Implications of the ACCORD Trial

Perspectives on Glycemic Control and CVD Risk?

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

Timeline:
- 1960
- 1970
- 1980
- 1990
- 2000
- 2010
Remember the History of Clinical Trials
The Serial Position Effect

- Serial position effect
  - Recall varies as a function of an item's serial or temporal position
  - Initially described by German psychologist Herman Ebbinghaus
- 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 intensive Rx
- Potential for increase risk (hypo)
- No reduction in 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>
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<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>
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Complications Risk in Diabetes
The Impact of Intensive Glycemic Control

DM Kendall. International Diabetes Center
DCCT and UKPDS
Glycemic Control and Microvascular Risk

Complications Risk in Diabetes
The Impact of Intensive Glycemic Control

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

<table>
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<th>Hemoglobin A1c</th>
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<th>12</th>
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<tr>
<td>eAG – Glucose</td>
<td>126</td>
<td>154</td>
<td>183</td>
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DM Kendall. International Diabetes Center
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<td>Relative Risk of Complications</td>
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DM Kendall. *International Diabetes Center*
CVD Risk and Diabetes
Have We Become Too “Gluco-centric”?

ADA Standards of Care

• Section on glucose control:

• Section on CVD prevention:

• Mention of positive impact of glycemic control in section on CVD prevention:

ADA standards of care have not stated that glycemic control can limit CVD risk

Support the need for RCTs to assess the hypothesis

Standards of Medical Care in Diabetes – 2010
Diabetes Care 33 (Suppl 1), 2010
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

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<td>Mean Age</td>
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<td>Duration of T2DM</td>
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<td>35%</td>
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<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>
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<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>
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<tr>
<td>RRR Mortality</td>
<td><strong>1.22 (1.01 – 1.46)</strong>*</td>
<td>0.93 (0.83 – 1.06)</td>
<td>1.07 (0.80 – 1.42)</td>
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A Broader View of CVD and Diabetes
Implications of ACCORD, ADVANCE and VADT

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# A Broader View of CVD and Diabetes

Implications of ACCORD, ADVANCE and VADT

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Treatment Considerations
Risk – Benefit of Intensive Therapy in T2DM

If we knew what it was we were doing, it wouldn’t be research.”
-- Albert Einstein

• Do these findings suggest a need to alter glycemic targets?
  – Established benefit on microvascular disease at or below A1C of 7%
  – Limited evidence of CVD benefit

• Which patients benefit the most? The least?
  – Early vs. late intervention, younger vs. older, healthier vs not?
  – Not well tested in current trials (particularly in younger, healthier)
  – Higher baseline A1C (>8.5%) associated with higher risk of mortality

• Does A1C predict risk and/or benefit and/or mortality?
  – Is treatment strategy critical?
  – Impact of severe hypoglycemia?
Epidemiologic Relationships Between A1c and All-cause Mortality in the ACCORD Trial

• Does A1C achieved predict a risk for all-cause mortality?
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, Snehira K, 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
Ray KK. Lancet. 2009;373(9677):1765-72
Treatment Considerations
Risk – Benefit and Intensive Therapies

• Intensive glycemic control both early and late in diabetes
  – Significantly reduces the risk of microvascular complications
  – *May* reduce the risk of CVD events (meta-analyses)
  – Increases the risk of severe hypoglycemia, weight gain, HCE
  – *Does not* significantly increase mortality risk across studies

• Later intervention may limit the magnitude of these benefits

Selected higher risk individuals may be appropriate for less intensive treatment and individualized (higher) A1C targets

*Higher baseline A1C, limited response to intensive therapy*
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, MACP
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-
Intensive Glycemic Control in Diabetes: Implications of ACCORD, ADVANCE and VADT

• Glycemic targets in diabetes
  – Lowering A1C to < 7% significantly lowers the risk of microvascular complications in both type 1 and type 2 diabetes
  – More intensive glycemic control does not further reduce CVD risk

• Long-term follow-up suggests that A1C < 7% in the years following diagnosis is associated with a reduction in CVD risk

• Given these data, the general A1C target of < 7% appears reasonable
  – For selected patients lower or higher A1C targets may be appropriate

• For CVD risk reduction in patients with diabetes:
  – Continue to follow recommendations for BP, lipids, aspirin, tobacco

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
Perspectives on Glycemic Control to Prevent Complications 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)
Thank You