ACCORD Diabetes Trial[1] – Intensive versus Standard A1C Targets in T2DM

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

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% ♀; ~93.5kg 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, SCr >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 95% vs 87%, rosiglitazone 92% vs 58%, secretagogue (glimepiride, repaglinide) 87% vs 74%, insulin 77% vs 55%, acarbose 23% vs 5.1%, 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.

Outcome (1°, 2°, other) {color denotes risk or benefit}	**Intensive A1C Tx** n=5128	**Standard A1C Tx** n=5123	**ARI↑ / ARR↓** over ~3.5yrs	**NNT/NNH** over ~3.5yrs	**HR; (95% CI); p-value** (taken from Table 4 of trial)
A1C Achieved	6.4%	7.5%	-	-	-
CV event MI, stroke, CV death (1°)	352 (6.9%)	371 (7.2%)	↓ 0.3%	NS	0.90, (0.78-1.04); p=0.16
Death – any cause (2°)	257 (5.01%)* (↑ 54 deaths)	203 (3.96%)*	↑ 1.05%	**NNH= 95** CI 95% = 54 - 403	1.22, (1.01-1.46); p=0.04
Death - CV related (2°)	135 (2.6%)	94 (1.8%)	↑ 0.8%	NNH= 125	1.35, (1.04-1.76); p=0.02
Non-fatal MI (2°)	186 (3.6%)	235 (4.6%)	↓ 1%	NNT= 100	0.76, (0.62-0.92); p=0.004
Hypoglycemia					
- requiring medical assistance	538 (10.5%)	179 (3.5%)	↑ 7%	NNH= 14	p<0.001
- requiring any assistance	830 (16.2%)	261 (5.1%)	↑ 11.1%	NNH= 9	p<0.001
Weight gain >10kg	(27.8%)	(14.1%)	14%	NNH= 7	{↑ 3.5kg vs 0.4kg} p<0.001
Fluid Retention	(70.1%)	(66.8%)	3.4%	NNH= 30	

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)*

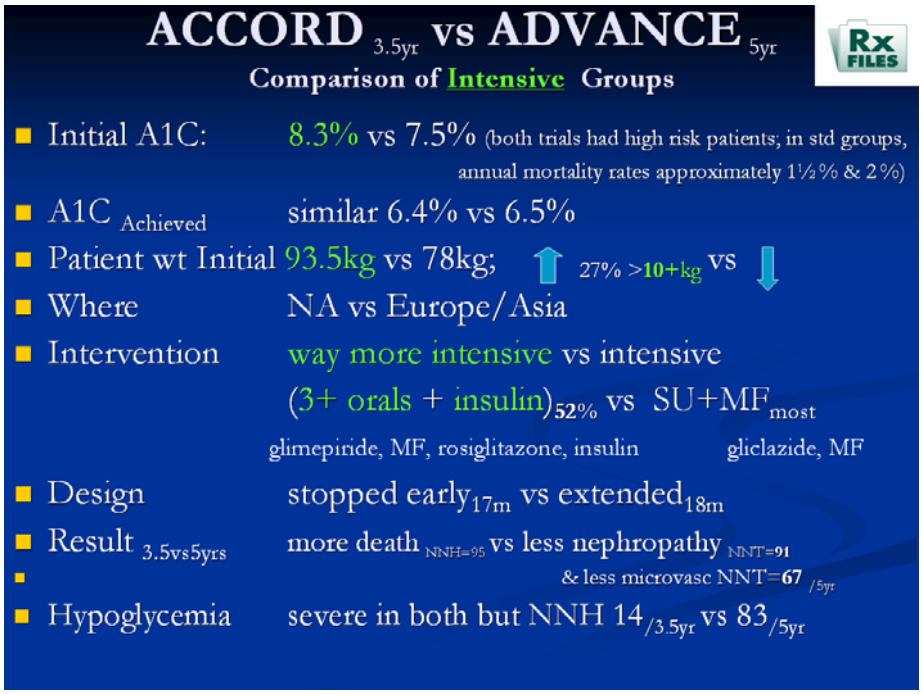
Considerations:

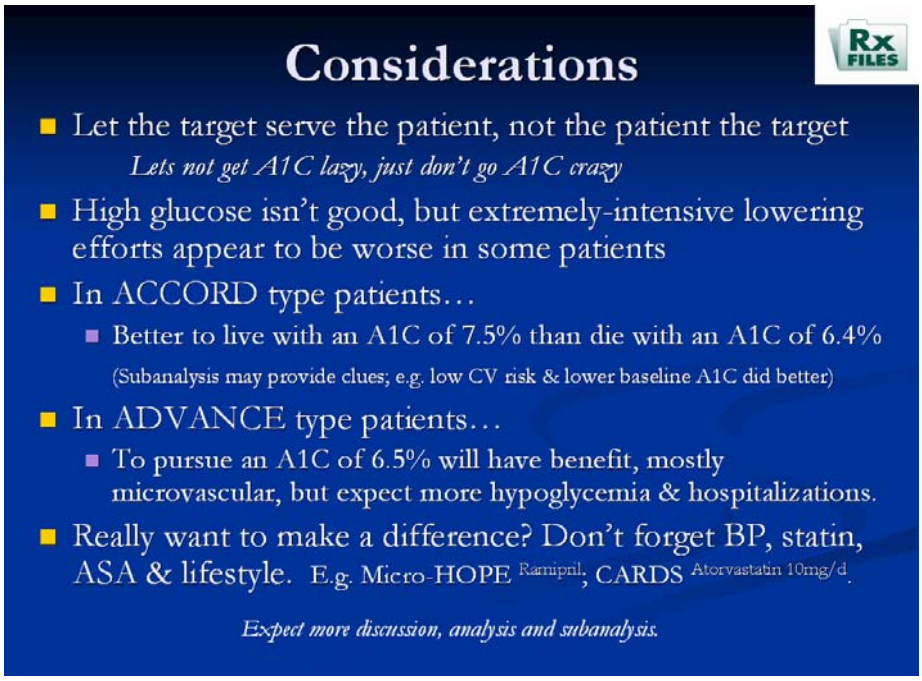
- Possible factors leading to ↑ death: the lower A1C level, magnitude &/or speed of A1C reduction, frequent changes in drug regimen, ↑ hypoglycemia/weight gain, adverse interactions, multiple hypoglycemics & ↑ doses used, ↑ insulin exposure.
- Two other trials, Steno-2 and ADVANCE targeted an A1C of 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.

See also RxFiles ADVANCE Trial Summary at www.rxfiles.ca





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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 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 = [illegible] 250/4 years
    - **NNH estimate = [illegible]** (95% CI [illegible])
    - Follow-up [illegible] intensive vs standard control x4years, there was 1 extra death
  - **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.

Trial now published (NEJM); see Trial Summary, June 2008.

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 n=11,140; , Origin & VA Diabetes).
  {Update, March 03, 2008: Preliminary ADVANCE-release suggests no ↑ in death; newer T2DM patients with lower baseline A1C & less intensive drug tx needed to lower A1C to 6.4%ave.}

Other:

- The T2DM population group is different from type 1 where intensive glycemic control has some evidence for lowering CV disease DCCT/EDIC; A1C=7.4 / 7.9. There are few & 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 avg at startup) in T2DM & microalbuminuria; multifactorial intervention {ASA, statin, ACEI, glycemic control (A1C=7.7%avg), 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 ACCORD type 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/nhlbi-06.htm ; www.RxFiles.ca; Advance: http://www.medscape.com/viewarticle/570243; http://www.nhlbi.nih.gov/health/prof/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