Glycemic Control and the Impact on CVD Risk in Diabetes

The Case for Intensive Glucose Control

David M. Kendall, MD
Chief Scientific and Medical Officer
Glucose and CVD Risk: From UGDP to ACCORD

• Glycemic Control and Complications
  – A Brief History of Clinical Trials
  – The Serial Position Effect – What We Remember

• Recent Clinical Trials – Diabetes and CVD
  – Implications of ACCORD, ADVANCE and VADT
  – Intensive glycemic control and mortality risk – is it real?

• A Path Forward
  – Is intensive glycemic control still appropriate?
  – A1C targets
    ▪ ADA, AHA, ACC Position Statement
    ▪ A practical perspective
Glycemic Control in Diabetes
A Brief History of Intervention Trials

- UGDP
- Oxford Steno Kroc Dallas Oslo
- DCCT
- VADT
- ADVANCE
- ACCORD
- UKPDS
- PROactive
- VACS
- Kumamoto
- SDIS
- RECORD
- BARI -2D
- EDIC

The History of Clinical Trials
Impact of the “Serial Position Effect”

• Serial Position Effect
  – Recall varies as a function of an item's serial or temporal position
  – Described by German psychologist Herman Ebbinghaus (1850-1909)

• Recency effect = greatest recall of the most recent data

• Primacy effect = better recall of an initial item increased rehearsal and commitment to long-term memory

We remember best what we learn first – and last

The Serial Position Effect
Microvascular Complications Risk in Diabetes

Primacy Effect:
- UGDP
  - No benefit from early intensive Rx
  - Increase in mortality with selected therapies

Recency Effect:
- ACCORD VADT
  - No benefit from late intensive Rx
  - Potential for increase risk (hypo)
  - No impact on CVD ? Mortality risk
Early Intensive Diabetes Therapy: Reduction in Microvascular Complications

<table>
<thead>
<tr>
<th></th>
<th>DCCT</th>
<th>Kumamoto</th>
<th>UKPDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>9 → 7.1%</td>
<td>9+ → 7.2%</td>
<td>8 → 7%</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>63%</td>
<td>69%</td>
<td>17-29%</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>54%</td>
<td>70%</td>
<td>24-33%</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>60%</td>
<td>Improved</td>
<td>-</td>
</tr>
<tr>
<td>CV disease</td>
<td>NS</td>
<td>-</td>
<td>16%</td>
</tr>
</tbody>
</table>

Complications Risk in Diabetes
The Impact of Intensive Glycemic Control

What is the impact of intensive glucose control on CVD risk?

<table>
<thead>
<tr>
<th>Hemoglobin A1c</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relative Risk</td>
<td>1.0</td>
<td>2.0</td>
<td>4.0</td>
<td>6.0</td>
<td>8.0</td>
<td>10</td>
<td>12</td>
</tr>
</tbody>
</table>

DM Kendall. International Diabetes Center
Complications Risk in Diabetes
The Impact of Intensive Glycemic Control

What is the impact of intensive glucose control on CVD risk?

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<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>eAG – Glucose</td>
<td>126</td>
<td>154</td>
<td>183</td>
<td>212</td>
<td>240</td>
<td>269</td>
<td>298</td>
</tr>
</tbody>
</table>

DM Kendall. International Diabetes Center
Glycemic Control in Type 2 Diabetes
A1c During UKPDS and UKPDS Follow Up

UKPDS. Lancet 1998;352:837–53
Myocardial Infarction Hazard Ratio
UKPDS Follow Up

Intensive (SU/Ins) vs Conventional Glucose Control

HR (95%CI)

1.4
1.2
1.0
0.8
0.6
0.4
1997 1999 2001 2003 2005 2007

MI
HR=0.84 p=0.052

HR=0.85 p=0.014

UKPDS Follow Up
Initial Intensive Therapy and Risk of MI

Proportion with event

Years since randomization

Risk reduction 15% (3-26%)
p=0.014

P=0.01

UKPDS Follow Up
Initial Intensive Therapy and Mortality

Intensive (SU/Ins) vs Conventional Glucose Control

Hazard ratio for mortality

HR = 0.94
$p = 0.44$

HR = 0.87
$p = 0.006$

After Median 8.5 Years Post-trial Follow-up

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>RRR:</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>P:</td>
<td>0.029</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR:</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td>P:</td>
<td>0.0099</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR:</td>
<td>16%</td>
</tr>
<tr>
<td></td>
<td>P:</td>
<td>0.052</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR:</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>P:</td>
<td>0.44</td>
</tr>
</tbody>
</table>

RRR = Relative Risk Reduction, P = Log-rank

DCCT/EDIC: Early Intensive Glycemic Control Reduces Risk of CAD in Type 1 Diabetes

No evidence of reduction in CVD risk observed in DCCT

Early intensive therapy reduced CVD risk more than 10 years after the intervention

Glycemic Control and CVD Risk in Type 2 Diabetes

Implications of ACCORD, ADVANCE and VADT
Research Questions
ACCORD, ADVANCE and VADT

• ACCORD
  – In middle aged/older people with T2DM at high risk for CVD, does a strategy targeting A1C < 6.0% vs 7.5% reduce CVD risk?

