A Fork in the Road: Navigating Through New Terrain

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Spokane, Washington
Chairperson, Professional Practice Committee
American Diabetes Association
Disclosure - Duality of Interest

• Consultant, Advisory Board
  – Amylin Pharmaceuticals, Boehringer Ingelheim, Eli Lilly

• Speakers Bureau
  – Amylin, Eli Lilly, Merck, Novo Nordisk, sanofi-aventis
Complications Risk in Diabetes
The Impact of Intensive Glycemic Control

DM Kendall. International Diabetes Center
Cardiovascular Disease and Diabetes

~65% of deaths are due to CV disease

Coronary heart disease deaths ↑2- to 4-fold

Stroke risk ↑2- to 4-fold

Heart failure ↑2- to 5-fold

Cardiovascular complications of T2DM

T2DM = type 2 diabetes mellitus

Bell DSH. *Diabetes Care*. 2003;26:2433-41
Glycemic Control for Vascular Complications: Is Late Too Late?

Years of Diabetes Diagnosis
# Glycemic Control for Vascular 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>DCCT</td>
<td>1441</td>
<td>&lt;5</td>
<td>9.0%</td>
<td>6.5</td>
<td>1993</td>
</tr>
<tr>
<td>Stockholm (SDIS)</td>
<td>102</td>
<td>~18</td>
<td>9.4%</td>
<td>7</td>
<td>1993</td>
</tr>
<tr>
<td>EDIC</td>
<td>1394</td>
<td>~10</td>
<td>7.1-8%</td>
<td>10+</td>
<td>2000+</td>
</tr>
<tr>
<td><strong>Type 2 Diabetes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UGDP</td>
<td>823</td>
<td>&lt;1</td>
<td>~7%</td>
<td>~5</td>
<td>1971</td>
</tr>
<tr>
<td>Kumamoto</td>
<td>110</td>
<td>2-10</td>
<td>9.4</td>
<td>8</td>
<td>1995</td>
</tr>
<tr>
<td>VACSDM</td>
<td>153</td>
<td>8</td>
<td>9.3</td>
<td>1 ½</td>
<td>1995</td>
</tr>
<tr>
<td>UKPDS</td>
<td>5102</td>
<td>&lt;1</td>
<td>~9%</td>
<td>10</td>
<td>1998/2008</td>
</tr>
<tr>
<td>Accord</td>
<td>10251</td>
<td>10</td>
<td>8.3</td>
<td>3 ½</td>
<td>2008</td>
</tr>
<tr>
<td>Advance</td>
<td>11140</td>
<td>8</td>
<td>7.5</td>
<td>5</td>
<td>2008</td>
</tr>
<tr>
<td>VADT</td>
<td>1791</td>
<td>11+</td>
<td>9.4</td>
<td>6</td>
<td>2008</td>
</tr>
</tbody>
</table>
## 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>7.9 → 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% (NS)</td>
</tr>
</tbody>
</table>

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

Stockholm Diabetes Intervention Study
Is Late Intervention for Glycemic Control of Benefit?

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

The Durable Effect of Early Intervention
Long Term Follow up from EDIC and UKPDS

Follow up cohort with similar glycemic control for 4-10+ years
A1C achieved = ~8.0%

Retinopathy Incidence (%)

Glycemic Control for Prevention of Macrovascular Complications:

- ACCORD
- VADT
- ADVANCE
- UKPDS + EDIC
- UKPDS
- VA
- UGDP
- Kumamoto

Years of Diabetes Diagnosis:

- At Risk
- Diabetes
- 5
- 10
- 15
- 20+
Comparison of Recent Glycemia Trials
ACCORD, ADVANCE and VADT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACCORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10,251</td>
</tr>
<tr>
<td>Mean Age</td>
<td>62</td>
</tr>
<tr>
<td>Duration of T2DM</td>
<td>10 yr</td>
</tr>
<tr>
<td>History of CVD</td>
<td>35%</td>
</tr>
<tr>
<td>BMI</td>
<td>32</td>
</tr>
<tr>
<td>Baseline A1C</td>
<td>8.3%</td>
</tr>
<tr>
<td>A1C Achieved</td>
<td>6.4% vs. 7.5%</td>
</tr>
<tr>
<td>RRR CVD Events</td>
<td>0.90 (0.78 – 1.04)</td>
</tr>
<tr>
<td>RRR Mortality</td>
<td>1.22 (1.01 – 1.46)*</td>
</tr>
</tbody>
</table>

