Update on Diabetes - 2010

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Editor, Journal of Diabetes
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New York, NY
Multiplicities of interest

- My patients with diabetes
- Consultant/advisor: BMS/Astra Zeneca, Merck, Novartis, Dainippon Sumitomo Pharma America, Forest Laboratories, Boehringer Ingelheim, Biodel, Medtronics
- Speaker: Merck, NovoNordisk, GSK, Boehringer Ingelheim, Medtronics
- Stockholder: Baxter International, CVS Caremark, Roche Holdings, St Jude Medical, Novartis
Update on Diabetes - 2010

- Diabetes epidemiology
- ACCORD glycemia: further understanding of outcome
  - Hypoglycemia effect
  - Different A1c-outcome relationship of standard vs. intensive arms
  - Microvascular effects
- ACCORD lipids and blood pressure
- Understanding A1c use for diagnosis and for treatment
- Type 1 diabetes treatment: The STAR-3 trial
Diabetes prevalence: Spain

Valdés et al Med Clin (Barc) 2007 129 352
Diabetes prevalence: US (percent)

National Diabetes Surveillance System. Available at: http://www.cdc.gov/diabetes
Diabetes prevalence: Asia (percent)

Ramachandran et al. Lancet 2010; 375: 408–18
Diabetes prevalence: world(/10^6)

Meetoo et al. British Journal of Nursing 2007;16:1002
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Action to Control Cardiovascular Risk in Diabetes (ACCORD): Severe Hypoglycemia

- Annual rates: intensive 3.3% vs. standard 1.1%.
- Interaction of hypoglycemia with treatment:
  - 9,546 persons without severe hypoglycemia
    - Mortality risk 24% ↑ in intensive treatment group
  - 705 persons with ≥1 severe hypoglycemia
    - Mortality ~3-fold greater than among those not experiencing hypoglycemia
    - Mortality risk 60% ↓ in intensive treatment group

ACCORD: severe hypoglycemia

Bonds et al. BMJ 2010;340:b4909
Hypoglycemia vs. mortality: metaregression analysis

<table>
<thead>
<tr>
<th></th>
<th>Mortality Odds Ratio</th>
<th>Severe hypoglycemia, % ↑ in intervention groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proactive, UKPDS, ADVANCE</td>
<td>↓ 0.08 to 0.24</td>
<td>0.2-0.8%</td>
</tr>
<tr>
<td>ACCORD, VADT</td>
<td>↑ 0.24 to 0.36</td>
<td>1.5-3.0%</td>
</tr>
</tbody>
</table>
## ACCORD: mortality

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVD death</td>
<td>135</td>
<td>94</td>
</tr>
<tr>
<td>Unexpected/sudden</td>
<td>86</td>
<td>67</td>
</tr>
<tr>
<td>Myocardial</td>
<td>19</td>
<td>13</td>
</tr>
</tbody>
</table>

Two thirds were unexpected/sudden death

<table>
<thead>
<tr>
<th></th>
<th>Intensive</th>
<th>Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV procedure</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Stroke</td>
<td>9</td>
<td>11</td>
</tr>
<tr>
<td>Other CVD</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>
Adverse effect of insulin intensification from oral monotherapy, mortality risk vs. A1c, n=20,005

Currie et al. Lancet, 2010
ACCORD: mortality vs. on-trial A1c

Higher mortality on standard treatment with A1c >8% or <7%

Higher mortality on intensive treatment with:
- Lesser 1-year A1c ↓
- Worse mean A1c

