ADVANCE Trial 1,2,3: Is intensive glucose control with a glinidazide based regimen better than standard glucose control with a non-glucidazide based regimen in high risk, but not too hard to control T2DM?

**Trial Methodology**

- **Who was in the trial?**
  - n=11,140; ~8yr hx of T2DM; age 66yr; 42% women; lower baseline A1C, 7.5%; FBG=8.5 mmol/L; weight=78 kg; BMI=28
  - only 4% North American; 32% had hx of CV disease; etablished a 6wk pre-trial run-in period (13.5% withdrew after run-in)
  - Inclusion: age >55; T2DM onset at age >30; a history of macrovascular or microvascular disease or 1+ additional risk factors
  - Exclusion: definite indication for, or contraindication to, any study treatments or a definite indication for long-term insulin at time of study entry
  - (also, of 12,877 registered for a 6 week run in period; 13.5% withdrew & 11,140 went on to study randomization)

- **A1C Target:**
  - Intensive group: ≤6.5%
  - Standard group: ≤7% depending on local guidelines; randomized controlled; not blinded.

- **Intervention drugs:**
  - **Gliclazide** modified release 90/50%+22% (DIAMICRON MR 30 to 120mg) 70.4% @ 120mg dose 6% = baseline share of other drugs
  - other sulfonylureas 13% vs 67%; sequential addition of metformin 74% vs 67%; glitazones 17% vs 11%; acarbose 19% vs 13%; insulin 40% vs 24% (basal +/- short acting insulin)

- **Primary (1°) Endpoints:**
  - Composites of major macrovascular (CV death, non-fatal MI/stroke) & major microvascular events (new/worsening nephropathy or retinopathy). {1° endpoints reviewed by independent End Point Adjudication Committee; blinded.}

- **Sponsored by:**
  - Servier but investigators independent. Conducted in: Asia 37%, Australasia 13%, Europe 45%, North America 4%.

**Results – after 5 years follow-up**

<table>
<thead>
<tr>
<th>Outcome (1°, 2°, other) (color denotes risk or benefit)</th>
<th>Intensive A1C Tx n=5571</th>
<th>Standard A1C Tx n=5569</th>
<th>ARR / ARI over ~5yrs</th>
<th>NNT/NNH over ~5yrs</th>
<th>HR, (95% CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C Achieved</td>
<td>6.5%</td>
<td>7.3%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Macro or Microvascular Event (1°)</td>
<td>1009 (18.1%)</td>
<td>1116 (20.0%)</td>
<td>↓ 1.9%</td>
<td>53 CI: 30-226</td>
<td>0.90, (0.82-0.98) p=0.01</td>
</tr>
<tr>
<td>Major Macrovascular Events (1°) (CV death, nonfatal MI, nonfatal stroke)</td>
<td>557 (10%)</td>
<td>590 (10.6%)</td>
<td>↓ 0.6%</td>
<td>ns</td>
<td>0.94, (0.84-1.06) p=0.32</td>
</tr>
<tr>
<td>Major Microvascular Events (nephropathy, retinopathy) (1°)</td>
<td>526 (9.4%)</td>
<td>605 (10.9%)</td>
<td>↓ 1.5%</td>
<td>67 CI: 38-264</td>
<td>0.86, (0.77-0.97) p=0.01</td>
</tr>
<tr>
<td>Death – all cause</td>
<td>498 (8.9%)</td>
<td>533 (9.6%)</td>
<td>↓ 0.7%</td>
<td>ns</td>
<td>0.93, (0.83-1.06) p=0.28</td>
</tr>
<tr>
<td>Death – CV associated</td>
<td>253 (4.5%)</td>
<td>289 (5.2%)</td>
<td>↓ 0.7%</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td>Nephropathy: new/worsening</td>
<td>230 (4.1%)</td>
<td>292 (5.2%)</td>
<td>↓ 1.1%</td>
<td>91 CI: 53-314</td>
<td>0.79, (0.66-0.93) p=0.02</td>
</tr>
<tr>
<td>Microalbuminuria: new/worsening</td>
<td>1318 (23.7%)</td>
<td>1434 (25.7%)</td>
<td>↓ 2%</td>
<td>50 CI: 28-251</td>
<td>0.91, (0.85-0.98) p=0.02</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>332 (6.0%)</td>
<td>349 (6.3%)</td>
<td>↓ 0.3%</td>
<td>ns</td>
<td>-</td>
</tr>
<tr>
<td>Hospitalization – any cause</td>
<td>2501 (44.9%)</td>
<td>2381 (42.8%)</td>
<td>↑ 2.1%</td>
<td>42 CI: 25-388</td>
<td>1.07, (1.01-1.13); p=0.03</td>
</tr>
<tr>
<td>Hypoglycemia – Severe</td>
<td>150 (2.7%)</td>
<td>81 (1.5%)</td>
<td>↑ 1.2%</td>
<td>83 CI: 58-150</td>
<td>1.86, (1.42-2.40) p&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemia – Severe events per 100 patient yr</td>
<td>0.7 (or 3.5 / 5yr)</td>
<td>0.4 (or 2 / 5yr)</td>
<td></td>
<td>(↑ hospitalizations due to severe hypoglycemia: 1.1% vs 0.7%/p=0.04)</td>
<td></td>
</tr>
<tr>
<td>Minor: events per 100 patient yr</td>
<td>120 (or 60 / 5yr)</td>
<td>90 (or 45 / 5yr)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Weight loss (mean)</td>
<td>Loss of ~ 0.1kg</td>
<td>Loss of ~ 1kg</td>
<td>-</td>
<td>(↑ 0.7kg vs standard Tx)</td>
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</tbody>
</table>