• ADVANCE
  – Among individuals with T2DM are micro and macrovascular events be reduced by intensive glucose control (A1C<6.5%)?
    ▪ As compared to conventional Rx (community standard)

• VADT
  – In older males (VAMC) with established T2DM what is the relative effect of conventional vs. intensive glycemic control on CVD risk?
    ▪ Longstanding T2DM uncontrolled on oral agents and/or insulin
## Comparison of Recent Glycemia Trials
### ACCORD, ADVANCE and VADT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
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<tbody>
<tr>
<td>N</td>
<td>10,251</td>
<td>11,140</td>
<td>1,791</td>
</tr>
<tr>
<td>Mean Age</td>
<td>62</td>
<td>66</td>
<td>60.4</td>
</tr>
<tr>
<td>Duration of T2DM</td>
<td>10 yr</td>
<td>8 yr</td>
<td>11.5 yr</td>
</tr>
<tr>
<td>History of CVD</td>
<td>35%</td>
<td>32%</td>
<td>40%</td>
</tr>
<tr>
<td>BMI</td>
<td>32</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>Baseline A1C</td>
<td>8.3%</td>
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## Comparison of Recent Glycemia Trials

**ACCORD, ADVANCE and VADT**

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<td>9.4%</td>
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<tr>
<td>A1C Achieved</td>
<td>6.4% vs. 7.5%</td>
<td>6.5% vs. 7.3%</td>
<td>6.9% vs. 8.4%</td>
</tr>
<tr>
<td>RRR CVD Events</td>
<td>0.90 (0.78 – 1.04)</td>
<td>0.94 (0.84 – 1.06)</td>
<td>0.88 (0.74 – 1.05)</td>
</tr>
<tr>
<td>RRR Mortality</td>
<td>1.22 (1.01 – 1.46)*</td>
<td>0.93 (0.83 – 1.06)</td>
<td>1.07 (0.80 – 1.42)</td>
</tr>
</tbody>
</table>

## A Broader View of Complications and Diabetes: Implications of ACCORD, ADVANCE and VADT

<table>
<thead>
<tr>
<th>Study</th>
<th>A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>9 → 7.9 → 7</td>
</tr>
<tr>
<td>DCCT/EDIC</td>
<td>9  → 7.1</td>
</tr>
<tr>
<td>ACCORD</td>
<td>7.5  → 6.4</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>7.3  → 6.5</td>
</tr>
<tr>
<td>VADT</td>
<td>8.4  → 6.9</td>
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A Broader View of Complications and Diabetes
Implications of ACCORD, ADVANCE and VADT

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<thead>
<tr>
<th>Study</th>
<th>A1C</th>
<th>Microvascular</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>9 → 7.9 → 7</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>DCCT/EDIC</td>
<td>9 → 7.1</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>ACCORD</td>
<td>7.5 → 6.4</td>
<td>↓</td>
<td>↔</td>
<td>↑ ?</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>7.3 → 6.5</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>VADT</td>
<td>8.4 → 6.9</td>
<td>↓</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>


Median A1C Before & After Transition

Median A1C pre-post transition: 7.5 → 7.6
Mean A1C pre-post transition: 7.7 → 7.8

