The Glycemia–Cardiovascular Disease Hypothesis

DO RECENT CLINICAL TRIALS RESOLVE THE QUESTION?

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In 1965, Sir Austin Bradford Hill proposed the types of evidence to be examined to assess whether associations between exposure and disease in population-based epidemiologic studies may be causal: strength, consistency, and specificity of association between exposure and disease occurrence; temporality in that exposure precedes disease; biological gradient where higher level of exposure is associated with higher rate of disease; biological plausibility and coherence of the findings with other knowledge; and experimental evidence showing that reducing exposure reduces subsequent disease.¹ Although some methodologists have suggested alternate approaches to considering causality, Hill's evidence of causality is a foundation of how we think about interpreting epidemiologic data.

For over 5 decades, observational epidemiologic studies have documented associations between glycemia and clinical macrovascular disease (i.e., cardiovascular diseases [CVD] like myocardial infarction and cardiac death). Persons with diabetes have 2–4 times the risk of CVD than persons without diabetes; associations persist when controlling for other CVD risk factors such as cholesterol and blood pressure; diabetes often precedes CVD onset; there is a “dose-response” relationship between glycemia level and CVD outcomes; and there is biological plausibility of a causal relationship.^{2–5} Thus, a glycemia–cardiovascular causal hypothesis has been supported by evidence for every item in Hill's list, except one: experimental evidence. If we lower glycemia, will we reduce CVD events? This question can definitively be answered only by a randomized controlled clinical trial—an experimental design.

To date, 5 large clinical trials have examined the question in persons with type 2 diabetes mellitus (T2DM). In the 1960s, the University Group Diabetes Program (UGDP) trial was conducted to determine effects of various treatments on outcomes in 823 persons with newly diagnosed T2DM. Participants randomly assigned to tolbutamide (a first-generation sulfonylurea) unexpectedly experienced higher CVD death rates than participants assigned to the other 3 arms: placebo, fixed-dose insulin, or variable-dose insulin. This finding engendered substantial controversy, including whether the methods were sound and whether tolbutamide was safe. Further, glycemia reduction (including the largest difference between the placebo and the variable insulin groups) did not result in a difference in cardiovascular outcomes.⁶

In the late 1990s, the United Kingdom Prospective Diabetes Study (UKPDS) trial in 3,867 persons with newly diagnosed T2DM reported that participants randomly assigned to intensive

glycemia lowering with sulfonylureas or insulin experienced a lower combined diabetes end point comprising both microvascular and macrovascular diseases than participants assigned to standard glycemia treatment. CVD outcomes were not significantly different, although a lower rate of myocardial infarction neared significance,⁷ which became significant during posttrial follow-up.⁸

This year, results were reported from 3 large randomized clinical trials testing intensive glycemia lowering compared with standard treatment on CVD events in persons with diabetes: Action to Control Cardiovascular Disease in Diabetes (ACCORD), the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT).

In the ACCORD trial, 10,251 participants with T2DM and either clinical CVD or at least 2 additional CVD risk factors were randomly assigned to an intensive strategy using available

medications and lifestyle approaches to control glycemia to near-normal levels (glycated hemoglobin goal less than 6%) or to a strategy of standard control (glycated hemoglobin goal 7.0% to 7.9%). The intensive glycemia strategy was stopped early because of

significantly higher all-cause mortality than the standard strategy; there was also significantly higher CVD mortality.⁹

In the ADVANCE trial, 11,140 participants with T2DM and a history of major macro- or microvascular disease or at least one other vascular risk factor were randomly assigned to intensive glycemia lowering (glycated hemoglobin goal less than 6.5%) using gliclazide modified release (a sulfonylurea) as first-line treatment and other drugs as step-up treatment or to standard control. Results showed a significant reduction in a composite of micro- and macrovascular outcomes but no significant effect on CVD events.¹⁰

In the VADT trial, 1,700 persons with T2DM and glycated hemoglobin of 7.5% or higher were randomly assigned to stepped-care therapy targeting glycated hemoglobin less than 6% or a standard goal of symptom-free glycated hemoglobin of 8–9%.¹¹ The VADT found no significant reduction in a composite outcome of CVD events.¹²

There have now been 5 large randomized clinical trials examining the glycemia–cardiovascular hypothesis, none of which provided experimental evidence that lowering glycemia will reduce CVD events during the treatment period. Based on epidemiologic evidence, the average achieved differences in glycated hemoglobin between randomized groups—0.8% in ADVANCE (1.3% by 4 years), 0.9% in UGDP, 1.1% in ACCORD, and 1.5% in VADT—

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were predicted to translate into reduced CVD events. However, not only were CVD events not reduced, some strategies for intensive glycemia lowering were harmful.

Do the consistent negative results of these trials negate the glycemia–cardiovascular causal hypothesis? Not necessarily. These trials did not just test whether lowering glycemia reduces CVD events. They tested whether specific strategies to lower glycemia reduced CVD events, and they tested those strategies in specific population groups selected to be at elevated risk.

