Microvascular Complications in Diabetes:
Perspectives on Glycemic Control to Prevent Microvascular Complications

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Chief Scientific and Medical Officer

Glycemic Control for Microvascular Complications: Is Late Too Late?

<table>
<thead>
<tr>
<th>Type 1 Diabetes</th>
<th>N</th>
<th>Duration of Diabetes</th>
<th>Baseline A1C</th>
<th>Follow Up (Yrs)</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stockholm</td>
<td>152</td>
<td>~18</td>
<td>6.4%</td>
<td>7</td>
<td>1995</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kumamoto</td>
<td>158</td>
<td>2-13</td>
<td>9.4%</td>
<td>0</td>
<td>1995</td>
</tr>
<tr>
<td>UGDP</td>
<td>116</td>
<td>~11</td>
<td>~7% (145 mg/dl)</td>
<td>~5</td>
<td>1971</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>11140</td>
<td>8</td>
<td>7.5%</td>
<td>5</td>
<td>2008</td>
</tr>
</tbody>
</table>

The Serial Position Effect
Microvascular Complications Risk in Diabetes

Discussion Outline:
Glycemia and Microvascular Complications

- Clinical Trials - A Brief History
  - Intensive glucose control and microvascular disease risk
  - A brief reminder of the Serial Position Effect
- Early vs. Late Intervention – A Clinical Perspective
  - EARLY = DCCT, UKPDS, Kumamoto
  - LATE = ACCORD, ADVANCE, VADT and SDIS
  - Updates from ACCORD
- A Rational Clinical Approach
  - Balancing Risk – Benefit with intensive glycemic control

Glycemic Control for Microvascular Complications: Is Late Too Late?
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The Impact of Early Intervention

Early Intensive Diabetes Therapy: Reduction in Microvascular Complications

Complications Risk in Diabetes

The Impact of Intensive Glycemic Control

DCCT and UKPDS Glycemic Control and Microvascular Risk

Early Intervention – Is It Truly Early? Benefit in Primary and Secondary Prevention

- Reduction in microvascular disease risk
  - Occurred with both primary and secondary prevention
  - Effect observed in DCCT, UKPDS and Kumamoto
Glycemic Control for Microvascular Complications: Is Late Too Late?

**Enduring Impact of Early Intervention**
EDIC and UKPDS

The Durable Effect of Early Intervention
EDIC and UKPDS
Follow up cohort with similar glycemic control for 4-10+ years
A1C achieved = ~8.0%


Glycemic Control for Microvascular Complications: Is Late Too Late?
The Impact Late Intervention

VADT: Effect of Intensive Glucose Lowering on Microvascular Complications in T2DM

<table>
<thead>
<tr>
<th>Complication</th>
<th>Microvascular Event</th>
<th>Impact in VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIABETIC RETINOPATHY</td>
<td>Proliferative retinopathy</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Nondiabetic</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Diabetic (n=104)</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Diabetic (n=497)</td>
<td>P=0.07</td>
</tr>
<tr>
<td>DIABETIC NEPHROPATHY</td>
<td>Doubling of serum creatinine</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Micro to macroalbuminuria</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Normal to micro/macroalbuminuria</td>
<td>P=0.02</td>
</tr>
<tr>
<td>DIABETIC NEUROPATHY</td>
<td>Peripheral neuropathy</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Autonomic neuropathy</td>
<td>P=0.07</td>
</tr>
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</table>

VADT Correction on Microalbuminuria

"On further examination of the data on albuminuria from the VADT we found that the data set that we used to evaluate the progression of disease was constructed improperly."

- As a result, the rates of progression to microalbuminuria and macroalbuminuria were reported (incorrectly).

"Both progression from normal to microalbuminuria or macroalbuminuria (P = 0.03) and progression from either normal or microalbuminuria to macroalbuminuria (P = 0.04) favor intensive treatment."

- Any progression of albuminuria is now statistically significant (P<0.01)

"We appreciate the opportunity to update our results."

