**Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes**

ADVANCE Trial N Engl J Med 2008;358:2560-72 (June 12)

**Study Type:** POEM

**Purpose:** Does lowering HbA1c to a target of 6.5% or less reduce cardiovascular events in a broad cross-section of patients with type 2 diabetes?

**Study Duration:** mean follow-up 5 years

**Trial Design:** randomized, double-blinded, intention-to-treat, multicenter (215 centers in 20 countries including USA)

**Treatment Groups:** 6-week run-in period with a fixed dose perindopril/indapamide combination to assess efficacy and compliance; patients were then randomized to placebo or perindopril/indapamide and undergo an intensive glucose control to HbA1c < 6.5% or standard control; intensive therapy patients got gliclazide as their sulfonylurea – other therapy was individualized at the discretion of the investigators

**Patients:** 11,140 patients, mean age 66 years, 42% female, duration of DM is 8 years, only 4% from America, most from Europe (46%), starting HbA1c 7.5, baseline BP 145/80, BMI = 28

**Inclusion:** Type 2 patients with diagnosis at 30 years or older, at least 55 years of age, history of major macrovascular disease or microvascular disease or at least one other vascular risk factor, they took all HbA1c patients

**Exclusion:** long-term insulin therapy, contraindication to study medications

**Outcome Events:** Macrovascular events (death from CV causes, nonfatal MI, nonfatal stroke) + Microvascular events (new or worsening nephropathy, macroalbuminuria, double SCr, retinopathy)

Secondary causes: see below

1. **Are the results valid?**
   * randomized? Yes  
   * double-blinded? yes  
   * were groups similar? Yes  
   * all patients accounted for? yes

2. **What were the results?**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Therapy</th>
<th>Standard Therapy</th>
<th>P-value</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrovascular events</td>
<td>18.1%</td>
<td>20%</td>
<td>.01</td>
<td>1.9%</td>
<td>52</td>
</tr>
<tr>
<td>Microvascular Events</td>
<td>10%</td>
<td>10.6%</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephropathy new patients</td>
<td>9.4%</td>
<td>10.9%</td>
<td>.01</td>
<td>1.5%</td>
<td>67</td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>4.1%</td>
<td>5.2%</td>
<td>.01</td>
<td>1.1%</td>
<td>91</td>
</tr>
<tr>
<td>New onset microalbuminuria</td>
<td>23.7%</td>
<td>25.7%</td>
<td>NS</td>
<td>2%</td>
<td>50</td>
</tr>
<tr>
<td>Hospitalization due to hypoglycemia</td>
<td>1.1%</td>
<td>0.7%</td>
<td>.04</td>
<td>0.4% (ARI)</td>
<td>250 (NNH)</td>
</tr>
</tbody>
</table>

* all other secondary outcomes were not significant – all coronary events, stroke, heart failure, PVD, visual deterioration, neuropathy, cognitive decline, dementia

3. **Will the results help me?**
   * microvascular changes were at 2 years  
   * the main benefit for intensive control was in microvascular changes and these were realized in nephropathy, not in retinopathy  
   * no benefit in macrovascular change and therefore no change in death

**Conclusion:** Intensive glucose control reduced the primary composite outcome, but was realized only in nephropathy, defined as macroalbuminuria, death from renal causes, doubling of SCr. Of the nephropathy outcomes, the benefit is seen in the development of macroalbuminuria (DOE - NNT 83) and microalbuminuria (DOE - NNT 50) and not death from renal causes (POEM) or doubling of SCr. There was NO benefit for macrovascular outcomes (death from CV causes, nonfatal MI, nonfatal stroke). No difference was seen in all-cause death, stroke, heart failure, cognitive decline or dementia. Four out of 1000 patients treated, as in this study, would be hospitalized for hypoglycemia. Insulin use increased from 1.5% at baseline to 40% by the end of the trial.

**Kelso editorial:** The authors make an appeal that the poor result for macrovascular outcomes might be the small difference between the HbA1c between the intensive and standard groups. If the difference was larger, the benefit might be greater. They then appeal to an observational study that showed a 0.7% difference in HbA1c cuts the macrovascular disease rate by ~1/6th. They further try and justify the results based on the greater use of statins, BP lowering drugs, aspirin. We just can’t let go of it. Type 2 diabetes is NOT a sugar problem. It is a marker, not the cause. When will we learn!

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