# Comparison of Recent Glycemia Trials
## ACCORD, ADVANCE and VADT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<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>
<td>7.5%</td>
<td>9.4%</td>
</tr>
<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>
<th>Microvascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>9 → 7.9 → 7</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>DCCT/EDIC</td>
<td>9 → 7.1</td>
<td>↓ ↓</td>
</tr>
<tr>
<td>ACCORD</td>
<td>7.5 → 6.4</td>
<td>↔ / ↓</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>7.3 → 6.5</td>
<td>↓</td>
</tr>
<tr>
<td>VADT</td>
<td>8.4 → 6.9</td>
<td>↓</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>
<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>


Epidemiologic Relationships Between A1c and All-cause Mortality in the ACCORD Trial

- Does A1C achieved predict a risk for all-cause mortality?

Epidemiologic Relationships Between A1c & All-Cause Mortality

- Effects of Intensive Glucose Lowering in the Management of Patients with Type 2 Diabetes Mellitus in ACCORD
  - Baseline A1c >8.5% predicted 64% higher risk of death
    - ? Legacy from prior poor control
    - ? More B cell destruction
    - ? adherence
  - Also history of taking aspirin
  - Self-report of having neuropathy

## ACCORD Glycemia Trial: Cause of Cardiovascular Deaths

<table>
<thead>
<tr>
<th>Category</th>
<th>Intensive N (%)</th>
<th>Standard N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexpected/Presumed CVD</td>
<td>86 (1.7)</td>
<td>67 (1.3)</td>
</tr>
<tr>
<td>MI</td>
<td>19 (0.4)</td>
<td>13 (0.3)</td>
</tr>
<tr>
<td>CHF</td>
<td>23 (0.5)</td>
<td>16 (0.3)</td>
</tr>
<tr>
<td>CV Procedure</td>
<td>10 (0.2)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>4 (0.1)</td>
<td>10 (0.2)</td>
</tr>
<tr>
<td>Non-CV Procedure</td>
<td>1 (0.02)</td>
<td>3 (0.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>9 (0.2)</td>
<td>11 (0.2)</td>
</tr>
<tr>
<td>Other CVD</td>
<td>8 (0.2)</td>
<td>10 (0.2)</td>
</tr>
<tr>
<td><strong>Total CV</strong></td>
<td><strong>257</strong></td>
<td><strong>203</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>135</strong></td>
<td><strong>94</strong></td>
</tr>
</tbody>
</table>
Severe Hypoglycemia Requiring Medical Assistance

Intensive Group Annual Incidence Rate = 3.3%
Standard Group Annual Incidence Rate = 1.0%
ADVANCE: Severe Hypoglycemia and Adverse Clinical Outcomes

Intensive glycemic therapy increased all-cause and cardiovascular mortality because there was more overall hypoglycemia with intensive therapy.

Hypoglycemia and CV Disease

Hypoglycemia → Hemodynamic → Thrombotic → Ischemia

Hypoglycemia → Inflammatory

Arrhythmia → Inflammatory

Wright R et al Diabetes/ Metabolism Research and Reviews, 2008
Potential Mechanisms of Hypoglycemia-Induced Mortality

- Cardiac arrhythmias due to abnormal cardiac repolarization in high-risk patients (IHD, cardiac autonomic neuropathy)
- Increased thrombotic tendency/decreased thrombolysis
- Cardiovascular changes induced by catecholamines
  - Increased heart rate
  - Silent myocardial ischemia
  - Angina and myocardial infarction
Effect of Experimental Hypoglycemia on QT Interval

5.0 mM

QTc = 456 ms
HR = 66 bpm

2.5 mM

QTc = 610 ms
HR = 61 bpm
QT Interval in Subjects With Type 2 Diabetes During Experimental Hypoglycemia (2.5 mM)

Vascular disease and diabetes: is hypoglycaemia an aggravating factor?

