Acute Coronary Syndromes
Acute and Chronic treatment

- Everything!!!!!!!
- Invasive approach
- Thrombolysis
- Anti-platelet agents
- Betablockers
- ACE-I
- Statins

Mostly based on subgroup analyses
Multifactorial Intervention in type 2 Diabetes
Euro Heart Survey Diabetes and the Heart

Evidence based medicine
The combined use of β-blockade, RAA-inhibition, antiplatelets and statins if not contraindicated

Patients from all day practice
110 centers
in 25 countries
n= 4 961
Coronary artery disease
with or without diabetes

One year follow up by management

Multifactorial Intervention in type 2 Diabetes

Euro Heart Survey Diabetes and the Heart

Impact of Evidence Based Medicine (EBM) on 1-year mortality

### Patient management in Clinical Practice
#### Euro Heart Survey Diabetes and the Heart

<table>
<thead>
<tr>
<th>Variable</th>
<th>Target</th>
<th>Outside</th>
<th>Target</th>
<th>Outside</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>98-03</td>
<td>%</td>
<td>2007</td>
<td>%</td>
</tr>
<tr>
<td>Blood lipids (mmol/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n=589 Cholesterol</td>
<td>&lt;5.0</td>
<td>53</td>
<td>&lt;4.5</td>
<td>68</td>
</tr>
<tr>
<td>n=532 LDL</td>
<td>&lt;3.0</td>
<td>57</td>
<td>&lt;1.8</td>
<td>93</td>
</tr>
<tr>
<td>n=559 HDL</td>
<td>&lt;1.0</td>
<td>37</td>
<td>&lt;1.0</td>
<td>37</td>
</tr>
<tr>
<td>n=585 Triglycerides</td>
<td>&lt;2.0</td>
<td>39</td>
<td>&lt;1.7</td>
<td>57</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>&lt;140/90</td>
<td>27</td>
<td>&lt;130/80</td>
<td>56</td>
</tr>
<tr>
<td>FP-glucose (mmol/l)</td>
<td>&lt;7.2</td>
<td>54</td>
<td>&lt;6.0</td>
<td>83</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>&lt;7.0</td>
<td>23</td>
<td>&lt;6.5</td>
<td>32</td>
</tr>
</tbody>
</table>

(Anselmino and Rydén. Data on file)
The difficult task of glycaemic control in patients with acute coronary syndrome

Glucose ?
The difficult task of glycaemic control in patients with acute coronary syndrome

- Hyperglycemia
  - Admission
    - Preexisting diabetes
    - Stress
    - Oxidative stress
    - Myocardial ischemia
    - Platelet aggregation
      - FFA
      - PAI levels

- Normoglycemia
  - Hospital course
    - Intensive insulin therapy or non-insulin treatment

Increased in-hospital and long-term mortality rate

(Adapted after Abbate et al. Eur Heart Jour 2005;26:1245)
Cardiac metabolic support
Glucose-insulin-potassium (GIK)
Glucose-insulin-potassium in myocardial infarction

Metaanalysis of hospital mortality in placebo controlled studies

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>No. of Patients</th>
<th>GIK Mortality (%)</th>
<th>Control Mortality (%)</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 (95% CI) 0.72 (0.57 - 0.90)
One life saved for 20 treated
Glucose-insulin-potassium in myocardial infarction
The CREATE-ECLA study

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)
Glucose-insulin-potassium in myocardial infarction
The CREATE-ECLA study

CREATE-ECLA investigators JAMA 2005;293:437
The difficult task of glycemic control in patients with acute coronary syndrome

HYPERGLYCEMIA

- Preexisting diabetes
- Stress
- Myocardial ischemia

Intensive insulin therapy or non-insulin treatment

NORMOGLYCEMIA

Increased in-hospital and long-term mortality rate

(Oxidative stress, FFA, Platelet aggregation, PAI levels)

(Adapted after Abbate et al. Eur Heart Jour 2005;26:1245)
DIGAMI 1 - Study design

Inclusion criteria

- Suspect AMI
- Symptom <24 hours
- Diabetes + B-glucose >11 mmol/L
- or B-glucose >11 mmol/L

Study protocol

Inclusion criteria: High risk, Low risk, +/- prior insulin

Strata: Control (3 months), Insulin-glucose i.v., Insulin s.c. (12 months)

Phase: Preinclusion

Hospital

Follow up

(Malmberg, Rydén et al J Am Coll Card 1995; 26:57)
DIGAMI 1 – Metabolic control

HbA1c
All patients

HbA1c Reduction

Stratum 1

HbA1c Reduction
DIGAMI 1 - Mortality

All patients

Stratum 1
DIGAMI 2 - Study outline and objectives
Confirm DIGAMI 1
Infusion or long-term insulin important?