There are many remaining experimental questions that can be asked to examine the glycemia–cardiovascular hypothesis further:

- Might other treatment strategies reduce CVD in the population groups examined? For example, if newer glycemia-lowering agents became available, could CVD events be reduced?
- What would be the longer-term effect of glycemia-lowering strategies in lower-risk groups? UKPDS participants, who were newly-diagnosed with diabetes, saw a significant reduction in myocardial infarction after 10 years. In addition, ACCORD subgroup analyses found that participants without clinical CVD at baseline (35%) had a reduction in major CVD events and a lesser increase in mortality from the intensive strategy than participants with existing CVD.
- Would normalizing glycemia in persons with less severe hyperglycemia lower CVD event rates? The ACCORD subgroup with glycated hemoglobin 8.0% or less at baseline had a significant reduction in CVD events from the intensive strategy and no increased mortality.
- Could lifestyle approaches reduce glycemia sufficiently for a long enough time period to prevent CVD events in persons with diabetes? The LOOK AHEAD trial is examining effects on CVD outcomes of a lifestyle approach for weight loss in persons with T2DM (although it does not directly address the glycemia–cardiovascular question).¹³
- Would preventing diabetes in the first place reduce subsequent CVD rates? The Diabetes Prevention Program (DPP) showed that lifestyle approaches can reduce onset of T2DM in adults with impaired glucose tolerance,¹⁴ but could preventing diabetes through lifestyle changes be maintained long enough to affect CVD events? The DPP Outcomes Study is examining that question.¹⁵
- Would preventing impaired glucose tolerance early in life, even in childhood (perhaps by reducing obesity rates) prevent T2DM and lower subsequent CVD event rates?

As the glycemia–cardiovascular hypothesis is supported by evidence for almost every item in Hill's list, the lack of confirmation in experimental trials has been surprising. Should we abandon the glycemia–cardiovascular hypothesis for alternative explanations? For example, perhaps T2DM and CVD are caused by the same underlying mechanisms, rather than causally related to each other.^{15,16} Questions like those above, however, suggest that additional clinical research is warranted before we abandon the hypothesis. We also clearly need tri-directional translation among

population, clinical, and basic research so we can better understand the glycemia–cardiovascular relationship. **CTS**

Disclaimer

The views expressed in this commentary are those of the author and do not necessarily reflect the views of the National Heart, Lung, and Blood Institute/NIH or the ACCORD investigators.

REFERENCES

1. Hill AB. The environment and disease: Association or causation? *Proceedings of the Royal Society of Medicine*. 1965;58:295–300.
2. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. *BMJ*. 2006;332:73–78.
3. Selvin E, Marinopoulos S, Berkenblit G, et al. Meta-analysis: Glycosolated hemoglobin and cardiovascular disease in diabetes mellitus. *Ann Intern Med*. 2004;141:421–431.
4. Livitan EB, Song Y, Ford ES, Liu S. Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. *Arch Intern Med*. 2004;164:2147–2155.
5. Sundell J. Obesity and diabetes as risk factors for coronary artery disease: from the epidemiological aspect to the initial vascular mechanisms. *Diabetes Obes Metab*. 2005;7:9–20.
6. Goldner MG, Knatterud GL, Prout TE. Effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes III. Clinical implications of UGDP results. *JAMA*. 1971;218:1400–1410.
7. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*. 1998;352:837–853.
8. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil AW. 10-year follow-up of intensive glucose control in type 2 diabetes. *NEJM*. 2008; Sep. 10. [Epub ahead of print].
9. The ACCORD Study Group. Effects of intensive glucose lowering in type 2 diabetes. *NEJM*. 2008;358:2545–2559.
10. ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *NEJM*. 2008;358:2560–2572.
11. Abaira C, Duckworth W, McCarren M, et al. Design of the cooperative study on glycemic control and complications in diabetes mellitus type 2: Veterans Affairs Diabetes Trial. *J Diabetes Complications*. 2003;17:314–322.
12. ADA press release. Intensive blood glucose control yields no significant effect on CVD reduction in VA Diabetes Trial, June 8, 2008. www.diabetes.org/for-media/pr-intense-blood-glucose-control-yields-no-significant-effect-on-cvd-reduction.jsp. Accessed September 10, 2008.
13. The Look AHEAD Research Group. Look AHEAD (Action for Health in Diabetes): Design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials*. 2003;24:610–628.
14. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *NEJM*. 2002;346:393–403.
15. Ratner RE. An update on the Diabetes Prevention Program. *Endocr Pract*. 2006;12(Suppl 1):20–24.
16. Ceriello A, Motz E. Is oxidative stress the pathogenic mechanism underlying insulin resistance, diabetes, and cardiovascular disease? The Common Soil Hypothesis revisited. *Arterioscler Thromb Vasc Biol*. 2004;24:816–823.