Diabetes Mellitus, Insulin Resistance and ACS

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Outline

• Diabetes and CVD Risk
• CVD Risk Factor Differences
  — Blood Pressure
  — Lipids
  — Longer Term Glycemic Control (HbA1c)
  — Short Term Glycemic Control
• ACS Patients
  — Intravenous insulin protocols
  — Transition to subcutaneous insulin
  — Plans at Discharge
  — Follow-up post discharge
CHD Mortality and Hyperinsulinemia: Paris Prospective Study (n=943)

Diabetes and CVD Risk in Framingham Cohort
Age 35-64 Years--30 Year Follow-up

- CHD
- Stroke
- Int. Claudication
- Cardiac Failure
- CVD Total

Risk Ratio

Steno-2 Trial Results
Risk Factor Control in T2DM

Steno-2 Trial
Risk Factor Levels During Trial

Steno-2 Trial Results
All Cause Mortality in T2DM

Cumulative Incidence of Death (%)

Years of Follow-up

No. at Risk
Intensive therapy 80 78 75 72 65 62 57 39
Conventional therapy 80 80 77 69 63 51 43 30

RR=0.554  P=0.02

Diabetes and Lipid Extremes
Framingham Offspring
Men

Per cent

HDL-C<35  Total-C 240+  LDL-C 160+  Trig 250+  HDL-C<35
Non-Diabetic  Diabetic

p<0.001  p<0.001

Siegel Metabolism 1996; 96: 1267
Diabetes and Lipid Extremes Framingham Offspring Women

Siegel Metabolism 1996; 96: 1267
Risk Variables for a Metabolic Syndrome

- Fasting Glucose
- 2-Hour Glucose
- Body Mass Index
- Fasting Insulin
- 2-Hour Insulin
- HDL-C
- BP Diastolic
- BP Systolic
- Waist/Hip
- Trig

Meigs Diabetes 1997; 46:1594
Risk Variables for a Metabolic Syndrome

Hypertension

Central Metabolic Syndrome

Impaired Glucose Tolerance

Meigs Diabetes 1997; 46:1594
Natural History of Type 2 Diabetes

Insulin Sensitivity

Insulin Secretion

Kahn Diabetes 1994; 43: 1067
Typical Levels of Insulin Sensitivity

- White men
- Healthy women
- Postpartum pregnancy
- Aged, high CHO diet
- Mexican Americans
- Aged, ad lib diet
- Obese nondiabetic
- Women on OCP
- NIDDM

Insulin Sensitivity Index
($Si=10^{-4} \text{ min}^{-1} \text{ uU}^{-1} \text{ ml}^{-1}$)

Bergman Diabetes 1989; 38: 1518
Insulin Resistance and Atherosclerosis: Proposed Relationships

- Insulin resistance
  - Hyperinsulinemia
  - Impaired glucose tolerance
  - Hypertriglyceridemia
    - Decreased HDL-C
  - Essential hypertension

- Clinical diabetes

- Accelerated atherosclerosis

Reaven: Banting Lecture 1988
Insulin Resistance and Atherosclerosis: Proposed Relationships

- Hyperinsulinemia
- Impaired glucose tolerance
  - Stress & Catechols
  - Clinical diabetes
- Hypertriglyceridemia
  - Decreased HDL-C
- Essential hypertension

Accelerated atherosclerosis

- Insulin resistance
Lipid Metabolism and Insulin Resistance

Ginsberg JCI 2000; 106: 453
Adiposity and Vascular Inflammation

- Adipose cells
  - Interleukin-6
    - Interleukin -1
    - TNF alpha
    - TGF beta
    - C-reactive protein
    - Fibrinogen
    - CVD or Diabetes
  - +
  - -

Modified from Gabay NEJM 1999; 340: 448
Adipocyte, Weight Gain and Insulin Resistance

Wellen JCI 2003
# SICU Intensive Insulin Rx

## Leuven Trial (N=1548)

<table>
<thead>
<tr>
<th>Mortality Experience</th>
<th>Conventional Therapy</th>
<th>Intensive Insulin Therapy</th>
<th>Stat Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall 12 month</td>
<td>8%</td>
<td>4.6%</td>
<td>P=0.04</td>
</tr>
<tr>
<td>Overall 12 month (&gt;5 days SICU)</td>
<td>20.2%</td>
<td>10.6%</td>
<td>P=0.005</td>
</tr>
<tr>
<td>In-Hospital</td>
<td></td>
<td>↓ 34%</td>
<td></td>
</tr>
</tbody>
</table>

Insulin Therapy in ACS

• Diabetic patient proportion varies
• Infusions (usual care typical comparator)
  Insulin
  Glucose/Insulin/Potassium= (GIK)
• Varying lengths of intensive therapy
• Varying targets for glucose control
Death at 3 Days with Glucose-Insulin–Potassium Therapy in ST-Segment Elevation MI (OASIS-6 GIK and CREATE-ECLA)

<table>
<thead>
<tr>
<th>Factor</th>
<th>Levels</th>
<th>Relative Risk</th>
<th>Stat Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dL)</td>
<td>&lt;126</td>
<td>1.00</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>126-144</td>
<td>1.09</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;144</td>
<td>2.47</td>
<td></td>
</tr>
<tr>
<td>Potassium (mEq/L)</td>
<td>&lt;4</td>
<td>1.00</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>4-5</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;5</td>
<td>2.02</td>
<td></td>
</tr>
<tr>
<td>Fluid Balance</td>
<td>Negative</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neutral</td>
<td>1.14</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Positive</td>
<td>2.42</td>
<td></td>
</tr>
</tbody>
</table>