Diabetes Care 2010;33:983-990
## ACCCORD microvascular outcomes

### Table: ACCCORD microvascular outcomes

<table>
<thead>
<tr>
<th></th>
<th>Intensive glycaemia control</th>
<th>Standard glycaemia control</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>At transition to standard therapy (February, 2008)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>4517</td>
<td>4577</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>6.3% (5.9–7.0%)</td>
<td>7.6% (7.0–8.2%)</td>
<td></td>
</tr>
<tr>
<td>Fasting serum glucose</td>
<td>4232</td>
<td>4292</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>5.88 (4.94–7.33)</td>
<td>8.16 (6.66–9.93)</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>4524</td>
<td>4583</td>
<td>0.0144</td>
</tr>
<tr>
<td></td>
<td>127 (116–138)</td>
<td>128 (116–139)</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>4524</td>
<td>4583</td>
<td>0.0003</td>
</tr>
<tr>
<td></td>
<td>67 (60–74)</td>
<td>68 (61–75)</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol in women</td>
<td>1634</td>
<td>1633</td>
<td>0.0050</td>
</tr>
<tr>
<td></td>
<td>1.22 (1.04–1.45)</td>
<td>1.19 (1.01–1.40)</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol in men</td>
<td>2610</td>
<td>2682</td>
<td>0.0014</td>
</tr>
<tr>
<td></td>
<td>1.01 (0.85–1.22)</td>
<td>0.98 (0.83–1.17)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>4245</td>
<td>4316</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>1.43 (1.01–2.10)</td>
<td>1.59 (1.11–2.36)</td>
<td></td>
</tr>
<tr>
<td>Body-mass index (kg/m²)</td>
<td>3768</td>
<td>3789</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>33 (29–37)</td>
<td>32 (28–36)</td>
<td></td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>4395</td>
<td>4466</td>
<td>0.9612</td>
</tr>
<tr>
<td></td>
<td>87.5 (73.4–107.0)</td>
<td>87.5 (72.5–107.0)</td>
<td></td>
</tr>
<tr>
<td>Urine albumin:creatinine ratio</td>
<td>4297</td>
<td>4380</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>(mg/mmol)</td>
<td>1.19 (0.64–3.42)</td>
<td></td>
</tr>
</tbody>
</table>

Accord microvascular. Lancet 2010;376:419
Glycemic groups: to transition

<table>
<thead>
<tr>
<th>Glycemic group</th>
<th>Intensive Events/n</th>
<th>Intensive %</th>
<th>Standard Events/n</th>
<th>Standard %</th>
</tr>
</thead>
<tbody>
<tr>
<td>First composite</td>
<td>443/5107</td>
<td>8.7</td>
<td>444/5108</td>
<td>8.7</td>
</tr>
<tr>
<td>Second composite</td>
<td>1591/5107</td>
<td>31.2</td>
<td>1659/5108</td>
<td>32.5</td>
</tr>
<tr>
<td>Neph-1: incident microalbuminuria</td>
<td>399/3204</td>
<td>12.5</td>
<td>494/3232</td>
<td>15.3</td>
</tr>
<tr>
<td>Neph-2: incident macroalbuminuria</td>
<td>138/4334</td>
<td>3.2</td>
<td>199/4361</td>
<td>4.6</td>
</tr>
<tr>
<td>Neph-3: ESRD</td>
<td>911/5085</td>
<td>2.1</td>
<td>112/5108</td>
<td>2.2</td>
</tr>
<tr>
<td>Neph-4: doubling of SCr or &gt;20 U eGFR decrease</td>
<td>2701/5025</td>
<td>53.6</td>
<td>2627/5034</td>
<td>52.2</td>
</tr>
<tr>
<td>Neph-5: any of Neph-2, Neph-3, or Neph-4</td>
<td>2788/5107</td>
<td>54.6</td>
<td>2760/5108</td>
<td>54.0</td>
</tr>
<tr>
<td>Eye-1: photocoagulation or vitrectomy</td>
<td>350/4886</td>
<td>7.2</td>
<td>347/4910</td>
<td>7.1</td>
</tr>
<tr>
<td>Eye-2: cataract surgery</td>
<td>447/4886</td>
<td>9.1</td>
<td>495/4910</td>
<td>10.1</td>
</tr>
<tr>
<td>Eye-3: three-line worsened visual acuity</td>
<td>911/5085</td>
<td>17.9</td>
<td>951/5085</td>
<td>18.7</td>
</tr>
<tr>
<td>Eye-4: severe loss of vision*</td>
<td>258/4651</td>
<td>5.5</td>
<td>273/4689</td>
<td>5.8</td>
</tr>
<tr>
<td>Neuro-1: neuropathy (MNSI score &gt;2.0)</td>
<td>1277/2815</td>
<td>45.4</td>
<td>1338/2791</td>
<td>47.9</td>
</tr>
<tr>
<td>Neuro-2: loss of vibratory sensation</td>
<td>766/4209</td>
<td>18.2</td>
<td>805/4209</td>
<td>19.1</td>
</tr>
<tr>
<td>Neuro-3: loss of ankle jerk</td>
<td>1225/3298</td>
<td>37.1</td>
<td>1270/3265</td>
<td>38.9</td>
</tr>
<tr>
<td>Neuro-4: loss of sensation to light touch</td>
<td>424/4577</td>
<td>9.3</td>
<td>481/4564</td>
<td>10.5</td>
</tr>
</tbody>
</table>

