiborod M, Barret E, Ceriello A, Isley W, Mazzone T and Raskin P**

- Glucose levels should be part of evaluation of all patients with ACS (A)
- It is reasonable to consider intensive glucose control in patients with significant hyperglycemia (>10 mmol/L or >180 mg/dl) (B)
- Approximation towards normoglycemia seems as a reasonable goal (5.0 - 7.7 mmol/L or 90 - 140 mg/dl) (non-ICU <10 mmol/L) (C)
- Insulin intravenously is currently the most effective method of controlling blood glucose in intensive care and should be instituted as soon as feasible (non-ICU sc insulin) (B,C)
- Plans for future glucose control to be made for patients with diabetes, and impaired glucose tolerance (C)

**Guideline recommendations**

Diabetic patients with acute MI benefit from tight glucometabolic control. This may be accomplished by different treatment strategies.

(Deedwania et al. Circulation 2008;17:1610)
Future …

- Establish if metabolic modulation/control is beneficial or not (and time dependent) in ACS

  IMMEDIATE (GIK in ambulance, mortality)

  INTENSIVE (Insulin to target, ischemia size (MRI))

- Determine target glucose levels

- New treatment options

- New tools
Glycemic control and acute coronary syndromes
Summary of studies in patients with ACS and hyperglycemia

- Metabolic support with high dose GIK has no role in the treatment of ST-elevation AMI
- Hyperglycaemia is an important independent risk factor for events following AMI
- Diabetic patients should have an intensive glucose control after an AMI. Normalisation!? 
- Hypoglycaemic episodes during hospitalization do not influence long-term prognosis. Some patients more vulnerable
- Agents used for long-term glucose control may play an important role for future morbidity and mortality

New tools or regimens needed!
Management of cardiovascular disease

Acute coronary syndromes and intensive care

Time for question