Median A1C pre-post transition: 6.4 → 7.2
Mean A1C pre-post transition: 6.6 → 7.4
### Primary & Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Events</th>
<th>Intensive to Standard Hazard Ratio (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Transition</td>
<td>380</td>
<td>0.90 (0.78, 1.03)</td>
<td>0.13</td>
</tr>
<tr>
<td>All Follow-Up</td>
<td>503</td>
<td>0.91 (0.81, 1.03)</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>Nonfatal Myocardial Infarction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Transition</td>
<td>207</td>
<td>0.79 (0.66, 0.95)</td>
<td>0.01</td>
</tr>
<tr>
<td>All Follow-Up</td>
<td>287</td>
<td>0.82 (0.70, 0.96)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Nonfatal Stroke</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Transition</td>
<td>72</td>
<td>0.99 (0.72, 1.38)</td>
<td>0.98</td>
</tr>
<tr>
<td>All Follow-Up</td>
<td>82</td>
<td>0.87 (0.65, 1.17)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Cardiovascular Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Transition</td>
<td>140</td>
<td>1.27 (0.99, 1.63)</td>
<td>0.07</td>
</tr>
<tr>
<td>All Follow-Up</td>
<td>187</td>
<td>1.29 (1.04, 1.60)</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>All-Cause Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-Transition</td>
<td>283</td>
<td>1.21 (1.02, 1.44)</td>
<td>0.03</td>
</tr>
<tr>
<td>All Follow-Up</td>
<td>391</td>
<td>1.19 (1.03, 1.38)</td>
<td>0.02</td>
</tr>
</tbody>
</table>
Identifying Higher Risk Patients
Intensive Glycemic Control in Type 2 Diabetes

• Conventional Wisdom:
  – Older individuals with established CVD    NO
  – Those who achieved lower A1C values     NO
  – Use of intensive insulin                NO
  – Individuals with longer duration diabetes MAYBE

• Who May Be at Risk with more intensive Rx
  – Longstanding poor control               YES
  – History of severe hypoglycemia          YES
  – Those less responsive to intensive Rx   MAYBE
Effect on Mortality by Baseline Characteristics: An ACCORD Trial Post-hoc Analysis

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Standard Glycemia</th>
<th>Intensive Glycemia</th>
<th>Intensive to Standard Hazard Ratio</th>
<th>Interaction P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65 years</td>
<td>2.57% (3382)</td>
<td>3.68% (3397)</td>
<td>0.4049</td>
<td></td>
</tr>
<tr>
<td>65-69</td>
<td>4.86% (947)</td>
<td>6.08% (938)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70-74</td>
<td>7.08% (537)</td>
<td>7.75% (516)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75+</td>
<td>12.45% (257)</td>
<td>12.64% (277)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical History Characteristics</th>
<th>Standard Glycemia</th>
<th>Intensive Glycemia</th>
<th>Intensive to Standard Hazard Ratio</th>
<th>Interaction P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior CVD</td>
<td>5.66% (1783)</td>
<td>7.62% (1825)</td>
<td>0.5327</td>
<td></td>
</tr>
<tr>
<td>No Prior CVD</td>
<td>3.05% (3340)</td>
<td>3.57% (3303)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diab Dur 0-5 years</td>
<td>4.26% (1455)</td>
<td>4.34% (1474)</td>
<td>0.4461</td>
<td></td>
</tr>
<tr>
<td>6-10</td>
<td>3.15% (1459)</td>
<td>4.62% (1472)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-15</td>
<td>3.34% (987)</td>
<td>4.33% (971)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16+</td>
<td>5.18% (1178)</td>
<td>6.88% (1163)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of Neuropathy</td>
<td>4.11% (1410)</td>
<td>7.84% (1327)</td>
<td>0.0008</td>
<td></td>
</tr>
<tr>
<td>No Neuropathy</td>
<td>3.84% (3646)</td>
<td>4.10% (3708)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
<th>Standard Glycemia</th>
<th>Intensive Glycemia</th>
<th>Intensive to Standard Hazard Ratio</th>
<th>Interaction P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>On Insulin</td>
<td>4.81% (1829)</td>
<td>6.23% (1750)</td>
<td>0.6740</td>
<td></td>
</tr>
<tr>
<td>Not On Insulin</td>
<td>3.49% (3291)</td>
<td>4.38% (3376)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lab Values</th>
<th>Standard Glycemia</th>
<th>Intensive Glycemia</th>
<th>Intensive to Standard Hazard Ratio</th>
<th>Interaction P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c &lt; 7.5</td>
<td>4.40% (1022)</td>
<td>4.83% (1036)</td>
<td>0.0444</td>
<td></td>
</tr>
<tr>
<td>7.5 to 8.4</td>
<td>4.09% (2200)</td>
<td>4.18% (2226)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.5+</td>
<td>3.60% (1887)</td>
<td>6.14% (1857)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Calles Escandon J et al. *Diabetes Care* 2010
Epidemiologic Relationships Between A1c and All-cause Mortality in the ACCORD Trial

Excess risk with intensive strategy vs standard occurred above A1c 7%

Average A1c %

6 7 8 9

Linear Prediction

Intensive strategy

Standard strategy

Riddle M et al. Diabetes Care 2010
Hypoglycemia and Risk and Mortality: Two Conceptual Approaches