Table 1. Summary of haemodynamic responses to hypoglycaemia

<table>
<thead>
<tr>
<th>Haemodynamic modality</th>
<th>Response</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate Blood pressure</td>
<td>Increases Systolic BP increases Diastolic BP decreases Central pressure falls</td>
<td>$\beta_1$ adrenoceptor $\alpha$ and $\beta_2$ adrenoceptors</td>
</tr>
<tr>
<td>Cardiac output Myocardial contractility ECG changes</td>
<td>Increases Increases T wave flattening or inversion ST depression QT prolongation</td>
<td>$\beta_1$ adrenoceptor $\beta_1$ adrenoceptor $\beta$ adrenoceptor hypokalaemia</td>
</tr>
</tbody>
</table>
Hematologic and Inflammatory Responses to Acute Hypoglycemia

- Haemodynamic changes
  - ↑ Endothelin
  - ↑ Plasma viscosity
  - ↑ Factor VIII
  - ↑ vWF
  - Platelet activation
  - Neutrophil activation
  - ↑ CRP

  - Vasoconstriction
  - ↓ Blood flow
  - Capillary closure
  - ↑ Coagulation
  - Thrombosis
  - Endothelial damage
  - Atherogenesis

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

- Intensive Glycemic Control in Diabetes
  - Lowering A1C to < 7% significantly reduces the risk of microvascular complications in both type 1 and type 2 diabetes (DCCT, UKPDS, ACCORD)
  - *Does not* reduce the risk of CVD events in short term studies
  - *Does not* significantly increase mortality risk across studies (meta-analyses)

- Adverse effects of more intensive therapies
  - 3-fold greater rates of severe hypoglycemia and risk of significant weight gain
  - Increase in mortality risk in selected populations

*For some patients lower or higher A1C targets may be appropriate*

Identifying Higher Risk Patients
Intensive Glycemic Control in Type 2 Diabetes

• Conventional Wisdom:
  – Older individuals with established CVD \( \text{NO} \)
  – Those who achieved lower A1C values \( \text{NO} \)
  – Use of insulin therapy \( \text{MAYBE} \)
  – Individuals with long duration diabetes \( \text{MAYBE} \)

• Who May Be at Risk with more intensive Rx
  – Longstanding poor control \( \text{YES} \)
  – History of severe hypoglycemia \( \text{YES} \)
  – Those less responsive to intensive Rx \( \text{MAYBE} \)
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

And in the setting of multi-risk factor management
Glycemic Recommendations for Nonpregnant Adults with Diabetes

<table>
<thead>
<tr>
<th>A1C</th>
<th>&lt;7.0%*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprandial capillary plasma glucose</td>
<td>70–130 mg/dl* (3.9–7.2 mmol/l)</td>
</tr>
<tr>
<td>Peak postprandial capillary plasma glucose†</td>
<td>&lt;180 mg/dl* (&lt;10.0 mmol/l)</td>
</tr>
</tbody>
</table>

- Goals should be individualized based on*:
  - duration of diabetes
  - age/life expectancy
  - comorbid conditions
  - known CVD or advanced microvascular complications
  - hypoglycemia unawareness
  - individual patient considerations
- More or less stringent glycemic goals may be appropriate for individual patients.
- Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals.

Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak 1.5–2 h after a meal.
Managing Hypertension in Diabetes

Treatment Targets – Treatment Approaches
Implications of Recent Trials
Blood Pressure Goal in Diabetes
< 130 extrapolated from benefits in nephropathy

Viberti GC et al. JAMA, 1993
Lebovitz H et al. Kidney Int, 1994
Bakris GL. Hypertension, 1997

Estacio R et al. Diabetes Care, 2000
Type 2 Diabetes and Blood Pressure: BP Control and Risk in the ACCORD and ADVANCE Era

~ 15% reduction in risk for each 10 mm Hg decrease in SBP

ADVANCE Trial
Blood Pressure Intervention

- 11,140 subjects – Type 2 diabetes and HTN
  - Treated with fixed dose combo (ACEI-diuretic) vs usual care
  - Blood pressure differential ~5 mm Hg (140.3 vs 134.7)

Multi-Risk Factor Intervention in Diabetes: The ACCORD Trial

**BP Trial**
- **Intensive** (SBP<120)
- **Standard** (SBP<140)

**Lipid Trial**
- **Group A**
  - Statin only
  - 1383
- **Group B**
  - Statin+Fibrate
  - 1374

**Multi-drug therapy**
- Systematic titration
- Target driven approach

*Primary analysis compares marginals for main effects*

Effects of Intensive Blood Pressure Control
The ACCORD Trial

![Graph showing the effects of standard and intensive blood pressure control.](image)

Effects of Intensive Blood Pressure Control
The ACCORD Trial

More intensive control of SBP did not further reduce CVD risk in type 2 diabetes

The ACCORD Trial
Effects of Intensive Blood Pressure Control in Type 2 Diabetes

<table>
<thead>
<tr>
<th>Event</th>
<th>Intensive Events (%/yr)</th>
<th>Standard Events (%/yr)</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Events</td>
<td>208 (1.87)</td>
<td>237 (2.09)</td>
<td>0.88 (0.73-1.06)</td>
<td>0.20</td>
</tr>
<tr>
<td>Total Mortality</td>
<td>150 (1.28)</td>
<td>144 (1.19)</td>
<td>1.07 (0.85-1.35)</td>
<td>0.55</td>
</tr>
<tr>
<td>CV Death</td>
<td>60 (0.52)</td>
<td>58 (0.49)</td>
<td>1.06 (0.74-1.52)</td>
<td>0.74</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>126 (1.13)</td>
<td>146 (1.28)</td>
<td>0.87 (0.68-1.10)</td>
<td>0.25</td>
</tr>
<tr>
<td>Nonfatal Stroke</td>
<td>34 (0.30)</td>
<td>55 (0.47)</td>
<td>0.63 (0.41-0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>Total Stroke</td>
<td>36 (0.32)</td>
<td>62 (0.53)</td>
<td>0.59 (0.39-0.89)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Reduced rate of CVA and of progression of macroalbuminurinia with more intensive blood pressure lowering

### Table 2: Serious Adverse Events and Clinical Measures after Randomization.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intensive Therapy (N=2362)</th>
<th>Standard Therapy (N=2371)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Serious adverse events — no. (%)‡</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event attributed to blood-pressure medications</td>
<td>77 (3.3)</td>
<td>30 (1.27)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypotension</td>
<td>17 (0.7)</td>
<td>1 (0.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Syncope</td>
<td>12 (0.5)</td>
<td>5 (0.21)</td>
<td>0.10</td>
</tr>
<tr>
<td>Bradycardia or arrhythmia</td>
<td>12 (0.5)</td>
<td>3 (0.13)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>9 (0.4)</td>
<td>1 (0.04)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Adverse laboratory measures — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium &lt; 3.2 mmol/liter</td>
<td>49 (2.1)</td>
<td>27 (1.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Potassium &gt; 5.9 mmol/liter</td>
<td>73 (3.1)</td>
<td>72 (3.0)</td>
<td>0.93</td>
</tr>
<tr>
<td>Elevation in serum creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;1.5 mg/dl in men</td>
<td>304 (12.9)</td>
<td>199 (8.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;1.3 mg/dl in women</td>
<td>257 (10.9)</td>
<td>168 (7.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Estimated GFR &lt; 30 ml/min/1.73 m²</td>
<td>99 (4.2)</td>
<td>52 (2.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
SO WHAT BP SHOULD WE TARGET?
### Systolic BP Targets in Diabetes

