Disclosure to Participants

- Notice of Requirements For Successful Completion
  - Please refer to learning goals and objectives
  - Learners must attend the full activity and complete the evaluation in order to claim continuing education credit/hours

- Conflict of Interest (COI) and Financial Relationship Disclosures:
  - Presenter: Pat Rafferty, PharmD, BCPS, CDE – No COI/Financial Relationship to disclose

- Non-Endorsement of Products:
  - Accredited status does not imply endorsement by AADE, ANCC, ACPE or CDR of any commercial products displayed in conjunction with the educational activity

- Off-Label Use:
  - Participants will be notified by speakers if any product used for a purpose other than for which it was approved by the FDA is used.

Glycemic Control for patients with Cardiovascular Disease or at high risk for CVD: How low should we go?

CDC National Statistics Report 2014

- 29.1 million with Type 2 Diabetes in U.S.
- Cardiovascular death rates 1.7x higher in adults > 18 yo
- Hospital rates for MI 1.8 x higher
- Hospital rates for CVA 1.5x higher
- 65% of death due to Cardiovascular disease

Initial Treatment of Type 2 Diabetes

- UKPDS – 5102 newly diagnosed Type 2, 7.5% with CVD, 10 years treatment
- Intensive control (FPG < 108) vs. Standard control (FPG < 270)
- BP arm: INT 144/82, STD 154/87
- A1c achieved: INT 7.0, STD 7.9

Initial treatment of Type 1 Diabetes

- DCCT/EDIC – 1441 Type 1 patients, no prior CVD, dz duration < 1 year, mean age 27
- 6.5 years INT vs STD, 20+ years follow-up
- During DCCT – INT A1c 7.2, STD 9.1
- During EDIC – both arms A1c 8.0
Legacy Effect / Metabolic Memory?

- DCCT/EDIC – Risk decreased 42% (aggregate CVD risk), Decrease in MI/CVA/CV death by 57%
- UKPDS – INT arm – RRR 24% microvascular disease, 15% MI, 17% DM-related death
  – Metformin – dec. MI 33%, death 27%, micro 27%

DCCT/EDIC and CAN

All differences statistically significant.

Legacy Effect / Metabolic Memory

- If we accept the theory that cardiovascular effects of early, intensive glucose therapy result in tissue changes that can persist, we must also accept corollary that years of poor control may result in anatomic changes that are not easily reversed with intensive glycemic control.

ACCORD Trial

- 10251 Type 2, 40-79 with CVD or 55-79 with 2 CVD risk factors, A1c 7.5 – 9%
- A1c < 6.0% (INT) vs. 7-7.9% (STD)
- Lipid arm (statin + fibrate vs. statin)
- BP arm: SBP < 120 vs. < 140
- Trial stopped early – HR 1.22, 1.1 – 1.4%
  – 257 death (INT) vs. 203 deaths (STD)

ADVANCE Trial

- 11140 Type 2 patients, > 55yo with at least one CVD risk factor
- Gliclazide to achieve A1c ≤ 6.5
- BP: Perindopril/Indapamide vs. Placebo
  – Dec. Microvasc 14%, Dec. death 14%
- No difference found in Glucose arm of study

NEJM 2014;371:1392-1406
VADT Trial

- 1791 vets (97% male) with poorly controlled Type 2
- Goal absolute decrease A1c by 1.5% INT
- Metformin + Rosiglitazone (+/- Insulin)
- Glimeperide + Rosiglitazone (+/- Insulin)
- No effect on CV events or mortality

NEJM 2009;360:129-139

ACCORD ADVANCE VADT

<table>
<thead>
<tr>
<th>Study</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
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<tbody>
<tr>
<td>N</td>
<td>10,211</td>
<td>11,140</td>
<td>1,791</td>
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<tr>
<td>Age (years)</td>
<td>62</td>
<td>66</td>
<td>60</td>
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<tr>
<td>Duration of study (yrs)</td>
<td>3.5</td>
<td>3.0</td>
<td>3.6</td>
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<tr>
<td>Duration of DM (yrs)</td>
<td>10</td>
<td>8</td>
<td>11.5</td>
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<tr>
<td>INT A1c/STD A1c</td>
<td>6.4/7.5</td>
<td>6.4/7.0</td>
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<tr>
<td>CVD at baseline</td>
<td>32%</td>
<td>32%</td>
<td>40%</td>
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<tr>
<td>Primary CVD endpoint</td>
<td>↓10% (NS)</td>
<td>↓4% (NS)</td>
<td>↓13% (NS)</td>
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<tr>
<td>Mortality</td>
<td>↓22% (p=0.04)</td>
<td>↓7% (NS)</td>
<td>↓6.5% (NS)</td>
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<tr>
<td>CV Mortality</td>
<td>↓35% (p=0.02)</td>
<td>↓12% (NS)</td>
<td>↓25% (NS)</td>
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<tr>
<td>Renal Outcomes</td>
<td>Dec. 32%</td>
<td>Dec. 21%</td>
<td>Dec. 33%</td>
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NEJM 2009;360:129-139

ACCORD ADVANCE VADT

<table>
<thead>
<tr>
<th>Study</th>
<th>MicroVIE</th>
<th>CVD</th>
<th>Mortality</th>
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<tr>
<td>UKPDS</td>
<td>↓</td>
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<tr>
<td>DCCT/EDIC*</td>
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NEJM 2009;360:129-139

