**ACCORD Diabetes Trial** – Intensive versus Standard A1C Targets in T2DM

**UPDATE:** Trial now published - NEJM online - June 06, 2008. This provides further discussion now that the full publication is available. Preliminary trial results causing halting of trial discussed February 2008.

**Research Question:**
- This randomized control trial (RCT) sets out to test if there is a correlation between A1C and cardiovascular (CV) events, which has been hypothesized based on epidemiologic studies. (RCTs are a higher quality evidence than epidemiologic studies)
- In type 2 diabetes patients who have established CV disease or additional CV risk factors, does an intensive glycemic control strategy to target an A1C <6% decrease cardiovascular risk compared to a standard strategy to target an A1C of 7-7.9%?

**Trial Methodology**
- Who was in the trial? n=10,251; type 2 diabetes (T2DM); mean age 62.2yrs; mean A1C of 8.3%; 38% ♀; mean BMI 32
  - Inclusion: T2DM; A1C ≥7.5%; age 40-79yrs with CV disease ~35% or age 55-79 with anatomical evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least 2 additional CV risk factors (lipid, hypertension, current smoker or obesity).
  - Exclusion: frequent/recent hypoglycemia, unwilling to do home glucose monitoring or inject insulin, BMI >45, S Cr >133umol/L, other serious illness
  - 50 patients lost to follow up & 162 patients withdrew consent; fairly equally divided between groups, but slightly more in intensive group.
- Primary (1°) Outcome: non-fatal MI or stroke, or death from CV causes (the 1st occurrence of)
- Double two-by-two factorial design (2 other arms still ongoing are assessing: 1) aggressive vs standard (BP therapy); 2) [fenofibrate vs placebo] + simvastatin
- Sponsored by: the National Heart, Lung and Blood Institute (NHLBI); conducted in 77 centers across the USA & Canada

**Results**
- All cause death was ↑ in intensive A1C group necessitating halting of trial 17 months early (after ~3.5 years follow-up).
  - (Over 3.5 years: relative risk ↑ 22%; absolute risk ↑ 1.05%; NNH: for every 95 patients treated in the intensive A1C group, there was one extra death from any cause over 3.5 years compared to standard A1C treatment arm)
- Lower A1C was associated with ↑ exposure to drugs of every class & more frequent changes in drugs
  - metformin 86% vs 58%, fosglitazone 92% vs 58%, secretagogue (glimepiride, repaglinide) 87% vs 74%, insulin 77% vs 55%, incretin 18% vs 5%
  - 52% of intensive Tx were on 3 oral hypoglycemics + insulin vs 16% in standard Tx group; visits q2months vs q4months
- Subgroup: those with no previous CV event history & an A1C ≤8% was associated with fewer fatal & non-fatal CV events.
- Preliminary non-specified analysis did not suggest a causative association for ↑ death for the following:
  - severe hypoglycemia, different drug randomizations, weight change or other factors
  - Causes of death contributing to ↑ rate: CV disease related, cancer related, non-CV or cancer.

