

“Effects of Intensive Glucose Lowering in Type 2 Diabetes.”

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study Group

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Background

- There is a positive correlation between hemoglobin A1c levels and cardiovascular risk.
- Lower HgbA1c levels increases the risk of symptomatic hypoglycemia.
- The ADA (American Diabetes Association) recommends a target HgbA1c level of <7.0%.¹
- The AACE (American Association of Clinical Endocrinologists) recommends a target HgbA1c level of <6.5% (Grade B)²

Hypothesis

Intensive therapy to control hemoglobin a1c levels below 6.0% will reduce the incidence of cardiovascular events as compared to targeting a1c values between 7.0% and 7.9% in older and middle-aged patients with type 2 diabetes *and* either established cardiovascular disease or additional cardiovascular risk factors.

Study Design

Study type: Randomized controlled trial. Single-blinded study. Two-by-Two Factorial.

Setting: 77 clinical centers within 7 networks in US and Canada

Time period: Patients recruited from Jan 2001- June 2001 and Feb 2003 – Oct 2005. Patients were on therapy for a mean of 3.5 years. Study was ended early in February 2008 due to evidence of harm in intensive group.

Inclusion Criteria: Type 2 diabetes; HgbA1c >7.5; ages 40-79 with known cardiovascular disease or ages 55-79 with anatomic evidence of significant atherosclerosis, albuminuria, LVH, or at least two additional cardiovascular risk factors (dyslipidemia, hypertension, current smoker, or obesity).

Exclusion Criteria: Frequent or recent serious hypoglycemic events; unwillingness to perform home glucose monitoring; unwillingness to inject insulin; BMI >45; creatinine >1.5; other serious illness NOS

Randomization: 10,251 patients randomly assigned to comprehensive intensive therapy for goal HgbA1c <6.0% vs standard therapy for goal HgbA1c 7.0-7.9%.

- Additionally, 4733 patients were also randomized to receive intensive systolic blood pressure therapy for goal SBP <120 vs standard therapy for goal SBP <140.
- Also, 5518 patients were randomly assigned to receive fenofibrate vs placebo while maintaining good control of LDL with simvastatin.

Patient characteristics: Patients were similar in all evaluated characteristics, including age, gender, demographics, smoking status, blood pressure, creatinine level, previous medication use. (please refer to Table 1). Of all study participants, the median duration of diabetes was 10 years. Approximately 35% of all study subjects has a history of prior documented cardiovascular event. The average HgbA1c was 8.3% ± 1.1 in all groups at the beginning of the trial, with fasting serum glucose levels of 175 ± 56.

Outcomes:

- Primary Outcome: The first occurrence of non-fatal MI or nonfatal stroke, or death from cardiovascular causes (including MI, HF, arrhythmia, invasive intervention, surgery, stroke, other vascular disease).
- Secondary Outcome: Death from any cause.

Results:

- Within 4 months, median HgbA1c fell from 8.1% to 6.7% in intensive group and 7.5% in standard group. These levels maintained throughout the follow-up period.
- Intensive group had higher rates of hypoglycemia, weight gain and fluid retention (see Table 3)
- Study was stopped early due to increased rate of death from any cause in the intensive-therapy group.

The evidence

	Controls (Standard Therapy) Control Event Rate (CER)	Cases (Intensive Therapy) Experimental Event Rate (EER)	p Value	Relative Risk (RR) EER/CER	Relative Risk Reduction (RRR) 1 – RR	Absolute Risk Reduction (ARR) CER – EER	Number Needed to Treat (NNT) 1/ARR
All Primary Outcomes	371/5123 (7.2%)	352/5128 (6.9%)	0.16	0.958	0.042	0.3	3.33
Death from CV Cause	94/5123 (1.8%)	135/5128 (2.6%)	0.02	1.44	-0.44	-0.8	∞
Nonfatal MI	235/5123 (4.6%)	186/5128 (3.6%)	0.004	0.78	0.22	1.0	1
Nonfatal Stroke	61/5123 (1.2%)	67/5128 (1.3%)	0.74	1.08	-0.08	-0.1	∞
Death From Any Cause	203/5123 (4.0%)	257/5128 (5.0%)	0.04	1.25	-0.25	-1.0	∞
Fatal or Nonfatal CHF	124/5123 (2.4%)	152/5128 (3.0%)	0.17	1.25	-0.25	-0.6	∞

Comments

- Although the study was randomized and blinded from the investigators and statisticians, it was not a double-blind study. The physicians caring for the patients must be aware of their clinical groups in order to achieve the appropriate a1c level. It is unclear from the text whether or not the patients were also blinded (if they were aware of the protocol, they would obviously not be blinded as to the group since they required more initial clinic visits and more frequent monitoring).
- Patients from both groups had lower mortality overall as compared to epidemiology studies of similar patient populations.
- The intensive-therapy group had a relative increase in mortality of 22% and an absolute increase of 1.0%. This is equivalent to one extra death per 95 patients in those receiving intensive therapy for 3.5 years. The difference in mortality emerged 1-2 years after randomization
- The decrease in the rate of the primary outcome was noted towards the end of the study, after about 3 years. Suggests that if there is a benefit to intensive therapy, it may take several years to emerge. During that time, patients may have an increased risk of death, before the benefit is noted.
- Complications of the intensive therapy group included more frequent hypoglycemia events (16.2% vs 5.1%, p<0.001), greater incidence of weight gain of >10kg above baseline (27.8% vs 14.1%, p<0.001), and greater incidence of fluid retention (70.1% vs 66.8%, p<0.001).
- Annualized rate of hypoglycemic episodes requiring medical assistance was 3.1% in intensive group compared to 1.0% in standard therapy group.
- The mean weight gain in the intensive and standard groups was 3.5kg and 0.4kg, respectively.
- There was no controlling for the rate of decrease in HgbA1c, the magnitude of the reduction in HgbA1c, the number of medications received, or the number of medication adjustments made. Since the treating physician was given discretion in how to lower the subjects' HgbA1c, analyzes to discern which aspects of the intensive-therapy strategy caused the differences in mortality.
- The study also incorporated patients receiving intensive blood pressure control and/or the receipt of fenofibrate vs placebo. These are still masked. Therefore, with further sub-analysis, the data may reveal trends related to the combination of intensive glucose control and one of these additional therapies. This data is not yet released.

References

1. American Diabetes Association: Clinical Practice Recommendations 2008. Diabetes Care. January 2008. 31, supplement 1.
2. American Association of Clinical Endocrinologists. Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus. AACE Diabetes Mellitus Clinical Practice Guidelines Task Force. ENDOCRINE PRACTICE Vol 13 (Suppl 1) May/June 2007