**Does the Evidence Support SBP Targets < 130?**

<table>
<thead>
<tr>
<th>Trial</th>
<th>N</th>
<th>Mean SBP less intense</th>
<th>Mean SBP more intense</th>
<th>CVD Risk Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHEP</td>
<td>583</td>
<td>155*</td>
<td>143*</td>
<td>22-56%</td>
</tr>
<tr>
<td>Syst-Eur</td>
<td>492</td>
<td>162</td>
<td>153</td>
<td>62-69%</td>
</tr>
<tr>
<td>HOT</td>
<td>1,501</td>
<td>144**</td>
<td>140**</td>
<td>30-67%</td>
</tr>
<tr>
<td>UKPDS</td>
<td>1,148</td>
<td>154</td>
<td>144</td>
<td>32-44%</td>
</tr>
<tr>
<td>ABCD</td>
<td>470</td>
<td>138</td>
<td>132</td>
<td>No CVD reduction</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>11,140</td>
<td>140</td>
<td>135</td>
<td>8-14%</td>
</tr>
</tbody>
</table>

* Communication - Sara Pressel: mean BP at 3 yrs of F/U

** BP in diabetes + non-diabetes population
Why weren’t the BP targets changed?
No evidence of harm < 130.
Definite evidence of benefit < 140
ADVANCE suggested benefit < 135
If you target 140, then most people will be satisfied with close enough and not get < 140
Individualizing Goals: Decision Points

• # Drugs
  – Little evidence above three

• Orthostatic hypotension

• Side effects from medications
  – Dizziness
  – Bradycardia
  – Drug interactions

• How low is too low for diastolic blood pressure?
J-Shaped curve with Blood Pressure: INVEST

Bangalore S et al.
Circulation 122:2142, 2010
Proper Measurement of Blood Pressure

- Straight back chair
- Arm resting on table
- Center of cuff at heart line
- Feet flat on floor
Assure Proper Fit of Blood Pressure Cuff
Ambulatory BP Monitoring

- ABPM is warranted for evaluation of “white-coat” HTN in the absence of target organ injury.

- Ambulatory BP values are usually lower than clinic readings.

- Awake, individuals with hypertension have an average BP of <135/85 mmHg and during sleep <120/75 mmHg.

- BP drops by 10 to 20% during the night; if not, signals possible increased risk for cardiovascular events.
Managing Lipids in Diabetes

Treatment Targets – Treatment Approaches

Implications of ACCORD
## The ACCORD Trial
### Lipid Study Protocol

### BP Trial

<table>
<thead>
<tr>
<th>Intensive (SBP&lt;120)</th>
<th>Standard (SBP&lt;140)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive Glycemic Control (HbA1c&lt;6%)</td>
<td>1178</td>
</tr>
<tr>
<td>Standard Glycemic Control (HbA1c 7-7.9%)</td>
<td>1184</td>
</tr>
</tbody>
</table>

### Lipid Trial

<table>
<thead>
<tr>
<th>Group A Statin only</th>
<th>Group B Statin+Fibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenofibrate or Placebo</td>
<td>5128*</td>
</tr>
<tr>
<td>Background statin LDL 60-180 HDL &lt; 50 and TG &lt;750</td>
<td>5123*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2362*</th>
<th>2371*</th>
<th>2753*</th>
<th>2765*</th>
</tr>
</thead>
</table>

*Primary analysis compares marginals for main effects

The ACCORD Trial
Lipid Study – Effect on Plasma Lipids

Published at www.nejm.org March 14, 2010 (10.1056/NEJMoa1001286)
No significant added benefit (in reducing MI, stroke or CVD death) with addition of fibrate to statin therapy

Post-hoc analyses suggesting potential benefit in those with lowest HDL-c (< 34 mg/dl) and higher TG (> 204 mg/dl)