<table>
<thead>
<tr>
<th>Outcome (1°, 2°, other)</th>
<th>Intensive A1C Tx n=5128</th>
<th>Standard A1C Tx n=5123</th>
<th>ARI↑ / ARR↓ over ~3.5yrs</th>
<th>NNT/NNH over ~3.5yrs</th>
<th>HR; (95% CI); p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV event, MI, stroke, CV death (1°)</td>
<td>352 (6.9%)</td>
<td>371 (7.2%)</td>
<td>↓ 0.3%</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Death – any cause (2°)</td>
<td>257 (5.01%)* (154 deaths)</td>
<td>203 (3.96%)*</td>
<td>↑ 1.05%</td>
<td>NNH= 95 CI 95% = 54.403</td>
<td></td>
</tr>
<tr>
<td>Death - CV related (2°)</td>
<td>135 (2.6%)</td>
<td>94 (1.8%)</td>
<td>↑ 0.8%</td>
<td>NNH= 125</td>
<td></td>
</tr>
<tr>
<td>Non-fatal MI (2°)</td>
<td>186 (3.6%)</td>
<td>235 (4.6%)</td>
<td>↓ 1%</td>
<td>NNT= 100</td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia - requiring medical assistance</td>
<td>538 (10.5%)</td>
<td>179 (3.5%)</td>
<td>↑ 7%</td>
<td>NNH= 14</td>
<td></td>
</tr>
<tr>
<td>- requiring any assistance</td>
<td>830 (16.2%)</td>
<td>261 (5.1%)</td>
<td>↑ 11.1%</td>
<td>NNH= 9</td>
<td></td>
</tr>
<tr>
<td>Weight gain &gt;10kg</td>
<td>(27.8%)</td>
<td>(14.1%)</td>
<td>14%</td>
<td>NNH= 7</td>
<td></td>
</tr>
<tr>
<td>Fluid Retention</td>
<td>(70.1%)</td>
<td>(66.8%)</td>
<td>3.4%</td>
<td>NNH= 30</td>
<td></td>
</tr>
</tbody>
</table>

ARI= absolute risk increase ARR=absolute risk reduction BP= blood pressure CI 95%/ 95% confidence interval CV=cardiovascular MI=myocardial infarction NNT= number needed to treat to benefit one NNH= number needed to treat to harm one (both values calculated from raw event rates)*

**Considerations:**
- Possible factors leading to ↑ death: the lower A1C level, magnitude & speed of A1C reduction, frequent changes in drug regimen; ↑ hypoglycemia/weight gain, adverse interactions, multiple hypoglycemics & ↑ doses used, ↑ insulin exposure.
- Two other trials, Steno-2 and ADVANCE targeted an A1C of 6.5%, and had positive outcomes. This should be interpreted in context of the different populations admitted into the trials and the differences in drug regimens used.
- Mortality rates for ACCORD were lower compared to both ADVANCE* less ASA, statins & the general T2DM population N America.

**Bottom Line: Don’t get too A1C lazy or crazy.**
- Individualize treatment! When considering an A1C target, consider also the patient and the risk of the drug interventions.
- ACCORD, ADVANCE & UKPDS-33 suggest that glucose reduction has microvascular but not macrovascular benefit.
- Let the target serve the patient, not the patient the target! Remember the role of lifestyle, BP, lipids & ASA in risk reduction.
- In ACCORD T2DM type patients, a target A1C of 7-7.9% is better than a target of <6% (perhaps especially if they have a CV event history, a high initial A1C & ↑ weight [subgroup analysis]). A lower A1C may still offer advantages in lower risk patients and those who are able to achieve this with less intensive drug regimens. Also, based on Steno-2 and ADVANCE, an A1C of 6.5% would be reasonable in some patients. We await further subanalysis, discussion and trials to help clarify this issue.
**RxFiles.ca - Trial Summary**

**L. Regier, B. Jensen - June 12, 2008**

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### ACCORD 3.5yr vs ADVANCE 5yr

**Comparison of Intensive Groups**

- **Initial A1C:** 8.3% vs 7.5% (both trials had high-risk patients; in std groups, annual mortality rates approximately 1.5% & 2%)
- **A1C Achieved:** similar 6.4% vs 6.5%
- **Patient wt Initial:** 93.5kg vs 78kg; ↑ 27% >10+ kg vs ↓
- **Where:** NA vs Europe/Asia
- **Intervention:** way more intensive vs intensive (3+ orals + insulin)_{52} vs SU+MF_{most} glimepiride, MF, rosiglitazone, insulin glargine, MF
- **Design:** stopped early (7m vs extended 18m)
- **Result:** 3.5v5yrs more death NNH=96 vs less nephropathy NNH=67 & less microvascular NNH=67
- **Hypoglycemia:** severe in both but NNH 14 vs 83