ADVANCE Treatment Effect on Microvascular Outcomes

<table>
<thead>
<tr>
<th>Follow-up (months)</th>
<th>Intensive control</th>
<th>Standard control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>12</td>
<td>25</td>
<td>30</td>
</tr>
<tr>
<td>24</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>36</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>48</td>
<td>40</td>
<td>45</td>
</tr>
</tbody>
</table>

Stockholm Diabetes Intervention Study

How Late is too Late in T1DM?

SDIS Study Design
- Intensive insulin therapy – A1C 9.4 → 7.2
- Mean duration of diabetes at study entry ≈ 18 years
- Significant (but modest) reduction in rates of microvascular disease

When do "advanced" complications become too advanced?

Intensive Glycemic Control in Diabetes

Is It Safe? What are the Risks?

- Severe hypoglycemia risk
  - Increased ~3 fold with intensive therapy
  - ? predictor of adverse outcome/mortality (VADT, ACCORD)
- Increase in health care resource use
  - Increase near-term cost of care (clinic, education, meds, technology)
- Increased number and type of medications used
- Weight gain
  - Increase in body weight (~5-20 lbs)
  - Unknown long term impact on CV risk, risk factors
- Increased mortality risk?

Reducing the Risk of Complications

Intensive Glycemic Control in Type 1 Diabetes
A Final Note on ACCORD

Final Results - Microvascular and Eye Study Data

Conclusions – ACCORD Microvascular

• Intensive treatment of glycemia in the ACCORD cohort did not reduce the risk of composite measures of advanced microvascular outcomes

• Intensive therapy delayed the onset of albuminuria and some measures of eye complications and neuropathy

• Microvascular benefits of intensive therapy should be weighed against the potential for increased mortality, increased body weight, and the risk for severe hypoglycemia

ACCORD Eye Study Design

• Baseline and Year 4 comprehensive eye exams including:
  – Visual acuity measurements
  – Fundus photography of 7 standard stereoscopic fields
  – Central grading of the fundus photographs using the Early Treatment Diabetic Retinopathy Study (ETDRS) Classification of diabetic retinopathy

Summary of Microvascular Results

Through End of Study

<table>
<thead>
<tr>
<th>Glycemia</th>
<th>Blood Pressure</th>
<th>Lipid</th>
<th>N=2856 Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensive</td>
<td>Standard</td>
<td>Feno+statin</td>
</tr>
<tr>
<td>Intensive</td>
<td>9.2% (29/319)</td>
<td>8.1% (25/308)</td>
<td>5.3% (21/400)</td>
</tr>
<tr>
<td>Standard</td>
<td>11.4% (38/332)</td>
<td>9.4% (29/308)</td>
<td>7.6% (31/406)</td>
</tr>
<tr>
<td>TOTALS</td>
<td>10.4% (67/647)</td>
<td>8.8% (54/616)</td>
<td>6.5% (52/806)</td>
</tr>
</tbody>
</table>
ACCORD Eye Study
Conclusions

- **Intensive glycemia** and combination of fenofibrate and simvastatin reduced the proportion whose retinopathy progressed by about one-third
  - Effects were consistent across subgroups

- No statistically significant effect of **intensive blood pressure**
  - No subgroup with effect

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvascular</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UGDP</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>UKPDS</td>
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<tr>
<td>DCCT/EDIC</td>
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<td>SDIS</td>
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<tr>
<td>ACCORD</td>
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<tr>
<td>VADT</td>
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Treatment Considerations
Risk – Benefit and Intensive Therapies

"A few observations and much reasoning lead to error. Many observations and little reasoning lead to truth."

- Intensive glycemic control both early and late in diabetes
  - Significantly reduces the risk of microvascular complications
  - Increases the risk of severe hypoglycemia, weight gain, HCE
- Later intervention may limit the magnitude of these benefits on microvascular risk – and should be weighed against the potential mortality risk of very intensive intervention

Diabetes and Glycemic Control
A Rational Approach to Limit Complications

As low as possible
As early as possible
For as long as possible
As safely as possible
And as rationally as possible

Conclusions