Published at www.nejm.org March 14, 2010 (10.1056/NEJMoa1001286)
### Primary Outcome By Treatment Group and Baseline Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Fenofibrate % Events (# in grp)</th>
<th>Placebo % Events (# in grp)</th>
<th>Feno to Placebo Hazard Ratio</th>
<th>Interaction P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>10.5% (2765)</td>
<td>11.3% (2753)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LDL-c Tertile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=84 mg/dl</td>
<td>9.4% (938)</td>
<td>12.2% (891)</td>
<td></td>
<td>0.1212</td>
</tr>
<tr>
<td>85-111 mg/dl</td>
<td>9.9% (934)</td>
<td>11.2% (922)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=112 mg/dl</td>
<td>12.4% (877)</td>
<td>10.6% (927)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HDL-c Tertile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=34 mg/dl</td>
<td>12.2% (964)</td>
<td>15.6% (906)</td>
<td></td>
<td>0.2374</td>
</tr>
<tr>
<td>35-40 mg/dl</td>
<td>10.1% (860)</td>
<td>9.5% (866)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=41 mg/dl</td>
<td>9.1% (925)</td>
<td>9.0% (968)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Triglyceride Tertile</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=128 mg/dl</td>
<td>9.9% (891)</td>
<td>11.3% (939)</td>
<td></td>
<td>0.6422</td>
</tr>
<tr>
<td>129-203 mg/dl</td>
<td>10.5% (924)</td>
<td>9.9% (913)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=204 mg/dl</td>
<td>11.1% (934)</td>
<td>12.8% (888)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Trig/HDL combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG204+ /HDL&lt;=34</td>
<td>12.4% (485)</td>
<td>17.3% (456)</td>
<td></td>
<td>0.0567</td>
</tr>
<tr>
<td>All Others</td>
<td>10.1% (2264)</td>
<td>10.1% (2284)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>A1c Median</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1c &lt;= 8.0</td>
<td>8.7% (1324)</td>
<td>10.6% (1335)</td>
<td></td>
<td>0.2045</td>
</tr>
<tr>
<td>A1c 8.1+</td>
<td>12.2% (1435)</td>
<td>11.9% (1415)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Lab Measures During Follow-up

<table>
<thead>
<tr>
<th>Laboratory Measures (no. (%))</th>
<th>Fenofibrate (N=2765)</th>
<th>Placebo (N=2753)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT ever &gt; 3X ULN</td>
<td>52 (1.9%)</td>
<td>40 (1.5%)</td>
<td>0.21</td>
</tr>
<tr>
<td>ALT ever &gt; 5X ULN</td>
<td>16 (0.6%)</td>
<td>6 (0.2%)</td>
<td>0.03</td>
</tr>
<tr>
<td>CK ever &gt; 5X ULN</td>
<td>51 (1.9%)</td>
<td>59 (2.2%)</td>
<td>0.43</td>
</tr>
<tr>
<td>CK ever &gt; 10X ULN</td>
<td>10 (0.4%)</td>
<td>9 (0.3%)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Serum creatinine elevation

<table>
<thead>
<tr>
<th></th>
<th>Fenofibrate (N=2765)</th>
<th>Placebo (N=2753)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women ever &gt; 1.3 mg/dl</td>
<td>235 (27.9%)</td>
<td>157 (18.7%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Men ever &gt; 1.5 mg/dl</td>
<td>698 (36.7%)</td>
<td>350 (18.5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Post-randomization incidence of microalbuminuria ( > 30 to < 300 mg/g*): 1050 (38.2%) vs. 1137 (41.6%) (P = 0.01)

Post-randomization incidence of macroalbuminuria ( > 300 mg/g*): 289 (10.5%) vs. 337 (12.3%) (P = 0.03)
**ACCORD Eye Study: Fenofibrate decreased risk of progression of retinopathy**

**Table 2. Effects of Intensive Glycemic Control, Fenofibrate, and Intensive Blood-Pressure Control on Progression of Diabetic Retinopathy and Moderate Vision Loss.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Progression of Diabetic Retinopathy</th>
<th>Adjusted Odds Ratio (95% CI)</th>
<th>P Value</th>
<th>Moderate Vision Loss</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyslipidemia therapy†</td>
<td>0.60 (0.42–0.87)</td>
<td>0.006</td>
<td></td>
<td>0.95 (0.79–1.14)</td>
<td>0.57</td>
<td></td>
</tr>
<tr>
<td>With fenofibrate</td>
<td>52/806 (6.5)</td>
<td></td>
<td></td>
<td>227/956 (23.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With placebo</td>
<td>80/787 (10.2)</td>
<td></td>
<td></td>
<td>233/950 (24.5)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The ACCORD Study Group. NEJM 2010;363:233-244
Lowering LDL Cholesterol