CAUSE OF DEATH INTENSIVE GROUP STANDARD GROUP

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<tr>
<th>CAUSE OF DEATH</th>
<th>INTENSIVE GROUP</th>
<th>STANDARD GROUP</th>
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<tbody>
<tr>
<td>UNEXPECTED/PRESUMED CVD</td>
<td>86</td>
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<tr>
<td>MYOCARDIAL INFARCTION</td>
<td>19</td>
<td>13</td>
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<tr>
<td>CONGESTIVE HEART FAILURE</td>
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<td>16</td>
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<td>CARDIOVASCULAR PROCEDURE</td>
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<tr>
<td>SUDDEN DEATH</td>
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<td>10</td>
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<tr>
<td>STROKE</td>
<td>7</td>
<td>11</td>
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<tr>
<td>CANCER</td>
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<td>59</td>
</tr>
<tr>
<td>NON-CANCER/NON-CVD</td>
<td>50</td>
<td>36</td>
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<tr>
<td>INDETERMINATE</td>
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<tr>
<td>TOTAL</td>
<td>282</td>
<td>242</td>
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Diabetes Care 2008;31:1913-1919

Why increased mortality in ACCORD?

- Overly rapid decrease and maintenance of low A1c
- Effects of severe hypoglycemia
- High doses of (?) harmful medications
- Weight gain with intensive treatment
- Chance

Lower A1c in ACCORD

- Patients in INT group who failed to decrease A1c from baseline had greatest death risk
- Death in INT arm linked with A1c > 8.5%, risk lowest when A1c near 6%
- Increased risk in INT arm found for patients whose A1c decreased little or none
Hypoglycemia in ACCORD
- Found to contribute to 1 death in INT arm
- Patients with A1c 7-8% had most events of severe hypoglycemia
- Study design flaws:
  - Clinics not required to document BG in hypoglycemic events
  - Blood glucose not measured at time of death

**Doses of (?) Harmful Medications - SU**
- Nurses’ Health Study (2014) – 4902 women with Type 2 w/o CVD baseline
- Use of SU associated with inc. risk CHD, HR 2.15 for > 10 years use
- WHY? – Hypoglycemia, weight gain, loss of myocardial ischemic preconditioning
- WHY? – Effect of DM duration, loss of B-cell response?
Use of basal insulin

- ORIGIN trial – patients with short-duration T2 and high CV risk, tx basal insulin > 6yrs
  - NO effect on CV events or incidence of cancer
- Dose (0.2 – 0.5 units/kg) – too low for CV event?
- 47% on Metformin – counter effect?
- 59% with prior CV event

NEJM 2012;367:319-328

Use of TZDs

- FDA lifted CV restrictions on Rosiglitazone after RECORD trial
- PROactive found no increase in CV events
- Concerns: edema, bone fx, bladder cancer
- ACCORD – end of trial 95% Metformin, 87% SU, 92% TZD, 77% basal, 55% prandial
  - Exenatide available at the time – use??

NEJM 2012;367:319-328

Weight gain with Intensive treatment

- 28% of INT group gained ≥ 10kg, 14% of STD group in ACCORD
- ADVANCE: No reported weight gain
- VADT: STD group gained 9 pounds, INT group gained 18 pounds

NEJM 1999;341:1097-105

Chance finding in ACCORD?

- Analysis by Lachin found:
  - No significant difference in baseline factors
  - Risk of hypoglycemia increased as A1c increased
  - Mean A1c not the mechanism for increased mortality
  - Type 1 (false +) error – concern with early termination of glycemic arm of study
  - No biological mechanism yet found

Diabetes Care 2010;33:Issue 12
Meta-Analyses of Intensive Glycemic Control in Type 2 Diabetes

Boussageon (2011) – 13 trials – no benefit of INT glucose control on death – dec. risk of non-fatal MI and renal dz
Ray (2009) – 5 trials (33040 patients) – all Type 2, 17% decrease in non-fatal MI, 15% dec. in CVD events, no affect on CVA or all-cause mortality
Turnbull (2009) – 4 trials (27049 patients), all Type 2; 9% dec. risk of CVD events, 15% dec. risk of MI, mortality not affected

Meta-Analyses:  Friend or Foe?
Individualizing glycemic treatment

- Individualize A1c target before treatment
  - Patients with CAD at baseline vs. those with risk factors
- Individualize A1c target by response to therapy
  - Highest mortality in ACCORD in patients who failed to dec A1c by > 0.5% after 4-12 months therapy

Why bother to treat A1c aggressively in advanced T2 diabetes?

- Strong evidence for decrease in microvascular risk, especially renal
- Meta-analyses show decreased risk of CVD events, especially risk of MI
- Lowest possible A1c without risk of hypoglycemia and/or weight gain

Abbreviations

- ACCORD – The Action to Control Cardiovascular Risk in Diabetes Study
- ADVANCE – Action in Diabetes and Vascular Disease: Preterax + Diamicron Modified Release Controlled Evaluation
- UKPDS – UK Prospective Diabetes Study
Abbreviations

• VADT – Veterans Affairs Diabetes Trial
• PROactive – PROspective pioglitazone Clinical Trial in macroVascular Events
• ORIGIN – Outcome Reduction with an Initial Glargine Intervention

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