

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

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, rosiglitazone, insulins, 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**
 - **↑ all-cause deaths** (n=10,251) : **257 vs 203**
 - 14/1000/yr vs 11/1000/yr = 3 extra deaths/1000/year = **12 extra deaths/1000/4 years** ave length of trial
 - **NNH estimate = 80 / 4 years** (CI^{95%}: 50-280 approximate; await full data)
 - For every 80 patients treated with very intensive glycemic control x4years, there was 1 extra death
 - **Other**
 - **Primary outcome** 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 death
 - 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 (although odds are against this).

Other:

- The T2DM population group is different from type 1 where intensive glycemic control has some evidence for lowering CV disease DCCT; A1C=7.4. There are few and somewhat equivocal CV outcome trials in T2DM (UKPDS, ProACTIVE, RECORD preliminary).
- Although some have emphasized T2DM as “cardiac risk equivalent”, discussion surrounding this study emphasizes that degree of cardiac risk and recommended treatment strategies does vary for different patients with T2DM.
- These results will discourage physicians from having to pursue extreme regimens to achieve ultra low glucose targets.
- **STENO-2** follow-up trial Feb 7th, 2008: A small 13.3yr (n=160, age 55yr ave at startup) in T2DM & **microalbuminuria**; multifactorial intervention {ASA, statin, ACEI, glycemic control (A1C=7.7%ave), lifestyle} resulted in ↓ death NNT=5, ↓CV events HR=0.41, ↓renal & eye complications.
- Metformin is the only hypoglycemic with RCT evidence for ↓mortality UKPDS-34; in obese; A1C=7.4%; it will be interesting to know more regarding such specific drugs (controversial relative contraindications of heart failure and ↓renal function could be factors)

Take Home:

- **Individualize treatment!** Avoid overly intensive glycemic control in patients with high CV risk, especially if older & ≥10year history of T2DM. Weigh the potential benefit of glucose control with the risks of both hypoglycemia and/or hypoglycemic drugs/drug regimens with limited outcome evidence. *Let the target serve the patient, and not the patient the target.*
- **Remember A1C is only a surrogate marker & previous trials also show limitations of A1C on macrovascular outcomes.** UKPDS Clinical endpoints such as MI, stroke, death are more important. Thus, trials such as ACCORD are critical to evaluate the risks and benefits of the therapies we have to offer. *Drugs that do good things, can also do bad things.*
- **Stay active, eat well, keep weight in check & don't smoke!!!** Think blood pressure, statins, ASA & lifestyle!

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

Reference links: <http://www.theheart.org/article/842113.do>; <http://www.accordtrial.org/web/public/index.cfm>; <http://www.nih.gov/news/health/feb2008/nhbi-06.htm>; www.RxFiles.ca
<http://www.nhbi.nih.gov/health/press/heart/other/accord/remarks.pdf>; STENO-2 follow-up: <http://content.nejm.org/cgi/content/short/358/6/580>; Hypoglycemics Chart: <http://www.rxfiles.ca/acrobat/cht-diabetes.pdf>

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