**Considerations**

- **Limitations:**
  - treatment group had about 3x as much contact with health care providers; population 96% non-North American

- **Compared to ACCORD:**
  - ADVANCE patients were less obese baseline weight: 78kg vs 93.5 kg, had less weight gain 0.7 vs 3.5kg, had shorter hx of T2DM, 8yr vs 10yr, had a lower baseline A1C 7.5% vs 8.3%, were less likely to end up on insulin 40% vs 77%, statins 46% vs 88%, or glitazones 17% vs 91% - Overall aggressiveness of drug regimens/dosages was less in ADVANCE.
  - {in ACCORD, the aggressive A1C target group (target ≤6%; achieved 6.4%) was halted due to ↑ all cause death (NNH=95). See RxFiles ACCORD Trial Summary}

- **What we knew:**
  - - glucose control & ↓ A1C levels do not always reduce heart, stroke & death endpoints, UKPDS-33, ACCORD, VAQT, etc.
  - - glucose control does ↓ microvascular endpoints somewhat UKPDS-33 (retinal) with an ↑ risk of hypoglycemia

- **What we still don’t know:**
  - Does glidazide offer outcome advantages or disadvantages compared to other sulfonylureas?
  - What are the prime factors that predict likelihood of ↑ risk; e.g. ACCORD vs benefit with aggressive hypoglycemic regimens?
  - Would we see benefits or risks on CV or death endpoints if we were able do a study over a longer time frame?
  - Want more “bang for the buck” & less adverse events? Consider BP meds Micro-NOPE, statin CARDSHPS, ASA & lifestyle.

**What this study adds - Bottom Line**

- In ADVANCE type patients, pursuing an A1C of ≤ 6.5% over 5 yrs (with most patients on glidazide + metformin) is associated with:
  - a reduction in major microvascular events, particularly nephropathy, in 1 out of 67 patients
  - an ↑ risk of severe hypoglycemia in 1 out of 83 patients & an ↑ rate of hospitalization in 1 out of 42 patients
  - no benefit or risk on macrovascular outcomes (MI, CV death, non-fatal stroke) or all-cause death

- Taking into consideration both the ACCORD and ADVANCE trials, any discussion of proposed A1C targets will need to consider the patient, the risks of the disease and the adverse effects of the treatment intervention. Lowering A1C by 1% may be associated with benefit or risk (automatic benefit often quoted based on epidemiologic data can not be assumed).

*Individualize therapy. Let the target serve the patient, not the patient the target!*
2016, Dec - Update: ADVANCE-ON Follow-up Trial

- 8,494 ADVANCE participants followed for median of 5.4 additional years
- In-trial A1C differences disappeared by first post trial visit
- Reduction in ESKD persisted after 9.9 years; 29 vs 53 events; HR 0.54, p <0.01
  - Effect greater in earlier stage CKD, and at lower baseline SBP.
- No macrovascular benefit seen (e.g. death, CV death, major CV event)

Related RxFiles Links:
- For more, see www.RxFiles.ca

References continued from Page 1.

1 The ADVANCE Collaborative Group. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. NEJM 2008;Jun 6. Online: http://content.nejm.org/cgi/content/full/NEJMoa0802987?resourcetype=HWCIT