### Considerations

- **Let the target serve the patient, not the patient the target**
  - *Let not get A1C lazy, just don’t go A1C crazy*

- **High glucose isn’t good, but extremely-intensive lowering efforts appear to be worse in some patients**

- **In ACCORD type patients…**
  - Better to live with an A1C of 7.5% than die with an A1C of 6.4%
  - (Subanalysis may provide clues; e.g., low CV risk & lower baseline A1C did better)

- **In ADVANCE type patients…**
  - To pursue an A1C of 6.5% will have benefit, mostly microvascular, but expect more hypoglycemia & hospitalizations.

- **Really want to make a difference? Don’t forget BP, statin, ASA & lifestyle. E.g. Micro HOPE Rampali, CARDS Atorvastatin 10mg/d**

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### References:

4. Park K. How low to go with glucose control. [http://www.australianprescriber.com/magazine/32/2/30/1](http://www.australianprescriber.com/magazine/32/2/30/1)

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ACCORD Diabetes Trial – Intensive Glucose Arm Halted February 6th, 2008

{Mortality with an very intensive glucose lowering strategy in high CV risk T2DM patients}

Preliminary Information: Full trial results awaiting publication now published in the NEJM June 06, 2008.

Research Question:

- In patients with type 2 diabetes (T2DM) who are at high risk for heart attack and stroke, does an intensive glycemic control strategy to target A1C (<6%) decrease cardiovascular risk compared to a standard strategy to target an A1C of 7-7.9%?
- {Other arms of this trial, still ongoing, are evaluating blood pressure and lipid control strategies (120mmHg vs 140mmHg; treatment with diuretic + ACEi or beta blocker encouraged; simvastatin 20mg/day if 1° prevention, 40mg/day if 2° prevention; +/- fenofibrate ≤160mg/day); ASA ≤325mg/d was standard and everyone encouraged in lifestyle interventions. All patients will now be in standard glucose arm.}

Inclusion - Patients:

- n=10,251; with T2DM, with heart disease or at least 2 cardiovascular risk factors (↑BP, ↑cholesterol, obesity, smoking)
- Baseline averages: 10 year history of diabetes at enrolment; age 62; A1C levels 8.2% (somewhat higher than most T2DM)

Intervention:

- Both arms could select from same hypoglycemic options (metformin, glitazone, insulin, sulfonylureas, acarbose, exenatide)
- Intensive glucose lowering by using higher doses and/or more combinations of drugs, more intensive glucose monitoring and clinic visits every 2 months instead of every 4. The achieved A1C, Intensive vs Standard: 6.4% vs 7.5%

Preliminary Findings (after 2-7 years of therapy; on average 4 years):

- Intensive vs Standard
  - o ↑ all-cause deaths (n=10,251): 257 vs 203
  - 14/1000/yr vs 11/1000/yr = 3 extra deaths/1000/yr  = 12 extra deaths/1000/4 years, or 1 extra death/4 years of study (heart attack, stroke, CV death); overall event rates actually 10% lower in intensive group; however, CV event more likely to be fatal & more sudden
  - Researchers claim that no specific drug appears to explain the higher mortality rate; data awaited.

Preliminary Considerations:

- Researchers suggest that a less aggressive A1C target of 7-7.9% is preferred if high CV risk, older, & ~10yr history T2DM.
- Researchers note lower death rate overall in study than in general T2DM population; this may be largely due to better & more frequent care overall, lifestyle support, ASA, blood pressure and lipid interventions.
- Flexibility in choice of drugs, etc., suggests that the ACCORD trial is similar to the way physicians practice in real life.
- Results could reflect real risk or could be due to chance (Future trials may also help: Advance, ORIGIN, VA Diabetes).

Reference links:
- http://www.theheart.org/article/842113.do

In ACCORD type patients, better to live with an A1C of 7.5% than die with an A1C of 6.4%.