The Portland Diabetic Project: Hyperglycemia/Mortality Hypothesis

Perioperative Hyperglycemia increases the risk of mortality in patients undergoing CABG.
CABG Only 1987 - 2003

Mortality vs. Hyperglycemia

BG <200

1.6%
(n= 2886)

BG >200

6.0%
(n= 1073)

P<0.001
CABG Mortality by glucose sextile - 2003

- < 150: 0.6%
- 150 / 175: 1.4%
- 175 / 200: 2.4%
- 200 / 225: 4.0%
- 225 / 250: 5.6%
- > 250: 14%

P < 0.001

N = 3959

mg / dl
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Cardiac-related Mortality by BG quantile

- Cardiac-Related
- Non-Cardiac

mg / dl

< 150  150 / 175  175 / 200  200 / 225  225 / 250  >250

0%  5%  10%  15%

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### MVA of CABG Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-BG</td>
<td>&lt;0.001</td>
<td>1.02 (mg/dl)</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>&lt;0.001</td>
<td>5.7</td>
</tr>
<tr>
<td>Cardiogenic Shock</td>
<td>0.004</td>
<td>4.2</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.02</td>
<td>2.5</td>
</tr>
<tr>
<td>Reoperation</td>
<td>0.005</td>
<td>2.4</td>
</tr>
<tr>
<td>Operative Status</td>
<td>0.007</td>
<td>1.7</td>
</tr>
<tr>
<td>Age</td>
<td>0.003</td>
<td>1.05 / yr</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>0.002</td>
<td>3.1</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>0.01</td>
<td>0.98 / %</td>
</tr>
<tr>
<td>PVD / CVD</td>
<td>0.001</td>
<td>2.3</td>
</tr>
<tr>
<td>Hx Atrial Fibrillation</td>
<td>0.01</td>
<td>2.4</td>
</tr>
</tbody>
</table>

N = 2895

Area under the ROC curve = 0.891
Conclusion: AHA 1999

♥ Intraoperative and postoperative hyperglycemia in diabetics, adversely effects postoperative cardiac-related mortality in diabetic CABG patients

♥ Perioperative CABG mortality in diabetics might be reduced to that of the non-DM population through a CII infusion protocol which substantially and safely eliminates hyperglycemia.
Independent association of Isolated BG Measurements on Mortality

Hgb A-1C
BG-Preop
3-BG
BG-DOS
BG-POD1
BG-POD2
BG-POD3
Is Hyperglycemia in the peri-operative period associated with increased mortality in patients undergoing CABG?

Yes -- Independently associated:

Beyond 3rd POD in ICU and until 3rd POD on the floor

Mortality directly rises with 3-BG > 150 mg/dl

2x @ 150 - 175 mg/dl
4x @ 175 - 200 mg/dl
7x @ 200 - 225 mg/dl
8x @ 225 - 250 mg/dl
23x @ > 250 mg/dl
The Portland Diabetic Project: CII / Mortality Hypothesis

The Portland Protocol (Continuous Intravenous Insulin -- CII) lowers the incidence of mortality in patients undergoing CABG.
Insulin Infusions Reduce Mortality in Diabetic CABG Patients

Anthony P. Furnary, MD; Guangqiang Gao, MD;
Gary L. Grunkemeier, PhD; Kathryn J. Zerr, RN, MBA;
H. Storm Floten, MD; Albert Starr, MD

St Vincent Medical Center
Providence Health Systems

J Thorac Cardiovasc Surg 2003; 125:1007-21
Total CABG Patients 1987 - 2001: 13,649

Diabetic: 26%
Mean Age: 65
Sex: 65% male
Redo: 12%

n = 3,554
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Study Design

Non-randomized, Prospective interventional study

Two sequential groups:

- **Control n = 942**: Subcutaneous Insulin (SQI) q 4 hrs
  Target blood glucose < 200 mg/dl. 1987 - 1991

- **Study n = 2612**: Continuous Intravenous Insulin (CII)
  The “Portland CII Protocol”
  Titrated to target BG q 1-2 hrs. 1992 - 2001

✓ Endpoint: Hospital mortality
Overall Mortality = 3.2%

- Pump Failure: 54%
- Arrhythmia: 17%
- Neurologic: 19%
- Respiratory: 5%
- Renal Failure: 1%
- Infection: 3%
- Hemorrhage: 1%

Median = 11 days (0-68)
CABG Mortality: SQI vs. CII

- SQI: 5.3% (n=942)
- CII: 2.5% (n=2612)