Accord microvascular. Lancet 2010;376:419
Glycemic groups: to study end

Accord microvascular. Lancet 2010;376:419
Microalbuminuria vs. glycemia

HR (95% CI): 0.79 (0.69, 0.90)
P=0.0005

Accord microvascular. Lancet 2010;376:419
Macroalbuminuria vs. glycemia

Accord microvascular. Lancet 2010;376:419
Cataract surgery vs. glycemia

Accord microvascular. Lancet 2010;376:419
Loss of light touch vs. glycemia

Accord microvascular. Lancet 2010;376:419
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Association Between Small, Dense LDL and Insulin Resistance

Steady-State Plasma Glucose (mmol/L)

LDL-Size Phenotype

LDL-Cholesterol underestimates the number of LDL particles when levels of small LDL are increased.

Larger LDL
  More cholesterol/particle

Smaller LDL
  Less cholesterol/particle

- Apo B
- Cholesterol Ester

Similar LDL cholesterol

- Slower plasma clearance
- Greater artery uptake & retention
- Faster oxidation
- More particles
Helsinki Heart Study Effect of Gemfibrozil on Coronary Events at 5 Years

- **Diabetic Patients**
  - Placebo: 10.7
  - Gemfibrozil: 3.4 (68% Risk Reduction)
  - n=135, P < .2

- **Nondiabetic Patients**
  - Placebo: 4.1
  - Gemfibrozil: 2.7 (34% Risk Reduction)
  - n=3946, P < .02

SENDACAP Study Effect of Bezafibrate on Coronary Events at 5 Years

Diabetic Patients

Patients With a Documented MI or Ischemia (%)

Placebo Bezafibrate

n=164, P < .01

67% Risk Reduction

Gemfibrozil: CV Death, Nonfatal MI, and Stroke

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)

4900 assigned placebo

4895 assigned fenofibrate

5 withdrew consent
10 lost to follow-up

Status at close-out visit
4885 mortality status confirmed
4856 primary outcome status confirmed

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)

- Reduction in non-fatal MI, ↑CV mortality
- Reduction in total CVD, revascularization
- Effects on CVD after adjusting for concomitant statins
  - CHD events ↓ 19%: p = 0.01
  - Total CVD events ↓ 15%: p = 0.004
- Risk reduction associated with starting statins
  - CHD: ↓ 49% (p<0.001)
  - CVD: ↓ 26% (p = 0.004)

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD): renal and eye effects

- 2.6% more patients albuminuria regression or not progressing
- 1.6% fewer patients required laser photocoagulation
- Subset analysis: low HDL group greater benefit, particularly with high triglyceride

Fenofibrate Intervention and Event Lowering in Diabetes (FIELD)


Macular edema

Proliferative retinopathy
### ACCORD Randomization: glycemia, blood pressure, lipids