Diaz JAMA 2007; 298; 2399
Serum Potassium and Mortality in Acute MI (Cerner Database, n=38,689)

Diaz JAMA 2007; 298; 2399
Inpatient Insulin for ACS in CCU

Intravenous regular insulin
   Hourly glucose levels
   Re-adjust insulin dose hourly
   Higher doses of insulin
      Sepsis
      Catechols Rx
      Extreme obesity

Subcutaneous insulin
   Less acutely ill
   When oral feedings or meals
Traditional Subcutaneous insulin
  Sliding Scale Insulin (SSI)
  Regular or rapid acting Insulin before meals

Basal-Bolus Subcutaneous insulin
  Glargine
  0.4 mg/kg if glucose 140-200 mg/dl
  0.5 mg/kg if glucose 200-400 mg/dl
  Very rapid acting insulin before meals
    Total rapid-acting dose = total glargine
  Supplemental rapid-acting insulin before meals
    For glucose levels 150-200, 200-250, >250 mg/dl
Post Hospital Discharge
ACS Patient with Hyperglycemia

Is Insulin Needed?
Goal is HbA1c less than 7
Is Diabetes Education Needed?

Diet and Exercise
Oral Hypoglycemic Agents
  Metformin
    2-4 weeks to work
    only if Creat<1.3)
  Glipizide or other sulfonylureas
  Incretins (probably Rx by endocrinologist)
    DPP-4
    GLP drugs
Insulin regimens
  Glargine + before meal rapid acting
  Glargine + metformin
  70/30 insulin twice a day (2/3 dose in AM, 1/3 in PM)
### GRACE Registry
Predicting 6-Month Mortality after ACS Discharge

<table>
<thead>
<tr>
<th>Factor</th>
<th>Effect</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (10 yr)</td>
<td>10 yr</td>
<td>1.7 (1.63-1.84)</td>
</tr>
<tr>
<td>History of MI</td>
<td>yes/no</td>
<td>1.4 (1.20-1.59)</td>
</tr>
<tr>
<td>History of Cardiac Failure</td>
<td>yes/no</td>
<td>2.1 (1.80-2.47)</td>
</tr>
<tr>
<td>Pulse</td>
<td>30/min</td>
<td>1.3 (1.23-1.47)</td>
</tr>
<tr>
<td>BP systolic</td>
<td>20 mm</td>
<td>1.1 (1.06-1.17)</td>
</tr>
<tr>
<td>Creatinine serum</td>
<td>1 mg/dL</td>
<td>1.1 (1.12-1.23)</td>
</tr>
<tr>
<td>Cardiac enzyme elevation initially (y/n)</td>
<td>yes/no</td>
<td>1.5 (1.33-1.79)</td>
</tr>
<tr>
<td>ST segment depression</td>
<td>yes/no</td>
<td>1.5 (1.29-1.69)</td>
</tr>
<tr>
<td>No in-hospital PCI</td>
<td>yes/no</td>
<td>1.9 (1.30-1.88)</td>
</tr>
</tbody>
</table>

Eagle JAMA 2004; 291: 2727
Reducing CVD Risk
At ACS Discharge

• **Blood Pressure**
  
  US Goal in DM is < 130/80 mm/Hg  
  European guidelines consider albuminuria, eGFR  
  Use of 3 or more BP meds is common  
  In non-hyperglycemic pts  
  Beta blocker and thiazides may worsen glycemia

• **Lipids**
  
  US Goal has been LDL-C < 100 (possibly <70) mg/dl  
  Statin --moderate potency or high-potency  
  Triglycerides often elevated (> 200 mg/dl)  
  Diet and alcohol  
  Fibrates  
  Omega-3

• **Anti-platelet therapy**
PCI vs CABG in Diabetic Patients with Advanced CAD
FREEDOM Trial (n=1900)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>2 Years after Randomization</th>
<th>5 Years after Randomization</th>
<th>Patients with Event</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PCI</td>
<td>CABG</td>
<td>PCI</td>
<td>CABG</td>
</tr>
<tr>
<td>Primary composite†</td>
<td>121 (13.0)</td>
<td>108 (11.9)</td>
<td>200 (26.6)</td>
<td>146 (18.7)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>62 (6.7)</td>
<td>57 (6.3)</td>
<td>114 (16.3)</td>
<td>83 (10.9)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>62 (6.7)</td>
<td>42 (4.7)</td>
<td>98 (13.9)</td>
<td>48 (6.0)</td>
</tr>
<tr>
<td>Stroke</td>
<td>14 (1.5)</td>
<td>24 (2.7)</td>
<td>20 (2.4)</td>
<td>37 (5.2)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>9 (0.9)</td>
<td>12 (1.3)</td>
<td>73 (10.9)</td>
<td>52 (6.8)</td>
</tr>
</tbody>
</table>

Farkouh N Engl J Med 2012; 267: 2375
Summary
ACS with Insulin Resistance/Diabetes

• **Inpatient**
  - Insulin—target often 140 to 180 mg/dl
  - Potassium in normal range
  - Usual ACS care
  - Revascularization decision

• **Outpatient**
  - BP goal in USA <130/80 mm Hg
  - LDL-C goal in USA
    - <100 mg/dl (or <70 mg/dl)
    - moderate or high potency statin
  - HbA1c <7 with oral agents or insulins
  - Antiplatelet therapy
  - Revascularization decision