P < 0.0001
# Multivariable Analysis of Mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin Infusion</td>
<td>0.001</td>
<td>0.43</td>
</tr>
<tr>
<td>Cardiogenic Shock</td>
<td>&lt;0.001</td>
<td>5.5</td>
</tr>
<tr>
<td>Renal failure</td>
<td>&lt;0.001</td>
<td>3.5</td>
</tr>
<tr>
<td>Reoperation</td>
<td>&lt;0.001</td>
<td>2.8</td>
</tr>
<tr>
<td>Operative Status</td>
<td>&lt;0.001</td>
<td>2.5</td>
</tr>
<tr>
<td>Age</td>
<td>0.001</td>
<td>1.05 / yr</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>0.001</td>
<td>3.2</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>0.003</td>
<td>0.98 / %</td>
</tr>
<tr>
<td>PVD / CVD</td>
<td>0.002</td>
<td>2.1</td>
</tr>
<tr>
<td>Hx Atrial Fibrillation</td>
<td>0.05</td>
<td>2.0</td>
</tr>
</tbody>
</table>

N = 2933

Area under the ROC curve = 0.874
### MVA of Risk-Adjusted Mortality*

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>STS Risk score &lt; 0.001</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>(35 Risk Factors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin Infusion</td>
<td>0.005</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Area under the ROC curve = 0.839

*External Risk Adjustment (n = 2834)
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CABG Mortality by BG quantile

P<0.0001

< 150: 1.6%
150/175: 1.4%
175/200: 2.3%
200/225: 4.1%
225/250: 6.0%
>250: 15%

mg / dl
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Ischemic DM Myocardial Metabolism

↑BG

↓Glycolysis

△ Membrane dysfunction
★ Negatively Inotropic
↑Free Radicals
★ Direct Toxicity
✓ Arrhythmogenic
★ Endothelial dysfunction

90% FFA Utilization

↑MVO₂

↓O₂

Accumulation of B-Oxidized FFA Intermediaries

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Cardiac-related Mortality by BG quantile

Cardiac-Related
Non-Cardiac

< 150 150 / 175 175 / 200 200 / 225 225 / 250 >250

mg / dl
Cardiac-Related Mortality: SQI vs. CII

- SQI: 4.4% (n=942)
- CII: 1.6% (n=2612)

P < 0.0001
**Summary: AATS 2002**

- **CII** independently reduced absolute CABG mortality by 57% as compared to SQI controls.

- **CII** lowers the incidence of cardiac related mortality.

- **CII** reduced risk-adjusted mortality by 50%.

- **CII** adds an independently protective effect on mortality to the constellation of risk factors in the STS risk model.
Conclusions: AATS 2002

♥ DM not the true risk factor for death following CABG
♥ Myocardial glyco-metabolic state influences mortality.
♥ The protective effect of CII may stem from improved glyco-metabolic control which enhances the effective utilization of excess glucose to improve myocardial energetics.
♥ Insulin infusions should become the standard of care for glycometabolic control in DM CABG patients.
# MVA of CABG Mortality --2003

<table>
<thead>
<tr>
<th>Variable</th>
<th>P value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CII</td>
<td>0.001</td>
<td>0.4</td>
</tr>
<tr>
<td>Cardiogenic Shock</td>
<td>&lt;0.001</td>
<td>5.6</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.009</td>
<td>2.6</td>
</tr>
<tr>
<td>Reoperation</td>
<td>&lt;0.001</td>
<td>3.3</td>
</tr>
<tr>
<td>Operative Status</td>
<td>&lt;0.001</td>
<td>2.5</td>
</tr>
<tr>
<td>Age</td>
<td>0.002</td>
<td>1.04 / yr</td>
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<tr>
<td>Unstable Angina</td>
<td>0.002</td>
<td>2.9</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>0.002</td>
<td>0.98 / %</td>
</tr>
<tr>
<td>Hx PVD / CVD</td>
<td>0.001</td>
<td>2.2</td>
</tr>
<tr>
<td>Hx Atrial Fibrillation</td>
<td>0.004</td>
<td>2.5</td>
</tr>
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</table>

N = 3293

Area under the ROC curve = 0.868

Year:
- 87
- 89
- 91
- 93
- 95
- 97
- 99
- 2001
- 2003

Non-DM LOS 9% CII

Graph shows the DM CABG Mortality rates from 1987 to 2003, with non-diabetic patients (Non-DM) and diabetic patients (DM Pts.) compared.
Do Continuous intravenous insulin infusions (CII) in DM CABG patients reduce postoperative mortality?

Yes -- CII independently reduce mortality by 60%