<table>
<thead>
<tr>
<th>Glycaemia trial</th>
<th>Blood pressure trial</th>
<th>Lipid trial (all on simvastatin 20 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SBP&lt;120 mm Hg</td>
<td>SBP&lt;140 mm Hg</td>
</tr>
<tr>
<td>HbA(_{1c}) &lt;6.0%</td>
<td>1178</td>
<td>1193</td>
</tr>
<tr>
<td>HbA(_{1c}) 7.0–7.9%</td>
<td>1184</td>
<td>1178</td>
</tr>
<tr>
<td></td>
<td>2362</td>
<td>2371</td>
</tr>
</tbody>
</table>

Accord microvascular. Lancet 2010;376:419
## ACCORD Lipid: CVD outcomes

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Fenofibrate % of events (no. in group)</th>
<th>Placebo % of events (no. in group)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>10.52 (2765)</td>
<td>11.26 (2753)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HDL cholesterol</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤34 mg/dl</td>
<td>12.24 (964)</td>
<td>15.56 (906)</td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>35–40 mg/dl</td>
<td>10.12 (860)</td>
<td>9.47 (866)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥41 mg/dl</td>
<td>9.08 (925)</td>
<td>8.99 (968)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Triglycerides</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤128 mg/dl</td>
<td>9.88 (891)</td>
<td>11.29 (939)</td>
<td></td>
<td>0.64</td>
</tr>
<tr>
<td>129–203 mg/dl</td>
<td>10.50 (924)</td>
<td>9.86 (913)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥204 mg/dl</td>
<td>11.13 (934)</td>
<td>12.84 (888)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Triglyceride–HDL cholesterol combination</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride ≥204 mg/dl and HDL ≤34 mg/dl</td>
<td>12.37 (485)</td>
<td>17.32 (456)</td>
<td></td>
<td>0.06</td>
</tr>
<tr>
<td><strong>All others</strong></td>
<td>10.11 (2264)</td>
<td>10.11 (2284)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ACCORD Lipid: Retinopathy Progression

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1,148 patients with HTN and type 2 diabetes were allocated to tight (<150/85 mmHg; n=758) or less tight (<180/105 mmHg; n=390) BP control and followed for a median of 8.4 years. Mean BP achieved in tight control group was 144/82 mmHg and 154/87 mmHg for the less tight group.

UKPDS=United Kingdom Prospective Diabetes Study.

Major Outcomes of the HOT Trial: Diabetes Subgroup

Diastolic Target
- ≤90 mmHg (n=501)
- ≤85 mmHg (n=501)
- ≤80 mmHg (n=499)

DBP of ≤80 mmHg vs ≤90 mmHg resulted in a 51% reduction in major CV events.

HOT=Hypertension Optimal Treatment. Subgroup of 1,501 patients, mean age 62 years, with HTN and diabetes at baseline were randomized to target DBP of 90, 85, or 80 mmHg—and a low dose of acetylsalicylic acid or placebo. Felodipine was baseline therapy with the addition of ACEIs or β-blockers and diuretics as needed.

ACCORD blood pressure study

![Graph showing systolic pressure over years since randomization]

**Mean No. of Medications Prescribed**

- Intensive: 3.2, 3.4, 3.4, 3.5, 3.5, 3.5, 3.4, 3.4
- Standard: 1.9, 2.1, 2.1, 2.2, 2.2, 2.3, 2.3, 2.3

**No. of Patients**

- Intensive: 2174, 2071, 1973, 1792, 1150, 445, 156, 156
- Standard: 2208, 2136, 2077, 1860, 1241, 504, 203, 201