- Does not explain increased mortality in ACCORD
  - Severe hypoglycemia was recorded
  - No association between severe hypoglycemia and increased mortality with intensive treatment
  - Hypoglycemia increased risk of mortality independent of treatment approach

- Logically was a mediator of increased mortality in ACCORD
  - Severe hypoglycemia associated with higher mortality
  - Intensive intervention associated with more severe hypoglycemia
  - Not all moderate hypoglycemia collected or confirmed
  - Corroborative data
Lessons from ACCORD
Severe Hypoglycemia and Mortality Risk

<table>
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<tr>
<th></th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
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<tr>
<td>Severe Hypo (%/ year)</td>
<td>Intensive 3.1%</td>
<td>Intensive 0.7%</td>
<td>Intensive 12.0%</td>
</tr>
<tr>
<td></td>
<td>Standard 1.1%</td>
<td>Standard 0.4%</td>
<td>Standard 4.0%</td>
</tr>
</tbody>
</table>

Annual mortality

1+ severe hypo 4.9%
No severe hypo 1.3%, 1.0%

Bonds et al. BMJ 2010;340:b4909
VADT: Hazard Ratio for Primary Outcome in Intensive Arm by Duration of Diabetes

VADT - Time to First CVD Event
Baseline Coronary Artery Calcium Score

A Broader View of CVD and Diabetes
Implications of ACCORD, ADVANCE and VADT

“A few observation and much reasoning lead to error.
Many observations and a little reasoning to truth”

Alexis Carrel

Prevention of cardiovascular disease through glycemic control in type 2 diabetes: A meta-analysis of randomized clinical trials

E. Mannucci

Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials

Kousik K Ray, Sreenu Patel, Naveed Sattar

Intensive glucose control and macrovascular outcomes in type 2 diabetes

F. M. Turnbull · C. Abraira · R. J. Anderson · R. P. Byington · J. P. Chalmers · W. C. Duckworth · G. W. Evans · H. C. Gerstein · R. R. Holman · T. E. Moritz · B. C. Neal · T. Ninomiya · A. A. Patel · S. K. Paul · F. Travert · M. Woodward

Mannucci E et al. *Nutr Metab Cardiovasc Dis* epub ahead of print. 8 May 2009
Prevention of CVD Thru Glycemic Control
CVD Events and Mortality Risk

Intensive Glycemic Control in Diabetes: Implications of ACCORD, ADVANCE and VADT

POSITION STATEMENT

Intensive Glycemic Control and the Prevention of Cardiovascular Events: Implications of the ACCORD, ADVANCE, and VA Diabetes Trials

A position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association

Jay S. Skyler, MD, MACE
Richard Bergenstal, MD
Robert O. Bonow, MD, MACC, FAHA
John Buse, MD, PhD
Prakash Deedwania, MD, FACC, FAHA
Edwin A. M. Gale, MD
Barbara V. Howard, PhD
M. Sue Kirkman, MD
Mikhail Kosiborod, MD, FACC
Peter Reaven, MD
Robert S. Sherwin, MD

Association (ADA) to recommend an A1C goal of <7% for most adults with diabetes (6), recognizing that more or less stringent goals may be appropriate for certain patients. Whereas many epidemiologic studies and meta-analyses (7,8) have clearly shown a direct relationship be-
Glycemic Targets in Adults

• Lowering of A1C to at or below 7%
  – Significantly reduces risk of microvascular complications of diabetes
  – *Does not* reduces the risk of CVD events in short term studies
    ▪ But *does not* significantly increase mortality
  – If initiated soon after diagnosis, long-term reduction in CVD risk

• Analysis suggest a small (but incremental) benefit in microvascular outcomes with A1C values closer to normal
  – Later use of intensive treatment may reduce the magnitude of impact

*Higher and lower targets appropriate for some individuals*

*Individualization of targets essential*

Individualizing Glycemic Targets in Diabetes

- **6.0%**
  - Patient age
  - Disease duration
  - Comorbidities
  - Established Complications: None

- **7.0%**
  - Behavioral – social - economic
  - Higher motivation, knowledge
  - Greater self-care capacity, insight, support

- **8.0%**
  - Hypoglycemia risk
  - Less motivated, non-adherent
  - Limited self-care capacity, insight support

Diabetes and Glycemic Control
A Rational Approach to A1C Targets

As low as possible
As early as possible
For as long as possible
As safely as possible
And as rationally as possible
Intensive Glycemic Control and Complications Risk in Diabetes

…After observation and analysis, when you find that anything agrees with reason and is conducive to the good and benefit of one and all, then accept it and live up to it

Buddha (c. 563 - c. 483 BC)