- Primary goal = LDL cholesterol <100 mg/dl (LDL-C < 70 an option)
  - Statin (+MNT) added in those with known CVD or at higher risk
  - Alternative = 30-40% reduction in LDL-c

Targeting Triglycerides and HDL-c

- Low HDL-C + high TG = most common pattern of dyslipidemia
- Managing TG and HDL-C
  - Limited evidence that intervention with fibrate on top of statin further reduces CV risk (may be benefit for retinopathy and nephropathy)
  - Data of addition of niacin to statin remains under study
Antiplatelet Agents in Diabetes, 2011

**Primary Prevention (75–162 mg/day):**

- Type 1 or type 2 diabetes at increased CV risk (10 yr risk > 10%), including most men > 50 yr or women > 60 yr who have at least one additional major risk factor (family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria) (C)
- Aspirin should not be recommended for CVD prevention for adults with diabetes at low CVD risk (10-year CVD risk <5%) (C)
- In patients in these age-groups with multiple other risk factors (e.g. 10-year risk 5–10%), clinical judgment is required. (E)

**Secondary prevention (75–162 mg/day):**

- Use aspirin therapy as a secondary prevention strategy in those with diabetes with a history of CVD (A)
- For patients with CVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used. (B)

ADA Clinical Practice Recommendations, Diabetes Care, January 2011
### Basis for Change in Recommendation

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Relative risk</th>
<th>Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belch (2008)</td>
<td>2539</td>
<td>0.87</td>
<td>(0.49 - 1.87) NS</td>
</tr>
<tr>
<td>Ogawa (2008)</td>
<td>1276</td>
<td>1.09</td>
<td>(0.82-1.46) NS</td>
</tr>
</tbody>
</table>

Belch J et al. BMJ 2008; 357:a1840  
Ogawa H et al. JAMA
ADA – Summary of Recommendations for Adults with Diabetes

2011 Standards of Care

Treatment targets for diabetes as recommended remain unchanged as evidence supports:

1. Targeting A1C < 7% (for reduction in risk of microvascular disease)
2. SBP target < 130 supported by evidence of reduction in risk of stroke and microvascular disease progression
3. LDL lowering with statin (LDL<100 or ↓ 30-40%) — Further reduction in CVD risk (with added fibrate) of potential benefit if low HDL-c and high TG
Cardiovascular Events: Steno-2 vs ACCORD

Steno-2: Cardiovascular Events

ACCORD: 1° outcome (composite nonfatal MI, nonfatal CVA, CVD death)

Should treatment and goals be standardized or individualized?

some one lied to you!

one size does not fit all!!
Heterogeneity of Type 2 Diabetes

- Obese versus Lean
- Slowly progressive versus rapidly progressive
- Abnormal Fasting Glucose
- Abnormal Postprandial Glucose
- High Insulin Secretion or Low Insulin Secretion
- Insulin Resistance or High Insulin Sensitivity
- High CVD Risk or low CVD Risk
- CVD present or CVD absent
- CKD present or CKD absent
- Age of the patient

} Combination of both
Atherosclerosis Timeline

Endothelial Dysfunction

- Foam Cells
- Fatty Streak
- Intermediate Lesion
- Atheroma
- Fibrous Plaque
- Complicated Lesion/Rupture

From first decade
From third decade
From fourth decade

Growth mainly by lipid accumulation
Smooth muscle and collagen
Thrombosis, hematoma

Remember, the Vasculature is Like a Tree

Does it make sense to separate out complications between microvascular and macrovascular?

Field Study: Showed benefit of fenofibrate on retinopathy and neuropathy

ACE-I Therapy: benefits retinopathy, (in type 1), nephropathy and cardiovascular events (type 2)

Lipid lowering therapy: alters progression of neuropathy (in epidemiologic studies)
Thank You