## ACCORD blood pressure: risks

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>BP</th>
<th>↓ BP</th>
<th>↓ pulse</th>
<th>↑ K</th>
<th>K&lt;3.2</th>
<th>↑ crea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>2371</td>
<td>133/71</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>27</td>
<td>367</td>
</tr>
<tr>
<td>Intensive</td>
<td>2362</td>
<td>119/64</td>
<td>17</td>
<td>12</td>
<td>9</td>
<td>49</td>
<td>561</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Therapy (N=2363)</th>
<th>Standard Therapy (N=2371)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of events</td>
<td>%/yr</td>
<td>no. of events</td>
<td>%/yr</td>
<td></td>
</tr>
<tr>
<td>Primary outcome $^c$</td>
<td>208</td>
<td>1.87</td>
<td>237</td>
<td>2.09</td>
</tr>
<tr>
<td>Prespecified secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>126</td>
<td>1.13</td>
<td>146</td>
<td>1.28</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>36</td>
<td>0.32</td>
<td>62</td>
<td>0.53</td>
</tr>
<tr>
<td>Nonfatal</td>
<td>34</td>
<td>0.30</td>
<td>55</td>
<td>0.47</td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From any cause</td>
<td>150</td>
<td>1.28</td>
<td>144</td>
<td>1.19</td>
</tr>
<tr>
<td>From cardiovascular cause</td>
<td>60</td>
<td>0.52</td>
<td>58</td>
<td>0.49</td>
</tr>
<tr>
<td>Primary outcome plus revascularization or nonfatal heart failure</td>
<td>521</td>
<td>5.10</td>
<td>551</td>
<td>5.31</td>
</tr>
<tr>
<td>Major coronary disease event $^j$</td>
<td>253</td>
<td>2.31</td>
<td>270</td>
<td>2.41</td>
</tr>
<tr>
<td>Fatal or nonfatal heart failure</td>
<td>83</td>
<td>0.73</td>
<td>90</td>
<td>0.78</td>
</tr>
</tbody>
</table>

ADVANCE 2x2 factorial blood pressure and glycemia intervention

- Glycemic treatment: A1c 7.5% reduced 0.61%
- Perindopril/indapamide: 145/81 reduced 7/3

<table>
<thead>
<tr>
<th>Blood pressure\Glucose tx</th>
<th>intensive</th>
<th>standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perindopril/indapamide</td>
<td>2783</td>
<td>2786</td>
</tr>
<tr>
<td>Placebo</td>
<td>2788</td>
<td>2783</td>
</tr>
</tbody>
</table>

