



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 glycemc 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^o) 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
- 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 ^o , 2 ^o , 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 ^o)	352 (6.9%)	371 (7.2%)	↓ 0.3%	NS	0.90, (0.78-1.04); p=0.16
Death – any cause (2 ^o)	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 ^o)	135 (2.6%)	94 (1.8%)	↑ 0.8%	NNH= 125	1.35, (1.04-1.76); p=0.02
Non-fatal MI (2 ^o)	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 light of the lower risk populations treated 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). 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.

¹ ACCORD Study Group. Effects of Intensive Glucose Lowering in Type 2 Diabetes. NEJM 2008; Online June 09, 2008. www.nejm.org

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

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?resource-type=HWCIT>

² Dluhy RG, McMahon G. Intensive Glycemic Control in the ACCORD and ADVANCE Trials. Editorial: NEJM June 06, 2008. Online at <http://content.nejm.org/cgi/content/full/NEJM0804182?resource-type=HWCIT>

³ Cefalu WT. Glycemic Targets and Cardiovascular Disease. Editorial: NEJM June 06, 2008. Online at <http://content.nejm.org/cgi/content/full/NEJM0803831?resource-type=HWCIT>

⁴ Patel A; ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007 Sep 8;370(9590):829-40.

ACCORD_{3.5yr} vs ADVANCE_{5yr}

Comparison of Intensive Groups



- Initial A1C: 8.3% vs 7.5%
- 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 gliclazide, MF
- Design stopped early_{17m} vs extended_{18m}
- Result_{3.5vs5yrs} more death_{NNH=95} vs less nephropathy_{NNT=91}
& less microvasc_{NNT=67 /5yr}
- Hypoglycemia severe in both but NNH 14_{/3.5yr} vs 83_{/5yr}

Considerations



- Let the target serve the patient, not the patient the target
Lets 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_{Ramipril}, CARDS_{Atorvastatin 10mg/d}.

Expect more discussion, analysis and subanalysis.