Study protocol

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

Stratification
CV-risk
Prev. insulin

Follow up
1.9 ±1.0 years

Group 1
Insulin-Glucose infusion followed by
Multidose subcutaneous insulin

Group 2
Insulin-Glucose followed by
Conventional treatment

Group 3
Conventional treatment only

Patients no
1 253
474 (38%)
473 (38%)
306 (24%)

(Malmberg, Rydén et al Europ Heart J 2005;26:650)
Suspect MI + Type 2 diabetes or B-glucose >11 mmol/L

DIGAMI 2
Death/reinfarction/stroke

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

Group 1 vs Group 3
HR = 1.22 (0.95 - 1.56) p = 0.115

(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)
DIGAMI 2 – Blood glucose the first 24 hours

DIGAMI 15.4mmol/L

1. Insulin glucose infusion plus insulin
2. Insulin glucose infusion plus conventional treatment

(Data on file)
Glycemic control and acute coronary syndromes
Summary of studies in patients with ACS and hyperglycemia

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

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

Circulation 2008; 17:1610

<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 2</td>
<td>No significant</td>
<td>2-year mortality no difference</td>
</tr>
<tr>
<td></td>
<td>Target not reached intensive group</td>
<td></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”

(Deedwania et al. Circulation 2008;17:1610)
The difficult task of glycemic control in patients with acute coronary syndrome

Adapted after Abbate et al. Eur Heart Jour 2005;26:1245

HYPERGLYCEMIA

Preexisting diabetes
Stress
Myocardial ischemia
Oxidative stress
FFA
Platelet aggregation
PAI levels

HYPOGLYCEMIA

Intensive insulin therapy or non-insulin treatment
Renal failure
Malnutrition
Caloric intake
Associated diseases (Impaired counterregulation)

NORMOGLYCEMIA

INCREASED IN-HOSPITAL AND LONG-TERM MORTALITY RATE

(Adapted after Abbate et al. Eur Heart Jour 2005;26:1245)
Cardiac function during hypoglycemia- hemodynamic effects

Iv insulin (0.15U/kg) in six normal male subjects

(Fisher et al. Diabetologia 1987;30:841)
Cardiac function during hypoglycemi-arrytmogenic effects

Altered ventricular repolarization during hypoglycemia in patients with diabetes

Euglycemia

Hypoglycaemia

Prolonged repolarisation and prominent U-vave

QTC=456 ms
HR= 66 bpm

QTC=610 ms
HR= 61 bpm

(Marques et al. Diabet Med 1997;14:648)
Hyper- and hypoglycaemia and 2 year mortality risk in diabetic patients with acute coronary events.

- ≤3.0 mmol/L/ ≤55 mg/dl (n=44; 20 deaths) 1.93 (1.18-1.317)
- 3.1-6.5 mmol/L/ 56-119 mg/dl (n=364; 101 deaths) Referent
- ≥6.6 mmol/L/ ≥120 mg/dl (n=276; 107 deaths) 1.48 (1.09-1.99)

Adjusted data for clinical characteristics

Lowest blood glucose recorded during hospitalisation

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

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

Symptomatic hypoglycemia n=45

Total mortality
- **Unadjusted**
- **Adjusted**

Hypoglycaemic events seem to identify patients at high risk by other reasons such as lower body weight, CHF and longer diabetes duration.

Death/Stroke/Reinfarction
- **Unadjusted**
- **Adjusted**

(Mellbin et al. Heart 2009; 95:721)
Conclusions

Acute and Chronic treatment

- Everything!!!!!!!
- Invasive approach
- Thrombolysis
- Anti-platelet agents
- Betablockers
- ACE-I
- Statins

Mostly based on subgroup analyses

The need for insulin during and after a myocardial infarction

Accumulated evidence suggests

- Metabolic support with high dose GIK have no role in todays treatment of ST- elevation AMI
- Diabetic patients should have an intensive glucose control after an AMI. At least those with admission glucose ≥ 11mmol/l (DIGAMI 1)
- Optimal glucose levels and glucose lowering agent is not known

New tools or regimens needed!