Zoungas et al. Diabetes Care 2009;32:2068
<table>
<thead>
<tr>
<th>Event</th>
<th>Intensive glucose and perindopril-Indapamide</th>
<th>Standard glucose and perindopril-Indapamide</th>
<th>Intensive glucose and placebo</th>
<th>Standard glucose and placebo</th>
<th>$p_{interaction}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>2,783</td>
<td>2,786</td>
<td>2,788</td>
<td>2,783</td>
<td></td>
</tr>
<tr>
<td>Death from any cause</td>
<td></td>
<td></td>
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<tr>
<td>No. events</td>
<td>198</td>
<td>210</td>
<td>231</td>
<td>240</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.82 (0.68-0.99)</td>
<td>0.87 (0.72-1.04)</td>
<td>0.96 (0.80-1.15)</td>
<td>1.00 (reference)</td>
<td>0.90</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. events</td>
<td>104</td>
<td>107</td>
<td>121</td>
<td>136</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.76 (0.59-0.98)</td>
<td>0.78 (0.60-1.00)</td>
<td>0.89 (0.70-1.14)</td>
<td>1.00 (reference)</td>
<td>0.62</td>
</tr>
<tr>
<td>Major coronary heart events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. events</td>
<td>133</td>
<td>132</td>
<td>139</td>
<td>155</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.92 (0.77-1.10)</td>
<td>0.87 (0.73-1.04)</td>
<td>0.90 (0.71-1.13)</td>
<td>1.00 (reference)</td>
<td>0.47</td>
</tr>
<tr>
<td>Major cerebrovascular events</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. events</td>
<td>111</td>
<td>104</td>
<td>111</td>
<td>107</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>1.03 (0.79-1.35)</td>
<td>0.96 (0.73-1.26)</td>
<td>1.03 (0.79-1.35)</td>
<td>1.00 (reference)</td>
<td>0.85</td>
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<td>All renal events</td>
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<td>No. events</td>
<td>590</td>
<td>630</td>
<td>686</td>
<td>777</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.72 (0.65-0.81)</td>
<td>0.77 (0.69-0.85)</td>
<td>0.88 (0.79-0.97)</td>
<td>1.00 (reference)</td>
<td>0.33</td>
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<td>New or worsening nephropathy</td>
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<td>No. events</td>
<td>81</td>
<td>100</td>
<td>96</td>
<td>120</td>
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<tr>
<td>HR (95% CI)</td>
<td>0.67 (0.50-0.88)</td>
<td>0.82 (0.63-1.07)</td>
<td>0.80 (0.61-1.05)</td>
<td>1.00 (reference)</td>
<td>0.93</td>
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<tr>
<td>New or worsening retinopathy</td>
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<td></td>
<td></td>
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<td></td>
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<tr>
<td>No. events</td>
<td>147</td>
<td>142</td>
<td>133</td>
<td>153</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.96 (0.76-1.20)</td>
<td>0.92 (0.73-1.16)</td>
<td>0.86 (0.69-1.09)</td>
<td>1.00 (reference)</td>
<td>0.27</td>
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<tr>
<td>New onset of microalbuminuria</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. events</td>
<td>523</td>
<td>542</td>
<td>605</td>
<td>673</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.75 (0.67-0.84)</td>
<td>0.77 (0.68-0.86)</td>
<td>0.90 (0.80-1.00)</td>
<td>1.00 (reference)</td>
<td>0.29</td>
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<tr>
<td>New onset of macroalbuminuria</td>
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<td></td>
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</tr>
<tr>
<td>No. events</td>
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<td>74</td>
<td>73</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.46 (0.32-0.65)</td>
<td>0.77 (0.56-1.04)</td>
<td>0.77 (0.57-1.04)</td>
<td>1.00 (reference)</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Zoungas et al. Diabetes Care 2009;32:2068
ADVANCE: outcomes

Significant benefit with intensive glucose or ACEI-diuretic or both

Zoungas et al. Diabetes Care 2009;32:2068
ADVANCE: outcomes

Significant benefit only seen with combined intensive glucose and ACEI-diuretic group

Zoungas et al. Diabetes Care 2009;32:2068
ADVANCE: outcomes

Significant benefit only seen with combined intensive glucose and ACEI-diuretic group

Zoungas et al. Diabetes Care 2009;32:2068
Update on Diabetes - 2010

- Diabetes epidemiology
- ACCORD glycemia: further understanding of outcome
  - Hypoglycemia effect
  - Different A1c-outcome relationship of standard vs. intensive arms
  - Microvascular effects
- ACCORD lipids and blood pressure
- Understanding A1c use for diagnosis and for treatment
- Type 1 diabetes treatment: The STAR-3 trial
Factors influencing A1c

1. Erythropoiesis
2. Hemoglobin
3. Glycation
4. Erythrocyte destruction
5. Assay

Correlation of hemoglobin glycation with mean blood glucose
Correlation of hemoglobin glycation with mean blood glucose

Linear regressions for three individual patients with HbA1c levels that consistently tracked above (▲), near (□), or below (●) the population regression line.
“In [Framingham and NHANES] nondiabetic and NGT populations, the relationship between age and A1C remained ... adjusting for sex, BMI, fasting glucose, and 2-h postload glucose.”

Pani et al, Diabetes Care 2008; 31:1991
Diagnostic Criteria for Diabetes: use of A1c 6.5%?

2107 participants, mean age 69, AROC = 0.63

By age quartile:
Younger
Older

Rancho Bernardo Study: Kramer Diabetes Care 2010;33:101-3
64 persons developing diabetes over 10 yr: Baseline prevalence of A1c 5.7-6.4, FBG 100-125, 2hBG 140-199


Cederberg et al. Diabetes Care 2010;33:2077
Overlap of pre-diabetes by IFG and A1C in NHANES among U.S. adults without diabetes

A1C alone would reclassify 37.6 million Americans with IFG to not pre-diabetes but add 8.9 million without IFG (?IGT)

Using IFG as reference, pre-diabetes by A1C has 27% sensitivity, 93% specificity, 61% positive predictive value, and 77% negative predictive value

Mann et al. Diabetes Care 2010;33:2190
AACE STATEMENT ON USE OF A1c FOR DIAGNOSIS OF DIABETES

- A1c an ... optional ... criterion, not primary
- Use traditional glucose criteria when feasible
- Do not use A1c for DM1 or GDM
- A1C may be misleading in ethnic populations (for example, African American patients).
- A1C may be misleading ... hemoglobinopathy, Fe deficiency, hemolysis, thalassemia... hepatic, renal disease
- Use standardized, validated A1c assays

Endocrine Practice 2010; 16:155-6
FOR DEBATE

The proposed terminology ‘A_1c-derived average glucose’ is inherently imprecise and should not be adopted

Z. T. Bloomgarden • S. E. Inzucchi • E. Karnieli • D. Le Roith

Received: 15 March 2008 / Accepted: 20 March 2008
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Frequency analysis: Glucose grouping vs. A1c

N=623 insulin treated DM2: 7 point SMBG x 3 d vs. A1c

224 patients with MPG 110-140 mg/dl:
10% had A1c <6.0%
10% had A1c > 8.1%

Shrom, Choi, Ilag, Bloomgarden, Journal of Diabetes, 2010
Frequency analysis: A1c grouping vs. mean glucose

N=623 insulin treated DM2: 7 point SMBG x 3 d vs. A1c

260 patients with A1c 6.5-7.5%:
10% had MPG < 115 mg/dl
10% had MBG > 171 mg/dl

Shrom, Choi, Ilag, Bloomgarden, Journal of Diabetes, 2010
Update on Diabetes - 2010

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  - Microvascular effects
- ACCORD lipids and blood pressure
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- Type 1 diabetes treatment: The STAR-3 trial
Effectiveness of Sensor-Augmented Insulin-Pump Therapy in Type 1 Diabetes

Richard M. Bergenstal, M.D., William V. Tamborlane, M.D.,
Andrew Ahmann, M.D., John B. Buse, M.D., Ph.D., George Dailey, M.D.,
Stephen N. Davis, M.D., Carol Joyce, M.D., Tim Peoples, M.A.,
Bruce A. Perkins, M.D., M.P.H., John B. Welsh, M.D., Ph.D.,
Steven M. Willi, M.D., and Michael A. Wood, M.D., for the STAR 3 Study Group*

STAR 3 - multicenter, randomized, controlled trial
Results Over Time: Adults ≥ 19 years

Values are means ± SE. Comparisons between SAP group and MDI group are significant for each time period (P<0.001).
**A1C Reduction is Correlated with Increased Sensor Use**

Patients who used sensors ≥81% of the time reduced their mean A1C by 1.2% at 1 year vs. baseline.

Values are the difference between the means ± SE. \( p=0.003 \) for association between sensor wear and A1C reduction at 1 year. Only 7 participants had sensor use of 20% or less, with a change in A1C of -0.43 at 1 year vs. baseline.
STAR 3 Conclusions

Sensor-augmented insulin pump therapy resulted in:

A1C (mean) reduction 4x greater than MDI (0.8% v. 0.2%) without an increase in severe hypoglycemia
- SAP: from 8.3% to 7.5%
- MDI: from 8.3% to 8.1%

1.0% A1C (mean) reduction in adults

Patients wearing sensors ≥81% of the time reduced their mean A1C by 1.2% (reduction from baseline to 1 year)

Glycemic improvements were seen early (3 months) and were sustained at 1 year
Integrated Infusion Set and Sensor

Insertion device

Infusion of insulin in gel shows localization with no insulin reaching sensor

sensor  Infusion port
Update on Diabetes - 2010

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